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Review Article

# Kyphotic response alterations in perinatally underfed lactating dams

## Alteraciones de la respuesta cifótica en madres lactantes desnutridas perinatalmente

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**Resumen**

Durante la succión las crías reciben alimento, estimulación sensorial para su desarrollo corporal y protección para sobrevivir. En esta revisión se enfatizan las alteraciones en la postura cifótica de madres lactantes F1 con desnutrición perinatal y su expresión durante la succión. En un grupo de ratas gestantes F0 desnutridas (50%, G6-G12; 30%, G13-G19), se evaluó el impacto del ayuno en una incubadora (12 h), y en otro (F1), rotando (12h) entre las camadas a 2 madres lactantes, una con pezones ligados (días 1 al 24 de edad). Destete en el día 25 de edad, seguido por dieta balanceada hasta el día 90, cuando se evaluó su respuesta cifótica. Se cuantificaron (días 5-30 de edad) las dimensiones del cráneo, nariz-coxis, tarso-metatarso y falanges, eje bitemporal, peso corporal y apertura de párpados de las ratas F1. La desnutrición perinatal redujo significativamente el peso corporal, apertura de párpados y déficits del esqueleto, principalmente de la zona de inserción de la masa muscular dorsal toraco-abdominal, participante en la cifosis para lactar. Funcionalmente, esta postura provocó deficiencias del inmunomarcaje c-Fos en la sustancia gris central que controla la musculatura de la región nariz-coxis-falanges de las madres F1 desnutridas para la succión de sus crías (días 4 y 12). Las deficiencias en la respuesta cifótica afectan el desarrollo de las crías con posible daño cognitivo a largo plazo. Los hallazgos pueden ser relevantes para entender las alteraciones en la crianza de madres adolescentes usualmente de talla corta, en el inicio y frecuencia de la alimentación del neonato.

*Palabras clave:* Desnutrición temprana, Desarrollo físico, Postura cifótica, Ratas.

**Abstract**

In the rat, the mother provides the newborns with plenty of breastfeeding, sensory stimulation, and protection for survival. In this review, we emphasized the deficits in the kyphotic response of F1 lactating dams with pre- and neonatal undernutrition that interfere with the pups´ sucking activity and physical and brain development. One group (F0) compared the effects of gestational food restriction (50%, G6-G12; 30%, G13-G19) and postnatal undernutrition of F1 pups to investigate their physical development. To analyze the impact of early undernutrition on the physical development of F1 rats, prenatally underfed subjects were placed daily in an incubator (12 h) or by the rotation (12 h) of two dams, one with nipples-ligature (days 1-24) between litters. Weaning was at 25 days old, and rats followed a balanced diet until 90 days, when pregnant F1 dams were tested for the kyphotic response. Skull, nose-coccyx, tarsus-metatarsus, phalange lengths, bitemporal axis, body weight, and eyelid-opening were measured in F1 rats (days 5-30). Pre-and neonatally undernourished F1 subjects exhibited body weight and skeletal deficits at most of the ages than controls. Furthermore, the functional evaluation of the nose-coccyx and limb musculature for the kyphotic posture elicited in F1 mothers by active pups (days 4, 12) indicated that undernutrition interfered with the kyphotic response. Functionally, this posture disrupted c-Fos immunostaining at the periaqueductal gray of F1 dams and the pups´ body growth, brain sensory activity, and possibly later cognition. The findings may be relevant to understand long-term effects in adolescent human mothers, usually with short stature and poor interest in newborn breeding.

*Keywords:* Early undernutrition, Physical development, Kyphotic posture, Rats.

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## 1. Introduction

During the mother-litter bonds, the dam displays a complex adaptive motor outcome to provide the newborn with thermal, tactile, olfactory, and pheromonal stimulation through body licking, whisking movements, relevant vestibular activation during anogenital licking, retrieval, and nipple attachment maneuvers for suckling.[1-7] In the nest environment before a suckling bout, the newborns are attracted to maternal and nest volatile odors, ultrasound vocalizations, and residual milk gustatory components to stimulate the oxytocin in the dam prolactin secretions necessary for the synthesis and release of milk.[8] During a normal suckling response, the lactating dam exhibits, among other motor activities, a notorious kyphotic posture relevant for the nutrition, development, and protection of pups in the nest that gradually declines around weaning.[9] The newborns stimulate the dam´s ventral somatosensory region to provoke quietness or immobility, bilateral symmetry, hyperextended limbs with the ventral trunk over the pups, and arching back. This kyphotic response or posture for suckling depends on the long back musculature located in the nose-coccyx length area, modulated by the cortical discharge following the pyramidal tract, midbrain caudal periaqueductal gray (cPAG), cerebellum, vestibular nuclei, and spinal motoneurons to activate the long back muscles necessary for the kyphotic expression.[10-13] The current review emphasized, among other components of the maternal response, the keystone of the dam kyphotic response in perinatally underfed dams as a unique natural space for intense mother-pup bonding. In this regard, it is known that early in life, the crouching mother response occurs in a nest where the size, temperature, bedding material, milk, fecal, and urine traces, among other cues, play a capital influence for pups´ physical, and functional brain development.[7]

## 2. Early undernutrition and brain deficiencies

In the rat, perinatal undernutrition or malnutrition significantly interferes with brain growth and functions by reducing neurogenesis, myelination, and the number and density of dendritic branches, spines, and synaptic contacts.[14-22] These anatomical alterations are concurrent with early poor sensory influences resulting in an immature brain with an impaired sensory organization that may disturb the reception, transmission, encoding, and integration of ascending neuronal messages from the peripheral sensors to the cerebral cortex. This information organized in the cerebral cortex disrupts cortical-subcortical integration, resulting in deficient complex locomotion, self-grooming, suckling postural performance, and early social motivation and cognition.[23-27] Most of these early brain impairments are concurrent with a low body and brain weights, delayed ear and eye-opening, reduced body size, and lower weights of visceral measurements during adolescence and adulthood.[28-30]

This review aims to provide evidence that the disrupted physical development of perinatally underfed mothers interferes with the adaptive motor and postural responses of lactating F1 dams for newborn suckling activity. In summary, the use of the pre-and neonatal underfeeding models may be relevant to test the effects of refeeding syndrome and early sensory stimulation and to compare with other underfeeding procedures, among others[31] Furthermore, the use of this experimental model may be helpful to understand the origins and mechanisms underlying some human cognitive disorders, associated with disruptions in the maternal natural niche that impact the newborn physical and brain development during the disrupted adolescence, and early pregnancy.[27,32]

## 3. Perinatal undernutrition and physical development

Different experimental prenatal- and neonatal undernutrition or malnutrition models have consistently shown physical alterations in the progeny, such as lower body weight, delayed ear and eye-opening, delayed somatic bones formations, and altered striate muscles and functional parameters of body growth compared to controls, that may persist into adulthood.[28,33,34]

Thus, the embryonic and fetal periods are critical time windows as nutritional impairments can affect fetal growth by disrupting placental intrauterine development.[35] Furthermore, the prenatal effects are potentiated when undernutrition is prolonged during the pre-weaning stage.[30,34,36]

In a recent study, we analyzed the physical development of Wistar rats affected by perinatal food restriction[28] Thus, in one gestationally underfed group (UG), 12 F0 dams were fed from gestational day 6 (G6) to G12 with 50% (9.5 g) of the normal diet, from G13 to G19 with 70% (13.3 g) and with 100% (19 g) until parturition. After birth, food restriction of F1 dams continued by using a neonatally underfed paradigm (n=12), in which one of two mothers (F0) had ligated nipples (UL) and F1 pups (n=8 per litter) was interchanged every 12 h (at 08:00 and 2000 h) with a non-ligated control (NLC) lactating dam (F0) from postnatal days (PDs) 1-24 as described elsewhere.[37,38] Additionally, another group of F1 newborn rats was underfed by placing half of the litter (n=4 pups) into an incubator (UI), with sensory deprivation for 12 h a day from PDs 1-24. Controls of the incubator (CI) were only placed for 2 minutes on PD 1. In all groups, weaning was performed on PD 25, and after that, F1 rats were fed ad libitum and maintained in groups of 4-6 subjects until PD 90, when they were tested for the maternal kyphotic response. The physical development measurements in F1 rats were made with a special plastic anatomical tape (0.5 cm width) that included the skull, nose-coccyx, tarsus-metatarsus, phalange lengths, bitemporal axis, mean body size and eyelid-opening, which were compared with their controls.[28]

The results showed that skull and nose-coccyx lengths of F1 subjects related to the insertion of the musculature for the kyphosis in the CG, UL, and UI groups gradually increased during development with significant reductions in the UL and UI groups compared to the CG from PDs 5-30. The tail length and bitemporal axis comparisons, not relevant for dams´ crouching between the underfed male and female groups, indicated significant reductions in UL and UI females compared to controls from PDs 10-30. Furthermore, for tarsus-metatarsus and phalange length comparisons, significant decreases were observed between the experimental groups from PDs 5-30 (see Table). Additionally, the analysis between weight and height measurements showed a gradual weight loss during development in UL and UI groups compared to their controls. Moreover, the mean cerebral and body weights comparisons with controls at PD 90 were reduced; and the size length comparisons indicated a significant decrease in both underfed group values throughout the study (PDs 5-30). Finally, eyelid-opening of female pups in CG, UL, and UI groups was retarded only at PDs 13 and 14. In the case of male pups, the significant delay was from PDs 13-15.

In summary, the physical measurements related to the long-back musculature underlying the kyphotic response were negatively affected in the UI and UL subjects. However, comparisons of the impact of sensory deprivation (UI), or increased sensory stimulation (UL) on the physical measurements, were relevant only at PD 30 to interfere with the physical development of long-back muscle activity for nursing.[28] Additionally, these physical measurements are interesting for newborn care, as the delayed development of the nose-coccyx, tarsus-metatarsus, and phalanges lengths alters the kyphotic posture of dams during the suckling activity and affects the interactions with the progeny in the maternal niche.

| PDs | Sex | CG | UL | UI | CG | UL | UI |
|---|---|---|---|---|---|---|---|
| | | Nose-coccyx lengths | | | Tarsus-metatarsus and phalanges lengths | | |
| 5 | F | 7.25 ± 0.09 | 6.25 ± 0.06* | 6.45 ± 0.03* | 1.42 ± 0.01 | 1.19 ± 0.02* | 1.24 ± 0.02* |
| | M | 7.84 ± 0.07 | 6.42 ± 0.05* | 6.72 ± 0.04* | 1.52 ± 0.01 | 1.27 ± 0.02* | 1.26 ± 0.01* |
| 10 | F | 9.00 ± 0.09 | 7.70 ± 0.05* | 7.88 ± 0.04* | 2.04 ± 0.03[1] | 1.67 ± 0.02*[2] | 1.70 ± 0.04* |
| | M | 9.27 ± 0.04 | 7.92 ± 0.08* | 8.03 ± 0.07* | 2.25 ± 0.01 | 1.86 ± 0.02* | 1.86 ± 0.03* |
| 15 | F | 10.65 ± 0.14[1] | 8.81 ± 0.12* | 9.11 ± 0.07* | 2.55 ± 0.03 | 2.21 ± 0.02* | 2.50 ± 0.03[4] |
| | M | 11.40 ± 0.09 | 9.34 ± 0.11* | 9.16 ± 0.07* | 2.69 ± 0.02 | 2.26 ± 0.02* | 2.56 ± 0.02[4] |
| 20 | F | 12.05 ± 0.21[1] | 10.48 ± 0.17* | 10.90 ± 0.11* | 2.82 ± 0.03[1] | 2.59 ± 0.03* | 2.70 ± 0.04 |
| | M | 12.95 ± 0.10 | 11.03 ± 0.13* | 11.25 ± 0.10* | 2.98 ± 0.01 | 3.71 ± 0.50* | 2.77 ± 0.04* |
| 25 | F | 13.98 ± 0.14[1] | 12.30 ± 0.12 | 12.39 ± 0.04 | 3.25 ± 0.03 | 2.90 ± 0.02* | 3.32 ± 0.03[4] |
| | M | 15.02 ± 0.08 | 12.73 ± 0.16* | 12.48 ± 0.11* | 3.33 ± 0.02 | 3.00 ± 0.01* | 3.33 ± 0.04[4] |
| 30 | F | 15.41 ± 0.17 | 14.40 ± 0.18* | 13.91 ± 0.10* | 3.33 ± 0.02[1] | 3.10 ± 0.30* | 3.51 ± 0.03*[4] |
| | M | 15.30 ± 0.05 | 14.58 ± 0.15* | 13.85 ± 0.09* | 3.62 ± 0.02 | 3.04 ± 0.03* | 3.67 ± 0.02[4] |

Table. Mean (± SEM) of body lengths (cm) in CG, UG, and UI female and male pups on PDs 5-30. (n= 23 per condition). * p <0.001 CG vs. UL or CG vs. UI; ~ p <0.01 CG vs. UL or CG vs. UI; (1) p <0.01 F CG vs. M CG; (2) p < 0.01 F UL vs. M UL; (3) p < 0.01 F UI vs. M UI not shown; (4) p < 0.01 UL vs. UI.

## 4. Early undernutrition and kyphotic response

In the maternal niche of rats, the kyphotic response is a relevant component of maternal care, as it creates a unique environment for protection, nursing, sensory stimulation, and learning and memory.[39] Studies have shown that early malnourished or undernourished dams significantly diminished the time spent crouching over the pups.[38,40-42]However, when the present findings are compared with those studies, they do not give clear evidence on the types and durations of nursing postures, how they could impact newborn development, and their correlation with the neuronal central gray modulatory mechanisms, among others. A recent study analyzed the effects of prenatal undernutrition using different percentages of the normal diet. At birth, prenatally underfed females were fed by two dams, one with her nipples tied, that was rotated (12 h) between litters from PDs 1-24.22. Weaning was at PD 25, and F1 females were maintained in groups of 4-6 until reaching PD 90 when they were tested for maternal behavior. [39,41] Maternal behavior was recorded only at PDs 4 and 12, when nursing and motivation were highly expressed, also to limit the disruption of mother-litter bonds. Functionally, the main results indicated neuronal Fos-I deficiencies mainly in the prefrontal cortex with minor effects on the amygdala.[29] The behavioral components were previously evaluated in a similar experimental report and included different durations and types of kyphotic postures of dams defined as follows: low kyphosis, the duration of quiescent posture with partially arched back and most of the limbs extended incompletely; high kyphosis, the duration of crouching with a pronounced dorsal arch or ventroflexion. Most of the pups (4 or more) suckled (at least 2 min or more) while the dam was quietly immobile in a symmetric posture with a pronounced or slight back arch and rigid legs splayed over the pups. Partial kyphosis, the duration of partial crouching with no support of the forelimbs or the hind limbs while hovering over the pups with access to her ventrum; prone, the duration of lying over the pups without any leg support while the young suckled or the dam regrouped; regroup, corresponds to any dam movement over the pups while nursing.[43] The findings showed that on PDs 4 and 12, F1 dams exhibited unaffected low kyphosis and significant increments in the partial and prone kyphotic responses, which may restrict the pups' access to maternal care, the nipples, and milk intake. These alterations in the direct mother-litter bonds on PD 12 indicate that pre- and neonatal undernutrition interferes with the maternal response, including the high kyphotic posture and the passive or active motor activities of F1 dams in caring for their newborns, as described elsewhere.[41-43]

Additionally, these studies suggest that disruption with proprioceptive and tactile stimulation given by F1 dams to the pups during suckling may interfere with the release of growth factors involved in synaptic junctions that possibly result in long-term learning and social development of the pups.[44,45] Another point of interest concerns how the pups' activity causes deficiencies in the kyphotic posture of UG dams. Current data showed prolonged F1 latencies of pups regarding nipple attachment and suckling of UG F1 dams on PD 12, which may reflect disrupted neuromuscular activity. Thus, it is possible that the poor, intermittent sensorimotor cutaneous stimulation to the dam's ventral trunk is due to the significantly reduced weight and body size of pups, as well as to their weak muscular activity, making them unable to stimulate the dam's mobility and crouching posture for nursing. This assumption is supported by the fact that pups nursed by early UG dams decrease the frequency, duration, and intensity of suckling bouts, and often when the mother leaves the nest, they lay down scattered on the floor as a passive litter mass.[46,48,49] Additionally, early undernutrition significantly reduced muscle fibers and secondary myotubes and altered the growth ratio between the brain and masticatory muscle activity.[33,34] Furthermore, pups on perioral anesthesia during nursing show a reduced number of suckling bouts or hyperthermic pups that interfere with the tactile ventral stimulation and maternal behavior, including the kyphotic posture, during the first week after birth.[10,46,47] Another possible explanation for the kyphotic posture alterations is that prenatal- and neonatal food restriction in F1 female pups may result in long-term changes to the nursing response mechanisms. This is due to early damage to muscle development and the anatomical and functional development of the sensorimotor cortical and brainstem systems descending to the spinal cord motoneurons, which undergo an intense phase of cell proliferation during the first two weeks after birth.[34] Additionally, descending systems that modulate both limb movements and trunk axial muscles for passive or active lordosis and kyphotic postures mature during the gestational period.[12] Furthermore, the unsteady postural development of the trunk anticipates adult motor patterns, particularly the deficient stabilization of the trunk as a major factor in the development of limb hyperextension accompanying the F1 dam's kyphotic nursing posture.[49] Early underfed F1 dams also showed significantly reduced nest rating scores and anogenital licking on PDs 4 and 12 of lactation.[29,41]

### 4.1. Functional analysis of the kyphotic response

In the rat, the crouching posture is modulated mainly by tactile stimulation of the pups. The cPAG in its ventrolateral portions (cPAGvl) is an essential brain stem structure for suckling and kyphosis. It is also a locus of a notable increase in early gene c-Fos expression as a marker of neuronal activity underlying the kyphotic nursing posture. Thus, cPAGvl immunocytochemical staining in early underfed F1 dams on PDs 4 and 12 of the lactation periods exhibited significant bilateral cPAGvl reductions in the absence of the pups but slight increases when dams were exposed to their litter. By contrast, control dams exposed to control pups had a two-fold increment only in the presence of the litter. These findings suggest that the somatosensory cues of pups reared by early underfed dams are possibly suboptimal in frequency and intensity to achieve the threshold for the kyphotic nursing posture and milk release. Underfed pups significantly reduced movements' frequency, intensity, and duration during suckling bouts.[46] Furthermore, c-Fos immunostaining in the cPAGvl is related to the pups' suckling activity and the kyphotic posture of the dams.[13] The lack of correlation between the significant decrease in the cPAGvl immunostaining of UG and CG dams and the non-significant effects on high kyphosis on PD 4 of lactation may be explained by the absence of the impact provoked by the 4-h separation from pups < 10 days of age. These pups rarely left the nipple and maintained poor motor activity and suckling to stimulate the dam's ventrum compared to older pups.[23] Additionally, in early underfed dams, the cortical discharge descends following the pyramidal tract to reach the cPAGvl column, cerebellum, vestibular nuclei, reticulospinal tract, and spinal motoneurons that are affected by perinatal undernutrition, hence disturbing the posture of the trunk that precedes the dam's limb

movements for suckling.[12] The cPAGvl is the only structure in the brain that increases c-Fos immunolabeling after suckling behavior. It is related to emotional activity and autonomous components associated with stress and aggressive behavior, which also grow in rats with early food restriction.[13] Finally, our results support electrolytic lesion studies in the PAG, which inhibits the kyphotic response for nursing. These studies found the reduced duration of the kyphotic nursing posture, total nursing components, and diminished body weight gain in the newborn13 and UG dams.

In summary, the physical and functional alterations associated with perinatal undernutrition interfere with maternal nest rating scores and the kyphotic posture durations after suckling, reflecting deficiencies in the mother-litter bonds. Furthermore, the reduced ventrum somatosensory stimulation of underfed pups may affect the expression of Fos-IR at the brain stem cPAGvl of the lactating dams. In the context of the human societies of poor and underdeveloped countries, the experimental findings here may be of great interest because around 50% of the females early in life suffer different degrees of malnutrition or undernutrition, followed by reduced body growth compared with the well-fed female population. Today maternal food restriction in adolescents is a prevailing situation that contributes to the incidence of premature births and fetal growth retardation because of the competition for nutrients in the dyad. Moreover, the findings may be relevant to understanding adolescent human mothers' long-term effects, usually with short stature and poor interest in newborn breeding.

## 5. Conclusions

Alterations in the kyphotic postures of perinatally underfed lactating F1 dams were evaluated during the nursing of their litter. The findings indicate that lactating underfed dams are associated with long-back length reductions and functional activity. These alterations resulted in deficient nest rating scores and disrupted kyphotic nursing posture reflecting a critical deficiency in the mother-litter bonds. Furthermore, these dam's kyphotic alterations may result in significant decrements in pups' activity, diminished body weight gain, and delayed morpho-functional activity of muscle fibers in the offspring of UG dams. Moreover, current data may provoke long-term alterations in the kyphotic neuronal mechanisms associated with early undernutrition of the F1 UG dams.

Additionally, the reduced ventrum somatosensory stimulation provoked by the offspring of early underfed F1 dams interferes with the expression of Fos-IR in the brainstem cPAGvl neurons. However, further studies are required using the present or different underfeeding paradigms to identify the possible effects of cross-breeding underfed young. The findings suggest that the disrupted kyphotic posture interferes with the mother-litter bonds and may have long-term consequences on the pup´s cognitive disorders. In this regard, our results correlate well with the clinical evidence that maternal depletion of energy in adolescence leads to a deficient nutritional status at conception, altered fetus growth, preterm birth, and delayed breastfeeding with possible late cognitive disorders in the progeny.

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## 7. Disclosure statement

The authors declare no conflict of interest regarding the publication of this article.

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