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Nicotinic Modulation of Hippocampal Cell Signaling and Associated Effects on Learning and Memory

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Abstract

The hippocampus is a key brain structure involved in synaptic plasticity associated with long-term declarative memory formation. Importantly, nicotine and activation of nicotinic acetylcholine receptors (nAChRs) can alter hippocampal plasticity and these changes may occur through modulation of hippocampal kinases and transcription factors. Hippocampal kinases such as cAMP-dependent protein kinase (PKA), calcium/calmodulin-dependent protein kinases (CAMKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and c-jun N-terminal kinase 1 (JNK1), and the transcription factor cAMP-response element-binding protein (CREB) that are activated either directly or indirectly by nicotine may modulate hippocampal plasticity and in parallel hippocampus-dependent learning and memory. Evidence suggests that nicotine may alter hippocampus-dependent learning by changing the time and magnitude of activation of kinases and transcription factors normally involved in learning and by recruiting additional cell signaling molecules. Understanding how nicotine alters learning and memory will advance basic understanding of the neural substrates of learning and aid in understanding mental disorders that involve cognitive and learning deficits.

Keywords

Nicotine; Addiction; Learning and Memory; Hippocampus; Kinases; Cell Signaling

Introduction

Nicotinic acetylcholine receptors (nAChRs) are a class of ligand gated ion channels located throughout the central and peripheral nervous system that are composed of five subunits with seventeen identified subunit combinations [1–4]. The primary function of nAChRs is the gating of sodium and/or calcium (Ca^{2+}, [5–7]). In the hippocampus, the predominant nAChR subtypes are α7 nAChRs and α4β2 nAChRs [8, 9]; though there is also a high density of α5 subunits [10], which can combine to form α4β2α5 nAChRs. The nAChR subtypes are functionally different. For example, α4β2 nAChRs show high-affinity for

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nicotine and desensitize slowly, whereas α7 nAChRs show lower affinity to nicotine and desensitize relatively rapidly [1, 11]. In general, nAChRs are found on both pre- and post-synaptic locations [2–4] and nAChRs can be found on many different cell types [12, 13].

In the hippocampus, α7 and α4β2 nAChRs show differential localization on a variety of neurons. For example, in the mouse hippocampus, α4 nAChR subunit is mainly expressed in the pyramidal cell layer whereas it is less expressed in the stratum oriens (SO) and stratum radiatum (SR, [14]). Also, a high level of α4 nAChR subunits are expressed on astrocytes in the hippcocampal CA1 region [14, 15]. There is also evidence showing that SO and SR both express α4, α7 and β2 subunits of nAChRs in rats [16]. In rats, α4β2 nAChRs also greatly contribute to the activity of the interneurons in the SR and stratum lacunosum-moleculare (SLM) while not affecting interneurons of the pyramidal cells or SO in the CA1 and DG regions of the hippocampus [17, 18]. However, there is also another report showing that α4β2 nAChRs contribute little to the SR activation but contribute to the SLM activation [19]. Different results may be due to different rat strains used in these studies as mouse studies also show heterogeneity in the nAChR expression in different regions [14].

Even though nAChRs are ionotropic receptors, agonists acting at nAChRs can produce complex changes in neuronal function through changes in cell signaling cascades. This is in part due to the gaiting of Ca^{2+}, which can directly activate Ca^{2+}-dependent cell signaling cascades. In addition, localization of nAChRs on presynaptic terminals can trigger the release of neurotransmitters that can activate cell-signaling cascades. Stimulation of nAChRs can directly lead to the release of the following neurotransmitters: acetylcholine, glutamate, GABA, dopamine, norepinephrine, and serotonin [20–26]. Several of these neurotransmitters act on receptors to initiate cell-signaling cascades. Thus, agonists at nAChRs can both directly and indirectly mediate changes in cell-signaling. Because changes in cell-signaling are associated with lasting behavioral changes (see [27, 28] for reviews), nAChR agonists may have a substantial impact on behavior through altering cell signaling.

This review to will focus on the effects of nicotine on cell-signaling in the hippocampus. The hippocampus is involved in many behaviors but is most often associated with long-term declarative memory formation (see below). Multiple cell signaling cascades exist that are beyond the scope of our chapter. Instead, a brief overview of hippocampus involvement in learning, and plasticity will be followed by examination of nicotine-associated changes in hippocampal cAMP-dependent protein kinase (PKA), calcium/calmodulin-dependent protein kinases (CAMKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-jun N-terminal kinase 1 (JNK1), and cAMP-response element-binding protein (CREB), as there is evidence suggesting that nicotine modulates these cell signaling molecules in the hippocampus.

Effects of Nicotine on Hippocampus-Dependent Learning and Memory

The hippocampus is a unique brain region that has been repeatedly shown to be the epicenter of many forms of learning and memory such as episodic memory, spatial learning, contextual learning, and spatial working memory [29–32]. The hippocampus is comprised of three major subregions CA1, CA3 and the dentate gyrus (DG). The main input to the

hippocampus is received by the DG from the entorhinal cortex, which receives variety of information from different cortical areas via the perforant pathway (PP). The DG projects to CA3 via the mossy fiber pathway. CA3 axons form Schafer collaterals (SC) that project to CA1 and also form commissural fibers that connect to the contralateral hippocampus. CA1 projects to both the subiculum and deep layers of the entorhinal cortex to complete the loop. These pathways comprise the major connections that contribute to memory formation [33] and evidence suggests hippocampal subregions contribute to different stages memory formation. For example, the DG has been implicated in forming orthogonal representations of the input received from the entorhinal cortex and therefore, forming spatial memory and differentiating spatial locations [34–36]. Also, the pyramidal neurons in the CA3 region form an auto-associative network, which enables multimodal associations between different stimuli. Therefore, CA3 is thought to be necessary for formation of episodic memory and holding information in the spatial working memory [36]. Importantly, this region has been found to be responsible for the formation of odor-context [37] and shock–context associations [31], which are necessary components of hippocampus-dependent contextual fear conditioning. Finally, CA1 is thought to be involved in diverse functions such as temporal associations [38, 39], memory consolidation [40], and memory retrieval [41].

Effects of nicotine on Hippocampal LTP

In addition to the differential involvement of hippocampal subregions in the formation of hippocampus-dependent learning and memory, as described above, the hippocampal subregions are involved in different types of long-term potentiation (LTP). LTP is a form of neural plasticity that may underlie long-term memory formation [42, 43]. The regulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPARs) and N-methyl-D-aspartic acid (NMDARs) receptors is fundamental for induction of LTP. Specifically, during LTP induction, existing AMPARs are phosphorylated and additional AMPARs are inserted into post-synaptic membrane as a result of glutamate release from the pre-synaptic membrane, which leads to sodium (Na^+) influx into the post-synaptic cell [44–48]. The simultaneous increase in internal Na^+ concentration and glutamate binding at post-synaptic NMDARs removes the magnesium blockade of NMDARs and results in Ca^{2+} release into the cell [42, 49–51]. Increased levels of intracellular Ca^{2+} induce depolarization of the pre-synaptic neuron as well as protein activation, mRNA synthesis, and protein translation required for maintenance of LTP [52–58]. Many of the molecular targets and mechanisms necessary for LTP induction are also required for hippocampus-dependent spatial and contextual learning [59, 60].

As a nAChR agonist, nicotine binds and activates nAChRs, which in turn, leads to neurotransmitter release [12, 13, 61–65], activation of second-messenger systems via depolarization [12, 65, 66] and within-cell Ca^{2+} influx. Therefore, numerous studies have investigated the effects of nicotine and nAChRs on hippocampal LTP. These studies suggest that nicotine can alter cellular mechanisms that are responsible for the induction of LTP [67–72]. In support, there is evidence showing that several cell signaling cascades responsible for the induction and maintenance of LTP are affected by nicotine-induced increase in the within-cell Ca^{2+} levels ([73, 74]; see [75, 76] for reviews). Furthermore, several studies showed that nAChRs interact with AMPARs and NMDARs. For example,

nicotine increased mRNA expression and protein levels of AMPARs, NMDARs and metabotropic glutamate receptors (mGluRs, [77–79]). In addition, nicotine increased AMPA/NMDA receptor ratio in the ventral tegmental area dopaminergic neurons [80]. Also, recently, Tang et al. [81] found that nicotine increased AMPAR-mediated current amplitude in the prefrontal cortex and this effect was reversed by an α7-nAChR antagonist methyllycaconitine (MLA). This is similar to results from Mitsushima et al. [82]that found that α7-nAChR antagonism blocked learning-related CA1 synaptic plasticity. Finally, there is evidence showing that nAChR-AMPAR-NMDAR activity integration determines excitability of hippocampal CA1 neurons [83]. Specifically, Alkondon et al. [83] found that nAChR agonists resulted in both AMPAR- and NMDAR-mediated excitatory postsynaptic currents (EPSCs) at CA1 interneurons. In line with studies suggesting that nAChRs-AMPARs-NMDARs interact, there is evidence suggesting that activation of nAChRs can enhance LTP [84–86] and convert weak stimulation-induced short-term potentiation to LTP [67, 69, 70], and directly induce LTP [68, 71, 72]. For example, Fujii et al. [67] showed that induction of SC-CA1 pathway LTP was enhanced with both acute and chronic nicotine exposure. Just as withdrawal alters hippocampus-dependent learning [87–92], LTP may be sensitive to nicotine withdrawal. Specifically, Yamazaki et al. [93] showed that withdrawal from chronic nicotine abolished nicotinic modulation of LTP induction for 4 days; during this period acute nicotine was not able to lower LTP induction threshold. In sum, in support of the results showing that nicotine alters hippocampus-dependent learning and memory, these results clearly show that nicotine and nAChRs are heavily involved in the regulation of hippocampal LTP through mediation of glutamatergic AMPARs and NMDARs.

Effects of nicotine on Hippocampal-Dependent Learning

Nicotine can modulate several different types of hippocampus dependent learning and some of these effects change as nicotine administration transitions from acute to chronic and to withdrawal from chronic treatment. Numerous studies have investigated the effects of acute nicotine on learning and memory (e.g., [94–99]). Results from multiple studies have consistently demonstrated an enhancing effect of acute nicotine on the hippocampus-dependent contextual and trace fear conditioning, but not on the hippocampus-independent cued fear conditioning. There is also evidence suggesting that this effect is mediated by high affinity β2-containing nAChRs [100]. However, there is one study demonstrating a deficit in contextual fear conditioning as a result of acute nicotine injection [101]. This differential result may be a result of the different route of nicotine administration, species used, and the inverted-U dose response for nicotine [97]. Acute nicotine also enhanced other hippocampus-dependent learning. For example, Kenney and Gould [102] used a context pre-exposure paradigm in which the animals were given exposure to the context prior to receiving immediate shocks in the same contexts and found that acute nicotine enhanced the contextual preexposure effect. Furthermore, acute nicotine enhanced hippocampus-dependent spatial object recognition but resulted in deficits in the hippocampus-independent novel object recognition [89]. Finally, there is also evidence suggesting that acute nicotine improves spatial learning in Morris Water Maze [103, 104] and enhances spatial working memory in Radial Arm Maze [105–107].

While acute nicotine may model the initial effects of nicotine use, continuous nicotine administration can be used to investigate the chronic effects of nicotine on learning. Multiple studies have shown that chronic nicotine does not affect hippocampus-dependent fear conditioning [87, 88, 90–92] or spatial object recognition (Kenney et al., 2011). However, there is evidence showing that chronic nicotine administration enhances spatial working memory [103, 108, 109], but at least one study showed impaired spatial working memory with chronic administration [110]. This differential result might also arise from the differential chronic nicotine administration regimens used in these studies. For example, studies that found improved spatial working memory with chronic administration used repeated injections of nicotine [103, 108, 109], but Scerri et al. [110] found deficits in spatial memory with continuous administration of nicotine. Due to nicotine's short half-life in animals [111], it is possible that these two administration regimens may yield different results. While chronic nicotine was found to have no effects on hippocampus-dependent fear conditioning, withdrawal from chronic nicotine resulted in a deficit in the same form of learning [87–92]. In smokers, nicotine withdrawal-associated cognitive deficits may contribute to the high levels of relapse [45, 46, 51]. In sum, nicotine may initially enhance cognition but with continued use tolerance can develop and cognitive deficits emerge with cessation of treatment. These changes may contribute to nicotine addiction as even the pro-cognitive effects can lead to the formation of maladaptive drug-context association that support drug-seeking behavior [44, 47, 82, 90].

Effects of Nicotine on Hippocampal Kinases and Transcription Factors

Protein kinase A (PKA)

Since its discovery in 1960's, PKA (also known as cAMP-dependent protein kinase) has been implicated in intercellular processes that include regulation of other cell-signaling kinases and transcription factors (see [112] for a review). PKA consists of regulatory (RIα, RIβ, RIIα, RIIβ) and catalystic (Cα, Cβ, Cγ) subunits and responds to cAMP increases within the cell. Specifically, increased levels of cAMP lead to phosphorylation of PKA and its downstream targets, which can result in protein translation and long-term storage of the memory [113, 114]. Like other hippocampal kinases, PKA plays important roles in synaptic plasticity and learning and memory by activating subsequent downstream targets such as ERK1/2 and CREB (see [27, 28] for reviews). For example, pharmacological inhibition of PKA in the hippocampus disrupts long-term contextual memory [115–117] as well as spatial memory retention [104]. In addition, multiple studies have shown that PKA is required for the transition between early to late phase of LTP [57, 78, 118, 119]. In line with the results suggesting that PKA is critical for long-term memory formation, Abel et al. [118] showed that the genetically modified R(AB) mice with reduced hippocampal PKA phosphorylation exhibited impaired expression of long-term but not short-term hippocampus-dependent contextual fear conditioning. Overall, PKA has been repeatedly shown to be an important mediator in the processes that determine long-term hippocampal memory formation.

The relationship between PKA and nicotine and nAChRs is complex with PKA altering nAChR function and nicotine altering PKA signaling [120–128]; see [129] for a review). Importantly, PKA has been shown to be instrumental in modulating nAChRs and is linked to

desensitization and recovery from desensitization of these receptors. Nishizaki and Sumikawa [126] showed that PKA activation increases and PKA inhibition decreases the speed of nAChR desensitization. In line with these results, there is also evidence showing that PKA phosphorylates nAChRs on the α4 subunits [122, 124, 125, 127, 128] and PKA-dependent phosphorylation of nAChRs can lead to long-term desensitization of these receptors [130].

Just as PKA may alter nAChR function, nicotine may change PKA signaling associated with learning and plasticity. For example, Welsby et al. [131] showed that the PKA inhibitors H-89 and Rp-8-CPT-cAMPS blocked both chronic and acute-nicotine enhancement of LTP in the rat DG slices. In addition, Gould and colleagues [132] investigated PKA involvement in the effects of acute nicotine on hippocampus-dependent learning to determine how nicotine administration leads to stronger long-term memory. The results of this study showed that the PKA inhibitor PKI 14–22 amide, at a dose that did not disrupt learning in nicotine naïve mice, prevented the nicotine-induced enhancement of contextual fear conditioning when infused into the dorsal hippocampus. Furthermore, using a PKA kinase activity assay, Gould et al. [132] showed that nicotine administration shifted the timing of the peak PKA activity from 1 to 2 hour after training. These results suggest that nicotine may strengthen memories and enhance transition from short-term to long-term memory through changing PKA activation in the dorsal hippocampus. Overall, the above-mentioned results point to the importance of PKA in its mediating the effects of acute nicotine on hippocampus-dependent learning.

Calcium/calmodulin-dependent protein kinases (CaMKs)

Calcium/calmodulin-dependent protein kinases (CaMKs; [133]) are highly abundant in the neuronal cells and they play a key role in the modulation of glutamatergic synapses [134]. There are at least five types of neuronal CaMKs, CaMKI, CaMKII, CaMKIII, CaMKIV, and CaMK kinase [135], with CaMKII and CaMKIV being the most commonly studied subtypes in the field of learning and memory. The activation patterns of CaMKII and CaMKIV differ as CaMKII is mainly activated by Ca^{2+} influx through NMDA receptors [136] and CaMKIV activation is determined by both Ca^{2+} influx and phosphorylation by a CaMKIV kinase [137]. Similar to the other Ca^{2+} activated kinases, CaMKs have also been shown to be instrumental in hippocampal synaptic plasticity and hippocampus-dependent memory formation ([119, 138, 139]; see [134] for a review). For example, inhibition of CaMKII protein [140] and disruption of αCaMKII gene expression [141] blocked induction of hippocampal LTP whereas tetanic stimulation that induces LTP increased CaMKII levels in the hippocampal neurons [142]. Moreover, Huang and Kandel [119] showed that CaMKII is required for the early phase of LTP, a PKA-independent process that underlies short-term memory. This suggests CaMKII may involve both early and late stages of LTP and potentially modulates transition between these two phases. In addition to CaMKII, CaMKIV has been implicated to play a role in LTP as well. Kasahara et al. [135] showed a transient activity of CaMKIV as a result of high frequency stimulation (HFS) of the hippocampal neurons. The same study also demonstrated that HFS-induced hippocampal *c-fos* activity was reversed by a CaMKIV inhibitor. These results clearly show that CaMKs are involved in LTP.

In parallel with the studies showing the importance of CaMKs in hippocampal synaptic plasticity, there is also evidence that CaMKII is involved in hippocampus-dependent learning and memory. For example, Silva et al. [114] demonstrated that CaMKII deficient mutant mice show impaired spatial learning in the Morris Water Maze. Interestingly, there is also evidence indicating that transgenic mice that have a Ca^{2+}-independent form of CaMKII show impaired spatial learning in the Barnes Maze but normal contextual fear conditioning [143]. These mice also showed normal LTP but a shift in the frequency-response curve was observed towards LTD. These results suggest that CaMKII may be specific to the certain types of hippocampus-dependent learning. Also, in line with Huang and Kandel's [119] results suggesting CaMKII may be involved in the transition from short-term to long-term memory, Wang et al. [144] also showed that inhibition of forebrain αCaMKII activity in mice 10 mins after learning disrupted short-term memory but the same manipulation after 15 mins had no effects on learning.

Although CaMK involvement in the effects of nicotine on hippocampus-dependent learning is unknown, several studies have reported modulation of nAChRs by the CaMKs [145–148]. Specifically, there is evidence showing that Ca^{2+}-dependent upregulation of several nAChRs such as α3, α5, and α7 requires activation of CaMKII [145]. However, Ridley et al. [147] showed that upregulation of α3 nAChRs, but not α7 nAChRs, are sensitive to the inhibition of CaMKII depending on the upregulating agent. Specifically, while the CaMKII inhibitor KN-62 prevented upregulation of α7 nAChRs induced by KCl, KN-62 had no effect on the nicotine or 3,[(4-dimethylamino) cinnamylidene] anabaseine maleate (DMAC)-induced α7 nAChR upregulation. In contrast, KN-62 administration alone resulted in upregulation of α3 nAChRs. Also, nicotine can directly activate CaMKII [77, 146, 147] and this activation is mediated by the β2-containing nAChRs [149]. In addition to the direct activation of CaMKs, nicotine-induced phosphorylation of ERK1/2 has also been shown to be dependent on the CaMKII activity [150]. Given that CaMKs are sensitive to nicotine-induced changes and involved in both in nAChR modulation and LTP induction, they may also have modulatory roles in the nicotine's effects on hippocampus-dependent learning but this remains yet to be examined.

Extracellular signal-regulated kinases 1 and 2 (ERK1/2)

First identified as the kinase phosphorylating microtubule-associated protein-2 (MAP-2) in response to growth factor stimulation in 1980's [151], ERK1/2 (ERK1 is also known as Mapk3 and p44 MAPK, and ERK2 is also known as Mapk1 and p42 MAPK) is a subfamily within the mitogen-activated protein kinases (MAPKs). ERK1/2 is activated by several different factors such as growth factors, G protein-coupled receptors, and other MAPK kinases [152, 153] and it contributes to the activation of transcription factors such as CREB [154, 155]. Given its role in the Ca2+ mediated cell signaling cascades, ERK1/2 plays modulatory roles in LTP [79–81, 113, 155]. For example, Kandel and his colleagues [80] found that ERK has a critical role in the theta frequent stimulation-induced LTP, which requires PKA, by modulating excitability of hippocampal neurons. In addition, Winder et al. [80] showed that inhibition of ERK prevented PKA-dependent LTP while not affecting PKA-independent LTP elicited by a single train. Also, Coogan et al. [79] demonstrated that in addition to the high-frequency stimulation-induced LTP, ERK1/2 inhibitor PD98059

prevented LTP induced by the application of the metabotropic glutamate receptor (mGluR) agonist (S)-dihydrophenylglycine (S-DHPG) and the K+ channel blocker tetraethylammonium chloride (TEA-LTP). Moreover, there is evidence showing that LTP-induction through high frequency stimulation in CA1 region of the hippocampus activates ERK in an NMDA receptor activation-dependent manner [81]. These results draw a clear link between ERK1/2 activation and hippocampal LTP, demonstrating a critical regulatory role for ERK1/2 in hippocampal plasticity.

Numerous studies have also indicated that ERK1/2 plays a significant role in long-term memory formation ([154, 156–158]; see [27, 159, 160] for reviews). For example, contextual fear conditioning increased ERK1/2 phosphorylation in the hippocampus [154, 157, 161]. Furthermore, ERK1/2 activation is necessary for long-term memory formation as ERK2 knockdown mice showed long-term memory deficits in fear conditioning [162]. Another intermediary kinase group that is closely associated with ERK1/2 activity is the mitogen-activated extracellular signal-regulated kinases 1 and 2 (MEK1/2). As a MAPK kinase (MAPKK), MEK1/2 phosphorylates MAPKs such as ERK1/2 [153] and therefore, contributes to the formation and consolidation of long-term memory. Multiple studies have shown that inhibition of MEK1/2 resulted in contextual fear conditioning deficits [115, 154, 157, 161, 163]. In addition, genetically modified mice that lack MEK1/2 showed both deficits in contextual fear conditioning and reduced levels of ERK1/2 activity [164]. These results suggest that MEK1/2 and ERK1/2 activation is required for encoding and consolidation of hippocampus-dependent memories.

Independent of behavior, nicotine may alter phosphorylation states of ERK1/2 [165–167] reported that acute nicotine administration increased ERK1/2 phosphorylation in the hippocampus along with other brain regions involved in learning. Similarly, Dajas-Bailador et al. [120] found that acute nicotine increased ERK1/2 activity in hippocampal neuronal culture and this activation was completely reversed by PKA inhibitors, KT 5720 and H-89. There are several ways that nicotine can induce ERK1/2 phosphorylation. For example, nicotine may trigger Ca^{2+} influx into the cell through the activation of nAChRs. In line with this mechanism, Nakayama et al. [168] showed that L-Type voltage-sensitive Ca^{2+} channel antagonists prevented nicotine-induced ERK1/2 phosphorylation in PC12h cells. Moreover, the same study showed that while α7 nAChRs were active at lower doses of nicotine than required for the induction of ERK1/2 phosphorylation (1 μM), non-α7 nAChRs were functional at higher doses of nicotine (50 μM). Nakayama et al. [168] also found that although non-selective nAChRs d-tubocurarine (d-TC) inhibited the nicotine-induced ERK1/2 phosphorylation, the α7 subunit-selective inhibitor α-bungarotoxin had no effect. This suggests that non-α7 nAChRs may be involved in the in the nicotine-induced phosphorylation of ERK1/2. In line with Nakayama et al. [168] results, Dajas-Bailador et al. [120] found that nicotinic activation of ERK1/2 is also Ca^{2+} dependent in SH-SY5Y cells and hippocampal neurons as it was absent in a Ca^{2+}-free medium. However, in contrast to Nakayama et al. [168] results, they also found that phosphorylation of ERK1/2 induced by nicotine at 100 μM dose was prevented by the α7 nAChR inhibitor α-bungarotoxin. These contrasting results may arise from the fact that the Nakayama et al. [168] and Dajas-Bailador et al. [120] studies used different cell lines, PC12h, and SH-SY5Y cells and hippocampal neurons, respectively. It is also possible that α7 nAChRs mediate the nicotine-induced

phosphorylation of ERK1/2 at the lowest and highest doses while non-α7 nAChRs are only involved with the intermediate dose. Finally, nicotine exposure times may also contribute to the results as Nakayama et al. [168] used a substantially longer exposure time (5 mins) compared to Dajas-Bailador et al. ([120]; 40 s).

Compatible with the data suggesting that nicotinic activation of ERK1/2 is Ca^{2+} dependent, there is also evidence showing that nicotine's effect on ERK1/2 activity requires PKA activation. For example, two different selective PKA inhibitors, KT5720 and H-89, have been found to decrease nicotine-evoked increase in ERK1/2 activity [120]. Finally, nicotine has been shown to alter activation of a downstream target of ERK1/2, ELK1, in the hippocampus [169]; acute nicotine increased ELK1 activation in CA1 but not DG whereas chronic nicotine did not increase activation but increase total levels of ELK1 in CA1 [169]. In sum, these results demonstrate that nicotine alters ERK1/2 activity and suggest that nicotine's effects on ERK1/2 can involve PKA-mediated Ca^{2+} influx.

ERK1/2 also plays important roles in nicotine's effects on learning and memory (Wang et al. 2001). In support, Welsby et al. [131] found that inhibition of an activator of ERK1/2, MEK1/2, prevented acute nicotine-induced enhancement of LTP without affecting normal LTP. Raybuck and Gould [83] investigated the effects of a systemic dose of a selective ERK1/2 inhibitor, SL327, on acute nicotine enhancement of hippocampus-dependent learning. When co-administered with nicotine prior to training, a dose of SL327 subthreshold for disrupting learning eliminated the nicotine-induced enhancement of contextual fear conditioning. These results suggest that ERK1/2 phosphorylation is required for nicotine's effects on the acquisition of the hippocampus-dependent memories. Moreover, Gould et al. [165] showed that while both acute nicotine administration and learning separately increased ERK1/2 activity in the hippocampus, acute nicotine shifted the timing of the hippocampal learning-related ERK/1/2 peak activation from 2 to 3 h post-training. The nicotine-induced delay in the hippocampal ERK1/2 phosphorylation peak may result in a stronger encoding of the hippocampus-dependent contextual memories. This effect potentially depends on the activation of other cell signaling molecules such as CREB and JNK as previously Kenney et al. [170, 171] showed the involvement of these cell signaling targets in the acute-nicotine enhancement of hippocampus-dependent learning. Overall, these studies suggest that nicotine mediates hippocampal ERK1/2 activity and in turn, ERK1/2 activation is required for the effects of nicotine on hippocampal-dependent forms of learning. Due to the fact that CREB is one of ERK1/2's downstream targets, it is possible that ERK1/2 may exert nicotine's effects by increasing the activation of CREB.

c-jun-N terminal kinase (JNK)

The c-jun N-terminal kinase (JNK) group of MAPKs are encoded by three *Jnk* genes (*Jnk1*, *Jnk2*, and *Jnk3;* [172, 173]) and they are activated by variety of kinases in the MAPK cascade such as the c-jun N-terminal kinase kinases (JNKK1/2; see [172] for a review). JNK1 (also known as MAPK8) has been shown to have variety of roles in processes such as apoptosis [174–176] and brain development [177–179] as well as learning and memory ([170, 171, 180–182]; see [183] for a review).

Several studies have investigated the direct and indirect effects of JNK activity on LTP [182, 184, 185]. For example, JNK1 deficient knock-out mice have been found to have normal LTP [182]. In line with the KO studies, there is evidence showing that the JNK inhibitor SP600125 does not affect hippocampal LTP [184]. However, Wang et al. [185] found that the JNK inhibitor JNKI reversed the blockage of hippocampal LTP in the DG by both synthetic and endogenous amyloid β-peptide (Aβ). In addition, Costello et al., [184] showed the attenuation of Aβ-induced impairment of CA1 LTP by another JNK inhibitor, SP600125. There is also evidence showing that JNK are involved in long-term depression (LTD). Studies showed that the JNK inhibitor SP600125 reduced NMDA-induced LTD [186] and JNK1 KO mice showed impaired metabotropic glutamate receptor (mGluR)-induced LTD [182]. Overall, these results suggest that while JNK may not be directly involved in hippocampal synaptic plasticity, they indirectly modulate LTP and LTD.

Early studies seemed to suggest JNK may not be critically involved in hippocampal synaptic plasticity, however, recent evidence suggests that hippocampal JNK may play a role in learning and memory. For example, inhibition of JNK in the hippocampus by SP600125 enhanced short-term memory while disrupting encoding and retrieval of long-term memory in an inhibitory avoidance task [180]. However, in parallel with the effects of JNK on LTD, there is evidence showing that JNK negatively regulate hippocampus-dependent associative learning. In contrast to Bevilaqua et al.'s [180] results showing JNK inhibition-induced disruption of long-term avoidance learning, pharmacological inhibition of JNK using SP600125 resulted in enhancement of contextual fear learning [187]. Critically, using KO mice lacking *Jnk1* gene, Sherrin et al. [187] also showed that JNK1 regulates baseline learning. Although Sherrin et al.'s [187] results contradict Bevilaqua et al.'s [180] data, a recent study by Leach et al. [181] may reconcile these results. Leach et al. [181] found that JNK1-null knockout mice learned contextual fear conditioning similar to their wild-type littermates, however; they did not show the enhancement of contextual fear conditioning with increased numbers of conditioning trials that wild-type mice did. This suggests that JNK1 is differentially recruited based on strength of learning. Therefore, it is possible that different training procedures used by Bevilaqua et al.'s [180] and Sherrin et al. [187] led to different levels of JNK1 involvement.

As discussed, JNK has been shown to play modulatory roles in both hippocampal LTP and augmentation of hippocampus-dependent learning. Therefore, it is possible that JNK may also be involved in the acute nicotine-induced enhancement of hippocampus-dependent learning. In support, using RNA extraction and quantitative real-time reverse transcription-PCR, Kenney et al. [170] found that nicotine given during learning increased JNK1 mRNA expression in the hippocampus, but not in the cerebellum. The same study also found that pharmacological inhibition of JNK activation in the dorsal hippocampus using local infusions of the JNK inhibitor SP600125 prevented enhancement of contextual fear conditioning by acute nicotine and phosphorylation of JNK1 was increased in the dorsal, but not ventral, hippocampus from mice that showed nicotine enhancement of the learning. JNK1 activation following nicotine administration during learning is dependent on β2-containing nAChRs, as the JNK1 mRNA increase in the hippocampus was absent in β2 KO

animals [170]. Therefore, these results suggest that hippocampal JNK1 may be responsible for the nicotine-induced enhancement of hippocampus-dependent fear memories.

cAMP-response element-binding protein (CREB)

cAMP-response element-binding protein (CREB) is a gene transcription factor in the nucleus and lead to changes that can alter function of single neurons as well as whole neuronal circuits [188]. CREB has been shown to be activated by ERK1/2, CaMKII, and PKA (see [188, 189] for reviews). CREB expression plays a crucial role in synaptic plasticity [114, 161, 189–191]. For example, Trifilieff et al. [161] showed that hippocampal CA1 LTP was correlated with CREB activation in the CA1 region. In addition, reduced levels of CREB have been shown to result in deficits in hippocampal synaptic plasticity. For example, Bourtchuladze et al. [190] showed that LTP decayed to baseline in the hippocampal slices from mice lacking hippocampal CREB. Also, transgenic mice expressing a truncated version of the CREB-binding protein showed deficits in late-phase hippocampal plasticity [192]. Furthermore, transgenic mice overexpressing an active form of CREB exhibited stronger hippocampal LTP [193]. However, using mutant mice with reversible CREB deficiency in the CA1 region of the hippocampus, Pittenger et al. [194] showed that while some forms of late-phase LTP such as forskolin-induced and dopamine-regulated potentiation are more sensitive to the CREB interference, several other forms of late-phase LTP are not affected by this manipulation. Overall, these results suggest that CREB works as a positive modulator of hippocampal neural plasticity.

In line with the studies showing that hippocampal LTP is modulated by CREB expression, there are several studies demonstrating that, hippocampus-dependent learning is also modulated by hippocampal CREB. Moreover, there is evidence showing that CREB is phosphorylated in the hippocampus during radial arm maze training suggesting CREB is a molecular marker for spatial learning [195]. Also, reversible inhibition of CREB in the CA1 region of the hippocampus impaired spatial memory in Morris Water Maze [194]. Similarly, while CREB-deficient mutant mice exhibited impaired contextual fear conditioning [190, 196, 197], viral vector-induced insertion of an active form of CREB to CA1 or DG neurons enhanced hippocampus-dependent contextual fear conditioning [198]. Overall, the results from the experiments showing that CREB modulates both hippocampal LTP and learning and memory converge on the conclusion that CREB is one of the key elements controlling long-term hippocampus-dependent learning.

Importantly, there is evidence showing that nicotine directly mediates CREB activity. In support, Hu et al. [199] found that nicotine stimulation of the hippocampal cells enhanced CREB activation. Similarly, Nakayama et al. [168] found nicotine-induced phosphorylation of CREB in PC12h cells. Moreover, there is evidence showing that the increase of CREB phosphorylation during nicotine-conditioned place preference can be reversed by non-specific nAChR antagonist mecamylamine [200], which shows that nAChR activation may play a role in CREB phosphorylation. Interestingly, Chang and Berg [201] showed that while nicotinic-signaling activates CREB in ciliary ganglion neurons this happens only when voltage-gated channels are blocked. It is suggested that this is because nicotine sustains CREB activity through Ca^{2+} influx from the internal stores, while voltage gated

channels trigger the release of calcineurin and PP1 to terminate the CREB activation. These results suggest that nicotine has a direct impact on the cascade responsible for mediating CREB activity but this process is controlled by the voltage gated channels.

While CREB activation seems to be necessary for normal long-term memory formation, there is also evidence suggesting that CREB phosphorylation is required for the effects of nicotine on hippocampus-dependent learning. Specifically, using chromatin immunoprecipitation (ChIP), Kenney et al. [171] showed that nicotine and learning interact to increase phosphorylated CREB binding at the *jnk1* promoter region in the hippocampus but nicotine administration alone or learning alone had no effect. This effect was also found to be β2-containing nAChRs-dependent as the increased CREB binding was absent in genetically modified mice lacking the β2 nAChR subunit. This result is also consistent with the previous results showing that β2-containing nAChRs are also required for the nicotine's enhancing effects on hippocampus-dependent fear conditioning [100, 202, 203]. Taken together, these results suggest that CREB activation plays a crucial role in nicotine's effects on hippocampus-dependent learning. Also, Kenney et al.'s [171] results suggest that CREB may increase expression of JNK1 to strengthen the consolidation of hippocampus-dependent fear memories.

Conclusion

As reviewed, there is overwhelming evidence suggesting that hippocampal kinases and transcription factors are heavily modulated by nicotine and nAChR activation and in turn these cell-signaling cascades are responsible for nicotine's effects on hippocampal learning and plasticity. The studies discussed here suggest that hippocampal kinases such as PKA, ERK1/2, CaMKs, and JNK are activated directly or indirectly by Ca^{2+} influx and play modulatory roles in hippocampal plasticity. While some of these kinases are necessary for LTP (e.g. PKA) others indirectly modulate plasticity (e.g. JNK1). In parallel to their roles in synaptic plasticity, hippocampal kinases are crucial for hippocampus-dependent learning. Kinases such as PKA and ERK1/2 are either necessary for hippocampus-dependent learning or, like JNK, they may play a more modulatory role in learning. Finally, there is strong evidence suggesting that kinases and transcription factors are altered during the acute nicotine-induced enhancement of hippocampus-dependent learning and that these changes in activation are responsible for the enhancement of hippocampus-dependent learning by nicotine.

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List of Abbreviations

nAChRs	Nicotinic acetylcholine receptors
mGluR	metabotropic glutamate receptors
Ca^{2+}	calcium

SO	stratum oriens
SR	stratum radiatum
SLM	stratum lacunosum-moleculare
DG	dentate gyrus
PP	perforant pathway
SC	Schafer collaterals
PKA	cAMP-dependent protein kinase
CAMKs	calcium/calmodulin-dependent protein kinases
ERK1/2	extracellular signal-regulated kinases 1 and 2
JNK1	c-jun N-terminal kinase 1
CREB	cAMP-response element-binding protein
MEK1/2	mitogen-activated extracellular signal-regulated kinases 1 and 2
MAPKK	MAPK kinase
LTP	long-term potentiation
LTD	long-term depression
Aβ	amyloid β-peptide
ChIP	chromatin immunoprecipitation

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Highlights

- Different kinases regulate different LTP/synaptic plasticity processes
- Nicotine alters both hippocampal plasticity and learning
- Nicotine alters hippocampal cell signaling cascades
- Hippocampal kinases are altered during the acute nicotine-induced enhancement of learning