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Second messenger/signal transduction pathways in major mood disorders: moving from membrane to mechanism of action, part I: major depressive disorder

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The etiopathogenesis and treatment of major mood disorders have historically focused on modulation of monoaminergic (serotonin, norepinephrine, dopamine) and amino acid [γ-aminobutyric acid (GABA), glutamate] receptors at the plasma membrane. Although the activation and inhibition of these receptors acutely alter local neurotransmitter levels, their neuropsychiatric effects are not immediately observed. This time lag implicates intracellular neuroplasticity as primary in the mechanism of action of antidepressants and mood stabilizers. The modulation of intracellular second messenger/signal transduction cascades affects neurotrophic pathways that are both necessary and sufficient for monoaminergic and amino acid–based treatments. In this review, we will discuss the evidence in support of intracellular mediators in the pathophysiology and treatment of preclinical models of despair and major depressive disorder (MDD). More specifically, we will focus on the following pathways: cAMP/PKA/CREB, neurotrophin-mediated (MAPK and others), p11, Wnt/Fz/Dvl/GSK3β, and NFκB/ΔFosB. We will also discuss recent discoveries with rapidly acting antidepressants, which activate the mammalian target of rapamycin (mTOR) and release of inhibition on local translation via elongation factor stimulation. Throughout this discourse, we will highlight potential intracellular targets for therapeutic intervention. Finally, future clinical implications are discussed.

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Key words: depression, major depressive disorder, signal transduction, second messenger, intracellular cascades, antidepressants.

Clinical Implications

- Preclinical models of despair and clinical samples of major depressive disorder (MDD) reveal abnormalities in intracellular second messenger/signal transduction cascades. Some of these cascades include the following: cAMP/PKA/CREB, neurotrophin-mediated (MAPK and others), p11, Wnt/Fz/Dvl/GSK3β, and NFκB/ΔFosB.
- Deficiencies in intracellular second messenger/signal transduction pathways reverse in response to successful treatment with traditional (monoaminergic) antidepressants.
- The rapidly-acting antidepressant ketamine induce changes in alternative intracellular cascades, e.g. mTOR activation and release of translational inhibition, in dendritic spines. These cascades are believed to be stimulated through acute antagonism of NMDA receptor and a synaptic glutamate surge.
- Intracellular second messenger/signal transduction abnormalities and reversal with successful treatment may serve as nosologica endophenotypes and biomarkers of response, respectively, to improve diagnosis and facilitate antidepressant drug development among the heterogeneity inherent in MDD.

Introduction

The etiopathogenesis and treatment of the major mood disorders, major depressive disorder (MDD) and bipolar disorder (BD), have historically focused on the manipulation of monoaminergic (serotonin, norepinephrine, dopamine) and amino acid (γ-aminobutyric acid,
glutamate) neurotransmitters via the activation or inhibition of plasma membrane receptors. Albeit there are acute changes in local neurotransmitter levels in brain regions implicated in the pathophysiology of depression (cortex, hippocampus), antidepressant effects often require weeks to months. As a result, the “neurotransmitter imbalance” hypothesis of depression is at best incomplete. As will be displayed below, these medications ultimately elicit their effects through the activation/inhibition of intracellular signal transduction cascades. Additionally, more direct targeting of salient second messenger/signal transduction intermediates may provide more rapid and robust acting antidepressant effects than our cadre of currently available antidepressants. Also, by directly targeting these mediators, some off-target adverse events, eg, increasing serotonin levels in the gastrointestinal tract leading to dyspepsia or diarrhea, may be avoided.

In this first of two articles, we will review intracellular-mediated neuroplasticity in the pathophysiology of preclinical models of depressive-like behavior and MDD. Throughout, we will discuss progress-to-date on pathway manipulation in treatment, and at the end we will offer exciting areas for future pathophysiological studies and experimental therapeutics targeted at these intracellular neuromodulatory cascades.

### Intracellular Second Messenger/Signal Transduction Cascades

#### cAMP/PKA/CREB

As mentioned, the delayed efficacy of monoaminergic antidepressants suggests a mechanism of action that is not simply explained by a restoration of a “chemical imbalance” via reuptake inhibition. As early as the 1980s, several preclinical investigators examined the vital role of intracellular second messenger/signal transduction cascades in the pathophysiology and treatment of depression. This examination was led by the discovery that antidepressants elicit their intracellular effects through canonical second messenger systems. Elevated synaptic levels of serotonin and norepinephrine activate cognate postsynaptic seven-transmembrane G-protein coupled receptors. Norepinephrine-induced β2AR and β1AR and serotonin-induced 5-HT6, 5-HT1a, and 5-HT7 receptor activation are predominantly implicated (Figure 1).1,2 The intracellular domain of G-protein coupled receptors interacts with Gα/β, which, through their α subunit, stimulates/inhibits adenylyl cyclase (AC). AC converts ATP-to-cAMP, which activates protein kinase A (PKA).

AC activity is increased with both chronic antidepressant treatment3 and electroconvulsive seizures (ECS).4 PKA phosphorylates downstream effector proteins involved in cytoskeletal reorganization and transcription. Standard antidepressants also increase PKA activity in fractionated rat neocortex.4,5 The cAMP-response element binding (CREB) protein is the major transcription factor responsible for neurotrophic/protective mRNA transcription in this cascade. Like PKA, chronic antidepressants increase CREB mRNA and protein levels in the rat hippocampus.6 This increases expression of brain-derived neurotrophic factor (BDNF), especially in the hippocampal dentate gyrus.7 Transgenic CREB overexpression in the hippocampus has antidepressant-like effects in rodent models of despair, and phospho-CREB (the activated isoform) stimulates CRE-responsive gene expression with chronic antidepressant treatment.8

Due to aberrancies corrected by standard antidepressants, phosphodiesterase (PDE) dysfunction has been investigated in MDD. There are numerous PDE isoforms that have variable specificity for cAMP and cGMP; PDE4 is a brain-specific, cAMP-selective isofom that has been the most extensively studied in depression.9 As displayed by [11C]-rolipram positron emission tomography (PET), PDE4 levels are globally decreased (about 20% reduction in MDD).10 As a result, PDE inhibitors have been proposed as rational therapeutic targets. An inhibitor of PDE4, (RS)-4-[3-(cyclopentyloxy)-4-methoxy-phenyl]-2-pyrrolidin-2-one (rolipram), has antidepressant effects in both MDD11 and rodent models of despair.12,13 Our group is currently studying changes in PDE4 levels after a treatment course with the selective serotonin reuptake inhibitor (SSRI) citalopram as a potential biomarker of treatment response (ClinicalTrials.gov identifier: NCT00369798). Even though there have been no additional trials with rolipram for two decades due to severe nausea, several pharmaceutical companies have subtype-specific, better-tolerated PDE inhibitors in their armamentarium for potential testing as antidepressants.

#### Neurotrophins

Centrally acting neurotrophins bind cognate receptors and intracellularly activate their tyrosine kinase domain, which induces autophosphorylation and recruits adapter proteins (Figure 1). In one of the most well-studied intracellular cascades in neuroscience, BDNF binds to TrkB, which activates the following three cascades: (1) extracellular regulated kinase (ERK)/mitogen-activated protein kinase (MAPK), (2) phospholipase Cγ (PLCγ)/inositol triphosphate (IP3), and (3) phosphatidylinositol-3 kinase (PI3K) (as shown in Figure 1, except the PLCγ/IP3 cascade). In the ERK/MAPK cascade, TrkB autoactivation recruits several adapter proteins: Shc, Grb2, and Sos. Sos is a guanine nucleotide exchange factor that converts GDP into the more...
energetically rich GTP. This sequentially activates Ras and Raf, the first protein kinase in this cascade. Like PKA, the activation of ERK/MAPK stimulates the transcription of target genes responsible for cytoskeletal rearrangement, neurotransmitter secretion, reuptake, etc.

The most extensively studied neurotrophin in depression is BDNF (reviewed by Tanis and Duman). In brief, multiple stress-induction paradigms decrease hippocampal BDNF expression and cause depression-like behaviors. Antidepressant medications and electroconvulsive seizures (ECS) restore BDNF mRNA levels in the frontal cortex and hippocampus. Exogenous administration of BDNF into the midbrain and hippocampus also has antidepressant-like effects. Conditional BDNF knockout in the mouse forebrain impairs the antidepressant effects of desipramine on the forced swim test (FST). As a result, CNS BDNF expression is both necessary (based on inducible knockout experiments) and sufficient (from exogenous administration experiments) for antidepressant efficacy.

Vascular endothelial growth factor (VEGF) is another neurotrophin that has been investigated in depression. Stress decreases hippocampal VEGF levels. ECS restores VEGF expression and intracellular flux through its cognate receptor, Flk-1 (VEGFR2), via the proliferation of neural stem cells in the dentate gyrus and hippocampus.

Figure 1. Canonical signal transduction cascades in preclinical models of despair and major depressive disorder. On the left side of the figure, monoamine neurotransmitter binding to cognate receptors recruits G protein adapters to their intracellular C-terminal tail. This activates (G_s)/inhibits (G_i) the cAMP/PKA/CREB cascade. Adenylyl cyclase converts ATP-to-cAMP, which stimulates protein kinase A to phosphorylate CREB. Phospho-CREB translocates to the nucleus to stimulate transcription of target genes involved in neuroprotection, neurotransmission, and cytoskeletal dynamics. On the right, neurotrophins bind to their cognate receptor tyrosine kinases and induce the autophosphorylation of their intracellular domain(s). This recruits numerous adapter proteins to the plasma membrane and stimulates protein–protein interactions that culminate in the activation of Raf, a protein kinase. Raf activates the small molecule Ras to induce mitogen-activated protein kinase (MAPK). Like the cAMP/PKA/CREB cascade, the MAPK/ERK pathway culminates in nuclear translocation of transcription factors (including CREB) to the nucleus.

There is also cross-talk between these two cascades (as depicted in the middle of the figure) via phosphoinositides leading to Akt activation. Akt phosphorylates GSK-3β, which dissociates it from Axin and APC ("degradation complex"). This stabilizes β-catenin and facilitates its nuclear translocation. Please refer to the accompanying text for a discussion of intracellular second messenger/signal transduction aberrations in depression, normalizing responses with antidepressants, and experimental targets for future drug development.
recruitment of constituents of the mTORC1 signaling pathway. VEGF/Flik-1 signaling is also essential for the antidepressant effects of the SSRI fluoxetine. Next, exercise-induced alleviation of depression-like symptoms in rodents also activates VEGF/Flik-1. In a rodent transgenic system (upregulation of cAMP through an *Aplysia* Gs-coupled receptor), VEGF was necessary for an antidepressant-like effect in several stress-induction paradigms. In clinical studies, low plasma VEGF levels have been observed in suicide completers, and the antidepressant effects of total plasma VEGF levels have been observed in suicide groups. Research groups have investigated a putative role for glial-vesicular epidermal growth factor (GDNF) in depression. MDD patients display an age-dependent decrease in peripheral GDNF levels, which increases in response to treatment and normalizes during remission. In contrast, in a postmortem sample of recurrent depression, increased GDNF levels in parietal cortex were evident. Finally, in a study of rat glia cells, antidepressant-induced GDNF expression/secretion was mediated by β-arrestin-1/CREB transcription complex formation, and GDNF epigenetic regulation (promoter methylation and histone modification) had adaptive effects in stressed mice.

Other centrally expressed neurotrophins, e.g., nerve growth factor (NGF) and neurotrophin-3 (NT-3) and their cognate receptors TrkA, TrkC and p75NTR, are also under investigation in preclinical/clinical studies.

**p11**

p11 was initially found in a yeast two-hybrid screen as a 5-HT1B and 5-HT4 interactor. p11 mRNA and 5-HT1B receptor transcripts co-express in several brain areas salient for depression. p11 mRNA was compared in helpless H/Rouen mice (a genetic model of depression) versus non-helpless NH/Rouen mice, and, at baseline, p11 mRNA levels were decreased in the forebrain in the helpless H/Rouen mice. The antidepressants imipramine and tranylcypromine as well as ECS increase neocortical p11 mRNA levels. p11 knockout mice display biochemical, electrophysiological, and behavioral responses consistent with depression. Furthermore, the antidepressant effects of imipramine in p11−/− mice were reduced in these mice, and, when exposed to tail suspension and FST, they were more resistant to the antidepressant effects of exogenous BDNF. The transgenic overexpression of p11, on the other hand, increases resiliency to exogenous stress. BDNF increases p11 expression in a trkB and MAPK-dependent manner. Therefore, p11 is both necessary in the pathogenesis and sufficient for reversal of depressive behaviors.

The expression of p11 mRNA has also been examined in depressed suicide completers, which revealed down-regulation in the anterior cingulate cortex relative to non-depressed controls. Prefrontal p11 mRNA is also decreased in suicide completers relative to postmortem controls. Peripheral p11 mRNA levels are also decreased in suicidal attempters with comorbid MDD and posttraumatic stress disorder (PTSD) relative to non-attempters (but increased relative to PTSD alone and healthy volunteers in another sample).

In non-human primates, chronic treatment with fluoxetine significantly increased p11 in peripheral mononuclear cells temporally consistent with antidepressant onset (unpublished personal communication).
from R. Innis, MD, PhD, NIMH). To translate these findings into humans, our group is presently investigating if peripheral p11 levels increase in response to successful SSRI treatment as a potentially biologically salient biomarker of treatment response (Clinical-Trials.gov identifier: NCT00697268).

**Wnt/Fz/Dvl/GSK-3β**

The Wnt/frizzled/disheveled/glycogen synthase kinase-3 beta cascade has been studied in the pathophysiology and therapeutics of depression (Figure 2). (Of note, GSK-3β can also be activated by PI3 K and Akt; for a review, see Voleti and Duman.) In the canonical signal transduction cascade, Wnt binding to Fz recruits a low-density lipoprotein receptor–related protein (LRP) to the plasma membrane, which may be inhibited by cytosolic isoforms of Dkk. The Wnt-Fz ligand-receptor complex recruits the scaffolding protein Dvl, which, in turn, stimulates Ca²⁺-dependent and Ca²⁺-independent pathways. The Ca²⁺ dependent pathway activates, among other mediators, PKC and CAMKII. In addition to their more notorious effects on phosphoinositides, PKC crosstalk with the MAPK/ERK cascade promotes neuromodulatory gene transcription (as depicted in Figure 1). CAMKII binds Ca²⁺ and stimulates neuromodulatory gene transcription through CREB. In the Ca²⁺ independent arm, Dvl stimulates phosphorylation of GSK-3β (as described in Figure 1) and facilitates dissociation of the β-catenin degradation complex and β-catenin mediated gene transcription. Please refer to the accompanying text for a discussion of aberrations in depression, normalizing responses with successful antidepressant treatment, and potential experimental targets for future investigation. Fz, frizzled; LRP, low-density lipoprotein receptor-related protein; Dkk, Dickkopf; Dvl, disheveled; PKC, protein kinase C; MAPK, mitogen activated protein kinase; ERK, extracellular-regulated kinase; CAMKII, calcium-calmodulin dependent protein kinase II; CREB, cAMP-response element binding protein; LEF/TCF, lymphoid enhancer factor/T-cell factor; GSK-3β, glycogen synthase kinase-3 beta; APC, adenosis polyposis coli; β-Cat, beta-catenin.

Figure 2. Canonical Wnt/Fz/Dvl/GSK-3β signal transduction cascade. Wnts are secreted glycoproteins that are agonists for Fz receptors. Fz receptor stimulation recruits LRP to the plasma membrane, which may be inhibited by cytosolic isoforms of Dkk. The Wnt-Fz ligand-receptor complex recruits the scaffolding protein Dvl, which, in turn, stimulates Ca²⁺-dependent and Ca²⁺-independent pathways. The Ca²⁺ dependent pathway activates, among other mediators, PKC and CAMKII. In addition to their more notorious effects on phosphoinositides, PKC crosstalk with the MAPK/ERK cascade promotes neuromodulatory gene transcription (as depicted in Figure 1). CAMKII binds Ca²⁺ and stimulates neuromodulatory gene transcription through CREB. In the Ca²⁺ independent arm, Dvl stimulates phosphorylation of GSK-3β (as described in Figure 1) and facilitates dissociation of the β-catenin degradation complex and β-catenin mediated gene transcription. Please refer to the accompanying text for a discussion of aberrations in depression, normalizing responses with successful antidepressant treatment, and potential experimental targets for future investigation. Fz, frizzled; LRP, low-density lipoprotein receptor-related protein; Dkk, Dickkopf; Dvl, disheveled; PKC, protein kinase C; MAPK, mitogen activated protein kinase; ERK, extracellular-regulated kinase; CAMKII, calcium-calmodulin dependent protein kinase II; CREB, cAMP-response element binding protein; LEF/TCF, lymphoid enhancer factor/T-cell factor; GSK-3β, glycogen synthase kinase-3 beta; APC, adenosis polyposis coli; β-Cat, beta-catenin.
disorders, especially bipolar disorder after the discovery that lithium is a potent GSK-3β inhibitor. In preclinical models of despair, the heterozygous deletion of GSK-3β has antidepressant effects, and GSK-3 inhibitors (L803-mts and AR-A014418) mimicked these genetic effects. The phosphorylation of GSK-3β is increased by chronic administration of the antidepressants fluoxetine or venlafaxine. A depressive phenotype was also observed with overexpression of GSK3β in the NAcc, while a dominant-negative GSK3β isoform promoted resiliency.

Several other pathway intermediates are affected by antidepressant therapy. Wnt2 was increased by several antidepressants (including ECS) in a microarray study of a rodent model of despair. Additionally, Wnt2 transgenic overexpression in the hippocampus was sufficient to generate antidepressant-like effects. Wnt7b expression, on the other hand, was increased by atomoxetine and ECS. Fz9 levels were upregulated by the noradrenergic antidepressants atomoxetine and venlafaxine but not by SSRIs. Blockade of a disheveled isoform, Dvl2 [via both overexpression of a dominant-negative isoform and intra-nucleus accum-bens (NAcc) inhibitor infusion], decreased resiliency to social defeat and other modalities for inducing despair.

To our knowledge, there have been no CNS-penetrant small molecule modulators of the Wnt/Fz/Dvl/GSK-3β pathway that have been tested in psychiatric disorders. We seek translation of these interesting rodent findings into the pathophysiology and experimental therapeutics of MDD. Due to this signal transduction/second messenger system’s involvement in numerous cellular pathways, especially mitogenesis, translational studies will need to pay close attention to toxicity and side effect profiles.

**NF-κB/ΔFosB**

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor that has been most extensively studied in immunology but also plays a functional role in synaptic processes underlying learning and memory. After demonstrating its function in instrumental and other forms of motivated learning, several groups have investigated NF-κB induction of ΔFosB, a truncated version of the immediate-early transcription factor FosB, in rodent models of despair. Lipopolysaccharide-exposed rodents have a delayed increase in immunostaining for ΔFosB that parallels the onset of increased immobility on the FST and reduced sucrose consumption (a preclinical marker of anhedonia). Serum response factor (SRF), another transcription factor, decreases ΔFosB in the NAcc in response to chronic social defeat. In addition, genetic deletion of NAcc SRF decreased resiliency to stress.

Several studies have demonstrated that ΔFosB expression correlates with antidepressant-like effects. In an elegant study using different mouse strains genetically engineered to produce FosB +/− ΔFosB, the ΔFosB haplotype (+/Δ) strain had increased depressive-like behaviors relative to wild-type and the double knock-in (Δ/Δ), which displayed less anxiety in the open field test. ΔFosB expression increased in multiple rat brain regions, eg, dorsal raphe nucleus, frontal cortex, hippocampus, and basolateral amygdala, with standard antidepressants (sertraline and desipramine) and vagal nerve stimulation (VNS). Interestingly, VNS appeared to have a larger effect and affected some brain regions not observed with traditional antidepressants (nucleus tractus solitarius and locus ceruleus).

**mTOR**

As the activation of intracellular neuromodulatory cascades is critical for the mechanism of action of standard antidepressants, several recent studies have elucidated the mechanisms underlying the rapidly acting antidepressant effects of glutamate-based medications such as ketamine. Li et al. discerned that the activation of mammalian target of rapamycin (mTOR) was necessary for ketamine’s antidepressant effects (Figure 3). A case report in a single treatment-resistant depressed patient revealed that intravenous ketamine increased peripheral mTOR expression on a time course that coincided with its rapid antidepressant effects. Like ketamine, the proprietary mGluR2/3 antagonist, LY341495, rapidly (within 1 h) activated mTOR and downstream pathway constituents (p70S6K, 4E-BP1) and subsequently (24 h later) increased levels of postsynaptic density proteins (PSD-95, GluR1, synapsin 1). These antidepressant effects of LY341495 were reversed by the mTOR inhibitor rapamycin.

**eEF2K/CAMKIII**

Finally, the release of inhibition on local translation in dendritic spines has emerged as an exciting intracellular target of ketamine. Autry et al. reported that subanesthetic doses of ketamine released inhibition of translation by deactivating eukaryotic elongation factor 2 kinase (eEF2K)/calcium-calmodulin protein kinase type III (CAMKIII) (Figure 3). The ensuing dephosphorylation of eEF2 removes tonic inhibition on BDNF translation in the hippocampus, thereby increasing BDNF levels and concomitant TrkB receptor activation. The deactivation of eEF2K and stimulation of eEF2

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**NR**

M. J. Niciu et al.
(therby increasing central BDNF levels) has emerged as a novel rational therapeutic target in MDD.\textsuperscript{76}

**Conclusions**

In this article, we have reviewed the evidence for intracellular second messenger/signal transduction cascades in preclinical models of despair and MDD. Monoamine reuptake inhibition by traditional antidepressants occurs immediately, but the behavioral effects take much longer, which implicates intracellular processes in their mechanism of action. Traditional monoaminergic antidepressants indirectly stimulate multiple intracellular cascades, and this may ultimately dilute their antidepressant efficacy on the neural circuitry that is involved in depression via off-target stimulation/inhibition. In addition, these medications have proven inadequate in real world effectiveness trials such as STAR*D\textsuperscript{77} and CO-MED.\textsuperscript{78} This should come as no surprise, as only 5–10\% of CNS neurons use monoamines as their primarily neurotransmitter, while 50\% use glutamate. Glutamate-based antidepressants are more rapidly acting and have larger effect sizes in clinical trials.\textsuperscript{79,80} Two of the most promising candidates for future drug development based on preclinical studies with ketamine are mTOR and eEF2K/eEF2. As reviewed, both of these molecules are critical in central BDNF signaling (mTOR possibly downstream of BDNF and eEF2K/eEF2 in local BDNF translation). As promising as this seems, we must remain vigilant for toxicity/adverse events, as (1) mTOR is a protooncogene and overactive in autoimmune disorders (where its overactivity may be suppressed clinically with rapamycin), and (2) chronic stimulation of eEF2 may...
lead to excessive translation of off-target proteins. (Of note, we suggest that monoaminergic antidepressants have not been associated with an increased risk of cancer because their biological effects are more indirect and likely less potent on these intracellular cascades.)

The mood disorders field is sorely in need of biologically salient measures to improve our existing nosology and monitor treatment response, which, at present, is based only on patient report and clinical impression. Biologically informed therapeutics are routinely used in other fields of medicine such as cardiology and oncology, but, unfortunately, they remain elusive in psychiatry. Reliable measures of intracellular processes involved in depression may assist in developing a more accurate nosology among the heterogeneity inherent in the clinical diagnosis of MDD, eg, those patients who have underactive mTOR or eEF2 activity may have a "glutamate-based depression" and may benefit from glutamate-based therapies. Next, the development of peripheral measures of intracellular events may allow us to assess a more reliable and quantitative baseline and treatment response better than our current approach, eg, assessing baseline mTOR and eEF2K/eEF2 activity and monitoring change in activity with treatment.

In conclusion, we have garnered an adequate understanding of intracellular second messenger/signal transduction cascades in preclinical models of depression and MDD, and, in due time, these findings will likely be translated into the clinic in novel therapies and nosological biomarkers.

Disclosures

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