Published in final edited form as:

Semin Cell Dev Biol. 2009 June ; 20(4): 432–440. doi:10.1016/j.semcdb.2009.01.007.

Nicotinic modulation of synaptic transmission and plasticity in cortico-limbic circuits

Huibert D. Mansvelder^a, Marjolijn Mertz^{a,b}, and Lorna W. Role^{b,*}

^aDepartment of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research (CNCR), VU University Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands

^bDepartment of Neurobiology and Behavior, Center for Nervous Systems Disorders (CNS Disorders), SUNY, Stony Brook, NY 11794-5320, United States

Abstract

Nicotine is the principle addictive agent delivered via cigarette smoking. The addictive activity of nicotine is due to potent interactions with nicotinic acetylcholine receptors (nAChRs) on neurons in the reinforcement and reward circuits of the brain. Beyond its addictive actions, nicotine is thought to have positive effects on performance in working memory and short-term attention-related tasks. The brain areas involved in such behaviors are part of an extensive cortico-limbic network that includes relays between prefrontal cortex (PFC) and cingulate cortex (CC), hippocampus, amygdala, ventral tegmental area (VTA) and the nucleus accumbens (nAcc). Nicotine activates a broad array of nAChRs subtypes that can be targeted to pre- as well as peri- and post-synaptic locations in these areas. Thereby, nicotine not only excites different types of neurons, but it also perturbs baseline neuronal communication, alters synaptic properties and modulates synaptic plasticity.

In this review we focus on recent findings on nicotinic modulation of cortical circuits and their targets fields, which show that acute and transient activation of nicotinic receptors in cortico-limbic circuits triggers a series of events that affects cognitive performance in a long lasting manner. Understanding how nicotine induces long-term changes in synapses and alters plasticity in the cortico-limbic circuits is essential to determining how these areas interact in decoding fundamental aspects of cognition and reward.

Keywords

Nicotine; Cognition; Limbic; Acetylcholine; Synaptic plasticity

1. Introduction

Activation of nicotinic receptors regulates neuronal excitability and modulates synaptic transmission via direct mechanisms and by indirect mechanisms. Direct effects include activation of nicotine-gated cationic channels causing local depolarization. Indirect pathways involve the activation of nicotine-gated channels that are highly conductive to Ca^{2+} . Activation of such channels elicit Ca^{2+} dependent signaling cascades, additional Ca^{2+} release from internal stores and/or exocytosis. The nAChRs expressed in cortico-limbic circuits include nAChR channel subtypes of varying subunit composition that differ in how they contribute to tuning

synaptic plasticity by virtue of their distinct biophysical properties, pharmacological characteristics and differential targeting to specific somato-dendritic and axonal domains. This review attempts to fuse the results of recent studies of both the cellular and circuit mechanisms of nAChR activation to better understand how nicotine modifies cortico-limbic circuits underlying cognitive functions.

The stars of our discussion of cortico-limbic circuits are the layer 5 cortical pyramidal neurons and a selected subset of their many limbic targets, specifically the VTA, ventral hippocampus, amygdala and nAcc. Recent studies within the prefrontal cortex and at sites of prefrontal cortical projections have provided important new insights into the synaptic mechanisms by which nAChRs modulate the activity of cortico-limbic relays. Both inputs to and outputs from layer 5 cortical neurons and synapses within each of the aforementioned target fields are modulated by nAChR activation. The final outcome of nicotinic modulation at the synaptic, circuit and, ultimately, behavioral level, depends critically on the nAChR expression pattern, nAChR localization and nAChR subunit composition. These factors collaborate in nicotine's ability to cause long-term changes in the rules that govern synaptic plasticity in cortico-limbic circuits thereby altering cognitive performance and reward.

1.1. Subunit composition and localization of nicotinic acetylcholine receptors in cortico-limbic circuits

To date, a total of 12 genes encoding neuronal nAChRs subunits have been identified in an array of vertebrates and invertebrates (for review see [1]). Nine α -type subunits ($\alpha 2$ - $\alpha 10$ encoded by CHRNA2-10) and 3 non- α -type or β -type subunits ($\beta 2$ - $\beta 4$; CHRNB2-4) have been cloned and sequenced from multiple species [1,2, reviewed in 3,4-7]. The subunit composition of nAChRs varies depending on the brain region (for review see [1,7,8,9-12]). It is thought that the neuronal nAChRs assemble in a manner analogous to the muscle homolog, and hence are pentameric complexes of 2 α and 3 non- α -type subunits. However, several studies indicate that nAChR subunit stoichiometry may be more complicated, including pentamers of between 3 and 5 α -type subunits. Likewise, as acetylcholine (ACh) and other ligands bind at the α - γ and α - δ interface of muscle nAChRs, nicotinic ligands are proposed to bind at the interface of α and non- α subunits in neuronal nAChRs, although direct evidence for this idea is lacking. In any case, binding of the agonist is transduced into the gating of the receptors ion channel pore that is permeable to multiple cationic species (Na^+ , K^+ , Ca^{2+}) and even large organic cations such as tetraethylammonium (TEA) (for review see [13]). The relative permeability for specific cations depends on the subunit composition of the nAChRs complex. The $\alpha 7$ -containing nAChRs (written as $\alpha 7^*$), historically identified by their binding of α -bungarotoxin (αBgTx), are the champions of Ca^{2+} permeable nAChRs [14-17]. Heterologous expression of homomeric $\alpha 7^*$ nAChRs reveals fractional Ca^{2+} currents of 6-12% which is comparable to estimates of Ca^{2+} permeability of N-methyl-D-aspartate (NMDA) receptors [16,18,19] and considerably greater than that of heteromeric ($\alpha\beta$)* nAChRs, (2-5%) [20].

The majority of the CNS nAChRs are relatively high-affinity nicotine-binding sites, that include $\alpha 4$ and $\beta 2$ type subunits (aka $\alpha 4\beta 2^*$ nAChRs); the αBgTx -binding (i.e. $\alpha 7^*$ nAChRs) are the next most abundant (reviewed in [7]). Homomeric, $\alpha 7^*$ nAChRs, expressed in heterologous systems are the best studied of the $\alpha 7$ -containing nAChRs and are renowned for their relatively low agonist affinity and rapid desensitization kinetics in the presence of 100 μM ACh or higher. More recent work, especially by Papke and colleagues, have emphasized the multiple gating modes of $\alpha 7^*$ nAChRs noting in particular the activation of a non-desensitizing small amplitude current by ACh concentrations of 20 μM or lower [21,22]. Considering that ACh and choline, both activators of $\alpha 7$ -containing receptors are present in cerebrospinal fluid (CSF), it is possible that under normal physiological conditions, there is a tonic activation of $\alpha 7^*$ nAChRs. Higher concentrations of agonist might decrease the net

contribution of $\alpha 7^*$ nAChRs, thereby decreasing ligand-gated calcium influx, preventing cytotoxicity [22].

There is increasing evidence that native $\alpha 7^*$ nAChRs may contain non- $\alpha 7^*$ nAChR subunits [23-27, e.g. see, 28]. Studies of such heteromeric $\alpha 7^*$ nAChRs in neurons *in vivo* and *in vitro* indicate different pharmacological properties and desensitization kinetics compared to the homomeric $\alpha 7$ nAChRs [28,29].

The least abundant nAChR subunits in the CNS are $\alpha 9$ and $\alpha 10$ which, unlike most, are expressed in non-neural tissues and organs, (e.g. bone marrow, nasal epithelium, and embryonic blood cells) as well as in innervated sensory epithelia and ganglia [30,31]. $\beta 3$, $\alpha 5$ and $\alpha 6$, once considered orphan subunits, have now all been identified as components of native nAChRs in several brain regions. Their inclusion in nAChR complexes have been shown to confer important differences in agonist and antagonist profile, ion permeation, Ca^{2+} -permeability, rates of desensitization and, most recently, to influence axonal and dendritic targeting of nAChRs [25,32-35].

Anatomical, electrophysiological and neurochemical studies have long established that $\alpha 4\beta 2^*$ nAChRs and $\alpha 7^*$ nAChRs are the most abundant neuronal nAChRs and are present in the corticolimbic circuits upon which this review focuses. Key examples include studies demonstrating pre- and post-synaptic $\alpha 7^*$ or $\alpha 4\beta 2^*$ nAChRs in hippocampus [36-39], PFC [40]; somatosensory cortex [41], and the VTA [42]; (for reviews see: [7,43]). Binding studies revealed nAChR-binding sites over the length of axons and provided evidence for anterograde transport of nAChRs to synaptic terminals [44-47].

A rather elegant study quantified the locations of $\alpha 7^*$ nAChRs at synapses in the VTA [42]. The vast majority of $\alpha 7^*$ nAChRs were situated at pre- and peri-synaptic sites, with only ~10% located within the active zone or near a post-synaptic density. $\alpha 7^*$ nAChRs were found on vesicular glutamate transporter (vGluT) positive terminals that were devoid of vesicular cholinesterase transporter (VChat) staining, consistent with their localization on glutamatergic, not cholinergic, terminals. One of the main glutamatergic inputs to the VTA arises from the PFC: the presence of $\alpha 7^*$ nAChRs on these pre-synaptic terminals supports a cholinergic mechanism for regulating glutamatergic input to the VTA dopaminergic (DA) neurons [42].

In contrast to $\alpha 7^*$ nAChRs in VTA, the majority of which appear to be associated with pre-synaptic glutamatergic terminals, a wide variety of non- $\alpha 7^*$ nAChRs are expressed by the intrinsic DA and γ -aminobutyric acid (GABA) neurons within the VTA per se [42,48-55]. Most VTA GABAergic neurons express nAChRs that contain $\alpha 4$ and $\beta 2$ subunits, and are blocked by dihydro- β -erythroidine (DH β E) [52]. VTA dopamine neurons express at least three pharmacologically distinguishable nAChRs, only one of which is $\alpha 7^*$ nAChRs. [50,54-56].

The composition of nAChRs that are expressed by the VTA and targeted to their dopaminergic projections to the nAcc are probably the best defined in subunit composition of any native nAChR population [53,57,58]. Pharmacological and gene deletion studies have revealed that these nAChR complexes include $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$ and $\beta 2$ $\beta 3$ and $\beta 4$ subunits in various combinations [53,57,58]. A simplifying factor in the morass of nAChR subtypes detected in the nAcc is that the preponderance of nicotinic effects are due to activation of pre-synaptic nAChRs that modulate the dopaminergic vs. glutamatergic inputs. That is, the nAcc medium spiny neurons (MSN) *themselves* express little, if any, nAChRs.

The *lack* of $\alpha 7^*$ nAChRs on pre-synaptic dopaminergic inputs from VTA to nAcc contrasts with strong evidence for both $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs on convergent glutamatergic projections from the PFC and/or hippocampus [42,47]. In fact the differential targeting of $\alpha \beta^*$ nAChRs to dopaminergic inputs to nAcc vs. $\alpha 7^*$ nAChRs to glutamatergic pre-synaptic

sites is likely of key importance for the varied and activity dependent effects of nicotine on the dopaminergic drive to tonically active vs phasic firing nAcc neurons [59-61]. Overall, it is the distinctions amongst the various nAChR subtypes in the cortico-limbic circuits as described above that underlie the pleiotropic effects of nicotine on attention-related behaviors [54]. In the sustained presence of 100-500 nM nicotine as experienced by smokers plus with the varied levels of released ACh, the differential activation and desensitization kinetics of nAChR subtypes are likely to be strong determinants of exactly how the local circuitry is tuned [52, 56,62]. Of course there is still the complicating contribution of pre- and post-synaptic *muscarinic* AChRs in cortical limbic circuits, an important reminder that one must be circumspect in comparing the effects of nicotine vs. ACh in dissecting the mechanisms of cholinergic modulation of circuit activity.

Details of the localization and subunit composition of nAChRs in prefrontal cortex have also come into increasing resolution in recent years. In fact, one of the first reports of pre-synaptic nAChRs governing glutamatergic transmission in the CNS was conducted in frontal cortex [63-65]. The prefrontal cortex receives glutamatergic inputs from the medial dorsal nucleus of the thalamus [66]. These thalamo-cortical projections are excited by nicotine and give rise to a strong increase in glutamatergic inputs to layer 5 as well as layer 6 pyramidal neurons [65, 67,68]. Application of low levels of nicotine induces glutamate release in a manner that is largely dependent on a superthreshold activity (i.e. tetrodotoxin (TTX) sensitive) and on the presence of intact thalamo-cortical projections [65]. The profile of activation of thalamo-cortical inputs by low concentrations of agonist is consistent with an important role of $\alpha 2\beta 4^*$ nAChRs as is the loss of nicotinic modulation at thalamo-cortical inputs in $\beta 2^*$ nAChRs knock-out (KO) mice [65].

Support for modulatory effects of pre-synaptic nAChRs activation in the PFC comes from a variety of approaches including electrophysiological recordings and assay of release from isolated nerve terminals [40,69,70]. A recent study testing the relative contribution of $\beta 2^*$ nAChRs vs. $\alpha 7^*$ nAChRs on glutamatergic synaptosomes from PFC [69] demonstrated that both $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs appear to be important although each modulates excitatory amino acid (EAA) release via distinct mechanisms. $\alpha 7^*$ nAChRs are predominantly found on ryanodine positive terminals and activation of these channels leads to calcium-induced calcium release (CICR). The involvement of CICR that is coupled to pre-synaptic extracellular signal-regulated kinase (ERK2) activation and synapsin-1 phosphorylation provides a cellular mechanism for pre-synaptic facilitation in response to $\alpha 7^*$ nAChR activation. On the other hand, activation of non- $\alpha 7^*$ nAChRs increases release via recruitment of voltage-gated calcium channels (VGCCs), accounting for early observations that nAChR modulation of glutamatergic transmission in PFC is due, at least in part, to a TTX-sensitive mechanism. The participation of both $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs (which are likely $\alpha 4\beta 2^*$ nAChRs) in the facilitation of [^3H] D-aspartate release by distinct activity and Ca^{2+} -dependent mechanisms underscores the importance of recognizing that multiple nAChR signaling pathways converge to fine tune cortical circuits. Obviously, the presence of cholinergic input to the PFC and the regulation of local ACh release is a key to the modulatory role of cholinergic circuits in these regions. Considerable mystery *vis a vis* mechanism remains: it is not clear which of the various glutamatergic inputs to layer 5 pyramidal neurons express $\alpha 7^*$ nAChRs and/or non- $\alpha 7^*$ nAChRs, but direct nAChR gating of the layer 5 pyramidal neurons *per se* does not play an important role in nAChR modulation of PFC circuits. Thus, direct application of nicotine to layer 5 pyramidal neurons does not elicit detectable current, and single-cell PCR analysis of layer 5 pyramidal neurons did not detect mRNAs for even the most abundant nAChR subunits $\alpha 4$, $\beta 2$ and $\alpha 7$ [68]. In contrast, specific interneuron populations in PFC layer 5 do express nAChRs. Regular spiking non-pyramidal interneurons (RSNP) as well as low-threshold spiking interneurons (LTS) show inward currents upon direct nicotine application, and they express mRNA for $\alpha 4$, $\beta 2$ and $\alpha 7$ subunits [68].

A different picture arises for the location of nAChRs in layer 6 of prefrontal cortex. In rat, pyramidal neurons in this layer do express nAChRs and show prominent inward currents upon ACh application [67]. Specifically pyramidal neurons that project to the thalamus are excited by nicotine and pharmacological evidence suggests that these neurons express nAChRs that contain the $\alpha 5$ subunit. Whether layer 6 *interneurons* express nAChRs is unclear at this point, although glutamatergic inputs to fast spiking interneurons is greatly facilitated by nAChR stimulation [67]. Taken together, nAChRs are expressed in both output layers of the PFC, layer 5 and 6, but their distribution among pyramidal neurons and interneurons differs for the two layers. It will be important to learn how simultaneous activation of these receptors alters the total output of the PFC.

1.2. Nicotinic modulation of synaptic plasticity in selected cortico-limbic circuits

During initial phases of exposure to drugs of abuse and the acquisition of addiction, neuronal networks in brain areas involved in reward, such as the VTA, nAcc and PFC, undergo strong adaptations that lead to behavioral sensitization [71]. Lesioning dorsomedial PFC prevented the expression of cocaine sensitization in rats [72,73] and blocking dopamine receptors specifically in medial PFC prevented behavioral as well as neurochemical sensitization to cocaine [74]. Recently, it has become clear that nicotine, like other drugs of abuse, has lasting effects on cortico-limbic circuits and synapses [47,51,52,75-79].

Several recent studies have revealed that the effects of nicotine or acetylcholine on synaptic connections within neuronal networks can outlast nAChR stimulation and desensitization [47,75,80]. Long-term modulation of glutamatergic and GABAergic synaptic connections adds another level of complexity to nicotinic modulation of neuronal networks. In the following sections we consider evidence for longer lasting effects of nicotinic modulation in selected cortico-limbic regions.

1.2.1. Nicotinic modulation of synaptic plasticity in prefrontal cortex—Synaptic plasticity is critically important for cognitive function, and in particular, synaptic plasticity in the PFC has been directly associated with attention and working memory [81]. The relative timing of action potentials in pre- and post-synaptic neurons has a profound impact on the induction of long-term potentiation (LTP) or depression (LTD). When a pre-synaptic spike precedes a post-synaptic spike within a short time window of several tens of milliseconds, LTP is induced. The reverse order of spike timing results in LTD [82,83]. In mouse PFC, nicotine strongly affects this timing-dependent synaptic plasticity, which is called spike-timing-dependent plasticity (STDP). Stimulation of nicotinic AChRs in PFC modify STDP induced by pairing stimulation of the excitatory inputs to PFC layer 5 pyramidal neurons with post-synaptic spikes elicited 5 ms after each synaptic response [68]. This coordinated stimulation induced robust LTP; however, when the same stimulus paradigm was applied in the presence of nicotine concentrations experienced by smokers, LTP was eliminated and a depression of the excitatory inputs to these cells was observed. Which nAChRs on what neurons are responsible for this effect? As discussed above, mouse PFC layer 5 pyramidal neurons do not express nicotinic receptors themselves. Rather, the nAChRs involved in the nicotinic modulation of LTP induction increase inhibitory GABAergic inputs to the pyramidal cells, as the nicotinic modulation of plasticity was abolished by inhibitors of GABA type A (GABA_A) receptors. As described above, LTS and RSNP GABAergic interneurons found in the PFC layer 5 express nAChR subunits on their soma that activate these neurons when nicotine is present. FS interneurons are excited indirectly by nAChRs that increase glutamatergic excitation of those cells. Thus, nicotine exposure enhances inhibitory input to the layer 5 pyramidal neurons through both direct and indirect excitation of inhibitory GABA interneurons (Fig. 1).

Studies in other cortical areas indicate that increases in post-synaptic calcium concentration are critical for the induction of synaptic plasticity [84-86]. Using two-photon imaging of intracellular calcium levels, it was found that action potentials that propagated from the soma into the dendrites of layer 5 pyramidal cells elicited increases in dendritic calcium concentration. Nicotine enhanced the GABA input to the same dendrites, resulting in less calcium entry, likely due to failure of action potential back-propagation from the soma. Thus, nicotine suppresses post-synaptic calcium changes, thereby altering the conditions necessary for synaptic potentiation. Burst-like stimulation of the pyramidal cell in the presence of nicotine could restore post-synaptic calcium to concentrations comparable to those seen in the absence of nicotine, as well as the STDP, indicating that strong post-synaptic stimulation could overcome the nicotinic modulation [68,87].

It is somewhat counter intuitive that nicotine in PFC decreases the likelihood of LTP induction, given that nAChRs are generally excitatory and their activation in other brain areas has been shown to enhance LTP [36,51,88]. The activation of distributed nAChRs provides the PFC neuronal network with a wide range of computational possibilities, but the functional consequences of this modulation are hard to predict from these data alone. Nicotine alters the rules for synaptic plasticity resulting from timed pre-synaptic and post-synaptic activity and increases LTP threshold by reducing dendritic calcium signals. As such, the function of the medial PFC network will most likely change in the presence of nicotine. Most likely, distal apical dendrites of layer 5 pyramidal neurons in superficial layers will be more quantitatively affected by the nicotinic mechanisms we found to block STDP than the synapses that are located closer to the cell body. By reducing dendritic action potential propagation in apical dendrites, nicotine hampers communication between cell body and distal synapses in layer 5 pyramidal neurons. This potentially could strongly affect information processing in the neuronal network of the medial PFC as a whole, and will alter the output of the PFC. At the same time, increased activity in pyramidal neurons restores the conditions for STDP to occur. The presence of nicotine and increased threshold for STDP could reduce cognitive performance in healthy naive rodents [89]. Alternatively, since PFC neuronal activity could be increased during PFC-based cognitive behavior, nicotine may provide conditions under which signal-to-noise ratio in PFC information processing is enhanced, thereby improving cognitive performance [89,90]. It is possible that enhancing signal-to-noise for phasic activity within the PFC, rather than simply increasing excitability, could be an effective mechanism for cognition-enhancing drugs.

1.2.2. Critical periods of nicotinic modulation of synaptic plasticity in cortico-limbic circuits—The effects of nicotine exposure and/or the effects of disruption of nicotinic signaling during early critical periods have been demonstrated most clearly in studies of projections to and from cortex and thalamus (see [91,92] for recent reviews). Nicotine exposure early on alters the development of neuronal ensembles that subserve the transmission of information between primary sensory cortical areas and their corresponding thalamic nuclei (reviewed in [92,93]). Studies in the auditory system demonstrate an essential role for nAChRs in the refinement of thalamo-cortical projections and implicate $\alpha 4\beta 2^*$ nAChRs in the gating of auditory transmission [80,94]. Studies using nAChR subunit selective KO mice demonstrate distinct roles for both $\alpha 7^*$ nAChRs and $\beta 2^*$ nAChRs in the development of thalamo-cortical and cortico-thalamic projections, respectively (and see [92] for review, [95]). The observation that selective knock out during early critical periods can dramatically alter performance in a passive avoidance task in the adult underscores the key role of normal nAChR “tone” in neural development. In particularly elegant studies Berg and colleagues have demonstrated an essential role of early nicotinic signaling in the developmental switch of GABAergic transmission from excitatory to inhibitory [96].

1.2.3. Nicotinic modulation of synaptic plasticity in VTA—The PFC extends glutamatergic projections into numerous regions associated with the (meso)limbic system;

Layer 5 pyramidal neurons of the infra limbic (IL) and prelimbic (PL) main projection sites include: the ventral striatum (~25%), lateral hypothalamus (~25%), basal lateral amygdala (BLA; 8%) and the VTA(4%). The latter input arises primarily from layer 5 PFC. About 40% of the neurons in layer 6 project to the medial thalamus [97].

Nicotinic AChRs located in the VTA are critically involved in nicotine addiction (see [98] for recent review). Indeed, in rats, intra-VTA infusions of nicotine increase DA concentration in the nAcc [99], an effect thought to mediate the reinforcing properties of most addictive drugs [100]. Also, intra-VTA infusion of nicotinic antagonists blocks the effect of systemic nicotine injections on accumbal DA release [99] and disrupt nicotine self-administration [101]. Electrophysiological experiments demonstrate that nicotine is able to increase the firing rate of DA neurons both *in vitro* and *in vivo* [50,102,103]. Although actions on nAChRs located on GABAergic interneurons or glutamatergic terminals in the VTA, or on pedunculopontine neurons, have been proposed to contribute to these effects [52,104,105], somato-dendritic nAChRs expressed by VTA DA neurons remain good candidates for the primary reinforcing action of nicotine.

Glutamatergic transmission onto DA neurons is enhanced by activation of pre-synaptic nAChRs [42,51]. Interestingly, cholinergic synaptic terminals were not in close vicinity to glutamatergic terminals expressing $\alpha 7$ -containing nAChR, consistent with a “volume” mode of cholinergic signaling [42,106,107]. When nicotine arrives in the VTA, it stimulates glutamatergic terminals as well as dopamine neurons, thereby favoring conditions of pre- and post-synaptic paired activation and a Hebbian type of synaptic plasticity. Nicotine-induced pairing resulted in LTP of glutamatergic inputs [51]. Nicotine also induced LTP *in vivo* measured as an increase in AMPA/NMDA receptor ratio [76]. Together these findings suggest that synaptic plasticity in the VTA may be induced after smoking a single cigarette and most likely underlies the persistent effects of the drug on dopamine release in the nAcc and PFC.

The $\alpha 7^*$ nAChRs involved in this mechanism are not desensitized significantly by low nicotine concentrations associated with tobacco smoking [52,56]. However, the non- $\alpha 7^*$ nAChRs on GABAergic neurons undergo rapid desensitization within minutes after the start of nicotine exposure, and as a consequence, reduced the inhibitory input to the dopamine neurons [52, 56]. Desensitization of GABAergic neuron nAChRs not only prevents further activation by nicotine, but it also precludes the contribution of these receptors to endogenous cholinergic transmission [52]. Thereby, VTA dopamine neurons are disinhibited by desensitization of non- $\alpha 7^*$ nAChRs [52]. Despite their rapid desensitization properties, it was shown by using genetically engineered mice lacking $\beta 2$ subunits [103] or expressing $\alpha 4$ subunits hypersensitive to nicotine [108] that these subunits are very important for nicotine addiction.

The dopaminergic projections from the VTA to the nAcc are studied with multiple subtypes of nAChRs that modulate accumbens dopamine release. Indeed, the dopaminergic nerve terminals in the striatum have as many as five different nAChR subtypes ($\alpha 4\beta 2$, $\alpha 4\alpha 5\beta 2$, $\alpha 4\alpha 6\beta 2\beta 3$, $\alpha 6\beta 2\beta 3$ and $\alpha 6\beta 2$) with different pharmacological properties. Although this elaborate array of nAChRs in accumbens is consistent with fine-tuned control of striatal dopamine release the role of these receptors in encoding nicotine addiction is less clear (reviewed in [109]).

1.2.4. Nicotinic modulation of cortico-accumbens circuits—The nucleus accumbens comprise GABAergic medium spiny and aspiny neurons and a small population of cholinergic interneurons. Apart from input of intrinsic GABAergic interneurons, the MSN is regulated by glutamatergic inputs from the PFC, hippocampus and the amygdala and dopaminergic neurons from the VTA. Add to this the unknown, but likely significant modulation of MSN activity by

tonic levels of ACh throughout the striatum. Studies of cholinergic influences on striatal activity emphasize the contribution of muscarinic AChRs, rather than nAChRs [110,111].

The multiple relays projecting to the nAcc encode a wide range of sensory context for integration by the striatum and, ultimately, for the output of motivated behaviors. Such inputs convey emotional salience of positive and negative valence (VTA, amygdala), executive function (PFC), and novelty relative to prior experience (ventral hippocampus/subiculum). Electrophysiological studies in nAcc demonstrate that the glutamatergic projections from PFC and ventral hippocampus are important in the regulatory excitatory tone of the output of MSN [112-116].

The tuning of activity and the extent of glutamatergic input to the nAcc from PFC vs. hippocampus and amygdala are important in both the filtering and detection of inputs. The convergence of these inputs in the nAcc is thought to be a synaptic substrate of information gating [114]. Of particular importance *vis a vis* the role of this gating circuit in attention and working memory deficits is recent work of Grace and colleagues recording *in vivo* from rat ventral hippocampus, nAcc and PFC in concert [128]. These studies reveal that the initiation of ventral hippocampus drive of the nAcc requires activity from PFC. Thus, at low levels of activation the ventral hippocampus regulates nAcc activity in concert with a “permissive action” of the PFC. Interestingly the latter influence appears to be indirect, requiring the activation of D2 dopamine receptors. The level of ventral hippocampus drive is also critical: if ventral hippocampus input is sufficient to induce LTP, PFC activity is no longer required for ventral hippocampus-nAcc activation. Since both the amount of dopamine release and the extent of glutamatergic transmission in the nAcc are strongly regulated by nAChRs, it is not surprising that nicotinic actions in nAcc are state dependent and complex [128].

Indeed the effects of nicotine administration on nAcc firing as recorded *in vitro* and *in vivo* are far from straightforward ([59-61,117], and for review see [118]). Recent *in vivo* recordings in our lab examined the effects of nicotine on ventral hippocampus to nAcc circuits in genetically modified mice testing for the degree of coherence between hippocampus and nAcc firing before and after nicotine administration. Preliminary findings indicate that the pattern of phasic bursting activity in the nAcc and the degree of hippocampus-nAcc coherence are strongly affected by nicotine and that the altered patterns of activity can persist long after the removal of nicotine from the system (unpublished: M. Nason and LWR).

To address the mechanism(s) that might underlie sustained effects of nicotine at ventral hippocampus to nAcc synapses, we moved to a gene chimeric, ventral hippocampus microslice plus wild type (WT) nAcc co-culture [47]. These studies document that in WT-WT ventral hippocampus to nAcc circuits there is strong pre-synaptic nAChR-mediated control on glutamatergic transmission. Although both $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs participate in nicotine-induced synaptic facilitation at ventral hippocampus to nAcc synapses, it is the $\alpha 7^*$ nAChRs that mediate the long lasting potentiation of ventral hippocampus activity [47]. Thus selective blockade of pre-synaptic $\alpha 7^*$ nAChRs or studies of chimeric cultures of $\alpha 7^*$ KO ventral hippocampus with WT nAcc neurons reveal only a transient facilitation of glutamate release. Something about $\alpha 7^*$ nAChRs converts the transient effects of nicotine into long lasting changes in synaptic transmission (see discussion below and [47]).

1.2.5. Nicotinic modulation of synaptic plasticity in hippocampal and cortico-amygdala circuits—Pairing of nicotine with activity potently modulates transmission and alters the probability of LTP in hippocampus and at cortico-amygdala synapses as well. In the hippocampus, nicotine by itself induces LTP at a minority of the glutamatergic synapses. However, nicotine paired with a subthreshold induction protocol induces synaptic plasticity at the majority of glutamatergic synapses [36,88,119]. Activation of post-synaptic nAChRs on

CA1 pyramidal neurons can boost short-term plasticity into LTP in Schaffer collateral synapses [36]. Activating nAChRs on interneurons that synapse on pyramidal neurons can prevent LTP in glutamatergic synapses [36]. Thus, timing and localization of nAChR activity in the hippocampus can determine whether LTP will occur or not. These different types of nicotinic modulation of LTP may contribute to the well-known effects of nicotine on learning and memory. Since CA1 pyramidal neurons in the ventral hippocampus project to the PFC [120], modulation of synaptic plasticity in the CA1 area by nicotine may also participate in the effects of nicotine on attention performance.

Nicotine has long been known to modulate activity in the amygdala [121] and prenatal exposure to nicotine has been strongly linked with difficulties in emotional behaviors later in life [92]. Cholinergic neurons from the basal forebrain send projections to several nuclei in the amygdala with the lateral and basolateral nuclei receiving particularly strong inputs [122,123]. Modulation of cortico-amygdala input by ACh influences BLA output to other limbic structures, including the nAcc, thereby altering emotional salience of learned experiences and reinforcement of motivated behaviors (for reviews see [124,125]). Recent studies demonstrate that the effects of nicotine exposure on amygdala circuits far outlast the time of nicotine administration [75,126]. Even a single trial, low-dose, exposure to nicotine can elicit lasting facilitation of cortical inputs to the BLA [75]. Pharmacological studies in WT and nAChR subunit KO mice reveal that activation of pre-synaptic $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs, facilitates glutamatergic transmission in an activity-dependent manner. With low-frequency stimulation of cortical inputs nicotine elicits robust facilitation of transmission at most cortico-BLA synapses and synaptic strength remains elevated for 15-30 min after nicotine washout. Most striking is the observation that nicotine reduces the threshold for activation of long-term potentiation of cortico-BLA synapses evoked by patterned (theta burst) stimulation [75].

1.3. What are the mechanisms by which nicotine alters the code of synaptic plasticity?

At this point, we hope to have convinced you that the diversity of nAChRs is not a perverse fluke of molecular redundancy, but rather a rich substrate for synaptic tuning. There is little doubt that the distinct biophysical (Ca^{2+} permeability, kinetics) and pharmacological properties (affinity, desensitization) as well as the cellular localization of nAChRs are important determinants of how cholinergic tone regulates circuit activity. Three key features should be emphasized. First, despite the high agonist affinity of some nAChRs and the rapid rates of desensitization of others, neither receptor occupancy nor the probability of opening are “maxed out” at baseline ACh concentrations or with a cigarette or two added to the soup. Second, there are likely multiple mechanisms that are involved in turning a transient increase in nAChR activation to long-term alterations in synaptic plasticity. That is, yes, the effects of nicotine at individual synapses, in complex circuits and on behavior are long lasting. Third, there are critical windows of nAChR activation where too much or too little can be catastrophic (for elegant examples see [92,95,96]). We conclude with a discussion of possible mechanisms that might underlie some of the long-term effects of nicotinic AChR activation and a brief summary of potential disease relevance.

1.3.1. Role of calcium signaling in nAChR-stimulated transmitter release—From the above discussion it is clear that despite the high affinity of $\beta 2^*$ nAChRs for nicotine and the inactivation that occurs with an $\text{IC}_{50} \sim 1\text{-}60\text{ nM}$ [62], the concentrations of nicotine due to smoking (100-500 nM) cause little desensitization of $\alpha 7^*$ nAChRs ($\text{IC}_{50} \sim 7\text{ }\mu\text{M}$) [36,51,127]. Furthermore, the targeting of both of these types of receptors to axons and axon terminals establishes an ideal impedance ratio. Thus, a little activation goes a long way. Gating of $\alpha \beta^*$ (or non- $\alpha 7^*$) nAChRs leads to local depolarization and activation of voltage gated Ca^{2+} channels (VGCC) [69]. Gating of $\alpha 7^*$ nAChRs at low agonist concentrations results in a slow non-desensitizing, influx of Ca^{2+} directly through these high Ca^{2+} permeability channels. With

the rise in Ca^{2+} , more Ca^{2+} may be released from intracellular Ca^{2+} -stores (CICR) [129,130]. Phasic activation Ca^{2+} signaling can lead in turn to stable activation of pre-synaptic Ca^{2+} /calmodulin kinase (CAMKII), perhaps supporting the 1-10 s bursts of multiquantal release as described at mossy fiber CA3 synapses. Long-term stable changes in probability of release (10 min to 1 h) by nicotine, as well as sustained changes in synaptic transmission appear to require coordinate pre- and post-synaptic activity that can be boosted by nAChR activation [51,52, 68,75]. In initial studies examining changes in Ca^{2+} signaling directly in axonal projections from PFC and ventral hippocampus microslices, we find that application of nicotine elicits an immediate rise in internal calcium at 2-5 μm “hotspots” along the axons. This initial response is followed by a further increase in Ca^{2+} at these sites after 2-3 min which persists with oscillatory periods of 1-2 min for at least 30 min after nicotine application (unpublished data: MM, HM and LWR). The long lasting Ca^{2+} signaling is blocked by antagonists of $\alpha 7^*$ nAChRs and is not seen in preparations from $\alpha 7$ KO animals. Recent studies from other labs also stress the differences in the contribution of $\beta 2^*$ nAChRs compared to $\alpha 7^*$ nAChRs on glutamate release from PFC synaptosomes. $\alpha 7^*$ nAChRs appear to link into downstream signaling cascades that allow longer term and different profiles of Ca^{2+} oscillations [69]. ERK1/2 is increased after activation of $\alpha 7^*$ nAChRs with peak values after 1.5 to 3 minutes. This correlates with an increase in phosphorylation of synapsin-1 which increases the size of the ready releasable pool. Fig. 2 illustrates the convergence of these findings in a model, which is of course, only a model. Nonetheless from the cellular to the circuit level studies, there is increasing evidence that nAChR can (somehow) exert profound and long term changes in synaptic plasticity.

2. Summary

Recent studies emphasize new and previously unappreciated aspects of nAChR signaling in the CNS. The effects can be long lasting, appear in critical periods during development and, if altered, may result in lifelong changes in behaviors subject to cholinergic modulation. Indeed, studies of several CNS disorders have implicated a role for cholinergic circuits in the normal functioning and maintenance of central circuits underlying attention, cognitive performance, motivation and memory. The role of cholinergic signaling in the brain may be quite complex, dependent on oscillatory signaling at synapses and in circuits. Rather than turning systems on or off, it appears that cholinergic tuning involves changes in the balance between inhibitory and excitatory inputs. In this manner, nAChRs participate in more subtle but crucial aspects of modulating synaptic plasticity.

References

- [1]. Le Novère N, Corringer PJ, Changeux JP. The diversity of subunit composition in nAChRs: evolutionary origins, physiologic and pharmacologic consequences. *J Neurobiol* 2002;53(4):447–56. [PubMed: 12436412]
- [2]. Chavez-Noriega LE, Crona JH, Washburn MS, Urrutia A, Elliott KJ, Johnson EC. Pharmacological characterization of recombinant human neuronal nicotinic acetylcholine receptors $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, $\alpha 8$, $\alpha 9$, $\alpha 10$, $\alpha 11$, $\alpha 12$, $\alpha 13$, $\alpha 14$, $\alpha 15$, $\alpha 16$, $\alpha 17$, $\alpha 18$, $\alpha 19$, $\alpha 20$, $\alpha 21$, $\alpha 22$, $\alpha 23$, $\alpha 24$, $\alpha 25$, $\alpha 26$, $\alpha 27$, $\alpha 28$, $\alpha 29$, $\alpha 30$, $\alpha 31$, $\alpha 32$, $\alpha 33$, $\alpha 34$, $\alpha 35$, $\alpha 36$, $\alpha 37$, $\alpha 38$, $\alpha 39$, $\alpha 40$, $\alpha 41$, $\alpha 42$, $\alpha 43$, $\alpha 44$, $\alpha 45$, $\alpha 46$, $\alpha 47$, $\alpha 48$, $\alpha 49$, $\alpha 50$, $\alpha 51$, $\alpha 52$, $\alpha 53$, $\alpha 54$, $\alpha 55$, $\alpha 56$, $\alpha 57$, $\alpha 58$, $\alpha 59$, $\alpha 60$, $\alpha 61$, $\alpha 62$, $\alpha 63$, $\alpha 64$, $\alpha 65$, $\alpha 66$, $\alpha 67$, $\alpha 68$, $\alpha 69$, $\alpha 70$, $\alpha 71$, $\alpha 72$, $\alpha 73$, $\alpha 74$, $\alpha 75$, $\alpha 76$, $\alpha 77$, $\alpha 78$, $\alpha 79$, $\alpha 80$, $\alpha 81$, $\alpha 82$, $\alpha 83$, $\alpha 84$, $\alpha 85$, $\alpha 86$, $\alpha 87$, $\alpha 88$, $\alpha 89$, $\alpha 90$, $\alpha 91$, $\alpha 92$, $\alpha 93$, $\alpha 94$, $\alpha 95$, $\alpha 96$, $\alpha 97$, $\alpha 98$, $\alpha 99$, $\alpha 100$, $\alpha 101$, $\alpha 102$, $\alpha 103$, $\alpha 104$, $\alpha 105$, $\alpha 106$, $\alpha 107$, $\alpha 108$, $\alpha 109$, $\alpha 110$, $\alpha 111$, $\alpha 112$, $\alpha 113$, $\alpha 114$, $\alpha 115$, $\alpha 116$, $\alpha 117$, $\alpha 118$, $\alpha 119$, $\alpha 120$, $\alpha 121$, $\alpha 122$, $\alpha 123$, $\alpha 124$, $\alpha 125$, $\alpha 126$, $\alpha 127$, $\alpha 128$, $\alpha 129$, $\alpha 130$, $\alpha 131$, $\alpha 132$, $\alpha 133$, $\alpha 134$, $\alpha 135$, $\alpha 136$, $\alpha 137$, $\alpha 138$, $\alpha 139$, $\alpha 140$, $\alpha 141$, $\alpha 142$, $\alpha 143$, $\alpha 144$, $\alpha 145$, $\alpha 146$, $\alpha 147$, $\alpha 148$, $\alpha 149$, $\alpha 150$, $\alpha 151$, $\alpha 152$, $\alpha 153$, $\alpha 154$, $\alpha 155$, $\alpha 156$, $\alpha 157$, $\alpha 158$, $\alpha 159$, $\alpha 160$, $\alpha 161$, $\alpha 162$, $\alpha 163$, $\alpha 164$, $\alpha 165$, $\alpha 166$, $\alpha 167$, $\alpha 168$, $\alpha 169$, $\alpha 170$, $\alpha 171$, $\alpha 172$, $\alpha 173$, $\alpha 174$, $\alpha 175$, $\alpha 176$, $\alpha 177$, $\alpha 178$, $\alpha 179$, $\alpha 180$, $\alpha 181$, $\alpha 182$, $\alpha 183$, $\alpha 184$, $\alpha 185$, $\alpha 186$, $\alpha 187$, $\alpha 188$, $\alpha 189$, $\alpha 190$, $\alpha 191$, $\alpha 192$, $\alpha 193$, $\alpha 194$, $\alpha 195$, $\alpha 196$, $\alpha 197$, $\alpha 198$, $\alpha 199$, $\alpha 200$, $\alpha 201$, $\alpha 202$, $\alpha 203$, $\alpha 204$, $\alpha 205$, $\alpha 206$, $\alpha 207$, $\alpha 208$, $\alpha 209$, $\alpha 210$, $\alpha 211$, $\alpha 212$, $\alpha 213$, $\alpha 214$, $\alpha 215$, $\alpha 216$, $\alpha 217$, $\alpha 218$, $\alpha 219$, $\alpha 220$, $\alpha 221$, $\alpha 222$, $\alpha 223$, $\alpha 224$, $\alpha 225$, $\alpha 226$, $\alpha 227$, $\alpha 228$, $\alpha 229$, $\alpha 230$, $\alpha 231$, $\alpha 232$, $\alpha 233$, $\alpha 234$, $\alpha 235$, $\alpha 236$, $\alpha 237$, $\alpha 238$, $\alpha 239$, $\alpha 240$, $\alpha 241$, $\alpha 242$, $\alpha 243$, $\alpha 244$, $\alpha 245$, $\alpha 246$, $\alpha 247$, $\alpha 248$, $\alpha 249$, $\alpha 250$, $\alpha 251$, $\alpha 252$, $\alpha 253$, $\alpha 254$, $\alpha 255$, $\alpha 256$, $\alpha 257$, $\alpha 258$, $\alpha 259$, $\alpha 260$, $\alpha 261$, $\alpha 262$, $\alpha 263$, $\alpha 264$, $\alpha 265$, $\alpha 266$, $\alpha 267$, $\alpha 268$, $\alpha 269$, $\alpha 270$, $\alpha 271$, $\alpha 272$, $\alpha 273$, $\alpha 274$, $\alpha 275$, $\alpha 276$, $\alpha 277$, $\alpha 278$, $\alpha 279$, $\alpha 280$, $\alpha 281$, $\alpha 282$, $\alpha 283$, $\alpha 284$, $\alpha 285$, $\alpha 286$, $\alpha 287$, $\alpha 288$, $\alpha 289$, $\alpha 290$, $\alpha 291$, $\alpha 292$, $\alpha 293$, $\alpha 294$, $\alpha 295$, $\alpha 296$, $\alpha 297$, $\alpha 298$, $\alpha 299$, $\alpha 300$, $\alpha 301$, $\alpha 302$, $\alpha 303$, $\alpha 304$, $\alpha 305$, $\alpha 306$, $\alpha 307$, $\alpha 308$, $\alpha 309$, $\alpha 310$, $\alpha 311$, $\alpha 312$, $\alpha 313$, $\alpha 314$, $\alpha 315$, $\alpha 316$, $\alpha 317$, $\alpha 318$, $\alpha 319$, $\alpha 320$, $\alpha 321$, $\alpha 322$, $\alpha 323$, $\alpha 324$, $\alpha 325$, $\alpha 326$, $\alpha 327$, $\alpha 328$, $\alpha 329$, $\alpha 330$, $\alpha 331$, $\alpha 332$, $\alpha 333$, $\alpha 334$, $\alpha 335$, $\alpha 336$, $\alpha 337$, $\alpha 338$, $\alpha 339$, $\alpha 340$, $\alpha 341$, $\alpha 342$, $\alpha 343$, $\alpha 344$, $\alpha 345$, $\alpha 346$, $\alpha 347$, $\alpha 348$, $\alpha 349$, $\alpha 350$, $\alpha 351$, $\alpha 352$, $\alpha 353$, $\alpha 354$, $\alpha 355$, $\alpha 356$, $\alpha 357$, $\alpha 358$, $\alpha 359$, $\alpha 360$, $\alpha 361$, $\alpha 362$, $\alpha 363$, $\alpha 364$, $\alpha 365$, $\alpha 366$, $\alpha 367$, $\alpha 368$, $\alpha 369$, $\alpha 370$, $\alpha 371$, $\alpha 372$, $\alpha 373$, $\alpha 374$, $\alpha 375$, $\alpha 376$, $\alpha 377$, $\alpha 378$, $\alpha 379$, $\alpha 380$, $\alpha 381$, $\alpha 382$, $\alpha 383$, $\alpha 384$, $\alpha 385$, $\alpha 386$, $\alpha 387$, $\alpha 388$, $\alpha 389$, $\alpha 390$, $\alpha 391$, $\alpha 392$, $\alpha 393$, $\alpha 394$, $\alpha 395$, $\alpha 396$, $\alpha 397$, $\alpha 398$, $\alpha 399$, $\alpha 400$, $\alpha 401$, $\alpha 402$, $\alpha 403$, $\alpha 404$, $\alpha 405$, $\alpha 406$, $\alpha 407$, $\alpha 408$, $\alpha 409$, $\alpha 410$, $\alpha 411$, $\alpha 412$, $\alpha 413$, $\alpha 414$, $\alpha 415$, $\alpha 416$, $\alpha 417$, $\alpha 418$, $\alpha 419$, $\alpha 420$, $\alpha 421$, $\alpha 422$, $\alpha 423$, $\alpha 424$, $\alpha 425$, $\alpha 426$, $\alpha 427$, $\alpha 428$, $\alpha 429$, $\alpha 430$, $\alpha 431$, $\alpha 432$, $\alpha 433$, $\alpha 434$, $\alpha 435$, $\alpha 436$, $\alpha 437$, $\alpha 438$, $\alpha 439$, $\alpha 440$, $\alpha 441$, $\alpha 442$, $\alpha 443$, $\alpha 444$, $\alpha 445$, $\alpha 446$, $\alpha 447$, $\alpha 448$, $\alpha 449$, $\alpha 450$, $\alpha 451$, $\alpha 452$, $\alpha 453$, $\alpha 454$, $\alpha 455$, $\alpha 456$, $\alpha 457$, $\alpha 458$, $\alpha 459$, $\alpha 460$, $\alpha 461$, $\alpha 462$, $\alpha 463$, $\alpha 464$, $\alpha 465$, $\alpha 466$, $\alpha 467$, $\alpha 468$, $\alpha 469$, $\alpha 470$, $\alpha 471$, $\alpha 472$, $\alpha 473$, $\alpha 474$, $\alpha 475$, $\alpha 476$, $\alpha 477$, $\alpha 478$, $\alpha 479$, $\alpha 480$, $\alpha 481$, $\alpha 482$, $\alpha 483$, $\alpha 484$, $\alpha 485$, $\alpha 486$, $\alpha 487$, $\alpha 488$, $\alpha 489$, $\alpha 490$, $\alpha 491$, $\alpha 492$, $\alpha 493$, $\alpha 494$, $\alpha 495$, $\alpha 496$, $\alpha 497$, $\alpha 498$, $\alpha 499$, $\alpha 500$, $\alpha 501$, $\alpha 502$, $\alpha 503$, $\alpha 504$, $\alpha 505$, $\alpha 506$, $\alpha 507$, $\alpha 508$, $\alpha 509$, $\alpha 510$, $\alpha 511$, $\alpha 512$, $\alpha 513$, $\alpha 514$, $\alpha 515$, $\alpha 516$, $\alpha 517$, $\alpha 518$, $\alpha 519$, $\alpha 520$, $\alpha 521$, $\alpha 522$, $\alpha 523$, $\alpha 524$, $\alpha 525$, $\alpha 526$, $\alpha 527$, $\alpha 528$, $\alpha 529$, $\alpha 530$, $\alpha 531$, $\alpha 532$, $\alpha 533$, $\alpha 534$, $\alpha 535$, $\alpha 536$, $\alpha 537$, $\alpha 538$, $\alpha 539$, $\alpha 540$, $\alpha 541$, $\alpha 542$, $\alpha 543$, $\alpha 544$, $\alpha 545$, $\alpha 546$, $\alpha 547$, $\alpha 548$, $\alpha 549$, $\alpha 550$, $\alpha 551$, $\alpha 552$, $\alpha 553$, $\alpha 554$, $\alpha 555$, $\alpha 556$, $\alpha 557$, $\alpha 558$, $\alpha 559$, $\alpha 560$, $\alpha 561$, $\alpha 562$, $\alpha 563$, $\alpha 564$, $\alpha 565$, $\alpha 566$, $\alpha 567$, $\alpha 568$, $\alpha 569$, $\alpha 570$, $\alpha 571$, $\alpha 572$, $\alpha 573$, $\alpha 574$, $\alpha 575$, $\alpha 576$, $\alpha 577$, $\alpha 578$, $\alpha 579$, $\alpha 580$, $\alpha 581$, $\alpha 582$, $\alpha 583$, $\alpha 584$, $\alpha 585$, $\alpha 586$, $\alpha 587$, $\alpha 588$, $\alpha 589$, $\alpha 590$, $\alpha 591$, $\alpha 592$, $\alpha 593$, $\alpha 594$, $\alpha 595$, $\alpha 596$, $\alpha 597$, $\alpha 598$, $\alpha 599$, $\alpha 600$, $\alpha 601$, $\alpha 602$, $\alpha 603$, $\alpha 604$, $\alpha 605$, $\alpha 606$, $\alpha 607$, $\alpha 608$, $\alpha 609$, $\alpha 610$, $\alpha 611$, $\alpha 612$, $\alpha 613$, $\alpha 614$, $\alpha 615$, $\alpha 616$, $\alpha 617$, $\alpha 618$, $\alpha 619$, $\alpha 620$, $\alpha 621$, $\alpha 622$, $\alpha 623$, $\alpha 624$, $\alpha 625$, $\alpha 626$, $\alpha 627$, $\alpha 628$, $\alpha 629$, $\alpha 630$, $\alpha 631$, $\alpha 632$, $\alpha 633$, $\alpha 634$, $\alpha 635$, $\alpha 636$, $\alpha 637$, $\alpha 638$, $\alpha 639$, $\alpha 640$, $\alpha 641$, $\alpha 642$, $\alpha 643$, $\alpha 644$, $\alpha 645$, $\alpha 646$, $\alpha 647$, $\alpha 648$, $\alpha 649$, $\alpha 650$, $\alpha 651$, $\alpha 652$, $\alpha 653$, $\alpha 654$, $\alpha 655$, $\alpha 656$, $\alpha 657$, $\alpha 658$, $\alpha 659$, $\alpha 660$, $\alpha 661$, $\alpha 662$, $\alpha 663$, $\alpha 664$, $\alpha 665$, $\alpha 666$, $\alpha 667$, $\alpha 668$, $\alpha 669$, $\alpha 670$, $\alpha 671$, $\alpha 672$, $\alpha 673$, $\alpha 674$, $\alpha 675$, $\alpha 676$, $\alpha 677$, $\alpha 678$, $\alpha 679$, $\alpha 680$, $\alpha 681$, $\alpha 682$, $\alpha 683$, $\alpha 684$, $\alpha 685$, $\alpha 686$, $\alpha 687$, $\alpha 688$, $\alpha 689$, $\alpha 690$, $\alpha 691$, $\alpha 692$, $\alpha 693$, $\alpha 694$, $\alpha 695$, $\alpha 696$, $\alpha 697$, $\alpha 698$, $\alpha 699$, $\alpha 700$, $\alpha 701$, $\alpha 702$, $\alpha 703$, $\alpha 704$, $\alpha 705$, $\alpha 706$, $\alpha 707$, $\alpha 708$, $\alpha 709$, $\alpha 710$, $\alpha 711$, $\alpha 712$, $\alpha 713$, $\alpha 714$, $\alpha 715$, $\alpha 716$, $\alpha 717$, $\alpha 718$, $\alpha 719$, $\alpha 720$, $\alpha 721$, $\alpha 722$, $\alpha 723$, $\alpha 724$, $\alpha 725$, $\alpha 726$, $\alpha 727$, $\alpha 728$, $\alpha 729$, $\alpha 730$, $\alpha 731$, $\alpha 732$, $\alpha 733$, $\alpha 734$, $\alpha 735$, $\alpha 736$, $\alpha 737$, $\alpha 738$, $\alpha 739$, $\alpha 740$, $\alpha 741$, $\alpha 742$, $\alpha 743$, $\alpha 744$, $\alpha 745$, $\alpha 746$, $\alpha 747$, $\alpha 748$, $\alpha 749$, $\alpha 750$, $\alpha 751$, $\alpha 752$, $\alpha 753$, $\alpha 754$, $\alpha 755$, $\alpha 756$, $\alpha 757$, $\alpha 758$, $\alpha 759$, $\alpha 760$, $\alpha 761$, $\alpha 762$, $\alpha 763$, $\alpha 764$, $\alpha 765$, $\alpha 766$, $\alpha 767$, $\alpha 768$, $\alpha 769$, $\alpha 770$, $\alpha 771$, $\alpha 772$, $\alpha 773$, $\alpha 774$, $\alpha 775$, $\alpha 776$, $\alpha 777$, $\alpha 778$, $\alpha 779$, $\alpha 780$, $\alpha 781$, $\alpha 782$, $\alpha 783$, $\alpha 784$, $\alpha 785$, $\alpha 786$, $\alpha 787$, $\alpha 788$, $\alpha 789$, $\alpha 790$, $\alpha 791$, $\alpha 792$, $\alpha 793$, $\alpha 794$, $\alpha 795$, $\alpha 796$, $\alpha 797$, $\alpha 798$, $\alpha 799$, $\alpha 800$, $\alpha 801$, $\alpha 802$, $\alpha 803$, $\alpha 804$, $\alpha 805$, $\alpha 806$, $\alpha 807$, $\alpha 808$, $\alpha 809$, $\alpha 810$, $\alpha 811$, $\alpha 812$, $\alpha 813$, $\alpha 814$, $\alpha 815$, $\alpha 816$, $\alpha 817$, $\alpha 818$, $\alpha 819$, $\alpha 820$, $\alpha 821$, $\alpha 822$, $\alpha 823$, $\alpha 824$, $\alpha 825$, $\alpha 826$, $\alpha 827$, $\alpha 828$, $\alpha 829$, $\alpha 830$, $\alpha 831$, $\alpha 832$, $\alpha 833$, $\alpha 834$, $\alpha 835$, $\alpha 836$, $\alpha 837$, $\alpha 838$, $\alpha 839$, $\alpha 840$, $\alpha 841$, $\alpha 842$, $\alpha 843$, $\alpha 844$, $\alpha 845$, $\alpha 846$, $\alpha 847$, $\alpha 848$, $\alpha 849$, $\alpha 850$, $\alpha 851$, $\alpha 852$, $\alpha 853$, $\alpha 854$, $\alpha 855$, $\alpha 856$, $\alpha 857$, $\alpha 858$, $\alpha 859$, $\alpha 860$, $\alpha 861$, $\alpha 862$, $\alpha 863$, $\alpha 864$, $\alpha 865$, $\alpha 866$, $\alpha 867$, $\alpha 868$, $\alpha 869$, $\alpha 870$, $\alpha 871$, $\alpha 872$, $\alpha 873$, $\alpha 874$, $\alpha 875$, $\alpha 876$, $\alpha 877$, $\alpha 878$, $\alpha 879$, $\alpha 880$, $\alpha 881$, $\alpha 882$, $\alpha 883$, $\alpha 884$, $\alpha 885$, $\alpha 886$, $\alpha 887$, $\alpha 888$, $\alpha 889$, $\alpha 890$, $\alpha 891$, $\alpha 892$, $\alpha 893$, $\alpha 894$, $\alpha 895$, $\alpha 896$, $\alpha 897$, $\alpha 898$, $\alpha 899$, $\alpha 900$, $\alpha 901$, $\alpha 902$, $\alpha 903$, $\alpha 904$, $\alpha 905$, $\alpha 906$, $\alpha 907$, $\alpha 908$, $\alpha 909$, $\alpha 910$, $\alpha 911$, $\alpha 912$, $\alpha 913$, $\alpha 914$, $\alpha 915$, $\alpha 916$, $\alpha 917$, $\alpha 918$, $\alpha 919$, $\alpha 920$, $\alpha 921$, $\alpha 922$, $\alpha 923$, $\alpha 924$, $\alpha 925$, $\alpha 926$, $\alpha 927$, $\alpha 928$, $\alpha 929$, $\alpha 930$, $\alpha 931$, $\alpha 932$, $\alpha 933$, $\alpha 934$, $\alpha 935$, $\alpha 936$, $\alpha 937$, $\alpha 938$, $\alpha 939$, $\alpha 940$, $\alpha 941$, $\alpha 942$, $\alpha 943$, $\alpha 944$, $\alpha 945$, $\alpha 946$, $\alpha 947$, $\alpha 948$, $\alpha 949$, $\alpha 950$, $\alpha 951$, $\alpha 952$, $\alpha 953$, $\alpha 954$, $\alpha 955$, $\alpha 956$, $\alpha 957$, $\alpha 958$, $\alpha 959$, $\alpha 960$, $\alpha 961$, $\alpha 962$, $\alpha 963$, $\alpha 964$, $\alpha 965$, $\alpha 966$, $\alpha 967$, $\alpha 968$, $\alpha 969$, $\alpha 970$, $\alpha 971$, $\alpha 972$, $\alpha 973$, $\alpha 974$, $\alpha 975$, $\alpha 976$, $\alpha 977$, $\alpha 978$, $\alpha 979$, $\alpha 980$, $\alpha 981$, $\alpha 982$, $\alpha 983$, $\alpha 984$, $\alpha 985$, $\alpha 986$, $\alpha 987$, $\alpha 988$, $\alpha 989$, $\alpha 990$, $\alpha 991$, $\alpha 992$, $\alpha 993$, $\alpha 994$, $\alpha 995$, $\alpha 996$, $\alpha 997$, $\alpha 998$, $\alpha 999$, $\alpha 1000$, $\alpha 1001$, $\alpha 1002$, $\alpha 1003$, $\alpha 1004$, $\alpha 1005$, $\alpha 1006$, $\alpha 1007$, $\alpha 1008$, $\alpha 1009$, $\alpha 1010$, $\alpha 1011$, $\alpha 1012$, $\alpha 1013$, $\alpha 1014$, $\alpha 1015$, $\alpha 1016$, $\alpha 1017$, $\alpha 1018$, $\alpha 1019$, $\alpha 1020$, $\alpha 1021$, $\alpha 1022$, $\alpha 1023$, $\alpha 1024$, $\alpha 1025$, $\alpha 1026</$

- [7]. Millar NS, Gotti C. Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* 2009;56(1):237–46. [PubMed: 18723036]
- [8]. Grady SR, Murphy KL, Cao J, Marks MJ, McIntosh JM, Collins AC. Characterization of nicotinic agonist-induced [H-3] dopamine release from synaptosomes prepared from four mouse brain regions. *J Pharmacol Exp Ther* 2002;301(2):651–60. [PubMed: 11961070]
- [9]. McGehee DS. Nicotinic receptors and hippocampal synaptic plasticity... it's all in the timing. *Trends Neurosci* 2002;25(4):171. [PubMed: 11998680]
- [10]. Wonnacott S, Sidhpura N, Balfour DJK. Nicotine: from molecular mechanisms to behaviour. *Curr Opin Pharmacol* 2005;5(1):53. [PubMed: 15661626]
- [11]. Mineur YS, Picciotto MR. Genetics of nicotinic acetylcholine receptors: relevance to nicotine addiction. *Biochem Pharmacol* 2008;75(1):323–33. [PubMed: 17632086]
- [12]. Alkondon M, Albuquerque EX. The nicotinic acetylcholine receptor subtypes and their function in the hippocampus and cerebral cortex. *Prog Brain Res* 2004:109–20. [PubMed: 14650910]
- [13]. Fucile S. Ca^{2+} permeability of nicotinic acetylcholine receptors. *Cell Calcium* 2004;35(1):1. [PubMed: 14670366]
- [14]. Wonnacott S, Harrison R, Lunt G. Immunological cross-reactivity between the alpha-bungarotoxin-binding component from rat brain and nicotinic acetylcholine receptor. *J Neuroimmunol* 1982;3(1):1–13. [PubMed: 7096564]
- [15]. Clarke PB, Schwartz RD, Paul SM, Pert CB, Pert A. Nicotinic binding in rat brain: autoradiographic comparison of [3H]acetylcholine, [3H]nicotine, and [125I]-alpha-bungarotoxin. *J Neurosci* 1985;5(5):1307–15. [PubMed: 3998824]
- [16]. Dajas-Bailador F, Wonnacott S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. *Trends Pharmacol Sci* 2004;25(6):317. [PubMed: 15165747]
- [17]. Fucile S, Renzi M, Lauro C, Limatola C, Ciotti T, Eusebi F. Nicotinic cholinergic stimulation promotes survival and reduces motility of cultured rat cerebellar granule cells. *Neuroscience* 2004;127(1):53–61. [PubMed: 15219668]
- [18]. McGehee DS, Heath MJS, Gelber S, Devay P, Role LW. Nicotine enhancement of fast excitatory synaptic transmission in CNS by Presynaptic receptors. *Science* 1995;269(5231):1692–6. [PubMed: 7569895]
- [19]. Rogers M, Colquhoun LM, Patrick JW, Dani JA. Calcium flux through predominantly independent purinergic ATP and nicotinic acetylcholine receptors. *J Neurophysiol* 1997;77(3):1407–17. [PubMed: 9084606]
- [20]. Haghighi AP, Cooper E. A molecular link between inward rectification and calcium permeability of neuronal nicotinic acetylcholine alpha 3beta 4 and alpha 4beta 2 receptors. *J Neurosci* 2000;20(2):529–41. [PubMed: 10632582]
- [21]. Papke RL. Estimation of both the potency and efficacy of [alpha]7 nAChR agonists from single-concentration responses. *Life Sci* 2006;78(24):2812–9. [PubMed: 16343553]
- [22]. Papke RL, Meyer E, Nutter T, Uteshev VV. Alpha 7 receptor-selective agonists and modes of alpha 7 receptor activation. *Eur J Pharmacol* 2000;393(13):179–95. [PubMed: 10771012]
- [23]. El-Hajj RA, McKay SB, McKay DB. Pharmacological and immunological identification of native [alpha]7 nicotinic receptors: evidence for homomeric and heteromeric [alpha]7 receptors. *Life Sci* 2007;81(16):1317–22. [PubMed: 17928008]
- [24]. Jones S, Yakel JL. Functional nicotinic ACh receptors on interneurons in the rat hippocampus. *J Physiol (Lond)* 1997;504(3):603–10. [PubMed: 9401968]
- [25]. Ramirez-Latorre J, Yu CR, Qu X, Perin F, Karlin A, Role L. Functional contributions of [alpha]5 subunit to neuronal acetylcholine receptor channels. *Nature* 1996;380(6572):347–51. [PubMed: 8598930]
- [26]. Yu CR, Role LW. Functional contribution of the alpha 5 subunit to neuronal nicotinic channels expressed by chick sympathetic ganglion neurones. *J Physiol (Lond)* 1998;509(3):667–81. [PubMed: 9596790]
- [27]. Girod R, et al. Heteromeric complexes of alpha 5 and/or alpha 7 subunits—effects of calcium and potential role in nicotine-induced presynaptic facilitation. Molecular and functional diversity of ion channels and receptors 1999;868:578–90.

- [28]. Khiroug SS, Harkness PC, Lamb PW, Sudweeks SN, Khiroug L, Millar NS, et al. Rat nicotinic ACh receptor alpha7 and beta2 subunits co-assemble to form functional heteromeric nicotinic receptor channels. *J Physiol* 2002;540(2):425–34. [PubMed: 11956333]
- [29]. Yu CR, Role LW. Functional contribution of the alpha 7 subunit to multiple subtypes of nicotinic receptors in embryonic chick sympathetic neurones. *J Physiol (Lond)* 1998;509(3):651–65. [PubMed: 9596789]
- [30]. Elgoyhen AB, Vetter DE, Katz E, Rothlin CV, Heinemann SF, Boulter J. alpha 10: A determinant of nicotinic cholinergic receptor function in mammalian vestibular and cochlear mechanosensory hair cells. *Proc Natl Acad Sci USA* 2001;98(6):3501–6. [PubMed: 11248107]
- [31]. Elgoyhen AB, Johnson DS, Boulter J, Vetter DE, Heinemann S. [Alpha]9: An acetylcholine receptor with novel pharmacological properties expressed in rat cochlear hair cells. *Cell* 1994;79(4):705–15. [PubMed: 7954834]
- [32]. Kuryatov A, Onksen J, Lindstrom J. Roles of accessory subunits in {alpha}4{beta}2* nicotinic receptors. *Mol Pharmacol* 2008;74(1):132–43. [PubMed: 18381563]
- [33]. Gerzanich V, Wang F, Kuryatov A, Lindstrom J. Alpha 5 subunit alters desensitization, pharmacology, Ca⁺⁺ permeability and Ca⁺⁺ modulation of human neuronal alpha 3 nicotinic receptors. *J Pharmacol Exp Ther* 1998;286(1):311–20. [PubMed: 9655874]
- [34]. Kuryatov A, Olale F, Cooper J, Choi C, Lindstrom J. Human [alpha]6 AChR subtypes: subunit composition, assembly, and pharmacological responses. *Neuropharmacology* 2000;39(13):2570–90. [PubMed: 11044728]
- [35]. Fischer H, Orr-Urtreger A, Role LW, Huck S. Selective deletion of the {alpha}5 subunit differentially affects somatic-dendritic versus axonally targeted nicotinic ACh receptors in mouse. *J Physiol (Lond)* 2005;563(1):119–37. [PubMed: 15611037]
- [36]. Ji D, Lape R, Dani JA. Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity. *Neuron* 2001;31(1):131–41. [PubMed: 11498056]
- [37]. Fabian-Fine R, Skehel P, Errington ML, Davies HA, Sher E, Stewart MG, et al. Ultrastructural distribution of the {alpha}7 nicotinic acetylcholine receptor subunit rat hippocampus. *J Neurosci* 2001;21(20):7993–8003. [PubMed: 11588172]
- [38]. Ge SY, Dani JA. Nicotinic acetylcholine receptors at glutamate synapses facilitate long-term depression or potentiation. *J Neurosci* 2005;25(26):6084–91. [PubMed: 15987938]
- [39]. Alkondon M, Albuquerque EX. Nicotinic acetylcholine receptor alpha 7 and alpha 4 beta 2 subtypes differentially control GABAergic input to CA1 neurons in rat hippocampus. *J Neurophysiol* 2001;86(6):3043–55. [PubMed: 11731559]
- [40]. 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(1):628–32. [PubMed: 10414345]
- [41]. Levy RB, Aoki C. Alpha 7 Nicotinic acetylcholine receptors occur at postsynaptic densities of AMPA receptor-positive and -negative excitatory synapses in rat sensory cortex. *J Neurosci* 2002;22(12):5001–15. [PubMed: 12077196]
- [42]. Jones IW, Wonnacott S. Precise localization of {alpha}7 nicotinic acetylcholine receptors on glutamatergic axon terminals in the rat ventral tegmental area. *J Neurosci* 2004;24(50):11244–52. [PubMed: 15601930]
- [43]. Nashmi R, Lester H. CNS localization of neuronal nicotinic receptors. *J Mol Neurosci* 2006;30(1):181–4. [PubMed: 17192671]
- [44]. Hancock ML, Canetta SE, Role LW, Talmage DA. Presynaptic type III neuregulin1-ErbB signaling targets {alpha}7 nicotinic acetylcholine receptors to axons. *J Cell Biol* 2008;181(3):511–21. [PubMed: 18458158]
- [45]. Wonnacott S. Presynaptic nicotinic ACh receptors. *Trends Neurosci* 1997;20(2):92. [PubMed: 9023878]
- [46]. Clarke PB, Hamill GS, Nadi NS, Jacobowitz DM, Pert A. H-nicotine- and 125I-alpha-bungarotoxin-labeled nicotinic receptors in the interpeduncular nucleus of rats. II. Effects of habenular deafferentation. *J Comp Neurol* 1986;251(3):407–13. [PubMed: 3771837]
- [47]. Zhong C, Du C, Hancock M, Mertz M, Talmage DA, Role LW. Presynaptic type III neuregulin 1 is required for sustained enhancement of hippocampal transmission by nicotine and for axonal

- targeting of $\alpha 7$ nicotinic acetylcholine receptors. *J Neurosci* 2008;28(37):9111–6. [PubMed: 18784291]
- [48]. Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB. Nicotinic modulation of neuronal networks: from receptors to cognition. *Psychopharmacology* 2006;184(34):292–305. [PubMed: 16001117]
- [49]. Charpantier E, Barneoud P, Moser P, Besnard F, Sgard F. Nicotinic acetylcholine subunit mRNA expression in dopaminergic neurons of the rat substantia nigra and ventral tegmental area. *Neuroreport* 1998;9(13):3097–101. [PubMed: 9804323]
- [50]. Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. *Nature* 1997;390(6658):401–4. [PubMed: 9389479]
- [51]. Mansvelder HD, McGehee DS. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. *Neuron* 2000;27(2):349–57. [PubMed: 10985354]
- [52]. Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* 2002;33(6):905–19. [PubMed: 11906697]
- [53]. Champiaux N, Han ZY, Bessis A, Rossi FM, Zoli M, Marubio L, et al. Distribution and pharmacology of $\alpha 6$ -Containing nicotinic acetylcholine receptors analyzed with mutant mice. *J Neurosci* 2002;22(4):1208–17. [PubMed: 11850448]
- [54]. Pidoplichko VI, Noguchi J, Areola OO, Liang Y, Peterson J, Zhang T, et al. Nicotinic cholinergic synaptic mechanisms in the ventral tegmental area contribute to nicotine addiction. *Learn Mem* 2004;11(1):60–9. [PubMed: 14747518]
- [55]. 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(5):1452–63. [PubMed: 11222635]
- [56]. 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(8):3176–85. [PubMed: 12716925]
- [57]. 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(6):1526–35. [PubMed: 15155845]
- [58]. 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 $\beta 3$ subunit gene deletion. *Mol Pharmacol* 2005;67(6):2007–15. [PubMed: 15749993]
- [59]. Zhang H, Sulzer D. Frequency-dependent modulation of dopamine release by nicotine. *Nat Neurosci* 2004;7(6):581–2. [PubMed: 15146187]
- [60]. Rice ME, Cragg SJ. Nicotine amplifies reward-related dopamine signals in striatum. *Nat Neurosci* 2004;7(6):583–4. [PubMed: 15146188]
- [61]. Britt JP, McGehee DS. Presynaptic opioid and nicotinic receptor modulation of dopamine overflow in the nucleus accumbens. *J Neurosci* 2008;28(7):1672–81. [PubMed: 18272687]
- [62]. Frazier CJ, Rollins YD, Breese CR, Leonard S, Freedman R, Dunwiddie TV. acetylcholine activates an α -bungarotoxin-sensitive nicotinic current in rat hippocampal interneurons but not pyramidal cells. *J Neurosci* 1998;18(4):1187–95. [PubMed: 9454829]
- [63]. Gioanni Y, Rougeot C, Clarke PBS, 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(1):18–30. [PubMed: 9987008]
- [64]. Vidal C, Changeux JP. Nicotinic and muscarinic modulations of excitatory synaptic transmission in the rat prefrontal cortex in vitro. *Neuroscience* 1993;56(1):23–32. [PubMed: 7901807]
- [65]. Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. *Neuropsychopharmacology* 2003;28(2):216–25. [PubMed: 12589374]
- [66]. Groenewegen HJ, Uylings HB. The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog Brain Res* 2000;126:3–28. [PubMed: 11105636]

- [67]. Kassam SM, Herman PM, Goodfellow NM, Alves NC, Lambe EK. Developmental excitation of corticothalamic neurons by nicotinic acetylcholine receptors. *J Neurosci* 2008;28(35):8756–64. [PubMed: 18753377]
- [68]. 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(1):73–87. [PubMed: 17408579]
- [69]. Dickinson JA, Kew JNC, Wonnacott S. Presynaptic $\alpha 7$ and $\beta 2$ -containing nicotinic acetylcholine receptors modulate excitatory amino acid release from rat prefrontal cortex nerve terminals via distinct cellular mechanisms. *Mol Pharmacol* 2008;74(2):348–59. [PubMed: 18445710]
- [70]. Wang BW, Liao WN, Chang CT, Wang SJ. Facilitation of glutamate release by nicotine involves the activation of a Ca^{2+} /calmodulin signaling pathway in rat prefrontal cortex nerve terminals. *Synapse* 2006;59(8):491–501. [PubMed: 16565963]
- [71]. Vanderschuren LJ, Kalivas PW. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl)* 2000;151(23):99–120. [PubMed: 10972458]
- [72]. Yoshikawa T, Watanabe A, Shibuya H, Toru M. Involvement of the fimbria fornix in the initiation but not in the expression of methamphetamine-induced sensitization. *Pharmacol Biochem Behav* 1993;45(3):691–5. [PubMed: 8332627]
- [73]. Pierce RC, Reeder DC, Hicks J, Morgan ZR, Kalivas PW. Ibotenic acid lesions of the dorsal prefrontal cortex disrupt the expression of behavioral sensitization to cocaine. *Neuroscience* 1998;82(4):1103–14. [PubMed: 9466434]
- [74]. Beyer CE, Steketee JD. Cocaine sensitization: modulation by dopamine D2 receptors. *Cereb Cortex* 2002;12(5):526–35. [PubMed: 11950770]
- [75]. Jiang L, Role LW. Facilitation of cortico-amygdala synapses by nicotine: activity-dependent modulation of glutamatergic transmission. *J Neurophysiol* 2008;99(4):1988–99. [PubMed: 18272879]
- [76]. Saal D, Dong Y, Bonci A, Malenka RC. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 2003;37(4):577–82. [PubMed: 12597856]
- [77]. Ungless MA, Whistler JL, Malenka RC, Bonci A. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 2001;411(6837):583–7. [PubMed: 11385572]
- [78]. Thomas MJ, Beurrier C, Bonci A, Malenka RC. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci* 2001;4(12):1217–23. [PubMed: 11694884]
- [79]. Girod R, Role LW. Long-lasting enhancement of glutamatergic synaptic transmission by acetylcholine contrasts with response adaptation after exposure to low-level nicotine. *J Neurosci* 2001;21(14):5182–90. [PubMed: 11438593]
- [80]. Kawai H, Lazar R, Metherate R. Nicotinic control of axon excitability regulates thalamocortical transmission. *Nat Neurosci* 2007;10(9):1168–75. [PubMed: 17704774]
- [81]. Laroche S, Davis S, Jay TM. Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. *Hippocampus* 2000;10(4):438–46. [PubMed: 10985283]
- [82]. Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 1997;275(5297):213–5. [PubMed: 8985014]
- [83]. Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J Neurosci* 1998;18(24):10464–72. [PubMed: 9852584]
- [84]. Koester HJ, Sakmann B. Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials. *Proc Natl Acad Sci USA* 1998;95(16):9596–601. [PubMed: 9689126]
- [85]. Magee JC, Johnston D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 1997;275(5297):209–13. [PubMed: 8985013]
- [86]. Sjöström PJ, Nelson SB. Spike timing, calcium signals and synaptic plasticity. *Curr Opin Neurobiol* 2002;12(3):305–14. [PubMed: 12049938]
- [87]. McGehee DS. Nicotine and synaptic plasticity in prefrontal cortex. *Sci STKE* 2007;2007(399):e44.

- [88]. Fujii S, Ji Z, Morita N, Sumikawa K. Acute and chronic nicotine exposure differentially facilitate the induction of LTP. *Brain Res* 1999;846(1):137–43. [PubMed: 10536221]
- [89]. 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(8):1123–34. [PubMed: 17214974]
- [90]. Mirza NR, Stoleran IP. Nicotine enhances sustained attention in the rat under specific task conditions. *Psychopharmacology (Berl)* 1998;138(34):266–74. [PubMed: 9725748]
- [91]. Clarke PB. Nicotinic modulation of thalamocortical neurotransmission. *Prog Brain Res* 2004;145:253–60. [PubMed: 14650920]
- [92]. Heath CJ, Picciotto MR. Nicotine-induced plasticity during development: Modulation of the cholinergic system and long-term consequences for circuits involved in attention and sensory processing. *Neuropharmacology* 2009;56(1):254–62. [PubMed: 18692078]
- [93]. Metherate R, Hsieh CY. Synaptic mechanisms and cholinergic regulation in auditory cortex. *Prog Brain Res* 2004;145:143–56. [PubMed: 14650913]
- [94]. Aramakis VB, Hsieh CY, Leslie FM, Metherate R. A critical period for nicotine-induced disruption of synaptic development in rat auditory cortex. *J Neurosci* 2000;20(16):6106–16. [PubMed: 10934260]
- [95]. King SL, Marks MJ, Grady SR, Caldarone BJ, Koren AO, Mukhin AG, et al. Conditional expression in corticothalamic efferents reveals a developmental role for nicotinic acetylcholine receptors in modulation of passive avoidance behavior. *J Neurosci* 2003;23(9):3837–43. [PubMed: 12736354]
- [96]. Liu Z, Neff RA, Berg DK. Sequential interplay of nicotinic and GABAergic signaling guides neuronal development. *Science* 2006;314(5805):1610–3. [PubMed: 17158331]
- [97]. Gabbott P, Warner TA, Jays PRL, Salway P, Busby SJ. Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. *J Comp Neurol* 2005;492(2):145–77. [PubMed: 16196030]
- [98]. Markou A. Review. Neurobiology of nicotine dependence. *Phil Trans R Soc B: Biol Sci* 2008;363(1507):3159–68.
- [99]. Nisell M, Nomikos GG, Svensson TH. Infusion of nicotine in the ventral tegmental area or the nucleus accumbens of the rat differentially affects accumbal dopamine release. *Pharmacol Toxicol* 1994;75(6):348–52. [PubMed: 7534921]
- [100]. 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(14):5274–8. [PubMed: 2899326]
- [101]. Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res* 1994;653(12):278–84. [PubMed: 7982062]
- [102]. Grenhoff J, Aston-Jones G, Svensson TH. Nicotinic effects on the firing pattern of midbrain dopamine neurons. *Acta Physiol Scand* 1986;128(3):351–8. [PubMed: 3788613]
- [103]. Picciotto MR, Zoli M, Rimondini R, Léna C, Marubio LM, Pich EM, et al. Acetylcholine receptors containing the [beta]2 subunit are involved in the reinforcing properties of nicotine. *Nature* 1998;391(6663):173–7. [PubMed: 9428762]
- [104]. Nomikos GG, Schilström B, Hildebrand BE, Panagis G, Grenhoff J, Svensson TH. Role of alpha7 nicotinic receptors in nicotine dependence and implications for psychiatric illness. *Behav Brain Res* 2000;113(12):97–103. [PubMed: 10942036]
- [105]. Corrigall WA, Coen KM, Zhang J, Adamson KL. GABA mechanisms in the pedunculopontine tegmental nucleus influence particular aspects of nicotine self-administration selectively in the rat. *Psychopharmacology (Berl)* 2001;158(2):190–7. [PubMed: 11702093]
- [106]. Descarries L, Gisiger V, Steriade M. Diffuse transmission by acetylcholine in the CNS. *Prog Neurobiol* 1997;53(5):603–25. [PubMed: 9421837]
- [107]. Zoli M, Jansson A, Sykova E, Agnati LF, Fuxe K. Volume transmission in the CNS and its relevance for neuropsychopharmacology. *Trends Pharmacol Sci* 1999;20(4):142–50. [PubMed: 10322499]

- [108]. Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Labarca C, et al. Nicotine activation of $\alpha 4^*$ receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004;306(5698):1029–32. [PubMed: 15528443]
- [109]. Grady SR, Salminen O, Lavery 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(8):1235–46. [PubMed: 17825262]
- [110]. Lovinger DM, Partridge JG, Tang K-C. Plastic control of striatal glutamatergic transmission by ensemble actions of several neurotransmitters and targets for drugs of abuse. *Ann N Y Acad Sci* 2003;1003(1):226–40. [PubMed: 14684449]
- [111]. Wang Z, Kai L, Day M, Ronesi J, Yin HH, Ding J, et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. *Neuron* 2006;50(3):443–52. [PubMed: 16675398]
- [112]. Goto Y, O'Donnell P. Altered prefrontal cortex-nucleus accumbens information processing in a developmental animal model of schizophrenia. *Ann N Y Acad Sci* 2003;1003(1):398–401. [PubMed: 14684471]
- [113]. Goto Y, O'Donnell P. Network synchrony in the nucleus accumbens in vivo. *J Neurosci* 2001;21(12):4498–504. [PubMed: 11404437]
- [114]. Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res Rev* 2000;31(23):330–41. [PubMed: 10719160]
- [115]. O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J Neurosci* 1995;15(5 I):3622–39. [PubMed: 7751934]
- [116]. West AR, Floresco SB, Charara ALI, Rosenkranz JA, Grace AA. Electrophysiological interactions between striatal glutamatergic and dopaminergic systems. *Ann N Y Acad Sci* 2003;1003(1):53–74. [PubMed: 14684435]
- [117]. Zhou FM, Wilson CJ, Dani JA. Cholinergic interneuron characteristics and nicotinic properties in the striatum. *J Neurobiol* 2002;53(4):590–605. [PubMed: 12436423]
- [118]. Dani JA, Bertrand D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annu Rev Pharmacol Toxicol* 2007;47(1):699–729. [PubMed: 17009926]
- [119]. Mann EO, Greenfield SA. Novel modulatory mechanisms revealed by the sustained application of nicotine in the guinea-pig hippocampus in vitro. *J Physiol* 2003;551(Pt 2):539–50. [PubMed: 12815181]
- [120]. Jay TM, Witter MP. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *J Comp Neurol* 1991;313(4):574–86. [PubMed: 1783682]
- [121]. Woolf NJ, Eckenstein F, Butcher LL. Cholinergic systems in the rat-brain.1. Projections to the Limbic telencephalon. *Brain Res Bull* 1984;13(6):751–84. [PubMed: 6532518]
- [122]. Changeux JP, Bertrand D, Corringer P-J, Dehaene S, Edelstein S, Lena C, et al. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. *Brain Res Rev* 1998;26(23):198–216. [PubMed: 9651527]
- [123]. Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology* 1998;138(34):217–30. [PubMed: 9725745]
- [124]. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci* 2004;27:1–28. [PubMed: 15217324]
- [125]. Power AE, Vazdarjanova A, McGaugh JL. Muscarinic cholinergic influences in memory consolidation. *Neurobiol Learn Mem* 2003;80(3):178–93. [PubMed: 14521862]
- [126]. Huang Y-Y, Kandel ER, Levine A. Chronic nicotine exposure induces a long-lasting and pathway-specific facilitation of LTP in the amygdala. *Learn Mem* 2008;15(8):603–10. [PubMed: 18685152]
- [127]. Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacol Biochem Behav* 2001;70(4):439–46. [PubMed: 11796143]
- [128]. Belujon P, Grace AA. Critical role of the prefrontal cortex in the regulation of hippocampus-accumbens information flow. *J Neurosci* 2008;28(39):9797–805. [PubMed: 18815264]

- [129]. Sharma G, Grybko M, Vijayaraghavan S. Action Potential-Independent. Nicotinic receptor-mediated concerted release of multiple quanta at hippocampal CA3-mossy fiber synapses. *J Neurosci* 2008;28(10):2563–75. [PubMed: 18322100]
- [130]. Sharma G, Vijayaraghavan S. Modulation of presynaptic store calcium induces release of glutamate and postsynaptic firing. *Neuron* 2003;38(6):929–39. [PubMed: 12818178]

Fig. 1.**Model of nicotinic modulation of layer 5 pyramidal neuron in the PFC**

In layer 5 of the mouse PFC, nicotinic AChRs are expressed on thalamocortical projections (T: yellow ovals on presynaptic profiles) on the cell bodies of low-threshold-spiking GABAergic cells (LTS) and by the regular-spiking-non-pyramidal cells (RSNP). FS cells do not express nAChRs. The glutamatergic inputs from T are increased by nicotine application eliciting an increased excitatory drive to the pyramidal neurons (Pyr), the LTS and the FS components. In addition RSNP cells are directly depolarized by nicotine due to activation of somato-dendritic nAChRs expressed by these cells, without alteration of the excitatory input. Thus, in the PFC nAChR activation results in an increased excitatory drive to the LTS neurons due to both direct activation of somato-dendritic nAChRs and to the indirect enhancement of glutamatergic input to LTS via activation of presynaptic nAChRs. Increased activation of LTS

results in increased inhibitory tone from the LTS to layer 5 pyramidal neurons, such that overall effect translates into a net inhibition of the pyramidal cells activity.

Fig. 2.

Nicotinic receptors regulate presynaptic gain via both $\alpha 7^*$ nAChRs and non- $\alpha 7^*$ nAChRs. Presynaptic $\alpha 7^*$ and non- $\alpha 7^*$ nAChRs modulate glutamate release via two different mechanisms. Activation of non- $\alpha 7^*$ nAChRs (A-1) cause depolarization which activates voltage gated calcium channels (VGCC) (2), and elicits fusion and exocytosis (3). (B) Release of higher concentrations of ACh or addition of nicotine activates low affinity $\alpha 7^*$ nAChRs (4). Upon their activation (5) calcium enters through the channels which can lead to further increases in Ca^{2+} via mobilization from internal Ca^{2+} stores (calcium-induced calcium release (CICR)); 6. The high levels of calcium allow for phosphorylation of Ca^{2+} /calmodulin kinase (pCAMKII) (7) which may contribute to the sustained phase of elevated glutamate release (8).