

Perinatal serotonergic activity: A decisive factor in the control of food intake

Atividade serotoninérgica perinatal: um fator decisivo para o controle da ingestão alimentar

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ABSTRACT

The serotonergic system controls key events related to proper nervous system development. The neurotransmitter serotonin and the serotonin transporter are critical for this control. Availability of these components is minutely regulated during the development period, and the environment may affect their action on the nervous system. Environmental factors such as undernutrition and selective serotonin reuptake inhibitors may increase the availability of serotonin in the synaptic cleft and change its anorectic action. The physiological responses promoted by serotonin on intake control decrease when requested by acute stimuli or stress, demonstrating that animals or individuals develop adaptations in response to the environmental insults they experience during the development period. Diseases, such as anxiety and obesity, appear to be associated with the body's response to stress or stimulus, and require greater serotonergic system action. These findings demonstrate the importance of the level of serotonin in the perinatal period to the development of molecular and morphological aspects of food intake control, and its decisive role in understanding the possible environmental factors that cause diseases in adulthood.

Keywords: Eating. Malnutrition. Serotonin. Serotonin uptake inhibitors.

RESUMO

O sistema serotoninérgico apresenta funções no controle de eventos biológicos fundamentais para o desenvolvimento adequado do sistema nervoso. A serotonina e o transportador de serotonina são indispensáveis

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para esta função de controle. A disponibilidade destes componentes é precisamente regulada durante o período de desenvolvimento, e podem sofrer interferências provindas do ambiente alterando sua ação sobre o sistema nervoso. A desnutrição, a inibição da recaptção da serotonina a partir de fármacos e mudanças na expressão de gênica do transportador de serotonina na gestação e lactação podem induzir o aumento de serotonina alterando sua ação anorexígena. As respostas fisiológicas desempenhadas pela serotonina no controle da ingestão exibem uma resistência quando requisitadas por estímulos ou estresses agudos, demonstrando que os animais ou indivíduos desenvolvem adaptações de acordo com as agressões ambientais sofridas no período de desenvolvimento. Patologias como, ansiedade e obesidade, parecem estar associadas à resposta do organismo a um estresse ou estímulo, necessitando de uma maior ação do sistema serotoninérgico. Estes achados demonstram a importância do conteúdo da serotonina no período perinatal ao desenvolvimento de aspectos moleculares e morfológicos do controle da ingestão alimentar, e sua função determinante para a compreensão das possíveis influências ambientais causadoras de patologias na vida adulta.

Palavras-chave: Ingestão de alimentos. Desnutrição. Serotonina. Inibidores da captação de serotonina.

INTRODUCTION

The serotonergic system is essential for the proper development of the nervous system. Serotonin or 5-Hydroxytryptamine (5-HT) and Serotonin Transporter (SERT) are essential for nervous system ontogenesis and maturation [1]. Environmental factors, such as malnutrition, selective serotonin reuptake inhibition, and changes in the expression of the serotonin transporter gene during the early stages of development may increase central serotonin availability, delay in satiety the trigger associated with hyperphagia, and reduce its anorexigenic effects in adult organisms [2-4]. However, despite the numerous studies conducted in recent years, the origin of the physiological and molecular mechanisms controlled by the serotonergic system has not been totally clarified. This review article focuses on the influence of serotonergic activity during the development period on food intake control.

Critical development period and phenotypic plasticity

Phenotypic plasticity is established to develop a central function on the etiology of chronic-degenerative diseases associated with the hypothesis of the development-related origin of health and disease. The risk of developing chronic diseases is closely related to the environment in which an individual developed

and his lifestyle in adulthood. Phenotypic plasticity is considered an adaptive process that allows the refinement of development patterns and mechanisms according to the surrounding environment. From the adaptive perspective, an individual will be benefitted by his ability to adapt to the environment [5].

Pieces of evidence of these adaptations in humans were demonstrated in 1970 by Ravelli *et al.* [6]. The Dutch Famine consisted of a period of food scarcity experienced by pregnant women during World War II (1944-1945). In adulthood, approximately 300,000 men exhibited changes in body composition, depending on the time in which they, as fetuses, had been exposed to maternal malnutrition. If malnutrition occurred in the last trimester of pregnancy, these individuals would have a low incidence of obesity. However, if it occurred in the first trimester, they would have a higher incidence of obesity [6].

In the 1960s Neel [7] described the 'thrifty genotype hypothesis', proposing that some populations were more susceptible to insulin resistance because of its possible relationship with environmental or genetic factors. The body's adaptation could benefit individuals who were exposed to food scarcity [7]. Some hypotheses had been explored by Neel [7], leading to a greater understanding of the importance of the gestation and breastfeeding periods to disease susceptibility in adult life. Certain subjects, such as metabolic programming and critical

development period, related to this knowledge resulted in a greater understanding of some diseases, such as diabetes and obesity.

The critical period represents a development window that cannot be inverted or repeated later on. Faster organization processes are more easily modified or interrupted [8]. Unlike the maintenance period, physiological processes during development do not have a uniform rate of emergence and duration. All processes exhibit critical periods whose importance and duration will depend on their variation rates. In the embryonic brain, many physiological events accelerate, slow down, or end their activities in a short period of time. The concept of vulnerability implies that the organization process is subject to perturbations that influence their rate of emergence or duration [9].

The nervous system development period consists of biological events, such as cell proliferation and differentiation, neuron migration, myelination, and synaptogenesis, which act on the organization and specialization of many brain structures [9]. During this period, they are extremely sensitive to environmental stimuli [8]. In humans the critical period starts in the prenatal phase, especially the last trimester of pregnancy, and continues until age five years. In rodents this phase lasts three weeks, starting at birth, the breastfeeding period [9].

Epidemiological studies have found a correlation between the critical development period and the onset of metabolic diseases in adulthood. One of the first hypotheses suggested by Hales & Barker [10], the thrifty phenotype hypothesis, proposes that stimuli or insults that occur during pregnancy, the perinatal period, and breastfeeding can promote physiological and metabolic adaptations. These adaptations may increase the provision of nutrients for the development of vital organs, such as the brain, in detriment of other organs. In the short run, the body would be able to adapt to the environment in order to survive. However, in the long run, these adaptations would increase the

body's susceptibility to disease. The studies on the thrifty phenotype hypothesis associate poor fetal and infant growth with higher susceptibility to low glucose tolerance and the metabolic syndrome in adulthood. A key issue for the discussion of this hypothesis is the proportion in which subjacent mechanisms are genetic or environmental [10].

During the study of the thrifty genotype and metabolic programming hypotheses, a new theoretical model is proposed by Wells [5], associating growth from childhood to adulthood to the risk of cardiovascular diseases in adulthood. In this hypothesis, birth weight is considered a 'metabolic capacity' index in which organ structure and function during intrauterine life and childhood promote homeostasis maintenance. According to this model, body and fat tissue growth are predictors of higher metabolic load just like low birth weight is a predictor of low metabolic capacity [5].

The theoretical models are inserted in the fetal origins of adult disease or phenotypic plasticity hypotheses. According to Gluckman *et al.* [11], genetic predisposition associated with environmental stimuli during development influences adaptive responses to the environment and increases susceptibility to disease in adulthood. Thus, phenotypic plasticity represents organisms' responses to different environmental conditions that generate a series of distinct phenotypes (morphological or physiological states) potentially expressed by a genotype [11]. To adjust cell processes according to environmental changes, epigenetic programming allows hereditary and reversible change of gene expression without changing the DNA sequence [12]. Epigenetic regulation may "program" genetic information and cell fate, and determine body, including brain, functionality. These mechanisms allow adaptive responses to environmental changes and optimize the chances of survival and reproduction [12]. In mammals, the signs that induce development plasticity are mediated during the fetal and neonatal period [12]. The

induction of phenotypic changes in offspring promoted by the mother may involve changes in the epigenome secondary to changes in DNA methyltransferase activity and histone structures [12]. In this review we describe the environmental influences that are associated with serotonin level in the central nervous system, such as malnutrition, selective serotonin reuptake inhibition, and change in serotonin transport gene expression during the development period. These influences promote structural, physiological, and behavioral changes, especially in food intake control.

Serotonergic system and development

Serotonin or 5-hydroxytryptamine is a monoamine widely distributed in the central nervous system. During development, it acts as a cell signaling agent, neuromodulator, hormone, and neurotransmitter, and its function may vary depending on the region in which it is located and the body's development and maturation phase. This molecule influences the induction of neurogenesis, neuronal differentiation, and synaptogenesis, and allows self-regulation of serotonergic neurons and development of target tissues [13]. Control of these biological events is essential for the proper development of the central nervous system. The first studies were able to identify the central serotonin level, morphology of its neurons, and components of this neurotransmission system, the enzyme Tryptophan Hydroxylase (TPH), the Serotonin Transporter (SERT), and the presence of serotonin [1,14-16].

In the human brain, 5-HT neurons first appear in the brainstem in the fifth week of intrauterine life [14]. Brain levels of 5-HT increase during intrauterine life until age two years, stabilize for a few years, then peaks at age five years [17]. In rodents serotonergic neurons appear between days 10 and 12 of intrauterine life, with serotonin synthesis detected one day

after their appearance; they complete their maturation at the end of the critical period [1,15]. After their appearance, serotonergic neurons emerge from the raphe nuclei in order to modulate the development and maturation of neuronal circuits in the hypothalamus, nucleus of the solitary tract, and cerebral cortex [15,18,19].

Since serotonin is hydrophilic and does not cross the blood-brain barrier, it must be synthesized in the brain from the essential amino acid tryptophan. This amino acid must be present in the diet as the body cannot synthesize it [20]. Central serotonin synthesis occurs mainly in serotonergic neurons of the dorsal raphe nucleus. Plasma tryptophan is either free or bound to albumin. Once it enters the neuron, tryptophan is hydrolyzed to 5-Hydroxytryptophan (5-HTP) by the enzyme TPH-2 present in the central nervous system [16]. Next, 5-HTP is decarboxylated by the enzyme aromatic L-amino acid decarboxylase to form serotonin.

After its synthesis in raphe neurons, serotonin is stored in vesicles present in pre-synaptic neurons. When free in the synaptic gap, 5-HT can act in its receptors, but after this interaction, its action ends. One of the degradation pathways of serotonin is performed by the enzymes monoamine oxidase A and B, breaking down serotonin into 5-hydroxyindoleacetic acid [21]. A second mechanism of serotonin degradation regards its reuptake by its transporter, located in the pre-synaptic membrane [22]. SERT is the main agent responsible for the regulation of 5-HT levels in the synaptic gap. The function of this cell membrane protein is to reuptake 5-HT that has not been broken down by monoamine oxidase in the synaptic gap and transfer it to the inside of the pre-synaptic neurons [22]. Active removal increases the speed in which the levels of neurotransmitter in the synaptic gap decrease, restricting the effects of 5-HT to smaller areas, and recycles some of the neurotransmitter released in the synapse for later use [22]. By changing its conformation, SERT moves one

or more serotonin molecules per cycle, unlike transmembrane channels, which remain open or closed. This allows molecules to exit the lipid-bilayered membrane.

Serotonin levels during nervous system development are minutely regulated, allowing early detection of intense serotonergic immunoreactivity [1]. During gestation, the placenta can synthesize and transport serotonin using a complex system of maternal conversion of tryptophan, the amino acid precursor of serotonin, into serotonin, releasing it in the fetal circulation [23]. A prenatal increase in tryptophan availability may prevent hyperinnervation of serotonergic neurons. This increase delays the development of serotonergic axons and reduces the synthesis of 5-HT [24]. Serotonergic innervation goes through hyperinnervation phases or temporary expression of some serotonergic receptors, which may be decisive for the participation of serotonin on the development and plasticity of the central nervous system. In mammals, the final density and distribution of serotonergic terminals are shaped during the postnatal maturation of the central nervous system [1]. Excess 5-HT during embryogenesis in SERT knockout animals reversibly reduces the radial migration speed of cortical pyramidal neurons, affecting the arborization of these neural circuits. The receptor 5-HT₆, expressed in pyramidal neuron progenitors when activated, replicates the effects of serotonergic stimulation [19]. These findings support the hypothesis that serotonergic homeostasis deregulation during development may affect the formation of the neocortical circuit and contribute to increase susceptibility to psychiatric disorders [19]. However, initiation of growth and innervation of serotonergic neurons may be an important inductor of structural and behavioral abnormalities.

Serotonergic neurons are widely distributed in rodent brain. Its projections originate at the raphe nuclei, located along the brainstem midline, and consist of numerous and distinctive groups of neurons that organize themselves, sending

out ascending and descending projections [1,25]. Two groups of serotonergic neurons seem to have distinct maturation pattern and migration. The rostral group, formed by the dorsal, caudal linear, and median raphe nuclei send predominantly rostral projections to the thalamus and hypothalamus. On the other hand, the caudal group formed by the nuclei raphe pallidus, raphe obscurus, and raphe magnus projects more caudally and ventrally to innervate the spinal cord and cerebellum [1,25]. Because of its widespread distribution in the central nervous system, serotonin influences many mammalian physiological spheres, from cardiovascular, respiratory, gastrointestinal, pain sensitivity, and thermogenic regulation to appetite, circadian rhythm, eating and sexual behavior, humor, locomotion, sleep, learning, and memory [26].

The development of the serotonergic properties of raphe neurons, such as serotonin synthesis, reuptake, and storage depend on a positive feedback system based on the presence of small amounts of 5-HT in order to initiate its own synthesis and stimulate the development of these properties, even in neurons that normally do not produce 5-HT [27]. This mechanism may be responsible for the quick development of serotonergic neurons and for the transitory presence of 5-HT in some neurons during development [15]. The synthesis of 5-HT from tryptophan increases in response to the frequency of electrical stimulation of the serotonergic cell body [16,22]. Short-term requirements for higher 5-HT synthesis may occur by changing the kinetic properties of TPH without the need to increase TPH level [28]. Serotonergic neurotransmission balance may present an increase in its metabolic processes in order to adapt to the demands made by environmental stimuli and aggressions.

Serotonin and food intake

Diet may be primarily considered a regulatory behavior whose function is to provide

energy to the body tissues, a critical process for survival [29]. The Solitary Tract Nucleus (STN) and the hypothalamus are considered the centers for detecting and responding to signs of hunger and satiety. The first central nervous system region to receive visceral sensory information from the oral cavity and peripheral regions is the STN, especially from the vagus nerve. The STN controls the beginning and end of digestion, and meal size [29]. The information that arrives at this nucleus is processed and transmitted to other brain areas, such as the hypothalamus and parabrachial complex, through direct or reciprocal connections [30-32]. The afferents received by the lateral parabrachial nucleus from the STN may be involved in visceral sensory responses [32]. These neuronal projections are an important pathway to suppress food intake. Stimulation of lateral parabrachial nucleus fibers reduces food intake [32]. Moreover, the STN sends the visceral information it receives to hypothalamic centers of homeostatic control, and receives descendent projections from the lateral hypothalamus and Paraventricular Nucleus [30,31]. The arcuate, ventromedial, dorsomedial, and paraventricular nuclei, and the lateral hypothalamus area are associated energy balance regulation [18]. The hypothalamus receives vagal afferents from the gastrointestinal tract, pancreas, liver, and adipose tissue, and integrates the information received from these organs and tissues with central information on hunger and satiety [18].

Serotonin is intimately related to food intake and seems to have an inverse relationship with energy intake as it reduces food intake by stimulating satiety in rats [33]. In the hypothalamus high serotonin levels promote satiety and low levels promote food intake [33]. The serotonergic neurons from the raphe nuclei send projections to the hypothalamus in order to control aspects of food intake, such as macronutrient selection and meal size, and energy balance for maintaining body weight [18,33]. The STN and the hypothalamus receive Neuronal populations that express neuropeptide

Y (NPY), Cocaine- and Amphetamine-Regulated Transcript (CART), Agouti-Related Protein (AgRP), and Proopiomelanocortin (POMC). The POMC neurons of the STN are activated by vagal afferents and satietogenic signals that limit food intake [32]. Stimulation of the AgRP and NPY neurons encourages food intake and reduces energy expenditure, while stimulation of the POMC and CART neurons reduces food intake and increases energy expenditure [18]. These responses may be mediated by serotonergic receptors [34]. Divided into seven classes (5HT₁ to 5HT₇) and 14 subtypes, the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors present serotonergic action on food intake [28,34,35]. The central use of 8-OH-DPAT, 5-HT_{1A} agonist, induced hyperphagia [35]. The 5HT_{1B} receptors expressed in serotonergic neurons act as self-receptors, inhibiting adenylyl cyclase, hyperpolarizing the neuron and reducing serotonin release [34]. The 5HT_{2C} receptors seem to modulate meal size and duration of food intake behavior [33]. In the arcuate nucleus of the hypothalamus, 5-HT hyperpolarizes and inhibits AgRP neurons, promoting inhibition of the POMC cells through 5-HT_{1B} receptors, and acts on 5-HT_{2C}, activating POMC neurons modulating food intake [34]. The rhythm of serotonergic activity in relation to food intake is associated with the transition of the day/night light cycles, as reflected by temporal changes in response to the 5-HT_{1B} receptor in the medial hypothalamus and in the release and use of endogenous 5-HT. Smaller serotonergic activity begins at the start of the activation of the food intake period, exactly on the transition of the light/dark light cycles [36]. At the beginning of the dark cycle, the active period for food intake in rodents, serotonergic stimulation more effectively suppresses food intake and particularly, carbohydrate intake [36]. The genes responsible for regulating serotonergic action, such as the gene *slc6a14*, which codifies sodium- and chloride-dependent amino acid transporters, and the gene *5-htr_{2c}*, which codifies the 5-HT_{2C} receptor, may be determinants of children's food intake control

and nutritional status. The gene *slc6a14* regulates tryptophan availability for serotonin synthesis. Children aged 7 to 8 years with *slc6a14* (rs2312054) and *slc6a14* (rs12391221) polymorphisms in leukocytes have higher food intake [4]. This finding may indicate a possible association between these polymorphisms in adulthood obesity.

The interaction between nutrition in the critical development period, serotonin action, and repercussions in adulthood has been documented by many researchers [2,9,37-40]. Perinatal malnutrition is one of the environmental factors responsible for structural and functional changes in central nervous system development, such as fewer neurons, and changes in neuronal shape and neurotransmitter levels [2,41]. The serotonergic system is greatly influenced by perinatal malnutrition [2]. The brain levels of serotonin increase during the postnatal period and adulthood of animals submitted to perinatal protein malnutrition. These changes may be related to higher levels of tryptophan in the brain and to the activity of 5-TPH, confirming the need of finely controlling 5-HT availability in the brain during the critical development period [2]. These changes may stem from response changes in serotonin neurotransmission.

Perinatal protein malnutrition seems to reduce weight gain and food intake in rats [37-40]. These animals gain less weight as they grow and have lower weight in adulthood. Despite this lower body weight, perinatal protein malnutrition increases food intake [37,38]. In the neonatal period, protein malnutrition reduced masticatory efficiency, weakening and delaying masticatory muscle maturation and the associated neuronal circuit [39]. A functional change associated with neonatal malnutrition and food intake seems to decrease the inhibitory effects of tryptophan on food intake in adulthood [40]. This resistance to the inhibitory effects of serotonin has also been observed in malnourished animals in gestation and lactation when submitted to acute fenfluramine

administration [37]. Serotonin control on food intake seems to fail when protein intake during the critical development period is sufficiently low.

Understanding the regulation of gene expression, such as the mechanism of induction of different phenotypes promoted by maternal diet during the critical period, allows a better understanding of the relationship between serotonin and control of food intake. The absence of serotonin reuptake mechanism in SERT knockout animals increases the extracellular levels of serotonin [42]. Despite the hypophagic characteristic of 5-HT, these animals have an obese phenotype in adulthood [43]. The mechanism associated with this obese phenotype in these animals has yet to be completely understood. These obese rodents are not hyperphagic, but they present changes in their exploratory behavior, such as low physical activity in their cages [43]. This obese phenotype may be reverted in animals when SERT is upregulated, demonstrating a possible consequence of low extracellular levels of brain serotonin secondary to higher SERT expression. Animals with upregulated SERT have low body weight and no changes in food intake [44,45].

Some pharmaceuticals, such as fenfluramine, can increase 5-HT levels by stimulating vesicular release and inhibiting reuptake, which promotes hypophagia, smaller meals, and higher intervals between meals in rodents [37]. The function of fenfluramine is to suppress food intake and facilitate weight loss by increasing metabolic rate [37]. Pharmacological or genetic SERT inhibition also evidences the inhibition of food intake. Higher serotonin levels promoted by selective serotonin reuptake inhibitors result in lower food intake. Fluoxetine increases serotonin in the hypothalamus and its hypophagic action [33].

Exposure to selective serotonin reuptake inhibitors during lactation reduces body weight and food intake [3,46]. The use of citalopram during lactation decreased growth and delayed the maturation of rodents' physical

characteristics [47]. The body weight of rodents exposed to fluoxetine was 22% lower at age 21 days [46]. The low body weight phenotype persisted to adulthood in neonatal animals exposed to fluoxetine [3]. In rodents, fluoxetine increases serotonin, stimulating satiety, which reduces food intake and body weight [33]. The development of the appetite regulation pathways in the hypothalamus occur predominantly after birth [48]. These pieces of evidence indicate that the postnatal period is important for food intake programming in rodents.

Physiological responses present a resisted response to acute stimuli or stress, demonstrating that these organisms develop adaptations according to the manipulations they experience during development periods or critical periods, which cannot be resolved depending on the demands of a new environment. The development of anxiety, obesity, and other diseases seems to be associated with an organism's need to respond to a stress or stimulus that requires higher action of its control systems, such as the serotonergic system. These findings show the importance of perinatal serotonin in the development of molecular and morphological components in food intake control, and its determinant function for understanding the possible environmental influences that cause diseases in adulthood.

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