Psychopharmacology (2006) 184: 292–305
DOI 10.1007/s00213-005-0070-z

REVIEW

Huibert D. Mansvelder · Karlijn I. van Aerde · Jonathan J. Couey · Arjen B. Brussaard

Nicotinic modulation of neuronal networks: from receptors to cognition

Received: 12 January 2005 / Accepted: 9 May 2005 / Published online: 2 July 2005

Abstract *Rationale:* Nicotine affects many aspects of human cognition, including attention and memory. Activation of nicotinic acetylcholine receptors (nAChRs) in neuronal networks modulates activity and information processing during cognitive tasks, which can be observed in electroencephalograms (EEGs) and functional magnetic resonance imaging studies. *Objectives:* In this review, we will address aspects of nAChR functioning as well as synaptic and cellular modulation important for nicotinic impact on neuronal networks that ultimately underlie its effects on cognition. Although we will focus on general mechanisms, an emphasis will be put on attention behavior and nicotinic modulation of prefrontal cortex. In addition, we will discuss how nicotinic effects at the neuronal level could be related to its effects on the cognitive level through the study of electrical oscillations as observed in EEGs and brain slices. *Results/Conclusions:* Very little is known about mechanisms of how nAChR activation leads to a modification of electrical oscillation frequencies in EEGs. The results of studies using pharmacological interventions and transgenic animals implicate some nAChR types in aspects of cognition, but neuronal mechanisms are only poorly understood. We are only beginning to understand how nAChR distribution in neuronal networks impacts network functioning. Unveiling receptor and neuronal mechanisms important for nicotinic modulation of cognition will be instrumental for treatments of human disorders in which cholinergic signaling have been implicated, such as schizophrenia, attention deficit/hyperactivity disorder, and addiction.

H. D. Mansvelder (✉) · K. I. van Aerde · J. J. Couey · A. B. Brussaard
Department of Experimental Neurophysiology,
Center for Neurogenomics and Cognitive Research (CNCR),
Vrije Universiteit Amsterdam,
De Boelelaan 1085,
1081 HV Amsterdam, The Netherlands
e-mail: huib@cncr.vu.nl

Keywords Nicotine · Acetylcholine · Receptors · Desensitization · Neuronal networks · Synaptic plasticity · EEG · Oscillations · Cognition · Addiction

Introduction

Nicotine has been shown to improve cognitive function in humans and other primates as well as in rodents (Levin and Simon 1998; Rezvani and Levin 2001; Stein et al. 1998; Stolerman et al. 1995). Particularly, performance on attention and working memory tasks is improved by nicotine. Most likely, this results from nicotinic effects on multiple brain areas, such as hippocampus, amygdala, and prefrontal cortex (PFC). One of the brain areas that has been implicated to be involved in attention and working memory is a collection of brain areas in the frontal lobe that covers about 30% of the entire human cortex (Groenewegen and Uylings 2000): the PFC. The PFC is also involved in executive control over behavior, and it has been argued that these PFC functions combine to temporally organize goal-directed behavior (Everitt et al. 2001; Fuster 2000a,b; Goldman-Rakic 1995; Miller 2000). By acting on nicotinic acetylcholine receptors (nAChRs) in the PFC, nicotine activates the PFC neuronal network (Gil et al. 1997; Gioanni et al. 1999; Lambe et al. 2003; Vidal and Changeux 1993).

In an electroencephalogram (EEG) from human or rodent brain, oscillatory electrical activity at different frequencies can be distinguished. These oscillations are the result of synchronized activity in the cortical neuronal network in which interneurons play an instrumental role (Buhl et al. 1998; Cobb et al. 1995; Fisahn et al. 1998; Whittington et al. 1995). The different frequencies correspond to different behavioral states and cognitive processing. Nicotine has been shown to increase EEG frequencies associated with arousal and reduce those associated with relaxed wakefulness (Kadoya et al. 1994; Lindgren et al. 1999). In addition, functional magnetic resonance imaging (fMRI) studies have shown increased activation of frontal networks by nicotine administration during attention tasks

(Lawrence et al. 2002). These data together suggest that nicotine's effects on cognition result from a subtle modulation of the cortical network whereby synchronized activity at higher frequencies is facilitated. Here we will review recent neurophysiological studies on nicotinic modulation of neuronal networks, with a particular focus on the PFC. This literature survey shows that, depending on the brain area, nicotine modulates multiple neuron types within a given network, often by activating cellular- and subcellular-specific nAChR subtypes, each with their own activation and desensitization properties. We argue that this type of complex neuronal network modulation by nicotine is a general phenomenon in the brain, and we will discuss how this may underlie the effects of nicotine on EEG signals and cognition. Given the limited amount of data available in the literature on nicotinic mechanisms at the cellular and network level in the PFC, we will present a putative model of nicotinic modulation of the PFC circuitry partly based on data obtained from other brain areas involved in cognitive effects of nicotine, such as hippocampus, amygdala, and ventral tegmental area (VTA).

Nicotine enhances PFC-dependent cognition

Tobacco and nicotine have complex effects on human performance, determined in part by whether human subjects are in a state of tobacco deprivation. In nicotine-deprived individuals, an impaired attention and cognitive ability may become apparent within 12 h of smoking cessation, whereas nicotine administration (either via smoking or via transdermal deposition) may reverse such deficits to pre-abstinence levels (Ernst et al. 2001). In a variety of human disorders, such as attention deficit/hyperactivity disorder (ADHD) and schizophrenia, nicotinic drugs may act beneficial on attention and sensory gating (Newhouse et al. 2004; Potter and Newhouse 2004). A significantly higher percentage of adults and adolescents that have been diagnosed with ADHD smoke compared with unaffected human subjects and have a lower chance of quitting smoking (Lambert and Hartsough 1998). Also, among schizophrenic patients, smoking rates are much higher (90%) compared to the general population (20–30%) (Lohr and Flynn 1992; Picciotto et al. 2000), and nicotine may ameliorate some of the major cognitive deficits associated with this disease (Martin et al. 2004; Newhouse et al. 2004). Although this review focuses on nicotinic mechanisms, it should be pointed out that tobacco smoke actually contains many more substances than nicotine alone, which could have effects on cognition as well.

Nicotine, the addictive substance in tobacco, may exert its cognitive effects by modulating activity in one or more cortical regions associated with mechanisms of sustained attention (Coull 1998; Sarter et al. 2001), including the prefrontal, parietal, and occipital cortex (Cabeza and Nyberg 2000; Rueckert and Grafman 1996, 1998), but the amygdala and hippocampus also play a role (Levin 2002; Newhouse et al. 2004). This is in line with the idea that sustained attention is crucially dependent on the ascending cholinergic (ACh) system originating in the basal forebrain and projecting to most of the cortex (Everitt and Robbins 1997; Muir et al. 1995). fMRI studies have shown that nicotine improves attention in smokers by extra activation of the cortical areas traditionally associated with visual attention, arousal, and motor activation (Lawrence et al. 2002). This is particularly true for schizophrenic patients who smoke (Jacobsen et al. 2004). Also, in nonsmokers, nicotine appears to produce an increased fMRI signal in the anterior cingulate, superior frontal cortex, and superior parietal cortex, which suggests that nicotine may alter neuronal activity in a distributed neural network associated with online task monitoring and attention and arousal (Kumari et al. 2003).

The putative effects of nicotine on cognition has also been observed in smokers as well as nonsmokers in a series of other cognitive performance tests, including those for visual attention (two-letter search task) and working memory (N-back tasks) (Ernst et al. 2001). It is interesting to note that working memory performance appeared to be related to smoking history (i.e., smokers performed most poorly and never-smokers best). Thus, trait-like differences in some cognitive domains, such as working memory, may exist in smokers vs. nonsmokers, which in turn may be long-term effects or etiological factors related to smoking (Ernst et al. 2001).

It is debated whether improved performance associated with relief from nicotine in abstinent smokers should be considered as cognitive enhancement (Newhouse et al. 2004). Indeed, many studies show performance impairment by nicotine in nonsmokers (Newhouse et al. 2004). In line with this, chronic cigarette smoking generally does not improve cognitive processing (Ascioglu et al. 2004), whereas nicotine deprivation tends to affect cognitive performance (Havermans et al. 2003). It is likely that transient exposure and long-term exposure to nicotine affect neuronal circuits in the brain very differently.

To understand how nicotine exerts these effects on cognitive performance, its short-term and long-term impacts on neuronal circuitries involved have to be assessed. However, we are only beginning to understand some of the processes involved. Several factors can be distinguished in how nicotine can alter neuronal network properties and information processing, and these factors press for an analysis at multiple levels of organization. First, how a neuronal network will be affected by nAChR activation depends on which neurons in the network express nAChRs: interneurons, pyramidal neurons, or other types of neurons (Alkondon and Albuquerque 2004; Ji et al. 2001; Mansvelder and McGehee 2002). Second, the subcellular location where these receptors are expressed will strongly impact neuronal and synaptic modulation (MacDermott et al. 1999; McGehee and Role 1996; Wonnacott et al. 2005). The receptors can be located on the cell body, presynaptic terminals, or at postsynaptic sites on dendrites. Third, the type or types of nAChRs that are expressed will determine how the network is affected by nicotinic modulation: activation and desensitization kinetics, agonist sensitivity, and single channel conductance (Gotti and Clementi 2004; Hogg et al.

2003; Klink et al. 2001; Wooltorton et al. 2003). Fourth, whether cholinergic signaling in the network occurs through direct synaptic or indirect nonsynaptic transmission will also impact nicotinic modulation. These factors will all combine to alter neuronal network properties.

Nicotinic acetylcholine receptors

nAChRs are cation-selective, ligand-gated channels whose endogenous agonist is acetylcholine (ACh). Neuronal nAChRs are pentameric combinations of 12 genetically distinct homologous subunits (α2–α10 and β2–β4), each combination potentially having a distinct single channel conductance, agonist sensitivity, and activation/desensitization kinetics (McGehee and Role 1995). Most nAChRs are assumed to be heterooligomeric (i.e., composed from various combinations of α and β subunits), and there is evidence that some α subunits also form homooligomeric proteins (Drisdel and Green 2000; McGehee and Role 1995). An open nicotinic receptor channel allows the movement of Na^+, K^+, and Ca^{2+} across the cell membrane, and at resting membrane potential of a typical cortical cell, this manifests as a depolarizing current. The calcium permeability of nAChRs is generally thought to play a crucial role in the central effects of nicotine (Dajas-Bailador and Wonnacott 2004), and it has been long established that the subunit composition of the nAChRs influences their intrinsic calcium permeability (McGehee and Role 1995). Indeed, a significant proportion of the total charge passing through nAChRs is carried by calcium; in heteromeric nAChRs composed of α and β subunits, the fractional calcium current is 2–5%. Homomeric α7 nAChRs exhibit a much larger fractional calcium current (6–12%) that appears similar to NMDA receptors (Burnashev 1998; Burnashev et al. 1995; Fucile 2004).

Early on, in nicotine-binding studies in the brain, two distinct nicotine-binding sites in the brain were recognized with very different affinities. The α4β2-containing nAChRs were identified as the high-affinity nicotine-binding site, whereas the neuronal bungarotoxin (αBTX) sensitive α7-containing nAChRs represent the low-affinity nicotine-binding sites (Couturier et al. 1990; McGehee and Role 1995; Seguela et al. 1993). Analysis of mRNA content of neurons showed that neurons in different brain areas express many more subunits (Charpantier et al. 1998; Klink et al. 2001; Porter et al. 1999). Recently, in studies using sub-micromolar concentrations of nicotine, concentrations experienced by smokers, it has become clear that the physiological importance of high- and low-affinity nicotine-binding sites may not so much be found in the activation properties of nAChRs but more in desensitization properties (Mansvelder and McGehee 2002; Wooltorton et al. 2003). At these low nicotine concentrations (100–250 nM), both α4β2 nAChRs and α7 nAChRs are activated, but α4β2 nAChRs desensitize much more. At 250 nM α4β2 nAChRs are completely desensitized within minutes, whereas α7 nAChRs are not and remain available for activation (Mansvelder and McGehee 2002; Wooltorton et al. 2003). Thus, both activation and desensitization properties have to be considered when trying to understand nicotinic modulation of neuronal networks.

Synaptic and nonsynaptic cholinergic transmission

Neurons can communicate via both synaptic and nonsynaptic transmission. The percentage of GABAergic and glutamatergic axons that terminate on a postsynaptic site approaches 100% (Seguela et al. 1990; Umbriaco et al. 1994, 1995). In contrast, ultrastructural analyses of monoaminergic, including acetylcholinergic, nerve terminals in the cortex (Audet et al. 1988, 1989) and hippocampus (Vizi and Kiss 1998) show that most of these nerve terminals do not make contact with a postsynaptic density. These terminals are equipped for vesicle release despite not making direct synaptic contacts (Descarries and Mechawar 2000; Seguela et al. 1989, 1990).

Cholinergic transmission is present in the early developing rat parietal cortex already at birth (Descarries et al. 1997; Mechawar and Descarries 2001). In the first 2 weeks after birth, the cholinergic innervation can be seen to increase greatly both in number of varicosities and number of branches per axon. However, the association of these new cholinergic terminals to postsynaptic densities (<15%) remains constant throughout adulthood (Mechawar et al. 2002). These studies point to a role for cholinergic volume transmission during development of the cortex. Cholinergic innervation has been reported to be almost exclusively extrasynaptic in several areas of the rat brain including the parietal cortex (Mechawar et al. 2002; Umbriaco et al. 1994), hippocampus (Umbriaco et al. 1995), neostriatum (Contant et al. 1996), visual sensory, and parietal cortices (Avendano et al. 1996; Turrini et al. 2001). Recently, it was shown that presynaptic nAChRs on glutamatergic terminals are not associated with cholinergic synapses, which is consistent with the paracrine delivery of ACh (Jones and Wonnacott 2004). The coexistence of synaptic and nonsynaptic cholinergic transmission in the central nervous system (CNS) has wide-ranging implications for our understanding of how nicotinic receptors affect neuronal networks, especially taking differences in activation and desensitization properties of nAChRs into account (Mansvelder et al. 2002; Quick and Lester 2002). In nonsynaptic transmission, the ACh concentration will be much lower and the buildup of these concentrations will be much slower than in synapses. Therefore, the rate of activation and desensitization of nAChRs will be very different under these conditions. As a consequence, α7-containing nAChRs can desensitize much less under these concentration regimes than, for instance, α4β2 nAChRs (Mansvelder et al. 2002; Quick and Lester 2002; Wooltorton et al. 2003). This is surprising because α7-containing nAChRs desensitize very rapidly during fast application of agonists, whereas α4β2 nAChRs desensitize much less under those conditions.

Location of nicotinic receptors in hippocampus, amygdala, and cortex

Nicotinic receptors are ion channels, and as such, their subcellular localization is critical to understanding their physiological impact on neuronal activity. nAChRs have been shown to modulate presynaptic glutamate release (Gray et al. 1996; MacDermott et al. 1999; McGehee et al. 1995; McGehee and Role 1996). In addition, nAChRs can modulate GABAergic transmission in multiple brain areas, such as VTA, thalamus, cortex, and hippocampus (Alkondon et al. 1997, 2000; Fisher et al. 1998; Lena and Changeux 1997; Lena et al. 1993; Mansvelder and McGehee 2002; Radcliffe et al. 1999). Modulation of γ-aminobutyric acid (GABA) neurons by nAChRs has been most extensively studied in the hippocampus, where GABAergic interneurons express multiple nAChR subtypes (Alkondon and Albuquerque 2004; Alkondon et al. 1997, 1999; Frazier et al. 1998; Ji and Dani 2000; Jones and Yakel 1997; McQuiston and Madison 1999). There is evidence for nAChR expression both on presynaptic terminals, where they directly modulate GABA release, independent of action potential firing (Fisher et al. 1998; Lu et al. 1999; Radcliffe et al. 1999), and away from synaptic terminals, where modulation of GABA release is dependent on action potential firing (Alkondon et al. 1997, 1999; Frazier et al. 1998). The expression of nAChRs is dependent on the interneuron subtype (Alkondon and Albuquerque 2004; McQuiston and Madison 1999).

Activation of nAChRs on cortical and hippocampal interneurons results either in inhibition or disinhibition of pyramidal neurons (Alkondon et al. 2000; Ji and Dani 2000; Ji et al. 2001). Inhibition is likely to be induced via nAChR-mediated increase in the GABAergic transmission directly onto pyramidal cells. Disinhibition of pyramidal neurons results from an increase of inhibitory GABAergic transmission to GABAergic interneurons by activation of nAChRs. Consequently, pyramidal neurons may receive less GABAergic input and are disinhibited.

In the amygdala, both GABAergic and glutamatergic transmission are enhanced by nicotine (Barazangi and Role 2001). nAChRs were found to be present on presynaptic locations in both glutamatergic and GABAergic synapses. Immunostaining with antibodies against different types of nAChRs showed that in these projections, α4, α7, and β2 subunits are expressed (Barazangi and Role 2001). Most likely, the presynaptic nAChRs on the projections from the olfactory bulb play a role in the working memory impairments observed when α4β2 and α7 antagonists are locally infused into the amygdala (Levin 2002).

There are significantly less data on nicotinic modulation of different types of neurons in the PFC. As in other parts of the neocortex, the PFC has a layered structure in which most of the cells are pyramidal. In rodents, several pyramidal and interneuron cell types have been identified physiologically, morphologically, as well as immunocytochemically (Gabbott et al. 1997, 2003; Kawaguchi 1993; 1995; Kawaguchi and Kondo 2002). In rat, thalamocortical inputs impinge on pyramidal neurons in layer V as well as in more superficial layers in the PFC. These inputs have been shown to be modulated by α4β2-containing nAChRs (Gil et al. 1997; Gioanni et al. 1999; Lambe et al. 2003; Vidal and Changeux 1993). Nicotinic modulation of thalamocortical projections by α4β2-containing nAChRs appears to be a general phenomenon in the cortex (Metherate 2004). If glutamatergic thalamocortical projections also terminate on interneurons in the PFC, these may also be modulated by α4β2-containing nAChRs (Fig. 1a).

An elegant study in the rat motor cortex revealed distinct interneuron subtypes, which both express nAChR mRNA for α4, α5, and β2 subunits and showed somatic nicotinic currents (Porter et al. 1999). Pyramidal cells, as well as interneurons expressing either parvalbumin or somatostatin, showed no effect of agonist application in this study. Interneurons expressing vasoactive intestinal peptide (VIP) and cholecystokinin (CCK) did show nicotinic currents, and pharmacological analysis implicated non-α7 nAChRs. In human cerebral cortical slices, bipolar and multipolar interneurons exhibited either α7 or α4β2 nAChR-mediated currents (Alkondon et al. 2000). Rat PFC interneurons have been characterized extensively in medial and lateral agranular cortex and anterior cingulate cortex (Kawaguchi and Kubota 1996, 1997), but nicotinic effects on these neurons have not been tested. With specific interneuron subtypes and thalamic inputs to pyramidal cells regulated by nAChRs, as in other cortical areas, nicotinic modulation of PFC neuronal networks may be similar to that in other cortical areas and hippocampus (Fig. 1a). In this way, nicotinic signaling could serve to fine-tune microcircuit function through inhibitory and disinhibitory mechanisms. However, this conclusion awaits experimental testing.

An interesting but seldom addressed aspect of cholinergic signaling in the cortex is the role of cholinergic interneurons in cortical microcircuit function. Cholinergic interneurons in the nucleus accumbens (NAc) can affect GABAergic transmission within the NAc itself via nAChR activation (de Rover et al. 2002). In addition, these cholinergic interneurons could be important in lasting changes in microcircuitries that affect animal behavior, because their intrinsic firing properties are altered during behavioral sensitization to amphetamine (de Rover et al. 2004). Furthermore, it is known from immunohistochemical data that a small fraction of bipolar interneurons in layer II/III of the sensory and motor cortices are cholinergic (Houser et al. 1985). A more recent study using single cell reverse transcriptase polymerase chain reaction (RT-PCR) found a subgroup of cortical interneurons that were positive for vasoactive intestinal protein and calretinin, and were also positive for choline acetyltransferase (ChAT) transcripts (Cauli et al. 1997). These same VIP-positive cells were shown to be the main interneuron subtype also expressing nicotinic currents and nAChR mRNA (Porter et al. 1999). In addition, the NINDS GENSAT BAC Transgenics Project found ChAT-positive staining in almost every part of the cortex, including the PFC (http://www.gensat.org/makeconnection.jsp). The putative presence of cholinergic interneurons in the PFC introduces the possibility of

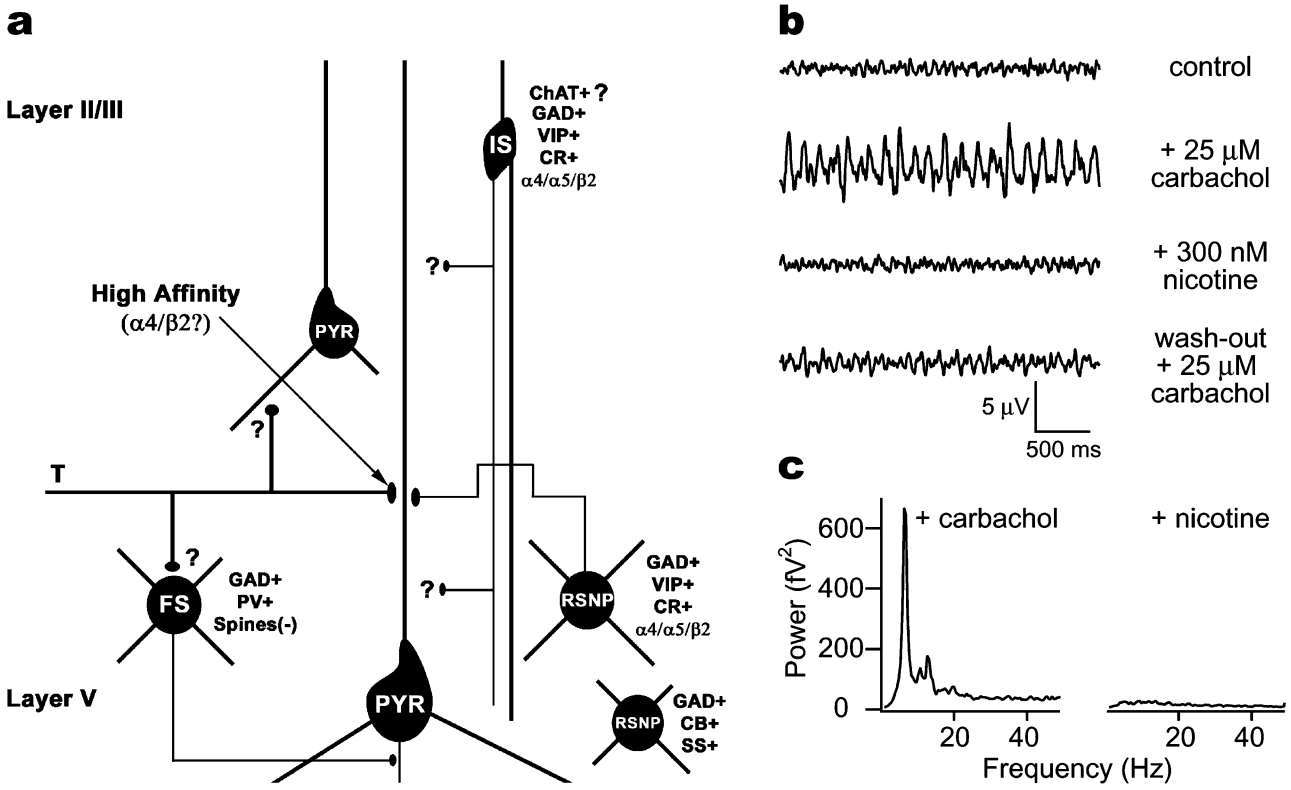

Fig. 1 Putative prefrontal cortex (PFC) neuronal network model and electrophysiological properties. **a** Cells are designated by electrophysiological profile on the soma as (*PYR*) pyramidal, regular-spiking nonpyramidal (*RSNP*), irregular spiking (*IR*), or fast spiking (*FS*). Putative connections of thalamic inputs (*T*) and interneurons to layer V pyramidal neurons are indicated by "*?*". In other cortical areas, FS cells make axoaxonic synapses whereas RSNP tend to contact dendrites. Expression of mRNA is denoted in text next to soma as vasoactive intestinal protein (*VIP*), somatostatin (*SS*), calretinin (*CR*), calbindin (CB), parvalbumin (*PV*), glutamic acid decarboxylase (*GAD*), nAChRs, and ChAT (choline acetyl transferase). Cells or connections with known nAChR expression are denoted by *arrows* and appropriate text. **b** Example traces of extracellular field recordings in deep layers of rat mPFC. From 3-week-old Wistar rat, coronal slices (450-μm thickness) of mPFC (infralimbic and prelimbic PFC) were prepared and extracellular recordings started after 1 h of incubation at room temperature (oxygenated ACSF containing 2 mM $CaCl_2$ and 2 mM $MgCl_2$). In control solution, no rhythmic activity was seen. Both application of the cholinergic agonist carbachol (25 μM) induced oscillatory activity, which was abolished when nicotine (10 μM) was applied in the presence of carbachol (n=8). After washout of nicotine, carbachol partially restored oscillatory activity. **c** Power spectra of carbachol-induced oscillations and after nicotine application. Note the peaks at 6–13 Hz in carbachol, which were absent in the presence of nicotine

nicotine-induced ACh release independent of release from cholinergic terminals that originate from lower brain areas. Because the PFC is implicated in behavioral sensitization (see below), intrinsic properties of cholinergic interneurons and ACh release in the PFC could also be modified during behavioral sensitization, as we found in the NAc (de Rover et al. 2004).

Figure 1a shows a putative rodent PFC circuitry and locations of nAChRs as found in the PFC (Alkondon et al. 2000; Lambe et al. 2003; Metherate 2004) and other cortical areas. Note that functional connections and projection areas of interneurons are currently unknown, as well as whether interneurons express nAChRs or not. Also, which PFC layers, let alone which neurons, in rodents express α7 nAChRs is not known.

Nicotinic ACh receptors and synaptic plasticity in VTA

In recent years, several studies in different brain areas have revealed that effects of nicotine or ACh on synaptic connections within neuronal networks can outlast nAChR stimulation and desensitization (Dani et al. 2001; Ji et al. 2001; Mansvelder et al. 2002; Mansvelder and McGehee 2000). Long-term modulation of glutamatergic and GABAergic synaptic connections adds another level of complexity to nicotinic modulation of neuronal networks. This will be shortly illustrated with results obtained on nicotinic modulation of reward areas. More extensive reviews on nicotinic modulation of VTA circuitry have appeared elsewhere (Fagen et al. 2003; Mansvelder et al. 2003; Mansvelder and McGehee 2002).

During initial phases of exposure to drugs of abuse and the acquisition of addiction, neuronal networks in brain areas involved in reward, such as the VTA, NAc, and PFC, undergo strong adaptations that lead to behavioral sensitization (Vanderschuren and Kalivas 2000). Lesioning dorsomedial PFC prevented the expression of cocaine sensitization in rats (Pierce et al. 1998; Yoshikawa et al. 1993), and blocking dopamine receptors, specifically in medial PFC (mPFC), prevented behavioral as well as neurochemical sensitization to cocaine (Beyer and Steketee

2002). Recently, it has become clear that drugs of abuse have lasting effects on VTA and NAc glutamatergic synapses (Mansvelder et al. 2002; Mansvelder and McGehee 2000; Saal et al. 2003; Thomas et al. 2001; Ungless et al. 2001). Given the executive functions the PFC has in behavior, which play an important role in the development of addiction (Everitt et al. 2001; Robbins and Everitt 1999), studies need to be performed that address lasting changes in PFC neuronal network that could underlie nicotine addiction.

In the VTA, nAChRs are expressed on dopamine neurons, GABA neurons, and glutamatergic terminals (Champtiaux et al. 2002; Charpantier et al. 1998; Klink et al. 2001; Mansvelder et al. 2002; Mansvelder and McGehee 2000; Pidoplichko et al. 1997, 2004). VTA dopamine neurons express three pharmacologically identifiable nAChRs, one that is likely a homomeric α7 nAChR and two that do not contain the α7 subunit. A majority of DA neurons express nAChRs that can be blocked by mecamylamine (MEC), whereas less than half of the DA neurons express α7 nAChRs (Klink et al. 2001; Pidoplichko et al. 1997, 2004; Wooltorton et al. 2003). GABA neurons in the VTA express a similar variety of nAChR subunits. As with dopamine neurons, only a minority of GABA neurons express α7 nAChRs (Wooltorton et al. 2003). Most of the VTA GABA neurons express nAChRs that most likely contain α4 and β2 subunits, which are blocked by dihydro-β-erythroidine (DHβE) (Mansvelder et al. 2002).

Glutamatergic transmission onto DA neurons is enhanced by activation of presynaptic nAChRs (Jones and Wonnacott 2004; Mansvelder and McGehee 2000). Interestingly, cholinergic synaptic terminals were not in close vicinity to glutamatergic terminals expressing α7-containing nAChR, consistent with a "volume" mode of cholinergic signaling (Descarries et al. 1997; Jones and Wonnacott 2004; Zoli et al. 1999). When nicotine arrives in the VTA, it stimulates glutamatergic terminals as well as dopamine neurons, thereby favoring conditions of pre- and postsynaptic paired activation and a Hebbian type of synaptic plasticity. Nicotine-induced pairing resulted in long-term potentiation (LTP) of glutamatergic inputs (Mansvelder and McGehee 2000). Nicotine also induced LTP in vivo measured as an increase in AMPA/NMDA receptor ratio (Saal et al. 2003). Together, these findings suggest that synaptic plasticity in the VTA may be induced after smoking a single cigarette and most likely underlies the persistent effects of the drug on dopamine release in the NAc and PFC.

The α7-containing nAChRs involved in this mechanism are not desensitized significantly by low nicotine concentrations associated with tobacco smoking (Mansvelder et al. 2002; Wooltorton et al. 2003). However, the non-α7 nAChRs on GABA neurons undergo rapid desensitization within minutes after the start of nicotine exposure, and as a consequence, reduced the inhibitory input to the dopamine neurons (Mansvelder et al. 2002; Wooltorton et al. 2003). Desensitization GABA neuron nAChRs not only prevents further activation by nicotine, it also precludes the contribution of these receptors to endogenous cholinergic transmission (Mansvelder et al. 2002). Thereby, VTA dopamine neurons are disinhibited by desensitization of non-α7 type nAChRs (Mansvelder et al. 2002). Despite their rapid desensitization properties, it was shown by using genetically engineered mice lacking β2 subunits (Picciotto et al. 1998) or expressing α4 subunits hypersensitive to nicotine (Tapper et al. 2004) that these subunits are very important for nicotine addiction.

Nicotinic ACh receptors and synaptic plasticity in other brain areas

Currently, it is unknown whether long-term modulation of synaptic connections by nicotine occurs within the PFC. As a matter of fact, data on long-term modulation of synaptic contacts by nicotine anywhere in the neocortex are lacking. However, nicotine does modulate synaptic plasticity in brain areas other than the VTA. In rat spinal cord, the α7 subunit containing nAChR affects the induction of synaptic plasticity (Genzen and McGehee 2003). In the absence of nicotine, pairing of pre- and postsynaptic activity in dorsal horn neurons induces LTP in some of the neurons. With nicotine, the prevalence of LTP induction was enhanced. In the hippocampus, in a minority of the glutamatergic synapses, nicotine induces LTP by itself, but in most of the glutamatergic synapses, nicotine modulates the induction of synaptic plasticity (Fujii et al. 1999; Ji et al. 2001; Mann and Greenfield 2003). Activation of postsynaptic nAChRs on CA1 pyramidal neurons can boost short-term plasticity into LTP in Schaffer collateral synapses (Ji et al. 2001). Activating nAChRs on interneurons that synapse on pyramidal neurons can prevent LTP in glutamatergic synapses (Ji et al. 2001). Thus, timing and localization of nAChR activity in the hippocampus can determine whether LTP will occur or not. These types of nicotinic mechanisms on LTP induction may contribute to the well-known effects of nicotine on learning and memory. Because CA1 pyramidal neurons in the ventral hippocampus project to the PFC (Jay and Witter 1991), modulation of synaptic plasticity in the CA1 area by nicotine may participate in the effects of nicotine on attention performance.

In developing immature hippocampus, nicotinic receptors containing α7 subunits can activate "silent" synapses that show a low probability of being active and turn them into high probability synapses (Maggi et al. 2003). Schaffer collateral to CA1 synapses that have a high probability of being active during development can be down-regulated by α7- and β2-containing nAChRs (Maggi et al. 2004). These findings suggest that nicotinic receptors also can play a role during postnatal development of excitatory glutamatergic connections and can contribute to shaping the hippocampal neuronal circuitry.

Effect of nicotine on neuronal networks: brain slices

Alterations in neuronal network properties by nicotinic modulation of excitatory and inhibitory neurons will result in changes in overall network activity, which ultimately underlies the alterations in cognitive performance observed with nicotine. Neuronal network activity can be studied in brain slices in vitro but can also be measured in EEG recordings in vivo. In both cases, a summation of excitatory and inhibitory currents following synaptic transmission in cortical or hippocampal networks is monitored. When both excitatory and inhibitory activities occur in an alternate synchronized fashion, electrical oscillations are observed (Buhl et al. 1998; Cobb et al. 1995; Fisahn et al. 1998; Traub et al. 1999; Whittington et al. 1995). In the hippocampus, fast network oscillations can result from recurrent synaptic feedback loops between pyramidal neurons and fast-spiking interneurons that target perisomatic regions of pyramidal neurons (Mann and Paulsen 2005; Mann et al. 2005). These GABAergic interneurons can provide rhythmic inhibition in pyramidal neurons, and they are synchronized by recurrent excitation. Pyramidal neurons and interneurons will fire action potentials phase-locked to the field oscillations, but at different phases of the oscillation. As a result, inhibitory and excitatory synaptic potentials will also occur time-locked to the field oscillation (Fisahn et al. 1998). Therefore, the location of nAChRs in these synaptically connected loops of neurons is going to determine how network oscillations are affected by nicotine. For instance, activation of nAChRs on fast-spiking interneurons could increase the excitability of these neurons such that they start to fire with shorter intervals. This may increase the frequency of field oscillations or increase the likelihood that the network starts to oscillate due to postinhibitory rebound activity in pyramidal neurons. However, the opposite outcome could also be imagined. If increased excitability of GABAergic interneurons occurs to the extent that pyramidal neurons can no longer escape synaptic inhibition, oscillatory network activity might be suppressed.

A human EEG can show synchronous network activity of multiple frequencies and different duration, both short bursts of synchronous activity such as high-voltage spindles (HVSs), as well as stable baseline oscillations. Various behavioral states such as arousal and cognitive activity are correlated with specific frequency bands in EEGs. In awake cats, for instance, 35–45 Hz (gamma-band) activity occurs during focused attention (Bouyer et al. 1987).

Electrical oscillations in field potential recordings are also observed in brain slices. From in vitro experiments, it became apparent that synchronized activity by networks of interneurons as well as by networks of pyramidal neurons drives oscillations (Beierlein et al. 2000; Blatow et al. 2003; Fisahn et al. 1998; Traub et al. 1999; Whittington et al. 1995). In vitro experiments enable the study of neuronal and synaptic mechanisms that underlie nicotinic modulation of network synchronization and oscillations that potentially correspond to cognitive states in vivo. Oscillations can be induced in brain slices by metabotropic glutamate receptor (mGluR) agonists, such as DHPG, and muscarinic agonists (Buhl et al. 1998; Fisahn et al. 1998; Whittington et al. 1995). Current studies in our laboratory indicate that this also applies to rat mPFC slices (Fig. 1b, c). Interestingly, during visual attention tasks, ACh release in the mPFC increases (Passetti et al. 2000), suggesting that cholinergic signaling, network oscillations, and attention are correlated.

Whether nicotine induces network oscillations by itself is not settled. One study reported that nicotine did not induce hippocampal oscillations (Williams and Kauer 1997), but recently, it was suggested that nicotine may be able to induce oscillations in the hippocampus (Murray et al. 2003). Part of these oscillations could be blocked by the muscarinic antagonist atropine, but slow rhythmic activity was atropine insensitive. In a preliminary set of experiments, we find that 300 nM nicotine suppresses carbachol-induced oscillations (6–13 Hz) in brain slices of rat mPFC (n=5; Fig. 1b, c), in line with nicotinic effects on rodent EEG (see below). It will be interesting to find out what mechanisms underlie this reduction of network oscillations and to investigate whether network oscillations induced by mGluR agonists instead of carbachol could be affected differently by nicotine.

Effect of nicotine on neuronal networks: EEG

Analysis of EEG data shows that specific frequency bands are correlated with different behavioral states. Delta and theta oscillations are prominent during slow-wave sleep (delta<4 Hz, theta 4–7 Hz), alpha oscillations are associated with relaxed wakefulness often recorded with the subject's eyes closed (alpha 8–14 Hz), and beta and gamma oscillations are seen during intense mental activity (beta 14–30 Hz, gamma 30–90 Hz). Administration of nicotine through cigarettes or dermal patches modulates cortical activity in EEG recordings. In both naive subjects (Foulds et al. 1994) and smoking subjects that abstained from smoking for several hours (Kadoya et al. 1994; Lindgren et al. 1999; Roth and Battig 1991), nicotine induced an acceleration of synchronized cortical activity with an increase of the dominant frequency in the alpha band. The power of lower frequency bands decreased (Kadoya et al. 1994; Lindgren et al. 1999). In rat EEG studies, moderate to high doses of nicotine (0.2–0.4 mg/kg s.c.) decreased not only the power of lower frequency bands theta and delta, but also beta frequencies (Ferger and Kuschinsky 1997). This is partly consistent with human EEG data (Kadoya et al. 1994; Lindgren et al. 1999), but changes in alpha frequencies were not addressed. Possibly, concentration profiles of nicotine reached in the brain when administered by patch or smoking in humans are different from subcutaneous injection in rats. However, in rat mPFC slices, oscillations are also reduced by low concentrations of nicotine (Fig. 1b, c).

It is also clear now that the effects of quitting smoking on EEG activation and attention may last for several weeks and are likely to be more severe with, for instance, stress

(Gilbert et al. 2004). Thus, whereas nicotine abstinence was shown to be associated with decreases in cognitive performance, and EEG activation, these effects of quitting did not show any tendency to resolve across 31 days of abstinence. Moreover, EEG deactivation and heart rate slowing were greater during a math task (high stress) than during relaxation (low stress). Finally, individuals high in traits for depression or nicotine dependence experienced greater EEG deactivation following abstinence, especially in the right hemisphere during the stressful task. The latter alludes to the fact that individual differences may exist in humans, and that a prior history of smoking may clearly affect future therapeutic perspectives when it comes to considering nicotinic treatment of human pathologies (Harris et al. 2004; Newhouse et al. 2004).

In addition to its effects on sustained oscillations in EEG, nicotine also affects HVSs observed in both rat and human frontal cortex, which are believed to be important for information storage (Contreras et al. 1997; Jakala et al. 1997). HVSs are bursts of 6–12 Hz oscillations lasting for approximately 0.5–3 s. They occur most often during slow-wave sleep, low arousal, and low vigilant states (drowsiness) and are virtually absent in awake states (Buzsaki et al. 1990; Contreras et al. 1997; Gais et al. 2002). Injection of nicotine suppresses the duration and frequency of HVS occurrence in rodents (Radek 1993; Riekkinen et al. 1993). Lesioning of cholinergic inputs to the cortex from the basal nucleus increases HVS (Bringmann 1996; Riekkinen et al. 1992) as occurs during natural cholinergic cell loss during aging (Riekkinen et al. 1992). In humans, declarative learning tasks lead to an increase in HVS in frontal cortex during slow-wave sleep, believed to be important for consolidation of declarative memories. Interestingly, human subjects injected with a cholinesterase inhibitor before sleep showed no consolidation of declarative memories (Gais and Born 2004; Gais et al. 2002), suggesting that ACh levels need to be low for memory consolidation. Thus, elevated levels of nicotine in a smoker's blood stream during sleep may be unfavorable for memory consolidation. Because spindle-like oscillations can also be recorded in brain slices (Jacobsen et al. 2001; Tancredi et al. 2000), this preparation could serve to investigate the neuronal mechanisms underlying nicotine's effect on HVS and memory consolidation.

Nicotinic receptor subtypes underlying nicotinic modulation of cognition in rodents

Endogenous cholinergic signaling in the PFC is important to cognitive processing. When α7-selective antagonist αBTX (McGehee and Role 1995; Seguela et al. 1993) or β2-selective antagonist DHβE (Alkondon and Albuquerque 1993; Luetje et al. 1990; McGehee and Role 1995) are injected into the prelimbic area of rat PFC, delayed response tasks requiring effortful processing for response selection are hampered, whereas general working memory and memory processes are unimpaired (Granon et al. 1995). Thus, although nAChR activation in sensory cortical brain areas may contribute to improved behavioral performance in sensory-cognitive tasks by enhancing sensory responsiveness (Metherate 2004), the endogenous nAChR activation in the PFC of rats appears to distinctly control executive functions. This was confirmed in studies where cholinergic transmission in the mPFC was reduced by injection of the cholinergic immunotoxin 192 IgG-saporin (SAP) (McGaughy et al. 2002). In the *five-choice serial reaction time task* (5-CSRTT), a behavioral paradigm that tests for attention performance, rats injected with SAP and reduced ACh efflux in the medial frontal cortex showed impaired attentional function (McGaughy et al. 2002).

As rats, mice may also show complex behaviors geared toward far-removed goals, which depend primarily on PFC function. The effects of endogenous activation of nicotinic transmission in this species have been assessed by means of genetic deletion of β2-containing nAChR (Granon et al. 2003). It was found that PFC-based cognitive functions in these mutant mice, such as spatiotemporal organization of locomotor behavior, together with conflict resolution and social interactions, were clearly affected and dissociated from unimpaired memory and anxiety. Because the behavior of β2-mutant mice resembled that exhibited by rats with lesions of the prefrontal (and cingulate) cortex, it seems that endogenous activation of nAChR in the PFC in rodents is involved in supervisory planning of locomotor and conflict resolution behavior.

In contrast to endogenous activation of nAChRs in the PFC, the behavioral effects of exogenous activation of nAChRs in PFC have been more difficult to assess. After intracranial microinfusion of nicotine in the mPFC, rats showed an improved performance via an increase in accuracy in the 5-CSRTT. Moreover, this effect appeared to be PFC specific because injections in hippocampus showed no effect (Hahn et al. 2003). However, in another study, intraperitoneal injections of nicotine decreased reaction time and increased anticipatory responses in the 5-CSRTT, but showed no effect on accuracy (Blondel et al. 1999). These differences could result from subtle variations in the behavioral paradigm such as stimulus duration. The effects of nicotine in the 5-CSRTT were antagonized by the nonselective nAChR antagonist MEC and β2-selective DHβE, but not by methyllycaconitine (MLA, more selective for α7-containing nAChRs) (Blondel et al. 2000), which may suggest that α7-containing nAChRs are less likely to mediate these behavioral effects of exogenous nicotine (but see below). Although effects of nicotine on other cognitive tasks have been reported, nicotine improvement of tasks assessing attentional performance are most consistently seen (Blondel et al. 1999, 2000). Also, in mice tested in a modified version of the 5-CSRTT with graded levels of difficulty, it was found that nicotine produced a consistent reduction in the level of omissions and thus a demonstrable improvement in attention behavior (Young et al. 2004). Thus, sustained attention behavior in rodents, which includes proper target detection, time-related performance, and appropriate reaction time of higher order cognitive processing, is likely to improve both in acute as well as in chronic nicotine treatment paradigms.

One problem faced when identifying nAChR subtypes underlying the beneficial effects of nicotine on sustained attention is the current lack of truly selective compounds and difficulties of producing more nAChR subtype-specific drugs. Hence, various laboratories have recently taken a transgenic approach to delineate the nAChR receptor subtypes involved in PFC-based cognition (Cordero-Erausquin et al. 2000). In a hallmark study in this respect, Young et al. (2004) examined the performance of α7 nAChR knockout mice in the 5-SCRTT and found that these mutants not only acquired the task more slowly than their wild-type littermates, but on attained asymptotic performance, they also exhibited a higher level of omissions. Even in a simpler version of 5-SCRTT, the α7 knockout mice performed less well (Young et al. 2004). Importantly, these mice were previously shown to behave normally in a number of other behavioral tests, including contextual and fear conditioning, spatial memory, and anxiety tests (Paylor et al. 1998).

Several studies have previously indicated that α7 nAChRs may be crucial in attention performance, and more specifically, in sensory gating (Martin et al. 2004). Schizophrenic patients and their unaffected relatives show reduced auditory gating. Genetic analysis shows that this was linked to chromosome 15q14, in a region proximal to the α7 locus. However, studies on α7 nAChR-mediated improvement of sensory gating in animal models for schizophrenia clearly show that this aspect of the attention phenotype is not located in the PFC but rather in the hippocampus (Martin et al. 2004). DBA/2 inbred mice, which display a reduced α7 nAChR density in CA3, show sensory gating deficits that can be ameliorated with partial α7 agonists (Stevens et al. 1996, 1998). Surprisingly, α7 nAChR knockout mice did not show any sensory gating deficits in a prepulse inhibition model (Paylor et al. 1998). Although the test used by Paylor et al. (1998) is different from that used in Stevens' studies, to date, there is no satisfying explanation for the discrepancy in outcome. Possibly, compensatory mechanisms, such as alterations in nAChR density, distribution, and/or subtype, may account for different results between pharmacological studies and genetic mutant mice studies (Young et al. 2004).

Nicotinic receptor subtypes underlying nicotinic modulation of cognition in primates and humans

The distribution of nicotine binding in monkeys corresponds broadly to the patterns observed in rodents, but the distribution of the binding sites for αBTX appears larger in the brains of rhesus monkeys than in rodent brains, suggesting a more important role of α7 receptors in primates (Han et al. 2003). αBTX binding was dense in layer I of most cortical areas, and a moderate labeling was found in layers V and VI of the prefrontal and other frontal cortices (Han et al. 2003). Also, in monkeys, nicotine and other agonists of nAChRs improve cognitive performance, in particular, visual recognition memory (Katner et al. 2004). In rhesus monkeys trained to perform a battery of six behavioral tasks, nicotine improved performance on tests that assay visual recognition memory, spatial working memory, and visuospatial associative memory. MEC impaired visuospatial associative memory (Katner et al. 2004). Further, ballistic and fine motor performance was not significantly improved by nicotine, although fine motor performance appeared impaired by MEC. It was not investigated further to which extent nAChR activation in PFC was specifically involved in this study, but visual recognition is likely to involve frontal cortices.

Monkeys that have previously received a chronic low dose of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) may develop attentional deficits, and it has been reported that SIB-1553A, a novel agonist with selectivity for β4-containing nAChRs, may counteract this type of cognitive deficit (Schneider et al. 2003). It is of particular interest that at lower doses, SIB-1553A appeared more effective in improving attentional deficits in monkeys associated with chronic MPTP exposure, whereas at higher doses, SIB-1553A appeared to effectively improve both attentional and memory performances (Schneider et al. 2003). As in rodents, various types of cognitive brain functions appear to also be under control of nAChRs in the primate PFC. However, although some attention functions were tested, albeit under extreme circumstances (Schneider et al. 2003), it is less clear to what extent sustained attention behavior is affected by nAChR activation in this species. Moreover, the putative predominant involvement of one particular α-subunit nAChR subtype at present cannot be confirmed.

A major challenge in mechanistically understanding nicotinic actions on cognition is to pinpoint nAChR location in neuronal networks. At present, it is unknown where in the PFC the α7-containing nAChRs that facilitate sustained attention behavior may be localized. Many options are open. The effects could be mediated by α7-containing nAChRs on interneurons in the PFC, as has been shown in other cortical areas both in rodents and human ortex (Alkondon and Albuquerque 2004; Alkondon et al. 2000). Interestingly, α7 nAChR immunoreactivity in the PFC of patients with schizophrenia may be reduced, whereas α4, α3, or α2 immunoreactivity or α7 mRNA expression appeared comparable to those observed in unaffected subjects (Martin-Ruiz et al. 2003). Alternatively, α7 nAChR involved in sustained attention could be located on corticocortical efferent terminals in the PFC. Then again, the effects could be less direct. For instance, α7-containing nAChRs are abundantly present in the VTA, as described above (Jones and Wonnacott 2004; Klink et al. 2001; Mansvelder and McGehee 2000; Pidoplichko et al. 1997). Activation of these receptors increases firing rates of dopamine and GABA neurons, some of which project to the PFC, thereby potentially altering PFC function. Further research will have to target these types of questions.

Non-α7 nAChRs may be involved in nicotinic effects on attention. In a recent mutational analysis study of the nAChR α4 subunit gene in a cohort of human subjects with

ADHD, a significant association was found for a 5′ intron 2 single nucleotide polymorphism of the α4 gene and severe attention problems. The location of the polymorphism was compatible with pre-mRNA instability or splicing (Todd et al. 2003). The latter may imply that genetically distinct subtypes of ADHD may exist and that attention problems in these patients in the future may be treated with α4-selective agonists.

Conclusion and future directions

The primary focus of this review was to address neuronal network mechanisms underlying nicotinic modulation of PFC function. An understanding of the role of nAChRs in PFC function requires the integration of information on different subtypes of nAChRs, their location, and how their activation affects neuronal circuitries. Much fundamental data on the PFC neuronal circuitry and nicotinic modulation thereof are currently lacking. For instance, what interneuron types present and what physiological characteristics they have are only extensively studied in certain areas of the rodent frontal cortex (Gabbott et al. 1997, 2003; Kawaguchi and Kondo 2002). Very little is known about how the circuitry is synaptically wired (Gabbott et al. 2003). This is of major importance for understanding the impact of nAChR location on the network. Very few studies have reported on the short-term or long-term consequences of nAChR activation on PFC function, and in particular, its neuronal network circuitry processing. This is surprising because in our view, this will be essential for understanding the role of nAChR in cognitive behavior in rodents, primates, and humans.

The involvement of specific nAChR subtypes in cognition is important and receives much attention because of the potential benefits of nicotine in treating human pathology (Levin 2002). In brain areas other than the PFC, such as hippocampus and VTA, much progress has been made in recent years to pinpoint the location of nAChRs and to tease out the acute and longer lasting effects of nicotine on the microcircuitry. For nicotinic effects on sustained attention behavior, synaptic mechanisms in the PFC are likely to be crucial. Also here, novel transgenic animal models, especially inducible and cell-type-specific knockouts are currently necessary to facilitate addressing these questions in the future. Little data are available linking cellular and synaptic effects of nicotine to neuronal network functioning and synchronized activity, which ultimately underlies cognition. We believe that understanding mechanisms underlying synchronized neuronal network activity and understanding cellular and synaptic mechanisms responsible for nicotinic modulation of this network activity will be instrumental for understanding nicotine's effect on cognition. Studying neuronal network oscillations and cellular mechanisms in brain slices may contribute to start bridging the knowledge gap between nAChR activation and nicotinic effects on EEG signals.

Acknowledgements The authors thank Dr. Ole Paulsen for critically reading the manuscript and Dr. Lorna Role for discussions. This work was supported by grants from the Netherlands Royal Academy of Sciences (HDM) and Netherlands Organization for Scientific Research (NWO) (HDM, ABB).

References

Alkondon M, Albuquerque EX (1993) Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons. I. Pharmacological and functional evidence for distinct structural subtypes. J Pharmacol Exp Ther 265:1455–1473

Alkondon M, Albuquerque EX (2004) The nicotinic acetylcholine receptor subtypes and their function in the hippocampus and cerebral cortex. Prog Brain Res 145:109–120

Alkondon M, Pereira EF, Barbosa CT, Albuquerque EX (1997) Neuronal nicotinic acetylcholine receptor activation modulates gamma-aminobutyric acid release from CA1 neurons of rat hippocampal slices. J Pharmacol Exp Ther 283:1396–1411

Alkondon M, Pereira EF, Eisenberg HM, Albuquerque EX (1999) Choline and selective antagonists identify two subtypes of nicotinic acetylcholine receptors that modulate GABA release from CA1 interneurons in rat hippocampal slices. J Neurosci 19:2693–2705

Alkondon M, Pereira EF, Eisenberg HM, Albuquerque EX (2000) Nicotinic receptor activation in human cerebral cortical interneurons: a mechanism for inhibition and disinhibition of neuronal networks. J Neurosci 20:66–75

Ascioglu M, Dolu N, Golgeli A, Suer C, Ozesmi C (2004) Effects of cigarette smoking on cognitive processing. Int J Neurosci 114:381–390

Audet MA, Doucet G, Oleskevich S, Descarries L (1988) Quantified regional and laminar distribution of the noradrenaline innervation in the anterior half of the adult rat cerebral cortex. J Comp Neurol 274:307–318

Audet MA, Descarries L, Doucet G (1989) Quantified regional and laminar distribution of the serotonin innervation in the anterior half of adult rat cerebral cortex. J Chem Neuroanat 2:29–44

Avendano C, Umbriaco D, Dykes RW, Descarries L (1996) Acetylcholine innervation of sensory and motor neocortical areas inadult cat: a choline acetyltransferase immunohistochemical study. J Chem Neuroanat 11:113–130

Barazangi N, Role LW (2001) Nicotine-induced enhancement of glutamatergic and GABAergic synaptic transmission in the mouse amygdala. J Neurophysiol 86:463–474

Beierlein M, Gibson JR, Connors BW (2000) A network of electrically coupled interneurons drives synchronized inhibition in neocortex. Nat Neurosci 3:904–910

Beyer CE, Steketee JD (2002) Cocaine sensitization: modulation by dopamine D2 receptors. Cereb Cortex 12:526–535

Blatow M, Rozov A, Katona I, Hormuzdi SG, Meyer AH, Whittington MA, Caputi A, Monyer H (2003) A novel network of multipolar bursting interneurons generates theta frequency oscillations in neocortex. Neuron 38:805–817

Blondel A, Simon H, Sanger DJ, Moser P (1999) The effect of repeated nicotine administration on the performance of drug-naive rats in a five-choice serial reaction time task. Behav Pharmacol 10:665–673

Blondel A, Sanger DJ, Moser PC (2000) Characterisation of the effects of nicotine in the five-choice serial reaction time task in rats: antagonist studies. Psychopharmacology (Berl) 149:293–305

Bouyer JJ, Montaron MF, Vahnee JM, Albert MP, Rougeul A (1987) Anatomical localization of cortical beta rhythms in cat. Neuroscience 22:863–869

Bringmann A (1996) Behaviour-related effects of nicotine on slow EEG waves in basal nucleus-lesioned rats. Naunyn Schmiedebergs Arch Pharmacol 353:168–174

Buhl EH, Tamas G, Fisahn A (1998) Cholinergic activation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. J Physiol 513:117–126
Burnashev N (1998) Calcium permeability of ligand-gated channels. Cell Calcium 24:325–332
Burnashev N, Zhou Z, Neher E, Sakmann B (1995) Fractional calcium currents through recombinant GluR channels of the NMDA, AMPA and kainate receptor subtypes. J Physiol 485(Pt 2):403–418
Buzsaki G, Laszlovszky I, Lajtha A, Vadasz C (1990) Spike-and-wave neocortical patterns in rats: genetic and aminergic control. Neuroscience 38:323–333
Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12:1–47
Cauli B, Audinat E, Lambolez B, Angulo MC, Ropert N, Tsuzuki K, Hestrin S, Rossier J (1997) Molecular and physiological diversity of cortical nonpyramidal cells. J Neurosci 17:3894–3906
Champtiaux N, Han ZY, Bessis A, Rossi FM, Zoli M, Marubio L, McIntosh JM, Changeux JP (2002) Distribution and pharmacology of alpha 6-containing nicotinic acetylcholine receptors analyzed with mutant mice. J Neurosci 22:1208–1217
Charpantier E, Barneoud P, Moser P, Besnard F, Sgard F (1998) Nicotinic acetylcholine subunit mRNA expression in dopaminergic neurons of the rat substantia nigra and ventral tegmental area. NeuroReport 9:3097–3101
Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 378:75–78
Contant C, Umbriaco D, Garcia S, Watkins KC, Descarries L (1996) Ultrastructural characterization of the acetylcholine innervation in adult rat neostriatum. Neuroscience 71:937–947
Contreras D, Destexhe A, Sejnowski TJ, Steriade M (1997) Spatiotemporal patterns of spindle oscillations in cortex and thalamus. J Neurosci 17:1179–1196
Cordero-Erausquin M, Marubio LM, Klink R, Changeux JP (2000) Nicotinic receptor function: new perspectives from knockout mice. Trends Pharmacol Sci 21:211–217
Coull JT (1998) Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol 55:343–361
Couturier S, Bertrand D, Matter JM, Hernandez MC, Bertrand S, Millar N, Valera S, Barkas T, Ballivet M (1990) A neuronal nicotinic acetylcholine receptor subunit (alpha 7) is developmentally regulated and forms a homo-oligomeric channel blocked by alpha-BTX. Neuron 5:847–856
Dajas-Bailador F, Wonnacott S (2004) Nicotinic acetylcholine receptors and the regulation of neuronal signalling. Trends Pharmacol Sci 25:317–324
Dani JA, Ji D, Zhou FM (2001) Synaptic plasticity and nicotine addiction. Neuron 31:349–352
de Rover M, Lodder JC, Kits KS, Schoffelmeer AN, Brussaard AB (2002) Cholinergic modulation of nucleus accumbens medium spiny neurons. Eur J Neurosci 16:2279–2290
de Rover M, Mansvelder HD, Lodder JC, Wardeh G, Schoffelmeer AN, Brussaard AB (2004) Long-lasting nicotinic modulation of GABAergic synaptic transmission in the rat nucleus accumbens associated with behavioural sensitization to amphetamine. Eur J Neurosci 19:2859–2870
Descarries L, Mechawar N (2000) Ultrastructural evidence for diffuse transmission by monoamine and acetylcholine neurons of the central nervous system. Prog Brain Res 125:27–47
Descarries L, Gisiger V, Steriade M (1997) Diffuse transmission by acetylcholine in the CNS. Prog Neurobiol 53:603–625
Drisdel RC, Green WN (2000) Neuronal alpha-bungarotoxin receptors are alpha7 subunit homomers. J Neurosci 20:133–139
Ernst M, Heishman SJ, Spurgeon L, London ED (2001) Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 25:313–319
Everitt BJ, Robbins TW (1997) Central cholinergic systems and cognition. Annu Rev Psychol 48:649–684
Everitt BJ, Dickinson A, Robbins TW (2001) The neuropsychological basis of addictive behaviour. Brain Res Brain Res Rev 36:129–138
Fagen ZM, Mansvelder HD, Keath JR, McGehee DS (2003) Short- and long-term modulation of synaptic inputs to brain reward areas by nicotine. Ann N Y Acad Sci 1003:185–195
Ferger B, Kuschinsky K (1997) Biochemical studies support the assumption that dopamine plays a minor role in the EEG effects of nicotine. Psychopharmacology (Berl) 129:192–196
Fisahn A, Pike FG, Buhl EH, Paulsen O (1998) Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. Nature 394:186–189
Fisher JL, Pidoplichko VI, Dani JA (1998) Nicotine modifies the activity of ventral tegmental area dopaminergic neurons and hippocampal GABAergic neurons. J Physiol Paris 92:209–213
Foulds J, McSorley K, Sneddon J, Feyerabend C, Jarvis MJ, Russell MA (1994) Effect of subcutaneous nicotine injections of EEG alpha frequency in non-smokers: a placebo-controlled pilot study. Psychopharmacology (Berl) 115:163–166
Frazier CJ, Rollins YD, Breese CR, Leonard S, Freedman R, Dunwiddie TV (1998) Acetylcholine activates an alpha-bungarotoxin-sensitive nicotinic current in rat hippocampal interneurons, but not pyramidal cells. J Neurosci 18:1187–1195
Fucile S (2004) Ca2+ permeability of nicotinic acetylcholine receptors. Cell Calcium 35:1–8
Fujii S, Ji Z, Morita N, Sumikawa K (1999) Acute and chronic nicotine exposure differentially facilitate the induction of LTP. Brain Res 846:137–143
Fuster JM (2000a) Executive frontal functions. Exp Brain Res 133: 66–70
Fuster JM (2000b) Prefrontal neurons in networks of executive memory. Brain Res Bull 52:331–336
Gabbott PL, Dickie BG, Vaid RR, Headlam AJ, Bacon SJ (1997) Local-circuit neurones in the medial prefrontal cortex (areas 25, 32 and 24b) in the rat: morphology and quantitative distribution. J Comp Neurol 377:465–499
Gabbott PL, Warner TA, Jays PR, Bacon SJ (2003) Areal and synaptic interconnectivity of prelimbic (area 32), infralimbic (area 25) and insular cortices in the rat. Brain Res 993:59–71
Gais S, Born J (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc Natl Acad Sci U S A 101:2140–2144
Gais S, Molle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830–6834
Genzen JR, McGehee DS (2003) Short- and long-term enhancement of excitatory transmission in the spinal cord dorsal horn by nicotinic acetylcholine receptors. Proc Natl Acad Sci U S A 100:6807–6812
Gil Z, Connors BW, Amitai Y (1997) Differential regulation of neocortical synapses by neuromodulators and activity. Neuron 19:679–686
Gilbert D, McClernon J, Rabinovich N, Sugai C, Plath L, Asgaard G, Zuo Y, Huggenvik J, Botros N (2004) Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. Nicotine Tob Res 6:249–267
Gioanni Y, Rougeot C, Clarke PB, Lepouse C, Thierry AM, Vidal C (1999) Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamocortical transmission. Eur J Neurosci 11:18–30
Goldman-Rakic PS (1995) Cellular basis of working memory. Neuron 14:477–485
Gotti C, Clementi F (2004) Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 74:363–396
Granon S, Poucet B, Thinus-Blanc C, Changeux JP, Vidal C (1995) Nicotinic and muscarinic receptors in the rat prefrontal cortex: differential roles in working memory, response selection and effortful processing. Psychopharmacology (Berl) 119:139–144
Granon S, Faure P, Changeux JP (2003) Executive and social behaviors under nicotinic receptor regulation. Proc Natl Acad Sci U S A 100:9596–9601

Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383:713–716

Groenewegen HJ, Uylings HB (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 126:3–28

Hahn B, Shoaib M, Stolerman IP (2003) Involvement of the prefrontal cortex but not the dorsal hippocampus in the attention-enhancing effects of nicotine in rats. Psychopharmacology (Berl) 168:271–279

Han ZY, Zoli M, Cardona A, Bourgeois JP, Changeux JP, Le Novere N (2003) Localization of [3H]nicotine, [3H]cytisine, [3H] epibatidine, and [125I]alpha-bungarotoxin binding sites in the brain of *Macaca mulatta*. J Comp Neurol 461:49–60

Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, Zerbe G, Freedman R (2004) Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 29:1378–1385

Havermans RC, Debaere S, Smulders FT, Wiers RW, Jansen AT (2003) Effect of cue exposure, urge to smoke, and nicotine deprivation on cognitive performance in smokers. Psychol Addict Behav 17:336–339

Hogg RC, Raggenbass M, Bertrand D (2003) Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol 147:1–46

Houser CR, Crawford GD, Salvaterra PM, Vaughn JE (1985) Immunocytochemical localization of choline acetyltransferase in rat cerebral cortex: a study of cholinergic neurons and synapses. J Comp Neurol 234:17–34

Jacobsen RB, Ulrich D, Huguenard JR (2001) GABA(B) and NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. J Neurophysiol 86:1365–1375

Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal JH (2004) Nicotine effects on brain function and functional connectivity in schizophrenia. Biol Psychiatry 55: 850–858

Jakala P, Puolivali J, Bjorklund M, Koivisto E, Riekkinen P Jr (1997) Activation of acetylcholine receptors and 5-HT2 receptors have additive effects in the suppression of neocortical high-voltage spindles in aged rats. Psychopharmacology (Berl) 132: 270–280

Jay TM, Witter MP (1991) Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris-leucoagglutinin*. J Comp Neurol 313:574–586

Ji D, Dani JA (2000) Inhibition and disinhibition of pyramidal neurons by activation of nicotinic receptors on hippocampal interneurons. J Neurophysiol 83:2682–2690

Ji D, Lape R, Dani JA (2001) Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity. Neuron 31:131–141

Jones S, Yakel JL (1997) Functional nicotinic ACh receptors on interneurones in the rat hippocampus. J Physiol 504(Pt 3):603–610

Jones IW, Wonnacott S (2004) Precise localization of alpha7 nicotinic acetylcholine receptors on glutamatergic axon terminals in the rat ventral tegmental area. J Neurosci 24:11244–11252

Kadoya C, Domino EF, Matsuoka S (1994) Relationship of electroencephalographic and cardiovascular changes to plasma nicotine levels in tobacco smokers. Clin Pharmacol Ther 55: 370–377

Katner SN, Davis SA, Kirsten AJ, Taffe MA (2004) Effects of nicotine and mecamylamine on cognition in rhesus monkeys. Psychopharmacology (Berl) 175:225–240

Kawaguchi Y (1993) Groupings of nonpyramidal and pyramidal cells with specific physiological and morphological characteristics in rat frontal cortex. J Neurophysiol 69:416–431

Kawaguchi Y (1995) Physiological subgroups of nonpyramidal cells with specific morphological characteristics in layer II/III of rat frontal cortex. J Neurosci 15:2638–2655

Kawaguchi Y, Kubota Y (1996) Physiological and morphological identification of somatostatin- or vasoactive intestinal polypeptide-containing cells among GABAergic cell subtypes in rat frontal cortex. J Neurosci 16:2701–2715

Kawaguchi Y, Kubota Y (1997) GABAergic cell subtypes and their synaptic connections in rat frontal cortex. Cereb Cortex 7:476–486

Kawaguchi Y, Kondo S (2002) Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. J Neurocytol 31:277–287

Klink R, de Kerchove d'Exaerde A, Zoli M, Changeux JP (2001) Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. J Neurosci 21: 1452–1463

Kumari V, Gray JA, Ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E, Vythelingum GN, Williams SC, Simmons A, Sharma T (2003) Cognitive effects of nicotine in humans: an fMRI study. NeuroImage 19:1002–1013

Lambe EK, Picciotto MR, Aghajanian GK (2003) Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology 28:216–225

Lambert NM, Hartsough CS (1998) Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. J Learn Disabil 31:533–544

Lawrence NS, Ross TJ, Stein EA (2002) Cognitive mechanisms of nicotine on visual attention. Neuron 36:539–548

Lena C, Changeux JP (1997) Role of Ca2+ ions in nicotinic facilitation of GABA release in mouse thalamus. J Neurosci 17:576–585

Lena C, Changeux JP, Mulle C (1993) Evidence for "preterminal" nicotinic receptors on GABAergic axons in the rat interpeduncular nucleus. J Neurosci 13:2680–2688

Levin ED (2002) Nicotinic receptor subtypes and cognitive function. J Neurobiol 53:633–640

Levin ED, Simon BB (1998) Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology (Berl) 138: 217–230

Lindgren M, Molander L, Verbaan C, Lunell E, Rosen I (1999) Electroencephalographic effects of intravenous nicotine—a dose–response study. Psychopharmacology (Berl) 145:342–350

Lohr JB, Flynn K (1992) Smoking and schizophrenia. Schizophr Res 8:93–102

Lu Y, Marks MJ, Collins AC (1999) Desensitization of nicotinic agonist-induced [3H]gamma-aminobutyric acid release from mouse brain synaptosomes is produced by subactivating concentrations of agonists. J Pharmacol Exp Ther 291:1127–1134

Luetje CW, Patrick J, Seguela P (1990) Nicotine receptors in the mammalian brain. FASEB J 4:2753–2760

MacDermott AB, Role LW, Siegelbaum SA (1999) Presynaptic ionotropic receptors and the control of transmitter release. Annu Rev Neurosci 22:443–485

Maggi L, Le Magueresse C, Changeux JP, Cherubini E (2003) Nicotine activates immature "silent" connections in the developing hippocampus. Proc Natl Acad Sci U S A 100: 2059–2064

Maggi L, Sola E, Minneci F, Le Magueresse C, Changeux JP, Cherubini E (2004) Persistent decrease in synaptic efficacy induced by nicotine at Schaffer collateral-CA1 synapses in the immature rat hippocampus. J Physiol 559:863–874

Mann EO, Greenfield SA (2003) Novel modulatory mechanisms revealed by the sustained application of nicotine in the guinea-pig hippocampus in vitro. J Physiol 551:539–550

Mann EO, Paulsen O (2005) Mechanisms underlying gamma ('40 Hz') network oscillations in the hippocampus—a mini-review. Prog Biophys Mol Biol 87:67–76

Mann EO, Suckling JM, Hajos N, Greenfield SA, Paulsen O (2005) Perisomatic feedback inhibition underlies cholinergically induced fast network oscillations in the rat hippocampus in vitro. Neuron 45:105–117

Mansvelder HD, McGehee DS (2000) Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron 27:349–357

Mansvelder HD, McGehee DS (2002) Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol 53:606–617
Mansvelder HD, Keath JR, McGehee DS (2002) Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 33:905–919
Mansvelder HD, De Rover M, McGehee DS, Brussaard AB (2003) Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction. Eur J Pharmacol 480:117–123
Martin LF, Kem WR, Freedman R (2004) Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. Psychopharmacology (Berl) 174:54–64
Martin-Ruiz CM, Haroutunian VH, Long P, Young AH, Davis KL, Perry EK, Court JA (2003) Dementia rating and nicotinic receptor expression in the prefrontal cortex in schizophrenia. Biol Psychiatry 54:1222–1233
McGaughy J, Dalley JW, Morrison CH, Everitt BJ, Robbins TW (2002) Selective behavioral and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192 IgG-saporin on attentional performance in a five-choice serial reaction time task. J Neurosci 22:1905–1913
McGehee DS, Role LW (1995) Physiological diversity of nicotinic acetylcholine receptors expressed by vertebrate neurons. Annu Rev Physiol 57:521–546
McGehee DS, Role LW (1996) Presynaptic ionotropic receptors. Curr Opin Neurobiol 6:342–349
McGehee DS, Heath MJ, Gelber S, Devay P, Role LW (1995) Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science 269:1692–1696
McQuiston AR, Madison DV (1999) Nicotinic receptor activation excites distinct subtypes of interneurons in the rat hippocampus. J Neurosci 19:2887–2896
Mechawar N, Descarries L (2001) The cholinergic innervation develops early and rapidly in the rat cerebral cortex: a quantitative immunocytochemical study. Neuroscience 108:555–567
Mechawar N, Watkins KC, Descarries L (2002) Ultrastructural features of the acetylcholine innervation in the developing parietal cortex of rat. J Comp Neurol 443:250–258
Metherate R (2004) Nicotinic acetylcholine receptors in sensory cortex. Learn Mem 11:50–59
Miller EK (2000) The prefrontal cortex and cognitive control. Nat Rev Neurosci 1:59–65
Muir JL, Everitt BJ, Robbins TW (1995) Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. Psychopharmacology (Berl) 118:82–92
Murray HJ, Muhia MW, Cunningham MO, Davies CH, Whittington MA (2003) Nicotine-induced rhythmic activity in the CA3 region of the rat hippocampus in vitro. Abstract Viewer Society for Neuroscience
Newhouse PA, Potter A, Singh A (2004) Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 4:36–46
Passetti F, Dalley JW, O'Connell MT, Everitt BJ, Robbins TW (2000) Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attentional task. Eur J Neurosci 12:3051–3058
Paylor R, Nguyen M, Crawley JN, Patrick J, Beaudet A, Orr-Urtreger A (1998) Alpha7 nicotinic receptor subunits are not necessary for hippocampal-dependent learning or sensorimotor gating: a behavioral characterization of Acra7-deficient mice. Learn Mem 5:302–316
Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, Fuxe K, Changeux JP (1998) Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 391:173–177
Picciotto MR, Caldarone BJ, King SL, Zachariou V (2000) Nicotinic receptors in the brain. Links between molecular biology and behavior. Neuropsychopharmacology 22:451–465
Pidoplichko VI, DeBiasi M, Williams JT, Dani JA (1997) Nicotine activates and desensitizes midbrain dopamine neurons. Nature 390:401–404
Pidoplichko VI, Noguchi J, Areola OO, Liang Y, Peterson J, Zhang T, Dani JA (2004) Nicotinic cholinergic synaptic mechanisms in the ventral tegmental area contribute to nicotine addiction. Learn Mem 11:60–69
Pierce RC, Reeder DC, Hicks J, Morgan ZR, Kalivas PW (1998) Ibotenic acid lesions of the dorsal prefrontal cortex disrupt the expression of behavioral sensitization to cocaine. Neuroscience 82:1103–1114
Porter JT, Cauli B, Tsuzuki K, Lambolez B, Rossier J, Audinat E (1999) Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. J Neurosci 19:5228–5235
Potter AS, Newhouse PA (2004) Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) 176: 182–194
Quick MW, Lester RA (2002) Desensitization of neuronal nicotinic receptors. J Neurobiol 53:457–478
Radcliffe KA, Fisher JL, Gray R, Dani JA (1999) Nicotinic modulation of glutamate and GABA synaptic transmission of hippocampal neurons. Ann N Y Acad Sci 868:591–610
Radek RJ (1993) Effects of nicotine on cortical high voltage spindles in rats. Brain Res 625:23–28
Rezvani AH, Levin ED (2001) Cognitive effects of nicotine. Biol Psychiatry 49:258–267
Riekkinen P Jr, Riekkinen M, Sirvio J, Miettinen R, Riekkinen P (1992) Loss of cholinergic neurons in the nucleus basalis induces neocortical electroencephalographic and passive avoidance deficits. Neuroscience 47:823–831
Riekkinen P Jr, Riekkinen M, Sirvio J (1993) Effects of nicotine on neocortical electrical activity in rats. J Pharmacol Exp Ther 267:776–784
Robbins TW, Everitt BJ (1999) Drug addiction: bad habits add up. Nature 398:567–570
Roth N, Battig K (1991) Effects of cigarette smoking upon frequencies of EEG alpha rhythm and finger tapping. Psychopharmacology (Berl) 105:186–190
Rueckert L, Grafman J (1996) Sustained attention deficits in patients with right frontal lesions. Neuropsychologia 34:953–963
Rueckert L, Grafman J (1998) Sustained attention deficits in patients with lesions of posterior cortex. Neuropsychologia 36:653–660
Saal D, Dong Y, Bonci A, Malenka RC (2003) Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron 37:577–582
Sarter M, Givens B, Bruno JP (2001) The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Res Brain Res Rev 35:146–160
Schneider JS, Tinker JP, Menzaghi F, Lloyd GK (2003) The subtype-selective nicotinic acetylcholine receptor agonist SIB-1553A improves both attention and memory components of a spatial working memory task in chronic low dose 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys. J Pharmacol Exp Ther 306:401–406
Seguela P, Watkins KC, Descarries L (1989) Ultrastructural relationships of serotonin axon terminals in the cerebral cortex of the adult rat. J Comp Neurol 289:129–142
Seguela P, Watkins KC, Geffard M, Descarries L (1990) Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. Neuroscience 35:249–264
Seguela P, Wadiche J, Dineley-Miller K, Dani JA, Patrick JW (1993) Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. J Neurosci 13:596–604
Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS (1998) Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. Am J Psychiatry 155:1009–1015

Stevens KE, Freedman R, Collins AC, Hall M, Leonard S, Marks MJ, Rose GM (1996) Genetic correlation of inhibitory gating of hippocampal auditory evoked response and alpha-bungarotoxin-binding nicotinic cholinergic receptors in inbred mouse strains. Neuropsychopharmacology 15:152–162

Stevens KE, Kem WR, Mahnir VM, Freedman R (1998) Selective alpha7-nicotinic agonists normalize inhibition of auditory response in DBA mice. Psychopharmacology (Berl) 136:320–327

Stolerman IP, Mirza NR, Shoaib M (1995) Nicotine psychopharmacology: addiction, cognition and neuroadaptation. Med Res Rev 15:47–72

Tancredi V, Biagini G, D'Antuono M, Louvel J, Pumain R, Avoli M (2000) Spindle-like thalamocortical synchronization in a rat brain slice preparation. J Neurophysiol 84:1093–1097

Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Labarca C, Whiteaker P, Marks MJ, Collins AC, Lester HA (2004) Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. Science 306:1029–1032

Thomas MJ, Beurrier C, Bonci A, Malenka RC (2001) Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. Nat Neurosci 4:1217–1223

Todd RD, Lobos EA, Sun LW, Neuman RJ (2003) Mutational analysis of the nicotinic acetylcholine receptor alpha 4 subunit gene in attention deficit/hyperactivity disorder: evidence for association of an intronic polymorphism with attention problems. Mol Psychiatry 8:103–108

Traub RD, Jefferys JGR, Whittington MA (1999) Fast oscillations in cortical circuits. MIT Press, Cambridge, MA

Turrini P, Casu MA, Wong TP, De Koninck Y, Ribeiro-da-Silva A, Cuello AC (2001) Cholinergic nerve terminals establish classical synapses in the rat cerebral cortex: synaptic pattern and age-related atrophy. Neuroscience 105:277–285

Umbriaco D, Watkins KC, Descarries L, Cozzari C, Hartman BK (1994) Ultrastructural and morphometric features of the acetylcholine innervation in adult rat parietal cortex: an electron microscopic study in serial sections. J Comp Neurol 348:351–373

Umbriaco D, Garcia S, Beaulieu C, Descarries L (1995) Relational features of acetylcholine, noradrenaline, serotonin and GABA axon terminals in the stratum radiatum of adult rat hippocampus (CA1). Hippocampus 5:605–620

Ungless MA, Whistler JL, Malenka RC, Bonci A (2001) Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. Nature 411:583–587

Vanderschuren LJ, Kalivas PW (2000) Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology (Berl) 151:99–120

Vidal C, Changeux JP (1993) Nicotinic and muscarinic modulations of excitatory synaptic transmission in the rat prefrontal cortex in vitro. Neuroscience 56:23–32

Vizi ES, Kiss JP (1998) Neurochemistry and pharmacology of the major hippocampal transmitter systems: synaptic and nonsynaptic interactions. Hippocampus 8:566–607

Whittington MA, Traub RD, Jefferys JG (1995) Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. Nature 373:612–615

Williams JH, Kauer JA (1997) Properties of carbachol-induced oscillatory activity in rat hippocampus. J Neurophysiol 78:2631–2640

Wonnacott S, Sidhpura N, Balfour DJ (2005) Nicotine: from molecular mechanisms to behaviour. Curr Opin Pharmacol 5:53–59

Wooltorton JR, Pidoplichko VI, Broide RS, Dani JA (2003) Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci 23:3176–3185

Yoshikawa T, Watanabe A, Shibuya H, Toru M (1993) Involvement of the fimbria fornix in the initiation but not in the expression of methamphetamine-induced sensitization. Pharmacol Biochem Behav 45:691–695

Young JW, Finlayson K, Spratt C, Marston HM, Crawford N, Kelly JS, Sharkey J (2004) Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. Neuropsychopharmacology 29:891–900

Zoli M, Jansson A, Sykova E, Agnati LF, Fuxe K (1999) Volume transmission in the CNS and its relevance for neuropsychopharmacology. Trends Pharmacol Sci 20:142–150