



Revista de Psiquiatría y Salud Mental

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EDITORIAL

Glutamatergic antidepressants? The intriguing antidepressant properties of ketamine[☆]

¿Antidepressivos glutamatérgicos? Las sorprendentes propiedades antidepressivas 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.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,^{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

[☆] Please cite this article as: Artigas F. ¿Antidepressivos glutamatérgicos? Las sorprendentes propiedades antidepressivas de la quetamina. Rev Psiquiatr Salud Ment (Barc.). 2011;4:183-6.

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(serotonin, catecholamines, histamine, acetylcholine, neuropeptides, nitrous oxide, endogenous cannabinoids, etc.) are primarily compounds that modulate the amino acid-mediated transmission.

Glutamate is the neurotransmitter of projection neurons in the cerebral cortex and most of the subcortical regions, such as the thalamus, the hippocampus, and the amygdala, with the exception of the basal ganglia (caudate-putamen, globus pallidus, and related structures) that use the inhibitory neurotransmitter GABA to communicate. Compared to the tens of thousands of millions of glutamatergic neurons in the human brain, the monoaminergic neurons (serotonin, noradrenaline, dopamine) represent a minimal percentage—there are about 250,000 serotonergic neurons in the human brain. As neuroanatomy and neuroimaging studies have shown, however, monoaminergic neurons reach most areas of the brain because of their extensive branching. This morphological feature differentiates them from the glutamatergic projection neurons, the axons of which have much more restricted neuronal targets.

The actions of glutamate are divided into (1) ionotropic, mediated by AMPA, NMDA, and kainate receptors, ion channels that Na^+ and Ca^{2+} cations permeate, and (2) metabotropic, mediated by G protein-coupled membrane receptors (mGluR1–mGluR8), analogous to the monoaminergic receptors. For years, NMDA receptors have been implicated in neuroplasticity phenomena, among which the *long-term potentiation (LTP)* processes involved in memory are prominent. These receptors have an ion channel made up of 4 subunits and allow Ca^{2+} ions to pass through under neuronal depolarisation conditions—that is, when the neuron has already been activated by glutamate itself via AMPA receptors or else by other excitatory neurotransmitters.

The NMDA receptor has various binding sites, among which is the binding site for glutamate itself and competitive antagonists, such as APV. It also has regulatory sites, such as the glycine binding site and a binding site inside the Mg^{2+} ion channel, as well as another for the so-called non-competitive antagonists, such as ketamine and phencyclidine—the dissociative anaesthetics that are used as pharmacological models of schizophrenia because of their ability to mimic some symptoms of the disease in healthy individuals and to exacerbate the condition of schizophrenic patients.^{5,6} The physiological activation of NMDA receptors by glutamate causes Ca^{2+} ions to flow into the neuron, which activates various intraneuronal signalling processes involved in neurotransmission, including the LTP processes mentioned above. When activation is excessive, however, excitotoxic phenomena occur, resulting in neuronal death secondary to a massive inflow of Ca^{2+} ions.

Paradoxically, systemic administration of non-competitive glutamate antagonists, such as MK-801, ketamine, or phencyclidine, results in increased glutamatergic neuron activity in the cortex and subcortical areas,^{7–10} an effect explained by the fact that they act preferentially on NMDA receptors located in cortical and/or subcortical interneurons.¹¹

In addition to these changes at the neurochemical level and in cortical neuron activity, non-competitive NMDA antagonists such as phencyclidine induce striking changes in cortical network functioning. In animal experimentation, intravenous administration of

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.⁸ These effects are analogous to those produced by other hallucinations-inducing psychotomimetic agents like DOI (5-HT_{23A} receptor agonist, with actions analogous to those of LSD and other natural hallucinogens, such as mescaline, psilocybin, and 5-methoxy-dimethyltryptamine).¹²

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.¹³ 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.¹⁴ A case of complete and persistent remission following an acute course of ketamine has been reported.¹⁵ 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.¹⁶ 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.¹⁷

These clinical results with ketamine are coincident with those obtained with deep brain stimulation of the cingulate cortex (Brodmann areas 24 and 25)^{2–4} 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 agonist antipsychotic drugs are being developed.^{18,19} 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.²⁰

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,^{7–10} which

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^{7,9,21} 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 described²² (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.²² 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.

Financing

This work has been financed by the SAF2007-62378 project and by the Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).

Conflict of interest

The author has no conflict of interest to declare.

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