EDITORIAL

Glutamatergic antidepressants? The intriguing antidepressant properties of ketamine

¿Antidepresivos glutamatérgicos? Las sorprendentes propiedades antidepresivas de la quetamina

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Current limitations in treatment of depression

The existing antidepressant drugs, which are based on reuptake of the monoamines serotonin and/or noradrenaline, have 2 major drawbacks: slow action and low effectiveness. Although most controlled clinical trials report about a 60% response rate after 6 weeks of therapy (initial severity reduced by half), data from the STAR*D naturalistic trial with almost 2900 patients has a less promising panorama, with response and remission rates of 47% and 30%, respectively, after 8 weeks of therapy with the selective serotonin reuptake inhibitor citalopram.\textsuperscript{1} Moreover, because the efficacy of antidepressant drugs diminishes as the disease progresses, the array of therapeutic options becomes limited to the more aggressive strategies, such as electroconvulsive therapy or—more recently—deep brain stimulation,\textsuperscript{2-4} which are effective in cases of greater resistance to drug therapy.

Finding new therapeutic targets that overcome the current limitations in treatment of depression is one of the supreme challenges in Neuropsychopharmacology. Both public research entities and pharmaceutical companies themselves are supporting efforts to identify new therapeutic targets, on the basis of which more effective drugs could be developed. In this connection, the author wishes to highlight the European Union's Innovative Medicines Initiative-Joint Undertaking (IMI-JU) conference, which included the New Medications in Depression and Schizophrenia (NEWMEDS) program, as a transnational research endeavour. Within Spain, research in this field is supported through the activities of CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental/Network of Biomedical Research Centres in Mental Health). The joint efforts of basic and clinical researchers along with interactions between the public and private sectors are bound to produce results in the not-too-distant future, even in spite of the current obvious budget constraints. This editorial reflects recent interest in glutamatergic neurotransmission as a target for development of new antidepressant drugs that, based on enhanced functioning of monoaminergic systems, act more quickly and are more effective than the current drugs.

Glutamatergic neurotransmission: NMDA antagonists

Glutamate is the most abundant neurotransmitter in the mammalian brain; glutamate and gamma-aminobutyric acid (GABA), the inhibitory amino acid, together constitute the essential elements of interneuronal communication. The other compounds involved in brain neurotransmission

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phencyclidine markedly reduces low-frequency oscillations—an effect reversed by classic (haloperidol) and atypical antipsychotics (clozapine), which indicates, as well that such effects are clearly related to their psychotomimetic actions. These effects are analogous to those produced by other hallucinations-inducing psychotomimetic agents like DOI (5-HT2A receptor agonist, with actions analogous to those of LSD and other natural hallucinogens, such as mescaline, psilocybin, and 5-methoxy-dimethyltryptamine).

**Ketamine’s intriguing antidepressant properties**

In addition to the psychotomimetic effects of the non-competitive NMDA glutamate receptor antagonists, there have been reports in recent years of the antidepressant effects of one of them—ketamine, which has become an abused drug thanks to its euphoria-inducing properties. This has led to NMDA receptors being studied as possible therapeutic targets in the development of antidepressants.

In fact, an early pilot study showed that intravenous administration of low-dose ketamine (0.5 mg/kg IV) to 9 patients hospitalised with unipolar and bipolar depression produced rapid antidepressant effects, with a maximum effect at 72 h post-administration that, in some patients, lasted up to 2 weeks. Subsequent trials conducted by the same group confirmed the initial results, showing that ketamine induced a response in 71% of patients resistant to conventional treatments. A case of complete and persistent remission following an acute course of ketamine has been reported. These trials have been independently replicated—even at lower doses (0.2 mg/kg IV) than in the initial trials—in a naturalistic study on patients with marked suicidal ideation, which reported a reduction in total score from 40 to 15 in 4 h on the Montgomery-Asberg (MADRS) scale. Intravenous ketamine infusion entails minimal side effects, even at doses much higher (5 mg/kg) than those used in the above-mentioned trials, and a low incidence of the appearance of psychotic symptoms.

These clinical results with ketamine are coincident with those obtained with deep brain stimulation of the cingulate cortex (Brodmann areas 24 and 25) and show that it is possible to obtain a much more rapid and successful antidepressant effect than that achieved using conventional monoamine reuptake inhibitor drugs.

They also highlight the important role of glutamatergic neurotransmission in the treatment of depression—just the same as in schizophrenia, where glutamate metabotropic receptor agonistantipsychotic drugs are being developed. Ketamine’s antidepressant efficacy is generating a wave of preclinical and clinical research on the actions of glutamate; this comes on top of research on this neurotransmitter already conducted in schizophrenia and other psychiatric disorders.

**Ketamine’s mechanism of action**

Most effects of the non-competitive NMDA antagonists (ketamine, phencyclidine, MK-801) are reversed or prevented with antipsychotic drug treatment,
indicates a clear association with the psychotomimetic actions of these compounds. It is not known, however, which of ketamine’s cellular- and circuit-level actions are responsible for its antidepressant effects, which are seen at doses lower than those responsible for its psychotomimetic effects.

This effect does not appear to result from the increase in monoamines caused by these compounds because such increases are also seen following administration of reuptake inhibitors, the clinical effects of which are much slower and less effective. In the different clinical trials that have been published, the patients who were responsive to ketamine had been treated previously with reuptake inhibitors; this also supports the idea that ketamine’s effects are not mediated by an increase in monoaminergic neurotransmission. Ketamine’s mechanism of action is unknown at this time; however, intracellular signalling mechanisms distinct from those activated by the monoamines are beginning to be described (see below). Research that is currently underway is bound to lead to the discovery of the molecular mechanisms, circuits, and areas of the brain that are responsible for ketamine’s antidepressant effect.

New therapeutic targets linked to NMDA receptors

Studies conducted in the 1990s showed that treatment with the classic antidepressant drugs induced changes in NMA receptor expression and function (see review in Ref. 23), which fuelled the clinical and research communities’ interest in compounds acting on this receptor and instigated the above-mentioned clinical trials. Because of its pharmacological characteristics, potential for abuse, and psychotomimetic effects, ketamine is not used routinely—even though its antidepressant effects are obvious. This has prompted a great many research groups to throw themselves into studying the cellular-level actions of ketamine. It has been reported that a single dose of ketamine induces increased intraneuronal signalling by mammalian target of rapamycin (mTOR) which, in rats, translates to an increased number of dendritic spines on prefrontal cortex pyramidal neurons and, therefore, enhanced synaptic connectivity. It is not known, however, whether ketamine could affect the functioning of brain circuits involving areas usually associated with depressive symptomatology, such as the prefrontal cortex itself, the hippocampus, and the amygdala. The extent to which ketamine’s antidepressant effect is due to its previously known actions on the activity of neuronal elements and brain circuits, as well as in studies on animal behaviour, is also unknown, for these actions were elicited at doses much higher than those used in the clinical trials.

In summary, ketamine’s antidepressant effects have brought to light the importance of glutamatergic neurotransmission and NMDA receptors in the treatment of depression. Public and private researches in this field are sure to lead to the discovery of new antidepressant drugs that overcome the limitations of current drugs in terms of efficacy and speed of action.

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Conflict of interest

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