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Neuromodulation by Acetylcholine: Examples from Schizophrenia and Depression

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Abstract

The contribution of acetylcholine to psychiatric illnesses remains an area of active research. For example, increased understanding of mechanisms underlying cholinergic modulation of cortical function has provided insight into attentional dysfunction in schizophrenia. Acetylcholine normally enhances cortical sensitivity to external stimuli and decreases corticocortical communication, increasing focused attention. However, increases in ACh signaling can lead to symptoms related to anxiety and depression. For example, while stress-induced ACh release can result in adaptive responses to environmental stimuli, chronic elevations in cholinergic signaling may produce maladaptive behaviors. Here, we review several innovations in human imaging, molecular genetics and physiological control of circuits that have begun to identify mechanisms linking altered cholinergic neuromodulation to schizophrenia and depression.

Introduction

Acetylcholine (ACh) is a potent regulator of neuronal activity throughout the peripheral and central nervous system [1,2]; however, the specific contributions of cholinergic neuromodulation to circuit function in the healthy brain and in psychiatric illness have been difficult to dissect, due to its pleiotropic actions on neuronal excitability, synaptic transmission, and network dynamics. In the last few years, technological innovations in the areas of molecular genetics, physiology, and human imaging have provided new ways to understand how neuromodulation shapes circuits and behavior. In this review, we outline recent progress in understanding how cholinergic signaling contributes to circuits involved in two groups of psychiatric disorders, schizophrenia and major depressive disorder (MDD).

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Continued technical innovation will continue to bring us closer to the ideal of translating fundamental neuronal mechanisms to the understanding and treatment of psychiatric illness.

Cholinergic sources and receptors

The two sources of ACh in the CNS are (1) projection nuclei that diffusely innervate distal areas and (2) local interneurons that are interspersed among their cellular targets. Cholinergic projection nuclei include the pedunculopontine (PPT) and laterodorsal (LDT) tegmental areas and the basal forebrain complex, including the medial septum [3–5]. In contrast, cholinergic interneurons are typified by the tonically active cells of the striatum and nucleus accumbens [6]. There is also evidence for a small population of cholinergic interneurons in the neocortex [7,8] and hippocampus [9].

The actions of ACh are mediated by two major classes of receptors: metabotropic muscarinic receptors (mAChRs) and ionotropic nicotinic receptors (nAChRs) [reviewed in 10,11]. Briefly, mAChRs are G protein-coupled and categorized by signaling through either $G\alpha_q$ (M1, M3, M5 subtypes) or $G\alpha_i$ (M2, M4 subtypes). In contrast, nAChRs function as nonselective, excitatory cation channels and occur as either homomeric or heteromeric assemblies of a large family of alpha- ($\alpha 2$-$\alpha 7$) and beta- ($\beta 2$-$\beta 4$) subunits.

Considerable debate has focused on whether cholinergic signaling occurs via traditional synapses with closely apposed pre- and postsynaptic membranes or via volume transmission mediated by diffusion through the extracellular space [12,13]. While a detailed discussion of this topic is beyond the present scope, several studies have suggested that ACh acts primarily by volume transmission. There is an anatomical mismatch between the sites of ACh release and the location of cholinergic receptors [14–16], and extracellular levels of ACh fluctuate in a manner that appears to be inconsistent with localized clearance of a synaptic transmitter [17–19]. More recently, however, it has become clear that volume transmission may be insufficient for the rapid transfer of cholinergic signals measured using electrochemical recordings in behavioral tasks such as prefrontal cortex (PFC)-dependent cue-detection or sustained attention [20,21]. In addition, optogenetic stimulation of endogenous Ach release has revealed fast excitatory transients mediated by nAChRs in neocortical GABAergic interneurons [22–24]. These rapid cholinergic signals are a key element in a cortical network underlying auditory fear learning [25]. The development of tools allowing more precise stimulation of ACh neurons *in vivo* [22–24] has been an innovation that has already altered our view of cholinergic neuromodulation.

Cholinergic function and dysfunction in neuropsychiatric disease

The neuromodulatory effects of ACh signaling are critical for normal function of numerous brain systems. Accordingly, abnormalities in the cholinergic system are known to contribute to a number of psychiatric and neurological illnesses. In the periphery, autoantibodies to muscle nAChRs contribute to myasthenia gravis [26,27]. Moreover, loss of cholinergic neurons and receptors in the brain contribute to the cognitive decline in Alzheimer's disease [28] and may contribute to the progression of Alzheimer's and Parkinson's disease [29]. More recently, advances in understanding the modulation of ACh signaling in cortical and subcortical circuits has revived interest in understanding how cholinergic dysfunction may

contribute to psychiatric illnesses such as schizophrenia and depression. Here, we will review the evidence for cholinergic involvement in these two disorders.

ACh in schizophrenia and attention

Schizophrenia consists of positive symptoms, such as disordered thoughts, delusions, and hallucinations, and negative symptoms, such as blunted affect and social withdrawal. In addition, cognitive disturbances including reduced attention and working memory are frequently present [30]. Prevailing hypotheses of the pathophysiology underlying schizophrenia have largely focused on monoamines like dopamine and serotonin. However, there is increasing evidence from clinical and preclinical studies that aberrant ACh signaling may also contribute to the disease.

Epidemiological studies have long shown that schizophrenics exhibit higher rates of tobacco smoking than the general population, suggesting that patients may use nicotine (an agonist of nAChRs) for self-medication [31,32]. Moreover, genome-wide association studies link copy number variations of a locus containing the α7 nAChR with elevated risk for schizophrenia [33]. Indeed, reduced α7 nAChR expression has been observed in the hippocampus and cingulate cortex of post-mortem brains from schizophrenic patients [34,35]. In addition, individuals with schizophrenia show greatly decreased upregulation of high affinity nAChRs as a result of smoking compared to control subjects, suggesting that the high rates of smoking in schizophrenia may be influenced by the diminished effect of nicotine on this cholinergic receptor subclass [31,32]. However, these findings are partially confounded by observations that antipsychotic treatment may also reduce nAChR binding [36]. Nicotinic stimulation produces well known enhancements of attention and working memory [37,38]; however, nAChR agonists have yielded mixed results in clinical trials, and pharmacotherapies directed at nicotinic signaling remain an area of active research [39].

Aberrant signaling through mAChRs is also implicated in schizophrenia, as postmortem studies of patients have revealed a decrease in expression of these receptors throughout the brain, including the prefrontal cortex and hippocampus [40–42]. Perhaps more telling is the observation that muscarinic antagonists produce psychosis-like symptoms in healthy individuals and exacerbate existing symptoms in schizophrenia patients [43,44]. Notably, a recent study of the mixed M1/M4 agonist xanomeline found significant cognitive improvements in patients, though peripheral side effects continue to pose problems for muscarinic-based therapies [45].

Despite these clinical observations, mechanistic links between the cellular actions of ACh and the pathophysiology of schizophrenia have been difficult to establish. Instead, current research has focused largely on the contribution of cholinergic activity to normal behaviors that are known to be disrupted in schizophrenic patients, such as attention and working memory.

Cholinergic activity in the rodent neocortex has been linked to control of circuits underlying attention, cue detection, and short-term memory, cognitive abilities that are disrupted in schizophrenic patients [30]. Lesions of cholinergic inputs arising from the basal forebrain impair tests of sustained attention [46–48]. In addition, stimulation ofα4β2 nAChRs in the

medial prefrontal cortex enhances performance in a visual attention task [49], while genetic deletion of these receptors in the mPFC impairs visual attention [50] and auditory discrimination [51]. Similarly, stimulation of α7 nAChRs in PFC modulates glutamatergic signaling through NMDA receptors, influencing circuits important for working memory performance [52]. Notably, transient rises in prefrontal ACh are significantly correlated with cue detection, suggesting that the temporal dynamics of cholinergic signaling are also critical for normal behavior [20]. In primates, locally applied ACh enhances the attentional modulation of neuronal activity in the primary visual cortex, while the muscarinic antagonist scopolamine reduces the effects of attention [53]. Similarly, optogenetic activation of cholinergic neurons in the basal forebrain enhanced visual responsiveness in mouse cortex and improved performance on a visual discrimination task [54]. Taken together, these findings suggest that cholinergic actions across both ionotropic and metabotropic receptors and diverse brain areas contribute to cognitive processing.

At the cellular level, ACh increases the excitability of many classes of neurons, including pyramidal cells and dendrite-targeting GABAergic interneurons via activation of both mAChRs and nAChRs [22,55–59]. ACh also modulates synaptic transmission. Activation of α4β2 nAChRs on thalamocortical terminals enhances glutamate release in both sensory and association cortex [60–62], whereas activation of mAChRs on terminals of soma-targeting parvalbumin-expressing interneurons decreases the probability of GABA release [63]. GABAergic inhibition normally reduces the response of cortical neurons to feed-forward excitation [64,65], and decreased GABA release therefore enhances the ability of thalamocortical inputs to stimulate pyramidal neuron firing [63]. In contrast, mAChRs located on pyramidal cell axon terminals suppress cortico-cortical transmission [60,62,66,67]. The simultaneous enhancement of feed-forward inputs from the thalamus and suppression of intra-cortical feed-back may increase the “signal-to-noise” ratio in cortical networks [68]. The most recent data therefore suggest that the role of cholinergic modulation in the cortex is to make neurons more sensitive to external stimuli, thereby increasing focused attention to sensory input (Fig. 1).

Acetylcholine signaling in stress and depression

As in schizophrenia, the primary medications for MDD target the monoamine system, but the contribution of the cholinergic system to affective disorders is becoming more evident. Recently, human imaging studies have revived the idea, first proposed in the 1970’s [69], that increased cholinergic signaling can contribute to depression. Peripheral administration of the acetylcholinesterase (AChE) antagonist physostigmine induces symptoms of anxiety and depression in human subjects by decreasing the breakdown of ACh and increasing levels of the neurotransmitter in the brain [70]. Furthermore, in SPECT imaging studies, individuals with major depressive disorder or bipolar disorder who are actively depressed have lower availability for the radiotracer 5IA binding to nAChRs throughout the brain. This result is observed despite the absence of altered nAChR number in postmortem cortical tissue [71,72]. Increasing ACh levels in human brain by physostigmine challenge also displaces 5IA binding [73]. Thus, individuals who are actively depressed appear to have significantly higher levels of extracellular ACh than healthy subjects, suggesting that increased ACh signaling may contribute to the etiology of depression.

Rodent studies confirm that increasing ACh levels by treating with physostigmine acutely can induce anxiety- and depression-like behaviors, whereas chronic treatment with the serotonergic antidepressant fluoxetine increases levels and activity of AChE, particularly in the hippocampus [74]. Local administration of physostigmine or knockdown of AChE in the hippocampus is sufficient to increase anxiety- and depression-like behaviors that can be reversed by administration of fluoxetine, suggesting that they are consistent with symptoms of depression [74]. Taken together, these studies show that hyperactive ACh signaling in hippocampus can contribute to depressive symptoms.

The effects of increasing ACh release on the dynamics of hippocampal activity are complex, and the specific alterations linked to regulation of depression-like symptoms are unclear. Increasing ACh signaling in the CA1 region of the hippocampus using physostigmine in a hippocampal slice results in depolarization of postsynaptic interneurons, mediated through M2/M3 mAChRs [75]. Optogenetic stimulation of cholinergic terminals in CA1 also increases activity of α4/β2* nAChRs and depolarizes a subpopulation of GABAergic interneurons in the stratum lacunosum moleculare [23], suggesting that one mechanism underlying the effects of cholinergic signaling on anxiety and depression may be activation of inhibitory interneurons. In contrast, lower levels of cholinergic stimulation in CA1 hyperpolarizes a subset of interneurons via M4 mAChRs and entrains others into a rhythmic bursting pattern [75]. Elevated ACh may therefore modulate hippocampal activity by switching CA1 networks from a quiescent or stable bursting state, to a more depolarized state with a higher level of firing.

Cholinergic signaling in the hippocampus, amygdala, prefrontal cortex (PFC), and striatum modulates behavioral responses to stressors [76–80]. Despite the fact that global and hippocampal increases in ACh tone result in anxiety- and depression-like behaviors [74], the effects of cholinergic signaling on stress-related behaviors are complex and vary across brain areas. Stress induces release of ACh in the hippocampus and PFC [81] but not the amygdala [82], perhaps because the basal firing rate of medial septal neurons innervating the amygdala is high [83] and stress cannot further increase ACh levels. Similarly, basal ACh tone in the striatum is high due to tonic firing of intrinsic cholinergic interneurons, and behaviorally relevant stimuli result in a pause in their firing leading to cue-dependent learning [84]. These findings suggest that healthy behavior is dependent on appropriately balanced cholinergic signaling across brain regions (Fig. 2).

Supporting this view, stress impairs PFC-mediated working memory [85], but cholinergic signaling through α7-type nAChRs is important for tuning glutamatergic signaling in the dorsolateral PFC and improving working memory [52]. Accordingly, both stress [18] and relief from stress [82] can increase ACh levels in the PFC. Similarly, silencing striatal cholinergic interneurons leads to depression-like behaviors [80]. Thus, increased ACh signaling in the brain may have differential effects (Fig. 2) depending on whether there is already high cholinergic tone in a particular brain area at baseline (amygdala, striatum), and whether the brain area is involved in avoidance behaviors (amygdala, hippocampus) or adaptive coping behaviors (PFC, striatum).

The ability to withdraw from stressful stimuli and decrease exploration in response to an immediate threat is likely to be highly favored in evolution. Following chronic stress, this adaptive response can lead to maladaptive induction of a depression-like state [86,87]. Exposure to an acute stress may lead to adaptive behavioral responses mediated through ACh release in the hippocampus, whereas chronic increases in ACh signaling can lead to mood disorders, perhaps by evoking synaptic plasticity in different neuronal subtypes throughout the hippocampus [88] and contributing to encoding memories of stimuli associated with stressful events [89]. Similarly, plasticity in the amygdala strengthens associations between environmental cues and stressful events and therefore is also likely to contribute to maladaptive learning leading to mood and anxiety disorders [78,90].

CONCLUSIONS

Despite decades of work, a complete understanding of the role of ACh in brain function remains elusive. However, recent methodological advances for monitoring and manipulating cholinergic systems have broadened our knowledge of the cellular mechanisms underlying ACh signaling. Similarly, new human imaging studies have highlighted the role for distinct cholinergic systems in behavior. One principal conclusion to be drawn from the wealth of current data is that cholinergic modulation is best viewed as the synergistic alteration of neuronal function at the synaptic, cellular, and network levels. Thus, improved therapies for neuropsychiatric disorders such as schizophrenia and depression will require interventions directed at specific cholinergic receptor subtypes and cell classes. For example, GABAergic interneurons provide an intriguing focus for their role in linking nAChR activity, cortical circuit function, and behavior. Future research directions must continue to emphasize the interactions of clinical and preclinical studies, ultimately bridging bench and bedside.

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Highlights

ACh boosts attention by enhancing sensory stimuli and decreasing cortico-cortical communication.

Increased ACh signaling can lead to symptoms of depression in humans and animal models.

Novel techniques have helped elucidate the role of ACh in schizophrenia and depression.

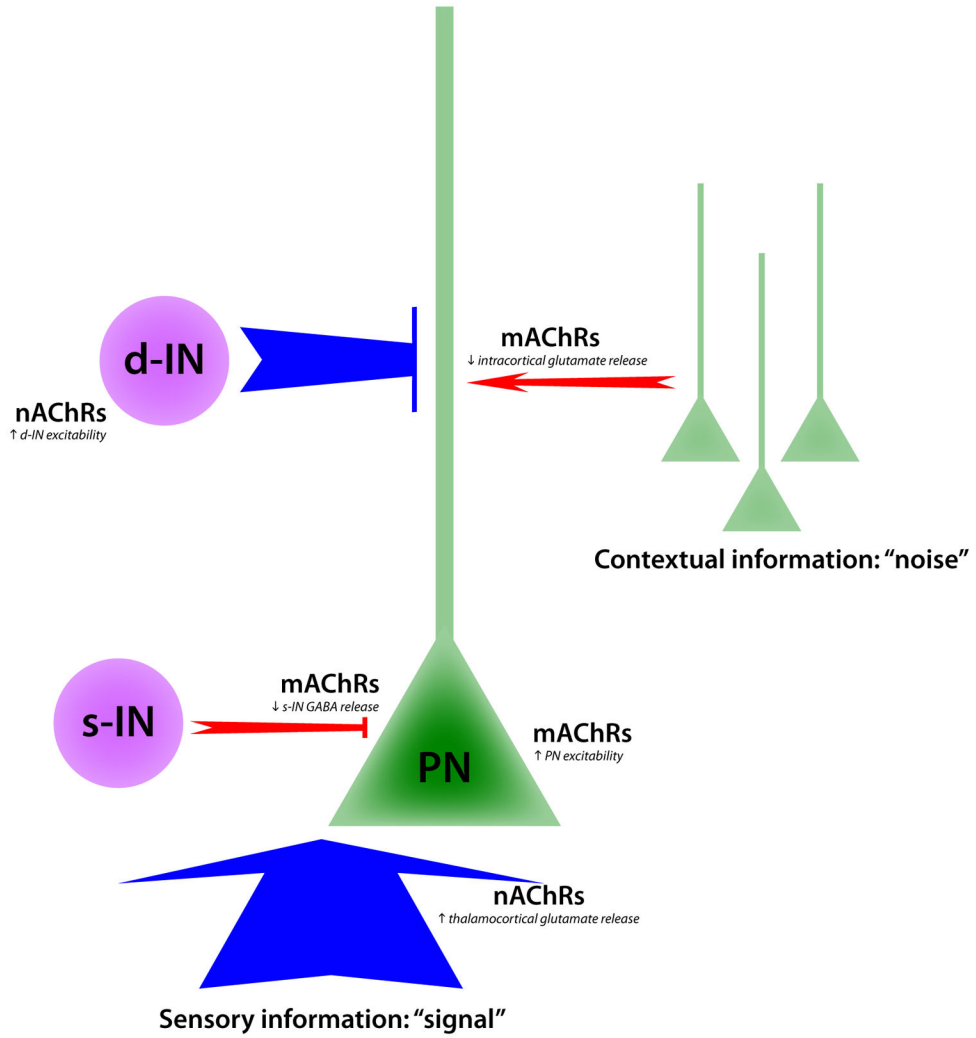

Figure 1.

Circuit mechanisms underlying cholinergic modulation of attention. In the schematic, ACh enhances sensory-evoked signals and limits the impact of noisy contextual inputs by strengthening pathways shown in blue and weakening pathways shown in red. Activation of nAChRs increases glutamate release from thalamocortical afferents, while mAChR activity increases the excitability of pyramidal neurons (PNs) and reduces GABA release from soma-targeting interneurons (s-INs). At the same time, mAChRs reduce intracortical glutamate release while nAChRs increase the excitability of dendrite-targeting interneurons (d-INs) that regulate synaptic integration. increases the release of glutamate from thalamocortical terminals.

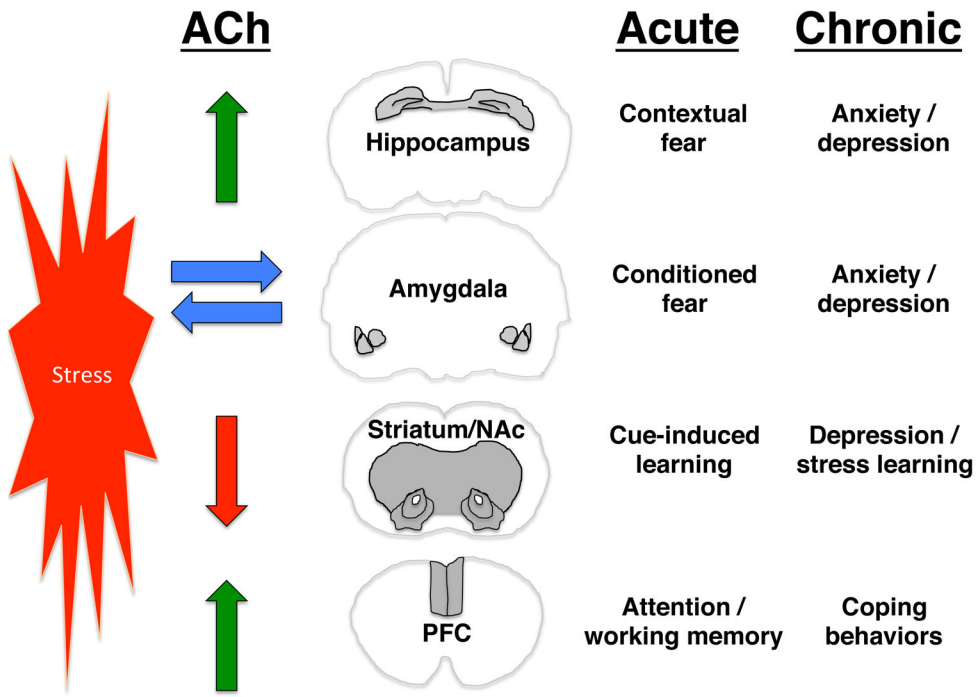

Figure 2.

Circuits involved in cholinergic modulation of mood and anxiety. The schematic demonstrates the differential effects of stress on ACh release. Stress induces increases in ACh release in the hippocampus and prefrontal cortex (PFC), has less of an effect on the already high levels of ACh in the amygdala, and decreases firing of the cholinergic interneurons in the striatum/nucleus accumbens (NAc). Relief of stress also increases ACh release in the PFC. The acute effects of stress-induced changes in ACh signaling area likely to be adaptive and to lead to behaviors that promote learning to change behavior and avoid stressors, whereas chronic stress may result in maladaptive plasticity downstream of ACh signaling that can lead to anxiety and mood disorders.