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Proof of Concept Trials in Bipolar Disorder and Major Depressive Disorder: A Translational Perspective in the Search for Improved Treatments

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Abstract

A better understanding of the neurobiology of mood disorders, informed by preclinical research and bidirectionally translated to clinical research is critical for the future development of new and effective treatments. Recently, diverse new targets/compounds have been specifically tested in preclinical models and in proof-of-concept studies, with potential relevance as treatments for mood disorders. Most of the evidence comes from case reports, case series, or controlled proof-of-concept studies, some with small sample sizes. These include (1) the opioid neuropeptide system, (2) the purinergic system, (3) the glutamatergic system, (4) the tachykinin neuropeptide system, (5) the cholinergic system (muscarinic system), and (6) intracellular signaling pathways. These targets may be of substantial interest in defining future directions in drug development, as well as in developing the next generation of therapeutic agents for the treatment of mood disorders. Overall, further study of these and similar drugs may lead to a better understanding of relevant and clinically useful drug targets in the treatment of these devastating illnesses.

Keywords

cholinergic; depression; glutamate; mood disorders; novel treatments; pathophysiology

Introduction

Worldwide, bipolar disorder (BPD) and major depressive disorder (MDD) are among the most disabling of all non-communicable illnesses. These heterogeneous, chronic, and severe disorders are associated with persistent subsyndromal symptoms and frequent episode relapses and recurrences [1–3]. However, treatment of both disorders remains inadequate for many patients. For instance, the Sequenced Treatment Alternatives to Relieve Depression

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Disclosure

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(STAR*D) study noted that only one-third of patients with MDD achieved remission after an adequate trial with a traditional antidepressant agent [4]. Similarly, a large-scale study funded by the National Institute of Mental Health (NIMH) failed to find significant benefit to adding antidepressants to mood stabilizers in patients with BPD-I or II depression over the course of 26 weeks [4;5]. Thus, the development of new, effective, and better-tolerated therapeutic approaches with a more rapid onset of action is critical.

To achieve this objective, a variety of compounds targeting diverse new systems have been proposed and have been or are being tested; many of these may ultimately result in new and improved treatments for mood disorders (see Figure 1). Here, we describe studies evaluating some of these potentially promising targets. Specifically, we review: (1) the opioid neuropeptide system, (2) the purinergic system, (3) the glutamatergic system, (4) the tachykinin neuropeptide system, (5) the cholinergic system (muscarinic system), and (6) intracellular signaling pathways. Other putative targets not covered in this review include the melatonergic system, the glucocorticoid system and bioenergetics and oxidative stress. This paper reviews data on new compounds that have shown antimanic or antidepressant effects in subjects with mood disorders or similar effects in preclinical animal models. It is important to mention at the outset that the extrapolation of animal studies to humans requires cautious interpretation. However, such studies may provide a better understanding of the neurobiology of mood disorders. This bi-directional research approach—whereby preclinical work can be translated to clinical research is—critical for the future development of new and effective treatments.

1. The Opioid Neuropeptide System

The dynorphin opioid neuropeptide family modulates diverse behavioral mechanisms such as mood, endocrine, motor, and cognitive function, and opioid peptides and their receptors are potential candidates for the development of novel treatments for mood disorders. Three types of opioid receptors have been described in the pathophysiology of mood disorders: delta (δ), mu (μ), and kappa (κ). These receptors are coupled to different intracellular effector systems and are widespread in the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC). Notably, opioid receptors are coexpressed in brain areas implicated in the pathophysiology of mood disorders [6]. For instance, patients with depression and anxiety were found to have lower serum β -endorphin levels [7]. A significant decrease in pro-dynorphin mRNA expression levels was also noted in subjects with BPD [8]. In addition, antidepressants have been shown to reverse stress-related changes in dynorphin levels in diverse limbic brain areas [9;10].

Kappa opiate receptor activation induces depressive symptoms in humans and animals [11], as well as psychotomimetic effects [12;13]. In preclinical models, the kappa opioid receptor agonist Salvinorin-A (*Salvia divinorum*) induced depressive-like behaviors [14], while the receptor antagonist MCL-144B caused antidepressant-like effects [15;16]. These agents have also been associated with preclinical anticonvulsant and antiepileptic effects (reviewed in [6]).

Kappa opiate receptor stimulation also decreases dopaminergic function in different brain areas [17]. In animal models of depression, the opioid antagonist naloxone blocked the antidepressant-like effects of tricyclic antidepressants and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine [18;19]. In clinical studies, the partial kappa agonist pentazocine (Talwin) adjunctively showed rapid antimanic effects in subjects with BPD without arousing depressive symptoms [20]. No selective kappa agonists have been clinically evaluated as monotherapy in subjects with BPD.

Few studies have described the efficacy of opioid agonists such as oxymorphone and buprenorphine in treatment-resistant MDD [21–23]. Buprenorphine—which appears to exert antidepressant effects in certain individuals [21]—is often described as a mixed mu/kappa antagonist, although compelling evidence suggests it is actually a partial kappa agonist. Mu receptors are densely present in diverse brain regions involved in stress response and emotional regulation. Animal studies suggest that mu opioid receptor agonists have antidepressant-like effects [24–26]. For instance, the synthetic opioid tramadol, an atypical agent that binds weakly to mu receptors, showed antidepressant-like effects in diverse animal models [27–29]. Small clinical studies of individuals with treatment-resistant MDD further noted that it appeared to have antidepressant/antisuicidal effects [30;31] and similar antidepressant effects to venlafaxine [32]. In terms of circuitry of depression and opioid receptors, a PET study by Kennedy and colleagues [33] reported dysregulated endogenous opioid emotion regulation circuitry in women with MDD. They found that sustained sadness was associated with significant decreases in mu-opioid receptor binding potential in the left inferior temporal cortex; these findings correlated with negative affect ratings. In addition, it was observed that those patients who did not respond to a 10-week course of the antidepressant fluoxetine had increased mu-opioid system activation, while responders displayed responses more closely related to those of controls (mean deactivations of opioid neurotransmission) [33].

Delta receptors have a high affinity for the endogenous opioid peptide proenkephalin. In animal models, proenkephalin-knockout mice displayed increased anxiety- and depressive-like behaviors, and diverse delta receptor agonists appear to have antidepressant-like properties [34], including SNC80 [35]. Interestingly, acute treatment of rodents with a delta opioid agonist simultaneously increased expression of brain derived neurotrophic factor (BDNF) and produced antidepressant-like effects [36]. Selective delta-opioid receptor agonists have antidepressant-like effects in models such as the forced swim test [36–39]. Receptor localization studies have shown that delta-opioid receptors reside in areas of the brain implicated in mood regulation [40–43]. For example, localization of the delta-opioid receptor in the amygdala is consistent with the modulation of anxiety states, whereas localization in cortex and hippocampus, regions associated with depression, is consistent with potential antidepressant action. Chronic but not acute treatment with imipramine significantly decreased the density and affinity of delta-opioid receptor agonist-opioid receptors in striatum of the rat brain. The decrease was confirmed by delta-opioid receptor immunostaining [44]. RB101, an inhibitor of enkephalin-degrading enzymes, produces antinociceptive, antidepressant, and anxiolytic effects in rodents, without typical opioid-related negative side effects [45]. The antidepressant-like and anxiolytic effects of RB101 appear to be mediated only through the delta-opioid receptor.

2. The Purinergic System

Purinergic neurotransmission is regulated by the neurotransmitter adenosine triphosphate (ATP) and the neuromodulator adenosine. The system modulates dopamine, gamma aminobutyric acid (GABA), and serotonin [46], and purines control sleep, motor activity, appetite, cognition, memory, and social interaction [47]. Adenosine acts mostly through adenosine 1 and 2A receptors. In animal models, it induces antidepressant-like and anticonvulsant effects [46;48]. In animal studies, adenosine agonists exert sedative, anticonvulsant, anti-aggressive, and antipsychotic properties [49]. In contrast, adenosine antagonists such as caffeine increase irritability, anxiety, and insomnia in individuals with BPD [50].

Purinergic system dysfunction has long been implicated in the pathophysiology of BPD [47]. Early clinical studies showed that enhanced excretion of uric acid was associated with

remission of manic symptoms [51]. Plasma uric acid levels have also been found to be higher during the manic phase of BPD, but not during the depressive or euthymic phases [52], suggesting that increased uric acid may represent a state rather than a trait marker of mania in BPD. Recently, increased uric acid levels were described in drug-naïve subjects with BPD who were experiencing their first manic episode [53]. In addition, a recent nationwide population-based study involving more than 24,000 subjects with BPD found an increased risk of gout among patients with BPD [54]. Relatedly, the P2RX7 (purinergic receptor P2X, ligand-gated ion channel, 7) gene has been described as a candidate gene for both MDD and BPD, because of repeated associations with the rs2230912 (Gln460Arg) polymorphism [55;56].

The purinergic modulator allopurinol, widely used to treat gout, was recently shown to induce antimanic effects in three different clinical studies [57–59]. One study assessed the antimanic effects of adjunctive allopurinol for eight weeks [57], and noted a difference between allopurinol and placebo at endpoint. Another recent, double-blind, placebo-controlled study evaluated the efficacy of allopurinol, dipyridamole, and placebo added to lithium in 180 subjects with BPD during a manic episode [59]; antipsychotics were not allowed during the trial. Allopurinol significantly decreased manic symptoms after four weeks compared to dipyridamole and placebo, and the antimanic effects of allopurinol were directly correlated with decreased plasma uric acid levels [59].

3. The Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter in the brain, and is present in three different cell compartments: the pre- and post-synaptic neurons and glial cells; together these comprise the “tripartite glutamatergic synapse” [60] (see Figure 2). Glutamate modulates several functions, including memory, learning, and synaptic plasticity [61–64].

Glutamate receptor subtypes include a group of pharmacologically distinct ligand-gated ion channels (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors) and the eight G-protein coupled metabotropic receptors. Increased synaptic levels of glutamate can lead to excitotoxic levels after an insult, leading to increased extrasynaptic glutamate [65]. Several glutamate ionotropic receptors and their respective subunits have been identified: NMDA (NR1, NR2, NR2B, NR2C, NR2D, NR3A, and NR3B subunits), AMPA (GluR1, GluR2, GluR3, and GluR4) and kainate (GluR5, GluR6, GluR7, KA1, and KA2).

The Effects of Mood Stabilizers on the Glutamatergic System

Notably, several mood stabilizers—typically used to treat patients with BPD—indirectly or directly affect the glutamatergic system. For instance, the classic mood stabilizer lithium alters glutamate uptake [66], glutamate receptor expression and function [67–71], vesicular glutamate transporter 1 (VGLUT1) expression, and presynaptic glutamate release [72–74]. Similarly, the mood stabilizer valproate (VPA) alters VGLUT1 expression and presynaptic glutamate release [75;76], increases excitatory amino-acid transporter (EAAT) expression [77;78], and alters glutamate receptor expression and function [67;79–85].

In addition, prolonged treatment—both in vitro and in vivo—with therapeutically relevant concentrations of either lithium and VPA downregulates AMPA GluR1 synaptic expression in hippocampus [86]. Additional support for the therapeutic relevance of these data is provided by recent studies indicating that AMPA receptor antagonists attenuate several “manic-like” behaviors produced by amphetamine administration [87].

Of all the medications currently used to treat mood disorders, lamotrigine—an anticonvulsant that also has mood stabilizing properties—probably has the most direct effect on the glutamatergic system. Lamotrigine inhibits the release of glutamate in the hippocampus of rats [88], and increases AMPA subunit receptor expression [79]. Lamotrigine may also inhibit the excessive release of glutamate via its limiting effects at P-type and N-type calcium channels, potassium channels, and sodium channels [89]. However, it is important to note that while lamotrigine is associated with modest efficacy in the treatment of bipolar depression [90], its clinical utility has been questioned [91].

Ionotropic Glutamate Receptors: NMDA

Preclinical evidence suggests that NMDA receptor antagonists display antidepressant-like effects in different models (reviewed in [92,93]). For instance, the NMDA antagonist dizocilpine (MK-801) and CGP 37849 have consistently shown antidepressant-like effects as monotherapy or when combined with traditional antidepressants [94–98]. Also, NR2A knockout mice showed highly robust anxiolytic- and antidepressant-like phenotypes [99], and GluR1 knockout mice displayed increased depressive-like behaviors (learned helplessness) [100].

Ketamine—The high affinity NMDA receptor antagonist ketamine increases presynaptic release of glutamate by increasing glutamatergic neuron firing after disinhibiting gamma aminobutyric acid (GABA)ergic inputs [101]. In animal models, ketamine displayed anxiolytic and antidepressant effects [102–106].

Notably, ketamine's antidepressant effects have been tested in several clinical trials for both MDD and bipolar depression. In the first small, preliminary investigation [107], significant antidepressant effects were noted within 72 hours after ketamine infusion in treatment-resistant patients with MDD. In a double-blind, crossover, placebo-controlled study evaluating patients with treatment-resistant MDD, a rapid (within two hours) and relatively sustained (one to two weeks) antidepressant effect was noted after a single infusion of ketamine [108]. More than 70% of patients responded to ketamine (50% improvement) at 24 hours after infusion, and 35% maintained a sustained response after one week of treatment. It is important to note that the response rates (71%) 24 hours after infusion with ketamine were similar to those observed after six to eight weeks of therapy with standard monoaminergic-based antidepressants (65%) [109]. Ketamine was superior to placebo on the 21-item HAM-D from 110 minutes through seven days after the single infusion. This finding has since been replicated in several other, albeit uncontrolled, studies [110–112]; the magnitude and time-frame of response to ketamine in these studies was similar to the previous controlled studies. Several variables have been found to predict initial antidepressant response to ketamine, including family history of alcohol dependence [111], and increased pretreatment rostral ACC activity [113]. More recently, anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task was found to predict antidepressant response to ketamine [114]. In contrast, plasma BDNF levels—which other studies have noted is associated with antidepressant response to chronic treatment with standard antidepressants [115]—were not associated with initial antidepressant response to a single dose of ketamine [116].

More recently, ketamine has been studied in bipolar depression [117]. In that study, subjects receiving ketamine had significant improvement in depressive symptoms compared to patients receiving placebo within 40 minutes after infusion; these effects remained significant through Day 3, and up to Day 7 in those who completed both phases of the study. Of the 17 subjects treated with ketamine, 56% met response criteria at 40 minutes post-infusion, and 44% met response criteria and 31% met remission criteria the day following

ketamine infusion. Seventy-one percent of all subjects responded to ketamine at some point during the study.

Ketamine has also been found to have significant antisuicidal effects [118;119]. In the study by Price and colleagues, 26 patients with treatment-resistant MDD were found to have significant reductions on the suicidality item of the MADRS 24 hours after a single infusion of ketamine. In the study by Diazgranados and colleagues, 33 subjects with treatment-resistant MDD received a single open-label infusion of ketamine and were rated at baseline and at 40, 80, 120, and 230 minutes post-infusion. Suicidal ideation scores significantly decreased on the Scale for Suicide Ideation (SSI) and suicidality items of depression rating scales within 40 minutes after infusion, and this effect remained significant through the first four hours post-infusion. Measures of depression, anxiety, and hopelessness were significantly improved at all time points. In addition to confirming the findings of the first study, the second study demonstrated that suicidal ideation was improved as soon as 40 minutes post-infusion, a finding with enormous public health implications. Controlled studies are necessary to confirm ketamine's rapid antisuicidal properties.

Because of the inherent propensity of ketamine to produce cognitive deficits and psychotomimetic effects, its use at this time remains limited to the research setting. Studies with more selective subtype NMDA antagonists are underway, in order to determine whether these have antidepressant effects that can occur safely without causing ketamine's undesirable side effects. A recent, double-blind, randomized, placebo-controlled clinical trial evaluating the NMDAR-2B subunit-selective antagonist CP-101,606 found that this agent induced significant and relatively rapid antidepressant effects (by Day 5) in patients with treatment-resistant MDD, but with evidence of psychomimetic properties [120]. As a result, the CP-101,606 research program was discontinued. However, additional clinical studies with subunit NMDR-2A and -2B antagonists are underway or completed and include AZD6765 (AstraZeneca Pharmaceuticals, completed) and EVT 101 (Evotec Neurosciences; ongoing). In addition to determining the efficacy of these agents in treatment-resistant MDD, these studies should also shed some light on the issue of rapidity of onset of antidepressant action.

It is also interesting to note that ketamine's rapid antidepressant effects may occur by increasing AMPA throughput, as suggested by behavioral studies showing that blockade of AMPA activation limit the antidepressant effects of ketamine [104]. It is thus possible that targeting AMPA receptors more directly, or AMPA's downstream pathways, would yield similar antidepressant effects to ketamine but without its psychomimetic effects. This preclinical work has been further extended to suggest that mammalian target of rapamycin (mTOR)-dependent synapse formation underlies ketamine's rapid antidepressant properties [121]. In an elegant series of studies, investigators from the Duman laboratory demonstrated that ketamine rapidly activates the mTOR pathway, leading to increased synaptic signaling proteins and increased number and function of new spine synapses in the prefrontal cortex of rats.

Ionotropic Glutamate Receptors: AMPA

AMPA receptors are a subfamily of ionotropic glutamate receptors that mediate the fast excitatory component of neurotransmission. AMPA receptor potentiators have been tested in preclinical models of mood disorders. This class of agents limits receptor desensitization and/or deactivation rates [122]. It includes AMPAkinase, which have displayed antidepressant-like effects in different models [79;123;124]. AMPA receptor trafficking is believed to modulate the antidepressant-like effects of AMPA potentiators by exerting a key role in regulating synaptic strength and behavioral plasticity [125].

Interestingly, in animal studies the AMPAkinic Ampalex showed antidepressant-like effects [126]. Clinically, AMPA receptor antagonists such as GYKI 53773 and LY 300164 have been studied as potential anticonvulsants in Phase III trials. The competitive AMPA receptor antagonist NS1209 was found to induce more rapid and consistent anticonvulsant effects than diazepam in animal models [127], and showed good central nervous system (CNS) bioavailability and tolerability in Phase I/II clinical trials. It has been also evaluated in refractory status epilepticus [128]. Clinical testing of NS-1209 in the treatment of refractory status epilepticus has been initiated, but no results are yet available [129].

Riluzole—Riluzole is blood-brain-penetrant glutamatergic agent with well-defined neuroprotective properties and is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS). Riluzole increases membrane insertion and AMPA trafficking (mostly GluR1 and GluR2), thus limiting glutamate release. Riluzole also increases glutamate reuptake and enhances neurotrophin synthesis [130;131].

In preclinical studies, pretreatment with 10 mg/kg riluzole (but not 3 mg/kg) moderately decreased amphetamine-induced hyperlocomotion [132], suggesting a potential antimanic effect. Enhanced ¹³C-glucose metabolism in the hippocampus and prefrontal cortex was also described after 21 days of treatment with riluzole [133].

In open-label clinical studies, riluzole showed significant antidepressant efficacy and good tolerability in patients with treatment-resistant MDD as well as those with bipolar depression. In MDD, 13 patients (68%) completed the trial, and all displayed significant improvement in both depressive and anxiety symptoms at Week 6 [134]. Another study found that riluzole induced antidepressant effects after one week of treatment, decreasing HAM-D scores 36% among completers [135]. Riluzole was also tested in 14 patients with bipolar depression as add-on therapy to lithium for eight weeks. Patients in that study had a significant decrease in MADRS scores [136]. Another recent, small, open-label, add-on study of 14 subjects with bipolar depression found that riluzole significantly reduced HAM-D scores [137].

Metabotropic Glutamate Receptors (mGluRs)

There is considerable interest in the potential psychiatric applications of mGluR agonists and antagonists (reviewed in [138]). The mGluR family includes eight receptor subtypes (mGluR1 to GluR8) separated into three groups based on their agonist selectivity, second messenger systems coupled-receptor, and sequence homology. Group I mGluRs (mGluR1 and mGluR5) are coupled to the phospholipase C signal transduction pathway, while Group II (mGluR2 and mGluR3) and III (mGluR4 and mGluR6 to mGluR8) receptor activity inhibits the adenylyl cyclase signal transduction pathway.

Group I mGluRs have functionally important interactions with NMDA receptors to modulate postsynaptic excitability. The mGluRs are involved in the early phase of memory formation and the mechanism of long-term depression [139–141]. The Group I mGluR5 antagonists MPEP (2-methyl-6-[phenylethynyl]-pyridine) and MTEP ([2-methyl-1,3-thiazol-4-yl]ethynyl]pyridine) have shown antidepressant-like activity in the modified forced swim test in rats [142], tail suspension test in mice [142], and olfactory bulbectomized rats [143]. Furthermore, MPEP treatment was recently found to increase hippocampal mRNA levels [144]. The mGluR1 antagonist EMQMCM ([3-ethyl-2-methyl-quinolin-6-yl]-(4-methoxy-cyclohexyl)-methanone methanesulfonate) was active in the modified forced swim test in rats and in the tail suspension test in mice [145].

The mode of antidepressant-like activity of mGluR1 or -5 antagonists is uncertain; some have suggested that mGluR5 inhibitors might produce a final effect that is similar to that

evoked by NMDA antagonists, which are known to display antidepressant-like effects. It is also possible that mGluR5 antagonists could exert antidepressant properties by acting on Group 1 mGluRs on glial cells and reducing the hypothesized overactivation of extrasynaptic NMDA receptors [146]. However, studies of the non-benzodiazepine anxiolytic fenobam, a potent and selective mGluR5 antagonist, were discontinued because of psychostimulant effects that occurred with its use [147]. The mGluR5 positive allosteric modulator 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) was found to be brain penetrant and to reverse amphetamine-induced locomotor activity and amphetamine-induced deficits in prepulse inhibition in rats, two models thought to be sensitive to antipsychotic treatment [148]. Should this compound result in an antipsychotic drug for clinical use, it is likely that it will be used clinically during manic episodes. Also currently underway is a trial for treatment-resistant MDD with an mGluR5 allosteric antagonist (RO4917523, Roche); this trial is also examining the rapidity of onset of antidepressant action.

Group II mGluR2, mGluR2/3 are negatively linked to the adenylyl cyclase signal transduction pathway and decrease glutamate release, especially under conditions of glutamate excess in the synapse; moreover, they regulate glutamate transmission by postsynaptic mechanisms. Group II mGluRs agonists (e.g., LY341495) dose-dependently decreased the immobility time of mice in the tail suspension test and reduced immobility time and increased swimming behavior without affecting climbing behavior in rats [149]. In addition, MGS-0039 has been reported to be effective in the learned helplessness model of depression [150] and to increase cell proliferation in the adult mouse hippocampus [151]. AMPA receptor activation is believed to be responsible at least in part for the antidepressant-like activity of Group II mGluR antagonists; the AMPA antagonist NBQX blocked the antidepressant-like activity of MGS-0039 in the tail suspension test in mice [152]. Consistent with this notion, a recent study 24-week, randomized, double-blind, placebo-controlled trial of adjunctive NAC, a drug that indirectly increases mGluR2 stimulation by raising extrasynaptic glutamate levels [153], found that this agent had antidepressant effects in patients with BPD [154].

Pilc and colleagues demonstrated that a selective Group III mGluR agonist (ACPT-I, [1S, 3R,4S]-1-aminocyclopentane-1,3,4-tricarboxylic acid) and an mGluR8 agonist (RS-PPG, [RS]-4-phosphonophenylglycine) for this receptor had antidepressant-like effects in the forced swim test in rats [155]. Additional proof for the involvement of Group II mGluRs comes from studies showing that mGluR7 knockout in mice produced antidepressant-like effects in the forced swim test and in the tail suspension test [156], and that Group III mGluR agonists had antidepressant effects in the behavioral despair test [157]. While the mGluR5 antagonists and Group II mGluR antagonists are promising compounds with considerable potential antidepressant-like activity, no Group III mGluR agonists have been clinically tested or studied in animal models of mania,

4. The Tachykinin Neuropeptide System

Several preclinical and clinical studies have investigated the potential therapeutic role of the tachykinin neuropeptide system in mood disorders. These neuropeptides include substance P (SP), neurokinin A, neurokinin B, and their respective receptors (NK1, NK2, NK3). The activity of these neuropeptides involves G-protein coupled receptor activity, increasing intracellular calcium via phospholipase C, and the diacylglycerol (DAG) signaling cascade [158]. These act as neuromodulators and neurotransmitters, and interact directly with the monoaminergic system in diverse brain areas implicated in mood regulation and emotion-processing [159]. Alterations in this system have been implicated in the pathophysiology of

BPD. For instance, increased SP has been described in the CSF and serum of subjects experiencing a major depressive episode [159].

In preclinical models, the use of tachykinin antagonists—especially those associated with NK2 receptor regulation—induced antidepressant-like effects in several paradigms [160–163]. Interestingly, some of these agents are believed to potentiate the therapeutic effects of selective serotonin reuptake inhibitors (SSRIs). In addition, the TAC1 gene (tachykinin 1, SP) located at 7q21.3 encodes SP and neurokinin A, and TAC1 knockout mice showed decreased depression- and anxiety-related behaviors in diverse paradigms [164].

Several neurokinin receptor antagonists have been tested in Phase II and III trials, with conflicting results. Three different NK1 receptor antagonists—MK869, L759274, and CP122721—reduced depressive symptoms compared to placebo in randomized, double-blind, Phase II clinical trials; both MK869 and CP122721 were associated with fewer adverse effects than the active comparator (paroxetine or fluoxetine) [165;166]. However, the efficacy of MK869 was not replicated in another multi-site, placebo-controlled, Phase III trial [167]. Three other studies that investigated NK1 and NK3 receptor antagonists found that these agents had no antidepressant efficacy compared to active agents or placebo [166;168]. The NK1 receptor antagonist orvepitant (GW823296; GlaxoSmithKline) study in MDD was terminated to allow assessment of isolated events of seizure during the program. Similarly, a six-week Phase II trial with the NK3 receptor antagonist SR142801 (osantetan) found that it was no more effective than placebo or paroxetine [169]. However, in recent Phase III trials, the NK2 receptor antagonist SR48968 (saredudant) showed significant antidepressant effects during depressive episodes in a group of adult and elderly patients with MDD [159].

5. The Cholinergic System

Several decades ago, Janowsky proposed the “cholinergic-adrenergic imbalance hypothesis” of BPD, which suggested that cholinergic dysfunction was key to the pathophysiology of mood disorders [170]. On a genetic level, there is still little evidence that cholinergic system dysregulation is involved in mood disorders. One study found an association between 19 cholinergic genes and BPD [171]. In addition, decreased muscarinic type 2 receptor binding was noted in the anterior cingulate cortex of individuals with BPD in a PET study [172]. Animal studies found that rats bred for increased muscarinic receptor sensitivity showed a behavioral phenotype similar to patients with depression (e.g., lethargy, lack of pleasure, and behavioral despair) [173]. In humans, cholinergic hyperactivity results in a worsening of depressive symptoms in patients with MDD [170]. Experiments add further support to this theory, as neuroendocrine and pupillary responses to cholinergic activity were found to be enhanced in depressed subjects [174] and attenuated in manic subjects [175]; improvement of manic symptoms with lithium and valproate led to normalization of pupillary responses.

Early clinical studies by Kasper and colleagues (1981) found that the anticholinergic drug biperiden had significant antidepressant properties [176]. A small controlled trial with the short-acting cholinesterase inhibitor physostigmine in mania showed that this agent had rapid, but not sustained, antimanic efficacy after single or multiple injections [177;178]. Also, the long-acting cholinesterase inhibitor donepezil, added on to mood stabilizers, demonstrated rapid and significant antimanic effects in more than half of subjects with treatment-resistant mania [179]. Two recent double-blind studies investigated the antimuscarinic drug scopolamine hydrobromide in MDD and bipolar depression [180;181]. In both trials, rapid antidepressant effects (within three to five days) were noted. Finally, it is of note that scopolamine appears to produce larger antidepressant and antianxiety effects in women than in men [182]. When reviewing the results of trials with agents like these that

produce noticeable effects, it is important to note that future studies would be expected to include active comparators, given that these types of agents demonstrate effects that could potentially unmask the blinding.

6. Intracellular Signaling Pathways

Glycogen Synthase Kinase-3 (GSK-3)

GSK-3 is a highly active and multifunctional serine/threonine kinase that regulates diverse signaling pathways (eg, the phosphoinositide 3-kinase pathway, the Wnt pathway, protein kinase A (PKA), and protein kinase C (PKC)). In general, elevated activity of GSK-3 is proapoptotic, whereas GSK-3 inhibition attenuates or prevents apoptosis. Lithium and other mood stabilizers have been shown to directly target GSK-3 activity [183;184]. Lithium also induces neurotrophic and neuroprotective effects in rodents, in part due to GSK-3 inhibition (reviewed in [185]). Mice overexpressing a constitutively active form of GSK-3 β in the brain displayed enhanced locomotor activity as well as decreased habituation in the open field test. In contrast, a recent study focusing specifically on GSK-3 α found that GSK-3 α knockout mice showed decreased exploratory activity, decreased immobility time in the forced swim test, and reduced aggressive behavior, among other phenotypes [186]. Another study found that the GSK-3 inhibitor AR-A014418 induced significant antidepressant-like effects in the forced swim test and attenuated D-amphetamine-induced hyperlocomotion [187;188].

In monocytes from a small group of symptomatic patients with BPD, serine phosphorylation of both GSK-3 α and GSK-3 β was lower than in healthy controls [189]. Notably, reduced serine phosphorylation of GSK-3 correlated significantly with severity of manic and depressive symptoms, suggesting that GSK-3 activity was affected by mood states. Studies of several other cohorts measuring the expression of GSK-3 mRNA and proteins generated inconsistent results. One study found that total GSK-3 levels tended to be higher in BPD-I than healthy controls in a Chinese population (unpublished data), while another study found that GSK-3 mRNA levels were lower in the peripheral blood mononuclear cells (PBMCs) of teenage suicide victims, and that GSK-3 protein levels were lower in platelets of patients with BPD [190]. Li and colleagues recently reported that levels of GSK-3 α and GSK-3 β in a group of bipolar manic subjects were higher than healthy controls [191]. They also noted that the improvement of manic symptoms during eight weeks of treatment with lithium, valproate, and atypical antipsychotics was associated with a significant increase in the inhibitory serine phosphorylation of GSK-3, but not total GSK-3 levels. This finding is in line with preclinical data suggesting that GSK-3 inhibition via increased serine phosphorylation is a response of GSK-3 to the psychotropics used to treat BPD, and supports the notion that GSK-3 is a promising molecular target in the pharmacological treatment of BPD.

Presently, no blood-brain-penetrant GSK-selective inhibitor has been clinically tested in proof-of-principle studies in mood disorders. It is important to mention, however, that the use of GSK-3 inhibitors would be limited by GSK-3's involvement with diverse pathways and multiple substrates that may induce side effects and/or toxicity [192].

PKC Signaling Cascade

PKC plays a key role in regulating neuronal excitability, neurotransmitter release, and plasticity. PKC isoforms differ in their structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity. Diverse studies support the direct involvement of PKC and its substrates in the pathophysiology and therapeutics of mood disorders [193–198]. In preclinical models, lithium and valproate have been found to directly regulate PKC,

and the PKC inhibitor tamoxifen was found to limit amphetamine-induced hyperactivity in a large open field [199].

A recent clinical trial provided further evidence for the involvement of this system in bipolar mania. Although well known for its anti-estrogenic properties, tamoxifen is also a potent PKC inhibitor at high concentrations. A single-blind study showed that tamoxifen had significant antimanic effects in five of seven BPD subjects [200]. Another four-week, three-arm, double-blind, placebo-controlled, add-on study involving 13 women compared the antimanic efficacy of tamoxifen with medroxyprogesterone acetate and placebo. Greater improvement in manic and positive symptoms of psychosis was noted in patients receiving tamoxifen than in those receiving placebo; all patients received concomitant lithium or valproate [201]. These preliminary results were subsequently confirmed in two three-week, double-blind, placebo-controlled, monotherapy studies [202;203]. Both studies showed that tamoxifen had superior antimanic efficacy compared to placebo, and that these therapeutic effects were not associated with sedative effects or increased risk of depression. However, some of tamoxifen's antimanic effects may be due to its anti-estrogen effects (see [204]). There is considerable enthusiasm for developing PKC inhibitors; one recently synthesized agent is endoxifen, which exhibits a fourfold higher PKC potency than tamoxifen [205]. However, it is not clear whether it also has anti-estrogen effects, a property that limits tamoxifen's usefulness in the long-term treatment of BPD.

Conclusion

Recent preclinical studies have investigated diverse targets/compounds and neurotransmitter and neuromodulatory systems that are now at the proof-of-concept stage. Here, we reviewed several agents for which there are recent and promising data. Ultimately, these may result in putative novel treatments for mood disorders. These include (1) the opioid neuropeptide system, (2) the purinergic system, (3) the glutamatergic system, (4) the tachykinin neuropeptide system, (5) the cholinergic system (muscarinic system), and (6) intracellular signaling pathways. It is important to note that none of these treatments have yet been shown to be safe and effective in the treatment of mood disorders. Also, important methodological differences exist regarding how specific compounds are evaluated. For instance, most of the evidence presented here comes from case reports, case series, or proof-of-concept studies, some with very small sample sizes. Key to future studies are such variables as what dose/plasma levels and time frames are consistent with clinical therapeutic effect, localization to brain regions implicated in the neurobiology of the disorder under consideration, and association with human genetic findings. However, given the global impact of these disorders, and the dearth of rapid-acting and effective treatments, a new generation of agents for the treatment of mood disorders is clearly needed. The evidence reviewed here can guide important future research in drug development for mood disorders and, ultimately, have a tremendous positive impact on public health worldwide.

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Figure 1. Putative therapeutic targets for mood disorders

The dynorphin opioid system, the purinergic system, the glutamatergic system (AMPA receptors, NMDA receptors, and mGluRs), the tachykinin neuropeptide system, and the cholinergic system are all promising targets for the development of novel therapeutics for the treatment of mood disorders. Other promising targets not reviewed in this chapter include the AA cascade, the melatonergic system, the glucocorticoid system, oxidative stress, bioenergetics, and mitochondrial activity.

Abbreviations: AA: arachidonic acid; AMPA: α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; CREB: cyclic AMP response element-binding; DAG: diacylglycerol; IP3: inositol triphosphate; mGluR: metabotropic glutamate receptor; NK: neurokinin; NMDA: N-methyl-D-aspartate; PIP-2: Phosphatidylinositol 4,5-bisphosphate; PKA: protein kinase A; PLA-2: phospholipase A2; PLC: phospholipase C; PSD: post-synaptic density; TNF: tumor necrosis factor.

Figure 2. Pathophysiological basis and potential therapeutic targets for mood disorders involving glutamatergic neurotransmission

Ketamine preferentially targets postsynaptic AMPA/NMDA receptors, while riluzole's antidepressant effects occur through direct regulation, mostly at presynaptic voltage-operated channels and glia. All potential targets for new, improved glutamatergic agents are described below.

Presynaptic targets: Before release, Glu is packaged into vesicles by VGLUTs, which control glutamate concentration produced in the synaptic vesicles (**Target I**). Activation of voltage-gated sodium channels (**Target II**) and VOCCs (**Target III**) depolarizes the plasma membrane, allowing for the influx of sodium (through depolarization of axon terminals) and calcium (through interaction with the SNARE proteins) (**Target IV**), leading to the fusion of synaptic vesicles and the consequent release of Glu into the synaptic cleft. The type II mGluRs (mGlu2/3) are also present presynaptically (**Target V**), and may directly limit the synaptic release of Glu. These mGluRs also mediate feedback inhibition of Glu release, thus decreasing the activity of Glu synaptic terminals when the activation of presynaptic receptors reaches a certain level.

Glia: Glu can also be directly released from glial cells, regulating synaptic activity pre- and post-synaptically (**Target VI**). After its release, large amounts of Glu are rapidly distributed across the synaptic cleft, where it can bind to glutamate receptors in the postsynaptic regions. The remaining unbound Glu is rapidly removed from the synaptic cleft to the presynaptic neuron mostly by glia and EAATs. The glial transporters EAAT1 (also known in rodents as GLAST) and EAAT2 (or GLT-1) are essential for blocking pathological increases in Glu levels (**Target VII**). Glial Glu transporter expression is upregulated by neuronal activity. Notably, the expression of Glu transporters by glial cells and their anatomical arrangement within the synaptic cleft can be dynamically and reversibly modified, and can directly regulate their ability to scavenge Glu.

Postsynaptic neuron: AMPARs (GluR1–4) mediate fast Glu neurotransmission and play a major role in learning and memory through critical regulation of calcium metabolism, plasticity, and oxidative stress. When activated, these receptors open the transmembrane pore, thus allowing the influx of sodium and the consequent depolarization of the neuronal membrane (**Target VIII**).

The NMDAR channel includes the subunits NR1, NR2 (NR2A–NR2D), and NR3 (NR3A and NR3B). Glu's binding sites have been described mostly in the NR2 subunit, whereas the NR1 subunit is the site for its co-agonist, glycine. NR2A and NR2B subunit receptors are

both highly expressed in brain areas implicated in mood regulation, but NMDA receptors containing NR2A mediate faster neurotransmission than NR2B receptors (**Target IX**). The mGluRs include eight receptor subtypes (mGluR1 to mGluR8) classified in three groups (I-III) based on their sequence homology and effectors. The mGluRs in Group I, including mGluR1 and mGluR5, stimulate the breakdown of phosphoinositide phospholipids in the cell plasma membrane. mGluRs in Groups II (including mGluR2/3) and III (including mGluRs 4, 6, 7, and 8) limit the generation of cAMP by activating inhibitory G- proteins. While Group I receptors are coupled to the phospholipase C signal transduction pathway, Group II and III mGluRs are both coupled in an inhibitory manner to the adenylyl cyclase pathway, which is involved in regulating the release of Glu or other neurotransmitters such as GABA (**Target X**).

KARs are involved in excitatory neurotransmission by activating postsynaptic receptors, and in inhibitory neurotransmission by modulating GABA release. There are five types of KAR subunits: GluR5 (GRIK1), GluR6 (GRIK2), GluR7 (GRIK3), KA1 (GRIK4), and KA2 (GRIK5). GluR5–7 can form heteromers; KA1 and KA2 can only form functional receptors by binding with one of the GluR5–7 subunits. KARs have a more limited distribution in the brain than AMPARs and NMDARs, and their function is not well defined; they are believed to affect synaptic signaling and plasticity less than AMPARs (**Target XI**).

Cytoplasmic PSD-enriched intracellular molecules (e.g. PSD93) interact with Glu receptors at the synaptic membrane to modulate receptor activity and signal transduction. PSD95 and similar scaffolding molecules link the NMDARs with intracellular enzymes that regulate signaling, and also provide a physical connection between diverse neurotransmitter systems to synchronize information from different effectors (**Target XII**).

Finally, recent preclinical work suggests that the mammalian target of rapamycin (mTOR)-dependent synapse formation underlies ketamine's rapid antidepressant properties [121] (**not shown**).

Abbreviations: AMPA: -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; cAMP: cyclic adenosine monophosphate; EAAT: excitatory amino-acid transporters; GABA: gamma-aminobutyric acid; Glu: Glutamate; Gly: Glycine; KA: kainate; NMDA: N-methyl-D-aspartate; PSD: postsynaptic density; PSVR: presynaptic voltage-operated release; mGluRs: metabotropic Glu receptors; SNARE: soluble N-ethylmaleimide-sensitive factor attachment receptor; VGLUTs: vesicular Glu transporters.