

Unmet needs in psychiatry and emerging novel pharmacological agents

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ABSTRACT

Despite huge amount of efforts and resources spent to improve the pharmacotherapeutic tools to treat major psychiatric disorders such as depression and schizophrenia, there still exist unmet needs in the field. Treatment resistance, non-adherence, and severe adverse effects such as diabetes mellitus type II, extrapyramidal side effects, etc. are among the unmet needs commonly faced by clinicians, probably due to the fact that the pathophysiology of both schizophrenia and depression have not been fully elucidated. Today, neither the monoamine hypothesis of depression nor the dopamine hypothesis of schizophrenia explains either disorder in full. In spite of its widespread presence throughout the brain, the glutamatergic system has remained almost unexplored with respect to drug discovery for psychiatric illnesses.

Recently, the promising outcomes of intravenous use of ketamine to overcome resistance to antidepressant treatment and the administration of a nitroprusside infusion to address resistance to antipsychotics in the treatment of schizophrenia have drawn attention to the glutamatergic system.

Keywords: depression, schizophrenia, drug therapy, treatment-resistant, ketamine, nitroprusside

Depression is particularly important among psychiatric disorders, as it is a globally prevalent health problem affecting approximately one fifth of the world's population and it can lead to irreversible complications such as suicide. The World Health Organization predicts that depression will be the second leading cause of death associated with stress and cardiovascular complications by 2020. However, currently still very little is known about

neurobiological alterations underlying the pathophysiology of depression. The most widely used treatment approach in the world, to treat depression, is the use of antidepressants. The major difficulty in clinical practice is the latency period of 3-4 weeks before the benefits of antidepressants are observed. Considering the suicidal predisposition of depression patients, a waiting period of a couple of week is a serious risk. This is the problem emphasized in both the Star*D and StepBD studies (1,2). Another problem associated with the pharmacotherapy of depression is that full remission rates achieved by currently available antidepressants are limited to only one third of patients who use these medications. Other issues in the drug treatment of depressive patients are the lower rates of remission, relapses, and recurrences. These treatment obstacles should be principal impulses for research in antidepressant drug discovery.

Different theories regarding the pathophysiology of depression have already been argued extensively. Since the 1970's the monoamine hypothesis, which can be qualified as the primary hypothesis for relevant scientific work, has claimed that insufficiency of monoamine derived neurotransmitters, especially noradrenaline, serotonin and to a lesser extent dopamine, is the cause of depression. The monoamine hypothesis has afforded researchers a valuable opportunity to pay more attention to monoamine neurotransmitters such as noradrenaline, dopamine and serotonin, and to better explain the mode of action of antidepressants through augmentation of neurotransmission via one or more of those monoamine neurotransmitters; this theory has actually become elementary in our understanding of depression. Lately, a possible role of neurotrophic factors in the pathogenesis of depression, the important role of brain-derived neurotrophic factors, and possible changes in neural plasticity have been discussed. One of the most prominent neurotransmitter systems in the brain appears to utilize glutamate, when the neurobiology of depression is explored from the aspect of

neurotrophic factors and neural plasticity (3,4).

Glutamate is the most common excitatory neurotransmitter in the brain. The system where glutamate exerts its activity in presynaptic neurons, postsynaptic neurons, and glial cells collectively is called the “triple glutamatergic synapse.” The glutamate-glutamine cycle plays an important role in the regulation of presynaptic and postsynaptic ionotropic as well as metabotropic receptors of glutamate. Glutamate is converted to glutamine in glial cells and reabsorbed by presynaptic neurons, where it is reconverted to glutamate. Synaptic plasticity and neurotransmission are believed to be regulated through AMPA receptors located in postsynaptic glutamatergic neurons. Similarly, glutamate has been shown to have an important role in the neuromodulation of kainite receptors. Presynaptic and postsynaptic metabotropic glutamate receptors, or mGluRs, remain in mutual interaction with glial cells. Those receptors have been demonstrated to attenuate cellular neurotoxicity as well as NMDA receptor activity. They can control vesicular glutamate transporters, glutamate level in the synaptic cleft, and glutamatergic receptor activity. Excitatory amino-acid transporters, usually existing in glial cells, have been shown to control the glutamate level in the synaptic cleft and ionotropic receptor activation, thus playing a role in the activity of postsynaptic density proteins (5,6).

The glutamatergic system is in mutual interaction with cytokines triggered by altered microglial serotonin metabolism as well as the quantity of inflammatory mediators such as chemokines, apoptosis factors and oxidative damage indicators such as reactive oxygen species and nitrogen metabolites. Accompanying the increasing amounts of the above mentioned substances, glutamate release increases whereas its reuptake is lessened; thus accumulation of glutamate in the synaptic cleft reinforces the role of the aforementioned factors in the pathogenesis of depression. An increase in glutamatergic activity, with the contribution of proinflammatory cytokines, leads to excitotoxicity (7). Following these discoveries, the glutamatergic system has become a subject of detailed research

regarding the pathophysiology of depression. The association of glial glutamate reuptake with neuroinflammation (8), nitric oxide (NO) and calcium mediated increase in glutamate release induced by astrocyte-derived cytokines (9), tapered reuptake of glutamate due to increased tumor necrosis factor alpha (TNF-alpha) levels in oligodendrocytes (10), increased glutamate release from astrocytes (11) as well as the relation between reactive oxygen species and glutamate levels (12) have attracted attention to the role of the glutamatergic system in the pathophysiology of depression. Receptors taking part in glutamatergic system activity are of importance too. Glutamate conjugates to ionotropic receptors such as N-Methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and kainite as well as mGluRs with numerous subtypes. NMDA receptors, which have been demonstrated to cause excitotoxicity upon hyperactivation, are the most studied receptors within the context of depression neurobiology (7,13,14).

There is increasing evidence addressing the role of the glutamatergic system both in the neuropathology and the treatment of major depression. As is known, the glutamatergic system is the most spread and important excitatory system in the brain. Conversely, it is interesting that so far no antidepressant drugs have been discovered that directly affect the glutamatergic system. At this time, however, we may point to the future discovery of new antidepressant drugs that act through the glutamatergic system, a usually neglected field of interest. Some new drug entities are already being investigated for the treatment of depression and schizophrenia, by utilizing glutamatergic system receptors (NMDA antagonists, ampakines as well as agonists and antagonists of mGluRs) and mechanisms changing the glutamate level in the synaptic cleft (15,16). In this context, medium sized phase II clinical trials with NMDA receptor antagonists such as AZD6765 and GLYX-13 have been completed (17,18). Some drugs like ceftriaxone and riluzole have some evidence about their potential activity on glutamate. These drugs are

known to have glutamate transporters that are similar to serotonergic transporters. Riluzole, a drug officially indicated for amyotrophic lateral sclerosis, also has shown efficacy in the treatment of depression, unipolar depression, bipolar disorder, and anxiety disorders. However, open-label design has been the common important limitation of those studies that have been conducted to date. There has been no large-size randomized placebo-controlled clinical study conducted with riluzole, appraising its efficacy and safety in the treatment of unipolar depression or bipolar disorder (19,20). Another glutamatergic approach is to study new drug entities acting on metabotropic glutamate receptors such as mGlu5 and mGlu2/3. Clinical trials with respect to drug candidates acting on those receptors are still ongoing (21,22).

Ketamine, an NMDA receptor antagonist is one of the most noteworthy compounds to arise out of the mechanisms mentioned above. Studies specifically conducted about its use in depression treatment were published first in 2000. Those studies carried out by Berman et al. have demonstrated that an antidepressant effect began within hours of use, yet this transient antidepressant effect wore off in a length of time from days to weeks (23). In 2005, Zarate et al. reported consistent findings revealing that an onset of antidepressant effect within 24 hours was reproducible in 70% of the recruited patient population and also observed in bipolar disorder cases of similar severity (24). Recently, single dose ketamine administration has been shown to provide a fast and sustainable antidepressant effect. Ketamine is an anesthetic agent for both human and veterinary use, blocking the glutamatergic neural transmission at the NMDA receptor level (6,25). Its mode of action has been completely clarified by a recently published study. Basic science research in rats has shown that ketamine readily activates “the mammalian target of rapamycin” (mTOR) pathway” that is one of many neural transmission pathways (26,27). This brand new approach has been construed as revolutionary and has set new therapeutic trends in antidepressant drug discovery. Therefore, a number of studies have been published, coming up with

repeated results confirming the rapid antidepressant action of ketamine in treatment resistant patients. The rapid antidepressant action of ketamine, which appears to be a potential solution of a leading pharmacotherapeutic problem in the treatment of depression made us wonder if such drugs could be beneficial for special patient populations like treatment resistant patients and a number of studies have been carried out in this respect (6,28).

However, there exist a set of drawbacks on the way to routine use of ketamine in treatment resistant depression. Firstly, ketamine is an anesthetic agent requiring patient-specific dose titration and caution during its use. Moreover, it has serious side effects requiring monitoring of vital signs such as blood pressure and pulse rate of patients. In addition, ketamine produces significant psychological side effects impacting on cognition and perception.

Schizophrenia is one of the leading illnesses of psychiatry and is the second important disorders, followed by depression.. Although a long way has been covered in pharmacotherapy of schizophrenia in 63 years, since Delay & Deniker of 1950, a number of unmet needs are known to exist. In particular, resistance to treatment and lack of efficacy of existing antipsychotics on the negative symptoms of schizophrenia have remained as important issues. Although for today, clozapine is effective in about half to 2/3 of treatment resistant patients, unfortunately neither clozapine nor the rest of the antipsychotics have significant efficacy on the negative symptoms of schizophrenia. The researches about treatment of negative symptoms are presently rather focused on the glutamatergic system. Researches on bitopertin are the one example of these efforts. Like ketamine, which is on trial for treatment resistant depression, an antihypertensive/vasodilator agent, namely sodium nitroprusside that has been in use for resistant schizophrenia and its negative symptoms, should be mentioned. Among those studies, a placebo-controlled clinical trial by Hallak et al. has reported rapid and permanent regression of symptoms in resistant schizophrenic patients, who were administered sodium nitroprusside infusion (29). This paper has provided a breathing space for

clinicians, who have been feeling desperate in the field of schizophrenia. Though the small size of sampling of this study was a notable limitation, it would be a new potential and may expand horizons of the pharmacotherapy of schizophrenia. If confirmed by new studies, the findings of this scientific work could provide a novel initiative about the relationship between the observed NMDA receptor hypofunction and the negative and cognitive symptoms of schizophrenia. Despite the fact that their findings are inconsistent, clinical studies that have been conducted about endogenous ligands like D-serine and glycine functioning as allosteric modulators, can be considered as another approach reinforcing NMDA receptor functionality (30).

Excitation of NMDA receptors results in cellular Ca^{+2} influx via a receptor gated ion channel. Ca^{+2} influx activates all enzymatic systems, including NOS and NO synthesis mounts up, respectively. NO synthesis is mediated by NOS, which converts L-arginine to NO and L-citrulline. NO is a retrograde messenger in gas form; it diffuses into presynaptic neurons and activates soluble guanylate cyclase to modulate the synthesis of cGMP and release of neurotransmitters. NO also plays a role in the modulation of neuroplasticity and acts like a free radical at excess levels (31).

Nitric oxide is a highly reactive molecule possessing an uncoupled electron and mimicking free radicals. NO in gas form reacts with oxygen so as to give nitrogen dioxide, which in turn reacts with a free radical donor called anionic superoxide in aqueous solution form to yield peroxynitrites. Peroxynitrite is a highly reactive compound that oxidizes mammalian cells. Peroxynitrite is inactivated either by superoxide anions or oxyhemoglobin. Thus, NO is associated with the negative symptoms of schizophrenia while it is affiliated with the adverse effects arising from the production of reactive oxygen species. Post-mortem studies carried out in schizophrenic patients have provided findings about oxidative stress. An increase in NOS expression has been shown in the cerebellar tissues of schizophrenic patients. Recent evidence suggests that oxidative stress processes might play a

relevant role in the pathogenic mechanism(s) underlying many major psychiatric disorders, including depression. Reactive oxygen and nitrogen species have been shown to modulate levels and activity of noradrenaline (norepinephrine), serotonin, dopamine and glutamate, the principal neurotransmitters involved in the neurobiology of depression (12). Despite the lack of clarity, it has been thought that this increase could be associated with a decline in NMDA receptor functions and in consequence, a probability for NO to have an important role in the pathophysiology of schizophrenia has been supposed.

Sodium nitroprusside is an antihypertensive drug that has vasodilator-effects. It owes its principal activity to being a NO donor, so that it raises NO synthesis. When administered to schizophrenic patients via infusion, NO production escalates, so the tissue levels increase directly, without mediation by NMDA receptors in brain. It is a prominent finding that a single dose administration of nitroprusside in schizophrenia patients provides amelioration in symptoms that lasts up to 2 weeks. It is highly likely that a single dose sodium nitroprusside infusion given to treatment resistant schizophrenia patients yielded a rapid and weeks-long improvement just like ketamine, an NMDA receptor antagonist, provided in treatment resistant depression. The effects of nitroprusside on schizophrenia symptoms could be explained by an increase in cerebral perfusion due to vasodilatation. Studies have proven that the blood stream in frontal and temporal cortex, which are concluded to be related to the negative symptoms of schizophrenia, decay in schizophrenia patients when compared to healthy controls (32). This finding provides additional evidence for NMDA receptor hypofunction in schizophrenia. The above mentioned results are consistent as far as the positive therapeutic effects of NMDA are concerned. The effect of nitroprusside should be repeatedly observed in additional clinical trials with sufficient sample size of schizophrenic patients, for confirmation.

In conclusion, although there are still numerous unmet needs and pending problems in the

treatment of depression and schizophrenia as two cardinal illnesses of psychiatry, it is hopeful to have ongoing phase II and phase III clinical trials (mostly phase II) on new drug entities exerting activity through the glutamatergic system or NO to have been proceeding quickly and accumulating data in a positive direction, to our knowledge.

There have been ongoing studies on a novel modified formulation of ketamine, an anesthetic agent, to be used in the treatment of depression. The so-called esketamine formulation is considered to be safer when compared to ketamine in terms of causing hallucinations and delirium, in addition with low abuse potential. Esketamine as being developed to be applied via intranasal with one out of twelve dose of ketamine, is still in its phase 2 trial. Ketamine with its rapid antidepressant action profile on setting within hours, is superior to the current medications that are generally required to be used at least for a month to exert their antidepressant effects. With this rapid action profile, great advantage can be provided in the treatment for prevention of suicide, financial losses and finally reduction in wastage of time and effort. As it is well known, depressed patients with high risk of suicide are required to be hospitalized for several months due to the fact that there is an increased risk of suicide, one of the most common, highly serious and irreversible complication of depression, with delayed effects of the current antidepressant therapies. Moreover, the majority of the outpatients are not able to work efficiently and even unable to work for several weeks due to the lack of the treatment of the disease. Thus, novel nasal

esketamine treatment might appear to be a breakthrough in the treatment of depression (33).

Nevertheless, the above mentioned drugs need years to be commercially available even if everything goes well with the completion of phase III clinical trials, NDA licensing, and acquiring marketing authorizations. We conclude that the relevant official bodies of national health authorities should evaluate and amend the regulations to favor ketamine and nitroprusside administration, provided that the approval of a second psychiatrist is obtained as well as the written consent of the patient and/or the patient's guardian are procured and the necessary safety precautions are taken. Such a step will minimize the serious risks associated with treatment resistance, such as suicides, recurrent hospitalizations, etc., but would require urgent resolution.

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