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Tactile Stimulation on Adulthood Modifies the HPA Axis, Neurotrophic Factors, and GFAP Signaling Reverting Depression-Like Behavior in Female Rats

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Abstract

Depression is a common psychiatric disease which pharmacological treatment relieves symptoms, but still far from ideal. Tactile stimulation (TS) has shown beneficial influences in neuropsychiatric disorders, but the mechanism of action is not clear. Here, we evaluated the TS influence when applied on adult female rats previously exposed to a reserpine-induced depression-like animal model. Immediately after reserpine model (1 mg/kg/mL, 1×/day, for 3 days), female *Wistar* rats were submitted to TS (15 min, 3×/day, for 8 days) or not (unhandled). Imipramine (10 mg/kg/mL) was used as positive control. After behavioral assessments, animals were euthanized to collect plasma and prefrontal cortex (PFC). Behavioral observations in the forced swimming test, splash test, and sucrose preference confirmed the reserpine-induced depression-like behavior, which was reversed by TS. Our findings showed that reserpine increased plasma levels of adrenocorticotropic hormone and corticosterone, decreased brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B, and increased proBDNF immunoreactivity in the PFC, which were also reversed by TS. Moreover, TS reestablished glial fibrillary acidic protein and glucocorticoid receptor levels, decreased by reserpine in PFC, while glial cell line–derived neurotrophic factor was increased by TS per se. Our outcomes are showing that TS applied in adulthood exerts a beneficial influence in depression-like behaviors, modulating the HPA axis and regulating neurotrophic factors more effectively than imipramine. Based on this, our proposal is that TS, in the long term, could be considered a new therapeutic strategy for neuropsychiatric disorders improvement in adult life, which may represent an interesting contribution to conventional pharmacological treatment.

Keywords Reserpine · Handling · BDNF · Hypothalamus-pituitary-adrenal axis

Introduction

Depression is the most common and serious mental disorder, characterized by depressed mood, persistent sadness, loss of interest, and cognitive impairments [1, 2]. According to World Health Organization, it is estimated that 300 million people are affected, and women are more likely to experience depression than men, considering that one-third of women will experience a major depressive episode in their lifetime [2]. The pathophysiology of depression had been involved with impairments in the monoaminergic system, and the pharmacological treatment is mainly based on drugs that can increase the brain levels of monoamines, as occurs with imipramine, a tricyclic antidepressant, whose mechanism of action consists in inhibit the brain neuronal transporter of both noradrenaline and serotonin [3]. However, these pharmacotherapies have been related to slow onset or low response rates which limit their application [4–6]. Based on this, recent hypotheses have proposed that interactions among monoaminergic systems, neurotrophins [7, 8], and glucocorticoid (GC) signaling dysregulation can lead towards symptoms of depression [9].

While the monoaminergic system, especially serotonin, is closely related to neurotrophic factors [10, 11], brain-derived neurotrophic factor (BDNF) is the main and most abundant

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neurotrophin in the brain and is critically involved in the maintenance of the neurogenesis, neuronal survival, and plasticity. Inadequate regulation of BDNF may be related to depression-like behaviors [12] since BDNF can regulate serotonin signaling and reuptake, because its receptor, TrkB, is also present on serotonergic neurons [13]. As a precursor of BDNF form, proBDNF is known to play opposing influences, since it acts on the neuronal death regulation via its receptor $p75^{NTR}$. In this sense, an upregulation on this factor has been related to the mood disorders development in rodents [14]. On the other hand, glial cell line–derived neurotrophic factor (GDNF) promotes differentiation and protection to dopaminergic and serotonergic neurons [15, 16], facilitating the neurites growth to different neuronal types [17, 18]. Decreased brain and plasma levels of GDNF in patients and rodents have been related to mood disorders [19, 20], and also the glial fibrillary acidic protein (GFAP) levels were found to be reduced in the brain of rodents submitted to depression models [21, 22]. Moreover, it was recently described that decreasing levels of GFAP could cause an astrocyte hypotrophy and the astrocytes are known as nutrient suppliers to neurons and are involved in the synaptic development and signalization processes [23].

Depression has also been related to a dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis. GC is synthesized and secreted by adrenal glands in response to HPA axis. Following the HPA axis activation, the corticotrophin-release-hormone (CRH) is activated in the hypothalamus, increasing the adrenocorticotrophic hormone (ACTH) release, which results in the adrenal glands secreting GC, such as corticosterone in rodents [24]. The glucocorticoid receptor (GR) plays a key role in negative feedback to the HPA axis, and alterations in this receptor in cortico-limbic areas, such as prefrontal cortex (PFC), amygdala, and hippocampus, may be related to depressive disorders due to altering the GC secretion [25, 26]. Furthermore, GR is closely involved in the biosynthesis regulation of both serotonin [27] and noradrenaline [28], since it is present on noradrenergic and serotonergic neurons [29]. Additionally, increased secretion of GC negatively regulates the BDNF pathways, impairing the brain synaptic plasticity by spine density and neurogenesis downregulation [30], which may be a possible mechanism to explain the GC involvement on depression.

Growing evidence from experimental studies has suggested that non-pharmacological treatments, including physical exercise and environmental enrichment, can exert neuroprotective effects and improve depression-like symptoms by changing the BDNF and the glucocorticoid signaling [31, 32]. In line with this, tactile stimulation (TS) constitutes a simple procedure that can modify the brain organization by increasing neurogenesis [33] and neuroplasticity [34] in the hippocampus, improving anxiety-like behaviors [35], and preventing preference to addictive drugs [36, 37] and depression-like behaviors [38] when applied during initial periods of development. Experimental studies also showed TS beneficial influence on the brain function, when applied in adult rats, preventing cortical lesion [39], and increasing neurotrophins and dendritic length [40].

In view of this, we evaluate the possible beneficial influence of TS on depression-like behaviors induced by reserpine, a promoter of monoaminergic dysfunction that acts by blocking irreversibly the vesicular monoamine transporter type 2, thus mimicking depression-like behaviors [41], thus assessing behavioral and HPA axis changes, and its reflexes on the molecular neurotrophic factors in the PFC.

Material and Methods

Animals and Experimental Procedures

Thirty-five female *Wistar* rats (60 days old) from the breeding facility of Universidade Federal de Santa Maria (UFSM), RS, Brazil, were kept in Plexiglas cages with free access to water and food in a room with controlled temperature (22 ± 1 °C) and on a 12-h light/dark cycle with lights on at 7:00 a.m. All procedures were performed in accordance with the Animal Ethics Committee (#2359150517) guidelines, affiliated to the National Council for the Control of Animal Experimentations (CONCEA), following international norms of care and animal maintenance.

Considering that female rats show increased susceptibility to different neuropsychiatric disorders, such as depression [6], we preferred to use female rats in the current study. First, female rats were randomly distributed in two experimental groups: vehicle ($n = 14$) and reserpine ($n = 21$). The animals received vehicle or reserpine (1 mg/kg/mL), subcutaneously (s.c.) once a day, for 3 consecutive days [42]. Immediately after the last vehicle/reserpine administration, animals were subdivided into five experimental groups ($n = 7$), to start the TS procedure (for 8 days) or not (unhandled; UH) as follows: group (I) vehicle-UH; group (II) vehicle-TS; group (III) reserpine-UH; group (IV) reserpine-TS; and group (V) reserpine-UH-imipramine (positive control). Following 8 days of TS, all the animals were submitted to behavioral evaluations; 30 min before of each test, the positive control group received one administration of imipramine, while all other experimental groups received NaCl 0.9% (imipramine vehicle) instead (Fig. 1).

Drugs and Drug Administration

Reserpine was obtained from Sigma (St. Louis, MO, USA). Reserpine was dissolved in glacial acetic acid (vehicle) and diluted to a final concentration of 0.5% acetic acid with distilled water. On postnatal day 60 (PND 60), the animals received a dose of 1 mg/kg/mL s.c. of reserpine or acetic acid

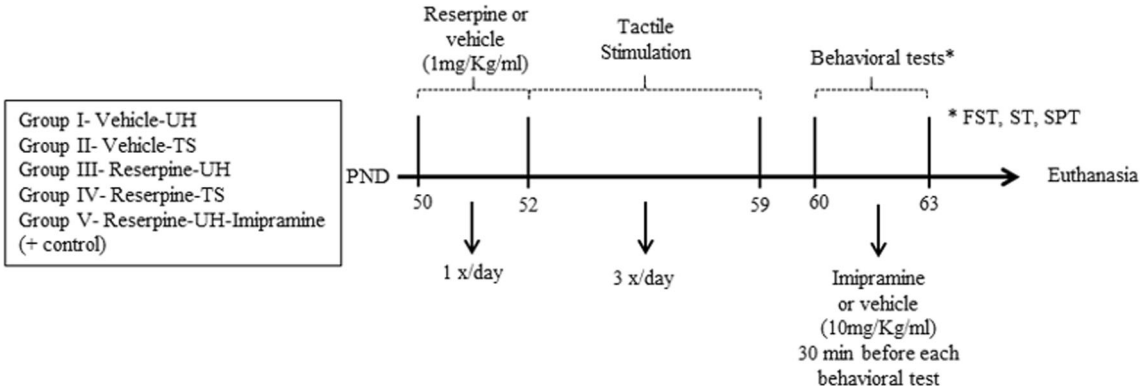

Fig. 1 Schematic representation of the experimental procedure for reserpine-induced depression and tactile stimulation treatment in female rats. Rats received reserpine (1 mg/kg/mL) or vehicle for 3 days, and then, tactile stimulation was performed for 8 days. Imipramine was used as positive control and only was administered 30 min before each behavioral test to the group reserpine-UH-imipramine. The remaining groups received NaCl 0.9% (imipramine vehicle) before behavioral testing. UH, unhandled; TS, tactile stimulation; PND, postnatal day; FST, forced swimming test; ST, splash test; SPT, sucrose preference test

0.5% once a day, for 3 consecutive days. This protocol of reserpine administration was used as the animal model to induce the depression-like symptoms [42]. Administrations were performed between 09:00 and 12:00 a.m. Imipramine (10 mg/kg/mL i.p.) was obtained from a local drug store and administered 30 min before performing each behavioral test. Imipramine vehicle (NaCl 0.9%) was administered to the other groups.

Tactile Stimulation

Immediately after the last administration of reserpine, TS was initiated. The procedure was based on Effenberg et al., with some modifications and consisted of removing the animals from home cage and petting them individually on the experimenter's lap with one hand for 15 min. The TS was applied 3 times per day between 09:00 a.m. and 04:00 p.m., for 8 days. After the procedures, the animals were returned to their home cages [40].

Behavioral Testing

Forced Swimming Test

Behavioral responses related to depression-like symptoms are experimentally assessed in the forced swimming test (FST) [43, 44]. On the first session, rats were forced to swim for a 15-min period (pretest session), and dried before returning to their home cages. Twenty-four hours following the pretest session, the animals were submitted again to the FST for 5 min (test session). Trained raters blinded to the experiment quantified immobility, climbing, and swimming time. The immobility was considered as no additional activity other than the required to keep the head above water. Climbing is defined as upward struggling movements of the forepaws at the side of the cylinder while movements around the cylinder are indicative of swimming time [43]. A decrease in the duration of immobility is indicative of an antidepressant-like effect.

Splash Test

The splash test consists of squirting a 10% sucrose solution on the rat's dorsal coat in its home cage. The sucrose solution dirties the coat and animals initiate grooming behavior. After the sucrose solution application, the time spent grooming (nose/face grooming, head washing, and body grooming) was recorded for 5 min as an index of self-care and motivational behavior [45, 46].

Sucrose Preference Test

In this test, the animals were allowed to consume 10% (*w*/*v*) sucrose/water solution or tap water in their home cage, individually. They were deprived of food and water for 12 h and then presented with two bottles containing either tap water or sweet solution. One-hour intake was measured by weighing bottles before and after the test [47]. The sucrose preference test (SPT) was calculated according to the following equation:

$$\mathrm{SPT} = \left(\frac{\text{Sucrose intake}}{\text{Sucrose intake} + \text{Water intake}}\right) \times 100$$

Tissue Preparations

Following 24 h of the last behavioral assessment, all animals were anesthetized (isoflurane, the dose to the effect) and euthanized by exsanguination. The blood (collected by cardiac puncture in heparinized tubes) was centrifuged at 3000*g*/15 min to obtain the plasma. Brains were removed and cut coronally at the caudal border of the olfactory tubercle to

remove the prefrontal cortex (PFC) [48] and stored in a freezer at − 80 °C for subsequent analysis.

Adrenocorticotropic Hormone and Corticosterone Assay

Quantification of adrenocorticotropic hormone (ACTH) and corticosterone levels were assessed in the plasma samples by ELISA using commercial kits (Sigma-Aldrich®, St. Louis, MO, USA, for ACTH and LDN® immunoassays and services, Nordhorn, Germany, for corticosterone), according to the manufacturer's instructions.

Molecular Assessments

Western Blotting

The PFC tissue was homogenized in a lysis buffer [49], and total protein concentration was determined according to Bicinchoninic Acid (BCA) Protein Assay Kit (Pierce, IL) using bovine serum albumin as standard. After, protein samples were separated by electrophoresis on a 10% or 12.5% polyacrylamide gel and electrotransferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, MA, USA). Non-specific binding sites were blocked and membranes were rinsed in buffer and incubated with primary antibodies: anti-β-actin (1:50000; Sigma-Aldrich, St. Louis, USA), anti-BDNF (1:1000; Abcam, Cambridge, UK), anti-proBDNF (1:500; Santa Cruz Biotechnology, CA, USA), anti-TrkB (1:500; Santa Cruz Biotechnology, CA, USA), anti-GDNF (1:1000; Santa Cruz Biotechnology, CA, USA), anti-GFAP (1:1000 Santa Cruz Biotechnology, CA, USA), and anti-GR (1:500; Santa Cruz Biotechnology, CA, USA), followed by anti-goat (1:10000; Santa Cruz Biotechnology, CA, USA) or anti-rabbit (1:20000; Santa Cruz Biotechnology, CA, USA) IgG horseradish peroxidase conjugate. Immunocomplexes were visualized using Luminata (Millipore, USA) according to the manufacturer's instructions. Film signals were digitally scanned (Chemidoc™ Imaging Systems) and then quantified using ImageJ software. β-actin was used as an internal control, so that data were standardized according to actin values.

Statistical Analysis

Levene's test was performed to verify the homogeneity of data. Two-way ANOVA (2 treatments (vehicle/reserpine) × 2 procedures (UH/TS)) followed by the Newman-Keuls post hoc test was used for all analysis, when appropriate. One-way ANOVA (1 treatment (reserpine) × 3 procedures (UH/TS/Imipramine)) followed by the Newman-Keuls post hoc test was used to compare the positive control and TS (only reserpine-treated groups). All data are expressed as means ± SEM. $p < 0.05$ was considered statistically significant for all comparisons made.

Results

Depression-Like Behavior Observed in the Forced Swimming Test

Two-way ANOVA revealed a significant influence of handling, reserpine administration, and an interaction of handling × reserpine on immobility ($F(1,24) = 223.93$, $p = 0.000$; $F(1,24) = 247.49$, $p = 0.000$; $F(1,24) = 19.93$, $p = 0.000$, respectively), swimming time ($F(1,24) = 18.59$, $p = 0.000$; $F(1,24) = 24.19$, $p = 0.000$; $F(1,24) = 12.83$, $p = 0.001$, respectively), and climbing time ($F(1,24) = 10.85$, $p = 0.000$; $F(1,24) = 18.50$, $p = 0.000$; $F(1,24) = 5.52$, $p = 0.000$, respectively).

The Newman-Keuls test showed that reserpine increased immobility and climbing time and reduced swimming time compared to vehicle-UH, while reserpine-TS animals showed reduced immobility and climbing time and increased swimming time when compared to the reserpine-UH group.

The post hoc test of one-way analysis showed that imipramine administration reduced immobility time when compared to reserpine-UH animals and increased immobility and climbing time when compared to reserpine-TS animals. Moreover, imipramine administration reduced the swimming time compared to reserpine-TS animals and increased this parameter when compared to reserpine-UH group (Fig. 2).

Anhedonia Behavior Was Observed in the Splash Test and Sucrose Consumption

In the splash test, two-way ANOVA revealed a significant influence of handling on latency time to grooming ($F(1,24) = 37.06$, $p = 0.000$, and grooming time $F(1,24) = 21.76$, $p = 0.000$). The post hoc of Newman-Keuls showed that TS per se reduced the latency to grooming when compared to the vehicle-UH group, while reserpine-UH animals increased latency to grooming when compared to the vehicle-UH and reserpine-TS groups. In grooming time, TS per se and reserpine-TS animals increased this behavior when compared to the vehicle-UH and reserpine-UH groups, respectively.

One-way analysis followed by the post hoc test showed imipramine administration reduced the latency to grooming, compared to reserpine-UH animals. Also, imipramine administration decreased the grooming time when compared to reserpine-TS group (Fig. 3a, b).

In the sucrose consumption, two-way ANOVA revealed a significant influence of handling, reserpine, and an interaction of handling × reserpine on sucrose consumption ($F(1,24) = 4.84$, $p = 0.003$; $F(1,24) = 4.15$, $p = 0.054$; and $F(1,24) = 7.41$,

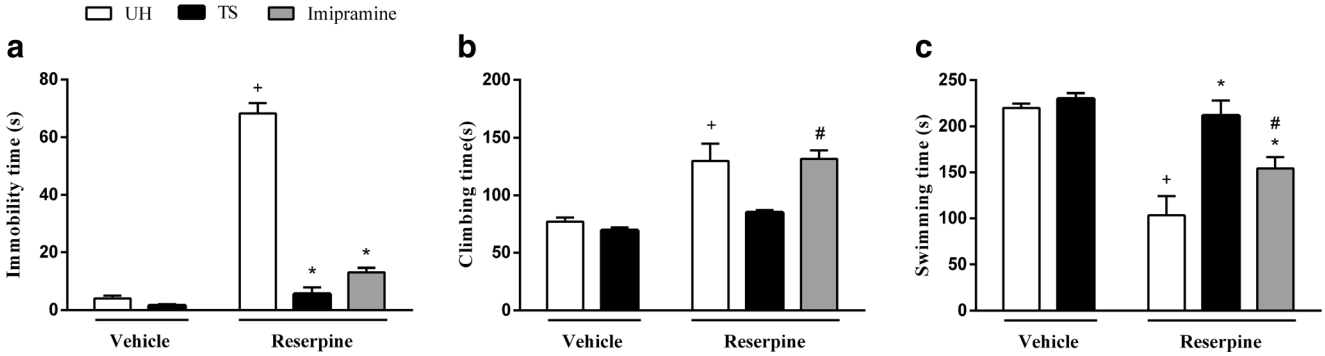

Fig. 2 Influence of reserpine and TS on immobility (**a**), climbing (**b**), and swimming time (**c**) measured in the forced swimming test (FST). Data are expressed as mean ± SEM ($n = 7$). Asterisk indicates significant difference from UH to TS or imipramine groups ($p < 0.05$). Plus sign indicates significant difference from vehicle to reserpine groups ($p < 0.05$). Number sign indicates significant difference from reserpine-TS to imipramine group ($p < 0.05$). UH, unhandled; TS, tactile stimulation

$p = 0.013$, respectively). The Newman-Keuls test showed that reserpine-UH animals reduced sucrose consumption compared to vehicle-UH and reserpine-TS group, while reserpine-TS reversed this parameter. The post hoc test of one-way analysis showed that imipramine administration increased sucrose consumption, compared to reserpine-UH animals, and had no difference in reserpine-TS animals (Fig. 3c).

Adrenal Weight, Body Weight, and Adrenal Weight/Body Weight Ratio

Two-way ANOVA revealed a significant main effect of handling in adrenal weight ($F(1,24) = 16.88$, $p = 0.000$) and adrenal weight/body weight ratio (AW/BW) ($F(1,24) = 17.96$, $p = 0.000$) while in the body weight was shown a significant main effect of handling × reserpine ($F(1,24) = 5.808$, $p = 0.025$).

The Newman-Keuls post hoc test showed that TS per se and reserpine-TS animals showed a decrease in adrenal weight and adrenal weight/body weight ratio when compared to vehicle-UH and reserpine-UH animals. The post hoc test of one-way analysis of imipramine administration showed higher adrenal weight/body weight ratio than reserpine-TS animals and had no difference when compared to reserpine-UH group (Table 1).

Adrenocorticotropic Hormone and Corticosterone Levels

Two-way ANOVA of ACTH revealed a significant main effect of handling ($F(1,24) = 52.84$, $p = 0.000$) and reserpine ($F(1,24) = 761.30$, $p = 0.000$). The Newman-Keuls post hoc test showed that reserpine-UH animals increased ACTH levels compared to vehicle-UH, while TS per se and reserpine-TS animals decreased these levels when compared to vehicle-UH and reserpine-UH animals, respectively. Also, reserpine-TS animals showed lower ACTH levels, compared to TS per se. The post hoc test of one-way analysis showed that imipramine administration decreased ACTH levels when compared to reserpine-UH and reserpine-TS animals (Fig. 4a).

Two-way ANOVA of corticosterone revealed a significant main effect of handling ($F(1,24) = 22.48$, $p = 0.000$) and reserpine ($F(1,24) = 531.32$, $p = 0.000$). The Newman-Keuls post hoc test showed that reserpine-UH animals increased

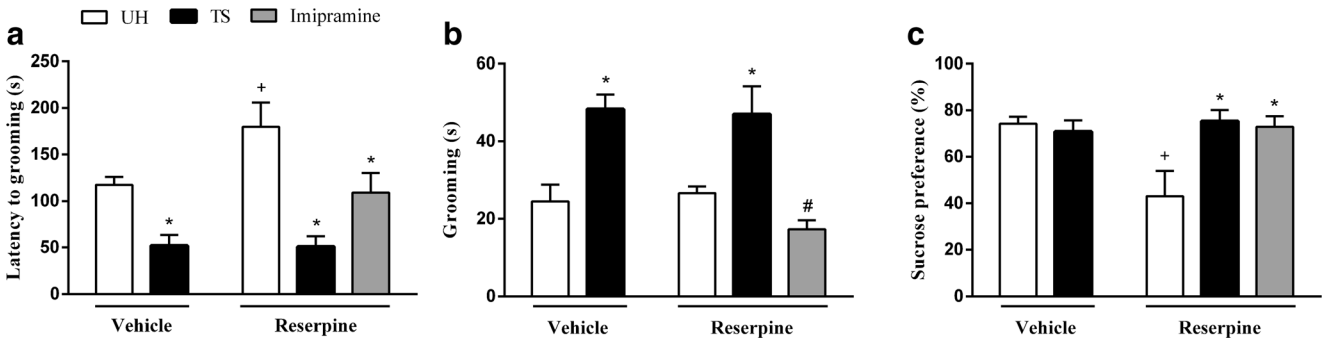

Fig. 3 Influence of reserpine and TS on anhedonia behavior. Latency to grooming (**a**) and grooming time (**b**) was measured in the splash test (ST), and sucrose preference percentage (**c**) was measured in the sucrose preference test (SPT). Data are expressed as mean ± SEM ($n = 7$). Asterisk indicates significant difference from UH to TS or imipramine groups ($p < 0.05$). Plus sign indicates significant difference from vehicle to reserpine groups ($p < 0.05$). Number sign indicates significant difference from reserpine-TS to imipramine group ($p < 0.05$). UH, unhandled; TS, tactile stimulation

Table 1 Effects of reserpine and TS on adrenal weight (AW), final body weight (BW), and adrenal weight/body weight ratio (AW/BW) in female rats

Treatment	Adrenal weight (g)	Body weight (g)	AW/BD (mg)
Vehicle-UH	0.1076 ± 0.005	237.66 ± 4.44	0.45 ± 0.020
Vehicle-TS	0.0908 ± 0.003*	262.16 ± 6.52	0.34 ± 0.012*
Reserpine-UH	0.1131 ± 0.001	251.83 ± 6.69	0.44 ± 0.007
Reserpine-TS	0.0959 ± 0.004*	242.16 ± 9.70	0.39 ± 0.020*
Imipramine	0.1050 ± 0.006	227.40 ± 8.28	0.46 ± 0.020*

UH, unhandled; *TS*, tactile stimulation; data are expressed as mean ± SEM; *indicates significant difference from UH to TS or imipramine groups ($p < 0.05$)

corticosterone levels when compared to vehicle-UH, while TS per se and reserpine-TS animals decreased these levels. Also, reserpine-TS animals had lower corticosterone levels when compared to TS per se. The post hoc test of one-way analysis showed that imipramine administration decreased corticosterone levels, compared to the reserpine-UH group, and had no difference when compared to reserpine-TS animals (Fig. 4b).

Molecular Parameters Analysis in Western Blotting

Two-way ANOVA of BDNF revealed a significant interaction between handling × reserpine ($F(1,24) = 6.97$, $p = 0.020$). The Newman-Keuls post hoc test showed that reserpine-UH animals decreased BDNF levels when compared to vehicle-UH and reserpine-TS animals. One-way analysis followed by the post hoc test showed that imipramine had no difference when compared to the other groups (Fig. 5a).

Two-way ANOVA of proBDNF revealed a significant main effect of handling ($F(1,24) = 8.39$, $p = 0.01$) and handling × reserpine ($F(1,24) = 5.37$, $p = 0.03$). The Newman-Keuls post hoc test showed that reserpine-UH animals increased proBDNF levels when compared to vehicle-UH and reserpine-TS animals. The post hoc test of one-way analysis showed that imipramine administration decreased proBDNF levels, compared to reserpine-UH, and had no difference when compared to reserpine-TS animals (Fig. 5b).

Two-way ANOVA of TrkB revealed a significant main effect of handling ($F(1,24) = 202.11$, $p = 0.000$), reserpine ($F(1,24) = 8.12$, $p = 0.014$), and handling × reserpine ($F(1,24) = 45.66$, $p = 0.000$). The Newman-Keuls post hoc test showed that reserpine-UH animals decreased TrkB levels when compared to vehicle-UH and reserpine-TS. TS per se increased TrkB levels when compared to the vehicle-UH group, while reserpine-TS animals showed TrkB higher levels, compared to TS per se and reserpine-UH animals. The post hoc test of one-way analysis showed that imipramine administration had no difference when compared to reserpine-UH animals, but decreased TrkB levels when compared to reserpine-TS animals (Fig. 5c).

Two-way ANOVA of GDNF revealed a significant main effect of handling ($F(1,24) = 22.69$, $p = 0.000$). The Newman-Keuls post hoc test showed that TS per se and reserpine-TS animals increased GDNF levels when compared with vehicle-UH and reserpine-UH animals. The post hoc test of one-way analysis showed that imipramine administration increased GDNF levels when compared to reserpine-UH and decreased these levels when compared to reserpine-TS animals (Fig. 5d).

Two-way ANOVA of GFAP revealed a significant main effect of reserpine ($F(1,24) = 5.56$, $p = 0.03$) and handling × reserpine ($F(1,24) = 8.90$, $p = 0.01$). The Newman-Keuls post hoc test showed that reserpine-UH animals decreased GFAP levels when compared with vehicle-UH and reserpine-TS animals. The post hoc test of one-way analysis showed that imipramine administration had no difference when compared to the other groups (Fig. 5e).

Two-way ANOVA of GR revealed a significant main effect of handling ($F(1,24) = 24.65$, $p = 0.001$) and handling × reserpine ($F(1,24) = 7.34$, $p = 0.02$). The Newman-Keuls post hoc test revealed that TS per se showed higher levels of GR when

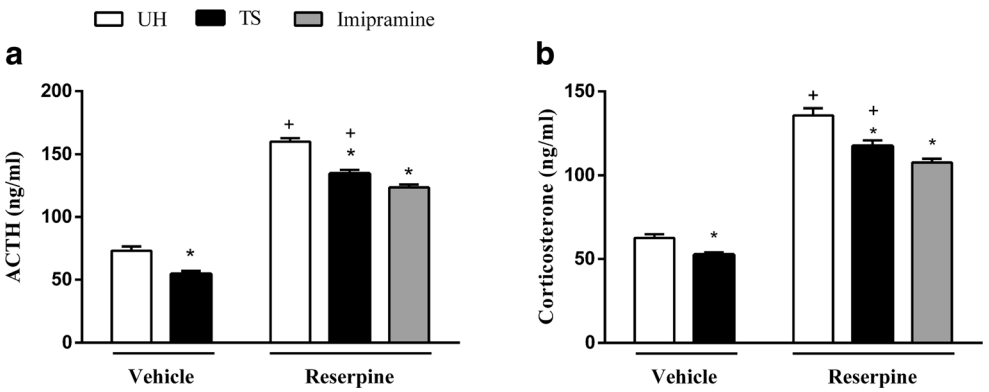

Fig. 4 Influence of reserpine and TS on ACTH and corticosterone in plasma. Data are expressed as mean ± SEM ($n = 7$). Asterisk indicates significant difference from UH to TS or imipramine groups ($p < 0.05$). Plus sign indicates significant difference from vehicle to reserpine groups ($p < 0.05$). Number sign indicates significant difference from reserpine-TS to imipramine group ($p < 0.05$). UH, unhandled; TS, tactile stimulation; ACTH, adrenocorticotrophic hormone

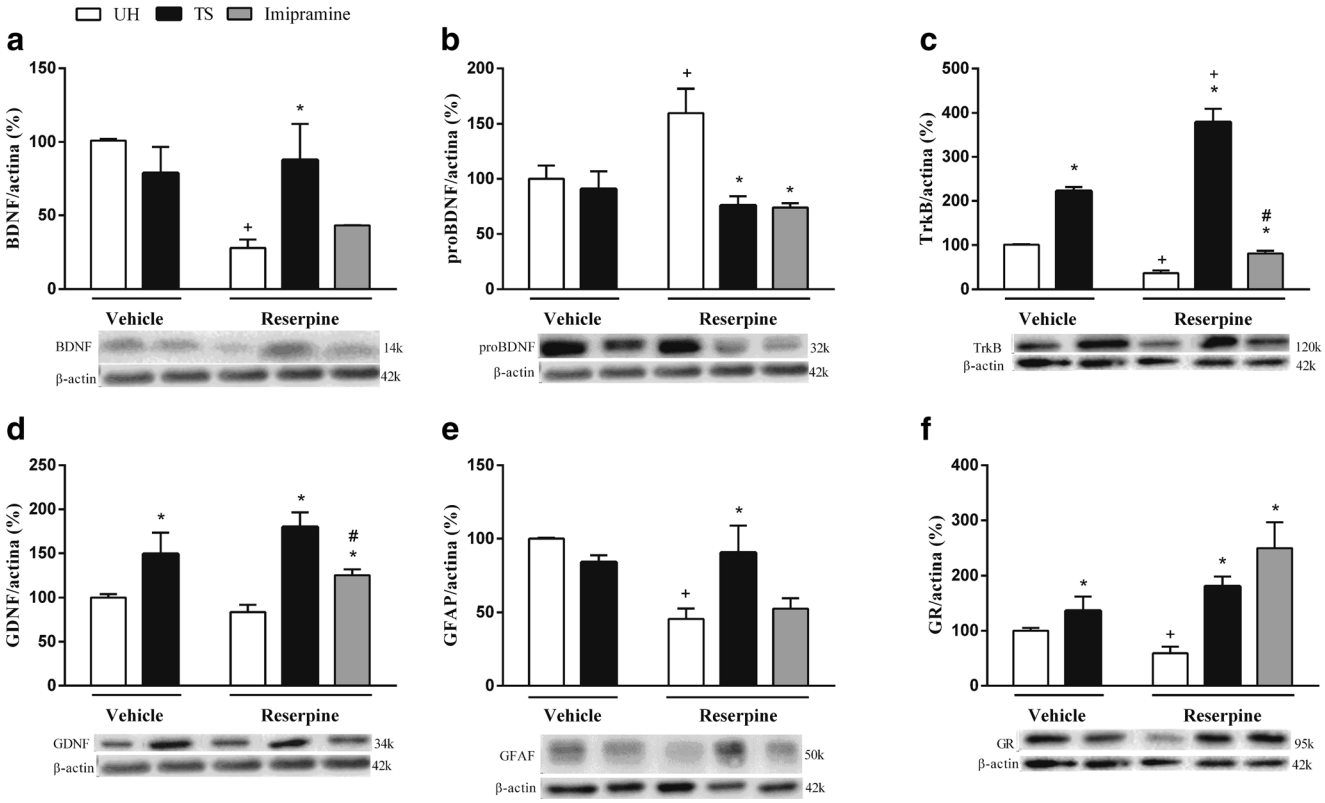

Fig. 5 Influence of reserpine and TS on BDNF (**a**), proBDNF (**b**), TrkB (**c**), GNDF (**d**), GFAP (**e**), and GR immunoreactivity (**f**) in the prefrontal cortex. Data are expressed as mean ± SEM ($n = 7$). Asterisk indicates significant difference from UH to TS or imipramine groups ($p < 0.05$). Plus sign indicates significant difference from vehicle to reserpine groups ($p < 0.05$). Number sign indicates significant difference from reserpine-TS to imipramine group ($p < 0.05$). UH, unhandled; TS, tactile stimulation; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillar acidic protein; GR, glucocorticoid receptor

compared to vehicle-UH animals, while reserpine-UH animals decreased GR levels when compared to vehicle-UH and reserpine-TS animals. The post hoc test of one-way analysis showed that imipramine increased these levels, compared to reserpine-UH, and had no difference when compared to reserpine-TS (Fig. 5f).

Discussion

Our study is showing that the tactile stimulation (TS) applied in adult animals reversed reserpine-induced depression-like behaviors, which were evidenced in the forced swim test (FST), splash test, and sucrose preference test. Furthermore, TS decreased adrenal weight, as well as the plasma levels of ACTH and corticosterone, thus reversing the decreased immunoreactivity of GR, GFAP, TrkB, proBDNF, and BDNF induced by reserpine administration. These findings are indicative that TS could reverse depressive behaviors by different pathways.

The FST is an experimental paradigm originally proposed to investigate beneficial effects of antidepressant drugs [43], in which reduced passive behaviors (immobility) and increased active behaviors (climbing and swimming) display the drug effect on depressive symptoms improvement [50], possibly through noradrenaline and serotonin system activation [51]. Here, TS and imipramine showed a reduction in the immobility time, thus increasing the swimming time in the FST. More precisely, imipramine also increased the climbing behavior. As this drug is a tricyclic antidepressant, it can reverse the depressive-like behavior, since the increase in the release of neurotransmitters such as noradrenaline and serotonin is directly associated with the climbing behavior enhancement [52]. Meanwhile, TS treatment increased only the swimming time, suggesting that the main effect of TS could be more dependent on serotoninergic system modulation. Despite that, more investigations about the monoaminergic system are needed. Besides FST, anhedonia behaviors (or hyposensitivity to pleasure) also have been employed to access the effectiveness of the antidepressant treatment [46, 53]. Here, both TS and imipramine administration reversed the increased latency time to grooming in the splash test, and the reduced sucrose consumption induced by reserpine.

Previous studies from our laboratory have shown the beneficial influence of TS applied during the neonatal period, which was able to reduce anhedonia in adult rats, preventing anxiety after stress exposure [54], improving benzodiazepine drugs responsiveness [55]. Moreover, TS presented itself as an

efficient tool against cocaine and amphetamine addiction [36, 37], also showing its effectiveness to increase the sertraline responsiveness in an animal model of depression [38]. Regarding the different objectives, our current findings primarily differ from these previous studies in two fundamental aspects: (i) TS was applied in adult animals; (ii) the beneficial influence of TS was effective to reverse reserpine-induced depression-like behaviors, while in previous studies the TS benefits were exclusively preventive. Although reserpine showed no reduction in grooming time in the splash test, TS increased this parameter per se and in the reserpine-TS group, confirming the hypothesis that TS exerts a beneficial approach to improve emotionality.

It is well known that women are more susceptible to develop depression symptoms [2]. Thus, we performed our research with female rats in order to mimic the human clinic. Although literature demonstrates that the estrous cycle has an important effect on depressive-like behaviors, since the estradiol can show antidepressant effects [56], female rodents are known to be more vulnerable to neuropsychiatric disorders models [6] and more responsive to the impacts upon modulation of the BDNF signaling and HPA axis [57, 58]. In the present study, TS treatment reduced ACTH and corticosterone levels in plasma, decreased adrenal glands weight, and increased GR immunoreactivity in PFC. Our findings are in accordance with previous studies showing that the glucocorticoid (GC) levels increase, deregulation in GR and the HPA axis hyperactivity were associated with depression-like behaviors [59, 60]. On the other hand, GR activation may improve the impaired HPA axis negative feedback and consequently, inhibit GC release. Such enhancement of GR levels in the brain, including PFC, is associated with decreased ACTH and corticosterone release and is considered pivotal to reduce depression-like behaviors since antidepressant treatment can reduce HPA axis activity by increasing GR expression, translocation, binding, and function [61, 62]. Our outcomes are in agreement with this evidence, given that TS applied during animals' adulthood showed the ability to decrease the HPA axis activity, minimizing the corticosteroid cascade, inciting the GR expression. Also, higher GR levels in the PFC after reserpine could explain the animals' depression-like behavior, whereas GR levels could be increased by TS or imipramine to regulate the GC release reversing the depression-like behavior. Together these findings may be linked to a better biological adaptation of the animal and a possible antidepressant effect, considering antidepressants can modify GR expression in brain areas such as the PFC [63].

Also, the GR changes in the PFC are directly associated with plasma GC release, and evidence demonstrated that GC exerts different influences on the PFC. Meanwhile, the increase of this hormone can impair the PFC neuronal architecture, thus facilitating the development of neuropsychiatric disorders such as depression [64, 65]. Similar to TS, the imipramine-induced reversion of depressive-like behaviors could be, at least partly, consequent to its influence on the hormones and GR levels, which is in accordance with previous findings, suggesting the antidepressant-like effects could be glucocorticoid-dependent [66, 67]. It is important to notice that HPA axis receives serotonergic input, acting as a regulator of behavior and emotion and the hyperactivity of the HPA axis can impair monoaminergic neurons, leading to a BDNF downregulation in the brain [68, 69]. Thus, an increase in glucocorticoid release could exert detrimental effects on CNS, reducing dendritic complexity, altering synaptic plasticity, and suppressing GDNF and BDNF expression, leading to atrophy and disruption of connectivity in cortex and hippocampus [70, 71].

Recent reports have shown that TS applied during the neonatal period and adulthood was able to increase trophic factor levels, including BDNF and fibroblast growth factor 2 in different brain areas, also increasing dendritic lengths after brain injury and enhancing memory performance of rodents [40, 72]. In the current study, TS applied in adult animals reversed the decreased reserpine-induced BDNF immunoreactivity, thus increasing TrkB and reducing proBDNF in the PFC, a brain area closely implicated in depression development [73, 74]. Indeed, BDNF signaling exerts an essential role on the maturation and survival of neurons, regulating neuropsychiatric-like behavioral phenotypes in adulthood [75]. In contrast, its precursor, proBDNF, can bind on $p75^{NTR}$ receptor inducing apoptosis, decreasing spine density and dendritic arbor [76, 77], thus facilitating depression-like behaviors. Moreover, BDNF-TrkB signaling also has demonstrated antidepressant activity similarly to our results, since the increase of TrkB levels in the brain tissue has been associated with depression improvement [78, 79]. Besides, BDNF signaling is crucial to the normal functioning of 5-HT_{2A} receptors, which are involved in the antidepressant activities [10]. In this sense, alterations in the conversion of proBDNF to BDNF together with reduced TrkB immunoreactivity, as observed in the reserpine-UH group, could explain the depression-like behaviors observed in this experimental group, while TS, and in minor proportion, imipramine, improved this signaling cascade and decreased the depression-like behavior.

Regarding imipramine, it is known that antidepressant drugs can increase BDNF/TrkB levels, thus helping to recover depression-like behaviors. However, our findings are showing that although imipramine has reduced the immobility time in TS-exposed animals, changes in BDNF/TrkB cascade were not observed in this experimental group. We believe this contradiction between the current outcomes and literature data can be only apparent considering the doses of imipramine and treatment time were in fact, different [80, 81].

Of particular importance, our findings also showed that reserpine exposure did not decrease GDNF levels in the PFC,

while TS and imipramine treatment increased the immunoreactivity of this molecular marker. GDNF is known to be an important factor for the survival and maintenance of dopaminergic and serotonergic neurons [82]. According to recent findings, all types of antidepressants, including imipramine, can modulate GDNF expression, possibly due to the increased extracellular level of 5-HT caused by antidepressant treatment, leading to increased ERK/MAPK activation and consequently stimulating the GDNF release [82, 83]. TS procedure increased this neurotrophic factor, suggesting the monoamines levels maintenance, which can be related to the depression-like behavior improvement. Studies have demonstrated that TS applied for 8 days can alter trophic factors in brain regions after a dopaminergic lesion, and that might have a direct relation between TS and dopaminergic release in the brain, and maybe other monoamines, which could contribute to improving psychiatry conditions such as depression [40, 84]. It is important to note that a limitation of our study was the absence of monoamines quantification in the PFC. Such an analysis could show the real monoamines reduction in the animals' brain and the possible recovery promoted by TS. This handling procedure showed similar, but subtly superior influences than those observed after imipramine administration. Thus, the continuity of studies approaching the TS as a therapeutic resource is still needed to better understand the relation among TS in adult animals, brain neurotrophic factors, and monoamines levels.

With similar functions to the neurotrophic factors, astrocytes are a type of glial cell responsible for providing energy, morphological, and metabolic support to neurons, and are also involved in differentiation, proliferation, and survival of neurons [85]. Reduced numbers of astrocytes have been related to different CNS diseases, including depression [22]. Likewise, GFAP, which is an essential marker of astrocytes and the major component of intermediate cytoskeletal filaments, presented reduced levels in both human and rodent depressed brain [86]. In our findings, reserpine reduced GFAP immunoreactivity in the PFC, while TS reestablished these levels. Decreased levels of GFAP also indicate a reduced number of astrocytes, and their hypofunction was recently associated with lower neuron survival and disruption in synaptic plasticity, which may be closely related to depression-like behavior [24] and literature data have shown that some antidepressant drugs can recover the astrocytes levels, ameliorating depression symptoms [24]. In our current findings, imipramine did not recover GFAP levels, but TS increased GFAP levels, enhancing reserpine-induced depression-like behaviors. In this sense, we suggest that TS can affect astrocytes proliferation and morphology, increasing synaptic plasticity and improving depression-like behaviors. Therefore, we hypothesized that the improvement in the HPA axis signaling caused by TS could enhance the function of neurotrophic factors and GFAP and consequently improve depression-like behavior in adult rats.

In summary, TS exerts a positive effect on the HPA axis signaling, which was reflected in the adrenal weight of animals, corticosterone release, and changes in GR expression in PFC. The protective cascade triggered by TS in adult female rats recovered the cortical levels of neurotrophic factors, such as BDNF, TrkB, GNDF, and GFAP, which were impaired by the reserpine-induced animal model of depression. Thus, to the best of our knowledge, the current study is demonstrating for the first time that TS can reverse depression-like behaviors in adult rats, through its influence on gene transcription, enhancing the neurogenesis. Also, the beneficial influence of TS was similar but subtly higher to those observed with the imipramine, a classical antidepressant drug. Our findings suggest that TS exerts a beneficial role on the psychological disorders of adult life and could be a practical approach in the human clinic, in the form of massage therapy, since this therapy consists in kinesthetic or sensory stimulation [87], contributing to the treatment of depression. Despite that, performing additional studies would be imperative to deepen the knowledge related to a possible involvement of the monoaminergic system succeeding the TS procedure.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Research Involving Animals All procedures were approved by the Animal Ethics Committee of the Federal University of Santa Maria and were carried out according to the Guidelines for Animal Experiments.

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