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Sertraline delays the somatic growth and reflex ontogeny in neonate rats

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Abstract

This study investigated the somatic maturation and ontogeny of reflexes in neonate rats treated with sertraline (Sert) during the suckling period. The animals were divided into four groups; three that received daily doses of Sert (5, 10 or 15 mg/kg s.c.; groups Sert5, Sert10, and Sert15, respectively), and a fourth group that received distilled water (Dw) (1 ml/kg/b.w.). Growth indicators (body weight, axis of the head and tail length) were measured daily, from the 1st to the 21st postnatal day. The reflexes (righting, free-fall righting, negative geotaxis, cliff avoidance, auditory startle response, vibrissa placing and palm grasp) and physical-feature maturation (ear unfolding, auditory conduit opening, irruption of the lower incisors and eye opening) were recorded each day of the animal's life. All groups were compared to the Dw group. The body weight gain was reduced in all the Sert groups. Moreover, a delay in the growth of the body length was observed in all the Sert groups. Higher Sert doses reduced the speed of growth in the tail length. The medio-lateral head axis reduced in Sert15 and Sert5 doses. Otherwise, Sert10 had a temporary acceleration in this growth, but the growth of the anteroposterior head axis had a delay in all the Sert groups. The highest doses induced a delay in physical-feature maturation. The palm grasp reflex (disappearance) was retarded in Sert10; cliff avoidance advanced in Sert10; negative-geotaxis and free-fall righting retarded in Sert15. The findings suggest that altered serotonergic system activity induced by sertraline early in life could play a role in the retardation of the somatic growth ontogeny as well as a delay in the maturation of some reflexes.

Keywords: 5-HT; Somatic growth; SSRI; Sertraline; Reflex development; Physical features

1. Introduction

Mounting experimental evidence suggests that serotonin (5-HT) influences embryogenesis and growth [1,2] by acting presumably as a developmental signal [3] or as a neurotropic factor [4,5]. Serotonin is one neurotransmitter occurring in mammal embryos [3,6]. The early appearance of tryptophan-hydroxylase—a 5-HT synthesis enzyme—found in 15-day old embryos reinforces the idea of precocious serotonergic activity in development [7]. In the rat a fast increase of serotonin occurs during prenatal and postnatal periods, and adult levels are observed at the end of the third week of life [8]. The timeline of these events is closely related to synaptogenesis [9]. Moreover, serotonin has a role in multiple physiological processes by exerting a modulatory effect as a neurotransmitter [9–11]. A recent study reports that rats treated with 5.7 dihydroxytryptamine (5.7-DHT) during the neonatal period presented a decrease in levels of 5-HT and 5-HIAA in the frontal cortex, striatum and hippocampus in adult life. However, this treatment did not affect dopaminergic neurons [12].

On the other hand, ill-treatment such as early malnutrition [13] or neonatal pharmacological manipulation induces neurobehavioral alterations in the organism, believed to be associated with the 5-HT neurotransmission system [14,15]. Many antidepressants—such as fluoxetine, citalopram or clomipramine—can influence food-intake behavior and their actions are performed through inhibition of the 5-HT synaptic reuptake [16–18]. Chronic administration of clomipramine to rats during the neonatal period resulted in adult behaviors similar to those observed in human depression [19,20]. In our

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laboratory, neonate rats treated with citalopram showed a retardation in somatic maturation and a reduction in body weight gain during the period of drug administration [21]; later, when the rats reached adult age, an increase in aggressiveness was observed [15]. A recent systematic review [22] evidenced several signs (such as insomnia, hypoglycemia, restless sleep, irritability, tremors) after in utero exposure to SSRIs. The authors suggested the occurrence of a neonatal, behavioral syndrome depended on the SSRI used by the mothers during the last trimester of pregnancy. Although not detected or only low SSRI serum levels have been found in children whose mothers received such drugs during pregnancy [23], the evidence above suggests that serotonergic changes early in life can modify the maturation of this neurotransmitter system and possibly induce neurobehavioral alterations. This evidence supports the hypothesis that pharmacological abuses early in life can modify the maturation of serotonergic neurotransmission, inducing neurobehavioral changes [20]. The objective in this study was to test the hypothesis that the administration of sertraline—one of the most potent SSRIs [24]—to rats during the suckling period induces changes to their somatic and sensory-motor development.

2. Material and methods

2.1. Animals

Wistar rats coming from the colony of the Nutrition Department—Federal University of Pernambuco—Brazil were coupled to obtain litters. During gestation until the end of the experiment, the animals were housed in polyethylene cages. Twenty-four hours after birth, pups from different mothers ($n=19$) were randomly distributed into litters of 6 neonates. When necessary, female rats were included in the litters to complete 6 pups, but they were not used in the tests. Each pup was labeled with a mark of methyl violet solution on the skin, for identification during the experiment. Each litter was breastfed by one of the dams until the 21st postnatal day (the birth day was considered Day Zero). The animals were maintained at a room temperature of 23±1 °C, on a light–dark cycle of 12/12 h (lights on 6:00 a.m. to 6:00 p.m.) with free access to food (Labina-Purina of Brazil) and water.

2.2. Pharmacological treatment and experimental groups

According to the experimental design, four groups of suckling, male rats were needed. Three groups received different doses of sertraline: group Sert5 (5 mg/kg, s.c., $n=25$); group Sert10 (10 mg/kg, s.c., $n=27$); group Sert15 (15 mg/kg, s.c., $n=17$), and a control group received an equivalent volume of distilled water; one rat of this group died during the experiment (Dw, $n=27$). Therefore, 96 rats were evaluated during the whole experiment. The occurrences of physical features, reflex-maturation and somatic growth were recorded. Sertraline (hydrochloride, Pfizer) was dissolved in distilled water and injected at a concentration of 1 ml/100 g b.w. The treatment was done daily from the 1st to 21st postnatal day (suckling period). In order to prevent identification of the groups during the experiment, a blind study was done. The animals of the different groups were simultaneously evaluated.

2.3. Physical features maturation

The observations of the physical features were made according to Smart and Dobbing [25] and Deiró et al. [21], and carried out daily between 10:00 a.m. and 12:00 a.m. during the suckling period. The following physical features were observed: unfolding of the external pinnae of both ears to the fully erect position; auditory conduit opening—internal auditory conduit opening of both ears; incisor irruption—the first visible and palpable crest of the lower incisors; and eye opening—when any visible break in the covering membrane of both eyes was detected. Maturation age of a particular feature was defined as the day when it occurred for the first time.

Table 1
Procedures for detection of reflexes maturation

Reflex	Stimulus	Response
Palmar grasp — PG	Palm of forepaw stroked gently with a paper clip.	Flexion of digits. As a maturation response, any or a very slight flexion must be seen. For this reflex, the disappearance date is registered.
Righting — R	Rat placed on back on a flat surface.	It turns over, to rest in ventral decubitus, with the four paws on the surface, in 10 s.
Vibrissa placing — VP	Rat held by the tail, head facing an edge of bench, vibrissa just touching vertical surface.	Lifts head and extends forepaws in the direction of the bench, making oriented "walking" movements to go far from the edge, in 10 s.
Cliff avoidance — CA	Rat put on edge of bench, with nose and forefeet just over edge.	Withdrawal of head and both forefeet from edge, moving away from "cliff", in 10 s.
Auditory startle — A*S*	Sudden sound stimulus by percussion with a metallic stick in a metal surface.	Body retraction, with a transitory immobility. The stimulus was given twice in each test, with a 1-min interval.
Negative geotaxis — NG	Rat placed with head downwards, on a 45° slope.	Turns to face up the slope, at least ≥130°, in 10 s.
Free-fall righting — FR	Rat held by the paws, back downwards, is dropped from 30 cm onto cotton–wool pad.	Turns body in mid-air, to land on all fours. All legs must be free of body on landing.

According to Smart and Dobbing [25].