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Review

Nicotinic modulation of hippocampal cell signaling and associated effects on learning and memory☆

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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.

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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.

Contents

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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1. 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 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, the 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 is 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 stratum pyramidale in the CA1 region 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 or inhibit 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.

1.1. 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].

1.2. 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 are 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