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From synapse to nucleus: novel targets for treating depression

Herbert E. Covington III[1], **Vincent Vialou**[1], and **Eric J. Nestler**[*]
Fishberg Dept of Neuroscience, Mount Sinai School of Medicine, New York, NY

Abstract

The need for newer compounds to treat depression is an ever-growing concern due to the enormous societal and financial ramifications of this disorder. Here, we review some of the candidate systems that could potentially be involved in depression, or an inherent resistance to depression termed resilience, and the numerous protein targets for these systems. A substantial body of literature provides strong evidence that neurotrophic factors, glutamate receptors, hypothalamic feeding peptides, nuclear hormone receptors, and epigenetic mechanisms, among others, will make for interesting targets when examining depressive behavior or resilience in preclinical models, and eventually clinical trials. Although some of these targets for depression already appear promising, new waves of more selective compounds for any molecular system should promote a better understanding of this complex disease and perhaps improved treatments.

1. Introduction

In addition to traditional agonists and antagonists that act predominantly at cellular membrane receptors, a surge in the number of specific compounds affecting intracellular proteins has recently been observed in experimental reports, furthering our understanding of, and putative treatments for, psychiatric and neurological diseases. While much remains to be learned concerning the roles of neurotransmitter systems and neuromodulatory peptides that act directly at the cell surface of neurons and glia, we postulate that the steady rise in compounds aimed at targeting intracellular mechanics reflects remarkable advances in neuroscience. Probing deeper into the mechanisms of cellular function reveals increasingly complex interactions between enzymes and structural proteins that mediate processes ranging from genomic regulation to cellular morphology. Unraveling the roles of particular intracellular signaling molecules, transcription factors, and chromatin modifying enzymes has elucidated cell-type specific events that may be dysregulated during disease states. Further advancements will undoubtedly lead to the generation of newer classes of compounds that are capable of targeting such cellular events, with the added potential of cell-type specificity. The fundamental goal of this strategy is to better treat psychiatric and neurological diseases in a timely manner without undesired negative side effects.

The need for improved antidepressant treatments is long-standing. Despite a steady increase in the number of people treated for depression over the past thirty years, the prevalence of the disorder remains stable. This, along with other factors, demonstrates the inadequacy of current

[1]These authors contributed equally to this work

[*]Address correspondence to: Eric J. Nestler, Fishberg Dept of Neuroscience, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1065, New York, NY 10029; eric.nestler@mssm.edu.

treatments and a lack of improvement over the conventional monoaminergic-based therapies discovered by serendipity decades ago (Healy, 1999; Kessler and Wang, 2008). In addition, available medications are slow to produce effects: mood elevation is seen only after several weeks of treatment, and severely depressed patients reach remission after an average of four successive treatments over 38 weeks (Rush et al., 2006). A need for maintenance therapies after a remission of symptoms is also typically warranted in patients that have a lifetime history of depressive episodes, comorbid anxiety disorder, substance abuse disorders, as well as those who are likely to experience frequent bouts of stress (Blier et al., 2007; Davis et al., 2007). A high lifetime prevalence rate (16.6%), with high rates of recurrence and morbidity, contribute substantially to the global burden of the disease which supports a need for newer medications with greater efficiency, faster onset of action, and improved tolerability (Berton and Nestler, 2006; Kessler and Wang, 2008; Rush, 2007).

A key obstacle in developing newer medications has been a limited knowledge of the pathophysiology of depression (Krishnan and Nestler, 2008). Indeed, there is a profound heterogeneity in the phenotype of depression (i.e., its clinical presentation, age of onset, course of illness, and treatment response), signifying that depression encompasses many different disease states with distinct etiologies (Berton and Nestler, 2006; Rush, 2007). Epidemiologic studies have found that depression is roughly 40% heritable, yet no specific genes have yet been identified definitively. In light of these problems, studies examining the role of gene-environment interactions on the emergence of particular symptoms or treatment responses have indicated several ‘susceptibility’ genes that may indicate a higher risk for major depressive disorder or resistance to treatment (Aan Het Rot et al., 2009; Lekman et al., 2008). Recent neuroimaging and post-mortem studies of human brain have advanced our knowledge of neural systems involved in depression, particularly brain areas that might underlie cognitive impairments and dysregulation of emotional processing (Drevets et al., 2008). As a complement to these findings, deep brain stimulation of the subgenual cingulate cortex or nucleus accumbens has been shown to alleviate some depressive symptoms in treatment-refractory patients (Mayberg et al., 2005; Schlaepfer et al., 2008).

Functional and morphological differences between brains of depressed and non-depressed subjects are likely to be derived from distinct molecular and cellular correlates (Manji et al., 2001). In clinical depression, and through the use of depression models in animals, numerous anomalies at the cellular level in distinct brain areas have indeed been revealed, which has in effect “opened the flood gates” for examining newer antidepressant targets (Berton and Nestler, 2006; Mathew et al., 2008). Also contributing to this wealth of potential new targets is the realization that the search for new antidepressants should not focus solely on mechanisms that prevent or reverse the deleterious effects of stress, but should also include mechanisms that promote resilience—continued health and well-being despite the onslaught of severe stress (Feder et al., 2009). Amongst such newer targets are amino acid neurotransmitter systems that are known for their dominant role in regulating neural activity and synaptic plasticity (e.g., glutamate and GABA), neurotrophic factors, and molecules that are readily induced by episodes of stress (e.g., CRF [corticotropin release factor] and glucocorticoids), neuropeptides that maintain homeostatic energy balance (e.g., hypothalamic feeding peptides), gonadal hormones that fluctuate over time, particularly in females (e.g., estrogen), as well as the abundance of downstream cellular effectors that affect genome-wide transcriptional outcomes (e.g., ΔFosB, CREB [cAMP response element binding protein], PDEs [phosphodiesterases], GSK-3ß [glycogen synthase kinase 3ß], and HDACs [histone deacetylases]). The majority of these potential targets are broadly expressed throughout the brain and have a diversity of functions. Therefore, the overwhelming challenge is to find specific targets that generate predicted outcomes, without producing adverse side effects. The development of allosteric modulators of receptor systems represents a particularly nice example of recent successes in drug discovery. Allosteric binding sites, when targeted, allow for increases or decreases in the

efficacy of endogenously available receptor ligand. Consequently, tolerance, dependence, and overdoses are less-frequently reported with allosteric pharmacological modulators. The best example of this principle is the popular $GABA_A$ positive allosteric modulators used to treat anxiety. Refining our understanding of the pathophysiology of depression and resilience, and uncovering novel antidepressant mechanisms, will ultimately lead to better therapeutic strategies for treating depressive syndromes.

In this review, we summarize our current understanding of depression and highlight examples of recent neural and molecular mechanisms implicated in this disorder. We focus on their therapeutic potential, and critically discuss their strengths and weaknesses in the light of recent preclinical and translational studies. Novel potential treatments for depression that are already actively in clinical trials (i.e., those that target receptors for CRF, vasopressin, glucocorticoids, and neurokinins) are discussed in other reviews (see Berton and Nestler, 2006; Mathew et al., 2008), and therefore are not covered here.

2. Neurotrophic factors and related signal transduction pathways

Sizeable morphological changes in the hippocampus have been reported in depressed humans and after chronic stress in animal models (Gould et al., 1997; Sapolsky, 1996). These observations have prompted the notion that depression might be associated with neuronal loss in this brain region (Sapolsky, 2000). One mechanism by which hippocampal impairments may correspond with depression is via the loss of neurotrophic factors and related signaling cascades. In addition, conventional antidepressant treatments have been shown to increase patterns of neurogenesis in the adult hippocampus, an effect that appears to be important for their antidepressant-like behavioral effects (Santarelli et al., 2003). However, given a lack of selective molecules that target specific signaling cascades involved in the process of hippocampal neurogenesis has made it difficult to achieve empirical assessments of their effects in preclinical depression models. Nonetheless, BDNF [brain-derived neurotrophic factor] is decreased in the hippocampus of depressed patients (Dwivedi et al., 2003) and by stress in animals, and multiple lines of experimental evidence have supported a role for BDNF in the behavioral effects of antidepressants in animals (Duman and Monteggia, 2006). In addition, BDNF polymorphisms can robustly alter its activity-dependant release, and may be linked to depression-related vulnerabilities in humans (Duncan et al., 2008; Gatt et al., 2009).

However, the effects of BDNF in other brain areas generate different behavioral outcomes, and increases in BDNF in the brain's reward circuitry may actually be pro-depressant (Berton et al., 2006). For example, infusion of BDNF into the ventral tegmental area (VTA) produces depression-like effects (Eisch et al., 2003). Likewise, an increase in BDNF protein levels in the VTA and its nucleus accumbens (NAc) target is triggered by chronic social defeat stress, and this increase is both necessary and sufficient to produce a depressive-like phenotype, while the selective knockout of BDNF from the VTA promotes resilience to stress (Berton et al., 2006; Krishnan et al., 2007). Thus, it is not surprising that broad forebrain deletions of BDNF or its TrkB receptor do not dramatically influence depression-like behaviors (Monteggia et al., 2007; Zorner et al., 2003) and that modulating BDNF or TrkB activity has proven to be clinically ineffective (Sen and Sanacora, 2008; Tanis et al., 2007). The limitations associated with modulating BDNF globally have prompted a revision of the neurotrophic hypothesis of depression, and highlights the difficulties of targeting such complex systems (Groves, 2007; Krishnan and Nestler, 2008).

Despite such difficulties, the neurotrophic hypothesis of depression has opened new doors for research strategies examining the mechanisms of depression and resilience. One example is the insight obtained from studies on the intracellular signaling pathways that are regulated by BDNF and other neurotrophic factors. BDNF activation of TrkB in turn activates several

intracellular cascades, including the Ras-Raf-ERK (extracellular-signal regulated kinase), phosphatidylinositol-3-kinase (PI3K)-AKT, and PLCγ (phospholipase Cγ) pathways. These distinct pathways converge on activating the transcription factor CREB, among many other actions. CREB then activates the transcription of numerous genes, including many of the neurotrophins. Not surprisingly, most of the proteins involved in neurotrophic signaling pathways, including ERK, AKT, PLCγ, and CREB, are regulated in animal models of depression or antidepressant treatments (Bolaños et al., 2003; Carlezon et al., 2005; Duman et al., 2007; Dwivedi et al., 2006; Dwivedi et al., 2008; Krishnan et al., 2008). Another potential target for achieving antidepressant effects may be via upregulation of the cAMP-CREB pathway through inhibition of any of several phosphodiesterases, which catalyze the breakdown of cAMP and increase BDNF expression (Fujimaki et al., 2000). Rolipram, a non-selective inhibitor of PDE4, has been reported to have antidepressant effects in depressed patients (Manji et al., 2003). Although these early trials were discontinued due to intense side effects (e.g., nausea and vomiting), efforts to develop safer drugs that target selective PDE isoforms continue [i.e., mice lacking PDE4D display antidepressant-like behaviors (Zhang et al., 2002)], and new PDE4 agents are in clinical trials for treating inflammatory diseases (Spina, 2008). PDEs 2, 5, 6, 10 and 11 all contain a GAF binding domain, and the GAF domain on PDEs 2, 5 and 6 have a higher affinity for cyclic guanosine monophosphate (cGMP) than for cAMP (Zoraghi et al., 2004), which serves to regulate catalytic activity upon association. By virtue of a large and well-defined structure, GAF domains provide a realistic theoretical target for constructing new ligands that function as agonists, or antagonists, and with a high degree of selectivity for particular PDEs (Martinez et al., 2002). Two compounds, sildenafil (a PDE5 inhibitor) and papaverine (an inhibitor of PDE10 among other subtypes), both appear to have anxiogenic effects in mice, indicating a hypothetical role for these enzymes in stabilizing mood (Hebb et al., 2008; Kurt et al., 2004).

Two recently characterized proteins, named SPROUTY (SPRY) and SPRED, have been shown to repress the action of fibroblast growth factor (FGF) and associated receptor tyrosine kinase-dependent signaling pathways (Bundschu et al., 2007; Cabrita and Christofori, 2008). Antagonism of these proteins has been postulated to be a potential therapeutic treatment for depression. SPRY2 is downregulated in the prefrontal cortex after chronic antidepressant treatment (Ongur et al., 2007), and disruption of this protein in the dorsal hippocampus has long-lasting effects on neurogenensis and depressive-like behavior (Dow et al., 2008). However, this protein, like many others, is enriched across several brain areas and its action may lead to different behavioral outcomes depending on its location. SPRY3, on the other hand, may be a more promising target in this regard (Minowada et al., 1999; Sanchez et al., 2008). As more inhibitors of SPRY (i.e., other modulators of FGF signaling) become increasingly available, their potential effects on depressive-like behavior, through their presumable effects on neurogensis and cellular plasticity, can begin to be fully addressed in preclinical models (Bachis et al., 2008).

The SPRED family of proteins specifically inhibits the Ras-ERK pathway in response to several growth factors, including vascular endothelial growth factor (VEGF) (Bundschu et al., 2007). Studies with *Spred1* knockout mice have demonstrated that this protein plays an important role in hippocampal-dependant learning and synaptic plasticity, making this an interesting target for antidepressant treatment (Denayer et al., 2008). Future studies should determine whether or not other family members of these proteins are selectively enriched in certain brain areas. It is promising that some of these proteins, such as SPRED3, are expressed predominantly in brain (Kato et al., 2003). However, until pharmacological agents are made available that alter their activity *in vivo*, it will remain challenging to unravel the promise in modulating SPRED in depressive-like behavioral responses.

The precursor of BDNF, proBDNF, is widely and abundantly expressed in adult brain and binds to the pan-neurotrophin receptor $p75^{NTR}$. Upon binding to $p75^{NTR}$, proBDNF can elicit long-term depression, reduce spine density in hippocampal neurons, and induce apopotosis in basal forebrain neurons (Martinowich et al., 2007; Volosin et al., 2006; Woo et al., 2005; Zagrebelsky et al., 2005). Control over the cleavage of proBDNF may thus represent a potentially relevant therapeutic target. Indeed, several recent studies have shown that the enzymes responsible for converting proBDNF to mature BDNF (i.e., tissue plasminogen activator [tPA], as well as several regulators of tPA like plasminogen activator inhibitor type 1 [PAI1], and p11, an activator of tPA) are implicated in depression (Martinowich et al., 2007; Tsai et al., 2008). Interestingly, the use of STATINs to treat hypercholesterolemia is reported to be associated with a reduction in the incidence of depression (Tsai, 2007). The mechanisms underlying an antidepressive effect of STATINs are currently unknown, but their inhibitory role over PAI1 might increase tPA activity, thereby increasing the cleavage of proBDNF into BDNF. Since tPA is expressed in the blood and the tPA-plasmin proteolytic cascade is involved in cardiovascular function, this approach may target a subset of depressed patients suffering from cardiovascular disease (Hou et al., 2009). Due to a lack of empirical data that support a role for STATINs, and their regulation of associated pathways, in depressive-like behavioral responses, more studies are necessary to build upon these claims. Additional neurotrophic factors, such as VEGF, FGF , and VGF (non-acronymic) have been implicated in the etiology and treatment of depression (Tsai et al., 2009; Evans et al. 2004; Warner-Schmidt and Duman, 2007). Such neurotrophic factors are induced by chronic antidepressant treatments in the hippocampus, while chronic stress reduces the expression of *vegf* (as well as its receptor *fllk-1*) and *fgf2* (as well as its receptor *fgfr1*) in this brain region (Heine et al., 2005; Turner et al., 2008). There are more than 20 endogenous ligands for FGF receptors alone (Reuss et al. 2003). Assessments of neurotrophic factor manipulations during ongoing conventional antidepressant treatments may be particularly valuable, given their prominent role in various forms of neuronal plasticity. All in all, a careful elucidation of the networks that rely on transcriptional regulation by these and other neurotrophic factors has tremendous potential for providing new therapeutic targets for the treatment of depression.

3. Glutamate acting drugs

Ever since the discovery in 1959 that D-cycloserine, a partial NMDA glutamate receptor agonist, has antidepressant effects, it has been generally accepted that the glutamatergic system contributes to the pathophysiology of depression (Crane, 1959; Pittenger et al., 2007). Many reports have highlighted alterations in glutamate signaling as well as changes in the expression of AMPA or NMDA receptor subunits in depression, although there are significant variations across brain areas, and the functional significance of these changes remains unclear (Feyissa et al., 2009; Karolewicz et al., 2009; Sanacora et al., 2008). No approved antidepressant treatment is currently based solely on targeting the glutamatergic system, although the glutamatergic agent riluzole is sometimes administered for its antidepressant effects. Originally developed as an anticonvulsant and subsequently granted approval by the FDA for treating amyotrophic lateral sclerosis, riluzole has recently been demonstrated to be a successful augmentation strategy in subjects with treatment resistant depression (Zarate et al., 2004).

In parallel, there is growing interest in the non-competitive NMDA receptor antagonist, ketamine, which produces a rapid and sustained antidepressant response in patients with treatment-resistant depression (Berman et al., 2000; Zarate et al., 2006; Aan Het Rot et al., 2009). Importantly, such effects of ketamine are seen at sub-psychomimetic doses of the drug. Moreover, ketamine produces a profound reduction in suicidality (Price et al., 2009). Based on findings with ketamine, there is interest in developing subtype-selective NMDA antagonists, particularly those that act through allosteric mechanisms. Allosteric modulators of glutamate receptors might have higher selectivity, retain the spatial and temporal aspects of endogenous

receptor activity, and avoid many of the drawbacks associated with more conventional ligands (Conn et al., 2009).

NMDA receptors are complex ion channels formed by the combination of two NR1 subunits that contain the glycine/D-serine co-agonist site, and two NR2 subunits, which contain the glutamate-binding site. Among the four NR2 subunits, NR2A and NR2B are expressed in forebrain. These subunits have different pharmacological properties and localization, and they play an important role in adjusting a cell's excitability threshold for synaptic modification (Yashiro and Philpot, 2008). Therefore, specific targeting of these distinct subunits may reveal useful antidepressant treatments. In this regard, CP-101,606 (an NR2B selective antagonist) is reported to produce rapid and robust antidepressant effects in patients with treatment-refractory depression with good tolerability and without producing dissociative reactions (Preskorn et al., 2008; Pittenger et al., 2007). Contrary to ketamine, which blocks the receptor-gated ion channel, CP-101,606 inhibits NMDA receptors through an allosteric mechanism (Mott et al., 1998), which may account for its fewer adverse side effects. Recent studies have indicated that activation of synaptic (or extrasynaptic) NMDA receptors can have apparently opposite effects on the function and survival of neurons (Hardingham et al., 2002). Specifically, it appears that activation of synaptic NMDA receptors promotes cell survival, in part through activation of CREB and BDNF, while extrasynaptic NMDA receptors initiate cell death. Pre-clinical studies have also revealed antidepressant-like effects of NMDA receptor partial agonists at the glycine/D-serine site (Pittenger et al., 2007).

AMPA and kainate ionotropic glutamate receptors represent additional potential drug targets (Lodge, 2009). AMPA receptors mediate fast excitatory postsynaptic currents in most neurons, however, the time course and amplitude of these effects depend on the subunit composition of the receptors, which vary across brain regions, neurons, and even synapses, which influences their role in synaptic plasticity and behavior (Kessels and Malinow, 2009). Allosteric modulators fail to rapidly desensitize AMPA receptors like full agonists do, and several classes of positive allosteric modulators of AMPA receptors increase BDNF expression levels, which can stimulate neurogenesis as well as neuronal sprouting in hippocampal neurons (O'Neill and Witkin, 2007). Such potentiation of AMPA receptors promotes antidepressant-like effects in rodents (Bleakman et al., 2007). In line with these findings, mice lacking the AMPA subunit GluR1 show depression-like behavior (Chourbaji et al., 2008). It is also possible that the antidepressant effects of ketamine are mediated in part through the activation of AMPA receptors (Maeng et al., 2008).

Despite these promising results, no clinical trial with AMPA receptor potentiators has yet succeeded as a result of their risk of toxicity (Mathew et al., 2008). Nonetheless, large-scale gene candidate studies have revealed an association between the GluR3 AMPA receptor and the K2 kainate receptor and suicidal ideation (Laje et al., 2007). Associations between the K4 kainate subunit and the outcome of antidepressant treatment have been identified as well (Paddock et al., 2007). Such pharmacogenomic approaches have further established a prominent role for the glutamatergic system in the neural effects of antidepressant treatment (Lekman et al., 2008).

AMPA receptors are highly regulated at the synapse via phosphorylation and their direct interaction with a multitude of proteins, particularly, the transmembrane AMPA receptor regulatory proteins (TARPs) and the recently discovered cornichon protein family, among many others like GRIP/ABP and PICK1 (Fig. 1). Targeting these proteins may be a feasible way to influence AMPA receptor function. TARPs are expressed exclusively in excitatory post-synaptic densities, which make them relatively selective for AMPA receptors (Tomita et al., 2003). TARPs mediate AMPA receptor surface expression and synaptic clustering (Tomita et al., 2003) and modulate the receptor's electrophysiological properties by slowing its

desensitization and deactivation (Korber et al., 2007;Priel et al., 2005). TARPs also control the pharmacological effects of AMPA receptor potentiators (Tomita et al., 2006) and antagonists (Cokic and Stein, 2008;Kott et al., 2007). Each TARP isoform displays a specific pattern of expression in brain. For instance, g3 and g8 are almost exclusively expressed in the cerebral cortex and hippocampus, respectively (Tomita et al., 2003). Recent studies implicate dysregulation of TARPγ2 mRNA in prefrontal cortex in bipolar disorder, further suggesting an involvement of these proteins in mood disorders (Silberberg et al., 2008). Cornichon homolog 2 and 3 (CNIH-2, -3) proteins are the main auxiliary subunits integrated into AMPA receptors complexes, at least in rodents (Schwenk et al., 2009). Similar to TARPs, cornichon proteins increase the expression of AMPA receptors and slow the kinetics of their deactivation and desensitization (Schwenk et al., 2009). The specific binding domains for enzymes, such as TARPs, remain rather elusive (Milstein and Nicoll, 2008). Thus, as information regarding the physical properties of these proteins becomes available, so may a future for compounds that have the ability to regulate their cellular functions.

These same approaches can be used to examine other components of the glutamatergic system, for instance, by targeting the receptor auxiliary protein NETO2 which functions to modulate kainite receptor channel properties (Zhang et al., 2009). More work is needed to fully explore this possibility (Gallyas et al., 2003; Zhang et al., 2009). Interestingly, blockade of K2 kainate subunits produces anxiolytic-like effects in rats, suggesting that this could be an adjunctive therapy for depression associated with high levels of anxiety (Alt et al., 2007).

Increasing evidence suggests that other aspects of glutamate signaling are regulated by stress or antidepressant treatments, including effects on presynaptic glutamate release and glutamate homeostasis via glial cells. Vesicular transporters for glutamate, SNARE complexes that mediate vesicle exocytosis, and plasma membrane glutamate transporters are under current investigation as potential targets in the treatment of depression (Sanacora et al., 2008).

A final glutamatergic strategy for treating depression may be through modulating metabotropic (G protein-coupled) glutamate receptors (Fig.1). One receptor in particular, mGluR5, increases neuronal excitability and potentiates NMDA-evoked currents, suggesting that antagonism of mGluR5 might dampen NMDA function. Indeed, MPEP and MTEP, selective mGluR5 allosteric antagonists, induce antidepressant effects in rodent models (Pilc et al., 2008). The antidepressant-like effects of MPEP are lost in mGluR5 knockout mice (Li et al., 2006). However, negative allosteric modulators of mGluR5, like MPEP, MTEP or fenobam, function like inverse agonists, and such actions might be the cause of cognitive deficits and psychotomimetic effects observed in some patients with severe anxiety after treatment with fenobam (Porter et al., 2005). The recent development of an mGluR5 partial allosteric antagonist might lead to the generation of improved drugs with fewer side effects (Rodriguez et al., 2005). Contrary to mGluR5, mGluR2 and mGluR3 negatively modulate glutamatergic neurotransmission. Preclinical studies have demonstrated that antagonists of these receptors may possess antidepressant-like effects when administered to rodents (Pilc et al., 2008). Such effects are prevented after blockade of AMPA receptors with NBQX, suggesting an AMPA-dependant antidepressant effect of these mGluRs (Bespalov et al., 2008;Pilc et al., 2008). Similarly, mGluR7 knockout mice generate antidepressant-like behaviors (Cryan et al., 2003).

Targeting glutamate receptors has the appeal of relieving depressive symptoms much faster than conventional monoaminergic strategies. In addition, the number of administrations or daily doses may be reduced based on the persistence of antidepressant effects after a single treatment, as observed with ketamine (Aan Het Rot et al., 2009). Problematic side effects of targeting ionotropic glutamate receptors arise from the acute disruptive effects (e.g., sedation and cognitive impairments) of strongly regulating glutamatergic synapses. Metabatropic

glutamate receptor acting drugs, however, are less likely to produce undesirable side effects due to their weaker, modulatory effects on excitatory synapses, and are currently in clinical trials for a number of neurological disorders (Marek, 2004; Moldrich et al., 2003).

4. Hypothalamic feeding peptides

Hypothalamic peptides are best known for their prominent role in the regulation of feeding behavior (Grossman, 1975; Hoebel and Teitelbaum, 1966). Recent studies have demonstrated that these peptides also contribute to emotional behavior (Nestler and Carlezon, 2006). The anhedonic and lethargy symptoms and significant changes in body weight that occur in many depressed patients suggest the involvement of hypothalamic mechanisms in a subtype of depression. For instance, orexin (hypocretin) stimulates feeding in response to energy deficiencies (Sakurai et al., 1998), and is critical for the antidepressant-like effects produced by calorie restriction in animals (Lutter et al., 2008a). Likewise, experimental treatments with this peptide promote antidepressant-like effects (Lutter et al., 2008a). Stimulation of hypothalamic orexin neurons appears to be mediated partly by the feeding-promoting gut hormone, grhelin, and its activation of growth hormone secretagogue receptor (GHSR, also known as the ghrelin receptor) on orexin neurons (Lutter et al., 2008b). Interestingly, social stress increases ghrelin secretion, indicating that this peptide may promote resilience (Lutter et al., 2008b). Mice lacking GSHRs display significant increases in stress-induced depressive-like behaviors (Lutter et al., 2008b). Targeting GHSRs to stimulate receptor function may therefore be a promising strategy for relieving symptoms of major depression, particularly when weight loss is a prominent symptom, as in anorexia nervosa (Lutter and Nestler, 2009).

Melanin-concentrating hormone (MCH) is another major orexigenic (pro-appetite) peptide. Like orexin, its expression is limited to a subset of lateral hypothalamic neurons. MCH activates the MCH_1 receptor, which is remarkably enriched in the NAc. (Humans also express an MCH_2 receptor, about which much less is known.) Targeted administration of MCH into the NAc, hypothalamus, or lateral ventricles robustly increases feeding behavior; whereas MCH_1 receptor antagonists produce the opposite effect (Georgescu et al., 2005). Interestingly, antagonism of MCH_1 receptors in the NAc promotes antidepressant-like effects, and similar actions are found in mice lacking these receptors (Georgescu et al., 2005). Over-expressing MCH is correspondingly pro-depressant (Shimazaki et al., 2006). Inhibiting MCH may therefore serve as an effective treatment in the subset of depressed patients that demonstrate weight gain.

Several other hypothalamic feeding peptides may also be targeted for treating depression. Of note are the anorexigenic peptides, including melanocortin (αMSH) and cocaine- and amphetamine-regulated transcript (CART), and the orexigenic peptides, ARP (agouti-related peptide) and NPY (neuropeptide Y). Preliminary evidence indicates that these peptides not only participate in the control of feeding behavior, but also regulate behavioral responses to emotional stimuli (Nestler and Carlezon, 2006). NPY, for example, is an attractive antidepressant target because of its expression in limbic circuits, as well as the hypothalamus (Karl and Herzog, 2007). Well-known for having a role in stress responses, NPY has been intensively examined in animal models and in clinical studies. Indeed, lower levels of NPY in CSF, plasma, and prefrontal cortex have been reported for depressed subjects as well as suicide victims (Caberlotto and Hurd, 2001; Widdowson et al., 1992). In support of these clinical findings, experimental decreases in NPY levels promote depressive-like behavioral responses in animals. Perhaps most encouraging are reports in mice and rats where stimulation of NPY neurotransmission produces antidepressant-like and anxiolytic-like effects. Two of the six known NPY receptors have received attention as potential mediators of the NPY-mediated antidepressant-like effects. For instance, activation of the primarily postsynaptic Y_1 receptor (that is highly expressed in the hippocampus and cerebral cortex) via intra-cranial

administration of the Y_1 selective agonist [Leu31;Pro34]PYY promotes antidepressant effects. Further confirming a role for this receptor are findings that direct hippocampal delivery of the Y_1 non-peptidic antagonists BIBP3226 or BIBO3304 prevents the antidepressant-like effects produced by NPY administration (Ishida et al., 2007). NPY Y_2 receptors could also be an interesting target for treating depressive symptoms due to its function as an inhibitory presynaptic autoreceptor, and by virtue of it being a heteroreceptor (Tschenett et al., 2003). Significant increases in the release of NPY are accomplished by deletion or blockade of Y_2 receptors. Consequently, Y_2 knockout mice or administration of the selective Y_2 receptor antagonist BIIE0246 reveals a promising anxiolytic- and antidepressant-like phenotype (Bacchi et al., 2006). Clinical trials for NPY-based compounds have already been initiated for the treatment of obesity.

5. Estrogen receptors

The odds of being diagnosed with a depressive or anxiety disorder is at least twice as high for women than for men (Earls, 1987). Fluctuations in endogenous levels of gonadal hormones during premenstrual, postpartum, and perimenopausal times often occur concomitant with changes in mood, which is exemplified by the two-to-five fold increase in incidence of depressive illnesses that occurs during the onset of menopause (Cohen et al., 2006; Freeman et al., 2006). As reviewed below, such hormonal events highlight a critical role for gonadal hormones in the regulation of affective behavioral responses. Indeed, strong evidence for a lack of estrogen receptor beta (ERß) activation in brain during depressive-like behavioral responses has been identified. Positive treatment outcomes in females with depressive illnesses can be deduced from reports on the robust antidepressant effects of estrogen-derived treatments when endogenous estrogen levels are low. Although the effects of estrogen levels during the course of depression in males is remains uncertain, data indicate that gonadectomy-related changes in mood within this population can be alleviated by estrogen treatments (Hughes et al., 2008).

Estrogen receptor alpha (ERα) and ERß are differentially expressed in brain, and have divergent roles regarding depressive-like behaviors. Agonist activity at ERα can positively regulate libido in females (Mazzucco et al., 2008; Walf and Frye, 2005). However, targeting ERß is well documented for its effect on a number of mood-related behaviors. Total knockout of ERß, and not ERα, significantly increases depressive- and anxiety-like behaviors (Imwalle et al., 2005; Krezel et al., 2001). Systemic administration of trilostane, a 3ß-hydroxysteroid dehydrogenase inhibitor, produces antidepressant-like effects in the forced swim test, an effect eliminated in mice lacking ERß (Koonce et al., 2009). ERß is highly expressed in serotonergic neurons of the dorsal raphe nucleus, and within the hippocampus and amygdala where antidepressant actions are considered to be important (Hu et al., 2005; Savitz et al., 2009). In the dorsal raphe, estrogen acts to increase tryptophan hydroxlase (the rate limiting enzyme in serotonin synthesis), and serotonin levels are decreased in the hippocampus of ERß knockout mice (Hiroi et al., 2006; Imwalle et al., 2005). Direct hippocampal activation of estrogen receptors promotes antidepressant- and antianxiety-like effects, and the hippocampus expresses more ERß than ERα (Shughrue et al., 1997; Walf and Frye, 2007). Recent clinical data support the promise of combining estrogen and serotonin modulators as an approach to treating depression in postmenopausal women (Wise et al., 2008). In fact, studies in women with severe postpartum depression have revealed surprising beneficial effects of estradiol treatments when administered alone that far exceed recovery rates after conventional antidepressant treatments (i.e., SSRIs). Gregoire et al. (1999) and Ahokas et al. (2001) both observed a significant reduction in depression scores in at least 80% of their patients treated with estradiol within 3 months or 2 weeks, respectively, after starting treatment. More clinical studies are required to elucidate the parameters of safe and successful estrogen treatment strategies; administration of estrogens that effectively push circulating levels above the

"normal" physiological range have no effects, or produce negative outcomes, on mood and cognition in both males and females (Galea et al., 2002; Patisaul et al., 2009).

An intriguing component of gonadal hormone-mediated effects on mood may be derived from their interaction with the hypothalamic-pituitary-adrenal "stress" axis. Estrogen dysregulation can lead to exacerbated stress responses (Walf and Frye, 2007; Young et al., 2000). Affective vulnerabilities to chronic environmental and social stressors may be reduced by estrogen treatments, and potentiated by low levels of endogenous estrogen (Gerrits et al., 2006; Young et al., 2000). Overall, it would appear that physiologically "normal" levels of estrogen positively regulate mood and increase resiliency to stress.

6. Epigenetic mechanisms

While all available antidepressant medications rapidly increase the activity of monoaminergic systems in brain, the mood-enhancing effects of these compounds require weeks of administration. Thus, the nature of drug-induced neural plasticity underlying the clinical actions of classical antidepressants has recently highlighted chromatin remodeling mechanisms as an essential process in these drugs' progressive therapeutic effects (Lee et al., 2006; Tsankova et al., 2006). Such epigenetic modifications can alter gene transcription in neurons in several ways, including covalent changes to DNA (e.g., DNA methylation) and to histone N-terminal tails (e.g., acetylation, methylation, phosphorylation, among many others). Environmental experiences that modify gene function through epigenetic mechanisms do so in the absence of altering the sequence of DNA, thereby providing a strong rationale for studying epigenetic changes in depression, which is particularly evident when considering the large number of inconsistent genetic association studies. In addition, chronic exposure to stress or antidepressant drugs influences histone acetylation and methylation in brain areas important for emotional processing (Tsankova et al., 2006).

At least two lines of evidence indicate how DNA methylation may play an important role in the emergence and alleviation of depression. In rodents, adult levels of hippocampal DNA methylation (of cytosine) are reported to be under the control of early rearing styles by the mother, with deficiencies in mother-pup interactions between post-natal days 1-10 effectively increasing DNA methylation of the glucocorticoid receptor gene, as well as increasing anxiety-like behaviors throughout the lifespan (Szyf et al., 2007; Weaver et al., 2004). By this mechanism, low amounts of maternal care reduce the expression of hippocampal glucocorticoid receptors. Such maternally induced increases in hippocampal DNA methylation in the pup can be attenuated by direct infusion of trichostatin A, an HDAC inhibitor (Weaver et al., 2004). In contrast, early life stress reduces the methylation of other gene promoters, such as that of the arginine vasopressin gene (*Avp*) in hypothalamus, which leads to life-long increases in AVP expression and perhaps to hypercortisolism (Murgatroyd et al., 2009).

A second line of evidence supports a prominent role for increasing global DNA methylation as a potential treatment for depression. *S*-Adenosyl-L-methionine (SAMe) functions as a donor of methyl groups for many cellular functions, including DNA methylation (Lieber and Packer, 2002). Clinical trials have examined the antidepressant effects of administering SAMe with promising results (Mischoulon and Fava, 2002). Because SAMe serves a number of important cellular functions (including a prominent role in the synthesis of monoamines), it is difficult to attribute any particular molecular effects of SAMe to one behavioral phenotype. Nonetheless, experimental work is beginning to provide critical insight regarding the brain areas, and the particular gene promoters, where altering levels of DNA methylation might be therapeutic for treating depression. For instance, chronic stress-induced increases in DNA methylation, within the NAc, occurs via a selective upregulation of certain DNA methyltransferases (LaPlant et al. 2009). Inhibiting DNA methyltransferase activity via

RG-108 infusion into this brain area has antidepressant-like effects. Data such as these indicate packaging and unpackaging of heterochromatic domains of the genome may be a stress-sensitive, and reversible, phenomenon.

In neuronal tissue, HDAC inhibitors increase histone acetylation through the inactivation of class I or class II HDACs, and thereby alter patterns of gene expression (Tsankova et al., 2007). In addition, histone acetylation, which is most often associated with activating transcription through its ability to relax 'condensed' areas of chromatin, appears sufficient to induce antidepressant effects in animals (Schroeder et al., 2007; Tsankova et al., 2006). One of these reports observed an increase in histone acetylation at certain BDNF gene promoters in the hippocampus after chronic imipramine treatment, and this increase in acetylation appears to be necessary for reversing a depressive-like phenotype induced by chronic stress (Tsankova et al., 2006). More recently, the direct infusion of more specific HDAC inhibitors into the NAc has been shown to induce potent antidepressant-like actions in several rodent models, and alter stress-induced patterns of gene expression in a similar manner to that of the conventional antidepressant fluoxetine (Covington et al., 2009). When examining particular genes in the NAc that are regulated by stress, and oppositely regulated by HDAC inhibitor, numerous potentially interesting gene targets for future scientific studies become apparent (Fig. 2). It should be noted, however, that inhibition of HDACs *via* systemic routes of administration would be expected to be accompanied by intolerable side effects, hence developmental efforts for more potent agents that are selective for specific HDACs may provide more promising results (Haggarty, 2005; Tsankova et al., 2007).

7. Conclusion

A considerable amount of knowledge has been gained since the original discovery of monoamines as a target for antidepressant treatments (Schildkraut, 1965). A multitude of diverse neurobiological systems have now been identified that could potentially be implicated in the pathophysiology of depression and its treatment. This diversity highlights the overwhelming heterogeneity of this complex disease and might represent a first step toward the development of novel drug targets for specific subtypes of depression. Unfortunately, animal models used to screen for newer compounds must first be validated according to the traditional effects produced by classical antidepressants, and thus the potential for false negative findings still remains a source of contention (Berton and Nestler, 2006). The incorporation of new behavioral approaches with a strong focus on neuroadaptive responses to stress has shown some success (Berton et al., 2006; Tsankova et al., 2006).

It is encouraging that there are many drugs in active clinical trials aimed at targeting a several different systems (e.g., corticotrophin-releasing factor, vasopressin, glucocorticoids, and neurokinin) (Mathew et al., 2008). Such trials incorporating mediators of glutamatergic activation appear to be particularly promising (Preskorn et al., 2008). Hypothalamic feeding peptides or hormones like estrogens may also soon find their way in the treatment of subtype-selective depression. The ability to regulate mood and the hypothalamic feeding system in both directions may provide the necessary tools for treating depressive symptoms that are also associated with dietary imbalances. With regard to the long-term stability of depressive symptoms, epigenetic modifications may also play a prominent role. Taken together, as scientific advances uncover the basic neurobiological mechanisms in diverse limbic brain regions that underlie the behavioral disturbances associated with distinct depression syndromes, it is anticipated that major advances in treatment will be achieved.

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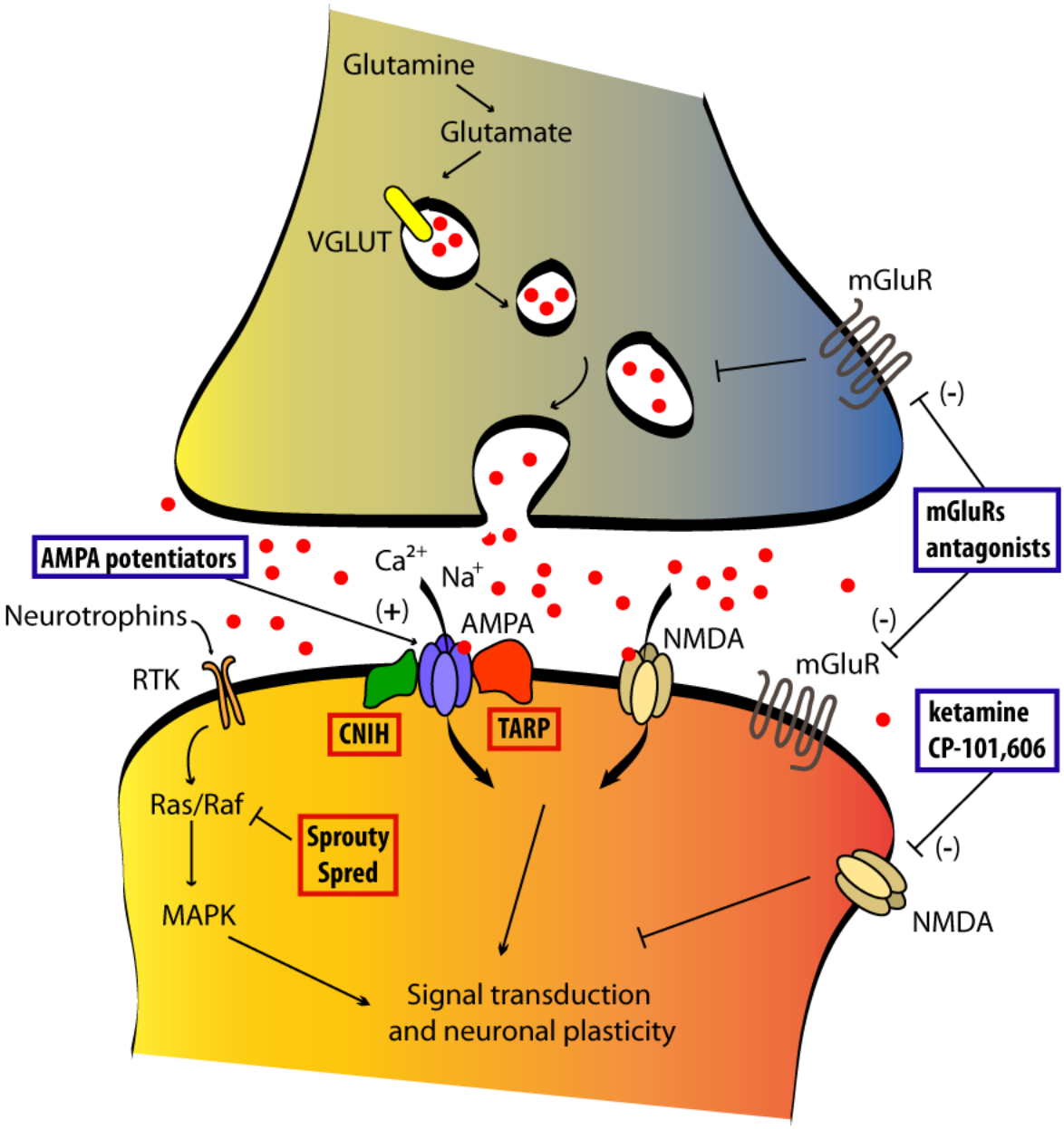

Figure 1.

Emerging antidepressant targets from neurotrophic and glutamatergic signaling pathways. Negative modulators of downstream neurotrophic signaling acting at SPROUTY and SPRED protein families represent potential mechanisms for increasing neurotrophic function. AMPA receptor potentiators and NMDA receptor allosteric modulators (with specific subunit selectivity) are now in clinical trials. Allosteric modulators of mGluRs are also being explored in preclinical studies. Modulators of AMPA receptor expression and function, such as TARPs and CNIH, represent potential therapeutic targets as well. Compounds under development for their antidepressants effect are shown in blue boxes. New target proteins are highlighted in red boxes. CNIH, cornichon homolog; MAPK, mitogen-activated protein kinase; RTK, receptor tyrosine kinase; TARP, transmembrane AMPAR regulatory proteins; VGLUT, vesicular glutamate transporter.

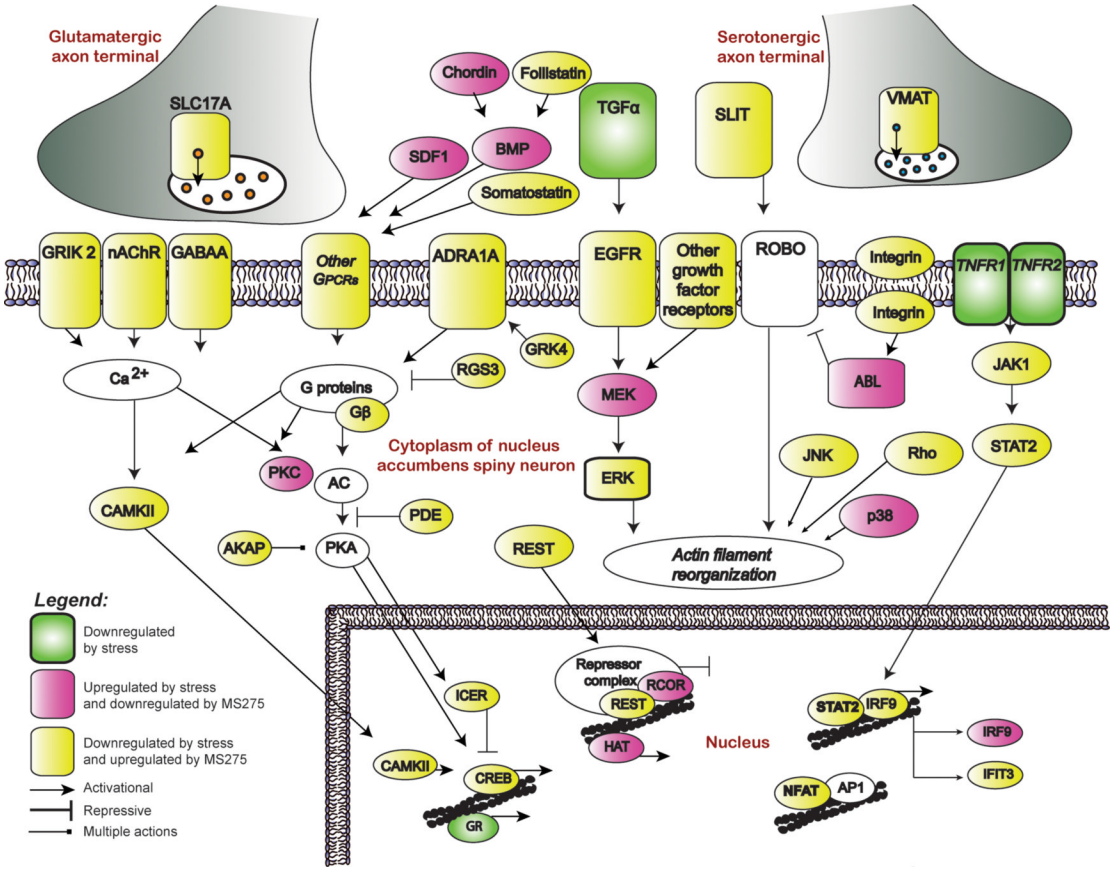

Figure 2.

Portrayed here is a molecular pathway analysis of genes regulated in the mouse nucleus accumbens by a direct infusion of the HDAC inhibitor MS-275 after chronic social defeat stress. Infusion of MS-275 promotes antidepressant-like behavioral responses and significantly regulates genes as revealed by microarray analysis. Examples of highly regulated molecular pathways that may provide novel targets for treating depression include genes that encode presynaptic vesicular proteins, plasma membrane receptors, intracellular signaling molecules, proteins that regulate the actin cytoskeleton, and the transcriptional regulatory machinery. Reprinted with permission from *The Journal of Neuroscience* (Covington et al., 2009).