

Reduction of intraspecific aggression in adult rats by neonatal treatment with a selective serotonin reuptake inhibitor

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Abstract

Most studies suggest that serotonin exerts an inhibitory control on the aggression process. According to experimental evidence, this amine also influences growth and development of the nervous tissue including serotonergic neurons. Thus, the possibility exists that increased serotonin availability in young animals facilitates a long-lasting effect on aggressive responses. The present study aimed to investigate the aggressive behavior of adult rats (90-120 days) treated from the 1st to the 19th postnatal day with citalopram (CIT), a selective serotonin reuptake inhibitor (20 mg/kg, *sc*, every 3 days). Aggressive behavior was induced by placing a pair of rats (matched by weight) in a box (20 x 20 x 20 cm), and submitting them to a 20-min session of electric footshocks (five 1.6-mA - 2-s current pulses, separated by a 4-min intershock interval). When compared to the control group (rats treated for the same period with equivalent volumes of saline solution), the CIT group presented a 41.4% reduction in the duration of aggressive response. The results indicate that the repeated administration of CIT early in life reduces the aggressive behavior in adulthood and suggest that the increased brain serotonergic activity could play a role in this effect.

Key words

- Aggression
- Serotonin
- Neonatal treatment
- Development

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Serotonin has been shown to have multiple functions as a neurotransmitter by exerting modulatory effects on neural excitability (1). There is mounting evidence of its participation in pain sensitivity, body thermoregulation, sleep, feeding behavior and mood (2). Brain areas known to be involved in emotional processes, such as hippocampus, hypothalamus, amygdala and cerebral cortex, are innervated by serotonergic pathways ascending from mesencephalic nuclei (3,4). Studies on animals and humans have

pointed out that the serotonergic system may play a role in several aggressive behaviors (4,5). An inverse relationship seems to exist between central serotonergic function and aggressiveness since reducing central serotonin levels facilitates aggression and this increased aggression is impaired by elevation of serotonin beyond normal levels (2,5). Also, the use of animal models of aggressiveness suggests that serotonin receptors are implicated in aggressive responses (4,6).

Furthermore, experimental evidence indicates that serotonin can influence embryogenesis and growth (7,8) presumably by acting as a developmental signal (9) or a neurotrophic factor (10). A role of serotonin in regulating the development of serotonin neurons themselves has also been demonstrated (7). Moreover, it is well known that very fast growth and development of the nervous system occurs during pregnancy and suckling and pharmacological or nutritional manipulations can induce drastic morphological and functional changes in this process. These changes can become irreversible depending on previous treatment and/or environmental factors (11,12). Thus, it is likely that the neural modifications induced by early serotonin treatment persist until adult life. As a consequence, the possibility exists that the use of serotonin agonists in the initial phase of life could have long-lasting effects on behaviors related to serotonergic function. Since, to our knowledge, there are no data concerning this point, the investigation of the possible long-term effects of early manipulation of the serotonergic system is highly desirable. The objective of the present study was to test the hypothesis that the administration of a selective serotonin reuptake inhibitor - citalopram (CIT) - to suckling rats induces changes in aggressiveness during adulthood.

Newborn male Wistar rats from the colony of the Department of Nutrition, Federal University of Pernambuco (Brazil), were assigned randomly to two groups (6 pups per litter) 24 h after birth. One group (CIT group, 16 rats) received citalopram (20 mg/kg, *sc*, dissolved in saline, 1 ml/kg; Lundbeck, Copenhagen, Denmark), and the other (control group, 24 rats) received an equivalent volume of saline (0.9% NaCl). The treatments were applied every 3 days from the 1st to the 19th postnatal day (suckling period). Body weights were determined on the 1st, 21st (weaning) and 90th-120th day. The animals were maintained at a room temperature of 23

± 1°C, on a light-dark cycle of 12/12 h (lights on at 7:00 a.m.), with free access to water and food. When they reached 90-120 days of age they were submitted to aggressiveness tests. The tests were performed in an acoustically isolated room using a box (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 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.

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, or b) they maintained evident physical contact (scratching, tooth baring and emission of characteristic vocalization). Data were compared by the two-tailed Student *t*-test (body weight) or by the Mann-Whitney U-test (aggressiveness) with the level of significance set at $P \leq 0.05$.

Compared to the controls (Table 1), CIT rats showed a reduction in body weight both on the 21st (46.8%, $P < 0.01$) and 90th-120th day (14.5%, $P < 0.01$). A significant difference in aggressive response was also observed (Table 2), with CIT rats presenting a reduced duration of aggressiveness (41.4% lower than control, $P < 0.02$).

The present study showed that chronic administration of CIT during the critical period of brain development impaired the weight evolution and reduced the aggres-

siveness of the rats. These effects may be related to an alteration of the serotonergic system occurring during development, as suggested by Palén et al. (8). In a study on chicken embryos, these authors observed that drugs acting on serotonin synthesis and release, or on the activation of serotonergic receptors may cause disturbances of growth and development in several tissues, including the nervous system, during embryogenesis. Some findings suggest improved neuronal development of serotonergic neurons of embryogenic nervous tissue treated with serotonin (7). Cultured serotonin neurons of embryogenic rat mesencephalon show an increased density and survival of serotonergic neurons (9). Although it is unknown whether this higher density of serotonin neurons persists until adult life, our data agree with this possibility. In fact the weight reduction found in the CIT group could be associated with the role of serotonin in feeding control by inhibiting food intake (13).

The reduced aggression duration during adulthood may be also related to the pharmacological manipulation of the serotonergic system during development, since a close relationship seems to exist between aggressiveness and the function of this neurotransmitter system (2,4). In this context, it is noteworthy that changes in emotional behavior have been already shown in both young and adult rats previously submitted to chronic nutritional injury (14), a condition which is known to alter brain serotonin concentration (15).

The reduction of aggressiveness presented by the CIT group could be related to the serotonergic action both at pre- and post-synaptic sites. Several studies have indicated such inhibitory role through the activation of serotonergic receptors (4).

In rats, the elevation of serotonin and 5-hydroxyindoleacetic acid levels in the amygdala, diencephalon and brain stem produced a reduction in the latency to muricidal behavior (16).

In the present study a nonspecific effect mediated by serotonin (such as the antinociceptive one) cannot be ruled out because of the high CIT dose used. However, the data support those obtained by others (17), who found a reduction of aggressive behavior in psychotic and borderline human patients treated with CIT. This anti-aggressiveness effect of CIT may be also related to its action on the serotonergic system. Increased serotonin concentration in the frontal cortex of adult rats has been observed after chronic treatment with high doses of CIT, the same as used here (20 mg kg⁻¹ day⁻¹, *ip*, for 14 days) (18). This point deserves attention since

Table 1 - Body weight of rats treated with citalopram or saline during suckling.

Rats received citalopram (20 mg/kg, sc; CIT group) or saline (0.9% NaCl, 1 ml/kg, sc; control group) every 3 days from the 1st to the 19th day of age. The animals were weighed on the 1st, 21st and 90th-120th day of age. The data are reported as mean ± SD. *P<0.01 compared to the control group at the same age (two-tailed Student t-test).

Experimental groups	Weight (g)		
	1st day	21st day	90th-120th day
Control group (N = 24)	7.2 ± 1.0	48.1 ± 7.3	334.1 ± 42.4
CIT group (N = 16)	7.0 ± 0.9	25.6 ± 5.2*	285.6 ± 31.0*

Table 2 - Aggressiveness of adult rats treated with citalopram or saline during suckling.

Rats received citalopram (20 mg/kg, sc; CIT group) or saline (0.9% NaCl, 1 ml/kg, sc; control group) every 3 days from the 1st to the 19th day of life. Later on, at 90-120 days of age, pairs of animals from the same group were submitted to a footshock session to elicit an aggressive response. The aggressive response was evaluated on the basis of time of aggression (900-s observation). Results are reported as median (Md) and 25 and 75 percentiles (PE₂₅₋₇₅). *P<0.02 compared to the control group (two-tailed Mann-Whitney U-test).

Experimental groups	Duration of aggressiveness (s)	
	Md	PE ₂₅₋₇₅
Control group (N = 24)	679.5	51.1-82.9
CIT group (N = 16)	398.0*	6.9-72.8

CIT inhibits the reuptake of serotonin, consequently increasing its synaptic availability and enhancing its inhibitory effect on aggressive behavior. On the other hand, the repeated administration of selective serotonin reuptake inhibitors can produce down-regulation both of the post- and presynaptic 5-HT_{1B} receptors, in this case improving the serotonin release (19). According to Saudou et al. (20), the 5-HT_{1B} receptors seem to be very important in the control of aggressive behavior, since mutant mice lacking these receptors presented exacerbated aggressiveness. The fact that CIT administered during suckling affected aggressive behavior much later in life suggests that 1) permanent mor-

phological and/or functional alterations were produced during the period of fast brain development, and 2) these alterations interfere with the behavioral responses of adult rats mediated by the serotonergic system.

Thus, the reduction of aggressiveness observed in the present study could be associated with neuroadaptive mechanisms developed during the neonatal period which last into adult life.

Further investigations demonstrating possible alterations of the serotonergic system as a consequence of pharmacological manipulation early in life are necessary to elucidate the mechanisms responsible for the behavioral changes observed in this study.

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