

Cholecalciferol abolishes depressive-like behavior and hippocampal glucocorticoid receptor impairment induced by chronic corticosterone administration in mice

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ABSTRACT

Several attempts have been made to understand the role of cholecalciferol (vitamin D₃) in the modulation of neuropsychiatric disorders. Notably, the deficiency of vitamin D₃ is considered a pandemic and has been postulated to enhance the risk of major depressive disorder (MDD). Therefore, this study aims to investigate the antidepressant-like effect of cholecalciferol in a mouse model of depression induced by corticosterone, and the possible role of glucocorticoid receptors (GR), NLRP3 and autophagic pathways in this effect. Corticosterone administration (20 mg/kg, p.o., for 21 days) significantly increased the immobility time and grooming latency, as well as reduced the total time spent grooming in mice subjected to the tail suspension test (TST) and splash test (ST), respectively. Importantly, these behavioral alterations were associated with reduced GR immunoreactivity in the hippocampus of mice. Conversely, the repeated administration of cholecalciferol (2.5 µg/kg, p.o.) in the last 7 days of corticosterone administration was effective to prevent the increased immobility time in the TST and the reduced time spent grooming in the ST, and partially abolished the increase in the grooming latency induced by corticosterone, suggesting its antidepressant-like effect. These behavioral effects were similar to those exerted by fluoxetine (10 mg/kg, p.o.). Moreover, the corticosterone-induced reduction on hippocampal GR immunoreactivity was not observed in mice treated with cholecalciferol. Additionally, cholecalciferol treatment *per se* reduced the immunoreactivity of NLRP3 inflammasome-related proteins ASC, caspase-1, and TXNIP in the hippocampus of mice. No alterations on hippocampal immunoreactivity of the autophagic-related proteins phospho-mTORC1, beclin-1, and LC3A/B were observed following cholecalciferol treatment and/or corticosterone administration. Collectively, our results provide insights into the effects of cholecalciferol in depression-related behaviors that seem to be related, at least in part, to GR modulation.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric disorder that affects > 350 million people, causing a high personal and socioeconomic burden (World Health Organization, 2017). It is well reported that chronic stress and hypothalamic-pituitary-adrenal (HPA) axis dysfunction are risk factors for MDD (Goodyer et al., 2000; Nowacki et al., 2020). Chronic stress can induce increased levels of glucocorticoids, namely cortisol in humans and corticosterone in rodents, which may damage the hippocampus, a region that presents a high density of glucocorticoids receptor (GR) crucial for HPA axis autoregulation and mood modulation (Anacker et al., 2011; Lee et al.,

2002). In keeping with these premises, exogenous corticosterone (CORT) administration in rodents has been proposed as a pharmacological stress model of depression that mimics the behavioral and neurochemical alterations associated with HPA dysfunction in the depressive state (Pazini et al., 2016; Rosa et al., 2014; Zhao et al., 2008).

Despite the numerous studies reporting that chronic stress underlies the genesis of MDD, the mechanisms by which glucocorticoids contribute to the depressive symptoms have not been entirely established. Compelling evidence indicates that glucocorticoids may induce a peripheral and central pro-inflammatory state that involves the stimulation of the nod-like receptor pyrin domain containing 3 (NLRP3), an intracellular multiprotein complex responsible for the inflammatory

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The involvement of GABAergic system in the antidepressant-like effect of agmatine

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Abstract

Considering the involvement of GABAergic system in the action of the fast-acting antidepressant ketamine, and that agmatine may exert an antidepressant-like effect through mechanisms similar to ketamine, the purpose of the present study was to evaluate the involvement of GABA_A and GABA_B receptors in the antidepressant-like effect of agmatine. The administration of muscimol (0.1 mg/kg, i.p., GABA_A receptor agonist) or diazepam (0.05 mg/kg, p.o., GABA_A receptor positive allosteric modulator) at doses that caused no effect in the tail suspension test (TST) combined with a subeffective dose of agmatine (0.0001 mg/kg, p.o.) produced a synergistic antidepressant-like effect in the TST. In another set of experiments, the administration of baclofen (1 mg/kg, i.p., GABA_B receptor agonist) abolished the reduction of immobility time in the TST elicited by agmatine (0.1 mg/kg, p.o., active dose). In another cohort of animals, treatment with NMDA (0.1 pmol/site, i.c.v.) prevented the antidepressant-like effect of the combined administration of agmatine and muscimol as well as ketamine and muscimol in the TST. Results suggest that the effect of agmatine in the TST may involve an activation of GABA_A receptors dependent on NMDA receptor inhibition, similar to ketamine, as well as modulation of GABA_B receptors.

Keywords Agmatine · Antidepressant · GABA · Ketamine · Tail suspension test

Introduction

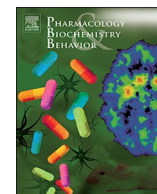
Major depressive disorder (MDD) is a debilitating psychiatric disorder that affects a considerable part of population around the world (Clevenger et al. 2018). Although its etiology is not completely understood, studies have demonstrated the involvement of GABAergic system in MDD. Indeed, postmortem evidence and preclinical studies have highlighted GABAergic abnormalities, such as a reduction in GABA in patients with depression (Bhagwagar et al. 2008; Price et al. 2009). In addition, the role of GABAergic system in the pathophysiology of MDD has been suggested by several studies that indicate (a) stress-related changes in GABAergic function (Biggio et al. 1990;

Banasr et al. 2017); (b) the ability of GABA agonists and antagonists to modulate the behavioral responses in models of depression in rodents (Song and Leonard 2005); (c) elevated GABA levels in rat thalamus following acute administration of tricyclic antidepressants (Korf and Venema 1983); (d) GABAergic abnormalities and genetic associations in depressed patients (Petty et al. 1999; Oh et al. 2012); and (e) evidence of clinical antidepressant efficacy by GABAergic drugs (Magni et al. 1989; Mohler 2012).

The treatment for MDD includes antidepressants, psychotherapy, or a combination of both (Spijker et al. 2013). However, it is common to observe low remission rates in patients with depression subjected to these therapies (Mathew and Charney 2009; Pigott et al. 2010), besides the high risk of relapse, with up to 85% of patients experiencing a recurrence after one MDD episode (Hardeveld et al. 2013). Considering that an important limitation of conventional therapy is the delay in the remission of depressive symptoms, great efforts have been carried out to find fast-acting antidepressant agents. Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, exerts a fast antidepressant effect in rats and

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The involvement of PI3K/Akt/mTOR/GSK3 β signaling pathways in the antidepressant-like effect of AZD6765

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ABSTRACT

AZD6765 (lanicemine) is a non-competitive NMDA receptor antagonist that induces a fast-acting antidepressant effect without presenting psychotomimetic effects. However, the mechanisms underlying its effects remain to be established. In this context, we demonstrated that a single administration of AZD6765 (1 mg/kg, i.p.) was able to induce an antidepressant-like effect in mice submitted to tail suspension test (TST), an effect reversed by LY294002 (a reversible PI3K inhibitor, 10 nmol/site, i.c.v.), wortmannin (an irreversible PI3K inhibitor, 0.1 μ g/site, i.c.v.) and rapamycin (a selective mTOR inhibitor, 0.2 nmol/site, i.c.v.). In addition, the administration of sub-effective doses of AZD6765 (0.1 mg/kg, i.p.) in combination with lithium chloride (non-selective GSK-3 β inhibitor, 10 mg/kg, p.o.) or AR-A014418 (selective GSK-3 β inhibitor, 0.01 μ g/site, i.c.v.) caused a synergistic antidepressant-like effect. These results suggest the involvement of PI3K/Akt/mTOR/GSK3 β signaling in the AZD6765 antidepressant-like effect. In addition, western blotting analysis showed an increased immunocontent of synapsin in the prefrontal cortex and a tendency to an increased immunocontent of this protein in the hippocampus 30 min after AZD6765 administration, but no significant effect of AZD6765 was observed in P70S6K (Thr³⁸⁹) phosphorylation and GluA1 immunocontent. A single dose of AZD6765 (3 mg/kg, i.p.), similarly to ketamine (1 mg/kg, i.p.), decreased the latency to feed in the novelty suppressed feeding (NSF) test, a behavioral paradigm that evaluates depression/anxiety-related behavior. This effect was reversed by rapamycin administration, suggesting the activation of mTOR signaling in the effect of AZD in the NSF test. In addition, a single administration of AZD6765 (1 mg/kg, i.p.) or ketamine (1 mg/kg, i.p.) reversed the depressive-like behavior induced by chronic unpredictable stress (CUS). Altogether, the results provide evidence for the fast-acting antidepressant profile of AZD6765, by a mechanism likely dependent on PI3K/Akt/mTOR/GSK3 β .

1. Introduction

NMDA receptors are a class of ionotropic glutamatergic receptors related to synaptic plasticity and cell survival (Glasgow et al., 2015). These receptors have been extensively studied in encephalic structures such as cerebral cortex and hippocampus and are highly implicated in psychiatric disorders such as major depressive disorder (MDD) (Hansen et al., 2014; Li et al., 2009). Glutamate excitotoxicity due to over-activation of these receptors has been implicated in the pathophysiology of these disorders (Fan and Raymond, 2007; Wang and Michaelis, 2010).

NMDA receptor antagonists have demonstrated beneficial effects for the treatment of MDD (Dang et al., 2014; Zarate et al., 2010).

Preclinical studies have reported that these antagonists exhibit antidepressant-like effect in several animal models of depression (Belzung, 2014; Li et al., 2010). An NMDA receptor antagonist that has emerged as a promising therapeutic agent is ketamine, a dissociative anesthetic that has demonstrated fast and long-lasting antidepressant effects when acutely administered at subanesthetic doses in patients suffering from severe MDD symptoms (Berman et al., 2000; Zarate et al., 2006; Zarate et al., 2013). The antidepressant response elicited by ketamine is proposed to be mediated by glutamate increase with the consequent stimulation of BDNF receptors, which leads to the activation of phosphatidylinositol 3-kinase (PI3K)/Akt, inhibition of glycogen synthase kinase-3 β (GSK3 β) and stimulation of mammalian target of rapamycin (mTOR) (Monteggia et al., 2013; Wohleb et al., 2017). The activation of

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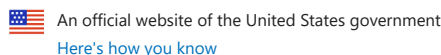
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Glibenclamide treatment prevents depressive-like behavior and memory impairment induced by chronic unpredictable stress in female mice

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Abstract

Glibenclamide is a second-generation sulfonylurea used in the treatment of Type 2 Diabetes Mellitus. The primary target of glibenclamide is ATP-sensitive potassium channels inhibition; however, other possible targets include the control of inflammation and blood-brain barrier permeability, which makes this compound potentially interesting for the management of brain-related disorders. Here, we showed that systemic treatment with glibenclamide (5 mg/kg, p.o., for 21 days) could prevent the behavioral despair and the cognitive dysfunction induced by chronic unpredictable stress (CUS) in mice. In nonhypoglycemic doses, glibenclamide attenuated the stress-induced weight loss, decreased adrenal weight, and prevented the increase in glucocorticoid receptors in the prefrontal cortex, suggesting an impact in hypothalamic-pituitary-adrenal (HPA) axis function. Additionally, we did not observe changes in Iba-1, NLRP3 and caspase-1 levels in the prefrontal cortex or hippocampus after CUS or glibenclamide treatment. Thus, this study suggests that chronic treatment with glibenclamide prevents the emotional and cognitive effects of chronic stress in female mice. On the other hand, the control of neuroinflammation and NLRP3 inflammasome pathway is not the major mechanism mediating these effects. The behavioral effects might be mediated, in part, by the normalization of glucocorticoid receptors and HPA axis.

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Antidepressant-like effect of guanosine involves activation of AMPA receptor and BDNF/TrkB signaling

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Abstract

Guanosine is a purine nucleoside that has been shown to exhibit antidepressant effects, but the mechanisms underlying its effect are not well established. We investigated if the antidepressant-like effect induced by guanosine in the tail suspension test (TST) in mice involves the modulation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, voltage-dependent calcium channel (VDCC), and brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB) pathway. We also evaluated if the antidepressant-like effect of guanosine is accompanied by an acute increase in hippocampal and prefrontocortical BDNF levels. Additionally, we investigated if the ability of guanosine to elicit a fast behavioral response in the novelty suppressed feeding (NSF) test is associated with morphological changes related to hippocampal synaptogenesis. The antidepressant-like effect of guanosine (0.05 mg/kg, p.o.) in the TST was prevented by DNQX (AMPA receptor antagonist), verapamil (VDCC blocker), K-252a (TrkB antagonist), or BDNF antibody. Increased P70S6K phosphorylation and higher synapsin I immuncontent in the hippocampus, but not in the prefrontal cortex, were observed 1 h after guanosine administration. Guanosine exerted an antidepressant-like effect 1, 6, and 24 h after its administration, an effect accompanied by increased hippocampal BDNF level. In the prefrontal cortex, BDNF level was increased only 1 h after guanosine treatment. Finally, guanosine was effective in the NSF test (after 1 h) but caused no alterations in dendritic spine density and remodeling in the ventral dentate gyrus (DG). Altogether, the results indicate that guanosine modulates targets known to be implicated in fast antidepressant behavioral responses (AMPA receptor, VDCC, and TrkB/BDNF pathway).

Keywords AMPA · BDNF · Dendritic spines · Depression · Guanosine

Priscila B. Rosa Graduated in Pharmacy with specialization in Clinical Analysis from the Federal University of Santa Catarina (2015), master's degree (2016) and doctorate (2020) from the post-graduate program in Biochemistry from the Federal University of Santa Catarina. Has experience in the fields of Neuropsychopharmacology and Biochemistry, mainly related to the investigation of the mechanisms involved in the antidepressant-like effect of neuromodulators, natural and synthetic products in animal models of depression.



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Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder with significant socioeconomic impact [1]. The pharmacotherapy for MDD has significant limitations, including