

Neonatal administration of sertraline reduces aggressiveness induced by shock in the paws (footshock) in adult rats.

Administração neonatal de sertralina diminui a agressividade induzida por choques elétricos nas patas em ratos adultos.

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ABSTRACT

This study investigated the aggressive behavior in 54 wistar adult males rats treated from the first to 21st days of life, with sertraline using 10 mg/Kg, 20 mg/Kg and 30 mg/Kg (sc, daily). The control group, constituted by 18 animals, received a distilled water (H₂O 0,9%) volume of solution. The Kruskal-Wallis test was used with $p < 0.05$ and expresses data in (median \pm SEM). Aggressiveness was induced by shock in the paws (footshock) (1.6-mA-2-s). Complete aggressiveness (CA) and Individual Complete aggressiveness (ICA) were appraised in 900 seconds. The sertraline group presented smaller time of CA (203,5 \pm 29,58; 6 \pm 9,79; 20 \pm 38,45) and ICA (304,5 \pm 37,69; 17,5 \pm 33,89; 79,5 \pm 39,28), when compared to the respective controls (233 \pm 34,54), (353 \pm 32,22). The animals treated with sertraline using 10 mg/Kg dose, didn't present statistics difference. Neonatal chronic treatment with sertraline reduced the aggressiveness in adult rats treated during the sucking period.

UNITERMS: Aggressiveness, footshock, serotonin, sertraline and suckle.

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RESUMO

Este trabalho avaliou o comportamento agressivo em 54 ratos wistar adultos machos tratados, do primeiro ao 21º dia de vida, com sertralina em doses de 10 mg/Kg, 20 mg/Kg e 30 mg/Kg (sc, diariamente). O grupo controle, constituído por 18 animais, recebeu um volume de solução de água destilada (H₂O, 0,9%). O teste Kruskal-Wallis foi utilizado, com ($p < 0,05$) e os dados apresentados em (mediana \pm erro padrão). Induziu-se agressividade por choque nas patas (1,6-mA-2-s). Agressividade completa (AC) e agressividade completa individual (ACI) foram avaliadas em 900 segundos. O grupo sertralina apresentou menor tempo de AC (203,5 \pm 29,58; 6 \pm 9,79; 20 \pm 38,45) e ACI (304,5 \pm 37,69; 17,5 \pm 33,89; 79,5 \pm 39,28), quando comparados aos respectivos controles (233 \pm 34,54) e (353 \pm 32,22). Os animais tratados com sertralina em dose de 10 mg/Kg, não apresentaram diferença significativa. Tratamento neonatal crônico com sertralina reduziu a agressividade de ratos adultos tratados no período de aleitamento.

UNITERMOS: Agressividade, footshock, serotonina, sertralina, aleitamento.

INTRODUCTION

The serotonergic neurotransmitters with several other neurochemistry factors is implied in the development of the nervous system (NS)⁽¹⁾ and it can influence in the expression of the emotional behavior, such as depression⁽²⁾, anxiety⁽³⁾ and aggressiveness⁽⁴⁾.

Studies have been indicating that the pharmacologic or nutritional manipulation in the nervous system during the period of initial development can provoke drastic alterations in morphologic⁽⁵⁾ functional⁽³⁾ and behavioral level⁽⁶⁾ and that those alterations can be irreversible, depending the period and the manipulation form⁽⁷⁾, it happens because the beginning of the nervous system development presents a very certain temporary and accelerated way sequence, divided in events, such as: neuronal division, differentiation, migration and synaptogenesis⁽⁸⁾.

These events determine the morphologic and functional definitive structure present in the adult⁽⁹⁾ and they are sensitive to the nutritional^(10,11) and pharmacological aggressions^(3,12).

The vulnerabilities of this physiologic system in the beginning of biological development allowed that is denominated of critical period of nervous

system development⁽¹³⁾. However, this period can vary among the species. In the man, it has beginning in the last gestational quarter continuing up until 2 to 4 years of life⁽¹⁴⁾ and in the rat, it corresponds to the three weeks of powder-native life that coincides with the suckling period⁽¹³⁾.

Experimental works indicates that itself 5-HT can influence the embryogenesis and the growth^(15,16), it possibly exercises a neurotrophic effect⁽¹⁷⁾ or presumably by acting as a developmental sign for the neurons development during the embryonic phase^(18, 19). Thus, the drugs administrated in the prenatal or powder-native phase can affect the serotonergic function^(9,13), such as the emotional behaviors⁽²⁰⁾.

Researchers make drugs use as instruments of nervous system manipulation especially, selective serotonin reuptake inhibitor (SSRIs) to make possible alterations and observe the biological phenomenons (5-HT)^(2,3,4,12), acting in the system membrane transporter and prolonging the serotonin action. These drugs increase the synaptic availability of 5-HT accentuating or facilitating its action^(21,22).

Some studies suggest that 5-HT inhibits the aggressive behavior^(4,21,23,24) and although, stimulate the development of researches in human; the obvious ethical limitations have been taking the

researchers to use the animal models. Among the several experimental models used for the aggressiveness study, there is that induces in rats aggressive behavior using electric shock in the paws (footshock)^(4,24).

The aggression induced by shock in the paws is considered defensive aggressive behavior. In spite of limitations, this method allows to reproduce behavioral aspects observed in several species besides the man^(4,24).

The 5-HT action in the aggressive behavior control was demonstrated through the use of drugs instruments, such as: fluoxetina, citalopram, among others. In this study, we used the sertraline, a selective serotonin reuptake inhibitor, for evaluation of the aggressive behavior.

METHOD

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 (Control group) received a volume of distilled water solution (H_2O - 0.9%) and the other (Sertraline group) received Sertraline in 3 (three) subgroups in agreement with the dose (10 mg/kg, 20 mg/Kg and 30 mg/Kg sc, dissolved in distilled water solution, 1 mg/kg). The treatments were applied every day from the 1st to the 21st postnatal day (suckling period). We make violet marks, daily; in the animals to identify the animals treated with the drug and the animals treated with distilled water. At final, we obtained 18 rats in each group.

Apparatus

A Skinner cage (20 x 20 x 20 cm) with the floor consisting of parallel metal bars (interbar

distance: 1.3 cm) connected to a scrambled electric current source. The test is in acoustically isolated room and consisted of placing a pair of rats from the same group (matched by weight) in the box, where they received a session of stimuli to induce aggressive responses.

Behavioral evaluation

The animals aged 90 days, weighing 310-330g, were evaluated with regard to aggressiveness behavior, using Skinner box with footshock. In this model each stimulus (an electric footshock) consisted of a 1.6-mA - 2-s current pulse. Each session lasted 20 min and included 5 stimuli separated by a 4-min interval. During the first 3 min of this interval, the duration of the aggressive response was measured with a digital chronometer. The total time of aggressive behavior observation was 900 s. In the last minute of each interval, the data were recorded and the equipment was checked. The aggressive response was defined as the presentation of at least one of the two following behaviors: a) the animals stood up on the hind paws facing each other in a threatening attitude but without direct contact (**Fig. 1**) or b) they maintained evident physical contact (scratching, tooth baring and emission of characteristic vocalization) (**Fig. 2**).



Fig. 1 – The animals maintaining evident physical contact.

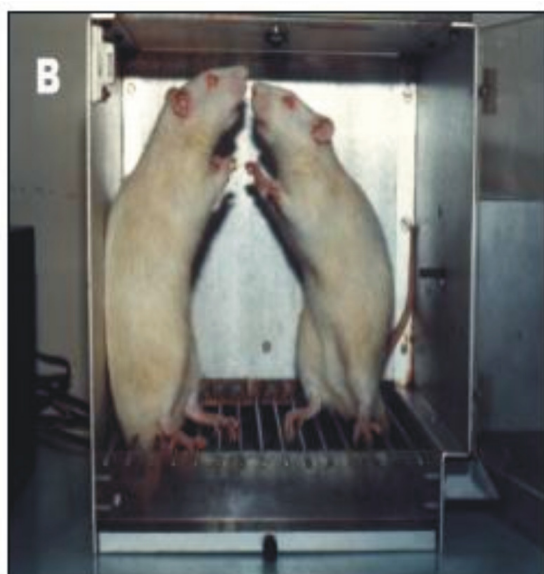


Fig. 2 – The animals stood up on the hind paws facing each other in a threatening attitude but without direct contact.

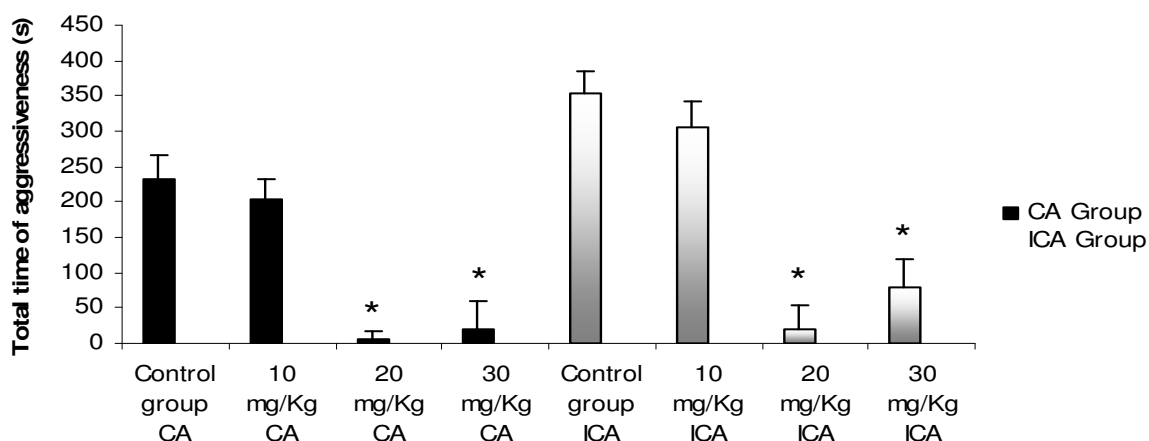
Data analysis

The behavioral parameters were expressed in (median \pm SEM) were analyzed by Kruskal-Wallis test. The significance level adopted for statistical tests was $p < 0.05$.

Results

There were a significant difference in aggressive response Sertraline rats presenting a reduced duration of aggressiveness in doses of 20 mg/kg and 30 mg/kg, represented in median (Md), minimum and maximum in the parameters complete aggressiveness (CA) ($203,5 \pm 29,58$; $6 \pm 9,79$; $20 \pm 38,45$) and individual complete aggressiveness (ICA) ($304,5 \pm 37,69$; $17,5 \pm 33,89$; $79,5 \pm 39,28$), when compared to the respective controls groups ($233 \pm 34,54$), ($353 \pm 32,22$), $p < 0,05$) (**Graph 1**). However, the treated animals with sertralina in dose of 10 mg/Kg, didn't present significant difference.

Aggressiveness



Graph 1. Measure of the Completes aggressiveness (CA) time and Individual completes aggressiveness (ICA) time induced by footshock; evaluated in seconds in the Skinner cage. Effect of the treatment with sertraline in the doses (10 mg/Kg, 20 mg/Kg and 30 mg/Kg daily, sc; n=18), during the critical period of nervous system development compared to the control group with distilled water (1 ml/100 g, daily; n=18). The behavioral parameters were expressed in median (Md) and analyzed by Kruskal-Wallis test. The significance level adopted for statistical tests was. * $p < 0.05$.

Discussion

The present study showed that chronic administration of Sertraline during the critical period of nervous system development reduced aggressiveness response in rats submitted to the foot electrical shock stimulus in doses of 20 mg/kg and 30 mg/kg, but didn't provoke alteration in dose of 10 mg/kg.

Our studies corroborate the Manhães de Castro *et al.*⁽⁴⁾ and Abumaria *et al.*⁽²⁵⁾.

Although the above-mentioned works have been accomplished with serotonergic drugs in the neonatal period, its necessary makes to point out some methodological differences. The first difference refers to the drug type administered and the used dose and second refers to the experimental model.

Manhães de Castro *et al.*⁽⁴⁾ used Citalopram (SSRI) with dose of 20 mg/kg, using Skinner cage experimental model, as in the present work. Abumaria *et al.*, 2007⁽²⁶⁾ made use of Citalopram (SSRI) in dose of 5 mg/kg and the experimental model was the resident intruder. This model consists of introducing inside of a cage an adult animal that is not of the same family during 1 to 3 minutes for 5 weeks. There is a suckling female in this cage. The female rat presents aggressive behaviors with the intruder's presence during the first 10 days after the childbirth⁽²⁵⁾.

The only founded study opposed to our results was Martins de Almeida *et al.*,⁽²⁵⁾. However, it was used an agonist drug, Metil-5-hidroxytriptamina maleate, that demonstrates high likeness for receptors 5-HT_{2A} and 5-HT_{2C} (ki=6.1 and 7.3, respectively). In this experiment, the mentioned drug was administered in the seventh post parturition day and behaviors registrations were made 10 minutes after each injection. There were methodological differences so much in the administered drug as in the administration period being important to point out that the pharmacokinetics properties of this nervous system instrument of manipulation was different from SSRI used in the previously mentioned works.

These last authors propose the 5-HT_{1a/1b} and 5-HT_{2a/2c} receptors stimulation has been decreasing the aggressive behavior in different animals models, because in cerebral areas such as hippocampus, area septal pre-optical, tonsil and periaqueductal grizzly mass exist an amount great 5-HT_{2a/2c} receptors. However, their results presented different effects with the Metil-5-Hidroxytriptamina maleate use in the 5-HT_{2a/2c} receptors in the different anatomical areas.

The stimulated areas were: central amygdaloid nucleus and median preoptic area⁽²⁵⁾. When injected inside of the central amygdaloid nucleus, this agonist drug increased the aggressive behavior observed by the frequency of the attacks by the resident females against the intruder. However this composition didn't have effects in the aggressive maternal behavior, when it was injected inside of the median preoptic area⁽²⁵⁾.

These authors suggest although the amygdale 5-HT_{2a/2c} receptors possibly increased the aggressive behavior in suckling female due to the changes result because the emotional fear state, which can to justify, besides the methodological differences, the opposition with the our results.

The found results in this study can be related to the increase due the SSRIs influence; the serotonin synaptic readiness and the functional acting in different areas of the brain⁽²⁷⁾. If pharmacologic manipulation happens in the critical period of nervous system development, it facilitates the occurrence of permanent alterations⁽²⁸⁾.

The experience with the experimental and clinical SSRIs use, as pharmacologic instrument research in cellular level; or as pharmacological therapy, there are evidences the serotonergic system involvement in the anatomic and functional genesis of the aggressiveness substratum^(12, 29).

Besides, it is necessary to consider the period happens the nervous system manipulation, because in the immature brain, many transmitters can act different from that in the mature brain, acting as regulators. Most of the monoaminas has been showing with that capacity, besides the

serotonina. It seems, in that phase, different recaptors subtypes can accomplish different functions. For example, in the serotonergic system, the 5-HT_{1c} receptor can regulate the cellular division, while the 5-HT_{1A} can regulate the neuronal differentiation. It suggests that the receptors pharmacologic manipulation in a development brain can result in permanent alterations⁽¹⁶⁾.

In spite of the studies shortage involving aggressiveness and SSRIs in the suckling period tested using the footshock model, the first hypothesis that the sertraline administration, in the beginning of the life, reduces the aggressive behavior in adult rats to corroborate the serotonergic mechanisms participation in the nervous circuits development involving in the aggressiveness emotional behavior.

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