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Antidepressant-like effects of ascorbic acid and ketamine involve modulation of $GABA_A$ and $GABA_B$ receptors

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ABSTRACT

Background: It has been suggested that dysregulation of γ-aminobutyric acid (GABA)-mediated neurotransmission is involved in the etiology of major depressive disorder and in the action of the fast-acting antidepressant ketamine. Considering that recent evidence has suggested that ascorbic acid may exert an antidepressant-like effect through mechanisms similar to ketamine, this study evaluated the involvement of $GABA_A$ and $GABA_B$ receptors in the antidepressant-like effect of ascorbic acid, comparing the results with those obtained with ketamine.

Methods: To investigate the involvement of $GABA_A$ in the antidepressant-like effect of ascorbic acid and ketamine in the tail suspension test (TST), mice were treated with a sub-effective dose of ascorbic acid (0.1 mg/kg, *po*), ketamine (0.1 mg/kg, *ip*) or vehicle and 30 minutes later, a sub-effective dose of muscimol (0.1 mg/kg, *ip*, $GABA_A$ receptor agonist) or vehicle was administered. In another set of experiments, mice were treated with ascorbic acid (1 mg/kg, *po*, active dose in the TST) or vehicle and 30 minutes later, baclofen (1 mg/kg, *ip*, $GABA_B$ receptor agonist) was administered. A similar experimental protocol was performed with ketamine (1 mg/kg, *ip*).

Results: The administration of muscimol combined with ascorbic acid or ketamine produced a synergistic antidepressant-like effect in the TST. Moreover, the antidepressant-like effects of ascorbic acid and ketamine were abolished by baclofen. There was no alteration in spontaneous locomotion in any experimental group.

Conclusions: Results indicate that the anti-immobility effect of ascorbic acid and ketamine in TST may involve an activation of $GABA_A$ receptors and a possible inhibition of $GABA_B$ receptors.

Introduction

Depression is a mood disorder that is a leading cause of disability, comorbidity and mortality worldwide [1]. It has a high social and economic impact [1,2], and affects up to 15% of the population at least once in their lifetime [3]. In the last 50 years, drugs that increase the synaptic availability of monoamines (serotonin, norepinephrine and dopamine) have been used for the treatment of depression, but they have some limitations because not all patients respond to treatment [4,5], a long time lag is necessary for clinical response to the treatment (usually 4–5 weeks), and there are side effects elicited by these agents [6].

It has been suggested that dysregulation of the inhibitory amino acid neurotransmitter γ-aminobutyric acid (GABA) is involved in the etiology of depression [7]. Depressive patients have been shown to present reduction in GABA concentration in different regions of the central nervous system (CNS), and effective treatments with antidepressants [8] or electroconvulsive therapy [9] increase GABA levels in the occipital cortex of depressive patients. Notably, GABAergic interneurons exert a significant influence on the neural networks responsible for controlling mood and cognitive function, and normalization of GABAergic neurotransmission leads to improvement in cognitive deficits observed in depressive individuals [7]. In addition, recent evidence has indicated that GABAergic system is implicated in the antidepressant activity of ketamine, an NMDA receptor antagonist that has been emerged as a novel fast-acting antidepressant, useful for the management of treatment-resistant depression [10–12]. Administration of ketamine was shown to increase GABA levels in

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the anterior cingulate in rats subjected to chronic unpredictable stress [13] and also in medial prefrontal cortex of depressive patients [14].

Ascorbic acid, a water-soluble antioxidant vitamin, commonly known as vitamin C, is a cofactor in several important biological enzyme reactions [15] and has neuroprotective and antioxidant properties [16]. Of particular interest, ascorbic acid has been suggested to play a role in mood regulation. Studies showed that plasma ascorbic acid levels were decreased in depressive patients [17] and that the treatment with ascorbic acid for 14 days was able to improve mood in healthy young adults [18]. Corroborating these findings, a randomized, double-blind, placebo-controlled pilot study revealed that ascorbic acid presents efficacy as an adjunct to fluoxetine therapy in pediatric major depressive disorder [19]. Consistent with clinical studies, our group demonstrated that ascorbic acid produces an antidepressant-like effect in the mouse tail suspension test (TST) and a synergistic antidepressant-like effect when administrated with conventional antidepressants in mice [20,21]. Importantly, we demonstrated that ascorbic acid exerts antidepressant-like effects through mechanisms similar to that of the fast-acting antidepressant ketamine [22]. Considering this background, the purpose of this study was to evaluate the involvement of the GABAergic system in the antidepressant-like effect of this neuromodulator in mice. Furthermore, we aimed to examine whether the antidepressant mechanism of ascorbic acid involving a possible modulation of the GABAergic system is comparable to the one triggered by ketamine.

Materials and methods

Animals

This study was performed using adult female Swiss mice (30–40 g), maintained at 20–22 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 7:00 a.m. Twenty four hours before the test, the cages were placed in the

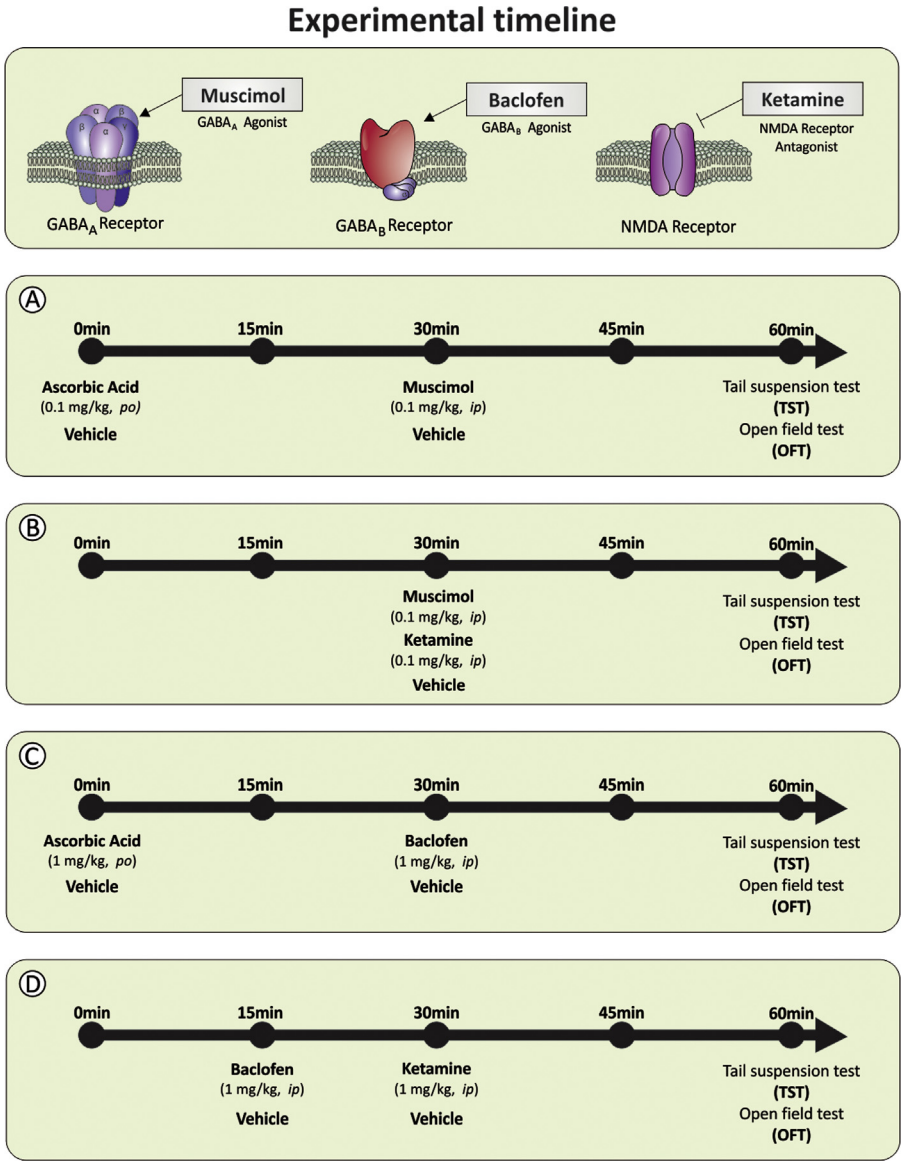

Fig. 1. Experimental timeline. A) Mice were treated with a sub-effective dose of ascorbic acid (0.1 mg/kg, *po*) or vehicle 30 min before administration of a sub-effective dose of muscimol (0.1 mg/kg, *ip*) or vehicle. After 30 min, they were subjected to behavioral tests. B) Mice were treated with a sub-effective dose of muscimol (0.1 mg/kg, *ip*), ketamine (0.1 mg/kg, *ip*) or vehicle 30 min before the behavioral tests. C) Mice were treated with ascorbic acid (1 mg/kg, *po*) or vehicle 30 min before administration of baclofen (1 mg/kg, *ip*). After 30 min, they were subjected to behavioral tests. D) Mice were treated with baclofen (1 mg/kg, *ip*), ketamine (1 mg/kg, *ip*) or vehicle 30 minutes before the behavioral tests.