HELSINGIN YLIOPISTO

Interactions of Ketamine with Opioids and Its Effects on BDNF and VEGF

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Ketamiini on tunnettu NMDA (N-metyyli-D-aspartaatti) -reseptorin antagonisti, jota käytetään laajasti nukutusaineena osana yleisanestesiaa, sekä kipulääkkeenä esimerkiksi postoperatiivisen kivun hoidossa. Matala-annoksinen ketamiini (<0.5 mg/kg) on tehokas kivunhoidon lääkkeenä ja kliinisessä käytössä se yhdistetään usein opioideihin, kuten morfiiniin. Aiemmat tutkimukset osoittavat, että ketamiinin samanaikainen annostelu opioidien kanssa saattaa nostaa sen plasmapitoisuutta, mikä puolestaan voi lisätä sen analgeettista tehokkuutta. Tällöin tyypillisten opioidien aiheuttamien haittavaikutusten, kuten opioiditoleranssin kehittymisen ja opioidien aiheuttaman hyperalgesian (OIH), riskit vähenevät, mikä voi parantaa pitkäaikaishoidon tuloksia.

Ketamiinin viimeisin keskeinen käyttöaihe on hoitoresistentin vaikean masennuksen hoito. Sen nopea antidepressiivinen vaikutus on yhdistetty neurotrofiinien, erityisesti aivoperäisen neurotrofisen tekijän (BDNF) ja verisuonikasvutekijän (VEGF), säätelyyn. Nämä neurotrofiinit ovat keskeisiä tekijöitä hermosolujen kasvussa ja synaptisessa välityksessä sekä neurogeneesissa, ja niiden matalat pitoisuudet on yhdistetty masennuksen ilmenemiseen. Ketamiinin on osoitettu lisäävään näiden neurotrofiinien pitoisuuksia, mikä voi kumota masennuksen aiheuttamia aivojen atrofisia muutoksia ja siten parantaa kognitiivisia toimintoja.

Masennuksesta kärsivillä potilailla on osoitettu usein myös vuorokausirytmin häiriöitä, joka voi edelleen vaikeuttaa oireita. Tutkimukset viittaavat siihen, että ketamiini voisi myös stabiloida vuorokausirytmiä, joka voisi siten liittyä sen masennuslääkinnälliseen vaikutusmekanismiin.

Tässä kirjallisuuskatsauksessa tarkastellaan ketamiinin monipuolisia ominaisuuksia masennuslääkkeenä, sekä sen toista keskeistä käyttöaihetta kivunhoidossa ja mahdollisia farmakologisia interaktioita opioiden kanssa yhteiskäytössä.

Ketamine is a well-known NMDA (N-Methyl-D-aspartate) receptor antagonist that is widely used as an anesthetic in general anesthesia and as an analgesic, particularly postoperative pain management. Low-dose ketamine (<0.5 mg/kg) is an effective analgesic and in clinical practice is often used in combination with opioids like morphine. Previous animal studies, followed by clinical research, suggest that ketamine inhibits the metabolism of morphine, thereby increasing its plasma concentrations. Evidence indicates that co-administration of ketamine with opioids can increase the plasma levels of ketamine as well potentially enhancing its analgesic effects. This decreases the side effects of opioid use, such as the risk of opioid tolerance and opioid induced hyperalgesia (OIH).

More recently, ketamine has been explored as a treatment for treatment-resistant major depressive disorder (MDD). Its antidepressant effects are linked to neurotrophic factor regulation, especially brain-derived-neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). These neurotrophic factors are significant in neuronal growth, synaptic transmission, and neurogenesis, and their low concentrations in the brain are associated with the manifestation of depression. Ketamine is shown to increase these levels of neurotrophic factors in human brain and therefore potentially reversing the atrophy changes associated with depression.

Patients with treatment-resistant depression have been shown to also suffer from circadian rhythm disruptions. Recent studies indicate that ketamine can stabilize circadian rhythm which could contribute to its antidepressant effects.

This literature review examines the versatile antidepressant properties of ketamine and explores its potential pharmacological interactions with opioids in pain management.

Table of contents

1 Introduction

The N-Methyl-D-aspartate receptor (NMDAR) antagonist ketamine is a drug used for multiple different indications in medicine. It was developed for use as an anesthetic in 1966 and stands out due to its' rare quality to create a dissociative anesthesia where the patient does not react to sensory stimuli but still maintains adequate circulation and ventilation (1). Ketamine has two stereoisomers S (+)- and R (-)-ketamine, where S-ketamine has a trading license in Finland for two preparations (5 mg/ml and 25 mg/ml) and two racemic ketamine products (both 50 mg/ml, other also 10 mg/ml) (2). In addition, to its use in general anesthesia, ketamine is exploited as analgesic especially in postoperative, neuropathic, and cancer pain treatment. The newest indication for ketamine is treatment resistant major depression. This review mainly focuses on ketamine's utilization in major depressive disorder (MDD).

Low-dose (< 0.5 mg/kg) ketamine has been used as a part of multimodal analgesia. It holds the beneficial properties to lessen cellular and molecular mechanisms behind different pain states, opioid tolerance, and opioid induced hyperalgesia (OIH) (3). For these purposes, ketamine has been studied to some extent. Cautious evidence exists that perioperative intravenous low-dose ketamine reduces postoperative pain and opioid consumption, which makes it more favorable in situations with greater background levels of pain (4). The use of opioids in relieving postoperative pain and cancer pain is crucial. Many side effects, including nausea and vomiting, respiratory depression, intense itching, tolerance, and OIH limit the applicability of opioids in mentioned conditions (5).

Depression is an extremely disabling illness and is prevalent among the population (6). Various treatment methods for severe depression have been extensively studied such as electroconvulsive therapy (ECT) in combination with conventional treatments, antidepressant drugs, and psychotherapy. Ketamine infusion as a treatment for depression is effective, rapid, and a suitable treatment possibility for previously treatment-resistant diagnosed depressions, alleviating suicidal thoughts, and treating depression in patients suffering from concurrent pain.

Ketamine exerts its therapeutic effects primarily by inhibiting the NMDA receptors and also by enhancing glutamatergic signaling. Disinhibition hypothesis suggests that ketamine induces excitatory cortical disinhibition, which subsequently promotes the

release of neurotrophic factors, notably brain-derived neurotrophic factor (BDNF) and Vascular endothelial growth factor (VEGF) (7).

BDNF is an important neurotrophic factor. It is involved in neuronal growth and proliferation, synaptic neurotransmission, and neuroplasticity. In the body, BDNF is present widely in central nervous system (CNS) such as hippocampus, hypothalamus, mesencephalon, brainstem, and spinal cord. It is also expressed in peripheral nervous system and other peripheral tissues such as blood platelets and skeletal muscles (8). VEGF is a pleiotropic growth factor and induces angiogenesis and lymphangiogenesis. It is found in circulatory system in endothelial cells lining blood vessels as well as in heart, lung, and kidney tissues (9). In human tissues VEGF is also found in skeletal muscles as well as BDNF (10). Therefore, these neurotransmitters are particularly crucial for understanding the application of ketamine in the treatment of depression.

It has been proposed that reduced brain levels of BDNF and VEGF are associated with depressive symptoms (11). Studies show that reduced levels take part in atrophy in the prefrontal cortex (PFC) and hippocampus and hippocampal neurogenesis. Treatment with typical antidepressants, such as SSRI- and SNRI-drugs, can partially reverse these deficits. Ketamine impacts rapidly as an antidepressant. In rodent studies it has been shown that ketamine increases BDNF and VEGF release as well as induces the perpetual release of insulin-like growth factor 1 (IGF-1).

Intravenous ketamine in subanesthetic concentrations is used for treatment-resistant depression. Recent studies show that the mechanism behind the effect of ketamine is by the activation of AMPA receptors and BDNF. The dose of ketamine in depression treatment has been the same with ketamine doses in pain management (<0.5 mg/kg). On the other hand, the results in clinical trials have been variable when using racemic ketamine, R-ketamine, or S-ketamine (12).

This literature review provides background information for a study I participated in. The study involved administering S-ketamine to healthy volunteers and evaluating its pharmacokinetic interactions with morphine, hydromorphone, and buprenorphine. In addition, the research examined the effects of ketamine on blood concentration of BDNF and VEGF levels, focusing on whether the pharmacological response of ketamine in relation to depression could be monitored by measuring growth factors in the blood. However, the analyses are not yet complete.

2 Pharmacological and Clinical Uses of Ketamine

2.1 The Clinical Roles of Ketamine

Ketamine was developed in the 1960s from phencyclidine. It was first used in Vietnam war as a field anesthetic due to its exceptional function of stimulating the blood circulation and not causing respiratory depression while creating dissociative anesthesia. Its use in chronic pain therapy began in 1990s while treating chronic pain patients it was discovered that ketamine could also be utilized as antidepressive drug (2).

Ketamine has several pharmacological targets which include γ-aminobutyric acid (GABA), dopamine, serotonin, sigma receptors as well as cholinergic receptors and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Some studies have shown that ketamine also interacts with opioid receptors (13,14). Though, it is important to note that the antidepressant, analgesic, and anesthetic attributes of ketamine are mostly through noncompetitive inhibition of N-methyl-D-aspartate (NMDA) receptors (15). NMDA-receptors are glutamatergic cation channels that pass calcium ions through (16). Ketamine is a racemic mixture combined of two optic stereoisomers S-ketamine and R-ketamine. S-ketamine binds to NMDA receptor with even 5 times higher affinity than R-ketamine and therefore is responsible for the analgesic and anesthetic effects in body. S-ketamine and ketamine are thus discussed together due to their similar qualities (17).

The effects of ketamine on the cardiovascular system are mostly sympathomimetic. It stimulates heart rate and increases arterial pressure at anesthetic and subanesthetic concentrations. Unlike other intravenous anesthetics, ketamine increases regional cerebral metabolism and blood flow, and so can possibly rise intracranial pressure (ICP) (1). Thus, the contraindications of ketamine are severe hypertension, intracranial pressure rise, pre-eclampsia, and eclampsia.

2.2 Pharmacokinetic and Pharmacodynamic Properties

Ketamine is a water- and lipid-soluble aryl-cycloalkylamine with a molecular mass of 238 g/mol and a pKa of 7.5. Systemic distribution of ketamine to brain and other well supplied tissues occurs rapidly after intravenous administration. It is widely distributed in the body due to its lipid solubility, with a plasma distribution volume of 2.3 l/kg. The pharmacokinetic key properties of ketamine are summarized in Table 1.

Ketamine is considered a complex drug due to its stereoisomers and many metabolites. The most extensive metabolite is norketamine. The majority of ketamine (80%) undergoes fast conversion to norketamine via demethylation (18). This process is mostly facilitated by liver enzymes CYP2B6 and CYP3A4. Subsequently, norketamine is further metabolized into dehydronorketamine (DHNK) and hydroxynorketamine (HNK). Whilst the liver functions as the primary site for the metabolism of ketamine, other organs i.e., kidneys, lungs and intestines may contribute to the process as well.

Ketamine has a high clearance rate (12–20 ml/min/kg), which is linked to high liver blood flow. Due to this, its' half-life is 2-3 hours (19).

Ketamine modulates both supraspinal and spinal pathways, influencing the processing of sensory input. The main effect is seen in thalamo-neocortical system, disrupting the communication between neocortex and thalamus. Anesthetic state of ketamine is primarily induced by blocking NMDA receptors. In addition, it has impacts on neurotransmitter systems, the most importantly glutamatergic system which is the preponderant factor in the antidepressant effects of ketamine (20).

The rapid antidepressant mechanisms of ketamine are closely tied to its pharmacokinetic properties, which enable rapid brain penetration and the formation of active metabolites. The modulation of BDNF signaling and enhancement of neuroplasticity by ketamine are crucial mechanisms for depression treatment (13).

Table 1. Pharmacokinetic properties of ketamine

Molecular mass	238 g/mol
pKa	7.5
Plasma distribution volume	2.3 l/kg
Clearance rate	12–20 ml/min/kg
Elimination half-life	2–3 h

3 Ketamine as an Analgesic

3.1 Co-administration With Opioids

As previously mentioned, ketamine is more commonly used as an anesthetic than an inducer and maintenance drug in general anesthesia. It can be used alone but mostly is combined with other anesthetics. In acute pain ketamine can be given in subanesthetic doses as a single agent especially in field conditions. However, when managing pain with spinal and epidural anesthesia, ketamine is often combined with opioids or local anesthetics such as ropivacaine or bupivacaine (2,21).

Patient-controlled analgesia (PCA) is a type of pain management where the patient him-/herself can dose a supplemental analgesic dose when needed. Recent studies show that adding ketamine with morphine or hydromorphone PCA provides an improvement in pain relief as well as reduces the opioid amount used (22). A study conducted by Bossard et al. (23) shows that ketamine and morphine may reduce synergistically pain response by decreasing the stimulus in nociceptive flexion reflex (RIII reflex). Other mechanisms behind this analgesic enhancement are studied as well but the conclusions remain inconclusive (24). However, results advocate further for use of ketamine in addition to traditional pain-relieving medications.

The NMDAR antagonism of ketamine is considered as the main mode of action for analgesic and opioid reducing effects. A theory introduced to enhance pain management suggests that the mechanism is related to pharmacokinetics.

3.2 Metabolic Pathways of Opioids

The metabolism of drugs in the body can be divided into four different main phases (0-III). In phase 0 the drug, i.e., an opioid, enters the cell. During phase I the drug is modified by the addition of a functional group, typically through enzymatic oxidation. A glutathione or glucuronide is added to a functional group in phase II. By the end of phase III, the drug has been transformed into a more hydrophilic molecule, allowing to exit the cell (17).

Morphine is a hydrophilic drug, undergoes metabolism primarily through conjugation to glucuronides. In phase I cytochrome P450 (CYP) enzymes catalyze morphine to metabolite normorphine, but this only account for 5% of metabolism.

3.3 Phase II Metabolism of Opioids

Most of the metabolism of morphine occurs through a hepatic pathway producing two main metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), of which M6G is an active analgesic and M3G is an inactive metabolite.

In humans, the enzyme responsible for converting morphine to M3G and M6G is called glucuronosyltransferase (UGT2B7). Glucuronidation is a process where lipophilic drugs are converted to hydrophilic metabolites and thereby can be excreted from the body via kidneys and urinary tract. This process is shown in figure 1.

M3G antagonizes the formation of M6G to small extent (25). In rodent studies it has been shown that ketamine increases morphine's analgesic effects by inhibiting morphine metabolism and reducing the formation of M3G (26). In addition, these findings are supported by the interindividual variability observed with the use of ketamine as part of multimodal analgesia.

Hydromorphone is another opioid that undergoes hepatic glucuronidation via UGT2B7 as well (27). Many other opioids such as oxycodone use the hepatic CYP450 enzymes for metabolism but with morphine and hydromorphone the pathway is insignificant (28).

Buprenorphine is metabolized through hepatic pathway but as well partially in the small intestine by glucuronidation and dealkylation. In some measures it is converted by CYP450 to norbuprenorphine. Both buprenorphine and norbuprenorphine undergo glucuronidation via UGT2B7 to form active metabolites (29).

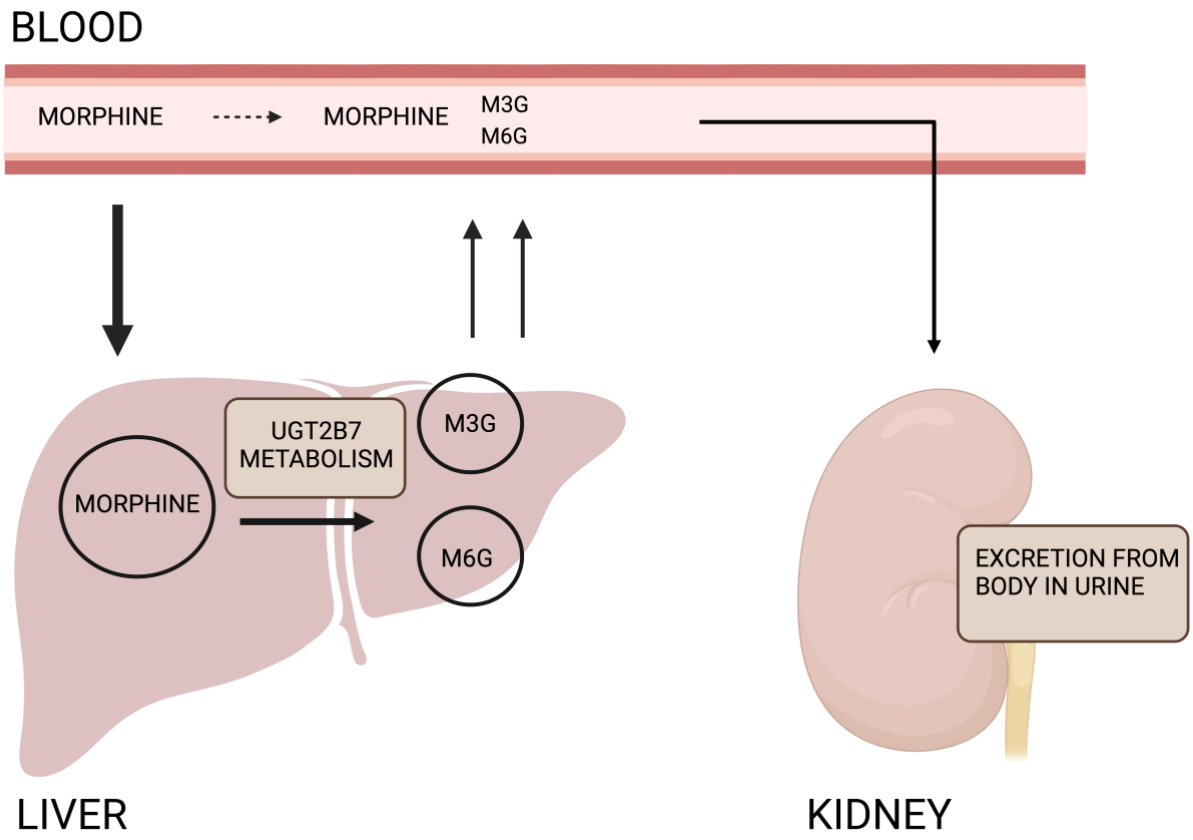

Figure 1. Morphine's metabolic pathway in body.

4 Neurotrophic Factors in Depression

4.1 BDNF and VEGF in Neuroplasticity

In the human brain, reduced levels of various neurotrophic factors, i.e., vascular endothelial growth factor (VEGF) and brain derived neurotrophic factor (BDNF), have been linked to the manifestation of depression. The level decrease leads to neuronal atrophy in prefrontal cortex and hippocampus. In rodent studies it has been pointed out that ketamine can rise the BDNF and VEGF release from pyramidal neurons in the medial prefrontal cortex and therefore accelerate their expression in PFC and hippocampus (30).

BDNF levels are significantly higher in human serum compared to plasma and cerebrospinal fluid. Over 90% of the BDNF present in blood is stored in platelets. Serum BDNF is primarily derived from blood platelets, which release it upon activation (8).

BDNF is a neurotrophic factor that targets motoneurons, sensory neurons and hippocampal neurons in the brain. It is a key factor in neuronal growth and engages as a neurotransmitter modulator as well as in the plasticity of neural network. This capability to create neuronal plasticity is why BDNF is believed to act as a factor in antidepressants' long-lasting effects (17). Decreased levels of BDNF are linked to multiple neurodegenerative diseases i.e., multiple sclerosis (MS) and Parkinson's disease and therefore can be described as a neuroprotective factor (31). Numerous studies show that BDNF is closely linked to the onset and progression of depression. Especially in women the deprivation of BDNF in amygdala is associated with MDD (32).

It is proposed that antidepressants such as SSRIs could bind to TrkB, the receptor of BDNF and thereby promote synaptic plasticity. Serum levels of BDNF in depression are often decreased and then increase with successful treatment. The coarse mechanism of BDNF mediated signaling is illustrated in Figures 2 and 3. However, due to significant interindividual variability, it is not a reliable marker in depression

diagnostics (33). With ketamine, the increased levels of BDNF are achieved by blocking NMDA receptors (34).

VEGF targets the motoneurons in brain. It is produced by vascular endothelial cells, neurons, astrocytes, and perivascular macrophages. VEGF's main ability is to stimulate blood vessel formation (angiogenesis) but apart from this, it also possesses strong properties in generating new nerve cells (neurogenesis), supporting the growth of nerve cells (neurotrophic), and shielding existing nerve cells (neuroprotective) (35). VEGF also contributes to various brain functions such as memory, learning and mood regulation. These effects are primarily mediated through a specific tyrosine kinase receptor known as fetal liver kinase 1 (Flk-1, also identified as VEGF receptor 2). It is important to note that VEGF levels in brain may not correlate with blood levels (30).

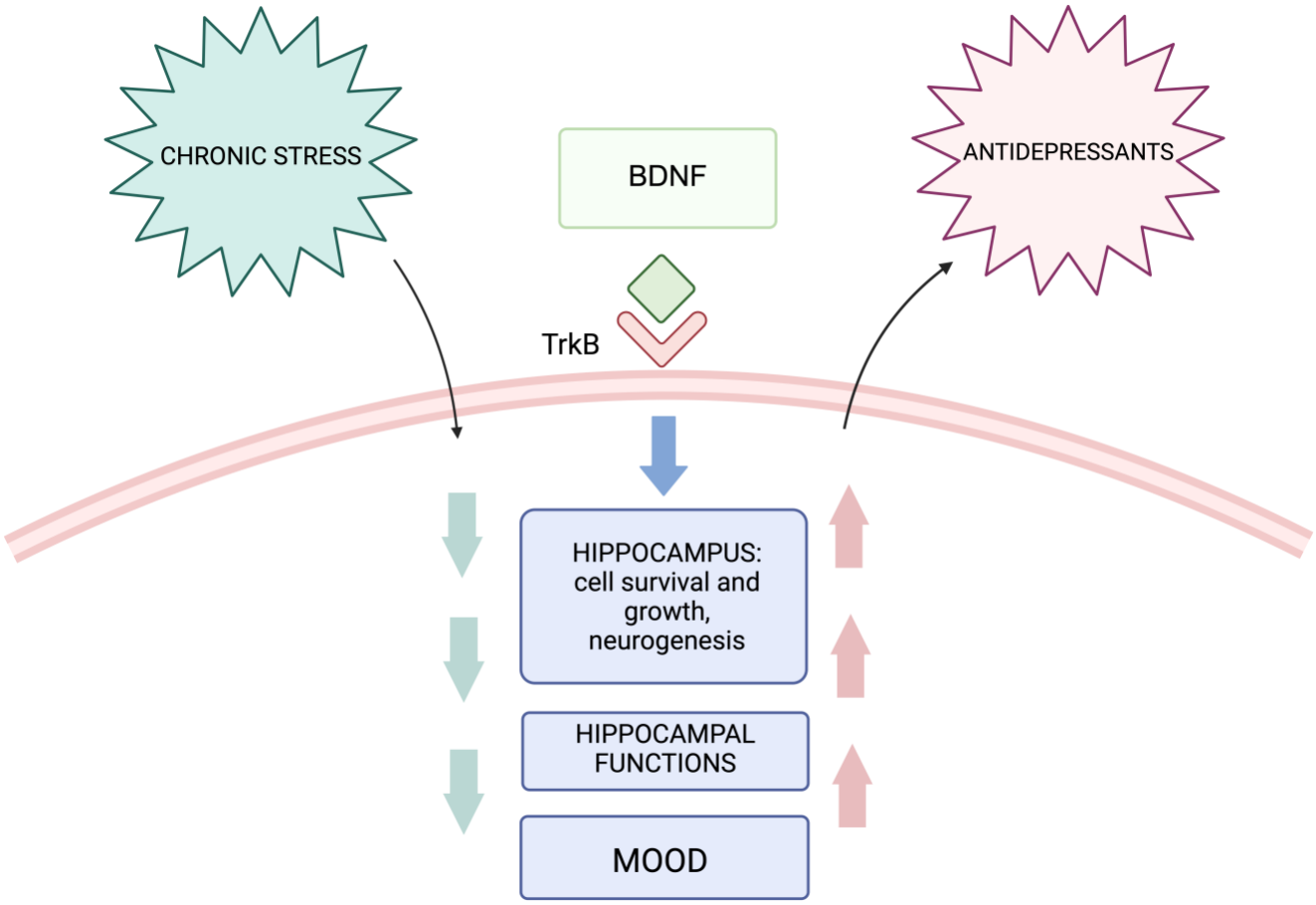

Figure 1. BDNF mediated pathway in brain with chronic stress and antidepressant effects in mood.

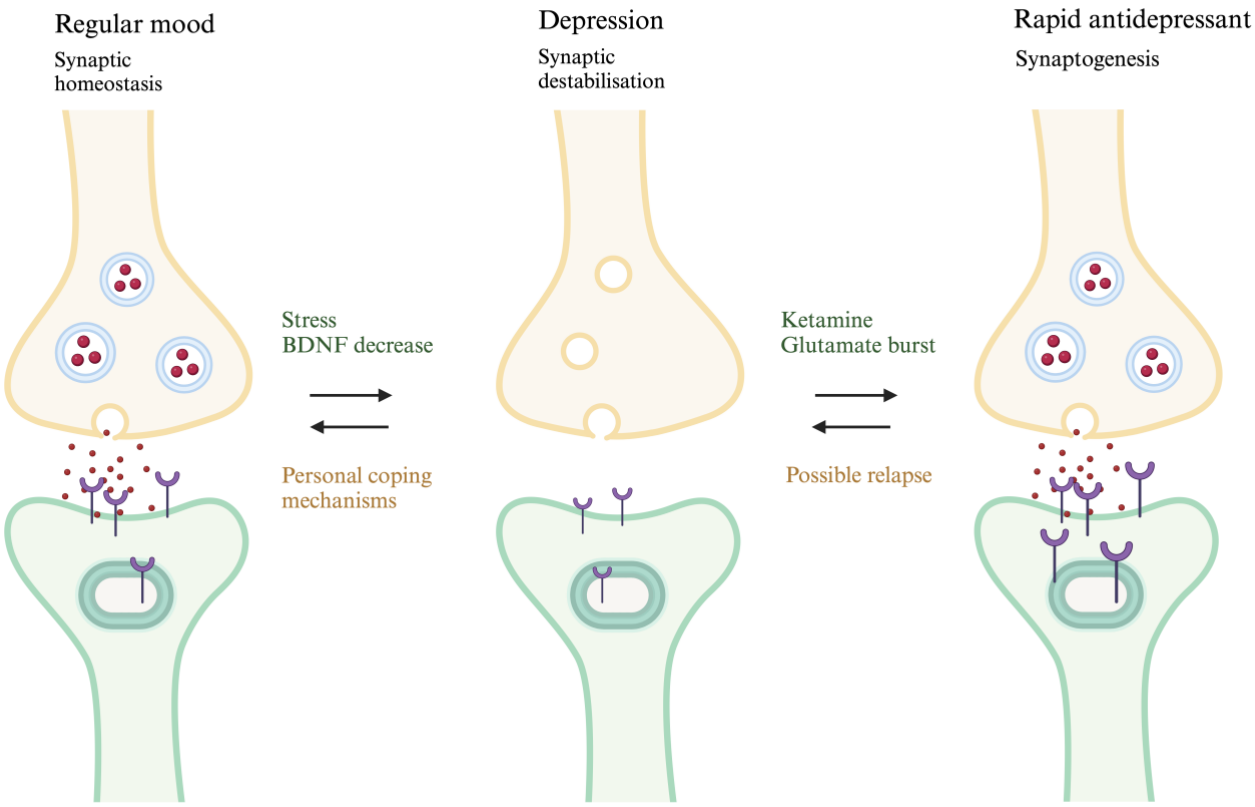

Figure 2. Synaptic changes in depression and antidepressants effect in neurotransmitter signaling,

5 Ketamine as an Antidepressant

5.1 Mechanisms of Ketamine in Treatment Resistant Depression

Large portion of depression patients remain treatment resistant despite the extensive range of antidepressants and high-quality therapy (36,37). The conventional theory of depression's pathophysiology is predominantly derived from pharmacological studies, which indicate that dysfunction in monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) is disrupted in individuals with depression (37). This has been partially confirmed through direct examination of systems using contemporary functional imaging methods (38). It is suggested that excitatory neurotransmitters, particularly brain glutamate and GABA systems are significantly behind the pathophysiology of depression (39). Altered glutamate and GABA levels have been detected in both human and animal studies. Significantly decreased levels were observed in regions such as PFC and anterior cingulate cortex (ACC), suggesting that disruptions in glutamatergic and GABAergic signaling, which affect neuronal plasticity and activity are pivotal to the pathophysiology of MDD. This also explains the pharmacological mechanism behind the antidepressant effects of ketamine by the rapid reversion of neurochemical disturbances by modulating glutamate and GABA systems' neurotransmission, promoting neuroplasticity and synaptogenesis. This further establishes the theory that a dysfunction in the glutamate and GABA systems are involved in the pathophysiology of depression (40). The effect of ketamine, where glutamate is released from postsynaptic neurons is shown in figure 4.

Ketamine infusion is used as an antidepressant treatment for treatment-resistant depression. It is suitable for both unipolar depression and bipolar affective disorder's depressive episodes. The ketamine infusion is administered 1-3 times a week. Possible side effects are classified into acute effects, such as anxiety, euphoria, and delusional states, and long-term effects, including a decline in cognitive performance and the increased risk of psychosis (41). The longest treatment period with ketamine infusion is reported at 1.5 years, where no severe side effects emerged. It is crucial to remember that prolonged ketamine infusion therapy is not far researched (42). An alternative option for intravenous ketamine is using S-ketamine in a nasal spray form (43).

Multiple clinical trials have shown that ketamine effects within 2 hours after given infusion and the antidepressant impacts last for approximately 7 days within patients that have tried at least two different antidepressants and yet have not attained the desired therapeutic response (44,45). Ketamine-induced euphoria is a short-term lasting effect where subject may feel a temporary "high." Patients suffering from major depression that received ketamine infusion as treatment purposes have reported that the experience of euphoria disappears shortly post infusion while lessening of depressive symptoms still occurs for multiple days (46).

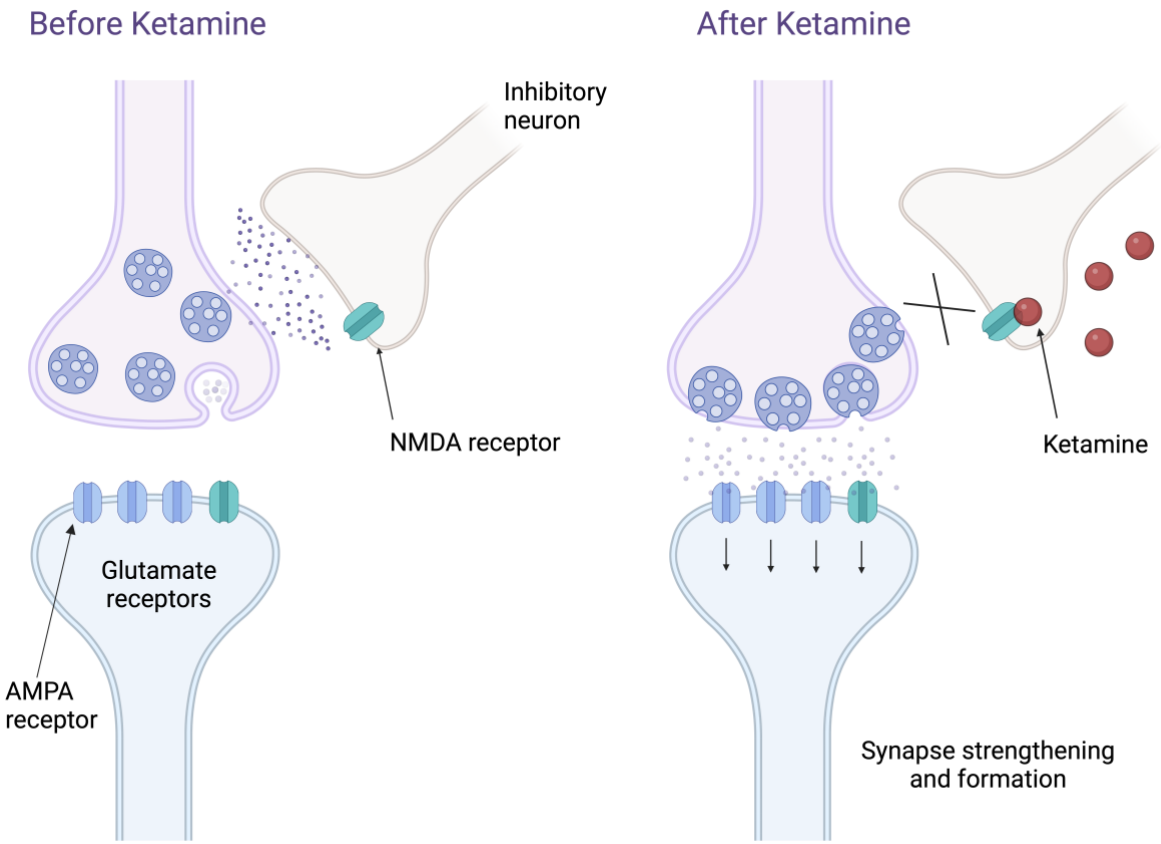

Figure 4. Ketamine blocking NMDA receptors induces glutamate burst from glutamergic synapses.

5.2 Clinical Administration and Efficacy of Ketamine in Depression

The anesthetic and analgesic effects of a single treatment with ketamine last for a few hours. Though the antidepressant effects of ketamine peak around 24 hours after treatment and maintains for couple of days. The short-acting but long-lasting effect of ketamine is believed to be like the regulation of sleep, facilitating of glutamatergic neurotransmission by the preferential blockade of NMDARs on GABAergic interneurons. This glutamatergic process is believed to induce the removal of inhibitory ones in pyramidal neurons, leading to heightened excitation and the release of BDNF. Eventually, cascade of BDNF activates cellular signaling pathways that support the formation of new synapses and adaptability of previously existing synapses. Compared to classical antidepressants where the full potent effect takes even multiple weeks to achieve, the rapid effects of ketamine in MDD patients are significant (47).

Based on previous clinical trials it is suggested that the effects of ketamine can be so rapid that the melioration of depressive symptoms starts even during the infusion. In the initial phase of its pharmacological effect, ketamine enhances the release of glutamate, boosts energy metabolism, and promotes the secretion of BDNF. This process also provokes the activation of numerous molecular pathways believed to play a role in intensive protein synthesis and the facilitation of synaptic plasticity. The emerge of psychomimetic and dissociative impacts after ketamine administration have been linked to the immediate surge in gamma oscillations. However, the prolonged and heightened gamma power effect of ketamine has been proposed as a potential indicator of ketamine-induced enhancement of synaptic strength (48). The studies suggest that ketamine-induced modulation of neural activity could be essential for the rapid antidepressant effect to work (49,50).

6 Circadian Rhythm

6.1 Overview of Circadian Rhythm

The pathophysiology of depression has been connected to dysfunction of circadian rhythm regulation. This is increasingly relevant as recent studies indicate that present-day's time cues (social zeitgebers) associated with modern lifestyles disrupt the circadian clock (47). Social zeitgebers are routines, activities, or social and personal relationships, for example eating meals or doing sports. Major depressive disorder is associated with circadian irregularities such as hormonal secretion changes and dysregulation of sleep.

Physiological and behavioral habits are preserved by circadian rhythms, 24-hour lasting patterns, that have derived in nearly everything in life (51). Cellular oscillators located in the suprachiasmatic nucleus (SCN) in the hypothalamus control circadian rhythms in mammals. Internal and external time cues together with signals from SCN create and conduct daily cycles (52).

Key clock gene expression habits were discovered in a study conducted by Li et al. These key clock genes are important for controlling all body's rhythms and more importantly it was noted in the study that depression patients' clock genes were not expressed correctly. This could explain many neural dysfunctions observed in major depressive disorder patients and therefore illustrate the symptoms associated with these patients (53).

6.2 Neurotrophic Mechanisms in Circadian Rhythm Regulation

Rodent studies have shown that BDNF levels in rats' frontal cortex and hippocampus fluctuate during a 24-hour cycle. The mechanisms of BDNF induction are both hormonal and influenced by the activity and light. BDNF levels rise in brain's visual cortex when the eyes open, suggesting that light acts as the sensory stimulus. In non-visual areas of the brain, hormonal differences, particularly corticosteroids, affect BDNF expression. In human studies it has been shown that plasma BDNF levels peak

in the morning and then decrease steadily throughout the day. This pattern is similar to cortisol, a hormone integral to the stress response, indicating a potential synergistic role supporting the cerebral functions (54). Yet other studies have observed an absence of daily variation of BDNF levels in women, attributing to the influence of differential sex hormones and discrepancies in the regulation of the hypothalamic-pituitary-adrenal axis between sexes (55). In recent study conducted by Ehrhardt et al, a circadian rhythm of plasma BDNF was not observed in male participants. However, serum BDNF level decrease during sleep was detected (56).
It has been suggested by data collected from human, animal, and neuronal cell studies that ketamine could modulate circadian rhythms (57). More closely ketamine possibly could reset abnormal clock genes and therefore stabilize circadian rhythms in MDD patients.

6.3 Effects of Ketamine on Circadian Rhythm

The pharmacological effects of drug administration are subject to modulation by various physiological functions. Circadian rhythm impacts these functions. However, it remains unclear how administering drugs at different times may directly affect these rhythms.

Rodent studies have explored this by administering ketamine during different phases: the rest (light) phase and the active (dark) phase. Rebuelto et al. (58) found that the pharmacological response of ketamine was longest when administered during the rest phase and shortest during the active phase. Similarly, research by Mihara et al. (59) demonstrated that ketamine administered during the rest phase induced phase advances of 65- and 153-minutes, while administration during the active phase caused phase delays of 43- and 235-minutes. These findings suggest that ketamine has opposing phase-shifting effects on circadian rhythms according to the time of the administration.

The findings conducted in rodent studies have been described in clinical studies as well. Zhuo et al. (60) created a protocol to test the hypothesis of administering ketamine during daytime and nighttime and compared the antidepressant effects. They anticipated that ketamine improves synaptic density and functional connectivity while

normalizing disrupted circadian rhythms. This would take place especially during nighttime administration similarly to previous rat study findings where ketamine induced phase advances in rest (dark) phases of rats.

Depression is known to disrupt sleep and circadian rhythm. However, limited research has been conducted on the effects of antidepressant drugs on circadian regulation highlighting a significant need for further investigation in this area.

7 Conclusions

This literature review highlights the unique role of ketamine in both pain management and treatment-resistant major depressive disorder.

Both topics are united by the relatively limited use of ketamine in clinical practice and the lack of extensive research on its role as an additive analgesic and an antidepressant.

In the realm of depression treatment, ketamine represents a significant factor due to its rapid-acting antidepressant effects, attributed to the modulation of neurotrophic factors, including BDNF and VEGF.

Furthermore, recent research into the effects of ketamine on circadian rhythms offers a new prospect to understanding its antidepressant mechanisms. Dysregulation of circadian rhythms is a common feature of depressive disorders and the potential of ketamine to support normal circadian stability represents a promising area for future research.

A limitation in this literature review is the deficiency of research on the optimal use of ketamine in depression treatment in order to get the best treatment response.

In conclusion, ketamine is a highly versatile drug for broader applications in both pain patients and the treatment depression. With further research, ketamine could become an increasingly valuable option in clinical practice.

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