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Perinatal undernutrition associated to experimental model of cerebral palsy increases adverse effects on chewing in young rats

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HIGHLIGHTS

- Experimental model of cerebral palsy reduced body weight.
- Perinatal undernutrition associated to cerebral palsy reduced feed intake in rats.
- Undernutrition and cerebral palsy altered the functional aspects of mastication.
- Undernutrition and cerebral palsy damaged the morphological aspects of mastication.
- Perinatal protein undernutrition accentuated the intensity of morphological and functional deficits in paralyzed animals.

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ABSTRACT

The aim of the present study was to investigate the effect of perinatal undernutrition on the sensorimotor pattern of chewing in rats submitted to cerebral palsy experimental model. A total of 60 male Wistar rats were randomly distributed into four groups: Nourished/Control (NC, n = 15), Nourished/Cerebral Palsy (NCP, n = 15); Undernourished/Control (UC, n = 15) and Undernourished/Cerebral Palsy (UCP, n = 15). Animals of cerebral palsy (CP) group were subjected to an experimental model based on the combination of perinatal anoxia associated with sensorimotor restriction of the hindlimb. In the rats were evaluated body weight gain, intake of breast milk, feed post-weaning consumption, parameters of the chewing, intra-oral sensitivity and muscle properties (muscle weight and distribution of types of fibers) of the masseter and digastric. Animals from undernourished CP group showed greater reduction in most data evaluated including body weight ($P < 0.05$), food intake post-weaning ($P < 0.05$), frequency of chewing cycles ($P < 0.05$), duration of the reactions of "taste" ($P < 0.05$), muscle weight and decrease of the proportion of type IIB fibers in the masseter muscle ($P < 0.05$). These results demonstrated in rats submitted a cerebral palsy that perinatal undernutrition intensifies the damage in morphological and functional parameters of chewing.

1. Introduction

Cerebral palsy (CP) is a sensory-motor dysfunction resulting from a static, nonprogressive injury that affects the central nervous system development [1]. Its prevalence is about 2 to 3.5 per 1000 live births and it's considered the most common cause of physical disability in childhood [2]. However, in underdeveloped and developing countries, the prevalence is higher for presenting more favorable conditions for the occurrence of chronic problems such as CP [3]. In this context, CP

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is estimated to be 5 to 10 times more common in most low- and middle-income countries [4], reaching 4 per 1000 live births [5]. Moreover, commonly in these countries, the CP is related to poor maternal and child nutrition conditions [6,7].

Several epidemiological and experimental studies have shown that environmental variations, such as the nutritional intake during early life can lead to phenotypic changes with permanent effects on the structure and function of physiological systems [8–10]. In this context, the concept of phenotypic plasticity emerges. This concept is the ability of an organism to react to the environmental challenges, changing its form, state, movement or pattern of it activity [11]. Undernutrition, especially protein undernutrition can result in changes in the maturation of the central nervous system, including impairments in the myelination [12] and in the development of neurological reflexes [13]. These damages in the nervous system are also observed in children with CP [14,15]. Thus, it is possible that poor nutritional status aggravates the primary effects of brain injury in children with cerebral palsy [16].

Poor nutritional status observed in children with neurological disorders, results from eating difficulties [17]. These difficulties are involved in the oral preparation of the food, including problems with drooling, sucking, chewing and swallowing [17]. The delay in development of masticatory function, particularly, reduces the coordination of movements of the jaw and the bite force during food intake [18,19]. Moreover, the damage to pyramidal system, observed in CP, can lead to changes in muscle tone, and cause lesions in the efferent patterns (motor), which can lead to hypertonia and affect muscles that elevate the jaw [20]. These abnormalities appear to be caused by damage in the development of neural circuitry involved in the modulation of the masticatory movements [21].

In mammals, morphological and functional maturation of chewing occurs during the critical period of development of the central nervous system, particularly during pregnancy and lactation [22]. During this period, there are changes in the pattern of food consumption marked by the transition from behavior of sucking for chewing [23]. In rats, the first chewing movements were observed on the twelfth day of postnatal life [22]. However, the maturation of adult pattern of chewing is completed in the twenty-first day of postnatal life [22,24]. During gestation and lactation, the deprivation in food supply may interfere with the development of vital functions for the body [25]. However, little is known about how nutritional factors, particularly protein undernutrition, is able to influence the development of the masticatory sequelae induced by CP.

In this context, there are some experimental models of cerebral palsy that try to reproduce the damage caused by this disease. These experimental models allow, within limits, extrapolation to humans [26]. Therefore, such models have contributed in building potential therapies aimed at minimizing the chronic inability of the disease. Studies show deleterious effects on skeletal muscle and in the organization of the primary somatosensory cortex (S1) resulting from neonatal anoxia combined with immobilization of hindlimbs in rats [27]. Therefore, replication of this model could clarify the impact caused on feeding behavior, in particular chewing.

It is observed that the nutritional insults and cerebral palsy induce severe structural and functional impairments of various organs and body systems, particularly in the structure and function of the stomatognathic system. However, it has not been reported in the literature so far how undernutrition associated with experimental model of cerebral palsy may influence the chewing. Thus, the objective of the study was to investigate the effects of perinatal undernutrition on the sensorimotor pattern of chewing in rats submitted to cerebral palsy experimental model. Our hypothesis is that perinatal undernutrition exacerbates the masticatory damage in rats submitted to CP experimental model by reduction of food intake post-weaning and amount of mandibular movements performed during mastication, together with changes in the intraoral sensitivity and morphological modifications of the digastric and masseter muscles. These mechanisms should be clarified to minimize injuries related the clinical status of the disturbance and also contribute in the rehabilitation of individuals affected by CP.

2. Materials and methods

The Guidelines for the Care and Use of Laboratory Animals were followed and all efforts were made to minimize animal discomfort and the number of animals used. The project was approved by the Ethical Committee of Animal Use (protocol 23076.025165/2014-10), Federal University of Pernambuco, Brazil.

2.1. Animals

A total of twenty (n = 20) albino female rats and ten (n = 10) albino male rats were obtained from the Department of Nutrition, Federal University of Pernambuco. Female rats were mated (2 females for 1 male). The day when spermatozoa were identified in vaginal smear was the conception day. The females rats were divided randomly into two experimental groups according to dietary manipulation: nourished (N, n = 10) and undernourished (U, n = 10). Dams were fed ad libitum during pregnancy and lactation. At birth, litters were adjusted to eight pups from mothers that were chosen at random. Male offspring were used in each litter and females were used only to standardize the size of each litter to eight pups. The pups were randomly divided into four groups, based on the induction of experimental cerebral palsy. The Nourished Control Group (NC, n = 15) consisted of pups whose mothers were fed 17% protein and were not submitted to the experimental model of cerebral palsy. The Nourished Cerebral Palsy Group (NCP, n = 15) composed of pups whose mothers were fed 17% protein and subjected to the cerebral palsy model. The Undernourished Control Group (UC, n = 15) consisted of pups whose mothers were fed 8% protein and were not submitted to the experimental model of cerebral palsy. Finally, the Undernourished Cerebral Palsy (UCP, n = 15) composed of pups whose mothers were fed 8% protein and were submitted to the experimental model of cerebral palsy. The experimental diets were performed based on the study of Reeves et al. [28]. The animals were maintained at a temperature of 22 ± 1 °C, light-dark cycle of 12/12 h (dark 18:00–06:00 h). The pups remain with their mothers until the end of the lactation period (P21).

Animals of the different experimental groups (NC; NCP; UC and UCP) used for behavioral and morphological analyses were randomly distributed. A total number of sixty pups were used for the analysis of body weight, milk intake and weight of the masseter and digastric muscles from which fifteen pups were attributed randomly to the NC, NCP, UC and UCP groups. From the total number of animals, forty pups were used for the analysis of chewing mandibular movements and food intake, from which ten pups were attributed randomly to the NC, NCP, UC and UCP groups. For the analyses of fiber types' proportion, twenty pups from the total number were selected randomly and equally distributed between the experimental groups with five pups each.

2.2. Experimental model of cerebral palsy

The experimental model of cerebral palsy was based in the method described by Strata et al. [29], Coq et al. [30] and Marcuzzo et al. [31]. Rats from Nourished CP and Undernourished CP groups were submitted to perinatal anoxia and a sensorimotor restriction of hindlimb with the objective of reproducing the lack of active movement observed in CP. Animals underwent two episodes of 12 min each one of post-natal anoxia at birth (P0) and the first day of postnatal life (P1). After two episodes of anoxia, from second day of postnatal life until the twenty-eighth day of postnatal life, rats were subjected sensorimotor restriction of hindlimb during 16 h per day.