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Novel Targets for Fast Antidepressant Responses: Possible Role of Endogenous Neuromodulators

Anderson Camargo[1], and Ana Lúcia S. Rodrigues[2]

Abstract

The available medications for the treatment of major depressive disorder have limitations, particularly their limited efficacy, delayed therapeutic effects, and the side effects associated with treatment. These issues highlight the need for better therapeutic agents that provide more efficacious and faster effects for the management of this disorder. Ketamine, an N-methyl-D-aspartate receptor antagonist, is the prototype for novel glutamate-based antidepressants that has been shown to cause a rapid and sustained antidepressant effect even in severe refractory depressive patients. Considering the importance of these findings, several studies have been conducted to elucidate the molecular targets for ketamine's effect. In addition, efforts are under way to characterize ketamine-like drugs. This review focuses particularly on evidence that endogenous glutamatergic neuromodulators may be able to modulate mood and to elicit fast antidepressant responses. Among these molecules, agmatine and creatine stand out as those with more published evidence of similarities with ketamine, but guanosine and ascorbic acid have also provided promising results. The possibility that these neuromodulators and ketamine have common neurobiological mechanisms, mainly the ability to activate mechanistic target of rapamycin and brain-derived neurotrophic factor signaling, and synthesis of synaptic proteins in the prefrontal cortex and/or hippocampus is presented and discussed.

Keywords

agmatine, ascorbic acid, creatine, fast-acting antidepressant, guanosine, ketamine

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Introduction

Major depressive disorder (MDD) is a common and chronic neuropsychiatric condition, characterized by affective and physiological impairments that cause a profound impact on the health of the affected individuals worldwide and a great economic burden.[1] The World Health Organization estimates that more than 300 million individuals are affected by MDD at present, and the number of individuals affected by this disorder increased by almost 20% in the last 10 years.[2] Given this scenario, MDD is now the leading cause of disability worldwide.

Despite the high prevalence of MDD, and the advances obtained in the last years in the comprehension of the neurobiological basis of this disorder, its treatment still represents a challenge. The limitations of the currently available antidepressants are related to their limited efficacy (only approximately 50% of the patients fail to achieve remission), the delayed therapeutic effects and a great number of adverse/side effects, which includes headaches, constipation, weight changes, and mainly sexual dysfunction.[1,3,4] These limitations are particularly problematic for patients with elevated risk for suicide. Noteworthy, it is estimated that up to 50% of the 800,000 suicides that occur per year worldwide are associated with MDD, and patients affected by this disorder are almost 20-fold more likely to die by suicide than the general population.[1,2,5] Therefore, appropriate and

[1]Neuroscience Postgraduate Program, Center of Biological Sciences, Universidade Federal de Santa Catarina, Florianópolis, Brazil
[2]Department of Biochemistry, Center of Biological Sciences, Universidade Federal de Santa Catarina, Florianópolis, Brazil

Corresponding author:
Ana Lúcia S. Rodrigues, Department of Biochemistry, Center of Biological Sciences, Universidade Federal de Santa Catarina, Florianópolis 88040-900, SC, Brazil.
Email: alsrodri@gmail.com

effective treatments are necessary to be established for a better management of this disorder. The most promising therapeutic strategy for this challenge emerged at the beginning of the 21st century, when Berman et al. demonstrated for the first time that the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine caused fast and long-lasting antidepressant effects.[6] This study represents the onset of a series of other studies that aimed at investigating the ability of ketamine to provide fast antidepressant responses, even in refractory patients, as well as those that have been focused on the investigation of the mechanisms underlying the fast antidepressant responses of ketamine.[7–11] Despite the promising effects of ketamine, its prolonged use has some limitations, mainly related to side effects and the possibility of neurotoxic effects upon chronic use. In addition to these drawbacks associated with ketamine's pharmacological/toxicological properties, the oral bioavailability of ketamine is slow.[12] Thereby, ketamine is generally administered by intravenous route in hospitalized patients.[13]

Novel drugs that may afford fast antidepressant responses have been extensively investigated. Here, we provide a brief history and overview of the development of antidepressant drugs, the discovery of ketamine, and novel targets for fast antidepressant responses, particularly the potential role of endogenous neuromodulators.

Beyond Monoamine-Based Therapies

The first hypothesis formulated to explain the neurobiology of MDD postulated that depressive symptoms occur as a consequence of reduced levels of monoamines in the synaptic cleft.[14] This assumption was based on serendipitous discoveries. Reserpine, an antihypertensive drug that causes noradrenaline depletion, was reported to cause depressive symptoms.[15,16] In parallel to this finding, the role of monoamines in MDD was further supported by discovery of the first antidepressant agents, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which have robust effects on monoaminergic transmission.[1] TCAs such as imipramine act by inhibiting the serotonin and noradrenaline reuptake, while MAOIs such as iproniazid inhibit MAO, an enzyme responsible for catabolizing the monoamines serotonin, noradrenaline, and dopamine. These events increase monoamine levels in the synaptic cleft, ultimately resulting in mood improvement in patients with MDD generally three to four weeks after the onset of the treatment.[1,17,18] The discovery of the mechanisms of imipramine and iproniazid was a crucial breakthrough for the development of monoaminergic hypothesis of MDD, which initially postulated that MDD could be due to low levels of noradrenaline in the synaptic cleft.[14,19] This hypothesis was extended to acknowledge that depressive symptoms may also be related to a deficiency of serotonin in the synaptic cleft in central nervous system (CNS).[20,21] These theories were reformulated, and subsequently, the monoaminergic theory was postulated suggesting that patients with MDD present a reduction of monoaminergic neurotransmitters (basically serotonin, noradrenaline, and dopamine) in the synaptic cleft.[22]

Fluoxetine, a selective serotonin reuptake inhibitors (SSRI) was discovered in 1984 in the Eli Lilly pharmaceutical company and went on sale in 1988 after some clinical reports confirming its efficacy in the MDD, along with the advantage of having fewer adverse/side effects when compared to TCAs and MAOIs.[23] In view of the growing need for agents to treat MDD and considering fluoxetine as prototype drug, other SSRIs were developed, but the delayed therapeutic effect is a key limitation of all of these drugs.

Although monoamine-based antidepressant agents reestablish monoamine levels within a few hours after administration, their therapeutic response only occurs lately, rendering the monoaminergic hypothesis of MDD overly simplistic.[1,3,24] It has recently been reported that serotonin may be co-released with glutamate in serotonergic neurons, and antidepressant agents appear to affect this mechanism.[25] This event is especially pronounced within the raphe nuclei, but not restricted to them. Particularly, acute administration of SSRIs blocks the serotonin transporter, increasing extracellular serotonin levels, which results in the activation of serotonin-1 A autoreceptors (5-HT_{1A}). As a consequence, the release of serotonin and glutamate is decreased in nerve terminals on the presynaptic neuron.[26,27] When autoreceptors desensitize, approximately two to three weeks after the onset of SSRIs intake, firing rates are restored, reestablishing the glutamatergic component.[28] Interestingly, the restoration of adequate synaptic levels of glutamate may contribute to the strengthening of excitatory synapses[29] and may result in antidepressant responses.[25]

According to the assumption that the monoaminergic system does not fully explain the pathophysiology of MDD and considering that the administration of NMDA receptor antagonists produces an antidepressant-like effect in rodents,[30] in 1999, Skolnick proposed that the antidepressants for the new millennium would be based on the glutamatergic system modulation.[31] At the beginning of 2000, Berman et al. published a groundbreaking study, which for the first time showed that it was possible to obtain fast (within 4 h) and long-lasting (for up to three days) antidepressant effects.[6] Following these findings, the rapid and efficacious antidepressant actions of ketamine were confirmed in a larger double-blind, placebo-controlled study by Zarate et al. that demonstrated a single subanesthetic dose of ketamine produced improvement of depressive symptoms in refractory depressive patients.[7] This effect was observed within 110 min and was sustained for up to seven days in most of

the patients. A great body of clinical evidence[32–34] and experimental studies[8,9,11,35] have demonstrated the rapid, robust, and sustained antidepressant-like effect elicited by ketamine, largely erasing any doubts on the antidepressant actions of this compound. The pronounced and extremely rapid antidepressant effect of ketamine contrasted with classical monoamine-based pharmacotherapy, which might take until four weeks to present the therapeutic effect.

Mechanisms Underlying the Fast-Acting Antidepressant Effect of Ketamine

The mechanisms of action by which ketamine exerts its rapid effects have been the subject of interest by many research groups, which have prospectively shown that the molecular targets for ketamine's effects go beyond the antagonism of NMDA receptors.[36] Notably, ketamine's rapid action seems to be triggered by antagonism of NMDA receptors in GABAergic interneurons, preventing the inhibitory action of this system on glutamatergic tonus.[37] In turn, glutamatergic neurons release glutamate in the synaptic cleft, which preferentially activates AMPA (alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid) receptors. Subsequently, AMPA receptors stimulation promotes a transient sodium influx that depolarizes the cell and activates the voltage-dependent calcium channels (VDCC).[10,37] The calcium entry by VDCC promotes exocytosis of synaptic vesicles containing the brain-derived neurotrophic factor (BDNF) in the synaptic cleft, which in turn, activates tropomyosin receptor kinase B (TrkB).[10] Upon activation, TrkB stimulates phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), which is followed by several events that culminate on the mechanistic target of rapamycin (mTOR) activation.[8,9,11,38–40]

mTOR regulates the initial steps for translation of proteins involved in the formation of new dendritic spines and synaptogenesis. Particularly, mTOR phosphorylates and activates 70-kDa ribosomal protein S6 kinase (p70S6K) and also phosphorylates and inactivates the eukaryotic initiation factor 4E-binding protein (4E-BP) facilitating translation initiation.[41,42] Among the proteins that have been functionally linked to the activation of mTOR signaling, stand out postsynaptic density protein-95 kDa (PSD-95), AMPA receptor subunit 1 (GluA1), and synapsin, which are required for the formation, maturation, and function of new synapses.[8,9] Given this background, the mTOR-mediated signaling pathway underpins the mechanism of action of fast-acting antidepressants responses. The pharmacological mechanisms that underlie the fast-acting antidepressant effect of ketamine are depicted in Figure 1.

Importantly, a completely different class of glutamate-based rapid-acting antidepressant agents, including NMDA receptor antagonists (CP-101,606/Traxoprodil, MK-0657/Rislenemdaz), glycine-binding site ligands (GLYX-13/Rapastinel), metabotropic glutamate receptor modulators (AZD2066), and other glutamatergic modulators (Riluzole) could have convergent effects on pro-synaptogenesis signaling pathway, like ketamine.[43]

The Potential Role of Endogenous Neuromodulators as Fast-Acting Antidepressants

Considering the limitation of widespread clinical use of ketamine, the search of compounds that might share similar mechanisms of action to ketamine emerges as a promising therapeutic strategy. Regarding this issue, our research group has focused on the investigation of the possible role of endogenous glutamatergic neuromodulators for fast antidepressant responses, namely agmatine, creatine, guanosine, and ascorbic acid.

Agmatine

Agmatine, an endogenous polyamine, is synthesized from L-arginine in a reaction catalyzed by the enzyme arginine decarboxylase and is catabolized by the enzyme agmatinase that converts agmatine into urea and putrescine.[44] Agmatine is an intermediary in the biosynthesis of polyamines, a pathway also related to the synthesis of important neurotransmitters, such as glutamate and GABA. Agmatine is widely distributed in mammalian tissues.[45] In the CNS, it is especially present in the cytoplasm in a network of neurons in the rostral brainstem and forebrain.[46] Noteworthy, agmatine is postulated to be a neuromodulator[47] that is taken up by presynaptic axon terminals, stored in synaptic vesicles (even as with other neurotransmitters such glutamate), and released upon membrane depolarization,[48–50] similar to classical neurotransmitters. Despite these features, no well-characterized receptor for agmatine was reported yet. The neuroprotective effects of agmatine were shown in a mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease[51,52] and in cultured cerebellar granule cells and hippocampal cells submitted to glutamate and/or NMDA-induced neurotoxicity[53,54] and corticosterone.[55] Agmatine also provides neuroprotective effects in a rat model of Alzheimer's disease induced by β-amyloid peptide (Aβ fragment 25-35)[56] and protected against memory impairment induced by streptozotocin[57,58] and lipopolysaccharide (LPS).[59] The mechanims underlying these neuroprotective effects of agmatine include antiexcitotoxic, antioxidant, antiapoptotic, and pro-survival properties,[51–59] which may be relevant for the ability of agmatine to afford protection against neurodegenerative and psychiatric diseases.

Notably, increased agmatine concentrations are evident in the serum of MDD patients[60] and reduced

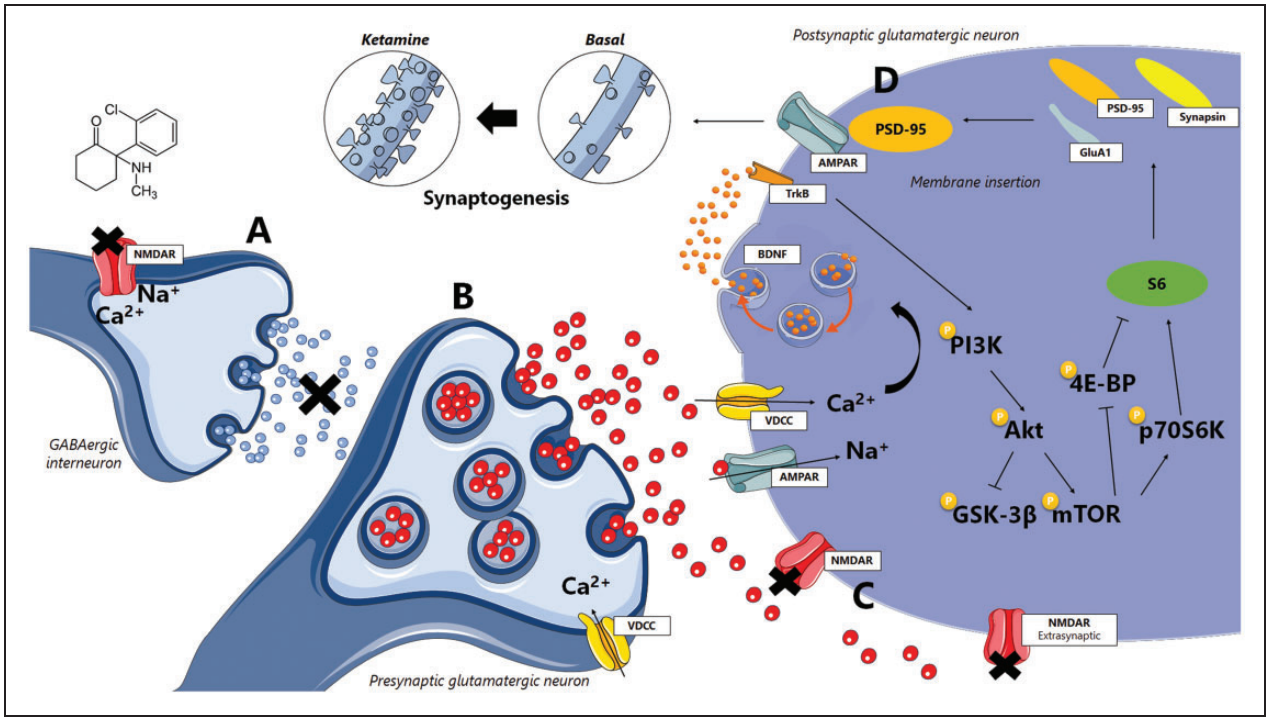

Figure 1. The proposed mechanism of action underlying the fast and sustained antidepressant effects of ketamine. It is postulated that ketamine acts antagonizing NMDAR in GABAergic interneurons (a), thereby decreasing inhibitory action of this system on glutamatergic tonus (b). Thus, glutamatergic neurons release glutamate-containing vesicles in the synaptic cleft, which preferentially activates AMPAR, since NMDAR is antagonized by ketamine (c). Upon activation, AMPAR induces a transient sodium influx that depolarizes the cell and activates VDCC, which induces exocytosis of BDNF-containing vesicles. Released BDNF, in turn, activates TrkB receptors. Upon activation, TrkB stimulates signaling pathways, particularly PI3K/Akt/mTOR-mediated pathway. This signaling pathway culminates in the synthesis of synaptic proteins such as synapsin, PSD-95 (which anchors AMPAR), and AMPAR subunit 1 (GluA1), which are inserted to the cell membrane, contributing to synaptogenesis and rapid antidepressant effect of ketamine (d). 4E-BP: eukaryotic initiation factor 4E-binding protein; Akt: protein kinase B; AMPAR: alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid receptor; BDNF: brain-derived neurotrophic factor; GluA1: AMPA receptor subunit 1; GSK-3β: glycogen synthase kinase 3β; mTOR: mechanistic target of rapamycin; NMDAR: N-methyl-D-aspartate receptor; p70S6K: 70 kDa ribosomal protein S6 kinase; PI3K: phosphatidylinositol 3-kinase; PSD-95: postsynaptic density protein-95 kDa; TrkB: tropomyosin receptor kinase B; VDCC: voltage-dependent calcium channels. Figure designed using images from Servier Medical Art and Mind the Graph.

concentrations of agmatine were shown in the cerebral cortex of suicides,[61] suggesting a role of this neuromodulator in the pathophysiology of MDD. In line with this finding, a clinical study showed the antidepressant effect of agmatine, but this study was carried out with only three patients.[62] Our research group and others have provided clear evidence that this compound has an antidepressant-like effect.[63–75] Zomkowski et al. showed the antidepressant-like effects of agmatine in behavioral tests predictive of antidepressant activity in mice, the forced swim test (FST) and tail suspension test (TST).[63] Subsequent studies reinforced the antidepressant-like effect of agmatine[64–68] involving interaction with nitrergic,[63,69] serotonergic,[65] and opioidergic systems.[66] In addition, the antidepressant-like effect elicited by the subchronic treatment with agmatine is dependent on the phosphorylation of protein kinase A (PKA), Akt, glycogen synthase kinase 3β (GSK-3β), and extracellular signal-regulated kinase (ERK1/2), with the subsequent activation of cyclic-AMP responsive-element binding protein (CREB), and transcription of BDNF.[70] The antidepressant-like response elicited by agmatine following its subchronic administration was also associated with synaptic proteins expression as well as the maintenance of the astrocytes and microglia integrity.[71]

The antidepressant-like effect of agmatine appears to involve inhibition of NMDA receptors,[69] since agmatine was able to enhance the antidepressant potency of the NMDA receptor antagonist MK-801 for up to 100 fold.[72] Subsequent studies investigated whether this compound could present fast-acting antidepressant response. Regarding this issue, Neis et al. demonstrated that the antidepressant-like effect of agmatine in the TST is dependent on the activation of AMPA and TrkB receptors, PI3K/mTOR signaling, and upregulation of synaptic proteins, in a way similar to ketamine.[73] Moreover,

the acute administration of agmatine at a very low dose by oral route was able to reverse the behavioral alterations induced by chronic unpredictable mild stress[74] and by chronic administration of corticosterone[75] in mice, suggesting that this compound may have fast-acting antidepressant properties. It is important to mention that these stress-induced models of depression are sensitive only to chronic, but not acute administration of conventional antidepressants. However, a single ketamine administration has been reported to be effective in these models of depression.[9,35] Reinforcing the notion that agmatine would have properties similar to ketamine, a single administration of agmatine or ketamine counteracted the depressive-like phenotype of CREB-regulated transcription coactivator 1 (Crtc1) knockout mice in the FST, suggesting that agmatine has a rapid antidepressant-like effect.[76] In HT22 hippocampal cell line, the combination of subthreshold concentrations of agmatine and ketamine produced cytoprotective effects against corticosterone-induced cell death by a mechanism dependent on Akt and mTOR/p70S6 kinase signaling pathway activation and increased expression of synaptic proteins.[55] Altogether, these findings suggest that agmatine may act as a ketamine-like compound, and further studies are important to investigate whether agmatine is able to afford rapid antidepressant effects in depressive patients. It is of particular interest considering that agmatine may be used even chronically at high doses without producing overt signs of toxicity.[77,78]

Creatine

Creatine, a supplement frequently used for ergogenic purpose, is widely distributed in mammalian tissues and has the potential to treat or mitigate a broad range of CNS diseases.[79] The creatine stores are found mainly in skeletal muscle, although substantial concentrations are also found in the brain.[80] Peripherally, the synthesis of this compound occurs initially in kidneys, from the amino acids glycine and L-arginine that undergo a reaction catalyzed by the enzyme L-arginine glycine amidinotransferase, resulting in ornithine and guanidinoacetate.[80] Subsequently, guanidinoacetate is transported to the liver where a methyl group from S-adenosyl-L-methionine is transferred to guanidinoacetate, forming creatine in a reaction catalyzed by guanidinoacetate-methyltransferase.[80,81] However, creatine is also synthesized in the CNS.[82] Noteworthy, creatine has been postulated to act as a neuromodulator synthesized and taken up by central neurons and released in an action-potential dependent manner, modulating various neurotransmitter systems and signaling pathways.[35,79,83–86] Notably, the neuroprotective effect of creatine was demonstrated by several lines of evidence, particularly in Parkinson's disease model induced by 6-hydroxydopamine and MPP^+,[87,88] in neurotoxicity induced by hyperammonemia,[89] as well as in glutamate-induced excitotoxicity and Alzheimer's disease model induced by β-amyloid peptide.[90] Furthermore, a growing body of clinical studies have also shown alterations in creatine levels in the brain of patients that exhibit depressive symptoms,[91–93] suggesting that this neuromodulator could exert an important role in the pathophysiology of MDD.

Remarkably, several preclinical studies reported the antidepressant-like effect of creatine in mice subjected to TST and FST.[35,85,86,94–97] This response is dependent on the modulation of dopaminergic,[94] serotonergic,[96] and noradrenergic systems [98] and also on the activation of PKA, protein kinase C (PKC), and mitogen-activated protein kinases (MAPKs).[86] Moreover, the coadministration of subeffective doses of creatine and NMDA antagonists MK-801 or ketamine elicited an antidepressant-like response in mice, suggesting a possible modulation of glutamatergic system.[95] The antidepressant effect of creatine on β-amyloid-treated mice was also demonstrated, a response associated with GSK-3β/Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway.[99]

In view of the results which show a similar effect between creatine and ketamine,[95,97] subsequent studies investigated whether creatine could be able to stimulate Akt/mTOR-mediated signaling pathway. Notably, creatine was able to increase Akt and mTOR phosphorylation in the hippocampus of mice.[85] Reinforcing the notion that creatine modulates PI3K/Akt/mTOR signaling, the antidepressant-like effect of creatine in mice submitted to TST was abolished by PI3K and mTOR inhibitors.[35,85] Interestingly, a single creatine administration was able to reverse corticosterone-induced depressive-like behavior, as well as increased mTOR and p70S6K phosphorylation, ultimately leading to increase on PSD-95 immunocontent in the hippocampus.[35] These effects were comparable to those results previously reported in the prefrontal cortex of rats administered with ketamine.[8,9] This evidence suggests that creatine could share with ketamine the ability to promote a fast antidepressant-like response. However, the antidepressant-like effect of creatine in the TST was not dependent on AMPA receptor activation, as opposed to ketamine.[10,95]

No evidence until now reports the ability of creatine to enhance the number and function of dendritic spines, an event that has been shown to be crucial for the rapid antidepressant responses. Therefore, future studies are necessary to ascertain the similarities between creatine and ketamine. Noteworthy, several clinical studies have also demonstrated the beneficial effects of creatine in patients with MDD.[100–105] Particularly, Lyoo et al. showed an improvement in depressive symptoms in 52 patients with MDD that received creatine combined with escitalopram for eight weeks, as early as week 2 of

treatment.[104] These findings were later reinforced by another study performed by Hellem et al., which showed that 14 patients with MDD in an eight-week open-label trial of daily creatine treatment presented a significant reduction in depressive symptomatology as early as week 2 when compared to baseline scores.[105] These studies suggest that creatine could present a faster antidepressant effect when compared to conventional antidepressants, but it remains to be established whether creatine could be able to afford a rapid-onset antidepressant response.

Guanosine

Guanosine is a guanine-based purine that has been recently proposed to be not only an intracellular signaling component but also an extracellular signaling molecule, which regulates important functions in the CNS.[106,107] In such a way, the guanosinergic system was postulated as a system in which guanosine could be the molecule with main biological activity.[106,108,109] These assumptions were supported by the fact that guanosine is released in the brain under physiological conditions and even more during pathological events, triggering widespread actions in several brain regions.[110] The main source of guanosine comes from astrocytes and neurons, which release nucleotides into the extracellular space that are rapidly catabolized by ecto-5′-nucleotidases forming this nucleoside.[109,111] Notably, while extracellular adenine-based purines are rapidly metabolized following an insult, guanosine concentration increases progressively, suggesting that it may be an endogenous neuroprotective agent.[110]

Indeed, a vast number of reports have shown the neuroprotective effect of guanosine against several injuries, including ischemia,[112–119] sepsis-induced cognitive impairment,[120] ammonia intoxication,[121] hepatic encephalopathy,[122] cytotoxicity induced by MPP^+ and 6-hydroxydopamine,[123,124] glutamate,[125] azide-induced oxidative damage,[126] methylmercury,[127] and LPS-induced inflammation.[128] Furthermore, the neuroprotective effect of guanosine was also demonstrated in animal models of Alzheimer's [129] and Parkinson's disease.[130] The mechanisms that underlie the neuroprotective effects of guanosine are associated with its ability to attenuate neuroinflammation and oxidative stress as well as to stimulate glutamate uptake.[124,125,131–133] Moreover, guanosine is supposed to exert its neuroprotective effects by synchronizing distinct signaling pathways such as PI3K/Akt and MAPKs signaling.[114,125,134] The neurotrophic effects of guanosine were also reported by several lines of evidence, which have demonstrated that this nucleoside is able to induce proliferation and differentiation, as well as stimulate the neurite arborization and outgrowth.[111,135–137] These effects may be underpinned by the guanosine's ability to promote synthesis and release of neurotrophic factors such as nerve growth factor (NGF), transforming growth factor beta (TGF-β), fibroblast growth factor 2 (FGF-2), and BDNF.[135–142] Despite the abovementioned studies, no receptor for guanosine was characterized until now.[143–145] However, guanosine is recognized as a glutamatergic neuromodulator.[146]

Noteworthy, plasma levels of guanosine were reduced in patients with MDD, suggesting that this nucleoside could play a role in the pathophysiology of MDD.[147] Accordingly, our research group demonstrated that guanosine produces an antidepressant-like effect in mice submitted to TST and FST.[137,148,149] Of note, the PI3K/Akt signaling pathway and its downstream target mTOR seem to be required for the behavioral response of guanosine.[148] In view of these findings, one may suppose that the mechanisms underlying the antidepressant-like response of guanosine are, at least in part, similar to those displayed by ketamine, which includes neurotrophic properties, the modulation of glutamatergic transmission, and the ability to stimulate the PI3K/Akt and mTOR-mediated signaling pathways. Noteworthy, reinforcing the notion that guanosine could share the mechanism of action of ketamine, a previous study reported that a single administration of a subeffective dose of guanosine combined with a subeffective dose of ketamine produced an antidepressant-like effect in the TST.[148] In addition, a recent study reported the augmentation effect of ketamine by guanosine in the novelty-suppressed feeding test by a mechanism dependent on mTOR signaling pathway.[150] Given this scenario, further studies are crucial to understand whether guanosine shares with ketamine a common mechanism of action and could present a fast-acting antidepressant effect.

Ascorbic Acid

Ascorbic acid, also known as vitamin C, is a water-soluble vitamin that occurs physiologically as the ascorbate anion. It exerts antioxidant activity and participates as a coenzyme in the production of proteins such as collagen, as well as in the synthesis of norepinephrine, serotonin, and carnitine.[151] This compound is synthetized in the majority of mammals, but humans are not able to synthetize it due to the absence of L-gulono-γ-lactone oxidase, a key enzyme for ascorbate biosynthesis. Therefore, humans should obtain ascorbic acid from foods and dietary supplements.[152]

Besides its function as a vitamin, ascorbic acid is a neuromodulator that modulates the glutamatergic and dopaminergic systems.[153] The first indication that ascorbic acid may exert an antidepressant effect was a case report published in 1980 that showed a reduction in the severity of depressive symptoms in a child with chronic hepatitis and under adrenocorticotropic hormone

therapy that received high doses of ascorbic acid.[154] Some subsequent clinical studies reinforce its potential as an antidepressant agent. Brody et al. reported that ascorbic acid was effective in decreasing scores on Beck Depression Inventories in healthy young adults.[155] In addition, lower depressive symptoms were observed in an elderly population on high dietary intake of vitamin C.[156] Pediatric patients treated for six months with fluoxetine and ascorbic acid presented a significant decrease in depressive symptoms when compared to the fluoxetine plus placebo group, further suggesting that ascorbic acid may afford beneficial effects on mood.[157] In line with this study, the administration of ascorbic acid with antidepressants decreased depression scores in 22 patients.[158] Preclinical studies have also supported the assumption that ascorbic acid may be effective as an antidepressant agent. The first preclinical study that showed that ascorbic acid might elicit antidepressant-like effects was published in 2009 by our research group. The administration of ascorbic acid to mice caused an antidepressant-like effect in TST by a mechanism dependent on the monoaminergic systems.[158] In addition, a synergistic antidepressant-like effect was found when ascorbic acid was administered in combination with conventional antidepressants.[159] Subsequent studies from our group indicated several targets for the antidepressant-like effects of ascorbic acid: (a) inhibition of NMDA receptors and the L-arginine-NO-cyclic guanosine 3,5-monophosphate pathway;[160] (b) inhibition of potassium channels;[161] (c) activation of phosphatidylinositol-3 kinase (PI3K) and mTOR signaling pathway, inhibition of GSK-3β, and induction of heme oxygenase-1;[162] (d) modulation of $GABA_A$ and $GABA_B$ receptors;[163] (e) activation of the opioid system.[164] Moreover, the administration of ascorbic acid elicited antidepressant-like effects in mice subjected to several models of depression, namely chronic unpredictable stress,[165] acute restraint stress,[166] and administration of the proinflammatory cytokine TNF-α.[167] Considering that the antidepressant-like effect of ascorbic acid is associated with the modulation of mTOR signaling pathway,[162] the possibility of ascorbic acid exerts a fast antidepressant-like effect in a way similar to ketamine deserves further investigation. Therefore, the characterization of the antidepressant behavioral response provided by ascorbic acid and its ability to modulate hippocampal synaptic plasticity is under investigation in our laboratory.

Conclusions and Future Directions

Although ketamine is able to produce fast-onset responses following a single administration even to severely depressed individuals, its side effects and the possibility of neurotoxicity upon chronic administration have led to the investigation of novel fast-acting antidepressant agents. Our research group has focused on the investigation of endogenous mood modulators that may act as ketamine-like compounds. We provide evidence from preclinical studies that the endogenous glutamatergic neuromodulators agmatine and creatine have antidepressant behavioral profile similar to ketamine, besides presenting the ability to elicit antidepressant response by activating mTOR signaling pathway and/or acutely increasing synaptic proteins and BDNF levels in the hippocampus (creatine and agmatine) and prefrontal cortex (agmatine). Moreover, there is evidence under way in our laboratory indicating that guanosine and ascorbic acid also have the potential to afford antidepressant responses similar to ketamine. Considering that all of these compounds are safe even upon chronic use and exert these effects at very low doses, we consider that they are promising compounds to be tested in clinical studies. A particular interesting approach would be the investigation of the augmentation effect of low doses of ketamine by these compounds in order to provide efficacious fast-acting antidepressant response with lesser side effects.

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ORCID iD

Ana Lúcia S. Rodrigues https://orcid.org/0000-0001-6285-8780

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