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REVIEW

Roles of cholinergic receptors during attentional modulation of cue detection

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Abstract

Basal forebrain corticopetal cholinergic neurons are known to be necessary for normal attentional processing. Alterations of cholinergic system functioning have been associated with several neuropsychiatric diseases, such as Alzheimer's disease and schizophrenia, in which attentional dysfunction is thought to be a key contributing factor. Loss of cortical cholinergic inputs impairs performance in attention-demanding tasks. Moreover, measures of acetylcholine with microdialysis and, more recently, of choline with enzyme-coated microelectrodes have begun to elucidate the precise cognitive demands that activate the cholinergic system on distinct time scales. However, the receptor actions following acetylcholine release under attentionally-challenging conditions are only beginning to be understood. The present review is designed to summarize the evidence regarding the actions of acetylcholine at muscarinic and nicotinic receptors under cognitively challenging conditions in order to evaluate the functions mediated by these two different cholinergic receptor classes. Moreover, evidence that supports beneficial effects of muscarinic muscarinic-1 receptor agonists and selective nicotinic receptor subtype agonists for cognitive processing will be discussed. Finally, some challenges and limitations of targeting the cholinergic system for treating cognitive deficits along with future research directions will be mentioned. In conclusion, multiple aspects of cholinergic neurotransmission must be considered when attempting to restore function of this neuromodulatory system.

Key words: 192 IgG-saporin; Acetylcholinesterase inhibitors; Alzheimer's disease; Attention; Basal forebrain; Muscarinic; Nicotinic; Protein kinase C; Prefrontal cortex; Schizophrenia

Core tip: The corticopetal cholinergic system is critical for normal attentional processing. Disruption of this system is associated with cognitive deficits in several disorders. Thus, restoration of cortical cholinergic neurotransmission represents a reasonable target for treating some cognitive disorders. Evidence is presented that the muscarinic muscarinic-1 receptor and nicotinic receptor subtypes appear to be key targets for future investigations related to treating cognitive disorders. Future research into muscarinic-nicotinic receptor interactions, along with the role of second messenger systems, is needed to further develop appropriate strategies for restoring cortical cholinergic neurotransmission.

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INTRODUCTION

Cortically-projecting cholinergic neurons originate from the nucleus basalis of Meynert and substantia innominata within the basal forebrain[1]. Numerous hypotheses have been put forth proposing that the cortical cholinergic sys-

tem is critical for the selection and subsequent processing of stimuli[2,3]. Several other theories have proposed roles for cortical cholinergic inputs in learning and memory[4,5], but the focus of this review will be with regard to the contribution of these pathways to attention. Several cortical regions, including prefrontal cortex, posterior parietal cortex and some somatosensory cortical areas[6], are thought to be sites where acetylcholine can modulate neural activity to impact aspects of attentional processing[2,7,8]. The evidence in support of these hypotheses has come from multiple experimental approaches.

In rats, intrabasalis infusions of excitotoxic compounds that preferentially destroyed cholinergic neurons tended to produce larger deficits in tasks that placed greater demands on attentional processing[9,10]. The immunotoxin, 192 IgG-saporin, which destroys cortically-projecting basal forebrain cholinergic neurons, has been an important tool for studying the impact of loss of the cholinergic system on attention[11]. Intrabasalis infusions of 192 IgG-saporin decrease signal detection accuracy in attention-demanding tasks[12-14]. Measures of acetylcholine using microdialysis techniques have found elevations in acetylcholine associated with attention-demanding tasks compared with procedures that control for motoric or motivational aspects of performance[15-17]. More recently, enzyme-coated microelectrodes have been used to measure choline and acetylcholine release on a much shorter time scale[18,19]. Experiments employing these techniques have shown that there are cholinergic transients on different timescales during cue detection tasks[20,21]. Moreover, these transients tend to occur during a transition from a trial when no signal is perceived to a trial when a signal is detected and the appropriate response rules are then activated[22]. Thus, the previous evidence has supported the idea that cortical acetylcholine contributes importantly to aspects of cue detection and variations in cognitive demands. Despite these important findings, the most effective pharmacological strategies to activate cholinergic neurons to restore normal functioning remain unclear. The goal of the present review is to summarize some key findings regarding the activation of muscarinic and nicotinic receptors during cue detection and to suggest future research areas that may facilitate the development of drug treatments aimed at restoring normal cholinergic neurotransmission.

ACETYLCHOLINE AND ALZHEIMER'S DISEASE: CURRENT CHOLINERGIC DRUG TREATMENTS

Alzheimer's disease is characterized, in early stages, by deficits in attentional[23,24] and mnemonic processing[4]. Loss of cholinergic neurons in the basal forebrain has been implicated in the cognitive deficits associated with Alzheimer's disease[4,25]. A wide variety of neuropathological changes have been noted in Alzheimer's disease, with the major features including the development of β-amyloid-induced plaques and neurofibrillary tangles, although the exact contribution of these features to disease progression has remained controversial[26,27].

Interestingly, alterations of cholinergic functioning appear to interact with many of the key neuropathological changes in Alzheimer's disease[28]. For example, elevated levels of amyloid-β42 suppresses acetylcholine synthesis[29,30]. Immunotoxic lesions of cholinergic neurons alter amyloid precursor protein secretion[31]. In animal models, loss of muscarinic-1 (M1) receptor stimulation exacerbates the development of plaques and tangles[32]. Conversely, muscarinic M1/M3 receptor stimulation decreases amyloid-β42 levels[33]. Similarly, recent reports have shown that α7 nicotinic receptor agonists can also decrease amyloid-β42 levels[34,35]. Thus, the available evidence suggests, broadly, that there is a negative correlation between neuropathological features leading to plaques and activity of the cholinergic system. Thus, it is possible that restoration of optimal cholinergic functioning could assist in improving other aspects of Alzheimer's disease. The relationship between the cholinergic system and tangles is less well-characterized. In patients with Alzheimer's disease, choline acetyltranferase-positive basal forebrain neurons do show tau pathology[36]. Elevated levels of tau can be neurotoxic to M1/M3-containing neurons, an effect thought to be related to the high affinity of tau for these receptors[37]. Activation of M1 receptors appears to lessen tau pathology, while nicotinic receptor stimulation can exacerbate tau pathology[38]. Thus, although cholinergic restoration may be beneficial, approaches that provide more modest levels of cholinergic stimulation may limit adverse effects.

Given the loss of cholinergic functioning in Alzheimer's disease, it is not surprising that restoring these pathways has received considerable attention to treat the cognitive deficits. Drugs that inhibit acetylcholinesterase (AChE), the enzyme that deactivates acetylcholine, have been used to treat Alzheimer's disease. The original approved AChE inhibitor approved for treatment of Alzheimer's disease, tacrine, was associated with a relatively high incidence of side effects, including hepatotoxicity[39]. The newer generation of AChE inhibitors, donepezil, galantamine, and rivastigmine, provide modest beneficial effects with a lower rate and severity of side effects compared with tacrine[40]. Additionally, a n-methyl-*D*-aspartate (NMDA) receptor antagonist, memantine, has been approved and appears to have beneficial effects when administered later in the progression of Alzheimer's disease[41]. The limited beneficial effects of the AChE inhibitors may be due to the widespread action these compounds have on multiple cholinergic receptors. A focus on more specific actions at certain cholinergic receptor subtypes may yield improved treatments for the cognitive deficits in Alzheimer's disease. Additionally, efforts to facilitate the action of acetylcholine binding, such as through allosteric receptor agonists or compounds that sensitize specific cholinergic receptors, may be beneficial.

MUSCARINIC RECEPTORS

Five muscarinic receptor subtypes have been characterized, M1-M5[42]. The M1, M3 and M5 receptors are primarily coupled to G_q proteins and can upregulate phospholipase C and activate inositol triphosphate, which can inhibit potassium currents[43]. The M2 and M4 receptors are coupled to G_i or G_o proteins, typically having inhibitory effects. The M1 and M2 receptors have been most carefully studied with respect to cognition. Generally, the M1 receptors are located postsynaptically whereas the M2 receptors are most predominantly located in presynaptically, serving as autoreceptors to inhibit acetylcholine release[44]. Many experiments have demonstrated that M1 receptor blockade can impair aspects of learning and memory[45-49]. With regard to attention, a muscarinic M1 antagonist did not affect performance in a task that required a simultaneous discrimination when visual stimuli were presented in one of two locations[50]. However, in a successive visual discrimination, when a visual stimulus is presented (or not) from a single location, M1 receptor blockade did decrease performance and this decrease in performance was seen at lower doses when a visual distracter was presented[51]. Thus, the M1 receptor system may not be essential when explicit attentional demands are minimal, but may be more likely to be recruited as task demands increase, such as in a successive discrimination task[52]. These findings are consistent with other results indicating that loss of cortical cholinergic inputs does not yield deficits following manipulations of any single attentional task parameter, but impairments are observed when multiple parameters are adjusted to increase explicit attentional demands[53]. Electrophysiological experiments have provided further evidence about neural processes that are supported by muscarinic M1 receptors. For example, muscarinic M1 receptors are sufficient for acetylcholine-induced prolonged cortical pyramidal cell excitability and at least partially contribute to transient inhibitory and excitatory activity in different cortical neurons[54]. Moreover, M1 receptor deficient mice show less of a shift toward a frequency coupled with stimulation of the basal forebrain, suggesting that the muscarinic M1 receptor is important for auditory cortical experience dependent plasticity[55]. Collectively, the data provide strong support that modulation of the muscarinic M1 receptor critically contributes to several processes that are important for normal learning.

Muscarinic M2 receptor antagonists enhance performance in several measures of working memory, including in radial arm maze win-shift and win-stay tasks and delayed nonmatching to position tasks[46,56]. Moreover, M2 receptor antagonists can enhance memory in aged animals[57]. Not surprisingly, M2 receptor antagonists increase acetylcholine release[57,58], although it is unknown whether this is the mechanism underlying enhanced memory performance following muscarinic M2 receptor blockade. Blockade of muscarinic M2 receptors has also been shown to enhance long-term potentiation, which may contribute to the reported cognitive benefits of drugs that act in this manner[59]. The effects of muscarinic M2 receptor antagonist administration on measures of attention have not been examined. Thus, the extent to which attentional enhancement may contribute to the memory improvement following muscarinic M2 receptor blockade remains unclear.

There is growing evidence that other muscarinic receptor subtypes contribute to aspects of cognition. For example, muscarinic M3 receptor knockout mice display deficits in contextual fear conditioning[60]. The development of more selective muscarinic toxins should greatly enhance the ability to study the roles of specific muscarinic receptor subtypes. These toxins have been used to show that inhibition of muscarinic M1 receptors, but not M4 receptors, in the dorsomedial striatum disrupts place reversal learning[48].

NICOTINIC RECEPTORS

When acetycholine binds to nicotinic receptors, release of several neurotransmitters is promoted and several processes are activated, including elevation of intracellular calcium levels[61-63]. There are two predominant neuronal nicotinic receptor subtypes, those containing $\alpha4\beta2$ subunits and those containing the $\alpha7$ subunit. The $\alpha4\beta2$ subtype has a higher affinity for nicotine compared with the $\alpha7$ subtype[64]. The available evidence suggests that $\alpha7$- and $\alpha4\beta2$-subunit containing receptors are located pre- and postsynaptically in the brain, with a larger proportion of these receptors located presynaptically[65,66].

Many experiments have examined the role of nicotinic receptors in attention. There appears to be sharp age-related differences in the effects of nicotine exposure on cognition. In rodents, prenatal nicotine exposure produces attentional impairments[41]. Adolescent nicotine exposure impairs attention[67,68] and learning[69,70]. In adults, acute nicotine exposure can have beneficial effects, although nicotine-induced performance improvement is occasionally observed during specific task conditions[71,72]. Moreover, impairments in attentional performance have been reported following nicotinic receptor blockade, however, changes in variables thought to reflect nonspecific aspects of performance have complicated the interpretation of these data[73,74]. Chronic nicotine exposure, on the other hand, appears to robustly enhance performance in attention-demanding tasks in rats[75], similar to findings in human smokers[76].

The exact mechanisms of nicotine-induced attentional enhancement in adults are beginning to become better understood. A recently published experiment failed to find effects of nicotine or a selective nicotinic $\alpha4\beta2$ receptor agonist, S 38232, on a well-trained attention task. However, when attentional demands were increased, the $\alpha4\beta2$ receptor agonist, but not nicotine, enhanced attentional performance[77]. Examination of putative cholinergic transients in the prefrontal cortex found that the $\alpha4\beta2$ receptor agonist produced a faster rise time and steeper decay compared with nicotine[77]. Subsequent experiments showed that nicotine and blockade of $\alpha7$

nicotinic receptors also enhanced performance, suggesting that the actions of nicotine at α7 nicotinic receptors may slow the rise time and decay of cholinergic transients, which may be a critical factor for enhancement of attentional performance under taxing conditions[77]. Recent data have supported the idea that agents, such as sazetidine-A, which desensitizes α4β2 nicotinic receptors, can enhance attentional performance and reverse deficits induced by blockade of NMDA or muscarinic receptors[78,79]. Thus, the available data provide strong evidence that α4β2 nicotinic receptors are important targets for regulating attentional performance.

Several studies have begun to examine the role of nicotinic α7 receptor agonists in attention[80]. Nicotinic α7 nicotinic receptor knock-out mice are not different from controls during baseline performance of the five-choice serial reaction time task, but do demonstrate elevated omissions when task demands are increased[81]. Moreover, α7 nicotinic receptor agonists facilitate aspects of pre-attentive processing[82,83]. However, α4β2 receptor agonists, but not α7 agonists, can reverse vigilance decrements in the five choice serial reaction time task[84]. Thus, there is evidence that nicotinic α7 receptor agonists can facilitate attention, although additional work is needed to clarify the aspects and conditions under which attentional processing can be enhanced by these compounds.

INTERACTIONS BETWEEN MUSCARINIC AND NICOTINIC RECEPTORS: PHARMACOLOGICAL EVIDENCE

Administration of cholinergic receptor-specific drugs has been used to study the relationship between muscarinic and nicotinic receptors. Several experiments have demonstrated that co-administration of muscarinic and nicotinic receptor antagonists, at doses that do not have effects when either receptor is blocked alone, can disrupt performance in attention- and memory-demanding tasks[73,85,86]. Moreover, as mentioned above, attentional impairments following blockade of muscarinic receptors can be overcome by drugs that desensitize α4β2 nicotinic receptors[79]. The ability of muscarinic, particularly M1 receptor agonists, to restore attentional processing following nicotinic receptor blockade has not been well-characterized. Collectively, the available evidence suggests that decreasing cholinergic receptor activity at multiple subtypes can have a synergistic negative effect on attentional performance and that agonism, increasing the activity of α4β2 nicotinic receptors, can overcome attentional deficits following muscarinic receptor blockade. Notably, reversing the effects of muscarinic receptor blockade on attentional processing is not exclusively accomplished by α4β2 nicotinic receptor agonists[87]. Nicotinic receptor agonists can also reverse scopolamine-induced deficits in measures of memory[88], although the focus of this review is primarily on attentional processing.

FUTURE RESEARCH DIRECTIONS: RESTORING CHOLINERGIC NEUROTRANSMISSION

Modes of cholinergic neurotransmission

Actions at cholinergic receptors have traditionally thought to reflect "volume" transmission, reflecting sensitivity to acetylcholine levels beyond the synapse. Part of the evidence in support of this idea is the location of cholinergic receptors, with nicotinic receptors predominantly located presynaptically and relatively few cholinergic varicosities forming classical synapses onto muscarinic M1 receptors in cortical pyramidal cells[89]. However, the use of choline-sensitive microelectrodes has provided evidence that phasic acetylcholine release, over several seconds, can predict aspects of trial-by-trial attentional performance[20,22,90]. Thus, there is developing evidence that acetylcholine may act on multiple time scales[21]. The functional implications of these different modes of transmission are not well-understood. Given these findings, treatments that maintain or facilitate cholinergic transmission modes by binding to allosteric sites on cholinergic receptors may be beneficial.

Allosteric agonists have considerable potential for treating cognitive deficits associated with cholinergic dysfunction. Several of these compounds have been thoroughly discussed in other reviews[91-93] so only a few allosteric ligands will be highlighted in this review to illustrate the progress and challenges with this approach. One compound in clinical trials for treating Alzheimer's disease and schizophrenia is the nicotinic α7 receptor-sensitizing agent, EVP-6124. This compound can enhance mnemonic processing, though its effects on attention remain less clear[94]. Although the precise mechanism of action of EVP-6124 is unclear, it is hypothesized that at least two pockets within the channel must be bound to activate the α7 receptor and that low doses of EVP-6124 can fill a small portion of the sites, allowing the same level of endogenous acetylcholine to activate more α7 nicotinic receptors[94]. Another compound that has been shown to have beneficial effects in rodent models of attentional dysfunction is the α4β2 agent, sazetidine-A[78]. Curiously, this compound initially stimulates and then desensitizes α4β2 receptors. Additional studies of the impact of this drug on acetylcholine and glutamate release may yield further insights into the exact mechanisms through which sazetidine-A can reverse attentional deficits. With regard to positive allosteric modulators of muscarinic receptors, challenges have existed with developing sufficiently targeted compounds[91], although more recent reports provide encouraging progress[95]. Overall, the positive results observed with initial allosteric agonists, along with novel insights about cholinergic transmission modes and potential disease-modifying effects of restoring cholinergic transmission, all lend support to the importance of further research with cholinergic receptor positive allosteric modulators.

Contributions of second messenger systems to attentional processing

As mentioned above, activation of both muscarinic and nicotinic receptors can induce further intracellular signaling cascades. The role of second messenger systems in attentional processing remains poorly understood. These systems may contribute to activation of response rules following cue detection or engagement of top-down mechanisms that guide attention. For example, inhibition of protein kinase A in the prefrontal cortex impairs attentional performance[96]. Protein kinase C (PKC) is activated by muscarinic M1 receptors and is lower in patients with Alzheimer's disease[97-99]. Moreover, as Alzheimer's disease progresses, there is increased M1 receptor/G-protein decoupling, suggesting that drugs targeting the muscarinic M1 receptor may only be effective in early disease stages[100]. Furthermore, this M1 receptor/G-protein decoupling correlates with the loss of PKC activity in Alzheimer's disease[100]. PKC inhibition impairs signal detection in attention-demanding tasks in rats, a finding consistent with the idea that lower PKC activity may contribute to attentional deficits during early stages of Alzheimer's disease[51]. These findings support the idea that PKC activators may be beneficial for Alzheimer's disease[101,102]. These preliminary experiments suggest that a focus on the role of second messenger systems is likely to provide insight into modulation of attentional processing and may offer useful targets for treating some cognitive disorders.

CONCLUSION

The muscarinic and nicotinic receptor systems are well-known to contribute to cognitive processing and to be disrupted in diseases characterized by cognitive deficits. Surprisingly, there are relatively few studies that examine combined agonism of muscarinic M1 receptor and nicotinic receptor subtypes in treating attentional deficits. The benefits derived from this approach will likely be determined, at least in part, by the ability to normalize cholinergic neurotransmission on multiple time scales. Allosteric agonists may be beneficial for achieving this goal. It will also be important to maintain the effects of cholinergic signaling on downstream signaling, such as PKC activation. Collectively, these approaches may yield greater benefits for cognitive disorders associated with corticopetal cholinergic dysfunction.

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