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Activity of mitochondrial respiratory chain is increased by chronic administration of antidepressants

Scaini G, Maggi DD, De-Nês BT, Gonçalves CL, Ferreira GK, Teodorak BP, Bez GD, Ferreira GC, Schuck PF, Quevedo J, Streck EL. Activity of mitochondrial respiratory chain is increased by chronic administration of antidepressants.

Objective: Depressive disorders, including major depression, are serious and disabling for affected patients. Although the neurobiological understanding of major depressive disorder focuses mainly on the monoamine hypothesis, the exact pathophysiology of depression is not fully understood.
Methods: Animals received daily intra-peritoneal injections of paroxetine (10 mg/kg), nortriptyline (15 mg/kg) or venlafaxine (10 mg/kg) in 1.0 ml/kg volume for 15 days. Twelve hours after the last injection, the rats were killed by decapitation, where the brain was removed and homogenised. The activities of mitochondrial respiratory chain complexes in different brain structures were measured.
Results: We first verified that chronic administration of paroxetine increased complex I activity in prefrontal cortex, hippocampus, striatum and cerebral cortex. In addition, complex II activity was increased by the same drug in hippocampus, striatum and cerebral cortex and complex IV activity in prefrontal cortex. Furthermore, chronic administration of nortriptyline increased complex II activity in hippocampus and striatum and complex IV activity in prefrontal cortex, striatum and cerebral cortex. Finally, chronic administration of venlafaxine increased complex II activity in hippocampus, striatum and cerebral cortex and complex IV activity in prefrontal cortex.
Conclusion: On the basis of the present findings, it is tempting to speculate that an increase in brain energy metabolism by the antidepressant paroxetine, nortriptyline and venlafaxine could play a role in the mechanism of action of these drugs. These data corroborate with other studies suggesting that some antidepressants modulate brain energy metabolism.

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Introduction

Major depressive is the most prevalent mental disorder with an estimated prevalence of 13.5–21.2% (1–3). It is believed that 5% of the population suffers from depression (4). Together with schizophrenia, depression is responsible for 60% of suicides worldwide and it is predicted to be the second main cause of disability in 2020, regardless of the age and the gender of the patient (5).

The pathophysiological mechanisms and the pharmacological treatment of major depressive disorder focus mainly on the monoamine hypothesis (6). This hypothesis predicts that the major depression results from a dysregulation of neurotransmission by serotonin, norepinephrine and dopamine, and the treatments are based on normalising the reduced levels of these neurotransmitters (7). In fact, almost all clinically used antidepressants increase

the extracellular concentrations of serotonin or norepinephrine by inhibiting their reuptake from the synapse or by blocking their degradation by inhibiting monoamine oxidase activity (8,9). Furthermore, monoamine-based antidepressants remain the first line of therapy for depression, but their long therapeutic delays and low remission rates (about 30%) have encouraged the search for more effective agents (10).

The treatment of depression was revolutionised by the discovery of monoamine oxidase inhibitors and tricyclic antidepressants. Since then, the availability of newer drugs with less adverse effects has greatly increased the ability to safely treat a significant number of patients (11). Although commonly used antidepressants, such as the selective serotonin (5-HT) reuptake inhibitor (SSRI), are often effective, full efficacy is only apparent after several weeks, and many patients only partially respond (12–14).

Paroxetine is functionally classified as an SSRI, which enhances serotonergic transmission by blocking the pre-synaptic active membrane transport mechanism for the reuptake of serotonin and consequently increases serotonergic activity at the post-synaptic receptor (15,16). Nortriptyline is a metabolite of amitriptyline with several putative pharmacological mechanisms including blockade of norepinephrine and serotonin uptake, blockade of sodium channels and sympathetic blockade and antagonism of *N*-methyl-D-aspartate glutamate receptors (16). Venlafaxine is used as the inhibitor of both serotonin and norepinephrine. The primary function of venlafaxine is to protect the transport of serotonin and norepinephrine at the synapse, thus increasing the concentration of both monoamines within the synapse (17).

Tissues with high-energy demands, such as the brain, contain a large number of mitochondria, being therefore more susceptible to the reduction of aerobic metabolism. Mitochondria are intracellular organelles that play a crucial role in adenosine triphosphate (ATP) production (18). Most cell energy is obtained through oxidative phosphorylation, a process requiring the action of various enzyme complexes located in the inner mitochondrial membrane, that is the mitochondrial respiratory chain (19). Mitochondrial dysfunction has been shown to be involved in the pathogenesis of a number of diseases affecting the brain, such as dementia, cerebral ischemia, Alzheimer's disease and Parkinson's disease (20–26). In this context, several recent works also support the hypothesis that energy impairment is involved in the pathophysiology of depression (27–30).

Therefore, on the basis of the hypothesis that energy impairment may be involved in the pathophysiology of depression, in the present work, we evaluated the activities of the mitochondrial respiratory chain complexes in the brain of rats and submitted the chronic administration of paroxetine, nortriptyline and venlafaxine.

Materials and methods

Animals

Adult and male Wistar rats (250–300 g) were obtained from Central Animal House of the Universidade do Extremo Sul Catarinense. They were caged in group of five with free access to food and water and were maintained on a 12-h light–dark cycle (lights on 07:00), at a temperature of 23 ± 1 °C. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior recommendations for animal care, with the approval of the Ethics Committee from Universidade do Extremo Sul Catarinense.

Drugs

Animals received daily intra-peritoneal injections of paroxetine (10 mg/kg), nortriptyline (15 mg/kg) or venlafaxine (10 mg/kg) in 1.0 ml/kg volume for 15 days ($n = 6$ animals per group). All drugs were dissolved in saline solution (vehicle). Control animals received the vehicle (1.0 ml/kg). The selection of this regimen was based on previous studies showing important neurochemical and antidepressant effects for both the drugs (31–35).

Tissue and homogenate preparation

Twelve hours after the last injection, the rats were killed by decapitation, the brain was removed and the prefrontal cortex, hippocampus, striatum, cerebellum and cerebral cortex were homogenised (1:10, w/v) in SETH buffer, pH 7.4 (250 mM sucrose, 2 mM EDTA (ethylene diamine tetraacetic acid), 10 mM Trizma base, 50 IU/ml heparin). The homogenates were centrifuged at $800 \times g$ for 10 min and the supernatants kept at −70 °C until used for enzymes activity determination. The maximal period between homogenate preparation and enzyme analysis was always less than five days. Protein content was determined by the method described by Lowry and colleagues (36) using bovine serum albumin as the standard.

Activities of mitochondrial respiratory chain enzymes

NADH (nicotinamide adenine dinucleotide) dehydrogenase (complex I) was evaluated by the method

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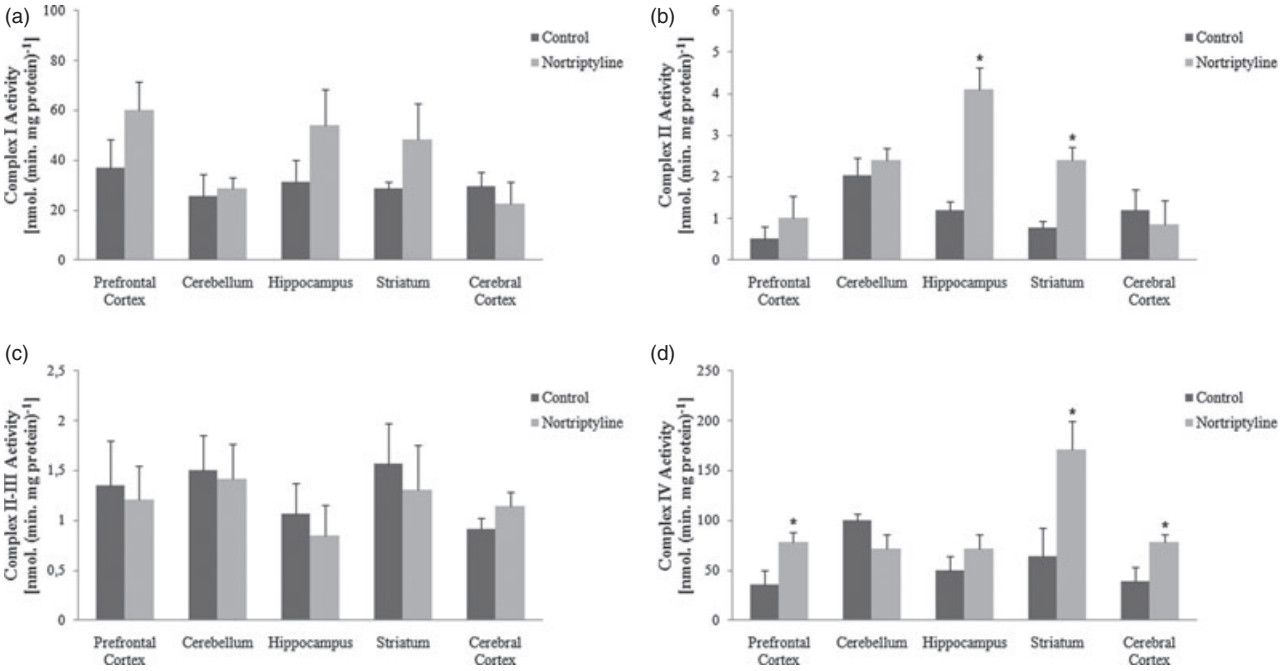

Fig. 1. Effects of nortriptyline chronic administration on mitochondrial respiratory chain complex I activity (a), complex II activity (b), complex II–III activity (c) and complex IV activity (d) in the prefrontal cortex, cerebellum, hippocampus, striatum and cerebral cortex of rats ($n = 6$). *$p < 0.01$ versus saline group, according to ANOVA followed by the Student's t-test.

described by Cassina and Radi (37) by the rate of NADH-dependent ferricyanide reduction at $\lambda =$ 420 nm. The activities of succinate-2,6-dichloroindophenol (DCIP)-oxidoreductase (complex II) and succinate:cytochrome *c* oxido-reductase (complex II–III) were determined by the method described by Fischer and colleagues (38). Complex II activity was measured by following the decrease in absorbance because of the reduction of 2,6-DCIP at $\lambda = 600$ nm. Complex II–III activity was measured by cytochrome *c* reduction from succinate at $\lambda = 550$ nm. The activity of cytochrome *c* oxidase (complex IV) was assayed according to the method described by Rustin and colleagues (39), measured by following the decrease in absorbance because of the oxidation of previously reduced cytochrome *c* at $\lambda = 550$ nm. The activities of the mitochondrial respiratory chain complexes were calculated as nanomole per minute milligram protein.

Statistical analysis

Data were analysed by Student's t-test when F was significant. All analyses were performed using the Statistical Package for the Social Science (SPSS) software.

Results

It was first investigated the respiratory chain complex activities in the presence of nortriptyline in homogenates from prefrontal cortex, hippocampus, striatum, cerebellum and cerebral cortex from rat brain. Figure 1 shows that rats administered with this antidepressant presented an increase in complex II activity in hippocampus and striatum, whereas prefrontal cortex, cerebellum and cerebral cortex were not affected (Fig. 1b). Furthermore, complex IV activity was increased in prefrontal cortex, striatum and cerebral cortex, without affecting cerebellum and hippocampus (Fig. 1d). On the other hand, chronic administration of nortriptyline did not affect complex I and II–III activities in the tested cerebral structures (Fig. 1a and c, respectively).

The next set of experiments was performed in order to evaluate the effect of paroxetine on the respiratory chain complex activities. Figure 2 shows that chronic administration of paroxetine increased complex I activity in prefrontal cortex, hippocampus, striatum and cerebral cortex, while cerebellum was not affected (Fig. 2a). In addition, complex II activity was increased by this antidepressant in hippocampus, striatum and cerebral cortex (Fig. 2b) and complex IV activity was increased in prefrontal cortex (Fig. 2d), with no effect on other brain structures. In contrast, complex II–III activity was not altered by paroxetine administration in either tested structure (Fig. 2c).

Finally, we tested the influence of chronic administration of venlafaxine on the respiratory chain complexes activities. It can be seen in Fig. 3 that complex

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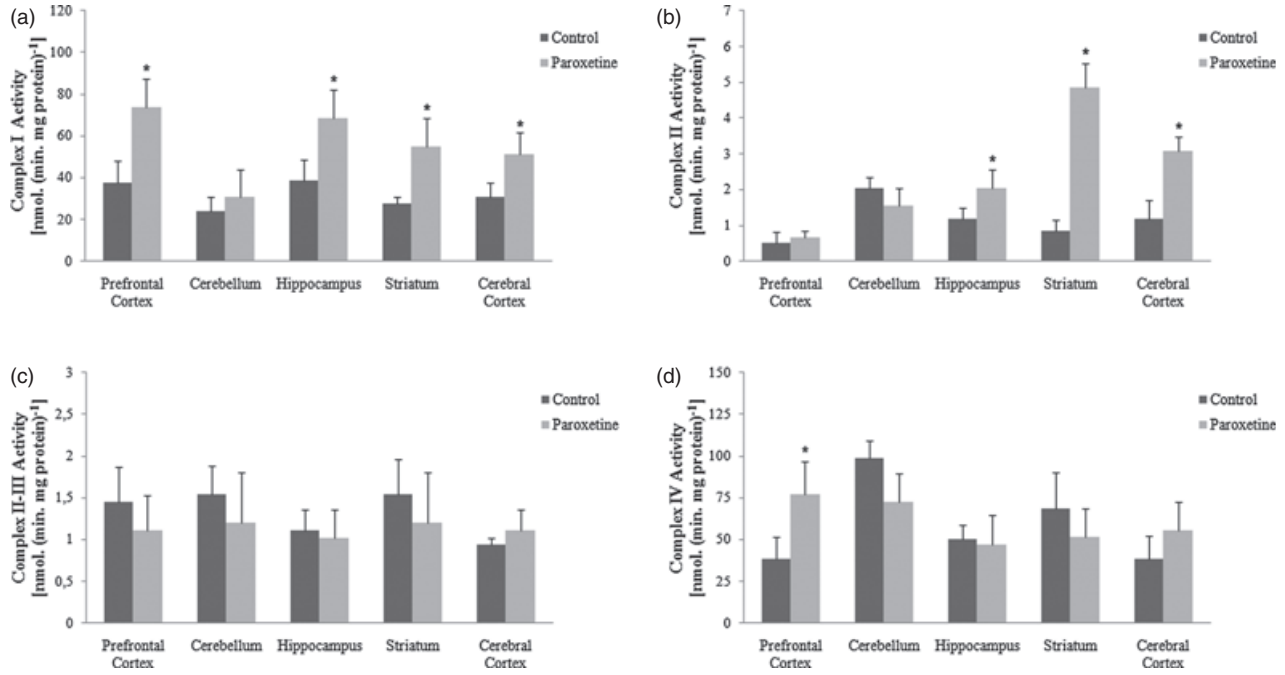

Fig. 2. Effects of paroxetine chronic administration on mitochondrial respiratory chain complex I activity (a), complex II activity (b), complex II–III activity (c) and complex IV activity (d) in the prefrontal cortex, cerebellum, hippocampus, striatum and cerebral cortex of rats ($n = 6$). *$p < 0.01$ versus saline group, according to ANOVA followed by the Student's t-test.

II activity was increased in hippocampus, striatum and cerebral cortex of rats administered with venlafaxine (Fig. 3b), while complex IV activity was increased only in prefrontal cortex (Fig. 3d). On the other hand, respiratory chain complex I and II–III activities were not altered by paroxetine administration in either tested structures (Fig. 3a and c, respectively).

Discussion

Mitochondrial oxidative phosphorylation is the major ATP-producing pathway, which supplies up to 95% of the total energy requirement in the cells (40). In most organisms, the mitochondrial respiratory chain is composed of four enzyme complexes, where electron transport drives translocation of protons from the mitochondrial matrix to the intermembrane space. The dissipation of this proton gradient generated through ATP synthase catalyses the formation of ATP by the phosphorylation of ADP (adenosine diphosphate) (41).

Damage to the mitochondrial electron transport chain has been suggested to play an important factor in the pathogenesis of some psychiatric disorders (42,43), including major depression. Indeed, Gardner and colleagues (44) showed a significant decrease of mitochondrial ATP production rates and mitochondrial enzyme ratios in the muscle of major depressive disorder patients. Considering that life stressors may contribute to the development of depression, chronic stress has been used as an animal model of depression. In this scenario, it has been reported that brain Na^+, K^+-ATPase and respiratory chain complexes I, III and IV activities are inhibited after chronic variate stress in rats (45,46) and that complexes I–III and II–III of mitochondrial respiratory chain are inhibited in the rat brain after chronic stress (43). Assis and colleagues (47) also reported that acute administration of ketamine and imipramine increased creatine kinase activity in the brain of rats.

In the present study, we observed that chronic administration of nortriptyline, paroxetine and venlafaxine increased respiratory chain complexes activities in the prefrontal cortex, hippocampus, striatum and cerebral cortex of rats. Our data are in agreement with previous works showing that chronic administration of paroxetine modulate brain energy metabolism in rats, by increasing creatine kinase activity in prefrontal cortex, hippocampus and striatum, and increasing citrate synthase and succinate dehydrogenase activities in prefrontal cortex, hippocampus, striatum and cerebral cortex of rats (48,49).

Several studies showed that paroxetine, venlafaxine and nortriptyline produced anti-immobility effects in the forced swimming test, suggesting an antidepressant-like action in mice and rats (32,35,50,51). Interestingly, some evidence point out to the possibility that other drugs used for the

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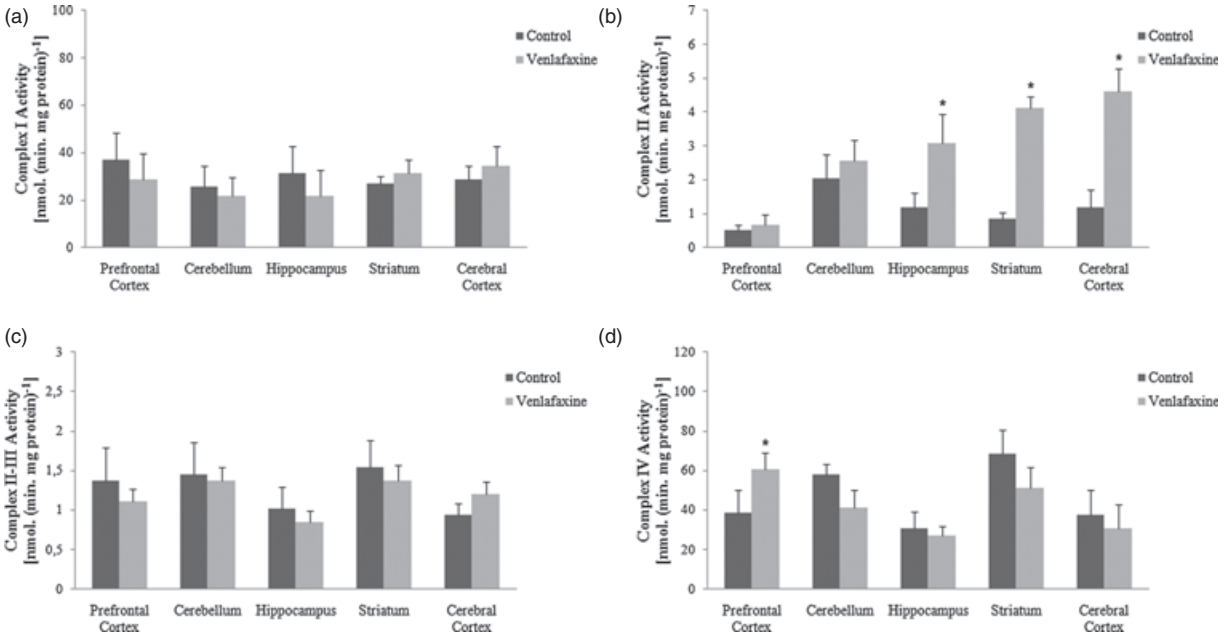

Fig. 3. Effects of venlafaxine chronic administration on mitochondrial respiratory chain complex I activity (a), complex II activity (b), complex II–III activity (c) and complex IV activity (d) in the prefrontal cortex, cerebellum, hippocampus, striatum and cerebral cortex of rats ($n = 6$). *$p < 0.01$ versus saline group, according to ANOVA followed by the Student's t-test.

treatment of mental disorders also modulate energy metabolism, including fluoxetine (45). Furthermore, electroconvulsive shock, which is also used as therapy for depression, was shown to elicit energetic disturbance in rats, by decreasing Na^+, K^+-ATPase and creatine kinase activities (52,53).

Paroxetine enhances serotonergic transmission by blocking the presynaptic active membrane transport mechanism for the reuptake of serotonin (15,16), nortriptyline blocks norepinephrine and serotonin uptake, and venlafaxine is an inhibitor of both serotonin and norepinephrine transport (16,17). Taking together the present findings and other reports showing that fluoxetine (which also acts on the serotonergic synapse) modulate brain metabolism, we speculate whether alterations in serotonergic synapse caused by these drugs are related to the biochemical effects, especially the increase in several parameters of energy metabolism in the brain.

Most antidepressants need chronic administration before they achieve clinical effects; the mechanisms involved in this delay are not known, but their therapeutic efficacy is probably mediated by long-term molecular adaptations. In this context, several studies showed that some antidepressants, such as venlafaxine, alter the gene expression profile of human cells. For example, it has been reported that venlafaxine altered the expression of genes implicated in ionic homeostasis and genes associated with cell survival, neural plasticity, signal transduction and metabolism (54). On the other hand, nortriptyline modulated the expression of cytoskeleton proteins and carbohydrate metabolism, as well as proteins involved in rats and synaptic transmission and neurite morphogenesis pathways (55). Paroxetine also increased expression or modification of several proteins, including sepiapterin reductase, which controls the production of tetrahydrobiopterin, an essential cofactor for the synthesis of many neurotransmitters (56).

In conclusion, we demonstrated that mitochondrial respiratory chain enzymes are activated in brain of adult rats after chronic administration of paroxetine, nortriptyline and venlafaxine. Considering that energy impairment may be involved in the pathophysiology of depressive disorders, we speculate that an increase in brain energy metabolism by antidepressant drugs could play a role in the mechanism of action of these drugs. These data corroborate with other studies suggesting that some antidepressants modulate brain energy metabolism.

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