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Behavioral-Cognitive Targets for Cholinergic Enhancement

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Abstract

Cholinergic mechanisms have long been considered a promising target for enhancing cognitive functions. Two distinct yet interacting components of cholinergic activity have been proposed to mediate specific cognitive functions. Transient spikes in cholinergic activity mediate the detection of cues in situations involving attentional mode shifts. More slowly changing cholinergic neuromodulation of cortical circuitry regulates task compliance specifically in response to performance challenges. Increases in cholinergic neuromodulation enhances the generation of cholinergic transients via stimulation of $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors. Stimulation of these receptors stabilizes attentional performance and increases cue detection rates. Adjunctive treatment with agonists or modulators at these receptors is predicted to benefit unstable attentional performance and low cue detection rates that are common to several brain disorders.

Introduction

Cholinergic mechanisms have been considered a favorable target for enhancing cognitive functions and capacities since early experiments indicated modest, if complex effects of acetylcholinesterase (AChE) inhibitors on memory [1–4]. In the 1990s, accumulating evidence supported the more specific hypothesis that cholinergic activity is necessary for attentional performance [5,6••] and the effects of AChE inhibitors again suggested that cholinergic mechanisms can be pharmacologically enhanced to benefit cognitive, specifically attentional performance [7••,8].

However, the complex pre- and postsynaptic effects of AChE inhibitors and also a second major group of drugs used to test cholinergic functions, namely antagonists at muscarinic acetylcholine receptors (mAChRs), have limited the interpretation of the neuronal and cognitive mechanisms by which these drugs affect cognition. AChE inhibition yields very high extracellular levels of acetylcholine (ACh), reaching several 1000% increases over baseline [9]. As a result, ACh stimulates M2 autoreceptors which silences presynaptic signaling. In addition, levels of stimulation of postsynaptic mAChRs as well as nicotinic

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Conflict of Interest

The author does not have any conflict of interest.

acetylcholine receptors (nAChRs) reach relatively high, supraphysiological tonic levels, with some receptor subtypes likely undergoing downregulation while others increase in number and affinity. Together, it is difficult to see how these effects of AChE inhibitors enhance cholinergic neurotransmission and related functions, particularly if it is the case that cholinergic neurotransmission is not primarily characterized by volume-transmission [10].

Likewise, administration of non-selective mAChR antagonists such as scopolamine or atropine results in extremely high extracellular concentrations of ACh as these drugs block presynaptic M2 mAChRs [e.g., 11]. While also blocking postsynaptic mAChRs, high extracellular ACh levels resulting from M2 antagonism extensively stimulate postsynaptic nAChRs. Therefore, a rather bizarre state of cholinergic neurotransmission results from administering drugs such as atropine or scopolamine.

Although effects of these compounds continue to support the premise that cholinergic mechanisms are a target for cognition enhancement in general and for attentional functions in particular [e.g., 12,13•], due to the complexity of effects of these drugs the development of specific hypotheses describing relationships between defined cholinergic mechanisms and cognitive processes have not evolved until recently. Evidence generated by studies designed to monitor and manipulate defined components of cholinergic neurotransmission have begun forming the basis for such hypotheses.

As will be detailed below, such cholinergic-cognitive relationships have emerged from research utilizing established as well as novel methods to monitor presynaptic ACh release, as well as from more selective pharmacological tools and optogenetic methods to probe pre- and postsynaptic cholinergic mechanisms. Here we will focus on the regulation and functions of the basal forebrain cholinergic projection system to the cortex, largely because the cognitive operations that depend on activity in septohippocampal and brainstem cholinergic systems, as well as striatal cholinergic interneurons, have remained less well defined. Specific attentional operations can now be mapped onto different components of cholinergic neurotransmission and receptor groups, and these mappings allow us to deduce opportunities for pharmacological cognition enhancement from these mappings [for a discussion of such mappings see 14]. Specifically, our evidence supports two separate yet interacting components of cortical cholinergic activity (Figure 1). Cholinergic transients mediate the detection of cues in certain contexts (below), and cholinergic neuromodulation upregulates the cortical circuitry that generates such transients as a function of demands on attentional control (top-down). $\alpha 4\beta 2^*$ nAChRs link these two mechanisms and, therefore, stimulation of these receptors serve as a defined cholinergic target for enhancing, or attenuating impairments of, the ability to detect and incorporate external cues to guide ongoing behavior.

Cue detection forced by cholinergic transients

In broadest terms, attention concerns the detection and selection of relevant cues from the outside world [for a definition of ‘detection’ see 15], to do so over extended periods of time (sustained attention), and to switch between cues of different modalities or occurring in different locations, while maintaining cue-related response rules in working memory

(divided attention). This focus on attention ignores bottom-up detection processes, as triggered by new, salient, and unexpected cues.

Cortical cholinergic signaling is required for diverse aspects of attention [13••,16–18]. Substantial evidence concerning the role of cholinergic signaling in rodents and humans performing a sustained attention task (SAT) has supported relatively specific hypotheses about the aspects of attention that are mediated via cholinergic activity. This task consists of a random order of cued and non-cued trials and requires discrete responses to cues (reporting the presence or absence of the cue; hits or misses) as well as reporting the absence of cues (“blank” trials; correct rejections or false alarms). Hits and correct rejections are rewarded while incorrect responses trigger the onset of the intertrial interval. Using different task parameters, rats and mice perform at comparable levels while humans exhibit substantially higher detection rates and, in contrast to rodents, respond to visual distractors by adopting a more conservative criterion [19,20].

Removal of cortical cholinergic inputs in rodents robustly and permanently reduced the number of detections (or hits) while completely sparing the rate of correct rejections [6••]. This finding, recently confirmed in humans with PET-defined decreases in the density of cortical cholinergic inputs [21], suggests that cholinergic activity is selectively required to detect cues in such contexts. We therefore tested the hypothesis that cued trials yielding hits are consistently associated with increases in cholinergic activity using real-time electrochemical recordings of cholinergic activity. As expected, brief, trial-based increases in cholinergic activity (“transients”) were not observed in cued trials that were missed and not in blank trials. Such transients were only found in cued trials yielding hits, but not on all such trials. Such transients were only observed in cue-hit trials when they followed factual or perceived blanks (“incongruent hits”). Transients were not observed during consecutive hits [22].

Non-cue trial performance does not involve cue detection and cue-triggered implementation of behavior and thus performing a correct rejection may be considered the default response mode while monitoring the cue source. For a subsequent cue to be detected, the cue needs to (re-)activate the cue-associated response rule and to force an appropriate response. Consecutive hits do not require such a mode shift unless long intertrial intervals spontaneously evoke a spontaneous reversal to the default mode [23••].

Because cholinergic transients are evoked only by cues that are part of incongruent hits, the actual perception of cues and their “insertion” into frontal circuitry likely does not depend on cholinergic activity. Rather, cholinergic transients force cue-directed behavior, that is, detection [15] in cued trials that require a departure from the default response mode. We recently confirmed this hypothesis in part by showing that optogenetic generation of transients during non-cue events strikingly increased the number of false alarms (or erroneous “claims” for hits; H. Gritton et al., in preparation).

All cues yielding hits, irrespective of trial sequence, also evoke glutamatergic transients that likely originate from thalamic afferents [Fig. 1; 24,25]. These glutamatergic signals may be speculated to “insert” cue information into cortical circuitry. Although glutamatergic

transients are necessary for the generation of cholinergic transients, they are not sufficient, as glutamatergic transients also occur during consecutive hits that are not associated with cholinergic transients. It is possible that cholinergic transients are actively suppressed during consecutive hits rather than actively generated during incongruent hits, to avoid overly biasing cortical circuitry toward detections and to maintain flexibility for accurately responding to different trial types (see also the discussion of cognitive constructs below).

Cholinergic neuromodulation

Attentional performance elevates prefrontal extracellular ACh levels measured by *in vivo* microdialysis. Moreover, presentation of a distractor reduces hits as well as correct rejections yet such impaired performance was shown to be associated with augmented levels of ACh. In addition, higher levels of ACh predicted greater resistance against the detrimental performance effects of the distractor [26]. Passetti and colleagues [27] demonstrated that higher cortical ACh levels were correlated with the completion of a greater number of task trials. *Vice versa*, in rats that exhibit, as a trait, relatively unstable attentional performance, characterized by frequent switches frequently between above and at-chance levels of performance, performance-associated ACh levels failed to show the typical increases [28]. These results have supported the hypothesis that extracellular ACh levels, known to reflect presynaptic ACh release, vary as a function of demands on attentional control [29,30].

While beyond the scope of this discussion, there are important technical and conceptual questions about the nature of the cholinergic signal monitored by microdialysis and potential relationships with cholinergic transients. The present evidence supports the view that ACh levels in dialysate collections are not, or not detectably, confounded by cholinergic transients. Furthermore, results from experiments using methods that allow analyzing dialysates based on one-minute collections continue to support the validity of the characterization of this component of cholinergic activity as neuromodulation [for discussion of these issues see 31].

As illustrated in Figure 1, separate populations of neurons are speculated to be the source of cholinergic transients and of cholinergic neuromodulation, respectively [32]. Moreover, cholinergic neuromodulation impacts the generation of transients by stimulating $\alpha 4\beta 2^*$ nAChR expressed by glutamatergic terminals [24,25]. In other words, high levels of cholinergic neuromodulation, or pharmacological stimulation of these receptors, improve detection performance by enhancing the (glutamatergic) “insertion” of the cue into cortical circuitry (see above), thereby enhancing the likelihood, rise time and amplitude of cholinergic transients [33]. Stimulation of $\alpha 4\beta 2^*$ nAChR was also found to improve the attentional performance of rats exhibiting poor attentional control as a trait [28]. The demonstration of efficacy of $\alpha 4\beta 2^*$ nAChR agonists in adult ADHD patients [34,35] is consistent with the hypothesis that mimicking or enhancing cholinergic neuromodulation through these receptors is a viable target for improving attentional performance.

Cholinergic enhancement: cognitive constructs

A task-independent, theoretical conceptualization of the cognitive mechanisms hypothesized to be targets for cholinergic enhancement suggests that cholinergic transients reduce the uncertainty of reporting the presence of a cue while increases in cholinergic neuromodulation benefit task compliance by, as explained below, decreasing opportunity costs. Reflecting the impact of cholinergic neuromodulation on transient generation (Fig. 1 and above), enhanced task compliance benefits detection in rats [36].

Conceptually, the operator's degree of certainty about the presence of a cue and thus the validity of reporting a hit is related to the response bias as calculated in accordance with signal detection theory. Consecutive hits, involving consecutive rewards, maximize certainty about the presence of cues and the validity of scoring hits, thus yielding a temporarily more "risky" response criterion. In this scheme, incongruent hits are associated with relatively high uncertainty about the validity of a detection response and with a propensity for staying - conservatively - with the default response. Cholinergic transients act to reduce such detection uncertainty and therefore force the detection process specifically in such trials. Given this hypothesis, the absence of cholinergic transients during consecutive hits is advantageous, as the presence of transients would unduly bias the operator toward a highly "risky" response bias. The finding that optogenetic generation of cholinergic transients during non-cued trials yields a high rate of false alarms (above) is consistent with this perspective [36•].

Performing an ongoing task involves the mental calculation of the utility of such performance relative to alternative action [termed 'opportunity costs'; 37]. This theory considers attentional effort, high distractibility, fatigue or boredom as subjective expressions of accumulating opportunity costs, rendering alternative action increasingly likely. Obviously, incentives to stay on task versus engaging in alternative action figure significantly into such calculation. Increases in levels of cholinergic neuromodulation reduce opportunity costs as indicated by the findings that particularly high levels of ACh release have been observed in motivated rats that do not omit many trials even while their performance is challenged by a distractor [26], and that the degree of attentional task compliance is correlated with cortical ACh levels [27]. Conversely, this hypothesis predicts that rats exhibiting limited increases in cholinergic neuromodulation during attentional performance ["sign trackers"; 28] rapidly accumulate opportunity costs and thus exhibit poor task compliance. Indeed, these rats were unable to maintain stable performance and shift, in cycles lasting about three minutes, between good and poor levels of performance. Another example originates from research on humans expressing a subcapacity variant of cholinergic presynaptic synapses; these subjects are more readily engaging in alternative action than subjects expressing the wild type version [38].

Conclusions: Cognitive-behavioral targets for cognition enhancement

This discussion does not cover the potential for cognition enhancement that results from stimulation of mAChRs because this research has largely focused on documenting effects of drugs in a wide range of tasks and therefore the cognitive processes potentially enhanced by

agonists or modulators acting at mAChRs require conceptualization [39]. In contrast, as discussed in this article, cognitive targets for drugs acting at major subtypes of nAChRs, $\alpha 4\beta 2^*$ nAChRs, can be defined. *Agonists or positive modulators at these receptors are predicted to enhance task compliance specifically in the presence of performance challenges and when alternative action is possible. Furthermore, and partly dependent on this effect, cue detection rates will benefit, specifically when task- and trial switches lower the operator's certainty about the presence of cues.* Importantly, the non-selective agonist nicotine is less likely to generate such enhancements, in part because nicotine also stimulates $\alpha 7$ nAChRs which disrupts the fine-temporal orchestration of cholinergic transients [33]. As agonists at $\alpha 4\beta 2^*$ nAChRs have reached Phase II clinical studies, compounds are available for assessing the validity of this specific prediction in humans.

Finally, low attentional task compliance and relatively poor rates of detection of behaviorally significant cues are fundamental impairments common to many neuro-psychiatric disorders [40–44]. Therefore, adjunctive treatment with agonists or positive modulators at $\alpha 4\beta 2^*$ nAChRs is expected to benefit the cognitive status of a wide range of patients.

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Highlights

- Cholinergic “double duty”: modulation versus transients.
- Attentional task compliance and cue detection rates depend on cholinergic activity.
- Stimulation of $\alpha 4\beta 2^*$ nAChRs reverses poor attentional performance.

Figure 1.

Schematic illustration of circuitry generating neuromodulatory and transient cholinergic activity in the cortex. The figure is not intended to illustrate anatomical details but to capture essential aspects of our current understanding of the regulation of cortical cholinergic activity. Cholinergic projections to the cortex arise from the nucleus basalis of Meynert (nbM), the substantia innominata (SI) and the horizontal nucleus of the diagonal band (HDB) of the basal forebrain. The precise origin of cholinergic projections in these regions depends on the cortical target region; however, all subregions contribute to cortical

innervation. In prefrontal cortex (PFC), cholinergic neurons contact GABAergic inhibitory interneurons (in black) and pyramidal cells and, as illustrated, both innervation patterns influence cortical (glutamatergic) output. Direct cholinergic regulation of cortical efferents may be primarily mediated by muscarinic (m)AChRs (not indicated). In the cortex, two types of cholinergic activity likely originate from separate neurons in the basal forebrain (see also magnified inset). First, for certain cues to be detected, these cues need to evoke a brief cholinergic release event (termed “transients”). Cue-evoked glutamate release from mediodorsal thalamic (MD) input is necessary but not sufficient to evoke such cholinergic transients. The exact mechanisms underlying glutamatergic-cholinergic transient interactions are unknown. The neuromodulatory component of cholinergic activity influences glutamatergic-cholinergic transients primarily via stimulation of $\alpha 4\beta 2^*$ nAChR expressed by glutamatergic terminals (references in text; note that other thalamic inputs to cortical neurons are not shown). The exact temporal resolution of variations in neuromodulatory activity remains unclear and may depend on the functional context but is presently assumed to be on the scale of tens of seconds to minute(s) (the lower part of the figure is reproduced, with permission, from Figure 2 in Ref. 43).