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Ceren Sahin, Serdar Dursun, Mesut Cetin & Feyza Aricioglu

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# The Neuroinflammation Perspective of Depression: Reuniting the Outstanding Mechanisms of the Pathophysiology

Ceren Sahin[1], Serdar Dursun[2], Mesut Cetin[3], Feyza Aricioglu[1]

**ABSTRACT:**

The neuroinflammation perspective of depression: reuniting the outstanding mechanisms of the pathophysiology

Major Depressive Disorder (MDD) is a serious mental health problem that leads to patients' disability and has huge impact on social and economic burden to society. The current available medications for the treatment of depression are mainly targeted on enhancing monoamine neurotransmission. However, antidepressant treatments are still lacking high efficacy in many cases which is associated with low treatment response and remission rates. However, the latest knowledge regarding the pathophysiology of depression indicates that depression is developed by highly complex and integrated mechanisms in which monoaminergic deficiency could only be part of. The paradigm is now shifting from monoaminergic hypothesis to significance of other novel mechanisms that could possibly play substantial role for the development of depression in a highly inter-related manner. In fact, neuroinflammation, amongst other mechanisms does seem to be a key pathological component by having impact on certain pathway pathologies including glutamatergic neurotransmission, oxidative processes, neurotropic factors, neurotransmitter metabolism, and glucocorticoid functions in the central nervous system (CNS) and in the periphery, thereby triggers the pathological alterations that is thought to contribute to the development of depression. The neuroinflammation comprehends the processes exampled from excessive pro-inflammatory cytokine release to activation of microglia and indolamine 2,3-dioxygenase (IDO) pathway, excessive glutamatergic neurotransmission, hyperactive hypothalamus-pituitary-adrenal (HPA) axis, decreased neurogenesis and synaptic plasticity. In fact, the antidepressant effect of ketamine as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist might be at least partially linked to inflammatory modulations. The significance of inflammation in depression is not only mentioned by the literature of basic researches from a mechanistic aspect but also by the possible clinical implications suggested by the clinical reports. Although the exact role of inflammation in depression and its clinical translation have not been determined yet, the inflammation-mediated point of view might provide novel insights for improving the diagnosis at clinic (e.g., inflammatory biomarkers), predicting antidepressant treatment response and thereby re-evaluating the treatment strategy. Moreover, with all that, the inflammation aspect raises the question for the possible significance of utilizing anti-inflammatory approaches in the treatment of depression.

**Keywords:** depression, inflammation, neuroinflammation, cytokine, microglia, glutamate, ketamine

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[1]Marmara University, School of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul - Turkey
[2]University of Alberta, Department of Psychiatry, Edmonton, Alberta, Canada
[3]GATA Haydarpasa Training Hospital, Department of Psychiatry, Istanbul - Turkey

**Corresponding author:**
Prof. Dr. Feyza Arıcıoğlu,
Marmara Üniversitesi, Eczacılık Fakültesi, Farmakoloji Anabilim Dalı ve Psikofarmakoloji Araştırma Birimi, Haydarpaşa, 34668, İstanbul - Türkiye

**Phone:** +90-216-418-9573

**Fax:** +90-216-345-2952

**E-mail address:**
faricioglu@marmara.edu.tr,
feyza.aricioglu@gmail.com

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## INTRODUCTION

Major Depressive Disorder (MDD) is a common debilitating and to some extend life-threating psychiatric disease with having huge impact on social and economic burden to society worldwide. According to the World Health Organization (WHO) global burden of disease report (updated in 2004); MDD is estimated to be the first line cause for disability and death followed by ischemic heart disease by 2030[1].

Today, it has been more than a half century since an iminodibenzyl compound having a tricyclic structure was firstly proposed to have antidepressant properties which thereafter formed the origin of tricyclic antidepressants (TCAs) and let to the first FDA approval of a tricyclic agent, imipramine, for the treatment of depression in 1959[2].

Further discoveries on TCAs revealing that these molecules blocked noradrenaline and serotonin re-uptake in addition to the findings regarding the deficiency of brain serotonin levels in depressed patients, brought up the conjecture of 'monoamine hypothesis' in depression[3-5]. In regard with this notion, subsequent treatment approaches that are specifically or non-specifically targeted to enhance monoaminergic neurotransmission have been developed with the aim of improving treatment response and also in some cases precluding undesirable side effects. Such approaches still utilized today include monoamine oxidase (MAO) inhibitors (e.g., moclobemide), dopamine reuptake inhibitor (e.g., bupropion), selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine), serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g., venlafaxine), noradrenaline reuptake inhibitors (NARIs) (e.g., reboxetine). There are also atypical multi-receptor targeted approaches including blockage of specific serotonergic (5-HT2C) receptors in combination with adrenergic receptors (mirtazapine) or melatonergic receptors (agomelatine). Most recently, agents with multi-modal serotonergic action profile which compromised of serotonin reuptake inhibition (SRI) in addition to multi-target serotonergic receptor actions are now being used in the treatment of depression with suggested superior effects due to their multi-modal mechanism of action profile (e.g., vortioxetine, vilazodone) which still remains in uncertainty in the clinic. The reader is referred to the comprehensive review by Millan et al. (2015) for further information regarding to the history and evaluation of pharmacotherapy available for the treatment of depression[6].

As briefly highlighted above, the current available medications for the treatment of depression remain to be mainly restricted to monoaminergic hypothesis despite the considerable amount of time elapsed from back then. However, unfortunately, the treatment options that we hold on utilizing today, still lack in high efficacy in many cases (60%-65%) leading to low treatment response and remission rate even after combination therapy[7,8]. On the other hand, there is an ongoing conflict with current medications regarding their delayed effect on improving the symptoms (requires several weeks, at least) even though they increase the brain monoamine levels rapidly. This is not only a problem for patients to be not able to recover in due time but it also leads to patients' poor adherence which may further results in giving up the treatment.

Therefore, the current knowledge clearly guides us that the pathophysiology of depression cannot be easily explained by the monoaminergic basis per se, rather it seems to be developed by much more complex and integrated mechanisms in which monoaminergic deficiency could only be part of. At this point, the paradigm is now shifting from monoaminergic hypothesis to significance of other novel mechanisms such as neuroinflammation, glutamatergic dysregulations and decreased neurogenesis that could possibly play substantial role for the development of depression in a highly interrelated manner which may further drive altered monoaminergic neurotransmitter metabolism (Figure 1). In this short review, we aim to highlight the inter-relation of these mechanisms from a 'neuroinflammation-mediated' point of view.

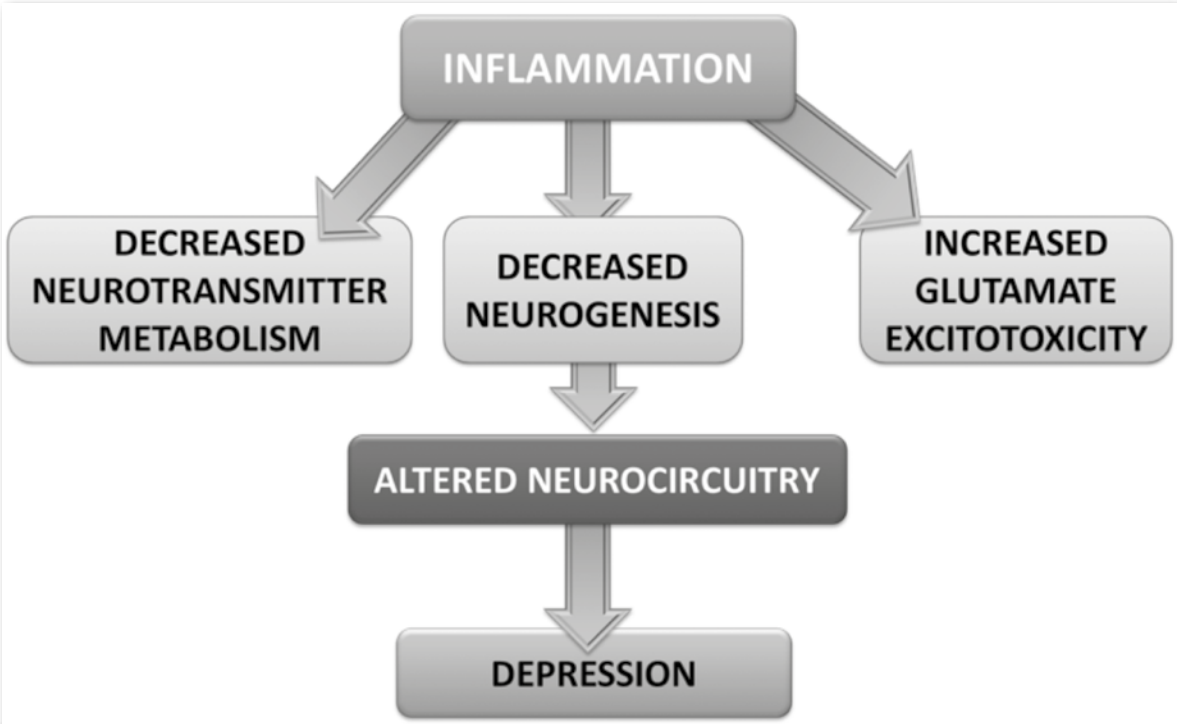


**Figure 1: The inflammation as a key mediator for the development of depression.**

**Why Neuroinflammation in Depression?**

Today, there is growing consensus suggesting that inflammatory processes are highly related with the occurrence of depression[9-11]. Individuals with immune and/or inflammatory diseases such as rheumatoid arthritis, diabetes, systemic lupus erythamotosus, psoriasis and cardiovascular diseases have been reported to have depressive symptoms[12-15]. On the other hand, basic and clinical studies have shown that cytokines, as main mediators of inflammatory responses, are elevated in depression[16-18]. Furthermore, certain anti-inflammatory approaches can reduce depressive symptoms[19,20], whereas antidepressant treatments can alleviate the elevated levels of cytokines in some cases[21-23]. Therefore it has been postulated that there might be a reciprocal relationship between ongoing inflammatory processes and depression[24]. In fact, at present, it has become more than a postulation particularly by the evidence of experimental studies shedding some light on how inflammation interacts with other mechanisms including glutamatergic neurotransmission, oxidative processes, neurotropic factors, neurotransmitter metabolism and glucocorticoid functions in the central nervous system (CNS) and in periphery at a molecular basis and trigger the pathological alterations that is thought to contribute to the development of depression[24,25]. Speaking of the inflammation in the brain brings up the term 'neuroinflammation' which is presented when inflammation reaches to the CNS either by the communication of peripheral immune mediators with brain (cytokines entering the brain) due to an inflammatory condition in the periphery (e.g., infection, disease) or microglial activation directly via psychological stress or other factors[11]. In this review, neuroinflammation in depression is overviewed by its role as a key mediator on major integrated pathway pathologies; microglial activation, excessive glutamatergic neurotransmission, hyperactive hypothalamus-pituitary-adrenal (HPA) axis, decreased neurogenesis, and altered neurotransmitter metabolism (Figure 2).

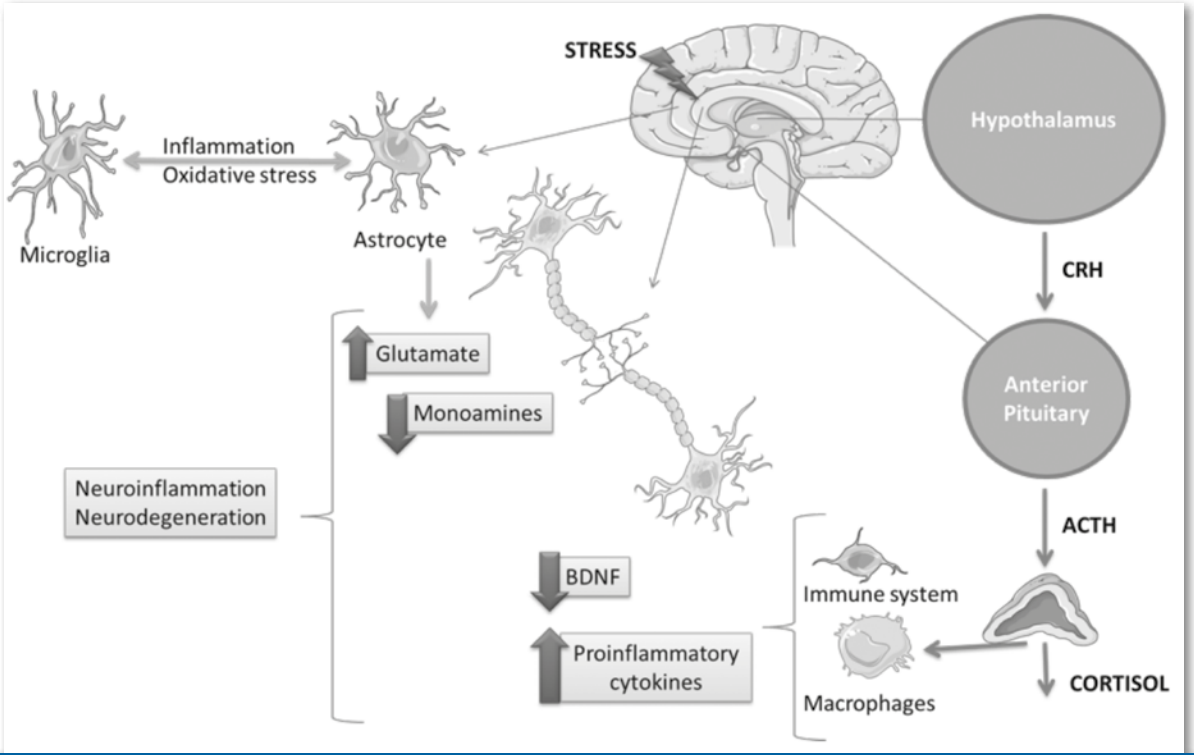


**Figure 2: Major integrated pathway pathologies in depression.**

### A Pathway from Microglial Activation to Excessive Glutamate

At present, it is well-reported that microglia are activated in chronic stress and depression[26,28]. Besides, microglial activation was reported in postmortem brain studies of suicide victims[29]. Microglia, one of the specific types of the glial cells in brain, are responsible for maintaining the CNS homeostasis in their resting state unless they are activated[30]. However, once encountered with danger signals that reach the brain (infection, dying cells, immune communication) they act as the as resident macrophages in the CNS playing a 'double-edged sword' 30 with trophic or destructive functions as depicted in Figure 3. Certain pathological events triggered by microglia activation are not only restricted to excessive release of pro-inflammatory cytokines (e.g., TNF-α, IL-1, and IL-6) but also includes increased glutamate levels and certain neurotoxic compounds and free radicals that are all highly involved with depression[11,30-32].

The activation of microglia and the subsequent release of cytokines at a cellular level are mainly based on triggering pattern recognition receptors located on the cell membrane such as Toll-Like and purinergic receptors by pathogen or damage associated molecular patterns which leads to the production of pro-inflammatory cytokines via nuclear factor kappa-B (NFκB) and mitogen activated protein kinase (MAPK) signaling. The activation of these cascades results in direct release of certain cytokines such as TNF-α and IL-6. However, inflammasome formation of Nod-like protein 3 (NLRP3), a cytosolic pattern recognition receptor, is required for caspase-1 activation which mediates IL-1β and IL-18 release[33]. Within the last years, NLRP3 inflammasome activation and its possible role as a candidate initiator mechanism for the treatment of depression has been under investigation by a growing number of encouraging studies[27,34-36].

Excessive pro-inflammatory cytokines activate indolamine 2,3-dioxygenase (IDO), an enzyme converting tryptophan, the precursor of

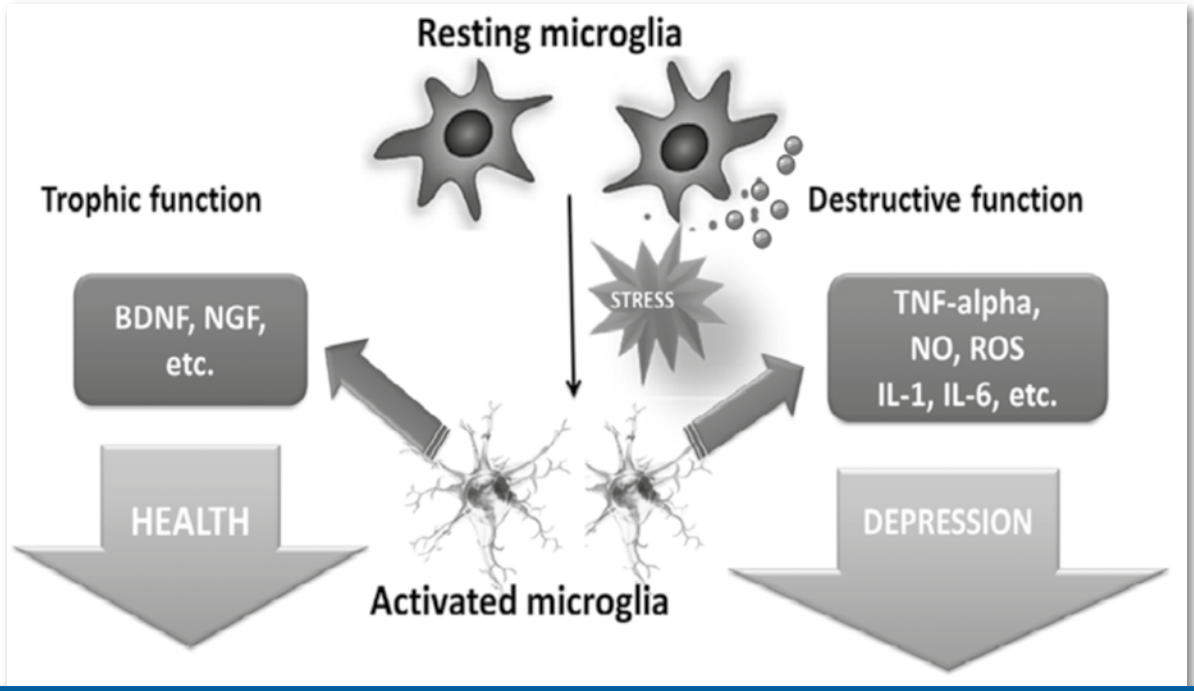


**Figure 3: The dual role of activated microglia.**

5-hydroxytriptamine (5-HT), into kynurenine, therefore shift the balance of tryptophan metabolism from 5-HT to kynurenine which in turn leads reduced serotonin bioavailability[37]. Kynurenine is further metabolized by a microglial enzyme, kynurenine mono-oxygenase, into neurotoxic 3-hydroxykynurenine and subsequent quinolinic acid, an N-methyl-D-aspartate (NMDA) receptor agonist that consequently leads to excessive glutamatergic neurotransmission thereby contributing to glutamate excitotoxicity in depression[38,39]. This notion is supported by the findings that depressive patients have higher plasma ratio of kynurenine to tryptophan compared to healthy controls[31] and the inhibition of IDO improves depressive-like behaviors induced by LPS manipulation[40].

It is noteworthy to indicate that the pathway highlighted for microglia here, is also valid for the peripheral innate immune cells meaning that if there is an ongoing inflammatory process in the periphery, the activation of innate immune cells results in the production and release of pro-inflammatory cytokines in the same manner. As in the CNS, excessive cytokines trigger IDO and consequently kynurenine in the periphery which is followed by peripheral communication to brain. Not only cytokines but also kynurenine can enter the brain via several ways which contributes to the activation of microglia, therefore, quinolinic acid formation, glutamate release and other subsequent destructive events including excessive NMDA receptor activation and neurotoxicity[31]. Therefore, this peripheral aspect that is apart from microglia activation due to central events within the brain (e.g., psychological stress) is also essential for the neuroinflammation-mediated pathophysiology of depression.

## Engaging the Brain with Periphery: Hyperactive Hypothalamus-Pituitary-Adrenal (HPA) Axis

Hypothalamus-pituitary-adrenal (HPA) axis hyperactivity is another important component for the pathophysiology of depression which is highly related with cytokine-mediated inflammatory processes[41,42]. Pro-inflammatory cytokines has been shown to stimulate HPA axis by both directly

activating CRH and subsequently increasing ACTH and cortisol and also disrupting negative feedback regulation via the inhibition of glucocorticoid receptors[10,43,44]. In the case of an inflammatory condition, cortisol and parasympathetic nervous system inputs (e.g., via the vagus nerve) are responsible for decreasing inflammatory responses on relevant immune cells via the inhibition of NF-κB, therefore producing an anti-inflammatory state in the body. However, when there is prolonged inflammation due to chronic disease or stress, excessive inflammatory cytokines disrupt glucocorticoid receptor functioning via the activation p38 MAPK pathway thereby NF-κB is rescued from the negative regulation of cortisol which in turn exaggerates the cytokine production and relevant inflammatory responses even more[10,44-46]. In addition, by activating p38 MAPK pathway, cytokines upregulates serotonin transporter (SERT) in the brain, which is considered to further contributing the serotonin deficiency in addition to tryptophan starvation due to IDO activation, highlighted above[10]. Therefore, excessive cytokine release might result in altered serotonin metabolism by the mentioned separate branches of mechanisms in depression. Moreover, high plasma glucocorticoid levels are associated with reduced brain-derived neurotrophic factor (BDNF) levels, atrophy of pyramidal cells in the hippocampus and prefrontal cortex which are accompanied by depressive symptoms[47,48].

**Ketamine and Neuroinflammation: Is There a Gap or Bridge Between?**

As overviewed above, excessive quinolinic acid and glutamate releases as chain reactions in neuroinflammatory processes, results in the over-activation of extrasynaptic NMDA receptors and subsequent glutamate excitotoxicity which is one of the most dominant pathway pathology seen in depression. The clinical discovery of ketamine's rapid antidepressant effect as a non-competitive NMDA receptor antagonist[49], has broaden the view of modulating glutamatergic neurotransmission as a highly potential novel treatment approach for depression along with the aim of identifying molecular mechanisms driving this robust effect.

The key mechanisms responsible for the rapid antidepressant effect of ketamine are considered to be mainly mediated by the activation of the mammalian target of rapamycin (mTOR) pathway, and subsequently rapid increase in BNDF production which further leads to post-synaptic protein translation such as PSD95, synapsin, GluA1 that are essential for enhanced synaptic signaling and new synapse formation (synaptogenesis)[50-52].

There is evidence that ketamine blocks NMDA receptors located on gamma-aminobutyric acid (GABA)-ergic interneurons resulting in an increased glutamate outflow[53]. Thus, the inhibition of NMDA receptors allows more glutamate transmission via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors which is considered to be an essential mechanism for the ketamine's rapid antidepressant effect[51]. The activation of AMPA receptors results in rapid sodium entry and membrane depolarization which triggers downstream events of signal transduction including mTOR activation, eukaryotic elongation factor 2 kinase (eEF2K) inhibition, increased BDNF translation and postsynaptic density protein expression[25,51,54,55].

Activation of mTOR rescues eEF2 from its inhibitory kinase eEF2K, which upregulates BDNF translation. BDNF, by binding tyrosine kinase B (TrkB) receptors, in turn activates mTOR signaling via phosphoinositide 3-kinase (PI3K)-AKT cascade which further enhances BDNF release by demonstrating a positive feedback mechanism. Based on the knowledge regarding the crucial roles of eEF2 on enhancing BDNF mediated neurotrophic processes, eEF2K inhibitors are currently under investigation in depression[55].

It has been shown that inhibition of glycogen synthase kinase-3 (GSK-3) is also involved in the rapid antidepressant effects of ketamine by the findings that ketamine inhibits GSK-3 activity and antidepressant-like effect of ketamine was potentiated when combined with lithium, a preferentially GSK-3 inhibitor[56,57].

Since ketamine has certain restrictive psychotomimetic characteristic and therefore, the potential therapeutic effect would almost hardly be mentioned in the clinic, novel compounds targeting different aspects of glutamatergic system and lacking psychotomimetic (also known as psychotogenic) properties have been under investigation in depression as follows: NMDA receptor antagonists (e.g., zinc, magnesium, scopolamine, guanosine, amantadine, dextrometorphan), glutamate release inhibitors (e.g., riluzole, lamotrigine, sarcosine), AMPA potantiators (e.g., tianeptin, aniracetam, LY392098, LY451616), metabotropic glutamate 2/3 (mGlu2/3) receptor antagonists (e.g., LY341495), selective NMDA receptor subtype 2B (NR2B) antagonists (e.g., CP-101, CP-606), partial NMDA receptor agonists (e.g., D-serin, D-cycloserine, GLYX-13) some of which are depicted in Figure 4. Further information regarding the current situation with the novel candidates modulating glutamatergic system can be found in the detailed review by Deutschenbaur et al.[58].

Today, there is growing body of evidence suggesting that ketamine may also possess anti-inflammatory properties that could contribute to its antidepressant effect. It was previously reported that ketamine downregulated cytokine expression induced by LPS manipulation in macrophage cells[59]. In addition, ketamine was shown to alleviate depressive-like behavior induced by LPS administration via AMPA receptor activation[60]. However, the improved behavioral effect obtained by ketamine in such neuroinflammation-mediated depression model was not accompanied with reduced cytokine response. On the other hand, in a more recent study, ketamine was shown to decrease pro-inflammatory cytokines induced by

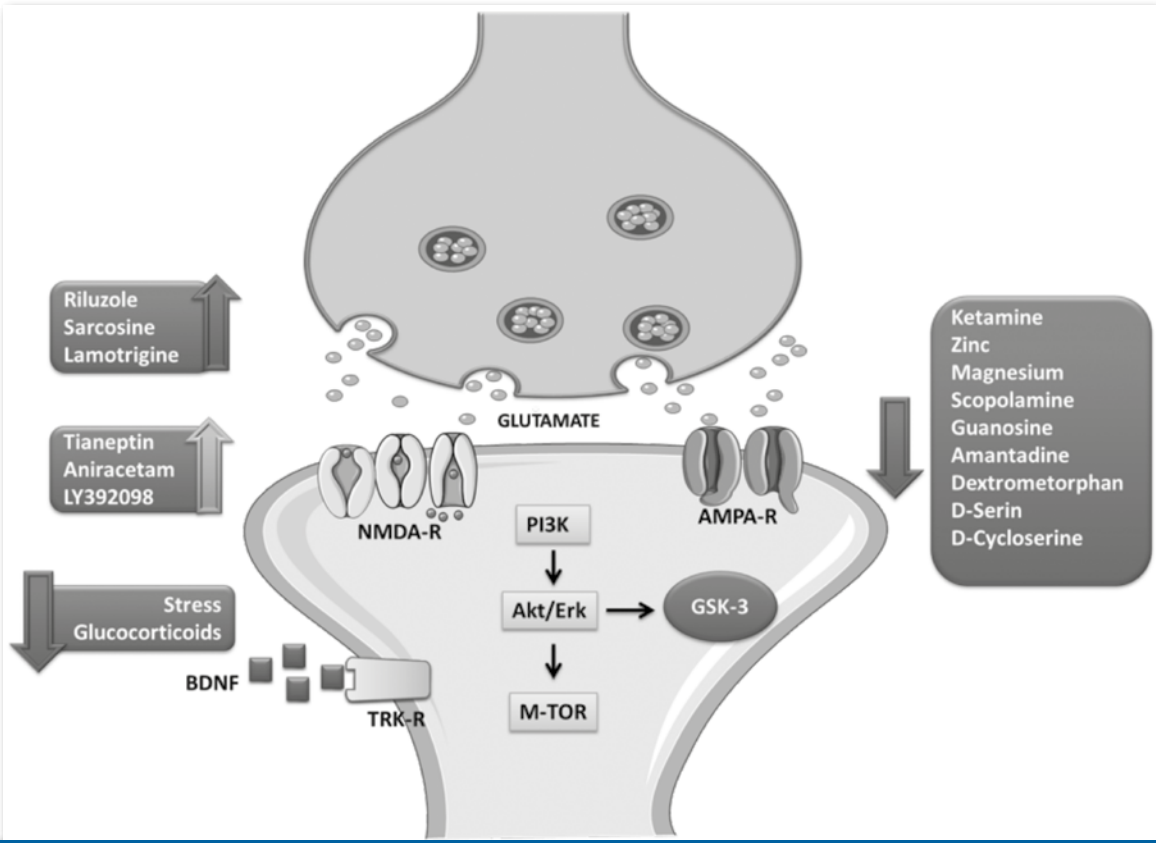


**Figure 4: Examples of different treatment approaches targeting glutamatergic neurotransmission: NMDA receptor antagonists (e.g., ketamine, zinc, magnesium, scopolamine, guanosine, amantadine, dextrometorphan), NMDA receptor partial agonists (D-serin, D-cycloserine), glutamate release inhibitors (e.g., riluzole, lamotrigine, sarcosine), AMPA receptor enhancers (e.g. tianeptin, aniracetam, LY392098) (Adapted from Deutschenbaur et al, 2016).**

maternal deprivation model and this was in accordance with ketamine's antidepressant-like effects[61]. These findings were concluded as the glutamatergic modulators could also be of interests for decreasing inflammatory responses or microglial activation in depression which requires further investigation at present. Therefore, the findings indicating that the antidepressant effects provided by ketamine might be also coupled with its proposed anti-inflammatory properties, direct us to the importance of understanding the possible mechanisms orchestrating neuroinflammation and glutamate exitotoxicity as potential targets in depression[11,24].

## CONCLUSION

At present, growing body of evidence from not only basic studies but also from clinical research points out the significance of inflammation in depression: A recent meta-analysis suggests that increased inflammatory markers predict antidepressant treatment resistance in depressed patients[62]. The data examination from 35 different clinical studies revealed that patients with persistently elevated TNF-α levels do not respond to antidepressant treatments whereas treatment responders are associated with decreased levels of TNF-α. In addition, treatment with antidepressants results in reduced IL-6 levels however, that is unrelated with treatment response[62]. These findings guide us to the importance of utilizing biochemical tests for determining the levels of inflammatory markers for possibly helping the diagnosis and improve the treatment success in refractory patients. Thereby, the idea follows as the non-responders with higher inflammatory markers might benefit from anti-inflammatory agents. Likewise, infliximab, a TNF-α antagonist, has recently been reported to improve depressive symptoms in refractory patients having high baseline inflammatory biomarkers[63].

Besides, non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated for their potential effects as adjunctive therapies in depression. Amongst other NSAIDs, perhaps the data of celecoxib still stands for the most evident one especially by a recent meta-analysis suggesting that adding celecoxib in addition to antidepressant treatment demonstrates higher treatment response and remission rate in MDD patients[64].

Taken together by the clinical point of view, although the role of inflammation in depression and its possible clinical implications have not been determined yet, but still inflammation aspect of depression holds promise for predicting antidepressant treatment response and raising question to the possible significance of utilizing anti-inflammatory approaches in the treatment of depression.

## References:


1. http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf
2. Kuhn R. Treatment of depressive states with an iminodibenzyl derivative (G 22355). Schweiz Med Wochenschr 1957;87(35-36):1135-40. (German)
3. Axelrod J, Whitby LG, Hertting G. Effect of psychotropic drugs on the uptake of H3-norepinephrine by tissues. Science 1961;133(3450):383-4. [CrossRef]
4. Ross SB, Renyi AL. Inhibition of the uptake of tritiated catecholamines by antidepressant and related agents. Eur J Pharmacol 1967;2(3):181-6. [CrossRef]
5. Carlsson A, Corrodi H, Fuxe K, Hökfelt T. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-alpha-ethyl-meta-tyramine. Eur J Pharmacol 1969;5(4):357-66. [CrossRef]
6. Millan MJ, Goodwin GM, Meyer-Lindenberg A, Ove Ogren S. Learning from the past and looking to the future: emerging perspectives for improving the treatment of psychiatric disorders. Eur Neuropsychopharmacol 2015;25(5):599-656. [CrossRef]
7. Block SG, Nemeroff CB. Emerging antidepressants to treat major depressive disorder. Asian J Psychiatr 2014;12:7-16. [CrossRef]
8. Montes JM, Ferrando L, Saiz-Ruiz J. Remission in major depression with two antidepressant mechanisms: results from a naturalistic study. J Affect Disord 2004;79(1-3):229-34. [CrossRef]
9. Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain Behav Immun 2003;17(Suppl. 1):S119-S24. [CrossRef]

10. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27(1):24-31. [CrossRef]

11. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. Neuroscience 2015;300:141-54. [CrossRef]

12. Ceretta LB, Réus GZ, Abelaira HM, Jornada LK, Schwalm MT, Hoepers NJ, et al. Increased prevalence of mood disorders and suicidal ideation in type 2 diabetic patients. Acta Diabetol 2012;49 (Suppl. 1):S227-S34. [CrossRef]

13. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, et al. Mood disorders in the medically ill: scientiŞc review and recommendations. Biol Psychiatry 2005;58(3):175-89. [CrossRef]

14. Hoyo-Becerra C, Schlaak JF, Hermann DM. Insights from interferon-alpha-related depression for the pathogenesis of depression associated with inşammation. Brain Behav Immun 2014;42:222-31. [CrossRef]

15. Kim WK, Shin D, Song WO. Depression and its comorbid conditions more serious in women than in men in the United States. J Womens Health 2015;24(12):978-85. [CrossRef]

16. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. [CrossRef]

17. O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine proŞles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. J Psychiatr Res 2007;41(3-4):326-31. [CrossRef]

18. Song C, Halbreich U, Han C, Leonard BE, Luo H. Imbalance between pro- and anti-inşammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: the effect of electroacupuncture or şuoxetine treatment. Pharmacopsychiatry 2009;42(5):182-8. [CrossRef]

19. Na KS, Lee KJ, Lee JS, Cho YS, Jung HY. Efficacy of adjunctive celecoxib treatment for patients with major depressive disorder: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2014;48:79-85. [CrossRef]

20. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367(9504):29-35. [CrossRef]

21. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 2011;36(12):2452-9. [CrossRef]

22. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 2000;22(4):370-9. [CrossRef]

23. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. Int J Neuropsychopharmacol 2002;5(4):401-12. [CrossRef]

24. Kaster MP, Moretti M, Cunha MP, Rodrigues AL. Novel approaches for the management of depressive disorders. Eur J Pharmacol 2016;771:236-40. [CrossRef]

25. Cai S, Huang S, Hao W. New hypothesis and treatment targets of depression: an integrated view of key findings. Neurosci Bull 2015;31(1):61-74. [CrossRef]

26. Hinwood M, Tynan RJ, Charnley JL, Beynon SB, Day TA, Walker FR. Chronic stress induced remodeling of the prefrontal cortex: structural re-organization of microglia and the inhibitory effect of minocycline. Cereb Cortex 2013;23(8):1784-97. [CrossRef]

27. Pan Y, Chen XY, Zhang QY, Kong LD. Microglial NLRP3 inflammasome activation mediates IL-1beta-related inflammation in prefrontal cortex of depressive rats. Brain Behav Immun 2014;41:90-100. [CrossRef]

28. Tynan RJ, Naicker S, Hinwood M, Nalivaiko E, Buller KM, Pow DV, et al. Chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav Immun 2010;24(7):1058-68. [CrossRef]

29. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression isassociated with suicide. J Psychiatr Res 2008;42(2):151-7. [CrossRef]

30. Kato TA, Kanba S. Are microglia minding us? Digging up the unconscious mind-brain relationship from a neuropsychoanalytic approach. Front Hum Neurosci 2013;7:1-13. [CrossRef]

31. Dantzer R, Walker AK. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? J Neural Transm (Vienna) 2014;121(8):925-32. [CrossRef]

32. Steiner J, Bogerts B, Sarnyai Z, Walter M, Gos T, Bernstein HG, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: Potential role of glial NMDA receptor modulators and impaired blood-brain barrier integrity. World J Biol Psychiatry 2012;13(7):482-92. [CrossRef]

33. Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression and systemic illnesses. Brain Behav Immun 2013;31:105-14. [CrossRef]

34. Alcocer-Gómez E, de Miguel M, Casas-Barquero N, Nú-ez-Vasco J, Sánchez-Alcazar JA, Fernández-Rodríguez A, et al. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. Brain Behav Immun 2014;36:111-7. [CrossRef]

35. Liu B, Xu C, Wu X, Liu F, Du Y, Sun J, et al. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience 2015;294:193-205. [CrossRef]

36. Zhang Y, Liu L, Peng YL, Liu YZ, Wu TY, Shen XL, et al. Involvement of inflammasome activation in lipopolysaccharide-induced mice depressive-like behaviors. CNS Neurosci Ther 2014;20(2):119-24. [CrossRef]

37. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35 (3):702-21. [CrossRef]

38. Heyes MP, Achim CL, Wiley CA, Major EO, Saito K, Markey SP. Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. Biochem J 1996;320(Pt 2):595-7. [CrossRef]

39. Mathews DC, Henter ID, Zarate CA. Targeting the glutamatergic system to treat major depressive disorder: rationale and progress to date. Drugs 2012;72(10):1313-33. [CrossRef]

40. O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 2009;14(5):511-22. [CrossRef]

41. Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. Ann N Y Acad Sci 2009;1179:86-105. [CrossRef]

42. Stetler C, Miller GE. Depression and hypothalamic–pituitary–adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011;73(2):114-26. [CrossRef]

43. Berkenbosch F, Van Oers J, del Rey A, Tilders F, Besedovsky H. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science 1987;238(4826):524-6. [CrossRef]

44. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;65(9):732-41. [CrossRef]

45. McKay LI, Cidlowski JA. Molecular control of immune/inşammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocr Rev 1999;20(4):435-59.

46. Wang X, Wu H, Miller AH. Interleukin-1 alpha (IL-alpha) induced activation of p38 mitogen-activated kinase inhibits glucocorticoid receptor function. Mol Psychiatry 2004;9(1):65-75. [CrossRef]

47. Wellman CL. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J Neurobiol 2001;49(3):245-53. [CrossRef]

48. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 1995;15(3):1768-77.

49. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47(4):351-4. [CrossRef]

50. Iadarola ND, Niciu MJ, Richards EM, Vande Voort JL, Ballard ED, Lundin NB, et al. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. Ther Adv Chronic Dis 2015;6(3):97-114. [CrossRef]

51. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010;329(5994):959-64. [CrossRef]

52. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat Rev Drug Discov 2008;7(5):426-37. [CrossRef]

53. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997;17(8):2921-7.

54. Hashimoto K. Role of the mTOR signaling pathway in the rapid antidepressant action of ketamine. Expert Rev Neurother 2011;11(1):33-6. [CrossRef]

55. Monteggia LM, Gideons E, Kavalali ET. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. Biol Psychiatry 2013,73(12):1199-203. [CrossRef]

56. Beurel E, Song L, Jope RS. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. Mol Psychiatry 2011;16(11):1068-70. [CrossRef]

57. Liu RJ, Fuchikami M, Dwyer JM, Lepack AE, Duman RS, Aghajanian GK. GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of subthreshold doses of ketamine. Neuropsychopharmacology 2013;38(11):2268-77. [CrossRef]

58. Deutschenbaur L, Beck J, Kiyhankhadiv A, Mühlhauser M, Borgwardt S, Walter M, et al. Role of calcium, glutamate and NMDA in major depression and therapeutic application. Prog Neuropsychopharmacol Biol Psychiatry 2016;64:325-33. [CrossRef]

59. Wu GJ, Chen TL, Ueng YF, Chen RM. Ketamine inhibits tumor necrosis factor-alpha and interleukin-6 gene expressions in lipopolysaccharide-stimulated macrophages through suppression of toll-like receptor 4-mediated c-Jun N-terminal kinase phosphorylation and activator protein-1 activation. Toxicol Appl Pharmacol 2008; 228(1):105-13. [CrossRef]

60. Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, et al. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology 2013;38(9):1609-16. [CrossRef]

61. Reus GZ, Nacif MP, Abelaira HM, Tomaz DB, dos Santos MA, Carlessi AS, et al. Ketamine ameliorates depressive-like behaviors and immune alterations in adult rats following maternal deprivation. Neurosci Lett 2015;584:83-7. [CrossRef]

62. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur Neuropsychopharmacol 2015;25(10):1532-43. [CrossRef]

63. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist inşiximab for treatment-resistant depression: the role of baseline inşammatory biomarkers. JAMA Psychiatry 2013;70(1):31-41. [CrossRef]

64. Faridhosseini F, Sadeghi R, Farid L, Pourgholami M. Celecoxib: a new augmentation strategy for depressive mood episodes. A systematic review and meta-analysis of randomized placebo-controlled trials. Hum Psychopharmacol 2014;29(3):216-23. [CrossRef]