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Why Ketamine is A New Treatment of Resistant Depression?

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Abstract

Ketamine is increasingly used as a treatment for resistant unipolar or bipolar depression. It is distinguished by its pharmacology of traditional antidepressants. It is a non-competitive antagonist ionotropic N-methyl-D-aspartate (R-NMDA) receptor of L-glutamate which binds to the "phencyclidine" site of this calcium channel. The best-known hypothesis of the mechanism of ketamine in depression is that it causes "bursts" of glutamate following the disinhibition of cortical GABAergic interneurons: the tonic triggering of these GABAergic interneurons would be driven by the receptors NMDA, and the active state of the open channel. Rapid antidepressant response to NMDA receptor antagonist would be associated with glutamate "bursts" and synaptogenesis in mPFC.

Keywords: Extracellular signal-regulated kinases; ketamine; N-methyl-D-aspartate receptor; resistant depression;

What is resistant depression?

Depression is treatable, whatever its typology, is a type of multi factorial disorder that requires several strategies to overcome it: pharmacological, psychotherapeutic, social, etc.

It is the same for the major resistant depression. However, in these cases, we simply need to be steadfast and persistent in order to find the most effective treatments for the patient who experiences untold suffering to experience the improvement he needs. On the other hand, we cannot forget that antidepressants, taken at the appropriate doses and for a minimum of 6 weeks, generally offer proven efficacy, but when this is not the case, when the patient perceives that his discomfort is still present installed and devoured, desolation becomes absolute. Moreover, the patient may experience a loss of confidence in his doctor and become skeptical about trying a new treatment.

The definition of the most commonly used resistant depression is based on the failure of at least two successful antidepressant treatment trials conducted in terms of dose and duration [1]. The lack of response to previous antidepressant treatments should be evaluated using specific instruments that can accurately define the level of therapeutic resistance. Many sociodemographic and clinical factors (psychiatric or somatic comorbidities) are classically associated with therapeutic resistance. The goal of any treatment for major depression is to achieve complete clinical remission [2]. The persistence of so-called residual symptoms leads to an increased risk of relapse and recurrence, thus facilitating the development of therapeutic resistance. However, we must ask the question, if we are not in front of a patient with bipolar depression who usually very poorly responds to antidepressants [3]. Conventional antidepressants are not suitable for all patients, because of their mechanism of action which involves intervening on the neurotransmitters, at the level of the synapses, thus on the surface of the cells. It is therefore necessary to focus not only on the external signal, but also on possible intracellular deregulation. Antidepressants always take time to act, so it is likely that something happens downstream of the synapses [4].The place of intracellular signaling cascades has long been the subject of research, clinical studies have shown the presence of Elk-1 (Extracellular signal-regulated kinases) in the blood of depressive patients [5], and a high level of Elk-1 was associated with a bad prognosis. In the blood, changes in Elk-1 are correlated with the clinical response, making it possible to define Elk-1 as a blood biomarker that is easy to follow over time. It could be a good indicator of the prognosis of depression and help the therapeutic decision such as the anticipated change of treatment to avoid therapeutic failure.

Ketamine in resistant depression

Ketamine (2-(2-chlorophenyl)-(1-methylamino)-cyclohexanone) is a non-competitive antagonist ionotropic N-methyl-D-aspartate (R-NMDA) receptor of L-glutamate binds to the "phencyclidine" site of this calcium channel. It is a dissociative general anesthetic fast acting whose hallucinogenic properties have made it an addictive popular drug the name of "Special K"[6]. Ketamine, used as a general anesthetic, has been shown to be effective in several studies to quickly relieve depressive symptoms when administered at low sub-anesthetic doses. Most of these studies used an intravenous dose of 0.5 mg / kg [7].

A dose-response study was conducted with 99 people with treatment-resistant depression in six research centers [8]. Four single doses of ketamine (given by injection) - 0.1 mg / kg, 0.2 mg / kg, 0.5 mg / kg and 1.0 mg / kg - were compared to "active" placebo which induces side effects, the absence of which could lead participants to realize that they are not receiving the drug to be tested, potentially biasing their perception of symptom improvement. Participants continued to take antidepressant treatments during the study period. Neither they nor the research staff knew who took the placebo or the drug and at what doses. Depression was measured with a 6-item version of the Hamilton

Depression Scale. Other instruments measured aspects of mood and suicidal thoughts. Dissociative symptoms such as memory loss and the feeling of detachment from reality were assessed during and after the ketamine infusion, and vital signs were measured after treatment and at all follow-up visits. Comparison of dosage levels, adjusted for various factors that may influence the results, showed an improvement for doses of 0.5 mg / kg and 1.0 mg / kg only. The two lower doses did not provide significant symptomatic relief, although some improvement was observed in some participants at the lowest dose of 0.1 mg / kg. In most participants receiving the higher doses, the benefits of treatment began to decrease by the third day and were no longer detectable after five days. There was no significant difference in the occurrence of adverse events among all study participants. These results confirm the clinical observation that a single dose, the most studied dose of 0.5 mg / kg, is not suitable for all, as some patients may require a lower than average dose; and each patient needs a personalized treatment plan that can include ketamine and other medications, as well as psychotherapy. Further research should focus on the efficacy of repeated doses of ketamine, as well as the possibility that higher doses require less frequent administrations.

A first study [9] confirmed by others since that date, showed that ketamine has an amazing antidepressant effect. Indeed, several double-blind placebo-controlled clinical trials have suggested that a single low dose of ketamine (0.5 mg / kg administered intravenously in 40 minutes, a dose below the anesthetic dose) exerts rapid antidepressant activity (within 72 hours after injection) and persistent (for 1 week) in depressed patients resistant to classic antidepressant treatment [10]. In addition, ketamine also decreases suicidal thoughts and therefore suicidal risk [11]. However, the mechanisms leading to such antidepressant action are probably more complex than the simple blockade of L-glutamate NMDA receptors and have not been clearly defined so far [12].

Molecular mechanism proposed for the antidepressant effect of ketamine

Neuronal atrophy and synaptic loss in depression

Brain imaging studies of depressed patients provide strong arguments because of a constant decrease in the volume of the cortical and limbic cerebral regions - like the medial prefrontal cortex (mPFC) and the hippocampus - which control emotions, mood and cognition, suggesting that neuronal atrophy is related to the prescription period of treatment [13]. Rodent studies have provided detailed evidence of neuronal atrophy, of synaptic density reduction and cell loss in models of depression and stress (CMS) [14]. The BDNF was of interest particular with regard to the atrophy of neuronal connections as this factor neurotrophic is required for early neuronal development and for survival and neuronal function, including synaptic plasticity, in the adult brain [15]. Under normal conditions, stimulation of the presynaptic neuron releases the neuronal glutamate, leading to activation of AMPA glutamate receptors postsynaptic and membrane depolarization; this causes the activation of several intracellular pathways, including the BDNF-TrkB signaling pathway (kinase-related tropomyosin B), and the mTORC1 pathway (target of rapamycin complex 1) in the hippocampus and median prefrontal cortex (mPFC)[16]. These pathways are essential for the regulation of plastic synaptic, a fundamental adaptive learning mechanism that includes the maturation (increased diameter of dendritic spines) and the increase in the number of synapses (synaptogenesis) [17]. This process requires a synthesis of the neuronal synaptic proteins, including GluA1 subunits of glutamatergic AMPA and PSD 95 receptors. Repeated stress decreases BDNF and mTORC1 signaling in part via positive regulation of the negative regulator REDD1 (regulating DNA damage and repair), which decreases the synthesis of synaptic proteins and thus contributes to a decrease in the number of synapses. Other proteins involved in regulating synaptic plasticity include GSK3 and protein phosphatase 1 (PP1).

Molecular mechanism of rapid antidepressant action of ketamine in mPFC

The best-known hypothesis of the mechanism of ketamine is that it causes "bursts" of glutamate following the disinhibition of cortical GABAergic interneurons: the tonic triggering of these GABAergic interneurons would be driven by the receptors NMDA, and the active state of the open channel (i.e., after release of Mg2 + channel ions) would allow ketamine to attach to the PCP site and block channel activity [18]. These glutamate bursts would stimulate post-synaptic AMPA receptors, which would cause neuronal membrane depolarization and Ca2 + channel activation (VDCC), leading to BDNF release and TrkB / Akt signal stimulation. This would activate mTORC1 signaling and trigger an increased synthesis of the proteins necessary for maturation and synapse formation (e.g., GluA1 and PSD95) [19]. Under conditions where release of BDNF is blocked (such as knock-in mice possessing the BDNF Val66Met allele with increased risk of depression) or neutralized (using an antibody), or in which mTORC1 signaling is blocked (infusion of rapamycin in mPFC), we observe well that synaptic and behavioral effects of ketamine are blocked [20, 21]. Relapse to a depressive state would be associated with a decrease in synapses on mPFC neurons, which could occur during chronic stress, imbalance in endocrine hormones (cortisol), estrogen, inflammatory cytokines, or metabolic and cardiovascular diseases [17].

Antidepressant mechanism of ketamine: link with neurotransmission of glutamate, GABA and serotonin in preclinical studies

Neurochemical (glutamate, GABA and 5-HT) and behavioral changes induced by the administration of an infra-anesthetic dose of ketamine, focusing on rodents, animal models of depression in rats or mice used in numerous published studies. Rapid antidepressant response to NMDA receptor antagonist would be associated with glutamate "bursts" and synaptogenesis in mPFC. The implication of the balance of excitatory (glutamate, serotonin) and inhibitory (GABA) neurotransmission in the glutamate - mPFC / serotonin - dorsal raphe nucleus (NRD) in rodent studies seems to be relevant [22].

Conclusion

The mechanism of the antidepressant effects of ketamine involves many receptors, forming an important network whose elements must be detailed. Here we focused on the R-NMDA, R-AMPA, R-GABAA and serotoninergic receptors. Ketamine is a calcium channel blocker of R-NMDA. Although the role of the GluN1 subunit in the antidepressant effects of ketamine is still a subject under discussion, the GluN2A and GluN2B subunits seem to be essential for this purpose because ketamine blocks the R-NMDAs containing the subunits. The theory of disinhibition of the antidepressant activity of ketamine suggests selective blockade of R-NMDA located on GABAergic interneurons, leading to an inhibition rise of pyramidal neurons of the cortex, thus improving their excitatory electrical activity. The selective blocking or elimination of this subunit located on the pyramidal neurons contributes to the rapid increase of synaptic excitatory impulses on these neurons to induce antidepressant effects.

From a clinical point of view, ketamine seems interesting to quickly exit a major depressive episode including bipolar. However this action is limited in time (about 15 days) and does not involve a switch to hypomania or mania. This may be of great benefit in bipolar depression in which conventional antidepressants should be used with caution.

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