Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Behavioral-cognitive targets for cholinergic enhancement

Martin Sarter

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 α4β2* 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.

Addresses
University of Michigan, Department of Psychology, 4030 East Hall, 530 Church Street, Ann Arbor, MI 48109, United States

Corresponding author: Sarter, Martin (msarter@umich.edu)

Current Opinion in Behavioral Sciences 2015, **4**:22–26

This review comes from a themed issue on **Cognitive enhancement**

Edited by **Barbara J Sahakian** and **Arthur F Kramer**

For a complete overview see the Issue and the Editorial

Available online 15th January 2015

http://dx.doi.org/10.1016/j.cobeha.2015.01.004

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 presynaptic 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 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 presynaptic 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 septo-hippocampal 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). α4β2* 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.

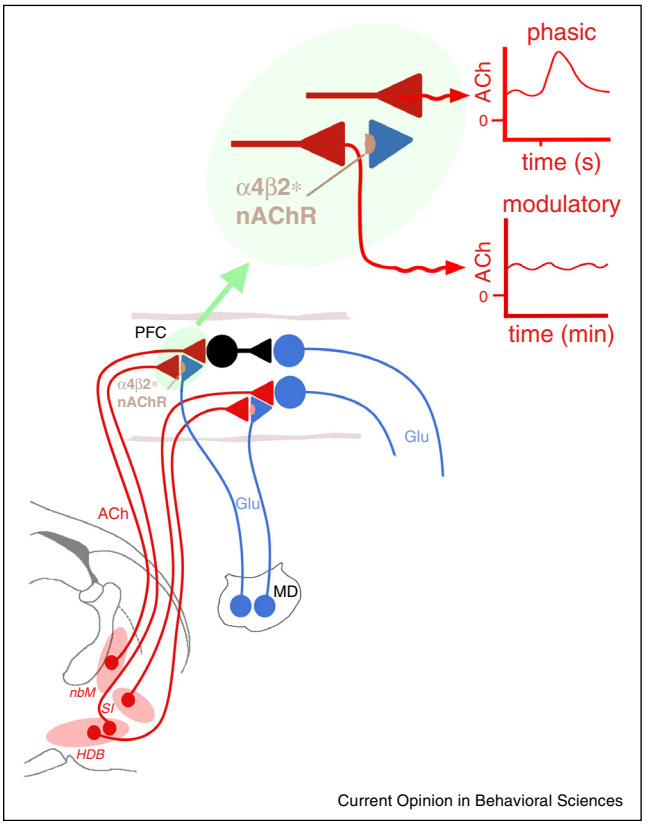
Cue detection forced by cholinergic transients

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

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 innominate (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 α4β2* 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 Fig. 2 in Ref. [43]