Biochemical Pharmacology 78 (2009) 744–755

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Nicotinic acetylcholine receptors and the ascending dopamine pathways

Phil D. Livingstone, Susan Wonnacott *

Department of Biology & Biochemistry, University of Bath, Bath BA2 7AY, UK

ARTICLE INFO

Article history:
Received 7 April 2009
Accepted 4 June 2009

Keywords:
Nicotine
Acetylcholine
Midbrain
Nucleus accumbens
Prefrontal cortex

ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are widely expressed in midbrain dopamine neurons that project to dorsal striatum, nucleus accumbens and prefrontal cortex. Thus nAChRs can influence the functions of these three pathways, notably motor control, 'reward' and executive function, respectively. Diverse subtypes of nAChRs have been identified on dopamine cell bodies and terminals as well as on neighbouring afferents and interneurons. Here we review the molecular and cellular mechanisms through which nAChRs exert their influence on these pathways in rodents.

Contents

1. Introduction

The association of nicotine with tobacco addiction has stimulated particular interest in how nicotine interacts with the 'reward' pathways of the brain. Most attention has been given to the ascending dopaminergic pathways that arise in the midbrain and project to aspects of the basal ganglia and prefrontal cortex (PFC; Fig. 1). In addition to mediating the reinforcing properties of addictive substances, dopamine is also central to the fine control of movement governed by the basal ganglia, whereas its actions in the PFC are critically important to 'executive' function [1,2]. This includes working memory, behavioural flexibility and decision making, and the PFC is also involved with the anticipation of reward [3,4].

Nicotine interacts with the dopamine systems via nicotinic acetylcholine receptors (nAChRs), a family of ligand-gated pentameric cation channels constituted from at least nine α and β subunits (α2–7 and β2–4) expressed in the mammalian brain [5]. nAChR subtypes can differ in their sensitivities to nicotine or acetylcholine (ACh), their channel characteristics (including their propensity to desensitise) and their cellular distribution. A high relative permeability to Ca^{2+}, a notable characteristic of the α7 nAChR subtype, enables nAChRs to interface with a variety of

Abbreviations: αBgt, alpha-bungarotoxin; CPu, caudate putamen; CREB, cyclic AMP response element binding protein; DARPP-32, dopamine and cyclic AMP regulated phosphoprotein of 32 kDa; DHβE, dihydrobetaerythroidine; ELK, Ets-like transcription factor; EPSC, excitatory postsynaptic current; ERK, extracellular signal-regulated kinase; FSCV, fast-scan cyclic voltammetry; GABA, gamma-aminobutyric acid; iGluR, ionotropic glutamate receptor; IPSC, inhibitory postsynaptic current; LDTn, laterodorsal tegmental nucleus; LTP, long-term potentiation; MLA, methyllycaconitine; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; PKA, protein kinase A; PPn, pedunculopontine tegmental nucleus; RRF, retrorubral field; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area.

* Corresponding author. Tel.: +44 (0)1225 386391; fax: +44 (0)1225 386779.
E-mail address: bsssw@bath.ac.uk (S. Wonnacott).

0006-2952/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2009.06.004

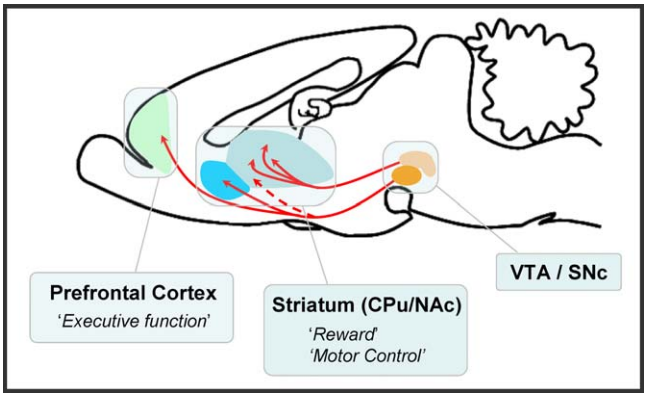


Fig. 1. Major ascending dopamine pathways of the rodent brain. Projections arise from cell bodies of the mesencephalon from one of two regions, the ventral tegmental area (VTA, orange) or substantia nigra pars compacta (SNc, including the retrorubral field, light orange). The caudate putamen (CPu) or dorsal striatum (light blue) is innervated by dopaminergic neurons from the SNc forming the nigrostriatal pathway and, to a lesser extent, from the VTA (dashed line). Two major dopamine pathways originate in the VTA; the mesolimbic pathway that terminates in the nucleus accumbens (NAc, dark blue) and the mesocortical pathway in the prefrontal cortex (green). For more anatomical detail see Appendix A.

intracellular Ca^{2+}-dependent mechanisms [6]. The localisation of nAChRs on dopamine cell bodies in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) allows nicotine to directly modulate dopaminergic cell firing. Additionally, nAChRs on dopamine terminals can influence transmitter release. nAChRs present on afferents projecting to the VTA and SNc or to the terminal fields can also influence the activity of dopaminergic neurons. The nicotinic modulation of dopamine release has generated interest in nAChRs as therapeutic targets for conditions involving dopaminergic dysfunction, including schizophrenia, attention deficit hyperactivity disorder, Parkinson's disease, Alzheimer's disease and age-related cognitive impairment [7–10].

In this review we focus on the mechanisms through which nAChRs modulate the activity of dopamine neurons of the principal ascending pathways (Fig. 1). We will consider nicotinic influences on somatodendritic and terminal fields, with the aim of integrating the diverse studies on nAChR actions. As the majority of this work have been undertaken in rodents, we will focus on these species. Although much of this research has been driven by the desire to understand nicotine addiction or the potential of nAChRs as therapeutic targets, the underlying physiological roles of nAChRs and the influence of their endogenous agonist ACh is also considered. Because nAChRs alter the firing pattern of dopaminergic neurons and dopamine release, this is often the endpoint of research studies. However, dopamine levels determine several critical downstream signals. Therefore the molecular and cellular consequences of dopamine release in response to nicotinic modulation will also be briefly explored.

2. Nicotinic regulation at the level of the dopaminergic cell bodies

Of the three anatomically defined groups of mesencephalic dopamine neurons (see Appendix A), those of the VTA and SNc have been extensively studied with respect to the roles of nicotine and nAChRs. These neurons are tonically active, firing single action potentials at low frequency ('irregular single spike firing' [11]). In addition to increases in single spike firing rate, these neurons can switch to a burst firing mode in which rapid bursts of action potentials serve to "boost the gain of neural signalling" of important or novel events [12,13]. A switch from tonic to burst firing is observed during presentation of a rewarding stimulus [14] and this switch occurs in response to nicotine [15,16]. ACh, glutamate and GABA, as well as dopamine itself, determine the excitability of dopaminergic cell bodies, and orchestrate changes in firing rate. nAChRs on dopamine cell bodies, local interneurons and afferent terminals play a significant role in this process by responding to endogenous transmitter or exogenous nicotine (Fig. 2A).

In the rodent VTA/SNc, *in situ* hybridisation and single-cell RT-PCR have revealed the expression in dopaminergic cell bodies of α3–α7, β2 and β3 nAChR subunits (note the relative lack of α2 and β4 only). α4, β2, α7 and β4 subunits were found in GABAergic interneurons and/or in other non-dopaminergic cells [17,18] (Fig. 2B). 6-Hydroxydopamine lesions to mimic dopaminergic cell loss in Parkinson's disease preferentially decrease the expression of α5, α6 and β3 nAChR subunits in the rat SNc [19]. The VTA expresses the same complement of nAChR subunit mRNAs as SNc but in a slightly lower percentage of neurons [18]. These findings suggest that the dopaminergic neurons are likely to be well endowed with a great diversity of nAChR subtypes, but mRNA expression data are not informative about nAChR subunit composition or subcellular distribution.

There are functional nAChRs on dopaminergic cell bodies both in SNc [20] and VTA [21,22]; autoradiographical evidence for the labelling of these neurons with [^{3}H]nicotine supports the presence of high affinity (β2-containing) nAChRs [23] and colocalisation of αbungarotoxin (αBgt) with tyrosine hydroxylase corroborates the presence of α7 nAChRs [24]. More detailed pharmacological analysis, in conjunction with single cell PCR and comparison of tissue from null mutant mice lacking a particular subunit, has provided evidence for both α-conotoxinMII-sensitive and -insensitive nicotine- and ACh-evoked currents (tentatively ascribed the subunit composition $\alpha4\alpha6\beta3(\beta2)_2$ and $(\alpha4)_2\alpha5(\beta2)_2$, respectively), as well as α7 nAChR-mediated responses [17].

The main influence of nAChRs expressed on cell bodies of dopamine neurons is to modulate the rate of action potential firing and consequent level of dopamine released at synapses [25]. Cholinergic inputs to the SNc arise in the pedunculopontine tegmental nucleus (PPn) and those to the VTA are from both the PPn and the laterodorsal tegmental nucleus (LDTn) [26,27]. Burst firing in dopaminergic neurons is dependent on inputs from the LDTn [28]. Evidence for the importance of endogenous nicotinic signalling comes from knockouts of β2 or α7 nAChR subunits in which spontaneous firing in VTA dopaminergic neurons is altered, either by attenuation of high frequencies and high bursts (β2 −/−) or reduction of other, more subtle firing modes (α7 −/−) [25] (Fig. 2C). Selective re-expression of the β2 subunit in the VTA of β2 −/− mice restored normal frequency and bursting patterns of action potential firing to these neurons. Thus both α7 and β2* nAChRs (where * denotes additional unspecified subunits) are implicated, with the latter having the more prominent role.

Focus on the VTA reflects the importance given to this region with respect to reward-related events, including responding to nicotine [29–31]. Lack of nicotine self-administration in β2 knockout mice has led to the conclusion that β2 subunit-containing nAChRs are critical for nicotine addiction [32] and a necessary and sufficient role for both α4β2* and α6β2* nAChRs in the VTA in nicotine self-administration has been demonstrated [33]. The importance of α6* nAChRs is highlighted in a study of mice in which these receptors harbour a gain of function mutation. This results in increased firing rates in VTA and SNc dopaminergic neurons, compared to wild type controls, in response to nicotine [34]. It would be interesting to know how this mutation affects nicotine self-administration, with respect to rate of acquisition and rate of responding.

How does the predominance given to β2* nAChRs in the above studies relate to the view that burst firing is largely influenced by NMDA receptors on dopamine cell bodies, activated by glutamate released from afferents from the PFC [13,35]? In this model nicotine increases burst firing via stimulation of presynaptic α7

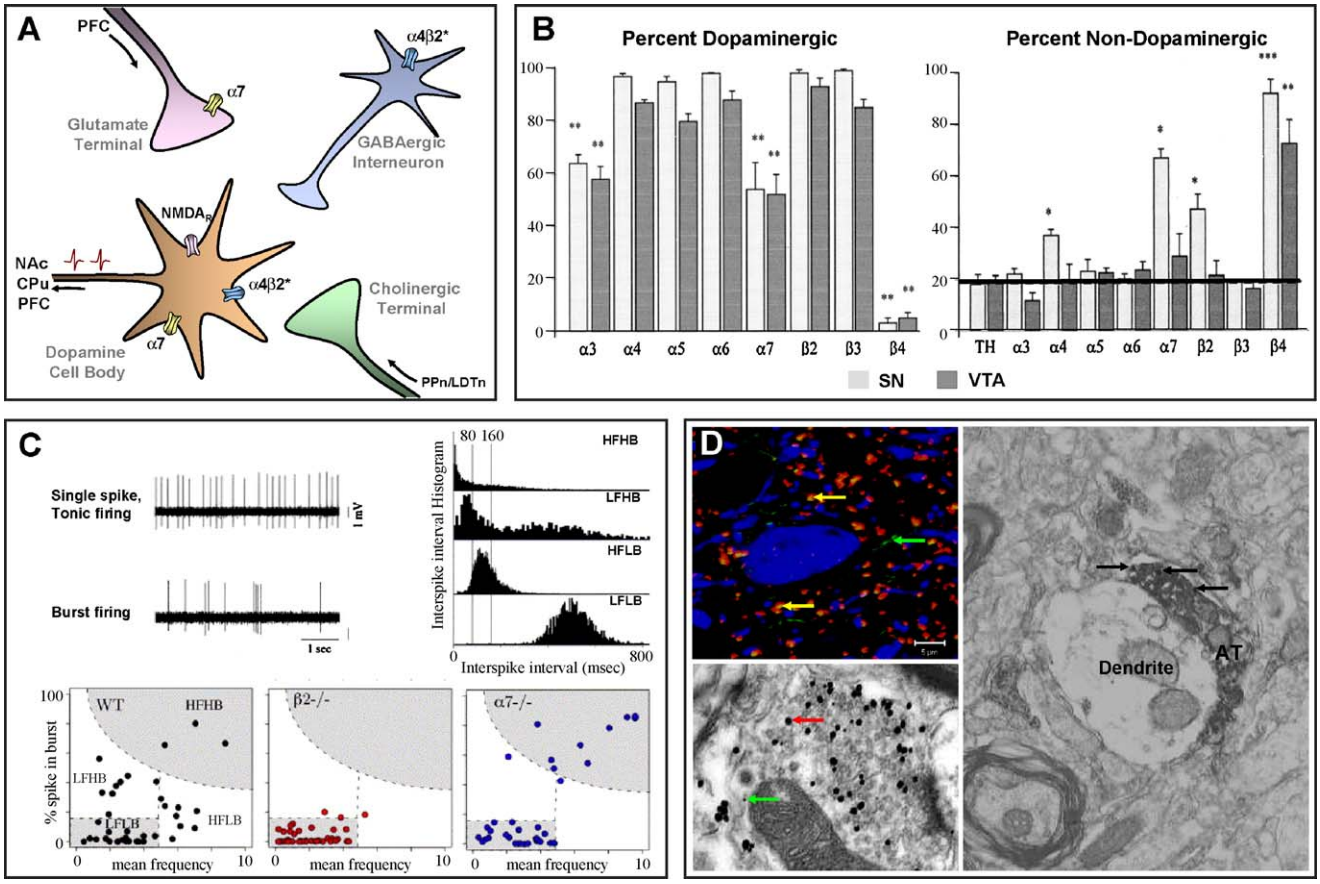


Fig. 2. Contribution of nAChRs to dopamine cell firing in the VTA/SNc. (A) Model indicating the key locations of α4β2* and α7 nAChR subtypes. ACh is released from terminals of projections from pedunculopontine and laterodorsal tegmental nuclei (PPn and LDTn). GABAergic interneurons bear α4β2* nAChRs and glutamate afferents from the prefrontal cortex (PFC) and elsewhere express α7 nAChRs (α7 nAChRs might also be present on GABAergic interneurons and afferents, not shown). NMDA receptors on dopamine cell bodies determine firing patterns. (B) Expression of nAChR subunit mRNA in tyrosine hydroxylase positive (dopaminergic) and negative (non-dopaminergic) neurons using *in situ* hybridisation. Many dopaminergic neurons in the SN/VTA express nAChR subunits (left side). The relative expression of subunits in non-dopaminergic cells (right side) shows significant expression of α4, α7 and β2 in SN and β4 in SN/VTA. Horizontal black bar denotes sensitivity limit for tyrosine hydroxylase-negative cells (modified from [18]). (C) VTA dopamine cell firing modes and changes observed in nAChR subunit knockout mice. Single cell in vivo electrophysiology recordings from a dopaminergic neuron show tonic and burst firing patterns (top left). Four firing modes in wild type (WT) mice (top right) consist of high or low frequencies (HF or LF) with high or low bursting activity (HB or LB). Frequency of spikes plotted against percentage of spikes in a burst (bottom) shows the distribution of the four firing modes in WT VTA (lower left panel). The HFHB mode is absent in β2 subunit knockout mice (red; middle panel) whereas in VTA from α7 knockout mice the HFHB mode is preserved (blue; right panel; reproduced from [25], with permission from Elsevier). (D) Localisation of α7 nAChRs using α-bungarotoxin (αBgt) in rat VTA. Top left shows α7 nAChRs (alexa fluor 488-conjugated αBgt, green arrow), vesicular glutamate transporter 2 (VGluT2), a marker of glutamate terminals (red) and tyrosine hydroxylase (blue) in fixed sections. Yellow arrows indicate examples of colocalisation of α7 nAChRs with VGluT2. Bottom left panel, subcellular colocalisation of biotinylated αBgt (small black particles, green arrow) and VGluT1/2 (large black particles, red arrow), using anti-biotin 1 nm gold and secondary antibodies to vGluT1/2 conjugated to large gold particles, respectively. An axon terminal is decorated with particles of both sizes, indicative of colocalisation. Right panel, in an aldehyde-fixed section of VTA α7 nAChRs labelled with biotinylated αBgt and anti-biotin gold, followed by silver enhancement (black particles, some indicated by arrows), are found in a vGluT1/2-immunopositive axon terminal (AT; revealed by diaminobenzidine reaction product) (I.W. Jones and S. Wonnacott, unpublished).

nAChRs on the glutamate afferents. There is immunocytochemical evidence for α7 nAChRs on glutamate terminals in the VTA [24] (Fig. 2D), supporting functional evidence that nicotine can sustain long-lasting presynaptic facilitation and NMDA receptor-dependent long-term potentiation [30,36]. In vivo single cell recordings from rat VTA indicated that β2* nAChRs contribute to increased firing rate but not bursting [37]. However, systemic nicotine was unable to alter the firing mode of dopaminergic neurons in the VTA in β2 −/− mice, an effect reversed by re-expression of the β2 subunit in this region [25]. Thus in β2 −/− mice, activation of α7 nAChRs is insufficient to elicit burst firing. Conversely, the observation that α7 −/− mice can switch to burst firing following systemic nicotine also emphasises the importance of β2* nAChRs in this phenomenon. A caveat to this interpretation is that excitability in the VTA may be altered in α7 knockout animals, for example, α7 nAChRs may also be expressed by VTA GABAergic neurons [17,24] and/or regulation of the excitability of glutamatergic afferents may be compromised by the absence of α7-mediated inhibition of pyramidal outputs from the PFC [38,39].

A concerted hypothesis for the nicotinic control of burst firing [40] posits that nicotine rapidly and preferentially desensitises α4β2 nAChRs on GABAergic interneurons [41], relieving inhibition of midbrain dopamine neurons while maintaining a sustained activation of α7 nAChRs on dopaminergic cell bodies as well as glutamate terminals [30]. β2* nAChRs on dopamine cell bodies provide a coincident depolarisation that enhances excitability, and this is necessary for LTP and/or to drive changes in firing pattern. Thus multiple nAChR subtypes play essential and complex roles in modulating the repertoire of firing patterns in midbrain dopamine neurons and a balance of activation and desensitisation of nAChRs is critical [42]. However our understanding of their roles is incomplete: for example, the contribution of α7 nAChRs on GABAergic neurons is unclear. The regulation of burst firing is further complicated by the possibility that somatodendritic dopamine release can promote glutamate release in the VTA, presumably by acting at D1 receptors on glutamatergic afferents [43,44]. In addition to the well characterised nicotinic modulation of dopamine release in the terminal regions, nicotine also

promotes somatodendritic dopamine release in the VTA/SNc [45]. Moreover, endogenous nicotinic signalling must be disentangled from responses to acute versus chronic nicotine, made more challenging by the complex pharmacodynamics and pharmacokinetics of modelling human nicotine consumption through cigarette smoking (see [46]). Extrapolation between in vivo and in vitro studies is also problematic as inherent firing patterns may not be preserved in the latter. A recent study [16] overcame this problem by recording firing patterns from midbrain dopamine neurons of freely moving rats in vivo and subsequently reproducing the same firing rates in striatal slices in vitro, allowing measurement of dopamine release probability across the striatum during firing modes representative of nicotine administration in the midbrain.

3. The nicotinic modulation of dopamine release in the dorsal striatum and NAc

The firing rates of midbrain dopaminergic neurons are the major determinants of dopamine release in the terminal fields. Basal firing patterns maintain a low concentration of extracellular dopamine whereas burst firing efficiently increases dopamine concentration in a spatially and temporally circumscribed manner [47]. As discussed above, nAChRs in the SNc and VTA influence the firing rates of these neurons and the VTA is the locus of action of systemically administered nicotine with respect to increased dopamine release in the NAc [29–31,48]. However, local application of nicotine to the NAc or dorsal striatum in vivo increases dopamine overflow [49,50], and striatal dopamine terminals express multiple nAChR subtypes that promote the release of radiolabelled dopamine from in vitro preparations (synaptosomes or prisms; Fig. 3A). The presynaptic regulation of dopamine release has been extensively studied [51,52].

Selective pharmacological tools, immunoprecipitation, knockout mice and lesion studies have contributed to defining the subunit composition of presynaptic nAChRs on dopamine terminals [17,53–55]. β2 subunits are ubiquitous in these nAChRs; α4β2* and α6β2* subtypes can be distinguished on the basis of their differential sensitivity to α-conotoxinMII (Fig. 3C). These have been further subdivided into five β2-containing nAChRs: α4β2, α4α5β2, α6β2, α6β2β3 and α4α6β2β3 [52], with the α4α6β2β3 subtype deduced to have the highest sensitivity to nicotine [56]. These presynaptic receptor subtypes are consistent with mRNA expression in the dopaminergic cell bodies of the VTA/SNc [17,18]; Fig. 2B. Segregation of α6-containing and α4(non-α6)-containing nAChRs to distinct populations of dopaminergic fibres with different firing patterns has been proposed [57]. nAChR

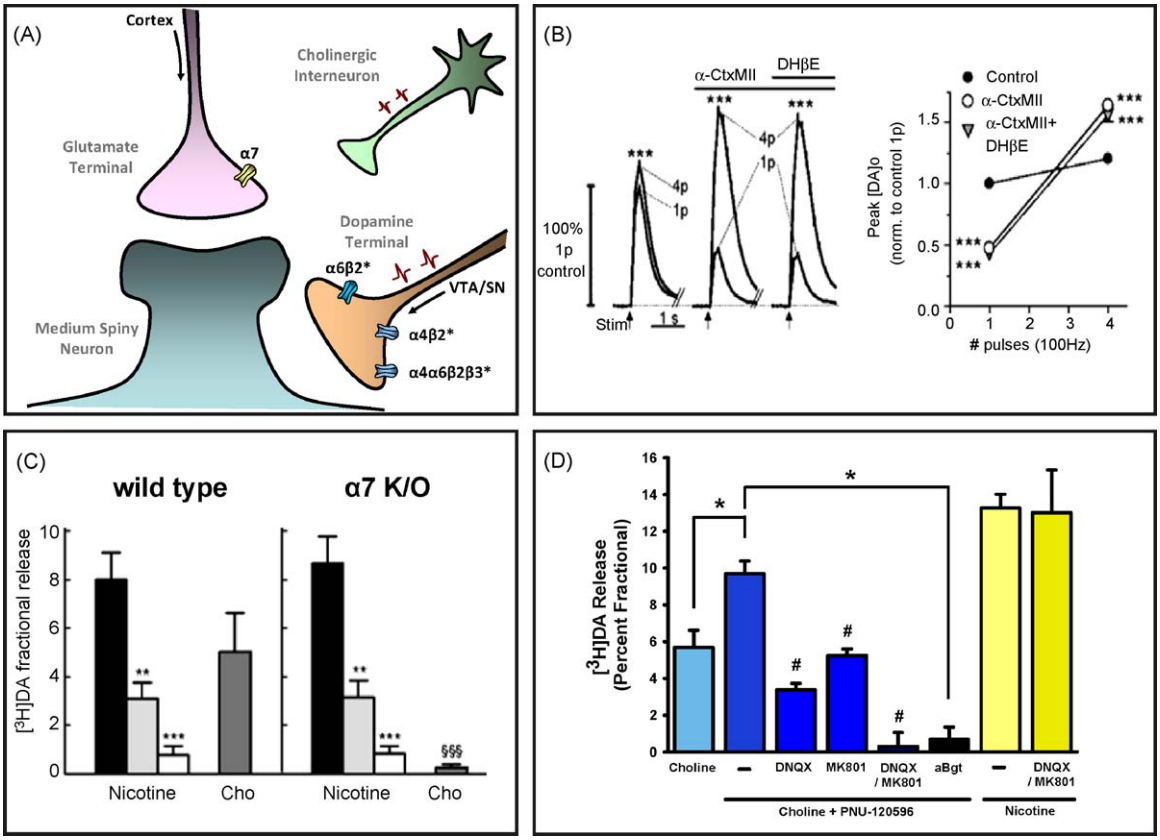


Fig. 3. Heterogeneity of presynaptic nicotinic receptors modulating striatal dopamine release. (A) Model of nAChRs on dopamine and glutamate afferents. Dopamine terminal from ventral tegmental area (VTA) or substantia nigra pars compacta (SNc) forms a synapse with a GABAergic striatal medium spiny neuron. nAChRs of the α4β2* and α6β2* subtypes, including α4α6β2β3*, are situated on dopamine terminals (they are not necessarily colocalised on the same terminal) and α7 nAChRs reside on glutamate terminals. Tonically active cholinergic interneuron firing is coupled with dopamine cell firing. GABA interneurons are omitted for clarity. (B) Effect of electrical pulse stimulation of nucleus accumbens coronal slices on extracellular dopamine concentration measured using fast-scan cyclic voltammetry. nAChR antagonists (DHβE and α-conotoxinMII) enhance the difference between responses to one and four pulses (100 Hz; left side). Peak height (right side) highlights the increased contrast in dopamine release produced by blockade of β2* (DHβE) or α6* (α-conotoxinMII) nAChRs, an effect mimicked by nicotine (not shown). (Reproduced from [84], with permission from Nature Publishing Group.) (C) Evidence for β2* and α7 nAChRs facilitating [^{3}H]dopamine release in mouse striatal prisms. Inhibition of responses to 1 μM nicotine by α-conotoxinMII (light grey bars) or DHβE (open bars) or in wild type mice implicates both α6 and non-α6 nAChR subtypes. Their contribution is unchanged in α7 knockout (K/O) mice. Choline-evoked responses in wild type mice are absent in α7 knockout animals. (Reproduced from [70], with permission from Springer Publishing.) (D) Contribution of α7 nAChR to rat striatal [^{3}H]dopamine release in tissue prisms. Choline (3 mM), with or without the allosteric modulator PNU-120596 (10 μM blue bars) increases release of [^{3}H]dopamine in an αBgt-sensitive manner. The $AMPA_R$/$Kainate_R$ antagonist DNQX (200 μM) and the $NMDA_R$ antagonist MK801 (5 μM) partially inhibit choline plus PNU-120596-mediated release and fully attenuate the effect when combined. [^{3}H]dopamine release evoked by nicotine (1 μM) is insensitive (yellow bars) to DNQX or MK801. (Modified from [69].)

heterogeneity is further enhanced by the variable stoichiometry of the $\alpha4\beta2$ subtype, with the $(\alpha4)_2(\beta2)_3$ configuration conferring higher sensitivity to ACh than $(\alpha4)_3(\beta2)_2$ [58,59]. Evidently in a nAChR pentamer the fifth 'accessory' subunit that does not contribute directly to the agonist binding sites nevertheless influences the sensitivity of the nAChR to agonist. In heterologous expression systems the switch from low to high sensitivity stoichiometry is promoted by exposure to chronic nicotine [58]. Similar stoichiometric variation can be anticipated for the $\alpha6\beta2$ nAChR subtype; multiple stoichiometries may contribute to the biphasic nature of ACh-stimulated $^{86}Rb^+$ efflux (a neurochemical assay of ion flux through open nAChR channels) from mouse striatal synaptosomes [60].

Despite the expression of $\alpha7$ nAChR subunit mRNA in a proportion of midbrain dopaminergic neurons (Fig. 2B), there is little evidence for the presence of $\alpha7$ nAChRs on dopamine terminals, as judged by their inability to influence [^{3}H]dopamine release from isolated nerve terminals [61–63]. Therefore this subtype may be restricted to somatodendritic regions of dopamine neurons. However, presynaptic nAChRs capable of modulating dopamine release in the striatum are not exclusively expressed on striatal dopaminergic terminals and in vitro approaches using more intact tissue preparations (slices, or prisms) can reveal neighbouring influences arising from the nicotinic modulation of other neurotransmitters, and a role for $\alpha7$ nAChRs is seen in this context.

The presence of $\alpha7$ nAChRs on glutamatergic afferents was initially inferred from the ability of a variety of antagonists selective for $\alpha7$ nAChRs or ionotropic glutamate receptors (iGluR) to partially inhibit [^{3}H]dopamine release evoked by the nicotinic agonist anatoxin-A in rat striatal prisms [64]. This arrangement is consistent with the release of [^{3}H]D-aspartate in response to activation of $\alpha7$ nAChRs and the release of [^{3}H]dopamine following stimulation of iGluRs observed in striatal synaptosome preparations [65–67]. Subsequently, the availability of novel $\alpha7$ nAChR-selective agonists, antagonists, and positive allosteric modulators has confirmed that $\alpha7$ nAChRs induce [^{3}H]dopamine release in striatal preparations [68,69] (Fig. 3D), and this response is absent in $\alpha7$ knockout mice [70] (Fig. 3C). The modulation of striatal dopamine release by two local populations of nAChRs ($\alpha7$ and non-$\alpha7$) is also observed in vivo. Administration of drugs directly into the striatum by reverse dialysis in freely moving rats resulted in a partial blockade of nicotine- or anatoxin-A-induced dopamine overflow by methyllycaconitine (MLA), an antagonist that is relatively selective for $\alpha7$ nAChRs, or α-Bgt [71,72].

Neuronal architecture of the striatum is well defined (Fig. 3A): dopamine terminals form typical symmetric synapses onto the dendritic spines and shafts of medium spiny GABAergic neurons of the striatum. These neurons are principally influenced by cortico-striatal glutamatergic afferents that make asymmetric synapses onto the heads of dendritic spines [73,74]. Thus glutamatergic terminals are in close proximity to dopaminergic boutons to facilitate transmitter crosstalk. In addition to GABAergic projection neurons, the striatum also contains a small population of GABAergic interneurons [75]. The nicotinic facilitation of [^{3}H]GABA release from mouse striatal synaptosomes has implicated $\alpha4\beta2^*$ and $\alpha4\alpha5\beta2^*$ nAChRs on GABAergic terminals, from comparison of nAChR subunit null mutant mice [76]. It is unclear if these receptors indirectly modulate dopamine release, although the influence of dopamine on local GABA release is well documented [77,78]. There is no evidence that striatal cholinergic interneurons, the source of endogenous agonist, are modulated by nAChRs [79] although $\alpha7$ and $\beta2$ subunit mRNA has been detected in these cells [80].

Given the diversity of presynaptic nAChR subtypes in the striatum, and their propensity to facilitate the release of dopamine and other transmitters, one has to consider what their physiological function might be. This is particularly intriguing in light of the dominant role of midbrain nAChRs in driving the firing patterns of dopamine neurons and the coupling between rate of action potential firing and dopamine release. At rest, tonic regular firing occurs at a rate of 2–5 Hz, this can increase to bursts of action potentials having a frequency of 15–100 Hz during 'reward presentation' [14] but firing can also 'pause', and this phenomenon is observed during reward omission [81]. Insight into the contributions of presynaptic nAChRs to dopamine release from active neurons has come from the application of fast-scan cyclic voltammetry (FSCV) to monitor endogenous dopamine release from coronal striatal slices with subsecond temporal resolution [16,82,83]. Typical firing rates can be simulated by electrical stimulation of striatal slices in vitro.

These experiments have led to the proposition that presynaptic nAChRs act as a 'filter' to enhance the contrast between different firing patterns with respect to dopamine release [16,84]. Thus during low frequency action potential firing in dopaminergic afferents, presynaptic $\beta2^*$ nAChRs are activated by ACh released from tonically active cholinergic interneurons, and increase dopamine release, ensuring that it is sustained throughout this mode of firing [85]. Desensitisation of nAChRs is avoided by the rapid turnover of ACh due to acetylcholinesterase activity. When dopaminergic firing pauses, so do the cholinergic interneurons and dopamine release is reduced. Burst firing in dopaminergic axons is also accompanied by a pause in cholinergic activity; sustained dopamine release is observed without the intervention of presynaptic nAChRs [83] (Fig. 3B). The lack of nicotinic potentiation of dopamine release during burst firing is proposed to avoid depletion of the readily releasable pool of neurotransmitter. It is noteworthy that neither GABA nor glutamate promotes dopamine release measured using FCSV, despite the evidence for $\beta2^*$ and $\alpha7$ nAChRs on striatal GABAergic terminals and glutamatergic afferents respectively [86,87].

In this model, the effects of nicotine on dopamine release are opposite to those of endogenous ACh [82,83]. Thus responses to tonic low frequency stimulation are reduced in magnitude whereas phasic bursts of action potentials result in increased levels of dopamine. This paradoxical action reflects the propensity of nicotine to desensitise $\beta2^*$ nAChRs. nAChR antagonists produce similar effects (Fig. 3B), which could explain, in part, the failure of DHβE to have any effect on nicotine self-administration when locally infused into the NAc of rats [29]. Thus nicotine, by its contrasting effects in response to tonic and phasic firing patterns, could enhance the salience of rewarding information and this might be germane to its addiction liability. Prior chronic nicotine treatment in vivo resulted in increased dopamine release (monitored by FSCV) in response to burst firing in striatal slices, compared with tissue from untreated controls. However, this response was reduced (rather than enhanced as in Fig. 3B) by the $\alpha6\beta2^*$-selective nAChR antagonist α-conotoxinMII [88]. It is possible that this ex vivo analysis may reflect the initial withdrawn state.

The use of α-conotoxinMII highlights the importance of $\alpha6\beta2^*$ nAChRs in regulating striatal dopamine release [88]. The striatum can be subdivided anatomically and functionally (see Appendix A) and there is evidence for $\alpha6\beta2^*$ having a greater role in the NAc than in the dorsal striatum [57,83]. A similar conclusion was reached by Drenan et al. [34] using 'knock-in' mice with gain of function $\alpha6\beta2^*$ nAChRs that are hypersensitive to agonist. The mice are hyperactive and acute administration of a low dose of nicotine produces locomotor activation. In contrast wildtype mice are insensitive to low nicotine doses and exhibit locomotor depression in response to higher doses. The behavioural phenotype of the mutant mice is consistent with enhanced dopamine release and may reflect enhanced responding to novelty (exploratory

behaviour) governed by the mesolimbic pathway [34]. A striking difference between the shell of the NAc and dorsal striatum with respect to dopamine release probability was shown using FSCV [16]. The extent to which α6β2* nAChRs contribute to this difference is not known. It would be illuminating to know the effect of gain of function α6β2* nAChRs on endogenous dopamine release evoked by tonic versus phasic stimulation of striatal slices. One can speculate that the mutated receptors would be less prone to desensitisation and hence they could initially enhance release during bursts but this would be unsustainable due to pool depletion and synaptic depression [84]. Further studies are required to establish the contribution of presynaptic nAChRs to dopamine release in vivo.

4. Nicotinic receptor-mediated facilitation of dopamine release in the PFC

It is now well-established that rodents have a functional prefrontal cortex able to perform many of the same rudimentary processes seen in primates and humans [89], including aspects of cognition, motor and reward anticipation [90,91] (see Appendix A). Changes in dopamine, glutamate and GABA transmission in this region can lead to cognitive or attentional impairment, resulting in conditions such as schizophrenia and attention deficit hyperactivity disorder [92–95] and an imbalance in prefrontal dopamine versus glutamate systems underpins many hypotheses regarding the development of schizophrenia [96]. The potential of nAChRs in the PFC to modulate these neurotransmitter systems has prompted characterisation of their properties (Fig. 4A).

Local administration of nicotine into the rat PFC improves attentional performance in the five-choice serial reaction time task [97], consistent with the presence of functional nAChRs in this brain region. However, the PFC has been relatively neglected with respect to the characterisation of nAChR subtypes present. Many earlier studies into nAChR distribution either failed to examine the anterior frontal cortex or did not distinguish it from the rest of the frontal cortex. Comparison of the autoradiographical distributions of [^{3}H]nicotine and [^{125}I]αBgt binding, specific labels for β2* and α7 nAChR subtypes, provided evidence for the presence of both classes of nAChR, with complimentary distributions, in the PFC in saggital rat brain sections [98].

Immunoprecipitation experiments to define the nAChR subunits present in rat PFC tissue identified α4, α5 and β2 but levels of α6 or β3 subunits did not reach significance [69] (Fig. 4B). Moreover, although nicotine induces [^{3}H]dopamine release from PFC prisms and this is blocked by DHβE, indicative of β2* nAChRs, it is insensitive to α-conotoxinMII [69,99]. Therefore, in contrast to striatum, α6* nAChRs are absent from PFC. Because α-conotoxinMII blocks both α6β2* and α3β2* nAChRs, this result also excludes the latter subtype so a more limited portfolio of nAChR subtypes (comprised of α4, α5 and β2 subunits only) exists to modulate dopamine release. Thus mesocortical projections have arisen from a population of dopamine neurons in the VTA that is distinct from those giving rise to the mesolimbic pathway [17].

The glutamatergic pyramidal cells in layer V of the PFC do not express functional nAChRs [39] but nicotine increases spontaneous excitatory postsynaptic currents (EPSCs) in these cells, attributed to its ability to increase glutamate release from neighbouring afferents [39,100,101]. Thalamocortical glutamatergic afferents projecting to layer V of the PFC are endowed with functional β2* nAChRs [100,101] (Fig. 4C). Indeed, stimulation of PFC synaptosomes with a β2-selective agonist increases the release of [^{3}H]D-aspartate, consistent with the location of β2* nAChRs on glutamatergic terminals [102]. In the rat PFC α7 nAChRs have also been localised to glutamatergic terminals, as well as GABAergic terminals and cell bodies [103]. α7 nAChR agonists also induce [^{3}H]D-aspartate release from PFC synaptosomes, but via a distinct cellular mechanism compared with β2* nAChRs [102]. It is not known if α7 and β2* nAChRs co-exist on the same glutamate terminals.

Nicotinic modulation of GABAergic transmission also contributes to PFC activity. A diverse array of GABAergic interneuron types exist in rat PFC [104,105]. These can be crudely separated into two classes; fast spiking and non-fast spiking. Single cell mRNA analysis indicates that in the mouse PFC non-fast spiking interneurons express α4, β2 and α7 nAChR subunits, whereas fast spiking cells do not express any of these nAChR subunits but can be influenced by nicotinic potentiation of excitatory inputs [39]. This study focused on the ability of nicotine to increase inhibitory postsynaptic currents (IPSCs) (Fig. 4D) and reduce LTP in layer V pyramidal cells, due to augmented release of GABA from interneurons. As a result, the threshold for spike-time dependant plasticity in layer V pyramidal cells of the medial PFC is increased. Potentially, this modulation of the PFC neuronal network by nicotine can change the rules for synaptic plasticity [39]. Such a mechanism could enhance the accuracy of rodents when performing cognitive tasks but in both rats and humans this depends on the baseline cognitive state [106,107].

Dopamine and glutamate systems can act in synergy with GABA to control pyramidal cell excitability [108–110] and nicotine has been instrumental in revealing the nicotinic modulation of these interactions, but how is this achieved by the endogenous transmitters ACh and choline? Activation of α4β2* nAChRs residing on prefrontal dopaminergic and glutamatergic afferents is proposed to result in the release of ACh from cholinergic projections to the PFC from the nucleus basalis of Meynert [111,112]. The known changes in tonic to phasic release of ACh from these neurons during increased performance in a cue detection task may permit alterations in GABAergic interneuron firing, hence affecting PFC network function [113]. It is noteworthy that muscarinic receptors in the PFC can also increase GABA release and depress pyramidal cell excitability [114].

Dopamine is a prominent modulator of executive function [115] and nicotine delivered systemically [116] or locally [50] elicits dopamine release in the medial PFC in conscious, freely moving rats. To address the subtypes of nAChR responsible within the PFC, subtype-selective agonists have been employed. Local delivery of either β2*- or α7-selective agonist into the rat medial PFC increased dopamine overflow measured by microdialysis, implying a positive role for both β2* and α7 nAChRs on dopamine release, in agreement with in vitro data for release from PFC prisms [69]. The in vitro experiments indicate that the action of α7 nAChRs is indirect, requiring the intervention of glutamate release to activate ionotropic glutamate receptors, as previously described for striatum (Fig. 3D). The novel α7 nAChR-selective positive allosteric modulator PNU-120596 enhanced responses to α7 nAChR agonist in vitro and in vivo. This modulator can be used to detect the presence of endogenous agonist in vivo, as it is ineffective at activating α7 nAChRs on its own [117]. Interestingly, PNU-120596 elicited dopamine overflow in the medial PFC when administered systemically, and this response was attenuated by systemic MLA, but it was ineffective when delivered locally into the PFC [69] (Fig. 4E). Tonic cholinergic activity, possibly arising from the pontine nuclei projecting to the VTA (Fig. 2A), may account for the extracortical stimulation. However, during cognitive performance (not encompassed in Livingstone et al. [69]) ACh would be released in the PFC [113] allowing locally administered PNU-120596 to become effective in releasing dopamine under these conditions. Hence positive allosteric

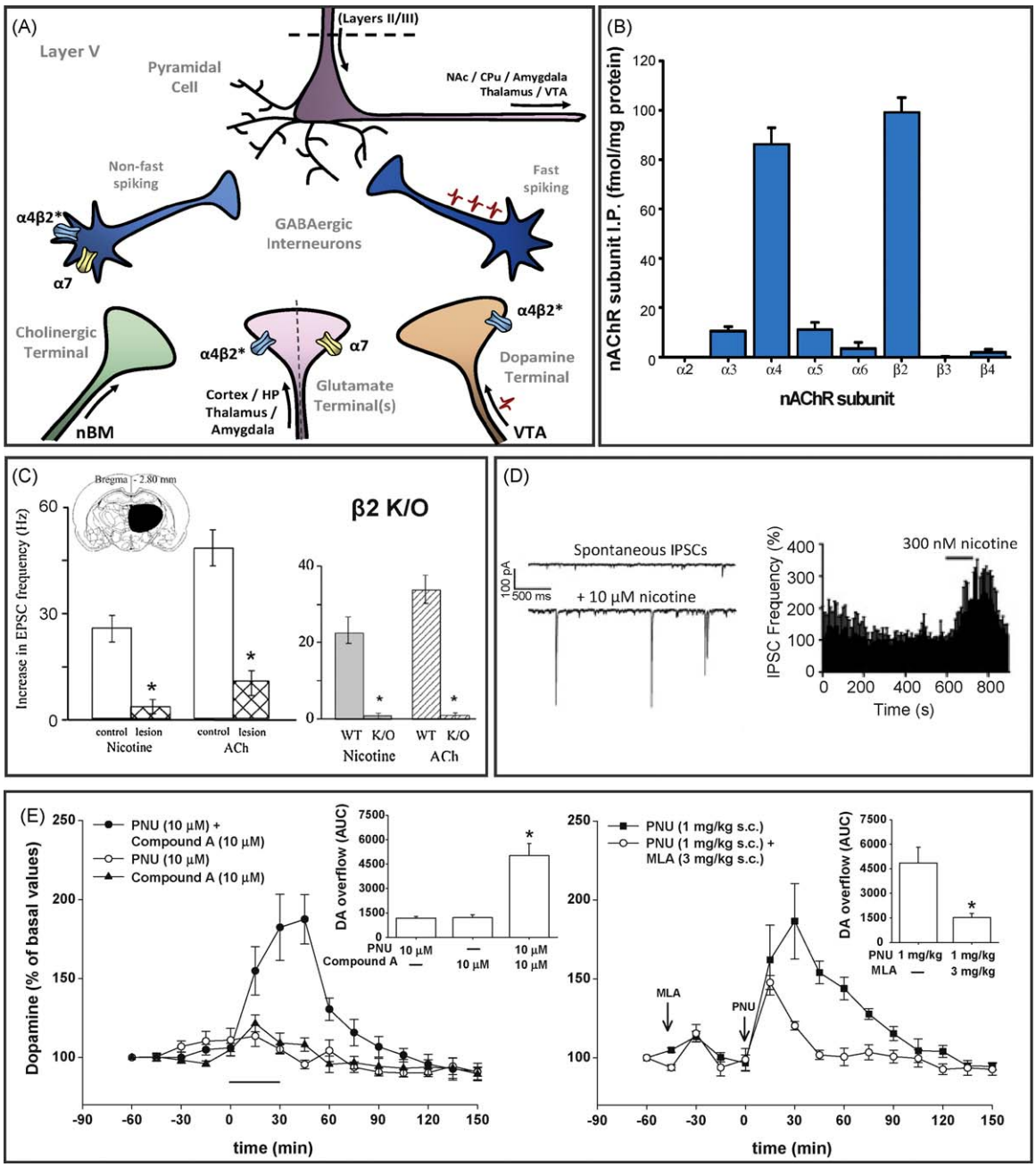


Fig. 4. nAChRs in the PFC. (A) Converging afferents and interneurons bearing nAChRs influence PFC glutamatergic pyramidal cells in PFC layer V. Two categories of GABAergic interneurons, fast spiking and non-fast spiking, are distinguished; only non-fast spiking interneurons express nAChRs (β2* and α7) (these interneurons also project to pyramidal cell apical dendrite in layers II/III). Presynaptic α7 or α4β2* nAChRs may be segregated to distinct populations of glutamatergic afferents (dashed line). Dopamine terminals express α4β2* nAChRs and are in proximity to glutamatergic afferents bearing α7 nAChRs. Cholinergic innervation is from the nucleus basalis of Meynert (nBM). Reciprocal crosstalk between glutamate, dopamine and GABA neurons affects activity and synaptic plasticity in the projection neurons (pyramidal cells). (B) Immunoprecipitation of nAChR subunits from rat PFC using subtype-selective antibodies. Modified from [69]. (C) Nicotine and ACh increase excitatory postsynaptic currents (EPSCs) in single pyramidal cells. These responses are sensitive to thalamic lesions (left, insert: section showing extent of lesion, black) and are absent in β2 nAChR subunit knockout (K/O) mice (right), compared to wild type (WT). (Reproduced from [101], with permission from Nature Publishing Group.) (D) Nicotine also increases inhibitory postsynaptic currents (IPSCs) in PFC layer V pyramidal neurons. Both high (10 μM, left) and low (300 nM, right) nicotine concentrations augment spontaneous IPSC frequency. (Reproduced from [39], with permission from Elsevier.) (E) α7 nAChRs increase dopamine overflow in medial PFC in freely moving rats. Local perfusion (bar) of a subthreshold concentration of the α7 nAChR selective agonist Compound A plus the positive allosteric modulator PNU-120596 increases dopamine overflow whereas PNU-120596 alone had no effect (left). Systemic administration of PNU-120596 does increase dopamine overflow and this is attenuated by systemic methyllycaconitine (MLA, right). Modified from [69].

modulators of α7 nAChRs have therapeutic potential for restoring cognitive deficits in conditions involving PFC dysfunction [10]. Indeed, a role for α7 nAChRs in PFC function is implicit in the deficits in attention and working memory performance in knock-out mice lacking this nAChR subunit [118,119], although it is unclear in these studies if the critical α7 nAChRs are located in the PFC or elsewhere in the brain.

5. Downstream consequences of dopamine release

The previous sections have established that dopamine release in the terminal fields of the ascending dopamine pathways is influenced by a variety of nAChR subtypes on dopaminergic cell bodies, terminals and neighbouring neurons. Postsynaptic dopamine receptor activation results in numerous downstream

responses, including phosphorylation of strategic proteins and changes in gene expression, and results in altered target cell excitability. Here we briefly consider the impact of nAChR activation on these downstream effectors.

In the striatum, dopamine can increase the excitability of medium spiny neurons of the striatonigral direct pathway via dopamine D1 receptors and can suppress those neurons of the striatopallidal indirect pathway, mainly via dopamine D2 receptor activation [120,121]. The key effector protein, downstream of D1 receptors and inhibited by D2 receptor activation, is protein kinase A (PKA) [108,121,122]. Activation of PKA phosphorylates dopamine- and cyclic AMP-regulated phosphoprotein of 32 kDa (DARPP-32) at Thr34, making it a potent inhibitor of protein phosphatase 1. This protein is abundant in all medium spiny neurons and operates as a 'molecular switch' [123,124]. The status of DARPP-32 can ultimately result in changes in the excitability of medium spiny neurons. Longer term changes may reflect the function of DARPP-32 as a critical modulator of ERK, ELK and CREB signalling [123,125].

Nicotine has been reported to alter DARPP-32 activity, in vitro and in vivo. In mouse striatal slices in vitro, nicotine produced differential, concentration-dependent changes in DARPP-32 activity, reflecting the activation of D2 and D1 receptors by low and high dopamine concentrations, respectively [126]. D2 activation was attributed to low nicotine concentrations activating $\alpha4\beta2$ nAChRs on dopaminergic terminals whereas higher nicotine concentrations were inferred to also activate $\alpha7$ nAChRs on neighbouring glutamate afferents, resulting in greater dopamine release (see Fig. 3A). In vivo, nicotine, like other psychostimulants, increases the phosphorylation of ERK in the NAc and prefrontal cortex in a D1-dependant manner [127]. ERK phosphorylation has an important impact on synaptic plasticity by increasing gene transcription in the postsynaptic neuron and this occurs in the NAc as a direct consequence of DARPP-32 phosphorylation [125]. Increased phosphorylation of CREB accompanies DARPP-32 phosphorylation in the NAc in response to pyschostimulant administration [128]. CREB acts as a transcription factor to alter gene expression of immediate early genes such as c-Fos. Nicotine administration (systemic, or locally into the VTA) increases c-Fos transcription in the NAc [129,130]. Such changes allow for a reduced excitability threshold in the medium spiny neurons of the direct pathway and behavioural adaptations to administered drugs such as cocaine [131].

Chronic nicotine produces a complex set of changes in phosphorylation [132] and expression of immediate early genes [133–136], perhaps most notably in NAc. Persistent increases in FosB expression were observed in NAc of rats following periadolescant nicotine exposure [136]. Accumulation of a long-lived truncated form of FosB, deltaFosB, following drug administration (including nicotine) [135] has been proposed as a sustained molecular change that contributes to the persistence of drug dependence and the propensity to relapse [137]. The loci of action of nicotine in these in vivo treatments are likely to be complex but the overall contribution of mesolimbic nAChR activation to downstream effectors in medium spiny neurons of the striatum will depend on the opposing actions of dopamine upon both D1 and D2 receptors of the direct and indirect pathways [126,138] as well as D2 autoreceptors on dopaminergic nerve terminals [139].

In the PFC the role of DARPP-32 is less clear than in striatum. Neither changes in ERK phosphorylation [125] nor increases in excitability of fast spiking GABAergic interneurons [140] depend on the phosphorylation of DARPP-32. It is likely that pathways involving DARPP-32 and ERK in the PFC are less integrated than in the NAc. The ability of dopamine in vitro to increase ERK phosphorylation in the PFC is sufficient to induce LTP in pyramidal cells, when NMDA receptors are also activated [141]. However, there is some evidence for negative regulation through DARPP-32: D2 receptors on pyramidal neurons are coupled to DARPP-32, resulting in reduced excitability [142]. How nAChRs in the PFC interface with these signalling pathways remains to be determined.

6. Concluding remarks

From this review of the literature it is striking that nAChRs can influence dopamine pathways in a variety of ways, reflecting their subcellular localisation: somatodendritic, presynaptic or on neighbouring neurons. Their influence ranges from key roles in determining firing rates to modulating transmitter release and enhancing the contrast between different firing modes, achieved through a delicate balance between activated and desensitised states of nAChR subtypes. The consequences of these actions include short and long-term changes in downstream effector molecules. The different modes of nicotine administration (acute, repeated or sustained) impact on all these parameters. We have highlighted, where there is evidence, the contrasting roles of nicotine and the endogenous agonist, ACh. Although a wealth of details have been accrued in recent years there remain many gaps in our knowledge, particularly of how cellular mechanisms elucidated in vitro are integrated in the functioning of the brain in vivo. nAChRs in additional neuronal circuits will also influence the behaviour of the dopamine system, for example in addiction. Further studies are needed to enhance our understanding of the physiologically relevant nAChR-mediated mechanisms, their contributions to disease and therapy, and how these mechanisms are hijacked by nicotine, leading to addiction.

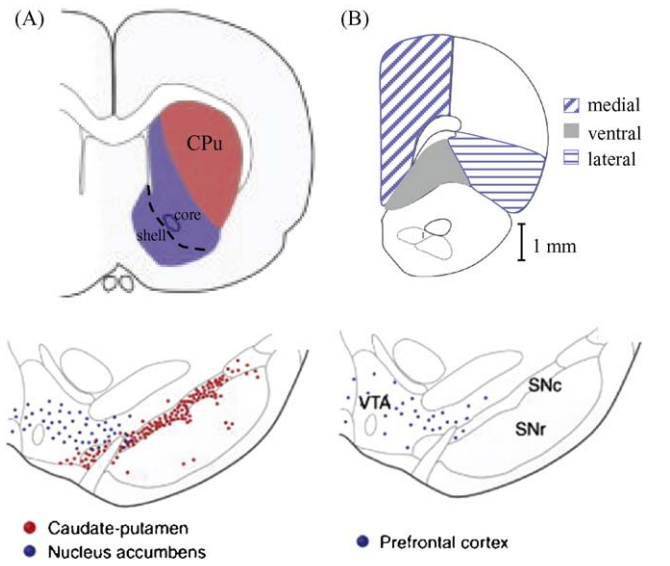
Acknowledgements

Due to space constraints we have been unable to cite all original papers and we apologise to authors whose work in this area has been omitted. Work in our laboratory is supported by grants from the Biological and Biotechnological Sciences Research Council (BBSRC; BBS/B/15600) and The Parkinson's Disease Society (G-0613) to SW and a postgraduate studentship from the BBSRC to PDL.

Appendix A. Anatomical subdivisions of principal regions in the ascending dopamine pathways in rodents

A.1. Midbrain dopamine cell body groups

Identification and classification of the major dopamine neurons in the rodent brain over forty years ago [143] led to the numbering of cell groups A8–A16. Three of these, A8–A10 in the mesencephalon, are the focus of this review. Both A8 and A9 project to the dorsal striatum and correspond to the retrorubral field and substantia nigra pars compacta (SNc), respectively [144]. We refer to these two groups simply as nigral dopamine cells of the nigrostriatal pathway in this review as they are not distinguished in any of the literature discussed and the retrorubral field is considered to be an anatomical extension of the SNc [145]. The substantia nigra pars reticulata (SNr) contains very few dopaminergic neurons. A10 is more commonly known as the ventral tegmental area (VTA) [144,146] and we use the latter term throughout this article, in line with the many studies investigating nAChRs in this region. It should be noted that although the use of A8–A10 is not common in the nAChR-dopamine field, the nomenclature is still current.



Adapted from [142], with permission from Elsevier

Fig. A1.

A.2. Striatum

The dorsal striatum, or caudate putamen (CPu), has a major involvement in motor co-ordination, a faculty impaired in Parkinson's disease [147]. A role for the dorsal striatum in executive functions has also been suggested in rodents and this relies on prefrontal glutamatergic afferents to the CPu [148]. Dopamine afferents arise from the SNc and, to a lesser extent, from the VTA [149] (see Fig. A1, part A, red dots indicate dopaminergic cell bodies that project to CPu). Both innervate multiple areas of the dorsal striatum, due to extensive axonal arborisation [146]. The nucleus accumbens (NAc) comprises the subdivisions referred to as core and shell (see Fig. A, upper panel). NAc core is considered to be ventral striatum but is distinct from CPu in that it receives almost all of its dopaminergic input from the VTA, as does NAc shell [149] (see Fig. A1, part A, purple dots). The NAc and CPu together are typically referred to as 'striatum', particularly in neurochemical experiments. The shell is more limbic in character, constituting a transitional zone between the extended amygdala and the NAc core [150]. The NAc core itself is involved with the increased locomotor properties of psychostimulants hence resembles the dorsal striatum [151,152]. As several drugs of abuse, including nicotine, increase dopamine release in the NAc to a greater extent than in the CPu [153], the mesolimbic dopamine system has been considered to be of critical importance in drug 'reward' or addiction.

Acutely, systemic nicotine preferentially increases dopamine overflow in the NAc shell, mainly by acting at nAChRs in the VTA [154]. This complements observations that dopamine release in the NAc shell predominates during the acquisition phase of responding to psychostimulants [155]. The differential responses of shell and core may reflect differences in the dopamine release probabilities in these regions [16]. A switch to dopamine release predominating in the NAc core is observed in response to repeated nicotine intake [156]. This switch is also observed in response to other psychostimulants [152,157]. NAc core dopamine release is associated with continued drug-seeking behaviour and the transition to dependence that occurs in the longer term [155–157].

A.3. Prefrontal Cortex

Once considered a unique feature of primates and termed the frontal granular cortex, the existence of a PFC in rodents had been viewed as controversial but is now clearly defined. A shift from cytoarchitectonic criteria to consideration of specific connections and functional characteristics as defining properties has supported a strong case for the rodent PFC [89]. Dopamine projections to the prefrontal cortex in rodents arise almost exclusively from the VTA with very limited evidence of afferents from the SNc [144] (see Fig. A1, part B, purple). Reciprocal projections from the PFC to the VTA are a principal source of glutamatergic afferents that are poised to modulate the activity of ascending dopamine neurons [38]. The rat PFC can be subdivided into lateral, ventral and medial aspects (see Fig. A1, part B, upper panel). The lateral and ventral PFC encompass the orbitofrontal cortical areas and are required for odour working memory, feeding, hyperactivity and social behaviours [89]. The medial PFC includes the prelimbic area; lesions greatly impair acquisition and retention in working memory tasks and reduce the ability to shift attention from one set of cues to another (set shifting) as well as reducing the ability to carry out specific motor tasks that require planning, such as food hoarding [89]. Functionally, the rat mPFC is most similar to the dorsolateral PFC in primates, based on lesion and behavioural studies [158]. In mice also, lesions of the prelimbic area reduces adaptation to novel objects and environments requiring decision making and this is supportive of a PFC region able to modulate higher function. The attentional control needed to learn new rules in tasks involving set shifting has been shown in mice to depend on the medial PFC [159]. Demonstration of a functional PFC in both rat and mouse provides useful models for investigating behavioural, genetic or developmental alterations that relate to human disorders of the PFC such as schizophrenia and ADHD.

References

[1] Jay TM. Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. Prog Neurobiol 2003;69:375–90.
[2] Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci 2004;5:483–94.
[3] Floresco SB, Magyar O. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berl) 2006;188:567–85.
[4] Schultz W. Behavioral theories and the neurophysiology of reward. Annu Rev Psychol 2006;57:87–115.
[5] Gotti C, Zoli M, Clementi F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. Trends Pharmacol Sci 2006;27:482–91.
[6] Dajas-Bailador F, Wonnacott S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. Trends Pharmacol Sci 2004;25:317–24.
[7] Mehler-Wex C, Riederer P, Gerlach M. Dopaminergic dysbalance in distinct basal ganglia neurocircuits: implications for the pathophysiology of Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder. Neurotox Res 2006;10:167–79.
[8] Levin ED, Rezvani AH. Nicotinic interactions with antipsychotic drugs, models of schizophrenia and impacts on cognitive function. Biochem Pharmacol 2007;74:1182–91.
[9] Quik M, O'Leary K, Tanner CM. Nicotine and Parkinson's disease: implications for therapy. Mov Disord 2008;23:1641–52.
[10] Timmermann DB, Gronlien JH, Kohlhaas KL, Nielsen EO, Dam E, Jorgensen TD, et al. An allosteric modulator of the alpha7 nicotinic acetylcholine receptor possessing cognition-enhancing properties in vivo. J Pharmacol Exp Ther 2007;323:294–307.
[11] Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: single spike firing. J Neurosci 1984;4:2866–76.
[12] Cooper DC. The significance of action potential bursting in the brain reward circuit. Neurochem Int 2002;41:333–40.
[13] Chergui K, Charlety PJ, Akaoka H, Saunier CF, Brunet JL, Buda M, et al. Tonic activation of NMDA receptors causes spontaneous burst discharge of rat midbrain dopamine neurons in vivo. Eur J Neurosci 1993;5:137–44.
[14] Hyland BI, Reynolds JN, Hay J, Perk CG, Miller R. Firing modes of midbrain dopamine cells in the freely moving rat. Neuroscience 2002;114:475–92.
[15] Grenhoff J, Aston-Jones G, Svensson TH. Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol Scand 1986;128:351–8.

[16] Zhang T, Zhang L, Liang Y, Siapas AG, Zhou FM, Dani JA. Dopamine signaling differences in the nucleus accumbens and dorsal striatum exploited by nicotine. J Neurosci 2009;29:4035–43.
[17] Klink R, de Kerchove d'Exaerde A, Zoli M, Changeux JP. Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. J Neurosci 2001;21:1452–63.
[18] Azam L, Winzer-Serhan UH, Chen Y, Leslie FM. Expression of neuronal nicotinic acetylcholine receptor subunit mRNAs within midbrain dopamine neurons. J Comp Neurol 2002;444:260–74.
[19] Elliott KJ, Jones JM, Sacaan AI, Lloyd GK, Corey-Naeve J. 6-Hydroxydopamine lesion of rat nigrostriatal dopaminergic neurons differentially affects nicotinic acetylcholine receptor subunit mRNA expression. J Mol Neurosci 1998;10:251–60.
[20] Clarke PB, Hommer DW, Pert A, Skirboll LR. Electrophysiological actions of nicotine on substantia nigra single units. Br J Pharmacol 1985;85:827–35.
[21] Calabresi P, Lacey MG, North RA. Nicotinic excitation of rat ventral tegmental neurones in vitro studied by intracellular recording. Br J Pharmacol 1989;98:135–40.
[22] Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. Nature 1997;390:401–4.
[23] Clarke PB, Pert A. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res 1985;348:355–8.
[24] Jones IW, Wonnacott S. Precise localization of alpha7 nicotinic acetylcholine receptors on glutamatergic axon terminals in the rat ventral tegmental area. J Neurosci 2004;24:11244–52.
[25] Mameli-Engvall M, Evrard A, Pons S, Maskos U, Svensson TH, Changeux JP, et al. Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. Neuron 2006;50:911–21.
[26] Maskos U. The cholinergic mesopontine tegmentum is a relatively neglected nicotinic master modulator of the dopaminergic system: relevance to drugs of abuse and pathology. Br J Pharmacol 2008;153(Suppl 1):S438–45.
[27] Mena-Segovia J, Winn P, Bolam JP. Cholinergic modulation of midbrain dopaminergic systems. Brain Res Rev 2008;58:265–71.
[28] Lodge DJ, Grace AA. The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. Proc Natl Acad Sci USA 2006;103:5167–72.
[29] Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res 1994;653:278–84.
[30] Mansvelder HD, McGehee DS. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron 2000;27:349–57.
[31] Sombers LA, Beyene M, Carelli RM, Mark Wightman R. Synaptic overflow of dopamine in the nucleus accumbens arises from neuronal activity in the ventral tegmental area. J Neurosci 2009;29:1735–42.
[32] Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, et al. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 1998;391:173–7.
[33] Pons S, Fattore L, Cossu G, Tolu S, Porcu E, McIntosh JM, et al. Crucial role of alpha4 and alpha6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. J Neurosci 2008;28:12318–27.
[34] Drenan RM, Grady SR, Whiteaker P, McClure-Begley T, McKinney S, Miwa JM, et al. In vivo activation of midbrain dopamine neurons via sensitized, high-affinity alpha6* nicotinic acetylcholine receptors. Neuron 2008;60:123–36.
[35] Tong ZY, Overton PG, Clark D. Antagonism of NMDA receptors but not AMPA/kainate receptors blocks bursting in dopaminergic neurons induced by electrical stimulation of the prefrontal cortex. J Neural Transm 1996;103:889–904.
[36] Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 2002;33:905–19.
[37] Schilstrom B, Rawal N, Mameli-Engvall M, Nomikos GG, Svensson TH. Dual effects of nicotine on dopamine neurons mediated by different nicotinic receptor subtypes. Int J Neuropsychopharmacol 2003;6:1–11.
[38] Carr DB, Sesack SR. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. J Neurosci 2000;20:3864–73.
[39] Couey JJ, Meredith RM, Spijker S, Poorthuis RB, Smit AB, Brussaard AB, et al. Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. Neuron 2007;54:73–87.
[40] McKay DB, Chang C, Gonzalez TF, McKay SB, El-Hajj RA, Bryant DL, et al. Analogs of methyllycaconitine as novel noncompetitive inhibitors of nicotinic receptors: pharmacological characterization, computational modeling, and pharmacophore development. Mol Pharmacol 2007;71:1288–97.
[41] Wooltorton JR, Pidoplichko VI, Broide RS, Dani JA. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci 2003;23:3176–85.
[42] Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not "either/or": activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. Prog Neurobiol 2008;84:329–42.
[43] Kalivas PW, Duffy P. D1 receptors modulate glutamate transmission in the ventral tegmental area. J Neurosci 1995;15:5379–88.
[44] Wolf ME, Xue CJ. Amphetamine and D1 dopamine receptor agonists produce biphasic effects on glutamate efflux in rat ventral tegmental area: modification by repeated amphetamine administration. J Neurochem 1998;70:198–209.
[45] Rahman S, Zhang J, Corrigall WA. Effects of acute and chronic nicotine on somatodendritic dopamine release of the rat ventral tegmental area: in vivo microdialysis study. Neurosci Lett 2003;348:61–4.
[46] Barik J, Wonnacott S. Nicotine psychopharmacology. Molecular and cellular mechanisms of action of nicotine in the CNS. Springer Publishing; 2009. p. 173–208.
[47] Goto Y, Otani S, Grace AA. The Yin and Yang of dopamine release: a new perspective. Neuropharmacology 2007;53:583–7.
[48] Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 1986;132:337–8.
[49] Toth E, Sershen H, Hashim A, Vizi ES, Lajtha A. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid. Neurochem Res 1992;17:265–71.
[50] Marshall DL, Redfern PH, Wonnacott S. Presynaptic nicotinic modulation of dopamine release in the three ascending pathways studied by in vivo microdialysis: comparison of naive and chronic nicotine-treated rats. J Neurochem 1997;68:1511–9.
[51] Wonnacott S. Presynaptic nicotinic ACh receptors. Trends Neurosci 1997;20:92–8.
[52] Grady SR, Salminen O, Laverty DC, Whiteaker P, McIntosh JM, Collins AC, et al. The subtypes of nicotinic acetylcholine receptors on dopaminergic terminals of mouse striatum. Biochem Pharmacol 2007;74:1235–46.
[53] Le Novere N, Zoli M, Changeux JP. Neuronal nicotinic receptor alpha 6 subunit mRNA is selectively concentrated in catecholaminergic nuclei of the rat brain. Eur J Neurosci 1996;8:2428–39.
[54] Quik M, Sum JD, Whiteaker P, McCallum SE, Marks MJ, Musachio J, et al. Differential declines in striatal nicotinic receptor subtype function after nigrostriatal damage in mice. Mol Pharmacol 2003;63:1169–79.
[55] Gotti C, Moretti M, Clementi F, Riganti L, McIntosh JM, Collins AC, et al. Expression of nigrostriatal alpha 6-containing nicotinic acetylcholine receptors is selectively reduced, but not eliminated, by beta3 subunit gene deletion. Mol Pharmacol 2005;67:2007–15.
[56] Salminen O, Drapeau JA, McIntosh JM, Collins AC, Marks MJ, Grady SR. Pharmacology of alpha-conotoxin MII-sensitive subtypes of nicotinic acetylcholine receptors isolated by breeding of null mutant mice. Mol Pharmacol 2007;71:1563–71.
[57] Meyer EL, Yoshikami D, McIntosh JM. The neuronal nicotinic acetylcholine receptors alpha4* and alpha6* differentially modulate dopamine release in mouse striatal slices. J Neurochem 2008;105:1761–9.
[58] Nelson ME, Kuryatov A, Choi CH, Zhou Y, Lindstrom J. Alternate stoichiometries of alpha4beta2 nicotinic acetylcholine receptors. Mol Pharmacol 2003;63:332–41.
[59] Moroni M, Zwart R, Sher E, Cassels BK, Bermudez I. alpha4beta2 nicotinic receptors with high and low acetylcholine sensitivity: pharmacology, stoichiometry, and sensitivity to long-term exposure to nicotine. Mol Pharmacol 2006;70:755–68.
[60] Marks MJ, Meinerz NM, Drago J, Collins AC. Gene targeting demonstrates that alpha4 nicotinic acetylcholine receptor subunits contribute to expression of diverse [^{3}H]epibatidine binding sites and components of biphasic ^{86}Rb+ efflux with high and low sensitivity to stimulation by acetylcholine. Neuropharmacology 2007;53:390–405.
[61] Grady S, Marks MJ, Wonnacott S, Collins AC. Characterization of nicotinic receptor-mediated [^{3}H]dopamine release from synaptosomes prepared from mouse striatum. J Neurochem 1992;59:848–56.
[62] Mogg AJ, Whiteaker P, McIntosh JM, Marks M, Collins AC, Wonnacott S. Methyllycaconitine is a potent antagonist of alpha-conotoxin-MII-sensitive presynaptic nicotinic acetylcholine receptors in rat striatum. J Pharmacol Exp Ther 2002;302:197–204.
[63] Salminen O, Murphy KL, McIntosh JM, Drago J, Marks MJ, Collins AC, et al. Subunit composition and pharmacology of two classes of striatal presynaptic nicotinic acetylcholine receptors mediating dopamine release in mice. Mol Pharmacol 2004;65:1526–35.
[64] Kaiser S, Wonnacott S. alpha-bungarotoxin-sensitive nicotinic receptors indirectly modulate [^{3}H]dopamine release in rat striatal slices via glutamate release. Mol Pharmacol 2000;58:312–8.
[65] Marchi M, Risso F, Viola C, Cavazzani P, Raiteri M. Direct evidence that release-stimulating alpha7* nicotinic cholinergic receptors are localized on human and rat brain glutamatergic axon terminals. J Neurochem 2002;80:1071–8.
[66] Wang JK. Presynaptic glutamate receptors modulate dopamine release from striatal synaptosomes. J Neurochem 1991;57:819–22.
[67] Desce JM, Godeheu G, Galli T, Artaud F, Cheramy A, Glowinski J. L-Glutamate-evoked release of dopamine from synaptosomes of the rat striatum: involvement of AMPA and N-methyl-D-aspartate receptors. Neuroscience 1992;47:333–9.
[68] Innocent N, Livingstone PD, Hone A, Kimura A, Young T, Whiteaker P, et al. alpha-Conotoxin ArIB[V11L, V16D] is a potent and selective antagonist at rat and human native alpha7 nicotinic acetylcholine receptors. J Pharmacol Exp Ther 2008;327:529–37.
[69] Livingstone PD, Srinivasan J, Kew JN, Dawson LA, Gotti C, Moretti M, et al. alpha7 and non-alpha7 nicotinic acetylcholine receptors modulate dopamine release in vitro and in vivo in the rat prefrontal cortex. Eur J Neurosci 2009;29:529–50.
[70] Quarta D, Naylor CG, Barik J, Fernandes C, Wonnacott S, Stolerman IP. Drug discrimination and neurochemical studies in alpha7 null mutant mice: tests

for the role of nicotinic alpha7 receptors in dopamine release. Psychopharmacology (Berl) 2009;203:399–410.
[71] Lecca D, Shim I, Costa E, Javaid JI. Striatal application of nicotine, but not of lobeline, attenuates dopamine release in freely moving rats. Neuropharmacology 2000;39:88–98.
[72] Campos F, Duran R, Vidal L, Faro LR, Alfonso M. In vivo effects of the anatoxin-a on striatal dopamine release. Neurochem Res 2006;31:491–501.
[73] Freund TF, Powell JF, Smith AD. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience 1984;13:1189–215.
[74] Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends Neurosci 1990;13:259–65.
[75] Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurones: chemical, physiological and morphological characterization. Trends Neurosci 1995;18:527–35.
[76] McClure-Begley TD, King NM, Collins AC, Stitzel JA, Wehner JM, Butt CM. Acetylcholine-stimulated [^{3}H]GABA release from mouse brain synaptosomes is modulated by alpha4beta2 and alpha4alpha5beta2 nicotinic receptor subtypes. Mol Pharmacol 2009;75:918–26.
[77] Bernath S, Zigmond MJ. Dopamine may influence striatal GABA release via three separate mechanisms. Brain Res 1989;476:373–6.
[78] Harsing Jr LG, Zigmond MJ. Dopaminergic inhibition of striatal GABA release after 6-hydroxydopamine. Brain Res 1996;738:142–5.
[79] Araujo DM, Lapchak PA, Collier B, Quirion R. Characterization of N-[^{3}H]methylcarbamylcholine binding sites and effect of N-methylcarbamylcholine on acetylcholine release in rat brain. J Neurochem 1988;51:292–9.
[80] Azam L, Winzer-Serhan U, Leslie FM. Co-expression of alpha7 and beta2 nicotinic acetylcholine receptor subunit mRNAs within rat brain cholinergic neurons. Neuroscience 2003;119:965–77.
[81] Tobler PN, Dickinson A, Schultz W. Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J Neurosci 2003;23:10402–10.
[82] Zhou FM, Liang Y, Dani JA. Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. Nat Neurosci 2001;4:1224–9.
[83] Exley R, Clements MA, Hartung H, McIntosh JM, Cragg SJ. alpha6-Containing nicotinic acetylcholine receptors dominate the nicotine control of dopamine neurotransmission in nucleus accumbens. Neuropsychopharmacology 2008;33:2158–66.
[84] Exley R, Cragg SJ. Presynaptic nicotinic receptors: a dynamic and diverse cholinergic filter of striatal dopamine neurotransmission. Br J Pharmacol 2008;153(Suppl. 1):S283–97.
[85] Rice ME, Cragg SJ. Nicotine amplifies reward-related dopamine signals in striatum. Nat Neurosci 2004;7:583–4.
[86] Avshalumov MV, Chen BT, Marshall SP, Pena DM, Rice ME. Glutamate-dependent inhibition of dopamine release in striatum is mediated by a new diffusible messenger, H_2O_2. J Neurosci 2003;23:2744–50.
[87] Cragg SJ. Variable dopamine release probability and short-term plasticity between functional domains of the primate striatum. J Neurosci 2003;23:4378–85.
[88] Perez XA, Bordia T, McIntosh JM, Grady SR, Quik M. Long-term nicotine treatment differentially regulates striatal alpha6alpha4beta2* and alpha6(-nonalpha4)beta2* nAChR expression and function. Mol Pharmacol 2008;74:844–53.
[89] Uylings HB, Groenewegen HJ, Kolb B. Do rats have a prefrontal cortex? Behav Brain Res 2003;146:3–17.
[90] Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB. Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology (Berl) 2006;184:292–305.
[91] Seamans JK, Lapish CC, Durstewitz D. Comparing the prefrontal cortex of rats and primates: insights from electrophysiology. Neurotox Res 2008;14:249–62.
[92] Takahata R, Moghaddam B. Activation of glutamate neurotransmission in the prefrontal cortex sustains the motoric and dopaminergic effects of phencyclidine. Neuropsychopharmacology 2003;28:1117–24.
[93] Toda M, Abi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. Curr Psychiatry Rep 2007;9:329–36.
[94] Levy F. Pharmacological and therapeutic directions in ADHD: specificity in the PFC. Behav Brain Funct 2008;4:12.
[95] Lodge DJ, Behrens MM, Grace AA. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. J Neurosci 2009;29:2344–54.
[96] Gainetdinov RR, Mohn AR, Caron MG. Genetic animal models: focus on schizophrenia. Trends Neurosci 2001;24:527–33.
[97] Hahn B, Shoaib M, Stolerman IP. Involvement of the prefrontal cortex but not the dorsal hippocampus in the attention-enhancing effects of nicotine in rats. Psychopharmacology (Berl) 2003;168:271–9.
[98] Clarke PB, Schwartz RD, Paul SM, Pert CB, Pert A. Nicotinic binding in rat brain: autoradiographic comparison of [^{3}H]acetylcholine, [^{3}H]nicotine, and [^{125}I]-alpha-bungarotoxin. J Neurosci 1985;5:1307–15.
[99] Cao YJ, Surowy CS, Puttfarcken PS. Different nicotinic acetylcholine receptor subtypes mediating striatal and prefrontal cortical [^{3}H]dopamine release. Neuropharmacology 2005;48:72–9.
[100] Gioanni Y, Rougeot C, Clarke PB, Lepouse C, Thierry AM, Vidal C. Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamo-cortical transmission. Eur J Neurosci 1999;11:18–30.
[101] Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology 2003;28:216–25.
[102] Dickinson JA, Kew JN, Wonnacott S. Presynaptic alpha7 and beta2-containing nicotinic acetylcholine receptors modulate excitatory amino acid release from rat prefrontal cortex nerve terminals via distinct cellular mechanisms. Mol Pharmacol 2008;74:348–59.
[103] Lubin M, Erisir A, Aoki C. Ultrastructural immunolocalization of the alpha 7 nAChR subunit in guinea pig medial prefrontal cortex. Ann N Y Acad Sci 1999;868:628–32.
[104] Gabbott PL, Dickie BG, Vaid RR, Headlam AJ, Bacon SJ. Local-circuit neurones in the medial prefrontal cortex (areas 25, 32 and 24b) in the rat: morphology and quantitative distribution. J Comp Neurol 1997;377:465–99.
[105] Kawaguchi Y, Kondo S. Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. J Neurocytol 2002;31:277–87.
[106] Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 2004;4:36–46.
[107] Day M, Pan JB, Buckley MJ, Cronin E, Hollingsworth PR, Hirst WD, et al. Differential effects of ciproxifan and nicotine on impulsivity and attention measures in the 5-choice serial reaction time test. Biochem Pharmacol 2007;73:1123–34.
[108] Tseng KY, O'Donnell P. Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. J Neurosci 2004;24:5131–9.
[109] Del Arco A, Mora F. Glutamate-dopamine in vivo interaction in the prefrontal cortex modulates the release of dopamine and acetylcholine in the nucleus accumbens of the awake rat. J Neural Transm 2005;112:97–109.
[110] Gao C, Wolf ME. Dopamine receptors regulate NMDA receptor surface expression in prefrontal cortex neurons. J Neurochem 2008;106:2489–501.
[111] Briand LA, Gritton H, Howe WM, Young DA, Sarter M. Modulators in concert for cognition: modulator interactions in the prefrontal cortex. Prog Neurobiol 2007;83:69–91.
[112] Parikh V, Man K, Decker MW, Sarter M. Glutamatergic contributions to nicotinic acetylcholine receptor agonist-evoked cholinergic transients in the prefrontal cortex. J Neurosci 2008;28:3769–80.
[113] Parikh V, Sarter M. Cholinergic mediation of attention: contributions of phasic and tonic increases in prefrontal cholinergic activity. Ann N Y Acad Sci 2008;1129:225–35.
[114] Zheng F, Johnson SW. Metabotropic glutamate and muscarinic cholinergic receptor-mediated preferential inhibition of N-methyl-D-aspartate component of transmissions in rat ventral tegmental area. Neuroscience 2003;116:1013–20.
[115] Schultz W. Getting formal with dopamine and reward. Neuron 2002;36:241–63.
[116] Nisell M, Nomikos GG, Hertel P, Panagis G, Svensson TH. Condition-independent sensitization of locomotor stimulation and mesocortical dopamine release following chronic nicotine treatment in the rat. Synapse 1996;22:369–81.
[117] Hurst RS, Hajos M, Raggenbass M, Wall TM, Higdon NR, Lawson JA, et al. A novel positive allosteric modulator of the alpha7 neuronal nicotinic acetylcholine receptor: in vitro and in vivo characterization. J Neurosci 2005;25:4396–405.
[118] Hoyle E, Genn RF, Fernandes C, Stolerman IP. Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. Psychopharmacology (Berl) 2006;189:211–23.
[119] Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, et al. Impaired attention is central to the cognitive deficits observed in alpha7 deficient mice. Eur Neuropsychopharmacol 2007;17:145–55.
[120] Lindskog M, Svenningsson P, Fredholm BB, Greengard P, Fisone G. Activation of dopamine D2 receptors decreases DARPP-32 phosphorylation in striatonigral and striatopallidal projection neurons via different mechanisms. Neuroscience 1999;88:1005–8.
[121] Flores-Hernandez J, Hernandez S, Snyder GL, Yan Z, Fienberg AA, Moss SJ, et al. D(1) dopamine receptor activation reduces GABA(A) receptor currents in neostriatal neurons through a PKA/DARPP-32/PP1 signaling cascade. J Neurophysiol 2000;83:2996–3004.
[122] Inoue Y, Yao L, Hopf FW, Fan P, Jiang Z, Bonci A, et al. Nicotine and ethanol activate protein kinase a synergistically via Gi beta gamma subunits in nucleus accumbens/ventral tegmental cocultures: the role of dopamine D1/D2 and adenosine A2A receptors. J Pharmacol Exp Ther 2007;322:23–9.
[123] Gould TD, Manji HK. DARPP-32: a molecular switch at the nexus of reward pathway plasticity. Proc Natl Acad Sci USA 2005;102:253–4.
[124] Svenningsson P, Nairn AC, Greengard P. DARPP-32 mediates the actions of multiple drugs of abuse. Aaps J 2005;7:E353–60.
[125] Valjent E, Pascoli V, Svenningsson P, Paul S, Enslen H, Corvol JC, et al. Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. Proc Natl Acad Sci USA 2005;102:491–6.
[126] Hamada M, Higashi H, Nairn AC, Greengard P, Nishi A. Differential regulation of dopamine D1 and D2 signaling by nicotine in neostriatal neurons. J Neurochem 2004;90:1094–103.
[127] Valjent E, Pages C, Herve D, Girault JA, Caboche J. Addictive and non-addictive drugs induce distinct and specific patterns of ERK activation in mouse brain. Eur J Neurosci 2004;19:1826–36.

[128] Tropea TF, Kosofsky BE, Rajadhyaksha AM. Enhanced CREB and DARPP-32 phosphorylation in the nucleus accumbens and CREB, ERK, and GluR1 phosphorylation in the dorsal hippocampus is associated with cocaine-conditioned place preference behavior. J Neurochem 2008;106:1780–90.
[129] Panagis G, Nisell M, Nomikos GG, Chergui K, Svensson TH. Nicotine injections into the ventral tegmental area increase locomotion and Fos-like immunoreactivity in the nucleus accumbens of the rat. Brain Res 1996; 730:133–42.
[130] Salminen O, Seppa T, Gaddnas H, Ahtee L. The effects of acute nicotine on the metabolism of dopamine and the expression of Fos protein in striatal and limbic brain areas of rats during chronic nicotine infusion and its withdrawal. J Neurosci 1999;19:8145–51.
[131] Dong Y, Green T, Saal D, Marie H, Neve R, Nestler EJ, et al. CREB modulates excitability of nucleus accumbens neurons. Nat Neurosci 2006;9:475–7.
[132] Brunzell DH, Russell DS, Picciotto MR. In vivo nicotine treatment regulates mesocorticolimbic CREB and ERK signaling in C57Bl/6J mice. J Neurochem 2003;84:1431–41.
[133] Nisell M, Nomikos GG, Chergui K, Grillner P, Svensson TH. Chronic nicotine enhances basal and nicotine-induced Fos immunoreactivity preferentially in the medial prefrontal cortex of the rat. Neuropsychopharmacology 1997;17: 151–61.
[134] Pagliusi SR, Tessari M, DeVevey S, Chiamulera C, Pich EM. The reinforcing properties of nicotine are associated with a specific patterning of c-fos expression in the rat brain. Eur J Neurosci 1996;8:2247–56.
[135] Marttila K, Raattamaa H, Ahtee L. Effects of chronic nicotine administration and its withdrawal on striatal FosB/DeltaFosB and c-Fos expression in rats and mice. Neuropharmacology 2006;51:44–51.
[136] Soderstrom K, Qin W, Williams H, Taylor DA, McMillen BA. Nicotine increases FosB expression within a subset of reward- and memory-related brain regions during both peri- and post-adolescence. Psychopharmacology (Berl) 2007;191:891–7.
[137] Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001;2:119–28.
[138] Smith Y, Bevan MD, Shink E, Bolam JP. Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 1998;86:353–87.
[139] Grilli M, Zappettini S, Zoli M, Marchi M. Pre-synaptic nicotinic and D(2) receptors functionally interact on dopaminergic nerve endings of rat and mouse nucleus accumbens. J Neurochem 2009;108:1507–14.
[140] Trantham-Davidson H, Kroner S, Seamans JK. Dopamine modulation of prefrontal cortex interneurons occurs independently of DARPP-32. Cereb Cortex 2007;18:951–8.
[141] Kolomiets B, Marzo A, Caboche J, Vanhoutte P, Otani S. Background dopamine concentration dependently facilitates long-term potentiation in rat prefrontal cortex through postsynaptic activation of extracellular signal-regulated kinases. Cereb Cortex; in press.
[142] Trantham-Davidson H, Neely LC, Lavin A, Seamans JK. Mechanisms underlying differential D1 versus D2 dopamine receptor regulation of inhibition in prefrontal cortex. J Neurosci 2004;24:10652–9.
[143] Dahlstroem A, Fuxe K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol Scand Suppl 1964;(Suppl. 232):1–55.
[144] Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci 2007;30:194–202.
[145] Ungerstedt U. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol Scand Suppl 1971;367:1–48.
[146] Matsuda W, Furuta T, Nakamura KC, Hioki H, Fujiyama F, Arai R, et al. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J Neurosci 2009;29:444–53.
[147] Thomas B, Beal MF. Parkinson's disease. Hum Mol Genet 2007;16(Spec No. 2):R183–94.
[148] Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. J Neurosci 2007;27:8161–5.
[149] Beckstead RM, Domesick VB, Nauta WJ. Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res 1979;175:191–217.
[150] Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 1991;41:89–125.
[151] Zahm DS, Brog JS. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. Neuroscience 1992;50:751–67.
[152] Sellings LH, Clarke PB. Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. J Neurosci 2003;23:6295–303.
[153] Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 1988;85:5274–8.
[154] Balfour DJ, Wright AE, Benwell ME, Birrell CE. The putative role of extrasynaptic mesolimbic dopamine in the neurobiology of nicotine dependence. Behav Brain Res 2000;113:73–83.
[155] Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res 2002;137:75–114.
[156] Wonnacott S, Sidhpura N, Balfour DJ. Nicotine: from molecular mechanisms to behaviour. Curr Opin Pharmacol 2005;5:53–9.
[157] Ito R, Robbins TW, Everitt BJ. Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. Nat Neurosci 2004;7:389–97.
[158] Kolb B. Functions of the frontal cortex of the rat: a comparative review. Brain Res 1984;320:65–98.
[159] Bissonette GB, Martins GJ, Franz TM, Harper ES, Schoenbaum G, Powell EM. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. J Neurosci 2008;28:11124–30.