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Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction

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Abstract

Nicotine reinforces smoking behaviour by activating nicotinic acetylcholine receptors in the midbrain dopaminergic reward centres. Upstream of the dopaminergic neurons nicotine induces long-term potentiation of the excitatory input to dopamine cells in the ventral tegmental area, and depresses inhibitory inputs. Both effects of nicotine were shown to last much longer than the nicotine exposure and together will activate the dopaminergic ventral tegmental area projection toward the nucleus accumbens. However, downstream of dopamine, effects of nicotine are also likely to occur. Cholinergic interneurons within the nucleus accumbens are important in the tonic control of the γ-amino buteric acid (GABA) nucleus accumbens output neurons, which project back to the ventral tegmental area. The nicotinic acetylcholine receptors that mediate this control are likely to desensitise upon preexposure to the nicotine concentrations found in the blood of smokers. Thus, synaptic mechanisms both upstream and downstream of dopamine release are potentially important factors contributing to the etiology of nicotine addiction.

Keywords: Nicotine; Addiction; Ventral tegmental area; Nucleus accumbens; Acetylcholine; Dopamine

1. Introduction

Tobacco use in the western society is estimated to be the largest single cause of premature death (Peto et al., 1992). Nicotine is the main addictive component of tobacco that motivates continued use despite the harmful effects. Nicotinic acetylcholine receptors are widely distributed throughout the mammalian central nervous system, where they normally respond to acetylcholine and modulate neuronal excitability and synaptic communication. Nicotinic receptors are structurally diverse and mediate a variety of physiological effects. Presynaptic and preterminal nicotinic acetylcholine receptors enhance neurotransmitter release (MacDermott et al., 1999; McGehee et al., 1995; McGehee and Role, 1995; Wonnacott, 1997). Postsynaptic and somatic nicotinic acetylcholine receptors mediate a small proportion of fast excitatory transmission and modulate cytoplasmic second messenger systems. Although the impact of nicotine obtained from tobacco is not completely understood, a considerable portion of nicotine's addictive power is attributable to actions ventral tegmental area into the nucleus accumbens is considered to be an important component in the reinforcement of rewarding behaviours, and nicotine along with other drugs of abuse usurp this process to motivate drug seeking and other behaviours associated with addiction. Physiologically relevant nicotine concentrations have been shown to activate both pre- and postsynaptic nicotinic acetylcholine receptors (MacDermott et al., 1999; McGehee et al., 1995; McGehee and Role, 1995; Wonnacott, 1997). Important extensions of this work indicate that both activation and desensitisation of diverse nicotinic acetylcholine receptors may be crucial factors underlying the effects of nicotine on the ventral tegmental area (Mansvelder et al., 2002; Mansvelder and McGehee, 2000) and the nucleus accumbens (de Rover et al., 2002).

This perspective-report will outline what is currently known about nicotinic modulation of synaptic transmission in these reward areas. Given their reciprocal connection, we will attempt to integrate the different effects of nicotine exposure.

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Our strongest insight into the cellular effects of first exposure to nicotine upstream of dopamine neurons comes from the recent studies on the ventral tegmental area (Mansvelder et al., 2002; Mansvelder and McGehee, 2000; Pidoplichko et al., 1997). These findings indicate differential distribution of nicotinic acetylcholine receptor subtypes on γ-amino buteric acid (GABA) inputs, glutamate terminals, and dopaminergic neurons within this nucleus and highlight the importance of carefully delineating potential differences in receptor activation and desensitisation when investigating the effects of nicotine.

Downstream of the dopaminergic projection in the nucleus accumbens, nicotinic acetylcholine receptors are also expressed, and a recent study on the endogenous cholinergic modulation of the feed-forward inhibition of GABA output neurons in this brain area from our lab (de Rover et al., 2002) puts new insight into how shifting the balance between GABA and glutamatergic synaptic transmission may further contribute to alterations in reward behaviour. These studies provide a base for future studies elucidating the synaptic mechanisms underlying the onset of nicotine addiction.

2. Nicotinic receptors in brain reward areas

Nicotinic receptors are pentameric membrane proteins that include two or more agonist binding sites and a central aqueous pore. Agonist binding results in a conformational change that leads to ion flux through the pore, inducing a depolarisation and increased excitability. Pharmacological and ligand-binding studies have demonstrated considerable diversity in neuronal nicotinic acetylcholine receptor subtypes. To date, 12 neuronal nicotinic acetylcholine receptor subunit genes have been identified, α2–10 and β2–4. The α subunits are required for ligand binding while the β subunits are structural.

In the ventral tegmental area, dopamine neurons, GABA neurons and glutamatergic terminals express nicotinic acetylcholine receptors. The dopamine neurons express a variety of mRNAs ranging from α2–7 to β2–4 and the expression level of each subunit varies within the cell population (Champtiaux et al., 2002; Charpantier et al., 1998; Klink et al., 2001). These mRNAs result in three pharmacological identifiable nicotinic acetylcholine receptors, one that is likely a homomeric α7 receptor and two that do not contain the α7 subunit. A majority of DA neurons express nicotinic acetylcholine receptors that can be blocked by mecamylamine at concentrations that block non-α7 containing nicotinic acetylcholine receptors selectively, whereas less than half of the DA neurons express nicotinic acetylcholine receptors containing α7 (Klink et al., 2001; Pidoplichko et al., 1997; Wooltorton et al., 2003).

GABA neurons in the ventral tegmental area express a similar variety of nicotinic acetylcholine receptor subunit mRNA, but in contrast to DA neurons, α7 was not found at all (Klink et al., 2001). Thus, the majority of the GABA neurons in the ventral tegmental area express nicotinic acetylcholine receptors that most likely contain α4 and β2 subunits, which are also blocked by mecamylamine or dihydro-β-erythroidine hydrobromide (DHβE) (Mansvelder et al., 2002).

The ventral tegmental area receives glutamatergic synaptic input primarily from the prefrontal cortex. This input has been suggested to provide the major excitatory control of ventral tegmental area neuron activity and ultimately DA release in the nucleus accumbens (Johnson et al., 1992; Kalivas et al., 1989; Sesack and Pickel, 1992; Suaud-Chagny et al., 1992; Taber and Fibiger, 1995). Focal administration of the NMDA receptor antagonist 2-amino-5-phosphonovalerate (APV) within the ventral tegmental area in vivo inhibits nicotine-induced increases in DA release within the nucleus accumbens (Schilstrom et al., 1998a), suggesting that nicotinic modulation of glutamatergic transmission contributes to the enhancement of ventral tegmental area DA output. Thus, the presynaptic terminals of the glutamatergic inputs to mesoaccumbens DA neurons in the ventral tegmental area most likely express nicotinic acetylcholine receptors. Indeed, in brain slice recordings from ventral tegmental area DA neurons, glutamatergic transmission onto these neurons is enhanced by low concentrations of nicotine and this enhancement is unaffected by tetrodotoxin (TTX), which blocks action potential firing. The latter finding suggests that the nicotinic acetylcholine receptors mediating this effect are situated locally in the ventral tegmental area, on the presynaptic glutamatergic terminals (Mansvelder and McGehee, 2000). These nicotinic acetylcholine receptors are sensitive to methyllycaconitine citrate (MLA), a selective inhibitor of nicotinic acetylcholine receptors that contain the α7 subunit (Alkondon and Albuquerque, 1993; Seguela et al., 1993). In vivo focal injection of methyllycaconitine citrate (MLA) into the ventral tegmental area also prevents nicotine-induced increases in accumbal DA release (Schilstrom et al., 1998b). Nicotinic acetylcholine receptors consisting of α7 subunits are well-suited for modulating synaptic transmission since they have a high calcium permeability, and this calcium flux occurs at resting membrane potentials when activated by agonists (McGehee and Role, 1995; Seguela et al., 1993).

Nicotinic receptor distribution on different types of neurons in the nucleus accumbens is less well studied. We recently reported that GABAergic interneurons in the nucleus accumbens express functional nicotinic acetylcholine receptors that promote action potential firing and that are sensitive to mecamylamine (de Rover et al., 2002), which suggests that they are a non-α7 subtype. Cholinergic interneurons most likely do not express nicotinic acetylcholine receptors, and it remains uncertain whether medium spiny output neurons express nicotinic acetylcholine receptors.

There is a considerable diversity in the nicotine sensitivity of the different receptor subtypes, which underlies

differences in channel activation and subsequent desensitisation in the continued presence of nicotine (Mansvelder et al., 2002; Wooltorton et al., 2003). As behavioural reinforcement by nicotine is likely a combination of these phenomena, each of the receptor properties and alterations therein need to be investigated, in order for us to understand both short and long-term effects of nicotine in the brain.

3. The addictive power of nicotine

In survey studies of human adolescents, the initial symptoms of nicotine dependence can be present after smoking of only a few cigarettes (DiFranza et al., 2000), i.e. before the onset of daily smoking. This demonstrates that human adolescents may become nicotine-dependent after occasional use of nicotine for a short period of time. These findings are consistent with the observation from cellular studies that profound changes in the synaptic physiology of the brain reward system can be observed after a single exposure to nicotine (Mansvelder and McGehee, 2000). This is likely true for most drugs of abuse, since a single exposure to amphetamines and morphine can also cause long-term changes in both behaviour and neurochemistry (Vanderschuren et al., 1999, 2001), and a single administration of cocaine to neonatal rats can induce long-term potentiation of the excitatory inputs to ventral tegmental area dopamine neurons that persists for up to 10 days (Ungless et al., 2001). Consistent with the idea that this phenomenon contributes to the effects of many abused substances, a single administration of alcohol, amphetamine, nicotine or acute stress induced long-term potentiation of excitatory inputs to dopamine neurons (Saal et al., 2003). Thus, the very first exposure to an addictive substance may leave its mark in the brain for a long time. But how is this achieved?

4. Synaptic mechanisms underlying nicotine addiction

Like humans, rodents readily self-administer nicotine when the opportunity is presented in the laboratory. Despite the widespread expression of nicotinic acetylcholine receptors throughout the brain, the activation of nicotinic acetylcholine receptors within the ventral tegmental area is critically important in the rewarding effect of nicotine (Nisell et al., 1994; Schilstrom et al., 1998b).

It is remarkable that while a single exposure to nicotine increases dopamine release in the nucleus accumbens from ventral tegmental area dopamine neurons for more than an hour in vivo (Di Chiara and Imperato, 1988), the nicotinic acetylcholine receptors on the dopamine neurons desensitise in seconds to minutes in the presence of nicotine (Pidoplichko et al., 1997; Wooltorton et al., 2003). During cigarette smoking, blood nicotine levels reach 300–500 nM several minutes after the initial smoking and concentrations close to 250 nM are sustained for 10 min or more thereafter (Henningfield et al., 1993). Such a time course of nicotine, when reaching the ventral tegmental area, will activate the high-affinity nicotinic acetylcholine receptors on ventral tegmental area dopamine neurons. However, following activation, even with nicotine concentrations as low as 100–500 nM, the somatic non-α7 nicotinic acetylcholine receptors will completely desensitise within seconds (Pidoplichko et al., 1997; Wooltorton et al., 2003), and thus cannot account for the long lasting increase in dopamine release observed in vivo upon a single nicotine exposure.

The idea that a change in synaptic strength within the ventral tegmental area may underlie the persistent effects of nicotine was supported by observation that nicotine-induced increases in dopamine release in nucleus accumbens were inhibited by an intra-ventral tegmental area injection of the NMDA glutamate receptor antagonist, APV (Schilstrom et al., 1998a). The NMDA receptor-dependence of long-term potentiation suggested a link to the effects of nicotine, but it was not clear if or how a single nicotine exposure might induce long-term plasticity. This leads to the investigation of functional nicotinic acetylcholine receptor expression within the ventral tegmental area microcircuitry, with particular focus on the possible role of presynaptic nicotinic receptors. Indeed, presynaptic nicotinic receptors have been shown to enhance both GABA and glutamate transmission in many brain regions (Wonnacott, 1997). Ventral tegmental area dopamine neurons receive excitatory glutamatergic input primarily from prefrontal cortex, in addition to the pedunculopontine and laterodorsal tegmental nuclei (Omelchenko and Sesack, 2002; Sesack and Pickel, 1992; Taber et al., 1995). Inhibitory GABAergic drive to the ventral tegmental area dopamine neurons arises from local interneurons and projections from nucleus accumbens and the ventral pallidum (Kalivas et al., 1993; Steffensen et al., 1998; Walaas and Fonnum, 1980). Thus, dopamine neuron excitability ultimately arises from the activity of these excitatory and inhibitory inputs, in combination with the intrinsic excitation of the dopamine neurons themselves. Our recent work (Mansvelder et al., 2002; Mansvelder and McGehee, 2000) has identified two synaptic mechanisms by which nicotine may have persistent stimulatory effects on the ventral tegmental area dopamine neurons, i.e. nicotine induced long-term potentiation of the excitatory glutamatergic input and nicotine-induced depression of GABAergic transmission within the ventral tegmental area.

5. First nicotine exposure of the ventral tegmental area

Nicotinic receptors are present on the presynaptic glutamatergic terminals in the ventral tegmental area (Mansvelder and McGehee, 2000). When nicotine arrives in the ventral tegmental area, it stimulates these glutamatergic terminals directly, in addition to activation of postsynaptic nicotine effects on dopamine neurons, thereby favouring

conditions of paired electrical stimulation of the pre- and postsynaptic partners. In fact, in our experiments, nicotine could replace presynaptic stimulation completely in long-term potentiation induction protocols. Most noteworthy, long-term potentiation was induced at very low concentration of nicotine, in the range of that experienced by smokers, and a nicotine exposure of 200 s was sufficient. While postsynaptic nicotinic acetylcholine receptors can directly excite dopamine neurons, these studies did not find a significant contribution of postsynaptic nicotinic acetylcholine receptors to long-term potentiation induction. It is important to note that this does not rule out a contribution of postsynaptic nicotinic acetylcholine receptors to long-term plasticity, as this has been reported in hippocampus where a weak presynaptic stimulation could lead to long-term potentiation when administered concomitantly with nicotine nicotinic acetylcholine receptor activation (Ji et al., 2001). Further evidence for the induction of long-term potentiation by nicotine comes from the study by Saal et al. (2003) showing that a single systemic nicotine injection induced an increase in the AMPA/NMDA receptor ratio, a measure of long-term potentiation expression. Together these findings suggest that synaptic plasticity in the ventral tegmental area may be induced after smoking a single cigarette and most likely underlies the persistent effects of the drug on dopamine release in the nucleus accumbens.

The nicotinic acetylcholine receptors involved in this mechanism contain the α7 subunit, and the low nicotine concentrations associated with tobacco use do not induce significant desensitisation of these receptors (Mansvelder et al., 2002; Wooltorton et al., 2003). Indeed, while a 10-min exposure to 250 nM nicotine completely desensitised the nicotinic acetylcholine receptors of dopamine (or GABA, see below) neurons, it still continues to activate the presynaptic nicotinic acetylcholine receptors on the glutamatergic terminals (Mansvelder et al., 2002).

In addition to excitatory inputs, dopamine neurons are under inhibitory control, predominantly by GABAergic interneurones within the ventral tegmental area and by projecting GABA-fibers from other brain areas, including the nucleus accumbens (Kalivas et al., 1993; Steffensen et al., 1998; Walaas and Fonnum, 1980). Activation of the nicotinic acetylcholine receptors expressed by the GABA interneurones in the ventral tegmental area, by exogenous nicotine, initially causes an increase in firing rate (Mansvelder et al., 2002), which may offset some of the excitatory effects of nicotine during the initial stages of nicotine exposure of the neuronal network. However, since these nicotinic acetylcholine receptors are of the non-α7 type, rapid desensitisation of these receptors will occur within minutes after the start of nicotine exposure, and as a consequence, the inhibitory input to the dopamine neurons will bediminished.

Desensitisation of the nicotinic acetylcholine receptors of the GABA neurons not only prevents further activation by nicotine, it also precludes the contribution of these receptors to endogenous cholinergic transmission (Mansvelder et al., 2002). As the majority of the endogenous cholinergic inputs to the ventral tegmental area appear to contact GABA rather than dopaminergic neurons in the ventral tegmental area (Fiorillo and Williams, 2000; Garzon et al., 1999), the functional significance of this second synaptic pathway of 'upstream' nicotine modulation is thought to be of major importance.

Finally, it is possible that the reduction in GABAergic transmission would also help to promote long-term potentiation induction, as it would favour depolarisation of the dopamine neurons. Together, these two presynaptic nicotine receptor-mediated effects ensure that a limited exposure to nicotine is sufficient to induce lasting changes in the circuitry of the mesolimbic reward system. At this point, it is unknown how these synaptic connections are affected in the ventral tegmental area after long-term exposure to nicotine, when animals are self-administering nicotine, and whether these cellular mechanisms play a role in the addicted brain.

6. Nicotine effects in the nucleus accumbens

The nucleus accumbens contain acetylcholine-releasing interneurones, presumed to play a regulatory role in the electrical activity of medium spiny output neurons. In our lab, it was found recently that GABA-mediated inhibition of the output neurons is facilitated by activation of nicotinic acetylcholine receptors and suppressed via activation of muscarinic acetylcholine receptors (de Rover et al., 2002). The physiological significance of this finding was substantiated by recording from pairs of neurons in which the functional connection between cholinergic neurons and output neurons was monitored. Driving the cholinergic neurons at physiological firing frequencies leads to stimulation of GABA inhibition of the output neurons via activation of nicotinic acetylcholine receptors of the non-α7 subtype being expressed by GABA interneurons innervating the medium spiny output neurons of the nucleus accumbens (i.e. 'feed-forward' inhibition). In contrast, glutamatergic excitation of output neurons was inhibited by activation of muscarinic acetylcholine receptors but was insensitive to activation of nicotinic acetylcholine receptors.

In general, cholinergic neurons make diffuse projections that sparsely innervate relatively broad areas. In the ventral striatum, however, the cholinergic neurons are interneurones that provide very dense local innervation. About 2% of the ventral striatal neurons are cholinergic and they provide an ongoing acetylcholine signal by firing action potentials tonically at about 2–5 Hz. The normally high acetylcholinesterase concentration in the striatum rapidly terminates the endogenous acetylcholine signal, and thereby minimizes desensitisation of nicotinic acetylcholine receptors (Zhou et al., 2001).

7. Downstream effects of cigarette smoking?

However, what will happen when nicotine arrives in the nucleus accumbens following cigarette smoking? Without doubt, it will facilitate the so-called feed-forward inhibition while leaving the excitatory input to the output neurons relatively unaffected. Initially, nicotine exposure may therefore lead to a reduction of the GABA output coming from the nucleus accumbens. Whether this in turn would reinforce or prolong the initial dopamine surge from the ventral tegmental area needs to be investigated.

Second, since nicotine will not be broken down by endogenous acetylcholinesterase, and since the nicotinic acetylcholine receptors involved in facilitating the feed-forward inhibition in the nucleus accumbens are of the non-α7 type, these receptors will be rapidly desensitised. If nothing else, this would limit any further endogenous cholinergic regulation of the synaptic circuitry, i.e. it would uncouple the intrinsic functional microcircuitry from endogenous acetylcholine release (Fig. 1) (de Rover et al., 2002), as was shown for the ventral tegmental area (Mansvelder et al., 2002) and the hippocampus (Frazier et al., 1998; Hefft et al., 1999).

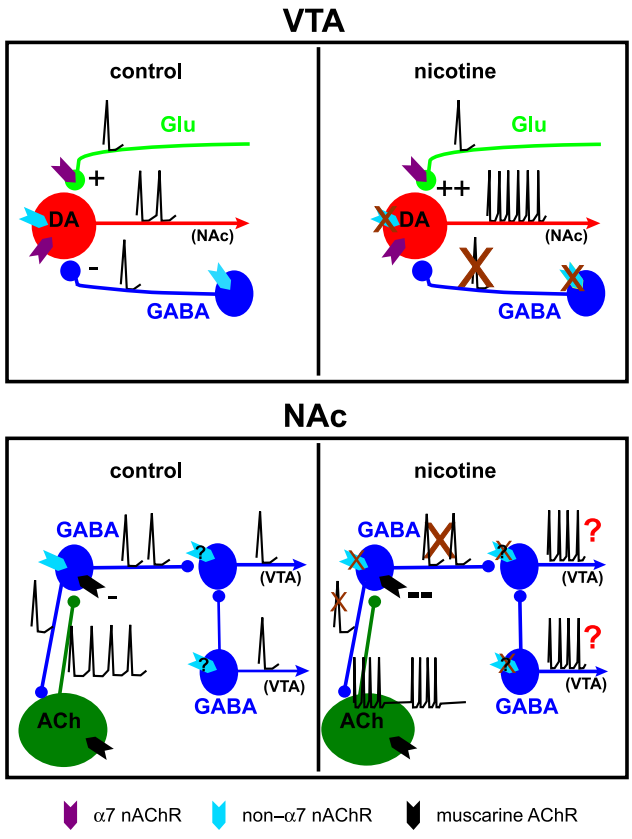

Fig. 1. Simplified schematic of the microcircuitry of ventral tegmental area and NAc before and after smoking a cigarette. Shown are excitatory and inhibitory synaptic inputs to the primary cell types with the proposed cellular locations of nicotinic and muscarinic receptors. On the left is the control situation, i.e. before the first exposure to nicotine. On the right is the situation after 5–10 min of nicotine exposure, at a concentration that is normally found in the blood after smoking a single cigarette. For details, see text.

Third, the spontaneous firing frequency of cholinergic neurons is under control of both a muscarinic and a nicotinic receptor pathway in a bi-directional manner. Under basal conditions (i.e. without nicotine), there is a substantial endogenous tone of acetylcholine in the nucleus accumbens shown with slice electrophysiology (de Rover et al., 2002) and in vivo microdialysis of acetylcholine release in the ventral striatum (Rada et al., 1994). The presence of nicotine will desensitise nicotinic acetylcholine receptors and shift the balance of cholinergic autoregulation toward the influence of muscarinic receptors, which induce a so-called bursting behaviour of the cholinergic neurons (nicotinic acetylcholine receptor activity induce slow regular firing). While this model is speculative, the important physiological role of nicotinic acetylcholine receptors in ventral striatal microcircuitry strongly suggests that significant alterations will occur in the firing pattern of the cholinergic neurons within the nucleus accumbens and therefore also in the time course of endogenous acetylcholine release.

The new step in our understanding of the regulation of the nucleus accumbens is that these data show that the cholinergic interneurones in the nucleus accumbens may directly, i.e. downstream of dopaminergic neurotransmission, control the excitability of the GABAergic output neurons. The schematic model in Fig. 1 illustrates this.

Thus far, the evidence for synaptic connectivity mediating endogenous cholinergic modulation of the GABA (inter)-neuronal network of the nucleus accumbens is lacking (de Rover et al., 2002). Hence, volume acetylcholine transmission acting on extrasynaptic nicotinic acetylcholine receptors (Vizi, 2000; Zoli et al., 1999) may regulate the output of the nucleus accumbens projection neurons. Future experiments to sort out the mechanisms that may regulate extracellular acetylcholine concentration in the nucleus accumbens, and/or hydrolysis of acetylcholine via activity of acetylcholinesterase (Mansvelder et al., 2002), may shed novel insight into this mechanism. However, the above line of arguments make more likely that smoking a cigarette will have direct 'downstream' effects within the nucleus accumbens.

8. Downstream cholinergic modulation in behavioural sensitization

As mentioned above, a common feature of many addictive drugs, including nicotine is that they increase dopamine levels in the nucleus accumbens via an initial effect in the ventral tegmental area. Although some drugs of abuse alter dopamine metabolism or reuptake to increase dopamine levels in the nucleus accumbens, nicotine (Mansvelder and McGehee, 2000) and also cocaine (Ungless et al., 2001) appear to alter primarily the activity of ventral tegmental area neurons to enhance dopamine release. This type of observation without further behavioural verification might

leave us with the impression that in order to become behaviourally sensitised to addictive drugs, the upstream regulation of the dopamine pathway is primarily important.

However, downstream cholinergic modulation by nicotine in the nucleus accumbens may be of crucial importance (Hikida et al., 2003; Schoffelmeer et al., 2002). Hikida et al. showed that immunotoxin-mediated ablation of the nucleus accumbens cholinergic neurons enhanced not only the sensitivity to morphine in conditioned place preference but also negative reinforcement of morphine withdrawal in conditioned place aversion. Remarkably, when acetylcholinesterase inhibitors were applied in animals in which the cholinergic cells were not ablated, they observed a suppression of both cocaine- and morphine-induced conditioned place preference and also a block of the induction and persistence of cocaine-evoked hyperlocomotion. Importantly, this cholinesterase inhibition was abolished by ablation of the nucleus accumbens cholinergic neurons. These results demonstrate that some aspects of cocaine and morphine addiction are mediated by potentiating the actions of acetylcholine released from the nucleus accumbens cholinergic neurons. Behavioural sensitisation to cocaine and amphetamine also depends on endogenously released acetylcholine in the nucleus accumbens (Schoffelmeer et al., 2002), therefore, nicotinic acetylcholine receptors in reward areas may play a more general role in the behavioural aspects of addiction.

9. Concluding remarks

Nicotinic receptors have been implicated in a variety of brain functions, including neuronal development, learning and memory formation, and reward. Although there are substantial data indicating that nicotinic acetylcholine receptor subunits are found in many brain regions, until recently, the precise cellular roles of these subunits in neuronal functions have remained elusive. While nicotinic acetylcholine receptors are still thought to primarily serve a modulatory role in the brain by regulating neurotransmitter release from nerve terminals, new evidence has revealed that nicotinic acetylcholine receptors also function in a postsynaptic role by mediating fast acetylcholine-mediated synaptic transmission in the hippocampus and in the sensory cortex, and are found at somatodendritic as well as nerve terminal sites in the reward system (Jones et al., 1999). As we have shown here, it is possible that activation and/or desensitisation of presynaptic and postsynaptic nicotinic acetylcholine receptors intermingle in mediating alterations in the efficacy of synaptic transmission in the reward brain regions.

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