Associative Learning, the Hippocampus, and Nicotine Addiction

Jennifer A. Davis and Thomas J. Gould*

Department of Psychology, Center for Substance Abuse Research, Temple University, Philadelphia, PA 19122, USA

Abstract: The abuse liability of nicotine is comparable to or greater than that of a variety of addictive substances. However, the reinforcing and/or rewarding properties of addictive substances other than nicotine far outweigh the reinforcing and/or rewarding effects associated with nicotine use. These data suggest that, in addition to the intrinsic reinforcing effects of nicotine, other factors may contribute to nicotine addiction. One such factor is associative learning, or rather, the ability of nicotine to alter learning and memory processes that may underlie addiction. The present paper presents an overview of the role of learning in nicotine addiction. In addition, recent advances in the identification of behavioral processes, neural substrates, and cellular and molecular substrates that underlie nicotine-associated alterations in learning are reviewed. Particular attention has been paid to research that describes the role of the hippocampus and hippocampus-dependent learning processes in nicotine addiction.

Keywords: Acetylcholine, nicotine, withdrawal, addiction, learning, hippocampus, CREB, ERK.

NICOTINE ADDICTION: HEALTH RISKS, STATISTICS, AND CONTRIBUTING FACTORS

Health risks associated with smoking include heart disease, lung disease, stroke [1], and cancers of the esophagus, lungs, trachea, stomach, cervix, and pancreas [2]. Given the negative effects of smoking on health, it is not surprising that approximately 438,000 smoking-related deaths are reported each year in the United States alone [2], and nearly one-third of annual cancer-related deaths can be attributed to smoking [2]. Despite the well-known deleterious effects of smoking on health, the Centers for Disease Control reported in 2005 [3] that 20% of adults in the United States are smokers. Reports that 42.5% of this 20% of adults in the United States attempted to quit during the previous year are encouraging in the face of these grim statistics [3]. However, they also underscore the difficulty of quitting smoking, which can be attributed to the strong addictive effects of nicotine, the primary component in cigarettes that motivates individuals to continue smoking. Furthermore, data indicating that less than 10% of individuals who attempt to quit are successful for one year [4, 5] underscore inadequacies in current smoking cessation therapies.

Like other drugs of abuse, nicotine use produces effects that are both rewarding and reinforcing and produces withdrawal-associated changes in somatic, affective, and cognitive processes [see 6-8 for reviews]. Among the reinforcing effects of the drug are decreased anxiety, enhancements in cognitive processes, and a sense of euphoria [see 8, 9 for reviews]. Attainment of the rewarding properties of nicotine and avoidance of the aversive symptoms associated with withdrawal from nicotine, which include bradycardia, insomnia, gastrointestinal discomfort, increased appetite, cravings, restlessness, irritability, depressed mood, anxiety, and cognitive deficits [10-15], are thought to contribute to sustained nicotine use.

*Address correspondence to this author at the Department of Psychology, Weiss Hall, Temple University, Philadelphia, PA 19122, USA; Tel: (215) 204-7495; Fax: (215) 204-5539; E-mail: tgould@temple.edu

The importance of alterations in learning, memory, and synaptic plasticity in addiction is an area of increased focus in addiction research, though not a primary focus of many nicotine addiction studies. In a 2005 review [16], Steven Hyman wrote that, "...addiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them", (p. 1414). This statement broadly reflects a growing consensus from numerous laboratories [see 16-21 for reviews]. Studies have shown that associative and cognitive processes involved in learning are also involved in addiction [see 22-25 for reviews], that common neural structures are involved in both addiction and learning [26-28], and that cell signaling molecules involved in learning [see 29-31 for reviews] are also involved in addiction [16-19]. The ability of addictive substances such as nicotine to hijack the neural substrates of learning would explain the ability of these substances to produce long-lasting and maladaptive behavioral and cellular changes that maintain addiction. The present paper presents an overview of the role of learning in nicotine addiction and a review of behavioral processes, neural substrates (with emphasis on the hippocampus), and cellular and molecular substrates that underlie nicotine-associated alterations in learning.

THE ROLE OF LEARNING AND MEMORY IN NICOTINE ADDICTION

Studies and theories have suggested that both reflexive associative learning and cognitively-mediated (i.e., requiring awareness) learning contribute to the development of nicotine addiction [23, 24]. There are multiple ways in which learning-related changes could facilitate the development of addiction. Both reflexive and cognitively mediated associations could form between the rewarding effects of nicotine and environmental stimuli [32-35 and see 22 for review]. Some of these associations can be described in terms of classical conditioning; stimuli that are associated with smoking function as conditioned stimuli (CS), and the reinforcing effects of nicotine, including decreased anxiety and euphoria, function as unconditioned stimuli (US). Once associations

1874-4737/08 $55.00+.00

are formed between these CSs and USs, subsequent exposure to smoking-related CSs comes to elicit a conditioned response (CR) such as drug-seeking behavior that may ultimately lead to smoking.

In addition to the formation of maladaptive associations that support nicotine addiction, direct effects of nicotine on learning could contribute to nicotine addiction as well [9]. The ability of nicotine to initially enhance some types of learning may in itself be reinforcing. This ability to enhance learning could also contribute to nicotine addiction by facilitating the formation of maladaptive associations, such as drug-context associations, that lead to drug-seeking behavior. Furthermore, effects of nicotine withdrawal on learning may contribute to addiction [9]. Adaptive changes that occur during chronic nicotine administration likely underlie disrupted learning seen during nicotine withdrawal. Relapse could occur in attempts to ameliorate these withdrawal-associated deficits in learning and learning-related processes. In the following sections, we will briefly review evidence supporting the role of these types of learning-related changes in the development and maintenance of nicotine addiction.

Support for the role of associative learning in nicotine addiction has come from studies indicating that increased cravings and physiological responses can be elicited with the presentation of previously neutral stimuli that were paired with smoking [36]. Likewise, withdrawn smokers and smokers who had not abstained from tobacco reported higher levels of craving following the presentation of images of smoking-related stimuli (e.g., a lighter) than following the presentation of non-smoking stimuli [26-28] (and see [22, 37] for reviews). Further demonstrating the importance of drug-stimulus associations in nicotine addiction, animals increase intravenous self-administration of nicotine when presented with stimuli that were previously paired with nicotine administration [38-40 for reviews] and decrease intravenous self-administration of nicotine in the absence of such conditioned stimuli [33, 40 for reviews]. Thus, formation of drug-stimuli associations and the ability of nicotine to enhance the reinforcing value of nonpharmacologic stimuli [41, 42] may lead to development and maintenance of behaviors that support nicotine addiction.

In addition to the ability of the effects of nicotine to be associated with discrete cues, associations with diffuse contextual cues can also support nicotine addiction. For example, animals will exhibit a preference for a context that was previously paired with nicotine administration [43-46]. Such data suggest that animals that receive nicotine can form an association between the drug or, rather, the reinforcing effects of the drug and the context in which they received nicotine. In support, a variety of studies have demonstrated that environmental stimuli can both maintain and reinstate drug-seeking/drug-taking behavior [32-35, 47, 48 and see 39, 40 for reviews]. Furthermore, contextual cues associated with smoking elicit cravings in smokers [49-51]. Thus, associations with either discrete stimuli or diffuse contextual stimuli can trigger physiological and behavior responses that can drive nicotine addiction.

Similar to the formation of associations between smoking-related stimuli and the effects of nicotine, direct effects of nicotine on behavioral and neural substrates of learning may contribute to nicotine addiction. These direct effects of nicotine could differentially affect learning as administration shifts from initial (or acute) to chronic administration and then to withdrawn administration. Research suggests that acute nicotine use is associated with the enhancement of learning and memory [see 9, 52-55 for reviews]. This effect of nicotine could reinforce smoking behavior by virtue of the implicit reward associated with enhanced learning and memory. In addition, acute nicotine use could augment the formation of maladaptive associations between smoking-related stimuli and the rewarding effects of the drug, thereby amplifying the conditioned value of some smoking cues [see 22 for review].

Chronic use, in the case of most drugs of abuse, contributes to addiction by eliciting increased drug consumption in order to overcome the tolerance that develops to the acute rewarding effects of the abused drug following repeated exposure [see 56 for review]. While there is some evidence that tolerance develops to the acute enhancing effect of nicotine on learning and memory as acute nicotine use transitions to chronic use [57, 58], there is little evidence for a direct role of this behavioral effect in nicotine addiction. Research suggests [see 59 for review] that, rather than increasing nicotine consumption over time, chronic smokers consume the same number of cigarettes each day on average, thereby maintaining a near-constant plasma nicotine level. These data suggest that individuals continue to smoke, not to overcome tolerance, but to avoid the symptoms that characterize the nicotine withdrawal syndrome. Among these symptoms are deficits in learning and memory [14, 57, 60]. Such deficits may also contribute to relapse as individuals who are attempting to quit may smoke again in an effort to ameliorate this effect of nicotine withdrawal.

THE HIPPOCAMPUS: A NEURAL SUBSTRATE FOR NICOTINE ADDICTION?

Studies indicating that the presentation of smoking-related stimuli to smokers is associated with the activation of brain regions that are involved in addictive processes and learning processes [26-28 and see 22, 37 for reviews] suggest that addiction and learning and memory may share neural substrates. Among the regions that have been identified as potential substrates for both processes are structures that comprise the mesocorticolimbic system, including the nucleus accumbens, the ventral tegmental area, the hippocampus, and the amygdala. Research examining the role of the ventral tegmental area and nucleus accumbens in nicotine addiction indicates that activation of nicotinic acetylcholine receptors (nAChRs) located in the ventral tegmental area results in an increase in dopamine release in the nucleus accumbens [see 61 for review]. Although a number of neurotransmitter systems other than the dopaminergic system may contribute to the rewarding effects of nicotine [see 62 for review], research indicates that this increase in accumbal dopamine release is critical for the rewarding properties of the drug [see 63 for review]. Within this system, it is suggested [64-66 and see 25 for review] that the amygdala and the hippocampus, a structure that is heavily involved in the formation of long-term declarative memories [see 67 for review], function to lay down representations of stimuli (CSs) that are associated with the rewarding effects of nicotine (USs). Subsequent exposure to these CSs comes to elicit a CR (i.e., smoking). Indeed, recent studies indicate that hip-

pocampal pathways and amygdalar pathways are critical for cue-elicited drug-seeking/taking [65, 68, 69 and see 70 for review]. The former (i.e., hippocampal pathways) are highly implicated in drug-seeking/taking that is elicited by contextual stimuli. In addition, the role of the hippocampus in strengthening synaptic connections in efferent areas that are also involved in addiction suggest that drug-induced changes in hippocampal function could produce long-lasting functional changes in these areas [20]. These properties of the hippocampus make the hippocampus an intriguing area to study in regards to nicotine addiction.

One behavioral paradigm that has proven useful in examining the role of hippocampus-dependent associations between contextual stimuli and the reinforcing effects of drugs of abuse is context reinstatement. Context reinstatement refers to the ability of contextual stimuli that were previously paired with a discrete cue that signaled drug availability to reinstate drug self-administration [71]. Although limited, there is evidence from research utilizing animals that self-administration of cocaine, alcohol, and speed-balls and/or drug-seeking can be elicited by exposure to a previously drug-paired (i.e., self-administration trained) context [69, 72-75]. Furthermore, lesions of the dorsal hippocampus prevent context reinstatement of cocaine administration [69] suggesting a critical role for the structure in context-elicited cocaine use and, perhaps, in context-elicited use of other drugs of abuse.

Support for a role of contextual stimuli in nicotine addiction has come from human research. A number of studies have demonstrated that contextual cues, cues that act as occasion-setters for smoking availability, can elicit nicotine cravings in smokers [49-51]. Such data suggest that the formation of hippocampus-dependent associations between contextual cues that are related to smoking and the reinforcing effects of nicotine may be important in maintaining smoking behavior and in relapse during periods of abstinence.

The role of the hippocampus in nicotine addiction likely extends beyond its role in the formation of associations between certain types of environmental stimuli (e.g., the smoking context) and the rewarding effects of nicotine. nAChRs in the hippocampus may mediate the direct effects of nicotine on learning and memory. To date, a majority of behavioral research has employed acute nicotine administration to examine the impact of nicotine on hippocampus-dependent forms of learning [see 9, 53-55 for reviews] including avoidance conditioning [76-80], delayed matching to sample performance [81, 82], working memory performance in the radial-arm maze and Morris Water Maze [83-85], and contextual and trace fear conditioning [57, 86-95]. The results overwhelmingly suggest that acute administration of nicotine dose-dependently enhances performance and/or learning of these tasks. Additional support for the role of the hippocampus in the acute effects of nicotine on learning and memory has come from studies indicating that acute nicotine administration alters long term potentiation (LTP), a persistent increase in synaptic strength that is widely considered a mechanism by which learning and memory occurs in the brain [see 96, 97 for reviews]. Briefly, acute nicotine administration decreases the threshold for LTP induction in the hippocampus [98-103] and can induce hippocampal LTP direcly [104, 105].

Although numerous paradigms can be used to illustrate the effects of nicotine on hippocampus-dependent learning, the present review will focus on fear conditioning. In fear conditioning, subjects are trained using temporally contiguous pairings of a CS, such as a tone, and an aversive US, such as a footshock. Two associations form as a result of training, an association between the training context and the US (called contextual fear conditioning) and an association between the CS and the US (called cued fear conditioning). The former association requires the hippocampus, while the latter association does not [106-108]. Fear conditioning has proven to be useful in studying the effects of nicotine on learning and memory for multiple reasons: 1) The task allows researchers to examine two types of learning within one animal: contextual learning and cued learning. 2) Fear conditioning is rapidly acquired; thus, one can easily examine the effects of acute nicotine administration, chronic nicotine administration, and withdrawal from chronic nicotine administration on this type of learning, 3) The neural and molecular substrates of fear conditioning have largely been identified [29 and see 31, 109, 110 for reviews], which facilitates identification of potential biological targets for nicotine that underlie the effects of nicotine on learning.

Previous research indicates that acute nicotine administration enhances contextual fear conditioning [57, 86-95]. In contrast, chronic administration of a dose of nicotine that produces plasma nicotine levels that are similar to those produced by an acute dose of nicotine that enhances contextual fear conditioning has no effect on the task [57]. These data suggest that behavioral tolerance develops to this effect of acute nicotine with chronic exposure to the drug. Finally, withdrawal from chronic administration of this dose of nicotine is associated with impairments in contextual fear conditioning [57, 86, 111, 112]. Of note, all three patterns of nicotine administration did not affect cued fear conditioning. Thus, only the portion of the fear conditioning task that depends upon the hippocampus [106-108] is affected by nicotine administration. These results suggest that the effects of nicotine on contextual fear conditioning and, perhaps, learning and memory in general are mediated by nAChRs in the hippocampus and/or a connected structure. However, limited studies have directly assessed the role of hippocampal nAChRs in the acute effects of nicotine on learning [76, 113], and no studies have examined the role of the hippocampus in the effects of acute, chronic, and withdrawal from chronic nicotine on learning and memory directly until now.

HIPPOCAMPAL nAChR INVOLVEMENT IN THE EFFECTS OF NICOTINE ON LEARNING AND MEMORY

Recent work from our lab has demonstrated that the action of nicotine at dorsal hippocampal nAChRs is sufficient to enhance contextual fear conditioning using direct infusion techniques [114]. In initial experiments, acute nicotine bilaterally infused into the dorsal hippocampus dose-dependently enhanced contextual fear conditioning, while nicotine infusions above or below the dorsal hippocampus had no effect on contextual fear conditioning. The latter findings provide strong evidence that the action of the nicotine at

dorsal hippocampal nAChRs rather than at nAChRs in surrounding brain regions underlies this effect of the drug on learning. An additional study assessing the effect of acute intrahippocampal nicotine on cued fear conditioning refuted an alternative interpretation of the data positing that the enhancing effects of acute nicotine infusions on contextual fear conditioning reflect alterations in non-associative processes, such as locomotor activity, arousal, or attentional processes rather than alterations in associative contextual learning. If the nicotine produced its effects on contextual fear conditioning *via* alterations in non-associative processes, then cued fear conditioning should have been similarly impacted by administration of the drug. This result was not seen; conditioning to the CS was unaffected by intrahippocampal nicotine.

Results indicating that acute intrahippocampal nicotine infusions enhanced learning suggest that the effect of chronic nicotine on contextual fear conditioning [57] may also be mediated by nAChRs in the hippocampus. Therefore, to assess the role of hippocampal nAChRs in the effect of chronic nicotine on the task, mice received 14 days of continuous intrahippocampal infusion of a dose of nicotine matched to the acute intrahippocampal dose that had enhanced learning.[1] Mice were trained on the 13th day and tested on the 14th day. Consistent with previous results using chronic systemic nicotine administration [57], chronic intrahippocampal nicotine administration had no effect on contextual conditioning. These data suggest that tolerance may develop to the enhancing effect of acute intrahippocampal nicotine on contextual fear conditioning with chronic exposure to the drug. Furthermore, these data suggest that chronic nicotine exposure alters hippocampal function such that the action of the drug at hippocampal nAChRs no longer produces the same behavioral effect as was seen with acute nicotine infusions. In support, chronic nicotine exposure is associated with prolonged nAChR desensitization and increases in nAChR density in the hippocampus and throughout the brain [e.g., 115-121]. It is hypothesized that these chronic nicotine-associated neural adaptations and related alterations in second-messenger signaling underlie nicotine withdrawal symptoms during periods of abstinence. Thus, nicotine withdrawal-associated deficits in contextual learning may also be mediated by changes in the hippocampus.

To directly test if the hippocampus is critically involved in withdrawal-associated deficits in contextual fear conditioning, mice treated for 12 days with chronic intrahippocampal infusion of nicotine were withdrawn for twenty-four hours prior to training.[2] As with mice withdrawn for twenty-four hours from chronic systemic nicotine [57], mice withdrawn from chronic intrahippocampal nicotine demonstrated deficits in contextual fear conditioning. There was no effect of withdrawal from chronic intrahippocampal nicotine on cued fear conditioning, suggesting that withdrawal-associated deficits in contextual fear conditioning reflect alterations in associative learning rather than non-associative processes. In addition, withdrawal from chronic infusion of nicotine into cortical regions above or thalamic regions below the dorsal hippocampus did not alter learning. Taken together, then, the data suggest that chronic nicotine treatment followed by withdrawal from chronic nicotine alters neural function in the dorsal hippocampus leading to deficits in hippocampus-dependent learning and memory. These alterations may occur at the receptor level and/or at the level of second messenger signaling molecules.

HIPPOCAMPAL nAChR SUBTYPE INVOLVEMENT IN THE EFFECTS OF ACUTE, CHRONIC, AND WITHDRAWAL FROM CHRONIC NICOTINE ON LEARNING AND MEMORY

nAChRs are a family of pentameric receptors that are densely located in both the central nervous system and the peripheral nervous system. nAChRs are either homomeric, consisting of α (α2 – α10) subunits, or heteromeric, consisting of a combination of α and β (β2 – β4) subunits [see 122-125]. A large number of nAChR subtypes have been identified to date. However, two subtypes, the α4β2* nAChRs (* may include additional subunits) and the α7* nAChRs, comprise approximately 90% of nAChRs in the central nervous system [126-130]. The functional characteristics of these nAChR subtypes differ considerably. For example, α4β2* nAChRs desensitize more slowly than α7* nAChRs and have a higher affinity for both acetylcholine and nicotine than α7* nAChRs [122, 129, 131, 132]. Differences in functional characteristics, localization, and density [127, 129, 131, 133, 134] likely underlie the divergent roles of α4β2* nAChRs and α7* nAChRs in the somatic, affective, and cognitive effects of nicotine. Thus, identifying the role each nAChR subtype plays in the effects of acute nicotine and withdrawal from chronic nicotine on learning and memory should advance understanding of nicotine addiction and aid in development of therapeutics for nicotine addiction.

Although numerous studies have examined if neuronal nAChRs are critically involved in a variety of forms of hippocampus-dependent learning and memory [e.g., 76, 86, 135-137], only a few studies have assessed the role of nAChR subtypes in the acute effects of nicotine on learning and memory [86, 87, 95]. To this end, we and others have utilized nAChR subtype selective antagonists [87] and nAChR subunit knockout mice [86, 95] to determine if α4β2* and/or α7* nAChRs are necessary for the enhancing effect of acute nicotine on hippocampus-dependent fear conditioning. Briefly, a study [87] that utilized dihydro-beta-erythroidine (DHβE), a nAChR antagonist that preferentially binds α4β2* nAChRs, and methyllycaconitine (MLA), a nAChR antagonist that acts preferentially α7* nAChRs, indicated that α4β2* but not α7* nAChRs are critically involved in the enhancing effect of nicotine on hippocampus-dependent learning; MLA had no effect, and DHβE blocked the enhancing effect of acute nicotine on contextual fear conditioning. Studies demonstrating that acute nicotine fails to enhance hippocampus-dependent fear conditioning in β2 nAChR subunit knockout mice but not α7 nAChR subunit knockout mice provide additional support for this conclusion [86, 95].

[1]Davis JA, Gould TJ. Hippocampal involvement in the effects of acute, chronic, and withdrawal from chronic nicotine on contextual fear conditioning. Annual Meeting of the Society for Neuroscience 2006 published abstract, Atlanta, GA.

[2]Davis JA, Gould TJ. Hippocampal involvement in the effects of acute, chronic, and withdrawal from chronic nicotine on contextual fear conditioning. Annual Meeting of the Society for Neuroscience 2006 published abstract, Atlanta, GA.

A recent study from our lab [114] extended this conclusion by examining if dorsal hippocampal α4β2* nAChRs and/or α7* nAChRs mediate the effect of acute systemic nicotine on contextual fear conditioning. Specifically, we determined if intrahippocampal infusions of either DHβE or MLA would block the enhancing effect of acute systemic nicotine on contextual fear conditioning. Mice receiving intrahippocampal DHβE and acute systemic nicotine demonstrated significantly lower levels of contextual conditioning than mice that received intrahippocampal saline and acute systemic nicotine and similar levels of contextual fear conditioning to saline-treated controls. In contrast, mice that received intrahippocampal MLA and acute systemic nicotine demonstrated levels of contextual fear conditioning that were similar to mice that received intrahippocampal saline and acute systemic nicotine. There was no effect of intrahippocampal administration of either antagonist alone on freezing in response to the training context. Thus, the action of nicotine at DHβE-sensitive nAChRs but not MLA-sensitive nAChRs in the dorsal hippocampus is necessary for acute nicotine-associated enhancement of contextual fear conditioning.

Just as β2-subunit containing nAChRs are involved in the acute effects of nicotine on contextual learning, these receptors appear to be involved in the effects of withdrawal from nicotine on contextual learning. Previous research suggests that β2 subunit-containing nAChRs are involved in some of the symptoms that characterize nicotine withdrawal, including impaired attention [138], increases in anxiety [139], writhing [140], and anhedonia [141]. In addition, a recent study from our lab has examined the involvement of nAChR subtypes in both spontaneous nicotine withdrawal-associated deficits and nAChR antagonist precipitated withdrawal-associated deficits in learning and memory. Precipitated withdrawal deficits in contextual fear conditioning were evident in mice treated chronically with systemic nicotine for 14 days following a pretraining intraperitoneal injection of DHβE but not MLA [111]. Similarly, β2 knockout mice failed to demonstrate nicotine withdrawal-associated deficits in contextual fear conditioning, while α7 knockout mice withdrawn from chronic nicotine administration demonstrated deficits in contextual fear conditioning. Taken together, these data suggest that alterations in α4β2* nAChRs underlie nicotine withdrawal-associated deficits in contextual fear conditioning. However, it is not clear if hippocampal α4β2* nAChRs are the critical population of α4β2* nAChRs through which chronic nicotine exposure and the subsequent removal of nicotine produces its impairing effect on learning and memory. Thus, the role of hippocampal α4β2* nAChRs in the effect of withdrawal from chronic nicotine on contextual fear conditioning was investigated.[3] Mice treated chronically with systemic nicotine or saline for 14 days received a pretraining bilateral infusion of DHβE into the dorsal hippocampus. Although intrahippocampal DHβE had no effect on contextual fear conditioning in mice treated chronically with systemic saline, intrahippocampal administration of the nAChR antagonist to mice treated chronically with systemic nicotine resulted in deficits in the task. These data suggest that dorsal hippocampal α4β2* nAChRs may be critically involved in nicotine withdrawal-associated deficits in contextual fear conditioning. Furthermore, these data suggest that behavioral tolerance to the enhancing effect of nicotine on contextual conditioning that is seen during chronic nicotine treatment and withdrawal-associated deficits in the task likely reflect alterations in dorsal hippocampal α4β2* nAChRs and/or related cell signaling.

Studies indicating that acute intrahippocampal nicotine enhances [76, 113 and 114] and withdrawal from intrahippocampal nicotine impairs[4] learning and memory suggest that the action of nicotine at hippocampal nAChRs is sufficient to alter associative learning processes. The data reviewed in this section extend these findings by suggesting that the action of nicotine at hippocampal α4β2* nAChRs is not only sufficient, but it is necessary for the effects of nicotine on learning and memory under systemic conditions. In other words, the enhancing effect of nicotine on learning and the impairing effect of nicotine withdrawal on learning requires the action of nicotine at hippocampal α4β2* nAChRs. Identification of nAChR subtypes that are involved in the effects of nicotine will aid in understanding if withdrawal is due to change in receptor function, changes in down-stream cell signaling cascades, or changes in both.

RECEPTOR-LEVEL CORRELATES THAT MAY UNDERLIE THE EFFECTS OF NICOTINE ON HIPPOCAMPUS-DEPENDENT LEARNING AND MEMORY

The effects of acute nicotine, chronic nicotine, and withdrawal from chronic nicotine on nAChR function and density have been described previously (see [122, 124, 142, 143] for reviews). Briefly, nAChRs can exist in three functional conformations: closed or inactive, open or active, and desensitized. Binding of agonists, such as endogenous acetylcholine and exogenous nicotine, to closed or inactive nAChRs induces a structural change that causes the ion channel to open. Selected ions, including calcium, enter the cell as a result of this change in the structural conformation of the nAChR, and neurotransmitter release and the activation of second messengers can result [see 144-148]. Following activation, agonist binding can induce a second conformational change, which leads to desensitization of the receptor. Desensitized receptors bind with higher affinity but are refractory to activation by agonists [143]. Desensitization can either be brief, as is the case with acute nicotine administration, or long-lasting, as is the case with chronic nicotine administration. This long-lasting nAChR desensitization may underlie the increase in nAChR density [116, 120, 149 but see 142] that is seen during and following chronic nicotine exposure [116, 150-159].

Research suggests that following a period of chronic nicotine exposure nAChRs can recover function (i.e., can be activated by agonist) in the absence of nicotine [160]. The combined effect of this functional recovery and chronic nicotine-associated increases in nAChR density that persist for up to 8 days in the absence of nicotine [152, 161, 162 and

[3]Davis JA, Gould TJ. Nicotine withdrawal-associated deficits in contextual fear conditioning are mediated by hippocampal α4β2 nAChRs. Annual Meeting of the Society for Neuroscience abstract in press, San Diego, CA.

[4]Davis JA, Gould TJ. Hippocampal involvement in the effects of acute, chronic, and withdrawal from chronic nicotine administration on contextual fear conditioning. Annual Meeting of the Society for Neuroscience 2006 abstract, Atlanta, GA.

see 142, 143 for reviews] is thought to underlie reported sensitized behavioral and physiological responses to nicotine during nicotine withdrawal [163-167]. Likewise, these nAChR-level alterations could underlie the aversive effects of nicotine withdrawal and the behavioral effects of nicotine that contribute to dependence [168].

Alterations in the function and number of nAChRs, specifically hippocampal DHβE-sensitive nAChRs, may contribute to the effects of acute nicotine, chronic nicotine, and withdrawal from chronic nicotine on learning and memory. It should be noted, however, that changes in receptor function associated with chronic nicotine treatment may not be the only factor contributing to the behavioral changes seen with chronic nicotine treatment. Specifically, a dissociation between the effects of chronic nicotine treatment on nAChR binding and tolerance has been demonstrated [169-171]. Tolerance for the acute effects of nicotine on Y-maze locomotor activity and rears was lost after 8 days, tolerance to the acute effects of nicotine on body temperature was lost after 12-16 days, and tolerance to the acute effects of nicotine on heart rate was lost after 20 days [170]. In contrast, nicotine binding returned to control levels after 8 days, and α-bungarotoxin binding (i.e., α7* nAChR binding) returned to control levels after only 4 days. Furthermore, the kinetics of nicotine administration altered nAChR binding and influenced the development of tolerance for the effects of nicotine on respiratory rate, acoustic startle response, Y-maze crosses and rears, heart rate, and body temperature; but the relationship between the timing of nicotine delivery and tolerance was opposite of the relationship between delivery timing and nAChR binding [171]. Specifically, mice that received chronic nicotine for 10 days *via* pulsed delivery showed greater tolerance but less extensive nAChR binding changes than mice that received an identical amount of chronic nicotine but received it continuously. Thus, long-term behavioral changes can be maintained independent of nAChR changes that occur with chronic nicotine treatment. It remains to be seen if the changes that underlie tolerance are the same changes that underlie withdrawal. Nonetheless, these findings suggest that alterations that extend beyond the level of nAChRs, including alterations in cell signaling, may contribute to the long-term effects of nicotine on learning and memory.

SECOND MESSENGER-LEVEL CORRELATES THAT MAY UNDERLIE THE EFFECTS OF NICOTINE ON LEARNING AND MEMORY

Although direct evidence supporting a role for alterations in hippocampal cell signaling molecules in the effects of nicotine on hippocampus-dependent learning is limited, recent evidence suggests that acute nicotine administration is associated with increased activation of second messenger signaling molecules and transcription factors, including protein kinase A, ERK, and CREB [98-105, 172-179], that are heavily involved in learning and memory [see 29-31 for reviews]. In addition, a recent study suggests that acute nicotine administration augments learning-related cell signaling in the hippocampus to enhance learning and memory [175]. The researchers demonstrated that systemic administration of a dose of SL327, a drug that inhibits activation of ERK, that did not impair contextual fear conditioning (i.e., a subthreshold dose) blocked the enhancing effect of acute nicotine administration on learning.

Chronic nicotine-associated tolerance and nicotine withdrawal-associated deficits in hippocampus-dependent learning and memory may be associated with concomitant alterations in hippocampal learning-related cell signaling as well. Although the effects of chronic nicotine and withdrawal from chronic nicotine administration on second messenger signaling and gene transcription are not well-studied, there is some evidence to support this hypothesis; in contrast to the effect of acute nicotine on CREB phosphorylation (i.e., acute nicotine-associated increase CREB activation; 178), chronic nicotine exposure may have little effect on phosphorylated CREB levels [180-182], and nicotine withdrawal may be associated with decreases in CREB activation [181, 182].

Like ERK [183-186], CREB has been shown to be critically involved in contextual fear conditioning [see 29, 187-189]. Thus, as tolerance develops for the effects of nicotine on cell signaling molecules and gene transcription factors involved in learning (such as ERK and CREB), tolerance may also develop for the effects of nicotine on learning. Likewise, nicotine withdrawal-associated alterations in behavior such as deficits in learning, which are opposite to the behavioral effects of acute nicotine administration, may reflect alterations in second-messenger signaling and gene transcription that are opposite to those seen with acute nicotine administration. Clearly, research that examines the relationship between changes in cell signaling and changes in learning and memory as nicotine administration transitions from acute to chronic to withdrawal is needed.

SUMMARY

Changes in learning and memory play a central role in nicotine addiction. The effects of nicotine can become associated with discrete cues and contextual cues that can lead to craving and drug-seeking/drug-taking behaviors [68, 69, 72-74]. In addition, nicotine exerts direct effects of learning that could support nicotine addiction. Previous research indicates that acute nicotine administration enhances, chronic nicotine administration has no effect, and withdrawal from chronic nicotine administration impairs hippocampus-dependent learning and memory [see 9 for review]. Such data suggest that the initial cognitive enhancing effects of nicotine may reinforce nicotine administration, and as tolerance develops, nicotine intake may be maintained to avoid withdrawal-associated cognitive deficits. In addition, individuals who are attempting to quit may begin to smoke again in an effort to ameliorate nicotine withdrawal-associated deficits in learning and memory.

The effects of nicotine on learning and memory are mediated by α4β2* nAChRs in the hippocampus [86, 87, 95 114][5] and may involve changes in cell signaling molecules that underlie long-term memory [98-105, 172-179]. Such data suggest that smoking cessation therapies that target α4β2* nAChRs may be efficacious at ameliorating nicotine withdrawal-associated learning and memory deficits and

[5]See also Davis JA, Gould TJ. Nicotine withdrawal-associated deficits in contextual fear conditioning are mediated by hippocampal α4β2 nAChRs. Annual Meeting of the Society for Neuroscience abstract in press, San Diego, CA.

ameliorating cue-elicited cravings. Indeed, early reports suggest that long-term cessation rates associated with the use of varenicline, a partial α4β2* nAChR agonist and full α7* nAChR agonist [190] that has recently been approved by the Federal Drug Administration for use as a smoking cessation therapy, are significantly greater than long-term cessation rates associated with bupriopion treatment (see [191] for review). Research that further elucidates the role of alterations in nAChRs and cell signaling in the effects of nicotine on learning, memory, and other processes should lead to the development of novel therapeutics for nicotine addiction.

Key Learning Objectives:

Many factors contribute to the development and maintenance of addiction. This review presents an overview of the role of learning and synaptic plasticity in nicotine addiction with emphasis on the behavioral changes that occur with nicotine administration and the underlying neural substrates that contribute to these changes.

Future Research Questions:

Does withdrawal from chronic nicotine produce alterations in learning and memory through changes in receptor function and/or changes in cell signaling cascades? Also, what therapeutic interventions will ameliorate nicotine withdrawal-associated disruption of learning and are these drugs equally effective for other withdrawal symptoms?

ACKNOWLEDGEMENTS

The authors would like to acknowledge grant support from the National Institute on Drug Abuse (DA017949 TG), National Institute on Alcohol Abuse and Alcoholism (DA017949 TG), and the National Cancer Institute (P5084718 PI: Caryn Lerman Ph.D) has supported some of the work referenced in this review. Jennifer Davis was supported by a NIH/NIDA predoctoral fellowship (DA021949).

REFERENCES

[1] World Health Organization. The world health report: 2003: shaping the future. (Monograph-W-HQ). Geneva: World Health Organization 2003; Retrieved March 14, 2005 from http://whqlibdoc.who.int/publications/2003/9241562439.pdf.

[2] American Cancer Society. Cancer prevention and early detection facts & figures 2007 (Publication No. 860007). Atlanta, GA: American Cancer Society 2007.

[3] Centers for Disease Control. Tobacco use among adults—United States, 2005. Morbidity and Mortality Weekly Report 2005; 55: 1145–1148. Retrieved April 21, 2007, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5542a1.htm.

[4] Lee CW, Kahende, J. Factors associated with successful smoking cessation in the United States, 2000. Am J Public Health 2007; 97: 1503-9.

[5] McIlVain H, Susman JL, Davis C, Gilbert C. Physician counseling for smoking cessation: is the glass half empty? J Fam Pract 1995; 40: 148-52.

[6] Baker TB, Brandon TH, Chassin L. Motivational influences on cigarette smoking. Annu Rev Psychol 2004; 55: 463-91.

[7] Kenny PJ, Markou A. Neurobiology of the nicotine withdrawal syndrome. Pharmacol Biochem Behav 2001; 70: 531-49.

[8] Picciotto MR. Common aspects of the action of nicotine and other drugs of abuse. Drug Alcohol Depend 1998; 51: 165-72.

[9] Gould TJ. Nicotine and hippocampus-dependent learning: Implications for addiction. Mol Neurobiol 2006; 34: 93-107.

[10] Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal. A replication and extension. Arch Gen Psychiatry 1991; 48: 52-9.

[11] Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol Psychiatry 2005; 57: 56-66.

[12] Kumari V, Gray JA. Smoking withdrawal, nicotine dependence and prepulse inhibition of the acoustic startle reflex. Psychopharmacology 1999; 141: 11-5.

[13] Paul RH, Brickman AM, Cohen RA, *et al*. Cognitive status of young and older cigarette smokers: data from the international brain database. J Clin Neurosci 2006; 13: 457-65.

[14] Snyder FR, Davis FC, Henningfield JE. The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 1989; 23: 259-66.

[15] Mendrek A, Monterosso J, Simon SL, *et al*. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. Addict Behav 2006; 31:833-44.

[16] Hyman SE. Addiction: a disease of learning and memory. Am J Psychiatry 2005; 162: 1414-22.

[17] Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. Neuron 2000; 25: 515-32.

[18] Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2001; 2: 695-703.

[19] Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: The role of reward-related learning and memory. Annu Rev Neurosci 2006; 29: 565-98.

[20] Kelley AE. Memory and addiction: Shared neural circuitry and molecular mechanisms. Neuron 2004; 44: 161-79.

[21] Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol 2002; 53: 606-17.

[22] Chiamulara C. Cue reactivity in nicotine and tobacco dependence: a "multiple-action" model of nicotine as a primary reinforcement and as an enhancer of the effects of smoking-associated stimuli. Brain Res Brain Res Rev 2005; 48: 74-97.

[23] Hogarth L, Duka T. Human nicotine conditioning requires explicit contingency knowledge: is addictive behavior cognitively mediated? Psychopharmacology 2006; 184: 553-66.

[24] Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev 1990; 97: 147-68.

[25] White NA. Addictive drugs as reinforcers: multiple partial actions on memory systems. Addiction 1996; 91: 921-49.

[26] Due DL, Huettel SA, Hall WG, Rubin DC. Activation of mesolimbic and visuospatial neural circuits elicited by smoking cues: evidence from functional magnetic resonance imaging. Am J Psychiatry 2002; 159: 954-60.

[27] Franklin TR, Wang Z, Wang J, *et al*. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: A perfusion fMRI study. Neuropsychopharmacology 2007; 32(11): 2301-9.

[28] Geier A, Mucha RF, Pauli P. Appetitive nature of drug cues confirmed with physiological measures in a model using pictures of smoking. Psychopharmacology 2000; 147: 306-13.

[29] Abel T, Lattal KM. Molecular mechanisms of memory acquisition, consolidation, and retrieval. Curr Opin Neurobiol 2001; 11: 180-87.

[30] Lattal KM, Abel T. Different requirements for protein synthesis in acquisition and extinction of spatial preferences and context-evoked fear. J Neurosci 2001; 21: 5773-80.

[31] Schafe GE, Nader K, Blair HT, Ledoux JE. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. Trends Neurosci 2001; 24: 540-46.

[32] LeSage MG, Burroughs D, Dugek M, Keyler DE, Pentel PR. Reinstatement of nicotine self-administration in rats by presentation of nicotine-paired stimuli, but not nicotine priming. Pharmacol Biochem Behav 2004; 79: 507-13.

[33] Caggiula AR, Donny EC, Chaudhri N, Perkins KA, Evans-Martin FF, Sved AF. Importance of nonpharmacological factors in nicotine self-administration. Physiol Behav 2002; 77: 683-7.

[34] Cohen C, Perrault G, Griebel G, Soubrie P. Nicotine-associated cues maintain nicotine-seeking behavior in rat several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR 141716). Neuropsychopharmacology 2005; 20: 145-55.

[35] Donny EC, Chaudhri N, Caggiula AR, *et al*. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. Psychopharmacology 2003; 169: 68-76.

[36] Lazev AB, Herzog TA, Brandon TH. Classical conditions of environmental cues to cigarette smoking. Exp Clin Psychopharmacol 1999; 7: 56-63.
[37] Bevins RA, Palmatier MI. Extending the role of associative learning processes in nicotine addiction. Behav Cogn Neurosci Rev 2004; 3*:* 143-58.
[38] Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. Science 1981; 214: 573-5.
[39] Caggiula AR, Donny EC, White AR, *et al*. Cue dependency of nicotine self-administration and smoking. Pharmacol Biochem Behav 2001; 70: 515-30.
[40] Le Foll B, Goldberg SR. Nicotine as a typical drug of abuse in experimental animals and humans. Psychopharmacology 2006; 184: 367-81.
[41] Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. Psychopharmacology 2006; 184: 353-66.
[42] Palmatier MI, Evans-Martin FF, Hoffman A, *et al*. Dissociating the primary reinforcing and reinforcement-enhancing effects of nicotine using rat self-administration paradigm with concurrently available drug and environmental reinforcers. Psychopharmacology 2006; 184: 391-400.
[43] Fudala PJ, Teoh KW, Iwamoto ET. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 1985; 22: 237-41.
[44] Grabus SD, Martin BR, Batman AM, Tyndale RF, Sellers E, Damaj MI. Nicotine physical dependence and tolerance in the mouse following chronic oral administration. Psychopharmacology 2004; 178: 183-92.
[45] Horan B, Smith M, Gardner EL, Lepore M, Ashby CR. (-)-Nicotine produces conditioned place preference in Lewis but not Fischer 344 rats. Synapse 1997; 26: 93-94.
[46] Walters CL, Brown S, Changeux J, Martin B, Damaj MI. The β2 but not α7 subunit of the nicotinic acetylcholine receptor is required for nicotine-conditioned place preference in mice. Psychopharmacology 2006; 184: 339-44.
[47] Liu X, Caggiula AR, Yee SK, Nobuta H, Poland RE, Pechnick RN. Reinstatment of nicotine-seeking behavior by drug-associated stimuli after extinction in rats. Psychopharmacology 2006; 184: 417-25.
[48] Liu X, Caggiula AR, Yee SK, *et al*. Mecamylamine attenuates cue-induced reinstatement of nicotine seeking behavior in rats. Neuropsychopharmacology 2007; 32: 710-8.
[49] Dols M, Willems B, van den Hout M, Bittoun R. Smokers can learn to influence their urge to smoke. Addict Behav 2000; 25: 103-8.
[50] Dols M, van den Hout M, Kindt M, Willems B. The urge to smoke depends on the expectation of smoking. Addiction 2002; 97: 87-93.
[51] Thewissen R, Snijders SJ, Havermans RC, van den Hout M, Jansen A. Renewal of cue-elicited urge to smoke: implications for cue exposure treatment. Behav Res Ther 2006; 44: 1441-9.
[52] Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol 2002; 53: 633-9.
[53] Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology 1998; 138: 217-30.
[54] Rezvani AH, Levin ED. Cognitive effects of nicotine. Biol Psychiatry 2001; 49: 258-67.
[55] Tinsley MR, Quinn JJ, Fanselow MS. The role of muscarinic and nicotinic cholinergic neurotransmission in aversive conditioning: Comparing Pavlovian fear conditioning and inhibitory avoidance. Learn Mem 2004; 11: 35-42.
[56] Nestler E.J. Molecular mechanisms of drug addiction. J Neurosci 1992; 12: 2439-50.
[57] Davis JA, James JR, Siegel SJ, Gould TJ. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. J Neurosci 2005; 25: 8708 – 13.
[58] Welzl H, Alessandri A, Oettinger R, Battig K. The effects of long-term nicotine treatment on locomotion, exploration and memory in young and old rats. Psychopharmacology 1988; 96: 317-23.
[59] Jarvis MJ. Why people smoke. BMJ 2004; 328: 277-79.
[60] Kleinman KM, Vaughn RL, Christ S. Effects of cigarette smoking and smoking deprivation on paired-associate learning of high and low meaningful nonsense syllables. Psychol Rep 1973; 32: 963-6.
[61] Laviolette SR, van der Kooy D. The neurobiology of nicotine addiction: bridging the gap from molecules to behavior. Nat Rev Neurosci 2004; 5: 55-65.
[62] Fagen ZM, Mansvelder HD, Keath JR, McGehee DS. Short- and long- term modulation of synaptic inputs to brain reward areas by nicotine. Ann N Y Acad Sci 2003; 1003: 185-95.
[63] Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol 2000; 393: 295-314.
[64] Ito R, Robbins TW, McNaughton BL, Everitt BJ. Selective excitotoxic lesions of the hippocampus and basolateral amygdala have dissociable effects on appetitive cue and place conditioning based on path integration in a novel Y-maze procedure. Eur J Neurosci 2006; 23: 3071-80.
[65] Rogers JL, See RE. Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. Neurobiol Learn Mem 2007; 87: 688-92.
[66] Stouffer EM, White NM. Roles of learning and motivation in preference behavior: mediation by entorhinal cortex, dorsal and ventral hippocampus. Hippocampus 2007; 17: 147-60.
[67] Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 1992; 99: 195-231.
[68] Black YD, Green-Jordan K, Eichenbaum HB, Kantak KM. Hippocampal memory system function and the regulation of cocaine self-administration behavior in rats. Behav Brain Res 2004; 151: 225-38.
[69] Fuchs RA, Evans KA, Ledford CC, *et al*. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 2005; 30: 296-309.
[70] See RE. Neural substrates of cocaine-cue associations that trigger relapse. Eur J Pharmacol 2005; 526: 140-6.
[71] Bouton ME, Bolles RC. Contextual control of the extinction of conditioned fear. Learn Motiv 1979; 10: 445-66.
[72] Alleweireldt AT, Weber SM, Neisenwander JL. Passive exposure to contextual discriminative stimulus reinstates cocaine-seeking behavior in rats. Pharmacol Biochem Behav 2001; 69: 555-60.
[73] Crombag HS, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. Neuropsychopharmacology 2002; 27: 1006-15.
[74] Crombag HS, Shaham Y. Renewal of drug-seeking by contextual cues after prolonged extinction in rats. Behav Neurosci 2002; 116: 169-73.
[75] Zironi I, Burattini C, Aicardi G, Janak PH. Context is a trigger for relapse to alcohol. Behav Brain Res 2006; 167: 150-5.
[76] Barros DM, RamireZ MR, Dos Reis EA, Izquierdo I. Participation of hippocampal nicotinic receptors in acquisition, consolidation and retrieval of memory for one trial inhibitory avoidance in rats. Neuroscience 2004; 126: 651-6.
[77] Bovet D, Bovet-Nitti F, Oliverio A. Effects of nicotine on avoidance conditioning of inbred strains of mice. Psychopharmacologia 1966; 10: 1-5.
[78] Brioni JD, Arneric SP. Nicotinic receptor agonists facilitate retention of avoidance training: participation of dopaminergic mechanisms. Behav Neural Biol 1993; 59: 57-62.
[79] Oliverio A. Effects of mecamylamine on avoidance conditioning and maze learning in mice. J Pharmacol Exp Ther 1966; 154: 350-6.
[80] Zarrindast M, Sadegh M, Shafaghi B. Effects of nicotine on memory retrieval in mice. Eur J Pharmacol 1996; 295: 1-6.
[81] Buccafusco JJ, Prendergast MA, Terry AV, Jackson WJ. Cognitive effects of nicotinic cholinergic receptor agonists in nonhuman primates. Drug Develop Res 1996; 38: 196-203.
[82] Elrod K, Buccafusco JJ, Jackson WJ. Nicotine enhances delayed matching-to-sample performance by primates. Life Sci 1988; 43: 277-87.
[83] Levin ED, Kaplan S, Boardman A. Acute nicotine interactions with nicotinic and muscarinic agonists: working memory and reference memory effects in the 16-arm radial maze. Behav Pharmacol 1997; 8: 236-42.
[84] Levin ED, Torry, D. Acute and chronic nicotine effects on working memory in aged rats. Psychopharmacology 1996; 123: 88-97.
[85] Socci DJ, Sanberg PR, Arendash GW. Nicotine enhances Morris water maze performance in young and aged rats. Neurobiol Aging 1995; 16: 857-60.

[86] Davis JA, Gould TJ. β2 subunit-containing nicotinic receptors mediate the enhancing effect of nicotine on trace cued fear conditioning in C57BL/6 mice. Psychopharmacology 2007; 190: 343-52.
[87] Davis JA, Gould TJ. The effects of DHBE and MLA on nicotine-induced enhancement of contextual fear conditioning. Psychopharmacology 2006; 184: 345-52.
[88] Davis JA, Porter J, Gould TJ. Nicotine enhances both foreground and background contextual fear conditioning. Neurosci Lett 2006; 394: 202-5.
[89] Feiro O, Gould TJ. The interactive effects of nicotinic and muscarinic cholinergic receptor inhibition on fear conditioning in young and aged C57BL/6 mice. Pharmacol Biochem Behav 2005; 80: 251-62.
[90] Gould TJ. Nicotine produces a within subject enhancement of contextual fear conditioning in C57BL/6 mice independent of sex. Integ Physio Behav Sci 2003: 38: 124-32.
[91] Gould TJ, Feiro O, Moore D. Nicotine enhances trace cued fear conditioning but not delay cued fear conditioning in C57BL/6 mice. Behav Brain Res 2004; 155: 167-73.
[92] Gould TJ, Higgins JS. Nicotine Enhances Contextual Fear Conditioning in C57BL/6J Mice at 1 and 7 Days Post-Training. Neurobiol Learn Mem 2003; 80: 147-57.
[93] Gould TJ, Lommock JA. Nicotine enhances contextual fear conditioning and ameliorates ethanol-induced deficits in contextual fear conditioning. Behav Neurosci 2003; 117: 1276-82.
[94] Gould TJ, Wehner JM. Nicotine enhancement of contextual fear conditioning. Behav Brain Res 1999; 102: 31-9.
[95] Wehner JM, Keller JJ, Keller AB, *et al.* Role of neuronal nicotinic receptors in the effects of nicotine and ethanol on contextual fear conditioning. Neuroscience 2004; 129: 11-24.
[96] Lynch MA. Long-term potentiation and memory. Physiol Rev 2004; 84: 87-136.
[97] Malenka RC, Nicoll RA. Long-term potentiation—a decade of progress? Science 1999; 285: 1870-974.
[98] Fujii S, Ji Z, Morita N, Sumikawa K. Acute and chronic nicotine exposure differentially facilitate the induction of LTP. Brain Res 1999; 846: 137-43.
[99] Fujii S, Ji Z, Sumikawa K. 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 2000; 286: 134-8.
[100] Fujii S, Jia Y, Yang A, Sumikawa K. Nicotine reverses GABAergic inhibition of long-term potentiation induction in the hippocampal CA1 region. Brain Res 2000; 863: 259-65.
[101] Fujii S, Sumikawa K. Acute and chronic nicotine exposure reverses age-related declines in the induction of long-term potentiation in the rat hippocampus. Brain Res 2001; 894: 347-53.
[102] Matsuyama S, Matsumoto A. 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 2003; 93: 180-7.
[103] Yamazaki Y, Hamaue N, Sumikawa K. Nicotine compensates for the loss of cholinergic function to enhance long-term potentiation. Brain Res 2002; 946: 148-52.
[104] He J, Deng CY, Chen RZ, Zhu XN, Yu JP. Long-term potentiation induced by nicotine in CA1 region of hippocampal slice is Ca(2+)-dependent. Acta Pharmacol Sin 2000; 21: 429-32.
[105] He J, Deng CY, Zhu XN, Yu JP, Chen RZ. Different synaptic mechanisms of long-term potentiation induced by nicotine and tetanic stimulation in hippocampal CA1 region of rats. Acta Pharmacol Sin 2003; 24: 398-402.
[106] Kim JJ, Rison RA, Fanselow MS. Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. Behav Neurosci 1993; 107: 1093-8.
[107] Logue SF, Paylor R, Wehner JM. Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. Behav Neurosci 1997; 111: 104-13.
[108] Phillips RG, Ledoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 1992; 106: 274-85.
[109] Fanselow MS. Contextual fear, gestalt memories, and the hippocampus. Behav Brain Res 2000; 110: 73-81.
[110] Maren S. Neurobiology of Pavolvian fear conditoning. Annu Rev Neurosci 2001; 24: 897-931.
[111] Portugal GS, Kenney JW, Gould TJ. β2 subunit containing acetylcholine receptors mediate nicotine withdrawal deficits in the acquisition of contextual fear conditioning. Neurobiol Learn Mem 2007, electronic publication ahead of press (June 19).
[112] Portugal GS, Gould TJ. Bupropion Dose-Dependently Reverses Nicotine Withdrawal Deficits in Contextual Fear Conditioning. Pharmacol Biochem Behav 2007; 88(2): 179-87.
[113] Sharifzadeh M, Tavasoli M, Naghdi N, Ghanbari A, Amini M, Roghani A. Post-training intrahippocampal infusion of nicotine prevents spatial memory retention deficits induced by the cyclooxygenase-2-specific inhibitor celecoxib in rats. J Neurochem 2005; 95: 1078-90.
[114] Davis JA, Kenny JW, Gould TJ. Hippocampal α4β2* nAChR involvement in the enhancing effect of acute nicotine on contextual fear conditioning. J Neurosci 2007; 27(40): 10870-7.
[115] Fenster CP, Rains MF, Noerager B, Quick MW, Lester RA. Influence of subunit composition on desensitization of neuronal acetylcholine receptors at low concentrations of nicotine. J Neurosci 1997; 17: 5747-59.
[116] Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. J Pharmacol Exp Ther 1983; 226: 817-25.
[117] Marks MJ, Rowell PP, Cao J, Grady SR, McCallum SE, Collins AC. Subsets of acetylcholine-stimulated $^{86}Rb^{+}$ efflux and [^{125}I]-epibatidine binding sites in C57BL/6 mouse brain are differentially affected by chronic nicotine treatment. Neuropharmacology 2004; 46: 1141-57.
[118] Olale F, Gerzanich V, Kurytatov A, Wang F, Lindstrom, J. Chronic nicotine exposure differentially affects the function of human α3, α4, and α7 neuronal nicotinic receptor subtypes. J Pharmacol Exp Ther 1997; 283: 675-83.
[119] Peng X, Gerzanich V, Anand R, Wang F, Lindstron J. Chronic nicotine treatment up-regulates α3 and α7 acetylcholine receptor subtypes expressed by the human neuroblastoma cell line SH-SY5Y. Mol Pharmacol 1997; 51: 776-84.
[120] Schwartz RD, Kellar KJ. *In vivo* regulation of [^{3}H] acetylcholine recognition sites in brain by nicotinic cholinergic drugs. J Neurochem 1985; 45: 427-33.
[121] Wooltorton JR, Pidoplichko VI, Broide RS, Dani JA. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci 2003; 23: 3176-85.
[122] Decker MW, Brioni JD, Bannon AW, Arneric SP. Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics. Life Sci 1995; 56: 545-70.
[123] Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol 2003; 146: 1-46.
[124] Jones S, Sudweeks S, Yakel JL. Nicotinic receptors in the brain: correlating physiology with function. Trends Neurosci 1999; 22: 555-61.
[125] Mcgehee DS. Molecular diversity of neuronal nicotinic acetylcholine receptors. Ann N Y Acad Sci 1999; 868: 565-77.
[126] Couturier S, Bertrand D, Matter J, *et al*. A neuronal nicotinic acetylcholine receptor subunit (α7) is developmentally regulated and forms a homo-oligomeric channel blocked by α-BTX. Neuron 1990; 5: 847-56.
[127] Flores CM, Rogers SW, Pabreza LA, Wolfe BB, Kellar KJ. A subtype of nicotinic cholinergic receptor in rat brain is composed of alpha 4 and beta 2 subunits and is up-regulated by chronic nicotine treatment. Mol Pharmacol 1992; 41: 31-7.
[128] Perry DC, Xiao Y, Nguyen HN, Musachio JL, Davila-Garcia MI, Kellar KJ. Measuring nicotinic receptors with characteristics of A4B2, A3B2, and A3B4 subtypes in rat tissues by autoradiography. J Neurochem 2002; 82: 468-81.
[129] Seguela P, Wadiche J, Dineley-Miller K, Dani JA, Patrick JW. Molecular cloning, functional properties, and distribution of rat brain α7: a nicotinic cation channel highly permeable to calcium. J Neurosci 1993; 13: 596-604.
[130] Wada E, Wada K, Boulter J, *et al*. Distribution of alpha2, alpha3, alpha4, and beta2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J Comp Neurol 1988; 284: 314-35.
[131] Alkondon M, Albuquerque EX. Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons. I. Pharmacological and func-

tional evidence for distinct structural subtypes. J Pharmacol Exp Ther 1993; 265: 1455-73.
[132] Ramirez-Latorre J, Crabtree G, Turner J, Role L. In Arneric SP, Brioni JD Eds., Neuronal nicotinic receptors: Pharmacology and therapeutic opportunities. New York, NY: Wiley-Liss 1998; 43-64.
[133] Dominguez del Toro E, Juiz JM, Peng X, Lindstrom J, Criado M. Immunocytochemical localization of the alpha 7 subunit of the nicotinic acetylcholine receptor in the rat central nervous system. J Comp Neurol 1994; 15: 325-42.
[134] Picciotto M, Zoli M, Lena C, *et al*. Abnormal avoidance learning in mice lacking functional high-affinity nicotine receptor in the brain. Nature 1995; 374: 65-7.
[135] Caldarone BJ, Duman CH, Picciotto MR. Fear conditioning and latent inhibition in mice lacking the high affinity subclass of nicotinic acetylcholine receptors in the brain. Neurpharmacology 2000; 39: 2779-84.
[136] Nott A, Levin ED. Dorsal hippocampal alpha7 and alpha4beta2 nicotinic receptors and memory. Brain Res 2006; 1081: 72-8.
[137] Paylor R, Nguyen M, Crawley JN, Patrick J, Beaudet A, Orr-Urtreger A. α7 nicotinic receptor subunits are not necessary for hippocampal-dependent learning or sensorimotor gating: A behavioral characterization of Acra7-deficient mice. Neurobiol Learn Mem 1998; 5: 302-16.
[138] Shoaib M, Bizarro L. Deficits in a sustained attention task following nicotine withdrawal in rats. Psychopharmacology 2005; 178: 211-22.
[139] Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther 2003; 307: 526-34.
[140] Malin DH, Lake JR, Upchurch TP, Shenoi M, Rajan N, Schweinle WE. Nicotine abstinence syndrome precipitated by the competitive nicotinic antagonist dihydro-beta-erythroidine. Pharmacol Biochem Behav 1998; 60: 609-13.
[141] Bruijnzeel AW, Markou, A. Adaptations in cholinergic transmission in the ventral tegmental area associated with the affective signs of nicotine withdrawal in rats. Neuropharmacology 2004; 47: 572-9.
[142] Gentry CL, Lukas RJ. Regulation of nicotinic acetylcholine receptor numbers and function by chronic nicotine exposure. Curr Drug Targets CNS Neurol Disord 2002; 1: 359-85.
[143] Marks MJ. In Arneric SP, Brioni JD Eds., Neuronal nicotinic receptors: Pharmacology and therapeutic opportunities. New York, NY: Wiley-Liss 1998; 65-80.
[144] Dajas-Bailador FA, Soliakov L, Wonnacott S. Nicotine activates the extracellular signal-regulated kinase ½ *via* the α7 nicotinic acetylcholine receptor and protein kinase A, in SH-SY5Y cells and hippocampal neurones. J Neurochem 2002; 80: 520-30.
[145] Dajas-Bailador F, Wonnacott S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. Trends Pharmacol Sci 2004; 25: 317-24.
[146] Kaiser S, Wonnacott S. In Arneric SP, Brioni JD Eds., Neuronal nicotinic receptors: Pharmacology and therapeutic opportunities. New York, NY: Wiley-Liss 1998; 141-60.
[147] Wonnacott S. Presynaptic nicotinic ACh receptors. Trends Neurosci 1997; 20: 92-8.
[148] Wonnacott S, Irons J, Rapier C, Thorne B, Lunt GG. Presynaptic modulation of transmitter release by nicotinic receptors. Prog Brain Res 1989; 79: 157-63.
[149] Fenster CP, Whitworth TL, Sheffield EB, Quick MW, Lester RA. Upregulation of surface α4β2 nicotinic receptors is initiated by receptor desensitization after chronic exposure to nicotine. J Neurosci 1999; 19: 4804-14.
[150] Collins AC, Luo Y, Selvaag S, Marks MJ. Sensitivity to nicotine and brain nicotinic receptors are altered by chronic nicotine and mecamylamine infusion. J Pharmacol Exp Ther 1994; 271: 125-33.
[151] Collins AC, Marks MJ. Chronic nicotine exposure and brain nicotinic receptors: influence of genetic factors. Prog Brain Res 1989; 79: 137-46.
[152] Collins AC, Romm E, Wehner JM. Nicotine tolerance: an analysis of the time course of its development and loss in the rat. Psychopharmacology 1988; 96: 7-14.
[153] Marks MJ, Campbell SM, Romm E, Collins AC. Genotype influences the development of tolerance to nicotine in the mouse. J Pharmacol Exp Ther 1991; 259: 392-402.
[154] Nguyen HN, Rasmussen BA, Perry DC. Subtype-selective upregulation by chronic nicotine of high affinity nicotinic receptors in rat brain demonstrated by receptor autoradiography. J Pharmacol Exp Ther 2003; 307: 1090-7.
[155] Pauly JR, Marks MJ, Gross SD, Collins AC. An autoradiographic analysis of cholinergic receptors in mouse brain after chronic nicotine treatment. J Pharmacol Exp Ther 1991; 258: 1127-36.
[156] Pauly JR, Marks MJ, Robinson SF, van de Kamp JL, Collins AC. Chronic nicotine and mecamylamine treatment increase brain nicotinic receptor binding without changing A4 or B2 mRNA levels. J Pharmacol Exp Ther 1996; 278: 361-9.
[157] Peng X, Gerzanich V, Anand R, Whiting PJ, Lindstrom J. Nicotine-induced in crease in neuronal nicotinic receptors results from a decrease in the rate of receptor turnover. J Pharmacol Exp Ther 1994; 46: 523-30.
[158] Perry DC, Davila-Garcia MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. J Pharmacol Exp Ther 1999; 289: 1545-52.
[159] Whiteaker P, Sharples CGV, Wonnacott S. Agonist-induced upregulation of α4β2 nicotinic acetylcholine receptors in M10 cells: pharmacological and spatial definition. Mol Pharmacol 1998; 53: 950-62.
[160] Marks MJ, Stitzel JA, Collins AC. Time course study of the effects of chronic nicotine infusion on drug response and brain receptors. J Pharmacol Exp Ther 1985; 235: 619-28.
[161] Gentry CL, Wilkins LH, Lukas RJ. Effects of prolonged nicotinic ligand exposure on function of heterologously expressed, human α4β2- and α4β4-nicotinic acetylcholine receptors. J Pharmacol Exp Ther 2003; 304: 206-16.
[162] Pietila K, Lahde T, Attila M, Ahtee L, Nordberg A. Regulation of nicotinic receptors in the brain of mice withdrawn from chronic oral nicotine treatment. Naunyn-Schmiedeberg's Arch Pharmacol 1998; 357: 176-82.
[163] Arnold HM, Nelson CL, Sarter M, Bruno JP. Sensitization of cortical acetylcholine release by repeated administration of nicotine in rats. Psychopharmacology 2003; 165: 346-58.
[164] Balfour DJK, Benwell MEM, Birrell CE, Kelly RJ, Al-Aloul M. Sensitization of the mesoaccubens dopamine response to nicotine. Pharmacol Biochem Behav 1998; 59: 1021-30.
[165] Domino EF. Nicotine induced behavioral locomotor sensitization. Prog Neuro-Psychopharmacol Biol Psychiatry 2000; 25: 59-71.
[166] Kempsill FEG, Pratt JA. Mecamylamine but not the α7 receptor antagonist α-bungarotoxin blocks sensitization to the locomotor stimulant effects of nicotine. Br J Pharmacol 2000; 131: 997-1003.
[167] Shim I, Kim H, Kim Y, *et al*. Role of nitric oxide synthase inhibitors and NMDA receptor antagonist in nicotine-induced behavioral sensitization in the rat. Eur J Pharmacol 2002; 443: 119-24.
[168] Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron 1996; 16: 905-8.
[169] Marks MJ, Collins AC. Tolerance, cross-tolerance, and receptors after chronic nicotine or oxotremorine. Pharmacol Biochem Behav 1985; 22: 283-91.
[170] Marks MJ, Stitzel JA, Collins AC. Time course study of the effects of chronic nicotine infusion on drug response and brain receptors. J Pharmacol Exp Ther 1985; 235: 619-28.
[171] Marks MJ, Romm, E, Collins AC. Mouse brain ATPase activities after chronic nicotine infusion. Biochem Pharmacol 1987; 36: 3318-20.
[172] Chang KT, Berg DK. Voltage-gated channels block nicotinic regulation of CREB phosphorylation and gene expression in neurons. Neuron 2001; 32: 855-65.
[173] Hu M, Liu QL, Chang KT, Berg DK. Nicotinic regulation of CREB activation in hippocampal neurons by glutamatergic and nonglutamatergic pathways. Mol Cell Neurosci 2002; 21: 616-25.
[174] Nakayama H, Numakawa T, Ikeuchi T, Hatanaka H. Nicotine-induced phosphorylation of extracellular signal-regulated protein kinase and creb in pc12h cells. J Neurochem 2001; 79: 489-98.
[175] Raybuck JR, Gould TJ. Extracellular signal-regulated kinase involvement in the enhancement of contextual fear conditioning by nicotine. Behav Neurosci 2007; 121(5): 1119-24.
[176] Tang K, Wu H, Mahata SK, O'Connor DT. A crucial role for the mitogen-activated protein kinase pathway in nicotinic cholinergic signaling to secretory protein transcription in pheochromocytoma cells. Mol Pharmacol 1998; 54: 59-69.
[177] Valjent E, Pages C, Herve D, Girault J, Caboche J. Addictive and non-addictive drugs induce distinct and specific patterns of ERK activation in mouse brain. European J Neurosci 2004; 19: 1826-36.

[178] Walters CL, Cleck JN, Kuo Y, Blendy JA. μ-Opioid receptor and CREB activation are required for nicotine reward. Neuron 2005; 46: 933-43.

[179] Wang J, Chen Y, Zhu X, Chen R. 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 2005; 22: 685-90.

[180] Brunzell DH, Russell DS, Picciotto MR. *In vivo* nicotine treatment regulates mesocroticolimbic CREB and ERK signaling in C57Bl/6J mice. J Neurochem 2003; 84: 1431-41.

[181] Pandey Sc, Roy A, Xu T, Mittal N. Effects of protracted nicotine exposure and withdrawal on the expression and phosphorylation of the creb gene transcription factor in rat brain. J Neurochem 2001; 77: 943-52.

[182] Pluzarev O, Pandey SC. Modulation of CREB expression and phosphorylation in the rat nucleus accumbens during nicotine exposure and withdrawal. J Neurosci Res 2004; 77: 884-91.

[183] Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. The MAPK cascade is required for mammalian associative learning. Nat Neurosci 1998; 1: 602-9.

[184] Selcher JC, Atkins CM, Trzaskos JM, Paylor R, Sweatt JD. A necessity for MAP kinase activation in mammalian spatial learning. Learn Mem 1999; 6: 478-90.

[185] Sweatt JD. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. J Neurochem 2001; 76: 1-10.

[186] Sweatt JD. Mitogen-activated protein kinases in synaptic plasticity and memory. Curr Opin Neurobiol 2004; 14: 311-7.

[187] Abel T, Kandel E. Positive and negative regulatory mechanisms that mediate long-term memory storage. Brain Res Brain Res Rev 1998; 26: 360-78.

[188] Adams JP, Sweatt JD. Molecular psychology: roles for the ERK MAP kinase cascade in memory. Annu Rev Pharmacol Toxicol 2002; 42: 135-63.

[189] Selcher JC, Weeber EJ, Varga AW, Sweatt JD, Swank M. Protein kinase signal transduction cascades in mammalian associative conditioning. Neuroscientist 2002; 8: 122-31.

[190] Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol 2006; 70:801-5.

[191] Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochran Database Syst Rev 2007; 2: 1-25.

Received: August 5, 2007 Revised: August 31, 2007 Accepted: September 1, 2007