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NEW INSIGHTS INTO MOLECULAR TARGETS FOR DEPRESSION

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ABSTRACT
Major depressive disorder is a heritable neuropsychiatric syndrome characterized by relatively subtle cellular and molecular alterations localized to a complex network of neural substrates. Various forms of psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT) are currently the most commonly used antidepressant treatments. Despite adequate care with currently available treatments, up to 70% of depressed patients have residual symptoms, and, even with more aggressive therapies, 20% or more may show only a limited response. The need for newer compounds to treat depression is still an ever growing concern due to the enormous societal and famifications of depression. This review covers all the monoaminergic (SSRI/5-HT1A antagonists, SSRI/5-HT2C antagonists, SSRI/alpha-2 adrenergic antagonists, triple reuptake inhibitors, dopamine agonists, targeting GABA) and beyond monoaminergic strategies including corticotropin-releasing factor (CRF)-1 receptor antagonists, Inhibition of glucocorticoid function, substance P (Nk-1) antagonists, MCH1 receptor antagonists, Gal3 receptor antagonists, arginine vasopressin as the potential novel targets for depression.. However, To be the most successful novel target it shouldn't only demonstrate preclinical antidepressant like effects, but also target the unmet clinical needs and lead to long-term disease modification.
KEY WORDS: Depression, Antidepressant, GABA, Monoamine, Molecular target, Corticotropin-releasing factor

INTRODUCTION

Depression is one of the top ten causes of morbidity and mortality, afflicting up to 20% of the world's population[1,2]. In addition to its social toll, the economic burden of depression contributes approximately $44 billion in lost productivity annually in the United States[3]. The symptoms of depression are chronic, recurring, and life threatening[2]. Despite adequate care with currently available treatments, up to 70% of depressed patients have residual symptoms, and, even with more aggressive therapies, 20% or more may show only a limited response[4,5]. Rather than being the exception, recurrent episodes are the rule, and there are few evidence-based approaches to help clinicians maintain a patient's antidepressant response. Persistent depression is associated with an increase in substance and alcohol abuse, an increased risk for suicide and for cardiovascular disease. Thus, improved treatments for depression are urgently needed[6].

Current Antidepressant Treatments

Despite the relative lack of knowledge of the aetiology and pathophysiology of depression, there are good treatments for it, with most patients showing significant improvement with optimal treatment. Mild depression responds to different forms of psychotherapy. Mild and more severe forms of depression respond to a host of antidepressant medications, with a combination of medication and psychotherapy providing optimal treatment. Electroconvulsive therapy (shock treatment) is one of most effective treatments for depression, but is usually reserved for the more severely ill due to the availability of numerous pharmacotherapies. The utility of other so-called somatic therapies is under investigation. Almost all of the available medications for depression are based on chance discoveries that were made more than half a century ago. Most of today's medications are based on the tricyclic antidepressants, which are believed to act by inhibiting the plasma membrane transporters for serotonin and/or noradrenaline[7,8]. Current pharmacological antidepressant treatments improve depressive symptoms through complex mechanisms that are themselves incompletely understood[9]. The need for newer compounds to treat depression is an ever growing concern due to the enormous societal and famifications of depression[10]. These older medications provided a template for the development of newer classes of antidepressant, including the SSRIs (selective serotonin reuptake inhibitors), NRIs (noradrenaline reuptake inhibitors) and SNRIs (serotonin and noradrenaline reuptake inhibitors). However, as these newer medications have the same mechanism of action as the older tricyclics, their intrinsic efficacy and range of patients for whom treatment is successful remain the same. The older monoamine oxidase inhibitors, which reduce the enzymatic breakdown of serotonin and noradrenaline, are also still used today with great success. Although today's treatments for depression are generally safe and effective, they are far from ideal. Therefore there is still a great need for faster acting, safer and more effective treatments for depression[11].

The Search For Novel Antidepressants

Various forms of psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT) are currently the most commonly used antidepressant treatments. Serendipitous discoveries and/or a limited understanding of the neurobiology of depression which largely focused on the monoaminergic neurotransmitter systems led to the development of many of these treatments. As knowledge of the neuroscience of depression advances, a number of novel targets for antidepressant treatment are being uncovered and actively investigated. Generally, these treatments fall into three major categories: first, medications that optimize the modulation of monoaminergic neurotransmitters; second, medications that target monoamine neurotransmitter and neuromodulatory systems; and third, devices that produce focal electrical brain stimulation targeting brain regions implicated in the pathophysiology of depression[6]. In this review, we discuss these treatments and highlight those that hold the most promise.

Monoaminergic Strategies

The monoamine hypothesis of depression postulates that the etiology and pathogenesis of depression arises from central deficiencies in serotonin, norepinephrine, and/or dopamine. Correspondingly, current pharmacotherapies have been developed in an effort to amend these alterations in monoaminergic systems (e.g., SSRIs, SNRIs). Regardless of their mechanism of action, however, a drawback of all marketed antidepressants is the 3- to 5-week delay necessary to achieve therapeutic efficacy. This lag time is thought to reflect the time required for desensitization of the receptors regulating monoamine release (e.g., 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{1A} and α2 adrenergic receptors). To potentially accelerate the onset of

antidepressant action as well as limit unwanted side effects current drug development strategies are focusing on designing new antidepressants with dual and/or triple modes of action. These approaches, along with examples of preclinical and clinical studies, will be highlighted in the following sections.

SSRI/5-HT$_{1A}$ antagonists

The delayed clinical efficacy of SSRIs is believed to result, to a large extent, from the indirect activation of somatodendritic 5-HT$_{1A}$ autoreceptors. A profound body of preclinical literature indicates that acute SSRI treatment increases serotonin levels in various brain regions including the dorsal raphe nuclei. This elevation in serotonin engages inhibitory 5-HT$_{1A}$ autoreceptors residing in the dorsal raphe to inhibit 5-HT cell firing and dampen subsequent 5-HT release in terminal serotonergic brain regions[12]. However, following long-term SSRI treatment (14–21 d) 5-HT$_{1A}$ autoreceptors desensitize resulting in more pronounced elevations in serotonin levels compared to acute treatment[13,14]. These data suggest that a strategy combining SSRIs with 5-HT$_{1A}$ receptor antagonists would produce robust and more rapid increases in central serotonin levels and likely yield an antidepressant with an accelerated onset of activity. This neurochemical hypothesis is supported by a plethora of microdialysis studies demonstrating that pretreatment with selective 5-HT$_{1A}$ antagonists such as WAY-100635 augments SSRI- and SNRI-induced changes in cortical serotonin levels[15].

Preclinical models sensitive to the behavioral effects of serotonergics corroborate these findings as 5-HT$_{1A}$ antagonism is reported to potentiate the antidepressant-like effects of SSRIs in the rodent resident-intruder, social interaction, and schedule-induced polydipsia assays[16-18]. Clinical data using this combination strategy demonstrate that the antidepressant activity of SSRIs is accelerated and/or enhanced when combined with the mixed 5-HT$_{1A}$/alpha adrenoceptor antagonist, pindolol[19]. As some of these dual acting SSRI/5-HT$_{1A}$ compounds begin their clinical evaluation, it may only be a matter of time to determine whether this approach will represent the newest generation of antidepressants.

SSRI/5-HT$_{2C}$ antagonists

Desensitization of 5-HT$_{2C}$ receptors is routinely reported following chronic SSRI treatment. However, the overall contribution of this molecular change to the antidepressant effects of SSRIs is not well understood. Recent data suggest that 5-HT$_{2C}$ receptor inactivation may play a role in augmenting the neurochemical and behavioral effects of antidepressants. Using *in vivo* microdialysis techniques in rats, Cremers et al. and others showed that the selective 5-HT$_{2C}$ antagonists, SB 242084 and RS102221, and the nonselective 5-HT$_{2C}$ receptor antagonists, ketanserin and irindalone, potentiate the neurochemical effects of SSRIs on hippocampal and cortical serotonin levels[20,21]. Despite the robust neurochemical effects when these agents are combined, 5-HT$_{2C}$ receptor antagonism alone has no significant effects on extracellular serotonin[21,22]. Similar to the reported neurochemical effects, this serotonergic combination produces marked augmentation of the antidepressant-like effects of SSRIs in behavioral models of depression and anxiety including the mouse tail suspension test (TST) and schedule-induced polydipsia assay[20,22]. Complementary studies done in 5-HT$_{2C}$ receptor null mutant mice show enhanced neurochemical and behavioral (TST) responses to fluoxetine compared to their wild-type littermates[22]. Overall, these preclinical data show that 5-HT$_{2C}$ antagonism augments the neurochemical and behavioral effects of SSRIs. Moreover, these data highlight a novel strategy of combining both targets, either in a single molecular entity or as adjunctive therapy to already marketed SSRIs, for the potential treatment of depressive disorders.

SSRI/alpha-2 adrenergic antagonists

The success of SNRIs in the clinic underscores the importance of elevating both norepinephrine and serotonin in the treatment of depression. However, a strategy that targets noradrenergic autoreceptors may have merit in augmenting the neurochemical effects of conventional antidepressants. Several classes of antidepressants, particularly norepinephrine reuptake inhibitors such as reboxetine (Edronax) and the SNRIs, acutely elevate extracellular levels of norepinephrine. The release of norepinephrine can activate presynaptic alpha-2 adrenergic autoreceptors located on both norepinephrine and dopamine cells causing blunted noradrenergic and dopaminergic responses, respectively. Thus, antidepressants, when given in combination with agents that "turn off " alpha-2 autoreceptors, can potentially elevate levels of all three monoamines. Neurochemical validation of this hypothesis comes from microdialysis studies showing that alpha-2 adrenergic antagonists markedly potentiate the ability of antidepressants to increase extracellular levels of norepinephrine, serotonin, and dopamine, depending on the brain region examined[23]. Although there are essentially no published data showing that this particular combination strategy is efficacious in preclinical behavioral models of depression, the data from microdialysis studies suggest that alpha-2 adrenergic antagonism may strengthen the neurochemical effects of antidepressants, and may improve the efficacy of antidepressants in humans[24]. In addition, nonselective alpha-2 adrenergic receptors antagonists such as mirtazapine (Remeron) are reported to possess modest antidepressant activity in their own right[25]. Finally, clinical studies emphasize that combining SSRIs with nonselective alpha-2 receptor antagonists actually shortens the time required to achieve antidepressant activity[26,27].

Collectively, these data have ignited considerable chemistry efforts to design and synthesize novel antidepressant molecules that combine monoamine reuptake inhibition with alpha-2 adrenergic receptor antagonism[28,29].

Triple Reuptake Inhibitors

Triple reuptake inhibitors block synaptic reuptake of 5- HT, NE, and DA. Animal studies have demonstrated antidepressant-like effects for several of these compounds[30-35]. DOV 216 303, one such agent, was found to be safe and tolerable during short-term use in a Phase 1, open-label study[35]. Tesofensine (NS 2330), another compound, has shown modest preliminary safety and efficacy in treating the motor symptoms of Parkinson's Disease (PD)[36], but clinical data in treating depression are unavailable. The success, however, of these compounds as well as the strategy and benefit of combing inhibition of all three monoamines into a single molecule is still awaiting evaluation in human patients.

Additional Multitarget, Monoamine Strategies

Both transporter and inhibitory autoreceptor mechanisms strictly control the release of biogenic amines into the extracellular environment. For instance, 5 HT$_{1A}$ and 5-HT$_{1B}$ receptors are somatodendritic and terminal autoreceptors, respectively, regulating levels of central serotonin levels. Blockade of 5-HT$_{1B}$ receptors alone has been shown to acutely increase levels of serotonin in the guinea pig frontal cortex and hippocampus as well as augment the effects of SSRIs on serotonin levels[37]. Combining the selective 5-HT$_{1A}$ antagonist, WAY-100635, with the 5-HT$_{1B}$ receptor antagonist, SB-224289, produced marked elevations in serotonin levels in the guinea pig[38]. These results curiously suggest that combining 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor antagonism can elevate serotonin and, consequently, potentially be an effective strategy to treat depression. Additional examples of targeting multiple postsynaptic receptors as putative antidepressant agents include the 5-HT$_{1A}$ agonist/alpha-2 antagonist, sunepitron, the 5-HT$_{1A}$ agonist/dopamine D2 agonist, roxindole, and alpha-2 adrenergic antagonist/5-HT2 antagonist, mirtazapine[39]. In summary, these strategies seem to efficiently "tweak" the monoaminergic systems in the hopes of developing a more rapid acting antidepressant. However, much needed clinical data regarding the efficacy, safety,

and tolerability of such "dual-acting" compounds is eagerly awaited. Perhaps newer approaches targeting convergent, downstream components of the monoamine system (e.g., neurotrophins) and/or nonmonoaminergic systems including GABA and glutamate may ultimately prove beneficial in the clinical management of depression.

Dopamine agonists

Dopamine D2/D3 receptor agonists include pramipexole and ropinirole. Two placebo-controlled trials have confirmed that pramipexole is efficacious, safe, and tolerable in patients with bipolar depression[40,41]. Pramipexole may also be effective in treatment-resistant unipolar depression as demonstrated in an open-label study with long-term follow-up[42,43]. Ropinirole may have similar benefits in depression based on results from an open-label study[44].

Targeting Excitatory Amino Acids

The NMDA receptor is an ionotropic glutamate receptor with highest densities located in cortico-limbic regions of the brain. Extracellular glutamate concentrations are enhanced by various stressors, like tail pinch and restraint, and an involvement of the NMDA receptor became apparent in the modulation of stress-induced glutamate responses[45, 46]. Furthermore, chronic antidepressant administration can influence NMDA receptor function and receptor binding profiles, as well as generate regional alterations in mRNA expression that encodes multiple NMDA receptor subunits[47,48]. An extensive library of noncompetitive NMDA antagonists (e.g., MK-801, memantine, ketamine) that reduce glutamatergic transmission at the NMDA receptor have demonstrated antidepressant-like effects in animal models, including forced swim and tail suspension tests, inescapable stressors, and in learned helplessness[49,50].

With this in mind, the direction of major research efforts for the treatment of depression and affective disorders now encompasses the development of compounds that regulate the target-rich environment within the NMDA receptor complex.

Targeting GABA

GABA is the primary inhibitory neurotransmitter in the CNS. GABA has been implicated in a number of psychiatric disorders including schizophrenia and affective disorders. A number of studies have been carried out to assess the concentration of GABA in CSF or plasma in patients suffering from psychiatric disorders. The most consistent results are from studies in depressed patients.

A number of research groups have reported CSF levels of GABA to be significantly decreased in depressed patients[51-53]. Furthermore, studies of plasma levels of GABA in depressed patients concur with these findings[54]. Using proton magnetic resonance spectroscopy, Sanacora and colleagues have measured cortical GABA concentrations *in vivo*. Occipital cortex GABA concentrations in depressed patients were found to be significantly lower than in healthy controls[55]. Subsequent studies demonstrated that these low levels of GABA were normalized after SSRI treatment. Interestingly, low levels of GABA in plasma of depressed patients were not reversed by desipramine treatment[56]. The decreases in GABA observed in depressed patients do not appear to be associated with changes in GABA uptake binding sites. Neither GABA B receptors nor glutamic acid decarboxylase (GAD; biosynthetic enzyme for GABA) activity have been found to be altered in depressed suicide victims, whereas GABA A receptor binding in frontal cortex was increased in depressed suicide victims[57,58]. The putative role of GABA, GABA A, and GABA B receptors in depression could be mediated directly by GABA or via other neurotransmitter systems. There are pieces of evidence linking GABA B receptors to noradrenergic and serotonergic systems. For example, administration of GABA B receptor antagonists has also been demonstrated to cause downregulation of beta adrenoceptors, an effect common to chronic administration of a number of types of antidepressants[59,60]. The GABA B antagonist, phaclofen, as well as the GABA A receptor antagonist, bicuculline, increased norepinephrine release in the median preoptic nucleus *in vivo*. Conversely, locally applied agonists of GABA A and GABA B receptors (muscimol and baclofen, respectively) decreased dialysate levels of norepinephrine in the same area. These data indicate that GABA A and GABA B receptors are involved in the control of norepinephrine release in this part of the rat brain[61]. Local infusion of the GABA A receptor antagonist, bicuculline, increases serotonin release in the dorsal raphe, indicating that GABA afferents exert a tonic inhibitory influence on serotonin neurones in the dorsal raphe[62]. In terms of behavioral effects of GABAergic drugs, the profile of the GABA B antagonist, CGP56433 in the forced swim test indicates a serotoninmediated effect; CGP56433 decreases immobility and increases swimming, a profile comparable with fluoxetine[63].

Thus, GABA is strongly implicated in depression such that GABA receptors are potential targets for the development of novel antidepressants

Novel Pharmacological Targets: Beyond Monoamines

In the area of depression research, interest in central peptide systems has focused on the high-profile efforts targeting receptors of the central substance P [neurokinin 1 (NK1)] and corticotropin-releasing factor (CRF1) systems. This has led to the development of numerous compounds now in clinical trials for depression. In addition to NK1 and CRF1, however, interest has also fallen on receptors involved in mediating the effects of other central peptidergic systems. These include examples such as melanin-concentrating hormone (MCH) and arginine vasopressin.

Corticotropin-releasing factor (CRF)-1 receptor antagonists

Increased activity of the hypothalamic–pituitary–adrenal (HPA) axis is a major component of the mammalian endocrine stress response. Following a stressful encounter, the neuropeptide CRF is secreted into the hypothalamohypophysial portal circulation where it acts to stimulate the release of adrenocorticotropin (ACTH) from the anterior pituitary. ACTH stimulates glucocorticoid production and release from the adrenal cortex. Stress (physical or emotional) can precipitate or worsen depression in vulnerable individuals. A burgeoning database links HPA axis activity and more specifically CRF to this process. Compared to nondepressed controls, depressed or depressed suicidal patients show increased HPA axis activity and elevated cerebrospinal fluid (CSF) CRF concentrations, increased paraventricular nucleus (PVN) CRF mRNA expression, and a larger number of CRF-expressing neurons in the PVN[64]. In healthy volunteers, desipramine reduces CSFCRF concentrations[65], and in depressed patients fluoxetine and ECT have shown similar effects[66]. These data suggest that antidepressant treatments with different mechanisms of action may ultimately reduce CRF activity as part of their mechanism of action. Consequently, research is focusing closely on the antidepressant potential of direct modulation of CRF neurotransmission.

Two main CRF receptor subtypes, CRF1 and CRF2, exist in the central nervous system (CNS). CRF binds more avidly to CRF1 receptors than to CRF2 receptors; urocortin is the preferred endogenous ligand for CRF2 receptors. Heightened anxiety-like behaviors in animals have been connected to the decreased activity of CRF2 receptors. Several CRF1 receptor antagonists possess anxiolytic-like and antidepressant-like effects in animal models[67]. R121919 showed encouraging antidepressant effects in humans but its development was discontinued as a result of potential liver toxicity[68]. CP-316 311, another CRF1 receptor antagonist, did not show significant antidepressant effects in a placebo-controlled and sertraline-controlled trial [69]; however, it is unclear whether the dose tested was sufficient to block CNS CRF1 receptors effectively. NBI-

34041, a third agent, has not yet been tested in depressed patients but in healthy humans has shown an ability to attenuate the endocrine stress response[70].

Inhibition of Glucocorticoid Function

Decreased synthesis or receptor blockade of adrenal glucocorticoids may have antidepressant effects. Ketaconozale, aminogluthemide, and metyrapone are agents that interfere with cortisol synthesis. All of these have shown some antidepressant potential, but adverse events have limited their development[71]. Mifepristone, also known as RU486, is a glucocorticoid 2 receptor antagonist that showed antidepressant efficacy in an early case series of patients with severe, chronic depression[72]. Two additional studies in patients with severe, psychotic depression (one open-label and one placebo-controlled) both found mifepristone to be safe and efficacious, with therapeutic effects seen within one week[73,74]. Because these benefits were primarily in psychotic symptoms and not in depressive symptoms, this agent may be more appropriate for treating psychotic depression.

Substance P (Nk-1) Antagonists

Neurokinins are neuropeptides involved in nociception and many other physiologic processes. Neurokinin receptors are extensively distributed in the CNS, and the most widely distributed receptor subtype is NK-1. Substance P binds to NK-1 receptors that are located in high density in the hypothalamus, periaqueductal gray matter, amygdala, locus ceruleus, and parabrachial nucleus[75]. Substance P-containing neurons contain 5HT and share projection targets with NE neurons[76,77]. A behavioral and physiologic stress response in animals has been associated with increases in substance P[78,79] and attenuated by the administration of an NK-1 antagonist[80,81]. After exposure to a stressful stimulus, patients with MDD or PTSD exhibit elevated CSF substance P concentrations[82]; decreased serum levels have been associated with an antidepressant response[83]. Preclinical studies show that various NK-1 receptor antagonists possess antidepressant-like effects and several have been tested in humans. Aprepitant (MK-869) showed antidepressant efficacy in an initial placebo-controlled trial[84], but subsequent controlled studies failed to confirm this finding[80]. L-759274 and CP-122721 demonstrated antidepressant effects in pilot studies[85,86], though replication has not been reported for either. GR-205171 has shown preliminary efficacy in social phobia[87] and antidepressant-like effects in an animal model[88].

MCH1 Receptor Antagonists

Melanin concentrating hormone is a lateral hypothalamic neuropeptide with a well-established role in the regulation of food intake and energy balance[89]. More recently, blockade of this target has been linked to antidepressant and anxiolytic properties in animal models[90], through enhancement of glutamaergic transmission in the shell of the nucleus accumbens (NuAcc)[91]. The NuAcc is central to the modulation of goal directed behaviors for natural rewards[92–94]. MCH seems to play an important role in the modulation of hypothalamic–NuAcc interactions, and therefore MCH1 antagonists may be able to modulate hedonic drive[95– 97]. In fact, making a parallel with paradoxical effects of CRF in the NuAcc on cue-triggered motivation for sucrose intake[98], one could speculate that MCH1 antagonists may actually stimulate palatable food intake as part of an enhancement of hedonic drive. In addition, MCH1 antagonists induce hippocampal neurogenesis after 4 weeks chronic treatment in the mouse, a process that has been associated with chronic antidepressant and chronic anxiolytic activity[99]. Finally, the MCH system is one of the many peptidergic pathways known to modulate the HPA axis[100]. Anhedonia, with loss of taste and appetite, and HPA axis overactivity are key features of melancholic depression. It is hypothesized that such patients may be a relevant target population for MCH1 antagonists. As this is a relatively new area, several outstanding questions remain: How does the MCH system interact with classical neurotransmitters in relevant disease state models? What is the impact of MCH2, a second MCH receptor in humans[101] (rodents have only one)? Is there any evidence that MCH1 plays a critical role in non-human primates? Even in the absence of answers to these questions, many companies are working on this target with at least one in phase I trials (for obesity as the primary indication). Progress toward the clinic has been slowed by difficulty in optimization of compounds with adequate cardiovascular safety as well as other 'drugability' issues[102].

Gal3 Receptor Antagonists

The neuropeptide galanin is widely distributed in the mammalian CNS and modulates multiple feeding, cognitive and affective behaviors. Pathological hyperactivity in the LC results in galanin release inhibiting dopaminergic pathways to the forebrain, resulting in reduced locomotor activity and anhedonia[103]. However, the co-storage and co-release of galanin and norepinephrine described in rodents CNS, is not seen in human LC[104], and the anatomical distribution of galanin in the brain differs significantly between rodents and higher primates[105]. Galanin is also known to be an inhibitory modulator of both acetylcholine and serotonin release in the rat hippocampus[106], arguing in favor of the potential usefulness of galanin antagonists for the treatment of depression. In rats, ECT increases galanin mRNA in the dorsal raphe nucleus and sleep deprivation augments galanin mRNA in the locus coeruleus[107] and in depressed patients, intravenous administration of galanin is followed by rapid and acute antidepressant like effects[108].

Arginine vasopressin

Arginine vasopressin (AVP) is a cyclic nonapeptide synthesized exclusively by neurosecretory cells of the CNS with a diverse array of biological functions based on differences in sites of release. AVP released into the portal circulation from the median eminence is also known to directly modulate CRF effects on ACTH release and the HPA axis. The central vasopressinergic system has been examined as a platform for psychiatric drug development, including depression[109]. The central vasopressinergic system acts on several key neural substrates underlying aspects of the depression endophenotype, including monaminergic systems and those regulating memory, pain sensitivity, synchronization of biological rhythms, the timing/quality of R.E.M. sleep, and regulation of fluid and electrolyte homeostasis[110]. Disturbances (hyperactivity) in vasopressinergic activity have also been reported clinically in patients with depression[111,112]. Together, this has led many to hypothesize the utility of central vasopressinergic receptor antagonism as a potentially novel antidepressant strategy.

CONCLUSION

Despite the efficacy of our currently available antidepressant medications and somatic therapies, residual depressive symptoms and relapse are common. This creates a challenge for the clinician as s/he seeks to completely eliminate symptoms and help patients fully recover. To reach these goals, improved treatment strategies are needed. Understanding the neurobiology of depression has helped researchers uncover a number of novel targets for antidepressant therapies. Over the next decade, proof-of-concept studies will be performed in the clinic for a wide array of mechanisms and the true validity of these novel strategies will be enlightening. This will not only include combination molecules taking further advantage of monoaminergic approaches but novel mechanisms yet to be tested in humans. Clearly, the current array of animal models for determining antidepressant activity has been useful in predicting therapeutic efficacy of multiple monoaminergic mechanisms. Notably, mechanisms that do not directly or indirectly modulate monoaminergic mechanisms remain to be fully validated and the development of further animal models may be necessary. In conclusion, the most successful novel approaches will be those that not only demonstrate preclinical antidepressant- like effects, but

those that target the unmet clinical needs and lead to long-term disease modification. For many of the approaches described in this review, clinical testing will determine the extent to which these approaches show distinct advantages over existing therapies and finally demonstrate the true innovation associated with these novel mechanisms.

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