Ketamine’s Legacy: New Targets for the Development of Rapid on Set Antidepressant Drugs

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Abstract

Major depressive disorder is a common, recurrent and disabling psychiatric disorder associated with significant morbidity and mortality. For half a century, the field of neuropsychopharmacology of depression has been dominated by the monoaminergic hypothesis, especially regarding the development of antidepressant drugs. However, the monoaminergic antidepressants have significant limitations; these drugs present a delayed onset of action (weeks to months), and a considerable fraction of patients do not respond to treatment even after several therapeutic attempts. In the last decade, compelling clinical evidence has demonstrated that a single sub anesthetic dose of the N-methyl-D-aspartate receptor (NMDAR) antagonist, ketamine, can induce a significant improvement of depressive symptoms within hours, even in situations of treatment-resistant depression. Furthermore, preclinical studies aiming to elucidate the biological mechanisms underpinning the antidepressant action of ketamine opened new perspectives into the neurobiology of depression and consequently to the emergence of important targets for the development of new antidepressant drugs. Ketamine seems to be the prototype for a new generation of antidepressants that can impact the clinical management of depression exerting their therapeutic effects within hours. Here, we are presenting some evidence regarding the efficacy, safety, and tolerability of ketamine. We also included a summary of the mechanisms underlying the rapid antidepressant effects of ketamine, and discussion of the contributions of these mechanisms for next-generation rapid-acting antidepressants: the called “legacy of ketamine”.

ABBREVIATIONS

WHO: World Health Organization; SSRIs: Selective Serotonin Reuptake Inhibitors; NIMH: National Institute of Mental Health; STAR*D study: Sequenced Treatment Alternatives to Relieve Depression; NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic Acid; MTOR: Mammalian Target of Rapamycin; BDNF: Brain Derived Neurotrophic Factor; eEF2: Eukaryotic Elongation Factor 2

INTRODUCTION

The World Health Organization (WHO) recognizes depression as the main cause of disability and loss of productive life years worldwide. Depression is a common mental disorder with about 350 million of people living with depression in the world. Depression often start at a young age, reduce people's functioning and is often recurrent [1,2]. Depression is also associated with increased risk of developing severe diseases, such as diabetes, atherosclerotic heart disease and cancer, and presents increased rates of suicide [3,4].

The 1950s was considered the “golden decade” of psychopharmacology due to the introduction of psychoactive drugs. Noteworthy, these drugs are still currently used. In this regard, the first advances in the pharmacotherapy of depression came from the discovery of the antidepressant properties of iproniazid, a monoamine oxidase inhibitor, originally prescribed for the treatment of tuberculosis. In sequence imipramine, the prototype of the tricyclic antidepressants, was developed [5,6]. In the late 1980s, fluoxetine was introduced in clinical practice, opening perspectives for the development of a new class of antidepressants called selective serotonin reuptake inhibitors (SSRIs) [7,8]. These antidepressants brought two major contributions to the field of psychiatry: i) provided a useful and relatively safe therapeutic tool for the care of depressed patients; ii) gave rise to the first aetiopathogenic hypotheses of depression, the monoaminergic theory [6].

Despite the initial excitement, in the last years, the effectiveness of monoaminergic pharmacotherapies for depression has been intensely questioned. In 2006, the National
Institute of Mental Health (NIMH) conducted a large clinical trial including more than 2500 patients from 41 clinical sites of the United States, to assess the effectiveness of currently antidepressant treatments, the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. The findings of this study were striking: they showed that less than one third of patients (27%) achieved remission of depressive symptoms within 12 weeks of treatment, and about 33% of patients did not achieve remission despite attempts up to four different schemes of antidepressant medications. Furthermore, in the subgroup of patients responding to treatment, the mean time to remission was 7 weeks, with little difference among the mono therapy regimens or with adjunctive medication [9-11]. Several other studies highlighted the limited effectiveness of monoaminergic antidepressant drugs and their delayed time of action [12,13]. Therefore, in view of the global burden of depression, there is a great need for more effective and rapid treatments for patients with this disease.

**DISCUSSION & CONCLUSION**

In the last decades several lines of evidence have highlighted the role of glutamatergic transmission dysfunction in the pathophysiology of depression. In other words, glutamatergic synapse presents attractive targets for the development of new antidepressant drugs [14]. In this context, based on clinical evidences, glutamatergic abnormalities were reported in the plasma, cerebrospinal fluid and brain areas of depressed patients [15,16]. Besides this, these abnormalities in glutamatergic transmission appear to be associated with important changes in brain cytoarchitecture and volumes observed in post-mortem studies and functional alterations in magnetic resonance imaging (MRI) of the brain of depressive patients [15,17,18].

Concurrently, preclinical studies have reported that different models of environmental stress promote significant disturbances on glutamate transmission, particularly in glutamate metabolism and reuptake. These changes are a result of the glial dysfunction induced by stress [18,19]. The increased extra synaptic levels of glutamate present two direct consequences: i) increased activation of metabotropic presynaptic receptors, which, in turn, inhibit the synaptic release of glutamate and the activation of synaptic receptors, and ii) activation of extra synaptic glutamate receptors, possibly the N-methyl-D-aspartate (NMDA) receptors containing the GluN2B subunit, which are associated with the activation of neuronal pro-apoptotic pathways and retraction of dendritic spines [20,21]. These evidences gave rise to the glutamatergic hypothesis of depression.

The investigation of the antidepressant effects of glutamatergic drugs is not new. Since 1959, Dr. George Crane and co-workers reported the antidepressant effect of the tuberculosatic agent D-cycloserine, based on the observation of mood improvement in patients treated with this drug [22]. Subsequently, it was determined that D-cycloserine mechanism of action includes a partial agonist effect at the glycine B site of NMDA receptors bearing the GluN2A and GluN2B subunits and a full agonist effect on NMDA receptors containing the GluN2C and GluN2D subunits [23,24]. However, the main findings about glutamatergic antidepressants came from trials conducted with ketamine from the 1990s.

Initially ketamine was used to study the glutamate synaptic dysfunction present in schizophrenia [25] and alcohol dependence [26]. When tested in depressed patients, ketamine promotes a surprisingly rapid and robust antidepressant effect [27]. In fact, the researchers were impressed by the rapid onset of action of ketamine, emerging in 2 to 4 hours after a single administration and inducing the complete remission of depressive symptoms within 24 hours in some patients [27–29]. Additionally, ketamine improved all symptoms of depression, including severe manifestations, such as suicidal ideation and catatonia [30,31]. Although some studies pointed out that the clinical benefits of a single dose of ketamine may last longer than 2 weeks [29], the maximal duration of the beneficial effects of ketamine are still unknown. Contrarily, some evidences showed that these effects may be as brief as 24 hours [32,33]. In fact, few studies have systematically followed patients beyond 72 hours post-ketamine [28]. The clinical variables predicting quick relapse, like those predicting sustained response should be an interesting topic for future research.

Despite the surprising therapeutic effect of ketamine, some limitations and risks have been associated to the use of this drug as an antidepressant. The core question when a potentially new medication (or a repurposed one) is being considered for clinical use is its safety. In this context, no toxicological studies have been conducted with ketamine in depressed patients. This is reinforced by the fact that little is known about the safety of repeated use of this drug in subanesthetic doses, i.e. doses responsible for the antidepressant effect of ketamine. In addition, some adverse effects have often been associated with the acute use of ketamine, particularly cognitive and dissociative symptoms, such as perceptual disturbances, confusion, euphoria, dizziness and increased libido. These symptoms generally appear within a few minutes after ketamine infusion, do not persisting for more than 2 hours [34,35]. Another important concern regarding the clinical use of ketamine is its potential for abuse. Ketamine or “Special K” is widely used as recreational drug to induce a dissociative state of relaxed wellbeing [36]. Ketamine abusers often administer higher and more frequent doses than the ones used to treat depression. This considerably increases the risk of adverse effects. Therefore, despite some studies have shown that the psychotomimetic effects of ketamine appear to be transient, concerns regarding abuse could lead to the therapeutic benefits being overlooked [29,36]. Thus, in a critical view, these questions make clear that ketamine is a strategy of “high-risk, high-gain” and justify the need for the development of better antidepressant treatments.

The investigation of the cellular mechanisms underpinning ketamine antidepressant action has a transformative impact on the development of new antidepressant drugs since they provide potential targets for drug development. In this field large contributions came from studies in animal models of depression (for more details please read [14]). In this context, ketamine appears to act through new mechanisms that are intrinsically linked to the neurobiological pathways of stress. Two (nonexclusive) hypotheses were developed for the antidepressant mechanism of ketamine [21]. The first hypothesis proposes that ketamine overlap the glutamatergic dysfunction involved in depression by stimulating synaptic glutamate
release and activation of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Once AMPA receptors signaling is potentiated, the ketamine downstream effect would be mediated by the activation of the pathway Akt/mammalian target of rapamycin (mTOR), resulting in a rapid and robust increase in the number and density of dendritic spines [37,38]. The second, in turn, suggests that NMDA receptors blockade (mainly at extra synaptic sites) would be critical for the antidepressant effects of ketamine. This could be explained by the fact that, in the context of glial dysfunction, excessive activation of these receptors would lead to the phosphorylation (and subsequent inhibition) of eukaryotic elongation factor 2 (eEF2), an essential factor for the translation of mRNA brain derived neurotrophic factor (BDNF) to its correspondent protein. Thus, the blockade of extra synaptic NMDA receptors by ketamine would increase BDNF synthesis and consequently the action of this neurotrophic factor on synaptic plasticity [39,40].

On the other hand, some studies have suggested that ketamine may act directly or indirectly on different targets beyond the glutamatergic system. In this context, it has been demonstrated that the ketamine effect is importantly linked to serotonergic neurotransmission. For example, the depletion of 5-HT by para-chlorophenylalanine (PCPA) or the blockade of 5-HT1A receptors can prevent the ketamine antidepressant effect [41]. Also, the microinjection of ketamine in the medial prefrontal cortex (mPFC) results in a marked increase in 5-HT extracellular concentrations in this area as well as increased c-Fos expression in the 5-HT neurons in the dorsal raphe nucleus, which was tightly correlated with its antidepressant efficacy [42,43]. Finally, there is interesting evidence that ketamine can directly bind to dopamine D2 receptors [44,45] and sigma 1/2 receptors [46], which must have a potential contribution for its behavioral effects.

Furthermore, recently, Zanos et al., 2016 demonstrated that the metabolism of ketamine to (2S, 6S; 2R, 6R)-hydroxynorketamine (HNK) is essential for its antidepressant effect. These researchers also found that the (2R, 6R)-HNK enantiomer exerts a rapid and sustained behavioral, electrophysiological and cellular antidepressant-related actions, without induce the typical ketamine-related side effects, such as dissociative and euphoric effects. Interestingly, the action of (2R,6R)-HNK seemingly did not depend of direct NMDA receptors inhibition, but involve early and sustained activation of AMPA receptors [47].

Therefore, the investigation of the mechanisms underpinning the antidepressant action of ketamine has fundamental importance for the development of new and better pharmacological therapies for depression. At this point of view, ketamine can be a prototype for a new generation of revolutionary antidepressant drugs.

In last recent years, based on studies of the glutamatergic synapse, other potential candidates for rapid and robust antidepressant effect have been emerged, such as GluN2B-selective NMDA receptor antagonists, glycine B partial agonists or antagonists, metabotropic glutamate receptor-2 antagonists, metabotropic glutamate receptor-5 antagonists, AMPAkinases, and drugs that induce the expression of glial glutamate transporters (riluzole) [for more details please read 48,49]. However, despite the therapeutic potential of these drugs, more information is still required for their broad clinical application in antidepressant therapy.

In conclusion, more than 50 years of research proposed that antidepressants should act on monoaminergic neurotransmission to produce their clinical effects. Based on these approach weeks to months would be necessary to their onset of action. Now, in the context of ketamine research it is clearly that a striking clinical improvement of depressive symptoms can be achieved within hours after ketamine administration. Furthermore, the antidepressant efficacy of ketamine does not depend on its direct action on monoamine targets. Overall, studies with ketamine allowed important advances in understanding the mechanisms involved in the pathophysiology of depression giving rise to the emergence of a new class of antidepressant medications, the rapid-acting antidepressants. Therefore, ketamine has proven to be a fundamental prototype for the development of new and improved alternatives for the treatment of depression that may have a transformative impact on the distress, disability, and public health burden associated with this disorder.

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