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Abstract

Major depressive disorder (MDD) affects approximately 17.3 million adults in the United States each year. For more than 50 years, the serotonin hypothesis of MDD, which hypothesizes that a deficiency of monoaminergic neurotransmitters results in depression, has been the foundation for neuropsychological research. However, studies reveal that only an estimated 50% of MDD patients respond to traditional, biogenic-amine-based antidepressants (ADs), like selective serotonin reuptake inhibitors (SSRIs). Research has noted that the neuroplasticity hypothesis, which posits that weakened excitatory synaptic transmission results in depression, offers an alternative mechanism by which ketamine-like drugs lacking the abuse liability and psychoactive effects of ketamine are able to induce AD-like effects. This study focuses on establishing the importance of the neuroplasticity hypothesis of MDD in relation to novel ADs and designing clinical trials that will help determine the most effective and fastest-acting MDD treatments. A compilation of studies involving rodent models of depression, MDD patients, and postmortem hippocampus analyses was examined in order to understand the relationship between long-standing theories and newer hypotheses of how depression manifests in rat and human brains. Research shows that because ketamine-like drugs, including L-655,708 and (2R,6R)-hydroxynorketamine (HNK), modulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression to promote neuroplasticity, the novel compounds induce AD-like effects within twenty-four hours and strengthen the brain's cortico-mesolimbic reward pathway in rodent models of depression. While the monoamine theory and the neuroplasticity theory of MDD focus on different mechanisms by which ADs reverse stress-induced changes in synaptic strength and hedonic behavior, the theories overlap to justify the ability of ketamine-like drugs,

which act as AMPAR potentiators, and biogenic-amine-based ADs to augment each other's activity. More clinical trials must be conducted in order to understand if and how the simultaneous administration of ketamine-like drugs and traditional ADs could result in shorter latency periods and higher efficacies in MDD therapies. Dual-drug treatments that maximize the synergism between long-standing and novel ADs may offer a new therapy method that would alleviate the severe depressive symptoms faced by a large population of treatment-resistant MDD patients.

Keywords: depression, monoamine, neuroplasticity, SSRIs, ketamine, ketamine-like drugs

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Introduction

MDD is a severe neuropsychiatric syndrome that affects approximately 16% of the world's population. To relieve the symptoms of the disorder, current pharmacological treatments target biogenic amine neurotransmitters that affect mood and behavior in the brain. Each treatment is based on a different hypothesis of MDD proposed by the scientific community. The most common of such theories is the monoamine hypothesis of depression, which states that a decrease in the release, synthesis, or receptor expression of monoamine neurotransmitters, especially serotonin, causes depression. For more than 50 years, researchers have relied upon the monoamine hypothesis of depression to develop traditional, biogenic-amine-based ADs, like SSRIs. However, according to Thompson et al. (2015)—who performed a meta-analysis on current trends in depression research—SSRIs are only effective in approximately 50% of MDD patients and have a latency period of up to 12 weeks (p. 280).

Due to the fact that only 70% of MDD patients are able to achieve complete remission with current therapy options, the neuroscience community recently launched itself into the search for a new hypothesis of MDD and a novel treatment option for MDD patients who are resistant to traditional ADs. In response to the debate on the cogency of the monoamine theory of MDD, Thompson et al. proposed a new model of MDD: the neuroplasticity hypothesis or the excitatory synapse hypothesis of MDD. The hypothesis is based on evidence that chronic stress damages synaptic strength in areas of the brain—including the nucleus accumbens (NAc), the ventral

tegmental area, the prefrontal cortex (PFC), the lateral habenula, the amygdala, and the hippocampus—that are associated with the control of reward behaviors (p. 281-287).

The novel neuroplasticity hypothesis of MDD offers a mechanism by which ketamine is able to induce rapid and robust AD-like effects in rodent and human models of depression. While ketamine does relieve depressive symptoms within twenty-four hours of a single administration, its abuse liability and psychoactive effects limit its clinical viability to treat traditional-AD-resistant MDD patients. However, according to Thompson et al., ketamine-like drugs, like L-655,708 and (2R,6R)-HNK, act via a similar mechanism as ketamine but lack the harmful side effects; ketamine-like drugs act as AMPAR potentiators in order to promote excitatory synaptic transmission in the brain, which induces neuroplasticity. The ability of ketamine-like drugs to influence both monoaminergic and glutamatergic systems within the brain indicates that there is an overlap between the monoamine hypothesis of MDD and the neuroplasticity hypothesis of MDD.

Preliminary research in rats has shown that traditional ADs and ketamine-like drugs may augment each other's activity, which suggests that the scientific community can develop new therapies for traditional-AD-resistant MDD patients by exploiting the synergism between the two classes of drugs. Because ketamine and ketamine-like drugs—including L-655,708, MRK-016, (2R,6R)-HNK, LY 451646, and LY 392098—modulate AMPAR expression to promote neuroplasticity, the novel compounds quickly induce AD-like effects and strengthen the brain's cortico-mesolimbic reward pathway. Simultaneous administration of ketamine-like drugs, which act as AMPAR potentiators, and traditional ADs, like SSRIs, could result in new MDD treatments with shorter latency periods and higher efficacies for MDD patients who are unable to achieve symptom relief with ADs that are based on the older, monoamine model of depression.

Neuroplasticity Hypothesis of Depression

The neuroplasticity theory proposed by Thompson et al. highlights the brain's ability to modify the function of its pathways and alter the strength of synaptic connections as a result of external stimuli such as chronic stress. By increasing cortical activity, the brain forms new neural connections to reverse the changes caused by chronic stress and MDD. The neuroplasticity hypothesis is supported by the findings of Duric et al. (2012), who studied the expression of synapse-related and glutamate-related genes in the hippocampi of MDD patients. Duric et al. claimed that pre-synaptic and post-synaptic genes involved in cytoskeletal rearrangement and glutamate receptor subtypes are dysregulated in the dentate gyrus (DG) and the CA1 area of the hippocampus of depressed individuals (p. 73). The idea that the dysregulation of synapses in the brain's reward pathway results in depression is central to the neuroplasticity hypothesis proposed by Thompson et al. (2015), who asserted that chronic stress changes the strength of glutamatergic synapses in locations of the brain like the hippocampus.

Duric et al. (2012) argued that long-term changes observed in MDD patients can be attributed to the downregulation of critical genes, like those that are involved in inducing synaptic plasticity and remodeling neuronal processes. While Duric et al. claimed that alterations of serotonin receptors *do* play a role in anhedonia seen in MDD patients, Thompson et al. (2015) and Gigliucci et al. (2013)—in a study that investigated the AD-like effects of ketamine in serotonin-depleted rats—found that in addition to altered monoamine levels in the brain's reward pathway, other factors like synaptic strength and brain-derived neurotrophic factor (BDNF) expression also influence the individuals' states of mind. Thompson et al. (2015) hypothesized

that “changes in excitatory synapses in regions” of the brain like the PFC and the hippocampus “interact with reward circuits in the cortico-mesolimbic system,” which influences the levels of neurotransmitters—like dopamine, glutamate, and γ-aminobutyric acid (GABA)—and alters neuronal activity (p. 286-287).

AD-Like Effects of Ketamine and Ketamine-Like Drugs

Research has shown that while chronic administration of traditional ADs like SSRIs can reverse depressive symptoms in MDD patients, acute administration of ketamine, which is the focus of the neuroplasticity hypothesis, is able to induce more robust AD-like effects in a shorter period of time. In the meta-analysis conducted on studies that investigated ketamine and other N-methyl-D-aspartate receptor (NMDAR) antagonists, Thompson et al. (2015) reported that there is substantial evidence that ketamine reduces depressive symptoms within one to two hours of administration and results in behavioral changes that can last for up to two weeks (p. 288). Thompson et al. further noted that in chronically stressed rodents, administration of ketamine restores feeding behaviors, food preferences, and social interaction, which is associated with reward and pleasure (p. 288).

In order to investigate ketamine’s AD capability in a human model of depression, Murrough et al. (2013) compared the AD effects of an acute administration of the sedative midazolam and the AD-like effects of an acute administration of ketamine on MDD patients. Murrough et al. found that the greater the time that had elapsed from the administration of ketamine or midazolam treatment, the greater the probability that a patient became a nonresponder—an individual who failed to demonstrate an increase of at least 50% in their score on the Montgomery-Åsberg Depression Rating Scale (MÅDRS)—when compared to their baseline score (p. 1137). However, when Murrough et al. compared treatment response with

treatment type, they found that individuals who received a single administration of ketamine were more likely to have a response, when compared to individuals who received a treatment of midazolam (p. 1137). While ketamine's and midazolam's AD-like effects decreased over time, ketamine was more likely to induce observable, positive changes in patients' moods, as qualified by the MÅDRS (p. 1137). Murrough et al. also noted that response rates between the ketamine and midazolam groups did not differ after seven days post-infusion, which indicated that the AD-like effects of ketamine were significantly reduced after seven days. However, ketamine still resulted in a greater likelihood of ketamine-treated patients having a Clinical Global Impression score lower than three (p. 1137). The substantiality of ketamine relies on its ability to induce faster and more robust symptom relief in MDD patients who show inadequate responses to traditional, clinical ADs.

In order to induce AD-like effects, ketamine increases neuronal activity in the cortico-mesolimbic pathway. In a study in which 20 MDD patients were administered a single infusion of ketamine hydrochloride, Cornwell et al. (2012) found that responders, who demonstrated rapid and extreme reduction in their depressive symptoms, showed an increase in stimulus-evoked somatosensory cortex (SS ctx) responses post-infusion of ketamine (p. 559). The results revealed a positive correlation between levels of plasma norketamine, which is an active metabolite of ketamine that has a longer half-life than ketamine, and increased cortical excitability (p. 559). The positive correlation observed in MDD patients supports the idea that there is a link between ketamine administration and increased cortical activity within the brain.

Currently, there are two proposed hypotheses of how ketamine inhibits NMDARs in order to lead to increased neuronal activity in the brain. According to Moghaddam et al. (1997), who studied ketamine's ability to activate glutamatergic neurotransmission in rats, one

hypothesis of ketamine's AD mechanism is that ketamine preferentially inhibits NMDARs that are located on GABAergic inhibitory interneurons (p. 2923). According to the meta-analysis conducted by Thompson et al. (2015), the preferential inhibition could be because of differences in the composition of NMDARs on GABAergic interneurons or because the interneurons themselves are more depolarized than other types of neurons, thus "relieving ion channel block by [magnesium ions] and allowing NMDARs to contribute more to [the neurons'] overall excitation" (p. 288). As a result of inhibiting NMDARs on GABAergic neurons, ketamine is able to induce a disinhibition or excitation of the neuronal population and potentiate a "surge of glutamate release" in both the NAc and the PFC (p. 288). However, in a study investigating the AD action of NMDAR antagonists on mice lacking NMDARs, Pozzi et al. (2014) found that ketamine is still able to induce AD-like effects in mice that do not have NMDARs in a subpopulation of GABAergic interneurons. According to Thompson et al. (2015), the study conducted by Pozzi et al. (2014) suggests that ketamine's AD-like actions do not rely on inhibiting NMDARs on GABAergic interneurons in the brain or that another type of interneuron is crucial in ketamine's mechanism.

According to Autry et al. (2011), who studied the effects of NMDAR blockade on behavioral AD responses in clinical trials, the second hypothesis of ketamine's AD mechanism is that ketamine inhibits ongoing NMDAR activation (p. 93). Since the ongoing activation of NMDARs is thought to suppress signaling cascades that promote synaptic transmission in excitatory neurons, Autry et al. argued that ketamine might promote the production and expression of proteins like AMPARs, which mediate excitatory synapses, by blocking the suppression of the excitatory signaling (p. 93).

Regardless of which of the two hypotheses, both of which focus on excitatory synapses, is more accurate, ketamine has been proven to induce rapid AD-like effects in depressive-like rats and depressed humans. However, while ketamine can induce AD-like effects after a single administration, the drug also causes harmful side effects. Traditional ADs and ketamine *both* result in side effects in MDD patients, but research has shown that ketamine often has a higher abuse liability and can result in psychoactive effects that hinder its clinical viability. Murrough et al. (2013), who studied ketamine's and midazolam's activity in MDD patients, emphasized that ketamine, which is an NMDAR antagonist, and midazolam, which is an anesthetic benzodiazepine, both induced adverse effects in treatment-resistant MDD patients (p. 1138). The fact that patients in the midazolam group demonstrated some side effects indicates that regardless of the class of drug administered to an MDD patient, some adverse effects like nausea and headache are likely to occur. However, because of ketamine's psychoactive effects and abuse liability, Murrough et al. observed hemodynamic changes and dissociative symptoms in the ketamine group (p. 1138). Murrough et al.'s findings suggest that ketamine's psychoactive effects were induced in the short term.

Due to the risks associated with administering pure ketamine to MDD patients in a clinical setting, researchers have been studying ketamine-like drugs—like ketamine metabolites or other compounds that increase synaptic strength—which act via similar mechanisms as ketamine but lack harmful side effects. The MDD-ketamine trials conducted by Cornwell et al. (2012) rely on the idea that in order to induce long-lasting changes in the brain's reward pathways, the next generation of ketamine-like drugs must increase cortical activity that will, in turn, allow the brain to form new neural connections to compensate for the changes caused by chronic stress and MDD. While Gigliucci et al. (2013), in their study with serotonin-depleted

rats, did prove that levels of monoamines like serotonin are still vital in ketamine's ability to elicit sustained AD activity, Cornwell et al. (2012) demonstrated how rapid and robust alleviation of depressive symptoms are a result of ketamine's ability to strengthen glutamatergic neurotransmission. Ketamine-like drugs that will be used as clinical ADs must act in a similar manner, by acting on glutamate pathways, to induce AD-like effects within twenty-four hours after an acute administration.

In order to determine the therapeutic implications of ketamine-like drugs, Fischell et al. (2015) studied L-655,708 and MRK-016, both of which are ketamine-like drugs, on the behavior of chronically stressed rats. The research team found that within twenty-four hours of administration of 0.7 milligrams (mg)/kilogram (kg) of L-655,708—which is an α5-selective negative allosteric modulator of GABA type A receptors ($GABA_ARs$)—the chronic restraint stress (CRS) rats showed levels of social interaction and sucrose preference that were similar to their baseline levels (p. 2501). The team also reported that within twenty-four hours of administration of MRK-016, all CRS rats demonstrated restored sucrose preference and social interaction levels (p. 2502). Fischell et al. claimed that L-655,708 and MRK-016 both reversed stress-induced changes in less than twenty-four hours for the Sprague Dawley rats *without* producing any detectable side effects (p. 2502).

In a similar study that specifically investigated the AD effects of ketamine metabolites, Zanos et al. (2016) assessed the effects of (S)-ketamine and (R)-ketamine enantiomers (p. 481). The researchers noted that, of the broad range of ketamine metabolites, experiments using rats have shown that (2S,6S;2R,6R)-HNK plays a major role in ketamine's AD properties (p. 482). After a series of experiments using a rodent model of depression, Zanos et al. found that (R)-ketamine had a greater potency as an AD and that an NMDAR inhibition-independent

mechanism is likely the explanation for ketamine's AD properties (p. 482). Zanos et al. emphasized that (2R,6R)-HNK has "greater antidepressant actions" than (2S,6S)-HNK (p. 483), which indicates that the former ketamine metabolite demonstrates more clinical viability.

Like Fischell et al. (2015), Zanos et al. (2016) demonstrated how ketamine-like drugs lack ketamine's abuse liability but induce AD-like effects. Both teams also concluded that while ketamine inhibits NMDARs to increase excitatory glutamate synaptic transmission, ketamine-like drugs—including L-655,708, MRK-016, and (2R,6R)-HNK—do not necessarily inhibit NMDARs and may induce increases in the expression of AMPAR-mediated pathways. Fischell et al. (2015) reported that decreases in GluA1 protein, which is a subunit of AMPARs, expression is associated with the neurological and behavioral stress-induced changes seen in MDD patients—such as "weakened excitatory synaptic transmission at [hippocampus temporoammonic-CA1 (TA-CA1)] synapses and altered hedonic behavior," respectively (p. 2505). After analyzing how L-655,708 influenced a rodent model of depression, Fischell et al. concluded that α5-subunit-selective negative allosteric modulators, like L-655,708, display high AD efficacy on an electrophysiological, behavioral, and molecular level (p. 2505).

Partial inverse agonists with a low affinity for the benzodiazepine binding site of α5-containing $GABA_A$Rs—including L-655,708—are able to demonstrate potential therapeutic effects with a minimal likelihood of producing negative adverse effects, such as anxiety. According to Fischell et al., drugs that specifically target α5-containing $GABA_A$Rs are able to alter and strengthen activity within cortico-mesolimbic circuits without adversely affecting other neurological circuits (p. 2506). The researchers suggested that the ability of "$GABA_A$R negative allosteric modulators and ketamine to promote activity accounts for their shared" AD effects because their "activity strengthens excitatory synapses via convergence onto common activity-

dependent signaling pathways" (p. 2507). Unlike ineffective SSRIs and the easily-abused ketamine, L-655,708 and MRK-016 induce selective AD effects within twenty-four hours of a single administration and represent a novel, clinically-viable treatment for MDD.

AMPAR-Mediated AD Pathways

In addition to investigating the behavioral and synaptic changes that ketamine and ketamine-like drugs induce, researchers have conducted studies to understand the mechanism or pathway by which the drugs act. In one such study, Cornwell et al. (2012), analyzed the AD-like effects of ketamine hydrochloride on MDD patients. The team found that NMDAR inhibition has been proven to increase spontaneous gamma oscillation activity in the SS ctx. According to Cornwell et al., NMDAR antagonists like ketamine have been known to typically increase spontaneous γ activity in the SS ctx just after drug administration, when "psychotomimetic symptoms are most prominent" (p. 559). Cornwell et al.'s study, in particular, showed that in responders and nonresponders, hours after ketamine infusion, there was no increase in spontaneous SS ctx γ activity (p. 559). These results indicate that increases in spontaneous SS γ activity that result from ketamine administration are likely more important to NMDAR antagonism's acute, psychoactive effects than they are to the long-term AD effects.

In a similar study that focused on ketamine metabolites instead of pure ketamine, Zanos et al. (2016) found similar evidence that ketamine metabolites, like (2R,6R)-HNK and (2S,6S)-HNK, both activated AMPARs but acted independent of NMDAR inhibition in order to induce AD effects. While research teams like Thompson et al. (2015)—who conducted the meta-analysis on current depression research—focused on NMDAR antagonists' ability to quickly restore stress-induced excitatory synaptic strength, other research teams like Fischell et al.

(2015)—who studied the AD-like effects of ketamine-like drugs on rats— focused on how drugs that aim to strengthen weakened AMPAR-mediated signaling are able to exert AD effects.

Fischell et al.'s analyses of brain slices from stressed rats, L-655,708-treated CRS rats, and vehicle-treated stressed rats confirmed that chronic stress at TA-CA1 synapses suppresses AMPAR-mediated signaling but does not affect NMDAR-mediated signaling (p. 2504). Fischell et al. claimed that L-655,708 is able to restore excitatory neurotransmission at the stress-sensitive TA-CA1 synapses by reversing the impairment of AMPAR-mediated signaling (p. 2504-2505). These results suggest that ketamine-like drugs, like L-655,708, are able to demonstrate AD effects via an NMDAR-independent mechanism, which is a similar idea to that proposed by the aforementioned Zanos et al. (2016).

In a similar study investigating the effects of a ketamine-like drug that acts as an AMPAR potentiator or positive modulator, Lindholm et al. (2012) discovered that acute LY 451646 treatment neither increased nor decreased mRNA levels of the tropomyosin receptor kinase B (TrkB) receptor (p. 5). However, Lindholm et al. did note that chronic LY 451646 treatment, with a dose of 0.5 mg/kg, increased TrkB mRNA levels in the DG and the CA4 and CA3 areas of the hippocampus (p. 5). TrkB is a receptor for BDNF and, in turn, is involved in neuronal survival and differentiation. The increase of TrkB by LY 451646 indicates that AMPARs are vital in the brain's mechanisms to promote neuroplasticity.

As mentioned previously, in a study that was more broadly conducted on the effects of ketamine hydrochloride on MDD patients, Cornwell et al. (2012) found that NMDAR antagonists' ability to increase spontaneous SS ctx γ activity was limited to a short period of time directly after the drug was taken (p. 559). Cornwell et al. suggested that since increases in spontaneous SS ctx γ were not seen in responders and nonresponders, "the immediate effects of

NMDAR antagonism might not be sufficient to elicit rapid clinical improvements" (p. 559). The researchers claimed that elevated cortical excitability six to seven hours post-infusion was not caused by ketamine-induced disinhibition of glutamatergic neurons or differences in extracellular glutamate levels between responders and nonresponders (p. 559-560). While "ketamine-induced disinhibition and increased glutamatergic activity are too transient" to directly ameliorate depressive symptoms, both processes could "trigger critical plastic changes at excitatory synapses that mediate" the increases in cortical excitability seen in responders (p. 560). According to the team, due to the fact that AMPAR-mediated neurotransmission plays a role in recruiting GABAergic interneurons, increased stimulus-evoked γ-band responses in SS ctx might confirm "enhanced AMPAR-mediated glutamatergic drive of interneuronal networks" (p. 560).

The study by Cornwell et al. raises the notion that if NMDAR antagonism is not a starting point for therapeutically altering cortical circuitry to benefit MDD patients, newly developed ADs could focus on directly triggering synaptic potentiation rather than indirectly via NMDAR antagonists. Thus, Cornwell et al.'s findings suggest that ketamine's AD-like effects rely on "enhanced non-NMDAR-mediated glutamatergic neurotransmission through synaptic potentiation" (p. 560). However, further research is needed to determine whether increased cortical excitability is associated with response to MDD therapies in general or is specific to glutamatergic drugs and to investigate the roles that AMPARs and NMDARs play in plastic changes within the human brain.

Overlap Between the Monoamine and Neuroplasticity Hypotheses of MDD

As researchers have investigated the mechanism by which ketamine and ketamine-like drugs potentiate excitatory synaptic transmission, some teams have also evaluated the role that monoamine neurotransmitters play in the drugs' AD-like activity. In such studies, researchers

investigated how biogenic-amine pathways intersect with glutamatergic or AMPAR-mediated systems that increase neuroplasticity.

In one such study that evaluated the interaction of AMPAR potentiators and traditional ADs in mice, Li et al. (2003) claimed that while LY 392098 increased the potency of the tricyclic AD imipramine, the AMPAR potentiator did not alter concentrations of imipramine in the brain (p. 425). While SSRIs like fluoxetine rely on the increased synaptic availability of a biogenic amine like serotonin, Li et al.'s results suggest that LY 392098's ability to induce increases in the potencies of conventional ADs in the forced swim test (FST) is a result of downstream effects that are produced by increased synaptic availability of biogenic amines combining with pathways that have been stimulated by the activation of AMPARs (p. 427). The team's findings suggest that the neuroplasticity hypotheses of MDD and the monoamine hypotheses of MDD converge. Li et al. argued that, in the case of LY 392098 and ketamine, each drug relies on biogenic amines like serotonin in order to maximize their AD properties.

Like Li et al., Gigliucci et al. (2013)—in their study on serotonin-depleted rats—found that while ketamine did not alter serotonin levels in the frontal cortex, serotonin depletion "attenuated the AD-like effect of ketamine" (p. 161). In the study, there was an increase in immobility for the rats that were serotonin-depleted, stress-exposed, and ketamine-treated when compared to the rats that were serotonin-depleted, non-stressed, and ketamine-treated (p. 161). Gigliucci et al. suggested that the timing of ketamine administration and the dose administered can either enhance or hinder the drug's AD effects (p. 163). According to the team, ketamine promotes neuronal changes that enhance the efficacy of central serotonin in synapses; however, further research using the FST must be conducted to understand the role of serotonin in relation to emerging views of depression and ADs (p. 165).

In a similar investigation of the AD-like effects of ketamine and fluoxetine on depressive mice, Pham et al. (2017) found that both ketamine and fluoxetine increase extracellular serotonin levels in the medial PFC (p. 202). The team concluded that in a rodent model of depression, serotonin plays a role in ketamine's behavioral activity, the AD-like activity of ketamine recruits the neural circuit involving the PFC and the brainstem dorsal raphe nucleus (DRN), and ketamine's ability to act like an AD requires the activation of AMPARs on the DRN (p. 204). According to Pham et al., the AD-like activity of ketamine, rather than that of fluoxetine, relies on interactions between serotonergic *and* glutamatergic systems within the medial PFC (p. 208). These results, like those of Gigliucci et al. (2013), indicate that ketamine's ability to induce rapid AD-like activity relies not only on glutamatergic systems that regulate neuroplasticity but also on serotonergic systems that regulate the levels of monoamine neurotransmitters.

Based on the research conducted by Li et al. (2003), Gigliucci et al. (2013), and Pham et al. (2017), while the long-standing monoamine theory of MDD is often discussed in a separate context from the neuroplasticity hypothesis of MDD, both have substantial overlap. The monoamine theory focuses on how increases in monoaminergic neurotransmitter levels positively impact mood and behavior, while the neuroplasticity hypothesis draws attention to the fact that strengthening glutamatergic synapses can support the brain's reward pathway as a whole. Despite their different focuses, the monoamine theory and the neuroplasticity theory overlap in their discussion of the brain's complex network of communication; levels of monoamines like serotonin *and* neuronal pathways that increase synaptic strength are vital in ketamine's and ketamine-like drugs' ability to elicit sustained AD activity.

Synergism Between AMPAR Potentiators and Biogenic-Amine-Based ADs

In addition to supporting the idea regarding an overlap between the monoamine hypothesis of MDD and the neuroplasticity hypothesis of MDD, preliminary research indicates that drugs based on both hypotheses may interact to produce AD effects that are faster and more robust than either class of drugs alone. Studies demonstrate a synergism between ketamine-like drugs—based on the neuroplasticity hypothesis—that activate AMPARs to promote AD-effects in the cortico-mesolimbic reward pathway and traditional ADs—based on the monoamine hypothesis—that alter biogenic amine levels in synaptic clefts. In one such study that investigated the interaction of AMPAR potentiators and traditional ADs, Li et al. (2003) observed that LY 392098 reduced the minimal effective dose of seven traditional ADs, including rolipram, citalopram, duloxetine, imipramine, nisoxetine, tranylcypromine, and fluoxetine (p. 423). Li et al. also observed that LY 392098 increased the relative potency of all seven of the aforementioned ADs, excluding tranylcypromine (p. 423). Li et al. concluded that the synergism between AMPAR potentiators like LY 392098 and conventional ADs like SSRIs suggests that in order to increase the efficacy of commonly prescribed AD medications, like fluoxetine or Prozac, combination therapies that combine the original AD with an AMPAR potentiator would be more successful than administering the original ADs alone.

Mackowiak et al. (2002)—who also studied the activity of an AMPAR-potentiating ketamine-like drug but used a rodent model of depression—claimed that one mg/kg of LY 404187, which is a racemic AMPAR potentiator, increased the number of BDNF-positive cells in the DG when administered chronically, over the course of seven days (p. 4). Li et al. (2003) claimed that AMPAR potentiators and conventional ADs like fluoxetine demonstrate a synergism when administered together. One probable explanation for the synergism between novel AMPAR potentiators and traditional ADs is increased BDNF expression, which, as shown

by Mackowiak et al. (2002), can result from AMPAR potentiators acting on the DG and hippocampus.

Conclusion

The synergism between AMPAR potentiators like LY 392098 and conventional ADs like SSRIs suggests that in order to increase the efficacy of commonly prescribed AD medications for MDD patients, combination therapies that combine traditional ADs with an AMPAR potentiator would be more successful than administering the original ADs alone. While ketamine is often classified as an NMDAR antagonist or inhibitor, the drug can be described more accurately as an AMPAR potentiator. As seen in the study conducted by Zanos et. al (2016), (2R,6R)-HNK, a ketamine metabolite that lacks harmful side effects, induces AD effects via sustained activation of AMPARs; such research further suggests that ketamine's and ketamine-like drugs' AD effects rely on their ability to interact with AMPARs. After conducting a study on serotonin-depleted rats, Gigliucci et al. (2013) also noted that ketamine's AD effects rely on AMPAR activation. Fischell et al. (2015), who studied the activity of ketamine-like drugs on rats, reported that L-655,708, an α5-selective negative allosteric modulator of $GABA_A$Rs, is able to act as a ketamine-like AMPAR potentiator that reverses stress-induced changes in hedonic behavior.

Since ketamine can be classified as an AMPAR potentiator, it can be considered as a compound that can increase the potency of conventional ADs and a compound whose potency can be increased by conventional ADs. While studies have shown that a single administration of ketamine or ketamine-like drugs—like the NMDAR antagonist esketamine that has been recently marketed as a novel AD—has had longer-lasting AD effects compared to chronic administration

of traditional ADs, it is possible that the AD effects of ketamine-like drugs, specifically AMPAR-potentiating drugs, can be increased further by combining the drugs with a traditional AD. Such a combination would extend the relief MDD patients receive from a single dose of their AD medication.

Future studies investigating the AD effects of a dual-drug treatment with an AMPAR-potentiating ketamine-like drug and a biogenic-amine-based AD must be conducted on rats *and* MDD patients. As seen by Duric et al. (2012), who studied the expression of synapse-related genes in rats' and MDD patients' hippocampi, chronic stress does not induce the same alterations in serotonin receptor expression in rats as in humans. In the study, Duric et al. found that chronic unpredictable stress (CUS) and AD treatment did not alter the expression of *HTR* genes, which are involved in coding for serotonin receptors, in the same way that MDD alters the expression of synapse-related genes in humans (p. 78). The research team acknowledged the fact that MDD manifests uniquely in different species. Even though animal models of depression like CUS rodents are similar to MDD in humans, chronic stress does not result in the same exact changes in animals as it does in humans.

In order to develop novel AD treatments that are more robust than currently prescribed AD drugs, future studies must not only investigate how ketamine-like drugs and traditional ADs interact within the human body but also what doses are needed for acute administrations of the dual-drug treatment. Longitudinal studies are needed to understand both the short-term and long-term effects that the dual-drug treatments will have on MDD patients' mood and hedonic motivation. The dual-drug treatments, which would maximize the synergism between long-standing and novel ADs, may offer a new therapy method that would attenuate the severe depressive symptoms faced by a large population of treatment-resistant MDD patients.

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