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Nicotine and Hippocampus-Dependent Learning

Implications for Addiction

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Abstract

Addiction is a complex disorder because many factors contribute to the development and maintenance of addiction. One factor is learning. For example, drug–context associations that develop during drug use could facilitate drug craving upon re-exposure to contexts previously associated with drugs. Additionally, deficits in cognitive processes associated with withdrawal could precipitate relapse in attempts to ameliorate those deficits. Because addiction and learning involve common neural areas and cell signaling cascades, addiction-related changes in processes underlying plasticity may contribute to addiction. This article examines similarities between addiction and learning at the behavioral, neural, and cellular levels, with emphasis on the neural substrates underlying the effects of acute nicotine, chronic nicotine, and withdrawal from chronic nicotine on hippocampus-dependent contextual learning.

Index Entries: Learning; addiction; acetylcholine; nicotine; hippocampus; contextual fear conditioning; CREB; MAPK; withdrawal; plasticity.

Introduction

Despite overwhelming evidence for the adverse health effects of smoking, 68.8 million Americans use tobacco products and 400,000 tobacco-related deaths occur in the United States each year *(1)*. Animal models have shown that nicotine has strong reinforcing properties, that abstinence from nicotine after chronic nicotine treatment produces withdrawal symptoms, and that exposure to environments where drug use occurs result in reinstatement of nicotine-seeking behavior (for review, *see* refs. *2–4*). Nicotine withdrawal studies with rodents have identified multiple withdrawal-related changes in somatic and affective responses. In both mice and rats, nicotine withdrawal resulted in the expression of somatic withdrawal behaviors such as head

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shakes and paw tremors *(5,6)*. Additionally, nicotine withdrawal was shown to be anxiogenic in mice *(6,7)* and was associated with a marked decrease in brain reward function in rats *(8)*. Nicotine withdrawal also disrupted cognition-related functioning in rodents, as measured by the ability to sensory-gate stimuli *(9)*. However, this effect may be dose-dependent *(7)*.

In humans, nicotine withdrawal is associated with anger, anxiety, difficulty concentrating, increased appetite, and agitation *(10)*. Additionally, smoking cessation is associated with disruption of sensory gating *(11–13)* and cognitive function *(14–16)*. The reduction of negative symptoms associated with nicotine withdrawal may motivate continued tobacco use and relapse *(17)*. However, the expression and severity of withdrawal symptoms may depend on multiple factors, including age, genetics, environment, and mental health *(17–21)*. Therefore, there may not be a universal symptom of nicotine withdrawal. Rather, a range of symptoms, including disrupted cognition, may characterize nicotine withdrawal. Increasing efforts have focused not only on understanding the effects of withdrawal on cognitive processes (e.g., learning) but also on understanding the role of learning in addiction. This article examines the role of learning and memory in addiction, with emphasis on the neural substrates underlying the effects of acute nicotine, chronic nicotine, and withdrawal from chronic nicotine on hippocampus-dependent contextual learning.

Neural and Cellular Correlates of Learning, Memory, and Addiction

In addition to the reinforcing properties of nicotine and the somatic withdrawal symptoms that help to maintain nicotine addiction, changes in the neural substrates of learning and memory may also contribute to the development and maintenance of addiction. Tremendous overlap exists between the neural and cellular substrates of learning and the neural and cellular substrates of addiction. The ability of drugs of abuse to interact with and alter the neural substrates of learning may contribute to the strong addictive properties of these drugs. Furthermore, drugs of abuse may have an especially strong impact on the declarative memory system. The declarative memory system allows for recollection of facts and events *(22)*; these types of memories comprise the personal history of individuals. Neural areas involved in declarative memory include the medial prefrontal cortex, hippocampus, parahippocampal regions, amygdala, and nucleus accumbens *(23–27)*. These areas are also involved in addiction. For example, addiction is associated with alterations in cortical function that may lead to disrupted decision processes and compulsive drug use *(28,29)*. Furthermore, Bechara *(30)* proposed that the amygdala may become hypersensitive to reward during addiction, and this overactivation of the amygdala may lead to altered regulation of ventromedial prefrontal cortical activity involved in decision making. Additionally, numerous studies have shown involvement of the amygdala in the formation of drug–cue associations (for review, *see* ref. *31*) and involvement of the nucleus accumbens, which is part of the reward circuitry *(32)*, in drug-seeking behavior *(33–35)*.

Finally, the hippocampus may process contextual drug associations that contribute to context-evoked craving and drug-seeking behavior. Inactivation of the hippocampus with tetrodotoxin prevented context-stimulated reinstatement of cocaine-seeking behavior *(36)*, and θ-wave stimulation of the hippocampus produced cocaine-seeking behavior *(37)*. Although this is not a complete list of brain areas involved in addiction, multiple groups have proposed that these areas form an interconnected system involved in drug addiction *(31,38–41)*. Therefore, because the declarative memory system is critically involved in processing and storing the memories that provide individuals with a personal history, the ability of drugs of abuse to co-opt the declarative memory system may

partially explain the strong addictive nature of these drugs.

Just as learning and addiction share similar neural substrates, learning and addiction also share similar cellular and molecular substrates. Tremendous headway has been made in identifying the cell signaling cascades involved in learning and synaptic plasticity. Briefly, numerous studies have demonstrated that protein kinase A (PKA), mitogen-activated protein kinase/extracellular-regulated kinase (MAPK/ERK), calcium/calmodulin protein kinase II (CaMKII), and the gene transcription factor cyclic adenosine monophosphate (cAMP)-response-element-binding protein (CREB) are critically involved in learning and synaptic plasticity *(42–47)*. These same substrates are involved in addiction. Infusion of a PKA inhibitor into the nucleus accumbens decreased cocaine self-administration, and infusion of a PKA activator increased self-administration of cocaine in rats *(48,49)*. In *Drosophila*, sensitization after repeated nicotine exposure was associated with increased levels of cAMP, implicating the cAMP/PKA pathway in this behavioral effect *(50)*. Furthermore, infusion of either a CaMKII inhibitor into the nucleus accumbens or an ERK inhibitor into the ventral tegmental area disrupted the development of behavioral sensitization to cocaine *(51,52)*, and inhibition of ERK phosphorylation in the central amygdala decreased cocaine-seeking behavior *(53)*. Changes in ERK activation may also contribute to alcoholism; withdrawal from ethanol was associated with increased ERK activation in multiple brain regions, including the amygdala and hippocampus *(54)*.

Changes in kinase levels can lead to changes in gene expression. The gene transcription factor CREB is activated by multiple kinases, including PKA and MAPK (for review, *see* refs. *55* and *56*). Therefore, the involvement of PKA and MAPK in addiction suggests a role for CREB as well. Evidence for the involvement of CREB in addiction comes from studies demonstrating that withdrawal from nicotine is associated with altered levels of phosphorylated and total CREB in the nucleus accumbens *(57)*, inhibition of CREB in the nucleus accumbens increased the rewarding properties of cocaine *(58)*, and chronic morphine administration decreased levels of CREB in the nucleus accumbens *(59)*. Therefore, learning and addiction activate similar cell signaling cascades and neural areas, and the ability of drugs of abuse to alter cell-signaling cascades involved in synaptic plasticity may lead to long-lasting behavioral changes. It is important to determine how activation of cell signaling cascades changes as drug administration changes from acute to chronic to withdrawal as well as to determine if activation and expression patterns vary across brain regions.

Learning and Memory and Nicotine Addiction

Similarly to other drugs of abuse, learning contributes to development and maintenance of nicotine addiction. Multiple studies have demonstrated that conditioned place preference can be established for a context associated with nicotine administration *(60–65)*. Whereas factors such as genetics and age may influence the development of conditioned place preference to nicotine, these studies clearly show that associations between the effects of nicotine and an environment can be conditioned. The ability to form strong but maladaptive associations between drug use and contextual stimuli may contribute to addiction and relapse by triggering context-specific drug craving and drug seeking. Specifically, researchers have proposed that nicotine reinforcement involves enhancement of associations with non-nicotine stimuli that eventually become reinforcers *(66)*. These non-nicotine stimuli could contribute to continued nicotine use. Smoking can be maintained by environmental stimuli *(67,68)*, and acquisition of nicotine self-administration in animal models is enhanced by pairing nicotine delivery with non-nicotine stimuli *(69–72)*. Additionally, during extinction of nicotine

self-administration, the presence of a non-nicotine stimulus previously paired with nicotine sustains pressing of a lever previously associated with nicotine *(67,72)*. These data suggest that these learned associations may contribute to resistance to extinction of nicotine self-administration. Furthermore, these studies together provide strong evidence for the role of learning in nicotine addiction.

Research demonstrating that environmental stimuli impact addiction *(36)* and the potential involvement of declarative memory processes in addiction *(73)* has led our lab to examine the effects of nicotine on contextual fear conditioning, a form of hippocampus-dependent learning *(74,75)* that may model declarative memory processes. Nicotine has multiple effects on learning that may contribute to the development and maintenance of addiction to nicotine. Acute nicotine, which may model the initial effects of smoking, enhances learning *(76–81)*. This positive effect of nicotine could facilitate continued drug use. Additionally, cognitive enhancing properties of nicotine could facilitate the formation of maladaptive drug–context associations that can lead to context-evoked cravings. Furthermore, if tolerance to the cognitive enhancing effects of nicotine develops, then greater amounts of nicotine may be consumed to compensate. This increased consumption could increase the addictive liability of nicotine. Finally, because withdrawal is associated with deficits in cognition, relapse may occur to ameliorate these deficits. Our work has focused on understanding the effects of acute nicotine treatment, chronic nicotine treatment, and withdrawal from chronic nicotine treatment on contextual conditioning and on the underlying nicotinic acetylcholinergic receptor (nAChR) subtypes and cell signaling cascades mediating the effects of nicotine on contextual fear conditioning. Because nAChR subtypes have different functional properties, a brief review of nAChRs follows to preface the discussion of behavioral effects of nicotine and the underlying neural substrates that may be involved.

Nicotinic Acetylcholinergic Receptor

nAChRs are a class of ligand-gated ion channels assembled from five subunits. Seventeen identified subunits that are differentially expressed in the central nervous system and peripheral nervous system have been identified *(82–85)*. Whereas the α4β2 and α7 nAChRs are similar because they are the predominant nAChR subtypes in the central nervous system, they differ in their functional properties *(86–88)*. α4β2 nAChR subtypes show high affinity for nicotine, desensitize slowly, and show long-lasting inhibition by mecamylamine, a broad spectrum nAChR antagonist *(85,89,90)*. Conversely, α7 nAChR subtypes show lower affinity for nicotine and a high affinity for α-bungarotoxin, desensitize rapidly, and show shortlasting inhibition by mecamylamine *(85, 89,91–94)*. Because nAChRs have different functional properties, nAChR subtypes may differentially contribute to the effects of nicotine on learning and addiction.

Both the α7 and α4β2 nAChR subtypes have properties that could contribute to cellular changes associated with learning and addiction. Both subtypes are located in the hippocampus, and α4β2 and α7 nAChRs are expressed pre- and postsynaptically, suggesting that these receptor subtypes could modulate both pre- and postsynaptic processes involved in synaptic plasticity. Furthmore, α4β2 and α7 nAChRs are calcium-permeable, which could enhance activation of second messengers involved in synaptic plasticity *(86–88,94–103)*. Some studies have suggested that the α7 and α4β2 nAChR subtypes may mediate different behavioral processes *(104,105)*. For example, activation of non-α7 nAChRs enhanced long-term potentiation, and inhibition of α7 nAChR subtypes enhanced long-term potentiation *(106)*. These data suggest that nicotine binding at these nAChR subtypes may differentially affect learning processes. Understanding the role of nAChR subtypes in the effects of acute, chronic, and withdrawal from chronic nicotine aids in understanding the behavioral effects of nicotine from receptor activation to molecular changes.

Acute Nicotine

We have used fear conditioning to examine the behavioral and neural effects of acute nicotine administration on contextual and noncontextual learning. In fear conditioning, animals form an association between a discrete auditory conditioned stimulus (CS) and a foot-shock unconditioned stimulus (US; i.e., cued fear conditioning) and between the training context and the US (i.e., contextual fear conditioning). Learning to associate the context with the US is hippocampus- and amygdala-dependent *(74,75)*. 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 *(75)*. Therefore, fear conditioning allows for the assessment of both hippocampus-dependent and hippocampus-independent learning in the same animal after a single training session.

A large body of work has examined both the neurocircuitry (reviewed in ref. *107*) and the associated mechanisms of plasticity (e.g., ref. *55*) that supports contextual fear conditioning, making contextual fear conditioning an excellent behavioral paradigm for examining the effects of nicotine on hippocampus-dependent learning. We have shown that acute nicotine enhances contextual fear conditioning *(76–79)*. This enhancement is long-lasting and expressed in the absence of nicotine *(79)*. Conversely, acute nicotine does not enhance the hippocampus-independent association between the auditory CS and the foot-shock US *(76,79)*, even when the difficulty of the task is increased *(108)*. Because nicotine enhances hippocampus-dependent contextual fear conditioning but not hippocampus-independent cued fear conditioning, nicotine may alter hippocampal function or the function of areas that project to the hippocampus during contextual fear conditioning. The neural, cellular, and molecular mechanisms involved in the long-lasting enhancement of contextual conditioning by nicotine are unknown.

Nicotine enhances contextual fear conditioning, and this enhancement is blocked by nAChR antagonists. However, nAChR antagonists administered alone do not disrupt contextual fear conditioning *(76–78,109)*, suggesting that nAChRs mediate the facilitation of contextual fear conditioning but are not essential for this form of learning. Studies with nAChR knockout mice have also suggested that activation of specific nAChR subtypes is not necessary for fear conditioning. Mice lacking either the α7 or the β2 nAChR subunit did not show deficits in conditioned fear *(110,111)*. Neither study examined whether nicotine could enhance fear conditioning in the knockout mice. However, it has since been demonstrated that β2-null mutant mice do not show enhancement of contextual fear conditioning by nicotine. Conversely, α7- and β4-null mutant mice that received nicotine demonstrated enhanced contextual fear conditioning *(112)*. We reported similar results using the α4β2 nAChR antagonist dihydro-β-erythroidine and α7 nAChR antagonist methyllycaconitine; dihydro-β-erythroidine blocked the nicotine enhancement of contextual fear conditioning, but methyllycaconitine did not; neither antagonist disrupted contextual fear conditioning when administered alone *(113)*. Together, these studies indicate that the α4β2 nAChR subtype is involved in the enhancement of contextual conditioning by nicotine.

The neural and molecular mechanisms recruited by nicotine to enhance contextual conditioning are not well known. Long-term memory is believed to be mediated by changes in gene expression that are induced by the activation of intracellular signaling pathways (reviewed in ref. *55*). Many of these signaling pathways are activated by calcium. One way in which acute nicotine binding at nAChRs may enhance learning is through interacting with glutamatergic processes to enhance calcium-mediated cell signaling. Nicotine could facilitate glutamate processes thorough presynaptic-mediated glutamate release *(114–116)*. It is also possible that nAChR activation facilitates postsynaptic-mediated glutamate processes involved in learning.

We recently found that co-antagonism of either nAChRs and AMPA glutamate receptors

or nAChRs and *N*-methyl-D-aspartate (NMDA) glutamate receptors with subthreshold doses of antagonists disrupted contextual fear conditioning *(117)*. These findings suggest that nAChRs may mediate processes that are similar or parallel to processes mediated by AMPARs and NMDARs. NMDARs, which are involved in contextual fear conditioning *(118–122)*, require cell depolarization to be activated. It is possible that nicotine enhances contextual fear conditioning by activating nAChRs that contribute to the membrane depolarization necessary for activating NMDAR-mediated processes. For example, nicotine can mediate changes in synaptic current independent of glutamate receptors and can mediate postsynaptic events *(93,115,123–131)*. Additionally, nAChRs have been localized on postsynaptic densities *(132,133)*. These findings suggest that nAChRs can support some fast excitatory synaptic transmission in the absence of glutamate and could play a significant role in NMDAR-dependent synaptic plasticity by contributing to the concurrent membrane depolarization necessary for NMDAR function. Additionally, increased calcium influx mediated by nAChRs *(98,99, 134–136)* could also facilitate learning by directly activating calcium-mediated cell signaling cascades involved in learning that are also activated by NMDARs.

Multiple studies have shown that nicotine can activate cellular and molecular processes that are involved in the chain of events linking synaptic activity to long-lasting changes associated with gene expression *(106,137–141)*. For example, the MAPK family has been implicated in synaptic plasticity and learning tasks, including contextual conditioning *(45,142–147)*. Nicotine-stimulated changes in calcium influx and in the release of calcium internal stores can activate kinases such as MAPK and CaMKII/IV as well as transcription factors such as CREB *(94,103,148,149)*. In mice, 0.4 mg/kg of acute nicotine increased ERK phosphorylation in area CA2 of the hippocampus *(150)*. Additionally, micro-array studies found nicotine administration was also associated with altered gene expression of several members of the MAPK family *(151,152)*. It remains to be determined whether acute nicotine enhances contextual fear conditioning through enhancement of cell signaling cascades involved in synaptic plasticity.

Chronic Nicotine

As reviewed previously, studies have shown that acute nicotine dose-dependently enhances hippocampus-dependent contextual fear conditioning *(76,77,112,153)*. Because withdrawal effects are commonly the opposite of acute drug action *(154)*, we investigated whether chronic nicotine results in tolerance for the effects of nicotine on contextual fear conditioning and whether withdrawal from chronic nicotine disrupts contextual fear conditioning. We found that an acute dose of nicotine and a chronic dose of nicotine that produced the same plasma nicotine levels did not produce the same behavioral effects; acute nicotine treatment enhanced contextual fear conditioning, whereas chronic nicotine treatment failed to enhance contextual fear conditioning *(153)*. Notably, plasma nicotine levels in mice treated acutely and chronically with nicotine were within the range of plasma nicotine levels (10–50 ng/mL) demonstrated by smokers *(155,156)*. These results suggest that with chronic administration of nicotine, neural adaptation occurs, resulting in tolerance for the effects of nicotine on contextual conditioning; however, the underlying neural changes are unknown.

Although the changes that may contribute to the tolerance observed for effects of nicotine treatment on contextual fear conditioning have not been examined, studies have examined the effects of chronic nicotine on intracellular signaling in multiple brain regions. Chronic nicotine was associated with increased levels of phosphorylated ERK in the prefrontal frontal cortex and decreased ERK levels in the amygdala *(157)*. This study also found that chronic nicotine treatment decreased levels of phosphorylated CREB (pCREB) in the nucleus accumbens and decreased total CREB in the

prefrontal cortex. Similarly, another study found that chronic nicotine was associated with increased MAPK activity in the prefrontal cortex *(152)*. It remains to be determined whether chronic nicotine treatment and contextual fear conditioning interact to alter cell-signaling cascades in a manner different than when chronic nicotine is administered without conditioning.

Nicotine Withdrawal

Neural adaptation that occurs during chronic nicotine administration may result in deficits when nicotine is withdrawn. This has been demonstrated for contextual conditioning; mice withdrawn from chronic nicotine treatment demonstrated deficits in contextual fear conditioning compared to their saline-treated counterparts when conditioned 24 h after removal of nicotine *(153)*. It is possible that relapse occurs in smokers after withdrawal from nicotine as an attempt to ameliorate learning-related deficits. For example, an acute challenge dose of nicotine reversed the deficit in contextual conditioning observed in mice withdrawn from chronic nicotine *(153)*.

The neural mechanisms altered during nicotine withdrawal that are responsible for the disruption of contextual fear conditioning are unknown. Changes may occur at both the receptor level and at the level of cell signaling cascades. In support of the former, chronic nicotine exposure was accompanied by an increase in nAChR binding sites *(90,158–160)* and by nAChR desensitization *(90,91,161–163)*. The increases in nAChR binding sites may be a compensatory mechanism induced by nAChR desensitization *(158,162)*. Evidence from pharmacokinetic studies of nicotine has suggested that periods of nicotine abstinence may result in recovery of function for some of the desensitized nAChRs (for review, *see* refs. *4, 155,* and *156*). For example, Gentry and colleagues *(164)* demonstrated in vitro that desensitized nAChRs recovered function after nicotine removal. Therefore, receptor level changes may account for the behavioral tolerance demonstrated by mice treated chronically with nicotine and for deficits in contextual fear conditioning associated with withdrawal from chronic nicotine.

As reviewed previously, numerous nAChR subtypes exist (for further review, *see* ref. *165*), and alterations in the function and number of any receptor subtype may account for behavioral changes. Research has shown that the acute effects of nicotine on contextual fear conditioning are mediated by α4β2 nAChRs *(112,113)*; however, it is unknown whether the effect of chronic nicotine and withdrawal from chronic nicotine on contextual fear conditioning are also mediated by α4β2 nAChRs. Marks and colleagues *(153)* reported that chronic nicotine, at a dose that produces comparable plasma nicotine levels as those associated with nicotine withdrawal-related deficits in contextual fear conditioning, results in half-maximal upregulation of α4β2 nAChRs *(159)*. Furthermore, β2-null mutant mice did not show upregulation of nAChRs after chronic nicotine treatment *(166)*. These findings suggest that alterations in α4β2 nAChR function and/or number that occur with chronic nicotine treatment may contribute to the nicotine withdrawal-associated changes in contextual fear conditioning *(153)*. This is an important topic for further study.

In addition to identifying the nAChRs involved in the effects of nicotine withdrawal on contextual fear conditioning, identifying changes in cell signaling cascades that could potentially underlie the effects of nicotine withdrawal on contextual fear conditioning is also important for understanding the effects of nicotine withdrawal on cognition and developing possible therapeutic agents. Studies that have examined the effects of nicotine withdrawal on cell signaling provide potential targets for changes that may cause the nicotine withdrawal-associated deficits in contextual fear conditioning. For example, mecamylamine-precipitated withdrawal from chronic nicotine treatment increased basal and stimulated adenylyl cyclase activity in the amygdala

(167). Withdrawal from nicotine may also be associated with changes in activation of gene transcription factors. Twenty-four hours after nicotine withdrawal, increased levels of pCREB were found in the ventral tegmental area and increased levels of total CREB were found in the nucleus accumbens *(157)*. Another series of studies found that 18 h after chronic intermittent nicotine exposure, pCREB was reduced in the cingulated cortex, piriform cortex, parietal cortex, and amygdala *(168)*. Additionally, pCREB levels were also reduced in the shell but not the core area of the nucleus accumbens *(57)*. The difference between this result and that of Brunzell and colleagues *(157)* may reflect methodological differences in nicotine administration. It remains to be determined whether withdrawal from nicotine differentially alters cell signaling when contextual learning occurs during the withdrawal. We have started experiments to test for possible interactions between nicotine withdrawal and contextual conditioning on cell signaling.

Conclusion

The effects of nicotine on cognition may support the development and maintenance of nicotine addiction through multiple mechanisms. We have demonstrated that acute nicotine enhances contextual learning. Therefore, the initial use of nicotine could facilitate cognitive processes, which may lead to repeated use and to the development of drug–context associations that could precipitate cravings. With repeated use, tolerance for the cognitive enhancing effects of nicotine may also lead to increased use and, therefore, to increased dependence. Finally, withdrawal from chronic nicotine disrupted contextual conditioning in mice. This deficit could be reversed with the administration of acute nicotine *(153)*. In humans, nicotine withdrawal deficits in cognitive function may contribute to relapse in an attempt to ameliorate the deficits. Whereas the α4β2 nAChRs have been identified as the nAChR mediating the acute effects of nicotine on contextual fear conditioning *(112,113)*, the nAChRs involved in the chronic and withdrawal effects of nicotine on contextual fear conditioning are unknown, as are the potential underlying cellular and molecular processes. Identifying the cellular adaptations responsible for behavioral changes in learning that occur with chronic nicotine and withdrawal from chronic nicotine treatment will increase understanding of learning and addiction and may lead to the development of more effective treatments to aid in smoking cessation.

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