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Cholinergic Regulation of Mood: From Basic and Clinical Studies to Emerging Therapeutics

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Abstract

Mood disorders are highly prevalent and are the leading cause of disability worldwide. The neurobiological mechanisms underlying depression remain poorly understood, although theories regarding dysfunction within various neurotransmitter systems have been postulated. Over 50 years ago, clinical studies suggested that increases in central acetylcholine could lead to depressed mood. Evidence has continued to accumulate suggesting that the cholinergic system plays a important role in mood regulation. In particular, the finding that the antimuscarinic agent, scopolamine, exerts fast-onset and sustained antidepressant effects in depressed humans has led to a renewal of interest in the cholinergic system as an important player in the neurochemistry of major depression and bipolar disorder. Here, we synthesize current knowledge regarding the modulation of mood by the central cholinergic system, drawing upon studies from human postmortem brain, neuroimaging, and drug challenge investigations, as well as animal model studies. First, we describe an illustrative series of early discoveries which suggest a role for acetylcholine in the pathophysiology of mood disorders. Then, we discuss more recent studies conducted in humans and/or animals which have identified roles for both acetylcholinergic muscarinic and nicotinic receptors in different mood states, and as targets for novel therapies.

INTRODUCTION

Mood disorders are the leading cause of disability worldwide. Two major categories of mood disorder, major depression and bipolar disorder, are estimated to occur in the general population at rates of 18% and 2–3%, respectively[1–3]. Dysfunction within various neurotransmitter systems, including the serotonergic, noradrenergic, dopaminergic, GABAergic, glutamatergic, and endorphinergic systems have been hypothesized to underlie mood disorders due to the mechanism of action of pharmacological treatments that target these systems, and biological findings[4–6]. The recent finding that the antimuscarinic agent, scopolamine, induces fast-onset and sustained antidepressant effects in depressed patients has renewed interest in understanding the role of the cholinergic nervous system in mood regulation[7–11].

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Drs. Dulawa and Janowsky declare no conflict of interest.

As early as 1950, clinical research observations suggested that increases in central acetylcholine (ACh) could lead to depressed mood[12–14]. In the 1970s, this possibility was further elaborated as the adrenergic-cholinergic balance hypothesis of mania and depression[15]. As proposed by Janowsky et al. (1972), this hypothesis posited that depression involved a central predominance of acetylcholinergic to noradrenergic tone, while mania resulted from the converse[15]. This theory was then reformulated as the catecholaminergic-cholinergic balance hypothesis of mania and depression, which integrated more recent findings incorporating the role of dopamine, a neurotransmitter integral to the regulation of mood[16].

Since the role of catecholamines, and dopamine in particular, have been reviewed previously[17–19], this review will primarily summarize current knowledge regarding the modulation of mood by the central cholinergic system. Human postmortem brain, neuroimaging, drug challenge, and animal model studies have examined the role of the cholinergic system in mood regulation. Here, we first describe an illustrative series of early discoveries which have suggested a role for acetylcholine in the pathophysiology of mood disorders. We will then discuss more recent studies conducted in humans and/or animals which have investigated the role of acetylcholinergic muscarinic and nicotinic receptors in different mood states, and as targets for therapeutics.

CHOLINERGIC REGULATION OF MOOD

Acetylcholinesterase Inhibitors, ACh receptor agonists, and ACh Precursor Effects on Mood in Humans

The earliest observations of a potential link between acetylcholine and depression were based on clinical observations of the effects of ACh receptor (AChR) agonists, which activate AChRs, and acetylcholinesterase inhibitors (AChEIs), which prevent the breakdown of ACh by acetylcholinesterases (AChEs). AChEIs compose a class of insecticides used in agriculture, and nerve agents used in wartime. Exposure to AChEIs increases acetylcholine levels in both the central nervous system and the periphery, causing toxic and potentially lethal respiratory, central nervous system, and cardiovascular effects.

Several early reports indicated that individuals exposed to AChEI insecticides or potential nerve agent weapons developed psychiatric symptoms including psychotic phenomena, anxiety, and most commonly, depression. In 1950, Rowntree et al. found that administration of the irreversible AChEI diisopropylflurophosphonate (DFP) to bipolar patients reduced manic symptoms and induced depression[12]. Furthermore, when administered to normal or depressed patients, DFP increased depressive symptoms and in some, activated psychotic symptoms. Gershon and Shaw (1961) reported that agricultural workers chronically exposed to AChEI insecticides became depressed or psychotic[13]. Bowers et al. (1964) tested the AChEI, EA 1701, in army volunteers and reported onset of depression[14]. Moreover, early animal behavioral pharmacological studies reported similar findings. For example, both the cholinergic muscarinic agonist arecoline and the AChEI physostigmine reduced rodent intracranial self–stimulation (ICSS), a measure of reward threshold[20, 21].

Subsequently, a number of investigators formally studied the psychiatric and behavioral effects of AChEI challenges (Table 1). Janowsky et al. (1973) reported that in patients with bipolar or major depressive disorder, an acute challenge with the centrally active and reversible AChEI, physostigmine, antagonized manic symptoms and induced depressive symptoms, including apathy, slowness of thought, and psychomotor retardation[22]. Similar studies replicated the antimanic effects of physostigmine in bipolar patients[23, 24]. Furthermore, an acute physostigmine challenge also precipitated depressive symptoms in psychiatric inpatients, especially those with a history of major depression[22]. Other reports indicated that physostigmine treatment also induces depressive symptoms in a minority of control subjects[25–27]. Recently, the AChEI donepezil was reported to induce more frequent relapse of depression in older patients with mild cognitive impairment[28, 29]. Furthermore, Altinyazer et al. (2016) showed that among individuals with major depression living in agricultural districts, red blood cell acetylcholinesterase activity levels negatively correlated with the number of past suicide attempts and hopelessness levels[30]. These reports are consistent with more recent SPECT imaging studies suggesting that levels of acetylcholine are increased throughout the brain in depressed unipolar and bipolar patients[31]. Thus, considerable evidence suggests that AChEIs reduce elevated mood during mania, increase depressive symptoms in depressed patients, and induce depression in euthymic individuals with a personal or family history of depression.

Acetylcholine precursors, such as deanol, choline, and lecithin, have also been reported to cause depression, and paradoxically hypomania in some cases. Tamminga et al. (1976) reported that choline precipitated depression in 2 out of 4 patients with tardive dyskinesia[32], and Growdon et al. (1977) reported that 2 out of 20 patients with tardive dyskinesia became withdrawn and apathetic[33]. Casey (1979) reported that high doses of deanol caused severe depression in 5 out of 33 movement disorder patients, and 3 of the 33 became hypomanic[34]. Overall, patients who developed mood symptoms had a history of affective disorder. Subsequent studies with the AChergic precursor citicoline showed mixed effects, with either no mood effects or reduced depressive symptoms when given along with agents including rivastigmine, citalopram, or lithium[35,36,37,38].

Procholinergic Agents Induce Biomarkers of Depression in Humans

Cholinergic agents including AChEIs and muscarinic agonists have also been reported to influence the expression of biomarkers linked to mood disorders, including effects on neuroendocrine measures, sleep, and pupillary size. Serum levels of adrenocorticotropic hormone (ACTH)[39, 40], cortisol[41–43], and beta endorphin[44–46], have been reported to be increased in depressed patients, as has cortisol non-suppression by dexamethasone. Similarly, increasing acetylcholine levels with physostigmine treatment has been reported to increase serum ACTH, cortisol, and beta endorphin[27, 47, 48]. Furthermore, physostigmine-induced increases in ACTH and beta endorphin were exaggerated in depressed patients compared to normal volunteers[49]. Physostigmine also induced non-suppression of cortisol by dexamethasone in normal adults[50]. Subsequently, a sex difference was reported in which low doses of physostigmine increased serum levels of ACTH and cortisol in females with a history of depression[51], but not in males.

Specific changes in sleep architecture are also endophenotypic markers of clinical depression observed in depressed patients and their asymptomatic relatives[52]. These changes include increases in rapid eye movement (REM) sleep duration, increases in REM density, reductions in REM latency, decreases in slow wave sleep, and disturbances in sleep continuity[52, 53, 54, 55]. These sleep alterations result in part from perturbations in the cholinergic system, with procholinergic influences inducing depression-relevant sleep effects[56]. Thus, the AChEI, galantamine, increases REM tonic activity and decreases REM latency[57]. Administration of procholinergic agents including physostigimine[58], donepezil[59], arecoline[60–63], or pilocarpine[64, 65] to controls reduces REM latency, and increases REM density. Furthermore, Laurer et al. (2004) found that the cholinergic muscarinic agonist RS 86 induced REM latency super-shortening in high risk individuals without a history of depression, and this was a predictor of a subsequent first major depressive episode[66]. Similarly, Perlis et al. (2002) discriminated control versus depressed patients by their response to donepezil. Controls showed no REM latency changes following low dose treatment, whereas depressed patients showed decreased REM latency[67]. Similarly, asymptomatic relatives of depressed patients showed a parallel vulnerability to cholinergic stimulation[67]. Furthermore, vulnerability to physostigmine-induced REM hypersensitivity is highly correlated in monozygotic twins, suggesting a genetic component to this phenomenon[68].

In contrast to the effects of cholinomimetic agents on sleep, several reports have indicated that the centrally active antimuscarinic, scopolamine, increases REM latency and suppresses REM density and duration in depressed patients[69, 70]. Furthermore, these scopolamine effects are evident following remission[71]. Thus, antagonizing muscarinic receptors produces effects on REM sleep that are opposite of those observed in depressed patients.

Another biomarker observed in depressed patients is pupillary sensitivity to cholinergic agonists. Depressed patients exhibited significantly greater reductions in pupillary diameter following administration of the muscarinic agonist pilocarpine than did controls, suggesting increased muscarinic sensitivity[72]. Conversely, a report by Sokolski and DeMet (2000) showed decreased pupillary sensitivity to pilocarpine in manic patients, a phenomenon which was reduced with lithium treatment[73].

AChEIs and ACh Agonist Effects on Mood in Rodents

Similar to findings in humans, a number of rodent studies have also demonstrated that treatment with AChEIs or cholinergic agonists induce depression-like behaviors (Table 2). Picciotto and colleages, as well as others, have shown that systemic administration of physostigmine to mice increases depression-like behaviors including social avoidance following social defeat[74], immobility in the forced swim test (FST)[75–77], and immobility in the tail suspension test (TST)[76, 78]. Furthermore, some of these pro-depressive effects were more pronounced in male than female mice[76, 77]. The pro-depressive effects of systemic physostigmine treatment in the TST were blocked by acute treatment with either scopolamine, a broad muscarinic antagonist, or mecamylamine, a broad nicotinic antagonist[74]. Additionally, physostigmine treatment increased anxiety-like behavior in mice, including time spent in the dark side of the light/dark box, and time spent in the center of the

open field[76, 77]. Treatment with either physostigmine or pilocarpine also decreased rates of intracranial self-stimulation (ICSS) of the ventral tegmental area (VTA), reflecting increased anhedonia[79]. These depressogenic effects of physostigmine are observed despite tight regulation of AChE through negative feedback pathways at the mRNA, protein, and activity levels. For example, significant adaptation has been observed following knockout of AChE isoforms[80], and exposure to AChEIs leads rapidly to upregulation of AChE mRNAs[81]. Furthermore, stress induces alternative splicing of AChE mRNAs and modulation of AChE activity[82, 83].

Local intracerebral drug infusion studies in rodents have implicated several brain regions in the depressogenic effects of procholinergic drug treatments. For example, intra-VTA infusion of physostigmine increased immobility time in the FST[75], decreased time spent on open arms in the elevated plus maze, and decreased sucrose preference[84], indicating increased anxiety and anhedonia, respectively. Furthermore, intra-VTA infusion of pilocarpine produced similar effects[84]. Conversely, intra-VTA infusion of scopolamine or mecamylamine decreased baseline immobility time in the FST, indicating antidepressant-like effects[75].

Mineur et al. (2013) assessed the effects of chronic fluoxetine treatment on AChE activity in multiple brain regions, and found that chronic fluoxetine increased AChE activity, specifically in the hippocampus[74]. To test the hypothesis that signaling at Ach receptors could contribute to depression-like behavior, physostigmine was infused locally into the hippocampus and behavior in the TST was assessed. Consistent with this hypothesis, intra-hippocampal physostigmine increased immobility, reflecting depression-like behavior[74]. Additionally, knockdown of AChE in the hippocampus using an adeno-associated virus (AAV) approach increased anxiety in the open field test and the light/dark test, and increased depression-like behavior in the FST, TST, and social defeat paradigm[74]. Additionally, 15 days of treatment with fluoxetine prevented the effects of viral hippocampal AChE knockdown in the social defeat paradigm[74].

Work by Chau et al. (2011) suggests that fluoxetine treatment produces antidepressant-like effects in the FST by reducing cholinergic activity in the nucleus accumbens (NAc)[85]. Specifically, intra-NAc infusions of fluoxetine reduced extracellular acetylcholine and increased active behavior in the FST[85]. Furthermore, exposure to the FST, a potent stressor, increased basal extracellular acetylcholine in the NAc shell for up to 14 days, while chronic fluoxetine treatment prevented this effect[85]. Similarly, intra-NAc infusions of the muscarinic acetylcholine receptor (AChR) agonist arecoline reduced active behavior[86], and intra-NAc infusions of neostigmine produced a conditioned taste aversion [87]. This depressant-like effect may be mediated in part through activation of muscarinic 1 acetylcholine receptors (M1-AChRs)[88], since blocking these postsynaptic receptors with the specific M1-AChR antagonist pirenzepine increased swimming in the FST[86]. On the other hand, activation of M2 acetylcholine autoreceptors, which are Gi-coupled, reduces ACh release and has antidepressant-like effects. Accordingly, the acetylcholine M2-AChR antagonist gallamine induces pro-depressant effects[86]. Finally, intra-NAc infusion of scopolamine increases active behavior in the FST, indicating an antidepressant-like effect[86]. However, Warner-Schmidt et al. (2012) reported that silencing cholinergic interneurons in the NAc induced a depression-

like phenotype in mice[89]. Since the cholinergic interneurons of the NAc synapse locally onto other neurons within the NAc, and are the only source of ACh in the striatum, these results appear to contrast with findings that intra-NAc scopolamine infusions produced antidepressant effects[86]. This inconsistency might be explained by the positioning of cholinergic interneurons within microcircuits of the NAc, which theoretically could preferentially influence M2-over M1-AChRs. In sum, AChRs in the VTA, hippocampus, and NAc appear to regulate depression-like behaviors in rodent models.

Muscarinic Effects of Physostigmine and Arecoline in Humans

Early studies suggested that muscarinic AChRs (M-AChRs) are important for the mood altering effects of acetylcholine. The depressogenic effects of low dose physostigmine were reversed by administration of atropine, a centrally active antimuscarinic agent[90], or scopolamine[91]. Direct muscarinic agonists have also been reported to reduce mood. Specifically, the direct muscarinic agonists arecoline[92, 93], and oxotremorine[94] worsened mood state in both euthymic and bipolar patients. Similarly, the M1-AChR agonist, RS 86, was reported to have antimanic effects[95].

Similarly, a series of studies specifically investigated whether the depression-like effects of physostigmine are mediated by muscarinic receptors, and whether these effects are mediated centrally or peripherally. Studies dissecting the mechanisms of action of physostigmine on behavioral, neuroendocrine, cardiovascular, and sleep measures have largely implicated central muscarinic receptors in these actions. Whereas centrally acting physostigmine causes significant behavioral, neuroendocrine, cardiovascular, and sleep effects in humans, equipotent doses of the non-centrally acting AChEI, neostigmine, does not[91, 96, 97]. Furthermore, these effects of physostigmine can be blocked by the centrally acting antimuscarinic agent, scopolamine[91], which is a high affinity antagonist at the five known muscarinic receptors and does not act at nicotinic receptors[98]. The effects of physostigmine are not prevented by treatment with the peripherally acting antimuscarinic agent, methscopolamine[91], suggesting a central effect.

Muscarinic Receptor Alterations in Mood Disorders

A body of research has explored central muscarinic receptor expression in controls, depressives and/or bipolar patients using in vivo imaging, positron emission tomography (PET), or radioligand binding in postmortem brain samples. Several reports have identified a reduction in M2-AChR and M4-AChR density in both bipolar and major depressive disorder patients. Activation of M2-AChRs or M4-AChRs, which are autoreceptors, reduces acetylcholine release from cholinergic terminals[99]. Thus, reduced expression of these receptors might increase Ach release. Cannon et al. (2006) used PET imaging to investigate central M2-AChR receptor density using [(18)F]FP-TZTP in unmedicated major depressive and bipolar disorder patients. They found that bipolar patients showed a lower distribution volume of M2-AChR in the anterior cingulate cortex (ACC) compared to both major depressive disorder and control groups[100]. This decrease in distribution volume could have resulted from reduced M2-AChR density or affinity, or increased endogeneous acetylcholine levels which could reduce radioligand binding to M2-AChRs. Indeed, increased central choline levels have been found in depressed patients[101, 102]. Studies applying the M2/4

receptor antagonist, [3H] AFDX-384, to post-mortem brain tissue from patients with major depressive or bipolar disorder also reported reduced M2-AChR and M4-AChR binding in Broadman's area 46 of the dorsolateral prefrontal cortex[103]. Furthermore, a decrease in binding of the M3-AChR antagonist, [3H]4-DAMP, in Broadman's area 10 indicated a decrease in M3-AChR expression in the rostral prefrontal cortex in bipolar patients[103]. More recently, Gibbons et al. (2016) measured M2-AChR and M4-AChR binding in Broadman's Area 24 and 46 of the dorsolateral prefrontal cortex using post-mortem tissue from controls, bipolar disorder patients, or major depressive patients[103]. Results showed that both M2-AChR and M4-AChR binding was lower in Broadman's area 24 and 46 of the dorsolateral prefrontal cortex in mood disorder patients relative to controls.

However, other reports have not replicated muscarinic receptor density changes in depression or bipolar disorder. For example, Zavitsanou et al (2005) assessed [(3)H]AF-DX 384 binding in the ACC to determine M2-AChR and M4-AChR binding in control, major depression, and bipolar patients[104]. However, no differences in receptor binding were found. Furthermore, an experiment using quantitative autoradiography to measure [(3)H]pirenzepine binding to M1-AChR and M4-AChR receptors in post-mortem tissue also found no difference in binding in bipolar and major depression groups compared to controls[105]. Additionally, a study using a [3H]4-DAMP radioligand binding assay which was modified to increase selectivity for the M3-AChR showed that cortical M3-AChR levels were not altered in major depression or bipolar disorder[106]. Heterogeneity in the etiology underlying mood disorders may be a factor leading to discrepant findings between studies[107, 108].

ANTIMUSCARINIC TREATMENT STUDIES

Fast-onset Antidepressant Effects of Scopolamine in Humans

In the early 1980's, Janowsky et al. (1983) proposed that centrally active anticholinergic drugs might be effective antidepressants[109, 110]. Although anticholinergics were reported to cause a "high" in recreational users[111–113], and scopolamine was found to be effective in antagonizing the behavioral, cardiovascular, sleep, and neuroendocrine effects of AChEIs[91], definitive proof that anticholinergics like scopolamine alleviated depression in humans remained elusive. In the next two decades, several randomized controlled trials (RCTs) assessed the effects of scopolamine or the antimuscarinic biperiden in depressed patients, but did not conclusively identify antidepressant effects of these drug treatments[114, 115]. However, Gillin et al. (1991) reported a small but significant antidepressant effect of scopolamine administered intramuscularly for three consecutive nights compared to placebo[116].

Studies published beginning in the mid-2000s by the National Institute of Mental Health (NIMH) Intramural Mood and Anxiety Disorders Program demonstrated that when administered at a higher dosage by the intravenous (i.v.) route, 4 μg/kg scopolamine exerted fast-onset antidepressant effects. After an open placebo infusion, major depressive disorder and bipolar patients received a series of three 15 min infusions of placebo followed by a series of three infusions of scopolamine, or the reverse sequence, each infusion pulsed 3–5 days apart. The placebo adjusted remission rate with scopolamine was 56%, with an onset of

3 days, persisting for at least 15 days[7]. Anti-cholinergic side effects were well tolerated. The same group replicated these findings in a major depressive group. Results showed that scopolamine also decreased anxiety, and produced larger reductions in anxiety symptoms in women than men[9]. Subsequent trials by the NIMH group have also shown the rapid-onset antidepressant effects of i.v. scopolamine, and identified characteristics of responders. Scopolamine induced antidepressant effects in treatment resistant major depressive and bipolar patients, and also produced larger antidepressant effects in treatment naïve patients[11]. Furthermore, scopolamine was more effective in patients with greater self-rated depressive symptoms at baseline[10]. In summary, i.v. infusion of scopolamine has been identified as a rapid-onset antidepressant with sustained effects for major depression and bipolar disorders. Also, one study by Khajavi et al. (2012) reported antidepressant effects of orally administered scopolamine. This study evaluated whether scopolamine could augment the effects of a classical antidepressant in major depressive disorder patients. In this RCT, a combination of the SSRI antidepressant citalopram (40 mg/day) plus oral scopolamine hydrobromide (1 mg/d) for six weeks was more effective (65% remission) than citalopram plus placebo (20% remission)[117].

Although a number of RTCs have demonstrated fast-onset antidepressant effects of scopolamine infusion in patients with unipolar or bipolar depression, none have reported any effects on mania symptoms. Based on the catecholaminergic-cholinergic balance hypothesis of mania and depression, scopolamine treatment might be expected to not only reduce depression, but possibly increase mania symptoms. The catecholaminergic-cholinergic balance hypothesis is also supported by work in rodents showing antidepressant-like effects of scopolamine treatment in normal or stressed animals. Future RTCs should be designed to assess the effects of scopolamine infusion on manic or hypomanic symptoms in bipolar patients, including those with rapid cycling.

Fast-onset Antidepressant-like Effects of Scopolamine in Rodents

A number of recent studies in rats and mice have shed light on the mechanisms by which scopolamine induces fast-onset antidepressant-like effects[118–121]. Similar to ketamine, a single, low dose injection of scopolamine in rodents rapidly induces an antidepressant-like behavioral response in several paradigms, including the FST[118–121], the chronic mild stress paradigm[119], the novelty-induced feeding paradigm[118, 120], the sucrose preference test[119], and learned helplessness[122, 123]. Acute scopolamine treatment induces molecular changes in the medial prefrontal cortex (mPFC). These effects include induction of brain-derived neurotrophic factor (BDNF) release[118], activation of mammalian target of rapamycin complex 1 (mTORC1), and increases in the number and function of spine synapses in layer V pyramidal neurons in the mPFC. These molecular changes induced by scopolamine have also been implicated in the fast-onset antidepressant effects of ketamine[124–126]. Pretreatment with a mTORC1 inhibitor or by a glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist blocks the antidepressant effects of scopolamine[121]. Scopolamine has been reported to initiate this molecular cascade by antagonizing the M1-AChR in the mPFC. Although both GABAergic (GAD67+) interneurons and glutamatergic (CaMKII+) interneurons in the mPFC express M1-AChR, viral-mediated knockdown of M1-AChR in GABAergic, but not glutamatergic, neurons

diminishes the antidepressant-like effects of scopolamine[120]. Further immunohistological and electrophysiological studies have shown that somatostatin interneurons in the mPFC highly express M1-AChR, and receptor knockdown studies demonstrated that M1-AChR expression in these neurons is required for the rapid antidepressant-like effects of scopolamine[120]. In addition, the antagonism of M1-AChR on somatostatin interneurons in the mPFC results in disinhibition of pyramidal glutamatergic neurons, leading to a burst of glutamate and downstream molecular pathways thought to mediate the antidepressant response through synaptogenesis[120]. More details regarding the molecular mechanisms mediating the rapid-onset antidepressant-like effects of scopolamine in rodents has been reviewed elsewhere[118].

The role of M2-AChRs in the mechanism of antidepressant action of scopolamine has also been investigated. Studies using M1-AChR or M2-AChR knockout mice treated with agonists that are preferentially selective for each of these receptors have shown that antagonists of M2 receptors, as well as M1 receptors, induce antidepressant-like effects[127]. Conversely, mice lacking M3-AChRs, M4-AChRs, or M5-AChRs do not show a reduced antidepressant-like response to scopolamine[127]. Thus, work to date suggests that M1-AChRs, and likely M2-AChRs, mediate the antidepressant-like effects of acute scopolamine treatment.

NICOTINIC REGULATION OF MOOD:

Nicotinic Treatment Studies in Humans:

Evidence suggests that nicotinic receptors also contribute significantly to the regulation of mood. Nicotine withdrawal due to cigarette smoking cessation has been well established to induce depression, anxiety, and dysphoria, which may continue for as long as 10 weeks[128, 129]. This especially occurs in subjects with a history of major depression[130, 131]. Furthermore, administration of nicotine using transdermal patches has been shown to alleviate depression during smoking cessation[132]. However, controlled studies assessing the effects of nicotine on depression in non-smokers are very rare. Of those, McClernon et al. (2006) found that chronic nicotine administration by patch produced antidepressant effects in non-smokers, compared to placebo[133]. Furthermore, Salin-Pascual et al. (1996) noted improvement in mood in major depression patients after only 2 days of treatment with nicotine patches[134]. Observations of improved mood following nicotine treatment[134, 135], or smoking, have led to the hypothesis that smoking nicotine tobacco is sometimes used to self-medicate symptoms of depression[136].

A small number of controlled studies have examined the effects of nicotinic agents besides nicotine in depressed patients. One study assessed the ability of CP-601,927, an α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist, to augment a sub-optimal antidepressant response to SSRIs; however, no therapeutic effect was found[137]. Furthermore, a meta-analysis of six randomized-controlled trials including 2067 participants failed to confirm preliminary positive evidence for the efficacy of nAChR antagonists in treatment-resistant depression[138]. For example, the non-selective, non-competitive antagonist of nAChRs, desmecamylamine (TC-5214) failed Phase III trials as a treatment for major depression[139]. Although no agents acting primarily at nicotinic receptors are currently in use

for the treatment of depression, it should be noted that many current antidepressants including tricyclics, SSRIs, and buproprion also act as α4β2 nAChR antagonists in cell-based assays[140, 141].

Nicotinic Treatment Studies in Rodents

Nicotine withdrawal-induced anhedonia in rodents provides a well validated model for aspects of major depression[142]. For example, the affective aspects of nicotine withdrawal can be assessed in rats and mice as elevations in brain-stimulation reward thresholds and conditioned place aversion. nAChR subtypes including the α5, α2, α3, and β4 subunits have been implicated in the aversive properties of nicotine withdrawal[143–146]. Furthermore, nicotine self-administration in rats results in an increase in the sensitivity of natural brain reward systems, detected by post-nicotine lowering of intracranial self-stimulation (ICSS) thresholds[147]. Surprisingly, nicotine-induced excitation of reward systems has been reported to persist for at least 36 days after cessation of nicotine self-administration had ceased[147]. Since nicotine increases serotonergic and noradrenergic neuronal activity and facilitates serotonin and noradrenaline release, the effects of coadministration of nicotine with SSRIs or noradrenaline reuptake inhibitors (NRIs) have been explored in preclinical studies. For example, nicotine enhances the antidepressant-like effects of low-dose citalopram or reboxetine in the FST in mice[148]. In addition, chronic mild stress-induced anhedonia can be alleviated by either nicotine or sertraline, but the two treatments did not have a synergistic effect[149].

Human Studies of Nicotinic Receptors

Like muscarinic receptors, nicotinic receptor function has also been reported to be altered in depressed patients. Single-photon emission computed tomography (SPECT) studies have found a reduction of β2 subunit-containing nAChR (β2* nAChR) availability across all brain regions in major depression patients compared to healthy controls. Furthermore, acutely depressed patients in this study were also found to have lower β2* nAChR availability than remitted patients[31]. This reduction in β2* nAChR availability in depressed patients has been suggested to result from increased central acetylcholine levels, which reduce the number of receptors available for binding to a SPECT ligand. For example, a SPECT study by Esterlis et al. (2013) showed that increases in ACh levels induced by physostigmine challenge reduces SPECT ligand binding[150]. Furthermore, a negative correlation between lifetime number of depressive episodes and β2* nAChR availability in temporal cortex, occipital cortex, thalamus, and striatum was reported in patients with major depressive disorder[31]. Consistent with findings in patients with major depression, a SPECT imaging study using [(123)I]5IA-85380 to quantify β2* nAChR total volume of distribution found significantly lower β2* nAChR availability (20–38% less) in subjects with bipolar depression compared to euthymic patients and controls in frontal, parietal, temporal, anterior cingulate cortex, hippocampus, amygdala, thalamus, and striatum[151]. In contrast, post-mortem studies using acetylcholine washout showed identical β2* nAChR density in controls, major depression patients, and bipolar disorder patients. Therefore, depressed and bipolar patients likely have increased endogeneous acetylcholine levels but similar β2* nAChR expression levels relative to controls.

Rodent Studies of Nicotinic Receptors

Rodent studies have also implicated nicotinic receptors in the regulation of depression-like behavior. However, differences between rats and mice have been found, with the antidepressant effects of nicotine being observed more frequently in rats. Nicotine treatment has antidepressant-like effects in several animal models of depression-like behavior, including the FST[152, 153], the TST[154] and the olfactory bulbectomy model[155]. Yet, the non-selective, non-competitive nicotinic antagonist mecamylamine also produces antidepressant-like effects in the FST in rodents[148, 156], a result which was not due to a generalized stimulant effect[157]. Furthermore, in rats exposed to chronic restraint stress, mecamylamine blocked depression-like behaviors including reductions in sucrose preference, increased anxiety, and hypothalamic pituitary adrenal hyperactivity[158]. However, a meta-analysis including six randomized-controlled trials examining effects of nAChR antagonists in treatment-resistant depression found no antidepressant effects[138].

Rodent studies suggest that targeting specific nAChR subtypes might provide a therapeutic strategy for treating depression[159]. Nicotinic antagonists at β2* or α7 nAChRs have been reported to have antidepressant-like effects in mice. The α7 nAChR antagonist methyllycaconite reduced immobility in the FST and TST, and decreased physostigmine-induced c-fos immunoreactivity in the hippocampus. These effects were observed in male, but not female, mice[76]. The α4β2 nAChR partial agonist varenicline showed antidepressant-like activity in the FST in two mouse strains, and also enhanced the effects of the SSRI sertraline[160]; α4β2 nAChR partial agonists may induce antidepressant-like effects by inducing dopamine release from VTA-NAc projections[161]. Furthermore, one small open-label study of varenicline augmentation was associated with significant improvement in mood in outpatient smokers with persistent depression[162]. However, the α4β2 nAChR partial agonist, CP-601,927, which was derived from varenicline, was not found to be effective in mouse models of antidepressant efficacy[163].

In a series of studies, Mineur et al. (2016) showed that viral-mediated knockdown of either the β2* or α7 nAChR subunit within specific brain regions induced robust antidepressant-like effects in several behavioral tests. Specifically, α7 subunit knockdown in the amygdala produced antidepressant-like effects in the TST[159], while β2* subunit knockdown produced antidepressant-like effects in the FST, TST, and the social defeat paradigm[159]. β2* subunit knockdown in the amygdala was also found to be critical for the antidepressant-like effects of the alpha2-noradrenergic receptor agonist guanfacine, while the antidepressant-like effects of the nicotinic partial agonist cytisine required noradrenergic signaling in the amygdala, highlighting an interaction between ACh and noradrenergic signaling in the regulation of depression-like behaviors in the mouse[164]. Furthermore, ACh signaling through α7 nAChRs in the hippocampus was reported to regulate depression-like behaviors when ACh levels are increased, which can occur under stressful conditions[76]. More work in humans and animals will be required to determine which nAChR subtypes provide the most promising targets for the treatment of mood disorders.

DISCUSSION:

We have highlighted a number of experiments which suggest that increasing central acetylcholine causes depression in humans and depression-like behaviors in animals. These results are remarkably consistent across species, and suggest that blocking or lowering acetylcholinesterase activity, increasing central acetylcholine levels, or stimulating specific cholinergic receptors, all lead to depression[15, 23, 24]. Furthermore, depression can be rapidly alleviated in humans by the pan-muscarinic receptor blocking agent, scopolamine[7, 9–11]. Depression-like behavior is also rapidly reduced by acute scopolamine treatment in rodent models[118–122]. Preclinical studies in rodents have made progress in understanding the specific muscarinic receptors, neural circuits, and molecular mechanisms by which altering cholinergic neurotransmission regulates affect[74, 76, 118–121, 159], and may provide novel therapeutics for mood disorders.

Work to date has also revealed an important role for nicotinic receptors in mood regulation. Extensive evidence has shown that nicotine withdrawal in both humans and animals produces a syndrome which includes symptoms of depression[142]. Furthermore, nicotine administration to rodents produces antidepressant-like effects[149], and several small studies suggest that nicotine may be antidepressant in nonsmokers[133, 135] in addition to those undergoing smoking cessation. Furthermore, nicotinic partial agonists and antagonists at β2* and α7 nAChRs, respectively, have antidepressant-like effects in mice[76, 159, 160], and one small study reported that varenicline augmentation improved mood in outpatient smokers with persistent depression[162]. Yet, it remains unclear whether activation, desensitization, or interference with temporally precise ACh signaling is more important for the antidepressant effects of nicotinic agents[165]. More work in humans and animals will be required to dissect the specific nicotinic receptor subtypes and that mediate the effects of Ach on mood, and could lead to the development of novel therapeutics.

The finding that scopolamine exerts a fast-onset and sustained antidepressant effects in humans has led to a renaissance of interest in the cholinergic system as an important factor in the neurochemistry of major depression and bipolar disorder. Controlled studies have indicated that acute i.v. treatment with scopolamine induces fast-onset and sustained antidepressant effects, even in treatment resistant patients with depression[7, 9–11]. Yet over the last decade, a far greater number of basic and clinical studies have investigated the therapeutic effects and mechanism of action of the NMDA antagonist, ketamine, compared to scopolamine[124–126]. Since no relative disadvantage of scopolamine regarding efficacy or safety has been reported compared to ketamine, and some common mechanisms of action have been identified, further investigation of the fast-onset antidepressant effects of scopolamine are highly warranted. Possibly, a subpopulation of depressed patients might respond to treatment with scopolamine who do not respond to classical antidepressants, ketamine, or nonpharmacological treatments. Furthermore, a better understanding of the mechanism of action of scopolamine could lead to the development of novel fast-onset antidepressants with improved efficacy and fewer side effects.

The reviewed literature indicates that scopolamine treatment produces rapid-onset antidepressant-like effects in rodents by antagonizing M1-AChRs on somatostatin

interneurons in the mPFC, resulting in disinhibition of pyramidal glutamatergic neurons, a glutamate surge, and ultimately an increase in synapses[120, 121]. On the other hand, activating M1-AChRs increases depression-like behaviors in humans and animals[86, 95, 166]. Stimulation of presynaptic M2-AChRs and M4-AChRs decreases acetylcholine release when activated, and hence agonists at these receptors might decrease depressive symptoms by reducing acetylcholine availability[99]. More work is needed to determine a potential role for M3–5-AChRs in the regulation of mood.

Animal studies have suggested that co-treatment with scopolamine and other antidepressants such as venlafaxine or noradrenaline reuptake inhibitors may potentiate antidepressant-like effects[167, 168]. As discussed above, more selective muscarinic or nicotinic agents such as M1-AChR antagonists, and nicotinic α7 and β2* agents, also require further investigation as potential therapeutics for the treatment of depression. Both nicotinic and muscarinic receptors also regulate other neurotransmitter systems implicated in mood regulation, including noradrenergic[169, 170], serotonergic[171–173], dopaminergic[84, 174], GABAergic[175–177], glutamaniergic[178–180] and cannabinoid[181] neurotransmitter systems. Investigation into how the acetylcholine neurotransmitter system interacts with other neurotransmitters, neuromodulators, and epigenetic factors to modulate mood state will be an important direction for future research.

CONCLUSIONS

The catecholaminergic-cholinergic balance hypothesis of depression and mania proposes that a central predominance of acetylcholinergic to catecholaminergic tone underlies depression, while mania results from the converse[15]. Evidence to date implicates higher central acetylcholine levels in depression, and antagonism of M1-AChRs by scopolamine in fast-onset antidepressant effects. Blockade of α7 nAChRs receptors and partial agonism of β2* nAChRs are also implicated in antidepressant-like effects. Future studies are needed to identify optimal pharmacological strategies for treating depression by harnessing the acetylcholinergic system.

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Box 1

Future research directions

1. Further explore potential antidepressant effects of nAChR agents in humans and animals.
2. Further elucidate the similarities and differences in the mechanisms of antidepressant action of scopolamine versus ketamine using animal models.
3. Longitudinal imaging studies assessing M2-AChR receptor expression during illness and remission.
4. Further elucidate the mechanism of action of scopolamine to identify novel targets for antidepressant development.
5. Identify biomarkers that identify responders to scopolamine versus ketamine treatment.
6. Replicate oral and i.v. trials of scopolamine in affective disorder patients.
7. Use human imaging studies and animal models to identify the neural circuits involved in scopolamine's fast-onset antidepressant effects.

Abbreviations: M2-AChR, muscarinic 2 acetylcholine receptor.

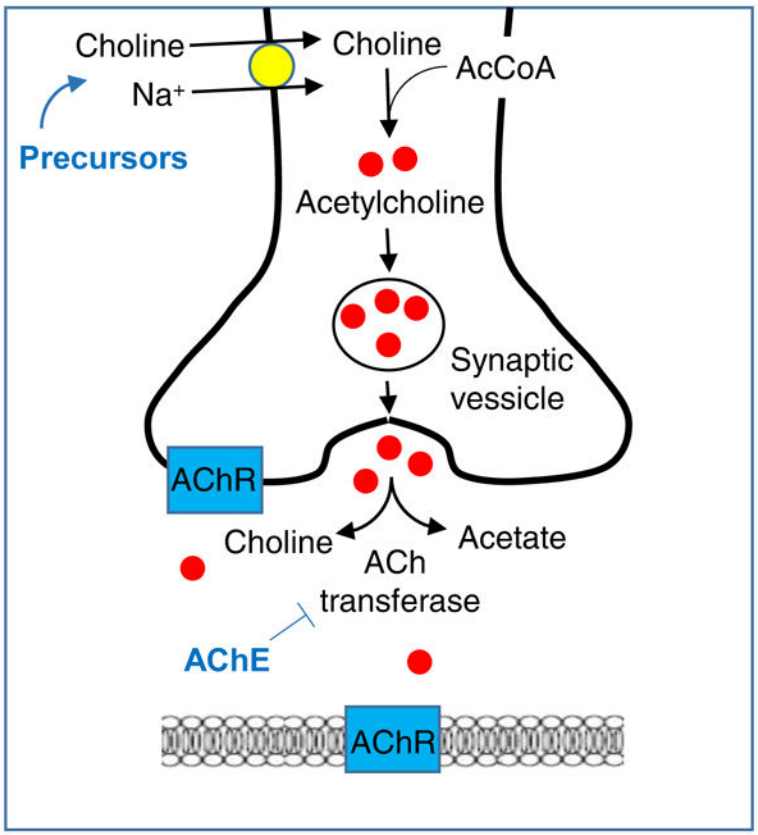

Figure 1.

Acetylcholine synthesis and degradation, and the actions of pharmacological interventions. Acetylcholine (ACh) is synthesized in neurons from choline and acetyl-coenzyme A by the enzyme acetyltransferase. ACh is protected from degradation by packaging within synaptic vesicles. ACh is released into the synaptic cleft where it acts upon pre- and postsynaptic muscarinic and nicotinic receptors, and degraded into choline and acetate by the enzyme acetylcholinesterase (AChE). Choline is recycled back into neurons. AChE inhibitors (AChEIs) such as physostigmine and donepezil prevent the breakdown of ACh. Precursors such as deanol and choline contribute to ACh synthesis. Abbreviations: AcCoA, acetyl coenzyme A; AChR, acetylcholine receptor.

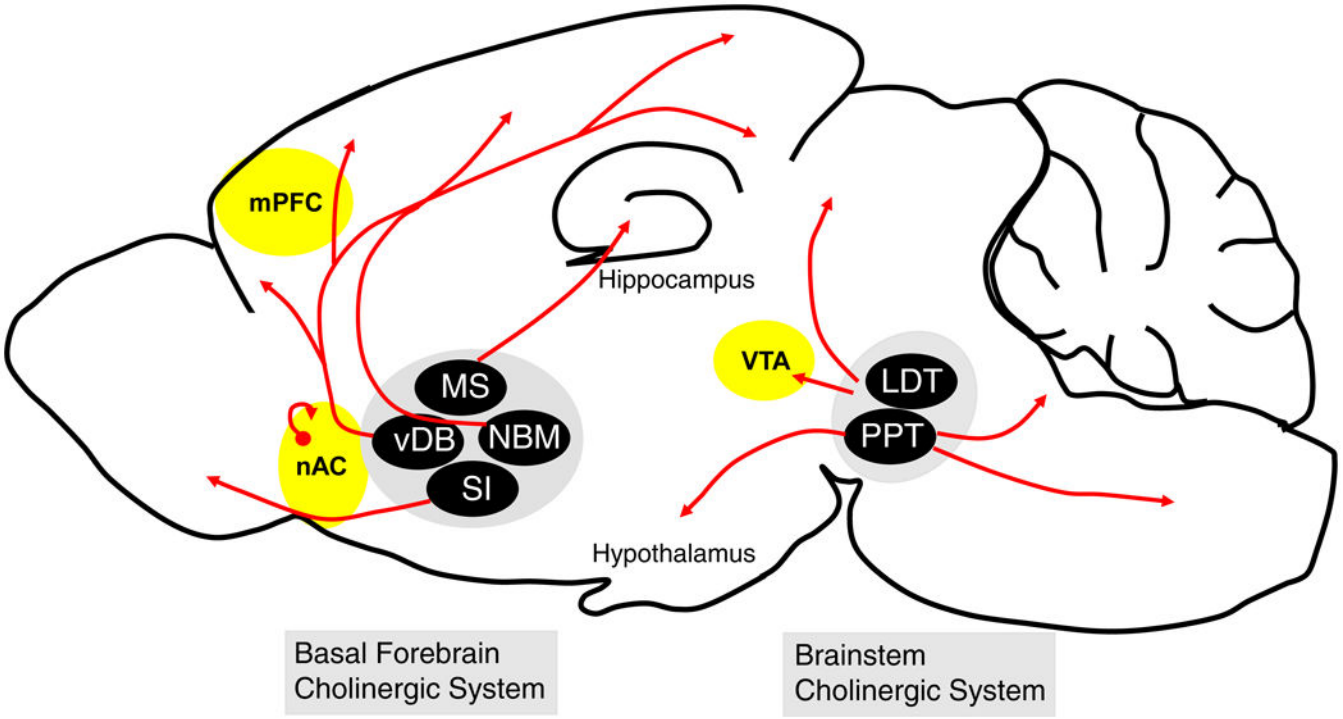

Figure 2.

Sites of action of scopolamine's rapid antidepressant-like effects within cholinergic circuitry. Rodent studies have shown that acute scopolamine treatment can induce fast-onset antidepressant effects when administered within the mPFC, nAC, and VTA (shown in yellow). Cholinergic innervation of the mPFC and VTA is supplied by the basal forebrain and brainstem cholinergic systems, respectively. The only source of acetylcholine within the nAC comes from local cholinergic interneurons (shown in red). Abbreviations: nAC, nucleus accumbens; mPFC, medial prefrontal cortex; VTA, ventral tegmental area; MS, medial septal nucleus; vDB, vertical diagonal band; NBM, nucleus basalis of Meynert; SI, substantia innominata; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus.

Table 1.

Summary of pharmacological evidence for cholinergic regulation of mood

Illness	Drug	Mechanism of action	Effect
Unipolar depression	Physostigmine	AChEI	Worsened depression[22]
	Arecoline	mAChR agonist	Worsened depression[182]
	Scopolamine	Antimuscarinic	Antidepressant[7, 9–11]
	Nicotine	nAChR agonist	Antidepressant in depressed non-smokers[134]
Bipolar depression	Physostigmine	AChEI	Worsened depression[22]
	Arecoline	mAChR agonist	Worsened depression[182]
	Scopolamine	Antimuscarinic	Antidepressant[7, 9–11]
Bipolar mania	Physostigmine	AChEI	Reduced mania[22–24]
	RS 86	M1-AChR agonist	Reduced mania[95]
Controls	Physostigmine	AChEI	Induced depression in those with positive history[25–27]
			Induced depression in marihuana-intoxicated controls[90]
	Donepezil	AChEI	Induced depression in cognitively impaired with positive history[28, 29]
	Deanol	ACh precursor	Induced depression or hypomania in those with positive history[183]
	Choline	ACh precursor	Induced depression in tardive dyskinesia patients[33]
	Arecoline	mAChR agonist	Induced depression in controls and euthymic bipolars patients[92], and Alzheimers disease[93]
	Oxotremorine	ACh agonist	Induced depression in Alzheimers disease[94]
	Nicotine	nAChR agonist	Antidepressant in non-smokers[133]

Abbreviations: ACh, acetylcholine; AChEI, acetylcholinesterase inhibitor; nAChR, nicotinic acetylcholine receptor; mAChR, muscarinic acetylcholine receptor; M1-AChR, muscarinic 1 acetylcholine receptor.

Table 2.

Effects of manipulations of the cholinergic system on depression-like behavior in rodents

Species	Drug	Mechanism	Route	Test	Effect
Mice	Physostigmine	AChEI	Systemic	FST	Depression-like[76–78]
				TST	Depression-like[74, 78]
			Intra-VTA	FST	Depression-like[75]
			Intra-Hipp	TST	Depression-like[74]
				Social defeat	Depression-like[74]
	Scopolamine	Antimuscarinic	Systemic	FST	Antidepressant-like[118–121]
				CMS	Antidepressant-like[119]
				LH	Antidepressant-like[122]
				NSF	Antidepressant-like[118, 120]
				SP	Antidepressant-like[119]
	Nicotine	nAChR agonist	Systemic	FST	Antidepressant-like[154, 156]
				TST	Antidepressant-like[154, 156]
	Mecamylamine	nAChR antagonist	Systemic	FST	Antidepressant-like[148, 156]
				TST	Antidepressant-like[156]
	Methyllycaconite	a7 nAChR antagonist	Systemic	FST	Antidepressant-like[76]
	Varenicline	a4b2 nAChR partial agonist	Systemic	FST	Antidepressant-like[160]
				TST	Antidepressant-like[76]
Rats	Physostigmine	AChEI	Systemic	FST	Depression-like[75]
			Intra-VTA	SP	Depression-like[84]
	Pilocarpine	mAChR agonist	Intra-VTA	FST	Depression-like[84]
	Scopolamine	Antimuscarinic	Intra-VTA	FST	Antidepressant-like[75]
	Mecamylamine	nAChR antagonist	Intra-VTA	FST	Antidepressant-like[75]
			Systemc	FST	Antidepressant-like[158]
				CMS	Antidepressant-like[158]
				SP	Antidepressant-like[158]
	Arecoline	mAChR agonist	Intra-NAc	FST	Depression-like[86]
	Pirenzepine	M1-AChR antagonist	Intra-NAc	FST	Antidepressant-like[86, 88]
	Gallamine	M2-AChR antagonist	Intra-NAc	FST	Depression-like[86]
	Scopolamine	Antimuscarinic	Intra-NAc	FST	Antidepressant-like[86]
	Nicotine	nAChR agonist	Systemic	FST	Antidepressant-like[152, 153]
				OBX	Antidepressant-like[155]

Abbreviations: AChEI, acetylcholinesterase inhibitor; nAChR, nicotinic acetylcholine receptor; mAChR, muscarinic acetylcholine receptor; M1-AChR, muscarinic 1 acetylcholine receptor; Intra-VTA, intra-ventral tegmental area; Intra-Hipp, intra-hippocampal; Intra-NAc, intra-nucleus accumbens; FST, forced swim test; TST, tail suspension test; SP, sucrose preference; CMS, chronic mild stress; LH, learned helplessness; NSF, novelty suppressed feeding.