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Effect of Perinatal Protein Malnutrition Under Serotonergic Control on Feeding Behavior: A Systematic Review

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Abstract: Protein malnutrition during the perinatal period leads to several morphological and physiological changes in the central nervous system whose main purpose is to prepare the body for environmental conditions. Several studies have been developed to explain the effects that malnutrition causes over feeding behavior in adults, and in particular on the role of the serotonergic system in this control. Thus, the objective of this systematic review was to assess emerging literature on the effects of perinatal malnutrition on the control of feeding behavior and the role of the serotonergic system in this control. The articles were researched in the virtual libraries Pubmed, Lilacs and Medline using as keywords: "Protein Malnutrition", "Feeding Behavior", "Serotonin Receptors", "Gestational malnutrition", "Perinatal undernutrition", "Fetal Nutrition Disorders" and "Serotonin". 261 articles in total were found. However, after excluding duplicates and analysis of the criteria for inclusion and exclusion 8 articles remained. Analysis of the articles showed that malnutrition in the perinatal period leads to changes in food preference in rats, in addition to delaying the point of satiety of these animals. It was also found that there is increased protein expression of c-fos groups forebrain neurons, increased expression of 5HT-1A receptors and increase in brain serotonin levels. These findings suggest that changes in eating behavior in malnourished animals can be brought about due to changes in the serotonergic system.

Keywords: Serotonin, Feeding Behavior, Protein Malnutrition

1. Introduction

Early in the life of mammals, there are phases in which intense physiological and structural changes in the nervous system occur, such as neurogenesis, synaptogenesis, and cell migration [1-3]. These phases have been termed critical periods of development [4]. The lack of nutrients during critical periods can promote the development of various types of diseases in the adult individual [5-7]. The main critical periods of development are the period of pregnancy and lactation [3, 8].

Studies to identify morphological and physiological changes in adulthood, resulting from assaults during the critical period, found an increase in the incidence of diabetes type II [6], increased visceral adiposity [9], hyperphagia, increased body weight, preference for palatable and high-fat diets, among others [10-12]. Furthermore, malnutrition during pregnancy or during lactation still entail changes in the serotonergic system, such as desensitization of 5HT-1B receptors and increased basal levels of brain serotonin, causing behavioral changes, which highlight the feeding behavior [7,13].

Feeding behavior is a complex mechanism that involves both central and peripheral stimuli that regulate hunger and satiety [14]. Among the various biomolecules that regulate feeding behavior [15], we can highlight some neurotransmitters such as some catecholamines [16-17], serotonin [18-19], Neuropeptide Y (NPY), a peptide related to Agouti (AgRP), Pro-opiomelanocortin (POMC) and Transcript Related to Cocaine and Amphetamine (CART) [20-24]. The different signals from different parts of the body are integrated into the central nervous system at the level of the hypothalamus and brainstem [25-27].

In recent years, several new studies have been conducted in order to associate malnutrition during perinatal period with changes in feeding behavior due to damage to the serotonergic system. Therefore, this study aimed to verify that association

through a systematic search investigating the publications of the last five years.

2. Method

This study deals with a systematic review of the literature. To this end, we selected original articles published in the last five years. The selection of items was held between October 18, 2014 until June 8, 2015 in the virtual libraries Pubmed, Scielo and Medline. The descriptors used were "Protein Malnutrition", "Feeding Behavior", "Serotonin Receptors", "Gestational malnutrition", "Perinatal undernutrition", "Fetal Nutrition Disorders" and "Serotonin".

Among all the articles found, all original ones that correlated malnutrition in the perinatal period with changes in feeding behavior and / or the central serotonergic system published in Portuguese, English or Spanish were included. As the exclusion criteria, we used review articles such as those articles that were published over five years ago and all articles published in languages other than Portuguese, English and Spanish. After application of exclusion and inclusion criteria, the remaining articles were arranged alphabetically for deletion of duplicates and analysis of the main results.

3. Results

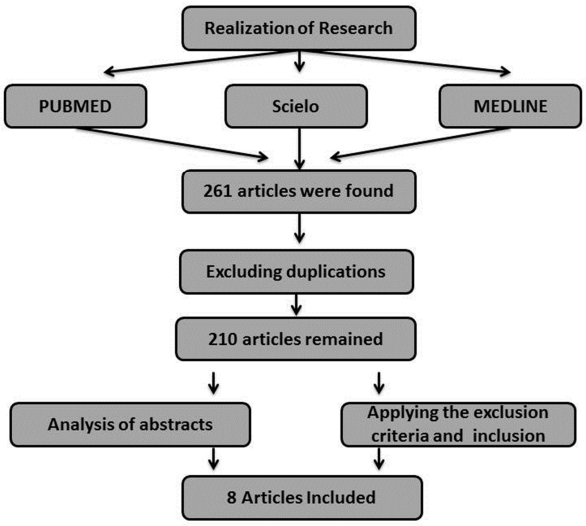

Figure 1. *Flowchart illustrating the steps of review.*

A total of 261 articles were found and distributed in the surveyed virtual libraries, 224 in Pubmed, 7 in Scielo and 30 in Medline. After applying the exclusion criteria and duplications found, eight articles remained. The steps of the review follow in Figure 1.

Table 1 shows the relationship between the set of words used with the number of articles found by the virtual library.

Table 1. *Relations between the keywords used and the number of articles obtained by virtual library.*

	Pubmed	Scielo	Medline	Total
Protein Malnutrition and Feeding Behavior	93	4	15	107
Protein Malnutrition and Serotonin Receptors	2	0	0	2
Feeding Behavior and serotonin receptors	99	3	1	95
Gestational malnutrition and Feeding Behavior	15	0	8	23
Perinatal undernutrition and Feeding Behavior	12	0	3	15
Fetal Nutrition Disorders and serotonin	3	0	3	6
TOTAL	224	7	30	261
TOTAL After duplications				210
TOTAL after the exclusion criteria				8

The types of malnutrition used were protein or caloric. Among the eight selected articles, six used the rat as experimental animal, another used a mouse and the last one used sheep. Among the six articles that have been performed in rats, the diets used to promote perinatal protein malnutrition showed variation in the concentration of casein. Thus, the control diet in two studies showed 17% casein and test diet was formulated with 8%. An article used 20% and 8% and another article used 22% and 0% casein to the test and control groups respectively. The two other articles used as malnutrition model a food restriction of 50%. This same pattern of 50% was applied to the study of sheep and another pattern of malnutrition under 40% of the reference consumed by the control group was used in the article that worked with mice. Articles found, the diets used, their respective objectives and key results are summarized in Table 2.

Table 2. *Main relevant aspects of the articles analyzed.*

Authors	Kind	Goals	Type of malnutrition / period	Main Results
Orozco-Solis et al., 2009	Rats	Analyze the feeding behavior of malnourished rats in the perinatal period	Protein malnutrition. Diet with 20% casein for the control group and 8% for the malnourished rats in the perinatal period.	During the first weeks after weaning malnourished pups had higher food consumption than the control group. Furthermore, it was found that malnourished animals had an increase in the size of meals and not increasing the number of meals.
Manjarrez-Gutiérrez et al., 2012	Rats	Check that intrauterine malnutrition can alter the tryptophan hydroxylase I and II expression to explain the accelerated serotonin synthesis seen	Calorie malnutrition. Standard diet for rats was administered in the control group and other diet with 50% of the standard	The intrauterine malnutrition increases the trunk brain serotonin levels such as increased expression of tryptophan hydroxylase I and reduces the expression of

Authors	Kind	Goals	Type of malnutrition / period	Main Results
		in malnourished animals.	nutrient was administered in the malnourished group	tryptophan-hydroxylase II.
da Silva et al., 2013	Rats	Analyze the effects of protein malnutrition in the period of pregnancy and lactation on s neurobiological mechanisms of food reward.	Diet with 17% casein for the control group and 8% for the malnourished group.	The protein malnutrition increases motivation for food reward and increases the protein expression of c-Fos in neurons in the basolateral amygdala and core, putamen, caudate nucleus, and dorsomedial nucleus of the hypothalamus.
Lira et al., 2014	Rats	Analyze the effects of perinatal malnutrition on the activation of the nucleus of the solitary tract in rats in response to food stimulation.	Diet with 17% casein for the control group and 8% for the malnourished group.	Animals that have suffered perinatal malnutrition had higher feed intake and increased activation of NTS in response to food stimuli
Rocha et al., 2014	Rats	Study the system ARC, PVN, and during NPY development of hypothalamic nuclei	Diet with 22% protein for the control group and 0% for the malnourished animals.	Protein malnutrition causes a delay in the distribution of NPY in the arcuate paraventricular-administration in rats.
Manuel-Apolina et al., 2014	Rats	Analyze the effects of intrauterine malnutrition on the expression of 5HT-1A receptors, D1 and D2, and Ob-Rb	Standard diet for rats was administered in the control group and other diet with 50% of the standard nutrient was administered in the malnourished group	An increase in the expression of 5HT-1A receptor and D2 on day 14, and Ob-Rb on day 14 and 90. There was a decrease in D1 receptor expression in the hypothalamic nuclei on the 14th day and increased on the 90th day.
Avraham et al., 2010	Mice	Examine whether supplementation with fish oil better morbidity and mortality associated with malnutrition and normalize endocannabinoids and monoaminergic systems involved in satiety and cognitive function in the hypothalamus and hippocampus	Standard diet to mice was administered in the control group and other diet with 40% of the standard nutrient was administered in the malnourished group	The fish oil supplement with increased lifetime and reduced cognitive decline in animals. In addition, it increased the levels of expression of genes for serotonin and dopamine in the malnourished group.
Nielsen et al., 2013	Sheep	Check that malnutrition in late pregnancy program to increase appetite and preference for high-fat foods in postnatal life.	Food standard (commercial plus) for the control group and sheep for the group test another diet with 50% of the standard diet of nutrients.	Malnourished sheep exhibit hyperphagia and preference for fatty and caloric foods.

4. Discussions

Several previous studies have correlated malnutrition in the perinatal period with permanent changes in different regions of the nervous system. The main findings suggest that malnourished animals show changes in the normal synthesis of serotonin and the identification of the biomolecule by their respective receptors [1, 18, 28]. Thus, the behavior in general, reflects the damage, whose principal behaviors affected are aggression [29], learning [30] and feeding behavior [13]. Feeding behavior is the result of interactions influenced by various central and peripheral stimuli that govern the search for food and hunger and satiety mechanisms [14]. This systematic review strengthens the literature, intensifying the hypothesis that the changes found in feeding behavior in early malnourished animals are due to changes in the serotonergic system.

Experimental studies with behavioral sequence of satiety in malnourished animals in the perinatal period have shown changes in eating behavior in adulthood, which led to increasing the size of the meal [7, 31]. The analysis of graphs of behavioral satiety sequence showed that malnourished animals showed a delay in satiety point, which consequently leads these animals to consume more food [7, 31], as shown in Figure 1. Similar results to these can be found in other previous studies, which have also undergone animals to protein malnutrition and found this delay in satiety [32-34].

Besides increasing the size of the meals, it was also observed that the protein malnutrition in the perinatal period leads to increased motivation for food reward and preference for palatable and rich-in-fat diets, in which these findings were observed in rats and sheep [9, 30]. The hedonic control of feeding behavior is regulated by different brain areas, such as the limbic system [35], cingulate and orbitofrontal cortex, mainly mediated by dopamine [36] and Serotonin [37]. Among these brain structures, the amygdala, caudate nucleus and the hypothalamus are involved in particular events related to the search for food reward. Therefore, besides investigating the motivation palatable food, da Silva and colleagues (2013) investigated the neuronal activation of undernourished rats in response to palatable food stimulus [30]. As a result, they observed increased neuronal activation in the basolateral amygdala and central core, putamen, caudate, and dorsomedial nucleus of the hypothalamus. These data seem to be in accordance with modifications of the motivation for palatable food intake.

Once the behavioral changes involved in food and food reward search may be triggered mainly by molecular modifications of dopaminergic and serotonergic pathways, it was found that in malnourished animals there was an increase

in gene expression for the 5HT-1A receptor such as an increase in serotonin levels and tryptophan hydroxylase I [28,38]. The 5HT-1A receptors are important receptors in satiety mechanism [39]. Studies show that stimulation of these receptors in the paraventricular nucleus of the hypothalamus reduces appetite, leading to satiety [18]. An increase of the number of these receptors associated with increased serotonin levels found suggests that there was a desensitization of the 5HT-1A receptors, since these animals showed a delay in satiety point [13].

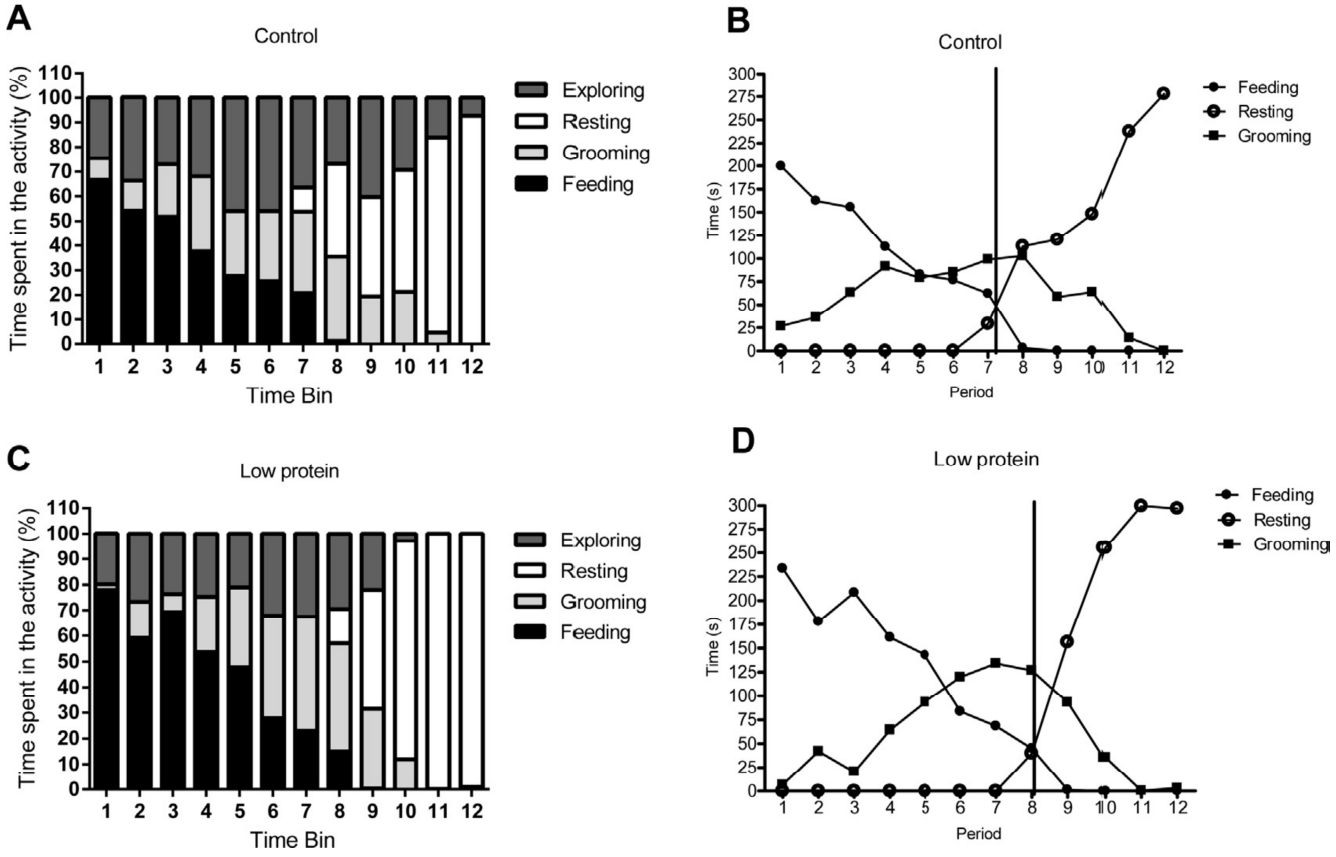

Figure 2. *Sequence of behavioral satiety in animals for 150 days old, subjected to perinatal malnutrition. (A) and (C) Power-supply frequency is not conduct in each period (5 min / period). (B) and (D) graphics that illustrate the crossing point between feeding behavior and rest. The vertical line indicates the point of satiety. (Lira, Almeida et al., 2014).*

Among the various biomolecules related to feeding behavior, there is Neuropeptide Y. Rocha *et al* (2014) verified that total protein malnutrition in the perinatal period leads in delayed maturation of the path of the arcuate NPY to the paraventricular nucleus, although it has not been consolidated the consequences of this event on feeding behavior [43].This neuropeptide is synthesized mainly by neurons in the arcuate nucleus of the hypothalamus. These neurons, when stimulated, cause starvation in animals [40]. An important receptor for regulating the release mechanism of NPY is the 5HT-1B receptor, which inhibits their synthesis. It is a presynaptic receptor expressed in various regions of the central nervous system, such as the hippocampus, cingulate gyrus, raphe nuclei and hypothalamic regions that govern feeding behavior, such as the paraventricular and ventromedial nucleus.

Another area affected by protein malnutrition in the perinatal period and that is also related to feeding behavior was the Nucleus of the Solitary Tract. It was verified that the NTS shows more activity in response to food in malnourished animals compared to the control group [31]. The NTS neurons receive information through various biomolecules and send dense projections to the lateral hypothalamus, taking action similar to electrical stimulation of the paraventricular nucleus of the hypothalamus [41-42]. It is noteworthy that the NTS receives afferents both from the gustatory pathways and from gastrointestinal neural pathways, which shows its importance in feeding behavior.

The damage that malnutrition causes in the serotonergic system, besides directly affecting the feeding behavior, causes impairment in memory mechanisms behavior [30]. This study verified through a food-motivational test that malnutrition interferes with the reward once the animal has a delay in storing the location of palatable food. This may happen due to the fact that malnutrition early in life affects the hippocampal formation [30]. Knowing that cognitive decline, Avraham *et al* (2010) developed a study with the purpose to check if the use of fish oil could reduce cognitive decline and normalize satiety signals evoked by serotonin and dopamine that malnourished mice present [44]. Therewith, it was found that the use of this oil not only reduces the cognitive decline and normalizes satiety signals but also increases the lifetime of animals. These findings, among others found in this review, deserve special

mention because it suggests that some of the effects observed due to malnutrition in the perinatal period can be mitigated.

5. Conclusions

Protein malnutrition in the perinatal period can promote changes in the control mechanisms of feeding behavior, including the serotonergic control. Such damage may involve hypothalamic nuclei, nucleus of the solitary tract, striatum, hippocampus, including other brain areas. Malnourished animals in the perinatal period have a higher consumption of pattern diet and increased motivation for food reward.

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