Review article

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

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Abstract

Chronic, incapacitating depression is quite prevalent. Although beneficial, current pharmacotherapies suffer from significant percentages of little/ no response and a lengthy therapeutic time lag. Rapid-acting antidepressants, such as the N-methyl-d-aspartate receptor (NMDAR) antagonist Ketamine, that activate many signaling pathways in ways different from those of conventional antidepressants containing are currently under investigation. Research into the neurobiology of ketamine and similar substances have attracted more attention because of potential they show for drastically enhancing therapy choices for depressed people. In this article, we summarise what scientists know thus far about fast-acting antidepressants and its effects neurons, brain circuits, and signaling pathways.

Introduction

Approximately five percent of the world's population is living with MDD, making it the main reason for disability everywhere [1]. Depression not only has a devastating impact on individuals' lives, but it also costs the US economy approximately $50 billion a year [2] because of decreased productivity at work and increased medical expenses. However, only about every 3rd patients react to their 1st trial of any particular medicine, and it often takes antidepressants 6 to 8 weeks to demonstrate benefit, even if good treatment is needed. Even after many tries, one-third of depressive people still don't 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.

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However, in the last 2 decades, major discoveries have started to solve this mystery.

It was first discovered that the anesthetic drug ketamine, only used so far in very high dosages, had an immediate effect of antidepressants at low, subanaesthetic levels [4]. More individuals which have not responded to conventional antidepressants have symptom relief within hours. The present article discusses the present level of research on antidepressant mechanisms of action, including major signaling pathways, developing knowledge of brain's function circuits, and the cutting edge techniques and drugs that are supporting researchers comprehend these processes.

Brain pathology during the depression

It is necessary to explore how depressed brain individuals differ from those who are not depressed to comprehend how medicines alleviate depressive symptoms. The many clinical manifestations that meet the criteria for MDD according to DSM of Mental Disorders [5] make it challenging to examine this subject. Varying subgroups of patients with MDD may have unique interactions among hypothesized mechanisms leading to depression. These mechanisms include abnormalities in metabolism [7], stress-response pathways [8], and inflammation [6]. Although the causes behind MDD are likely to be somewhat diverse, it seem to be some defining features of a depressive state that may lead to diagnosis markers.

The cingulate cortex, frontal cortex, and hippocampal volume are decreased in humans in neuroimaging studies related to mood regulation [9]. Grey matter is most affected, and there is evidence from people and animals that a glia loss is primarily responsible for this impact, along with a decrease in neuronal size [10, 11]. A reduction in cortical gray matter volume [12] is associated with reduced synapse number in the prefrontal cortex, detected in post-mortem tissues of depressed patients. The stress response's features including the overproduction of glutamate due to elevated corticosteroids, decrease in neurotrophic factors and increased activity of apoptotic signaling pathways are met with glial and neuronal atrophy [13].

Rapid-acting antidepressants may be helpful in treating depression because glia is an important glutamate neurotransmission regulator and their disturbance is caused by disruption of glutamate signaling. By retaining glutamate after it enters the synapse, glia inhibits glutamate signaling. When this process collapses, glutamate builds up outside of cells [14]. At

sufficiently high concentrations, this extra glutamate binds not only to its primary postsynaptic targets, the AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-d-aspartate) receptors (NMDARs) but also to presynaptic mGluRs (metabotropic glutamate receptors). By decreasing postsynaptic glutamatergic signaling and synaptic connection, activation of presynaptic metaboreceptors reduces synaptic glutamate release [15]. Neuroimaging studies in human support the idea is that higher levels of glutamate are met with decreased connectivity in anterior cingulate cortex. [16]. Additionally, deep brain stimulation (DBS) normalizes activity in the cingulate region 25 in depressive individuals [17].

By stimulating extrasynaptic NMDARs, an excess of extra-cellular glutamate may potentially have detrimental consequences on connection. Rapid-acting antidepressants may work by stimulating a signaling cascade that begins at these receptors. Dendritic-spine loss and dendritic atrophy are caused by many factors, including eEF2 phosphorylation and decreased levels of BDNF [14]. The rodent chronic stress model and post-mortem prefrontal cortex of depressed subjects showed an increase in DNA damage response 1, a negative regulator of mTORC1 pathway implied in synaptic protein synthesis. [18]. Consistent with human research revealing synaptic loss and neuronal atrophy in MDD patients, depressed animal models have put that dendritic structure degenerates as well [12]. Important information about the MOA of fast-acting antidepressants, which alleviate those same deficiencies means synapse loss mechanisms (Figure 1), may be gleaned from this glial pattern decreases in connection and synaptic function.
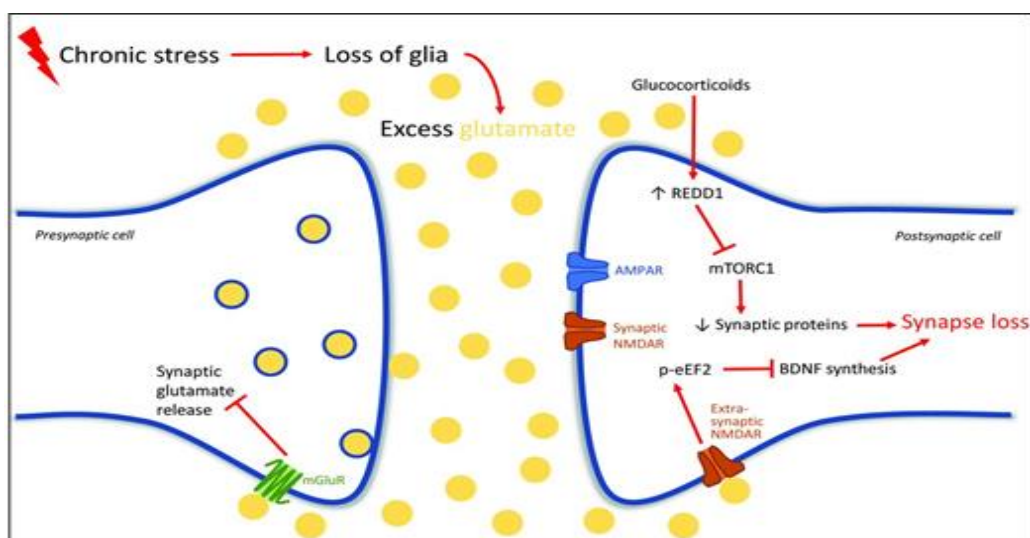

Figure 1. In depression, synapse loss mechanisms

MOA of presently available antidepressants

It was observed in the year 1950 that medications that blocked the monoamine neurotransmitter's reuptake had antidepressant action, albeit the specific mechanism remained unknown. This observation sparked the research and ultimately led to the creation of anti-depressants in widespread use today. Since all of these medications worked by elevating monoamine's synaptic levels. It is generally believed that more of these chemicals were the secret to their success. Pharmacologists have been capable of refining the first generation of monoaminergic antidepressants and tricyclics-but these drugs had undesirable side effects because of their lack of specificity in binding monoamines. Since their introduction in the late year 1980s, SSRIs and SNRIs have been widely considered the first-line therapy for depression [19].

Although the monoamine theory established the foundation for almost drug invention efforts in subsequent 40 years, this had limitations that were problems to rectify until advancements in the knowledge of pathophysiology of depression emerged in the last two decades. Even though monoaminergic medications improve monoamine availability after one effective dosage [20], the most disappointing clinical component of these treatments is the 6-8 week lengthy wait for the commencement of its antidepressant effects. The efficacy of these medications are mediated through some mechanism other than elevated monoamine levels. This rapid coupling of plastic and negative connections in depressed brain with the drugs effects requires field to do   more on   monoamine hypothesis following the investigation of ketamine's rapid antidepressant effect.

MOA of Ketamine

Ketamine, the most well-studied fast-acting antidepressant, is a significant advancement over monoaminergic drugs not only due to their rapid onset but also because it alleviates depressive symptoms in patients those do not respond to other changes, such as those do not respond to therapy of electroconvulsive and are therefore considered treatment resistant. [21]. However it has many disadvantages that stop it from being widely used. In particular, it has misuse potential (particularly at larger dosages) [22] and causes psychomimetic and dissociative side effects in the instant post-consumption period (1-2 h) in a significant number of patients [23]. Worryingly, Magnetic Resonance Imaging studies have met that those who regularly take high doses of ketamine have cortical shrinkage and neurotoxicity. Understanding how ketamine works in the brain is crucial for developing new agents which are safely for general use and might be useful from the drug's outstanding antidepressant characteristics.

The N-methyl-d-aspartate receptor (NMDAR) is a major transducer of glutamate signaling in brain and ionotropic glutamate receptor, and ketamine is a receptor antagonist. Studies in

rodents have found that their 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 mPFC [25]. Next evidence for the function of glutamate-AMPA activity is provided by the factuality of blocking AMPA receptors negates the drug's antidepressant effect [26]. 1st difficulty in trying to recognize how ketamine works is reconciling the fact that it increases glutamate signaling while being a medication that inhibits a glutamate receptor. Figure-2, The preferential binding of ketamine to NMDAR in its exposed conformation may be key to understanding this seeming contradiction.
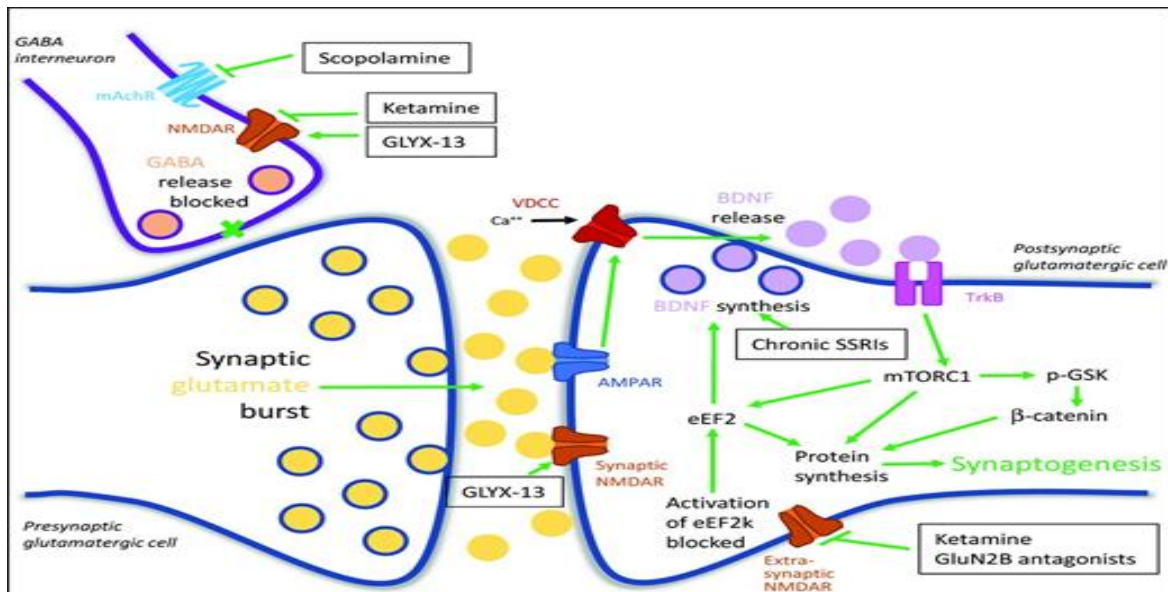

Figure 2: Pathways of Signaling associated with the respond to fast-acting antidepressants.

For example, low doses of ketamine bind preferentially to NMDAR of γ-Aminobutyric acid interneurons because these neurons have a more tonic firing rate compared to pyramidal neurons. When the NMDAR is blocked, the inhibitory cells cannot do their job, and glutamatergic pyramidal cell activity inhibition by interneurons is lifted [8]. By binding to all NMDARs, at higher doses, ketamine inhibits signaling of glutamate not only in interneurons but also in pyramidal neurons, so interference with glutamate neurotransmission is required to complete an antidepressant effect [25]. This disinhibition decision explains ketamine's glutamatergic effects.

Pyramidal neuron disinhibiting causes a glutamate burst, which sets off postsynaptic signaling issues that have effects on local networks in PFC and many other brain areas. Inhibiting AMPA receptors, the principal synaptic glutamate target also blocks ketamine's antidepressant effect [26]. By opening an ion channel, activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors results in postsynaptic cell depolarization. L-type VDCCs depolarization triggers the opening which in turn stimulates BDNF release [27], the BDNF binds to the receptor tropomyosin receptor kinase B and activates pathways of

mTORC1 signaling through TrkB [28, 29]. For ketamine to exert its antidepressant effects, it must first and foremost activate the chemical signals that stimulate dendritic spine formation and the plasticity of synapses.

Because of their shared involvement in cell growth control and varying aspects of energy metabolism (Figure 2) [30], the signaling issues that precede and follow BDNF release and mTORC1 activation are complex and intertwined. Ketamine's antidepressant impact is mediated via several key pathways. By eEF2 kinase (eEF2K) activation normally phosphorylates its target protein eEF2 in response to spontaneous synaptic glutamate release (except for action potential-evoked release), which is inhibited by ketamine, as shown by Autry et.al [31]. This assists in the induction of BDNF synthesis in the hippocampus. Ketamine blocks NMDARs, preventing the transmission of the signal that causes eEF2K to be activated concerning glutamate that has generated spontaneously. Inhibition of BDNF production by phosphorylated eEF2 is alleviated by ketamine's NMDA antagonism [32]. Although separate from pyramidal cell disinhibition theory, this action of N-methyl-D-aspartate antagonism may constitute a supplementary mechanism. Autry et. al [31] and some more [34] observed that ketamine had no impact on mTORC1 signaling, in contrast to our earlier work and results from numerous groups of research [28,33]. The mTORC1 signaling protein's phosphorylation is state-dependent and dynamic, so it's possible that many factors, such as animals' exposure to uncontrolled stress, species, brain region, method of dissection, and method of tissue preparation (synaptosome-enriched preparations versus crude homogenates), are to blame for this discrepancy.

Many studies have researched the NMDAR role containing the GluN2B subunit, which is activated by glutamate release (such as opposed to the GluN2A subunit, which responds to stimulated glutamate), lending credence to the hypothesis that antidepressant ketamine's effects are derived, at least in part, to planned glutamate release from blocking the response. Researchers have seen that GluN2B-selective antagonists have immediate antidepressant effects in rat models [26, 28] and depressed individuals [35]. Hall et.al found that selective inhibition of GluN2B potentiates the anti-depressant response, and selective deletion removes GluN2B subunit from the cortical pyramidal neurons, thereby blocking ketamine effects; however, these knockout mice display more motor deficits, making these behaviors difficult to explain [36]. Not only do GluN2B subunits activate concerning distinct glutamate release patterns, but they also appear to be more abundant in a distal region of postsynaptic neuron [37], and they convey a distinct intracellular signal's set. It seems that the plasticity-inducing glutamate neurotransmission effects 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 GluN2B consisting of NMDARs may have distinct behavioral implications, although ketamine doesn't bind preferentially to one isoform of GluN2 over another.

The Glycogen Synthase Kinase pathway (shown in Figure 2) is another mechanism besides ketamine regulates plasticity. To regulate the novel dendritic spine creation and other kinds of cellular plasticity, GSK regulates the loss 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 can be a result of BDNF release, which increases Akt, the protein that phosphorylates GSK, or this can be the result of mTORC1 activity activating S6 kinase, a protein that phosphorylates GSK [30]. However, the exact mechanism of this effect remains unclear.

The long-held belief that N-methyl-D-aspartate antagonism is ketamine's functional mechanism has currently been challenged by studies showing that just one metabolite of racemic (R, S) ketamine, (2R,6R)-hydroxynorketamine, is enough to obtain a strong antidepressant response, despite contrary reports that HNK lacks binding affinity for N-methyl-D-aspartate receptor [34]. This enantiomer of HNK, like racemic ketamine, has been demonstrated to rapidly boost glutamate signaling and install AMPA receptors into cell membranes [39]. New data, however, from another lab suggests that (2R, 6R)-hydroxynorketamine may function at N-methyl-D-aspartate receptors, although at greater dosages [40]. HNK may be better tolerated than ketamine by patients with depression because it has fewer side effects in rodent models, even though HNK operates through NMDARs.

Ketamine stimulates the translation of proteins required to form new synapses, such as the A MPA receptor subunit GluA1 [41], and hence increases dendritic spine formation and synaptic plasticity. Loss of dendritic spines is a sign of a 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 BDNF [43]. Multiple ketamine-influenced signaling pathways seem to converge on a crucial mechanism involved in the repair of synaptic plasticity.

Other rapid-acting antidepressant's Mechanisms of action

Understanding the required and sufficient circumstances to alleviate depression may be strengthened by comparing how the ketamine's mechanisms and other antidepressants align or vary. Researchers identified many fast-acting antidepressants in the last twenty years, some of

which are just as effective as ketamine. Although they all accomplish the same goal—increased plasticity and synaptogenesis—they do so in various ways (Figure-2).

Several drugs bind to NMDA receptors in pathways that are the most comparable to ketamine. The GluN2B selective modulator effects have been observed in depressed people [35] and animal models [26, 28]. Learn how these medications work for people with depression, we need further clinical trials. GLYX-13, tetrapeptide generated from antibody against the NMDAR, is another intriguing molecule. Analog to a partial agonist at the glycine location, GLYX-13 acts as the allosteric modulator. It operates as a modulator. It has a more selective binding profile, which may explain why it has a quick antidepressant effect with some adverse effects than ketamine. Similarly to ketamine, GLYX-13 boosts mTORC1 signalling, synapse quantity and PFC function [33]. To increase synaptic plasticity, GLYX-13 may operate either at postsynaptic NMDARs, like ketamine, or indirectly through NMDA receptors on GABA interneurons. This issue is presently being investigated by researchers. Now therapeutically studies are ongoing to more completely analyze the overall efficacy of GLYX-13 as a fast-acting antidepressant than ketamine [35].

At dosages as low as 4 micrograms per kilogram (g/kg) [44], scopolamine, an antagonist at the muscarinic Ach receptor (mAchR), has proven to have a fast effect of antidepressant in people. Scopolamine, like ketamine, enlarge mTORC1 signaling and development of novel dendritic spines in medial prefrontal cortex [45]. Interneurons are shown to produce mAchRs, and it has hypothesized 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 glutamatergic cells or GABAergic to show that scopolamine's antidepressant effect required the M1-AChRs on the GABAergic interneurons.

It's important to note that ketamine and monoaminergic antidepressants share some molecular effects, which suggests that latter may make use of same plasticity-dependent mechanisms that ketamine does, albeit in a roundabout and inefficient fashion that causes it to exert their antidepressant effect much more cautiously. The effects of fluoxetine [48] an SSRI, and ketamine [47] are prevented in mice engineered to produce mutant version of BDNF that hinders its expression. The agents vary in how it affect BDNF, however: Ketamine promotes fast, activity-dependent release of BDNF [27] and enhanced expression of BDNF [31] after single dosage, while usual antidepressant drugs only raise the expression but not the release of Brain-derived neurotrophic factor, and this happens only after chronic treatment for at minimum 14 days [49,50].

Involvement of Neural circuits in the fast-acting antidepressant's function

New technologies, like optogenetics, which allows for the frame-ups of particular brain circuits, are allowing for a clearer understanding of antidepressant circuit-level effects by shedding light on intra-cellular signaling pathways engaged by these drugs. Correspondents of human brain's mood-regulating cortical-limbic system have found in rodents and non-human primates [51] thanks to years of study. The mPFC (medial prefrontal cortex) is an essential component of limbic system and a major regulator of other limbic regions involved in emotion regulation. Emotional self-reflection and other self-conscious behaviors are concluded to involve the mPFC (medial prefrontal cortex) 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 brain and setting them to constantly stimulate at high frequency to alleviate depressive symptoms too other cognitive and affective ones. Subgenual cortex [region of the mPFC (medial prefrontal cortex)] that is hyperactive in depressive persons differentiated with controls as determined by functional magnetic resonance imaging [53, 54], is most consistently successful electrode insertion. Delivery of DBS to the cortex lowers the high glutamate-linked depression [55]. DBS inactivates targeted axons by diminishing presynaptic neurotransmitter pool.

Current research has seen that antidepressant behavioral and ketamine-like synaptic responses may be induced in rats using optogenetic glutamatergic neurons activation in mPFC, with intensity and time course comparable to ketamine. In addition, a directly ketamine infusion into the rat limbic cortex (hypothesized to affect human mPFC)   is adequate to produce an antidepressant effect similar to that of control, while neuronal silencing of the infralimbic PFC blocks the systemic effect of ketamine [56]. These investigations show that glutamatergic neurons in medial prefrontal cortex are essential for ketamine's antidepressant effect to take place.

Pyramidal neurons in in medial prefrontal cortex transmit axons to several other parts of brain, including hippocampus and dorsal raphe nucleus (DRN), researchers have started to investigate the glutamatergic projections significance from mPFC to these and other brain regions. Optogenetic stimulation of DRN axon terminals has used in conjunction with behavioral analysis to study mPFC to DRN projection. In rodents, activating this projection has proven to have an immediate antidepressant effect [57]. Using optogenetic stimulation, we discovered that activating prefrontal cortex ends in the dorsal raphe nucleus leads to more sustained antidepressant respond in the forced swim test twenty four hours later [58]. Further research showed that ketamine injected into the mPFC has effect of an antidepressant and that mPFC-

injected ketamine causes neuronal activity in dorsal raphe nucleus as measured by the cFos expression [59]. Taken as a whole, these data raise possibility that ketamine's antidepressant effect depends on the activation of the medial prefrontal cortex to dopamine reward network projection.

Ketamine's antidepressant impact may be related to its location in the ventral hippocampus. Current research has used DREADDs (designed receptors uniquely triggered by designer pharmaceuticals) to stimulate the ventral hippocampus to medial prefrontal cortex pathway, therefore simulating effects of ketamine as an antidepressant. It was seen that the ketamine's impact might be reversed by optogenetic inhibition of this route [60]. These findings are comprise with previous research demonstrating that ketamine also enlarges mTORC1 and Brain-derived neurotrophic factor expression in the prefrontal cortex of rats, suggesting that ketamine also increases plasticity in hippocampus. These investigations provide preliminary insights into ketamine-induced plasticity effects on particular brain regions and circuits; nevertheless, a detailed image of neural circuitry underpinning ketamine's action has so far emerged.

Discussion

Importantly, different from other antidepressants on the market, which predominantly influence serotonin transport and/or norepinephrine, this one primarily functions via glutamate. The fast antidepressant effects have in ketamine and some other medications, leading researchers to re-evaluate long-held hypotheses about the mechanisms by which antidepressants like this function. To re-evaluate the fast-acting drugs' effects, new neuroscientific methods have revealed the underlying intra-cellular signals and neural networks.

This article shows the present research on antidepressant mechanisms of action, including major signaling pathways, developing knowledge of cutting-edge techniques and the brain's function circuits, and agents assisting in the investigators comprehending these processes.

Conclusion

Since the research of fast-acting antidepressant and glutamate's central role, the scientific community has come a long way in its knowledge of the antidepressant's mechanisms. There is still a lack of complete understanding of intracellular signals that are responsible for efficacy of fast-acting antidepressants. Researchers may soon be able to test predictions concerning development of ketamine's impact, from N-methyl-D-aspartate antagonism to Brain-derived neurotrophic factor release and mTORC1 activation to synaptogenesis, thanks to a 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 large opportunities for research into 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.

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