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Agmatine as a novel candidate for rapid-onset antidepressant response

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Abstract

Major depressive disorder (MDD) is a disabling and highly prevalent mood disorder as well as a common cause of suicide. Chronic stress, inflammation, and intestinal dysbiosis have all been shown to play crucial roles in the pathophysiology of MDD. Although conventional antidepressants are widely used in the clinic, they can take weeks to months to produce therapeutic effects. The discovery that ketamine promotes fast and sustaining antidepressant responses is one of the most important breakthroughs in the pharmacotherapy of MDD. However, the adverse psychomimetic/dissociative and neurotoxic effects of ketamine discourage its chronic use. Therefore, agmatine, an endogenous glutamatergic modulator, has been postulated to elicit fast behavioral and synaptogenic effects by stimulating the mechanistic target of rapamycin complex 1 signaling pathway, similar to ketamine. However, recent evidence has demonstrated that the modulation of the NLR family pyrin domain containing 3 inflammasome and gut microbiota, which have been shown to play a crucial role in the pathophysiology of MDD, may also participate in the antidepressant-like effects of both ketamine and agmatine. This review seeks to provide evidence about the mechanisms that may underlie the fast antidepressant-like responses of agmatine in preclinical studies. Considering the anti-inflammatory properties of agmatine, it may also be further investigated as a useful compound for the management of MDD associated with a pro-inflammatory state. Moreover, the fast antidepressant-like response of agmatine noted in animal models should be investigated in clinical studies.

Key Words: Agmatine; Fast-acting antidepressants; Ketamine; Major depressive disorder; Microbiota-gut-brain axis; Neuroinflammation

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Core Tip: One of the main challenges in the advancement of antidepressant therapy is the establishment of safe and effective fast-acting antidepressants. Ketamine is a prototype for rapid-onset antidepressant responses. Agmatine has been shown to produce fast antidepressant-like effect by stimulating mechanistic target of rapamycin complex 1 signaling pathway, similar to ketamine. Moreover, NLR family pyrin domain containing 3 and microbiota-gut-brain axis may be novel targets for fast antidepressant responses. These targets have also been postulated to play a role in the antidepressant effect of both ketamine and agmatine.

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INTRODUCTION

Major depressive disorder (MDD) affects more than 300 million people and is a major cause of disability and suicidal deaths worldwide[1]. Despite the high prevalence of this psychiatric disorder, its neurobiological basis remains to be fully elucidated, and its treatment remains a challenge. Although the monoaminergic hypothesis of MDD has played a crucial role in its pharmacotherapy, it is now considered overly simplistic [2]. One of the limitations of this hypothesis is the fact that the drugs currently used to treat MDD exert their therapeutic effect only after 3-4 wk and many patients fail to respond to these drugs. Antidepressants also feature side effects that may include nausea, dizziness, insomnia, weight gain, sleep disturbances, and sexual dysfunction. This scenario underscores the strong demand for developing novel antidepressants with a fast antidepressant response, better efficacy, and fewer adverse effects[3,4].

In this regard, the year 2000 marked a turning point in the history of MDD pharmacotherapy, and Berman *et al*[5] showed for the first time that a single dose of ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, produced a fast-acting antidepressant response in MDD patients. This discovery was reinforced by several subsequent studies that demonstrated that a single dose of ketamine elicited rapid and long-lasting antidepressant effects, even in treatment-resistant patients with suicidal ideation[6-8]. Although the discovery of ketamine is considered the major breakthrough in MDD pharmacotherapy and opened new perspectives to manage refractory patients at risk of suicide, ketamine has knock-on effects that limit its widespread clinical use[9]. For these reasons, ketamine has emerged as a prototype for screening novel fast-acting antidepressant agents. Agmatine, an endogenous neuromodulator, shares some common molecular mechanisms with ketamine and the ability to elicit fast antidepressant-like effects in preclinical studies[10]. Therefore, agmatine could be a novel candidate to elicit fast antidepressant responses.

Therefore, this narrative review presents evidence that agmatine has a rapid antidepressant effect and provides an overview of the possible mechanisms underlying this effect versus those already described for ketamine. The PubMed, SCOPUS, and SciSearch databases were searched for original manuscripts and contemporary reviews published in English.

KETAMINE AS A PROTOTYPE RAPID-ACTING ANTIDEPRESSANT AGENT

A milestone for the development of drugs with a rapid antidepressant effect has emerged over the past two decades[5,6]. Berman *et al*[5] demonstrated for the first time that a single subanesthetic dose of ketamine elicited fast (within 4 h) and long-lasting (for up to 3 d) antidepressant effects in MDD patients. These findings were reinforced and extended by Zarate *et al*[6], who showed that a single dose of ketamine effectively improved the MDD symptoms in treatment-refractory patients, as evidenced by an effect observed within 110 min that was sustained for up to 7 d. Importantly, a rapid resolution of suicidal ideation after a single infusion of ketamine in patients with treatment-resistant MDD was also observed, supporting the premise that ketamine has

rapid beneficial effects even in severely depressed individuals at risk of suicide[7,8]. Due to the ability of ketamine to alleviate MDD symptoms, several research groups have investigated its underlying molecular mechanisms.

Although ketamine has been well characterized as an NMDA receptor antagonist, its molecular effects extend far beyond this level. It is worth noting that this drug has a window of therapeutic efficacy that surpasses its short half-life of a few hours[11,12]. Experimental studies have provided evidence that the antidepressant-like effect of ketamine depends on mechanistic target of rapamycin complex 1 (mTORC1) activation, a key pathway required for protein synthesis-dependent synaptic plasticity [13-15]. It has been postulated that ketamine, by antagonizing NMDA receptors in GABAergic interneurons, attenuates the inhibitory action of this system on glutamatergic tonus. This blockade causes the disinhibition of pyramidal cells, which causes a burst of glutamatergic transmission[11]. In particular, the glutamate released under these conditions preferentially stimulates alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) receptors, promoting a transient sodium influx that depolarizes the cell and activates the voltage-dependent calcium channels (VDCC). This event causes the exocytosis of synaptic vesicles containing the brain-derived neurotrophic factor (BDNF) in the synaptic cleft, as a result of calcium influx by VDCC [16].

BDNF activates tropomyosin receptor kinase B (TrkB), which stimulates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTORC1 signaling pathway[12]. In turn, mTORC1 controls the translation of proteins involved in new dendritic spine formation and synaptogenesis [*e.g.*, postsynaptic density protein-95 kDa (PSD-95), glutamate AMPA receptor subunit 1 (GluA1), and synapsin] by activating the 70-kDa ribosomal protein S6 kinase (p70S6K) and inhibiting the eukaryotic initiation factor 4E-binding protein[13,14,17]. Although mTORC1-dependent synaptogenesis induced by ketamine was first demonstrated in the prefrontal cortex of rodents[13,15], it has been shown that similar events also occur in the hippocampus[18-20]. Therefore, these findings suggest that targeting the mTORC1-driven signaling pathway may produce rapid-onset and long-lasting antidepressant-like responses. The molecular mechanisms underlying ketamine's antidepressant responses are shown in Figure 1.

Importantly, almost 20 years after the groundbreaking discovery that ketamine effectively produces rapid and sustained antidepressant effects, particularly in March 2019, the United States Food and Drug Administration approved the use of (S)-ketamine nasal spray (Spravato™) for treatment-resistant MDD. In the same year, (S)-ketamine nasal spray was approved for use in treatment-resistant depression in Europe[21]. Despite the fast and long-lasting antidepressant effects of ketamine, there is much concern about its abuse potential and serious adverse effects[9]. For this reason, ketamine is only available through a restricted distribution system, limiting its widespread clinical use. Although there are some drawbacks associated with its use, it may serve as a prototype for screening novel fast antidepressant agents. Given this scenario, the search for ketamine-like compounds has emerged as a promising therapeutic strategy. In this regard, our research group and others have shown that agmatine is also able to produce fast antidepressant responses and shares some mechanisms of action with ketamine[10].

AGMATINE AS A NOVEL CANDIDATE FOR FAST ANTIDEPRESSANT RESPONSES

Agmatine, a cationic amine produced from the L-arginine in a reaction catalyzed by the enzyme arginine decarboxylase, is widely distributed in human tissues, including the brain[22-24]. For almost a century, it was wrongly believed that agmatine was produced by bacteria, plants, and fish but not mammals[25]. Agmatine was "rediscovered" in 1994 during the search for an endogenous ligand for imidazoline binding sites[24]. In this study, a molecule was isolated from the mammalian brain and identified as agmatine[24]. This was the starting point for many studies that have evaluated the biological properties and possible beneficial effects of agmatine on a wide variety of diseases[26].

Soon after providing evidence of the presence of agmatine in mammalian nervous tissue, Piletz *et al*[27] documented its neuroprotective effects. The neuroprotective effects of agmatine reportedly involve protection mechanisms against excitotoxicity, since agmatine may block NMDA receptors and inhibit the increase in intracellular calcium concentrations in different neuronal cell cultures[28-30]. The NMDA receptor

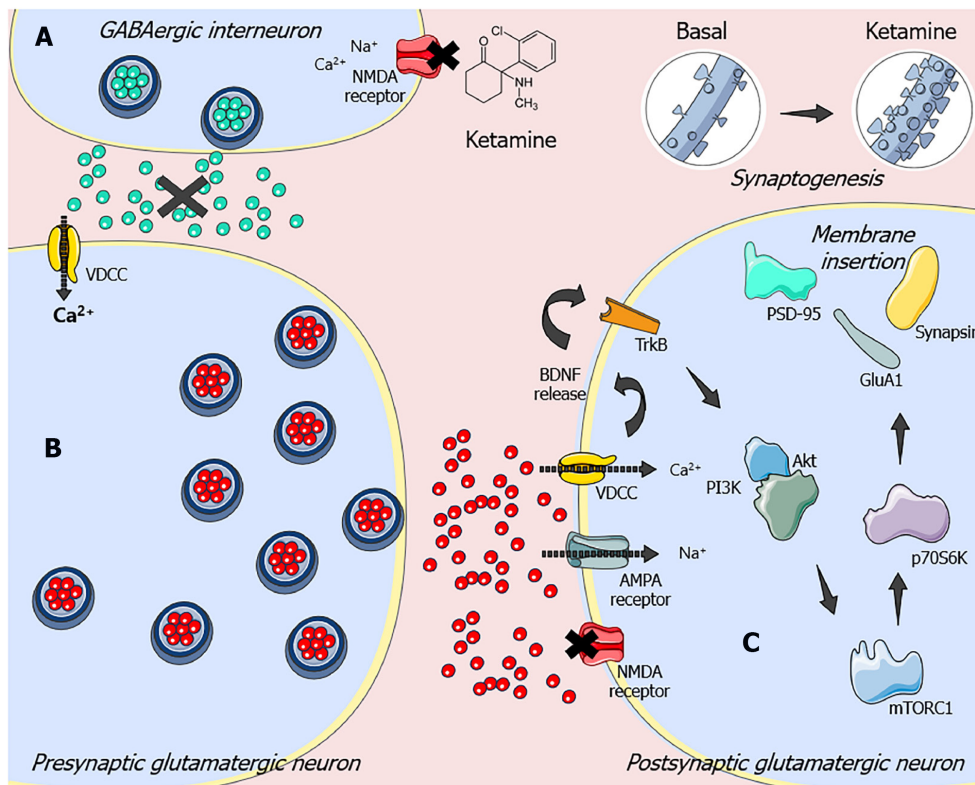


Figure 1 Supposed intracellular signaling pathway implicated in ketamine's antidepressant-like effects. A: Ketamine antagonizes N-methyl-D-aspartic acid receptors in GABAergic interneurons, which in turn attenuate the inhibitory action of this system on glutamatergic tonus. Subsequently, the disinhibition of pyramidal cells results in a burst of glutamatergic transmission; B: The glutamate released in the synaptic cleft preferentially stimulates alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) receptors, which promotes a transient sodium influx that depolarizes the neurons and activates voltage-dependent calcium channels. C: This event causes the exocytosis of synaptic vesicles containing brain-derived neurotrophic factor (BDNF) in the synaptic cleft[16,122]. BDNF culminates in protein kinase B activation that can phosphorylate and activate mechanistic target of rapamycin complex 1 (mTORC1). In turn, mTORC1 phosphorylates the 70-kDa ribosomal protein S6 kinase at Thr389, which regulates synaptic protein synthesis such as AMPA receptor subunit 1 and postsynaptic density-95, which contribute to dendritic spine formation and synaptogenesis[17,13]. NMDA: N-methyl-D-aspartic acid; AMPA: Alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid; BDNF: Brain-derived neurotrophic factor; VDCC: Voltage-dependent calcium channels; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; TrkB: Tropomyosin receptor kinase B; GluA1: Glutamate AMPA receptor subunit 1; mTORC1: mechanistic target of rapamycin complex 1; PSD-95: postsynaptic density protein-95 kDa.

is an ion channel controlled by glutamatergic excitation, which is essential for the normal functioning of the central nervous system (CNS), including cognitive function, locomotion, and breathing[31-33]. This type of receptor is located on the membranes of neuronal and glial cells[34], and is implicated in the development and maintenance of acute and chronic diseases of the CNS, such as stroke, Parkinson's disease, Alzheimer's disease, MDD, and schizophrenia[34]. Under excitotoxic conditions, the increase in extracellular glutamate intensifies NMDA receptor activation, causing an influx of Ca^{2+} and Na^{+} [34]. NMDA receptor stimulation also activates nitric oxide (NO) production pathways by activating nitric oxide synthase, thereby generating NO, one of the main mediators of cellular death[35,36]. The inhibition of NO synthesis is potentially beneficial in the treatment of brain disorders associated with its overproduction. Several studies have shown that the neuroprotective properties of agmatine in several neurodegenerative diseases are related to its ability to antagonize NMDA receptors and inhibit NO synthesis as well as its potential to counteract the effects of oxidative stress[37].

The first evidence of the antidepressant effects of agmatine was reported in a study that examined its impact on behavioral tests related to depression (immobility time in the tail suspension test and forced swimming test) in mice[38]. Since then, other studies have confirmed the antidepressant efficacy of agmatine in behavioral tests in rodents[39-41]. Subsequent studies implicated several molecular targets in the antidepressant effect of agmatine, namely the modulation of: (1) K^{+} channels[42]; (2) NO synthesis[43,44]; and (3) several neurotransmitter receptors including NMDA receptors[38,45], AMPA receptors[46,47], GABA receptors[48], serotonin receptors[49, 50], and opioid system receptors[51].

In 2010, a human clinical trial showed the safety of oral agmatine[52]. In 2013, Shopsin *et al*[53] provided the first evidence that agmatine may effectively treat MDD, but this study included only three patients. None of these three patients treated with agmatine relapsed after the joint administration of a serotonin-depleting drug, indicating that the mechanism underlying the antidepressant action of agmatine is likely unrelated to the serotonergic system[53]. It was also reported that 8-wk treatment with the standard antidepressant bupropion normalized plasma agmatine levels[54]. In brain autopsies of chronically depressed patients, Bernstein *et al*[55] reported a significant increase in agmatinase immunoreactivity in hippocampal neurons, suggesting the role of the agmatinergeric system in MDD pathophysiology. However, it was not possible to determine the exact reason why levels of this enzyme increased in hippocampal neurons due to the use of antidepressants.

In 2018, a gas chromatography–mass spectrometry study quantified agmatine levels in the brains of post-mortem humans who died by suicide and showed reduced agmatine levels in the suicide cortex regardless of these individuals formerly meeting the criteria for MDD versus controls[56].

Weiss *et al*[57] presented evidence of the activity of the agmatinergeric system in habenular nuclei and investigated the actions of agmatine and agmatinase in the rat and human habenular systems. It is important to highlight that the role of habenular nuclei in mental disorders, including MDD, has already been considered[58,59]. In this study, agmatine was demonstrated responsible for the strong decrease in the spontaneous action potential of medial habenular neurons by activating type I1 imidazoline receptors. It was also reported that increased activity of the agmatinergeric system in habenular nuclei may strengthen the dopaminergic activity of the midbrain. This evidence suggests dysregulation in the habenular-interpeduncular axis in patients with MDD[57].

In summary, these results present the possible role of agmatine in the neurobiology of MDD and highlight the possible benefits of agmatine as antidepressant therapy.

Recent evidence has also demonstrated the possible fast antidepressant-like actions of agmatine (Figure 2)[10]. In this context, Neis *et al*[46] reported that the antidepressant-like effect of agmatine administered orally to mice subjected to the tail suspension test is dependent on the modulation of molecular targets associated with the fast antidepressant-like effect displayed by ketamine. In particular, the antidepressant-like effect elicited by the acute administration of agmatine in the tail suspension test appears to involve inhibition of NMDA receptors since it enhanced the antidepressant potency of MK-801 (an NMDA receptor antagonist) up to 100-fold[60]. Moreover, the antidepressant-like effect of agmatine in the tail suspension test is dependent on AMPA and TrkB receptor activation since the administration of 6,7-dinitroquinoxaline-2,3-dione (DNQX; an AMPA receptor antagonist) or K-252a (a TrkB receptor antagonist) completely abolished its antidepressant-like response[46]. A single dose of agmatine also increased BDNF levels in the prefrontal cortex of mice, and its antidepressant-like effect in the tail suspension test was abrogated by the administration of anti-BDNF antibody. Of note, the antidepressant-like effect of agmatine is also dependent on PI3K/Akt/glycogen synthase kinase-3 β (GSK-3 β)/mTOR signaling. In particular, the administration of LY294002 (a PI3K inhibitor) or rapamycin (a selective mTOR inhibitor) completely abrogated the behavioral responses of agmatine in the tail suspension test. Combined treatment with a sub-effective dose of agmatine and lithium chloride (a non-selective GSK-3 β inhibitor) or AR-A014418 (a selective GSK-3 β inhibitor) produced an antidepressant-like effect in the tail suspension test[46]. Importantly, these behavioral responses were accompanied by an increase in BDNF, GluA1, and PSD-95 immunoccontent in the prefrontal cortex of mice[46].

Supporting the assumption that agmatine could elicit a fast antidepressant-like effect, a study by Neis *et al*[61] demonstrated that a single dose of agmatine effectively reversed the depressive-like behavior induced by chronic unpredictable stress. In this study, mice were exposed to the stress protocol for 14 d and received a single oral dose of agmatine, ketamine, or fluoxetine. The results indicated that a single dose of agmatine or ketamine (after 24 h), but not fluoxetine, counteracted the depressive-like behavior induced by the stress protocol in the tail suspension test[61].

Expanding upon these findings, Neis *et al*[62] reinforced the ability of agmatine to rapidly reverse the depressive-like behavior induced by the 21-d administration of corticosterone, a pharmacological model of stress in mice. In the tail suspension test, a single dose of agmatine or ketamine abolished the depressive-like behavior of mice chronically exposed to corticosterone. In addition, treatment increased GluA1 immunoccontent in the hippocampus of control animals[62]. Notably, a single dose of fluoxetine did not produce the same effects as ketamine or agmatine[62]. Chronic

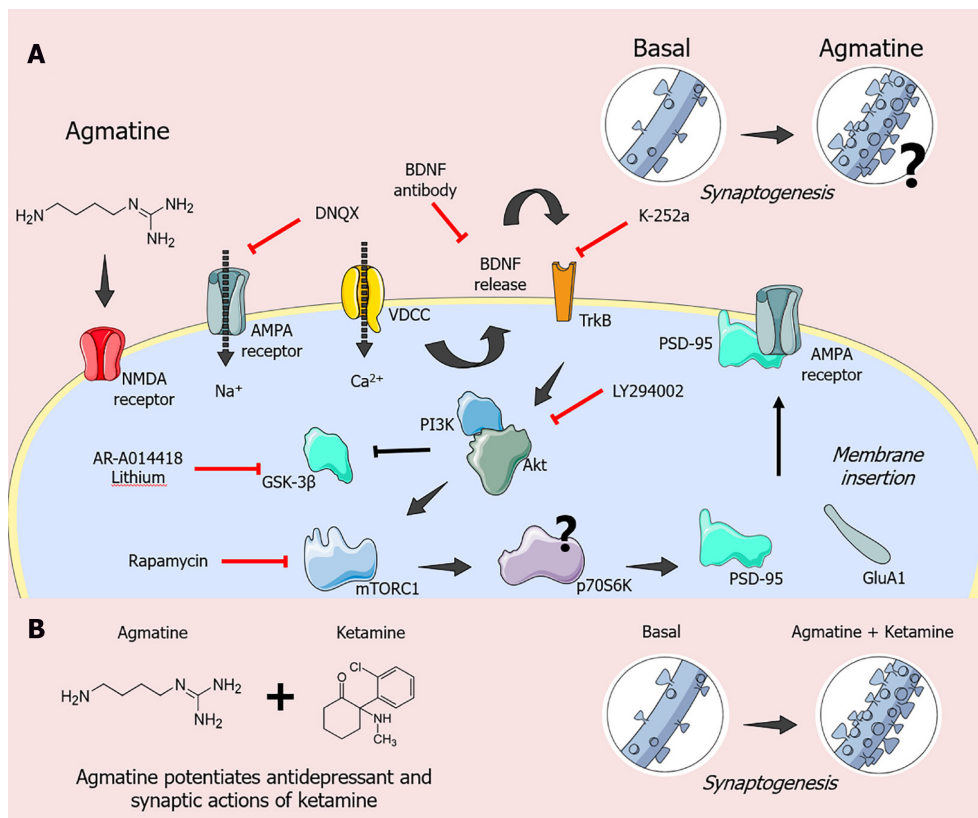


Figure 2 Putative signaling pathways implicated in the rapid-acting antidepressant-like effects of agmatine. A: The antidepressant-like effect elicited by the acute administration of agmatine in the tail suspension test appears to involve inhibition of N-methyl-D-aspartic acid (NMDA) receptors since it enhanced the antidepressant potency of MK-801 (an NMDA receptor antagonist) by up to 100-fold[60]. Moreover, agmatine's antidepressant-like effect in the tail suspension test is dependent on the activation of alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) and tropomyosin receptor kinase B (TrkB) receptors since the administration of 6,7-dinitroquinoxaline-2,3-dione (DNQX; an AMPA receptor antagonist) or K-252a (a TrkB receptor antagonist) completely abolished its antidepressant-like response. The antibody anti-brain-derived neurotrophic factor (BDNF) also abolished the antidepressant-like effect elicited by agmatine in the tail suspension test[46]. Of note, the antidepressant-like effect of agmatine is also dependent on phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase-3β/mechanistic target of rapamycin (mTOR) signaling. In particular, the administration of LY294002 (a PI3K inhibitor) or rapamycin (a selective mTOR inhibitor) completely abrogated the behavioral responses of agmatine in the tail suspension test. The combined treatment with a sub-effective dose of agmatine and lithium chloride (10 mg/kg, po; a non-selective GSK-3β inhibitor) or AR-A014418 (a selective GSK-3β inhibitor) produced an antidepressant-like effect in the tail suspension test[46]. Importantly, these behavioral responses were accompanied by an increase in the BDNF, glutamate AMPA receptor subunit 1 and postsynaptic density protein-95 kDa immunocontent in the prefrontal cortex of the mice[46]; B: Reinforcing the notion that ketamine and agmatine share common behavioral responses and molecular targets, the ability of agmatine to potentiate the antidepressant and synaptic actions of ketamine was also demonstrated[47]. In particular, the combined administration of subthreshold doses of agmatine and ketamine produced a fast (starting in 1 h) and sustained (lasting up to 7 d) antidepressant-like effect in the tail suspension test. These behavioral responses were associated with stimulation of the Akt/70-kDa ribosomal protein S6 kinase signaling pathway and increased synaptic protein synthesis in the prefrontal cortex in a time-dependent manner. More importantly, the combined administration of sub-effective doses of agmatine and ketamine raised the dendritic arbor and spine densities and effectively remodeled the dendritic spinal architecture in the prefrontal cortex[47]. NMDA: N-methyl-D-aspartic acid; AMPA: Alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid; BDNF: Brain-derived neurotrophic factor; VDCC: Voltage-dependent calcium channels; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; TrkB: Tropomyosin receptor kinase B; GluA1: Glutamate AMPA receptor subunit 1; mTORC1: mechanistic target of rapamycin complex 1; PSD-95: postsynaptic density protein-95 kDa; GSK-3β: Glycogen synthase kinase-3 β.

unpredictable stress and chronic corticosterone administration models are sensitive to chronic but not acute administration of conventional antidepressants, but a single dose of ketamine sufficiently produced antidepressant responses in these models[62]. Moreover, a single dose of agmatine or ketamine counteracted the depressive-like phenotype of cAMP-responsive element binding protein-regulated transcription coactivator 1 knockout mice in the forced swimming test, reinforcing the notion that agmatine could have a rapid antidepressant-like effect[63].

Subsequent studies provided novel evidence that a low-dose combination of ketamine plus agmatine produced neuroprotective, antidepressant-like, and synaptogenic effects[11,64,65]. A study using the HT-22 mouse hippocampal neuronal cell line reported that the combined use of sub-effective concentrations of ketamine and agmatine prevented the neuronal damage caused by corticosterone[64]. Of note, this effect was associated with increased phosphorylation of Akt (Ser⁴⁷³), p70S6K (Thr³⁸⁹), and PSD-95 immunocontent[65]. These data support the idea that ketamine

and agmatine share common molecular targets and could work in tandem to protect neuronal cells from the harmful effects of corticosterone by activating Akt/mTORC1/p70S6K signaling, resulting in synaptic protein expression[11,65].

Reinforcing these findings, Freitas *et al*[47] investigated the ability of agmatine to potentiate the effects of the antidepressant and synaptic actions of ketamine in mice. Of special interest, the combination of single subthreshold doses of ketamine and agmatine exerted antidepressant-like and pro-synaptogenic actions in a time-dependent manner. In particular, agmatine plus ketamine produced fast (1 and 24 h) and sustained (7-d) antidepressant-like effects in the tail suspension test[47]. Furthermore, this combined treatment increased p70S6K phosphorylation and GluA1 immunocontent in the prefrontal cortex 1 h after treatment. This same protocol increased the PSD-95 immunocontent, an effect that persisted for up to 7 d. The combined treatment also increased the complexity of the dendritic branches after 24 h, and this effect lasted up to 7 d. Likewise, ketamine plus agmatine treatment effectively increased the dendritic spine density after 1 h later, a response that lasted up to 24 h [47]. These results reinforce the notion that agmatine and ketamine share common molecular targets and expand the findings regarding the ability of agmatine to enhance the antidepressant-like and synaptic actions of ketamine[47].

Taken together, these results support the hypothesis that agmatine can act as a ketamine-like compound, and further studies are crucial to investigate whether the rapid antidepressant effects of agmatine are reproducible in patients with MDD. Moreover, the use of agmatine in the clinic would be highly promising owing to its safety, even at high doses, without evident effects of toxicity[26,52].

BEYOND mTORC1 HYPOTHESIS

In addition to focusing on the importance of the mTORC1-mediated signaling pathway for the antidepressant effect of agmatine, some studies investigated other signaling pathways that may play a role in its antidepressant effect. Understanding other pathways influenced by agmatine is important to its establishment as a therapeutic alternative in the clinical setting.

Regarding the factors that may influence the mechanisms associated with MDD symptoms, neuroinflammation has received much attention in recent years. Neuroinflammation reportedly plays an essential role in several neuropathologies, such as multiple sclerosis, Alzheimer's disease, and MDD[66,67]. It was demonstrated in both humans and animals that immunological challenges may induce depressive behavior [68]. It is important to note that, since the 1990s, several studies reported a strong correlation between MDD and peripheral inflammatory markers[69,70].

In the last few years, three meta-analyses aimed to better understand the relationship between neuroinflammation and the development/maintenance of MDD. Kappelmann *et al*[71] published a meta-analysis in 2018 that analyzed data from four randomized controlled studies that examined the effects of pro-inflammatory cytokine inhibitors. In these studies, adalimumab and etanercept were used, and both treatments improved depressive symptoms in patients. In 2019, a randomized clinical study showed more pronounced antidepressant results in patients with higher high-sensitivity C-reactive protein levels[72]. In this study, the use of anti-inflammatory drugs improved clinical signs of depression, such as motor retardation, suicidal thoughts, and depressed mood[72]. Another meta-analysis evaluated 36 studies and assessed the effects of anti-inflammatory drugs in almost 10000 patients[73]. The findings suggested that the use of anti-inflammatory drugs sufficiently reversed depressive symptoms. The latest meta-analysis combined 26 randomized clinical trials of over 1500 patients[74]. This study also verified the improvement in depressive symptoms in patients with anti-inflammatory agent use[74].

Therefore, inflammatory pathways play an important role in the development and maintenance of depressive symptoms. Increasing evidence has shown that agmatine also acts on neuroinflammatory-related pathways that may participate in rapid-onset antidepressant responses.

The early administration of agmatine for 7 d prevented the depressive-like behavior caused by lipopolysaccharide (LPS) challenge in mice[75]. Agmatine pretreatment counteracted LPS-induced neuroinflammation by preventing increases in interleukin (IL)-1 β and tumor necrosis factor (TNF)- α level in the murine brain. In addition, agmatine positively regulates BDNF levels in the hippocampus[75]. In another study, agmatine pretreatment also normalized LPS-induced sickness behavior in rats in addition to decreasing serum concentrations of IL-6 and TNF- α [76]. Zarifkar *et al*[77]

reported that agmatine prevented LPS-induced spatial memory impairment and hippocampal caspase-3 activation in LPS-treated rats. It is also noteworthy that agmatine effectively inhibited the LPS-induced production of nitrite and decreased body temperature in rats in a dose-dependent manner[78].

Notably, Neis *et al*[45] showed that agmatine effectively counteracted the depressive-like behavior induced by the pro-inflammatory cytokine TNF- α in mice. In this study, the combined treatment of sub-effective doses of agmatine and fluoxetine, imipramine, bupropion, MK-801, or 7-nitroindazole resulted in a synergistic antidepressant-like effect in mice subjected to TNF- α administration[45].

Agmatine also exhibits anti-inflammatory effects in other disease models. In particular, in a type 2 diabetes mellitus (T2DM) model induced by a high-fat diet for 12 wk, anxiety- and depressive-like behaviors were associated with an increase in pro-inflammatory cytokines, such as IL-6 and TNF- α , as well as a decrease in the BDNF immunocontent in the rat hippocampus[79]. These parameters were inhibited by agmatine treatment in the last 4 wk of the protocol. In this study, agmatine levels in the hippocampus of rats subjected to the T2DM protocol were significantly lower than those in the control animals[79].

In an Alzheimer's disease model, the administration of amyloid- β peptide ($A\beta_{1-42}$) to mice caused depressive-like behavior in the forced swimming test, an effect parallel to an increase in the pro-inflammatory cytokines IL-6 and TNF- α in the hippocampus [80]. Both depressive-like behavior and pro-inflammatory markers were reversed by agmatine treatment, suggesting that the anti-inflammatory properties of agmatine may be related to its antidepressant effect. Notably, this study also detected lower concentrations of agmatine in the brains of animals injected with $A\beta_{1-42}$ [80]. These data point to the action of agmatine in neuroinflammatory processes, as a pharmacological strategy to decrease depressive-like behavior, including that associated with comorbid diseases, such as T2DM and Alzheimer's disease.

It is important to note that the activation of various types of inflammasomes is a critical target in the inflammatory response. Inflammasomes are involved in the development of several neurological diseases, including MDD[81,82]. Among them, the NLR family pyrin domain containing 3 (NLRP3) inflammasome is the most closely related to MDD due to the exaggerated activation of inflammatory and immunological responses that contribute to the pathogenesis and progression of this disorder[83]. A compelling study reported that depressive-like behavior in mice subjected to LPS administration is related to NLRP3-dependent caspase-1 activation[84]. Accordingly, anxiety-like behavior reportedly occurs in rats exposed to neonatal inflammation or inflammatory stress early in life triggered by NLRP3 inflammasome activation in animals' brains[85]. Altogether, evidence suggests that the NLRP3 inflammasome plays an essential role in the neurobiology of MDD and may be a potential target for antidepressant treatment.

In this regard, ketamine was shown to exert an antidepressant effect in the LPS-induced model *via* suppressing the NLRP3 inflammasome and upregulating AMPA receptors[86]. Importantly, in this study, the authors postulated that ketamine might increase AMPA receptor expression through the NLRP3 inflammasome, suggesting that NLRP3 could be a target in fast-acting antidepressant treatment[86].

The possibility that agmatine exerts antidepressant effects by modulating neuroinflammatory mechanisms has also been investigated. Sahin *et al*[43] investigated the effects of agmatine in a model of restraint stress-induced depressive-like behavior. The authors demonstrated that agmatine rescued anti-inflammatory cytokine IL-4 and IL-10 levels that were impaired by stress[43]. Moreover, the 6-wk treatment with agmatine counteracted the depressive-like behavior of animals exposed to chronic unpredictable stress by suppressing NLRP3 and IL-1 β [43].

The exact role of the NLRP3 inflammasome-driven signaling pathway in MDD pathophysiology and antidepressant responses is still not well established. However, it has been proposed that the gut microbiota may influence activation of the NLRP3 inflammasome and neuroinflammatory processes through the microbiota-gut-brain axis.

The microbiome, a complex ecosystem in the human gut, includes bacteria, viruses, archaea, and fungi. The bacteria present in this system regulate aspects of the host's health, mainly brain development and functioning[87,88]. The microbiome is a dynamic structure that is affected by delivery type, sex, age, nutrition, stress, and medications[89]. These interferences can compromise the balance between pathogenic and commensal bacteria[90], promoting the development of a process called dysbiosis, which can change the permeability of the intestinal wall, allowing bacteria and their products to leak into the sterile cavity and activate the immune response[91]. Immune response activation increases the levels of pro-inflammatory cytokines, which, together

with other toxic metabolites, damage the blood–brain barrier and trigger neuroinflammation[92].

The immune and brain mechanisms involved in intestinal dysbiosis may include microglial activation[93]. Microglia are responsible for releasing pro-inflammatory cytokines in the brain when activated by stress, a mechanism that is altered in MDD [94,95]. On the other hand, a balanced and healthy microbiota can regulate the activation of these stress response pathways through the synthesis of hormones and neurotransmitters, minimizing the effects of such stressors[96].

Studies have shown that there is a “microbiota of MDD” due to the difference in composition between depressed patients and healthy controls. In a microbiome study of patients with MDD and irritable bowel syndrome, less bacterial diversity, an effect associated with increased levels of bacteria from the phylum Bacteroidetes, and increased colon inflammation were noted in patients compared to healthy controls [97]. In a Chinese cohort, the microbiota of patients with MDD showed higher concentration of Proteobacteria and decreased concentrations of Firmicutes[98].

Several studies have suggested the direct modulation of bacteria in the immune system. *Proteus mirabilis*, a proteobacterium, can activate the NLRP3 inflammasome and interleukin IL-1 β production[99]. Other components of Proteobacteria, such as the LPS produced by *Pseudomonas*, are related to the development of MDD symptoms *via* activation of the NLRP3 inflammasome and pro-inflammatory immunoglobulins[93]. In patients with MDD, an increase in some Bacteroidetes species (*Parabacteroidetes* and *Alistipes*) reportedly converts tryptophan to indole, which can influence the availability of tryptophan in the body and affect serotonergic balance[100]. Other studies confirmed an increase in *Alistipes* bacteria in patients with MDD, chronic fatigue syndrome, irritable bowel syndrome, and stress models[101,102].

The transplantation of fecal microbiota from patients diagnosed with MDD to germ-free microbiota mice triggered anxious-, anhedonic-, and depressive-like behaviors in the animals[103,104]. This evidence suggests that the depressive phenotype may be transmitted by gut microbiota. These data show a close relationship between the composition of the gut microbiota and brain health, mainly in the pathological mechanisms involved in the development and maintenance of depressive symptoms. Furthermore, the immune system/NLRP3 inflammasome acts as an intermediary between gut dysbiosis and brain function.

Some studies have suggested that the ability of ketamine to elicit antidepressant effects may be mediated, at least in part, by modulation of the microbiota-gut-brain axis. Two studies that investigated the effects of ketamine administration in the gut microbiota of mice following the social defeat stress model reported that the treatment attenuated the alterations in *Bacteroidales*, *Clostridiales*, *Ruminococcaceae*, *Deltaproteobacteria*, and *Mollicutes* bacterial levels in their feces[105,106]. Moreover, ketamine prevented the increase in the *Clostridium* and *Butyrivibrio* species induced by the stress model[105,106]. Other studies showed that ketamine significantly amplified the number of healthy bacteria and decreased the number of opportunistic pathogens in Wistar rats[107]. In an inflammatory model of LPS-induced depressive-like behavior, ketamine improved the diversity of the gut microbiota, positively regulating this microsystem[108]. Together, these data suggest that ketamine influences the composition of the microbiota, a response that may underlie its antidepressant-like effects.

The relationship between gut microbiota and agmatine levels has emerged and may play a role in the ability of gut microbiota to influence mental health. Agmatine is produced and released by gut bacteria of the human microbiome[109] and can be obtained from ingested food[110,111]. The composition of the intestinal microbiota influences agmatine availability in the gut lumen for absorption, and the majority of agmatine in humans is believed to be derived from bacterial sources[27]. Interestingly, agmatine may also be obtained from foodstuffs, particularly fermented foods such as alcoholic beverages (wine, beer, sake), which suggests the role of yeast in its production[109]. The filamentous fungus *Aspergillus oryzae*, which is widely used for the production of various Asian fermented foods, can enhance agmatine ingestion [112].

The consumption of fermented foods has beneficial effects on mental health[113]. The use of probiotics also reportedly exerts positive effects on depressive symptoms [114,115]. The possibility that agmatine is produced in the gut following the consumption of fermented foods and probiotics may account, at least in part, for its anti-inflammatory and antidepressant effects should be investigated in future studies.

Metformin, the mainstay therapy for T2DM, reportedly influences the diversity and composition of the gut microbiota[116]. This drug has recently been shown to act on *Escherichia coli*, elevating agmatine production and increases the longevity of

Caenorhabditis elegans[117]. Metformin has been shown to produce antidepressant effects in depressed patients with diabetes mellitus[118] and proposed as an adjunctive antidepressant approach in nondiabetic patients with MDD[119]. It remains to be determined whether agmatine levels are higher in individuals taking metformin and, if so, whether it contributes to the antidepressant effect observed with metformin treatment.

CONCLUSION

Agmatine, an endogenous cationic amine, exerted antidepressant effects in several preclinical studies[26,120]. Considering that the microbiota composition and consumption of fermented foods, or even some drugs such as metformin, may influence agmatine levels in the gut[27,109-119], it remains to be established whether agmatine derived from these sources may positively impact mood and exert antidepressant effects. Therefore, modulation of the microbiota and, consequently, gut agmatine levels may represent a novel approach to mood regulation.

In addition to the fact that agmatine may be synthesized by gut microbiota, several studies have indicated that it is safe even when administered at high doses as a nutraceutical. The sulfate salt of agmatine has been used for bodybuilding[27] and the management of neuropathic pain at doses as high as 2.6 g/day[121]. The fact that agmatine also exhibits several beneficial effects for a wide spectrum of diseases[27] suggests that it is a promising therapeutic strategy for the management of MDD and several comorbid diseases and inflammatory clinical conditions such as diabetes, obesity, pain, and neurodegenerative diseases. Of particular relevance, compelling preclinical evidence has indicated that agmatine has the ability to counteract several neuroinflammatory markers induced by models of depression and shares with ketamine the ability to elicit fast antidepressant responses[46,47,61,62,75-80]. The possibility that agmatine may afford a rapid antidepressant effect would give it an advantage over conventional antidepressants that require several weeks to alleviate depressive symptoms. In preclinical studies, agmatine elicited a synergistic effect with ketamine in mice subjected to animal models of depression as well as cell culture, and pharmacological evidence has pointed to similar molecular mechanisms of these drugs [46]. These properties of agmatine clearly warrant future clinical investigation of its beneficial effects for managing depressive symptoms as a monotherapy or adjunctive treatment. Therefore, clinical studies are warranted that investigate the possibility that agmatine may be combined with low doses of ketamine to diminish the side effects and provide synergistic antidepressant effects.

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