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UNDERSTANDING THE CONCEPT OF DEPRESSION AND PERSPECTIVES OF PHARMACOTHERAPEUTICS IN MODERN CONTEXT

Vikram Singh[1]* and Yogesh Kr. Sharma[1]

Maharaja Agrasen College of Pharmacy, Bharatpur 321205, Rajasthan, India.

***Corresponding Author: Vikram Singh**

Maharaja Agrasen College of Pharmacy, Bharatpur 321205, Rajasthan, India.

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ABSTRACT

Chronic, incapacitating depression is quite prevalent. Although beneficial, current pharmacotherapies suffer from significant percentages of little or no response and a lengthy therapeutic time lag. Rapid-acting antidepressants, such as the N-methyl-d-aspartate (NMDA) receptor (NMDAR) antagonist ketamine, that activate many signalling pathways in ways different from those of conventional antidepressants have been the subject of current study. Research into the neurobiology of ketamine and related substances has attracted a lot of attention because of the potential they show for drastically enhancing therapy choices for depressed people. In this article, we summarise what scientists know thus far about rapid-acting antidepressants and their effects on neurons, brain circuits, and signalling pathways.

KEYWORDS: AMPAR, GABAR, Major Depressive Disorder, mGluR, neural circuits.

INTRODUCTION

An estimated 5% of the world's population is living with major depressive disorder (MDD), making it the main cause of disability everywhere.[1] Depression not only has a devastating impact on individuals' lives, but it also costs the United States economy approximately $50 billion year[2] because to decreased productivity at work and increased medical expenses. However, only about a third of patients react to their first trial of any particular medicine, and it often takes antidepressants 6-8 weeks to demonstrate benefit, despite the widespread need for effective therapy. Even after trying many times, one third of depressive people still do not find relief with conventional antidepressants.[3] Not knowing the molecular processes behind antidepressant effects has been one of the main roadblocks to developing better drugs. But in the last two decades, major breakthroughs have started to solve this mystery.

It was first discovered that the anaesthetic drug ketamine, which had hitherto only been used in very high dosages, had an immediate antidepressant effect at low, subanesthetic levels.[4] Many individuals who have not responded to conventional antidepressants have symptom relief within hours. Importantly, unlike all other antidepressants on the market, which predominantly influence the transmission of serotonin and/or norepinephrine, this one primarily functions via glutamate. Rapid antidepressant effects have been seen in ketamine and a few other medications, leading researchers to reevaluate long-held hypotheses about the mechanisms by which antidepressants like these function. In order to reevaluate the effects of fast-acting drugs, new neuroscientific methods have revealed the underlying intracellular signals and neural networks.

This article will discuss the present state of research on antidepressant mechanisms of action, including major signalling pathways, the developing knowledge of the function of brain circuits, and the cutting-edge techniques and agents that are helping researchers comprehend these processes.

Brain pathology in depression

It is necessary to explore how the brains of depressed individuals vary from those who are not depressed in order to comprehend how antidepressants alleviate depressive symptoms. The many clinical manifestations that fulfil criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)[5] make it challenging to examine this subject. Different subgroups of individuals with MDD may have unique interactions amongst the mechanisms that have been hypothesised to cause depression. These mechanisms include abnormalities in inflammation[6], metabolism[7], and stress-response pathways.[8] Although the causes behind MDD are likely to be somewhat diverse, there are seem to be a few defining characteristics of the depressed state that serve as diagnostic markers.

Frontal cortex, cingulate cortex, and hippocampal volume have all been shown to be decreased in humans in neuroimaging studies related to mood regulation.[9] Grey matter is most affected, and there is evidence from both people and animals that a loss of glia is primarily responsible for this impact, along with a decrease in neuronal size.[10,11] A reduction in cortical grey matter volume[12] has been linked to a decrease in the number of synapses in the prefrontal cortex, which has been detected in postmortem tissue from depressive people. Several features of the stress response, including as the overproduction of glutamate due to elevated corticosteroids, the reduced expression of neurotrophic factors, and the enhanced activation of apoptotic signalling pathways, have been linked to glial and neuronal shrinkage.[13]

Rapid-acting antidepressants may be helpful in treating depression because glia are important regulators of glutamate neurotransmission and their disturbance leads to derangements in glutamatergic signalling. By sequestering glutamate after it has been released into the synapse, glia inhibit glutamate signalling. When this process breaks down, glutamate builds up outside of cells.[14] At sufficiently high concentrations, this extra glutamate binds not only to its primary postsynaptic targets, the -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors (NMDARs), but also to presynaptic metabotropic glutamate receptors (mGluRs). By decreasing postsynaptic glutamatergic signalling and synaptic connection, activation of these presynaptic metabotropic receptors decreases synaptic glutamate release.[15] Neuroimaging studies in humans support the concept that higher glutamate levels are associated with decreased functional connectivity in the anterior cingulate cortex.[16] In addition, effective therapy with deep brain stimulation (DBS) normalises increased activity in cingulate region 25 in depressive individuals.[17]

By stimulating extrasynaptic NMDARs, an excess of extracellular glutamate may potentially have detrimental consequences on connection. Rapid-acting antidepressants may work by stimulating a signalling cascade that begins at these receptors. Dendritic atrophy and dendritic-spine loss are caused by many factors, including phosphorylation of eukaryotic elongation factor-2 (eEF2) and decreased levels of brain-derived neurotrophic factor (BDNF).[14] Postmortem prefrontal cortex (PFC) of depressed subjects and rodent chronic stress models have shown an increase in REDD1, a negative regulator of the mammalian target of rapamycin complex 1 (mTORC1) pathway involved in synaptic protein synthesis.[18] Consistent with human research revealing synaptic loss and neuronal atrophy in MDD patients, animal models of depression have shown that dendritic structure degenerates as well.[12] Important insights into the mechanism of action of rapid-acting antidepressants, which alleviate those same deficiencies (Figure 1), may be gleaned from this model of glial loss leading to a reduction in connection and synaptic function.

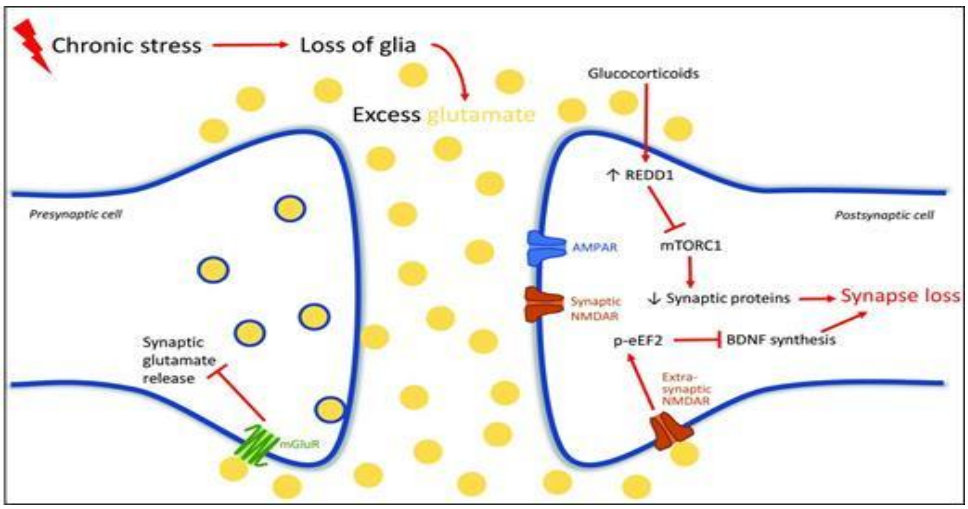

Figure 1: Mechanisms of Synapse Loss in Depression.

Mechanism of action of currently available antidepressants

In the 1950s, it was observed that medications that blocked the reuptake of monoamine neurotransmitters had antidepressant action, albeit the specific mechanism remained unknown. This observation sparked the study that would ultimately lead to the creation of the antidepressants in widespread use today. Since all of these medications worked by elevating synaptic levels of monoamines, it was widely believed that these higher concentrations of these chemicals were the secret to their success. Pharmacologists have been able to refine the first generation of monoaminergic antidepressants—monoamine reuptake inhibitors and tricyclics—but these drugs had undesirable side effects because of their lack of specificity in binding monoamines. Since their introduction in the late 1980s, selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-

reuptake inhibitors (SNRIs) have been widely considered the first-line therapy for depression.[19]

Although the monoamine theory established the foundation for most drug-discovery efforts in the subsequent 40 years, it had limitations that were difficult to rectify until advancements in the knowledge of depression pathophysiology emerged in the last two decades. Despite the fact that monoaminergic medications improve monoamine availability after a single effective dosage[20], the most disappointing clinical component of these treatments is the 6-8 week lengthy wait in the commencement of their antidepressant effects. The efficacy of these medications is clearly mediated by some mechanism other than elevated monoamine levels. In order to incorporate what is known about deficits of plasticity and connectivity in the depressed brain and the effect of rapid-acting agents on these pathways, the field had to move beyond the monoamine hypothesis after the discovery of ketamine's rapid-acting antidepressant activity.

Mechanism of action of ketamine

Ketamine, the most well-studied fast-acting antidepressant, is a significant improvement over monoaminergic agents not only due to its rapid onset but also because it alleviates depressive symptoms in patients who have not responded to other modalities, such as those who have not responded to electroconvulsive therapy and are therefore considered treatment-resistant.[21] But it has several limitations that prevent it from being widely used. In particular, it has misuse potential (particularly at larger dosages)[22] and induces dissociative and psychomimetic side effects in a significant percentage of patients in the immediate post-administration interval (1-2 h).[23] Worryingly, MRI studies have shown that those who regularly take large doses of ketamine have cortical shrinkage and neurotoxicity. Understanding how ketamine works in the brain is crucial for developing novel medicines that are safe for general use and might benefit from the drug's outstanding antidepressant characteristics.

The N-methyl-d-aspartate receptor (NMDAR) is an ionotropic glutamate receptor and a major transducer of glutamate signalling in the brain, and ketamine is an antagonist of this receptor. Studies in rodents have shown that its antidepressant effect is due in large part to a transitory burst of glutamate it causes in several brain areas immediately (30-60 min) after treatment, particularly in the medial prefrontal cortex (mPFC).[25] Further evidence for a function of glutamate-AMPA activity is provided by the fact that blocking AMPA receptors negates the drug's antidepressant effect.[26] The first difficulty in trying to understand how ketamine works is reconciling the fact that it increases glutamate signalling while being a medication that inhibits a glutamate receptor. The fact that ketamine preferentially binds to the NMDAR in its open conformation (Figure 2) may hold the key to understanding this seeming contradiction. It is hypothesised that low dosages of ketamine preferentially bind to NMDARs on -aminobutyric acid (GABA) interneurones due to the greater tonic firing rate of these neurons compared to pyramidal neurons. When the NMDAR is blocked, the inhibitory cells cannot do their job, and the tonic inhibition of glutamatergic pyramidal cell activity by interneurones is lifted.[8] By binding to all NMDARs, ketamine at higher concentrations inhibits glutamate signalling not only on interneurones but also on pyramidal neurones, interfering with the glutamate neurotransmission necessary to achieve an antidepressant effect.[25] This disinhibition hypothesis explains the observed glutamatergic effects of ketamine.

Disinhibition of pyramidal neurons causes a glutamate burst, which sets off postsynaptic signalling cascades that have effects on local networks in the prefrontal cortex and many other brain areas. Inhibiting AMPA receptors, the principal target of synaptic glutamate, also blocks ketamine's antidepressant effect.[26] By opening an ion channel, activation of AMPA receptors results in a depolarization of the postsynaptic cell. Depolarization triggers the opening of L-type voltage-gated calcium channels (VDCCs), which in turn stimulates the release of brain-derived neurotrophic factor (BDNF)[27], the binding of BDNF to its receptor tropomysin receptor kinase B (TrkB), and the activation of the mTORC1 signalling pathway through TrkB.[28,29] In order for ketamine to exert its antidepressant effects, it must first and foremost activate the chemical signals that stimulate the formation of dendritic spines and the plasticity of synapses.

Because of their shared involvement in varying aspects of energy metabolism and cell growth control (Figure 2)[30], the signalling cascades that precede and follow BDNF release and mTORC1 activation are complex and intertwined. It has been shown that ketamine's antidepressant impact is mediated via a number of key mediators of these pathways. Activation of eEF2 kinase (eEF2K), which normally phosphorylates its target protein, eEF2, in response to spontaneous synaptic glutamate release (as opposed to action potential evoked release), is inhibited by ketamine, as shown by Autry and colleagues.[31] This promotes the induction of BDNF synthesis in the hippocampus. Ketamine blocks NMDARs, preventing the transmission of the signal that causes eEF2K to be activated in response to glutamate that has been generated spontaneously. Inhibition of BDNF production by phosphorylated eEF2 is alleviated by ketamine's NMDA antagonism.[32] Although separate from the pyramidal-cell disinhibition theory, this action of NMDAR antagonism may constitute a supplementary mechanism. Autry and colleagues[31] and a few others[34] have observed that ketamine had no impact on mTORC1 signalling, in contrast to our earlier work and results from numerous other research groups.[28,33] The phosphorylation of mTORC1 signalling proteins is dynamic and state dependent, so it's possible that a

number of factors, such as the animals' exposure to uncontrolled stress, species, brain region, method of dissection, and method of tissue preparation (crude homogenates versus synaptosome-enriched preparations), are to blame for this discrepancy.

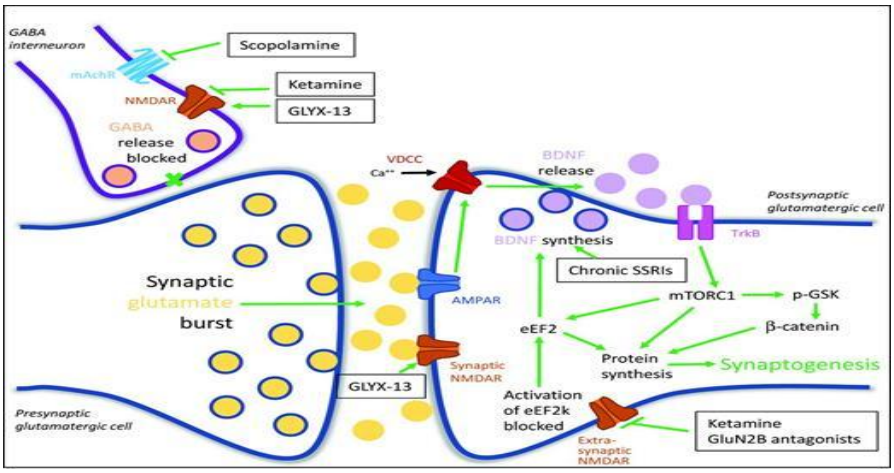

Figure 2: Signaling Pathways Involved in The Response to Rapid-Acting Antidepressants.

Numerous studies have looked into the role of NMDARs containing the GluN2B subunit, which is selectively activated by spontaneous glutamate release (in contrast to GluN2A subunits, which respond to action potential evoked glutamate), lending credence to the hypothesis that ketamine's antidepressant effects are derived, at least in part, from blocking the response to spontaneous glutamate release. Researchers have shown that GluN2B-selective antagonists have immediate antidepressant effects in rat models[26,28] and in depressed individuals.[35] Hall and colleagues found that GluN2B-selective inhibition produces a robust antidepressant response that occludes the antidepressant effect of ketamine by using a conditional knockout to remove the GluN2B subunit selectively from cortical pyramidal neurones; however, these knockout mice also display hyperlocomotor activity, making it difficult to interpret these behavioural findings.[36] Not only do GluN2B subunits activate in response to distinct glutamate release patterns, but they also seem to be more abundant in a distal region of the postsynaptic neuron[37], and they convey a distinct set of intracellular signals. It seems that the plasticity-inducing effects of glutamate neurotransmission are throttled by GluN2B-mediated signals, in particular at extrasynaptic NMDARs. Conditional deletion of GluN2B eliminates this barrier, allowing ketamine's effects on BDNF production and mTORC1 activation to be more easily concealed.[36] Inhibition of hyperactive extrasynaptic NMDARs containing GluN2B may have distinct behavioural implications, despite the fact that ketamine does not preferentially bind to one GluN2 isoform over the other.

The glycogen synthase kinase (GSK) pathway (shown in Figure 2) is another mechanism by which ketamine regulates plasticity. To regulate the creation of new dendritic spines and other kinds of cellular plasticity, GSK regulates the degradation of -catenin. Inactivating GSK by phosphorylation increases -catenin availability.[30] Rapidly increasing GSK phosphorylation is an action required for ketamine's antidepressant impact.[38] This impact may be a result of BDNF release, which increases Akt, a protein that phosphorylates GSK, or it may be the result of mTORC1 activity, which activates S6 kinase, a protein that phosphorylates GSK.[30] However, the exact mechanism of this effect remains unclear.

The long-held belief that NMDA antagonism is ketamine's functional mechanism has recently been challenged by studies showing that just one metabolite of racemic (R,S) ketamine, (2R,6R)-hydroxynorketamine (HNK), is enough to elicit a strong antidepressant response, despite contrary reports that HNK lacks binding affinity for the NMDAR.[34] This enantiomer of HNK, like racemic ketamine, has been demonstrated to rapidly boost glutamate signalling and install AMPA receptors into cell membranes.[39] New data, however, from another lab suggests that HNK may function at NMDARs, although at greater dosages.[40] HNK may be more tolerated by depressed patients than ketamine itself is due to its lower side effects in rodent models, even though HNK operates through NMDARs.

Ketamine stimulates translation of the proteins necessary to establish new synapses, such as the AMPA receptor subunit GluA1[41], and hence increases synaptic plasticity and dendritic spine formation. Loss of dendritic spines is a hallmark of the depressed brain, and ketamine treatment restores this loss within 24 hours in rodent models of depression generated by chronic stress.[42] Ketamine's antidepressant effect relies on the simultaneous stimulation of mTORC1 and the release of brain-derived neurotrophic factor (BDNF).[43] Multiple ketamine-influenced signalling pathways seem to converge on a crucial mechanism involved in the repair of synaptic plasticity.

Mechanisms of action of other rapid-acting antidepressants

Understanding the required and sufficient circumstances to alleviate depression may be strengthened by comparing how the mechanisms of ketamine and other antidepressants align or vary. In the last 20 years, researchers have identified a number of fast-acting antidepressants, some of which are just as effective as ketamine. Although they all accomplish the same goal—increased plasticity and synaptogenesis—they do so in different ways (Figure 2).

Several drugs that bind to NMDARs in ways that are most comparable to ketamine. Antidepressant effects of GluN2B selective modulators have been observed in both human patients with depression[35] and animal models.[26,28] To learn how effective these medications are in depressed individuals, we need further clinical trials. GLYX-13, a tetrapeptide generated from an antibody against the NMDAR, is another intriguing molecule. Similar to a partial agonist at the glycine location, GLYX-13 acts as an allosteric modulator of the NMDAR complex. It operates as a modulator and has a more selective binding profile, which may explain why it has a quick antidepressant effect with fewer adverse effects than ketamine. Similarly to ketamine, GLYX-13 boosts mTORC1 signalling and synapse quantity and function in the PFC.[33] To increase synaptic plasticity, GLYX-13 may operate either directly at postsynaptic NMDARs, like ketamine, or indirectly through NMDARs on GABA interneurones. This issue is presently being investigated by researchers. Clinical studies are now ongoing to more completely analyse the overall efficacy of GLYX-13 as a rapid-acting antidepressant than ketamine.[35]

At dosages as low as 4 micrograms per kilogramme (g/kg)[44], scopolamine, an antagonist at the muscarinic acetylcholine receptor (mAchR), has been shown to have a fast antidepressant effect in people. Scopolamine, like ketamine, increases mTORC1 signalling and the development of new dendritic spines in the medial prefrontal cortex (mPFC).[45] Interneurons are known to produce mAchRs, and it has been hypothesised that blocking these receptors, like ketamine blocking NMDARs, might disinhibit pyramidal cells.[39] Wohleb et al.[46] used viral-mediated silencing of the M1-AchR in either GABAergic or glutamatergic cells to show that the antidepressant effect of scopolamine required only the M1-AChRs on GABAergic interneurones.

It's also important to note that ketamine and monoaminergic antidepressants share some molecular effects, which suggests that the latter may make use of the same plasticity-dependent mechanisms that ketamine does, albeit in a roundabout and inefficient fashion that causes them to exert their antidepressant effect much more slowly. The antidepressant effects of ketamine[47] and fluoxetine[48], an SSRI, are prevented in mice engineered to produce a mutant version of BDNF that hinders its expression. The agents vary in how they affect BDNF, however: Ketamine promotes fast, activity-dependent release of BDNF[27] and enhanced expression of BDNF[31] after a single dosage, while usual antidepressant drugs only raise the expression but not the release of BDNF, and this happens only after chronic treatment for at least 2 weeks.[49,50]

Neural circuits involved in the function of rapid-acting antidepressants

New technologies, like as optogenetics, which allow for the manipulation of particular brain circuits, are allowing for a clearer understanding of the circuit level effects of antidepressants by shedding light on the intracellular signalling pathways engaged by these drugs. Correspondents of the human brain's mood-regulating cortical-limbic system have been found in non-human primates and rodent[51] thanks to years of study. The medial prefrontal cortex (mPFC) is an essential component of the limbic system and a major regulator of other limbic regions involved in emotion regulation. Emotional self-reflection and other self-referential behaviours are hypothesised to involve the medial prefrontal cortex (mPFC) in humans.[52] Depression's negative effects on self-evaluation, such as increased guilt and a diminished sense of value, may originate in the malfunctioning of the prefrontal cortex. DBS research has focused heavily on the mPFC's role in depression since this therapy involves implanting electrodes into the brain and setting them to constantly stimulate at a high frequency to alleviate depressive symptoms as well as other cognitive and affective ones. Subgenual cortex, a region of medial prefrontal cortex (mPFC) that is hyperactive in depressive patients compared with controls as determined by fMRI[53,54], has found to be the most consistently successful electrode insertion. Delivery of DBS to the cortex lowers the excess glutamate associated with depression.[55] DBS inactivates targeted axons by diminishing the presynaptic neurotransmitter pool.

Recent research has shown that ketamine-like synaptic and antidepressant behavioural responses may be induced in rats using optogenetic activation of glutamatergic neurones in the mPFC, with a time course and intensity comparable to that of ketamine. In addition, a direct infusion of ketamine into the rat infralimbic cortex, which is thought to be a correlate of the human mPFC, was sufficient to produce an antidepressant effect similar to that achieved when the drug is given systemically, and neuronal silencing of infralimbic PFC blocks the effect of systemic ketamine.[56] These investigations show that glutamatergic neurons in the medial prefrontal cortex (mPFC) are essential for ketamine's antidepressant effect to take place.

Given that pyramidal neurones in the mPFC transmit axons to many other parts of the brain, including the dorsal raphe nucleus (DRN) and hippocampus, researchers have started to investigate the significance of

glutamatergic projections from the mPFC to these and other brain regions. Optogenetic stimulation of DRN axon terminals has been used in conjunction with behavioural analysis to study the mPFC to DRN projection. In rodents, activating this projection has been shown to have an immediate antidepressant effect.[57] Using optogenetic stimulation, we discovered that activating PFC terminals in the DRN leads to a more sustained antidepressant response in the FST 24 hours later.[58] Further research showed that ketamine injected into the mPFC has an antidepressant effect, and that mPFC-injected ketamine causes neuronal activity in the DRN as measured by cFos expression.[59] Taken as a whole, these data raise the possibility that ketamine's antidepressant effect depends on activation of the medial prefrontal cortex to dopamine reward network projection.

Ketamine's antidepressant impact may possibly be related to its location in the ventral hippocampus. Recent research has used DREADDs (designed receptors uniquely triggered by designer pharmaceuticals) to stimulate the ventral hippocampus to medial prefrontal cortex pathway, therefore simulating the antidepressant effects of ketamine. It was also shown that the impact of ketamine might be reversed by the pharmacological or optogenetic inhibition of this route.[60] These findings are in line with previous research demonstrating that ketamine also increases mTORC1 and BDNF expression in the prefrontal cortex of rats, suggesting that ketamine also increases plasticity in the hippocampus. These investigations provide preliminary insights into the effects of ketamine-induced plasticity on particular brain regions and circuits; nevertheless, a detailed picture of the neural circuitry underpinning ketamine's action has yet to emerge.

CONCLUSION

Since the discovery of fast-acting antidepressants and glutamate's central role, the scientific community has come a long way in its knowledge of the mechanisms of antidepressants. There is still a lack of complete understanding of the intracellular signals that are responsible for the efficacy of fast-acting antidepressants. Researchers may soon be able to test predictions concerning the development of ketamine's impact, from NMDA antagonism to BDNF release and mTORC1 activation to synaptogenesis, thanks to more precise and subtle genetic changes in mice. With the advent of cell-type-specific viral vector systems and genetic changes, there will be even more opportunities for research into the cells that mediate these effects and how they alter the local circuits. These methods should help us better understand whether ketamine primarily works by blocking spontaneous glutamate transmission through GluN2B-containing NMDARs or by disinhibiting pyramidal cells. Finally, recent developments in optogenetic and chemogenetic methods are shedding light on the action of antidepressants by revealing the participation of certain circuits.

Conflict of interest

No conflict of interest is declared.

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REFERENCES

1. Ferrari A.J., Charlson F.J., Norman R.E., Patten S.B., Freedman G., Murray C.J.L. et al Burden of depressive disorders by country, sex, age, and year: findings from the Global Burden of Disease Study 2010. PLOS Med., 2013; 10: e1001547
2. Wang P.S., Simon G. and Kessler R.C. The economic burden of depression and the cost-effectiveness of treatment. Int. J. Methods Psychiatr. Res., 2003; 12: 22–33.
3. Gaynes B.N., Warden D., Trivedi M.H., Wisniewski S.R., Fava M. and Rush A.J. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr. Serv., 2009; 60: 1439–1445.
4. Berman R.M., Cappiello A., Anand A., Oren D.A., Heninger G.R., Charney D.S. et al Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry, 2000; 47: 351–354.
5. American Psychiatric Association. (2013) Diagnostic and Statistical Manual of Mental Disorders: DSM-5, American Psychiatric Association, Washington, D.C.
6. Iwata M., Ota K.T. and Duman R.S. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. Brain Behav. Immun., 2012; 31: 105–114.
7. Abdallah C.G., Jiang L., De Feyter H.M., Fasula M., Krystal J.H., Rothman D.L. et al Glutamate metabolism in major depressive disorder. Am. J. Psychiatry, 2014; 171: 1320–1327.
8. Duman R.S. Neurobiology of stress, depression, and rapid acting antidepressants: remodeling of synaptic connections. Depress. Anxiety, 2014; 31: 291–296.
9. Arnone D., McIntosh A.M., Ebmeier K.P., Munafò M.R. and Anderson I.M. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur. Neuropsychopharmacol., 2012; 22: 1–16.
10. Rajkowska G., Miguel-Hidalgo J.J., Wei J., Dilley G., Pittman S.D., Meltzer H.Y. et al Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol. Psychiatry, 1999; 45: 1085–1098.
11. Treadway M.T., Waskom M.L., Dillon D.G., Holmes A.J., Park M.T.M., Chakravarty M.M. et al Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression. Biol. Psychiatry, 2015; 77: 285–294.

12. Kang H.J., Voleti B., Hajszan T., Rajkowska G., Stockmeier C.A., Licznerski P. et al Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat. Med., 2012; 18: 1413–1417
13. Banasr M., Dwyer J.M. and Duman R.S. Cell atrophy and loss in depression: reversal by antidepressant treatment. Curr. Opin. Cell Biol., 2011; 23: 730–737.
14. Krystal J.H., Sanacora G. and Duman R.S. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol. Psychiatry, 2013; 73: 1133–1141.
15. Bonansco C., Couve A., Perea G., Ferradas C.Á., Roncagliolo M. and Fuenzalida M. Glutamate released spontaneously from astrocytes sets the threshold for synaptic plasticity. Eur. J. Neurosci., 2011; 33: 1483–1492.
16. Horn D.I., Yu C., Steiner J., Buchmann J., Kaufmann J., Osoba A. et al Glutamatergic and resting-state functional connectivity correlates of severity in major depression - the role of pregenual anterior cingulate cortex and anterior insula. Front. Syst. Neurosci., 2010; 4. https://doi.org/10.3389/fnsys.2010.00033. Google Scholar
17. Mayberg H.S., Lozano A.M., Voon V., McNeely H.E., Seminowicz D., Hamani C. et al (2005) Deep brain stimulation for treatment-resistant depression. Neuron, 45: 651–660
18. Ota K.T., Liu R.-J., Voleti B., Maldonado-Aviles J.G., Duric V., Iwata M. et al REDD1 is essential for stress-induced synaptic loss and depressive behavior. Nat. Med., 2014; 20: 531–535.
19. López-Muñoz F. and Alamo C. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. Curr. Pharm. Des., 2009; 15: 1563–1586.
20. Sanacora G., Treccani G. and Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology, 2012; 62: 63–77.
21. Ibrahim L., Diazgranados N., Luckenbaugh D.A., Machado-Vieira R., Baumann J., Mallinger A.G. et al Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2011; 35: 1155–1159.
22. Mahapatra DK, Bharti SK. Medicinal chemistry with pharmaceutical product development. CRC Press; 2019.
23. Zhang Y., Xu Z., Zhang S., Desrosiers A., Schottenfeld R.S. and Chawarski M.C. Profiles of psychiatric symptoms among amphetamine type stimulant and ketamine using inpatients in Wuhan, China. J. Psychiatr. Res., 2014; 53: 99–102.
24. Wang C., Zheng D., Xu J., Lam W. and Yew D.T. Brain damages in ketamine addicts as revealed by magnetic resonance imaging. Front. Neuroanat., 2013; 7: 23.
25. Moghaddam B., Adams B., Verma A. and Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J. Neurosci., 1997; 17: 2921–2927.
26. Maeng S., Zarate C.A. Jr, Du J., Schloesser R.J., McCammon J., Chen G. et al Cellular mechanisms underlying the antidepressant effects of ketamine: role of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol. Psychiatry, 2008; 63: 349–352.
27. Lepack A.E., Fuchikami M., Dwyer J.M., Banasr M. and Duman R.S. BDNF release is required for the behavioral actions of ketamine. Int. J. Neuropsychopharmacol., 2014; 18: pyu033.
28. Li N., Lee B., Liu R.-J., Banasr M., Dwyer J.M., Iwata M. et al mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science, 2010; 329: 959–964.
29. Jourdi H., Hsu Y.-T., Zhou M., Qin Q., Bi X. and Baudry M. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. J. Neurosci., 2009; 29: 8688–8697.
30. Duman R.S. and Voleti B. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci., 2012; 35: 47–56.
31. Autry A.E., Adachi M., Nosyreva E., Na E.S., Los M.F., Cheng P.-F. et al NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature, 2011; 475: 91–95.
32. Monteggia L.M., Gideons E. and Kavalali E.T. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. Biol. Psychiatry, 2013; 73: 1199–1203.
33. Liu R.-J., Duman C., Kato T., Hare B., Lopresto D., Bang E. et al GLYX-13 produces rapid antidepressant responses with key synaptic and behavioral effects distinct from ketamine. Neuropsychopharmacology, 2017; 42: 1231–1242.
34. Zanos P., Moaddel R., Morris P.J., Georgiou P., Fischell J., Elmer G.I. et al NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature, 2016; 533: 481–486. http://doi.org/10.1038/nature17998.
35. Preskorn S., Macaluso M., Mehra D.O.V., Zammit G., Moskal J.R., Burch R.M. et al Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. J. Psychiatr. Pract., 2015; 21: 140–149.
36. Miller O.H., Yang L., Wang C.-C., Hargroder E.A., Zhang Y., Delpire E. et al GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. Elife, 2014; 3: e03581.

37. Hardingham G.E. and Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nat. Rev. Neurosci., 2010; 11: 682–696.
38. Beurel E., Song L. and Jope R.S. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. Mol. Psychiatry, 2011; 16: 1068–1070.
39. Wohleb E.S., Gerhard D., Thomas A. and Duman R.S. Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. Curr. Neuropharmacol., 2016; 15: 11–20.
40. Suzuki K., Nosyreva E., Hunt K.W., Kavalali E.T. and Monteggia L.M. Effects of a ketamine metabolite on synaptic NMDAR function. Nature, 2017; 546: E1–E3.
41. Duman R.S., Aghajanian G.K., Sanacora G. and Krystal J.H. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat. Med., 2016; 22: 238–249.
42. Li N., Liu R.-J., Dwyer J.M., Banasr M., Lee B., Son H. et al Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol. Psychiatry, 2011; 69: 754–761.
43. Duman R.S. and Aghajanian G.K. Synaptic dysfunction in depression: potential therapeutic targets. Science, 2012; 338: 68–72.
44. Furey M.L. and Drevets W.C. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Arch. Gen. Psychiatry, 2006; 63: 1121–1129.
45. Voleti B., Navarria A., Liu R.-J., Banasr M., Li N., Terwilliger R. et al Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. Biol. Psychiatry, 2013; 74: 742–749.
46. Wohleb E.S., Wu M., Gerhard D.M., Taylor S.R., Picciotto M.R., Alreja M. et al GABA interneurons mediate the rapid antidepressant-like effects of scopolamine. J. Clin. Invest., 2016; 126: 2482–2494.
47. Liu R.-J., Lee F.S., Li X.-Y., Bambico F., Duman R.S. and Aghajanian G.K. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. Biol. Psychiatry, 2012; 71: 996–1005.
48. Bath K.G., Jing D.Q., Dincheva I., Neeb C.C., Pattwell S.S., Chao M.V. et al BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity. Neuropsychopharmacology, 2012; 37: 1297–1304.
49. Nibuya M., Morinobu S. and Duman R.S. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J. Neurosci., 1995; 15: 7539–7547.
50. Li G., Jing P., Liu Z., Li Z., Ma H., Tu W. et al (2017) Beneficial effect of fluoxetine treatment aganist psychological stress is mediated by increasing BDNF expression in selected brain areas. Oncotarget, https://doi.org/10.18632/oncotarget.17891 Google Scholar
51. Price J.L. and Drevets W.C. Neurocircuitry of mood disorders. Neuropsychopharmacology, 2009; 35: 192–216. Google Scholar Crossref
52. Beer J.S., Lombardo M.V. and Bhanji J.P. Roles of medial prefrontal cortex and orbitofrontal cortex in self-evaluation. J. Cogn. Neurosci., 2010; 22: 2108–2119.
53. Mayberg H.S., Lozano A.M., Voon V., McNeely H.E., Seminowicz D., Hamani C. et al Deep brain stimulation for treatment-resistant depression. Neuron, 2005; 45: 651–660.
54. Holtzheimer P.E. and Mayberg H.S. Deep brain stimulation for psychiatric disorders. Annu. Rev. Neurosci., 2011; 34: 289–307.
55. Iremonger K.J., Anderson T.R., Hu B. and Kiss Z.H.T. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J. Neurophysiol., 2006; 96: 613–621.
56. Fuchikami M., Thomas A., Liu R., Wohleb E.S., Land B.B., DiLeone R.J. et al Optogenetic stimulation of infralimbic PFC reproduces ketamine's rapid and sustained antidepressant actions. Proc. Natl. Acad. Sci. U.S.A., 2015; 112: 8106–8111.
57. Warden M.R., Selimbeyoglu A., Mirzabekov J.J., Lo M., Thompson K.R., Kim S.-Y. et al A prefrontal cortex-brainstem neuronal projection that controls response to behavioural challenge. Nature, 2012; 492: 428–432.
58. Thomas A.M., Hare B., Kato T., Fukumoto K., Liu R.-J., Aghajanian G.K. et al (2017) The Role of Medial Prefrontal Cortex Glutamatergic Projections in the Antidepressant Effect of Ketamine, Society for Neuroscience Annual Meeting, Washington, D.C.
59. Fukumoto K., Iijima M. and Chaki S. The antidepressant effects of an mGlu2/3 receptor antagonist and ketamine require AMPA receptor stimulation in the mPFC and subsequent activation of the 5-HT neurons in the DRN. Neuropsychopharmacology, 2015; 41: 1046–1056.
60. Carreno F.R., Donegan J.J., Boley A.M., Shah A., DeGuzman M., Frazer A. et al Activation of a ventral hippocampus-medial prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. Mol. Psychiatry, 2016; 21: 1298–1308.
61. Zhou W., Wang N., Yang C., Li X.M., Zhou Z.Q. and Yang J.J. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur. Psychiatry, 2014; 29: 419–423.