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Ketamine – mechanisms of action as an antidepressant

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Summary

Since the year 2000, ketamine and its enantiomers have been studied for their antidepressant effects. This paper will briefly summarise the journey of ketamine from an anaesthetic to an antidepressant. The text will present the key mechanisms of its action, as well as the actions of its metabolites. The aim of this article is to describe the role of specific groups of receptors in activation of important metabolic pathways and in production of factors such as mammalian target of rapamycin kinase (mTOR) and brain-derived neurotrophic factor (BDNF), in order to comprehensively present a potential link between ketamine, ketamine's enantiomers and its metabolites with terms such as neuroplasticity and antidepressant action. Another important part of this article is a summary of arguments for and against importance of specific mechanisms of ketamine action and to compare (S) and (R)-ketamine's potential to act as an antidepressant. This article may be particularly helpful for researchers in determining further research directions and serve as a summary of the current state of knowledge regarding the mechanisms of ketamine's action and the latest therapeutic possibilities in the treatment of affective disorders.

Key words: ketamine, antidepressants, depression

Introduction

Depression is a common illness, with an estimated 3.8% of the population affected worldwide [1, 2]. It is a serious medical and social problem, causing individual suffering, loss of productivity, increased health care costs, and high suicidal risk. Depression is a leading cause of disability around the world and is a major contributor to the overall global burden of disease [1, 2]. The number of patients receiving antidepressant treatment in increasing every year [2]. Despite the high prevalence of depressive disorders, their etiopathogenesis is not yet fully understood. Only 60–70% of patients suffering from this disorder respond to the standard antidepressant treatment, which means that treatment resistant depression (TRD), defined as lack of clinical improvement despite of at least two attempts of treatment with antidepressants at adequate dose from two

different groups with unique mechanisms of action, may be as prevalent as 1/3 of patients with clinical depression [3].

There are some therapeutic strategies dedicated to this group of patients. One of them is electroconvulsive therapy (ECT) during which patients undergo a series of several to over a dozen treatments under anaesthesia, with intervals of a few days between each session. This therapy brings good results; however, according to the guidelines of the APA (American Psychiatric Association), it should also be considered as a preferred method for certain patients (those experiencing a severe depressive episode with psychotic symptoms or food refusal) rather than solely as a "last-line" treatment [4]. Often, for patients suffering from treatment-resistant depression, augmentation is applied using compounds such as second-generation antipsychotics – particularly quetiapine, olanzapine, aripiprazole, and risperidone, lithium – recommended as an augmentation to antidepressants, among other reasons due to its anti-suicidal effects in this patient group [4, 5], and anti-inflammatory drugs (such as celecoxib) [6]. Psychotherapy is also important in this form of depression. However, each of these treatments carries potential side effects or may be contraindicated for specific patient groups, hence it is essential to continue searching for new, effective and safe therapies.

In 2019, FDA approved esketamine as an adjunctive treatment for treatment-resistant depression (TRD) in adults. Esketamine was approved under a risk evaluation and mitigation strategy (REMS) that requires administration under medical supervision. Both ketamine and esketamine are currently viable treatment options for TRD that offer the possibility of rapid symptom improvement [7]. The aim of this paper is to show ketamine's way from anaesthetic to novel antidepressant agent, and most importantly to present its potential antidepressant mechanisms of action.

Brief history of ketamine – from anaesthetic to antidepressant

In the 1950s, at Parke-Davis laboratories in Detroit, the search for an anaesthetic that would meet the needs of modern medicine began, which in 1958 led Victor Maddox to synthesis of phencyclidine, also known as PCP or, among those who abuse it, "Angel Dust" [8]. The anaesthetic effect of the new agent was promising, but in next years subsequent scientific publications have reported that some patients suffer significant agitation or psychosis-like state after anaesthesia with phencyclidine [9]. Side effects of PCP have led scientists to search for a better agent – among phencyclidine derivatives.

In 1962, Parke-Davis consultant – Calvine Stephens synthesized molecule built by specific cyclohexane moiety consisting of ketone and amine group. Later, this molecule was named Ketamine [10]. In 1964, Dr Edward Domino, who previously had conducted research on PCP, accepted the Parke-Davis offer to carry out research on ketamine's anaesthetic potential involving human participants. Considering he was not an anaesthesiologist, Dr Domino invited Professor of the University of Michigan – Dr Crossen – for cooperation, and they conducted the first ketamine administration on volunteer – one of the inmates from Jackson Prison in Michigan [11]. Further research

has reported promising results – ketamine compared to PCP less frequently induces adverse effects. Nevertheless, some of the respondents have described subjective experience of disembodied journey, and sensation of dissociation of one's body part, which is partially similar to some of the reports after PCP intake [12, 13].

Scientists were wondering how to denominate ketamine's unique effect which is underlying these patients' experiences. Primarily it was supposed to be "Schizophreniomimetic effect", but considering that this nomenclature may discredit new medicine, they did not decide to use this term. Instead, a new designation was proposed by Dr Domino's wife – Toni Domino, and new agent, referring to the sensation of being dissociated from one's body part [14], was named dissociative anaesthetic, and to these days, as proposed by Dr Domino, anaesthesia with ketamine is known as "dissociative anaesthesia". The beginnings of ketamine marketing date back to 1968, when it was introduced in Belgium for veterinary use, and in 1969 it became available by prescription in the United States under the name Ketalar.

Over the years, the use of ketamine in operating rooms began to be abandoned, partly due to the introduction of a new, very effective anaesthetic – propofol – in 1986. On the other hand, in the 1990s scientists dwelled on ketamine's molecular properties, especially its mechanism of action as non-competitive NMDA receptor inhibitor, which has led to discovery of its antihyperalgesic effect [15]. Because of it ketamine has been successfully used for counteracting side effects of remifentanil, which has been introduced in 1990s. The number of studies examining ketamine as a potential treatment for PTSD (post-traumatic stress disorder) has been increasing year by year. However, definitive conclusions regarding its efficacy for this indication are still lacking [16].

Ketamine has been studied for many years as a bronchodilator (particularly in the paediatric population) and appears to be effective in patients who do not respond to first-line treatments [17]. Currently, ketamine-based anaesthesia is widely used, especially in paediatric patients, due to its stable effects on the cardiovascular system [18]. Furthermore, ketamine therapy is being investigated as a potential strategy for managing chronic pain, including neuropathic pain [19]. Eventually, the first research results on ketamine use for depression treatment were published in 2000 year [20]. The research in this area proceeds, as it seems, now in 2025 the story of molecule once named ketamine is still not finished.

Ketamine's role in depression treatment

Ketamine is a racemic mixture of two enantiomers: (R)-ketamine and (S)-ketamine. The first clinical trials conducted on (R,S)-ketamine in the treatment of TRD (treatment-resistant depression) showed a rapid and significant antidepressant effect after a single intravenous dose [20], lasting approximately 72 hours after administration. Further research on (R,S)-ketamine showed significant antidepressant effect in 60–70% of patients with TRD [21, 22]. Studies have also emphasised significant reduction in suicidal ideations, tendencies and actions due to ketamine treatment. The pro-cognitive effect

of ketamine in patients suffering from TRD is important – its long-term administration has a positive effect on working memory, information processing speed, verbal learning and memory [23], as well as on visual memory and simple and complex working memory [24]. It has been indicated that a lower level of attention, measured using the CogState battery before initiating therapy in this group of patients, is a predictor of a good response to ketamine treatment [24].

Similarly, in patients with bipolar disorder, pro-cognitive effects of ketamine used in the treatment of depressive episodes have been noted. It is important to highlight that, in some patients, this effect occurs regardless of whether an antidepressant response is achieved or not [25]. In 2019 research on therapy with esketamine in nasal form for TRD was conducted [26]. The medicine was administered once per week or once per two weeks. The results were so promising that in the same year FDA approved esketamine in nasal spray for TRD treatment.

Currently, (R)-ketamine's therapeutic potential is under investigation, as well as there are ongoing comparative trials on (R,S)-ketamine and esketamine efficiency [27]. Nonetheless, the mechanisms of ketamine action as an antidepressant remain to be not fully uncovered. Yet we know that it is associated with glutamatergic system, GABA-ergic system as well as with mechanisms of neuroplasticity, including these linked with BDNF (brain-derived neurotrophic factor). The fast-acting excitatory receptors are particularly important for ketamine's anaesthetic (which was described in 1990s) and antidepressant action.

Impact of ketamine on NMDA and AMPA receptors

NMDA (N-methyl-D-aspartate) receptors belong to ionotropic, glutamate-activated receptor group (along with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and kainate receptors) [28], and they are located intra – and extrasynaptically. NMDA receptors play a key role in cell homeostasis maintenance via promoting both: cell apoptosis and cell survival. Therefore, activation of extrasynaptic NMDA receptors promotes process of apoptosis, via enhanced calcium ion influx into the cell body (NMDA receptors are permeable not only for Na^+ and K^+, but also for Ca^{2+} ions), whereas activation of intrasynaptic NMDA receptors promotes cell viability [29]. In basic neuronal activity, NMDA receptors are not primarily responsible for transmitting fast excitatory synaptic currents (it is main role of AMPA receptors), but they modulate this transmission [30]. It is due to their complex mechanism of activation – ion channels of NMDA receptor are blocked by Mg^{2+} ions – depending on depolarisation. It means that in physiological concentration Mg^{2+} ions are inside the receptor channel and make it impermeable to other ions, especially Ca^{2+} ions. For it to become preamble, a sufficient depolarisation must occur [31].

NMDA receptors are tetramers and can be composed of seven described subunits (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B). There is difference between subunits regarding their frequency of occurrence on different parts of neurons,

and on different neurons (for example, NMDA receptors located in extrasynaptic area considerably more frequently consist of GluN2B subunit) [32]. The structure (subunits composition) of NMDA receptor also determines its Mg^{2+} channel blockage potential, likewise its channel permeability for Ca^{2+} ions, which play a key role in glutamatergic system. For example, NMDA receptors built of GluN2A or GluN2B subunit are preamble for Ca^{2+} ions in lower depolarisation potential in comparison to other NMDA receptors [33]. Ketamine, like its predecessor – phencyclidine, appears to block NMDA receptors via an "open channel block" mechanism, thus it enters the ion channel and inhibits ion influx through it. This type of blockage could explain long lasting effect after ketamine intake since receptor inhibition terminates only after decomposition of inhibitor, but admittedly even for ketamine it occurs faster than in the case of its analogues – phencyclidine or MK-801 [34].

So-called psychiatric effects after ketamine administration – dissociative (or psychotomimetic) and antidepressant effects – occur predominantly at subanaesthetic doses [29]. Most likely, in small micromolar concentration ketamine inhibits less than 50% of NMDA receptors [35]. What is important, trials on animal models have proven that at anaesthetic dose ketamine does not cause antidepressant effect in rodents [36]. This phenomenon seems to be an effect of the difference between ketamine affinity to different NMDAR subtypes as well as difference between these subtypes' role in the CNS (central nervous system) functioning.

Next group of glutamate-activated ionotropic receptors essential for ketamine mechanism of action are AMPA receptors. Their main role in the CNS is to transmit fast excitatory currents, which occurs within milliseconds [37, 38]. Conduction velocity also depends on AMPA receptor subtype since – similarly to NMDARs – they are tetramers that can be composed of four subunits (GluA1–4) as heteromers or homomers [39]. AMPA receptors' channels facilitate Na^{+} ions influx into the cell as well as K^{+} ions efflux from the cell body. However, as it turns out some of AMPA receptor subtypes, likewise NMDARs, are preamble for Ca^{2+} ions and thus they play significant role in neuroplasticity as well, which is crucial for subsequent sections of this paper [40]. Furthermore, AMPA receptors impact NMDAR-mediated synaptic transmission, since depolarisation of the cell membrane caused by the influx of ions into the cell through AMPA receptors often serves as impulse for NMDA receptors, which are located on the same membrane, to activate due to removal of Mg^{2+} channel block [41]. The importance of AMPA receptors in the mechanism of action of ketamine is indicated, among others, by the mechanism of action of the (R)-ketamine metabolite – (2R,6R)-HNK (hydroxynorketamine), which will be discussed later in this paper.

Ketamine and neuroplasticity

Processes associated with neuroplasticity in patients suffering from depression underlie ketamine antidepressant effect. In 2023, the results of the first randomised trial on changes in neuroplasticity in patients with depression after ketamine administra-

tion were published. This trial was conducted with patients suffering from depression that previously had been treated with at least one antidepressant with no sufficient improvement, in order to compare fast therapeutic effect after ketamine administration in one group and placebo in another group regarding neuroplasticity changes in specific brain regions evaluated with putative neuroplasticity marker – MD-DTI (diffusion-tensor-imagining mean diffusivity) [42]. In the past, this method was found useful for research on remembering mechanisms, despite not being a direct measurement method, thus having its own limitations in neuroplasticity assay. Antidepressant effect was measured with the MADRS (Montgomery-Asberg Depression Rating Scale) and QIDS-SR (Quick Inventory of Depressive Symptomatology). Twenty-four hours after ketamine administration general clinical improvement was noticed – according to both scales. Neuroplasticity improvement, assessed based on the decrease in mean diffusivity in DTI in the left amygdala and left BA10 (Brodmann area 10) after ketamine administration, was a predictor of more robust clinical improvement, as estimated by the MADRS. In the right BA10 region, antidepressant response was correlated with estimated increased neuroplasticity, regardless of whether the group was treated with placebo or ketamine.. On the other hand, in the left and right hippocampus, correlation between marker opposite to this representing neuroplasticity (increase in mean diffusivity in DTI) and clinical improvement was noticed. The authors proposed some hypothetical explanations for this observation and emphasised that, due to the limitations of the MD-DTI method, an increase in mean diffusivity may not correspond to a decrease in neuroplasticity. The role of different cortex regions in antidepressant effect and neuroplasticity remains to be unclear and needs further research, but neuroplasticity in general appears to be key factor in fast antidepressant effect after ketamine administration.

A significant agent of signalling pathways detailed in a subsequent part of this paper is the growth factor BDNF (brain-derived neurotrophic factor), which is directly linked to protein synthesis via the mTOR (mammalian target of rapamycin) pathway and further – neuroplasticity. Previous research has shown that signalling via BDNF in specified hippocampal regions is crucial for antidepressant effect of medicines such as SSRIs or TCAs [43, 44]. It could be essential for ketamine action likewise, since it no longer causes fast antidepressant effect in animals, after BDNF neutraliser infusion into mPFC (medial prefrontal cortex) [45]. Moreover, recent studies have shown that in patients who have responded well to ketamine treatment, there was a statistically significant increase in BDNF blood levels compared to levels before ketamine administration. This correlation was proven only for ketamine although esketamine was also under examination in this study, but sample was not big enough to infer correctly [46]. An increase in BDNF level was also noticed in mice hippocampal tissue 30 minutes after ketamine infusion [47]. On the other hand, some studies suggest that among patients with bipolar disorder, experiencing a depressive episode which is resistant to classical antidepressant treatment, that undergo ketamine therapy, there is statistically significant decrease in serum BDNF levels at 7 and 14 days after ketamine administra-

tion in those who did not respond to treatment. This is a small study with potential risk of bias, such as the use of mood stabilisers by participants, which may affect serum BDNF levels (as lithium does). Nevertheless, if subsequent studies confirm a correlation between the decrease in serum BDNF levels and the lack of antidepressant response, this could support the significant role of BDNF in the mechanism of ketamine action [48]. Hypothetical mechanisms underlying improvement in neuroplasticity (some of which involve BDNF) will be delineated in the next part of this manuscript.

Ketamine mechanism of action according to disinhibition hypothesis

According to the PING (pyramidal-interneuron-gamma) model, increased amplitude of gamma bands is an electrophysiological indicator of glutamatergic transmission disinhibition in visual and motor cortex [49]. This electrophysiological phenomenon is repeatedly noticed after ketamine administration, hence disinhibition of pyramidal neuron transmitting in this context is suspected, but to confirm that further research is required [49, 50]. NMDA receptors are located on both presynaptic and postsynaptic glutamatergic neurons, as well as on GABAergic inhibitory interneurons. Besides that, there are AMPA receptors on postsynaptic glutamatergic neurons. It is hypothesised, that forebrain inhibitory interneurons firing frequency is higher than pyramidal neurons firing frequency, thus it seems reasonable to conclude that blockade of receptors responsible for glutamatergic transmission in both pyramidal neurons and interneurons will result in enhancement of glutamatergic signalling in the forebrain, especially throughout AMPA receptors, since they are not restricted by ketamine inhibition. Furthermore, ketamine appears to have higher affinity to NMDA receptors that consist of Glun2D subunit [51] – that occur at higher frequency on inhibitory interneurons, than on postsynaptic glutamatergic neurons. It is explanatory to the fact that ketamine, at subanaesthetic dose, induces fast antidepressant effect whereas at higher dose – while inhibition of NMDA receptors which regulate excitatory glutamatergic signalling occurs, antidepressant effect is not evoked [35]. Hypothetical mechanism that is proposed as one that could link neuroplasticity improvement and glutamatergic disinhibition among patients taking ketamine is that it is inhibiting NMDA receptors located on GABAergic inhibitory interneurons which results in enhanced glutamate release into the synaptic cleft leading to postsynaptic ionotropic AMPA receptors activation and BDNF release which promotes structural proteins synthesis via mTOR pathway, thus it eventuates in brain neuroplasticity improvement (see Figure 1) [52]. The significance of AMPA receptors is pointed out by a trial where administration of AMPA receptor antagonist resulted in absence of ketamine-induced antidepressant effect [53]. Referring to other studies on rats, the release of glutamate in the hippocampal CA1 region directly and proportionally to concentration increases the synthesis of BDNF in this area [54], which is strongly advocating for link between “disinhibition theory” and increased neuroplasticity brain regions crucial for MDD (major depressive disorder). Nonetheless there are number of publications which present evidence undermining

role of this hypothesis in ketamine-induced fast antidepressant effect, for instance there is evidence for its absence after ionotropic GABA antagonist – picrotoxin infusion prior to ketamine administration [47]. It is possible that the disinhibition theory, with its supporting and opposing arguments, provides only a partial description of the mechanism whose action results in the rapid antidepressant effect observed after ketamine administration.

Ketamine and inhibition of spontaneous glutamate release

An equally important or even crucial element in explanation of the action of this mechanism may be the hypothesis addressing the role of the glutamate spontaneous release inhibition and its impact on the antidepressant effect of ketamine. In the basal activity-state, spontaneous release of glutamate into the synaptic cleft occurs due to fusion of presynaptic vesicles [55]. It is proposed that in physiological state activation of postsynaptic NMDA receptors inhibits BDNF translation throughout eEF2K (eukaryotic elongation factor-2 kinase) activation, which eventually suppresses protein synthesis and neuroplasticity. eEF2 (eukaryotic elongation factor 2) catalyses ribosomal translocation which induces protein synthesis in neuroplasticity processes (see Figure 1) [56]. On the other hand, eEF2 kinase strongly promotes eEF2 phosphorylation, which turns it into inactive form. As it has been demonstrated, eEF2 phosphorylation rate depends on NMDA receptors, since their selective blockage results in decrease of phosphorylated eEF2 level [56]. The occurrence of this process has been experimentally proven in hippocampal neurons [56].

The pivotal role of the described mechanism has been highlighted by studies [57] that have proven that ketamine-induced fast antidepressant effect in mice measured by FST (forced swim test) is absent in eEF2K-knockout rodents as well as in BDNF-knockout rodents. It also does not occur after memantine administration [58], which is a non-competitive NMDA receptor inhibitor. It is suggested, that under the physiological concentration of Mg^{2+} inside ion canal, memantine does not inhibit NMDA receptor subunits involved in spontaneous glutamate release, whereas ketamine does [58].

Ketamine and direct extrasynaptic NMDA receptors blockage

There is a group of NMDA receptors which are located in extrasynaptic area. They are not activated by glutamate release into the synaptic cleft, but they are activated regularly by glutamate that surrounds receptor. Most extrasynaptic NMDARs consist of Glun2B subunits [32]. The activation of these receptors is dependent on EAAT2 (Excitatory amino acid transporter 2) that is

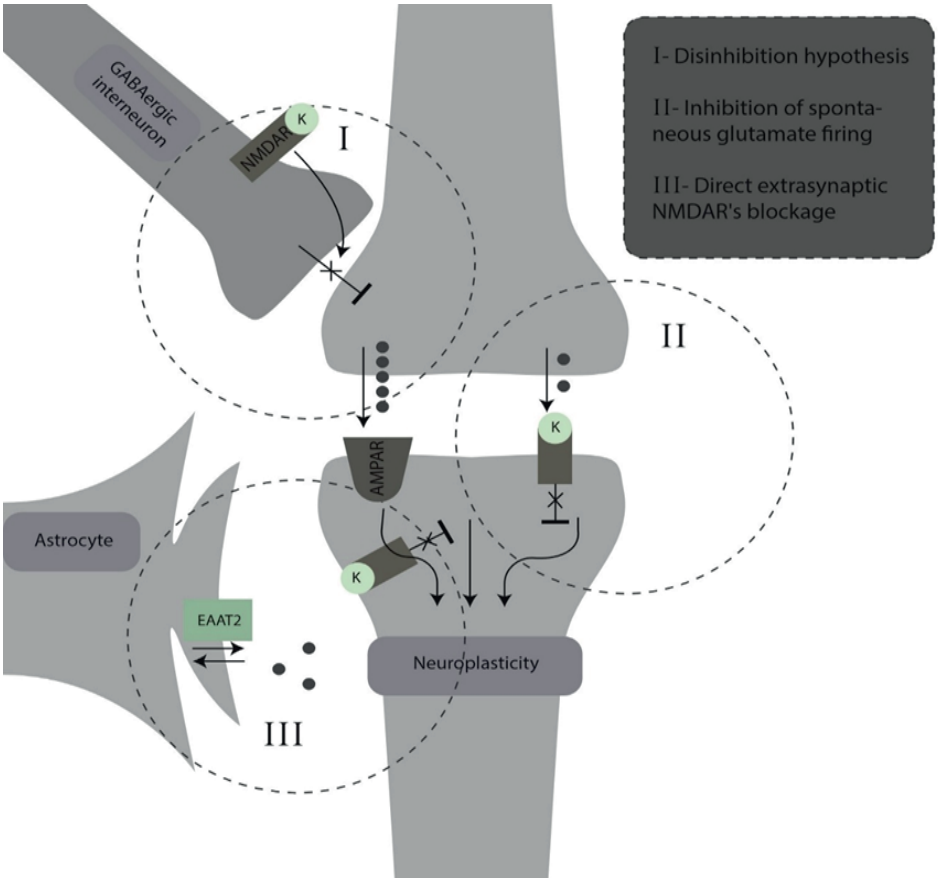

Figure 1. **Hypothetical mechanisms of action of ketamine promoting neuroplasticity**

located on adjacent glial cells [59] and mediates the flux of glutamate from extrasynaptic area into the astrocyte. Presumably, ketamine administration leads to increased glutamate concentration around extrasynaptical NMDA receptor, which results in EAAT2 upregulation [60]. In conditions of increased glutamate concentration in this area, extrasynaptic GluN2B-NMDARs are activated, leading to the inhibition of protein synthesis via mTOR in postsynaptic neurons [61]. Therefore, ketamine, by blocking this group of receptors, may be responsible for the disinhibition of the mTOR pathway and, consequently, for increasing neuronal neuroplasticity (see Figure 1). Key role of extrasynaptic NMDARs as target for ketamine action has been implicated, among others, by the research which has shown that the deletion of Glun2B receptor gene results in absence of antidepressant effect after ketamine administration in mice, nonetheless, it should be noted that impact of ketamine in this specific animal model might be altered due to its tendency for abnormal central nervous system functioning

[61]. Also, administration of selective Glun2B-containing NMDARs antagonist – similarly to ketamine – results in clinical antidepressant effect, which advocates for importance of previously mentioned mechanism [62].

Antidepressant potential of ketamine metabolites

Ketamine metabolites are also suggested as important contributors to its antidepressant effect. Metabolism of (S)-ketamine, as well as (R)-ketamine primarily occurs in the liver via cytochrome P450 enzymes to: norketamine, hydroxyketamine, dehydronorketamine, and hydroksynorketamine (HNK) [63, 64]. First, (S)-ketamine or (R)-ketamine is metabolised by CYP2B6 or CYP3A4 respectively to (S)-norketamine or (R)-norketamine. Next it is metabolised to (S)-dehydronorketamine or (R)-dehydronorketamine and finally to hydroxynorketamines (HNKs). Two main hydroxynorketamines are (2S,6S)-HNK and (2R,6R)-HNK – formed as a result of norketamine transformation by CYP2A6. These two hydroxynorketamines, among other ketamine metabolites, have drawn researchers' attention in terms of antidepressant action [64, 65].

Studies with rodents have shown that HNKs do not present anaesthetic effect after administration, in contrary to ketamine [66]. Nonetheless, fast antidepressant effect occurs after (2S,6S,2R,6R)-HNK administration, according to research findings [67]. Moreover, it has been proven experimentally that (2S,6S,2R,6R)-HNK is necessary for occurrence of fast antidepressant effect measured by FST. In this study on mice, instead of ketamine, (6,6)-dideuteroketamine has been administrated. This agent should analogise unmetabolised ketamine pharmacodynamics, but its metabolism should proceed differently. Indeed, its transformation to (2S,6S,2R,6R)-HNK is extensively reduced in comparison to ketamine. It appears that (6,6)-dideuteroketamine administration, unlike ketamine, does not induce fast antidepressant effect in mice measured with FST, which is advocating for (2S,6S,2R,6R)-HNK importance [67]. This metabolite is mixture of (2S,6S)-HNK and (2R,6R)-HNK which are derivatives of, respectively, (S)-ketamine and (R)-ketamine. In comparison, with the same brain concentration, (2R,6R)-ketamine exhibits greater antidepressant potential in rodents than (2S,6S)-ketamine, which may be one of the explanations why (R)-ketamine rather than (S)-ketamine is more potent as an antidepressant, nonetheless, within a higher brain-concentration (2S,6S)-ketamine exhibits antidepressant properties likewise [67]. Most of the research on (2S,6S,2R,6R)-HNK action, recognise its dose as a sufficient to cause antidepressant response, when it enables to reach maximum brain drug concentration on the 10 μmol/kg level. At this dose (2R,6R)-HNK does not act as NMDA inhibitor, on the other hand it leads to significant enhancement of frequency and amplitude of AMPAR-dependent EPSCs (excitatory postsynaptic currents) at C1 hippocampal region [67].

To confirm that antidepressant effect as a result of (2R,6R)-HNK infusion occurs due to AMPA receptor signalling in mice, the test was conducted – 10 minutes prior to (2R,6R)-HNK administration the AMPA antagonist – NBQX (2,3-dihydroxy-6-nitro-

7-sulfamoyl-benzo[f]quinoxaline-2,3-dione) was administered. Subsequently, the antidepressant effect was measured with FST, and appeared to be absent [67]. It may suggest that AMPA receptors play an important role in ketamine and its metabolites mechanisms of action as antidepressant. Another exam that underlines role of mentioned receptors in ketamine antidepressant response is quantitative encephalography, which allows to measure gamma-band power in humans as well as in rodents, which among others, correlates with AMPA receptors activation degree. Once again, research indicates a link between ketamine metabolites and AMPA receptors mediated antidepressant effect, since similarly to ketamine, (2R,6R)-HNK administration significantly increases gamma-bands power. Research reveals that 10 μmol/kg dose of (2R,6R)-HNK does not inhibit NMDAR-dependent EPSCs like it does with AMPAR-dependent ESPCs, but in higher dose – above 50 μmol/kg – it does. This may underline some additional dose-dependent properties of this metabolite in its high concentrations [68].

(S)-ketamine and (R)-ketamine in depression treatment

In the recent years, while ketamine, which is racemic mixture of two enantiomers – (R)-ketamine and (S)-ketamine (esketamine), have been reviewed for its fast antidepressant effect, both of its enantiomers appeared to exhibit different pharmacodynamic and clinical properties. For instance: (S)-ketamine exhibits stronger anaesthetic and analgesic effect in comparison to (R)-ketamine [69]. It has been suggested that it is due to (S)-ketamine's three times higher affinity to NMDA receptors, compared to (R)-ketamine [70]. Based on this fact it has been postulated that anaesthesia with (S)-ketamine may prove to be associated with less side effects, than with (R)-ketamine, since its target dose is smaller. Nonetheless, research has proven differently. In one of them side effects of treatment with (S)-ketamine and (R)-ketamine have been compared. Despite of considerably smaller dosage of (S)-ketamine compared to dosage of (R)-ketamine, mostly patients from (S)-ketamine group have been affected with psychotomimetic effect and agitation [71]. This and other research have proven that with anaesthetic doses (R)-ketamine is inflicted with lesser risk of adverse effects.

Nonetheless, in terms of studying ketamine antidepressant potential, which was described in 2000 [20], a number of researchers once again focused on (S)-ketamine because of its stronger binding with NMDA receptors. Eventually, the fast antidepressant effect after (S)-ketamine (dosed 0.2 mg/kg and 0.4 mg/kg) administration was confirmed. Adverse effects, including dissociation, agitation and hallucinations, were more pronounced at the higher dose, while the antidepressant effect was comparable [72]. Further research has shown its sufficient antidepressant effect, compared to the control group [73, 74]. Regarding strong evidence for (S)-ketamine treatment efficiency, in 2019 it was brought to market in US as well as in UE in nasal spray formula, dedicated for patients with treatment-resistant depression.

However, perhaps researchers have focused on the wrong enantiomers, as with anaesthesia and analgesia? Pre-clinical trials conducted in 2019 seem to implicate that

(R)-ketamine has greater antidepressant potential than (S)-ketamine [75, 76], as well as its better therapeutic profile in terms of adverse effects, which are major concern in (S)-ketamine therapy. Moreover, psychotomimetic effect potentially increases recreational (S)-ketamine misuse risk. Furthermore, research shows that with an animal model (S)-ketamine requires higher central nervous system concentration to induce antidepressant effect, compared to (R)-ketamine [67]. Notably, it is not a result of different bioavailability of two enantiomers, since research on rodents have shown that central nervous system drug concentration does not differ between enantiomers if adequate dose has been used [67].

The first pilot study on (R)-ketamine antidepressant effect in humans was conducted in 2020. There were seven participants – patients suffering from TRD, and five of them have been prescribed with antipsychotics [77]. Antidepressant effect, measured with Montgomery-Åsberg scale in first and in seventh day was promising, moreover, adverse effects typical for (S)-ketamine did not occur. Admittedly, this pilot study is flawed in certain aspects, which makes it difficult to draw a conclusion, but certainly it is a step towards a closer look on (R)-ketamine – potentially better antidepressant than (S)-ketamine.

Lateral habenula as key region for ketamine's action

Although, ketamine antidepressant effect has been known for a short time, recently there is growing interest in ketamine-induced inhibition of NMDA receptors of the lateral habenula, which is a part of the epithalamus. There are two significant pathways connecting a limbic system with a midbrain, the epithalamus is part of one of them. Another one – called main pathway – goes from frontal nasal area, through lateral preoptic area, lateral hypothalamus to ventral tegmental area, which is a part of midbrain [78]. Lateral habenula glutamatergic receptors may be activated in couple of ways, for instance as a result of GABA-ergic inhibitory neurons activation, triggered by psychological stress, which antagonise dopaminergic signalling in this area [79]. The lateral habenula is especially interesting in terms of psychiatric illnesses. First of all, it is one of a few regions that regulate both serotonergic and dopaminergic system. Moreover, it is the only region that, throughout a number of studies on animal depression models, persists to exhibit increased neuronal activity in brains of depressed-like animals according to these models [80–82].

It is revealing that common phrase used to characterise this region is "antireward brain system", therefore it is no wonder, regarding its features as well as research on animal models results, that the lateral habenula neurons are potential target for antidepressants, including ketamine. The results obtained from animal studies encouraged scientists to conduct experiments on lateral habenula activity in patients with depression. For instance, some analysis implicated that it is possible that lateral habenula volume correlates with occurrence of anhedonia in humans, however, it should be noted that, in this particular regressive analysis, sample size was modest, and lateral

habenula volume did not correlate with occurrence of other depressive symptoms [83]. Studies on animals show that ketamine administration directly to the lateral habenula of rodents induces antidepressant effect in a rat model of depression which is detectable 60 minutes after infusion, using the FST [82].

It is tempting to ask whether it is through NMDA blockade in this region that ketamine induces antidepressant effect. Bathing of brain slices consisting lateral habenula neurons in ketamine solution have shown that afterward NMDARs-dependent EPSCs are not inhibited, instead it results in complete NMDAR-mediated inhibition of spontaneous glutamate release, which shows that NMDARs are essential for ketamine antidepressant action in this area. On the other hand, administration of AMPAR inhibitor resulted in moderate inhibition of spontaneous glutamate release [82]. These results appear promising for better understanding of ketamine antidepressant action, but it should be noticed that for now antidepressant effect is confirmed only hour after ketamine administration into this structure, thus further research on the role of the lateral habenula in long-lasting fast antidepressant effect after ketamine administration in humans is needed. It should be underlined that strong correlation between administration of ketamine into the lateral habenula and antidepressant effect occurrence is only shown in animals. For recognition of the lateral habenula as significant as suggested earlier, further research with human participants is needed.

Recapitulation

Ketamine, as a non-classical antidepressant, by its mechanism of action addresses different hypothesis on pathogenesis and pathophysiology of depression. The mode of action of this new medicine is brought up as advocating for glutamatergic theory of depression righteousness, which emphasise concept of dysregulation of glutamatergic and GABA-ergic systems as potentially key factor for depression and anxiety disorders pathogenesis, among others in the central nervous system damaged by glutamatergic excitotoxity. Ketamine, by its influence on neural plasticity due to BDNF action, shifts balance between neurogenesis and neurodegeneration toward proliferation of neural cells. Also, its antiapoptotic action, due to calcium ions influx inhibition, promotes neuroplasticity processes overbalance.

Neurogenic theory of depression emphasises the significance of hippocampal neurogenesis disturbance in aetiology of depression in adults, which occurs for instance due to overactivity of the hypothalamus-pituitary-adrenal axis. The importance of this axis is also underlined in immunological theory of depression which propose immunological activation and inflammatory reaction as fundamental for depression development, partly due to cytokines' capability for overactivation of glutamatergic system, which leads to disturbance in neuroplasticity. Research shows that ketamine administration results in increasing of hippocampal BDNF level, as well as in other areas of CNN, which leads to propagation of neurogenesis processes

(also in other mechanisms than BDNF-related) and due to neuroplasticity counteracts degeneration caused by excessive glutamate release as a result of immune system activity. The manner in which ketamine mechanism of action corresponds with these theories appears to be premise for further research on its influence on the central nervous system, as this knowledge may be the way for better understanding of affective disorders themselves, which is one of the greatest challenges of modern psychiatry.

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