December 2004

Acetylcholine: II. Nicotinic Receptors

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CHAPTER 2.4

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Abstract

The nicotinic cholinergic system has been widely implicated in mediating learning and/or memory processes in human and nonhuman animals. This chapter highlights various areas of basic research in which stimulation or blockade of nicotinic acetylcholine receptors (nAChRs) has been shown to affect an animals performance in a variety of tasks thought to measure learning and memory. For example, under certain conditions, stimulation of nAChRs by nicotine (or other nAChRs agonists) can enhance working memory of primates as measured in a delayed matching-to-sample task. Attentional processes are also improved in rats as indexed by a five-choice serial reaction time task. Further, recent research suggests that stimulation of nAChRs by nicotine likely enhances the incentive salience of stimuli. We elaborate on a model by which this enhancement might occur and suggest that the role of this incentive mechanism in relation to learning and memory processes requires more empirical attention. Finally, there appears to be overlap in the processes by which nAChRs affect learning and memory. That is, enhanced incentive salience might be responsible for the increased attentional effects of nicotine, or vice versa. Subsequent research needs to refine the behavioral techniques so as better dissociate, if required, these mechanisms.

Introduction

A survey of the neuropharmacology literature would likely leave even the most critical individual convinced that nicotinic acetylcholine receptors (nAChRs) are involved in learning and/ or memory processes in human and nonhuman animals. For example, in humans nAChRs have been implicated in memory and learning difficulties displayed by patients suffering from Alzheimer's disease[66] and attention deficit disorder.[58] In rodent and nonhuman primate models, manipulation of nAChRs can alter performance in such learning tasks as radial-arm maze,[49,52,53,65] Morris water maze,[1,26] T-maze,[6] delayed matching[13] and nonmatching to sample,[38] delayed matching-to-position,[31] 5-choice serial reaction time,[11,41,64] environmental familiarization,[9] passive avoidance,[28,74] signal detection,[14] latent inhibition,[79] "learned helplessness",[36] and context conditioning.[40] In the past decade or so, there have been several thought-provoking reviews on the role of nAChRs in learning, cognition, and memory.[18,56,78] We encourage readers interested in this aspect of nicotinic receptor functioning to seek these other reviews because of the vastness of the relevant literature and the differences in emphasis between reviews—including the present review.

Neuronal nAChRs

Before any detailed discussion of the functional role of nAChRs in learning and memory processes, it may be helpful to provide a brief overview of the main subtypes of neuronal nAChRs and their neuroanatomical localization within the central nervous system (CNS). For a comprehensive review of brain nAChRs we refer the reader to Changeux *et al.*.[18]

Published in *From Messengers to Molecules: Memories Are Made of These,* edited by Gernot Riedel and Bettina Platt. Georgetown, TX (Landes Bioscience/Eurekah.com, 2003), pp. 113–124.

Table 1. Distribution of cholinergic neurons in the CNS

Descriptor	CNS Localization	Projection Areas
Ch1	medial septal nucleus	hippocampal complex, limbic cortex
Ch2	ventral nucleus of the diagonal band	hippocampal complex, limbic cortex
Ch3	horizontal limb nucleus of the diagonal band, magnocellular preoptic area	olfactory bulbs, limbic cortex, amygdala
Ch4	nucleus basalis of Meynert	amygdala, neocortex
Ch5, Ch6	pedunculopontine tegmental nucleus, laterodorsal tegmental nucleus, central gray, locus coeruleus	thalamus, substantia nigra (ventral tegmental area and pars compacta), reticular formation, locus coeruleus, cingulate gyrus, subicular cortices, medial prefrontal cortex
Ch7	medial habenula	interpeduncular nucleus
Ch8	parabigeminal nucleus	superior colliculus
Striatal	nucleus accumbens, olfactory tubercle, caudate, putamen, island of Calleja	local interneurons
Hypothalamic	hypothalamus	local interneurons, neocortex

Based on refs. 34, 62,63,98.

Subtypes

Nicotinic acetylcholine receptors are ligand-gated ion channels. This receptor is composed of five polypeptide subunits that form a barrel-like structure around a central ion channel.[21] In contrast to nAChRs located in the periphery which are composed of α1, β1, δ, ε, γ subunits, the standard configuration of the neuronal nAChRs include combinations of α and β sub-units. However, α7, α8, and α9 subunits can also form functional nAChRs that consist of a single subunit type.[25] Presently, the subunits α2–α7 and β2–β4 have been identified in the human brain and the distribution of these subunits in the human brain are presently being examined (see ref. 71 for a review of the nAChRs in the human brain). As in other receptor systems, much more work has examined the distribution of nAChR subunits in the rodent brain. In rodent models, the α3, α7, β2 subunits, and to a lesser extent the α4 subunit are expressed in the hippocampus (see ref. 73). The α2, α4, α5, α7, β2, and β4 subunits have been identified in the interpeduncular nucleus, and expression of the α3, α4, α7, and β2 subunits have been reported in the amygdala.[89] For a more detailed description of the distribution of the various subunits see Arneric *et al.*[2] and Shacka and Robinson.[89] Most of the neuronal nAChRs contain α4β2 or α7 subunits[37,90,94,99] and these are the subunits that have been most commonly studied in learning and memory tasks (see later). Although, this chapter focuses on the contribution of central nAChR processes in learning and memory, the role of nAChRs located in the peripheral nervous system should not be ignored (see ref. 89 for discussion of peripheral nAChRs).

Localization

Acetylcholine (ACh) is the endogenous transmitter substance that binds to functional nAChRs. Much of the research localizing these ACh-utilizing (cholinergic) neurons in the central nervous system has employed immunohistochemistry staining for choline acetyltransferase (ChAT); an enzyme required

for synthesis of ACh. Table 1 provides a summary of the CNS localization of major clusters of ChAT-containing neurons in mammals. Also, included in (Table 1) are some of the notable brain regions that receive projections from these cholinergic cells. The "Ch" nomenclature allows for simpler designation of diffuse collections of cholinergic neurons.[62,95] For example, Ch3 is located in the basal forebrain and includes neurons in the horizontal limb nucleus of the diagonal band and magnocellular preoptic area of the hypothalamus. We will reference back to this table when discussing the functional importance of nAChRs. For example, cholinergic input from Chl may affect learning by modulating α7* nAChRs in the hippocampus (see later). Because a comprehensive review of the cholinergic system is tangential to our goal, we refer the reader to the following reports for a more detailed discussion of the cholinergic system: Mesulam (refs. 62,63) and Woolf (ref. 98).

Memory

Manipulation of nAChRs has been shown to affect performance in a variety of tasks that assess memory functioning. In nonhuman animals, a majority of this work has been conducted in tasks designed to assess working memory processes. Working memory is defined by Feldman *et al.*.[34] as "encoding of task-specific information over short periods of time (e.g., within a single trial or test session)" (p. 272). The delayed matching-to-sample (DMTS) task is a commonly used preparation for assessing working memory. Briefly, in this task an animal is presented with a "sample" stimulus. Following a delay, the animal is presented with the sample stimulus and one or more novel stimuli. During this choice test, the animal is rewarded for choosing the sample stimulus. Thus, working memory processes are recruited to encode the information of the sample stimulus in order to make a correct response during the choice test. That is, working memory allows the animal to discriminate between the sample stimulus and the other stimuli.

The DMTS task has been widely used to examine the role of nAChRs. For example, Buccafusco *et al.*.[13] trained mature pig-tailed and rhesus monkeys on the DMTS task using colored lights as the stimuli. After acquisition training, the monkeys were tested at 4 different delays: zero, short, medium, and long. At the zero delay, the choice test occurred immediately following the presentation of the sample stimulus. The other delays were adjusted for each monkey's skill level; on average the short delay was 10.6 sec, the medium delay 39.4 sec, and the long delay 79.4 sec. Presumably, lengthening the delay impairs performance in this task because of the limited capacity of working memory processes.[31] Indeed, performance ranged from 97% correct after the zero delay to 58% correct after the long delay. In order to assess if stimulation of the nicotinic receptors could enhance working memory performance, the animals were administered ABT-418, a nAChR agonist (i.e., cholinergic channel activator). ABT-418 did not affect performance at the zero, short, or medium delays. However, at the long delay, DMTS performance was enhanced by treatment with ABT-418. After a washout period, all animals were tested with nicotine, an agonist at nAChRs with a high affinity for α4β2*.[20] Similar to ABT-418, nicotine enhanced performance only at the longest delay.

The inability of nAChR agonists to improve performance in the DMTS task at the shorter delays likely indicates that performance was near optimal levels at the shorter delays, thus making an improvement difficult to observe. However, improvement at the long delay suggests that stimulation of the nAChRs affected memory processes when strained. Recall that at the long delay performance was impaired (58% correct versus 97% correct after no delay). As mentioned earlier, impaired performance in this task after long delays is taken to suggest a disturbance in the capacity of working memory.[31] Thus, one possibility for the enhancement in performance is that the agonists stimulated working memory processes by enhancing the capacity to store the information of the sample stimuli. Given that a major component of working memory tasks involve attention,[12] another tenable and related possibility, is that attentional processes were enhanced such that the neural representation of the sample stimulus was stored/encoded more efficiently. Indeed, stimulation of nAChRs has been shown to enhance attentional processes (see later).

Further, there is a wealth of research examining the role of nAChRs in mediating performance in other tasks that include a working memory component. For example. Levin *et al.* .[53-55] has repeatedly found that chronic nicotine treatment enhances performance in a win-shift version of a radial arm maze. In this particular version of the task, the arms of the maze are baited and entries into arms that had been previously visited are scored as errors. The number of errors is taken as a measure of working memory function given that the rat must encode the information about the location of visited arms. Similar to chronic nicotine, AR-R17779, an agonist for the α7 subunit, enhances performance in this task.[57] Further, Felix and Levin[35] found that methyllycaconitine (MLA), an antagonist specific for the α7 subunit, or dihydro-β-erythroidine (DHBE), an antagonist with affinity for the α4β2* nAChR, infused into the ventral hippocampus impaired performance in the win-shift version of the radial-arm maze. This impairment suggests a role for hippocampal α4β2* and α7* nAChRs in working memory processes.

Interestingly, the greatest performance improvements resulting from stimulation of nAChRs are commonly reported in tasks that require effortful processing[38,84] or in tasks in which a deficit is produced.[29,56] For example, in the DMTS task described earlier, enhanced performance was not observed until the delay induced a severe deficit in performance. Similar findings have been reported using a novel-object detection task (also referred to as object recognition). In that task, a rat is presented with two identical sample objects. After a delay, the rat is presented with a novel object and one of the previously experienced objects. Rats display a tendency to interact more with the novel object than the familiar object when the delay is 1 h (i.e., delayed nonmatching-to-sample; see refs. 7 and 33). However, Puma *et al.*.[77] found that after a 24 h delay rats did not discriminate between the objects (i.e., equal time with the novel and familiar object). Administration of nicotine after exposure to the sample objects reversed this "deficit;" rats spent more time interacting with the novel object during the test that occurred 24 h later. Presumably, stimulation of the nAChRs enhanced the retention (consolidation) of the information about the sample objects during the long delay.[77] Nicotine has also been reported to enhance retention in a passive avoidance task.[74] Interestingly, in that study, mice lacking the β2 subunit of the nAChR did not show the nicotine-induced enhancement in retention, suggesting a role for this subunit in retention processes (e.g., consolidation, encoding, etc.).

Deficits in performance induced by lesions have also been reversed by nAChR stimulation. For example. Decker *et al.*.[29] found that lesions of the septal area, which reduced cholinergic input to the hippocampus (see Table 1), induced an impairment in a spatial discrimination version of a Morris water maze task. Administration of ABT-418 reversed the lesion-induced deficit, but had no effect on intact controls. Interestingly, this drug was subsequently tested by Potter *et al.*.[76] in patients with early to moderate Alzheimer's Disease, a disease which is accompanied by memory impairments and degeneration of the cholinergic system. ABT-418 treated patients tested on the Selective Reminding Task had improved recall across a 6 h testing period.

Interestingly, stimulation of nAChRs does not appear to affect performance in tasks that involve reference memory (i.e., use of the same information across trials).[12] For example, administration ofSIB-1553A, a β4* nAChR agonist, did not affect performance in mice that were trained to discriminate between a baited and unbaked arm of a T-maze.[12] Similarly, Levin *et al.*.[55] found that chronic nicotine treatment did not affect performance in a 16-arm radial maze in which specific arms were repeatedly unbaked. Further, Granon *et al.*.[38] reported that antagonism of nAChR by administration of neuronal bungarotoxin (NBT) did not affect performance in a reference memory component of a T-maze task; NBT, however, impaired working memory. Notably, mecamylamine, a noncompetitive nAChR antagonist, infused into the hippocampus did not affect reference memory, but impaired working memory.[67] This result suggests that nAChRs in the hippocampus are involved in mediating working memory, but not reference memory processes.

There clearly exists a wealth of research examining the role of nAChRs in mediating performance in a variety of tasks. Stimulation of nAChRs generally appear to enhance performance in working memory tasks and tasks that involve retention of information across a delay. Further, nAChR processes in work-

ing memory and retention (consolidation) mechanisms appear to be especially important in restoring performance induced by degeneration of the cholinergic system, whether the deficit is naturally occurring (i.e., aging) or induced by a lesion. From our reading of the literature, an important factor that may contribute to this restoration includes alterations in attentional processes mediated by nAChRs (see following section). Presumably, increasing attention to specific stimuli would result in better encoding of the information. In turn, this information would be neurally retained more effectively and be more readily available for future use. Further, in a later section (Rewarding/Incentive Effects), we propose another mechanism that may contribute to the enhanced performance observed with nicotinic receptor stimulation.

Attention

The cholinergic system has been implicated in mediating attentional processes in humans and nonhuman animals.[11,50,59,64,85,96] For example, in human studies, smoking a cigarette (e.g., nicotine administration) before presentation of a word list improved the number of words correctly recalled during a later test.[83,96] Specifically, Warburton *et al.*. found that more words from the latter part of the list were recalled; this pattern was consistent with an attentional explanation to the extent that attention diminishes towards the latter part of the list. Similarly, Rusted and Eaton-Williams[83] found that nicotine-induced accuracy improvements in word recall was related to the length of the word list. That is, a greater improvement was observed after presentation of a 30-item word list, than a 10-item word list. Nicotine delivered by a transdermal patch has also been shown to enhance performance in a Random Letter Generation task (e.g., participants required to name letters of the alphabet in a random order) and a Stroop test (e.g., participants required to read the ink color of color words), presumably by enhancing attentional processes.[59]

Nonhuman animal studies have also focused on nAChR involvement in attentional processes. The five-choice serial reaction time (5-CSRT) task has been used in rodents to assess the role of various nicotinic agonists and antagonists in attentional processes. Commonly, the apparatus used for this task includes a wall with five distinct holes, each with a light at the rear of the hole. During training, one of the five holes is illuminated for a brief duration. A correct response is registered for nose pokes during the period that the light is illuminated or for a fixed interval after the offset of the light. Daily training sessions usually include about 100 trials (i.e., random light illuminations). Thus, accurate performance in this task involves sustained attention and vigilance throughout the entire session.

Mirza and Stolerman[64] found that increasing the time between each light presentation resulted in a performance decrement, likely because prolonged vigilance was necessary to maintain correct responding. Nicotine administration reversed this deficit suggesting that attentional processes were enhanced. Interestingly, shortening the duration of the stimulus illumination (i.e., weakening the signal strength), decreased correct responding, and increased the latency to make a response.[11] According to the authors, this data pattern indicates that information processing, not necessarily attentional processing, is impaired. Under these conditions, nicotine administration did not enhance correct responding. Together these results suggest that stimulation of nAChRs by nicotine can enhance attentional processes, but may not necessarily affect informational processing (see ref. 92 for a review of the effects of nicotine in the 5-CSRT task). Further, using the short duration light stimulus, Blondel *et al.*[11] replicated the findings of Mirza and Stolerman[64] in that nicotine administration did not affect the number of correct responses. However, the authors did find that nicotine decreased the latency to make a correct response and increased anticipatory responses.

To further assess the role of the specific subunits of the nicotinic receptor that may contribute to attentional processes, Grottick and Higgins[41] assessed various compounds in rats that had failed to meet criterion during 5-CSRT task training. Presumably, attentional/vigilance processes in these rats were slightly impaired given that they had failed to meet the predetermined criterion. Rats were administered nicotine, AR-R 17779 (an α7* agonist), or SIB 1765F (an α4β2* agonist). Both nicotine and SIB 1765F improved

performance by increasing correct responding and enhancing reaction time. In contrast, AR-R 17779 did not affect correct responding. This data pattern was taken to suggest involvement of the α4β2, but not the α7 subunits, in mediating increased attention/vigilance. Additionally, SIB-1553A, a β4* nAChR agonist, had no effect on correct responding in the 5-CSRT task in aged rats, whereas performance in aged rats was enhanced by nicotine administration.[43] Taken together this work suggests that the β4* nAChR is not involved in attentional processes as measured in a 5-CSRT task.

In sum, performance on tasks designed to measure attention processes can be enhanced by stimulation of nicotinic receptors. Specifically, the α4 and β2 subunits appear to contribute to this enhancing effect. Notably, researchers have begun to examine the feasibility of using nAChR compounds as potential therapeutic agents for attention deficit/hyperactivity disorder (ADHD). Nicotine delivered by a transdermal patch to adults with ADHD showed some effect in aiding attentional processes;[58] however, further research in this area is required.

Rewarding/Incentive Effects

The nAChR agonist nicotine acts on dopaminergic pathways (see Fig. 1) implicated in the rewarding or the incentive-motivational effects of stimuli such as food, play, or copulatory opportunity.[70,88] Notably, nicotines action in this "incentive/approach system" and the conditioned effect associated with this action is used to explain the acquisition and maintenance of compulsive tobacco use,[44,45,80] and the over 95% relapse rate following abstinence without pharmacotherapy.[16,17] Animal models such as self-administration and intracranial self-stimulation have been employed to elucidate the behavioral and neurobiological processes underlying these effects of nicotine.[15,46,69,81] For example, rodents and nonhuman primates prepared with an intravenous catheter will press more on a lever that produces contiguous intravenous delivery of nicotine. The differential increase in responding (self-administration) maintained by nicotine requires normal functioning of the system outline in Figure 1. For example, nicotine self-administration in rats is decreased with bilateral 6-hydroxydopamine lesions of the dopaminergic projections between the ventral tegmental area (VTA) and nucleus accumbens,[23] or by infusions of a nAChR antagonist, DHβE, into the VTA.[24] Further, selective cholinergic lesioning of the pedunculopontine tegmental nucleus, a major cholinergic projection to the VTA, also attenuates nicotine self-administration.[51] Finally, mice lacking the β2 subunit fail to self-administer nicotine.[32]

Additional empirical work has implicated nAChRs located on the cell bodies in the VTA and on the terminals of glutamatergic projections from the prefrontal cortex to the VTA.[27,47,60] These excitatory glutamatergic projections stimulate VTA neurons resulting in dopamine release.[48] Theorists have suggested that this release of dopamine, especially in the nucleus accumbens, is important for various aspects of the rewarding/incentive effects of appetitive stimuli and the conditioned approach effects engendered by these stimuli (de Bruin, this book and refs. 3,10,27). Dopamine release in the nucleus accumbens is increased *in vitro* and *in vivo* with nicotine. This prolonged increase in dopamine release appears to be mediated by long-term potentiation of VTA cells containing NMDA receptors—a glutamate receptor selective for the agonist *N*-methyl-D-aspartate.[87] The α7* nAChRs located on the presynaptic terminals of projections from the prefrontal cortex are important for inducing this long-term potentiation in the VTA.[60,88] The α4β2* nAChR located on the cell bodies of VTA neurons quickly desensitize to the presence of nicotine and are unlikely to contribute to the long-term enhancement of dopamine release.[27,75]

Although there is a massive empirical literature studying the functional effects of dopamine release in this system, there is still disagreement as to its role in incentive-related behaviors. The following quote by Dani *et al.*.[27] provides a good summary that is consistent with our thinking and will serve as basis for suggesting a broad role of the nAChR-mediated neural plasticity of this system in learning and memory.

> "DA [dopamine] concentrations in the NAc [nucleus accumbens] are not a scalar indication of reward. More likely, the DA signal conveys novelty and reward expectation or serves to indicate the

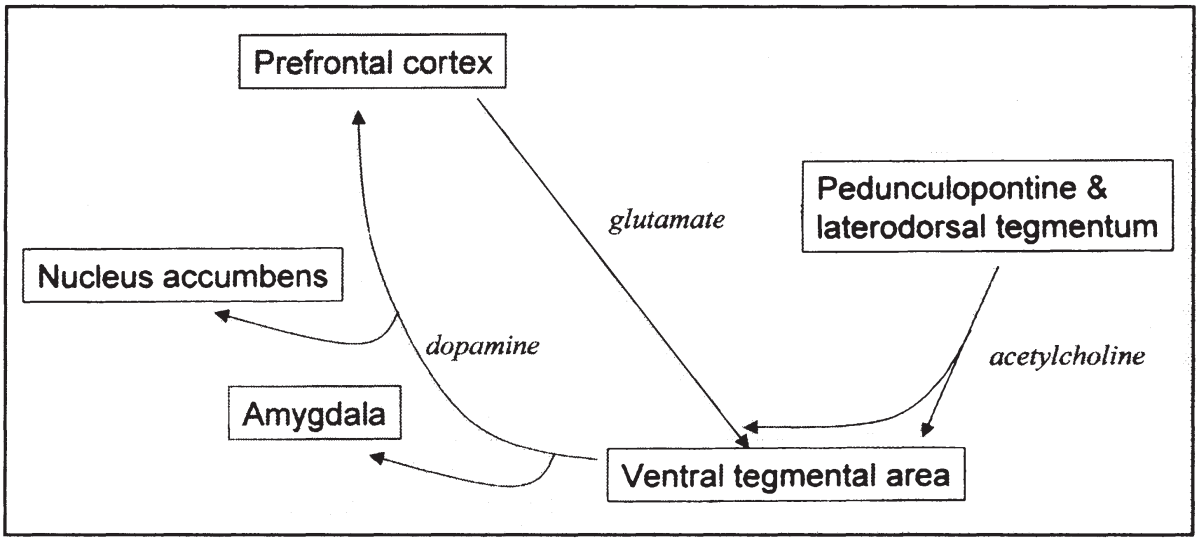

Figure 1. Diagram of the main pathways involved in nicotinic acetylcholine synaptic plasticity of the incentive-motivational (reward) system.

> deviation of the environmental input from the animal's expectations, which were constructed by experience. Thus, DA may participate in the ongoing associative learning of adaptive behaviors as an animal continually updates a construct of environmental salience" (p. 350).

This conceptualization suggests that the dopamine signal that is enhanced by nicotine's action on presynaptic terminals containing α7* nAChRs plays a role in neurally attributing incentive salience to the stimulus input from a continually changing environment. This neural attribution likely occurs through associative learning processes, broadly defined.[3]

Recent research by Caggiula and colleagues[15] provides an important behavioral example of this process. Briefly, rats were trained to self-administer nicotine such that when the response requirement was completed a 1-sec intravenous infusion of nicotine (0.03 mg/kg) was delivered; a 1-sec light co-occurred with the nicotine infusion. Upon establishing stable self-administration behavior, some rats were switched to an extinction phase in which saline replaced nicotine, but the 1-sec cue light still occurred. Although lever press rates decreased with the removal of nicotine, the nicotine-associated light still maintained responding well above controls receiving saline without the cue light. In a separate set of rats, the response-contingent nicotine infusion continued during the extinction phase, but the light signal was removed. Rates of nicotine self-administration also decreased in this group. Notably, the level of responding maintained by nicotine alone was comparable to that maintained by the cue light alone. This result is intriguing if one considers that the rate of behavior maintained by what is conceptualized as the primary reinforcer, nicotine, is similar to that controlled by a cue associated with the effects of nicotine. Caggiula *et al.*[15] concluded that, "nicotine promotes the establishment or magnifies the salience of conditioned reinforcers" (p. 526). We suggest that a plausible mechanism for this enhanced incentive salience is the action of nicotine on the α7* nAChRs located on glutamatergic presynaptic terminals of projections from the prefrontal cortex to the VTA. Of course, this proposal requires empirical attention.

Regardless of the specific neurobiological processes responsible for enhancing the incentive salience of stimuli, this enhancement provides an additional mechanism by which nAChR compounds may broadly affect learning and memory. For example, enhanced attention and/or vigilance (see earlier) may be, at least in part, the result of this process. Stimulus events that occur in the presence of nicotine (or other appropriately selective nAChR agonists) may acquire, or have potentiated, some appetitive property. Presumably this enhanced appetitive quality increases salience and may even require deeper processing given the acquired associations. Indeed, animals in a free-choice situation spend more time in a distinct environment that has been previously paired with appetitive stimuli.[4]

Enhanced/magnified incentive salience of cues may also play a role in die improved acquisition of new tasks observed with some nAChR agonists. For example, we found that acquisition of a T-maze visual discrimination task was faster in chronic nicotine-treated rats than in saline-treated rats.[6] Perhaps nicotine potentiated the incentive effects of the food used to reinforce correct arm choice (i.e., black arm). According to this formulation the incentive salience of the black arm may also be enhanced. That is, any conditioned reinforcing value acquired by the black-arm stimuli repeatedly associated with food may be increased by nicotine. Further, these conditioned effects may be stronger because the appetitive effects of food would also be enhanced (see earlier). Finally, the black-arm stimuli may acquire additional incentive salience by direct association with nicotine. The cumulative increase in the incentive salience of the stimulus events relevant to learning the discrimination thus enhanced acquisition rates relative to saline controls. Interestingly, reversal learning (white-arm now associated with food) was not altered by nicotine pretreatment. Perhaps, the effects of nicotine on the incentive salience require the stimulus events to be relatively novel (i.e., relatively little learning history). Or, perhaps the acquired increase in the incentive salience of black arm cues competed with white arm cues that were now becoming associated with food and nicotine after a long history on nonreinforcement in a manner similar to nonmagnified cues in the saline controls.

As a final note in this section, we found that enhanced acquisition in the T-maze task was predicted by activity in an inescapable novel environment; less reactive rats learned the discrimination faster (see ref. 6 and Fig. 1). Notably, past research on individual differences predicted by reactivity to inescapable novelty has implicated the mesocorticolimbic dopamine system.[82,86] The nAChR-mediated long-term potentiation of the VTA increases dopamine release within this system (see Fig. 1) and suggests a potential process responsible for the predictable difference in T-maze learning produced by nicotine. Of course, the speculations concerning incentive salience and the role of nAChR-mediated long-term potentiation in learning and memory require further research to provide independent evidence for the processes at a neurobiological and behavioral level.

Other Effects

Additional functional effects of nAChRs include alterations in pain, anxiety, appetite, depression, epilepsy, and motoric abilities. Although a comprehensive discussion of these effects is beyond the scope of the present review, their potential influence (direct or indirect) on learning and memory deserves mention. We will use as an example the locomotor effects of centrally located nAChRs. Most of the nonhuman animal research investigating attention, reward, or working memory include controls to assess whether the motoric effects of the nAChR ligand of interest could account for group differences. Such controls are important in that nAChR agonists can alter general locomotor activity.[8,42,61,68,92] Whether the change is locomotor suppression or stimulation depends on such factors as selectivity of ligand, dose, pretreatment or preexposure history, rodent strain, and environmental familiarity. Accordingly, if one is investigating the memory enhancing effects of, say, chronic nicotine, then an index of locomotor stimulation will be important. Arguably, these locomotor stimulant effects could enhance acquisition and performance in certain learning tasks perhaps by producing small decreases in the time between stimulus-outcome or behavior-outcome relations (i.e., improved temporal contiguity) inherent in learning situations.[72,93,97] Along these lines, it is interesting to note that the α4β2* nAChRs[42] and increased dopamine release in the nucleus accumbens[5] appear to be important for the locomotor stimulant effects of nicotine (see section on Reward/Incentive Effects). Likely, future research will begin to more specifically identify the links between the effects we have listed as "Other" and memory. Perhaps the anxiolytic effects of ABT 418[30] or nicotine[19] allow an animal to use neural processing resources released from this decrease in anxiety toward the learning/memory task prescribed by the experimenter.

Closing Remarks

Advances in molecular biology are clearly refining our understanding of the vast structural variation that exists in nAChRs. As these advances continue, so will our understanding of nAChR processes in learning and memory. For example, behavioral geneticists can further develop mutant mice with selective deletions of nAChR subunits. Extensive neurobiological and behavioral assessment of these mice will inform our theoretical models. Also, continued development of selective ligands will allow researchers to dissociate function and receptor subtypes. Finally, from our perspective, we need a better understanding of the psychological constructs measured by current animal models (e.g., radial arm maze, 5-CSRT) and we need further development of new animal models (see Jaffard and Marighetto in this book). Our discussion, for example, of the possibility that working memory models may also be measuring attentional processes highlights this need. If we do not fully understand what the dependent measures are indexing and the factors that affect those measures, we will always be unsure of whether the neurobiological process identified actually reflects the psychological construct (memory, learning, attention, reward, etc.) of interest.

Acknowledgements

We thank D. Taylor, K. Karthigeyan, and M. Palmatier, for their comments on an earlier version of this chapter. R. A. Bevins was supported by United States Public Health Service grant DA11893 while preparing this report; J. Besheer was supported by DA06092. Correspondence concerning this chapter should be addressed to Rick A. Bevins, Department of Psychology, University of Nebraska-Lincoln, Lincoln NE USA 68588-0308, or e-mail rbevins1@unl.edu

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