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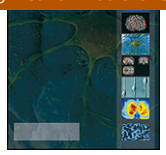

Olanzapine plus fluoxetine treatment increases Nt-3 protein levels in the rat prefrontal cortex

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ABSTRACT

Evidence is emerging for a role for neurotrophins in the treatment of mood disorders. In this study, we evaluated the effects of chronic administration of fluoxetine, olanzapine and the combination of fluoxetine/olanzapine on the brain-derived-neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) in the rat brain. Wistar rats received daily injections of olanzapine (3 or 6 mg/kg) and/or fluoxetine (12.5 or 25 mg/kg) for 28 days, and we evaluated for BDNF, NGF and NT-3 protein levels in the prefrontal cortex, hippocampus and amygdala. Our results showed that treatment with fluoxetine and olanzapine alone or in combination did not alter BDNF in the prefrontal cortex ($p = 0.37$), hippocampus ($p = 0.98$) and amygdala ($p = 0.57$) or NGF protein levels in the prefrontal cortex ($p = 0.72$), hippocampus ($p = 0.23$) and amygdala ($p = 0.64$), but NT-3 protein levels were increased by olanzapine 6 mg/kg/fluoxetine 25 mg/kg combination in the prefrontal cortex ($p = 0.03$), in the hippocampus ($p = 0.83$) and amygdala ($p = 0.88$) NT-3 protein levels did not alter. Finally, these findings further support the hypothesis that NT-3 could be involved in the effect of treatment with antipsychotic and antidepressant combination in mood disorders.

Bipolar disorder (BD) is a prevalent condition in adults determining a significant impairment in quality of life [27]. Bipolar depression represents a difficult-to-treat and disabling form of depression. Studies indicate that patients with BD spend more time in and take longer to recover from the depressive phase than the manic phase [33,47].

Olanzapine (OLZ) has demonstrated efficacy in the treatment of acute bipolar mania [59,61–63,65] stabilizing effects [11,60,62,65,66] and has been found to improve depressive symptoms in patients with schizophrenia [58,64]. In a controlled study of Shelton et al. [53] subjects with treatment-resistant depression received OLZ alone, fluoxetine (FLX) alone, or a combination of both. The combination was associated with significantly greater and faster improvement than was either drug alone. In a critical review, Fountoulakis et al. [26] show that several practice guidelines disagree on how best to initiate treatment of bipolar depression.

Neurotrophic factors, as such, brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) are critical regulators of the formation, survival, differentiation, and outgrowth of select peripheral and central neurons throughout adulthood [32,51] and plasticity of neural networks [28,32,51].

Since how the combination of OLZ and FLX modulates stabilizing effects centrally is little known, the present study was aimed to investigate physiological effects of the combination of OLZ and FLX on the BDNF, NT-3 and NGF protein levels in the prefrontal cortex, hippocampus and amygdala.

Male adult Wistar rats (60 days old) were obtained from UNESC (Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil) breeding colony. They were housed five per cage with food and water available ad libitum and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.). All experimental procedures involving animals were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care and with approval by local Ethics Committee under protocol number 510/2006.

Olanzapine (Zyprexa™) and Fluoxetine (Prozac™) were provided from Eli Lilly do Brasil Ltda, São Paulo, Brazil. Animals received daily intraperitoneal injections of OLZ (3 or 6 mg/kg), FLX (12.5 or 25 mg/kg) ($n = 10$) or combination of both drugs for 28 days. All the drugs were dissolved in Tween 1% solution (vehicle). Control animals received vehicle (1.0 ml/kg). After the chronic treatment

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the animals were killed by decapitation 24 h after the last injection and prefrontal cortex, hippocampus and amygdala were immediately removed and stored at −70 °C for biochemical analysis.

BDNF, NT-3 and NGF levels in prefrontal cortex, hippocampus and amygdala were measured by sandwich-ELISA, according to the manufacturer instructions (Chemicon, USA for BDNF and Millipore, USA & Canada for NT-3 and NGF). Briefly, rat prefrontal cortex, hippocampus and amygdala were homogenized in phosphate buffer solution (PBS) with protease inhibitor cocktail (Sigma). Microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluent and standard curve ranged from 7.8 to 500 pg/ml of BNDF, NT-3 or NGF. The plates were then washed four times with sample diluent and a monoclonal anti-BNDF, anti-NT-3 or anti-NGF rabbit antibody (diluted 1:1000 in sample diluent) was added to each well and incubated for 3 h at room temperature. After washing, a peroxidase conjugated anti-rabbit antibody (diluted 1:1000) was added to each well and incubated at room temperature for 1 h. After addition of streptavidin-enzyme, substrate and stop solution, the amount of each neurotrophin was determined by absorbance in 450 nm. The standard curve demonstrates a direct relationship between Optical Density (OD) and the concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard, as previously described by Lowry et al. [39].

All data are presented as mean ± S.E.M. Differences among experimental groups in the assessment of BDNF, NGF and NT-3 protein levels were determined by one-way ANOVA, followed by Tukey *post hoc* test when ANOVA was significant; $p < 0.05$ were considered to be statistical significant.

As depicted in Fig. 1A, the NT-3 protein levels did not alter in the hippocampus (Fig. 1A; $F_{(8-42)} = 0.51$; $p = 0.83$) and amygdala (Fig. 1A; $F_{(8-43)} = 0.45$; $p = 0.88$) after treatment with olanzapine or fluoxetine alone or in combination. However treatment with olanzapine at the dose of 6 mg/kg in combination with fluoxetine at the dose of 25 mg/kg we found an increase in NT-3 protein levels in the prefrontal cortex (Fig. 1A; $F_{(8-37)} = 2.4$; $p = 0.03$); but olanzapine or fluoxetine treatment alone did alter NT-3 protein levels in the prefrontal cortex.

The BDNF and NGF protein levels are illustrated in Fig. 1B and 1C, respectively. After treatment with olanzapine or fluoxetine alone or in combination, both BDNF and NGF protein levels did not alter in the prefrontal cortex (Fig. 1B; $F_{(8-46)} = 1.11$; $p = 0.37$; Fig. 1C; $F_{(8-24)} = 0.65$; $p = 0.72$), hippocampus (Fig. 1B; $F_{(8-51)} = 0.98$; $p = 0.45$; Fig. 1C; $F_{(8-18)} = 1.48$; $p = 0.23$) and amygdala (Fig. 1B; $F_{(8-47)} = 0.57$; $p = 0.79$; Fig. 1C; $F_{(8-18)} = 0.74$; $p = 0.64$).

In the present study we evaluated the effects of the antipsychotic OLZ and of the antidepressant FLX (alone or in combination) on the NT-3, BDNF and NGF protein levels in the rat brain. We showed that chronic treatment with FLX and OLZ in combination increased the NT-3 protein levels in the prefrontal cortex. Treatment with FLX and OLZ alone or in combination did not alter BDNF or NGF protein levels in the rat brain.

The hippocampus regulates hypothalamic–pituitary–adrenal (HPA) axis, and has connections with amygdala and prefrontal cortex. In addition, brain imaging studies have indicated volumes altered of the hippocampus, prefrontal cortex or amygdala in patients with major depression or bipolar disorder [14,20].

Several studies have highlighted the role of neurotrophins in the pathophysiology and treatment of psychiatric disorders [24]. The BDNF, NT-3 and NGF promote survival and cellular plasticity [4,38]. Reductions of BDNF have been found in serum humans with major depression, as well as in animal models [22,34], on the other hand, infusion of BDNF into dentate gyrus in rat hippocampus produces antidepressant effect [55]. Moreover, patients with schizophrenia and bipolar disorder showed reduced serum BDNF levels in relation to healthy volunteers [17,49,50], and it is known that antipsychotic, as well as mood stabilizers treatment are seems to alter levels of BDNF in rat hippocampus, in plasma and serum of patients with psychiatric disorders [9,29,49,50].In the present findings we showed that treatment with FLX and OLZ alone or in combination did not alter BDNF protein levels in the prefrontal cortex, hippocampus or amygdala. Our investigation did not confirm previous studies showed by other authors, who reported alteration in BDNF after treatment with FLX or OLZ. Lee et al. [35] showed that OLZ treatment (10–100 μM) increased basal BDNF gene promoter activity in a dose dependent manner and increased protein levels at high dose. In addition, OLZ increased BDNF levels in the cortex and hippocampus [18] and frontal cortex [10]. Also, FLX administration increased BDNF mRNA levels in the nucleus accumbens and hippocampus [42,43]. We cannot explain the reason for this different result, but similar discrepancies have been observed by the other author. In fact, plasma BDNF levels did not alter after 8 weeks of treatment with OLZ [31,67]. FLX also did not alter BDNF mRNA isoforms in the rat hippocampus [5,19]. FLX (10 mg/kg) increased BDNF protein levels in the frontal cortex, but not in the hippocampus, amygdala, olfactory, and brain stem [10]. Other study showed still that FLX treatment decrease BDNF mRNA expression in the rat hippocampus [41]. In other studies, OLZ decreased BDNF in the hippocampus and frontal cortex [7], and did not alleviate the decreases in RNA expression of BDNF and NGF produced by neonatal quinpirole treatment [15]. Furthermore, both BDNF and NGF seem to be activity-dependent [36]. In the present data, we did not see alterations in BDNF or NGF protein levels in the rat brain, suggesting that the effects by FLX and OLZ on the BDNF and NGF levels were not modulated by these neurotrophins, because they are activity-dependent.

NGF is very important to neuronal survival, neurite outgrowth and synapse formation [4] and has been shown an association between NGF and mood disorders or psychiatric diseases. In fact, NGF was found to be decreased in plasma in BD patients when compared to that seen with controls and BD individuals in mania had lower NGF levels than euthymic patients or controls [12]. NGF also has been found decreased in plasma, liquor or postmortem brains of schizophrenic patients [3,13,23]. On the other hand, the antipsychotics, haloperidol, chlorpromazine, risperidone and OLZ reduced BDNF and NGF protein levels in the striatum and hippocampus [48], in this study the authors showed that second-generation antipsychotics compared to first-generation antipsychotics are less deleterious on neurotrophic factors in the brain. In contrast, Parikn et al. [46], demonstrated that OLZ, but not the antipsychotic risperidone increased levels of NGF in the hippocampus. Additionally, administration of OLZ for 29 days at the doses of 3 and 15 mg/kg increased BDNF in the hippocampus and occipital cortex [7]. Discrepancies between studies may be related to route of drug administration.Little is known about antidepressants and NGF. In the present we did not show an alteration on NGF protein levels after treatment with FLX alone or in combination with OLZ. The antidepressants, amitriptyline and paroxetine also did not alter NGF serum concentrations from depressed patients [30]. However, it was recently demonstrated that intranasal NGF had significant antidepressant effects on animal models of depression [54]. On the other hand, NGF was reduced in brain regions of the Flinders Sensitive Line rat, a genetic animal model of depression [6]. In addition, an escitalopram-dependent NGF reduction in stressed rats was detectable in the cortex, but not in the frontal cortex, cerebellum and serum [52]. Moreover, the antidepressant fluvoxamine potentiated the NGF-induced neurite outgrowth [44] and desipramine or fluoxetine for 48 h elevated the NGF mRNA expression [37] in PC12 cells.

NT-3 is a neurotrophin that plays key roles in neuronal survival, differentiation, connectivity and plasticity [32,51]. Moreover, human studies have demonstrated participation of NT-3 in the pathophysiology of stress, major depression and BD [25,34,56].

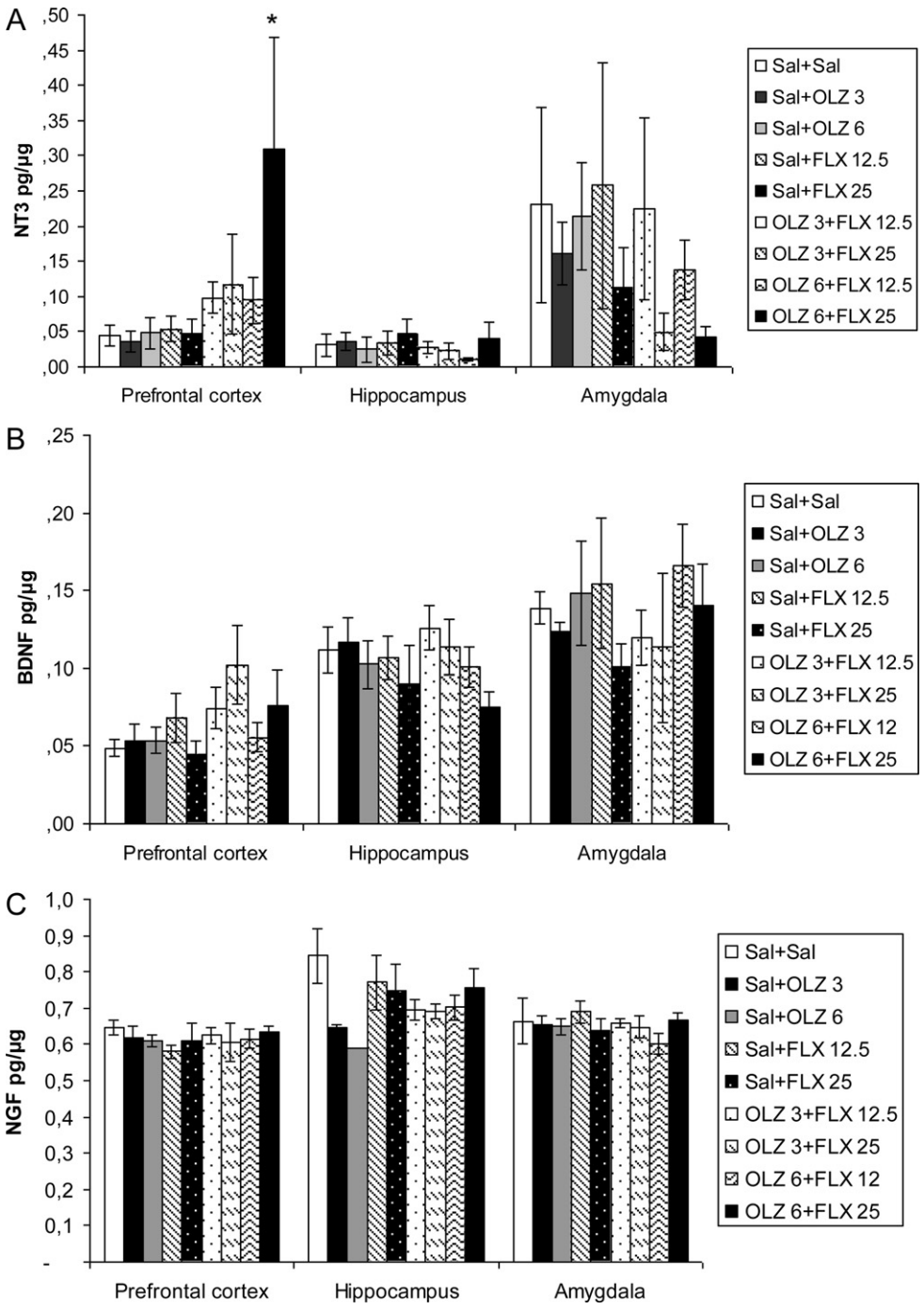

Fig. 1. Effects of the chronic administration of OLZ and FLX on the NT-3 (A), BDNF (B) and NGF (C) protein levels in the rat prefrontal cortex, hippocampus and amygdala ($n = 10$). Bars represent means ± S.E.M. $^*p < 0.05$ *vs.* saline according to ANOVA followed by Tukey *post hoc* test.

Interestingly, the present data shows that the combined administration of FLX and OLZ increased NT-3 protein levels in the prefrontal cortex. Lesions of the prefrontal cortex are associated with development of depression or aggression [8].

Serum NT-3 levels in drug-free and medicated patients with BD during manic and depressive episodes were increased when compared with controls [25]. A study conducted by Otsuki et al. [45] showed reduced expression levels of NT-3 mRNAs, but not in BDNF, NGF and neurotrophin-4 mRNAs in peripheral white blood cells in patients with major depressive disorder in a current depressive state, but not in a remissive state, suggesting that the changes in the NT-3 mRNAs might be state-dependent and associated with the pathophysiology of major depression. Our findings showed that FLX plus OLZ increased NT-3 protein levels, but not BDNF and NGF, suggesting that treatment with these drugs may be important to current depressive state. The gene expression for NT-3 was not affected by single or repeated administration of antidepressants drugs, including FLX [16]. Our study also showed that FLX alone did not alter NT-3 protein levels, but in combination with OLZ increased NT-3 protein levels. In fact, the combination of OLZ and FLX produces significantly greater and faster improvement than either drug alone in subjects with treatment-resistant depression [40]. Importantly, FLX is a potent hepatic enzyme inhibitor, but there was not found differences in hepatic enzymes in patients

with bipolar depressive episode treated with OLZ/FLX in combination [58], thus pharmacokinetic interaction may be involved in psychopharmacological effects.

Some studies have shown an association between neurotrophins and glucocorticoids [57]. It was shown an increase of NGF and NT-3 mRNA in the hippocampus by glucocorticoids, probably as a compensatory response to stress-induced damage [56]. Additionally a study showed that glucocorticoids exert biphasic effects on neuronal mitochondrial dynamics, with low levels potentiating and chronic high levels attenuating various aspects of mitochondrial function [21]. Studies from our group recently demonstrated that FLX and OLZ alone or in combination altered the creatine kinase and citrate synthase activities [1,2], which are involved with energy metabolism.

In conclusion, the present findings suggest that NT-3 may be involved in the therapeutic action of olanzapine/fluoxetine combination in mood disorders. Finally, future studies evaluating the combination of behavioral, neurochemical and dosing the plasmatic levels of FLX and OLZ, would be necessary and opportune to expand the present result.

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