

# *Treatment with sertraline from gestation until 21<sup>st</sup> day of post-natal life reduces in adult rats spent time in the elevated plus-maze open arms*

## Tratamento com sertralina a partir da gestação até 21<sup>o</sup> dia de vida pós-natal reduz, em ratos adultos, o tempo de permanência nos braços abertos no labirinto elevado em cruz

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### ABSTRACT:

This study investigated the behavioral anxiety in 21 Wistar adult male rats. It was administered sertraline in dose of 10 mg/Kg (sc) in 11 animals and an equivalent volume of saline (NaCl, 0,9%) in the control group (n = 10), from the 13<sup>th</sup> day of gestation to the third week of powder-native life. The anxiety was evaluated by plus-maze (PM) in the 90<sup>th</sup> day. The spent time in the open arms (OA) was used as anxiety index. T-test was used with  $p < 0.05$  and expresses data in mean  $\pm$  SEM. The animals treated with sertraline presented larger spent time in the OA ( $102,36 \pm 7,14$ ,  $p = 0,009$ ) compared to control group ( $60,40 \pm 5,75$ ). The sertraline chronic administration from gestation until neonatal third week showed smaller propensity to the anxiety induced by plus-maze test.

**KEY WORDS:** anxiety, plus-maze, serotonin, sertraline and neonatal.

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## RESUMO

Este estudo avaliou a ansiedade comportamental em 21 ratos Wistar adultos machos. A partir do 3º dia de gestação até a terceira semana de vida pós-natal, administrou-se sertralina em dose de 10 mg/Kg (sc) em 11 animais e um volume equivalente de salina (NaCl, 0,9%) no grupo controle (n = 10). No 90º dia, analisou-se a ansiedade pelo tempo de permanência dos animais nos braços abertos (BA) do labirinto elevado em cruz (LEC). O teste t foi utilizado, com ( $p < 0,05$ ) e os dados apresentados em média  $\pm$  erro padrão. Os animais tratados com sertralina apresentaram maior tempo de permanência nos braços abertos ( $102,36 \pm 7,14$ ,  $p = 0,009$ ), quando comparados ao grupo controle ( $60,40 \pm 5,75$ ). A administração crônica com sertralina a partir da gestação até a terceira semana de vida pós-natal apresentou menor susceptibilidade à ansiedade no modelo do LEC.

**PALAVRAS-CHAVE:** ansiedade, labirinto elevado em cruz, serotonina, sertralina, neonatal.

## INTRODUCTION

Studies involving growth and development of the central nervous system, using experimental models of laboratory are increasing. This has been happening because the some animals' nervous system seems to execute the same stages of the maturation in human <sup>(1)</sup>. The serotonergic system has participation in the emotional behavior <sup>(2)</sup>. Animals' models have contributed to demonstrate the role of serotonin (5-hidroxytryptamine, 5-HT) in affective disorders like anxiety <sup>(3,4)</sup>. Adult rats treated with selective serotonin reuptake inhibitor (SSRI) during the neonatal stage (days 1 to 21, suckling period) have demonstrated behavioral alterations in the elevated plus-maze, an experimental model of anxiety <sup>(5,6)</sup>. However, there aren't any discoveries in the literature, demonstrating any alteration starting from the gestation, continuing until the suckling period. Being made use of the pharmacologic tool, we can observe that in acute treatment, there is an increase in extracellular serotonin in several subcortical brain regions due to reuptake blockade <sup>(7)</sup> and in the chronic administration, there is an increase of extracellular concentrations of 5-HT at cortical and subcortical levels, and the long-term 5-HT reuptake blockade provokes desensitization of somatodendritic 5-HT<sub>1A</sub> and terminal 5-HT<sub>1B</sub> autoreceptors, respectively leading to a disinhibitory effect on raphe neurons firing and to reduced

feedback inhibition of 5-HT release <sup>(8,9)</sup>. Some studies show chronic administration of selective serotonin reuptake inhibitor (SSRI) during the suckling period induces several morphologic <sup>(10,11)</sup>, functional <sup>(12)</sup> and behavioral changes <sup>(13)</sup>. However, the data obtained in animal studies using SSRI antidepressants are still contradictory <sup>(14)</sup>, specifically, in concentration kind 1 to 1 (10 mg/Kg), using elevated plus-maze <sup>(15)</sup>. The objective of this study was test the hypothesis that the administration of a SSRI, sertraline, from the gestation to suckling phase, promotes changes in anxiety behavior in the elevated plus-maze in adult rats.

## MATERIAL AND METHODS

### ANIMALS

The animals were male Wistar rats maintained at a room temperature of  $23 \pm 2^\circ\text{C}$ , on a light-dark cycle of 12:12 hours (light on at 7:00 a.m.), with free access to water and food. The animals were assigned randomly to two groups (6 pups per litter) 24 h after birth. One group (Sertraline group) received sertraline (10 mg/kg, sc, dissolved in saline solution, 1 ml/kg), and the other (Control group) received an equivalent volume of saline (NaCl, 0.9%). The treatments were applied every day from the 13<sup>th</sup> day of gestation to the 21<sup>st</sup> postnatal day (suckling period). Body weights were

determined at 1st to the 21<sup>st</sup> (weaning) and 90th day.

## APPARATUS

A standard wooden elevated plus-maze apparatus consisting of 50 x 10 x 40-cm opposite closed arms and 50 x 10-cm open arms that radiated from a central 10 x 10-cm space was used. The apparatus was elevated to a height of 50 cm above floor level by a single support.

## BEHAVIORAL EVALUATION

The animals aged 90 days, weighing 310-330g, were evaluated with regard to anxiety behavior and locomotor activity, using elevated plus-maze. This model is based on the innate fear rodents have for open and elevated spaces <sup>(15)</sup>. Rats on the elevated plus-maze tend to avoid the open arms and prefer to stay in the enclosed arms. When confined to the open arms, rats show behavioral and physiological manifestations of fear, such as freezing, defecation, and increases in plasma corticosteroids <sup>(16)</sup>. The avoidance of the open arms occurs primarily because they prevent the rat from engaging in thigmotaxic behavior <sup>(17,18)</sup>. Thigmotaxis is a natural defensive response that keeps the rat in contact with a vertical surface, thereby avoiding predators <sup>(19)</sup>.

Each animal was placed in the central area of the maze facing one of the closed arms. The animals were observed for 5 min by a trained observer who sat quietly 1.5 m from the center of the maze and recorded the time spent in and the number of entries into each arm. An entry was recorded when the animal's four limbs had entered an arm. The observer was "blind" to the animal's condition.

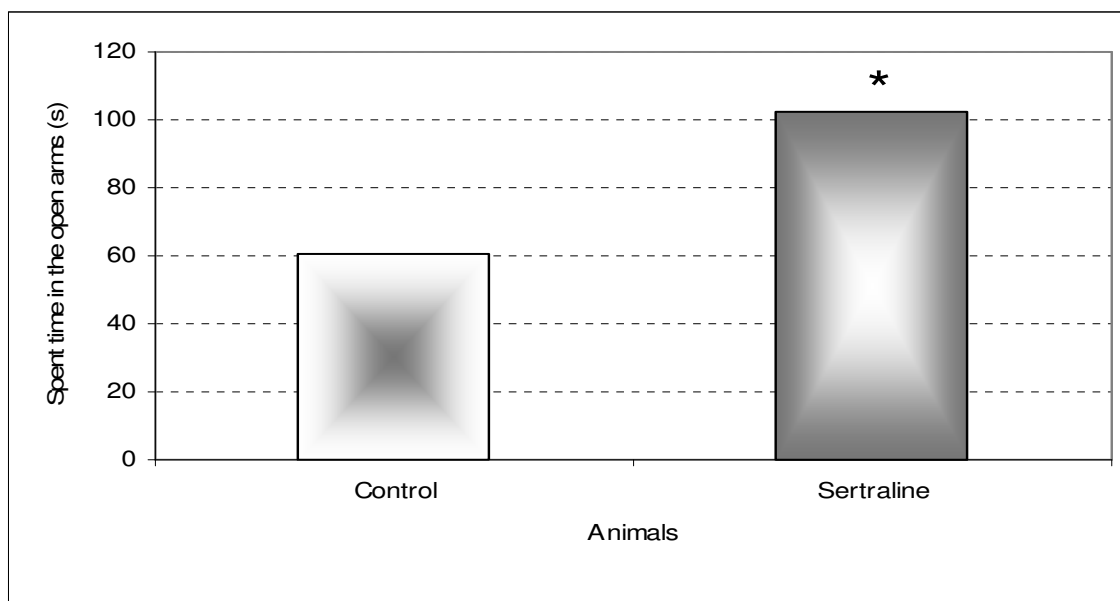
The anxiety evaluation was performed, observing the spent time in the open arms as anxiety index.

## DATA ANALYSIS

The spent time in the open arms was computed for each animal. The behavioral parameters (expresses mean  $\pm$  SEM) were analyzed by Student's "t" test. The significance level adopted for statistical tests was  $p < 0.05$ .

## RESULTS

Compared to the Control group, there was not statistical significance, in both stages, with time spent in the open arms of fluoxetine group. The animals treated with sertraline presented larger spent time in the OA ( $102,36 \pm 7,14$ ,  $p=0,009$ ) (**Graph 1**) compared to control group ( $60,40 \pm 5,75$ ).



**Graph. 1.** The spent time in the open arms. Evaluation in the elevated plus-maze. Sertraline chronic effect (10 mg/kg, sc, dissolved in saline solution, 1 ml/kg, n=11), during neonatal period compared to Control group treated with saline (NaCl 0,9%, 1ml/Kg, sc, daily, n=10). The behavioral parameters (expresses mean  $\pm$  SEM) was analyzed by Student's "t" test. The significance level adopted for statistical tests was  $p < 0.05$ .

## DISCUSSION

The chronic administration of sertraline, from the gestation until the end of critical period of development of the nervous system, reduces the anxiety behavior in the elevated plus maze experiment.

During chronic sertraline administration there is an increase of extracellular concentrations of 5-HT at cortical and subcortical levels, and the long-term 5-HT reuptake blockade provokes desensitization of somatodendritic 5-HT<sub>1A</sub> and terminal 5-HT<sub>1B</sub> autoreceptors, respectively leading to a disinhibitory effect on raphe neurons firing and to reduced feedback inhibition of 5-HT release (20,21,22).

However, the manipulation of the serotonergic neurotransmission still producing contradictory results in the anxiety, specifically, studies using antidepressants (23) and especially, if it involves SSRI in a concentration of 1 to 1, using experimental models of anxiety (14).

This study used sertraline from the gestation to the neonatal period as a tool for manipulation of the serotonin neurotransmission.

This work found anxiolytic profiles of anxiety experiment ( $p < 0.05$ ) with animals treated with sertraline, in the neonatal period, compared to the control groups. These results seem to indicate a sedative effect.

Differently from our work, Ansorge *et al.* (2004) found anxiogenic effect in mice tested in the elevated plus-maze. However, this work corroborate Silva and Brandão (2000) that used other SSRI, fluoxetine (10 mg/Kg, PO) in chronic administration and did not find effect in none of the measures space-time (entrance and exit of the arms or spent time in some of the elevated plus-maze's arms).

Although both works have been accomplished with SSRI, using the elevated plus-maze, it is make necessary to present some methodological differences. The first of them refers the lineage of the animal and the second to the period from pharmacologic treatment. In the first

work<sup>(6)</sup>, the animals were mice, while in our work the animals were rats and in the second<sup>(15)</sup>, fluoxetine administration did not happen in the neonatal period. Similar results, also using the elevated plus-maze, were presented before<sup>(23)</sup>.

Another question to be considered is the heterogeneity of symptoms presented by the anxiety disorder. The fluoxetine, for example, does not respond appropriately at treatment from widespread anxiety. However, it is used with effectiveness in compulsive obsessive disorder, social phobia, panic disturbance and nervous bulim<sup>(5)</sup>.

## CONCLUSION

The serotonin increases due to the selective serotonin reuptake inhibition action and functional acting in different areas of the brain<sup>(24)</sup>, specially, in the neonatal period, can facilitate permanent alterations<sup>(12)</sup>.

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