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Research Progress on the Application of PI3K/AKT Pathway in the Treatment of Depression

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Abstract:

Depression, also known as depressive disorder, is a common psychological disorder. The phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) signaling pathway can affect neurophysiological processes directly related to depression, such as synaptic transmission and neuroinflammatory response, by regulating downstream key molecules. This article explores the impact of the PI3K/AKT pathway on depression. Through comprehensive literature analysis, this article shows the main molecular mechanisms of the PI3K/AKT signaling pathway and emphasizes the regulatory role of this pathway in synaptic plasticity, neuroinflammation, and dopamine expression, which directly affect depression. By consulting the recent progress in the development of medicines for depression and figuring out the underlying mechanism, this article concludes that medicines based on the PI3K/AKT pathway have great potential. If the potential safety issues can be addressed and the efficacy of the medicine treatment can be further improved, depression patients worldwide could be largely cured with medicines that modulate the PI3K/AKT pathway.

Keywords: depression; PI3K/AKT; BDNF.

1. Introduction

Depression, also known as depressive disorder, is a kind of common mental disorder. Its core feature is that patients experience severe and persistent depressive emotions, and severe patients may exhibit self-harm, suicidal behavior, often accompanied by delusions, hallucinations, and other psychiatric symptoms. The causes of depression are complex and involve multiple mechanisms, some of which are not yet fully understood. Brain-derived neurotrophic factor (BDNF) is one of the key elements in the pathogenesis of depression. It can modulate its own downstream signaling pathways to influence depression.

The phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) signaling pathway is a downstream pathway of the BDNF pathway, which plays a crucial role in the life of cells. It can be activated by a variety of factors, influencing cell proliferation, differentiation, and apoptosis, and is deeply involved

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in cellular processes associated with depression. Meanwhile, experimental evidence suggests that this pathway is closely related to the incidence of depression. Therefore, exploring the role of the PI3K/AKT pathway is expected to discover new targets for depression treatment.

This study focuses on the PI3K/AKT pathway and explores its mechanism of action and the key enzymes and proteins involved. PI3K is activated by the receptor tyrosine kinase (Trk) produced by the BDNF upstream pathway, which is converted to phosphatidylinositol 3,4,5-triphosphate (PIP3) after a few reactions. PIP3 will then recruit AKT onto the cell membrane and activate it. After that, AKT can further drive downstream pathways by generating a second messenger. Key enzymes and proteins in this pathway include PI3K, AKT, and their downstream targets.

This paper uses the research methods of a literature review. By synthesizing the results of multiple studies, researchers can gain a general understanding of the role and specific mechanism of the PI3K/AKT pathway in depression, whether clear or not.

The primary objective of this study is to uncover the specific roles of key proteins and enzymes in the PI3K/AKT pathway in depression, therefore providing a basis for the development of subtype-specific targeted medicines. This allowed researchers to understand how each protein and enzyme causes depression at a pathophysiological level. For example, certain proteins may act as regulators, controlling the activation or inactivation of pathways, while enzymes may be responsible for catalyzing key biochemical reactions that affect synaptic plasticity – all of which are key factors in depression. Of course, there may be some more complex mechanisms of interaction between these enzymes and proteins, which call for further research.

The development of targeted medicines using molecules in the PI3K/AKT pathway as targets has a wide range of prospects and is likely to become a hot topic in the near future. As long as side effects can be overcome, medicines that target this signaling pathway could become the first choice for treating depression—either alone or in cocktail therapy.

2. Depression

Depression is a common psychological disorder that can be caused by a variety of factors, including genetic predisposition, neurochemical imbalances, and environmental stressors. It can lead to psychological distress, impaired cognitive function, social withdrawal, an increased risk of cardiovascular disease, and even suicide.

Current treatment modalities for depression include pharmacological treatment, psychotherapy, and neuromodulation. However, existing treatments still have limitations. Traditional antidepressants usually take 4-6 weeks to work, and the efficacy is affected by genetic polymorphisms that determine medicine metabolism [1].

3. BDNF

BDNF is a core member of the neurotrophic factor family and is widespread in the central nervous system (CNS). BDNF reduces neuronal cell apoptosis, promotes synaptic regeneration, and improves cognitive function.

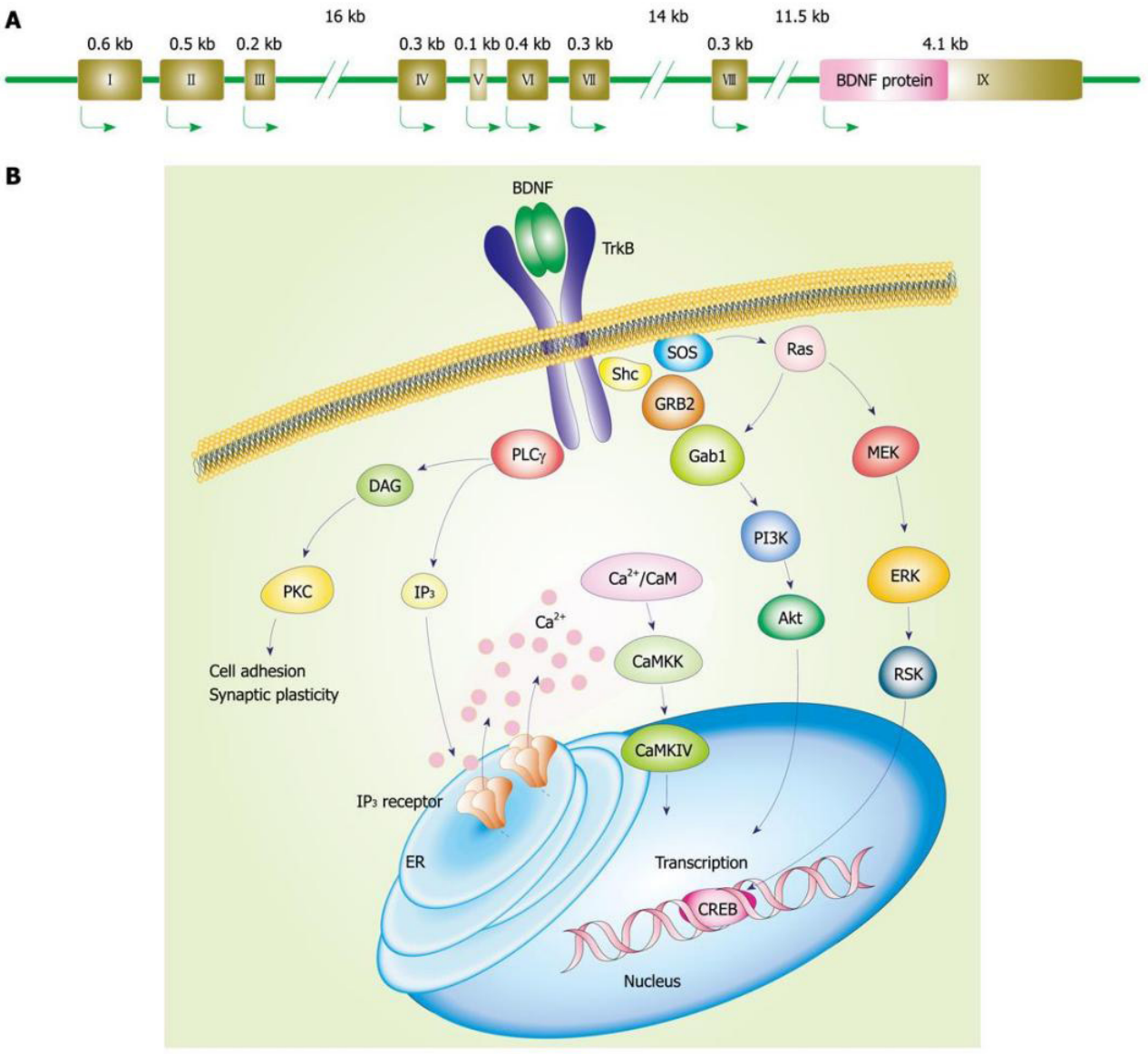

Fig. 1 BDNF gene and stimulated intracellular signaling cascades after activation of TrkB (A) Mouse and rat BDNF genes (B) Intracellular signaling after TrkB activation [2]

As shown in figure 1, by binding to the TrkB, BDNF induces TrkB dimerization and, at the same time, activates the intrinsic tyrosine kinase, which in turn phosphorylates and activates downstream signaling pathways.

The hippocampus is a central region of the brain. It is responsible for learning and memory. BDNF can act as a regulator to regulate the synaptic plasticity of neural synapses in the hippocampus through its downstream pathways. BDNF improves synaptic transmission efficiency by enhancing presynaptic membrane neurotransmitter release and postsynaptic membrane receptor sensitivity [3]. At the same time, BDNF also regulates the activity of dopaminergic and serotonergic neurons, affecting mood and reward systems. Neuroinflammation is an important pathological mechanism of neurodegenerative diseases, and BDNF can exert a neuroprotective effect by inhibiting microglial activation and reducing the release of pro-inflammatory factors.

4. PI3K/AKT pathway

4.1 PI3K and AKT

The PI3K family is lipid kinases that phosphorylate the hydroxyl group of phosphatidylinositol to produce a second messenger, such as PIP3. AKT is a serine/threonine kinase. It is the main downstream effector of PI3K. Activated AKT phosphorylates over 100 substrates to regulate

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the cell life cycle.

4.2 PI3K/AKT pathway

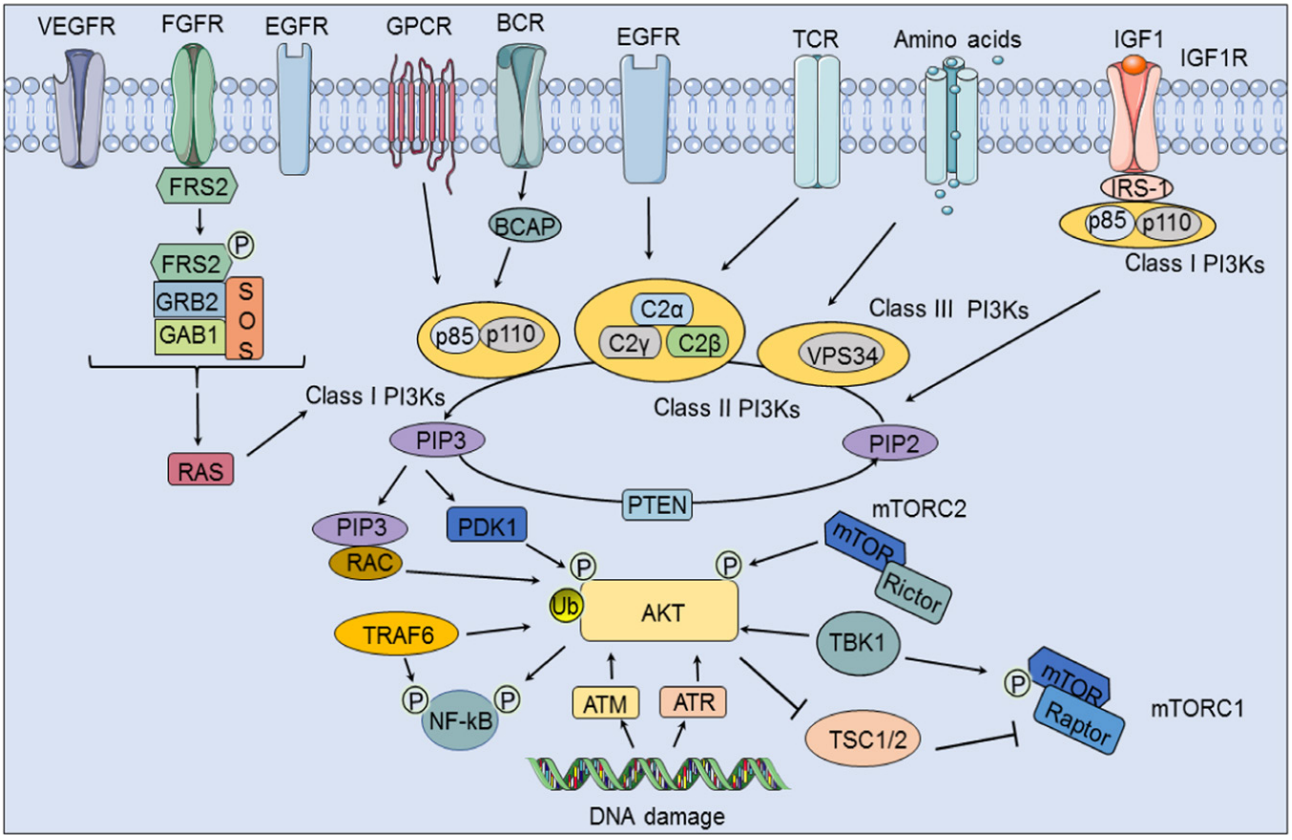

Fig. 2 Upstream activation of the PI3K/Akt signaling pathway [4]

The PI3K/AKT pathway constitutes a key signaling network that controls cellular homeostasis. It can be seen in figure 2, PI3K stimulated by growth factors generates PIP3, which recruits AKT to the cell membrane through its pleckstrin homology (PH) domain. Membrane-bound AKT is phosphorylated at the Thr308 and Ser473 sites for full activation [5]. Activated AKT inhibits apoptosis by inhibiting pro-apoptotic proteins and promotes cell cycle progression through mTORC1-mediated protein synthesis.

4.3 Regulating synaptic plasticity

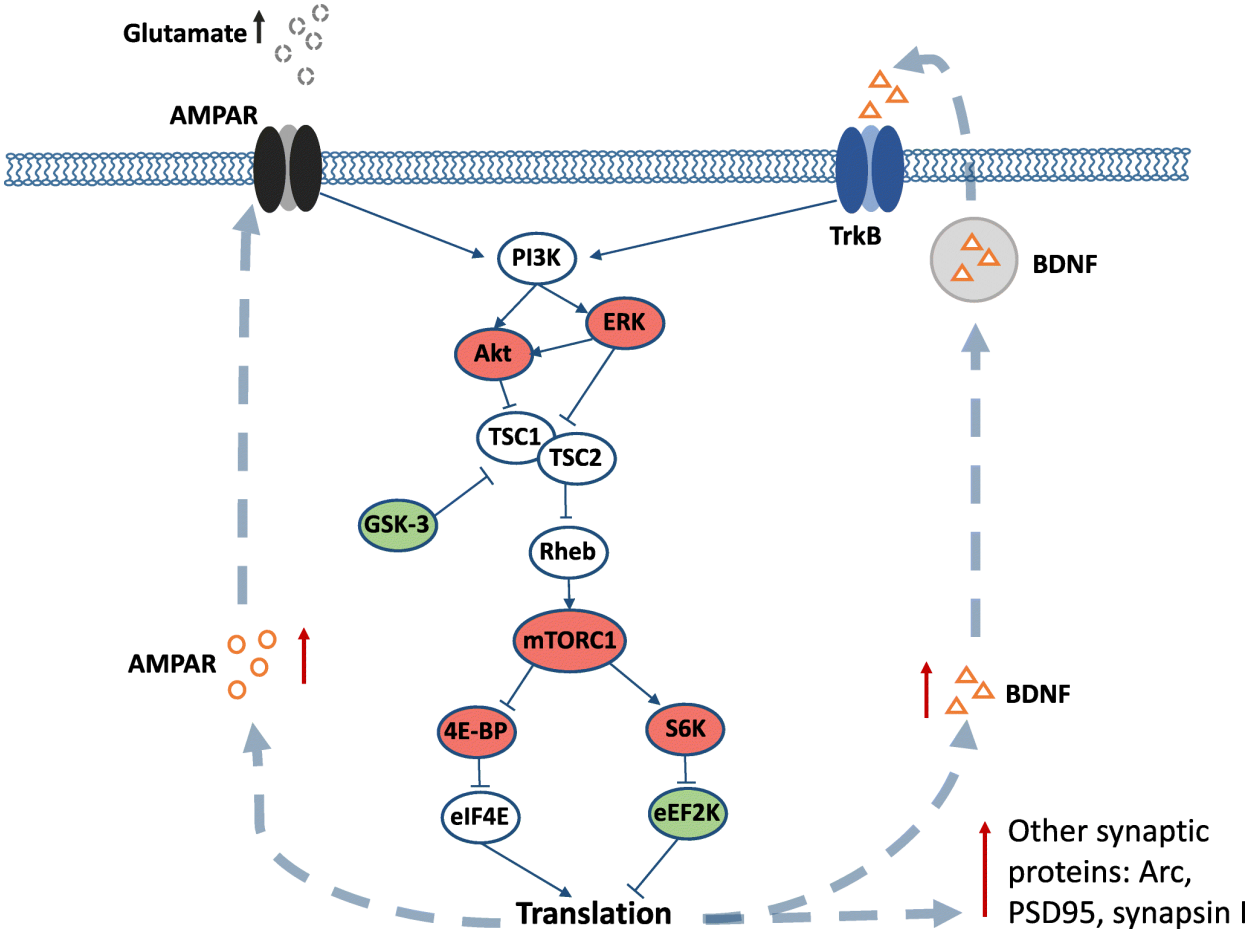

Fig. 3 Activation of the mTOR pathway [6]

As shown in figure 3, activated AKT inhibits its function by phosphorylating the tuberous sclerosis complex (TSC) 1/TSC2 complex, activating Rheb in the form of GTP binding, which originally inhibited Rheb, therefore activating mTORC1. The mTORC1 complex is a key integrator in central nervous system development.

The mTORC1 works in two ways. On the one hand, it phosphorylates eukaryotic translation initiation factor 4E-binding protein (4E-BP) and dissociates 4E-BP from eukaryotic initiation factor 4E (eIF4E). After the dissociation, eIF4E can form a translation initiation complex to initiate the translation of mRNA. On the other hand, it phosphorylates ribosomal protein S6 kinase (S6K), which in turn phosphorylates eukaryotic elongation factor-2 kinase (eEF2K) and inhibits the activity of eEF2K. Inhibited eEF2K will relieve its inhibition of eEF2 and promote the elongation of the polypeptide chain.

Translation products can be divided into three categories. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunit will be inserted into the postsynaptic membrane to enhance synaptic excitatory transmission. At the same time, the translation will produce more BDNF, forming a positive feedback loop.

Reduced levels of mTOR phosphorylation regulated by the PI3K/AKT signaling pathway affect the activation of p70S6K, further resulting in reduced transcription of several synaptic proteins [7].

However, animal models mimicking depression have shown that the effect of mTOR phosphorylation levels on depression is not monotonous. Recipients of dexamethasone (DEXA; 20 mg/kg) for 21 days showed depressive behavior while mTOR activity in their brains increased. In contrast, mice that were given higher or lower doses of DEXA did not exhibit these behaviors [8]. This unexpected result suggests that there may be some complex and still unknown mechanisms by which mTOR phosphorylation levels affect depression.

4.4 Inhibits inflammation

Dysregulation of the immune system, especially the inflammatory response, can lead to the onset of depression.

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The reason for this is that inflammation can lead to neuronal damage, glial damage, and reduced secretion of the monoamine transmitter serotonin (5-HT), which in turn leads to damage to neural connections in abnormal connections in brain regions.

The PI3K/AKT pathway could regulate microglial polarization, which in turn regulates neuroinflammation levels. It transforms microglia between the pro-inflammatory phenotype and the anti-inflammatory one, thereby inhibiting the inflammatory response that contributes to depression [9].

4.5 Maintains dopamine expression

Dopamine is responsible for transmitting information about excitement and happiness, and plays an important role in mood regulation. Patients with depression often have abnormalities in the function of their dopamine system, such as problems in the synthesis, release, or receptor binding of dopamine.

The PI3K/AKT pathway inhibits CREB phosphorylation and tissues enter the nucleus, thereby inhibiting CREB binding to CRE sites in the TH promoter region. In this case, TH transcription will be inhibited, weakening the TH inhibition of dopamine synthesis [10].

5. Strategies for the treatment of depression using the PI3K/AKT pathway

The PI3K/AKT pathway is able to synergize with other signaling pathways, such as the ERK/MAPK pathway, to modulate antidepressant responses. In the case of ketamine, it is an antidepressant that inhibits NMDA receptors and activates PI3K/AKT and ERK pathways in the lateral hypothalamic nucleus (LHb) to exert its long-lasting effects. This dual activation inhibits overactive neuronal burst firing – a hallmark of depression by promoting neurotrophic signaling and inhibiting pro-inflammatory cytokines. Specifically, ketamine promotes phosphorylation of AKT and ERK, which in turn upregulates the expression of BDNF and promotes CREB phosphorylation, thereby restoring synaptic plasticity [11]. However, this therapy has not yet become widespread because of ketamine's psychoactive side effects, such as dissociative and psychotomimetic effects, memory and cognitive impairment, and abuse [12]. Even with these deficiencies, future researchers can minimize side effects while improving efficacy by adjusting medicine dosages, selecting softer binding medicines, and even developing new medicines that target downstream effectors of the facilitating pathway.

6. Conclusion

This study demonstrates the effects of the PI3K/AKT pathway on depression. The PI3K/AKT pathway influences depression by affecting multiple mechanistic profiles such as synaptic plasticity, neuroinflammatory response, and dopamine expression. After understanding these mechanisms, medicine developers can conduct experiments to explore the effects of various medicines on the expression level, phosphorylation activity, and functional status of core molecules in key links of this pathway to screen highly effective antidepressants. Future research should focus on explaining the ununderstood mechanisms of Miqian, exploring synergies with other previously thought unrelated pathways, and identifying the metrics needed for personalized treatment. In addition, universal approaches such as optimizing medicine delivery systems and exploring combination therapies of multiple medicines can also effectively improve efficacy. If these problems are addressed, the PI3K/AKT pathway will realize its potential and become a key focus in the treatment of depression. The quality of life of existing depressed patients will be effectively improved, cured patients will be able to achieve clinical cure and significantly reduce the risk of recurrence, and those potential patients will be able to better prevent the deterioration of their condition.

References

[1] Harry Costello, Jonathan P Roiser, Robert Howard. Antidepressant medications in dementia: evidence and potential mechanisms of treatment-resistance. Psychological Medicine, 2023, 53(3): 654-667.

[2] Numakawa T, Yokomaku D, Richards M, Hori H, Adachi N, Kunugi H. Functional interactions between steroid hormones and neurotrophin BDNF. World Journal of Biological Chemistry, 2010, 1(5): 133-143.

[3] Shouhei Miyazaki, Yoshio Fujita, Hirotaka Oikawa, Hideo Takekoshi, Hideaki Soya, Masato Ogata, Takahiko Fujikawa. Combination of syringaresinol–di–O–β-d-glucoside and chlorogenic acid shows behavioral pharmacological anxiolytic activity and activation of hippocampal BDNF–TrkB signaling. Scientific Reports, 2020, 10(1).

[4] Yan He, Miaomiao Sun, Guogeng Zhang, Jing Yang, Kuisheng Chen, Wenwen Xu, Bin Li. Targeting PI3K/Akt signal transduction for cancer therapy. Signal Transduction and Target Therapy, 2021, 6(1): 425.

[5] Jichao Sun, Mo Chen. Navigating AKT-ivity across cellular compartments. Trends Cell Biology, 2025.

[6] Wenyan Cui,Yuping Ning, Wu Hong, Ju Wang Zhening Liu, Ming D. Li. Crosstalk Between Inflammation and Glutamate System in Depression: Signaling Pathway and Molecular

Biomarkers for Ketamine's Antidepressant Effect. Molecular Neurobiology, 2019, 56(5): 3484-3500.
[7] Ningning Guo, Xin Wang, Muran Xu, Jie Bai, Hao Yu, Le Zhang. PI3K/AKT signaling pathway: Molecular mechanisms and therapeutic potential in depression. Pharmacological Research, 2024, 206.
[8] Aisha Alhaddad, Asmaa Radwan, Noha A Mohamed, Eman T Mehanna, Yasser M Mostafa, Norhan M El-Sayed, Shaimaa A Fattah. Rosiglitazone Mitigates Dexamethasone-Induced Depression in Mice via Modulating Brain Glucose Metabolism and AMPK/mTOR Signaling Pathway. Biomedicines, 2023, 11(3): 860.
[9] MacRae F Linton, Javid J Moslehi, Vladimir R Babaev. Akt Signaling in Macrophage Polarization, Survival, and Atherosclerosis. International Journal of Molecular Sciences, 2019, 20(11): 2703.
[10] Wenfeng Hu, Jingjing Wu, Ting Ye, Zhuo Chen, Jinhua Tao, Lijuan Tong, Kai Ma, Jie Wen, Hui Wang, Chao Huang. Farnesoid X Receptor-Mediated Cytoplasmic Translocation of CRTC2 Disrupts CREB-BDNF Signaling in Hippocampal CA1 and Leads to the Development of Depression-Like Behaviors in Mice. International Journal of Neuropsychopharmacology, 2020, 23(10): 673-686.
[11] Z Zack Ma, Natalie J Guzikowski, Ji-Woon Kim, Ege T Kavalali, Lisa M Monteggia. Enhanced ERK activity extends ketamine's antidepressant effects by augmenting synaptic plasticity. Science, 2025, 388(6747): 646-655.
[12] Panos Zanos, Ruin Moaddel, Patrick J Morris, Lace M Riggs, Jaclyn N Highland, Polymnia Georgiou, Edna F R Pereira, Edson X Albuquerque, Craig J Thomas, Carlos A Zarate Jr, Todd D Gould. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacological Reviews, 2018, 70(3): 621-660.