eNeurobiología

Vol. 15 | Núm. 35 | ISSN 2007-3054 | DOI: 10.25009/eb.v15i37.2630
Recibido: 20/04/2024 | Aceptado: 20/05/2024 | Publicado: 25/05/2024

Research article

Maternal behavioral disorders associated with neuronal changes in the lateral habenula of pre- and neonatally underfed rats

Conducta maternal alterada asociada a cambios neuronales en la habénula lateral de ratas con desnutrición pre- y neonatal

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This article can be found at: https://eneurobiologia.uv.mx/index.php/eneurobiologia/article/view/2630

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Vol. 15 | Núm. 35 | ISSN 2007-3054 | DOI: 10.25009/eb.v15i37.2630
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Abstract
Studies in lactating rats show that early food restriction induces deficient long-term cognitive states including newborn care, motivation, and disturbed multimodal sensory information, allowing dams to make decisions that enable pup survival. This study found a correlation between certain cognitive responses of early underfed dams and damages on the lateral habenula nucleus (LHN), which underlies motivational responses. We investigated this relationship by restricting food from gestational days (G) 6 to 12 (50%) and G13 to 19 (30%) and providing a balanced diet from G20 to G21. After birth, pups were underfed by rotating two lactating dams, one with tied nipples, every 12 hours. Pups were weaned at 25 days of age and given an *ad libitum* diet. The F1 dams' motivation (nest ratings, retrieval latency, and anogenital licking) was assessed during 10 min daily on lactating days (LDs) 4 and 12 when they were 90 days old. After the assessment on LD12, dams were sacrificed, and their brains were processed (Golgi-Cox) to measure the dendritic arbors and perikaryon of multipolar neurons from LHN. Early underfed dams showed significant reductions in nest ratings and anogenital licking and prolonged pup-retrieval latencies, concurrent with significant decreases in the number and density of the dendritic arbors, as well as in the cross-sectional area and perikaryon perimeter. The hypotrophy of multipolar LHN neurons points to possible alterations in the excitability, encoding, and integration of brain-descending code signals that modulate maternal motivation.

Keywords: Perinatal undernutrition, maternal motivation, lateral habenula, rats.

Resumen
En la rata, la restricción perinatal de alimento provoca deficiencias cognitivas que alteran el cuidado maternal, la motivación y el ingreso sensorial para la crianza. En el estudio, se correlacionan respuestas de madres con desnutrición temprana, y el daño neuronal de la habénula lateral que regula estados motivacionales. Se utilizaron hembras gestantes con bajos porcentajes de alimento del día gestacional G) 6 al 12 (50%) y del G13 al 19 (30%), seguido de dieta balanceada del G20 al G21. Después del parto, las crías continuaron su desnutrición rotando cada 12 h a dos madres lactantes, una con pezones ligados. Destete en el día 25 de edad, seguido de dieta *ad libitum*. La motivación materna (construcción del nido, latencia de acarreo, y lamido anogenital) se evaluó (10 min), en los días 4 y 12 de lactancia en el día 90 de edad. En el día 12 de lactancia, después de la prueba de motivación, las madres se sacrificaron y se procesó su cerebro (Golgi-Cox) para evaluar dendritas y somas de neuronas multipolares de la habénula lateral. Las madres que fueron desnutridas redujeron significativamente la construcción del nido y el lamido anogenital, incrementando su latencia para el acarreo de crías. Estos cambios concurrieron con reducciones en el número y densidad de dendritas, área y perímetro neuronal. La hipotrofia neuronal en la habénula lateral sugiere alteraciones en la excitabilidad, codificación, e integración de señales descendentes que modulan la motivación materna.

Palabras clave: Desnutrición perinatal, motivación maternal, habénula lateral, ratas.

I. Introduction

Newborn rats give their nursing dams multimodal sensory cues such as frequent ventral cutaneous stimulation, to improve the efficiency of adaptive motor paradigms, and elicit internal motivational and emotional states. These states are highly expressed during the early stages of lactation and gradually decline near weaning.[1] In turn, the dams exhibit intense fur stimulation, body licking, whisking movements, retrieval, and vestibular activation during huddling and suckling, all essential for the pups 'physical and cognitive development.[2-4]

Perinatal food restriction in the rat elicits long-term deficiencies in maternal care, such as decreased nursing time, pup retrieval, and body licking, as well as increased non-maternal behaviors like exaggerated self-grooming which diminishes physical contact with the young. These alterations in maternal care result in adaptive deficiencies when the pups enter adulthood, including vulnerability to affective and motivational disorders.[5-7] Early undernutrition also interferes with the progeny´s neuronal development in several brain structures underlying cognitive responsiveness, as it reduces cell numbers, dendritic branching, and the formation of spines with small perikaryal alterations that restrict their connectivity and neuronal interactions at cortical and subcortical levels.[8-11]

Neuroanatomical and neurophysiological studies in rats have shown that the habenular nuclei in both the medial and lateral subdivisions, maintain wide interconnections with the neocortical layers, basal ganglia, and limbic, brainstem, and spinal motor neurons to modulate the cognitive aspects of pups retrieval, nest building and the nursing posture over pups.[10,12-17] Furthermore, focal bilateral electrolytic medial and lateral habenula lesions disrupted the expression of motivation, emotional and cognitive responses, and maternal responses for at least seven days.[7,18,19] By contrast is unknown the diffuse damage linked to perinatal undernutrition on lateral habenular nucleus (LHN) development and the motivation of lactating rats. Therefore, we hypothesize that the damage to multipolar neurons in this structure will interfere with the expression of some maternal components during two stages of motivation during lactation.

2. Materials and Methods

2.1 Subjects

Animals (n=20) were 90-day-old female Wistar rats (*Rattus norvegicus*,) descendants of a stock originally obtained from Harlan Sprague-Dawley, Inc., and raised in an animal colony at the Laboratory Animal Facility of the Institute of Neurobiology, National Autonomous University of Mexico (UNAM). The Local Animal Committee approved animal care and protocols. They were conducted under the guidelines for the care and use of mammals in Neuroscience and Behavioral Research.[20] Furthermore, animal care and protocols were approved by Local Animal Committees project 108.A and Official Mexican Standard NOM-062-Z00-199. Subjects were obtained from eight pregnant, nulliparous dams at 100-120 days of age (200-250 g). All animals were maintained in an automatically controlled room at 23 ± 2 ºC, 50% humidity on a 12-h light/dark cycle (lights on at 07:00 h), with *ad libitum* food (Purina chow) and water. For mating, groups of four virgin female rats were housed with two males of similar ages. Sperm-positive females were placed one week before delivery in plastic maternity cages (35 x 27 x 17 cm^3) with grill tops, and woodchip bedding. The day of birth was referred to as postnatal day 0. Twenty-four hours later, pups were weighed and sexed, and four females and four males from each litter were randomly distributed among dams to reduce possible genetic and nutritional differences that might influence the experimental results. The presence of bila-

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teral thoracic and abdominal lines of nipples, as well as a shorter anogenital distance in females were used as criteria for newborn sex recognition.

2.2 Nutritional Procedures

2.2.1. Control group (CG)

The CG (n=10) was formed by lactating F1 dams obtained from four litters normally nourished by well-fed mothers (G0) with free access to food and water during the gestation and lactation periods. After birth, pups were fed and handled by interchanging a pair of normally lactating mothers every 12 h for 24 days, as described elsewhere.[21] The female F1 dams obtained through this procedure were mated and subjected to maternal testing at 90 days of age.

2.2.2. Underfed group (UG)

The UG0 dams (n=10) came from four different litters. The standard food requirement was calculated by measuring food intake in four pregnant rats (200-250 g) every week for 24 days. Each week's resulting average food intake was the basal level used to calculate the food-intake percentage of UG females. Dams were fed from gestational day 6 (G6) to G12 with 50% (9.5 g) of the balanced diet (Purina chow), from G13 to G19 with 70% (13.3 g), and then with 100% (19 g) of the same diet from G2 until parturition to avoid fetal resorption or cannibalism of newborns. This protocol was chosen because neurogenesis of the cortical and subcortical maternal circuit and afferent connectivity occurs between G12 and G21.[22] After birth, prenatally underfed F1 female newborns were nursed by two lactating control dams. The main galactophorous ducts were subcutaneously tied in one of these dams. The two lactating mothers were interchanged every 12 h between litters from PDs 1 to 24. The CG and UG (F1) groups of dams were weaned at PD25, after which rats were given free access to water and food (Purina chow) (Figure 1). The F1 females were maintained in groups of 4-6 until reaching 90 days of age when they were tested for maternal behavior with their litters.[21] This cross-fostering procedure minimizes the effects of stress and maternal sensory deprivation on the pups. Approximately 80% of UG dams were undernourished during the light phase of the cycle. This study evaluates the effects of pre- and neonatal underfeeding paradigms on body and brain weights. Moreover, nest ratings, retrieval latency, and anogenital licking were used to measure the lactating dams´ motivational level. Additionally, in CG and UG F1 lactating dams we evaluated the dendritic density and dendritic orders of branches, as well as the cross-sectional area, and perikaryal perimeter of large multipolar LHN neurons at LD12. The neuronal parameters were correlated with the long-term cognitive performance of the mothers on lactating days (LDs) 4 and 12 when their motivational response is at its highest or lowest values respectively.[23,24]

The maternal response components were videotaped (10 min) in a sound-proof room under continuous dim illumination provided by a red lamp (100 W=130 cd, Philips Co., Amsterdam, Netherlands).

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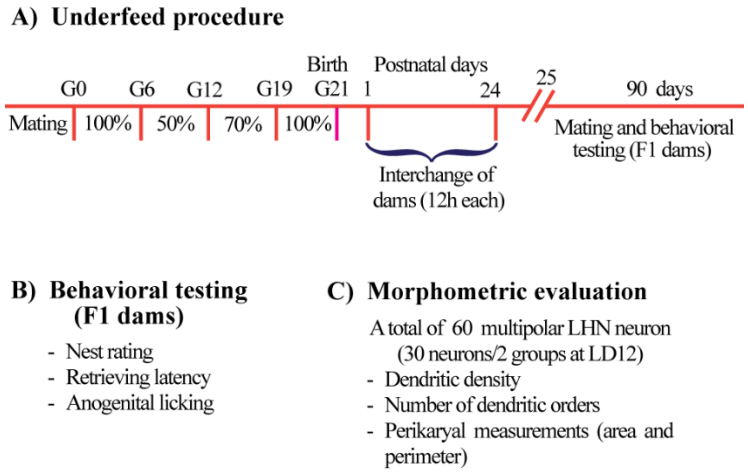

Figure 1. A) Underfeed procedure. B) Behavioral testing (nest ratings, retrieving latency, and anogenital licking) for (n=10) CG and UG dams at LDs 4 and 12. C) Morphometric evaluation of large multipolar LHN neurons in CG and UG at LD12 of dams.

2.3 Histology

The lactating dams were subjected to two dietary treatments (n=10, CG, and UG). After the maternal evaluation, body and brain weights were recorded at PD90, and LD12, to evaluate brain and behavioral development respectively. Afterwards, the dams were deeply anesthetized with ether and transcardially perfused with saline and then with buffered 4% paraformaldehyde (JT Baker, Co.), pH 7.4. Next, the dams were decapitated, and the brains were removed, weighted wet, cut into three coronal blocks, and immersed in Golgi-Cox solution for impregnation. Three weeks later, the blocks were dehydrated and embedded in low-viscosity nitrocellulose. Subsequently, they were cut into 120-150 µm coronal sections and serially mounted. The slides were coded to ensure blind evaluation concerning the dams age and dietary treatment. When digitizing neuronal images, the experimenter only had access to the code numbers, not the ages and nutritional treatments. The Paxinos and Watson atlas were used to identify and locate the LHN.[25] The anterior-posterior coordinates for the location of the LHN corresponded to values ranging from Bregma -2.12 to -3.80 mm. For each experimental group, 30 scattered and large multipolar LHN neurons were analyzed, broken up by fiber bundles of the stria medullaris.

2.4 Morphometric evaluation

After LD12, 60 well-impregnated multipolar LHN neurons per group (n = 30) with dendritic arbors confined to one section were evaluated for each experimental condition, age group, and neuronal parameter (Figure 2). Dendritic density was measured by placing the cell body and primary dendrites at the center of the first of a series of seven concentric rings (spaced at 40 µm intervals) and counting all dendritic intersections with larger individual rings. Dendritic order measurements were obtained by counting the number of 1^{sts}, 2nd, 3rd, 4th, and 5th dendritic orders. Dendritic branches leaving the cell body were defined as the first order, while those that branched from the former were considered second order, and so on. Additionally, the cross-sectional area and perikaryal perimeter of multipolar neurons were measured. In all cases neuronal measurements were obtained at a magnification of 40

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X using an image digitization system (Perception Analysis System by Human-Computer Interface, Cambridge, UK). No attempt was made to correct for compression of the three-dimensional dendritic arbor to a two-dimensional sketch since the relative differences between neurons remain constant when transformed from three to two dimensions. Furthermore, no stereological method was used because the dendritic arbor is confined to the tissue section. Additionally, the image analyzer performed some of the previously described calculations for the soma parameters.

2.5 Statistics

All measurements were analyzed with ANOVA comparisons (software *Statistica 7*): 1) Scores for body and brain weight of CG vs.UG dams were submitted to a normality and homogeneity of variance tests expressed as mean ± SD. Group measurements were analyzed with a one-way ANOVA. 2) For the maternal nest ratings, retrieval latency, and anogenital licking repeated measurements, a two-way ANOVA was used, 2 (dietary regimes) X 2 (ages). 3) The effects of undernutrition on the dendritic order and density of basilar branches of multipolar LHN neurons were analyzed using a two-way ANOVA, 2 (dietary conditions) X 5 (dendritic orders) or 7 (concentric rings). 4) The cross-sectional area and perimeter of perikaryal measurements from CG and UG rats were compared with a one-way ANOVA. The *post hoc* statistical comparisons between experimental groups were performed using the Fisher's (LSD) *post hoc* test. The alpha level for all comparisons was set at $p < 0.05$.

3. Results

3.1. Effects on body and brain weights of dams

Perinatal undernutrition affects the body and brain weights of lactating dams.

According to the ANOVA comparisons body and brain weight scores between CG and UG dams significantly decreased due to perinatal undernutrition (Table 1).

Table 1.
Mean ± SEM of body and brain weights of GC and UG dams (n = 10 /group).

Age (days)	Body weight CG		UG	Brain weight (LD12) CG	UG
90	290.00 ± 11.72		258.80 ± 4.52	1.92 ± 0.037	1.70 ± 0.31
Factor	df	F	p<	F	p<
Diet	1,8	6.16	0.037*	20.16	0.002*

3.2. Effects on maternal responses

Perinatal undernutrition disrupted the early and late motivational responses of dams.

3.2.1. Nest ratings of lactating dams

The ANOVA comparisons between groups indicated that nest ratings of UG F1 dams were significantly reduced, $F(1,14) = 38.95$, $p < 0.0001$, with no effects of age and interaction between factors. *Post hoc* comparisons indicated that on LDs 4 and 12 UG dams showed significantly reduced nest ratings ($p<0.05$) when compared with CG dams (Table 2).

3.2.2. Pup- retrieval latency

The ANOVA comparisons between groups showed prolonged significant retrieval latency exhibited by UG F1 dams. $F(1,14) = 9.45$,

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p<0.05. There were no effects of age and interaction between factors. *Post hoc* comparisons were only significant on LD12 (Table 2).

3.2.3. Maternal anogenital licking

The ANOVA analysis showed significant reductions in the UG group, F (1,14) = 10.96, *p*< 0.005, without effects on age and no interaction between factors. *Post hoc* comparisons were significantly reduced in the UG group on LDs 4 and 12 (Table 2).

Table 2.
Mean ± SEM of the maternal duration and latency of components recorded in CG and UG dams at LDs 4 and 12 (n = 10/group). * *p*<0.05.

Behavior	LD4		LD12	
	CG	UG	CG	UG
Nest ratings	2.63 ± 0.18	1.50 ± 0.19*	2.75 ± 0.16	1.88 ± 0.13*
Retrieval latency	386 ± 201	396 ± 295	284 ± 157	732 ± 198*
Anogenital licking	759 ± 60	369 ± 76*	681 ± 60	532 ± 99*

3.3. Morphometric analyses

Perinatal undernutrition disrupted the development of multipolar LHN neurons in lactating dams.

3.4. Effects on the dendritic arbor

The density of the dendritic circle crossings of multipolar LHN neurons of dams, measured as the number of dendrites with seven circles, showed significant reductions associated with the diet ($F_{1,58}$=24.901, p<0.0006) and the number of circles (7) ($F_{6,348}$=291.174; p<0.0001) without interaction between factors. *Post hoc* comparisons of dendritic crossings indicated that the UG of dams were significantly reduced (p<0.05) from the 2nd-5th number of circles on LD12 (Figure 2A).

The number of the dendritic orders of multipolar LHN neurons of dams indicated significant reductions associated with the diet ($F_{1,58}$=20.97, p<0.0002) and the dendritic orders (5) ($F_{4,232}$=254.091, p<0.00001. Moreover, a significant interaction between factors interaction ($F_{4,232}$) =3.492, p<0.008. *Post hoc* comparisons indicated that UG multipolar neurons showed significant reductions (p<0.05) in the 3rd, 4th, and the 5th dendritic orders on LD12 (Figure 2B).

3.5. Effects on perikaryal measurements

The ANOVA comparisons of the perikaryon area measurements showed significant reductions in the multipolar LHN neurons of the UG dams ($F_{1,58}$=543.97, p<0.001) (Figure 2C). ANOVA comparisons of the soma perimeter measures indicated significant reductions associated with diet ($F_{1,58}$=422.36, *p*<0.001).

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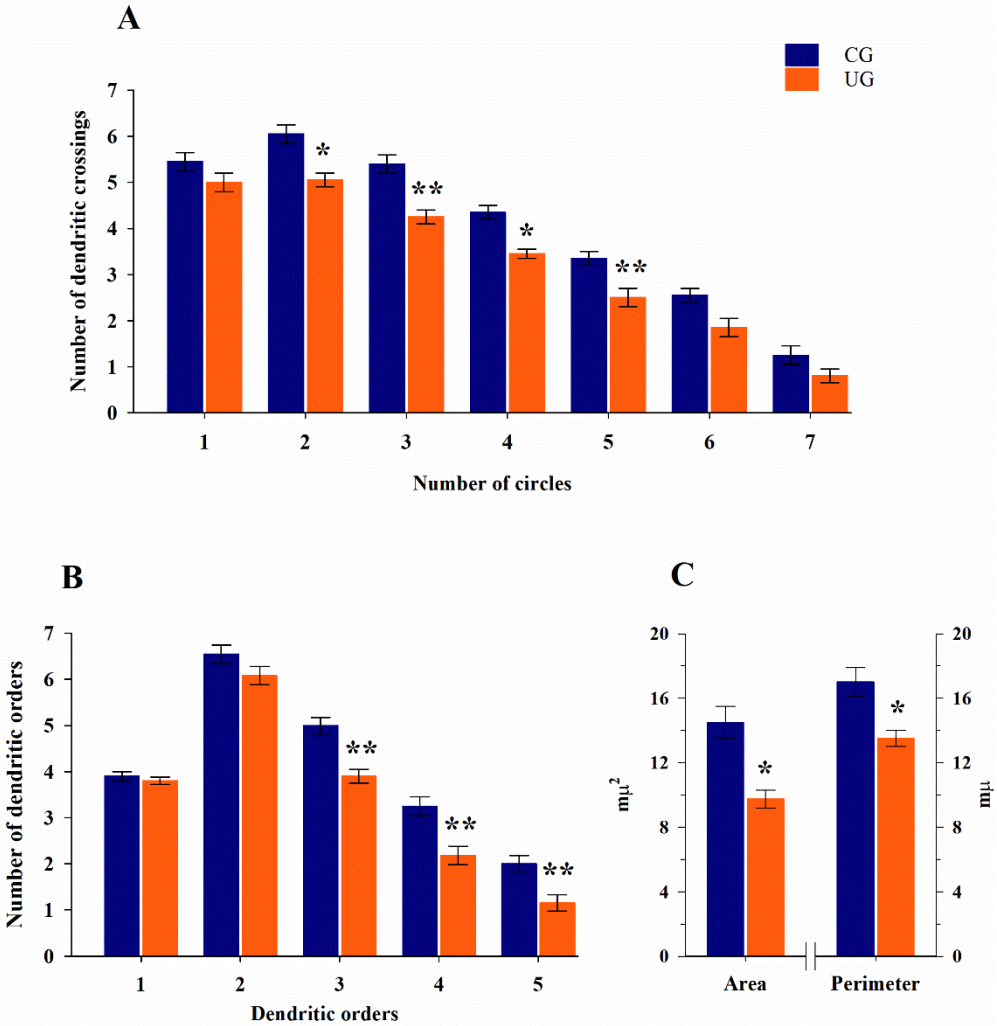

Figure 2. Mean values ± SEM at LD12 of A) Dendritic crossings, B) Dendritic orders, and C) Perikaryal measurements of multipolar LHN neurons during the development of CG and UG groups of dams. * $p<0.05$, ** $p<0.001$. Note the general significant decrements in the dendritic crossings, number of dendritic orders, and perikaryal values in the UG dams.

4. Discussion

The current findings showed that perinatal undernutrition induced significant reductions in body and brain weights of dams between G0 and LD25, and at 90 days of age, they were on a balanced diet and tested for maternal behavior. The prenatal undernutrition established in F0 dams included 30% to 50% food restriction (G6 to G20), which possibly interfered with the size and weight of the placenta and with fetal nutrition, as described elsewhere.[26,27] F1 pups from PDs 1 to 24 were underfed by rotating two well-fed lactating rats one with tied nipples between litters, resulting in significant sensory deficiencies in mother-litter interactions, tactile stimulation, and long-term cognitive outcomes.[7,21] These alterations are consistent with those in previous reports, suggesting that several factors, such as the abnormal

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structure and function of the placenta, and the reduced tactile sensitivity in altered mother-litter interactions, lead to decreased physical contact and pup licking with long-term behavioral consequences.[2,4] These findings also align with studies in isolate–reared rats, which were less attentive to their young, as they performed fewer pup retrievals and spent less time licking their pups.[28] Moreover, early undernutrition disrupts the release of various hormones and growth factors that promote proteins, body and cellular, glia, and brain synaptic development that impact body weight, which constitutes tangible evidence of the harmful effects of early food restriction.[14,29-31] Additionally, the present data showed that UG lactating dams exhibited significantly reduced motivational responses that interfered with the nurturing of their pups, as reflected by the decrease in nest ratings, anogenital licking on LDs 4 and 12, and retrieval latency on LD12. The findings of this study also indicated that both pre- and neonatal food restriction in UG dams resulted in consistent reductions in dendritic branch density and number of dendrites, from medial to the distal portions for the synaptic reception of the multipolar LHN area, compared with the CG of dams on LD12. Although we did not evaluate the number and distribution of afferent dendritic frameworks, previous reports have shown that the large diencephalic multipolar LHN substrate generated between G13 and G16 remains a well-conserved epithalamic structure that receives inputs from the medial prefrontal cortex, olfactory bulb, basal ganglia, and lateral hypothalamus between G14 and G16. This is generally concurrent with the rat´s cognitive motivational appearance.[32,33] LHN efferent projections reach the midbrain, brainstem, and spinal cord, modulating motor actions, stress, mood, and motivational decisions.[16,34] The motivational deficiencies of UG dams in this study could be partly associated with the development of LHN neurons and with the LHN hypotrophy caused by perinatal undernutrition. These deficiencies interfere with their modulatory influence upon the lower brainstem, disrupting the release of dopamine and serotonin neurons and the appearance of maternal-altered motor and cognitive responses for pups survival as described elsewhere.[32,35] Furthermore, motivational alterations in UG dams may be related to the pups´ delayed sensory development and the restricted environmental stimulation, both of which hindered the anatomical and functional development of the young.[2,4,36,37]

On G15, amniotic fluid in the rat uterus is constantly modified within a narrow range of conditions that the fetus needs to challenge in addition to the somatosensory and chemosensory cues that impact its brain development for a less stable environmental habitat. Thus, the fetus mainly responds to the activation of chemical signals that reach the brain through the placenta and travel through the immature embryonic olfactory and gustatory systems. These sensory systems advance in their development by birth and undergo rapid maturation. They also have increased plasticity to promote cognitive processes such as maternal odor and taste recognition, early learning, attentiveness, and motivation outcomes.[38-41] Several studies indicate that somatosensory in the rat input appears early during gestation, in contrast to the mainly postpartum origins of ear and eye-opening.[42] The role of this early tactile sensory system in prenatal cognitive development is still unspecified. Furthermore, early undernutrition significantly delays and restricts these sensory channels' anatomical and functional development.[7,9] However, how these sensory influences contribute to attention, mood, and motivational development later in life is still poorly understood.[2,15,43]

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In the rat, the olfactory bulb macro neurons (mitral and tufted cells) are formed between days G12 and G15. They gradually proliferate and increase their connectivity in the following prenatal days, achieving their functional maturity at birth.[41] However, their growth and morphological organization in layers occur after birth. The total physiological activity of macro neurons is achieved perinatally when wide interconnections with granule cells and precise interconnections within the olfactory glomeruli are established.[44] The neurogenetic processes of macro neurons continue in the olfactory bulb during the first three weeks of life, whereas interneurons undergo these processes even in adulthood.[45] Although olfactory bulb macro neurons are formed before birth, perinatal undernourishment at the LHN level may have long-lasting functional consequences on the maternal underfed motivational responses of underfed dams. These findings suggest that UG dams exhibit alterations relevant to newborn discrimination since olfaction is a fundamental sensory avenue for early adaptive responses such as precocious learning, motivation, and maternal care of the progeny.[44] Our findings showed long-term motivational deficiencies in early underfed lactating dams. These deficiencies are concurrent with not previously described LHN neuronal damages, possibly deteriorating the efferent cortico-subcortical signals underlying maternal developmental cognition. However, further studies are needed to understand how early food restriction and the associated delayed sensory development, may impact the morphological and functional brain substrate implicated in cognitive phenomena by using electrophysiological, anatomical, cellular, and molecular techniques.

5. Conclusion

Our findings showed that the perinatal underfeeding paradigm in this study which evaluates high or low maternal motivational responses, was associated with the hypotrophy of multipolar LHN neurons of UG dams. These neurons possibly relayed different code information from cortical and subcortical structures to modulate deficient maternal cognitive responses. The findings provide evidence that disrupted mother-newborn interactions due to perinatal food restriction may be a robust source of brain damage associated with potential psychiatric disorders, working memory impairment, decision-making, drug addiction, and altered affective behaviors. These anatomical and functional disorders of the brain, observed in the early underfed model of lactating dams, may be helpful to understanding the cognitive disarrays relating to perinatal nursing commonly observed in humans in underdeveloped countries. However, further studies using the current model may be challenged and needed by the exposure to different dietary paradigms, reaction to various novel environmental cues, underbrain disorders or associated with addictive drug exposure. Further studies are necessary to understand how the exposure in early life to food restriction adversity increases the vulnerability to several disorders including affective and reward dysfunctions.[46]

6. Acknowledgments

This work was partly supported by DGAPA/UNAM, IN200317. We thank Jessica González Norris for the editorial assistance and helpful suggestions, and V. Avalos for collecting data.

7. Conflict of interest

No conflict of interest was reported by the authors regarding this publication.

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Vol. 15 | Núm. 35 | ISSN 2007-3054 | DOI: 10.25009/eb.v15i37.2630
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Vol. 15 | Núm. 35 | ISSN 2007-3054 | DOI: 10.25009/eb.v15i37.2630
Recibido: 20/04/2024 | Aceptado: 20/05/2024 | Publicado: 25/05/2024

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