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Review

Smoking, nicotine and neuropsychiatric disorders

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ABSTRACT

Tobacco smoking is an extremely addictive and harmful form of nicotine (NIC) consumption, but unfortunately also the most prevalent. Although disproportionately high frequencies of smoking and its health consequences among psychiatric patients are widely known, the neurobiological background of this epidemiological association is still obscure. The diverse neuroactive effects of NIC and some other major tobacco smoke constituents in the central nervous system may underlie this association. This present paper summarizes the pharmacology of NIC and its receptors (nAChR) based on a systematic review of the literature. The role of the brain's reward system(s) in NIC addiction and the results of functional and structural neuroimaging studies on smoking-related states and behaviors (i.e. dependence, craving, withdrawal) are also discussed. In addition, the epidemiological, neurobiological, and genetic aspects of smoking in several specific neuropsychiatric disorders are reviewed and the clinical relevance of smoking in these disease states addressed.

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1. Basic pharmacology of nicotine and smoking

1.1. Pharmacology of nicotine

Nicotine (NIC) is an alkaloid present in tobacco leaves and in lower levels in other plants such as eggplant, tomato, potato, and green pepper, where it acts as a natural insecticide (Hukkanen et al., 2005; Doolittle et al., 1995; Gotti et al., 2006). NIC was first isolated from tobacco in 1828 by Posselt and Reimann (Henningfield and Zeller, 2006). Chemically, NIC is a weak base containing a pyridine and a pyrrolidine ring; each possesses a tertiary amine. The pK_a of the pyridine nitrogen is 3.04, whereas the pK_a of the pyrrolidine nitrogen is 7.84 at physiological temperature and ionic strength. With these characteristics, approximately 23% of NIC is nonionized at physiological pH and thus able to rapidly cross biological membranes (Brewer et al., 2004; Yildiz, 2004). The pH of the environment is a key regulatory factor in NIC traffic across biological membranes (Hukkanen et al., 2005). In an acidic environment NIC is in an ionized state and does not rapidly cross membranes. For example, because of the acidic pH of gastric juice there is little absorption of swallowed NIC (such as from NIC gum) in the stomach (Hukkanen et al., 2005; Metz et al., 2004). Smoke from tobaccos used in pipes and cigars is more alkaline (pH = 6.5 or more), and as a result, NIC is mostly unionized and well absorbed from the mouth (Hukkanen et al., 2005; Metz et al., 2004). The acidic smoke (pH = 5.5–6) of tobacco used in cigarettes dramatically reduces the absorption of NIC from the mouth (because NIC is primarily ionized at this pH), so cigarette smokers need to inhale cigarette fumes into their lungs. There the alkaline fluid (pH = 7.4) of the human lung's inner surface can buffer the acidic fumes to a neutral pH on the extremely large surface of the alveoli, allowing NIC to be absorbed into the pulmonary circulation (the lungs may also act as a depot for NIC, as was demonstrated in some studies) (Hukkanen et al., 2005; Metz et al., 2004; Brewer et al., 2004; Yildiz, 2004).

In the blood (at physiological pH 7.4) NIC is about 69% ionized and 31% unionized and its binding to plasma proteins is less than 5% (Hukkanen et al., 2005). NIC can easily pass through the blood–brain barrier by passive diffusion and perhaps by carrier-mediated transport (but the exact mechanisms are not clear) (Wang et al., 2005; Lockman et al., 2005). Chronic NIC administration does not appear to influence the kinetics of NIC uptake into the brain (Lockman et al., 2005). The plasma half-life ($t_{1/2}$) of NIC is approximately 2 h. In the brain, the distributional $t_{1/2}$ of NIC is

10 min. Distributional $t_{1/2}$ describes the time that it takes a NIC dose to fall 50% from its peak level in the brain as the NIC is distributed to other body compartments with a high affinity for NIC (for example, the liver, spleen, kidney, lung) (Hukkanen et al., 2005; Baker et al., 2004b; Pogocki et al., 2007). When the half-life of NIC was determined by urine excretion data, it was much longer (≈11 h). This could be explained by the slow release of NIC from body tissues (Hukkanen et al., 2005).

NIC is extensively metabolized in the liver to six primary metabolites (nicotine glucuronide, nicotine N-oxide, nornicotine, nicotine isomethonium ion, cotinine, 2-hydroxynicotine). The predominant pathway during first-pass metabolism yields cotinine (in humans 70–80% of NIC is metabolized to cotinine), which may have some relevance in the diverse neurobiological effects of smoking as a ligand of nicotinic acetylcholine receptors (nAChRs) (Hukkanen et al., 2005; Yildiz, 2004; O'Leary et al., 2008). Furthermore, there are several other indications that cotinine is a pharmacologically active substance. It has (1) neuro- and/or cell-protective effects in cell-culture models; (2) attention enhancing effects; (3) antipsychotic-like effects (in prepulse inhibition paradigm); (4) dopamine-releasing effects in striatal tissue samples, etc. (Buccafusco, 2004; Terry et al., 2005a; Riveles et al., 2008; O'Leary et al., 2008). Several enzymes play a role in NIC metabolism in the liver, such as some members of the cytochrome P450 enzyme family (CYP2A6 > CYP2B6 ≫ CYP2D6 subtypes), flavin-containing monooxygenase 3, amine N-methyltransferase, aldehyde oxidase and UDP-glucuronosyltransferases (Hukkanen et al., 2005). Unmetabolized NIC excretion via the urine only accounts for about 5% of total elimination (Matta et al., 2007; Le Houezec, 2003; Balbani and Montovani, 2005). Animal studies suggest that to a minor extent NIC is metabolized in extrahepatic tissues, too (e.g. kidney, lung, brain) (Hukkanen et al., 2005; Le Houezec, 2003). The rate of NIC metabolism is influenced by a lot of factors, such as age, gender, meal consumption, race, hepatic or renal diseases, pregnancy, tobacco ingredients (e.g. menthol, which inhibits both CYP2A6 activity and also the glucuronidation of NIC), or medication status (e.g. contraceptive use) (for details see Hukkanen et al., 2005; Matta et al., 2007). Tobacco smoking per se influences NIC metabolism. The clearance of NIC is slower (thus the half-life of NIC tends to be longer) in smokers compared with non-smokers (Hukkanen et al., 2005; Matta et al., 2007; Benowitz and Jacob, 2000). This phenomenon may be explained by the effect of β-nicotyrine (a smoke ingredient with CYP2A6 inhibitory activity) as well as NIC-evoked CYP2A6 mRNA and protein down-regulation in the liver (Hukkanen et al., 2005).

1.2. Pharmacology and health consequences of smoking

The vast majority of tobacco users (98%) nowadays are cigarette smokers, in contrast to the last decades of the 19th century, when tobacco chewing and cigar smoking were the predominant forms of tobacco use (and industrial cigarette making was only in its infancy) (Mitrouska et al., 2007; Koob and Le Moal, 2006). In many respects (vide infra) cigarette smoking is a highly effective form of NIC intake (compared to, for example, different kinds of nicotine replacement therapy (NRT)). First, bioavailability of NIC in cigarette fumes (80–90%) is higher than in different formulations of NRT (NIC-containing gum/nasal spray/lozenge and most forms of patches) (Hukkanen et al., 2005). Second, most forms of NRT deliver NIC into the systemic circulation more slowly than smoking (Hukkanen et al., 2005). NIC is absorbed from smoke into the circulation relatively quickly because of the large alveolar surface and large blood perfusion of the pulmonary circulation (Brewer et al., 2004). During smoking, high levels of NIC reach the brain in 10–20 s after a puff, faster than with intravenous administration (Hukkanen et al., 2005). Third, maximal venous blood concentration of NIC during cigarette smoking could reach a higher level than during the use of different forms of NRT (Hukkanen et al., 2005). Fourth, cigarette smokers can easily regulate their NIC intake by changing their smoking pattern (puff volume, number of puffs per cigarette, inter-puff interval, puff velocity, etc.) according to their NIC needs in contrast to users of other forms of NRT (i.e. patch or gum) (Hammond et al., 2006). This fact is highly significant because average smokers consume only 30% of the available tobacco in each cigarette; thus there is a large amount of "idle" NIC in every cigarette (Hammond et al., 2006). Routes of drug administration that enable a rapid drug entry into the brain increase the propensity of the given drug to induce addiction and are also associated with a greater feeling of euphoria. For example, smoked cocaine ('crack') is thought to be more addictive than snorted cocaine, and cocaine or heroin administered intravenously, rather than by snorting, results in greater self-reports of pleasure (Samaha et al., 2005; Samaha and Robinson, 2005). During smoking, NIC concentrations increase more rapidly and reach higher levels than with most forms of NRT (Hukkanen et al., 2005). Not surprisingly, therefore, NIC is highly addictive when inhaled from tobacco smoke, whereas NRT products (which deliver NIC slowly) are less likely to lead to addiction (Samaha et al., 2005; Samaha and Robinson, 2005). According to the above data those NRT forms which provide rapid NIC release (e.g. nasal spray, chewing gum) have greater potential to cause behavioral dependence compared to NRT forms that provide slower NIC release (e.g. NIC patch) (Hajek et al., 2007; West et al., 2000).

Tobacco contains approximately 2500 chemical compounds, while tobacco smoke consists of over 4000 compounds, so several compounds of smoke are generated by various mechanisms (combustion, pyrolysis, distillation) during the burning of tobacco (Baker, 1987; Newhouse et al., 2004a; Frishman et al., 2006). There is an exothermic combustion zone at the burning end of the cigarette, where the temperature is 700–950 °C. Below the combustion zone is the pyrolysis/distillation zone with a lower temperature (200–600 °C). Most smoke ingredients are generated in this area during endothermic reactions (Baker, 1987). The actual composition of cigarette smoke is influenced by many factors, such as characteristics of the cigarette paper and filter, column length of the tobacco rod, composition of the tobacco, etc. (Frishman et al., 2006). Tobacco smoke has two phases, the gaseous phase and the particulate phase. The gaseous and particular phases comprise 95% and 5% of the smoke's weight (Zevin and Benowitz, 1999). The gaseous phase contains inter alia nitrogen oxide, carbon monoxide, carbon dioxide, ammonia, nitrites, alcohols, ketones (acetone, butanone), volatile sulfur-containing compounds (hydrogen sulfide), hydrocarbons, aldehydes (formaldehyde and acetaldehyde), free radicals and other oxidants (hydrogen peroxide, superoxide anion and peroxynitrite). According to recent results, hydrogen peroxide probably has a role in airway tumorigenesis (Frishman et al., 2006; Zevin and Benowitz, 1999; Khan et al., 2008; Swan and Lessov-Schlaggar, 2007; Hatzinikolaou et al., 2006; Pryor and Stone, 1993). The particulate phase contains alkaloids, water, and tar (Frishman et al., 2006; Zevin and Benowitz, 1999). NIC is the most abundant alkaloid in tobacco (accounting for 95% of the total alkaloid content) (Cai et al., 2003). Minor alkaloids are anatabine, anabasine, and nornicotine; some of them – like NIC – possess agonist activity on nAChRs. Other tobacco smoke ingredients, such as nitrosamines (i.e. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN) and N-nitrosodiethylamine (DEN)) and cembranoids are also ligands of nAChRs (Zevin and Benowitz, 1999; Ayers et al., 2005; Schuller, 2007; Ferchmin et al., 2005, 2009; Cai et al., 2003). Tar consists of polycyclic aromatic hydrocarbons (PAH), metallic ions, several radioactive compounds, and free radicals, as well (Frishman et al., 2006; Swan and Lessov-Schlaggar, 2007; Pryor and Stone, 1993). The internal

documents of tobacco companies – which were disclosed by law in 1998 – have revealed that many ingredients of tobacco were added by cigarette manufacturers to mask the odor, visibility, or irritation effects of environmental tobacco smoke (i.e. vanillin, bergamot oil), to enhance bronchodilation (i.e. theobromine, caffeine), and to regulate pH, which increases the bioavailability of NIC, and temper the harsh feeling of the smoke (i.e. levulinic acid, ammonia, sugars). Overall additives made up 10% of the total weight of the cigarette (Talhout et al., 2006; Rabinoff et al., 2007; Connolly et al., 2000; Keithly et al., 2005; Hammond et al., 2006; Henningfield et al., 2004).

Environmental tobacco smoke is a combination of sidestream smoke (85%) and exhaled mainstream smoke (15%) (Ambrose and Barua, 2004). Mainstream smoke (the inhaled part of smoke) is the smaller portion (45%) of total smoke compared with sidestream smoke (55%) (sidestream smoke is the smoke emitted from the burning end of a cigarette) (Phillips et al., 2003). Sidestream smoke has a greater concentration of some toxic components (i.e. carbon monoxide, benzene, ammonia, and many carcinogens) than mainstream smoke (Phillips et al., 2003; Ambrose and Barua, 2004; Brownson et al., 1997). Moreover, in sidestream smoke, the amount of NIC is twice as high as in the mainstream smoke (Brownson et al., 1997). These differences between compounds concentrations in sidestream and mainstream smoke are caused by the less complete combustion in those regions from which sidestream smoke derives (Brownson et al., 1997). The above facts suggest that sidestream and mainstream smoke have comparable carcinogenic and cardiovascular risk heightening effects (Swan and Lessov-Schlaggar, 2007). Because smoke is diluted in the environmental air, a non-smoker is typically exposed to less tobacco smoke than an active smoker. Nevertheless, epidemiological investigations have clearly demonstrated the health risks of passive smoking, too (Swan and Lessov-Schlaggar, 2007; Barnoya and Glantz, 2005; Brownson et al., 1997; Venn and Britton, 2007; Subramanian and Govindan, 2007).

An average cigarette contains 10–14 mg NIC, but only 1–1.5 mg of NIC is absorbed systemically from the inhaled smoke of one cigarette (Hukkanen et al., 2005). When a cigarette is smoked, a large amount of NIC (≈35%) is destroyed by combustion and a similar amount of NIC is lost in non-inhaled smoke (Balbani and Montovani, 2005).

Many observations (see below) suggest that cigarette smoking is reinforced not only by NIC but also by nonnicotine chemical, behavioral and environmental factors, and NIC per se has merely a moderate addictive potential (Rose, 2006; Samaha et al., 2005; Samaha and Robinson, 2005; Talhout et al., 2007). For example, denicotinized cigarettes have been shown to reduce tobacco craving and some withdrawal symptoms during cessation and are comparable with NIC-containing cigarettes in terms of perceived reward (Dar and Frenk, 2004; Rose, 2006; Henningfield et al., 2005). Moreover, intravenous bolus injections of NIC elicit minimal feelings of reward, pure intravenous NIC self-administration has not been convincingly demonstrated among smokers, NIC has shown only a limited ability to induce self-administration in animals and conditioned place-preference (CPP) studies suggest that NIC has weak reinforcing effects. Finally NRT has limited efficacy as a cessation therapy and low addictive potential (Samaha et al., 2005; Samaha and Robinson, 2005; Talhout et al., 2007; Rose, 2006; Dar and Frenk, 2004; Henningfield et al., 2005; Le Foll and Goldberg, 2005). These findings have led to the hypothesis that, along with NIC, other addictive components are also present in tobacco smoke. Accordingly some cigarette tobacco ingredients (i.e. gamma-heptalactone, gamma-valerolactone, gamma-decalactone, delta-decalactone, gamma-dodecalactone, menthol, and β-nicotyrine) may decrease the metabolism of NIC via CYP2A6 inhibition, which could theoretically increase the addictive potential of NIC sourced from tobacco smoke (Hukkanen et al., 2005; Rabinoff et al., 2007). Moreover, some other ingredients of tobacco smoke have intrinsic addictive properties. For example, several studies raised the possibility that acetaldehyde has addictive features. First, acetaldehyde activates dopaminergic cells in the ventral tegmental area (VTA), which is a feature of many (but not all) addictive agents (Melis et al., 2005; Foddai et al., 2004; Talhout et al., 2007). Second, self-administration and conditioned place-preference tests in animals have shown that acetaldehyde has reinforcing properties (Talhout et al., 2007). Third, it seems that acetaldehyde – as the first metabolite of ethanol, produced by alcohol dehydrogenase and catalase – could strongly mediate the addictive potential of ethanol (Melis et al., 2007; Foddai et al., 2004). This is supported by the findings of many investigations. For example, the administration of acetaldehyde-chelating agent D-penicillamine decreases spontaneous ethanol drinking and ethanol-induced locomotor stimulation and conditioned place-preference in rodents, ethanol-induced place-preference is also inhibited by alcohol dehydrogenase blocking agent 4-methyl-pyrazole (4-MP), 4-MP also decreases ethanol-evoked dopaminergic cell firing in VTA and dopamine level increase in nucleus accumbens (NAcc), and salsolinol – the condensation product of acetaldehyde and dopamine – also has intrinsic reinforcing properties (Foddai et al., 2004; Rodd et al., 2008; Matsuzawa et al., 2000; Melis et al., 2007; Font et al., 2006). Acetaldehyde is generated from sugars in tobacco during combustion, so it may have a role as a co-addictive agent in tobacco smoke (Talhout et al., 2006, 2007). This theory is further bolstered by acetaldehyde's ability to facilitate the reinforcing effects of NIC (in self-administration paradigm) (Talhout et al., 2007). NIC does not possess any monoamine oxidase (MAO) inhibitory activity, but tobacco smoke contains various compounds (i.e. farnesylacetone, 2-naphthylamine, harman, and norharman) with marked MAO inhibitory properties (Lewis et al., 2007; Castagnoli et al., 2002). MAO-A and MAO-B are key enzymes in the degradation of monoamine neurotransmitters, such as dopamine, serotonin, and norephinephrine (van Amsterdam et al., 2006; Lewis et al., 2007; Guillem et al., 2005). Among smokers the activities of both monoamine oxidase isoforms (MAO-A and MAO-B) are reduced in the brain and also in peripheral organs (van Amsterdam et al., 2006; Lewis et al., 2007; Fowler et al., 1996a,b; Leroy et al., 2009). A longitudinal study by Harro et al. (2004) showed that both high and low platelet MAO activity is a risk factor for the initiation of smoking; thus the decreased MAO activity among smokers may not (merely) be genetic in origin (Harro et al., 2004). The same conclusion was drawn by Fowler et al. (1996a) in their previous study, as they failed to find any difference in MAO-B brain activity between groups of non-smokers and former smokers (Fowler et al., 1996a). Other studies have also found that decreased MAO activity in smokers appeared to be reversible, since its activity slowly recovered following smoking cessation (van Amsterdam et al., 2006; Harro et al., 2004; Fowler et al., 1996a). Moreover, findings about the effects of genetic polymorphisms in genes for MAO-A and MAO-B on smoking habits are unclear (Lewis et al., 2007; Tochigi et al., 2007). In recent years, several studies have revealed that self-administration of NIC is significantly increased by MAO inhibitor pretreatment. Furthermore MAO inhibitors maintained the repeated NIC treatment-induced increased locomotor activity (as a form of behavioral sensitizition) which is otherwise abolished following three periods of withdrawal (van Amsterdam et al., 2006; Lewis et al., 2007; Guillem et al., 2005; Villegier et al., 2003, 2007a,b). Moreover, treatment of rats with the non-selective monoamine oxidase inhibitor phenelzine enhances the discriminative stimulus effect of NIC (Wooters and Bardo, 2007). In addition, an NIC-induced increase of extracellular dopamine levels in the NAcc was enhanced by MAO inhibitor (tranylcypromine) pretreatment (addictive agents such as psychostimulants, NIC,

opiates, ethanol, and THC acutely increase the extracellular dopamine level in the NAcc, and this phenomenon is considered a possible neurochemical marker of their addictiveness) (Villegier et al., 2007b; Melis et al., 2005). Experiments by Villegier et al. (2007a,b) have shown that the α1-adrenergic receptor antagonist prazosine decreases the enhancing effects of MAO inhibitors on NIC self-administration and also tempers the enhancing effect of MAO inhibitor pretreatment on NIC-induced elevation of dopamine concentration in the NAcc. Furthermore, they also showed that an increase in NIC self-administration evoked by MAO inhibition is a dopamine-1 (D1) receptor dependent process (Villegier et al., 2007a,b). Recently, the repeated co-administration of an MAO inhibitor and NIC (but neither repeated NIC nor repeated MAO inhibitor administration alone) was also demonstrated to evoke a similar neurochemical response (enhanced cortical norepinephrine and serotonin release induced by D-amphetamine or para-chloroamphetamine, respectively) to that found in the repeated administration of various other compounds (cocaine, ethanol, morphine, amphetamine) from different groups of addictive agents (for details see Lanteri et al., 2008, 2009). Because MAO inhibitors are present in tobacco smoke and act synergically with NIC to produce a feeling of reward and also to cause addiction, the inhibition of MAO enzymes (alone or with NIC replacement therapy) could be helpful in enhancing cessation rates. Double-blind studies examining the efficacy of MAO-A or MAO-B inhibitors as cessation agents have provided promising results (Lewis et al., 2007; Frishman et al., 2006; George and Weinberger, 2008).

Both human and animal studies have observed that NIC administration enhances the reinforcing effects of rewarding stimuli. Moreover NIC withdrawal is associated with brain reward threshold elevation; thus the strong addictive nature of NIC – which has a relatively moderate euphorigenic effect – can partially be explained by its capacity to increase the salience of rewarding stimuli in the environment (Markou, 2008; Barr et al., 2008c; Attwood et al., 2009).

Smoking is widely known to have a marked and diverse deleterious effect on health. Inter alia smoking is associated with chronic obstructive pulmonary disease, various types of malignancies, hypertension, unfavorable changes in the lipoprotein profile, signs of inflammation (i.e. elevated levels of white blood cells and inflammatory markers such as CRP, IL-6 and TNF-α), altered blood coagulation (by stimulating platelet aggregation and reducing fibrinolysis), elevated risk of diabetes mellitus, increased risk of infective disorders (i.e. severe forms of influenza, pneumococcal disease, tuberculosis and wound infections), and also decreased fertility and elevated risk of spontaneous abortion (Yildiz, 2004; Burns, 2001; Gleerup and Winther, 1996; Catanzaro et al., 2007; Halperin et al., 2008; Bowman et al., 2007; Benowitz, 2008; Steptoe and Ussher, 2006; Eliasson, 2003). NIC and other nAChRs agonists in cigarette smoke appear to have an essential role in the pathogenesis of cancer and arteriosclerosis, which were previously believed to be caused primarily by other components of tobacco smoke (i.e. PAHs and nitrosamines) (Bersch et al., 2009; Wong et al., 2007; Egleton et al., 2008; Schuller, 2007, 2008; Cucina et al., 2008; Lau et al., 2006; Catanzaro et al., 2007; Knaapen et al., 2007; Ramos and Moorthy, 2005; Baird et al., 2005). Furthermore, recent genome-wide association studies have identified single nucleotide polymorphisms (SNP) in 15q24-25 locus (containing the genes for α3, α5 and β4 subunits of nAChRs), which are associated with the risk of lung cancer, arteriosclerosis, and NIC addiction (Thorgeirsson et al., 2008; Amos et al., 2008; Hung et al., 2008; Volkow et al., 2008). Although pure NIC may have damaging health effects, and NRT is frequently used longer than recommended, there is no doubt that long-term smoking is more harmful than long-term NIC administration alone (Etter, 2009; Hughes, 2008a).

1.3. Gender differences in nicotine action

A marked gender difference in smoking rates is reported from most parts of the world, because males are markedly over-represented among cigarette smokers (Pauly, 2008). Various human and animal studies have hinted that gender differences may play a role in the biological effects of NIC (Schnoll and Patterson, 2009; Pogun and Yararbas, 2009; Pauly, 2008). The development of NIC dependence among females after first use of NIC is more rapid than among males (Pogun and Yararbas, 2009). Moreover, females relapse more frequently following cue-induced drug craving (Pogun and Yararbas, 2009; Pauly, 2008). Differences between the sexes have also been found in the extent of chronic NIC administration-evoked nAChR upregulation. In addition, among female rodents self-administration is acquired at lower NIC doses than among males, furthermore the anxiolytic effects of NIC are also more pronounced among females than among males (see in details in Pogun and Yararbas, 2009). The reinforcing effect of NIC is probably lower among females than among males (Pogun and Yararbas, 2009; Pauly, 2008). Although there are some discrepancies in the literature, the metabolism of NIC has been found to be higher among females than among males (Hukkanen et al., 2005; Pogun and Yararbas, 2009). One of the most important practical consequence of the differences in NIC's effects between the sexes is that NIC replacement therapy (and probably bupropion) are less effective in females than males in promoting long-term smoking cessation (Schnoll and Patterson, 2009; Pogun and Yararbas, 2009; Pauly, 2008).

2. Nicotinic acetylcholine receptors (nAChRs)

2.1. Basic pharmacology of nAChRs

Acetylcholine (ACh) is one of the most ubiquitous signaling molecules found in nature (Gotti and Clementi, 2004). It is a phylogenetically ancient molecule; both ACh and the acetylcholine synthesizing enzyme, choline acetyltransferase, are found in a wide range of life forms (i.e. bacteria, plants, fungi, lichens, invertebrates, vertebrates) (Gotti and Clementi, 2004; Horiuchi et al., 2003). NIC is an agonist of nicotinic acetylcholine receptors (nAChRs), which are members of the Cys-loop ligand-gated ion channel (LGIC) family and respond to ACh as their endogenous ligand (furthermore, in the last decade choline – the precursor of acetylcholine and also the product of acetylcholine degradation – has been shown to have some direct effects on some kinds of nAChRs) (Cassels et al., 2005; Bertrand and Gopalakrishnan, 2007; Hogg et al., 2005; Alkondon and Albuquerque, 2006) In addition to NIC, a great number of other ligands of nAChRs (i.e. epibatidine, cytisine, α-bungarotoxin, methyllycaconitine and α-conotoxin) are provided by natural sources (Daly, 2005; Hogg and Bertrand, 2004). LGICs – like ACh – are phylogenetically ancient structures. Recent studies have revealed their presence in prokaryote organisms (Hilf and Dutzler, 2008, 2009; Bocquet et al., 2007; Tasneem et al., 2005; Zouridakis et al., 2009). The family of Cys-loop LGICs also includes GABA-A, GABA-C, glycine, zinc activated ZAC and 5-HT_3 receptors (Jensen et al., 2005; Farber et al., 2004; Hogg et al., 2005). The Cys-loop family is a member of the LGIC superfamily which has two other families (P2X receptors for ATP and glutamate-activated cation channel receptors). The members of the superfamily differ from each other in their subunit number and the number of transmembrane domains in one subunit (Hogg et al., 2005). The members of the Cys-loop family are formed from a pentameric assembly of subunits, each of which has four transmembrane spanning regions (Jensen et al., 2005; Arias and Bhumireddy, 2005; Hogg et al., 2005). The subunits are localized around the central ion-conducting pore, and the receptors gate the

flux of either the cations Na^+, K^+, and Ca^{2+} (nAChRs and 5-HT3R) or anions, such as Cl^- and HCO_3^- (GABA-A, GABA-C and glycine receptors) (Jensen et al., 2005; Arias and Bhumireddy, 2005). There are different molecular models (i.e. Monod–Wyman–Changeux or the "concerted two state model" and the "quaternary twist model") based on biochemical and structural investigations that could explain the functional states (active, resting and desensitized states, which differ from each others in their affinity to agonists/antagonists and in the level of conductance of ion channels) of nAChRs and the molecular mechanisms of the gating process (for details, see Changeux and Taly, 2008; Jensen et al., 2005; Taly et al., 2006; Giniatullin et al., 2005; Wang and Sun, 2005; Quick and Lester, 2002).

To date, seventeen nAChR subunits have been cloned in vertebrate species. A much greater diversity of nicotinic receptor subunits have been found in some non-vertebrates, for example at least 27 kinds of nAChR subunits are known in rhabditid nematode Caenorhabditis elegans (Jensen et al., 2005; Jones et al., 2007; Millar and Gotti, 2009; Blaxter, 1998). The nAChR subunits have been divided into muscle types (α1, β1, δ, γ and ε) and neuronal types (α2–α10 and β2–β4) (Jensen et al., 2005). Although the α10 subunit cannot form a functional homomeric receptor (see below), it can form a functional nAChR when co-expressed with the α9 subunit. Because the expression of the α9 subunit is limited mainly to extraneuronal tissues/organs (the olfactory epithelium, hair cells of the inner ear, lymphocytes, dorsal root ganglion cells, and epidermal basal cell and follicular central cell layers in the skin and pituitary gland), nAChRs containing α9 and α10 do not fall conveniently into the conventional classification of either muscle type or neuronal nAChRs (Jensen et al., 2005; Lips et al., 2005; Plazas et al., 2005; Baker et al., 2004a; Luebke et al., 2005; Millar and Gotti, 2009). The α8 subunit is expressed only in avian species (Jensen et al., 2005; Lips et al., 2005; Millar and Gotti, 2009).

The ligand (ACh) binding sites of the receptors comprise two parts (principal and complementary components) (Gotti et al., 2006a,b, 2007). In case of homopentameric (i.e. α7) receptors the same subunit carries – on its opposite sides – both the principal and the complementary components so at the interface between two identical subunits the complete ligand-binding site comes into existence (consequently homopentameric receptors have five identical ACh-binding sites per receptor molecule) (Gotti et al., 2006a,b, 2007). In case of heteropentameric receptors α (α2, α3, α4 or α6) subunits carry the principal components, and β subunits (β2 or β4) carry the complementary components of ligand-binding sites (consequently heteropentameric receptors have two identical ACh-binding sites per receptor molecule) (Gotti et al., 2006a,b, 2007). In this kind of formation of the ligand-binding site, the subunits are conventionally grouped into ligand-binding (α) subunits and structural (β, γ, ε, δ) subunits (Gotti et al., 2000). α5 and β3 subunits are unique in this classification because they carry neither the principal nor the complementary component of the ACh-binding site; consequently, they are considered accessory subunits (Gotti et al., 2007; Kuryatov et al., 2008). The presence of α5 or β3 subunits as a fifth subunit in heteromeric nAChRs are frequent in the brain (for example in $(\alpha4\beta2)_2\alpha5$ or $(\alpha6\beta2)_2\beta3$ receptors). The presence of these auxiliary subunits in the pentamer structure can change the neurochemical characteristics of the receptors (i.e. in regard to their Ca^{2+} permeability or sensitivity to activation by ACh). Furthermore, a recent investigation has revealed the absence of upregulation of α4β2α5 receptors after chronic NIC administration in the rodent brain in contrast to the massive upregulation of simple α4β2 receptors (Kuryatov et al., 2008; Mao et al., 2008; Gotti et al., 2006a,b, 2007; Tapia et al., 2007).

In addition to their classical ACh-binding site (the so-called orthosteric-binding site), both α7 and α4β2 nAChRs have allosteric-binding sites for their positive and negative modulators. For example, antihelmetic agent ivermectin, tyrosine kinase inhibitor genistein, 5-hydroxyindole, cholinesterase-inhibitor galantamine, or progesterone are allosteric modulators of α7 receptors, while progesterone, 17-β-estradiol, zinc and the thiazole analog LY-2087101 are allosteric modulators of α4β2 receptors (Bertrand and Gopalakrishnan, 2007; Hogg et al., 2005; Dani and Bertrand, 2007). Some peptides (i.e. lynx-1, an endogenous brain protein closely related in structure to bungarotoxins isolated from snake venom; SLURP-1 secreted by keratinocytes; and β-amyloid, a key protein in the pathobiology of Alzheimer's disease) are widely known to also have allosteric modulatory properties on nAChRs (Changeux and Taly, 2008; Bertrand and Gopalakrishnan, 2007; Hogg et al., 2005; Gotti et al., 2006a,b; Miwa et al., 2006).

Neuronal nAChR are heteropentamers composed of α subunits (α2, α3, α4, α5, α6) and β subunits (β2, β3, β4) or homopentamers of five α-subunits (e.g. α7, α8 or α9) or α heteropentamers (e.g. α7/α8 (in chicken) or α9/α10 (in mammals)). αβ heteropentamers are α-bungarotoxin insensitive, while α homo- and heteropentamers are α-bungarotoxin sensitive receptors (Lips et al., 2005; Plazas et al., 2005; Lindstrom, 2003; Gotti et al., 2006a,b, 2007). Not only can the α7 subunit form a homopentameric nAChR, but, according to some convincing recent results (which may partially contradict the above classification), the α7 subunits may co-assemble with β2 subunits to form a functional, naturally expressed heteromeric receptor (Liu et al., 2009; Son and Winzer-Serhan, 2008; Millar and Gotti, 2009).

The prevalent, naturally occurring stoichiometry of αβ heteromer nAChRs in the brain is $(\alpha)_2(\beta)_3$, but the $(\alpha)_3(\beta)_2$ stoichiometry could also occur both naturally and under some experimental conditions (using in vitro models) (Jensen et al., 2005; Tapia et al., 2007; Gotti et al., 2007; Kuryatov et al., 2008). The relative proportions of α and β subunits within the pentamer may alter various biochemical properties of the receptors. For example, $(\alpha4)_3(\beta2)_2$ and $(\alpha4)_2(\beta2)_3$ differ from each other in their permeability to Ca^{2+}, their affinity to agonists, and the velocity of their desensitization (Tapia et al., 2007; Gotti et al., 2007; Kuryatov et al., 2008; Moroni and Bermudez, 2006; Millar and Gotti, 2009). The stoichiometry of heteromeric α9/α10 nAChR is $(\alpha9)_2(\alpha10)_3$ (Plazas et al., 2005). The α9 and α9α10 nAChRs are characterized by mixed muscarinic/nicotinic pharmacological profiles significantly different from those of other nAChRs. Furthermore, genes of α9 and α10 subunits represent a distant, distinct, and peculiar early divergent branch within the nAChR gene family (Jensen et al., 2005; Plazas et al., 2005; Verbitsky et al., 2000).

Ca^{2+} permeability of a given nAChR depends on its subunit composition. α7–α10 subunits containing receptors have higher Ca^{2+} permeability compared to those nAChRs which are formed by α2–α6 subunits together with β2–β4 subunits (Fucile et al., 2006; Jensen et al., 2005).

Clearly, 12 different kinds of neuronal α and β subunits can combine in a great number of ways to homo- or heteropentamers, but in mammalian brain, two major subtypes of nAChRs are expressed: the α4β2* heteropentamer receptors (with a high affinity for NIC) and the α7 homopentamer receptors (with low affinity for NIC) (Jensen et al., 2005; Tapia et al., 2007; Gotti et al., 2006a; Kulak et al., 2006). The α4β2* subtype accounts for 90% of the brain's nAChRs with a high affinity for NIC (asterisk indicates that additional subunits such as α5 may be present in some of these AChRs) (Jensen et al., 2005; Tapia et al., 2007; Gotti et al., 2006a).

2.2. Neuroanatomical distribution of different nAChRs

The neuroanatomical distribution of different nAChRs is species dependent to some degree. Furthermore, relevant data are obtainable from studies using different methods (i.e. mRNA in

situ hybridization and/or immunoprecipitation and/or using subunit specific receptor ligands, etc.), thus only a brief survey of the issue is presented here (for a current review of the topic, see Millar and Gotti, 2009). The most abundant nAChR type ($\alpha4\beta2^*$ receptors) are present, inter alia, in the cortex, striatum, cerebellum, lateral geniculate nucleus, amygdala, superior colliculus, hippocampus, spinal cord, and thalamus. $\alpha7$ receptors are expressed with high density in the cortex, hippocampus and limbic regions and with low density in the thalamus and basal ganglia. Receptors containing $\alpha9$- and $\alpha10$ subunits are present in the dorsal root ganglia, the pars tuberalis of the pituitary gland and non-neuronal cells (see above), but not in the brain. $\alpha3\beta4^*$ receptors are mainly localized in the ganglions of the autonomic nervous system as well as in the adrenal medulla, medial habenula, pineal gland, dorsal medulla, cerebellum, interpeduncular nucleus, hippocampus and retina. $\alpha3\beta2^*$ receptors are expressed in different parts of the visual pathway, the cerebellum, and in monkey (but not rodent) striatum. $\alpha6^*$ receptors (probably mainly in $\alpha6\alpha4\beta2\beta3$ and $\alpha6\beta2\beta3$ subunit compositions) are distributed in the lateral geniculate nucleus, retina, locus coeruleus, VTA, striatum, reticular nucleus of the thalamus, and colliculus superior. Distribution of $\alpha2^*$ receptors are limited, but are present in the retina, nucleus interpeduncularis, and cortex (in $\alpha2\alpha4\beta2$ composition) (Jensen et al., 2005; Gotti et al., 2006a,b, 2007; Gaimarri et al., 2007; Quik et al., 2007; Millar and Gotti, 2009).

nAChRs are localized on cell bodies, axons, presynaptic terminals, postsynaptic densities and also on dendrites (Dani and Bertrand, 2007; Gahring and Rogers, 2006). Most nAChRs in the nervous system are at presynaptic localizations as autoreceptors in cholinergic, and as heteroreceptors in non-cholinergic (i.e. noradrenalinergic, dopaminergic, serotoninergic, GABAergic, glutamatergic) synapses, where they serve to modulate the release of neurotransmitters (Amtage et al., 2004; Raiteri, 2006; Exley and Cragg, 2008; Quarta et al., 2007; Lendvai and Vizi, 2008).

Nicotinic receptors are also expressed in non-neuronal cells of the CNS (i.e. astrocytes or microglial cells) and in some cell types of non-nervous systems (i.e. different cell types of placenta, epithelial and endothelial cells of lung, lymphocytes and macrophages) (Gahring and Rogers, 2006; Lips et al., 2005; Gotti and Clementi, 2004; Lendvai and Vizi, 2008).

2.3. Genetic variability in nAChRs genes and their associations with different aspects of nicotine addiction

The genetic determination of smoking-related behaviors is supported by several twin-studies (Portugal and Gould, 2008). According to these results, the heritability of NIC dependence ranges from 31% to 75%, and of persistent smoking from 39% to 82% (Portugal and Gould, 2008). The roles of different nAChRs subunits in different aspects of addiction and in NIC-evoked behavioral changes are also under intensive investigation. The application of molecular genetic approaches (i.e. genome-wide linkage analysis, genome-wide association analysis, candidate gene screening, genetic animal models (knock-out rodent strains)) have shed light on many aspects of this topic (Portugal and Gould, 2008; Mineur and Picciotto, 2008; Fowler et al., 2008). Genome-wide linkage studies have identified a number of potential susceptibility loci (i.e. located on chromosomes 1, 2, 6, 9, 11, 14, 17, 18, 19, 21) for NIC dependence (Mineur and Picciotto, 2008). Genome-wide and candidate gene association studies have found several SNPs in various nicotinic acetylcholine receptor subunit genes associated with smoking behavior. Some SNPs (i.e. rs1044396, rs1044397, rs3787137) in the CHRNA4 gene (it codes for $\alpha4$ subunit) are associated with smoking quantity or the risk of NIC dependence, while other SNPs in this gene (i.e. rs2236196, rs6122429) are associated with subjective responses to smoking (Portugal and Gould, 2008). The association between polymorphisms in the CHRNB2 gene (which codes for $\beta2$ subunit) and smoking habits seems less robust than in the case of CHRNA4, but some SNPs of this gene have also been observed to affect smoking behavior (i.e. rs2072660 is associated with a reduced risk for smoking initiation, and rs2072658 and rs2072660 are associated with altered subjective feelings about the negative effects of smoking) (Portugal and Gould, 2008). Several studies have suggested that various SNPs in the nicotinic receptor gene cluster (that comprises CHRNA3, CHRNA5 and CHRNB4 genes) on locus 15q25 and in another nicotinic receptor gene cluster (that comprises CHRNA6 and CHRNB3 genes) on locus 8p11 can also influence smoking habits (Portugal and Gould, 2008; Bierut et al., 2008; Hoft et al., 2009). Interestingly, SNPs in the gene for nicotinic acetylcholine receptor $\beta1$ subunit (CHRNB1) are also associated with smoking (paradoxically, this subunit is expressed only in the neuromuscular junction (and not in the central nervous system)) (Lou et al., 2006; Jensen et al., 2005; Millar and Gotti, 2009; Mineur and Picciotto, 2008; Lessov-Schlaggar et al., 2008).

Studies using different nAChR subunit knock-out (KO) rodent strains have also provided valuable information about the role of various subunits in NIC dependence and NIC-evoked effects. $\beta2$ subunit KO mice do not show the enhancing effects of NIC in hippocampus-dependent learning paradigms, nor do they self-administer NIC or show an NIC-induced increase in the firing rate of dopaminergic neurons or an NIC-evoked elevation in dopamine levels in the ventral striatum. Moreover, NIC-dependent $\beta2$ subunit KO mice displayed typical somatic signs after NIC withdrawal, suggesting that $\beta2$ subunits are not involved in the physical signs of NIC withdrawal. Intriguingly, studies with $\beta2$ KO mice and others using $\beta2$ subunit containing nAChR antagonists have suggested, however, that receptors containing $\beta2$ subunits have an important role in the affective components of NIC withdrawal (Portugal and Gould, 2008; Mineur and Picciotto, 2008; Jackson et al., 2008). The lentiviral vector-mediated $\beta2$ subunit gene delivery into the VTA in $\beta2$ KO mice reestablished both NIC self-administration and NIC-evoked increase in dopamine levels in the NAcc. These results further suggest the essential role of the $\beta2$ subunit in NIC addiction (Maskos et al., 2005; Portugal and Gould, 2008; Fowler et al., 2008). Given the frequent co-assembly of $\alpha4$ and $\beta2$ subunits (as $\alpha4\beta2^*$ nAChRs, see above), $\alpha4$ KO mice not surprisingly show similarities to $\beta2$ KO mice. For example, neither strain experienced an NIC-evoked elevation of striatal dopamine levels or an NIC-induced changes in body-temperature or locomotor activity, or NIC-induced analgesia in the hot-plate test (Portugal and Gould, 2008; Mineur and Picciotto, 2008; Marubio et al., 1999). NIC self-administration is also impaired in $\alpha4$ KO mice, but the lentiviral vector-mediated re-expression of $\alpha4$ subunit in the VTA restored NIC self-administration in $\alpha4$ KO mice strain (Pons et al., 2008). Interestingly Tapper et al. (2004), using a knock-in mice strain with a single point mutation ($Leu^{9'} \rightarrow Ala^{9'}$) in the $\alpha4$ subunit (this mutation renders $\alpha4^*$ nAChRs hypersensitive to NIC), showed that these mutant mice exhibit a 50-fold increase in sensitivity to the rewarding effects of NIC compared to wild-type mice, as measured by the conditioned place-preference paradigm (Tapper et al., 2004; Portugal and Gould, 2008; Mineur and Picciotto, 2008; Fowler et al., 2008). $\alpha6$ KO mice also showed loss of NIC self-administration behavior, and the lentiviral vector-mediated re-expression of this subunit in the VTA reestablished NIC self-administration in this KO strain. These results suggest that the $\alpha6$ subunit containing nAChRs (i.e. $\alpha6\beta2^*$) in the reward pathway play a crucial role in NIC reward (Pons et al., 2008). The knock-out of the $\alpha7$ subunit has no radical impact on NIC-evoked reward measured by conditioned place-preference or by self-administration paradigms. However, studies with the $\alpha7$ KO mice strain

suggest the role of the α7 subunit in physical (i.e. withdrawal-induced hyperalgesia or decreased locomotion) but not in affective signs of NIC withdrawal (Portugal and Gould, 2008; Mineur and Picciotto, 2008; Jackson et al., 2008; Pons et al., 2008; Walters et al., 2006). β4 subunit KO rodents display decreased somatic signs (i.e. changes in grooming, chewing, scratching, and tremors) of NIC withdrawal, which suggests this subunit may have a role in somatic symptoms after smoking cessation (Portugal and Gould, 2008; Mineur and Picciotto, 2008; Jackson et al., 2008; De Biasi and Salas, 2008).

2.4. Desensitization and upregulation of nAChRs

An aftermath of nAChRs agonist (i.e. NIC) administration is the desensitization (i.e. temporary inactivation) of both major types of brain nAChRs (α4β2 and α7) with markedly different velocities of desensitization in regard to the two main subtypes (in a range of seconds for α4β2 and milliseconds for α7) (Giniatullin et al., 2005; Léna and Changeux, 1998; Jacobsen et al., 2004; Prus et al., 2007; Robinson et al., 2006; Janhunen and Ahtee, 2007; Wooltorton et al., 2003; Picciotto et al., 2008). After agonist wash-out, the desensitized state of the α4β2 receptor ceases within minutes (Jacobsen et al., 2004; Picciotto et al., 2008). Acute tolerance to NIC caused by the desensitization of nAChRs was demonstrated in various in vivo (i.e. NIC-evoked prolactin release or nicotine-stimulated synaptosomal $^{86}Rb^{+}$ efflux) models and also in behavioral (i.e. discriminative stimulus or conditioned taste aversion) paradigms, allowing for the conclusion that NIC could act as a functional antagonist in vivo (Prus et al., 2007; Kuryatov et al., 2005; Robinson et al., 2006; Hulihan-Giblin et al., 1990; Vann et al., 2006). This functional antagonist effect of NIC has great relevance from a clinical perspective. For example, it may explain how both agonists and antagonists of nAChRs can have anti-depressant effects among patients with depression and in animal models of depression (George et al., 2008; Philip et al., 2009; Picciotto et al., 2008). Desensitization of nAChRs in different cell types of VTA is also very important in the regulation of activity of the mesolimbic reward pathway by NIC (see discussion below) (Picciotto et al., 2008; Wooltorton et al., 2003; Keath et al., 2007; Dani and Harris, 2005). One of the main supposed functions of nAChR desensitization is the protection of neurons from uncontrolled excitation. This theory is supported by a mutation leading to decreased desensitization of the α7 receptor, which is accompanied by the premature death of animals with this mutation (Wang and Sun, 2005; Mudo et al., 2007). Details about the molecular mechanisms underlying the desensitization of nicotinic receptors (i.e. receptor phosphorylation/dephosphorylation), characteristics of desensitization dependent on exposure time and/or ligand concentrations, and the diverse consequences of desensitization under physiological or pathological conditions can be found in Giniatullin et al. (2005), Wang and Sun (2005), Quick and Lester (2002).

The desensitization of nAChRs leads to a compensatory upregulation of nAChRs. Therefore, the chronic administration of both agonists and antagonists of nAChRs in vivo and in vitro lead to the upregulation of nAChRs (in contrast to the widely observed and accepted fact that cell membrane receptors are upregulated after antagonist administration and downregulated after agonist administration) (Gaimarri et al., 2007; Lloyd and Williams, 2000; Teaktong et al., 2004; Prus et al., 2007; Kuryatov et al., 2005; Wang and Sun, 2005; Gentry and Lukas, 2002; Hogg and Bertrand, 2007). The two most prevalent receptor subtypes in the CNS (α4β2 and α7) differ in the nature of their upregulation, while the upregulation of α4β2 nAChRs may require a shorter exposure and/or lower concentration of NIC to develop and is regionally more extended in the brain than the upregulation of α7 receptors (in consonance with this, β2 subunit knockout mice do not show upregulation of NIC binding sites) (Teaktong et al., 2004; Nuutinen et al., 2005, 2006; Picciotto et al., 2008; Ochoa and Lasalde-Dominicci, 2007; Corringer et al., 2006). In addition, the NIC concentration in the brain of smokers is probably not high enough to upregulate α7 receptors, since most studies have failed to demonstrate the upregulation of α7 receptors in the brains of smokers (only Teaktong et al. (2004) found an increase in α7 immunoreactive perikarya in the granular cell layer of the dentate gyrus – but not in other brain regions – of smokers) (Teaktong et al., 2004; Nuutinen et al., 2005, 2006; Picciotto et al., 2008; Ochoa and Lasalde-Dominicci, 2007; Corringer et al., 2006). However, the upregulation of the α6β2* receptor in vivo has not yet been clearly confirmed (since previous studies found no change or up- or down-regulation of these receptors after chronic NIC treatment). A recent in vitro study has found that α6β2 receptors need a higher concentration of NIC to its upregulation than α4β2 receptors, and the velocity of α6β2 upregulation is higher than for α4β2 receptors (Walsh et al., 2008; Picciotto et al., 2008). Apparently, regulation of the two main subtypes of α6* subunits containing receptors (α6α4β2* and α6 (non-α4) β2*) by NIC in the striatum differed because the α6α4β2* receptor was downregulated, while the α6 (non-α4) β2* receptor was upregulated after NIC treatment in rodents (Perez et al., 2008a,b). The upregulation characteristics of α3β2 receptors and the α4β2 receptors, measured in vitro, are also different from each other (Walsh et al., 2008). Upregulation of α4β2 nAChRs develops within week(s) after the initiation of NIC administration and ceases within 7 days in mice, 20 days in rats, and 8 weeks in humans after the termination of NIC administration in post-mortem studies (Picciotto et al., 2008; Mamede et al., 2007; Koylu et al., 1997; Pietilä et al., 1998; Sacco et al., 2004; Gentry and Lukas, 2002; Breese et al., 1997). An in vivo (SPECT) study also found the upregulation of nAChRs as a consequence of long-term NIC administration in baboons. In addition, recent in vivo investigations in humans have also confirmed both the upregulation of α4β2 receptors after chronic NIC administration (smoking) and the termination of upregulation after approximately 21 days of smoking cessation (Mamede et al., 2007; Staley et al., 2006; Wullner et al., 2008; Kassiou et al., 2001). While desensitized nAChRs have a greater affinity for agonists than their nondesensitized counterparts, it remains controversial whether the elevation of NIC binding sites after chronic NIC administration is the result of an increased rate of desensitized receptors or an increased number of functional, activatable nAChRs (Picciotto et al., 2008; Giniatullin et al., 2005). Recently, several studies have examined the mechanisms underlying nAChR upregulation, and the results of these studies implicate numerous different pathways in this process (Picciotto et al., 2008). NIC-induced receptor upregulation occurs by post-transcriptional mechanism(s), as several studies have found that chronic NIC administration was not associated with changes in mRNA levels of nAChRs subunits (Corringer et al., 2006; Millar and Harkness, 2008). The potential mechanisms of upregulation may be as follows: NIC (and other membrane-permeable ligands of nAChRs) acts as a pharmacological chaperone in the endoplasmatic reticulum (ER) to facilitate the assembly of subunits (Kuryatov et al., 2005; Wells, 2008); chronic NIC treatment causes an increased half-life of nAChRs in the surface membrane (Kuryatov et al., 2005; Peng et al., 1994); NIC induces conformational changes in surface-membrane nAChRs, and receptors in this novel conformational state are more sensitive to activation, desensitize more slowly, and have a higher affinity for epibatidine (Vallejo et al., 2005; Kuryatov et al., 2005; Wells, 2008); NIC acts in the ER as a "maturational enhancer" and promotes the transition from an immature oligomer receptor state into a state with higher metabolic stability (Sallette et al., 2005; Corringer et al., 2006; Gaimarri et al., 2007); NIC may decrease – both by a direct and a nAChR-mediated

manner – the process of protein degradation via modulation of the activity of the ubiquitin-proteasome system (UPS), and this newly discovered action of NIC could lead to increased protein (for example, nAChR and glutamate receptor) levels (Rezvani et al., 2007). In addition, chaperone-type proteins (such as VILIP-1, protein 14-3-3η, PICK-1, RIC-3, ubiquilin-1, BiP, and calnexin) could play a role in nAChR folding, assembly, and trafficking, and also in the modulation of receptor expression levels and the regulation of receptor sensitivity to agonists (Gaimarri et al., 2007; Wells, 2008; Millar, 2008).

2.5. Non-synaptic transmission through nAChRs

Neurons can communicate with each other via both synaptic and non-synaptic transmission. In non-synaptic communication (or so-called volume transmission), the nerve endings or nerve boutons release transmitters, but do not make synaptic contacts. The transmitter from these non-synaptic nerve endings or nerve boutons is therefore released into the extracellular space (ECS) and then may diffuse to relatively distant targets (i.e. to extrasynaptically located receptors or to receptors on non-neuronal cells) (Lendvai and Vizi, 2008; Vizi et al., 2004a; Vizi and Mike, 2006; Descarries et al., 1997). Not only non-synaptic nerve boutons may play a role in volume transmission, but transmitter transporters in reverse operation mode may also release transmitters into the ECS. Moreover, a leakage of transmitters from classic synapses into the ECS (a phenomenon called spillover) is known to occur (Vizi et al., 2004a). Non-synaptic transmission is considered the typical form of neurotransmission in monoaminergic (dopaminergic, serotonergic, and noradrenergic) and cholinergic systems, as evidenced by the following: nerve terminals and nerve boutons in these systems are mainly in a non-synaptic situation; the ACh degrading enzyme acetylcholinesterase (AChE) is frequently localized far from cholinergic nerve endings, which suggests that ACh may reach targets a great distance from its place of release; and nAChRs exist at non-synaptic sites (Lendvai and Vizi, 2008; Dani and Bertrand, 2007; Vizi et al., 2004a; Vizi and Mike, 2006). According to the assumption of Vizi et al. (2004a,b), the relatively low concentration of NIC in the brain during cigarette smoking may induce its neurobiological effects mainly via non-synaptic nAChRs, because these receptors are usually activated by lower ligand concentrations than their counterparts in synaptic localization (Vizi et al., 2004b; Lendvai and Vizi, 2008).

3. Mechanisms of nicotine's actions in the reward pathway(s) and the relevance of dopamine in nicotine addiction

3.1. Nicotine and the mesocorticolimbic dopamine system

The mesocorticolimbic dopamine system (MDS, sometimes referred to as the reward system) is regarded as the main morphological substrate of reward and reinforcement in the brain (Wonnacott et al., 2005; Nestler and Carlezon, 2006). Neuroanatomically the MDS is a neural circuitry that includes primarily the dopaminergic cells of the VTA and their projections to the nucleus accumbens (NAcc; also called ventral striatum), the prefrontal cortex (PFC), the amygdala, the ventral pallidum, and the hippocampus (Wonnacott et al., 2005; Nestler and Carlezon, 2006; Pierce and Kumaresan, 2006; Kalivas and Volkow, 2005). The dopaminergic neurons of the VTA are key players in the reward system, and dopamine release in NAcc is strongly associated with the administration of most drugs of abuse (i.e. ethanol, opiates, cannabinoids, phencyclidine, toluene (in inhalant abuse) and psychostimulants) (Pierce and Kumaresan, 2006; Riegel et al., 2007; Adinoff, 2004; Rose, 2007; Hutson et al., 2000; Britt and McGehee, 2008; Melis et al., 2005). Additionally, the MDS is also activated by different kinds of natural rewards, such as humor, sexual activity, food, positive social interactions, play, aesthetic artworks, pictures of loved ones, etc. (Sabatinelli et al., 2007; Cannon and Bseikri, 2004; Mobbs et al., 2003).

nAChRs are widely distributed in the reward pathway. Mostly α4β2α5 and α4β2α6α5 receptors are found on dopaminergic cell bodies in the VTA; α7 receptors in a smaller proportion also occur on the surface of these cells; a lot of α4β2α5 and a few α7 receptors are present on GABAergic cell bodies in the VTA; α7 receptors also appear on glutamatergic nerve endings in the VTA; α4β2* receptors are found on GABAergic nerve endings in the VTA; α4β2, α4β2α5, α6β2β3, α4α6β2β3 receptors occur on dopaminergic terminals in the NAcc; and α4β2* receptors appear on GABAergic nerve endings in the NAcc. Therefore, it is not surprising that like other substances of abuse, NIC can influence the activity of the reward pathway, resulting in an increased level of extracellular dopamine in the NAcc, striatum, and frontal cortex (Pierce and Kumaresan, 2006; Janhunen and Ahtee, 2007; Mameli-Engvall et al., 2006; Rose, 2007; Dani and Harris, 2005; Bednar et al., 2004; Picciotto, 2003; Picciotto et al., 2008; Fowler et al., 2008; Mansvelder et al., 2006; Pidoplichko et al., 2004; Exley et al., 2008). Studies of the usage of nAChRs antagonists have also underlined the direct effect of NIC on MDS. The administration of the nAChR antagonist mecamylamine (as a non-specific nAChR antagonist) into the VTA decreased the NIC-evoked dopamine release in the NAcc (although mecamylamine failed to reduce dopamine release when it was administered into the NAcc), while the administration of α7 antagonists (methyllycaconitine (MLA) or α-bungarotoxin) into the NAcc decreased the NIC-evoked dopamine release there (Pierce and Kumaresan, 2006; Janhunen and Ahtee, 2007; Walters et al., 2006; Papke et al., 2001; Fu et al., 2000; Rossi et al., 2005a,b). In animal studies, the systemic or intra-VTA administration of α4β2 nAChR antagonist dihydro-β-erythroidine (DHβE) decreased NIC self-administration and the rewarding effect of NIC in the conditioned place-preference paradigm, but α7 antagonist MLA had no effect on NIC-induced conditioned place-preference. Moreover, effects of MLA in the NIC self-administration paradigm were contradictory, which suggests that α4β2 receptors – compared with α7 receptors – have a bigger role in the mediation of rewarding effects of NIC (Laviolette and van der Kooy, 2003a,b, 2004; Picciotto et al., 2008; Fowler et al., 2008; Walters et al., 2006). Results of studies with genetically modified rodents (i.e. β2 subunit gene knock-out strain; β2 subunit gene knock-out strain with lentiviral mediated β2 gene transfer to reexpress β2 subunit; mouse strain with an α4 subunit variant with a point mutation which renders the α4 subunit containing nAChRs more sensitive to NIC; α7 subunit knock-out strain) offer further support for the supposition that α4β2 nAChRs are primarily responsible for mediating the rewarding effects of NIC (Picciotto et al., 2008; Fowler et al., 2008; Walters et al., 2006; McCallum et al., 2006).

The role of the MDS in NIC addiction is also reinforced by the results of anatomical or pharmacological blockades of MDS, while the disruption of dopaminergic neurons in reward pathway by 6-hydroxydopamine or the administration of dopamine antagonists is associated with decreased NIC self-administration and NIC-evoked conditioned place-preference (Laviolette and van der Kooy, 2004; Sellings et al., 2008; Spina et al., 2006). Interestingly, according to recent results by Sellings et al. (2008), aversive and rewarding effects of NIC are segregated anatomically in the NAcc: the core part of NAcc provides the anatomical substrate for the aversive effects, while the shell part of the NAcc provides the anatomical substrate for the rewarding effects of NIC (Sellings et al., 2008).

Electrophysiologically, dopaminergic neurons of VTA have three kinds of patterns of activity, namely an inactive state, a tonic firing state, and a burst-firing mode (Grace et al., 2007;

Maskos, 2008; Mameli-Engvall et al., 2006). Dopamine release in terminal regions of the MDS is dependent on the firing state of dopaminergic neurons of VTA. Phasic burst firing leads to massive dopamine release in the NAcc, while slow single-spike tonic activity leads to stable low-level baseline dopamine concentration in the NAcc (Grace et al., 2007; Maskos, 2008; Mameli-Engvall et al., 2006). Tonic firing is driven by the intrinsic membrane potential oscillations of dopaminergic cells in contrast to burst-firing, which is dependent on intact afferent innervation of dopaminergic cells of VTA (Grace et al., 2007; Maskos, 2008; Mameli-Engvall et al., 2006). The afferent innervation of the MDS is very complex, originates in the cerebral cortex and in various subcortical structures, and involves many kinds of neurotransmitters (for details see Pierce and Kumaresan, 2006; Kalivas and Volkow, 2005; Janhunen and Ahtee, 2007; Grace et al., 2007; Laviolette and van der Kooy, 2004). An important source of afferent innervation are two adjacent nuclei in the brainstem: the laterodorsal tegmental nucleus (LDT) and the pedunculopontine tegmental nucleus (PPT), which comprise mainly cholinergic neurons interspersed with GABAergic and glutamatergic neurons. All of these cell types send connections to the VTA (Wonnacott et al., 2005; Janhunen and Ahtee, 2007; Grace et al., 2007; Dani and Harris, 2005; Wonnacott, 2008; Maskos, 2008). The switch from tonic to burst-firing of dopaminergic neurons in the VTA is driven by glutamate afferents derived mainly from the PFC and the PPT (Grace et al., 2007; Maskos, 2008; Wonnacott, 2008). The afferent innervation of the VTA from the LDT permits this glutamate-driven switch from tonic activity to burst-firing (Grace et al., 2007; Maskos, 2008; Wonnacott, 2008). The neurotransmitter mediating this effect is probably ACh (Grace et al., 2007). Cholinergic brainstem nuclei are an important aspect of NIC addiction, while a lesion of the posterior part of the PPT, which innervates the VTA, causes an alteration in intravenous NIC administration. Natural (such as food and sex) and drug (opiate) rewards are also known to be influenced by PPT lesions (Laviolette and van der Kooy, 2004; Maskos, 2008; Alderson et al., 2006).

NIC has a deep impact on the activity of MDS. First of all, NIC administration in the VTA activates $\alpha4\beta2$ receptors on dopaminergic and GABAerg cells and on GABAerg terminals, and $\alpha7$ nAChRs on glutamatergic nerve terminals. Then, within minutes after the start of NIC exposure, $\alpha4\beta2$ receptors on GABAerg neurons and nerve terminals and on dopaminergic neurons undergo rapid desensitization (leading to a decrease in both GABA-mediated inhibition and direct activation of dopaminergic cells by NIC), but the concentration of NIC associated with smoking is not high enough to desensitize $\alpha7$-containing nAChRs on glutamatergic nerve endings. As a result, NIC is able to induce glutamate release in this stage too, which further activates dopaminergic cells of the VTA during prolonged NIC administration (i.e. smoking) (Janhunen and Ahtee, 2007; Dani and Harris, 2005; Picciotto et al., 2008; Fowler et al., 2008; Mansvelder et al., 2006; Pidoplichko et al., 2004; Keath et al., 2007). The net effect of NIC in the VTA thus results in an increased activity of dopaminergic cells and facilitates the switch from the tonic to the burst-firing mode of VTA dopaminergic neurons (Janhunen and Ahtee, 2007; Rose, 2007; Mameli-Engvall et al., 2006; Dani and Harris, 2005; Fowler et al., 2008; Zhang and Sulzer, 2004; Pidoplichko et al., 2004; Ikemoto, 2007). Dopamine release in the NAcc is influenced by NIC. Four types of nAChRs (see above) are present on dopaminergic nerve terminals in NAcc (where the endogenous ligand ACh is released from cholinergic interneurons of the NAcc). The administration of NIC desensitizes them, which then leads to both an increased release of dopamine during burst-firing, and a decreased release of dopamine during tonic low-frequency firing of dopaminergic cells (according to recent results, $\alpha6\beta2^*$ nAChRs are key players in the regulation of NIC-evoked dopamine release in the NAcc) (Janhunen and Ahtee, 2007; Britt and McGehee, 2008; Picciotto, 2003; Rice and Cragg, 2004; Zhang and Sulzer, 2004; Exley and Cragg, 2008; Exley et al., 2008; Mansvelder et al., 2003; Dani and Bertrand, 2007). Because dopaminergic cells in the VTA are in burst-firing mode in response to reward-predicting stimuli or in unpredicted-reward situations, NIC administration selectively enhances reward-related dopamine release (Britt and McGehee, 2008; Rice and Cragg, 2004; Exley et al., 2008; Schultz, 1997; Schultz, 2007).

Interestingly, differences are found in NIC-evoked dopamine release in the two main parts of the striatum. NIC administration excites dopaminergic neurons that innervate either the dorsal striatum (caudate-putamen) or ventral striatum (NAcc). NIC-evoked dopamine release, however, is more pronounced in the NAcc than in the dorsal striatum (which is densely innervated by dopaminergic afferents originating mainly in the substantia nigra and to a lesser degree in the VTA; NAcc on the other hand is innervated by dopaminergic afferents originating mainly in the VTA and to a lesser degree in the substantia nigra) (Zhang et al., 2009). In addition, NIC-evoked activation, measured by the expression of immediate early genes c-Fos and ΔFosB, is more pronounced in the terminal region of the mesocorticolimbic pathway (NAcc) than in the terminal region of nigrostriatal pathway (caudate-putamen region) (Janhunen and Ahtee, 2007). The NIC-evoked phasic burst-firing of dopaminergic neurons was recently shown to be associated with a greater dopamine efflux in the NAcc than in the dorsal striatum (while an NIC-evoked decrease in dopamine efflux was experienced in both areas during the tonic firing of dopaminergic neurons). Moreover, the differences in the expression of various nicotinic receptor subunits on afferent nerve endings and dopaminergic cell bodies in the VTA vs. the substantia nigra may also explain the divergent responses of dopaminergic neurons to NIC in these two nuclei (Zhang et al., 2009; Keath et al., 2007).

3.2. Nicotine and the habenular complex

NIC may have effects on other brain systems linked to reward processing (Rose, 2007). The habenular complex (HbCpl) is an epithalamic structure consisting of cholinergic cells and substance P-containing neurons in its medial part (medial habenula) and GABAergic and glutamatergic neurons in its lateral part (lateral habenula). The two parts are in a unidirectional relationship, with axons of some neurons of the medial habenula having en passant boutons in the lateral habenula (Lecourtier and Kelly, 2007; Rose, 2007). The HbCpl receives its main afferents – via the stria medullaris – from various brain areas and sends its main outputs – via the fasciculus retroflexus – to several brain areas, too (for details see Lecourtier and Kelly, 2007; De Biasi and Salas, 2008). VTA and NAcc – as main components of the dopaminergic reward pathway – are in anatomical connection with the HbPcl (Rose, 2007; De Biasi and Salas, 2008). The lateral habenula sends glutamatergic axons to the GABAergic cell population of the VTA, which provides local inhibitory input to the dopaminergic cells of the VTA. According to this structural connection, the electrical stimulation of neurons in the lateral habenula suppresses the activity of dopaminergic neurons in the VTA (Wonnacott et al., 2005; Hikosaka et al., 2008; Ji and Shepard, 2007; Morra, 2007; Lecourtier et al., 2008; Ungless, 2004). Interestingly, neurons of the lateral habenula are activated by a cue that predicts the absence of reward or by the omission of a predicted reward, but they are inactivated by an unpredicted reward. Consequently, their responses in reward-related situations were opposite to those of dopaminergic neurons of the VTA (Hikosaka et al., 2008; Morra, 2007; Schultz, 2007). The close functional and anatomical relationship of HbCpl to the mesolimbic dopaminergic system

(discussed above), the presence of nAChRs (mainly as α3β4 receptors) in large amounts in the medial habenula and interpeduncular nucleus (as one of the main output areas of the medial habenula), and the finding that the administration of 18-methoxycoronaridine (a selective α3β4 receptor antagonist) may decrease the self-administration of various addictive agents (i.e. morphine, alcohol, cocaine and metamphetamine) in animal studies seriously raise the possibility that the habenular complex is one of the neural systems involved in NIC addiction (De Biasi and Salas, 2008; Glick et al., 2008). In accordance with this theory, the intraperitoneal administration of 18-methoxycoronaridine caused a decrease in i.v. self-administration of NIC in rodents in a dose-dependent manner (Glick et al., 2000). The link between NIC and HbCpl are further supported by the selective toxicity of chronic NIC administration to the habenula and fasciculus retroflexus (Rose, 2007; Ciani et al., 2005). That knock-out strains either for β4 subunit, α2 subunit, or α5 subunit (which in addition to the α3 subunit are all highly expressed receptor subunits types in the medial habenula and/or in interpeduncular nucleus) show decreased somatic signs of nicotine withdrawal is in agreement with the idea that the habenular/interpeduncular system plays a major role in NIC dependence (Salas et al., 2009; De Biasi and Salas, 2008).

3.3. Nicotine and insula

The insular region has also emerged recently as an anatomical substrate of NIC addiction (Rose, 2007; Naqvi et al., 2007). Functional neuroimaging studies had previously described that the insula is activated by drug-related cue-elicited craving. Moreover, structural abnormalities of the insula have also been described in some forms of addiction (Rose, 2007; Naqvi et al., 2007; Contreras et al., 2007; Naqvi and Bechara, 2009). Contreras et al. (2007) found that the pharmacological inactivation of the insula in rodents was associated with impaired amphetamine-conditioned place-preference (Contreras et al., 2007; Naqvi and Bechara, 2009). Recently in their seminal paper, Naqvi et al. (2007) described how patients who had suffered a lesion in the insular region were more likely to abstain from smoking than patients who had suffered lesions in other brain regions (Naqvi et al., 2007).

3.4. Relevance of dopamine in nicotine addiction

Although a large body of results suggest that dopamine plays a crucial role in reward processing and/or the development of drug addiction, a number of caveats have been applied to this "evidence" from the start. First of all, dopaminergic neurons of the VTA (or at least a subpopulation of them) appear to increase their activity not only in response to unpredicted-reward or reward-predicting stimuli, but also in response to aversive stimuli. In addition, a great number of studies have found that aversive stimuli – like addictive stimuli – also elicit dopamine release in the ventral striatum (but results are ambiguous in this respect) (Brischoux et al., 2009; Roitman et al., 2008; Ungless, 2004; Horvitz, 2000). Moreover, in the tyrosine hydroxylase knock-out rodent (dopamine deficient mice) strain, dopamine did not prove necessary for hedonic responses evoked by opiate administration or for learned preferences for sweet tasting solutions over water (Berridge, 2007; Hyman et al., 2006; Hnasko et al., 2005). Hyperdopaminergic (dopamine transporter knockdown) mice also showed no difference compared with wild-type mice in hedonic reactions to sweet tasting solutions (Berridge, 2007; Britt and McGehee, 2008). The pharmacological (6-OHDA) lesion of the mesolimbic dopaminergic system is similarly not associated with the reduced hedonic impact of sweet taste. Furthermore the administration of dopamine receptor antagonists failed to decrease the hedonic impact of addictive agents in some studies. For example flupenthixol administration leads to decreased aversive rather than decreased rewarding effects of NIC, but this effect is only observable in an acute state of NIC exposure, and not after long-term NIC exposure (Sellings et al., 2008; Berridge, 1996, 2007; Laviolette and van der Kooy, 2003a,b; Tan et al., 2009). Based on the above and other non-detailed results, several experts have suggested that dopamine may mediate the phenomenon of "wanting" (expectation of reward) more than the phenomenon of "liking" (the hedonic impact of reward) (Berridge, 2007; Adinoff, 2004).

NIC administration increases dopamine levels in several brain areas (i.e. hippocampus, striatum, cingulate and frontal cortex, amygdala and pontine nuclei) (Singer et al., 2004; Cao et al., 2005a,b; Janhunen and Ahtee, 2007). Interestingly, during NIC withdrawal the level of extracellular dopamine decreases in NAcc, but rises in the PFC. While stressful situations and aversive stimuli are associated with increased dopamine levels in the PFC, this alteration could mediate aversive aspects of NIC withdrawal (De Biasi and Salas, 2008).

Not only does NIC have a radical effect on the brain's dopaminergic systems, but it also influences the release of many kinds of neurotransmitters (i.e. serotonin, noradrenaline, GABA, acetylcholine, glutamate, and endocannabinoids) and neuropeptides (i.e. CRF, endogenous opioids, and orexins). For details on the relevance of these diverse actions of NIC in various brain functions and in the development and maintenance of NIC dependence, (see De Biasi and Salas, 2008; Di Matteo et al., 2007; Touiki et al., 2007, 2008; Seth et al., 2002; Galindo-Charles et al., 2008; Rossi et al., 2005a,b; Grilli et al., 2005; Markou, 2007, 2008; Liechti and Markou, 2008; Kenny et al., 2009; Hahn and Stolerman, 2005; Erhardt et al., 2000; George et al., 2007; Xue and Domino, 2008; Chen et al., 2008b; Merritt et al., 2008; Pasumarthi and Fadel, 2008).

4. Results of structural and functional brain-imaging studies on the influence of nicotine/smoking on neural systems

4.1. Structural and morphological alterations of a smokers' brain

In recent years numerous studies have investigated structural brain abnormalities associated with smoking, smoking-related changes in global and regional brain activities, and NIC-evoked changes at the molecular levels in the brain. Several studies have reported generalized brain atrophy by computed tomography (CT) in smokers (Kubota et al., 1987; Akiyama et al., 1997; Hayee et al., 2003; Durazzo et al., 2007). In magnetic resonance imaging (MRI) studies brain atrophy, white matter lesions and lacunar infarcts are also described as a consequence of smoking (but the results are ambiguous). Moreover, cigarette smoking was identified as a risk factor for the progression of white matter lesions (Yamashita et al., 1996; Shintani et al., 1998; Swan et al., 2000; Longstreth et al., 2001; Swan and Lessov-Schlaggar, 2007; van Dijk et al., 2008).

4.1.1. Gray matter alterations in smokers

In a structural brain-imaging study by Brody et al. (2004a), reduction in gray-matter volumes and densities are described in the dorso- and ventrolateral prefrontal cortex, the left dorsal anterior cingulate cortex, and the right cerebellum among smokers compared with non-smokers (Brody et al., 2004a). Almeida et al. (2008) found decreased gray-matter densities in the posterior cingulum, precuneus, precentral gyri and right thalamus in an elderly smoker population, and the authors note that these areas are also affected in incipient Alzheimer's disease (Almeida et al., 2008). Gallinat et al. (2006) found no difference in whole-brain volume between smokers and non-smokers, but did find decreased

regional gray-matter volumes in thalamic, cuneal, precuneal, frontal and occipital cortical regions among smokers (Gallinat et al., 2006). Interestingly, no volume deficit was found in the ventral striatum—a key structure in reward processing (Gallinat et al., 2006).

Some theories have been developed about the etiology of smoking-related regional gray-matter abnormalities. For instance, because gray matter is particularly vulnerable to ischemia and smoking is associated with the decreased oxygen-carrying capacity of blood (via elevated blood carbon monoxide levels) and/or impaired lung function, the consequential ischemia of brain tissues may lead to gray-matter damage (Durazzo et al., 2007). Cigarette smoke containing reactive oxygen species (with its known damaging effects on cellular membranes, DNA, carbohydrates, etc.) may also contribute to structural brain abnormalities in smokers (Brody et al., 2004a; Gallinat et al., 2006; Durazzo et al., 2007). Reduced gray-matter volume among smokers may be associated with cognitive decline related to long-term smoking, as suggested by prospective epidemiological studies (Gallinat et al., 2006; Almeida et al., 2008; Paul et al., 2008; Sabia et al., 2008). Interestingly, studies with special populations (patients with schizophrenia or alcohol dependency) also reported smoking-related gray matter changes. Durazzo et al. (2007) reported that smoking in heavy drinkers is associated with decreased total gray matter and temporal gray-matter volumes (Durazzo et al., 2007). According to a recent study by Tregellas et al. (2007), smokers with schizophrenia have less gray-matter shrinkage in the superior temporal gyri and lateral prefrontal cortex than do non-smokers with schizophrenia, suggesting that smoking has some kind of neuroprotective effects in schizophrenia (Tregellas et al., 2007).

4.1.2. White matter alterations in smokers

White matter abnormalities are also described in smokers. Gazdzinski et al. (2005) found that smoking is associated with increased white matter volume in the temporal region in a population with alcohol dependence (Gazdzinski et al., 2005). The same study suggested that alterations in the white matter might be a result of NIC-induced cytotoxic cell swelling secondary to NIC-induced osmotic imbalances. Vasogenic swelling (as a consequence of NIC-induced blood–brain barrier damage) characterized by plasma fluid leaking into the parenchymal interstitial space was considered another possible culprit (the findings of Paul et al. (2008), however, challenge the vasogenic swelling theory) (Gazdzinski et al., 2005; Paul et al., 2008). In their diffusion tensor imaging study, Paul et al. (2008) found that NIC dependence was associated with significantly higher fractional anisotropy (FA) in the body and whole corpus callosum, and also a trend of higher FA in the splenium. This suggests a superior integrity of the white matter, although the explanation of these findings is scarce (Paul et al., 2008). Interestingly, higher FA was also found in the anterior cortical white matter and the internal capsule of both adolescent smokers and adolescent non-smokers with prenatal exposure to cigarette smoke compared to adolescent non-smokers with no prenatal exposure to cigarette smoke (Jacobsen et al., 2007). Gallinat et al. (2007) measured concentrations of N-acetylaspartate (NAA), which is considered a marker for neuronal and axonal integrity, in their magnetic resonance spectroscopy study and found it was significantly reduced in smokers compared to non-smokers in the left hippocampus, but not in the anterior cingulate cortex (Gallinat et al., 2007; Gujar et al., 2005). This result suggests a local neurotoxic effect of smoking on the hippocampus, which may explain cognitive decline associated with chronic smoking (Gujar et al., 2005; Anstey et al., 2007; Gallinat et al., 2007; Swan and Lessov-Schlaggar, 2007; Peters et al., 2008).

4.2. The effects of nicotine on brain activity

Although the direction of NIC administration-evoked changes in global cerebral blood flow (gCBF) is ambiguous, some results suggest a decreased gCBF as a consequence of chronic NIC administration and an increase of gCBF after acute NIC administration (Almeida et al., 2008). Studies using the Xe^{133} inhalation method or ^{99m}Tc-HMPAO-SPECT found a decrease in global cerebral or gray matter blood flow as an effect of chronic cigarette smoking with an increase after quitting in the long-term (Kubota et al., 1983; Rogers et al., 1983, 1985; Yamashita et al., 2000; Brody, 2006; Siennicki-Lantz et al., 2008). Using Doppler ultrasonography, Morioka et al. (1997) and Boyajian and Otis (2000) found an increase in the velocity of cerebral arterial blood flow as an acute consequence of smoking. Wennmalm (1982) using the N_2O-wash-in technique and Skinhoj et al. (1973) using the Xe^{133} intracarotid injection method also found increased CBF after NIC administration (Skinhoj et al., 1973; Wennmalm, 1982; Silvestrini et al., 1996; Morioka et al., 1997; Boyajian and Otis, 2000; Terborg et al., 2002; Brody, 2006).

PET studies by Cruickshank et al. (1989) and Ghatan et al. (1998) found a decrease in gCBF or no change in gCBF after NIC administration, but authors of another study (Nagata et al., 1995) have shown an increase in global CBF in one set of measurements but not in another test performed immediately afterward (Cruickshank et al., 1989; Ghatan et al., 1998; Stapleton et al., 2003; Nagata et al., 1995). The SPECT studies by Yamamoto et al. (2003) and Rourke et al. (1997) and the PET study by Rose et al. (1998) described a decline in global CBF after smoking, too (Rourke et al., 1997; Stapleton et al., 2003; Yamamoto et al., 2003). Shinohara et al. (2006) found with PET no significant changes in global CBF after NIC administration (smoking) in smokers, however they found a statistically significant inverse correlation between arterial NIC concentrations and CBF (Shinohara et al., 2006). Global cerebral glucose metabolism was also found diminished after NIC administration (Stapleton et al., 2003; Rose et al., 2007).

Changes in regional brain activity as a consequence of NIC administration have also been under intensive investigation. Functional brain-imaging studies measuring regional CBF (rCBF) or glucose metabolism have commonly reported that administration of NIC or smoking activate different parts of the frontal cortex, thalamus, visual system, ventral striatum and cerebellum, while most studies have found decreased brain activities in the anterior cingulate cortex, amygdala and the hippocampus (however, different studies frequently provide contradictory results) (Ghatan et al., 1998; Domino et al., 2000, 2004; Rose et al., 2003; Lee et al., 2005; Zubieta et al., 2005; Brody, 2006; Ray et al., 2008; Siennicki-Lantz et al., 2008; Tanabe et al., 2008). NIC also modulates reticular arousal system activity in a dose-dependent manner: low doses activate while higher doses depress the activity of the reticular system. Thus finding is in accordance with the stimulatory effect of low-dose and the inhibitory effect of high-dose NIC on arousal (Rose et al., 2003). Some results suggest that NIC-evoked changes in regional brain activities are dependent on smoking history (smokers vs. non-smokers) and also on laterality (right vs. left hemispherium) (Ray et al., 2008).

A recent fMRI study has shown that subsequent administration of NIC, compared to acute NIC administration, is associated with the activation of different parts of the brain in rodents (i.e. NAcc, hippocampus, ventral pallidum, PFC and ventral tegmentum) (Li et al., 2008). Hong et al. (2009b) in their MRI study found that the increased severity of NIC addiction was associated with a decreased strength in functional connectivity between the dorsal anterior cingulate cortex and the striatum in a resting (task-independent) state. The authors have raised the possibility that

this phenomenon may serve as a novel biomarker for NIC addiction (Hong et al., 2009b). Moreover, they also report that short-term NIC supplementation does not significantly affect the association described above, suggesting that NIC replacement does not necessarily correct NIC addiction-related network abnormalities. This may partially explain why NIC supplementation is not a highly effective therapy for smoking cessation (Hong et al., 2009b).

4.3. Functional brain-imaging studies on smoking abstinence and craving

The effect of smoking abstinence (and associated craving) on rCBF were also investigated by several studies. A recent investigation found no change in gCBF after overnight smoking abstinence but significant increases in rCBF in the anterior cingulate cortex and medial part of the orbitofrontal cortex (OFC) did occur. The study also found that abstinence-induced craving correlated with gCBF and increased rCBF (compared with satiety situation) in the right dorsolateral PFC, OFC, and insula, as well as in the left inferior frontal cortex, occipital cortex, anterior cingulate cortex, ventral striatum, thalamus, amygdala, bilateral hippocampus, and left caudate (Wang et al., 2007b). The same group investigated the effects of some functional polymorphisms in the dopaminergic and opioidergic pathways (DRD2-141 Ins/DelC; DRD2 C957T, OPRM1 A118G, COMT Val158Met polymorphism) on overnight abstinence-associated changes in rCBF. They found that carriers of the DelC variant of the DRD2-141 polymorphism, the Val/Val variant of the COMT polymorphism, or the AA variant of OPRM1 polymorphism have significantly greater abstinence-induced rCBF increases in regions previously linked with cigarette cravings (Ray et al., 2008; Wang et al., 2008). In conclusion, these results suggest that genetic polymorphisms with reduced dopaminergic tone, and those associated with increased endogenous opioid binding, may be linked with patterns of regional brain activation that may increase the risk of relapse (Ray et al., 2008; Wang et al., 2008).

Recently, Tanabe et al. (2008) found that overnight abstinence is not associated with rCBF changes in the thalamus, medial frontal cortex, and ventral striatum, although they did find a significant inverse correlation between rCBF in the thalamus and the severity of withdrawal symptoms measured by the Minnesota Withdrawal Scale. Domino et al. (2004) and Zubieta et al. (2005), in their previous articles, however, described a decrease in rCBF in the ventral striatum including nucleus accumbens after smoking a cigarette subsequent to overnight abstinence. Wang et al. (2007b), on the other hand, found a positive association between *increased* thalamic rCBF and abstinence-induced craving (Domino et al., 2004; Zubieta et al., 2005; Wang et al., 2007b; Tanabe et al., 2008). The decrease in overnight abstinence-induced craving after smoking a cigarette correlated with a decrease in rCBF in the anterior cingulate cortex and right hippocampus according to the results of Zubieta et al. (2005).

Changes in the brain activity of smokers associated with exposure to smoking-related visual cues (pictures, videos, 3D environment simulation) is also an intriguing topic in neuroimaging (Brody et al., 2007; Ray et al., 2008). Most studies have found that the presentation of smoking-related cues activates the visuospatial cortical system (i.e. cuneus, precuneus, occipital cortex) and attention (i.e. anterior cingulate cortex, prefrontal and parietal cortex) and reward circuits (i.e. amygdala, ventral striatum) (Brody, 2006; Brody et al., 2007; Franklin et al., 2007, 2009; Wang et al., 2007b; McClernon et al., 2008a; Ray et al., 2008). Some studies have also found that the activation of different regions (i.e. in the anterior cingulate cortex, right orbitofrontal cortex, left inferior occipital gyrus, left globus pallidus, right caudate, left inferior parietal lobe, and medial occipital lobes) by smoking-related cues are positively correlated with the level of NIC dependence and that the degree of cue-induced craving is associated with the extent to which the mesocorticolimbic region, midbrain and amygdala are activated (Ray et al., 2008). There are mixed results about the impact of abstinence (vs. smoking as usual situation) on the extent of brain activation induced by smoking-related cues (McClernon et al., 2009). Recently, Franklin et al. (2009) found that a well-known VNTR polymorphism in the 3′-untranslated region of the dopamine transporter gene (SLC6A3) has an effect on smoking cue-elicited activation in many brain areas (i.e. in the bilateral OFC and parahippocampal region, left ventral striatum, left dorsolateral PFC, right ventral medial PFC, fusiform gyrus, and superior temporal and frontal gyri). The results suggest that the carriers of the 9-repeat VNTR (the allele of which is associated with lower DAT expression) showed greater activation during exposure to smoking cues (vs. non-smoking cues) in the areas mentioned above compared with persons homozygous for the 10-repeat allele (Franklin et al., 2009). The brain regions most affected in different aspects of NIC dependence, as indicated by functional imaging studies, are rich in nAChRs (i.e. the ventral striatum, NAc, DLPFC, thalamus, inferior frontal cortex, visual cortex, and cerebellum) and these areas are also the key anatomical substrates of a wide range of cognitive processes (i.e. memory processes, attention, behavioral control, decision making, etc.) (Zubieta et al., 2005; Brody et al., 2007; Wang et al., 2007b; Tanabe et al., 2008).

While NIC has widely known procognitive effects, some neuroimaging studies have also focused on the impacts of NIC administration on brain activity during cognitive tasks (Brody, 2006). Results of these studies show that NIC administration during cognitive tasks has different effects on activity levels of the thalamus, visual cortex, ACC, prefrontal cortex, parietal cortex and the so-called "default system" (a network of brain regions that is active at rest and is deactivated during the performance of specific tasks. The default system consists of the medial frontal area, posterior cingulate cortex, and (pre)cuneal region) (for details see Brody, 2006; Hahn et al., 2007; Musso et al., 2007; Swan and Lessov-Schlaggar, 2007; Xu et al., 2007; Ray et al., 2008; Schilbach et al., 2008). Some of these studies have also found that the extent of activation is influenced by the smoking status of the probands and by the specific cognitive task used in the given study (Musso et al., 2007; Ray et al., 2008).

4.4. Results of brain-imaging studies on nAChRs

Imaging of nicotinic acetylcholine receptors (nAChRs) in the human brain is also an intensively investigated topic in neuroscience. Briefly, PET/SPECT studies have suggested the occurrence of an upregulation of $\alpha4\beta2^*$ nAChRs upon chronic nicotine exposure, normalization of $\alpha4\beta2^*$ receptor density after a few weeks abstinence in smokers, and nearly complete saturation of brain $\alpha4\beta2^*$ receptors during a typical daily pattern of smoking (Mamede et al., 2007; Brody et al., 2006b; Mukhin et al., 2008). Brody et al. (2009a,b) recently showed that smoking a denicotinized cigarette is not associated with pronounced receptor occupancy (Brody et al., 2009a). Therefore, NIC – and not other tobacco smoke ingredients – is responsible for the observed marked nAChR occupancy as a consequence of smoking regular cigarettes (Brody et al., 2009a). PET studies have also found an aging-associated decline in high-affinity nAChR densities in several brain regions (i.e. the thalamus, frontal/temporal/parietal/anterior cingulate/occipital cortex, and striatum), no significant difference in brain $\beta2^*$ nAChR availability between men and women non-smokers, and no change in $\beta2^*$ nAChR availability across the menstrual cycle (Brody et al., 2006b, 2009a; Staley et al., 2006; Cosgrove et al., 2007; Mamede et al., 2007; Mitsis et al.,

2008; Mukhin et al., 2008; Ray et al., 2008; Wullner et al., 2008). Preliminary results of a recent PET study by Le Foll et al. (2009) suggested that the baseline density of midbrain α4β2 receptors in squirrel monkeys may affect their motivation to self-administer NIC (Le Foll et al., 2009).

4.5. Neuroimaging studies on smoking-related changes in the dopaminergic system

Several neuroimaging studies were targeted at smoking-associated changes in the dopamine system. Salokangas et al. (2000) found enhanced [^{18}F]fluorodopa uptake in the basal ganglia among smokers, which suggests smoking-related, enhanced dopamine activity in the striatum (Salokangas et al., 2000). Most PET studies using D2/D3 receptor radiotracers [^{11}C]raclopride or [^{18}F]fallypride primarily found decreased radiotracer binding in the ventral striatum (but not in the extrastriatal brain regions) following cigarette smoking or consumption of gum containing NIC, which suggests an NIC-evoked dopamine release in these regions. This contradicts a PET study using [^{11}C]raclopride by Scott et al. (2007) and two SPECT study using [^{123}I]IBZM by Yang et al. (2006, 2008), which showed no difference in D2/D3 density in the striatum between male smokers and non-smokers (Brody et al., 2004b; Brody, 2006; Yang et al., 2006; Scott et al., 2007; Fehr et al., 2008; Takahashi et al., 2008; Yang et al., 2008).

Decreased ventral striatal D2 receptor availability has also been observed in patients with a dependence on other substances of abuse (i.e. alcohol, heroin, cocaine, and methamphetamine), and this change may also be detected after long-term cessation (Fehr et al., 2008; Volkow et al., 2009). The decreased radiotracer binding in bilateral putamen is maintained after a period of overnight abstinence in smokers (Fehr et al., 2008). Negative results in regard to decreased [^{11}C]raclopride binding potential after NIC consumption from animal and human PET studies are also published. However, the low-level of NIC dependence of the probands could bias the results of these studies, since some investigations have suggested that NIC administration in non-smokers is not associated with a significant decrease in radiotracer binding, a phenomenon that could refer to enhanced dopamine release in heavy smokers compared to light (or non-) smokers (Montgomery et al., 2007; Fehr et al., 2008; Takahashi et al., 2008). However, the relationship between the level of NIC dependence and the extent of dopamine release associated with smoking was not replicated by Fehr et al. (2008) in their recent article (Fehr et al., 2008).

According to a current PET study by Brody et al. (2009a,b), NIC is essential in the release of dopamine associated with smoking, while smoking denicotinized cigarettes is associated with a decreased level of dopamine release compared to smoking NIC-containing "normal" cigarettes (Brody et al., 2009b).

Genetic studies suggest that interindividual differences in smoking-related dopamine release is influenced by genetic variants of some genes related to dopaminerg neurotransmission. Individuals with the Val/Val genotype of COMT and/or with the 9-repeat allele for a VNTR in the DAT gene and/or with the short (7-repeat) allele of the dopamine D4 receptor gene VNTR in exon 3 had greater smoking-induced decreases in [11C]raclopride binding potential (as an indirect measure of dopamine release) in the striatum compared to individuals with the alternate genotypes (Brody et al., 2006a; Ray et al., 2008). Furthermore, a recent fMRI study reported that subjects with the Val/Val genotype of a COMT gene polymorphism exhibit better performances in N-back working memory tasks after cigarette smoking than after a 14 h abstinence period. Furthermore they showed a relative decrease in BOLD signal in bilateral DLPFC and dorsal cingulate/medial PFC during the working memory task after the abstinence period (compared to the activation of the affected regions after smoking). The observed changes in Val/Val carriers were not characteristic of subjects with the Met/Val or Met/Met genotypes of COMT (Loughead et al., 2008).

Striatal DAT density is decreased in smokers compared to non-smokers according to two SPECT studies using [^{99m}Tc] TRODAT. Because synaptic dopamine concentrations interfere with DAT density, these results are probably the consequence of increased synaptic levels of dopamine (Newberg et al., 2007; Yang et al., 2008). In contrast, in a previous SPECT study, Staley et al. (2001) did not find altered DAT density in the striatum of smokers compared to non-smokers. Discrepant results of this study are possibly due to the decreased selectivity of [^{123}I]β-CIT to DAT compared with [^{99m}Tc] TRODAT (Staley et al., 2001; Brody, 2006). Dagher et al. (2001) using PET measured decreased striatal D1 receptor binding in smokers, and this result was later affirmed by Yasuno et al. (2007) (Dagher et al., 2001; Staley et al., 2001; Yasuno et al., 2007). The latter study also suggested that after a long-term abstinence period, decreased D1 receptor density could recover (Yasuno et al., 2007). The results of imaging studies on changes in monoamine oxidase (MAO, one of the main dopamine-degrading enzymes) activity in smokers is discussed in chapter 1.2. (Fowler et al., 1996a,b, 2005; McClernon and Gilbert, 2004).

5. Connections between smoking and mental disorders and/or suicidal behavior

5.1. Epidemiology of smoking and nicotine dependence among smokers

Tobacco smoking, a global epidemic, is one of the greatest challenges of our time. Currently about 1.1 billion people are cigarette smokers worldwide, and their consumption is 5.5 trillion cigarettes annually (Jha et al., 2006; Proctor, 2004). Approximately 5 million people are killed a year by tobacco in the world, and the number of annual deaths will increase to 10 million by the year 2030 (Jha et al., 2006; Proctor, 2004).

Based on the National Comorbidity Survey estimates, the risk of becoming tobacco-dependent among smokers (namely among those who have tried tobacco at least once) is 32% higher than corresponding rates for heroin (23%), alcohol (15%) and cocaine (17%) (Anthony et al., 2005; Piasecki, 2006). In prospective studies, rates of relapse (after a smoking cessation attempt) are similar to those found after ending heroin or alcohol consumption, but some retrospective studies may yield more positive results (Caggiula et al., 2001; Henningfield et al., 1991; Piasecki, 2006; Frenk and Dar, 2000; Hughes et al., 2004). In summary, despite the well-known low euphorigenic effects of NIC compared to other drugs, it remains a highly addictive agent (Hughes, 2006; Caggiula et al., 2001; Barr et al., 2008a,b).

Not surprisingly, smokers with NIC dependence have greater mortality than smokers without NIC dependence (Hughes et al., 2006). In their recent review, Hughes et al. (2006) concluded that NIC dependence (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria) is one of the most frequent (prevalence of lifetime dependence: 19–37%; prevalence of current dependence: 9–13%, in American and German samples) and most fatal psychiatric disorders (30–50% of current smokers will die of a tobacco related disorder) (Hughes et al., 2006; Tonstad and Andrew Johnston, 2006). Surprisingly, their review showed that only about 50% of current smokers fulfilled DSM/ICD criteria for NIC dependence in contrast to previous studies where the prevalence of NIC dependence was approximately 90% among smokers (Hughes et al., 2006). Other authors emphasized that NIC dependence based on DSM-IV criteria is not closely associated with heavy smoking and/or long smoking history (Donny and Dierker, 2007; Dierker

et al., 2007). This problem arises from the generic application of DSM-IV criteria to determine dependence not only for NIC, but for all addictive agents. Some criteria for dependence in DSM-IV, however, are hard to interpret with respect to NIC (Hughes, 2004; Hughes et al., 2006). For example, because NIC is a legal and easily available addictive agent without the propensity to cause acute intoxication, the criterion "a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects" immediately appears problematic (Hughes, 2004; Hughes et al., 2006). Some other DSM-IV criteria (i.e. "important social, occupational, or recreational activities are given up or reduced because of substance use" and "a need for markedly increased amounts of the substance to achieve the desired effect") also rarely apply to smokers (Hughes, 2004; Hughes et al., 2006). Because of the known weaknesses of a DSM-IV and ICD-10-based diagnosis of NIC dependence, researchers prefer to use other criteria systems for establishing NIC dependence (Hughes et al., 2006).

5.2. Epidemiology of smoking in psychiatric patients

The smoking rates of patient groups suffering from various psychiatric disorders (e.g. schizophrenia or schizoaffective disorder, major depressive disorder, bipolar or panic disorder, alcohol/opiate/cocaine/cannabis dependence, attention deficit hyperactivity disorder, or posttraumatic stress disorder) are significantly higher than the smoking rates of the general population. Only a few psychiatric disorders, such as obsessive–compulsive disorder, catatonic subtype of schizophrenia, and autism spectrum disorders are associated with lower rates of smoking than in the average population (Zvolensky and Bernstein, 2005; Bejerot and Nylander, 2003; de Leon and Diaz, 2005; Vanable et al., 2003; Hughes et al., 1986; Wu et al., 2006; Dome et al., 2005; Hapke et al., 2005; Fu et al., 2007b; Bejerot and Humble, 1999; Beratis et al., 2001; Shoptaw et al., 2002; Patkar et al., 2006; Littleton et al., 2007; Agrawal et al., 2008; Wilens et al., 2008a,b). Astonishingly, the 7% of the overall population who have both a psychiatric disorder and are nicotine dependent consume 34% of all cigarettes smoked in the USA. Furthermore, individuals with a current psychiatric disorder (with or without NIC dependence) make up 30% of the population and consume 46% of all cigarettes smoked in the USA. These data emphasize the relevance of the comorbidity of NIC dependence and other psychiatric disorders (Grant et al., 2004). Most large-scale population-based studies have found bidirectional predictive associations between the initiation of several forms of mental disorders (primarily affective, anxious, disruptive and substance use disorders were screened in these studies) and smoking, while many kinds of primary mental disorders predict the subsequent onset of smoking, conversely, primary smoking can also predict the subsequent onset of many kinds of mental disorders (Kessler et al., 2007; Breslau et al., 2004a,b; John et al., 2004; Cuijpers et al., 2007; Griesler et al., 2008; Ismail et al., 2000). However, the ability of a mental disorder to predict a substance- (for example NIC) use disorder, has been more strongly substantiated (Kessler et al., 2007; Griesler et al., 2008; Glantz et al., 2009). Moreover, some authors also suggest that the prevalence of anxiety and affective disorders among former smokers is lower than among current smokers. In addition, a subsequent increase in the amount of smoking is more closely associated with a current mental disorder than a remitted one (Breslau et al., 2004b; John et al., 2004; Mykletun et al., 2008).

5.3. Smoking and suicide

A striking connection exists between smoking and suicidal behavior. Epidemiological studies in general and also studies in psychiatric patient populations suggest that smoking is associated with elevated risks of suicide attempts/ideation and/or completed suicide. Two prospective studies with large samples (50,000 US men and 300,000 US Army male personnel) showed that smoking is a risk factor for completed suicide after controlling for socio-demographic factors, but not for the presence of depression or a previous suicide attempt, two major risk factors for suicide (Miller et al., 2000a,b). Iwasaki et al. (2005), in their large-scale study with prospective design in a sample of Japanese men, also found a positive association between baseline smoking and completed suicide after controlling for some confounders (i.e. alcohol drinking habits, living with spouse, self-reported stress, and physical activity) but the study did not control for psychiatric diagnoses (Iwasaki et al., 2005). Bronisch et al. (2008), in their recent longitudinal study (with a 4-year follow-up period), investigated the smoking-suicide connection from a new perspective, namely the temporal relationship between smoking and suicidality. They found that both occasional smoking and non-dependent regular smoking and, in particular, NIC dependence at baseline were strongly associated with previous suicide ideation and suicide attempts (Bronisch et al., 2008). During the follow-up period, increased risks for new onset of suicide ideation and/or attempts – even after controlling for DSM-IV-based mood disorders – were positively associated with prior occasional and regular smoking (with or without NIC dependence). In contrast pre-existing suicidal ideations or attempts (assessed at baseline) were not associated with elevated risk for first onset of occasional/regular/dependent smoking during the follow-up period (Bronisch et al., 2008).

Tanskanen et al. (2000) in their prospective study also found a dose-dependent relationship between smoking and elevated risk for completed suicide even after adjusting for several confounding factors including "symptoms of depressed mood" and "symptoms of anxiety" (Tanskanen et al., 2000). In a recent longitudinal study by Breslau et al. (2005) the positive association between current daily cigarette smoking, but not past daily smoking, and increased risk for subsequent suicidal thoughts or attempts held even when potential confounding factors (i.e. prior suicidal behavior, current or past major depression, and current or past substance abuse) were taken into consideration (Breslau et al., 2005). Schneider et al. (2005) in their case–control study examined suicide attempters and found that among males, but not among females, current smoking was a risk factor for completed suicide after controlling for psychiatric disorders (Schneider et al., 2005). Riala et al. (2007a) found a similar gender related tendency in the connection between smoking and suicide in their large-scale prospective study. Regular smoking in early adolescence elevated the risk of completed suicide only among males, but it elevated the risk of hospital-treated suicide attempts in both genders (Riala et al., 2007a). Kessler et al. (2008), after a thorough statistical processing of data from the National Comorbidity Survey, reported that the highest level of smoking (early smoking initiation with lifetime NIC dependence, daily use, and dependence) was associated with suicide plans among suicide ideators (but not with other suicide-related outcomes such as suicide gestures or attempts). This result was independent of current smoking status, since among remitted smokers the above association was also detectable (Kessler et al., 2008). According to the authors this refutes a direct causal effect of NIC dependence itself on suicide plans, and instead refers to a causal association between the determinants of NIC dependence and suicide plans (Kessler et al., 2008). In their longitudinal study, Hemmingsson and Kriebel (2003) also found that smoking is a risk factor for suicide, but after the authors adjusted for some potential confounders (i.e. psychiatric diagnoses, "low emotional control", alcohol consumption and medication for nervous problems, drug use, etc.) the relationship was dissipated and was no longer significant (Hemmingsson and Kriebel, 2003). Kessler et al. (2007)

in their cross-sectional study and Boden et al. (2008) and McGee et al. (2005) in their longitudinal studies also found that while smoking is associated with a higher risk of suicide, after introducing new confounding variables (i.e. mental disorders or low levels of parental attachment) into the statistical analysis or using more sophisticated statistical methods in the processing of data, the positive association between smoking and suicidal behavior vanished (McGee et al., 2005; Boden et al., 2008; Kessler et al., 2007, 2008). Some of the above studies found that current smoking is more strongly associated with suicidal behavior than past smoking (Breslau et al., 2005; Miller et al., 2000b; Iwasaki et al., 2005; Rihmer et al., 2007), but others failed to confirm this result (Kessler et al., 2008). The majority of the above studies found a dose-dependent association between cigarette smoking and suicidal behavior (suicidal behavior was more frequent among heavy smokers than among light smokers) (Miller et al., 2000a,b; Tanskanen et al., 2000; Riala et al., 2007a; Iwasaki et al., 2005; Bronisch et al., 2008; Boden et al., 2008; Schneider et al., 2009). In addition to the results of the surveys discussed above, which were taken in non-clinical populations, the investigations by Tanskanen et al. (1998) and Malone et al. (2003) showed that smoking is also a risk factor for suicidal behavior in adult psychiatric patient populations and a similar result was also found by Rihmer et al. (2007) in a Hungarian adult outpatient population (Tanskanen et al., 1998; Malone et al., 2003; Rihmer et al., 2007). This relationship was observed by Riala et al. (2007b) in an adolescent psychiatric patient population, too (Riala et al., 2007b). In a psychological autopsy study by Schneider et al. (2009), current smoking was associated with an elevated risk of suicide in patients with personality disorders and substance use disorders, but interestingly, current smoking was associated with a decreased risk of suicide among individuals with affective disorders (Schneider et al., 2009). Blood and urine levels of NIC and cotinine were higher among smokers who committed suicide compared with smokers who died of non-suicide-related causes according to an autopsy study. This result suggests that cigarette smokers who have committed suicide smoked more heavily than other cigarette smokers (Moriya et al., 2007).

Different theories exist concerning the background of the connection between smoking and suicide. The common cause hypothesis suggests that smoking is a non-causal marker of elevated risk of suicidal behavior (i.e. both smoking and suicidal behavior have common risk factors, for example mental disorders or more distal causes for which current mental disorders serve as proxies) (Kessler et al., 2007; Hughes, 2008b). The mediation hypothesis states that smoking is a physical/psychological toxin that first leads to mental disorders and after it to elevated risk of suicide (Kessler et al., 2007; Hughes, 2008b). One version of mediation theory raises the possibility that smoking causes physical illnesses and then physical illness(es) increases the risk of suicide. Interestingly, patients with some pulmonary diseases (i.e. asthma and COPD) have an increased risk of mood and anxiety disorders. While cigarette smoking increases the risk of development and/or negatively influences the course of these disorders, the positive association between smoking and mental disorders and suicide may also partially materialize via the lung damaging effects of smoking (Shanmugam et al., 2007; Katon et al., 2007; Hasler et al., 2005; Wagena et al., 2005; Mannino and Buist, 2007; Hughes, 2008b). A third possible explanation of the smoking-suicide connection views smoking as a form of self-medication in an already existing mental disorder (which is a risk factor for suicide) (Hughes, 2008b). Presently, however, the validity of these theories is still uncertain (Hughes, 2008b). According to our current knowledge, the risk of suicidal behavior does not increase during/after cessation. Recently, however, some findings have suggested that the administration of some smoking cessation medications may elevate the risk of suicidal behavior (Hughes, 2008b; Christensen et al., 2007; McIntyre, 2008).

5.4. Different forms of nicotine administration and the risk of mental disorders

Recently Goodwin et al. (2008) have suggested that the route of NIC administration (smokeless tobacco or cigarette smoking) and NIC dependence (in contrast to non-dependence) have a profound impact on the relationship(s) between mood/anxiety disorders and NIC consumption. These results support the theory that smoking is not just a kind of NIC administration (Goodwin et al., 2008). The study processed data gained from NESARC (National Epidemiologic Survey for Alcohol and Related Conditions) with a representative sample of the adult US population (Goodwin et al., 2008). For subjects with NIC dependence, the use of smokeless tobacco was not associated with an increased likelihood of mood disorders, while smoking was. Interestingly, if subjects were not NIC-dependent, neither the use of smokeless tobacco nor cigarette smoking was associated with an increased likelihood of mood disorders. Among participants with NIC dependence the use of smokeless tobacco or smoking were associated with elevated likelihood of anxiety disorders, but among NIC non-dependent participants neither the use of smokeless tobacco nor smoking were associated with the increased likelihood of anxiety disorders (but NIC non-dependent smoking was associated with elevated risk of panic disorder) (Goodwin et al., 2008). These results suggest that smoking is not only a staggeringly addictive form of NIC consumption (discussed in detail in the chapter "Pharmacology and health consequences of smoking"), but is more closely associated with some forms of mental disorders than other modes of NIC administration (Goodwin et al., 2008).

6. Schizophrenia

6.1. Epidemiology and consequences of smoking in schizophrenia

de Leon and Diaz (2005) in their meta-analysis, which processed smoking epidemiological data of patient populations from different parts of the world, found that patients with schizophrenia have an approximately 5.3 times higher risk of being current smokers and a 3.1 times higher risk of ever smoking than people from the worldwide general population (de Leon and Diaz, 2005). The average current smoking rate was 62% among patients with schizophrenia according to this meta-analysis (de Leon and Diaz, 2005; Chapman et al., 2009). Although the elevated smoking rate in patients with schizophrenia is beyond dispute, a recent article calls attention to a strange publication trend: authors of many research articles or websites often report a more elevated rate of smoking in schizophrenia ("around," "up to," or "about" 90%) than was found in the above meta-analysis. These statements are dangerous, as clinicians reading these articles may conclude that almost all patients with schizophrenia smoke and that their smoking is intractable (Chapman et al., 2009).

The elevated smoking frequencies among patients with schizophrenia persists after correcting for such confounding factors as marital status, antipsychotic medication, institutionalization, socioeconomic status or alcohol and drug use (Lyons et al., 2002; Aguilar et al., 2005; Kumari and Postma, 2005). Heavy smoking, high NIC dependence, and lower smoking cessation rates are also more frequent among patients with schizophrenia compared to the general population (de Leon and Diaz, 2005). Furthermore, a recent study by Tidey et al. (2005) found that smokers with schizophrenia smoked cigarettes more "efficiently" compared to the control population (greater number of puffs per cigarette, shorter inter-puff intervals, and larger total cigarette puff

volumes in patients with schizophrenia vs. control) (Tidey et al., 2005). In accordance with this result, most, but not all, studies found that smokers with schizophrenia have higher blood or saliva levels of NIC and/or cotinine compared to controls matched for cigarette consumption (Bozikas et al., 2005; Strand and Nyback, 2005; Williams et al., 2005; Weinberger et al., 2007). An interaction between the metabolism of NIC and antipsychotics is improbable, since NIC is metabolized primarily by CYP2A6 and CYP2B6 enzymes, and these enzymes are not involved significantly in the metabolism of antipsychotics. Consequently, higher NIC levels among patients with schizophrenia are probably not a corollary of antipsychotic medication (Williams et al., 2005). Similar serum 3′-hydroxycotinine to cotinine ratios in patients with schizophrenia or schizoaffective disorder and in controls suggest that differences in the metabolism of NIC by the CYP2A6 enzyme among patients with schizophrenia are also unlikely; thus higher NIC levels in patients with schizophrenia compared to controls matched for cigarette consumption is not a metabolic effect, but the sequelae of the increased NIC intake per cigarette among patients (Williams et al., 2005).

Differences appear to exist between smokers with and without schizophrenia in their motivations to smoke (Gurpegui et al., 2007). Members of the patient group more frequently attributed their desire to smoke to the calming, mood-increasing, concentration- and agitation-heightening effects of smoking than did control persons (Gurpegui et al., 2007). Barr et al. (2008a) in their recent study showed that two motivation factors (“pleasure from the ritual of smoking” and “desire for stimulation”) were indicated more frequently by patients than controls, and scores on both these factors were in positive correlation with the chlorpromazine equivalent of the antipsychotic dose given to patients. Consequently, authors have suggested that increased motivation may be a response to counter side-effects of antipsychotic medication (Barr et al., 2008a). Furthermore, some data indicate that patients with schizophrenia are more prone to NIC addiction, while the increased reinforcing effects of smoking were found to be associated with this disorder (Spring et al., 2003; Weinberger et al., 2007).

Smoking initiation in general (on average in 77% of cases) precedes the onset of schizophrenia and unaffected co-twins or siblings of patients with schizophrenia are more often smokers and have more difficulty quitting than controls (Lyons et al., 2002; de Leon and Diaz, 2005; Smith et al., 2008). Furthermore, those patients with schizophrenia who started smoking at least 5 years before beginning psychiatric medication had a higher risk of becoming regular (daily) smoker than normal controls of comparable age (Diaz et al., 2008). In addition, several studies have reported that the level of schizotypy (which is genetically and developmentally linked to schizophrenia and considered a phenotypical variant of schizophrenia) among healthy subjects correlated positively with smoking habits (Kumari and Postma, 2005; Esterberg et al., 2007, 2009). Although, as mentioned above, smoking precedes the onset of schizophrenia in most cases, patients with schizophrenia or who are vulnerable to schizophrenia are more likely to initiate daily smoking after age 20 (when subjects of the general population rarely initiate daily smoking) (de Leon et al., 2002; Gurpegui et al., 2005; Diaz et al., 2008). These data suggest that probably (genetic) vulnerability to schizophrenia rather than schizophrenia per se or the prodromal period of schizophrenia is positively associated with smoking habits (Lyons et al., 2002; de Leon and Diaz, 2005; Kumari and Postma, 2005; Esterberg et al., 2007; Diaz et al., 2008). On the other hand, data are ambiguous about whether smoking status at baseline affects the chances of the onset of schizophrenia in longitudinal studies (Zammit et al., 2003, 2007; Weiser et al., 2004; Wiles et al., 2006).

The mortality rate is higher among patients with schizophrenia. Moreover, in recent decades this mortality gap between the patient and general population has been increasing (Auquier et al., 2006; Saha et al., 2007). Approximately two-thirds of the excess mortality can be accounted for by deaths caused by natural (non-suicide) causes (Goff et al., 2005; Auquier et al., 2006; Saha et al., 2007). Cardiovascular diseases are twofold more frequent among patients with schizophrenia, and are responsible for a large portion of premature deaths among patients (more premature deaths are caused by cardiovascular disorders than suicide in this patient population) (Hennekens et al., 2005). Patients with schizophrenia also have a higher rate of COPD (one of the leading cause of mortality worldwide, and one of its main risk factors is smoking) compared with the general population (Mannino and Kiriz, 2006; Mannino and Buist, 2007; Shanmugam et al., 2007). Because the rate of smoking is so high in individuals with schizophrenia, it is easy to conclude that smoking alongside other highly prevalent cardiovascular risk factors in schizophrenia (i.e. obesity, diabetes mellitus, and hypertension) may be a major cause of premature death in this population (Hennekens et al., 2005; Hennekens, 2007). Furthermore, smoking seems to correlate positively with elevated suicide risk in schizophrenia patient population, as it does in the general population (Miller et al., 2000a,b; Altamura et al., 2003; Potkin et al., 2003; Iancu et al., 2006; Limosin et al., 2007).

6.2. Self-medication theory

Although some kind of “consensus” exists among laymen and psychiatrists that smoking is used as a way of self-medicating in schizophrenia, the following facts contradict this theory. First, there is no significant inverse relationship between smoking and classical symptoms of schizophrenia. Moreover, most studies have found a positive relationship between smoking and the intensity of positive and negative symptoms of schizophrenia (although nAChR agonists could have a beneficial effect on cognitive symptoms of schizophrenia, see below). Second, smoking reduction or cessation in most studies had no major effect on the symptoms of schizophrenia. Third, as mentioned above, smoking precedes the onset of schizophrenia in most cases (de Leon et al., 2006; Esterberg et al., 2007). Since NIC administration causes dopamine release in many parts of the brain, and smoking may decrease dopamine D2 receptor upregulation in the striatum caused by typical antipsychotic medication, another hypothesis suggests that smoking may alleviate extrapyramidal side-effects of antipsychotics (i.e. akathisia, parkinsonism and tardive dyskinesia). Results of epidemiological studies in this regard, however, are ambiguous (in fact, with tardive dyskinesia, smoking seems to be a risk factor rather than a protective factor) (Silvestri et al., 2004; de Leon et al., 2006; Diehl et al., 2009). Nowadays, the role played by the tobacco companies in research on the “self-medication hypothesis” is clear. First, the tobacco industry directly funded research supporting the “self-medication hypothesis”. In addition, the tobacco industry also promoted research showing that patients with schizophrenia are less susceptible to the harmful health effects of smoking (Prochaska et al., 2008a).

6.3. The role of antipsychotics in smoking behavior

A complex relationship exists between antipsychotic medication and smoking. Since antipsychotics cause a dopamine receptor blockade which – at least theoretically – dampens NIC-evoked reward, antipsychotics could lead to higher NIC intake (smoking) among patients (Kelly and McCreadie, 2000). This assumption is strengthened by some studies which have found that haloperidol administration leads to increased smoking behavior, although

Brauer et al. (2001) reported the opposite (Brauer et al., 2001). Laviolette and van der Kooy (2003a) described how systemic or intra-NAcc administration of the antipsychoticagent flupenthixol decreased the aversive and increased the rewarding effectsof NIC, which suggests that dopamine receptor blockades by antipsychotics caninduce a unique phenotype extremely vulnerable to nicotine's rewarding properties (Laviolette and van der Kooy, 2003a).

Another aspect of the interaction between smoking and antipsychotic treatment is the accelerating effect of some ingredients of cigarette smoke (mainly polycyclic aromatic hydrocarbons) on the metabolism of several antipsychotics (i.e. clozapine, olanzapine, members of the phenotiazione group, and haloperidol), although smoking does not significantly change the metabolism of others (i.e. quetiapine, risperidone, ziprasidone, aripiprazole) (Desai et al., 2001; de Leon et al., 2006). Thus, not surprisingly, most investigations show that smoker patients with schizophrenia receive significantly higher neuroleptic doses compared with non-smoker patients with schizophrenia (Aguilar et al., 2005; de Leon et al., 2006).

6.4. Explanatory theories of elevated smoking rates among patients with schizophrenia

Several theories try to explain why smoking is more prevalent among patients with schizophrenia. According to the dopamine hypothesis of schizophrenia, patients with schizophrenia have a hypodopaminergic state in the prefrontal cortex (PFC), which could account for certain characteristic cognitive impairments in this disorder (Lewis and Gonzalez-Burgos, 2006; Guillin et al., 2007). In an animal model of schizophrenia, NIC or nAChR modulator galantamine administration elevated the level of dopamine in PFC, furthermore NIC alleviated impaired working memory in line with the normalization of the dopamine D1 receptor and dopamine levels in PFC. Therefore, molecules with nAChR agonist property may hypothetically restore dopaminergic disturbances in PFC in schizophrenia (Tsukada et al., 2005; Fallon et al., 2007; Schilstrom et al., 2007).

Excitation of VTA dopaminergic neurons is primarily dependent on glutamatergic innervation from the PFC, and in accordance with this, NMDA administration into the VTA activates the dopaminergic mesocorticolimbic fibers (Nisell et al., 1996; Ikemoto, 2004; Tseng et al., 2006; Wang et al., 2007a). Another theory of schizophrenia suggests a decreased activity of glutamatergic fibers projecting from the PFC onto mesencephalic dopaminergic nuclei (Knott et al., 2006; Lewis and Gonzalez-Burgos, 2006). nAChR agonists activate pre-synaptic α7-containing nAChRs on glutamatergic terminals in the VTA, resulting in an increased, evoked release of glutamate, which in turn, excites NMDA receptors on dopaminergic neurons in the VTA (Knott et al., 2006; Mansvelder et al., 2006; Fallon et al., 2007; Wang et al., 2007a). In line with this, the non-α7 nAChRs on GABA neurons undergo rapid desensitization within minutes after the start of NIC exposure, and as a consequence, reduce the inhibitory input to the dopaminergic neurons (Mansvelder et al., 2006). These two effects of NIC in the VTA lead to increased burst-firing of dopaminergic neurons and a release of DA in the nucleus accumbens and PFC (Nisell et al., 1996; Knott et al., 2006; Mansvelder et al., 2006; Fallon et al., 2007; Wang et al., 2007a). Moreover, chronic NIC administration upregulates the expression of subunits of NMDA-type glutamate receptor in PFC (where there is reduced NMDA receptor-mediated signaling in schizophrenia), which suggests that chronic NIC administration causes a hyperglutamatergic neurotransmission within the mesocorticolimbic dopaminergic circuitry (Lewis and Gonzalez-Burgos, 2006; Wang et al., 2007a). Another interesting link also exists between glutamate hypothesis of schizophrenia and NIC. The administration of molecules with NMDA receptor antagonist properties (i.e. ketamine, PCP) is widely know to cause either increased symptom severity among patients with schizophrenia or thought disorders and perceptual distortions among healthy individuals (Lewis and Gonzalez-Burgos, 2006; Pomarol-Clotet et al., 2006). Moreover, kynurenic acid – an endogenous tryptophan metabolite with NMDA receptor antagonist properties – could disrupt auditory gating and prepulse inhibition (see below in details). Furthermore, the brain tissue and cerebral spinal fluid of patients with schizophrenia contained elevated levels of kynurenic acid, which further suggests the relevancy of NMDA antagonists in the pathogenesis of schizophrenia (Shepard et al., 2003; Erhardt et al., 2004, 2007; Chess et al., 2007). Interestingly, kynurenic acid also exhibits antagonist properties on α7 nAChRs, and this activity of kynurenic acid is assumed to lead to working memory deficiency, a classical symptom of schizophrenia (Chess et al., 2007; Lewis and Gonzalez-Burgos, 2006).

6.5. Alterations of the cholinergic system in schizophrenia

The cholinergic system has been extensively researched in schizophrenia (Adams and Stevens, 2007). The number of cholinergic neurons is not altered significantly in the nucleus basalis Meynert, and laterodorsal tegmental nucleus of the brainstem, but is elevated in the pedunculopontine nucleus of the brainstem and decreased in the ventral striatum in patients with schizophrenia compared to controls (Garcia-Rill et al., 1995; Adams and Stevens, 2007; Berman et al., 2007). Cortical cholinesterase and choline acetyltransferase (ChAT) activity is unaltered, but ChAT activity is reduced in the pedunculopontine nucleus of patients with schizophrenia (Garcia-Rill et al., 1995; Berman et al., 2007). In addition, alterations in choline acetyltransferase and acetylcholinesterase activities were also described in the hippocampus, caudate, putamen, nucleus accumbens, thalamus and septal areas in patients with schizophrenia (Karson et al., 1993). nAChRs density changes are commonly reported in schizophrenia (see below). Furthermore, patients with schizophrenia have elevated levels of autoantibodies against many neurotransmitter receptors (i.e. nAChRs) (Margutti et al., 2006; Chandley et al., 2009). Post-mortem autoradiographic studies have revealed disturbances in the expression levels of α7 and α4β2 nAChRs in various cerebral areas of patients with schizophrenia. Results are more certain regarding α7 nAChRs, since most investigations suggest the expression of α7 nAChRs is decreased in the hippocampus, the reticular nucleus of the thalamus, and the prefrontal cortex (Freedman et al., 1995; Court et al., 1999; Guan et al., 1999; Martin-Ruiz et al., 2003; Adams and Stevens, 2007; Olincy and Stevens, 2007). Moreover, Marutle et al. (2001) observed that in the brain of patients with schizophrenia, a reduction in α-bungarotoxin (a ligand with a high affinity for α7 nAChR) binding in the cingulate cortex occurs. In addition, non-significant changes in α-bungarotoxin binding in the orbitofrontal (Br 11, 12, and 47) and posterior temporal (Br 20, 21, and 36) cortex have been described in comparison with controls (Marutle et al., 2001; Martin-Ruiz et al., 2003; Ripoll et al., 2004; Adams and Stevens, 2007). Only two studies did not find significantly decreased α7 antagonist (^{3H}-methyllycaconitine or ^{I125}-α-BTX) binding in the frontal cortex (Br 8/9 and Br 46), and one of these did not detect any significant decrease in the ^{3H}-methyllycaconitine binding in the hippocampus (Breese et al., 2000; Adams and Stevens, 2007; Mathew et al., 2007). Although most studies investigating α7 nAChR densities in the brains of patients with schizophrenia had no matched control groups for smoking, this methodological shortcoming probably would not lead to the observed decline in

the density of α7 nAChR, since in patient groups – given the higher prevalence of smoking among patients with schizophrenia (see above) – the expected smoking rates are higher, and should be accompanied by a rise in α7 nAChR density because of smoking-induced receptor upregulation (Freedman et al., 1995; Court et al., 1999). Unfortunately, results of studies that investigated mRNA levels for α7 receptors in different brain regions in schizophrenia are not closely correlated with the results of autoradiographic and western blot studies (Hemby et al., 2002; Martin-Ruiz et al., 2003; De Luca et al., 2006a,b; Adams and Stevens, 2007; Mathew et al., 2007). Three studies did not find any reduction in mRNA levels for α7 receptors in PFC. Furthermore, one study found increased and one study found unaltered mRNA levels for α7 receptor in hippocampal formation or in the adjacent entorhinal cortex among patients with schizophrenia compared to controls (De Luca et al., 2006a,b; Adams and Stevens, 2007; Mathew et al., 2007; Martin-Ruiz et al., 2003; Breese et al., 2000). Decreased α7 nAChR density in the reticular nucleus of the thalamus is thought to possibly lead to hallucinations (Behrendt, 2006). In addition, two selective α7 nAChR agonists (SSR180711 and PNU-282987), like antipsychotics, appear to activate the shell region of NAcc and the PFC—measured by early response gene (c-fos) activation. Both regions are affected in the pathophysiology of schizophrenia, and the activation of NAcc and medial PFC by antipsychotics is considered the basis for their therapeutic effects on symptoms of schizophrenia. This has led to the conclusion that α7 nAChR agonists could be potential antipsychotics (Hansen et al., 2007). Recent investigations of SSR180711 and TC-5619 (a selective α7 agonist) in various animal models of schizophrenia further support this assumption, and there is some suggestion that SSR180711 and TC-5619 may ameliorate cognitive dysfunction (Hashimoto et al., 2008; Barak et al., 2009; Thomsen et al., 2009; Hauser et al., 2009). Recently, Mathew et al. (2007) found an association between the allele and haplotype frequencies of schizophrenia-associated polymorphisms in the neuregulin 1 gene and decreased α7 nAChR expression measured by ^{I125}-α-BTX binding (parallel with decreased mRNA level for α7 receptor) in the PFC. This result increases the likelihood that α7 nAChR has a role in the pathogenesis of schizophrenia (Mathew et al., 2007). The link between decreased α7 nAChR density and schizophrenia is further supported by the discovery that phencyclidine (PCP) administration (as an experimental model of psychotic states) leads to decreased α7 nAChR expression in the mouse brain (Hashimoto et al., 2008).

Conflicting data are available on the density of α4β2 nAChR in schizophrenia (Adams and Stevens, 2007). Among patients with schizophrenia, the density of the α4β2 receptor is decreased in the hippocampus, no change occurs in the density of high-affinity nAChR in the thalamus, and the direction of change in α4β2 receptor's density in the striatum and the cortex is ambiguous (Freedman et al., 1995; Ripoll et al., 2004; Adams and Stevens, 2007). Breese et al. (2000) described an attenuated upregulation of α4β2 in the hippocampus, thalamus and caudate of patients with schizophrenia who smoke compared to control smokers (Breese et al., 2000). Further results by the same authors suggested that concomitant NIC and antipsychotic (haloperidol) administration-induced nAChR upregulation did not differ significantly from the NIC administration-induced receptor upregulation measured by [^{3}H]epibatidine binding in the cortex of rats (Breese et al., 2000; Ochoa and Lasalde-Dominicci, 2007). In contrast, Lee et al. (2001) found that NIC and antipsychotic (haloperidol) co-treatment was associated with a decreased α7 nAChR upregulation in the hippocampus and α4β2 nAChR upregulation in the thalamus compared to receptor upregulation induced by NIC treatment alone (Lee et al., 2001).

6.6. Genetic evidence for the role of nAChRs in schizophrenia

As mentioned, genetic investigations suggest that some polymorphisms in the region of the α7 subunit gene (CHRNA7) may be associated with sensory deficits in schizophrenia, while additional linkage of schizophrenia itself to the region 15q13-14 (the chromosomal localization of the α7 subunit gene) has been revealed in most – but not all – of investigated pedigrees (Ripoll et al., 2004; Adams and Stevens, 2007; Ochoa and Lasalde-Dominicci, 2007). In addition, a recent investigation found that a polymorphism (rs3087454) located in a putative repressor region upstream of CHRNA7 was significantly associated with schizophrenia (Stephens et al., 2009). Moreover, De Luca et al. (2006a,b) observed that genetic interaction between the α4 (CHRNA4) and β2 (CHRNB2) genes was significant in patients with schizophrenia, whereas when the two genes were investigated separately, neither was sufficient to confer susceptibility to schizophrenia (De Luca et al., 2006a,b; Adams and Stevens, 2007). The same investigators also found an association between heavy smoking and a genetic variant of CHRNA4 among patients with schizophrenia, although further studies are needed to confirm these findings (Adams and Stevens, 2007; Voineskos et al., 2007).

6.7. Antipsychotic treatment and the cholinergic system

Antipsychotic treatment has a wide range of effects on the cholinergic system (Terry et al., 2003; Levin et al., 2006; Terry and Gearhart, 2007; Terry and Mahadik, 2007). Although the opinion that second-generation antipsychotics (SGAs) are better than first-generation antipsychotics (FGAs) in point of their beneficial effects on cognition was widely accepted in the past, recent animal studies with long-term antipsychotics administration and some human studies also suggest that both FGAs and SGAs could have deleterious effects on memory functions (Levin and Rezvani, 2007; Terry and Mahadik, 2007). Considering that nicotinic cholinergic systems have an essential role in memory functions, the deteriorating effects of some antipsychotics on memory functions can presumably be linked to their possible actions on nicotinic cholinergic systems (Dani and Bertrand, 2007). Investigations seem to support this assumption. Risperidone significantly decreased the density of α7 nAChR in many brain areas (including in different parts of hippocampal formation) after 180 days of treatment in rats (Terry et al., 2005b). Olanzapine also significantly decreased the density of α7 nAChR in dentate gyrus after 90 (but not after 180) days of treatment (Terry et al., 2005b), while both haloperidol and risperidone decreased α7 nAChR density in other memory-related brain areas (frontal cortex and basal forebrain) after 90 days of treatment (Terry and Gearhart, 2007). Choline acetyltranferase (ChAT) levels are significantly decreased after 90 days of haloperidol treatment in the hippocampus, cortex and striatum in rats (Terry et al., 2003). Risperidone administration after 90 days also decreased ChAT levels in the hippocampus and striatum (but not in the cortex) in rats (Terry et al., 2003), while olanzapine or clozapine treatment for 90 days did not cause diminution in ChAT levels in the hippocampus, cortex and striatum (Terry et al., 2002, 2003). Investigations also showed that representative FGAs (haloperidol and chlopromazine) and SGAs (olanzapine and risperidone) do not affect high-affinity α4β2 nAChR density in the hippocampal formation, cortex and thalamic nuclei after their long-term (90 or 180 days) administration in rats (Terry et al., 2006; Galletly, 2009).

Another possible link between nicotinic cholinergic systems and antipsychotic treatment is that some antipsychotics, such as clozapine, chlorpromazine, haloperidol and quetiapine were shown to inhibit the function of nAChRs (Grinevich et al., 2009; Xu et al., 2006; Singhal et al., 2007).

6.8. The role of the nicotinic system in sensory processing

Sensory processing deficits have been frequently described in schizophrenia and they are correlated with some impairments commonly reported in schizophrenia patients (i.e. disturbances of thought and attention) (Adams and Stevens, 2007; Martin and Freedman, 2007; Thaker, 2007; Turetsky et al., 2007). Three experimental paradigms (P50 auditory gating test and prepulse inhibition in the acoustic startle test, and eye tracking tests, such as the smooth pursuit eye movement task and antisaccade task) are widely used to assess sensory processing deficits in schizophrenia (for a review, see Zanelli et al., 2005; Turetsky et al., 2007).

The aim of the P50 test is to measure with EEG the blocking of response to an auditory stimulus received immediately after a preceding (conditioning) auditory stimulus. Patients with schizophrenia showed an increased P50 ratio (the amplitude of the P50 to the second (test) stimulus divided by the amplitude of the P50 to the first (conditioning) stimulus) compared to control individuals without schizophrenia (Adler et al., 2004; Martin and Freedman, 2007; Turetsky et al., 2007). This aberration is already present at the first episode of psychosis. Furthermore, family members of patients with schizophrenia also have this aberration (de Wilde et al., 2007; Martin and Freedman, 2007). Impairment in the P50 test suggests that patients with schizophrenia have a decreased ability to filter information, and consequently are flooded by external and internal information, which could lead to personality decompensation (Adams and Stevens, 2007; Turetsky et al., 2007). The primary anatomical correlates of the P50 test are the hippocampus, the PFC and temporoparietal junction (Turetsky et al., 2007). Findings of decreased α7 nAChR density in the hippocampus in schizophrenia suggest that this nicotinic receptor plays an important role in the impairment of auditory gating (Leonard et al., 1998). Results of biochemical and genetic investigations also point to α7 nAChRs as the culprits responsible for impairment in the P50 paradigm of auditory gating among patients (inconsistencies in the results, however, leave open the question of whether variations in the gene encoding this subunit (CHRNA7) alter the risk of schizophrenia) (Leonard et al., 1998; Olincy et al., 2007; Zammit et al., 2007). The role of α7 subunits in schizophrenia is further supported by the results with the DBA/2 mouse strain, which exhibit decreased α7 nAChR expression in the hippocampus and also an impaired auditory gating (Martin and Freedman, 2007). In addition to some antipsychotics (i.e. clozapine and perhaps olanzapine), smoking, NIC-containing patches or gum, and the partial α7 agonist DMXB-A repair P50 deficiencies in schizophrenia (Ripoll et al., 2004; Martin and Freedman, 2007; Turetsky et al., 2007). NIC administration (like clozapine administration) has a positive effect on impaired sensory gating in the DBA/2 mouse strain, too (Levin et al., 2006; Olincy et al., 2007). Some data also point to the involvement of α4β2 nAChRs in the beneficial effect of NIC in the rodent model of auditory gating (Radek et al., 2006). In conclusion, these results suggest that NIC may have beneficial effects on extraneous information filtering in patients with schizophrenia (Olincy et al., 2007).

Patient with schizophrenia also have impairments in prepulse inhibition (PPI), which is a sensory motor gating probe (Thaker, 2007; Turetsky et al., 2007). In PPI, a weak "prepulse" stimulus, which precedes the "pulse" or "startling" stimulus by 30–500 ms, inhibits the motor response of the orbicularis oculi muscle (measured by EMG) to the "pulse" or "startling" stimulus (Kumari and Postma, 2005; Campbell et al., 2007; Thaker, 2007; Turetsky et al., 2007). Deficient (reduced) inhibition associated with the "prepulse" stimulus is reported among patients with schizophrenia and also among their unaffected family members (Kumari and Postma, 2005; Thaker, 2007; Turetsky et al., 2007). This deficiency correlates more strongly with cognitive abnormalities and thought disorder than with other schizophrenic symptoms (Kumari and Postma, 2005; Thaker, 2007; Turetsky et al., 2007). PPI impairment (like deficiency in the P50 test) also suggests problems of extraneous information filtering (Van den Buuse et al., 2003). NIC corrects PPI deficiency elicited by the NMDA-R antagonist phencyclidine (an agent which is capable of inducing psychotic symptoms) in animal studies and also repairs reduced PPI among patients with schizophrenia (Carls and Ruehter, 2006; Hong et al., 2008).

Abnormal smooth pursuit eye movement (SPEM) is a consistently observed neurophysiologic deficit in patients with schizophrenia and their relatives. Moreover, this impairment is not affected by dopamine D2 receptor antagonist antipsychotics (Tanabe et al., 2006; Thaker, 2007; Lencer et al., 2008), but is also attenuated by NIC administration (by cigarette smoking, NIC patch, or nasal spray) among patients with schizophrenia (Martin and Freedman, 2007). A recent fMRI study by Tanabe et al. (2006) showed that NIC improves abnormal SPEM in schizophrenia through modulation of hippocampal and anterior cingulate activity (Tanabe et al., 2006).

6.9. Nicotinic agents and AChE inhibitors as possible therapeutics for cognitive dysfunctions in schizophrenia

Results of some studies suggest that nAChR agonists may have a therapeutic role in the treatment of cognitive impairments (i.e. disturbances in attention and in verbal, visual and working memories) in schizophrenia, and in turn, smoking abstinence could lead to a deterioration of cognitive functions and psychomotor performance in this patient population (Sacco et al., 2005; Smith et al., 2006; Buchanan et al., 2007; Levin et al., 2006; Barr et al., 2008b). On the other hand, NIC also has beneficial effects on cognitive dysfunctions caused by antipsychotic therapy (Levin and Rezvani, 2006, 2007; Buchanan et al., 2007). Some studies investigating the effect of NIC on cognition have been conducted among smoker patients with schizophrenia; thus the results of these studies could be biased because of withdrawal symptoms and tachyphylaxis (rapidly decreasing response to a drug due to receptor desensitization). Studies investigating non-smoker patients with schizophrenia, however, have found that NIC has beneficial effects on cognitive functions (Harris et al., 2004; Barr et al., 2008b). While the procognitive effects of NIC are limited by tachyphylaxis and the possible toxicity of NIC (and other ingredients of cigarettes when the form of NIC intake is smoking), less toxic and more chronically effective cholinergic treatments are required (Buchanan et al., 2007). For example, the α7 nAChR partial agonist 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A, also known as GTS-21) amended cognitive functions in healthy persons and in various animal models (Martin et al., 2004; Olincy et al., 2007). In a small proof-of-concept trial, the administration DMXB-A had a positive effect on neurocognition in patients with schizophrenia. However, in a later phase-2 trial, investigators did not find any significant improvement in the cognitive functions of patients (but they found that DMXB-A has a therapeutic effect on the negative symptoms of schizophrenia) (Olincy et al., 2006, 2007; Freedman et al., 2008; Galletly, 2009). The procognitive effects of SSR180711 (a partial α7 nAChR agonist) and TC-5619 (a selective α7 agonist) in experimental models of schizophrenia have already been discussed above (Barak et al., 2009; Hauser et al., 2009).

Both nAChR and muscarinic AChRs (mAChRs) are involved in the pathophysiology of schizophrenia, while their agonists – at least in some studies – have procognitive effects in this population. Thus it would be reasonable to conclude that the administration of acetylcholinesterase inhibitors (AChEIs) also has favorable effects on neurocognitive functions in schizophrenia. Unfortunately,

according to the results of clinical studies, this supposed beneficial effect of AChEIs is far from proved (Buchanan et al., 2007, 2008; Chouinard et al., 2007; Green, 2007; Stip et al., 2007; Dyer et al., 2008; Freedman et al., 2008; Sellin et al., 2008; Galletly, 2009). Furthermore, favorable effects of AChEIs on core (positive and negative) symptoms of schizophrenia are also questionable. Only a few studies have suggested that some AChEIs have some beneficial effects on negative symptoms (Akhondzadeh et al., 2008; Buchanan et al., 2008; Conley et al., 2009; Sacco et al., 2008). Galantamine, in addition to its AChEI activity, is also a positive allosteric modulator of the $\alpha4\beta2$ and $\alpha7$ nAChRs. Among AChEIs, galantamine appears superior to donepezil and rivastigmine in its procognitive effect in schizophrenia. Considering these two facts together, it seems likely that the mere inhibition of AChE does not impact on cognitive dysfunctions in schizophrenia, but different kinds of nAChRs may be promising targets for further drug development (Buchanan et al., 2007; Villarroya et al., 2007; Galletly, 2009).

7. Affective disorders

7.1. Bipolar disorder

7.1.1. Epidemiology

Bipolar disorder is a chronic condition with recurring episodes of hypomania/mania and depression (Belmaker, 2004). The lifetime prevalence of bipolar I disorder (major depression with mania) is as high as 2.4%. However, if the bipolar II (major depression with hypomania, but not with mania) and the subthreshold cases were also considered, much higher lifetime prevalence rates of the broadly defined bipolar disorders, up to at least 7.2%, were reported (Rihmer and Angst, 2005). Several epidemiological data have unequivocally shown that the smoking rate among bipolar patients exceeds the smoking rate of the general population. In their classic article, Hughes et al. (1986) found that the prevalence of current smoking in bipolar patients in their psychiatric patient population was approximately 2.5 times higher than the smoking rate of the control population (70% vs. 30%, respectively) (Hughes et al., 1986). Lasser et al. (2000) – using data from the National Comorbidity Survey (a nationally representative sample of U.S. adults) – reported that the prevalence of current and life-time smoking among patients with bipolar disorder was 68.8% and 82.5% respectively (the prevalence of current and life-time smoking was 22.5% and 39.1% in the control population without mental illness) (Lasser et al., 2000). In a sample of psychiatric outpatients, Vanable et al. (2003) found that bipolar patients had higher smoking rates than patients with schizophrenia or major depression (66% vs. 63% vs. 60%, respectively) (Vanable et al., 2003). A recent article by Diaz et al. (2009) has also suggested that patients with a bipolar disorder have higher odds of ever and current smoking than individuals from the general population (Diaz et al., 2009). The association between bipolar disorder and elevated smoking rates is obviously true from the opposing perspective, too. For example, according to data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), an individual with NIC dependence has an approximately four times higher chance of suffering from bipolar-I disorder (Grant et al., 2004). Findings on the smoking rate of bipolar patients in other parts of the world are similar to the US samples. For example, in a Spanish sample, Gonzalez-Pinto et al. (1998) also found a higher life-time and point prevalence of smoking among patients with bipolar disorder compared to the control population, while Itkin et al. (2001) reported that the current smoking rate was 43% in a patient population with bipolar disorder from southern Israel, which was higher than the current smoking rate of control population (27.5%) and it was comparable to the smoking rate of patients with schizophrenia (45%). A study from Turkey also found higher smoking rates in bipolar patients (55.1%) than in the control population (47.3%) (although the difference was not statistically significant, perhaps because of the relatively small sample size and/or the high smoking rate in the general population). A Hungarian study also reported significantly higher rates of current and ever smoking among bipolar patients compared to the general population (Gonzalez-Pinto et al., 1998; Itkin et al., 2001; Uçok et al., 2004; Dome et al., 2005).

Data on successful cessation rates among patients with bipolar disorder are scarce and ambiguous. Some epidemiological studies have described decreased rates of successful cessation among patients with bipolar disorder, but a naturalistic treatment study did not find a lower quit rate in bipolar patient groups (Diaz et al., 2009; Lasser et al., 2000; Gershon Grand et al., 2007).

7.1.2. Smoking-related changes in clinical characteristics of bipolar disorder

A great number of studies also suggest that smoking habits may significantly influence the clinical characteristics of bipolar disorder. Berk et al. (2008) found that smoker patients with a current episode of mania showed poorer treatment response compared to their non-smoker counterparts. Moreover, they found that non-smokers had a significantly longer time to discontinuation from the trial for any reason (Berk et al., 2008). Waxmonsky et al. (2005) found in their cross-sectional study that bipolar patients who smoke have more (and more serious) previous episodes of both mania and depression compared to non-smokers with bipolar disorder (Waxmonsky et al., 2005). In addition they reported that smoking was positively associated with rapid-cycling, suicidal behavior, psychiatric comorbidity, and the use of alcohol, caffeine, and illicit drugs (Waxmonsky et al., 2005). In a retrospective study authors also found that a life-time history of smoking was significantly related to a more severe course of illness and elevated rates of comorbid psychiatric problems (Ostacher et al., 2006). Goldstein et al. (2008) also found positive relationships between smoking status and the severity of depressive episodes and higher rates of comorbid substance use disorder in a sample of adolescents with bipolar disorder (Goldstein et al., 2008). Some studies suggest that smokers with bipolar disorder are more vulnerable to psychotic episodes than non-smokers, but other studies failed to confirm this association (Waxmonsky et al., 2005; Corvin et al., 2001; Cassidy et al., 2002; Heffner et al., 2008). Not all investigations found similar results to the above; for example Heffner et al. (2008) found no association between smoking status and the severity and characteristics of bipolar disorder (i.e. rapid cycling, symptom severity) in a sample with an early course of bipolar disorder (data collection was conducted at the admission of patients with a first episode of mania) (Heffner et al., 2008). According to scarce data available in the literature, smoking status and cognitive functions are not closely related among bipolar patients (Law et al., 2009). Data are unclear regarding temporal relationships between the initiation of smoking and bipolar disorder. Some studies have found that the onset of smoking precedes the onset of bipolar disorder in most cases, but the results of other investigations do not support this result (Gonzalez-Pinto et al., 1998; Goldstein et al., 2008). Also uncertain is whether smoking is associated with an earlier onset of bipolar disorder (Waxmonsky et al., 2005; Goldstein et al., 2008; Ostacher et al., 2006; Heffner et al., 2008). The role of smoking in an elevated risk of suicide in bipolar disorder is also ambiguous. Some studies found that smoking is associated with a higher risk of suicidal behavior, but other studies have not confirmed this association (Waxmonsky et al., 2005; Goldstein et al., 2008; Ostacher et al., 2006; Neves et al., 2009; Oquendo et al., 2004; Valtonen et al., 2006; Marangell et al., 2006; Galfalvy et al., 2006).

Individuals suffering from bipolar disorder are well known to have an elevated risk of suicide mortality compared to the general population (Pompili et al., 2009). In addition, a recent literature review concluded that sufferers of bipolar disorder have an increased rate of premature death from natural causes (mainly by cardiovascular, respiratory, cerebrovascular, and endocrine disorders), too. Only a few studies have investigated cancer risk in this patient population, and results of these studies are unclear (Roshanaei-Moghaddam and Katon, 2009; BarChana et al., 2008; Carney and Jones, 2006). Results of investigations from different parts of the world suggest that the higher mortality rate in this patient population is a consequence not only of frequent obesity, metabolic syndrome, alcohol and other substance use, and poor diet, but also of smoking (Roshanaei-Moghaddam and Katon, 2009; Garcia-Portilla et al., 2009; Birkenaes et al., 2007; Salvi et al., 2008).

7.1.3. Relationships between the nicotinic system and bipolar disorder

Current knowledge about neurobiological relationships between the nicotinic system and bipolar disorder is scarce. Some findings suggest that patients with bipolar disorder with psychotic episode(s) in their medical history and also their unaffected relatives have deficits in P50 auditory gating (the P50 paradigm is discussed in details in the chapter on schizophrenia) (Schulze et al., 2007; Olincy and Martin, 2005; Hall et al., 2008; Sánchez-Morla et al., 2008). While deficiencies in the P50 response are associated with a potential susceptibility locus on chromosome 15q, which contains the α7 nicotinic receptor subunit gene cluster, the nicotinic system may be involved in the pathophysiology of bipolar disorder (Schulze et al., 2007; Olincy and Martin, 2005; Hall et al., 2008; Sánchez-Morla et al., 2008). The possible role of α7 nAChRs in bipolar disorder is further supported by the altered ratio of α7 and α7-like mRNA expression levels in the post-mortem prefrontal cortex of bipolar patients compared to controls (De Luca et al., 2006a,b). Genetic studies, however, have not fully supported the association between α7 nAChRs and bipolar disorder, since they have provided equivocal results on the association between genetic variants of the α7 nAChR gene (CHRNA7) and bipolar disorder (De Luca et al., 2006a,b; Serretti and Mandelli, 2008; Flomen et al., 2008; Flomen et al., 2006; Hong et al., 2004; Shi et al., 2007). The association of other nicotinic receptor genes with bipolar disorder has been poorly investigated, and existing results do not support a consistent association (Shi et al., 2007; Serretti and Mandelli, 2008; Lohoff et al., 2005; Kato, 2007).

7.2. Major depression

7.2.1. Epidemiology

Major depression, a serious public health problem associated with an increased risk of disability and mortality (according to estimates by the WHO, depression will be the second leading cause of disability worldwide in 2020), is a common diagnosis worldwide with a life-time prevalence 5–17% (Rihmer and Angst, 2005; Chachamovich et al., 2008; Ebmeier et al., 2006).

Results of epidemiological studies in general and clinical populations suggest a bidirectional positive relationship between smoking and major depression. For example, in the National Comorbidity Survey nearly 60% of individuals with a life-time history of depression were current or past smokers, while only 39% of the general population were current or past smokers (Lasser et al., 2000; Ziedonis et al., 2008). Additionally 16.5% of NIC-dependent individuals suffered from a current episode of major depression in the NESARC investigation, a rate several times higher than the rate of current major depression in the general population (2–7% in studies from different parts of the world) (Rihmer and Angst, 2005; Grant et al., 2004). In clinical smoking treatment studies, the life-time prevalence of major depression was much higher than in the general population (Covey et al., 1998). In most longitudinal and retrospective studies, smoking at baseline was associated with an elevated rate of onset of depression during the follow-up period, which may suggest that smoking could be a risk factor for depression. Most of these results also suggest that this relationship is more pronounced among females, although a study from Finland found the above association to be true only among males (Ziedonis et al., 2008; Steuber and Danner, 2006; Klungsøyr et al., 2006; Pasco et al., 2008; Pedersen and von Soest, 2009; Munafò et al., 2008; Korhonen et al., 2007; Husky et al., 2008). Conversely, depression may be a risk factor for the progression of smoking (Ziedonis et al., 2008; Pasco et al., 2008; Pedersen and von Soest, 2009). According to the current results of Leventhal et al. (2008, 2009), some depressive symptoms are more strongly linked with nicotine dependence than others (Leventhal et al., 2008, 2009). Namely, symptoms of the melancholic subtype of major depression are associated more strongly with NIC dependence than symptoms of atypical depression (melancholic and atypical depression are DSM-IV-based subtypes of major depression and differ from each other in some of their symptoms) (Leventhal et al., 2008, 2009).

However, data on the effect of depression on the success rate of quitting are mixed. Ziedonis et al. (2008) in a recent review concluded, based on data from smoking cessation trials published from 1988 to 2006, that smokers with a past history of depression have a similar chance of achieving short-term (less than 3 months) abstinence, but a decreased chance of achieving long-term abstinence (more than 6 months). This result pertained only to nonmedicated patients, while "the analysis was restricted to the participants randomized to the placebo or the alternative lowest intensity treatment arm of each study to remove the potential influence of any experimental interventions hypothesized to benefit depressive smokers specifically" (Ziedonis et al., 2008). A previous meta-analysis by Hitsman et al. (2003), which processed data from smoking cessation trials published from 1988 to 2000 and included patients on active arms of studies, concluded that depression history was not a risk factor for relapse. Later, the same authors reanalyzed the data restricting the meta-analysis to participants randomized to the least intensive treatment conditions and again failed to detect a relationship between depression history and relapse (Hitsman et al., 2003, 2004; Ziedonis et al., 2008; Japuntich et al., 2007). However, data on the effect of current depressive episodes on the success of cessation attempts are scarce. Based on the results of three published smoking treatment studies, Ziedonis et al. (2008) concluded that cessation intervention among patients with a current episode of depression resulted in a similar rate of abstinence to that among non-depressed smokers (Ziedonis et al., 2008). Conversely, in a recent study by Japuntich et al. (2007), current depression was a more strong predictor of short-term (1 week), but not long-term (3 months, 6 months) cessation failure than previous episode(s) of depression. Moreover, in a treatment study (NIC replacement therapy (NRT) vs. placebo), individuals on the placebo arm with a current episode of depression at baseline were significantly more likely to smoke at 12 months post-quit compared to non-depressed individuals on NRT or placebo arms or depressed individuals on NRT arm (Japuntich et al., 2007; Kinnunen et al., 2008). In contrast, those patients with a current episode of major depression who successfully stop smoking appear to have a greater chance of mood improvement compared to depressed patients who are unable to achieve abstinence (Blalock et al., 2008; Prochaska et al., 2008b). Additionally, in a recent population-based study authors found that smokers who had unsuccessfully attempted to quit in the past year experienced current depression at a higher rate than either smokers who had not attempted to quit in the past year or former smokers (successful quitters). Moreover, successful

quitters were less likely to be currently depressed than either unsuccessful quitters or non-quitters (McClave et al., 2009). Recurrent depression in medical history appears more closely related to cessation failure than a single episode of major depression (Ziedonis et al., 2008). Post-cessation depressive episodes are more frequent among individuals with previous episode(s) of depression than among individuals without depressive episode(s) in their medical history. Some results also suggest that an elevation in depressive symptoms during cessation is more closely associated with relapse than a baseline level of depression. Ziedonis et al. (2008) in their recent review, however, concluded that "it remains unclear whether depressive episodes during treatment contribute to relapse among depression vulnerable smokers" (Ziedonis et al., 2008; Hughes, 2007; Kinnunen et al., 2008; Catley et al., 2005; Killen et al., 2003). Results also suggest that a past or new episode of depression during cessation are linked to elevated levels of withdrawal symptoms and/or with a prolonged period of withdrawal (Strong et al., 2004; Covey et al., 1990, 1997, 1998; John et al., 2004; Breslau et al., 1992; Thorndike et al., 2008; Weinberger et al., 2009). Also in special populations (for example in patients admitted to hospital with acute cardiovascular events) depression at baseline was a predictor of smoking cessation failure (Thorndike et al., 2008; Perez et al., 2008a,b).

The elevated total (suicide and non-suicide (including cardiovascular)) mortality in patients with major depression is well documented (Surtees et al., 2008; Cuijpers and Schoevers, 2004; Rihmer, 2007; Pozuelo et al., 2009). Although some investigations also suggest that depression could be an "independent" risk factor for cardiovascular disorders and cancer, it is easy to imagine that an elevated rate of smoking in depression may further strengthen the association between depression and the increased risk of mortality (Surtees et al., 2008; Cuijpers and Schoevers, 2004; Pozuelo et al., 2009; Oerlemans et al., 2007).

7.2.2. Explaining theories of elevated smoking rates among patients with major depression

As discussed, results of epidemiological studies clearly suggest an elevated risk of smoking in people with mood disorders. Three explanations have been proposed for this association. The "self-medication theory" supposes that depression leads to smoking because NIC and/or other tobacco smoke ingredients have antidepressant effects, while the second theory holds that smoking and depression have common environmental or genetic risk factors, and the third that depression is the sequelae of smoking (while smoking leads to brain dysfunction) (Duncan and Rees, 2005).

The pathophysiological background of depression seems to be extremely complex. One of the several theories is the cholinergic hypothesis of depression (Picciotto et al., 2008). This is based on the results of the last decades, namely that physostigmine (an acetylcholinesterase inhibitor (AChE-I)) could exacerbate a depressed mood (although some later investigations with other AChE-I-s found the opposite trend) and that elevated choline (the rate-limiting precursor to acetylcholine) levels were found in the brains of patients with depression (Picciotto et al., 2008; Elgamal and MacQueen, 2008; Shytle et al., 2002). The neurobiological link between depression and the cholinergic system is also supported by the potent antidepressant activity of muscarinic antagonist scopolamine (furthermore some tricyclic antidepressant agents also have antimuscarinic actions). Moreover, investigations have found exaggerated neuroendocrine and pupillary responses among patients with mood disorders after administration of cholinomimetic agents. In addition, ACh facilitates the release of several stress-sensitive transmitter molecules (i.e. corticosterone, ACTH, and CRF) (Furey and Drevets, 2006; Shytle et al., 2002). The role of nAChRs in the pathophysiology of depression at first seems contradictory, since both nAChRs agonists/partial agonists (i.e. NIC, varenicline, cytisine, ispronicline) and nAChRs antagonists (i.e. mecamylamine, dihydro-β-erythroidine, methyllycaconitine) have antidepressant activities in both animal and human investigations (a recent article, however, reports that RJR-2403 (α4β2-selective agonist) and PNU-282987 (α7-selective agonist) lack efficacy in the forced swim test and the tail-suspension test in mice) (Picciotto et al., 2008; Philip et al., 2009; Lodge and Li, 2008; Patterson et al., 2009; George et al., 2008; Popik et al., 2003; Vázquez-Palacios et al., 2004; Rabenstein et al., 2006; McClernon et al., 2006; Malpass and Higgs, 2007; Rollema et al., 2009; Andreasen et al., 2008). Also importantly, several members of different families of antidepressants (i.e. amitriptyline, imipramine, fluoxetine, bupropion, nefazodone) have shown remarkable antagonist activity at nAChRs (Shytle et al., 2002; Pacher and Kecskemeti, 2004). The most probable and acknowledged explanation of the above contradiction is a hypothesis stating that the inhibition of nAChRs leads to the antidepressant effects of a given drug. The inhibition of nAChRs may be realized either directly (as in the case of nAChR antagonist administration) or indirectly (as in the case of desensitization of nAChRs as a consequence of nAChR agonists administration (this phenomenon is called functional antagonism)) (Picciotto et al., 2008; Andreasen and Redrobe, 2009; Lodge and Li, 2008; George et al., 2008). The significance of nAChRs in the pathophysiology of depression is further supported by the results of investigations with knock-out (KO) animals. For example α7 or β2 KO mice were insensitive to the antidepressant effects of mecamylamine (Rabenstein et al., 2006). In addition, Caldarone et al. (2004) demonstrated that β2 KO mice are resistant to the antidepressant effects of the tricyclic antidepressant amitriptyline in three types of behavioral depression models (tail-suspension, forced swim and learned helplessness tests). Moreover β2 KO mice were also resistant to amitriptyline-evoked hippocampal cell proliferation (which is also a common marker of antidepressant action); thus these results strongly suggest that the β2 subunit is involved in an antidepressant response to amitriptyline (Caldarone et al., 2004; Picciotto et al., 2008; Lodge and Li, 2008). The role of nAChRs in depression is further bolstered by findings that in different kinds of rodent strains (i.e. Flinders Sensitive rats or Fawn-Hooded rats) with depressive features or in rodents after olfactory bulbectomy (as a model of depression), altered neuronal nAChR densities were described (Tizabi et al., 2000; Tizabi et al., 2009; Slotkin and Seidler, 2006). Also remarkably, some antidepressants are effective smoking cessation agents, which suggests that depression and nicotine dependence may share some common neuronal substrates (Picciotto et al., 2008).

Several neurobiological theories have tried to explain the antidepressant impact of NIC (and other nAChRs agonists). For instance, the activation of hippocampal nAChRs (probably the α4β2 isoform) leads to increased neurogenesis in the hippocampus, which is considered a common action of antidepressants, as well. In consonance with this, chronic stress and depression is associated with decreased hippocampal volume (Millan, 2006; Gershon et al., 2007; Banasr and Duman, 2007). The antidepressant effect of NIC may also be linked to the monoaminergic theory of depression, since the activity of monoaminergic systems in the brain are deeply influenced by nAChRs (Andreasen and Redrobe, 2009; Millan, 2006). In this respect, the role of the dopaminergic reward system seems to be of paramount importance, since impaired function of it is associated with depression, and in line with this, smokers with depression may perceive NIC consumption more rewarding than smokers without depression (Spring et al., 2003; Cardenas et al., 2002; Martin-Soelch, 2009). Although results are not fully consistent, the exposure of a stressful environment on animals appears associated with increased, while chronic

administration of antidepressants is associated with decreased, activation of the amygdala (measured by c-fos immunoreactivity). Both cytisine (as a partial nAChR agonist) and mecamylamine (a non-selective nAChR antagonist) have antidepressant activities and their administration leads to decreased c-fos expressions in amygdala, which is in consonance with the above findings (Picciotto et al., 2008; Mineur et al., 2007; Cunningham et al., 2008; Roche et al., 2007; Andreasen et al., 2008). Popik et al. (2005) found that the chronic administration of NIC to Wistar rats leads to beta-adrenoceptor down-regulation in the cortex, which is also a common finding after chronic antidepressant treatment, electroconvulsive, and sleep deprivation treatments for depression (Popik et al., 2005; Millan, 2006). As noted previously, smoking is not equivalent to pure NIC administration, since tobacco smoke contains several other bioactive ingredients, some of which (i.e. harman or norharman with MAO inhibitory properties) also may have antidepressant effects (Lewis et al., 2007).

As discussed above, one theory suggests the "depressogenic" effect of some tobacco ingredients is responsible for the frequent co-occurrence of depression and smoking, and there are several results that support this. For example, Malone et al. (2003) reported that cigarette smoking is associated with impaired serotonin function (measured by CSF 5-HIAA levels and the fenfluramine challenge test) in depressed patients (Malone et al., 2003). Acute tryptophan depletion (ATD) has a mood-lowering effect in euthymic individuals with mood disorder in their personal medical history or family history (Spring et al., 2007). Recently, the depression-triggering effect of ATD was shown to be more pronounced in smokers with a history of major depression compared to their non-smoking counterparts (Spring et al., 2007). Chronic stress and depression are associated with the dysregulation of the hypothalamo–pituitary–adrenal (HPA) axis (Carroll et al., 2007). While smoking has a strong influence on the activity of the HPA axis, this effect could be another link between smoking and depression (Badrick et al., 2007; Mendelson et al., 2008; Chen et al., 2008a). Smoking-induced oxidative stress may also be responsible for the frequent co-occurrence of depression and smoking, while it seems obvious that increased oxidative stress occurs in major depression (and antidepressant treatment could reverse this oxidative imbalance) (Zafir et al., 2009; Pasco et al., 2008). Another possible mechanism of smoking-induced depression is related to chronic obstructive pulmonary disease (COPD). Smoking is a clear-cut risk factor for COPD, and the prevalence of depression among individuals with COPD is elevated compared to the general population (Decramer et al., 2008; Agusti and Soriano, 2008). The permanent state of systemic inflammation and/or the chronic hypoxia that are hallmarks of COPD may explain the elevated rate of mood disorders in the COPD population (see details in Decramer et al., 2008). Another theory states that smoking may provoke mood disturbances in smokers because of the appearances of acute NIC deprivation periods several times a day, and – in consonance with this – several studies found that smoking cessation is associated with decreased levels of stress and anxiety in the long run (Parrott, 2006; Aronson et al., 2008). A recent investigation by Aronson et al. (2008) has strengthened this theory, as the authors found – in contrast to the experiences of smokers – that heavy smoking is associated with greater negative affects, and this association is more pronounced on stressful days (Aronson et al., 2008).

As mentioned above, a third theory suggests that a common genetic or environmental vulnerability is responsible for the high co-occurrence of smoking and depression (Ziedonis et al., 2008). This theory is confirmed by twin-studies (Ziedonis et al., 2008; McCaffery et al., 2008; Fu et al., 2007a; Lyons et al., 2008; Korhonen et al., 2007). In conjunction with this, a few studies found that some genetic variations in genes of the dopaminergic pathway or in the gene of the μ-opioid receptor are associated with smoking-evoked mood effects. Data on the associations between susceptibility to major depression and polymorphisms of genes of nicotinic receptor subunits is scarce (Ziedonis et al., 2008; Perkins et al., 2008; López-León et al., 2008).

Another startling connection between smoking and depression is the association of NIC administration (smoking) during pregnancy and elevated vulnerability to mood disorders in offspring, according to results of both epidemiological studies and animal models. This association could be the consequence of NIC-evoked dramatic changes in the developing nervous system (Fergusson et al., 1998; Paz et al., 2007; Heath and Picciotto, 2009).

8. Alzheimer disease (AD)

8.1. Epidemiology

AD is the most frequent cause of dementia, accounting for 50–60% of all cases (Blennow et al., 2006). Most studies with case–control (retrospective) design have found that smoking is protective against AD, but prospective studies have shown that current, and not former, smoking is a risk factor for AD (Almeida et al., 2002; Reitz et al., 2007; Anstey et al., 2007; Purnell et al., 2009; Peters et al., 2008). The difference between the results of case–control and cohort studies may be due to survival bias, but a theoretical study contradicts this assumption (Almeida et al., 2002; Reitz et al., 2007; Debanne et al., 2007). In addition, in a recent article, authors found that smoking is associated with an elevated risk of AD or dementia only in those prospective studies where participants were younger (55–74 years old) at baseline (but not in those studies where participants were older (more than 75 years) at baseline). Selection bias in prospective studies may account for the above relationship between the age of study participants and the smoking-related risk of AD. Another possible explanation of the result, namely that smoking is harmful at younger ages but beneficial at older ages, was also offered (Hernán et al., 2008).

8.2. Neuropathological findings and alterations of the cholinergic (nicotinergic) system in AD

Extracellular β-amyloid senile plaques, intracellular neurofibrillary tangles (NFT, mainly composed of abnormally hyperphosphorylated tau protein), and neuronal loss are hallmark lesions of Alzheimer disease (Silvestrelli et al., 2006; Oddo and LaFerla, 2006).

Several neurotransmitter systems (i.e. noradrenergic, histaminergic, serotonergic, dopaminergic) are affected in AD, but the most consistently described change is the degeneration of the cholinergic system originating in the basal forebrain, i.e. cell loss in the nucleus basalis Meynerti and loss of cholinergic fibers in the cerebral cortex (mainly in temporal and frontal regions) in the hippocampus and amygdala. Moreover, the density of NFT in the nucleus basalis Meynerti is elevated and the ratio of different isoforms of tau protein are altered in AD patients compared to normal subjects (Lyness et al., 2003; Silvestrelli et al., 2006; Hogg and Bertrand, 2004; Carreiras and Marco, 2004; Frölich, 2002; Ladner and Lee, 1998; Mufson et al., 2008; Nelson et al., 2009; Mesulam et al., 2004). Relatively preserved cholinergic innervations of the thalamus (from the brainstem) and the striatum (from striatal interneurons) and some regions of cortex (anterior cingulum, primary visual, somatosensory and motor cortex) were reported in AD (Geula and Mesulam, 1996; Lane et al., 2006). Decreases in the levels of ACh in the cortex and hippocampus, and decreases in the levels of some enzymes of the cholinergic system (i.e. acetylcholine synthesizing enzyme, choline acetyltransferase (ChAT) in the cortex and in the hippocampus; and ACh hydrolyzing

enzime acetylcholinesterase (AChE) in the cortex) are also described in AD (Silvestrelli et al., 2006; Hogg and Bertrand, 2004; Lanari et al., 2006; Shinotoh et al., 2000; Geula and Mesulam, 1996; Kar and Quirion, 2004; Lane et al., 2004, 2006; Lyness et al., 2003; Carreiras and Marco, 2004; Sivaprakasam, 2006; Nordberg, 2006a,b; Frölich, 2002; Giménez-Llort et al., 2007). The direction of change in the level of high-affinity choline transporters in AD is contradictory, while the expression level of vesicular ACh transporter (VAChT) is not altered in AD (Okuda et al., 2000; Mufson et al., 2008). Decreased ChAT and AChE activities are in significant correlation with cognitive deficit and senile plaque numbers in AD (Hogg and Bertrand, 2004; Kar and Quirion, 2004; Nordberg, 2006a,b; Giacobini, 2003; Giménez-Llort et al., 2007; Perry et al., 1978). Butyrylcholinesterase (BuChE), also called serum cholinesterase or pseudo-cholinesterase, is another important enzyme of the cholinergic system which – like AChE – degrades ACh in the synaptic cleft (Musiał et al., 2007; Lane et al., 2006). In contrast to the level of AChE, the level of BuChE is elevated in the brain during the progression of AD, rendering meaningless the inhibition of AChE in severe AD—whilst activity of AChE is minimal in this stage. The selective inhibition of BuChE, however, could be a good therapeutic target in severe AD (Kamal et al., 2008; Musiał et al., 2007; Giacobini, 2003; Lane et al., 2006; Perry et al., 1978). Interestingly, degeneration of the brain's cholinergic system has also been observed in a number of other disorders with dementia, such as Down-syndrome, olivo-ponto cerebellar atrophy, Parkinson's disease, Jakob–Creutzfeld disease, progressive supranuclear palsy, Korsakoff's syndrome, chronic ethanol intake, and dementia pugilistica (Schliebs and Arendt, 2006). Surprisingly, patients with mild cognitive impairment (MCI) – the transition state between cognitive decline due to normal aging and dementia – have elevated levels of frontal cortical and hippocampal ChAT in post-mortem studies, and have unaltered cholinergic innervation (measured by ChAT-immunoreactive fiber and axon varicosity densities) in the superior frontal cortex in contrast to significantly reduced cholinergic innervation of the frontal cortex in AD (Nordberg, 2006a,b; Ikonomovic et al., 2007). The above results could suggest that a compensatory upregulation of the cholinergic system may delay the transition of MCI to AD (Nordberg, 2006a,b; Ikonomovic et al., 2007).

According to the results of different post-mortem studies, levels of the α7 nAChR protein are reduced or unaltered in the temporal cortex and decreased in the hippocampus of patients with AD, but the mRNA level of the α7 subunit is increased in the hippocampus (Nordberg, 2001; Yu et al., 2005; Guan et al., 2000; Martin-Ruiz et al., 1999). Results regarding the α7 nAChR protein levels in the frontal cortex are also ambiguous (Conejero-Goldberg et al., 2008; Ikonomovic et al., 2009). mRNA of the α7 subunit is upregulated in neurons of nucleus basalis in AD (but not in MCI), perhaps as a compensation of decreased cholinergic function. Moreover, the extent of increase in the α7 subunit mRNA level was inversely correlated to cognitive decline, although the upregulation of α7 nAChR could also be dangerous since α7 nAChR interacts with APP and amyloid-β. On the other hand, some results suggest that the administration of α7 agonists/antagonists may be protective against amyloid-β toxicity (Counts et al., 2007; Mufson et al., 2008; Søderman et al., 2008). α7 nAChRs also have a role in cerebrovascular amyloid angiopathy (the deposition of amyloid-β in the cerebral vessel's wall, which is significantly more frequent in AD compared to normal aging), while the expression of α7 nAChRs by smooth muscle cells in the walls of blood vessels may facilitate the selective accumulation of amyloid-β peptides in these cells (Clifford et al., 2008). In mouse models of AD, the expression levels of the α7 nAChR protein/mRNA in the brain are also unclear (levels are elevated in the hAChE-Tg, APP_{SWE}Tg, and APP_{SWE}/hAChE-Tg mouse strains, but decreased in the 3xTG-AD mouse strain) (Mousavi and Nordberg, 2006; Oddo et al., 2005). α7 nAChR expression of astrocytes appears elevated in both sporadic AD and AD caused by mutation of the APP (Yu et al., 2005). Although the direction of change in the density of α7 nAChRs in AD is uncertain, the α7 KO mouse strain shows impairment in some cognitive domains (i.e. attention, spatial memory, specific types of learning), which suggests the eminent role of this subunit in cognitive functions (Cincotta et al., 2008).

Results regarding α4β2 nAChR are more definite, while most studies found decreased levels of this receptor type in the cortex and hippocampus (Yu et al., 2005; Gotti et al., 2006; Gotti and Clementi, 2004). The mRNA level of the α4 subunit is unaltered in the nucleus basalis in AD (Counts et al., 2007). In a recent study, epibatidine (a potent but non-selective nAChR agonist) binding was decreased in various parts of the cortex (Brodmann areas 38, 39 and 46) in AD but not in MCI compared with control subjects without dementia (Sabbagh et al., 2006; White et al., 2006; Yogeeswari et al., 2006). The loss of nAChRs in post-mortem studies probably does not result from post-mortem artifacts, since PET and SPECT investigations also found decreased levels of (mainly α4β2) nAChRs in frontal, striatal, and medial temporal regions of the brain of AD patients (these changes seem rather characteristic of moderately severe AD and not mild AD) (Sabbagh et al., 2006; Oddo and LaFerla, 2006; Sabri et al., 2008; O'Brien et al., 2007; Ellis et al., 2008). Interestingly, two neuroimaging studies found a decreased level of α4β2 nAChR in patients with MCI (it is mentionable that the levels of high-affinity nAChRs are decreased during normal aging, too, in various cortical and subcortical areas according to previous post-mortem studies and a recent SPECT study) (Sabri et al., 2008; Mitsis et al., 2008; Terrière et al., 2008). C^{11}-nicotine binding in the brain, measured by PET, has a significant negative correlation with cognitive performance in AD (Kadir et al., 2006; Nordberg et al., 1995). In accordance with the decreased number of high-affinity nAChRs in AD, β2 knock-out mice show increased deficit in memory functions and increased cell loss in the hippocampus after intrahippocampal excitotoxic lesion. Moreover, the hippocampal remodeling after exposure to an enriched environment was decreased in the β2−/− strain (Zanardi et al., 2007).

Many other interesting aspects of the link between cholinergic system and AD exist. For example, β-amyloid can bind to α7 and α4β2 nAChRs. Furthermore, β-amyloid peptide can upregulate the expression of AChE. This can lead to decreased levels of acetylcholine, and consequently to impaired cholinergic neurotransmission. In addition, AChE can bind to β-amyloid (Aβ-AChE complexes are more toxic than Aβ fibrils alone). Moreover, AChE in this complex has elevated V_{max} and K_m values and has a decreased affinity to AChEIs, and is more resistant to the inhibitory effect of a high substrate concentration. Furthermore, according to results of PET and cell-culture studies, AChEI treatment has effects on nAChR density, while some forms of AD treatment (i.e. ginkgo biloba extract) may have a favorable effect on the non-amyloidogenic way of amyloid precursor protein (APP) processing. Also, activation of muscarinic M1 receptors promotes non-amyloidogenic processing of APP and decreases the hyperphosphorylation of tau protein, while chronic exposure to Aβ in vitro leads to upregulation of α7 nAChRs. Finally, peptide fragments from the C-terminus of the tailed (synaptic) isoforms of AChE have a striking homology and structural similarity to β-amyloid. These peptides bind to α7 nAChRs and alter the affinity of α7 nAChRs to their natural ligands and also upregulate α7 nAChRs. All the interactions mentioned above, however, are too complex to be discussed in detail here (Lane et al., 2006; Oddo and LaFerla, 2006; Liu and Wu, 2006; Dineley, 2007; Small et al., 2007; Kadir et al., 2008; Kadir et al., 2007; Nordberg, 2006a,b; Colciaghi et al., 2004; Inestrosa et al., 2008; Fisher, 2007; Bond et al., 2009; Greenfield et al., 2004; Perry et al., 2004).

8.3. Smoking effects on nAChR expression in AD

Smoking has various effects on nAChR expression in AD. Mousavi et al. (2003) found that the α4 nAChR subunit protein is significantly upregulated in the temporal cortex, while the α7 nAChR subunit protein showed a quasi significant upregulation in same region in AD patients who smoke compared to non-smoker AD patients. Protein levels of α3/α4/α7 nAChR subunits in the hippocampus, however, were independent of smoking status in AD patients (Mousavi et al., 2003; Picciotto and Zoli, 2008). In this study, the levels of α3/α4 but not α7 nAChR subunit proteins in the temporal cortex and all investigated receptor subunit (α3/α4/α7) proteins in the hippocampus in AD patients who smoke are still lower than levels in non-smoker and non-demented controls (Mousavi et al., 2003; Picciotto and Zoli, 2008). In accordance with the above results, cytisine (a α4 ligand) binding was higher in smokers with AD compared to non-smokers with AD in the temporal cortex, but not in the hippocampus or frontal cortex (Hellstrom-Lindahl et al., 2004). α-bungarotoxin (an α7 ligand) bindings were not significantly different in the frontal and temporal cortex or in the hippocampus of smokers with AD compared to non-smokers with AD (Hellstrom-Lindahl et al., 2004).

8.4. Effects of smoking or pure nicotine administration on AD pathology

Several studies have investigated the influence of smoking on AD pathology, but found inconsistent results. Court et al. (2005) demonstrated less β-amyloid pathology in the entorhinal cortex of smokers compared with non-smokers in a sample of elderly subjects free from neurological or psychiatric disorders. In this study, tau-type pathology was independent of smoking status (Court et al., 2005). Ulrich et al. (1997) found decreased senile plaque numbers in smokers compared with non-smokers in females, but also found a more severe NFT pathology in both sexes among smokers in an unselected sample of elderly subjects (Ulrich et al., 1997; Court et al., 2005; Oddo and LaFerla, 2006). Sabbagh et al. (2005) did not find an effect of smoking on neuropathologic markers (neuritic plaque and NFT numbers) in the mid-frontal cortex in an AD sample (Sabbagh et al., 2005). Perry et al. (2000) found that smokers have a diminished senile plaque formation in the entorhinal cortex and hippocampus, but NFT formation did not differ between smokers and non-smokers in an elderly population without dementia (Perry et al., 2000). Tyas et al. (2003) did not find a strong relationship between smoking and tau pathology, but did find that the numbers of neuritic plaque increased in the neocortex and hippocampus in current and former smokers. Interestingly, in very heavy smokers the plaque number was diminished in both the hippocampus and neocortex compared with heavy and medium smokers (Tyas et al., 2003; Oddo and LaFerla, 2006). Hellstrom-Lindahl et al. (2004) found that the levels of both soluble and insoluble Aβ 40 and Aβ 42 were significantly lower in the frontal and temporal cortex (but not in the hippocampus) of smokers without dementia compared with non-smokers without dementia. Among AD patients, levels of both insoluble and soluble Aβ 40 and Aβ 42 were significantly reduced in the frontal cortex of smokers compared with non-smokers, but in the temporal cortex and hippocampus only levels of insoluble and soluble Aβ 40 (but not soluble or insoluble Aβ 42) were significantly reduced in smokers with AD compared with non-smokers with AD (Hellstrom-Lindahl et al., 2004; Court et al., 2005). Hellström-Lindahl et al. (2008) have demonstrated that smoking status does not affect neprilysin (one of the main enzymes involved in β-amyloid degradation) levels in the brain of either patients with AD or control individuals; thus the lower levels of β-amyloid do not appear linked to an elevated level of amyloid degradation in smokers (Hellström-Lindahl et al., 2008).

In different mouse models of AD (i.e. using APP_{swe} or hAChE-Tg/APP_{swe} or J20 triple-APP mutation strains) the effect of chronic NIC administration on beta-amyloid pathology is ambiguous (Hedberg et al., 2008; Unger et al., 2006; Sabbagh et al., 2008).

Amyloid plaques arise from amyloid monomers through dimers, oligomers, protofibrils and fibrils in a multistep process called aggregation (Finder and Glockshuber, 2007). In vitro studies suggest that NIC binds directly to β-amyloid in its α-helical conformation and retards the amyloid aggregation process by inhibiting an α-helix → β-sheet conformational transformation of β-amyloid. Moreover NIC could disassemble the preformed amyloid fibrils and also facilitate – via both α7 and α4β2 nAChRs – the non-amyloidogenic alpha-secretase cleavage of the amyloid precursor protein (APP), which would release soluble sAPPα (considered neuroprotective) (Oddo and LaFerla, 2006; Unger et al., 2006; Estrada and Soto, 2007; Pogocki et al., 2007; Nordberg, 2006a,b; Mousavi and Hellström-Lindahl, 2009). Nornicotine – a major NIC metabolite – also binds to the β-amyloid peptide, which leads to the inhibition of amyloid aggregation (Dickerson and Janda, 2003; Oddo and LaFerla, 2006). NIC could also indirectly inhibit the formation of toxic β-amyloid fibrils via elevation of the transthyretin (TTR) levels in CSF (Raghu and Sivakumar, 2004). TTR could bind soluble β-amyloid and thereby prevent β-amyloids from aggregating to form toxic fibrils (Estrada and Soto, 2007; Raghu and Sivakumar, 2004; Sousa et al., 2007; Liu and Murphy, 2006). NIC may attenuate neurotoxic effects of extracellular β-amyloid via the facilitation of extracellular Aβ internalization and degradation in autophagic processes (Hung et al., 2009).

Unfortunately NIC has unfavorable effects on tau pathology as demonstrated by in vivo and in vitro animal studies (Oddo and LaFerla, 2006). For example, chronic administration of NIC (5 months via the drinking water) to 3xTG-AD mice resulted in elevated levels of tau phosphorylation, probably via the activation of p38-mitogen-activated protein kinase (Oddo et al., 2005). Furthermore, two in vitro studies have found similar results. In one of these two studies, Hellström-Lindahl et al. (2000) demonstrated that NIC or epibatidine (a non-selective nAChR agonist) treatment of the human neuroblastoma cell line SH-SY5Y led to an increased level of tau protein and also enhanced levels of tau phosphorylation (Hellström-Lindahl et al., 2000; Oddo and LaFerla, 2006). The other study found that NIC or Aβ42 (as a ligand for nAChRs, see above) or epibatidine administration-induced tau phosphorylation in SK-N-MC neuroblastoma cell line and in hippocampal synaptosomes. The effect of Aβ42 on tau phosphorylation was blocked by α7 antagonist pretreatment, suggesting a critical role for α7 nAChRs in Aβ42-induced tau phosphorylation. Results also suggested that proteins of the mitogen-activated protein kinase cascade (i.e. extracellular receptor kinases and c-Jun N-terminal kinase) play a role in the α7 nAChR-mediated Aβ42-induced tau phosphorylation (Wang et al., 2003; Oddo and LaFerla, 2006). In partial contrast to previous reports, Bitner et al. (2009) found that α7 agonist administration may also be protective against tau hyperphosphorylation. They found that the administration of a selective α7 agonist (A-582941) leads to the inhibition of glycogen synthase kinase3β (GSK3β)-mediated tau phosphorylation (Bitner et al., 2009). Recently, results of a human study by Chalmers et al. (2009) have further supported the possibility that the facilitation of the cholinergic transmission in the brain may lead to increased tau pathology (in this investigation the amount of hyperphosphorylated tau in the cerebral cortex of AD patients treated with AChEI was higher than had untreated AD patients) (Chalmers et al., 2009).

8.5. Smoking and cognitive decline

Many investigations found that chronic smoking accelerates cognitive decline (measured by a variety of markers of cognitive

function, i.e. working, arithmetic and prospective memory, auditory–verbal learning, psychomotor speed or cognitive flexibility) (Swan and Lessov-Schlaggar, 2007; Durazzo and Meyerhoff, 2007). Several factors could explain the link between tobacco smoking and the higher risk of cognitive decline. For instance, tobacco smoke contains lead, and chronic lead exposure is a well-known risk factor for cognitive deterioration. Another ingredient of tobacco smoke, cadmium, also has neurotoxic properties. Furthermore smokers have decreased levels of circulating antioxidants (vitamin C, carotene α and β, cryptoxanthin), and oxidative stress is closely linked to AD. Impaired lung function (a consequence of tobacco smoking) presents yet another risk state for cognitive decline. Smoking also seems to be a risk factor for silent and symptomatic vascular intracerebral lesions and decreased brain volume (Swan and Lessov-Schlaggar, 2007; Min et al., 2007). Although the accelerating effects of smoking on the development of AD and – principally – of cognitive decline generally appear unambiguous, NIC and some other agonists of nicotinic receptors have neuroprotective effects in many in vitro and in vivo models of neurotoxicity. NIC, however, could be toxic under some circumstances, mainly in during the administration of high doses or continuous administration, and especially during administration for developing neurons (Picciotto and Zoli, 2008; Egea et al., 2007; Shin et al., 2007; Shimohama et al., 1998). A wide range of mechanisms may underlie the neuroprotective effects of NIC (i.e. upregulation of growth factor (NGF and FGF-2) pathways, inhibition of apoptosis, oxidative stress reduction via different mechanisms, and influencing intracellular calcium dependent events). Moreover, NIC has a direct influence on AD pathology (see above) (Picciotto and Zoli, 2008; Pogocki et al., 2007; Dajas-Bailador and Wonnacott, 2004).

8.6. Nicotinic agents as possible therapeutics for cognitive decline in AD

The relevance of nAChRs in cognitive functions is bolstered by the results of studies with α7 or β2 subunit knock-out rodent strains and by the detrimental effects of nAChR antagonists on cognitive functions in animal and human studies (Cincotta et al., 2008; Newhouse et al., 2001). Although the impact of NIC on cognition in healthy individuals is doubtful, among patients with neurodegenerative diseases NIC clearly may have beneficial effects on cognitive functions (Sacco et al., 2004). A variety of investigations have studied the effects of administering NIC and α7 or α4β2 nAChR agonists (i.e. ABT-418, GTS-21, ispronicline (TC-1734)) on cognition in AD, MCI, and age-related cognitive decline. The results of these studies suggest that NIC has a more pronounced ameliorating effect on attention than memory performances in AD (Oddo and LaFerla, 2006; Levin et al., 2006). ABT-418 (an α4β2 agonist) has ameliorating effects on cognitive functions (i.e. on verbal and spatial learning) in AD (Pogocki et al., 2007; Sacco et al., 2004). Ispronicline (a partial α4β2 agonist) and NIC have favorable effects on cognitive functions in age-associated cognitive decline (Newhouse et al., 2004b; Dunbar et al., 2007). nAChR agonist treatment is probably more efficacious in MCI than in AD because nAChRs are preserved in MCI to a greater extent than in AD (Newhouse et al., 2004b).

8.7. Genetic findings

Several studies have explored the genetic background of the relationship between the cholinergic system and AD (Vasto et al., 2007; Cook et al., 2004). Investigations into the association between α4 subunit gene polymorphisms and AD have obtained dubious results. Studies of the associations between AD and polymorphisms in either gene encoding choline acetyltransferase (ChAT) or gene encoding butyrylcholinesterase (BuChE) have had similarly unclear outcomes (Vasto et al., 2007; Serretti et al., 2007; Piccardi et al., 2007). A recent study has shown that a genetic variation in the α7 subunit (CHRNA7) gene is associated with the risk of AD. An association between the presence of the T allele in the polymorphic site rs6494223 of the CHRNA7 gene and the risk of delusional symptoms in AD was also discovered by the same authors (Carson et al., 2008a,b). A noncoding polymorphism in the gene encoding β2 subunit was also observed to be significantly associated with susceptibility to AD (Cook et al., 2004).

9. Attention-deficit/hyperactivity disorder

9.1. Epidemiology

Attention-deficit/hyperactivity disorder (ADHD) is known to affect approximately 5–10% of children and continues into adulthood at a considerably high rate (range: 5–70%) among those who were diagnosed in childhood. Prevalence of ADHD is estimated at 3–5% of the adult population (Kalbag and Levin, 2005; Biederman, 2005). ADHD is highly comorbid with other psychiatric disorders such as anxiety, mood, and antisocial disorders in the adult population and anxiety, mood, conduct, and oppositional defiant disorders in the child/adolescent population (McGough et al., 2005; Biederman, 2005; Wilson and Levin, 2005).

Never-treated adults with ADHD are twice as likely to develop a substance use disorder (SUD), and if they have a comorbid bipolar disorder or juvenile conduct disorder, then the likelihood increases further. Moreover, children with ADHD have a four times greater risk of developing an SUD by adulthood (16% vs. 4% of control subjects) (Wilson and Levin, 2005; Wilens, 2006). Conversely, alcohol and drug dependent adolescents and adults suffer more often from ADHD than members of the general population (Gordon et al., 2004; Wilson and Levin, 2005; Wilens, 2004). ADHD itself appears to be a risk factor for later SUD, with a worse outcome, greater severity, longer duration, and more rapid transition from substance use to abuse and dependence (Wilens, 2006; Faraone et al., 2007; Wilson, 2007). High rates of ADHD have been reported in first-degree relatives of individuals with SUD and vice versa: parents of children with ADHD have an elevated risk for SUD (Wilson and Levin, 2005; Wilens, 2004, 2006).

Not only SUD in general, but smoking in particular is more common in both adolescent (19.0–46% vs. 10–24% for ADHD and non-ADHD) and adult (41–42% vs. 26% for ADHD and non-ADHD) ADHD populations. In addition, patients with ADHD are more likely to initiate smoking earlier than control persons (Humfleet et al., 2005; Monuteaux et al., 2007; Fuemmeler et al., 2007; McClernon and Kollins, 2008; Wilens et al., 2008b). Although ADHD is a risk factor for smoking even after controlling for confounding variables (i.e. psychiatric comorbidity), the increased risk of smoking is further elevated in the presence of comorbid conduct disorder, major depression, bipolar and anxiety disorders (Humfleet et al., 2005; Wilens et al., 2000; Molina and Pelham, 2003; Milberger et al., 1997). Moreover, smokers with ADHD compared with non-smokers with ADHD are at greater risk for subsequent use of other addictive agents besides NIC. In other words, NIC seems to be a gateway drug among patients with ADHD (Biederman et al., 2006b). Additionally, some results suggest that smokers with ADHD have elevated levels of NIC dependence compared to control smokers and the severity of ADHD is positively associated with the extent of smoking (but results are not completely clear in this regard) (McClernon and Kollins, 2008; Wilens et al., 2008b).

Quitting rates are lower among both adult and adolescent patients with ADHD than among patients without ADHD. Hyperactivity/impulsivity symptoms seem to be associated more strongly with cessation failure than inattention. Moreover, some

results suggest that quitting is associated with more severe withdrawal symptoms and disturbances in cognitive functions in ADHD populations (but results regarding the severity of withdrawal symptoms are not totally conclusive) (Humfleet et al., 2005; Upadhyaya, 2006; Pomerleau et al., 1995; McClernon et al., 2008b; McClernon and Kollins, 2008; Covey et al., 2008). Importantly, increases in attention deficit and hyperactivity–impulsivity symptoms measured by a self-report checklist during smoking cessation (with nicotine replacement therapy) predict the increased likelihood of relapse (Rukstalis et al., 2005).

Not only clinical diagnosis of ADHD, but symptoms of ADHD correlate positively with smoking in nonclinical (community) samples (Kollins et al., 2005; Fuemmeler et al., 2007; Barman et al., 2004; Lerman et al., 2001; Tercyak et al., 2002; McClernon and Kollins, 2008). There is some debate in the literature over whether hyperactivity/impulsivity or inattention is primarily accountable for elevated smoking rates in ADHD (and whether they increase the chance of NIC-dependence to a different extent in adolescence and young adulthood) (Burke et al., 2007; Diamond, 2005; Elkins et al., 2007; Rodriguez et al., 2008).

9.2. Neurobiological explanations of frequent co-occurrence of ADHD and smoking

There are numerous explanations for the elevated rate of smoking among patients with ADHD. First of all, the mechanism underlying NIC's ability to reduce symptoms of ADHD may be similar to that of medications (psychostimulants, atomoxetine and bupropion) used to treat this disorder, since they all have enhancing effects on dopaminergic and/or noradrenergic systems, which may suggest that smoking is a way of self-medicating in this patient population (Solhkhah et al., 2005; Wilens et al., 2005a,b; Sacco et al., 2004; Hahn and Stolerman, 2005; Cao et al., 2005a,b).

Elevated slow-wave (delta–theta) activity (the EEG sign of reduced arousal) is commonly described in children, adolescent, and adult populations with ADHD. This electrophysiological aberration could refer to decreased cholinergic activity, which may partially explain both the effectiveness of nicotinic agonists in the therapy of ADHD and the increased risk of smoking in ADHD (Rowe and Hermens, 2006). Furthermore, a reduction in the amplitude of the P300 wave is a frequently reported electrophysiological alteration in ADHD and nicotinic agonists are also known to increase P300 amplitude (Rowe and Hermens, 2006).

Furthermore, the possibility of a common genetic background accountable for the high comorbidity of smoking and ADHD may also emerge (Laucht et al., 2007; McClernon and Kollins, 2008). Most genetic investigations have found that some polymorphisms of the α4 nAChR subunit gene (CHRNA4) are associated with ADHD, while investigated polymorphisms of the CHRNA7 gene are not (Waldman and Gizer, 2006; McClernon and Kollins, 2008; Wallis et al., 2008). In addition, the smoking rate was found to be significantly higher among subjects who carried the A2 allele in *Taq1* A DRD2 polymorphism and exhibited at least six symptoms of hyperactivity–impulsivity than among carriers of the A1 allele; this result offers further support for a genetic explanation of the association between smoking and ADHD (McClernon and Kollins, 2008). The hypothesis that nicotinic receptors may play role in the pathophysiology of ADHD is strengthened by the presence of some symptoms of ADHD (such as inattention, lack of inhibitory control and hyperactivity) among β2 nAChR subunit KO mice. This mouse strain could thus serve as an animal model of ADHD (Granon and Changeux, 2006).

Previous studies showed that NIC exposure during pregnancy and/or postnatal parental smoking appear to be risk factors for ADHD in offspring, but some contradictions exist between survey results (Linnet et al., 2005; Langley et al., 2005; Kollins et al., 2009; Button et al., 2005; Thapar et al., 2003; Banerjee et al., 2007; Obel et al., 2009). This relationship is also influenced by genetic susceptibility (i.e. carriers of some genetic variations of DAT1 or DRD4 or CHRNA4 genes are more susceptible than non-carriers of these polymorphisms) (McClernon and Kollins, 2008). However, a very recent result seems to refute the causal relationship between prenatal exposure to tobacco smoke and elevated risk of ADHD. Thapar et al. (2009), with a clever experimental design, found that maternal smoking during pregnancy was a much stronger predictor of ADHD in offsprings in genetically related mother-offspring pairs compared to genetically unrelated mother-offspring pairs (in the latter case, mothers conceived through assisted reproduction technologies (i.e. oocyte donation or embryo donation)). This result suggests that the previously described association between in utero exposure to tobacco smoke ingredients and elevated risk of ADHD is mainly attributed to inherited factors and not to the harmful effects of tobacco smoke per se (Thapar et al., 2009).

Neuroimaging (PET, MRI, SPECT) studies have shown that striatal structures could be involved in the pathophysiology of ADHD (Krause et al., 2006). Although results are far from unequivocal, most studies have found an elevated expression of dopamine transporter (DAT) – expressed mainly in the striatum – among patients with ADHD compared to controls. This is especially true for those patients with ADHD who respond well to stimulant therapy (Krause et al., 2003, 2006; Madras et al., 2005; Hesse et al., 2009; Krause, 2008). It is important to note that smoking decreases DAT density among patients with ADHD, as do psychostimulants used to treat this disorder (Krause et al., 2003, 2006; Krause, 2008). DAT knockout mice have been found to exhibit striking, spontaneous behavioral hyperactivity, while psychostimulants have had an ameliorating effect on this KO strain (Mehler-Wex et al., 2006). Both these findings are at odds with the theory of increased DAT density in ADHD.

Although in non-ADHD samples, investigations have found that psychostimulant (methylphenidate or d-amphetamine) treatment increased ad libitum smoking, many studies of patients with ADHD have shown that stimulant (but not bupropion) treatment decreased the risk of SUD in general and smoking in particular (but some studies achieved the opposite results) (Rush et al., 2005; Wilens et al., 2008a, 2003; Whalen et al., 2003; Upadhyaya et al., 2005; Wilson and Levin, 2005; Wilens, 2006; Monuteaux et al., 2007; Cousins et al., 2001; Huizink et al., 2009; Huss et al., 2008; Katusic et al., 2005). In accordance with these results, there is some evidence from animal studies too that the treatment of adolescent rats with psychostimulant may reduce the risk of later SUD (Carlezon et al., 2003).

9.3. Nicotinic agents and AChE inhibitors as possible therapeutics for ADHD

Based on the above facts and the essential role played by the (nicotinic) cholinergic system in attention, motivation and cognitive functions, NIC can be assumed to have a possible therapeutic effect in ADHD (Sacco et al., 2004; Sarter et al., 2006; You et al., 2008; Inglis and Winn, 1995). According to this assumption, NIC and in some studies selective $\alpha_4\beta_2$ nAChR agonists (ABT-418 and ABT-089) have beneficial impacts on behavioral symptoms of ADHD and/or ADHD-related cognitive disturbances (measured by behavioral inhibition, delay aversion and sustained attention tasks) (Gehricke et al., 2006; Potter and Newhouse, 2004, 2008; Poltavski and Petros, 2006; Wilens et al., 2005a,b; Wilens and Decker, 2007; Levin et al., 2006; Potter et al., 2006). Studies investigating the effect of AChE inhibitors (donepezil or galantamine) on symptoms of ADHD have yielded inconsistent results (Wilens et al., 2005a; Doyle et al., 2006; Yoo

et al., 2007; Biederman et al., 2006a). The importance of cholinergic system in ADHD is further supported by recent data demonstrating that atomoxetine (an approved therapy for ADHD) increases cholinergic neurotransmission in cortical regions, and accordingly enhances memory functions measured by radial arm-maze and object recognition tests in rats (Tzavara et al., 2006).

10. Parkinson's disease (PD)

10.1. Epidemiology of smoking in PD

Most epidemiological studies (both with case–control and prospective design) and meta-analyses show that smokers present a lower risk of developing Parkinson's disease (PD), although some studies could not confirm this inverse relationship (Allam et al., 2002, 2004; Grandinetti et al., 1994; De Michele et al., 1996; Liou et al., 1997; Hellenbrand et al., 1997; McCann et al., 1998; Ritz et al., 2007). A recent preliminary study has shown that passive smoking could also protect against PD (Mellick et al., 2006). Two twin studies and one family-based study also support the inverse relationship between smoking and PD (Wirdefeldt et al., 2005; Tanner et al., 2002; Scott et al., 2005). The onset of PD symptoms, the time of diagnosis of PD, and the time at which levodopa treatment is introduced occurred at an older age in ever-smoking group compared with never-smoking group according to a recent investigation (although two other studies failed to find a relationship between smoking and later onset of PD) (De Reuck et al., 2005; Alves et al., 2004; Papapetropoulos et al., 2005). Another recent case–control study suggests that the protective effects of smoking, coffee drinking, and nonsteroidal anti-inflammatory drug (NSAID) consumption on the risk of PD are cumulative (Powers et al., 2008).

10.2. Regulation of the nigrostriatal pathway by nAChRs

NIC is important in promoting the release of DA in the nigrostriatal pathway, either by stimulation of dopaminergic neurons of the substantia nigra through its receptors (with $\alpha6\alpha4\beta2\beta3$ or $\alpha6\beta2\beta3$ or $\alpha7$ or $\alpha4\beta2$ subunit compositions) on cell bodies, or through its receptors (with $\alpha6\beta2^*$ ($\alpha6\alpha4\beta2^*$ or $\alpha6(non\alpha4)\beta2^*$) and $\alpha4\beta2^*$ ($\alpha4\beta2$, $\alpha4\alpha5\beta2$, $\alpha4\alpha2\beta2$) subunit compositions) on dopaminergic nerve terminals in the striatum ($\alpha7$ receptors are not present on striatal dopaminergic terminals) (Gotti and Clementi, 2004; Matsubayashi et al., 2004; Quik and McIntosh, 2006; Quik, 2004; Quik et al., 2007; Huang et al., 2009). Not only NIC but its main metabolite, cotinine, also has a dopamine-releasing effect in the nigrostriatal system (O'Leary et al., 2008).

The proportion of $\alpha6\beta2^*$ and $\alpha4\beta2^*$ receptors on striatal dopaminergic terminals is species dependent; in primates the larger proportion of these receptors are $\alpha6\beta2^*$ while in rodents it is $\alpha4\beta2^*$. Accordingly, during low-frequency firing of dopaminergic cells, dopamine release was mainly regulated by $\alpha3/\alpha6\beta2^*$ receptors in the primate dorsal and ventral putamen. During burst firing, both $\alpha3/\alpha6\beta2^*$ and $\alpha4\beta2^*$ regulate dopamine release in the ventral putamen, but neither of them regulate dopamine release in the dorsal putamen (Gotti and Clementi, 2004; McCallum et al., 2005; Quik et al., 2008; Perez et al., 2009). Elements of other transmitter systems that influence the activity of the nigrostriatal system contain nAChRs, too. For example, $\alpha7$ receptors are found on glutamatergic nerve endings in striatum, $\alpha4\beta2$ and $\alpha7$ receptors on cholinergic interneurons of the striatum, and $\alpha6\alpha4\beta2$ and $\alpha7$ and $\alpha4\beta2$ receptors on GABAergic neurons of the striatum (Gotti and Clementi, 2004; Quik and McIntosh, 2006; Quik, 2004). Results of experiments with different nAChR subunit knockout mice strains also support the role of nAChRs in the regulation of nigrostriatal dopaminergic activity, and show that receptors containing $\alpha6$, $\alpha4$, $\beta2$ subunits are essential to NIC-evoked dopamine release in rodent striatum (Quik and McIntosh, 2006).

10.3. Neuropathological findings and alterations of the nicotinergic system in PD

PD is a neurodegenerative disorder mainly characterized by degeneration of dopaminergic neurons in the substantia nigra and VTA with consequential dysfunction of the nigrostriatal and mesocorticolimbic pathways (Bosboom et al., 2004). Non-dopaminergic nuclei (i.e. serotonergic dorsal raphe nuclei or noradrenergic locus coeruleus) are also involved in the pathological process (Bosboom et al., 2004; Fornai et al., 2007; Zarow et al., 2003). Furthermore, the appearance of Lewy bodies (one of the pathological hallmarks of PD) and/or cell loss have been described in cholinergic nuclei (i.e. nucleus basalis (n. Meynert) and pedunculopontine nucleus) in PD (Bosboom et al., 2004; Zarow et al., 2003; Pahapill and Lozano, 2000; Jellinger, 1988). In addition, the pedunculopontine nucleus may play a role in the pathogenesis of some symptoms of PD (e.g. the degree of akinesia is associated with the extent of cholinergic cell loss in the pedunculopontine nucleus) and deep brain stimulation of this area seems to be effective in alleviating some symptoms of PD (Pahapill and Lozano, 2000; Nandi et al., 2002; Plaha and Gill, 2005; Winn, 2008).

Neuronal nAChR densities appear to be decreased among patients with PD in various areas of their brain. NIC binding was decreased in an autoradiography study by Court et al. (2000) in the postmortem caudatum and putamen of patients with PD (Court et al., 2000). Recently, three studies using PET or SPECT and iodinated or fluorinated derivatives of A-85380 as radioligands for $\beta2$ subunit containing nAChRs (i.e. $\alpha4\beta2$, $\alpha3\beta2$ and $\alpha6\beta2$ receptors) investigated the densities of nAChRs in patients with PD. All of the studies have found that the densities of the $\beta2$ subunit containing nAChRs were reduced in cortical and/or subcortical regions (i.e. striatum and substantia nigra) in non-demented PD patients compared to age-matched control individuals (Kas et al., 2009; Fujita et al., 2006; Oishi et al., 2007; Ward et al., 2008). Two studies using postmortem PD brains found that the A-85380 uptake was diminished in the striatum and thalamus, indicating $\alpha4\beta2$ receptor loss in these structures (Schmaljohann et al., 2006; Pimlott et al., 2004). α-conotoxinMII (which interacts with receptors containing $\alpha3$ and $\alpha6$ subunits) binding is decreased in the caudate and putamen of patients with Parkinson's disease (Quik et al., 2004). In contrast to previous studies, Martin-Ruiz et al. (2000) did not find changes in the expression level of $\alpha3$, $\alpha4$, $\alpha7$, and $\beta2$ subunits in the putamen of patients with PD (Martin-Ruiz et al., 2000). In the cerebral cortex of patients with PD, $\alpha4$ and $\alpha7$ subunit protein levels are decreased (Burghaus et al., 2003). The protein level of the $\alpha7$ subunit did not show a decrease in the caudatum or hippocampus in patients with PD. Furthermore, the level of the $\alpha7$ subunit was increased in the temporal cortex of patients with PD compared to control subjects (Guan et al., 2002; Ward et al., 2008). Densities of $\alpha2$-$\alpha6^*$ (but not $\alpha7$) nAChRs in the striatum are decreased in experimental animal models of PD too (i.e. in MPTP-lesioned primates and rodents), which further supports the role of nAChRs in the pathophysiology of PD (Quik, 2004). Different kinds of nAChRs in the striatum are also different in their vulnerability to nigrostriatal damage. $\alpha6\beta2^*$ receptors appear particularly vulnerable (within this group $\alpha6\alpha4\beta2^*$ receptors are more vulnerable than the $\alpha6(non\alpha4)\beta2^*$ subtype), while $\alpha4\beta2^*$ receptors are less vulnerable (i.e. their number is decreased only after severe nigrostriatal damage) (Huang et al., 2009; Bordia et al., 2007). In addition, $\alpha6\alpha4\beta2^*$ and $\alpha6(non\alpha4)\beta2^*$ receptors also differed from each other in their expression level

after chronic NIC treatment: α6(nonα4)β2* receptors were upregulated, while α6α4β2* were downregulated after long-term NIC administration in striatum (Perez et al., 2008a,b).

10.4. Neuroprotective effects of nicotine and other tobacco smoke ingredients in PD

The results of recent examinations suggest that striatal α4β2* and α3/α6β2* nAChR loss following experimental nigrostriatal damage could be prevented by long-term NIC administration before experimental lesion. Furthermore, NIC pretreatment is associated with a lesser dopaminergic dysfunction (measured by striatal tyrosine hydroxylase, dopamine transporter, vesicular monoamine transporter and dopamine levels) in the striatum after MPTP lesions in squirrel monkeys (Bordia et al., 2006; Quik et al., 2006; Huang et al., 2009). During high-dose (up to 105 mg/day) and long-term NIC therapy in patients with PD the dopamine transporter binding (measured by SPECT) in the basal ganglia decreased less than expected given the results of previous studies in PD patients without NIC treatment. This suggests that NIC-administration may lead to diminished striatal neuronal loss during the progression of PD (Itti et al., 2009). NIC also attenuates 6-hydroxydopamine (6-OHDA)-induced nigrostriatal neurodegeneration (6-OHDA administration is another experimental model of PD in addition to MPTP administration) (Grunblatt et al., 2000; Costa et al., 2001; Ryan et al., 2001). NIC is also protective against nigral dopaminergic nerve cell degeneration in a mechanically induced degeneration of the dopaminergic system (Janson and Moller, 1993; Janson et al., 1994). In addition, NIC may attenuate the salsolinol-induced apoptosis in a neuroblastoma cell population served as a model of the nigral dopaminergic cell population (salsolinol, a dopamine derivative with a selective toxic effect on the nigrostriatal dopaminergic system, has elevated concentrations in the liquor, brain tissue, and urine among patients with PD, and consequently, may be a possible marker of PD) (Copeland et al., 2007; Mravec, 2006). Furthermore, chronic NIC administration in rats slowed age-associated dopaminergic receptor loss in the nigrostriatal system (Prasad et al., 1994). A recent investigation concluded that NIC has more neuroprotective than neuroregenerative effects in experimental lesion models of PD in rodents and primates, while NIC administration protects against nigrostriatal damage (measured by changes in densities of nAChRs and dopamine transporter and behavioral deficits after lesion) only when given prior to lesioning, but not after nigrostriatal damage (Huang et al., 2009). NIC may be protective against PD via mechanisms other than direct control of the nigrostriatal dopamine pathway, since NIC has several kinds of neuroprotective properties. For example, NIC has direct antioxidant activity, moreover the activation of nAChRs may increase the expression of neurotrophic factors. In addition, NIC modulates the activity of the mitochondrial complex I of the electron transport chain which results in a reduction in reactive oxygene species production. Finally, NIC has anti-inflammatory effects (Quik, 2004; Mudo et al., 2007; Imamura et al., 2006; Xie et al., 2005; Park et al., 2007). Recently, NIC and another cigarette smoke component (hydroquinone) were also shown capable of inhibiting the process of α-synuclein fibrillation (Lewy bodies contain ubiquitin and fibrils of α-synuclein) (Hong et al., 2009a; Bisaglia et al., 2009). Inhibitors of α-synuclein fibrillation may be potential therapeutic agents for the prevention or control of PD (Hong et al., 2009a).

Other compounds in cigarette smoke besides NIC could be protective against PD. For example, some MAO enzyme inhibitors (harman, norharman, 2,3,6-trimethyl-1,4-naphthoquinone, 2-naphthylamine, and farnesylacetone) are found in cigarette smoke, and MAO inhibition is one known way to achieve symptomatic relief in PD (Herraiz and Chaparro, 2005; Khalil et al., 2006). Hydralazine, another component of cigarette smoke, has a significant effect in protecting dopaminergic nigrostriatal neurons from damage by MPTP (De Reuck et al., 2005). The elevated expression of some CYP enzymes (CYP2D6, CYP2E1, CYP2B6) in the brain as a consequence of exposure to components of cigarette smoke (including NIC) could be another mechanism of the peculiar neuroprotection offered by smoking, since these enzymes metabolise many xenobiotics (i.e. MPTP and related structures) that can cause PD-like syndromes (Miksys and Tyndale, 2006).

10.5. Nicotinic agents and AChE inhibitors as possible therapeutics for PD: results of clinical and animal studies

Although data from epidemiological investigations have identified mainly inverse relationships between smoking and PD, results of studies looking at the efficacy of NIC treatment on symptoms of PD are disappointing. Vieregge et al. (2001) investigated the effectiveness of transdermal NIC patches as an add-on treatment for symptoms of PD in their double-blind placebo-controlled trial and found no significant beneficial drug effects on motor and affective symptoms (Vieregge et al., 2001). Similarly, two other studies concluded that NIC administration is ineffective in treating either motor or cognitive deficits of PD (Clemens et al., 1995; Lemay et al., 2004; Allam et al., 2002). NIC treatment worsened motor symptoms of PD in one study (Ebersbach et al., 1999). Furthermore, SIB-1508Y, an α4β2 nAChR agonist agent (previously found effective in improving motor performance, attention, and alertness in animal models of PD), did not show beneficial effects on motor and cognitive disturbances of patients with PD (Parkinson Study Group, 2006). These findings are in accordance both with observations of no beneficial disease-modifying effects of smoking among patients with already diagnosed PD (i.e. among those who continued smoking after their diagnosis) and with the above discussed results from experimental animal models of PD by Huang et al. (2009) (Alves et al., 2004; Kandinov et al., 2007). Moreover, a recent prospective study found that current smoking (compared with non-smoking) at PD onset is associated with a more rapid cognitive deterioration in accordance with results of two previous cohort studies (Weisskopf et al., 2007; Ebmeier et al., 1990; Levy et al., 2002). The symptom-alleviating effect of NIC is also contradictory in animal models of PD, although some results from both primate and rodent models of PD show that NIC may reduce L-DOPA-induced dyskinesias or L-DOPA-induced cognitive deficits (L-DOPA is the gold standard for treating PD) (Quik et al., 2007; Bordia et al., 2008; Janhunen and Ahtee, 2007; Abdel-Salam, 2008; Decamp and Schneider, 2009). In partial contrast to the results discussed above, some case-reports and studies found that NIC has symptom-alleviating and cognition-improving effects in PD. Furthermore, a recent investigation found evidence that long-term and high-dose NIC administration is required to attain beneficial effects on symptoms of PD (Hanagasi et al., 2007; Kelton et al., 2000; Fagerstrom et al., 1994; Ishikawa and Miyatake, 1993; Villafane et al., 2007).

Evidence of serious cholinergic deficits in PD have raised the possibility that AChE-inhibitor therapy may be effective in the treatment of cognitive deterioration, which is very frequently associated with PD (Oertel et al., 2008). Placebo-controlled studies with donepezil and rivastigmine found that these two agents improve cognitive deficits without significant long-term worsening of motor symptoms in PD (Grace et al., 2009; Dodel et al., 2008; Oertel et al., 2008). In contrast, a recent study found that non-demented PD patients treated with galantamine (an agent with both AChE inhibitor and nAChRs allosteric modulator properties) did not show improvement in various aspects of cognition (i.e. attention, memory, visuospatial performance). Moreover, the rate of self-reported worsening of PD symptoms was higher in the

treatment arm compared to the placebo arm (Grace et al., 2009; Razay and Wilcock, 2008).

11. Discussion

Smoking is the most frequent and also the most harmful form of NIC consumption. In addition, NIC from tobacco smoke – based on the pharmacological properties of smoking – is extremely addictive compared to NIC from other possible sources (i.e. NIC replacement products). Considering the ubiquitous presence of nAChRs in various parts of the central nervous system, NIC not surprisingly has diverse effects on various brain functions, and influences the activity of several neurotransmitter systems. Moreover neuroimaging studies have found smoking-associated functional and structural changes in the brain. Strong epidemiological data suggest that smoking rates are higher among individuals with different kinds of psychiatric disorders compared to the general population. Furthermore, subjects with a current psychiatric disorder consume a disproportionally large part of tobacco products. Replicated findings suggest that smoking may be an independent risk factor for suicide. A growing body of results indicates that smoking may alter the clinical features of neuropsychiatric disorders and may also be partially responsible for elevated non-suicide mortality in patients with some of these diseases. Several possible mechanisms may explain the disease-modifying effects of smoking. First of all, pharmacological evidence points to the involvement of nAChRs in the regulation of different neural circuits. Second, changes in different levels of the cholinergic system (enzymes, transporters, and receptors) are described in neuropsychiatric disorders. Third, genetic findings indicate that some polymorphisms of nAChR genes are associated with an altered risk of both neuropsychiatric disorders and smoking behavior. In addition, not only NIC but some other ingredients of tobacco smoke are also known to have various direct neuroactive effects too. Because of the close relationship between the (nicotinic) cholinergic system and neuropsychiatric disorders, and also the possible role of self-medication in the elevated smoking rates in these disorders, several nicotinic agents were tested for therapeutic efficacy, and some were found to be useful in the treatment of these states. Finally, it should be mentioned that tobacco smoke contains many compounds (i.e. polycyclic aromatic hydrocarbons, carbon monoxide, and heavy metals) that either stimulate or inhibit CYP450 enzymes, so pharmacokinetic interactions between smoking and psychopharmacological agents are frequent and are worth considering (Zevin and Benowitz, 1999; Desai et al., 2001).

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