Mol Neurobiol (2008) 38:101–121
DOI 10.1007/s12035-008-8037-9

Modulation of Hippocampus-Dependent Learning and Synaptic Plasticity by Nicotine

Justin W. Kenney · Thomas J. Gould

Received: 22 May 2008 / Accepted: 25 July 2008 / Published online: 9 August 2008
© Humana Press Inc. 2008

Abstract A long-standing relationship between nicotinic acetylcholine receptors (nAChRs) and cognition exists. Drugs that act at nAChRs can have cognitive-enhancing effects and diseases that disrupt cognition such as Alzheimer's disease and schizophrenia are associated with altered nAChR function. Specifically, hippocampus-dependent learning is particularly sensitive to the effects of nicotine. However, the effects of nicotine on hippocampus-dependent learning vary not only with the doses of nicotine used and whether nicotine is administered acutely, chronically, or withdrawn after chronic nicotine treatment but also vary across different hippocampus-dependent tasks such as the Morris water maze, the radial arm maze, and contextual fear conditioning. In addition, nicotine has variable effects across different types of hippocampal long-term potentiation (LTP). Because different types of hippocampus-dependent learning and LTP involve different neural and molecular substrates, comparing the effects of nicotine across these paradigms can yield insights into the mechanisms that may underlie the effects of nicotine on learning and memory and aid in understanding the variable effects of nicotine on cognitive processes. This review compares and contrasts the effects of nicotine on hippocampus-dependent learning and LTP and briefly discusses how the effects of nicotine on learning could contribute to nicotine addiction.

Keywords Nicotine · Hippocampus · Learning · LTP · Addiction · Contextual learning · Fear conditioning · Nicotinic receptors · Acetylcholine

J. W. Kenney · T. J. Gould (✉)
Department of Psychology, Center for Substance Abuse Research,
Weiss Hall, Temple University,
Philadelphia, PA 19122, USA
e-mail: tgould@temple.edu

Introduction

Understanding the function of the hippocampus was revolutionized with the work of Penfield and Milner [1]. In the 1950s, an individual, now familiar to most psychologists and neuroscientists as patient HM, underwent a radical procedure to treat his epilepsy; bilateral medial temporal lobe tissue, including the hippocampus, was removed. Postoperatively, HM displayed anterograde amnesia and temporally graded retrograde amnesia [1]. Numerous studies of patient HM and others with similar neuronal damage revealed that the hippocampus plays a critical role in the transfer of short-term memories to long-term memories. Since these initial studies, research involving neuropsychological patients and animal models has further elucidated hippocampal function. It is clear that, in addition to playing a critical role in the formation of long-term memories, the hippocampus is critically involved in integrating and processing spatial and contextual information. Theories of hippocampal function have proposed that the hippocampus is involved in forming configural associations between stimuli such as those involved in learning a context or to navigate in space [2, 3]. The ability of the hippocampus to aid in the formation of long-term memories and to process configural information may be one reason that the hippocampus is believed to be important for declarative memory function. Declarative learning and memory processes are involved in defining who we are and anchor us to past events, places, and experiences [4]. Thus, the hippocampus is not only critically involved in learning but also plays an important role in defining the self. Diseases and drugs that disrupt these processes have a grave impact on daily function and could have long-lasting effects on an individual's behavior.

Disorders such as schizophrenia, Alzheimer's disease, and nicotine addiction are associated with alterations in cholinergic function in the hippocampus and in cognition. Schizophrenia is associated with hippocampal dysfunction [5] and changes in hippocampus-dependent cognitive processes such as contextual information processing [6]. Given that there is a particularly high incidence of smoking amongst patients with schizophrenia [7], a finding thought to be indicative of self-medication [8], understanding the effects of nicotine on contextual information processing may yield insights into this debilitating disorder. Alzheimer's disease has long been associated with loss of cholinergic function in the hippocampus [9, 10] and is associated with severe deficits in declarative memory. Furthermore, cholinergic drugs have been found to have beneficial effects for those with the disorder [11, 12] suggesting the importance of understanding how nicotine alters cholinergic processes. Finally, addiction in general has been linked to changes in hippocampal function [13–15], and nicotine addiction is no exception [16]. Given that changes in cholinergic processes and hippocampal function are associated with multiple diseases, understanding the effects of cholinergic drugs such as nicotine on hippocampus-dependent learning and synaptic plasticity will facilitate the development of treatments for such diseases.

An overarching goal of this review is to examine the similarities and differences in the behavioral and neural effects of nicotine on hippocampus-dependent learning and plasticity. To accomplish this goal, we will briefly review the structural and functional characteristics of nicotinic acetylcholinergic receptors (nAChRs), the hippocampus, the effects of acute, chronic, and withdrawal from chronic nicotine on synaptic plasticity as measured with long-term potentiation (LTP), and the effects of nicotine on hippocampus-dependent learning with particular emphasis on contextual learning[1]. Finally, as an example of how the effects of nicotine on hippocampus-dependent learning could contribute to a disease, we will examine the interaction between nicotine, learning, and addiction.

nAChRs

Nicotinic acetylcholinergic receptors are a class of ligand-gated ion channels that are assembled from five subunits out of at least 17 identified subunits and are differentially expressed in both the central and peripheral nervous systems [18–21]. Neuronal nAChRs have a pentameric structure and are comprised of either α (α7–α10) subunits or a combination of α (α2–α6) and β (β2–β4) subunits [22–25]. In the central nervous system, the α4β2* (which includes subclasses differentiated by the inclusion of α3, α5, or α6 subtypes [26, 27]) and α7 nAChRs are the two predominant nAChR subtypes [28, 29], but they have diverse functional properties [30–32]. α4β2* nAChR subtypes show high affinity for nicotine, desensitize slowly, and show long-lasting inhibition by mecamylamine (a broad-spectrum nAChR antagonist) [21, 33, 34]. Conversely, α7 nAChR subtypes show lower affinity for nicotine but high affinity for α-bungarotoxin, desensitize rapidly, and show short-lasting inhibition by mecamylamine [21, 34–38].

Both the α7 and α4β2* nAChR subtypes have properties that could contribute to the cognitive-enhancing effects of nicotine. For example, both nAChR subtypes are located in the hippocampus, both are expressed presynaptically and postsynaptically which suggests they could modulate both presynaptic and postsynaptic processes involved in synaptic plasticity and both gate calcium, which could enhance memory through activation of second messengers involved in synaptic plasticity or by facilitating neurotransmitter release [30–32, 35, 39–47]. Whereas both α7 and α4β2* nAChRs have properties that could contribute to the effects of nicotine on learning and memory, differences in their functional properties suggest that these receptors may have divergent influences on these cognitive properties. This possibility will be explored as we review the effects of nicotine on hippocampal LTP, spatial learning, spatial working memory, and contextual learning.

The Hippocampus

When compared to other areas of the brain, the hippocampus is structurally and functionally unique. In fact, the anatomical layout of the hippocampus may endow the structure with functional capacities necessary for certain forms of learning and memory. Unlike cortical areas that contain a large number of reciprocal connections, the hippocampus is primarily a unidirectional circuit (Fig. 1a). The structure and connectivity of the hippocampus is no doubt critical to the special information-processing capabilities that have been attributed to it. Information from a variety of unimodal and polymodal cortical areas projects to the entorhinal cortex, an area that provides input to the hippocampus. The primary output of the entorhinal cortex is to the dentate gyrus (DG) via the perforant pathway (PP) with secondary outputs projecting to the CA3 and CA1 regions. The granule cells of the DG give rise to the mossy fiber pathway that projects to the CA3 region. The outputs of the pyramidal cells of the CA3 region then form the Schafer collaterals (SC) that project to the CA1 region and

[1] Studies that use nicotine tartrate salt vary in whether they report doses based on salt weight or nicotine base weight. When studies reported doses as salt weight, we converted them to free base. If a study did not specify, we used the dose they reported. For a detailed discussion of this, see [17].

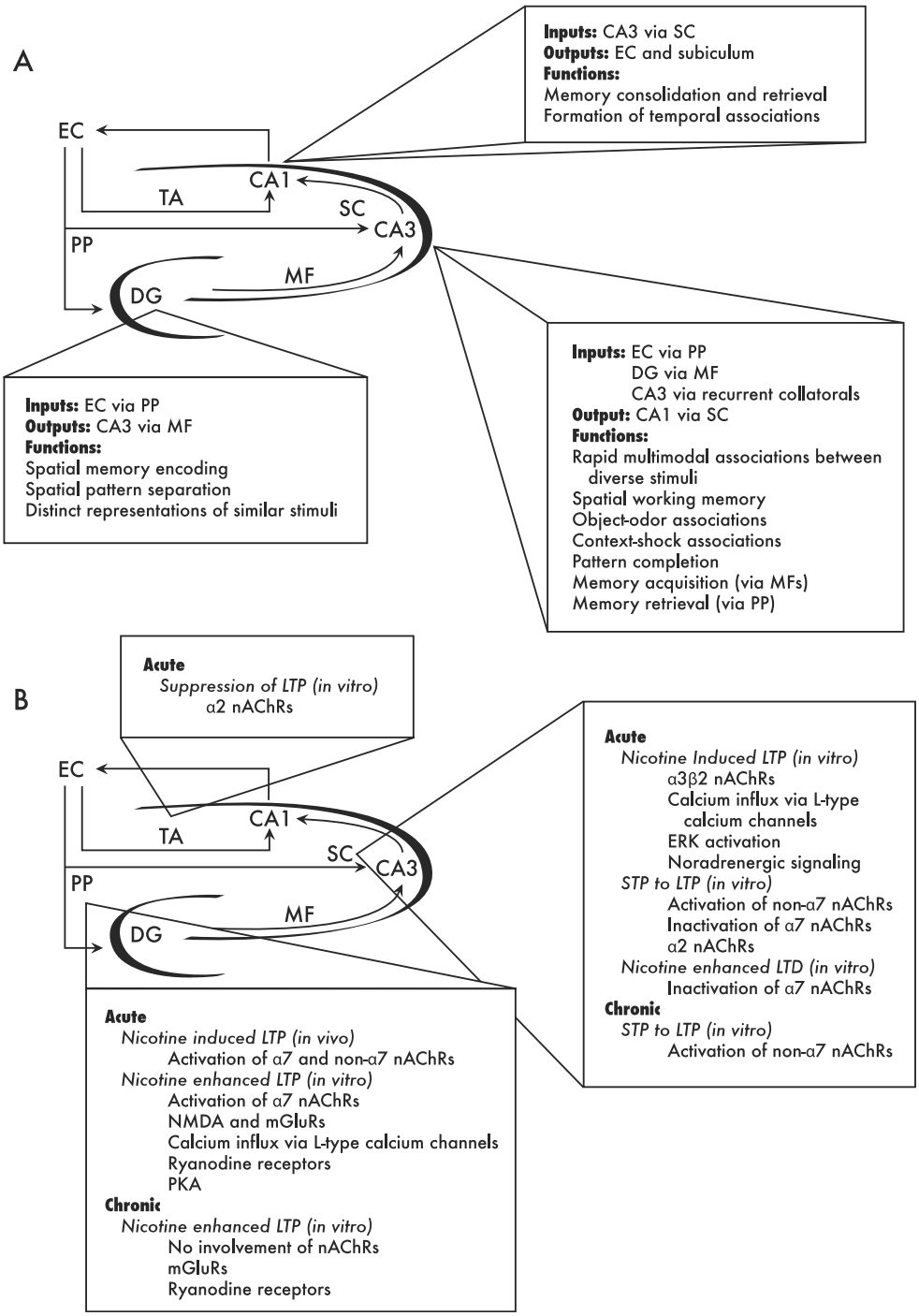

Fig. 1 The role different hippocampal subregions play in various aspects of learning and memory and the effects of nicotine on synaptic plasticity in these regions as measured by LTP (see text for details). **a** Inputs and outputs of three hippocampal subregions (DG, CA3, and CA1) and their involvement in various hippocampus-dependent learning and memory tasks. **b** The effects of nicotine on synaptic plasticity as measured by LTP and the involvement of various nAChR subtypes and other mechanisms in the PP–DG, SC-CA1, and TA-CA1 pathways. *EC*—entorhinal cortex, *DG*—dentate gyrus, *PP*—perforant pathway, *TA*—temporoammonic pathway, *MF*—mossy fibers, *SC*—Schaffer collaterals

the commissural fibers that connect to the contralateral hippocampus. CA1 pyramidal cells project back to the entorhinal cortex as well as to the subiculum, which then projects to the entorhinal cortex. Afferents from the entorhinal cortex form back projections that innervate the same cortical areas that initiated hippocampal activation via the entorhinal cortex. The connections described above comprise the major pathways of the hippocampus [for a detailed review, see 48].

Different regions of the hippocampus are thought to contribute, to varying extents, to diverse functions such as episodic memory, spatial learning, contextual learning, and working memory (Fig. 1a). Based on computational modeling, the DG is thought to be involved in forming orthogonal representations of input from the entorhinal cortex [49]. A prime example of this is the formation of specific nonoverlapping place cells in the DG from grid cells of the entorhinal cortex [50]. As would be expected,

DG lesions lead to deficits in the encoding of spatial memory [51] and in differentiating spatial locations in rodents [52]. Recent functional magnetic resonance imaging work in humans also suggests a role for the DG, in conjunction with the CA3 region, in forming distinct representations of subtly different stimuli [53].

The pyramidal cells of the CA3 region are unique in that a large portion of their input comes from recurrent collaterals forming an extensive autoassociative network. Such connections allow neurons of the CA3 region that are activated separately to become rapidly associated with one another. Thus, the CA3 region is thought to be important for making rapid multimodal associations between diverse stimuli, the hallmark of episodic memory, as well as holding spatial information in working memory [49]. In addition, the CA3 region has been found to be important for making associations between objects or odors and a context [54] and in associating a context with a shock [55]. A related function of the CA3 is its critical contribution to pattern completion, in which a fully detailed memory is recalled based on only a few inputs. A number of studies have demonstrated an integral role for the CA3 region in spatial pattern completion [56, 57]. Finally, inputs from the mossy fiber and perforant pathways into the CA3 region, respectively, are thought to be differentially involved in the acquisition and retrieval of a memory [51].

The CA1 region has been implicated in a number of functions including forming temporal associations, memory consolidation, and memory retrieval. Disruption of CA1 function alters the ability of animals to learn temporal patterns [58, 59] and retrieve spatial memories [60]. Given the large number of back projections from the CA1 region to cortical regions that have afferent connections with the hippocampus and that a number of theories of hippocampal functioning postulate that memory is consolidated to cortical regions over time ([61] but see [62]), it is not surprising that the CA1 has also been found to be important for the long-term consolidation of memory [63].

Nicotinic acetylcholine receptors are widely distributed throughout the hippocampus. α7 nAChRs are present in all hippocampal subregions, with the highest concentration in the DG [64]. α4 and β2 subunits are also located throughout the hippocampus, with the highest density in the DG and CA1 regions [65]. Nicotinic receptors are located on both glutamatergic pyramidal cells and GABAergic interneurons. On pyramidal neurons, α7 nAChRs are densely localized both presynaptically and postsynaptically with sparse somatic localization [64, 66] whereas β2-containing nAChRs are more densely localized postsynaptically and at the soma with less-dense presynaptic localization [66, 67]. In interneurons, α7 nAChRs are localized presynaptically [68] and both α7 and α4β2* nAChRs are localized to somatodendritic compartments [69–71]. The relative contribution of α7 and α4β2* nAChRs to interneuron activation depends on the interneuron subtype and layer within the hippocampus [69–71]. For example, in the CA1 region, most interneurons in the stratum pyramidale display little activation by nAChRs whereas interneurons in stratum oriens are modulated by both α7 and α4β2* nAChRs [69–71]. Thus, the net effect of nicotine on neural activity in the hippocampus is complex (see [70] for a more detailed discussion) as nicotine can modulate the transmission of information by altering both interneuron and pyramidal cell activation.

In summary, the regions of the hippocampal formation act in concert to quickly and efficiently process and encode episodic, spatial, contextual, and temporal memories. Understanding how the different hippocampal subregions contribute to memory formation can yield specific clues as to where nicotine may act in the hippocampus to alter learning and memory.

LTP

Long-term potentiation is a widely accepted model of synaptic plasticity that is thought to underlie learning and memory processes [72, 73]. LTP is manifested as increased synaptic efficiency lasting over an hour that is induced by brief high-frequency stimulation of presynaptic neurons [74]. Inducing LTP in vitro has proven to be a fruitful model in which the cellular and molecular mechanisms that support learning and memory can be easily investigated. Many of the molecules and mechanisms that have been found to be important for different aspects of LTP have subsequently been found to be important in spatial learning [75] and fear conditioning [76]. For instance, simple passive avoidance learning was found to induce LTP [77] and the same mechanism that maintains long-lasting LTP also maintains spatial memory [78]. Given this background, exploring the effects of nicotine on LTP may assist in our understanding of the cellular and molecular mechanisms that form the basis for the effects of nicotine on learning and memory.

In the hippocampus, acetylcholine is thought to modulate learning and memory by altering the oscillatory rhythms that result from the interaction of the various hippocampal subregions [79]. Altering such rhythms may result in an increase in the recruitment of various cell-signaling molecules known to be involved in synaptic plasticity as measured by LTP. To explore how nAChRs may alter such processes, studies have examined the effects of nicotine on LTP using high-frequency stimulation (HFS) of presynaptic neurons for induction (Fig. 1b). Many of the mechanisms that have been found to underlie HFS-induced LTP have been found to be important in learning and

memory tasks [75, 76]. Other studies have explored the effects of nicotine on short-term potentiation (STP), in which short bursts of HFS lead to a form of potentiation that degrades to baseline within minutes (also known as subthreshold stimulation), to determine if nicotine can change STP to LTP. A handful of studies have also looked at nicotine-induced LTP in vivo and in vitro in which the drug is applied or administered in the absence of tetanic stimulation yet results in LTP induction. Finally, the effect of chronic nicotine treatment and withdrawal prior to in vitro LTP induction has also been explored.

The various LTP induction protocols have been used to investigate the effects of nicotine on plasticity in different pathways of the hippocampus (Fig. 1b). The effect of nicotine on STP has been studied in the SC-CA1 pathway in which the afferents arise from the CA3 region and in the adjacent temporoammonic (TA)-CA1 pathway in which the afferents arise from the entorhinal cortex. In addition, the ability of nicotine to enhance HFS-induced LTP has been explored in the PP–DG pathway, which constitutes the main input from the entorhinal cortex to the hippocampus proper. Finally, nicotine-induced LTP has been explored in the SC-CA1 pathway in vitro and in the PP–DG pathway in vivo. These various hippocampal subregions and pathways are thought to contribute to the different aspects of learning and memory that the hippocampus supports [49]. Thus, understanding how nicotine affects LTP and STP and induces LTP in the different subregions may yield clues as to how nicotine alters different learning and memory processes.

LTP in the SC-CA1 Pathway

In the SC-CA1 pathway, nicotine has been found to induce LTP in the absence of tetanic stimulation, as well as facilitate LTP induction by subthreshold stimulation (i.e., turn STP into LTP). Nicotine-induced (1–10 μM; the concentration of nicotine in smokers reaches about 0.5 μM [80]) LTP was blocked by kappa-bungarotoxin, an α3- and β2-containing nAChR antagonist, suggesting an integral role for α3β2-containing nAChRs [81]. Furthermore, nicotine-induced LTP required calcium influx via L-type calcium channels [82] as well as the activation of mitogen-activated protein kinases [83]. However, unlike many types of tetanic-induced LTP, nicotine-induced LTP in the SC-CA1 pathway did not require *N*-methyl-D-aspartate (NMDA) receptor activation or retrograde signaling via nitrous oxide [84]. Thus, nicotine may facilitate calcium signaling such that NMDA-mediated calcium signaling is not necessary. In addition, nicotine may induce LTP by modulating the release of other neurotransmitters that may then increase synaptic efficiency, a contention that is supported by the fact that nicotine-induced LTP in the SC-CA1 pathway has been found to be dependent upon noradrenergic signaling [81].

Nicotine has also been found to decrease the threshold for LTP induction in the SC-CA1 pathway. Administration of 1–10 μM nicotine to hippocampal slices subjected to subthreshold stimulation resulted in LTP induction even though the stimulation only induced STP in control slices [85]. Subthreshold facilitation of LTP also occurred in the presence of non-α7 nAChR agonists (epibatidine and A85380) and an α7 nAChR antagonist (methyllycaconitine; MLA) [86, 87]. These findings suggest that the facilitation of synaptic plasticity by nicotine required both the activation of non-α7 nAChRs and the inactivation of α7 nAChRs. Recent work suggests that α2-containing nAChRs may also be important for this effect, as nicotine applied to hippocampal slices obtained from α2 nAChR knockout (KO) mice did not change STP into LTP [88].

There are at least three mechanisms by which nicotine may act to turn STP into LTP. The first mechanism is via disinhibition of pyramidal cells through alterations in the signaling of GABAergic interneurons. Activation of nAChRs localized to GABAergic interneurons has been found to increase activity in CA1 pyramidal cells, presumably via inhibiting other inhibitory interneurons that synapse directly onto pyramidal cells [69, 89]. Alternatively, a second manner by which nicotine might facilitate LTP induction is via a decrease in inhibitory interneuron activity that may occur following desensitization of nAChRs located on the interneurons [87, 88, 90]. Finally, a third possibility is that nicotine may act postsynaptically at CA1 pyramidal cells to reduce the threshold for LTP induction in the SC-CA1 pathway [91] by increasing calcium signaling or neuronal excitability.

Nicotine is not only capable of enhancing plasticity in the CA1 region but is also capable of decreasing synaptic efficiency. For example, in the SC-CA1 pathway, nicotine was found to enhance long-term depression [92] and decrease the likelihood of LTP induction [91, 93]. Whether nAChR activation resulted in potentiation or degradation of synaptic efficiency in the SC-CA1 pathway depended upon the timing of postsynaptic nAChR activation relative to SC stimulation [91, 93] and the type and location of nAChRs involved [69]. In addition, in the adjacent TA-CA1 pathway, nicotine suppressed the induction of LTP, an effect that appears to depend on the presence of α2 nAChRs [88]. Enhanced LTD could contribute to the enhancement of learning and memory by decreasing the contribution of neurons not involved in the encoding of the memory and thus increasing the signal-to-noise ratio of those neurons involved. Alternatively, if LTD decreases the efficiency of inhibitory processes, this could lead to

disinhibition of other cells resulting in increased learning-related activity. Thus, the effects of nicotine on synaptic plasticity in the CA1 region are multifaceted, with the overall effect of nicotine dependent upon a host of interactions between incoming stimulation via the temporoammonic pathway and SCs as well as the nAChR subtypes involved.

LTP in the PP–DG Pathway

In the PP–DG pathway, nicotine-induced LTP in vivo as well as enhanced HFS-induced LTP in vitro. Nicotine (1.1 mg/kg) induced LTP in vivo in anesthetized mice [94, 95]. In vivo LTP was partially induced by the administration of choline (an α7 nAChR agonist) or epibatidine and fully induced following the administration of both agonists. However, the dose of nicotine used to induce LTP is much higher than those required for the enhancement of learning and memory and approaches doses of nicotine that induce seizures in mice [96, 97]. Furthermore, the animals were anesthetized during LTP induction using urethane, an anesthetic that has been found to potentiate the function of α4β2 nAChRs [98]. Thus, the relationship between in vivo drug-induced LTP in the PP–DG pathway and the effects of nicotine on learning and memory are not altogether clear.

Nicotine (5 μM) has also been found to enhance HFS-induced LTP in the PP–DG pathway in vitro. This enhancement is dependent upon the action of nicotine at α7 nAChRs, as MLA but not DHβE (a high-affinity nAChR antagonist, e.g., α4β2 nAChRs) blocks the effect, and it is absent in α7 nAChR KO mice [99, 100]. The enhancement of LTP by nicotine also appears to depend on glutamatergic and calcium-mediated processes. Blocking either NMDA receptors or L-type calcium channels prevents the enhancement as does blocking ryanodine receptors but not IP3 receptors, both of which are involved in gating calcium release from intracellular stores [99]. Welsby et al. [99] suggest that stimulation of α7 nAChRs by nicotine prior to LTP induction fills ryanodine-receptor-sensitive stores with calcium, and following HFS there is a larger amount of calcium-induced calcium release from these stores leading to greater LTP. However, this may not be the only cellular process underlying the effect, as mGluRs as well as PKA activation have also been found to be important for the enhancement of LTP in the PP–DG pathway by nicotine [99, 100]. A comparison of these findings to those exploring the effects of nicotine on transforming STP into LTP in the SC-CA1 pathway suggests that the effects of nicotine in these two pathways involve different nAChR subtypes and rely upon different cellular processes.

LTP in Chronic Nicotine-Treated Animals

In addition to the effects of acute nicotine on LTP, chronic nicotine treatment and withdrawal following chronic nicotine could result in altered hippocampal function leading to changes in synaptic plasticity. Chronic nicotine administration in these experiments consisted of twice daily injections of 1 mg/kg of nicotine for 10–17 days. The last injection of nicotine occurred well before the brain was dissected such that no nicotine was present in the brain slice at the time of recording unless added. Thus, it is an open question as to whether these studies examined the effects of chronic nicotine administration or withdrawal from chronic nicotine. Nonetheless, in the SC-CA1 pathway of hippocampal slices obtained from rats treated with chronic nicotine, LTP could be induced with normally subthreshold stimulation protocols (i.e., such stimulation usually results in STP). This effect was blocked by the application of mecamylamine or DHβE [85, 86]. If acute nicotine (1 μM) was applied to slices taken from chronic nicotine-treated animals, the amount of stimulation needed to induce LTP was lower than that required in acute nicotine-treated slices obtained from chronic nicotine-naïve animals. However, unlike in naïve animals, MLA did not further facilitate subthreshold LTP in chronic nicotine-treated animals, suggesting that the α7 nAChRs may be thoroughly desensitized and therefore may no longer contribute to the facilitation of LTP following chronic treatment [86]. In contrast, non-α7 nAChRs may not be desensitized to the same extent as α7 nAChRs and therefore may contribute to LTP facilitation in slices obtained from chronic nicotine-treated animals. The effect of chronic nicotine treatment on the facilitation of subthreshold LTP in the SC-CA1 pathway may also be due to the upregulation of high-affinity nAChRs following chronic nicotine treatment [101–103]. An increase in high-affinity receptors may lead to a reduced threshold for LTP induction in the SC-CA1 pathway in chronic nicotine-treated animals by enhancing the effect of cholinergic signaling during subthreshold stimulation.

In rats withdrawn from chronic nicotine administration for 2 days, the ability for subthreshold stimulation to result in LTP in the SC-CA1 pathway was attenuated and after 23 days of withdrawal completely diminished [104]. Following 4 days of withdrawal, nicotine applied directly to slices no longer facilitated subthreshold stimulation, an effect that appears to be due in part to alterations in glutamate receptor function [104]. Furthermore, following withdrawal from chronic nicotine, α7 nAChRs on GABAergic interneurons are functionally upregulated, possibly leading to a decrease in overall activity that may contribute to the attenuated enhancement that occurs during withdrawal [104].

In the PP–DG pathway, enhanced LTP following HFS was found in slices obtained from chronic nicotine-treated animals. Unlike in slices obtained from naïve animals, the effect in chronic nicotine-treated animals does not appear to depend upon nAChR activation at the time of induction as the application of either MLA or mecamylamine prior to the tetanus did not block the enhancement [99, 100]. However, the enhancement of LTP in the PP–DG pathway of chronic nicotine-treated animals still required the activation of mGluRs and ryanodine receptors. This suggests that the enhancement of PP–DG LTP by chronic nicotine is due to alterations in processes downstream from nAChRs, such as calcium-mediated cell signaling [99]. Similar to the mechanism suggested for the effects of acute nicotine on LTP in this pathway, Welsby and colleagues [99] suggest that the enhanced LTP in the PP–DG pathway in the chronic nicotine-treated animals is a result of an increase in the amount of calcium in ryanodine-sensitive intracellular stores due to persistent nAChR activation before slices are prepared. The increased stores of calcium may then lead to greater calcium-induced calcium release following HFS and thus enhanced LTP. Overall, despite the paucity of studies exploring the effects of chronic nicotine on LTP induction in the various hippocampal subregions, it appears that acute and chronic nicotine act via overlapping yet subtly different mechanisms.

In summary, the various effects of nicotine on different LTP stimulation protocols in different areas of the hippocampus suggest a number of possible mechanisms by which nicotine may act to enhance learning and memory processes. Enhancement of HFS LTP in the PP–DG pathway by nicotine suggests that connections normally formed during learning may be stronger when formed in the presence of nicotine. Alternatively, the ability of nicotine to transform STP into LTP in the SC-CA1 pathway suggests that nicotine may either strengthen cell processes normally involved in learning or recruit additional processes. Such changes may lead to enhanced learning and plasticity via altered patterns of memory encoding, although it should be noted that the doses of nicotine used in the in vitro studies (1 μM in the SC-CA1 and 5 μM in the PP–DG pathway) are potentially higher than those concentrations of nicotine found in smokers of around 0.5 μM [80]; however, equating the nicotine concentration infused into a slice to those found in the plasma of smokers is contentious, and understanding how in vivo concentrations translate to in vitro preparations is an important issue. Finally, the relevance of nicotine-induced LTP to understanding the effects of nicotine on learning and memory are not altogether clear due to the indiscriminate nature of the LTP induction. Such effects may be important for other effects of nicotine, such as sensitization of reward pathways [105–107], alterations in psychiatric patients that use nicotine [8, 108], or protection against the effects of neurodegenerative diseases [109, 110].

The studies reviewed in the prior paragraphs also suggest that different nAChR subtypes modulate different types of LTP in the various subregions of the hippocampus. For example, the enhancement by nicotine of HFS LTP in the PP–DG pathway depends primarily upon the activation of α7 nAChRs, whereas the change from STP to LTP in the SC-CA1 pathway by nicotine involves both the desensitization of α7 nAChRs and the activation of non-α7 nAChRs. Thus, if activation of non-α7 (e.g., α4β2* nAChRs) receptors are found to be involved in the enhancement of a learning task, we can hypothesize based on the current evidence that the mechanism underlying this enhancement may be nicotine acting to turn STP into LTP in the SC-CA1 pathway as opposed to enhancing LTP in the PP–DG pathway. In this manner, LTP studies can suggest potential mechanisms involved in the effects of nicotine on learning.

Even with the studies reviewed here, considerable work remains to be done on understanding the effects of nicotine on LTP and how this relates to the effects of nicotine on learning and memory. For example, would nicotine facilitate subthreshold stimulation in the PP–DG pathway? Would nicotine enhance HFS-induced LTP in the SC-CA1 pathway? Can nicotine induce LTP in vivo at doses similar to those used to enhance learning and memory in conscious animals? Could nicotine enhance LTP or facilitate subthreshold stimulation in vitro at concentrations that more closely approximate those seen in smokers? Compared to HFS, would nicotine have similar effects using an LTP induction paradigm that approximates the firing patterns of neurons during learning [111], such as theta stimulation? Identifying how nicotine alters these various forms of LTP induction and identifying the receptor subtypes and signaling molecules involved will significantly further our understanding of how nicotine alters learning and memory processes.

Spatial Learning

A prediction that results from studies examining the effects of nicotine on LTP is that acute nicotine should enhance hippocampus-dependent learning. Indeed, nicotine enhances many types of hippocampus-dependent learning but the story is complex as effects vary across learning tasks. The Morris water maze is a hippocampus-dependent spatial learning task that requires animals to use extra maze cues to learn the location of a hidden platform in a pool of water [112]. Training generally takes several days and learning of the task is measured as a decreased latency to discover the hidden platform across sessions or as time spent in the

vicinity of the platform during a test session in which the platform has been removed. Both acute and chronic nicotine alter performance of this task, but results are not consistent across studies (Table 1). Acquisition of the Morris water maze takes multiple sessions. Thus, studies examining the effects of nicotine on acquisition of this task require nicotine administration over multiple days. This raises the question as to whether such studies are examining the effects of acute or chronic nicotine on acquisition of the task, which is a particularly important question because nicotine desensitizes nAChRs, although to different degrees depending on nAChR subunit composition and treatment duration [113].

In a study that administered 0.07 mg/kg nicotine once daily to young and aged rats starting 3 days prior to training and continuing throughout training, nicotine improved acquisition in the aged but not the young rats [114]. It should be noted that the young rats required 7 days of training (four sessions per day) whereas the aged rats required 14 days of training. Nicotine did improve recall or retention in the young but not the aged rats. However, in another study, young and aged rats administered 0.2 mg/kg nicotine before all Morris water maze sessions (two trials per day for 3 days) both showed no effect of nicotine [115].

The dose of nicotine and the treatment duration may determine whether nicotine enhances or disrupts spatial learning. In mice, administration of 0.7 mg/kg nicotine 4 days before training disrupted learning but administration of 0.35 or 0.7 mg/kg nicotine starting 5 days before training and continuing for the 4 days of training improved learning [116]. It is possible that the deficits seen in the group that received nicotine prior to but not during training could reflect some type of withdrawal effect; however, results from another study suggest that this may not be the case. Rats treated with 0.7 mg/kg nicotine twice daily either for 1 day at 10 days before training or for 10 days with the last treatment 24 h before training both showed enhanced acquisition of the Morris water maze [117]. Clearly, methodological differences, such as differences in strains, doses, and drug treatments, are important variables in the effects of nicotine on spatial learning but procedural differences across studies complicate direct comparisons.

Multiple studies suggest that the hippocampus may be the site of action for the effects of nicotine on spatial learning as measured with the Morris water maze. Rats trained in the Morris water maze (3 days, two trials per day) that received direct infusion of nicotine (1 μg) into the dorsal hippocampus immediately after the last trial showed enhanced recall [118]. In addition, α7 nAChRs in the hippocampus may be involved in acquisition of the Morris water maze. Mice that received bilateral hippocampal delivery of the rat α7 nAChR gene had a greater rate of acquisition than control mice but showed a similar level of

Table 1 The effects of nicotine on the water maze

Acute or chronic	Subjects	Pretreatment	Treatment during task	Dose of nicotine	ROA	Result	Study
Acute	Fischer 344 rat (4 and 24 months)	–	15 min prior to training	0.20 mg/kg	ip	No effect	[115]
Acute	Sprague-Dawley rat (male)	1 day (9 days before training) two per day	–	0.70 mg/kg	sc	0.70 mg/kg enhanced acquisition	[117]
Acute	Albino Wistar rat (male)	–	Following last training trial	0.5, 1.0, and 2.0 μg	Hipp infusion	1.0-μg infusion-enhanced memory retention	[118]
Acute	C57BL6 mice (male)	–	15 min prior to 4 days of training	0.35, 0.70 mg/kg	sc	0.70 mg/kg resulted in deficit on day 4 of training	[116]
Chronic	Sprague-Dawley rat (2–3 or 25–26 months, male)	3 days one per day	15 min prior to 7 (young) or 14 (aged) days of training	0.07 mg/kg	ip	0.07 mg/kg increased memory retention in young and enhanced acquisition in old rats	[114]
Chronic	Sprague-Dawley rat (male)	10 days two per day	–	0.70 mg/kg	sc	0.70 mg/kg enhanced acquisition	[117]
Chronic	Sprague-Dawley rat (male)	2 days	Continued chronic treatment through 8 days of training	0.25 or 4.0 mg/kg per day	sc osmotic minipump	4.0 mg/kg per day resulted in deficits in acquisition and retention	[120]
Chronic	C57BL6 mice (male)	5 days one per day	15 min prior to 4 days of training	0.35, 0.70 mg/kg	sc	0.35 and 0.70 mg/kg enhanced acquisition	[116]

ROA Route of administration, *ip* intraperitoneal, *sc* subcutaneous, *Hipp* hippocampus

learning [119]. Finally, the disruptive effects of nicotine on the Morris water maze may also be related to changes in hippocampal function; a 4-mg/kg per day treatment for 10 days disrupted acquisition of the Morris water maze and also decreased neurogenesis in the hippocampus [120]. Nicotine self-administration has also been shown to decrease neurogenesis and markers of synaptic plasticity in the hippocampus [121]. Together, these studies suggest that the hippocampus may be a critical site of action for the effects of nicotine on spatial learning. In addition, α7 nAChRs may modulate acquisition of spatial learning but it remains to be determined which nAChRs are involved in the effects of nicotine on Morris water maze learning.

Spatial Working Memory

Just as nicotine alters spatial learning, nicotine has also been shown to alter spatial working memory. The radial arm maze is a hippocampus-dependent task used to measure spatial working memory, in which subjects must remember the locations of baited versus unbaited arms [122]. A radial arm maze typically has eight or 16 arms, all or some of which are baited with food and placed in a room with a number of extra maze cues. Animals are placed in the center of the maze and allowed to explore the arms to obtain the food rewards. Entries to already-visited arms are scored as working memory errors and entries into arms not previously baited with food are scored as reference memory errors. Findings concerning the effect of acute nicotine on radial arm maze performance have been complex (Table 2). While a number of studies found that acute nicotine administration (0.07 or 0.14 mg/kg) improved performance in the radial arm maze in rats [123–125], others found either an effect in aged but not young rats [126] or variable effects across experiments [127, 128]. Furthermore, some studies found a lack of an effect at the same doses of nicotine as used in prior studies [129, 130] and one experiment found a trend towards a deficit [131].

In contrast to the variable effects with acute nicotine, chronic nicotine has been shown to improve radial arm maze performance. Studies have shown that multiple doses of chronic nicotine (3.4 mg/day (given via a Silastic pellet) or 5 and 12 mg/kg per day for 3 or 4 weeks) improve performance in the radial arm maze [126, 132–135]; however, two studies found no effect of treatment with 5 mg/kg per day for 4 weeks [136, 137]. It appears that the effects of chronic nicotine on this task remain after treatment stops as cessation of chronic nicotine treatment did not disrupt working memory but instead rats continued to outperform controls [132, 138].

Both α7 nAChRs and α4β2* nAChRs and the ventral hippocampus appear to be involved in spatial working memory and in the effects of nicotine on radial arm maze performance. Lesions of the ventral hippocampus blocked the effects of chronic nicotine on performance in the radial arm maze [134] and chronic nicotine reversed deficits induced by septohippocampal lesions [135]. Acute infusion of MLA or DHβE into the ventral hippocampus disrupted spatial working memory in the radial arm maze [139]. Furthermore, chronic infusion of DHβE into the ventral hippocampus also disrupted performance in the radial arm maze and nicotine ameliorated this deficit [131].

It is interesting that withdrawal from chronic nicotine does not disrupt performance in the radial arm maze [132, 138] in light of reports in humans that nicotine withdrawal disrupts working memory [140–142]. Most likely, different tasks are differentially affected by nicotine withdrawal due to the involvement of diverse neural areas and substrates in the various tasks. For example, the effects of nicotine on radial arm maze performance are mediated by the ventral hippocampus and chronic nicotine has been shown to increase nAChR number in the dorsal but not ventral hippocampus [117]. Thus, it is possible that the lack of withdrawal-associated disruption of radial arm maze performance could be related to a lack of change in ventral hippocampal nAChR number during chronic nicotine treatment. If this were the case and changes in nAChR number and/or function underlie withdrawal symptoms, then cognitive tasks that engage the dorsal hippocampus may be susceptible to the effects of withdrawal from chronic nicotine treatment.

The molecular mechanisms that may underlie the effect of nicotine on working memory have not yet been explored. Working memory generally relies upon fast neural transmission as information is kept online to assist in decision making [143]. Thus, neurotransmitter systems involved in such transmission, such as glutamate, acetylcholine, and GABA may underlie working memory by causing transitory changes in cell signaling similar to those involved in short-term memory. Given the interaction between nAChRs and glutamate (see "Contextual Learning" section), this would be a useful starting point for delineating the mechanisms by which nicotine alters spatial working memory. The mechanisms that underlie the effects of nicotine on working memory may contrast those that underlie the consolidation of long-term memories. Long-term memory is dependent upon gene transcription and protein synthesis [144, 145], processes that nicotine is capable of modifying [146, 147]. Therefore, nicotine likely alters working memory and long-term memory via distinct mechanisms. The mechanisms by which nicotine alters long-term memory has been explored using contextual learning as a model.

Table 2 The effects of nicotine on the radial arm maze

Acute or chronic	Subjects	Pretreatment	Treatment during task	Dose of nicotine	ROA	Result	Study
Acute	Sprague-Dawley (female) 16-arm maze	–	20 min prior to testing trials	0.07 and/or 0.14 mg/kg	sc	0.07 but not 0.14 mg/kg enhanced working but not reference memory	[124, 125, 129]
Acute	Sprague-Dawley (female)	–	20 min prior to testing trials	0.07, 0.14 mg/kg	sc	0.07 and 0.14 mg/kg enhanced WM	[123, 128]
Acute	Sprague-Dawley (female)	–	20 min prior to testing trials	0.035, 0.07, 0.14 mg/kg	sc	Linear dose-related enhancement of WM	[127]
Acute	Sprague-Dawley (2–4 months, female)	–	20 min before testing trials	0.035, 0.07, 0.14 mg/kg	sc	No effect	[130, 131]
Acute	Sprague-Dawley (3–7 or 24–29 months, male)	–	20 min prior to testing trials	0.035, 0.07, 0.14, mg/kg	sc	No effect in young; dose-dependent enhancement of WM in aged rats	[126]
Chronic	Sprague-Dawley (male and female)	–	Continuously through testing; none during withdrawal	3.4 mg/day	sc Silastic pellet	Chronic nicotine enhanced WM; enhancement persisted following 2 weeks of withdrawal	[132, 135]
Chronic	Sprague-Dawley (male)	3 weeks prior to training	–	3.4 mg/day	sc Silastic pellet	Enhanced WM following withdrawal	[138]
Chronic	Sprague-Dawley (female)	–	Continuously through testing; none during withdrawal	5, 12 mg/kg per day	sc osmotic minipump	Chronic nicotine enhanced WM; no effect following withdrawal	[133, 134]
Chronic	Sprague-Dawley (male; 3–7 or 24–28 months)	–	Continuously through testing (3–4 weeks); none during withdrawal	5 mg/kg per day	sc osmotic minipump	Chronic nicotine enhanced WM in young but not old rats; no effect following withdrawal	[126]
Chronic	Sprague-Dawley (female)	–	Continuously through testing	5 mg/kg per day	sc osmotic minipump	No effect	[136, 137]

Data are from eight-arm radial maze unless otherwise indicated.
ROA Route of administration, *WM* working memory, *sc* subcutaneous

Contextual Learning

Both spatial learning and contextual learning involve the hippocampus [2, 3] but, until recently, few studies have examined the effects of nicotinic acetylcholinergic influences on contextual learning [148–153]. As contextual learning and spatial learning involve different brain regions [154, 155], different neurotransmitter receptor subtypes [156–158], different cellular substrates [159–162], and different genes [163], nicotine may alter one form of hippocampus-dependent learning through different cellular and molecular mechanisms than those involved in another form of hippocampus-dependent learning. Thus, the pattern of effects of nicotine, whether it be acute, chronic, or withdrawal from chronic nicotine treatment, in spatial learning may not be the same as in contextual learning.

Fear conditioning has proven to be a powerful tool for examining the effects of nicotine on contextual learning. In fear conditioning, animals are trained to form an association between conditioned stimuli (CS) and a foot shock unconditioned stimulus (US). Conditioned stimuli can be a discrete stimulus such as a tone or a complex, configural stimulus such as a context. One session of two training trials produces robust learning of two different associations, the auditory CS–shock association (i.e., cued conditioning) and the training context–shock association (i.e., contextual conditioning). Commonly, 24 h after conditioning, the strength of the contextual association is tested by returning the conditioned animal to the training chamber and scoring freezing, a behavioral measure of fear. Later, the strength of the cued association is tested by placing the animal in an altered context chamber that has features that are distinct from the training chamber. In the altered context chamber, generalized freezing is first measured. If animals have formed a specific contextual association with the training context, levels of freezing to the altered context should be low. After assessing altered context freezing, the auditory CS is sounded and the strength of the auditory CS–shock association is measured.

This paradigm allows the investigator to measure two associations in the same subject; specifically a context–US association and a discrete cue–US association. Importantly, these two associations involve different neural substrates. Learning to associate the context with the US is hippocampus and amygdala dependent ([164, 165] reviewed in [166]); the dorsal hippocampus appears to be particularly important for forming contextual associations [167–169]. On the other hand, learning to associate the auditory CS with the foot shock US involves many of the same brain regions as contextual fear conditioning but not the hippocampus [164]. Thus, fear conditioning allows for the assessment of both hippocampus-dependent and hippocampus-independent learning in the same animal after a single training session. This not only allows experimenters to compare the effects of drugs on two different types of learning and potentially identify neural substrates involved in the effects of the drugs but also provides built-in controls that facilitate understanding of the drug effects. For example, if a drug alters both contextual and cued fear conditioning, this suggests that the drug is acting on processes common to both types of learning (e.g., common learning and neural processes, anxiety, shock sensitivity, attention, or locomotor activity). However, if a drug only alters contextual conditioning, this suggests that the drug is acting on processes specific to the context–US association.

Just as the neural substrates of fear conditioning are well defined, the underlying molecular substrates have also been identified [170]. NMDA receptors are critically involved in fear conditioning [171–173]. Activation of NMDA receptors can lead to activation of multiple cell signaling molecules involved in learning that include cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA), calmodulin kinase II, and extracellular-regulated kinase (ERK) [174–176]. Furthermore, both PKA and ERK can activate cAMP response element binding protein (CREB), a gene transcription factor involved in fear conditioning [177, 178]. The same molecular targets underlying fear conditioning have also been shown to be involved in LTP [76], and many of these substrates have been shown to be altered by nicotine [44, 47, 179]. Thus, the next step in identifying the cellular substrates of the effects of nicotine on contextual learning is to identify if nicotine administration during conditioning alters these substrates and in which brain region nicotine is acting to alter these processes.

Numerous studies have shown that nicotine given prior to training and testing enhances contextual fear conditioning but not cued fear conditioning in mice (Table 3) [148–151, 180–183], an effect that lasts at least 1 week [150]. These effects are dose dependent as a 0.09-mg/kg dose of nicotine that produces plasma nicotine levels in mice similar to those in smokers (of about 0.1 μM [184]) enhances learning [149, 150, 180, 181, 183, 184] but higher doses of nicotine disrupt contextual fear learning [148, 185]. The specificity of the effects of nicotine on contextual but not cued fear conditioning suggests that nicotine is not altering common processes that would affect both contextual and cued fear conditioning such as anxiety, locomotor activity, or attention. Furthermore, these behavioral results suggest that nicotine is either acting in the hippocampus or areas efferent or afferent of the hippocampus to enhance contextual conditioning. In support of direct effects in the hippocampus, infusion of nicotine (0.35 μg) into the hippocampus enhanced contextual fear conditioning but had no effect on cued fear conditioning [186]. Furthermore, infusions above the hippocampus into cortex or below the

Table 3 The effects of nicotine on contextual fear conditioning

Acute or chronic	Subjects	Pretreatment	Treatment during task	Dose of nicotine	ROA	Result	Study
Acute	C57BL6 mouse (male)	–	2–4 min before training and testing	0.1, 0.25, 0.5, 1.0 mg/kg	ip	0.5 mg/kg enhanced and 1.0 mg/kg caused deficits in CFC but not cued conditioning	[148, 190]
Acute	C57BL6 mouse (male and female)	–	2–4 min before training and/or testing	0.5 mg/kg	ip	0.5 mg/kg before training and testing enhanced CFC irrespective of sex	[151]
Acute	C57BL6 mouse (male)	–	2–5 min before training and testing but not 1 week retest	0.018, 0.044, 0.09, 0.13 mg/kg	ip	0.044 and 0.09 mg/kg enhanced CFC at 24 h and 1 week after training	[149, 150]
Acute	C57BL6 mouse (male, 2–3 months)	–	5 min before training and testing	0.09 mg/kg	ip	0.09 mg/kg enhanced CFC but not cued conditioning	[180, 181, 183, 184, 186, 199]
Acute	Wistar rat (male)	–	5 min before testing	0.21, 0.35 mg/kg	sc	0.21 and 0.35 mg/kg caused deficits in CFC	[185]
Acute	C57BL6 mouse (male, 2–3 months)	–	Immediately before training and testing	0.09, 0.18, 0.35 μg	Hipp infusion	0.35 μg enhanced CFC but not cued conditioning	[186]
Chronic	C57BL6 mouse (male, 2–3 months)	12 days	Continuously through training and testing; none during withdrawal	6.3 mg/kg per day	sc osmotic minipump	No effect of chronic nicotine; during withdrawal (1 day following end of chronic treatment): deficits in CFC but not cued conditioning	[184, 200, 203]
Chronic	Wistar rat (male)	6 days one per day	Last injection 5 min before training	0.21 mg/kg	sc	No effect	[185]
Chronic	Sprague-Dawley rat (male)	14 days two per day	None—training–testing 14 days following chronic treatment	Ramped from 0.5 to 1.1 mg/kg	sc	Enhanced CFC but no effect on cued conditioning 14 days following end of treatment	[204]

ROA Route of administration, *CFC* contextual fear conditioning, *ip* intraperitoneal, *sc* subcutaneous, *Hipp* hippocampus

hippocampus into thalamus, two areas that also have a high density of nAChRs [32, 65], were without effect on fear conditioning. These results strongly suggest that nicotine works in the hippocampus to enhance contextual fear conditioning and provides a target neural area to examine for nicotine-induced changes in cellular, molecular, and genetic processes during learning.

Once a neural area involved in the behavioral effects of nicotine on contextual fear conditioning is identified, the chain of underlying neurobiological events from the level of receptor activation to changes in protein activation and gene expression in that area can be studied. Nicotine is most likely altering contextual fear conditioning through actions at nAChRs. Whereas there are multiple nAChRs, the α7 and α4β2* nAChRs are the two predominant nAChRs in the central nervous system and both are highly expressed in the hippocampus [65, 187]. The broad-spectrum nAChR antagonist mecamylamine blocks the enhancement of contextual fear conditioning by nicotine [148]. While this suggests that nicotine is enhancing contextual fear conditioning through receptor-mediated processes, it also provides a hint as to what nAChR subtypes may be involved. Mecamylamine has higher affinity for α4β2* nAChRs than α7 nAChRs [34, 188]. This leads to a prediction that altering α4β2* nAChR function will alter the enhancement of contextual fear conditioning by acute nicotine. This has been tested both genetically and pharmacologically. The α4β2 nAChR antagonist DHβE blocked the enhancement of contextual fear conditioning by nicotine but the α7 nAChR antagonist MLA did not [180, 186]. In addition, no enhancement of contextual fear conditioning by nicotine was seen in β2 KO mice but enhancement was seen in α7 KO mice [189, 190]. Neither genetic disruption of nAChRs nor nAChR antagonists disrupted fear conditioning in young mice ([148, 152, 153, 180, 186, 189] but see [190]) suggesting that, unlike in the radial arm maze, nAChRs modulate contextual fear conditioning but activation of nAChRs is not necessary for fear conditioning to occur.

To further examine the involvement of both the hippocampus and α4β2* nAChRs in the enhancement of contextual fear conditioning, mice received direct infusion of DHβE into the hippocampus paired with systemic nicotine treatment. Systemic nicotine enhanced contextual fear conditioning in vehicle-infused mice, as would be expected based on prior results [148, 151, 181], but nicotine did not enhance contextual fear conditioning in mice that received hippocampal infusions of DHβE [186]. These results further support the argument that the hippocampus is critically involved in the effects of nicotine on contextual fear conditioning and that hippocampal α4β2* nAChRs mediate these effects. In addition, these results, in conjunction with the finding that nicotine infused into the hippocampus is sufficient to enhance contextual fear conditioning [186], demonstrate that nicotine is acting in the hippocampus and not in another structure in parallel to enhance contextual fear conditioning. If nicotine were acting in parallel in multiple areas to enhance contextual fear conditioning, inhibition of nAChRs in the hippocampus should not block the enhancement because nAChRs in areas working in parallel could still contribute to the enhancement of learning.

The cellular mechanism(s) through which nicotine enhances contextual learning are not yet clear. Nicotine both activates and desensitizes nAChRs [23, 25]. Thus, acute systemic nicotine may enhance contextual fear conditioning via activation, desensitization, or activation and subsequent desensitization of α4β2* nAChRs. However, if desensitization of α4β2* nAChRs is critical for the effect of acute systemic nicotine on contextual fear conditioning, then functional inactivation of these receptors should also enhance contextual fear conditioning. However, no deficits in fear conditioning were seen in β2 KO mice, mice treated with mecamylamine or DHβE [148, 152, 153, 180, 186, 189]. Thus, α4β2 nAChR activation or activation followed by desensitization must be the mechanism through which acute nicotine enhances contextual fear conditioning.

As stated, α4β2* nAChRs are not critically involved in contextual fear conditioning but instead modulate the learning. This suggests that, during contextual fear conditioning, nicotine may alter cell signaling pathways that underlie the learning. The glutamate system is critically involved in fear conditioning; inhibition of NMDA receptors disrupts fear conditioning [171–173]. If NMDA-receptor-mediated activation of PKA, ERK, and CREB underlie contextual fear conditioning, then modulation of these cell-signaling molecules by nicotine could enhance contextual conditioning. Multiple studies suggest that nAChRs and glutamate receptors may interact to support learning. nAChRs could contribute to the cellular depolarization necessary for NMDA receptor activation. Allen and colleagues [191] demonstrated that basal forebrain neurons, which provide the primary cholinergic innervation of the hippocampus, corelease acetylcholine and glutamate. It is possible that corelease of acetylcholine and glutamate could lead to nAChR facilitation of NMDA receptor activation. In support, numerous studies have shown that nAChRs mediate excitatory currents in hippocampal neurons [192–194]. In fact, Ji et al. [91] demonstrated that currents mediated by postsynaptic hippocampal pyramidal cell nAChRs could contribute to the depolarization necessary to remove the magnesium block of NMDA receptors.

Experimental data support the contention that the nAChR-mediated and glutamate-receptor-mediated processes interact during contextual fear conditioning. Whereas administration of the AMPA receptor antagonist NBQX

alone [195] or mecamylamine alone [148] did not alter fear conditioning, coadministration of NBQX and mecamylamine disrupted contextual fear conditioning [196]. This supports the hypothesis proposed by Ji et al. [91] that nAChRs in the hippocampus, similar to AMPA receptors, could contribute to the depolarization necessary to remove the magnesium block of NMDA receptors. In addition to interacting with AMPA receptors, nAChRs could also interact with NMDA receptors during contextual fear conditioning. In support, mice treated with a dose of the NMDA receptor antagonist MK801 that was subthreshold for altering fear conditioning showed disrupted contextual fear conditioning when also treated with mecamylamine [196]. Thus, mecamylamine, while having no effect on fear conditioning alone, shifts the dose response curve for MK801 disruption of fear conditioning to the left. This suggests that, during fear conditioning, nAChR and NMDA receptors may be mediating similar processes. Both nAChRs and NMDA receptors gate calcium and therefore both receptors could contribute to the activation of calcium-mediated cell signaling [31, 197]. Thus, during contextual fear conditioning, nAChRs and glutamate receptors may interact and support similar processes involved in the synaptic plasticity necessary for contextual fear conditioning. Nicotine may enhance contextual fear conditioning by increasing the contribution of nAChRs to those processes.

As stated earlier, both NMDA-receptor-mediated and nAChR-mediated processes can activate ERK and ERK is critically involved in contextual fear conditioning [47, 179, 198]. Hence, nicotine could enhance contextual fear conditioning by increasing signaling through the ERK pathway. In support, a dose of the ERK inhibitor SL327 that was subthreshold for disrupting contextual fear conditioning blocked the enhancement of contextual fear conditioning by nicotine [199]. Whereas further work is needed to fully elucidate the complete mechanisms involved in the enhancement of contextual fear conditioning by acute nicotine, to date, we know that nicotine acts in the hippocampus at α4β2* nAChRs to enhance contextual fear conditioning and that interactions between nAChRs and glutamate receptors may lead to enhanced activation of ERK and increased contextual fear conditioning.

In addition to acute nicotine interacting with learning processes to alter plasticity, chronic nicotine treatment may directly cause changes to the brain that result in altered learning. No enhancement of contextual learning was seen in mice treated chronically for 14 days with a dose of nicotine (6.3 mg/kg per day) that produced the same plasma nicotine level as the acute dose of nicotine (0.09 mg/kg) that enhanced learning and yielded plasma nicotine levels well within the range seen in smokers [184]. A similar noneffect of chronic nicotine on contextual fear conditioning was obtained in rats treated with 0.21 mg/kg per day via daily subcutaneous injections [185]. These results suggest that chronic nicotine treatment alters neural function and results in tolerance for the effects of nicotine on contextual fear conditioning.

If chronic nicotine alters hippocampal processes involved in contextual fear conditioning, then administration of a nAChR antagonist to mice treated chronically with nicotine may disrupt contextual fear conditioning. Furthermore, withdrawal of nicotine treatment could also disrupt contextual fear conditioning. Both scenarios have been demonstrated to be true. Whereas administration of DHβE to control mice before conditioning has no effect [180], administration of DHβE to mice treated chronically with nicotine disrupted contextual fear conditioning [200]. This suggests that chronic nicotine treatment alters neural function underlying contextual fear conditioning by modifying either nAChRs and/or processes mediated by nAChRs. Withdrawal studies also provide support for the contention that chronic nicotine treatment results in neural changes that alter contextual fear conditioning. Numerous studies have demonstrated that 24 h after withdrawal from 12 days of chronic nicotine treatment contextual but not cued fear conditioning was disrupted [183, 184, 200–203]. These findings suggest that withdrawal alters processes specific to contextual fear conditioning and not processes that could affect both cued and contextual fear conditioning. Thus, acute nicotine enhances contextual fear conditioning but chronic nicotine treatment produces neural adaptations that results in tolerance and withdrawal deficits in contextual conditioning when treatment terminates. Interestingly, contextual but not cued conditioning in rats is enhanced 2 weeks following termination of 14 days of twice daily injections using a ramping procedure from 0.5 to 1.1 mg/kg [204]. This suggests that withdrawal effects may not only dissipate but may rebound resulting in effects opposite of those that occur immediately following withdrawal. Further work needs to be done to identify when changes occur during withdrawal and how long they last.

It is currently unknown if the same processes that are involved in the enhancement of contextual fear conditioning by nicotine are altered by chronic nicotine treatment. It has been demonstrated, however, that the same nAChR subtypes involved in the effects of acute nicotine on contextual fear conditioning are involved in the nicotine withdrawal deficits in contextual fear conditioning. Mice lacking the β2 nAChR subunit did not show nicotine withdrawal disruption of contextual fear conditioning but wild-type littermates did and DHβE precipitated withdrawal [200]. In contrast, α7 nAChR KO mice displayed nicotine-withdrawal-induced disruption of contextual fear conditioning. These results suggest that both the acute effects of nicotine and changes in neural function that occur during chronic nicotine treatment are mediated by α4β2*

nAChRs. This is only the first step in exploring if the acute and chronic effects of nicotine on contextual fear conditioning involve the same substrates.

Nicotine, Contextual Learning, and Addiction

While the hippocampus is associated with learning and declarative processes, an increasing amount of work suggests that the hippocampus is also a substrate of addiction. Numerous studies have shown that the hippocampus is involved in developing context–drug associations. For instance, the dorsal hippocampus is involved in contextual reinstatement of cocaine-seeking behavior and the ventral hippocampus is involved in cued reinstatement of cocaine-seeking behavior [13]. In addition, inhibition of protein synthesis in the hippocampus disrupts morphine-conditioned place preference [205]. This result suggests that changes in gene expression in the hippocampus could contribute to addictive behaviors; this has been supported by multiple studies. Exposure to ethanol-associated contextual stimuli reinstated drug-seeking behavior and increased hippocampal c-fos expression in rats previously trained to self-administer ethanol [206]. Similarly, training in conditioned place preference for amphetamine increased c-fos expression in the hippocampus of rats [207]. Furthermore, extended training in a morphine-conditioned place preference paradigm altered gene expression in the hippocampus of rats [208]. Changes in gene expression are not limited to laboratory animals. An examination of gene expression in postmortem hippocampi from cocaine abusers found significant dysregulation of genes related to synaptic plasticity and neuronal structure [14], suggesting that drug abuse changes the function and structure of the hippocampus. These changes may underlie formation of maladaptive drug–cue associations. In support, smoking-related cues evoked changes in hippocampal activity in smokers but not nonsmokers [209–211]. Thus, drug-induced changes in hippocampal function could facilitate the formation of maladaptive drug–cue and drug–context associations that could facilitate cravings and continued use. Continued use could lead to further functional and structural changes in the hippocampus and other brain regions that could contribute to withdrawal symptoms as well as impaired decision making associated with addiction.

The hippocampus is one part of an interconnected network of neural structures involved in both learning and addiction. Thus, changes to the hippocampus may alter more than just hippocampal function. The hippocampus has efferent connections with many brain regions involved in addiction such as the amygdala, prefrontal cortex, and the ventral striatum [15, 212]. Because one function of the hippocampus is facilitating long-term memory storage in other areas, alterations in hippocampal function could also alter function in other areas involved in drug abuse and addiction. The hippocampus receives dopaminergic input from midbrain dopamine cells and in turn projects to the prefrontal cortex and ventral striatum, areas involved in behaviors such as impulse control, decision making, and reward evaluation [15]. Increased dopaminergic input to the hippocampus due to drug intake and subsequent output to areas important for behaviors related to addiction could result in the formation of strong maladaptive contextual associations. In support, it has been proposed that the hippocampus may provide information about novelty that stimulates dopamine release from the ventral tegmental area [213]. Thus, the effects of drugs of abuse, such as nicotine, on hippocampal function not only could contribute to addiction through facilitating the development of maladaptive associations that maintain drug-seeking behavior but may also facilitate the development of long-lasting changes in other structures involved in addiction.

The studies reviewed demonstrate how nicotine can alter synaptic plasticity and learning and also suggest how the effects of nicotine on learning could contribute to nicotine addiction. For example, acute nicotine enhances contextual conditioning via high-affinity nAChRs in the hippocampus, most likely $\alpha 4\beta 2^*$ nAChRs [186]. This ability of nicotine to enhance cognitive processes may reinforce repeated use while facilitating the development of drug–context associations that can trigger cravings. This possibility is supported by studies showing that animals will develop a learned preference for a context associated with nicotine [214–216]. Repeated nicotine use may transition into chronic use, which could alter neuronal function resulting in tolerance and cognitive deficits when nicotine is withdrawn. Data from studies in mice have shown that tolerance for the effects of nicotine on contextual conditioning develops with chronic administration and deficits occur when treatment ceases [184]. In addition, numerous studies of smokers have demonstrated that nicotine withdrawal disrupts cognitive function [141, 142, 217, 218]. These deficits, along with cued and context-evoked cravings, could lead to relapse. Not surprisingly, changes in cognition during abstinence are predictive of relapse [219]. Thus, examining how nicotine alters different types of learning will further our understanding of the neural substrates of learning and aid in understanding how nicotine-associated changes in behavior can lead to addiction.

Summary

In comparing the effects of nicotine on LTP, spatial learning, spatial working memory, and contextual learning, it is clear that the effects of nicotine vary across tasks.

Studies in LTP demonstrate that nicotine has differential effects on synaptic plasticity depending upon the hippocampal regions examined and the different nAChR subtypes involved. This may explain the range of effects of nicotine on different hippocampus-dependent tasks. For instance, whereas the dorsal hippocampus and $\alpha4\beta2$* nAChRs are involved in the enhancement of contextual fear conditioning by nicotine [186], the ventral hippocampus and both $\alpha7$ and $\alpha4\beta2$* nAChRs [136, 137, 220] appear to be involved with the effects of nicotine on spatial working memory. Thus, results from one type of hippocampus-dependent learning do not necessarily extend to other types of hippocampus-dependent learning. This should not be surprising because different types of hippocampus-dependent learning involve different neural and cellular substrates [154–161, 163, 221].

Overall, the findings discussed in this review provide insight into the molecular, cellular, and behavioral mechanisms by which nicotine alters declarative memory processes via changes in hippocampal function. These findings have implications for understanding schizophrenia, Alzheimer's disease, and, in particular, nicotine addiction. Such work lays the foundation for the development of new treatments for those afflicted with these potentially life-changing disorders.

Acknowledgements We thank Karen Coletti for assistance with the figure and acknowledge excellent suggestions from anonymous reviewers. Cited work from the authors' laboratory was funded in part by the National Institute on Drug Abuse (NIDA) grant DA017949 (TJG) and the National Institute on Alcohol Abuse and Alcoholism grant AA015515 (TJG). JWK was supported by NIDA training grant DA07237.

References

1. Penfield W, Milner B (1958) Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch Neurol Psychiatry 79(5):475–497
2. Rudy JW, O'Reilly RC (1999) Contextual fear conditioning, conjunctive representations, pattern completion, and the hippocampus. Behav Neurosci 113(5):867–880
3. Burgess N, Maguire EA, O'Keefe J (2002) The human hippocampus and spatial and episodic memory. Neuron 35(4):625–641
4. Eichenbaum H (1999) The hippocampus and mechanisms of declarative memory. Behav Brain Res 103(2):123–133
5. Antonova E et al (2004) The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 70(2–3):117–145
6. Boyer P et al (2007) Hippocampal abnormalities and memory deficits: new evidence of a strong pathophysiological link in schizophrenia. Brain Res Rev 54(1):92–112
7. Hughes JR et al (1986) Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 143(8):993–997
8. Kumari V, Postma P (2005) Nicotine use in schizophrenia: the self medication hypotheses. Neurosci Biobehav Rev 29(6):1021–1034
9. Muir JL (1997) Acetylcholine, aging, and Alzheimer's disease. Pharmacol Biochem Behav 56(4):687–696
10. Nordberg A (2001) Nicotinic receptor abnormalities of Alzheimer's disease: therapeutic implications. Biol Psychiatry 49 (3):200–210
11. Oddo S, LaFerla FM (2006) The role of nicotinic acetylcholine receptors in Alzheimer's disease. J Physiol Paris 99(2–3):172–179
12. Birks J (2006) Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev (1):CD005593
13. Rogers JL, See RE (2007) Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. Neurobiol Learn Mem 87 (4):688–692
14. Mash DC et al (2007) Gene expression in human hippocampus from cocaine abusers identifies genes which regulate extracellular matrix remodeling. PLoS ONE 2(11):e1187
15. Kelley AE (2004) Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron 44(1):161–179
16. Gould TJ (2006) Nicotine and hippocampus-dependent learning: implications for addiction. Mol Neurobiol 34(2):93–107
17. Matta SG et al (2007) Guidelines on nicotine dose selection for in vivo research. Psychopharmacology (Berl) 190(3):269–319
18. Le Novere N, Grutter T, Changeux JP (2002) Models of the extracellular domain of the nicotinic receptors and of agonist- and Ca2+-binding sites. Proc Natl Acad Sci USA 99(5):3210–3215
19. Rush R et al (2002) First and second transmembrane segments of alpha3, alpha4, beta2, and beta4 nicotinic acetylcholine receptor subunits influence the efficacy and potency of nicotine. Mol Pharmacol 61(6):1416–1422
20. Lena C, Changeux JP (1998) Allosteric nicotinic receptors, human pathologies. J Physiol Paris 92(2):63–74
21. Cordero-Erausquin M et al (2000) Nicotinic receptor function: new perspectives from knockout mice. Trends Pharmacol Sci 21 (6):211–217
22. McGehee DS (1999) Molecular diversity of neuronal nicotinic acetylcholine receptors. Ann N Y Acad Sci 868:565–577
23. Decker MW et al (1995) Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics. Life Sci 56(8):545–570
24. Hogg RC, Raggenbass M, Bertrand D (2003) Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol 147:1–46
25. Jones S, Sudweeks S, Yakel JL (1999) Nicotinic receptors in the brain: correlating physiology with function. Trends Neurosci 22 (12):555–561
26. Salminen O et al (2004) Subunit composition and pharmacology of two classes of striatal presynaptic nicotinic acetylcholine receptors mediating dopamine release in mice. Mol Pharmacol 65(6):1526–1535
27. Salminen O et al (2007) Pharmacology of alpha-conotoxin MII-sensitive subtypes of nicotinic acetylcholine receptors isolated by breeding of null mutant mice. Mol Pharmacol 71(6):1563–1571
28. Marks MJ, Collins AC (1982) Characterization of nicotine binding in mouse brain and comparison with the binding of alpha-bungarotoxin and quinuclidinyl benzilate. Mol Pharmacol 22(3):554–564
29. Whiteaker P et al (1999) An autoradiographic study of the distribution of binding sites for the novel alpha7-selective nicotinic radioligand [3H]-methyllycaconitine in the mouse brain. Eur J Neurosci 11(8):2689–2696
30. Broide RS, Leslie FM (1999) The alpha7 nicotinic acetylcholine receptor in neuronal plasticity. Mol Neurobiol 20(1):1–16
31. Wonnacott S (1997) Presynaptic nicotinic ACh receptors. Trends Neurosci 20(2):92–98

32. Perry DC et al (2002) Measuring nicotinic receptors with characteristics of alpha4beta2, alpha3beta2 and alpha3beta4 subtypes in rat tissues by autoradiography. J Neurochem 82 (3):468–481
33. Fenster CP et al (1997) Influence of subunit composition on desensitization of neuronal acetylcholine receptors at low concentrations of nicotine. J Neurosci 17(15):5747–5759
34. Papke RL, Sanberg PR, Shytle RD (2001) Analysis of mecamylamine stereoisomers on human nicotinic receptor subtypes. J Pharmacol Exp Ther 297(2):646–656
35. Berg DK, Conroy WG (2002) Nicotinic alpha 7 receptors: synaptic options and downstream signaling in neurons. J Neurobiol 53(4):512–523
36. Wooltorton JR et al (2003) Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci 23(8):3176–3185
37. Orr-Urtreger A et al (1997) Mice deficient in the alpha7 neuronal nicotinic acetylcholine receptor lack alpha-bungarotoxin binding sites and hippocampal fast nicotinic currents. J Neurosci 17 (23):9165–9171
38. Zhang ZW, Coggan JS, Berg DK (1996) Synaptic currents generated by neuronal acetylcholine receptors sensitive to alpha-bungarotoxin. Neuron 17(6):1231–1240
39. Barrantes GE, Westwick J, Wonnacott S (1994) Nicotinic acetylcholine receptors in primary cultures of hippocampal neurons: pharmacology and Ca++ permeability. Biochem Soc Trans 22(3):294S
40. Sorenson EM, Shiroyama T, Kitai ST (1998) Postsynaptic nicotinic receptors on dopaminergic neurons in the substantia nigra pars compacta of the rat. Neuroscience 87(3):659–673
41. Porter JT et al (1999) Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. J Neurosci 19 (13):5228–5235
42. Nomikos GG et al (2000) Role of alpha7 nicotinic receptors in nicotine dependence and implications for psychiatric illness. Behav Brain Res 113(1–2):97–103
43. Eilers H et al (1997) Functional deactivation of the major neuronal nicotinic receptor caused by nicotine and a protein kinase C-dependent mechanism. Mol Pharmacol 52(6):1105–1112
44. Dajas-Bailador FA, Soliakov L, Wonnacott S (2002) Nicotine activates the extracellular signal-regulated kinase 1/2 via the alpha7 nicotinic acetylcholine receptor and protein kinase A, in SH-SY5Y cells and hippocampal neurones. J Neurochem 80 (3):520–530
45. Barrantes GE et al (1995) Nicotine increases intracellular calcium in rat hippocampal neurons via voltage-gated calcium channels. Neurosci Lett 196(1–2):101–104
46. Sabban EL, Gueorguiev VD (2002) Effects of short- and long-term nicotine treatment on intracellular calcium and tyrosine hydroxylase gene expression. Ann N Y Acad Sci 971:39–44
47. Nakayama H et al (2001) Nicotine-induced phosphorylation of extracellular signal-regulated protein kinase and CREB in PC12h cells. J Neurochem 79(3):489–498
48. Amaral D, Lavenex P (2007) Hippocampal neuroanatomy. In: Anderson P et al (ed) The hippocampus book. Oxford University Press, New York, pp 37–114
49. Rolls ET, Kesner RP (2006) A computational theory of hippocampal function, and empirical tests of the theory. Prog Neurobiol 79(1):1–48
50. Jung MW, McNaughton BL (1993) Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 3 (2):165–182
51. Lee I, Kesner RP (2004) Encoding versus retrieval of spatial memory: double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus 14(1):66–76
52. Gilbert PE, Kesner RP, Lee I (2001) Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus 11(6):626–636
53. Bakker A et al (2008) Pattern separation in the human hippocampal CA3 and dentate gyrus. Science 319(5870):1640–1642
54. Gilbert PE, Kesner RP (2003) Localization of function within the dorsal hippocampus: the role of the CA3 subregion in paired-associate learning. Behav Neurosci 117(6):1385–1394
55. Daumas S et al (2005) Encoding, consolidation, and retrieval of contextual memory: differential involvement of dorsal CA3 and CA1 hippocampal subregions. Learn Mem 12(4):375–382
56. Nakazawa K et al (2002) Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 297 (5579):211–218
57. Gold AE, Kesner RP (2005) The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. Hippocampus 15(6):808–814
58. Huerta PT et al (2000) Formation of temporal memory requires NMDA receptors within CA1 pyramidal neurons. Neuron 25 (2):473–480
59. Hoge J, Kesner RP (2007) Role of CA3 and CA1 subregions of the dorsal hippocampus on temporal processing of objects. Neurobiol Learn Mem 88(2):225–231
60. Vago DR, Bevan A, Kesner RP (2007) The role of the direct perforant path input to the CA1 subregion of the dorsal hippocampus in memory retention and retrieval. Hippocampus 17(10):977–987
61. Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 55:51–86
62. Moscovitch M et al (2005) Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 207(1):35–66
63. Remondes M, Schuman EM (2004) Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory. Nature 431(7009):699–703
64. Fabian-Fine R et al (2001) Ultrastructural distribution of the alpha7 nicotinic acetylcholine receptor subunit in rat hippocampus. J Neurosci 21(20):7993–8003
65. Wada E et al (1989) Distribution of alpha 2, alpha 3, alpha 4, and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J Comp Neurol 284(2):314–335
66. Zarei MM et al (1999) Distributions of nicotinic acetylcholine receptor alpha7 and beta2 subunits on cultured hippocampal neurons. Neuroscience 88(3):755–764
67. Alkondon M, Pereira EF, Albuquerque EX (1996) Mapping the location of functional nicotinic and gamma-aminobutyric acid A receptors on hippocampal neurons. J Pharmacol Exp Ther 279 (3):1491–1506
68. Radcliffe KA et al (1999) Nicotinic modulation of glutamate and GABA synaptic transmission of hippocampal neurons. Ann N Y Acad Sci 868:591–610
69. Alkondon M, Albuquerque EX (2001) Nicotinic acetylcholine receptor alpha7 and alpha4beta2 subtypes differentially control GABAergic input to CA1 neurons in rat hippocampus. J Neurophysiol 86(6):3043–3055
70. Alkondon M, Albuquerque EX (2004) The nicotinic acetylcholine receptor subtypes and their function in the hippocampus and cerebral cortex. Prog Brain Res 145:109–120
71. McQuiston AR, Madison DV (1999) Nicotinic receptor activation excites distinct subtypes of interneurons in the rat hippocampus. J Neurosci 19(8):2887–2896
72. Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361 (6407):31–39

73. Martin SJ, Morris RG (2002) New life in an old idea: the synaptic plasticity and memory hypothesis revisited. Hippocampus 12(5):609–636
74. Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232 (2):331–356
75. Lynch MA (2004) Long-term potentiation and memory. Physiol Rev 84(1):87–136
76. Sigurdsson T et al (2007) Long-term potentiation in the amygdala: a cellular mechanism of fear learning and memory. Neuropharmacology 52(1):215–227
77. Whitlock JR et al (2006) Learning induces long-term potentiation in the hippocampus. Science 313(5790):1093–1097
78. Pastalkova E et al (2006) Storage of spatial information by the maintenance mechanism of LTP. Science 313(5790):1141–1144
79. Hasselmo ME (2006) The role of acetylcholine in learning and memory. Curr Opin Neurobiol 16(6):710–715
80. Benowitz NL, Porchet H, Jacob P 3rd (1989) Nicotine dependence and tolerance in man: pharmacokinetic and pharmacodynamic investigations. Prog Brain Res 79:279–287
81. Yu JP et al (2007) Noradrenaline release by activation of kappa-bungarotoxin-sensitive nicotinic acetylcholine receptors participates in long-term potentiation-like response induced by nicotine. Sheng Li Xue Bao 59(6):814–820
82. He J et al (2000) Long-term potentiation induced by nicotine in CA1 region of hippocampal slice is Ca(2+)-dependent. Acta Pharmacol Sin 21(5):429–432
83. Wang J et al (2001) Activation of p42/44 mitogen-activated protein kinase pathway in long-term potentiation induced by nicotine in hippocampal CA1 region in rats. Acta Pharmacol Sin 22(8):685–690
84. He J et al (2003) Different synaptic mechanisms of long-term potentiation induced by nicotine and tetanic stimulation in hippocampal CA1 region of rats. Acta Pharmacol Sin 24 (5):398–402
85. Fujii S et al (1999) Acute and chronic nicotine exposure differentially facilitate the induction of LTP. Brain Res 846 (1):137–143
86. Fujii S, Ji Z, Sumikawa K (2000) Inactivation of alpha7 ACh receptors and activation of non-alpha7 ACh receptors both contribute to long term potentiation induction in the hippocampal CA1 region. Neurosci Lett 286(2):134–138
87. Fujii S et al (2000) Nicotine reverses GABAergic inhibition of long-term potentiation induction in the hippocampal CA1 region. Brain Res 863(1–2):259–265
88. Nakauchi S et al (2007) Nicotine gates long-term potentiation in the hippocampal CA1 region via the activation of alpha2* nicotinic ACh receptors. Eur J Neurosci 25(9):2666–2681
89. Ji D, Dani JA (2000) Inhibition and disinhibition of pyramidal neurons by activation of nicotinic receptors on hippocampal interneurons. J Neurophysiol 83(5):2682–2690
90. Yamazaki Y et al (2005) Nicotine-induced switch in the nicotinic cholinergic mechanisms of facilitation of long-term potentiation induction. Eur J Neurosci 22(4):845–860
91. Ji D, Lape R, Dani JA (2001) Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity. Neuron 31(1):131–141
92. Fujii S, Sumikawa K (2001) Nicotine accelerates reversal of long-term potentiation and enhances long-term depression in the rat hippocampal CA1 region. Brain Res 894(2):340–346
93. Ge S, Dani JA (2005) Nicotinic acetylcholine receptors at glutamate synapses facilitate long-term depression or potentiation. J Neurosci 25(26):6084–6091
94. Matsuyama S, Matsumoto A (2003) Epibatidine induces long-term potentiation (LTP) via activation of alpha4beta2 nicotinic acetylcholine receptors (nAChRs) in vivo in the intact mouse dentate gyrus: both alpha7 and alpha4beta2 nAChRs essential to nicotinic LTP. J Pharmacol Sci 93(2):180–187
95. Matsuyama S et al (2000) Activation of nicotinic acetylcholine receptors induces long-term potentiation in vivo in the intact mouse dentate gyrus. Eur J Neurosci 12(10):3741–3747
96. Miner LL, Collins AC (1989) Strain comparison of nicotine-induced seizure sensitivity and nicotinic receptors. Pharmacol Biochem Behav 33(2):469–475
97. Salas R et al (2004) The alpha3 and beta4 nicotinic acetylcholine receptor subunits are necessary for nicotine-induced seizures and hypolocomotion in mice. Neuropharmacology 47(3):401–407
98. Hara K, Harris RA (2002) The anesthetic mechanism of urethane: the effects on neurotransmitter-gated ion channels. Anesth Analg 94(2):313–318, table of contents
99. Welsby P, Rowan M, Anwyl R (2006) Nicotinic receptor-mediated enhancement of long-term potentiation involves activation of metabotropic glutamate receptors and ryanodine-sensitive calcium stores in the dentate gyrus. Eur J Neurosci 24 (11):3109–3118
100. Welsby PJ, Rowan MJ, Anwyl R (2007) Beta-amyloid blocks high frequency stimulation induced LTP but not nicotine enhanced LTP. Neuropharmacology 53(1):188–195
101. Marks MJ et al (1992) Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. J Neurosci 12 (7):2765–2784
102. Gentry CL, Lukas RJ (2002) Regulation of nicotinic acetylcholine receptor numbers and function by chronic nicotine exposure. Curr Drug Targets CNS Neurol Disord 1(4):359–385
103. Nashmi R et al (2007) Chronic nicotine cell specifically upregulates functional alpha 4* nicotinic receptors: basis for both tolerance in midbrain and enhanced long-term potentiation in perforant path. J Neurosci 27(31):8202–8218
104. Yamazaki Y et al (2006) Nicotine withdrawal suppresses nicotinic modulation of long-term potentiation induction in the hippocampal CA1 region. Eur J Neurosci 24(10):2903–2916
105. Mansvelder HD, McGehee DS (2000) Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron 27 (2):349–357
106. Picciotto MR, Corrigall WA (2002) Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci 22(9):3338–33341
107. Robinson TE, Kolb B (2004) Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47(Suppl 1):33–46
108. Simosky JK, Stevens KE, Freedman R (2002) Nicotinic agonists and psychosis. Curr Drug Targets CNS Neurol Disord 1(2):149–162
109. Mudo G, Belluardo N, Fuxe K (2007) Nicotinic receptor agonists as neuroprotective/neurotrophic drugs. Progress in molecular mechanisms. J Neural Transm 114(1):135–147
110. Picciotto MR, Zoli M (2008) Neuroprotection via nAChRs: the role of nAChRs in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Front Biosci 13:492–504
111. Albensi BC et al (2007) Electrical stimulation protocols for hippocampal synaptic plasticity and neuronal hyper-excitability: are they effective or relevant? Exp Neurol 204(1):1–13
112. Morris RG et al (1982) Place navigation impaired in rats with hippocampal lesions. Nature 297(5868):681–683
113. Giniatullin R, Nistri A, Yakel JL (2005) Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci 28(7):371–378
114. Socci DJ, Sanberg PR, Arendash GW (1995) Nicotine enhances Morris water maze performance of young and aged rats. Neurobiol Aging 16(5):857–860

115. Attaway CM, Compton DM, Turner MD (1999) The effects of nicotine on learning and memory: a neuropsychological assessment in young and senescent Fischer 344 rats. Physiol Behav 67 (3):421–431
116. Bernal MC et al (1999) Effects of nicotine on spatial learning in C57BL mice. Behav Pharmacol 10(3):333–336
117. Abdulla FA et al (1996) Relationship between up-regulation of nicotine binding sites in rat brain and delayed cognitive enhancement observed after chronic or acute nicotinic receptor stimulation. Psychopharmacology (Berl) 124(4):323–331
118. Sharifzadeh M et al (2005) Post-training intrahippocampal infusion of nicotine prevents spatial memory retention deficits induced by the cyclo-oxygenase-2-specific inhibitor celecoxib in rats. J Neurochem 95(4):1078–1090
119. Ren K et al (2007) alpha7 Nicotinic receptor gene delivery into mouse hippocampal neurons leads to functional receptor expression, improved spatial memory-related performance, and tau hyperphosphorylation. Neuroscience 145(1):314–322
120. Scerri C et al (2006) The effects of chronic nicotine on spatial learning and bromodeoxyuridine incorporation into the dentate gyrus of the rat. Psychopharmacology (Berl) 184(3–4):540–546
121. Abrous DN et al (2002) Nicotine self-administration impairs hippocampal plasticity. J Neurosci 22(9):3656–3662
122. Meck WH, Church RM, Olton DS (1984) Hippocampus, time, and memory. Behav Neurosci 98(1):3–22
123. Levin E, Icenogle L, Farzad A (2005) Ketanserin attenuates nicotine-induced working memory improvement in rats. Pharmacol Biochem Behav 82(2):289–292
124. Levin ED, Kaplan S, Boardman A (1997) Acute nicotine interactions with nicotinic and muscarinic antagonists: working and reference memory effects in the 16-arm radial maze. Behav Pharmacol 8(2–3):236–242
125. Levin ED et al (1998) Nicotine–dizocilpine interactions and working and reference memory performance of rats in the radial-arm maze. Pharmacol Biochem Behav 61(3):335–340
126. Levin ED, Torry D (1996) Acute and chronic nicotine effects on working memory in aged rats. Psychopharmacology (Berl) 123 (1):88–97
127. Levin ED (1997) Chronic haloperidol administration does not block acute nicotine-induced improvements in radial-arm maze performance in the rat. Pharmacol Biochem Behav 58(4):899–902
128. Addy N, Levin ED (2002) Nicotine interactions with haloperidol, clozapine and risperidone and working memory function in rats. Neuropsychopharmacology 27(4):534–541
129. Levin ED et al (2003) Ventral hippocampal NMDA blockade and nicotinic effects on memory function. Brain Res Bull 61 (5):489–495
130. Kholdebarin E et al (2007) Interaction of nicotinic and histamine H(3) systems in the radial-arm maze repeated acquisition task. Eur J Pharmacol 569(1–2):64–69
131. Arthur D, Levin ED (2002) Chronic inhibition of alpha4beta2 nicotinic receptors in the ventral hippocampus of rats: impacts on memory and nicotine response. Psychopharmacology (Berl) 160 (2):140–145
132. Levin ED et al (1990) Chronic nicotine and withdrawal effects on radial-arm maze performance in rats. Behav Neural Biol 53 (2):269–276
133. Levin ED et al (1993) Chronic nicotinic stimulation and blockade effects on working memory. Behav Pharmacol 4 (2):179–182
134. Levin ED et al (1999) Ventral hippocampal ibotenic acid lesions block chronic nicotine-induced spatial working memory improvement in rats. Brain Res Cogn Brain Res 7(3):405–410
135. Levin ED et al (1993) Chronic nicotine reverses working memory deficits caused by lesions of the fimbria or medial basalocortical projection. Brain Res Cogn Brain Res 1(3):137–143
136. Bancroft A, Levin ED (2000) Ventral hippocampal alpha4beta2 nicotinic receptors and chronic nicotine effects on memory. Neuropharmacology 39(13):2770–2778
137. Bettany JH, Levin ED (2001) Ventral hippocampal alpha 7 nicotinic receptor blockade and chronic nicotine effects on memory performance in the radial-arm maze. Pharmacol Biochem Behav 70(4):467–474
138. Levin ED et al (1992) Persistence of chronic nicotine-induced cognitive facilitation. Behav Neural Biol 58(2):152–158
139. Levin ED et al (2002) Hippocampal alpha 7 and alpha 4 beta 2 nicotinic receptors and working memory. Neuroscience 109 (4):757–765
140. George TP et al (2002) Effects of smoking abstinence on visuospatial working memory function in schizophrenia. Neuropsychopharmacology 26(1):75–85
141. Jacobsen LK et al (2005) Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol Psychiatry 57(1):56–66
142. Mendrek A et al (2006) Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. Addict Behav 31(5):833–844
143. Durstewitz D, Seamans JK, Sejnowski TJ (2000) Neurocomputational models of working memory. Nat Neurosci 3(Suppl):1184–1191
144. Davis HP, Squire LR (1984) Protein synthesis and memory: a review. Psychol Bull 96(3):518–559
145. Hernandez PJ, Abel T (2008) The role of protein synthesis in memory consolidation: progress amid decades of debate. Neurobiol Learn Mem 89(3):293–311
146. Greenberg ME, Ziff EB, Greene LA (1986) Stimulation of neuronal acetylcholine receptors induces rapid gene transcription. Science 234(4772):80–83
147. Li MD et al (2004) Time-dependent changes in transcriptional profiles within five rat brain regions in response to nicotine treatment. Brain Res Mol Brain Res 132(2):168–180
148. Gould TJ, Wehner JM (1999) Nicotine enhancement of contextual fear conditioning. Behav Brain Res 102(1–2):31–39
149. Gould TJ, Lommock JA (2003) Nicotine enhances contextual fear conditioning and ameliorates ethanol-induced deficits in contextual fear conditioning. Behav Neurosci 117(6):1276–1282
150. Gould TJ, Higgins SJ (2003) Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. Neurobiol Learn Mem 80(2):147–157
151. Gould TJ (2003) Nicotine produces a within-subject enhancement of contextual fear conditioning in C57BL/6 mice independent of sex. Integr Physiol Behav Sci 38(2):124–132
152. Caldarone BJ, Duman CH, Picciotto MR (2000) Fear conditioning and latent inhibition in mice lacking the high affinity subclass of nicotinic acetylcholine receptors in the brain. Neuropharmacology 39(13):2779–2784
153. Paylor R et al (1998) Alpha7 nicotinic receptor subunits are not necessary for hippocampal-dependent learning or sensorimotor gating: a behavioral characterization of Acra7-deficient mice. Learn Mem 5(4–5):302–316
154. Burwell RD et al (2004) Corticohippocampal contributions to spatial and contextual learning. J Neurosci 24(15):3826–3836
155. Good M, Honey RC (1997) Dissociable effects of selective lesions to hippocampal subsystems on exploratory behavior, contextual learning, and spatial learning. Behav Neurosci 111 (3):487–493
156. El-Ghundi M et al (1999) Spatial learning deficit in dopamine D (1) receptor knockout mice. Eur J Pharmacol 383(2):95–106
157. Roberts AJ et al (2004) Mice lacking 5-HT receptors show specific impairments in contextual learning. Eur J Neurosci 19 (7):1913–1922

158. Voikar V et al (2004) Impaired behavioural flexibility and memory in mice lacking GDNF family receptor alpha2. Eur J Neurosci 20(1):308–312
159. Graves L et al (2002) Behavioral analysis of CREB alpha delta mutation on a B6/129 F1 hybrid background. Hippocampus 12 (1):18–26
160. Van Dam D et al (2000) Spatial learning, contextual fear conditioning and conditioned emotional response in Fmr1 knockout mice. Behav Brain Res 117(1–2):127–136
161. Peters M et al (2003) Loss of Ca2+/calmodulin kinase kinase beta affects the formation of some, but not all, types of hippocampus-dependent long-term memory. J Neurosci 23(30):9752–9760
162. Yasuda M, Mayford MR (2006) CaMKII activation in the entorhinal cortex disrupts previously encoded spatial memory. Neuron 50(2):309–318
163. Owen EH et al (1997) Assessment of learning by the Morris water task and fear conditioning in inbred mouse strains and F1 hybrids: implications of genetic background for single gene mutations and quantitative trait loci analyses. Neuroscience 80(4):1087–1099
164. Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106(2):274–285
165. Logue SF, Paylor R, Wehner JM (1997) Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. Behav Neurosci 111(1):104–113
166. Maren S (2001) Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci 24:897–931
167. Maren S, Aharonov G, Fanselow MS (1997) Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 88(2):261–274
168. Fanselow MS (2000) Contextual fear, gestalt memories, and the hippocampus. Behav Brain Res 110(1–2):73–81
169. Lopez-Fernandez MA et al (2007) Upregulation of polysialylated neural cell adhesion molecule in the dorsal hippocampus after contextual fear conditioning is involved in long-term memory formation. J Neurosci 27(17):4552–4561
170. Abel T, Lattal KM (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. Curr Opin Neurobiol 11 (2):180–187
171. Gould TJ, McCarthy MM, Keith RA (2002) MK-801 disrupts acquisition of contextual fear conditioning but enhances memory consolidation of cued fear conditioning. Behav Pharmacol 13 (4):287–294
172. Young SL, Bohenek DL, Fanselow MS (1994) NMDA processes mediate anterograde amnesia of contextual fear conditioning induced by hippocampal damage: immunization against amnesia by context preexposure. Behav Neurosci 108(1):19–29
173. Quinn JJ et al (2005) Dorsal hippocampus NMDA receptors differentially mediate trace and contextual fear conditioning. Hippocampus 15(5):665–674
174. Sindreu CB, Scheiner ZS, Storm DR (2007) Ca2+-stimulated adenylyl cyclases regulate ERK-dependent activation of MSK1 during fear conditioning. Neuron 53(1):79–89
175. Ohno M, Frankland PW, Silva AJ (2002) A pharmacogenetic inducible approach to the study of NMDA/alpha CaMKII signaling in synaptic plasticity. Curr Biol 12(8):654–656
176. Roberson ED, Sweatt JD (1996) Transient activation of cyclic AMP-dependent protein kinase during hippocampal long-term potentiation. J Biol Chem 271(48):30436–30441
177. Roberson ED et al (1999) The mitogen-activated protein kinase cascade couples PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus. J Neurosci 19(11):4337–4348
178. Nguyen PV, Woo NH (2003) Regulation of hippocampal synaptic plasticity by cyclic AMP-dependent protein kinases. Prog Neurobiol 71(6):401–437
179. Steiner RC, Heath CJ, Picciotto MR (2007) Nicotine-induced phosphorylation of ERK in mouse primary cortical neurons: evidence for involvement of glutamatergic signaling and CaM-KII. J Neurochem 103(2):666–678
180. Davis JA, Gould TJ (2006) The effects of DHBE and MLA on nicotine-induced enhancement of contextual fear conditioning in C57BL/6 mice. Psychopharmacology (Berl) 184(3–4):345–352
181. Davis JA, Porter J, Gould TJ (2006) Nicotine enhances both foreground and background contextual fear conditioning. Neurosci Lett 394(3):202–205
182. Gould TJ, Feiro O, Moore D (2004) Nicotine enhances trace cued fear conditioning but not delay cued fear conditioning in C57BL/6 mice. Behav Brain Res 155(1):167–173
183. Gulick D, Gould TJ (2007) Interactive effects of ethanol and nicotine on learning in C57BL/6J mice depend on both dose and duration of treatment. Psychopharmacology (Berl) 196:483–495
184. Davis JA et al (2005) Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. J Neurosci 25(38):8708–8713
185. Szyndler J et al (2001) The anxiolytic-like effect of nicotine undergoes rapid tolerance in a model of contextual fear conditioning in rats. Pharmacol Biochem Behav 69(3–4):511–518
186. Davis JA, Kenney JW, Gould TJ (2007) Hippocampal alpha4-beta2 nicotinic acetylcholine receptor involvement in the enhancing effect of acute nicotine on contextual fear conditioning. J Neurosci 27(40):10870–10877
187. Seguela P et al (1993) Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. J Neurosci 13(2):596–604
188. Chavez-Noriega LE et al (1997) Pharmacological characterization of recombinant human neuronal nicotinic acetylcholine receptors h alpha 2 beta 2, h alpha 2 beta 4, h alpha 3 beta 2, h alpha 3 beta 4, h alpha 4 beta 2, h alpha 4 beta 4 and h alpha 7 expressed in *Xenopus* oocytes. J Pharmacol Exp Ther 280(1):346–356
189. Davis JA, Gould TJ (2007) beta2 subunit-containing nicotinic receptors mediate the enhancing effect of nicotine on trace cued fear conditioning in C57BL/6 mice. Psychopharmacology (Berl) 190(3):343–352
190. Wehner JM et al (2004) Role of neuronal nicotinic receptors in the effects of nicotine and ethanol on contextual fear conditioning. Neuroscience 129(1):11–24
191. Allen TG, Abogadie FC, Brown DA (2006) Simultaneous release of glutamate and acetylcholine from single magnocellular "cholinergic" basal forebrain neurons. J Neurosci 26(5):1588–1595
192. Hefft S et al (1999) Synaptic transmission at nicotinic acetylcholine receptors in rat hippocampal organotypic cultures and slices. J Physiol 515(Pt 3):769–776
193. Alkondon M, Pereira EF, Albuquerque EX (2003) NMDA and AMPA receptors contribute to the nicotinic cholinergic excitation of CA1 interneurons in the rat hippocampus. J Neurophysiol 90 (3):1613–1625
194. Radcliffe KA, Dani JA (1998) Nicotinic stimulation produces multiple forms of increased glutamatergic synaptic transmission. J Neurosci 18(18):7075–7083
195. Lu Y, Wehner JM (1997) Enhancement of contextual fear-conditioning by putative (+/−)-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulators and *N*-methyl-D-aspartate (NMDA) receptor antagonists in DBA/2J mice. Brain Res 768(1–2):197–207
196. Gould TJ, Lewis MC (2005) Coantagonism of glutamate receptors and nicotinic acetylcholinergic receptors disrupts fear conditioning and latent inhibition of fear conditioning. Learn Mem 12(4):389–398
197. Fayuk D, Yakel JL (2007) Dendritic Ca2+ signalling due to activation of alpha 7-containing nicotinic acetylcholine receptors in rat hippocampal neurons. J Physiol 582(Pt 2):597–611

198. English JD, Sweatt JD (1996) Activation of p42 mitogen-activated protein kinase in hippocampal long term potentiation. J Biol Chem 271(40):24329–24332
199. Raybuck JD, Gould TJ (2007) Extracellular signal-regulated kinase 1/2 involvement in the enhancement of contextual fear conditioning by nicotine. Behav Neurosci 121(5):1119–1124
200. Portugal GS, Kenney JW, Gould TJ (2008) Beta2 subunit containing acetylcholine receptors mediate nicotine withdrawal deficits in the acquisition of contextual fear conditioning. Neurobiol Learn Mem 89(2):106–113
201. Davis JA, Gould TJ (2007) Atomoxetine reverses nicotine withdrawal-associated deficits in contextual fear conditioning. Neuropsychopharmacology 32(9):2011–2019
202. Portugal GS, Gould TJ (2007) Bupropion dose-dependently reverses nicotine withdrawal deficits in contextual fear conditioning. Pharmacol Biochem Behav 88(2):179–187
203. Andre JM et al (2008) Nicotine withdrawal disrupts both foreground and background contextual fear conditioning but not pre-pulse inhibition of the acoustic startle response in C57BL/6 mice. Behav Brain Res 190(2):174–181
204. Tian S et al (2008) Prior chronic nicotine impairs cued fear extinction but enhances contextual fear conditioning in rats. Neuroscience 153(4):935–943
205. Milekic MH et al (2006) Persistent disruption of an established morphine conditioned place preference. J Neurosci 26(11):3010–3020
206. Dayas CV et al (2007) Distinct patterns of neural activation associated with ethanol seeking: effects of naltrexone. Biol Psychiatry 61(8):979–989
207. Rademacher DJ et al (2006) The neural substrates of amphetamine conditioned place preference: implications for the formation of conditioned stimulus–reward associations. Eur J Neurosci 24(7):2089–2097
208. Marie-Claire C et al (2007) Sensitization to the conditioned rewarding effects of morphine modulates gene expression in rat hippocampus. Neuropharmacology 52(2):430–435
209. Due DL et al (2002) Activation in mesolimbic and visuospatial neural circuits elicited by smoking cues: evidence from functional magnetic resonance imaging. Am J Psychiatry 159 (6):954–960
210. Franklin TR et al (2007) Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. Neuropsychopharmacology 32(11):2301–2309
211. Zubieta JK et al (2005) Regional cerebral blood flow responses to smoking in tobacco smokers after overnight abstinence. Am J Psychiatry 162(3):567–577
212. Jones S, Bonci A (2005) Synaptic plasticity and drug addiction. Curr Opin Pharmacol 5(1):20–25
213. Lisman JE, Grace AA (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46(5):703–713
214. Fudala PJ, Teoh KW, Iwamoto ET (1985) Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 22(2):237–241
215. Walters CL et al (2006) The beta2 but not alpha7 subunit of the nicotinic acetylcholine receptor is required for nicotine-conditioned place preference in mice. Psychopharmacology (Berl) 184 (3–4):339–344
216. Wilkinson JL, Bevins RA (2008) Intravenous nicotine conditions a place preference in rats using an unbiased design. Pharmacol Biochem Behav 88(3):256–264
217. Kleinman KM, Vaughn RL, Christ TS (1973) Effects of cigarette smoking and smoking deprivation on paired-associate learning of high and low meaningful nonsense syllables. Psychol Rep 32 (3):963–966
218. Snyder FR, Davis FC, Henningfield JE (1989) The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 23(3):259–266
219. Rukstalis M et al (2005) Increases in hyperactive-impulsive symptoms predict relapse among smokers in nicotine replacement therapy. J Subst Abuse Treat 28(4):297–304
220. Felix R, Levin ED (1997) Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. Neuroscience 81(4):1009–1017
221. Bannerman DM et al (2003) Ventral hippocampal lesions affect anxiety but not spatial learning. Behav Brain Res 139(1–2):197–213