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REVIEW

Research Progress on the Mechanism of Ketamine in Neuropathic Pain Comorbid Depression

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Abstract: This review systematically summarizes the research progress of ketamine and its interaction with specific brain regions in the context of neuropathic pain comorbid with depression. As a non-competitive inhibitor of N-methyl-D-aspartate (NMDA) receptors, Ketamine exerts complex mechanisms and controversial topic. The structure and function of NMDA receptors, as well as the binding sites of ketamine, are summarized, and the hypothesis of disinhibition and neuroplasticity of ketamine's antidepressant effect is elaborated. The mechanism of key brain regions, such as hippocampus and anterior cingulate cortex, is discussed in detail, and the antidepressant effect of ketamine is explored from the perspective of transcriptomics. Finally, this review integrates bioinformatics, molecular biology and other interdisciplinary approaches to elucidate the therapeutic effects and potential mechanisms of ketamine in treating neuropathic pain and depression comorbidity, providing a comprehensive theoretical basis, new directions for subsequent research and novel insights for the clinical application of ketamine.

Keywords: ketamine, neuropathic pain, depression, specific brain regions

Introduction

According to the International Association for the Study of Pain, pain is defined as an unpleasant feeling and emotional experience that is associated with or close to real or potential tissue damage. Pain results from the interplay of psychological, emotional, behavioral, and social factors. Mere activity of sensory neurons and neural pathways does not constitute pain. Although pain typically serves an adaptive and protective role, its presence may also lead to negative consequences for physical function, mental health, and social well-being. Verbal description is only one mean of pain expressing, and challenges in linguistic communication do not negate the presence of pain experience in individuals or animals.[1,2]

Neuropathic pain (NP) is a type of chronic pain caused by damage to the somatosensory nervous system or harmful stimuli, and may be directly caused by an underlying disease. It is clinically manifested in the form of allodynia, hyperalgesia, and spontaneous pain. The mechanism of NP involves peripheral and central processes. The peripheral mechanisms include abnormal discharges from damaged peripheral sensory nerve fibers, discharges induced by aberrant neuronal interactions, and sympathetic nervous system hyperexcitability. The central mechanisms include the persistence and recurrence of pain that typically arises above the spinal cord.[3,4]

Epidemiological studies show that the proportion of chronic pain with neuropathic characteristics is about 7%–10%. Chronic neuropathic pain is more common in females (8% vs 5.7% in males) and people above 50 (8.9% vs 5.6% in those under 49). Pain most frequently affects the lower back and limbs, including both the lower and upper extremities. Conventional pharmacotherapy relieves only 30%–40% of NP patients.[5]

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The pain-depression dyad (PDD) describes a pathological condition characterized by the co-occurrence of pain and depression in the same individual. Studies have indicated that the prolonged transmission of nociceptive signals leads to structural and functional plastic changes in higher brain centers, such as the prefrontal cortex (PFC),[6] anterior cingulate cortex (ACC),[7] amygdala,[8] and hippocampus.[9] These areas are also involved in regulating emotional and cognitive functions, suggesting that pain signals in higher brain centers encompass not only nociceptive signals but also emotion-related components.[10] Clinical research has further highlighted that patients with neuropathic pain often exhibit mood disorders, including anxiety and depression, while patients with anxiety and depression are frequently accompanied by hypersensitivity to pain and hyperalgesia.[11] This exacerbates the vicious cycle between pain and emotional disorders. This comorbidity not only intensifies the patient's suffering but also poses significant challenges for treatment. However, the underlying mechanisms of this comorbidity remain under investigation. Therefore, identifying an appropriate entry point to explore the potential mechanisms between pain and depression could help in better understanding neuropathic pain.

Ketamine, an NMDA receptor antagonist, exhibits potent analgesia and rapid-durable antidepressant effects. Low-dose ketamine induces such effects in both human patients and animal models.[12,13] A clinical study[14] has shown that six ketamine infusions yielded response and remission rates of 68.0% and 50.5%, respectively. The rapid, robust antidepressant and antisuicidal effects observed within four hours of infusion were sustained. Literature[15] showed that ketamine will exhibit greater tolerability and safety in comparison to Electroconvulsive therapy (ECT). However, ketamine's mechanisms in NP with comorbid anxiety and depression remain unclear. While current research focuses mainly on NMDA receptors, its effects via other mechanisms and brain regional roles in its treatment need further study. In conclusion, advancements in understanding ketamine's application in NP with concurrent anxiety and depression are highly significant for clinical practice and research. A more thorough comprehension of ketamine's mechanisms could result in the development of more effective treatment strategies, thereby enhancing patients' quality of life.

In recent years, bioinformatics has become an invaluable tool in the treatment of a wide range of diseases. Through the analysis of extensive genomic and transcriptomic data, bioinformatics methods can uncover new biomarkers and therapeutic targets, facilitating precise medical interventions. Additionally, these techniques enable the extraction of valuable insights from large-scale biological datasets, offering direction for future experimental designs.[16]

Objective

Ketamine has complex mechanisms, and previous studies have suggested that ketamine may improve depressive symptoms by enhancing the expression of brain-derived neurotrophic factor (BDNF), which is beneficial for the growth and connection of neurons.[17] Research has also shown that ketamine can regulate the levels of monoamine neurotransmitters in the brain, such as dopamine, serotonin, and norepinephrine, thereby alleviating depressive symptoms.[18] Additionally, ketamine may exert its therapeutic effects by modulating inflammatory responses and oxidative stress in the brain.[19] Specific brain regions likely play significant roles in the treatment of NP comorbid with anxiety and depression through ketamine. Studies indicate that the lateral habenula (LHb), often referred to as the "anti-reward center" may be involved, where ketamine might act on NMDA receptors in this region to reduce cluster discharges, release inhibition on the reward center, and produce rapid antidepressant effects.[20] Furthermore, regions such as the hippocampus and cortex may also contribute to ketamine's antidepressant effects.[21] However, the precise mechanisms of these brain regions in ketamine's therapeutic action remain unclear.

This review aims to elucidate the mechanisms of ketamine and its interaction with specific brain regions in neuropathic pain comorbid with anxiety and depression, further research is needed. On one hand, animal and cellular experiments can be conducted to explore ketamine's impact on neuronal activity, neurotransmitter levels, inflammatory responses, and other factors in various brain regions, thereby revealing its mechanisms of action. From another perspective, clinical studies can evaluate the efficacy and safety of ketamine in regulating NP patients with anxiety and depression symptoms, and can also analyze functional changes in different brain regions, providing theoretical support for clinical application. In general, Understanding the role of ketamine and specific brain regions in neuropathic pain complicated with anxiety and depression is of key diagnostic and research value, which helps to formulate more

effective treatment programs. This study aims to systematically dissect the antidepressant mechanisms of ketamine by integrating molecular, hypothesis level, brain region neurocircuits, regional specificity and transcriptomic perspectives.

NMDA Receptor and Ketamine

The NMDA receptor, an ionotropic glutamate receptor prevalent in the central nervous system (brain and spinal cord), features a complex structure permeable to K^+, Na^+, and Ca^{2+}. A functional receptor requires the NR1 subunit, forming tetramers/pentamers with regulatory NR2 subunits. Different NR2 subtypes confer distinct regional distributions, physiological properties, and dual voltage- and ligand-gating mechanisms, rendering it a unique dual-gated channel.[22] Mediating slow, Ca^{2+}-permeable excitatory neurotransmission, NMDARs are implicated in neurodevelopmental, neuropsychiatric, neurological, and neurodegenerative disorders, making their modulation a therapeutic target for disease modification. During neurodevelopment, the receptors regulate neuronal survival, dendritic and axonal structural development, and participate in synaptic plasticity, playing a crucial role in the formation of neuronal circuits. They are critical receptors in learning and memory processes.

Ketamine is an NMDA receptor antagonist. Although the pharmacological correlation with its rapid (within hours of administration) antidepressant effects remains unclear, this antidepressant action is thought to depend on mechanisms involving excitatory synaptic enhancement. Activation of synaptic NMDARs is essential for inducing typical long-term potentiation (LTP), which leads to sustained increases in synaptic strength. Studies have shown[23] that through behavioral pharmacology, quantitative Western blotting of hippocampal synaptic proteins, and electrophysiological recordings from hippocampal slices, the hypothesis that rapid antidepressant effects require NMDAR activation has been validated. Fast-acting antidepressant compounds have a common downstream effect dependent on NMDAR activation, even though their initial pharmacological targets are not the same. Promoting the NMDAR signaling pathway or other strategies to enhance NMDAR dependent LTP-like synapses may be a useful antidepressant.

"Disinhibition" Hypothesis

The "disinhibition" hypothesis posits that ketamine's ability to alleviate depression stems from its capacity to remove metaphorical "clouds" within the brain. By reducing the activity of overly active inhibitory systems—referred to as the brain's "brakes"—ketamine helps to improve depressive symptoms. Specifically, at lower dosages, ketamine targets and blocks NMDA receptors located on GABAergic interneurons. This blockage decreases the inhibitory influence that these interneurons exert on glutamatergic pyramidal neurons, thereby promoting the release of glutamate (Figure 1A).

This hypothesis focuses on glutamatergic neurotransmission, and it is thought that the effect of ketamine may be related to inhibiting gamma-Aminobutyric interneurons in the prefrontal cortex and hippocampus, then triggering downstream glutamatergic excitation and affecting synaptic plasticity. In mouse experiments,[24] subanesthetic doses of ketamine rapidly increased glutamate content in the prefrontal cortex and hippocampus. This subanesthetic dose can enhance glutamate levels, but high anesthetic doses can cause a decrease in glutamate release, ketamine helps promote glutamate circulation in the PFC, and directly enhances glutamatergic neurotransmission in the medial prefrontal cortex (mPFC) and hippocampus. Inhibition of hippocampal GABAergic interneurons resulted in increased glutamate release,[25,26] and this phenomenon in hippocampal CA1 region had a direct dose-dependent effect on BDNF surrender and TrkB receptor expression and translocation. These identifications demonstrated a causal relationship between synaptic glutamate increase and BDNF release, thereby supporting the disinhibition hypothesis.

The mPFC, and its peak glutamate levels in the hippocampus are associated with postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptors (AMPAR) activation, AMPARs are ionic glutamate receptors that are uniquely involved in rapid synaptic transmission, and are also involved in synaptic plasticity. In mouse models, Inhibition of GLT-1, a glutamate transporter in glial cells, can produce antidepressant effects similar to those of ketamine[27] (Figure 1B); however, another study showed that inhibition of GLT-1 can hinder the antidepressant effects of ketamine and also affect downstream phosphorylation.[28] This phenomenon may be caused by unbalanced glutamate circulation, which leads to hyperexcitability and excitotoxicity. Ketamine enhances synaptic transmission driven by AMPAR, especially in the hippocampus.[29] The downstream response of AMPAR stimulation includes the release of BDNF, which interacts with the postsynaptic TrkB receptor. Current evidence suggests that even TrkB receptor antagonists can block the regulatory effects of ketamine.[30] Some

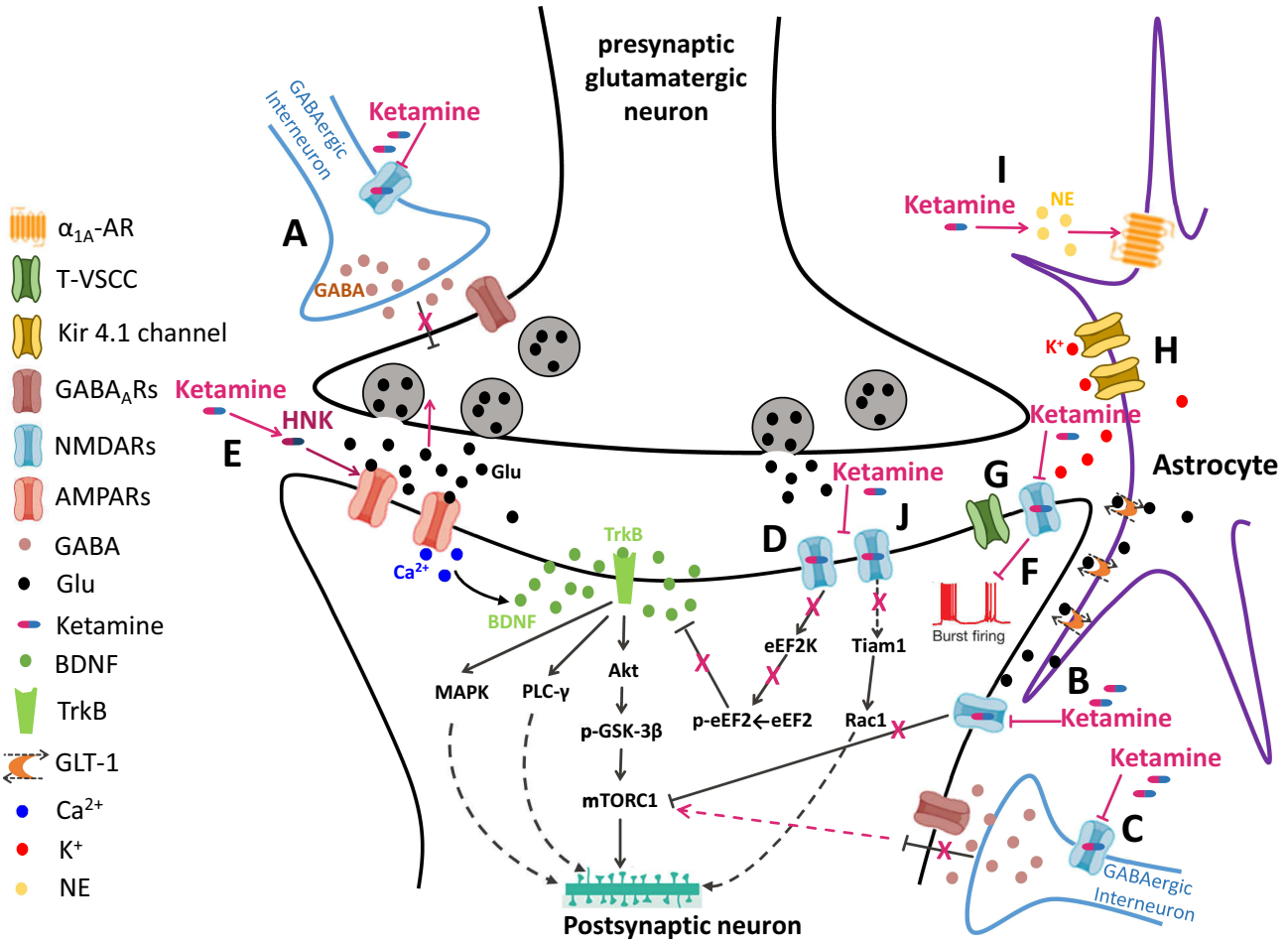

Figure 1 Converging synaptic signaling pathways underlying ketamine action. (**A**) The antidepressant mechanism of ketamine predominantly depends on its antagonistic action on NMDARs located in GABAergic interneurons, blocking the release of GABA. By inhibiting the release of GABA, the inhibition of pyramidal glutamatergic neurons is averted. As a result, glutamate is released, leading to the subsequent downstream consequences triggered by a sudden increase in glutamate levels. Glutamate then binds to postsynaptic AMPARs, enabling calcium to flow in, results in the release of BDNF from the postsynaptic membrane, triggering TrkB receptor signaling. The TrkB pathway and resulting rapid homeostatic synaptic plasticity are crucial for both ketamine's rapid and sustained actions. Activation of downstream mTOR causes structural plasticity, generating fast and long - lasting antidepressant effects. BDNF autocrine signaling directs downstream pathways like MAPK, PLC - γ, and PI3K - Akt. MAPK and PLC - γ are linked to synaptic plasticity, and PI3K - Akt to anti - apoptotic signaling and cell survival. (**B**) Ketamine is proposed to selectively block extrasynaptic GluN2B-containing NMDARs, which are tonically activated by low levels of ambient glutamate regulated by glutamate transporter 1 located on astrocytes. (**C**) The transient decrease in the excitatory drive of inhibitory interneuron-resident NMDARs mediated by ketamine is thought to inhibit the tonic release of GABA and relieve the activity of target excitatory neurons. The resulting increase in glutamatergic activity activates the downstream mammalian target of rapamycin (mTOR) function, leading to structural plasticity and producing rapid and sustained antidepressant effects. (**D**) Ketamine blocks NMDAR-mediated spontaneous neurotransmission, which inhibits eukaryotic elongation factor 2 kinase (eEF2K) activity, thus stopping the phosphorylation of its eEF2 substrate. (**E**) (2R,6R)-HNK increases AMPAR-dependent synaptic transmission. (**F**) A special firing pattern in the lateral habenula - burst firing is a sufficient condition for the occurrence of depression, and the effect of ketamine is to effectively prevent burst firing in this brain region. (**G**) T - VSCCs can serve as a novel antidepressant molecular target. (**H**) Another rapid antidepressant molecular target was revealed - the potassium ion channel Kir4.1 present in glial cells, which is crucial for triggering the burst firing of neurons. (**I**) The rapid elevation of NE by ketamine and the activation of astrocyte α1 - AR play an antidepressant role in sustained resilience. (**J**) Tiam1 links NMDARs stimulated by chronic pain to the activation of Rac1 in the ACC.

studies have shown that AMPAR activation is critical to ketamine's depression-fighting effects. In a sample of mice with depression, AMPAR inhibition reduces or completely removes ketamine's depression-fighting effects. Ketamine[31] (10 mg/kg, i.p) produced a rapid (1 hour) anti-depression effect in mice with chronic adrenocorticotropin (ACTH) and chronic and unpredictable stress (CUMS) induced depression. These responses to depression are associated with the regular expression of glutamate transporter-1 (GLT-1), glial fibrillary acidic protein (GFAP), BDNF, and phosphorylated eukaryotic expansion factor 2 (p-eEF2) in PrL-PFC. Excitatory neurons in PrL are less responsive to peripheral glutamate synaptic stimulation.

"Neuroplasticity" Hypothesis

The "neuroplasticity" hypothesis suggests that antidepressant effects are due to the increase in substances or connections in the brain that promote feelings of happiness. Ketamine is believed to trigger the production of substances that support

neuronal growth and synapse formation. Research has shown[32] that the glutamate system and structural plasticity hypothesis are central to the rapid and long-lasting antidepressant effects of new antidepressants. Hippocampal plasticity is one of the important mechanisms for the sustained antidepressant effect of ketamine. Ketamine may improve depressive symptoms by increasing the expression of BDNF, which in turn promotes neuronal growth and association. A single dose of ketamine dramatically increases synaptic function and the number of pyramidal cells in the prefrontal cortex, rapidly changing the synapses lost by these neurons due to chronic stress. Ketamine[33] enhances the synthesis and transport of AMPAR by activating the signaling pathway of BDNF and its receptor TrkB, thereby enhancing the excitability of synaptic transmission. It may improve depression by increasing the expression of neurotrophic factor BDNF in the brain to promote the growth and cohesion of neurons. The autocrine signaling of BDNF[34] relies on MAPK, PLC-γ and PI3K-Akt signaling pathways to lead the downstream signaling pathway. The MAPK and PLC-γ pathways are associated with synaptic plasticity, the PI3K-Akt pathways are associated with anti-apoptotic signaling and cell survival, and the signals conveyed by mTORC1 are also associated with synaptic plasticity and neurogenesis (Figure 1A).

Duman's lab has done research, which shows that the action of ketamine involves blocking the action of NMDARs on inhibitory interneurons.[35,36] For NMDARs expressed in these inhibitory neurons, their excitatory drive is temporarily weakened, and people feel that GABA tonic release is inhibited. The inhibitory activity of target excitatory neurons is stimulated, the glutamatergic activity is improved, the function of downstream mammalian target protein of rapamycin (mTOR) is activated, the formation of dendritic spines is increased, and the rapid and lasting antidepressant effect is not strong.[37,38] One-time administration of ketamine can rapidly improve the synaptic function of prefrontal cortex pyramidal neurons. Increase their numbers, and immediately adjust the synaptic loss that occurs in these neurons as a result of chronic stress (Figure 1C).

Detailed interpretation[39] of the synaptic signaling activity associated with the NMDA receptor by ketamine provides evidence that ketamine inhibits the tension-stimulated NMDA receptor, resulting in the blocking of these static calcium signals and the suppression of eEF2K activity (Figure 1D), leading to dephosphorylation of eEF2 and lifting restrictions on the synthesis of dendritic proteins, especially BDNF. Instead, BDNF activates the post-synaptic TrkB receptor to induce the addition of the AMPA receptor, which in turn creates a new type of synaptic improvement in the hippocampus, which is the basis for the rapid antidepressant effect. Research indicates[40] that astrocytes play a role in the pathophysiological process of major depression and the efficacy of antidepressant drugs through the regulation of synaptic plasticity supports the hypothesis that astrocyte atrophy is beneficial to the pathophysiological process of depression. The morphological changes of astrocytes may be one of the ways that ketamine rapidly improves depressive symptoms. The findings show[41] that ketamine has an antidepressant effect, and that synaptic plasticity through presynaptic promotion promotes fear of memory loss, which may give new ideas for the treatment of post-traumatic stress disorder (PTSD).

AMPAR and Ketamine

Studies[42] have shown that AMPAR promote rapid excitatory synaptic transmission in the central nervous system, and changes in synaptic plasticity of AMPAR are considered to be the basis for the long-term antidepressant effects of ketamine. Although ketamine and (2R,6R)-HNK do not alter the content of GluA1 and GluA2 AMPAR subunits in hippocampus 1 hour after treatment, both of them increase these subunits 24 hours after treatment in mice. These findings indicate that, the maintenance of AMPAR-induced synaptic strengthening—mediated by (2R,6R)-HNK via enhancing glutamate yield and AMPAR expression to boost AMPAR-dependent synaptic transmission—underlies the compound's persistent antidepressant effects. (Figure 1E). Evidence also shows that (2R,6R)-HNK modulates metabolic glutamate (mGlu) receptor signaling, stimulates mTOR and BDNF pathways, and enhances release of other neurotransmitters (serotonin, norepinephrine). The compound promotes structural plasticity via dendritic remodeling and influences additional processes—including inflammatory responses and mitochondrial function.

The Effects of Ketamine on Specific Brain Regions (Figure 2)

Lateral Habenula (LHb): A Key Brain Region in Ketamine's Antidepressant Action

Research[43] for the first time revealed that a special firing pattern in the LHb - the burst firing - is a sufficient condition for the development of depression, and the effect of ketamine is to effectively prevent burst firing in this brain region.

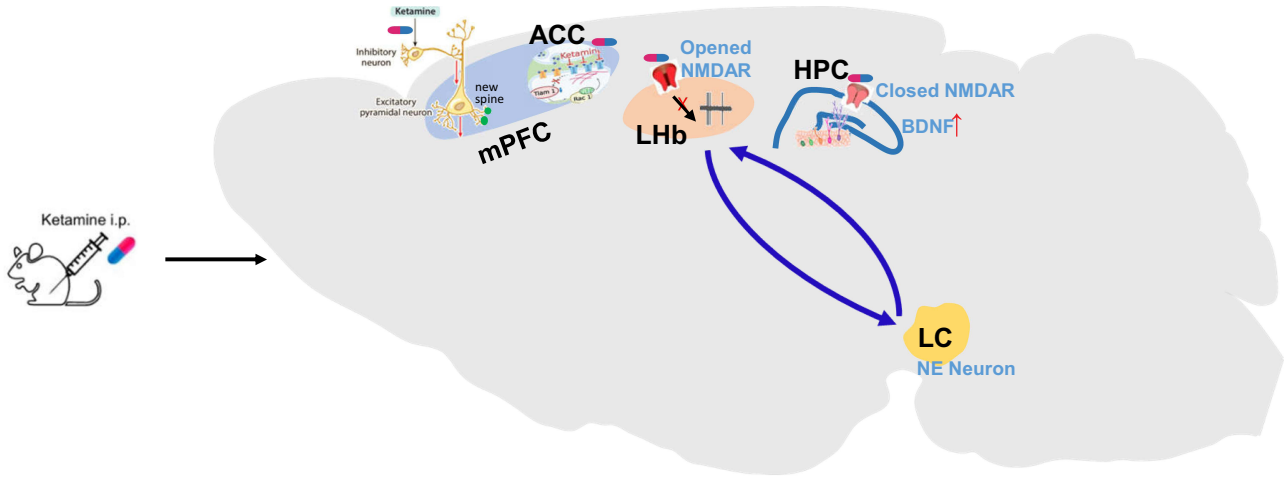

Figure 2 The effects of ketamine on various brain regions of rats with comorbid chronic pain and depression. Adapted from Borsellino P, Krider RI, Chea D, et al. Ketamine and the Disinhibition Hypothesis: neurotrophic Factor-Mediated Treatment of Depression. J Pharmaceuticals. 2023;16(5):742. Under Creative Commons License https://creativecommons.org/licenses/by/4.0/.[34]
Abbreviations: ACC, anterior cingulate cortex; HPC, hippocampus; LHb, lateral habenula; mPFC, medial prefrontal cortex; LC, locus coeruleus.

(Figure 1F) In addition to relying on NMDARs, the burst firing in the LHb also requires the hyperpolarization of the neuronal membrane potential and the coordinated action of low - voltage - sensitive T-type calcium channels (T-VSCCs). Locally blocking T-VSCCs in the LHb also produced rapid antidepressant effects. This finding indicates that T-VSCCs can serve as a novel antidepressant molecular target (Figure 1G). The research team led by Hu Hailan[44] further explored the molecular mechanisms leading to the hyperpolarization of LHb neurons and the increase in burst firing activity, revealing another rapid antidepressant molecular target the potassium ion channel Kir4.1 present in glial cells, which is crucial for triggering the burst firing of neurons (Figure 1H). When the potassium ion channel Kir4.1 is highly expressed in astrocytes, the ions released by neurons into the extracellular space are cleared more rapidly, leading to the hyperpolarization of neurons and subsequently triggering burst firing. A variety of typical depression-like behaviors were also observed in relevant mouse models. Subsequently, the researchers used RNA interference or dominant - negative mutations to specifically reduce the expression level of Kir4.1 or block its function in the astrocytes of the LHb, and found that the depressive behaviors were alleviated. The above findings demonstrate a causal relationship between the high expression of this potassium ion channel in the LHb and the formation of depression, and clarify a new molecular mechanism of depression onset - that is, the interaction between LHb neurons and glial cells is altered, triggering the burst firing of neurons and ultimately mediating depressive behaviors.

Studies have shown that in models of depression in rats and mice, blocking the explosive activity of the "anti-reward center" (LHb) on which NMDA relies can produce the rapid antidepressant effect of ketamine. In animals with similar depression, LHb neurons show a large increase in explosive activity, and this phenomenon is altered by ketamine. The understanding that light stimulation triggers LHb explosion, which leads to the behavioral characteristics of despair and anhedonia, suggests a basic model in which ketamine alleviates the inhibition of the downstream monoaminergic reward center by blocking the NMDA-dependent explosion of LHb neurons, thereby improving mood at a very rapid rate. This gives a framework for developing new, fast-acting antidepressants. Research[45] shows that the LHb is a brain region of great significance for the generation of stress and anxiety. Norepinephrine (NE) has always been associated with arousal, stress and anxiety, and it has been determined that the projection of NE to LHb comes from the locus coeruleus (LC). Current research results have established that the NE void inside LHb plays a role in arousal and anxiety. Calcium signaling in LHb astrocytes relies on α1A-adrenergic receptors and on a neural network between LHb and LC (Figure 2). LHb astrocytes mediate the second activation of local LHb neurons and the release of NE. Activating or inhibiting the calcium signals in LHb astrocytes respectively promoted or alleviated stress - induced depression - like behaviors. Research shows[46] the crucial role of the rapid elevation of NE by ketamine and the activation of astrocyte α1 - AR in

sustained resilience (Figure 1I), which may explain some alternative antidepressant interventions in rodent models and patients.

Ketamine has fundamentally changed the approach to treating depression, offering not only rapid but also long-lasting antidepressant effects. While its half-life in mice is only 13 minutes, its antidepressant benefits can persist for over 24 hours, a discrepancy that presents an intriguing biological puzzle and carries significant clinical relevance. Research has shown[46] that after a single systemic injection, ketamine continues to inhibit burst firing and block NMDARs in the LHb for up to a full day. This prolonged effect is not due to endocytosis, but instead arises from the use-dependent retention of ketamine within the NMDAR. By manipulating the interaction dynamics between ketamine and NMDARs at different plasma concentrations, we can control the duration of its antidepressant effects. These findings shed new light on the mechanisms responsible for ketamine's sustained antidepressant action, and provide a promising avenue for enhancing its clinical application by regulating the length of its effects based on its biophysical interactions with NMDARs. Research by Professor Hu Hailan's team at Zhejiang University has found that, once ketamine enters the depressed brain, it specifically targets the LHb, where NMDA receptors on LHb neurons serve as the initial target for ketamine's effects. In the context of neuropathic pain comorbid with anxiety and depression, the LHb may also play a critical role in ketamine's therapeutic effects. After administration of ketamine, neuronal activity in the LHb is initially suppressed, which may be a key step in alleviating anxiety and depressive symptoms. Furthermore, specific local knockout of NR1 (the NMDA receptor subunit) in the LHb of mice prevents the rapid antidepressant behavioral effects of ketamine, further confirming the crucial role of the LHb in ketamine's antidepressant action.

The influence of neural signaling on the LHb and depression: Under normal conditions, the LHb serves as the "anti-reward center" and its hyperactivity is linked to depressive-like behaviors. In the context of neuropathic pain, pain signals may exacerbate the abnormal activity in the LHb. Ketamine acts on the LHb, inhibiting the cluster firing of its neurons and thereby altering neural signal transmission. This not only alleviates depressive symptoms but may also impact comorbid anxiety symptoms. This mechanism of action could be a key pathway through which ketamine exerts its effects in cases of neuropathic pain comorbid with anxiety and depression.

Hippocampus: Regulation of Neuroplasticity

Ketamine is believed to promote neuroplasticity in the hippocampus. Studies have shown[47] that even a single dose of ketamine can significantly improve anxiety-like symptoms induced by stress, possibly through modulation of the GSK-3β/GR signaling pathway to enhance hippocampal synaptic plasticity. Chronic pain can induce depression,[48] severely affecting the patient's life quality, although the underlying mechanisms remain unclear. Chronic neuropathic pain has been shown to regulate the DNA methylation of target genes associated with neuroplasticity and emotional regulation, a process induced by DNA methyltransferases (DNMTs). Methylation changes in the BDNF gene in the hippocampus are crucial for both neuropathic pain and depression. In the context of comorbid anxiety and depression associated with neuropathic pain, hippocampal neuroplasticity may be impaired. Ketamine can improve hippocampal neuroplasticity through the modulation of the glutamatergic system and upregulation of neurotrophic factor expression. This helps restore normal connections and function between neurons, alleviating anxiety and depressive symptoms. Research has found that ketamine treatment leads to changes in molecular events related to neuroplasticity in hippocampal neurons, such as alterations in the expression and phosphorylation levels of AMPA receptor subunits. These changes may represent a specific manifestation of ketamine's effect on improving neuroplasticity. Studies have also shown that a single injection of ketamine selectively promotes neurogenesis in the ventral hippocampus of adult rats. Furthermore,[49] the ventral dominance induction of GluN2B subunits of NMDARs, p-mTOR, GluA1 subunits of AMPARs, and BDNF in the hippocampus may form the basis of ketamine's unique antidepressant effects.

The hippocampus has extensive neural connections with other brain regions, including the prefrontal cortex and LHb. In cases of comorbid anxiety and depression associated with neuropathic pain, interactions between these brain regions may become dysregulated. Ketamine acts on the hippocampus and may modulate the neural activity of the entire brain by affecting its connections with other regions, thereby improving anxiety and depressive symptoms. Numerous studies have shown that BDNF is highly expressed in the hippocampus and is essential for processes such as neuronal growth, differentiation, regeneration, and maintenance of physiological functions. Chronic pain and depression are both

associated with decreased levels of BDNF in the hippocampus.[50] By pharmacologically inducing increased BDNF expression in the hippocampus, ketamine exerts both antidepressant and analgesic effects, and these actions may be linked to changes in other brain regions.

Anterior Cingulate Cortex (ACC)

The ACC[51] is located on the medial surface of the cerebral hemisphere, above the corpus callosum, spanning its entire length, and includes subregions such as the subgenual, perigenual, and dorsal areas. The ACC is closely related to etiology, pathogenesis, and treatment of major depressive disorders.

As an important component of the limbic system, the ACC has extensive fiber connections with many cortical and subcortical structures, and it plays a central role in regulating emotions, affect, motivation, and other functions. Animal studies[52] have identified the ACC as a critical part of the medial pain system that mediates emotional responses. Additionally, the ACC receives nociceptive inputs from other pain-related cortical regions,[53] such as the primary somatosensory cortex (S1) and the insular cortex. Not only does the ACC receive widespread afferent input, but its efferent fibers are also broadly distributed. Deep pyramidal cells project to many subcortical structures, including the hypothalamus and periaqueductal gray matter. Reports also indicate that deep pyramidal cells in the ACC send descending projections to the spinal cord. It can be inferred that these extensive fiber connections likely contribute to the complex role of the ACC in processing pain and associated emotional disorders.

The Relationship Between the ACC and Chronic Pain-Related Anxiety and Depression

ACC is a well-known region involved in processing and modulating the emotional components of pain. Several animal studies have observed the significance of excessive ACC activity in the context of chronic pain.[54,55] Previous imaging studies[56] have shown that patients with neuropathic pain exhibit excessive activation of the ACC. Additionally, optogenetic activation of the ACC in mice has been found to induce anxiety- and depression-like behaviors.[57] When activated during chronic pain, the ACC serves as a key center for emotional disorders, making it an important target for understanding the underlying mechanisms of these conditions.

Neurons in the ACC form bidirectional connections with the amygdala,[58] which allows the ACC to receive input related to emotional fear and anxiety signals. This unique connectivity enables ACC neurons to integrate sensory input with anxiety signals. Chronic pain and anxiety may be mutually reinforcing, and the anterior cingulate cortex has an anatomical connection to the amygdala and other subcortical areas involved in emotional responses, which provides a theoretical basis for the anterior cingulate cortex's response to anxiety and fear associated with painful stimuli or experiences.[59] These findings support the idea that neuronal activity in the ACC can influence anxiety-related emotions. Research suggests[58] that synaptic LTP in the presynaptic neurons of the ACC may be a synaptic mechanism underlying anxiety-like behaviors in the context of chronic pain. The presence of presynaptic LTP enhances the input from the thalamus to the ACC neurons involved in the chronic pain response, leading to pain-related anxiety. Additionally, the presence of postsynaptic LTP (post-LTP) results in an additive effect from both forms of LTP, which further promotes the interaction between chronic pain and anxiety. Under depressive conditions, the ACC can undergo functional and morphological changes, positioning it as a critical brain region in neuropathic pain-induced depression, closely related to the pathophysiology of depression.

As a key processing hub in the limbic system, ACC receives nociceptive information projected from the thalamus[60] and somatosensory cortex,[61] as well as fear and anxiety-related signals from the amygdala.[62] This distinctive characteristic enables ACC neurons to combine sensory inputs from pain signals with anxiety-related data, playing a crucial role in the processing of pain and the associated anxiety and depression-like behaviors. Clinical MRI studies have shown that patients with neuropathic pain and concomitant emotional dysfunction exhibit reduced gray matter volume in the ACC and enhanced hemodynamic signals.[63,64] Furthermore, bilateral anterior cingulate corticectomy[65] has been shown to alleviate both neuropathic pain and major depressive disorder in patients. In animal models of neuropathic pain, increased c-fos expression and synaptic plasticity in the ACC indicate abnormal activation of this region.[66] Local silencing of the ACC or inhibition of ACC LTP[67] has been demonstrated to effectively reduce neuropathic pain and its associated anxiety and depression-like behaviors.

Both domestic and international studies have confirmed that the ACC is closely associated with pain and emotional disorders. However, the molecular mechanisms by which nociceptive signals activate the ACC, leading to synaptic plasticity changes, remain unclear. Studies have shown[68] that a single dose of ketamine can persistently inhibit the overactivity of ACC neurons in chronic pain, and the antagonistic effect of NMDA receptors in ACC is beneficial to the inhibition of ketamine on aversive change in chronic pain. Seed stimulation analysis was used to explore the activation of subgenual anterior cingulate cortex (sgACC) dependent task. Assessment of inter-group differences and changes before and after convalescence,[69] compared with the control group, patients with major depression showed higher sgACC activation levels for favorable and reverse monetary rewards, which were associated with anhedonia and anxiety, respectively, and major depressive disorder (MDD) patients showed higher functional connectivity of resting state between the hippocampus and sgACC. This was related to sgACC overactivation of favorable rewards, but not reverse rewards, and ultimately ketamine reduced sgACC overactivation of favorable rewards, not reverse rewards. These findings suggest a neural mechanism for ketamine's antidepressant effects, namely the rapid reduction of abnormal sgACC's hyperresponsiveness to positive incentives.

Studies have shown[12] that Tiam1 correlates chronic pain-stimulated NMDARs with Rac1 activation in ACC, which regulates synaptic structural plasticity through actin and spinal remodeling. Synaptic NMDAR stabilizes functional plasticity, which can lead to ACC overactivity and depression-like behavior (Figure 1J). Ketamine addresses depression-like behaviors associated with chronic pain by preventing maladaptive plasticity induced by tiam1 in the anterior cingulate cortex. Therefore, ketamine may promote its sustained antidepressant like effects by suppressing the structural and functional plasticity of synapses induced by Tiam1 in ACC neurons, which may be the basis for depression-like behaviors induced by chronic pain.

Prefrontal Cortex (PFC)

Glutamatergic signaling in the mPFC mediates ketamine-induced synaptic plasticity, which is critical for its rapid antidepressant effects. Subanesthetic amounts of ketamine can trigger abnormal glutamatergic explosion in mPFC, and inhibition of mPFC neurons can block the antidepressant effect of ketamine. More evidence of the critical significance of mPFC has been provided by photogenetic studies. It has been shown that light stimulation of pyramidal neurons expressing camk2a in mPFC can re-produce the rapid and long-lasting antidepressant behavior of ketamine.[70] mPFC is a central hub that can shape activities in a distributed network of output structures, including stress-regulating behaviors and autonomic responses. Research[71] suggests that the antidepressant effect of ketamine is due to the increase of glutamate in the medial prefrontal cortex, which stimulates the projection of the prefrontal lobe to the medial dorsal nucleus and locus coeruleus, thereby stimulating the release of serotonin and noradrenaline in the same region. The time frame for the effects of the two monoamines on the antidepressant response to ketamine appears to be different.

Studies[72] have shown that ketamine can rapidly improve the signaling within mPFC, even after ketamine is metabolized and cleaned, it still causes continuous morphological and physiological changes, subanesthetic doses of ketamine will increase the glutamate in mPFC, and then AMPA receptors are activated, BDNF is released, within 30 to 60 minutes. mTORC1 signaling is enhanced. Studies have also found[73] that activation of specific neuronal types in the prefrontal cortex, such as DRD1-expressing neurons, can produce ketamine-like rapid antidepressant effects, suggesting that ketamine may interact with specific neuronal populations in the prefrontal cortex to exert its anxiolytic and antidepressant effects.

Ketamine Antidepressant Effects: A Transcriptomic Perspective

Transcriptomics, as a powerful research tool, provides new insights into understanding the mechanisms of ketamine in treating pain-related depression. A number of studies have suggested that transcriptomics plays a critical role in ketamine's therapeutic effects for pain-related depression. Transcriptomics is the study of the complete set of transcripts in a specific cell or tissue at a particular time, offering valuable information about gene expression regulation mechanisms and biological processes. Studies[74] explored the susceptibility of depressive-like behavior development under chronic pain conditions by identifying key genes or cellular mechanisms. The researchers used genome-wide RNA sequencing to detect transcriptomic signatures of the hippocampus, a region responsible for regulating mood and stress

responses, in male mice that suffered from chronic inflammatory pain. Based on behavioral tests, pain-plagued animals were divided into two groups: "Tough" and "fragile", as verified by RNA-seq bioinformatic interpretation and qPCR, hippocampus genes are implicated in neuroinflammation, cell delay/neurogenesis, and impaired blood-brain barrier integrity. Another study[75] found that Sema4a was significantly upregulated in both male mice and humans under conditions of emotional changes, playing a crucial role in the onset of mood disorders. Overall, these results place the amygdala-cingulate pathway at the core of pain-depression comorbidity, highlighting the role of Sema4a and myelin damage in emotional regulation.

According to the research results,[76] KEGG analysis shows that cholinergic synapses and estrogen signaling pathways in the ACC play a key role in NP, and gradually more and more according to.[77] The ACC region is enhanced by estrogen receptor-β / PKA and G protein-coupled estrogen receptor-1 / protein kinase B pathways that promote emotional distress, promote synaptic plasticity facilitated by NMDAR, and the cholinergic system[78] modulates NP through restrained delivery of muscarinic M1 receptors facilitated by activation of GABA. In addition to calcium signaling, the GO analysis also focused on the activity of voltage-gated potassium channels (Kv). Gao[79] found that the excessive movement of NP-related cingulate pyramidal neurons was related to the current reduction induced by Kv2, and the efficacy limit of Kv2 was able to reduce the excessive movement of nerves and produce analgesic consequences. It was also observed[80] that there are many adhesion molecules and vesicles in the GO profile, and that synaptic adhesion molecules are important in the control of synaptic growth, neural circuits and behavior, and that in the NP case, activation of the anterior cingulate cortex changes the number of specific adhesion molecules. Nerve cell adhesion molecule-1[81] underpins behavioral sensitivities through spinal tissue and NMDAR-dependent LTP, Cav-1 plays a key role in synapse generation and plasticity. Yang[82] demonstrated for the first time that Cav-1 in ACC neurons directly binds to N-methyl-D-aspartate receptor 2B subunit (NR2B) to improve the NR2B surface level in ACC, thereby stimulating ERK/CREB signaling channels and regulating chronic neuropathic pain.

In the antidepressant process of ketamine, significant changes in the transcriptomics of the ACC have been observed. The transcriptomics of the ACC holds great potential as a therapeutic target. Through transcriptomic analysis, the molecular mechanisms of disease can be identified, and new drug targets can be discovered. In depression, dysfunction of the ACC is closely related to executive dysfunction and comorbid depression in chronic pain conditions. Therefore, intervening in the transcriptomic changes of the ACC may become a novel strategy for treating depression. Studies[83] found that major depressive disorder is a disease associated with circadian rhythm disruption and a high suicide rate. Low-dose ketamine KT and sleep deprivation SD, two fast-acting antidepressants, can significantly reduce the depressive symptoms of patients within 24 hours. To solve this problem, we conducted a contrastive transcriptomic analysis to identify the candidate genes and associated channels shared by KT and SD. This investigation confirmed the potential efficacy of the biological clock in the rapid response of antidepressants. These distinctions may lead to new research directions that may be useful in planning chronopharmacological protocols for the regulation of major depression. In summary, the transcriptomics of the ACC provides new perspectives and potential therapeutic targets for the treatment of depression.

Concluding Remarks

In summary, ketamine holds significant research value and clinical importance in the treatment of neuropathic pain comorbid with anxiety and depression. A bibliometric analysis[84] revealed that over the past two decades, research on ketamine and its enantiomers for antidepressant effects has surged, culminating in the approval of esketamine nasal spray for treatment-resistant depression. Ketamine's rapid antidepressant action has prompted investigations into its mechanisms and the development of new antidepressants with reduced side effects. Future studies should focus on further investigating the mechanisms of ketamine's action, developing safer and more effective novel antidepressants, and providing better treatment options for patients.

In future research, it is crucial to explore the mechanisms of ketamine's action in neuropathic pain comorbid with anxiety and depression. First, the specific relationships between ketamine and different brain regions need to be further clarified. Although the roles of the LHb and hippocampus in ketamine's antidepressant effects are well-established, the mechanisms of action in other brain regions, including the PFC, ACC, and amygdala, as well as how they affect the

functional connectivity between brain regions and the balance of neural circuits, remain to be further explored and discussed. To address these gaps, future studies should integrate functional MRI (fMRI) with viral tracing techniques to map both structural and functional connectivity of the PFC-ACC-amygdala circuit during ketamine treatment. Additionally, optogenetic or chemogenetic manipulation of specific neuronal populations in these regions will enable causal validation of how ketamine modulates neural circuit balance underlying its therapeutic effects.

Secondly, research into the antidepressant mechanism of ketamine through ACC transcriptomics should continue, with a focus on more precisely understanding the relationship between ketamine and ACC transcriptomics. Although it is known that ketamine induces significant changes in ACC transcriptomics during the antidepressant process, the specific genes involved, how these genes interact, and how they influence the onset and development of depression remain unclear. Advanced transcriptomics technologies, such as single-cell RNA sequencing, can be employed for in-depth analysis of different cell types within the ACC to identify the specific cell types and gene targets affected by ketamine. Studies suggest that different cell types in the brain may play distinct roles in the onset and treatment of depression, and single-cell RNA sequencing can reveal ketamine's effects on specific cell types, providing a basis for precision medicine.

In conclusion, future research should focus on exploring ketamine's mechanisms of action and clinical applications. Through interdisciplinary collaboration and innovation, more effective and safer treatment options can be provided for patients with neuropathic pain comorbid with anxiety and depression.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Ethical Approval

Given that this manuscript is a review, which does not entail any new experiments on human or animal subjects, the statement of ethical approval is not applicable.

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Author Contributions

Conceptualization, QM L, SM L, XF L and BY Q; Study design, QM L, SM L; Execution, QM L, XF L; Analysis and Interpretation, QM L, SM L, XF L and BY Q; Writing-Original Draft, QM L and SM L; Writing-Review & Editing; QM L, XF L and BY Q; Funding Acquisition, BY Q, XF L. All authors contributed to the study conception and design. All authors edited and approved the final manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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