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Review Article

Current concepts of pathogenesis of depressive disorder: A literature review

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Abstract

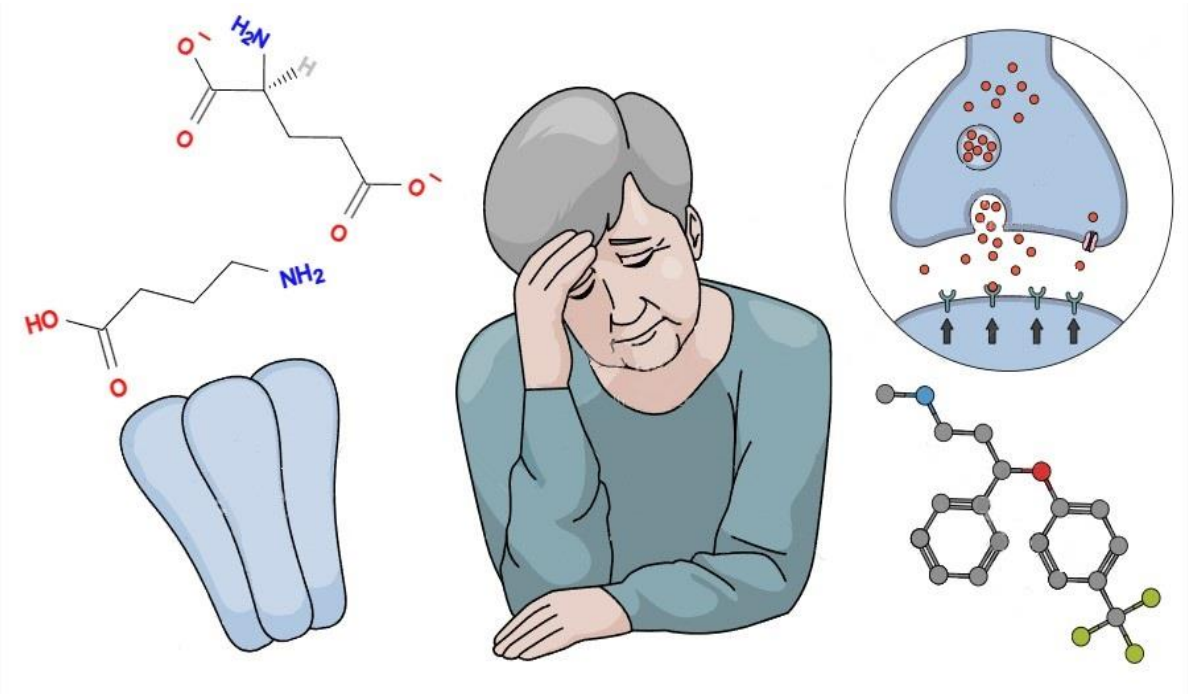
Introduction: Despite the high prevalence of depressive disorders, the pathogenesis of depression has not been fully established. Recently, a significant number of works have been published demonstrating mechanisms of development of this pathology that differ from classic monoaminergic theory. In-depth study of such mechanisms can be used as new approaches to the design of more advanced antidepressant drugs.

Materials and Methods: A search of literary sources was conducted in Google Scholar, PubMed and Cochrane databases using keywords in English: “pathogenesis of depression”, “major depressive disorder”, “β-arrestin”, “glutamate depression”, “GABA and depression”, and “neuroinflammation”. The exclusion criteria were sources published earlier than 2015. At the first step, 127 sources were chosen, but after excluding papers containing duplicated or not up-to-date information, only 40 articles were included in the review. The obtained data were briefly summarized in the form of a review article.

Results and Discussion: Translational MRI data indicate that hippocampal volume loss in depression is likely due to a disruption in serotonin-dependent neuroplasticity, which is reversible with SSRI treatment. It is believed that the therapeutic effect of these drugs is not due to a direct effect on symptoms, but rather to a restructuring of neuronal energy metabolism due to increased serotonin levels, which initiates restorative processes in the brain. β-arrestin pathway is alternative to classic in G-proteins, and some data suggest that β-arrestin-2 expression is exactly the key component of fluoxetine’s mechanism of action. Current research reveals structural, functional, and neurochemical abnormalities in GABA- and glutamate-dependent neurons that can lead to impaired signaling in the cerebral cortex and hippocampus. According to current concepts, the molecular mechanisms of these changes are associated with stress-induced excitotoxic effects, occurring against a background of elevated levels of adrenal glucocorticoids and inflammatory cytokines. Current data confirm the key role of neuroinflammation in the development of depression. Animal models of depression consistently show elevated levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α). Multiple psychosocial stressors have been shown to accelerate the development of neuroinflammation, which, in turn, contributes to the progression of major depressive disorder.

Conclusion: Despite a significant amount of research in this area, the role of additional factors in the pathogenesis of depression continues to be actively explored. Established pathogenetic models do not fully explain the disorder’s clinical heterogeneity, and current research focuses on clarifying the contribution of less studied elements, including immune dysfunction, oxidative stress, and the complex interactions between various neurotransmitter systems that go beyond the classical monoamine hypothesis.

Graphical Abstract



Keywords

GABA, serotonin, glutamate, exititoxicity, β-arrestin, depression, neuroinflammation

Introduction

Depression is a chronic mental disorder characterized by hypothymia, cognitive deficits, and motor retardation (Cui 2015; Fee et al. 2017). Depressive disorders affect an average of 13.3% of the population worldwide (Wu and Zhang 2023), and major depressive disorder (MDD) may affect one in five people during their lifetime (Ménard et al. 2016). The pathogenesis of depression is currently viewed through the prism of complex disorders. The multifactorial and heterogeneous nature of depression, driven by a combination of genetic and environmental factors, continues to hinder a full understanding of its pathophysiological mechanisms. Three main theoretical models occupy a key place in the modern scientific paradigm: the monoamine hypothesis, the concept of impaired neuroplasticity, and the theory of hypothalamic-pituitary-adrenal axis dysfunction (Wang et al. 2022). The central place belongs to dysregulation of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal systems, serotonergic deficiency, as well as chronic inflammation and abnormalities of the immune response as key pathogenetic links (Troubat et al. 2021). This complex pathobiochemical background, affecting cytokines, hormones and neuropeptides, continues to be actively studied. In-depth study of pathophysiology opens the way for new therapeutic strategies (Li et al. 2021), which is especially relevant in light of frequent therapeutic resistance, stimulating the search for original pharmacological and psychological targets (Kverno et al. 2021). The relationship between affective disorders and oxidative stress is being studied separately, with antioxidants (glutathione, coenzyme Q10, etc.) acting as indicators, and restoration of their balance serving as a marker of successful treatment (Harsanyi et al. 2022). Hormones and neuropeptides also exert their influence, closely interacting with the serotonergic, dopaminergic, noradrenergic, and GABAergic systems.

Despite the high prevalence of the disease and amount of underlying mechanisms described, the pathogenesis of depression has not been fully established yet, as a result of which almost half of patients with depression experience insufficient effect of antidepressants (Li et al. 2021). A better understanding of the mechanisms of pathogenesis of depressive disorder will help to find more effective treatment options. This is why it is so important to highlight these aspects.

Aim of the study

Analysis of modern literature data on the features of molecular mechanisms of depressive disorders development for target-oriented search for new drugs.

Materials and Methods

A search of literary sources was conducted in Google Scholar, PubMed and Cochrane databases using keywords in English: “pathogenesis of depression”, “major depressive disorder”, “β-arrestin”, “glutamate depression”, “GABA and depression”, and ”neuroinflammation”. The exclusion criteria were sources published earlier than 2015. At the first step 127 sources were chosen, but after excluding papers containing duplicated or not up-to-date information, only 40 articles were included in the review. The obtained data were briefly summarized in the form of a review article.

Results and Discussion

Classic monoamine theory

The monoamine theory of depression pathogenesis, based on the depletion of vesicular stores of norepinephrine and serotonin, has been the main theory in psychiatry since the 1960s. According to the literature, the dopaminergic system is not directly involved in MDD, but the afferent regulation of its functioning is impaired (Grace 2016; Belujon & Grace 2017). Opposing effects on behavior in anxiety and depression are also noted, mediated by the activation of α_2-adrenaline and H-cholinergic receptors containing β_2-subunit in the amygdala (Mineur et al. 2021). Over the past six decades, research into the pathophysiology of depression has focused on 5-hydroxytryptophan and serotonergic neurotransmission (Dell’Osso et al. 2016). Translational magnetic resonance imaging data in animals suggest that the decrease in neuronal density and size and the reduction in hippocampal volume in patients with depression may be associated with changes in serotonin-modulated neuroplasticity that can be restored by selective serotonin reuptake inhibitors (SSRIs) (Kraus et al. 2017). According to some studies, SSRIs do not act directly on depressive symptoms, but alter the energy homeostasis of nerve cells by increasing the concentration of serotonin in the synaptic cleft, and their therapeutic effect is due to the compensatory capacity of the brain to restore homeostasis (Andrews et al. 2015).

β-arrestin pathway

Other mechanisms of dysthymia development are currently being studied. As is known, GPCRs activate G proteins in response to allosteric stimulation (Smith et al. 2018). For their adaptation to the action of a constant stimulus, the process of desensitization of active receptors is necessary (Cahill et al. 2017). One of its stages is the phosphorylation of receptors through serine-threonine kinases and their preparation for binding to arrestin-1 (Kumari et al. 2016), which blocks further signal transmission through G proteins and redirects the signal to alternative pathways (Fig. 1), such as β-arrestin (Kumari et al. 2017). It is noted that taking fluvoxamine in MDD reduces the expression of β-arrestin in the hippocampus, while the use of imipramine and desipramine increases it (Tejeda-Martínez et al. 2024). Li et al. (2020), using a chronic stress model of depression, suggest that β-arrestin-2 expression is a key component of fluoxetine's mechanism of action, as β-arrestin-2 knockout mice do not respond to 10 mg/kg fluoxetine treatment in terms of immobility time in the forced swim test, serotonin concentrations and hippocampal neurogenesis.

Involvement of GABA-ergic synaptic transmission and exitotoxicity of glutamate

A study of the neurobiological basis of damage to synaptic transmission in the central nervous system using magnetic resonance spectroscopy and positron emission tomography (Lener et al. 2017) showed that not only excitatory glutamatergic but also inhibitory GABA-ergic interneurons play a decisive role in the pathogenesis of affective disorders (Duman et al. 2019). Structural, functional, and neurochemical deficits in GABA- and glutamate-dependent nerve cells have been demonstrated (Fig. 2), which can lead to deterioration of signal integrity in the cortex and hippocampus (Abdallah et al. 2014). The molecular mechanisms of these changes are believed to be associated with stress-induced excitotoxic effects in combination with increased levels of adrenal glucocorticoids and inflammatory cytokines (Duman et al. 2019). Currently, a positive allosteric modulator of neurosteroid $GABA_A$ receptors, allopregnanolone, is known, which exhibits antidepressant and anxiolytic effects (Zorumski et al. 2019). Studies have also been conducted on the modulation of $GABA_B$ receptors for the treatment of depression (Alexander 2017).

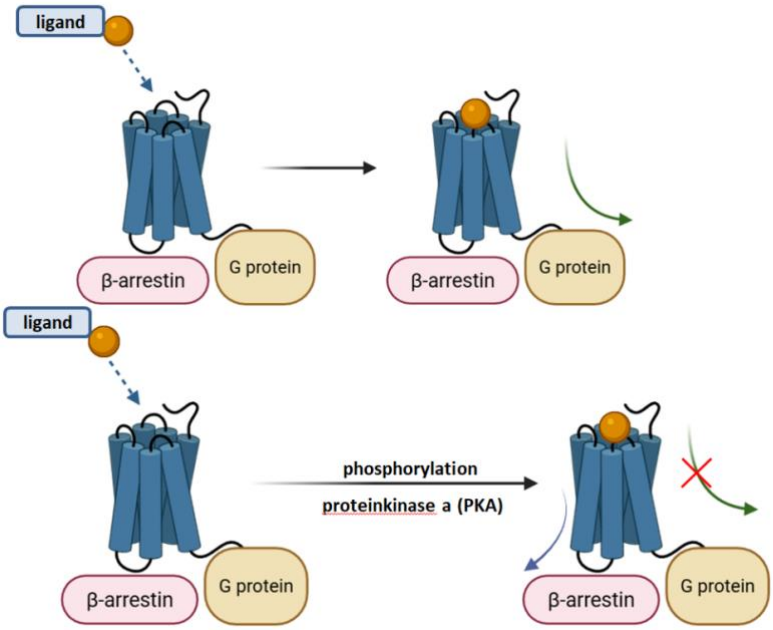


Figure 1. β-arrestin pathway.

Ionotropic (NMDAR, AMPAR and kainate receptors) and metabotropic (mGluRs) glutamate receptors play an important role in the genesis of affective disorders. A decrease in the level of N-methyl-D-aspartate in the dorsolateral, dorsoanterolateral and dorsomedial prefrontal cortex and anterior cingulate cortex in people suffering from MDD has been established (Henter et al. 2018), as well as atrophy of glutamatetergic neurons in the areas of the central nervous system that control mood and emotions – the limbic system and cortex (Duman et al. 2019). According to Dean et al. (2021), glutamate levels were increased in the occipital cortex of patients suffering from depression. It is noteworthy that some genes responsible for the expression of glutamate (the $GRIA_3$ gene encoding AMPAR; the $GRIK_2$ and $GRIK_4$ genes encoding kainate receptors and the GRM_7 gene responsible for mGluRs) were found to be involved in the genesis of dysthymia (De Sousa et al. 2017). It is worth noting that these genes are responsible to a greater extent for the genesis of bipolar affective disorder than MDD (Gerhard et al. 2016). Ketamine, as an NMDA antagonist, is able to induce a rapid reduction in depressive symptoms (within hours), restore synaptic connections in the prefrontal cortex and reverse molecular deficits caused by chronic stress (Dean et al. 2021). This properties of ketamine have now led to the initiation of a number of studies investigating various fast glutamatergic agents in the treatment of depressive disorder (Hess et al. 2022; Fan et al. 2023; Borbély et al. 2022).

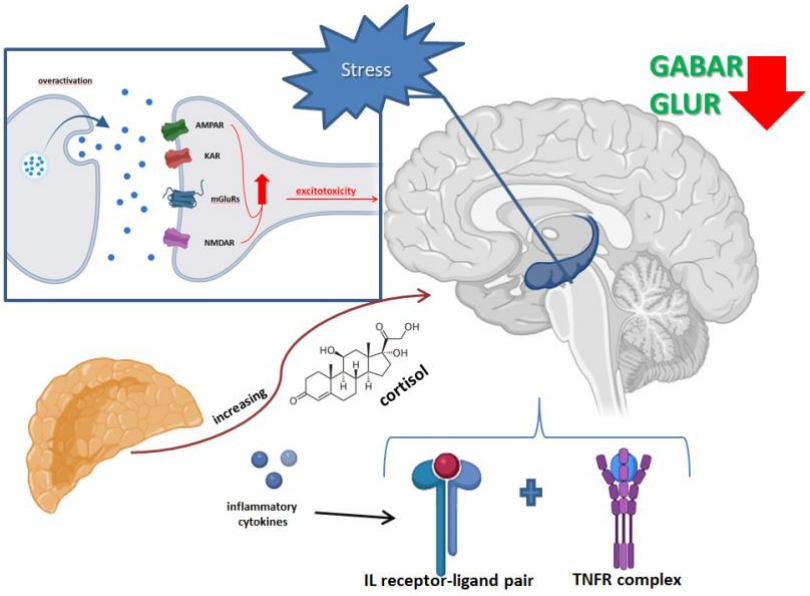


Figure 2. GABA- and glutamatergic systems in affective disorders.

Contribution of neuroinflammation

Finally, according to recent studies, one of the key roles in the pathogenesis of depression belongs to neuroinflammation processes. Multiple psychosocial stressors have been shown to accelerate the development of neuroinflammation, and ongoing neuroinflammation can contribute to the progression of MDD (Won et al. 2021). Peripheral levels of IL-1β, IL-6, and TNF-α are consistently increased in animal models of depression (Hodes et al. 2014). Various forms of animal stress (chronic mild stress, learned helplessness, repetitive stress of social interaction) induce a melancholic phenotype of depression, increase insulin insensitivity and levels of proinflammatory cytokines. For example, Haapakoski et al. (2014) found a strong correlation between depression and increased titers of peripheral inflammatory markers (IL-6 and C-reactive protein) in cerebrospinal fluid samples. Hodes et al. (2015) found that peripheral IL-6 levels were 27-fold higher in susceptible mice compared to resistant mice after repeated social interaction stress. Administration of an IL-6 monoclonal antibody 5 minutes before the stress procedure prevented the development of social avoidance (Hassamal 2023). In a meta-analysis, the use of various drugs, including nonsteroidal anti-inflammatory drugs (celecoxib, naproxen, aspirin), cytokine inhibitors, statins, and minocycline, significantly improved depressive symptoms in some patients with MDD (Köhler-Forsberg et al. 2019).

Conclusion

Despite the fact that depressive disorders have been known for a long time, their treatment at the present stage causes significant difficulties due to the diversity of pathogenetic pathways underlying the development of this pathology. At the present stage, the role of the serotonergic system, excitotoxic action of glutamate, disorders in the work of the GABA-ergic link, as well as the β-arrestin pathway and neuroinflammatory processes is emphasized. At the same time, the pathogenesis of depressive disorder is still being actively studied and the role of other links in the pathological process has yet to be established.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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The study was carried out within the framework of a state assignment, registration number 1024022800309-1-3.5.2;3.1.5;3.1.6.

Data availability

All of the data that support the findings of this study are available in the main text.

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