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Review Article

Effects of perinatal undernutrition on juvenile play development of rats

Efectos de la desnutrición perinatal en el desarrollo del juego juvenil de ratas

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Resumen

En la rata el juego social es una respuesta innata, necesaria para promover el desarrollo de habilidades motrices, el rango social y el aprendizaje de respuestas esenciales para sobrevivir. Asimismo, el desarrollo del juego es un proceso complejo donde los protagonistas son expuestos a múltiples influencias sensoriales, y estresores ambientales incluyendo entre otros al aislamiento materno breve y el aporte de alimento. Tanto la malnutrición como la desnutrición perinatal afectan el desarrollo cerebral y sus funciones, al reducir el número de neuronas, depósito de mielina, número de dendritas y los contactos sinápticos en diversas estructuras corticales y subcorticales que participan en la integración del juego social. En esta revisión se analiza el impacto de diferentes modelos experimentales de restricción de alimento, y cómo el deficiente desarrollo sensorial asociado en diferentes áreas cerebrales pudiera impactar la transmisión, codificación de señales e integración de la actividad neuronal involucrada en el procesado del juego juvenil. Los hallazgos revisados pudieran ser relevantes para la comprensión de las alteraciones en el desarrollo del juego social, dependiente del trastorno sensorial causado por la restricción temprana de alimento. Estas alteraciones interfieren con mecanismos relacionados con la obtención de habilidades motoras, experiencia temprana y la cognición que pueden reconocerse durante la juventud y la adultez.

Palabras clave: Desnutrición perinatal, desarrollo sensorial y juego, ratas.

Abstract

In rats, juvenile play is an innate behavior that improves motor skills, builds social ranking, and provides basic learning experiences for survival. Juvenile play is also a complex process in which the animals are exposed to multisensory signals and environmental stressors, including maternal separation and perinatal food restriction. Perinatal malnutrition or undernutrition impedes brain growth and functions by decreasing neurogenesis, myelination, and the number of dendritic and synaptic contacts at different cortical and subcortical brain areas subserving juvenile play combinations. In this review we examined, in the rat, the impact of experimental models of perinatal food restriction, and how disordered sensory activities at different brain levels may disrupt the transmission, encoding and integration of the neuronal activity underlying the complex expression of juvenile play. Moreover, current findings may be relevant to understand how the sensory impairments provoked by perinatal undernutrition and its associated stressors may alter the mechanisms involved in motor skill development, early-life experiences and cognition as observed in youth and adulthood.

Keywords: Early undernutrition, sensory and play development, rats.

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I. Introduction

In mammalian species the neuronal mechanisms underlying juvenile play and reproductive-like functions are integrated in the cortical and subcortical brain structures that evoke motivation, autonomic states, refined movement displacements and postural adaptive responses.[1-4] Juvenile play is a sexually dimorphic, pleasurable, voluntary activity that consists in abundant stereotyped movements initiated when the animal is relaxed and healthy.[5,6] Furthermore, juvenile play is a complex social response in which the participants are exposed to several multisensory environmental signals and conditions that may influence the organization and expression of late non-social behaviors like flight, hunting, fighting, and reproductive activities, among others.[7,8] Unfortunately, evidence about the neuronal mechanisms underlying basic juvenile neuromotor activity in healthy and in handicapped and rehabilitated subjects is sometimes contradictory, as diverse non-physiological procedures, ages, and species have been used.[9,10]

In rodents, perinatal food restriction and the associated impoverishment of neonatal sensory stimulation are some of the non-genetic factors that may interfere with early brain development and are determinants for social behavioral disruption in adulthood.[11,12] In the rat, perinatal undernutrition or malnutrition significantly interferes with brain development and functions by reducing neurogenesis, myelination, and the number and density of dendritic arbors, spines and synaptic contacts in different areas of the brain.[13-19] These anatomical alterations associated with early sensory deficiencies result in an immature brain with impaired sensory and hormonal organization that affects an animal's response to environmental demands.[20] Furthermore, brain alterations may disturb the transmission, encoding and integration of ascending neuronal information from the peripheral receptors to the cerebral cortex, affecting the integration of reflex, locomotor and social motivational activities including juvenile play responses.[2,21-30] The aim of this review was to analyze and compare the effects of different perinatal food restriction procedures, the associated impaired sensory maturation, and the role of mother-litter bond deficiencies in the mechanisms underlying the juvenile play development of rats.

2. Undernutrition and juvenile play development

2.1. Effects of olfactory and cortical influences

Several reports showed that in the study of play fighting in rats, bilateral olfactory bulbectomy or induced anosmia by zinc-sulfate olfactory mucosa painting, at 23 or 24 days of age, did not affect the frequency of play fighting and play initiation by males, but slightly increased the frequency of play fighting without affecting play initiation in females. These findings suggested that early modulatory influences of the olfactory bulbs in the cortical and limbic structures and their association with amygdala activation were not especially relevant for play fighting expression.[31] However, when total decorticated rats were assessed in like-lesioned pairs, the frequency of pinning—in which one rat stands over a supine partner during play fighting—was reduced about by 50%, and average pin durations were shorter. Furthermore, separate tests of play solicitation behaviors did not identify any differences between controls and decorticated subjects suggesting that play motivation remained intact. Although studies in neonatal decorticate rats indicate little effects on rough-and-tumble play, these may be explained by

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moderate impairments in motor-postural control and/or reduced cortical somatosensory excitability.[32] Additionally, from postnatal days (PDs) 25 to 40, decorticate rats exhibited a 50% decrease in juvenile play fighting but increased the types of defensive responses compared to controls. The findings suggest that the cerebral cortex may interfere with the defensive responses of juvenile rats with prolonged ventral-ventral contact during play fighting.[33] However, other studies have analyzed the effects of cortical and subcortical diffuse neuronal damages associated with neonatal undernutrition and sensory deprivation in the rat. The results showed that the total mean frequency of boxing, wrestling, and pinning markedly increased in male and female rats from PDs 20 to 60. Moreover, females exhibited an increase in juvenile play and during the interaction in pairs in the prepuberal period.[34] These findings suggested that early food restriction and sensory deprivation were concurrent with reduced maternal anogenital licking and body contacts directed to the newborns which may have interfered with the somatosensory diffuse cortical and subcortical brain maturation, including the structures underlying juvenile play at peripheral and central modulatory mechanisms.[19,27,30,31,35-37]

In summary, the findings of these studies indicated that modulatory influences in the cortical and limbic structures via the olfactory bulbs and amygdala activation did not seem to be particularly relevant for juvenile play expression in rats. Furthermore, the findings showed that complete cerebral cortex removal decreases juvenile play fighting responses by 50% compared with sham-control subjects. Additionally, the diffuse cortical damages elicited by neonatal undernutrition also reduced play behavior in pairs or groups of rats, although food restriction and sensory stimulation increased the mean number of total dorsal body contacts, compared with pins directed to the nape and flank areas, which were significantly reduced (Fig.1).[10] The effects of juvenile play on neonatal decorticate rats may be also explained by moderate impairments in motor cortical control mechanisms, as exhibited by increases in diverse types of defensive responses.[32]

The preweaning growth of young rats is highly dependent on intense mother/litter bonds that impact both maternal care activities and the newborn’s somatosensory and motor development including play performance. In this regard recent studies indicated that the maternal motivation of F1 underfed lactating dam’s changes throughout lactation. Thus, when maternal motivation was evaluated at PD 90, by recording deficiencies in retrieving, handling shavings, and crouching posture at PDs 4 and 12, the motivation of F1dams for pups was high (day 4) or declining at PD 12. Additionally, maternal motivation was correlated with c-Fos immunostaining of neurons in the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) when pups were removed from the dams 90 min after suckling. The findings showed that early underfed dams had Fos-I neuronal deficiencies in the mPFC, with minor effects on the BLA, possibly because the sensory cues required to evoke maternal motivation and possible the juvenile play motivation were suboptimal and/or due to deficient maternal network electrical transmission that are relevant to trigger deficient cognitive mother-litter bonds, mutually interfered with the neuronal network of adolescent rats for further play development.[38] Current findings support the role of the maternal prefrontal cortex in the integration of sensory signals transmitted from different olfactory, visual, somatosensory, and auditory neuronal routes, with the limbic structures regulating the internal emotional states. Moreover, these sensory avenues are essential for cognitive spatiotemporal performance, such as maternal care, social play, attentiveness, and locomotor activity. Specifically, the mPFC, BLA and cerebellar vermis play an important role in maternal memory consolidation, decision making and conditioned learning.[4,21,23,39-42] Studies in early underfed F1dams have evaluated the anatomical effects of reduction (Golgi-Cox) on the distal dendritic segments of layer III pyramidal neurons, perikaryon measurements, and the number of dendritic spines in the anterior cingulate cortex (ACC), mPFC and BLA.[38,43] In the newborn, the ACC, mPFC and BLA are a part of the neuronal networks associated with social play development, maternal response, motivation, and emotional states, among others.[6] Unfortunately, current knowledge about how perinatal undernutrition influences juvenile play motivation is still limited. There is little information on the specific anatomical network damages underlying the motivational responses integrated at the brainstem level. Moreover, how they are possibly combined with the deficient multisensory arousal systems, and the origins of the autonomic nervous substrate associated with visceral activities and basic coordinated movements involved in juvenile play development.

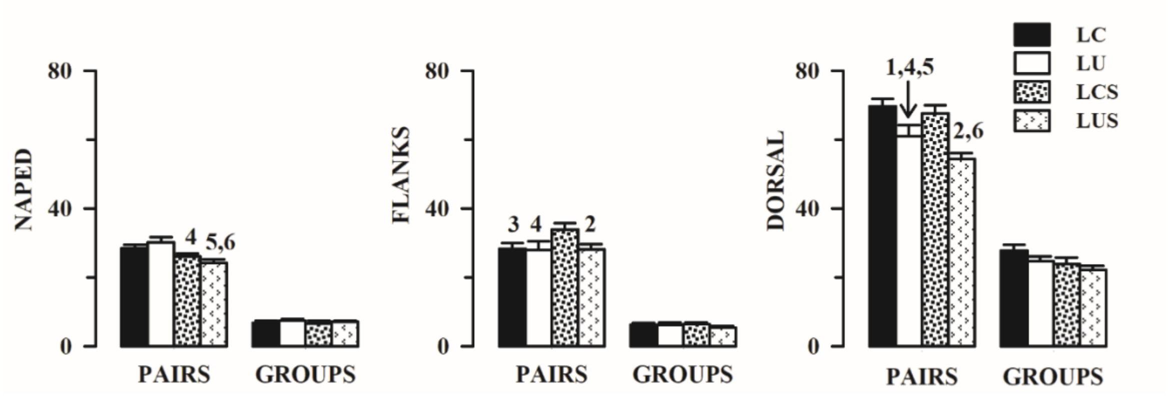

Figure 1. Mean values ± of total body contacts directed at partners during the play in pairs or groups. Note the higher values in the dorsal area in the play in pairs and groups, with reductions in the LU and LUS groups, and minor values directed at other areas. Numbers above bars indicate different statistical comparisons (LC vs LU1, LCS vs LUS2, LC vs LCS3, LCS vs LU4, LU vs LUS5, LUS vs LC6).[10]

2.2. Effects of somatosensory influence

Maternal somatosensory stimulation is a relevant source of influence to modulate the expression of specific adaptive motor responses in young rats, including maternal anogenital licking, huddling, grooming, suckling, and retrieving. These responses are elicited by sensitive skin receptors located in strategic areas of the pup's body. adaptive motor responses including reflex activity, locomotion, posture for retrieving, and juvenile play development, among others.[5,10,22,25,44-49] In this context, a series of experiments have shown the relevant effects somatosensory stimulation of the skin to evoke juvenile play in rats. For example, local xylocaine anesthesia of the dorsal body surface of rats reduced the frequency of pinning during play performance, by 35% to 70%, while motivation to play remained intact. The findings suggested that dorsal body surface anesthetization decreased the stimulation of somatosensory receptors that trigger juvenile play expression. Thus, when untreated rats were paired with locally anesthetized rats, the untreated rats consistently pinned the dorsal body area of

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anesthetized rats more than vice versa but maintaining the motivational play response.[25]

Another point of interest to study the role of somatosensory influence was to analyze if during juvenile play in pairs or groups of subjects (n=4 per group) of the same sex, the somatosensory contacts given by F1 underfed rats at the nape, flanks, and the hairy dorsal skin areas to invite a partner to play, could have different effects on the frequency of hairy skin pinning throughout the testing sessions from PDs 15 to 60. According to several studies, pinning is a reliable indicator to measure juvenile play components in rats.[6] Findings on the total number of pins given by an early F1 underfed rat to a partner showed that pins to the nape and flanks were unaffected or poorly activated, whereas pins to the hairy dorsal area decreased. Moreover, pinning increased more during juvenile play in pairs than in groups with perinatal undernutrition.[10] Additionally, the effects of early handling for 5 min from PDs 1-7, and the exposure to a sensory-enriched environment for 30 min a day from PDs 8 to 30 to ameliorate the effects of the underfeeding maneuvers, were evaluated. The results indicated significant increments in the number of pins directed to the dorsal body area of the sham-ligated, underfed, sensory-stimulated controls (LCS) versus the nipple-ligated, and sensory stimulated (LUS) rats playing in pairs, with negligible effects on contacts directed to the other skin areas during group play (Fig. 1). Additionally, this peculiar profile of hairy skin contacts may be explained because early undernutrition reduces the pleasantness of tactile stimulation, which in turn interferes with juvenile play.[50] The findings in LUS versus LCS group reductions may be related to a lower number of somatosensory receptors in dorsal skin or to low tactile skin excitability that diminishes the sense of pleasantness required to elicit juvenile play in underfed partners that did not receive relevant early sensory stimulation (Fig. 1).[51] In line with this assumption, several studies have suggested that sensory deprivation associated with perinatal undernutrition may lead to an increase in high-frequency (60 kHz) ultrasonic calls and that sensory deprivation may cause an incomplete or distorted sensory image of cortical neuronal representation during ontogenetic development, thus affecting juvenile play performance.[10,49,52,53] Furthermore, movement restriction decreases the number and distribution of spines along apical shafts of layer V pyramidal cells in the prefrontal and sensory cortices (rapid Golgi), the hippocampus and the basolateral amygdala (Golgi-Cox) in peripubertal rats, probably due to the stress from the restriction maneuver, which affects play expression.[54,55] In summary the experimental findings showed that the dorsal skin area of early underfed rats may have a reduced number of somatosensory receptors and/or reduced excitability to evoke play behavior compared with other skin body regions. Furthermore, xylocaine anesthetization of the dorsal body surface of rats reduced the frequency of pinning by 35% to 70% with intact motivation to play compared with saline control subjects.

2.3. Thalamic relays and juvenile play behavior

Juvenile play in rats has also been evaluated by discrete electrolytic lesions in different key thalamic nuclei associated with the sensory modulation of ascending electrical signals reaching specific sensory regions of the cerebral cortex.[25,56] Discrete lesions to the parafascicular or posterior thalamic regions significantly decrease the frequency of pinning in juvenile rats, while sparse lesions interfere with the motivation to play. Similar lesions placed within the ventrobasal thalamic nucleus have minimal effects on both pinning and play solicitation, whereas electrolytic lesions within ventrolateral aspects of the brain stem significantly reduce pinning, with no effects on play motivation. These findings

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are inconclusive because the behavioral experiments used to evaluate the potential damage mechanisms may be more anatomically and functionally complicated. However, the overall pattern of results indicates that these thalamic areas may be involved in the sensory modulatory mechanisms underlying juvenile play.[25] Additionally, similar studies showed that rough-and tumble social play, evaluated by the frequency of pinning, was significantly reduced in the dorsomedial thalamus and parafascicular region of juvenile rats by 33% and 73%, respectively. Moreover, the parafascicular lesions elicited effects on average pin durations, making them 105% longer than those of controls; and lesions in the parafascicular but not in the dorsomedial regions reduced play solicitation behaviors.[57] These results of discrete thalamic lesions and juvenile play development indicated that the changes were limited because the site, extension of lesions, and lack of basic neuronal excitatory/inhibitory thalamic connectivity were not well-known.

Additionally, several studies have suggested that the thalamic reticular nucleus (TRN) and the lateral thalamic nucleus (LTN) are also associated with the control of sensory afferent transmission.[58] In this regard, the use of neonatal undernutrition in rats by transferring half of the litter (n=4) from the nest to an incubator for 12 h a day from PDs 1 to 23 resulted in significant reductions of the cell body and dendritic field areas (Golgi-Cox), as well as in the number of dendritic branches of TRN neurons, with no significant differences between groups when similar neuronal measurements in the LTN were evaluated.[56] In summary these findings suggest that discrete thalamic electrolytic lesions may result in variable deficiencies in juvenile play performance. Furthermore, they provide additional information of neuronal alterations in some of the thalamic nuclei associated with sensory transmission in early underfed rats. These morphofunctional alterations may disrupt the sensory ascending modulatory mechanisms underlying social play development.[1,10] However, more experimental data on the modulatory thalamic sensory relays under different developmental conditions are needed to understand the role of ascending/descending neuronal discharges in triggering autonomic and motor-powered juvenile play expression in rats.

2.4. Effects of auditory stimulation on juvenile performance

A study of juvenile play development in rats with early auditory deficiencies showed that a punctured tympanic bilateral membrane with the pinna of the ear folded over the ear opening significantly reduced juvenile play.[25] In other experiments, an analysis of high-frequency 50-kHz ultrasonic vocalizations (USVs) emitted by pairs of control rats before and during juvenile play revealed that auditory interactions were significantly abundant and associated with a confident affective state eliciting communicative playful body contacts with the partner.[59] Furthermore, when both partners in a playing pair were devocalized, the frequency of playful attacks was significantly disrupted. When play was assessed between a vocal and a non-vocal partner, rats preferred to play with the one able to vocalize. By contrast, in a similar study 50 kHz calls by juvenile rats did not signal playful interactions compared with adult rats.[59] The findings suggest that in juvenile rats, 50 kHz USVs play a small role in maintaining a playful mood and generating auditory signals to one another during play fighting. In general, the authors conclude that vocalizations have a slight role in juvenile play but serve a more significant role in modulating adult interactions between strangers, allowing for the tactical mitigation of the risk of aggression.[59] Additionally, malnourished male rats fed with a deficient diet (6% casein) before mating and during pregnancy and tested for USVs after brief nest isolation or cooling conditions at PDs 7, 9 and 11, were compared with well-nourished pups (25% casein). Thus, prenatally malnourished pups emitted a smaller variety of calls, with fewer ascending USVs at PDs 7 and 9, and greater descending USVs at PD 11. The findings reflect altered interactions in central brain structures and functional maturation that may predict deficits in adaptive behavior including juvenile play at later ages.[60]

According to previous morphological studies on neonatal undernourishment in rats, in which half of the litter (4 out of 8 pups) were removed from the nest and placed in an incubator (12 h) from PDs 1-23, Golgi-Cox-stained bipolar neurons in the medial superior olive presented alterations in the dendritic arbor and binaural modulatory interactions with the auditory axon terminals.[61] These findings may anticipate that the modulatory system at the first relays of the auditory pathway may disrupt the central integration of the afferent auditory signals of play involved in the binaural interactions between the axon terminals, and the ipsilateral and contralateral dendritic arbors probably interfere play expression. Unfortunately, this underfeeding paradigm has not been used to evaluate its effects on play development in the juvenile rat. In summary, the 50 kHz USVs emitted by pairs of well-fed rats before and during juvenile playful interactions were significantly abundant and associated with certain affective states with the partner. Furthermore, prenatally malnourished pups emitted a smaller variety of calls, with fewer ascending USVs at PDs 7 and 9, and greater descending USVs at PD 11. The findings may indicate altered interactions in central brain structures, and functional disorders that may result in long-term brain deficits that affect juvenile play expression.

2.5. The hippocampus and juvenile play development

The hippocampus is a brain structure necessary for spatial learning, memory and attentive responses that requires relevant environmental sensory information during play activity, particularly somatosensory, visual, and auditory signals.[62,63] Moreover, the hippocampus is overly sensitive to the noxious influence of different stressors such as early food restriction and sensory deprivation.[19] Thus, prenatally and neonatally undernourished rats tested as adults in an 8-arm and then a 16-arm radial maze showed significantly more error distributions in the complex maze and in the time taken to make the choices in the spatial memory task compared with the well-fed controls.[64] These behavioral deficiencies were correlated with morphometric alterations (according to rapid Golgi) in the hippocampal growth of 2-month-old rats fed with a low protein diet (8% casein) for 6, 12 and 18 months, compared with age-matched control rats and recovered rats, which were nourished first with a low protein diet (8% casein) and then with a normal diet (25% casein) for 6 months. The total number of granular hilar neurons of CA1 and CA3 pyramidal cells was significantly decreased in malnourished adult rats, including the food recovered group not tested during the juvenile stage. Additionally, early undernourished adult subjects exhibited impaired high-frequency electrical stimulation of hippocampal dentate granule cells to produce long-term potentiation and visuospatial learning compared with their controls, suggesting a clear dysfunction associated with early malnutrition in adult hippocampal behavioral activities, perhaps related to juvenile play performance.[39,65,66] However, the role of hippocampal system deficits caused by perinatal undernutrition in juvenile play development requires further investigation, particularly to understand the neuronal circuits involved in play and the long-term

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consequences of these deficits on cognition in healthy subject and subjects with brain disorders.[67] In line with the above, studies on the neurophysiological interactions between the prefrontal cortex and hippocampus have determined that when the correlation or synchronicity of these interactions is disrupted, they cause alterations in cognition, emotions, fear and anxiety like in psychiatric disease.[68] Additionally, these studies are consistent with experimental evidence that, in the parietal association cortex, thalamo-cortical projections for recruiting and spindling-like responses, elicited by repetitive (6-9 sec) stimulation of the centrum medianum-parafascicular complex, the intralaminar thalamic nuclei that are synchronized and mutually connected for predictive behavioral responses.[69] These cortical and subcortical structures are a part of the complex neuronal networks involved in the expression of social play in rats. Unfortunately, the functional interactions between these brain structures associated with early food restriction during the play routine have not been clearly elucidated.

2.6. Effects of visual stimulation

Several studies on play fighting behavior of blinded or sighted juvenile rats used the brief paired-encounter procedure, in which rats were observed in large or small chambers on alternate days from PDs 28-43. The findings showed no significant differences in play behavior regardless of pair composition or chamber size.[70] The authors conclude that vision is not relevant for initiating or maintaining play fighting. Play behavior in rats initiates after the opening of the ears and eyes around PD 18, reaches a peak at PD 20, and then gradually declines until PDs 30-40, remaining stable until adulthood.[71] This behavioral sequence is concurrent with the development of the morphological visual pathway and the maturation of electrophysiological evoked cortical responses.[21,72] In this context, a possible explanation for the lack of effects of vision on juvenile play performance may be that the researchers evaluated play behavior at a late stage (PDs 28-43), when play activity was already reduced and stabler.[6,73] In a similar study the effects of optic enucleation on play fighting were evaluated in infant golden hamsters from PDs 30-36. The authors noted that the differences in pinning, play fighting and grooming time, as well as in the percentage of time spent in play fighting and the amount of locomotion between blind-blind, blind-intact, and intact-intact dyads were small and statistically insignificant.[74] It is possible that in other species the lack of vision may be compensated by sensory systems that are more closely related to the physical contact stimulation that play performance requires. Additionally, juvenile rats living under dim light conditions and tested for play behavior when exposed to an intensely lit arena showed suppressed pinning and decreased boxing/wrestling social responses. The findings indicate that social responses in adolescent rats may be disrupted by distinct levels of environmental organization or light conditions, even when the visual system is not damaged.[7] In summary, the role of early undernutrition and its interaction with sight impairments during juvenile play is still poorly understood.

3. Mother-litter bond influences

In mammals, mother-litter interactions play a fundamental role in species preservation by eliciting plastic brain changes in the mother to produce maternal behavior adaptive mechanisms directed to the newborn for their survival and brain and behavioral development.[19,75] Several studies have shown that perinatal undernutrition causes lasting deficits in maternal care, including reduced nest building, nursing time, retrieval responses, licking of pups, and number of contacts with pups, compared to controls.[11] In

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this context, rat pups emit different USVs that may serve as a powerful means of communication with the mother to promote their physiological development. These vocalizations have been studied under several distressing and motivational situations, such as separation from the dam (frequency range from 30 to 50 kHz) and exposure of the newborns to cold, acute isolation, and pain cues at 22 kHz.[76-78] Furthermore, USVs for communication may be altered by perinatal malnutrition (6% casein) and associated damage to various immature brain structures when compared with well-nourished controls (25 % casein).[60] From other studies, it is known that brain stem areas associated with swallowing, breathing, and laryngeal motor innervations are also necessary for phonation.[79,80] Neuroanatomical tracing studies provide a description of the central brain stem connections of the axons within the superior and recurrent laryngeal nerves, the latter with a special motor innervation to the intrinsic laryngeal muscles arising from the caudal ambiguous nucleus (AMBc) motoneurons.[81,82] These muscles and the vocal cord morphology change in neonatally underfed rat pups.[83] A pioneer study of USV recordings in malnourished rats indicated that pup USVs reduced the dam's nursing motivation in association with reduced olfactory, visual, and auditory stimuli to localize, retrieve and protect the young in a safe nest environment.[60] In a complementary Golgi-Cox morphometric study, our group evaluated the impact of perinatal undernutrition and the salutary effects of daily body massage stimulation (10 min) from PDs 4-15 on AMBc multipolar motoneuron development.[84] These motoneurons were related to the laryngeal intrinsic muscle innervation to produce USVs in neonatal rats.[82] The results indicated that multipolar motoneuron dendritic scores were reduced in both number and density at PDs 8, 12 and 15 in the underfed subjects. Moreover, the somatic massage stimulation of pups for a daily 10 min span (PDs 4 to 15) increased the body weight and the values of morphological parameters in both experimental groups, although the dendritic arbors of underfed and massage-stimulated rats only reduced their values at PD 15.[84] In summary, these experimental findings showed that USV alterations associated with perinatal malnutrition or early undernutrition disrupted the mother-litter bonds. Moreover, the USV alterations were associated with neuronal damage in various brain structures underlying the integration of neonatal vocal communication at critical stages of life. Additionally, the 50 kHz USV descending pattern of perinatally underfed rats was reduced and not modified by early massage stimulation.[84] The current findings indicate that perinatal food restriction disrupts the sensory morpho-functional brain organization subserving phonation and affects the USV calls emitted during juvenile play expression of rats, in association with other concurrent environmental factors during lactation and prepuberal stages. In this regard, our findings are in line with recent studies on the memory processes and anxiety-like behavior severely interfered when early undernutrition was induced by the large litter sizes exposure.[85]

4. Perinatal stress and juvenile play development

Another point of interest concerns to the role of the perinatal underfeeding paradigm as a stressor agent affecting the anatomical and behavioral mother-infant interactions by increasing the release of glucocorticoids, which reprogram the Hypothalamic-Pituitary-Adrenal (HPA) axis of the newborn to present non-adaptive juvenile play responses.[86] In this regard, it is known that during the first week of a rat's life there is a period of low or no stress response to hypothermia, electric shock, or brief periods of maternal separation. This depends on the immaturity of the portal blood

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vessels arising from the hypothalamic median eminence or the maturation of distinct cell types in the anterior pituitary gland of rats.[87,88] In a recent study of play development in the rat the underfeeding paradigm was initiated in F0 dams during gestation by 50% to 70% of food restriction.10 which affected the placental weight and functions causing deficiencies in fetal nutrition and growth as previously described.[89] Additionally, from PDs 1 to 24, F1 underfed pups spent 12 h with a nipple-ligated dam and 12 h with a normally lactating mother, where they received maternal sensory stimulation in the encounter that ameliorated their low body weight and/or reduced food consumption.[90] Thereafter, UG F1 virgins slightly increased food consumption and body weight through a balanced diet from PDs 25 to 90, without compensating the low body weight, which was associated with their juvenile play deficiencies and disrupted bonding interactions with the foster pups.[91] Although the effects of brief neonatal separation from the mother on early development were attenuated in this study, the effects of gestational stress were not prevented. Thus, a prenatal stress component may affect the connections of pyramidal and multipolar neurons within the juvenile play networks, increasing the glucocorticoid levels that reprogram the HPA axis of the early underfed young to provide non-adaptive social behavioral responses.[92] This assumption may be supported by the long-term deficiencies associated with early undernutrition and social stressors in juvenile play response, disturbed social interactions, increased responses to novelty, deficient learning, decreased exploratory behavior and brain disorders in adulthood.[67,93] The current data suggest that early food restriction results in long-term impoverished maternal responses that may correlate with different hypoplastic neuronal effects on the juvenile play relays, which may significantly and differentially affect the thresholds and propagation of action potentials, disrupting the synaptic plasticity underlying early cognitive responses such as juvenile play expression. In summary of the neuronal interactions occurring during the juvenile play expression in rats is grossly depicted in Figure 2.

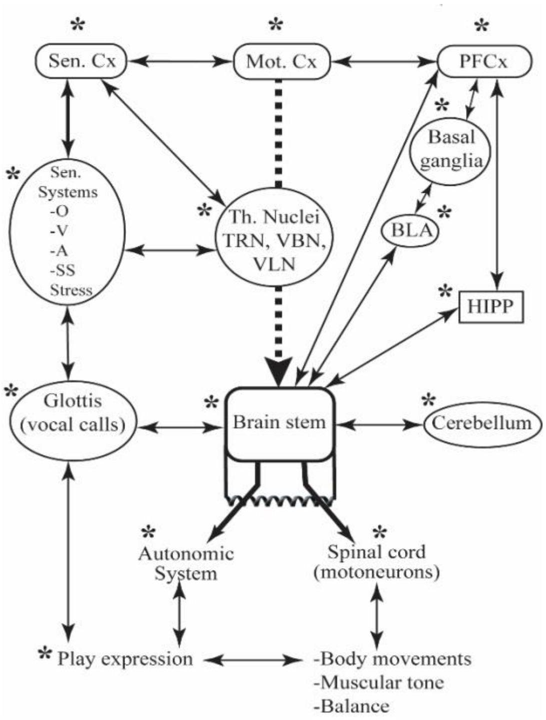

Figure 2. Schematic neuronal cortical/subcortical relay interactions occurring during the juvenile play expression of rats. Asterisks, indicate places where early food restriction interfered the neuronal play development. See text for abbreviations. Data partly taken from.[38]

5. Conclusions

The aim of this review was to analyze and compare the effects of different procedures of perinatal food restriction in rats and the associated sensory maturation impairment and mother-litter bond deficiencies on the mechanisms underlying juvenile play performance. In summary, deficits in the maturation of the olfactory, gustatory, visual, somatosensory, and auditory systems of newborns, commonly seen in early food restriction protocols, severely disrupt brain development and functions. Moreover, repeated separation of pups from the dams as an early stressor interferes with the sensory communication required to achieve early experience and develop motor abilities for the juvenile play expression of the progeny. Additionally, deficient mother-litter bonds early in life may also affect the pup’s brain growth, behavioral repertoire, and adaptive stress responses, all of which have been associated with mental disorders and the propensity for addictions at later ages. Furthermore, because the neuronal mechanisms underlying social play and maternal-like responses varies with the activation of ancient subcortical and cortical structures eliciting autonomic and motivational states, the study of social play may be relevant to modulate motoric skill abilities and defensive environmental adaptive responses. Most of our knowledge on synaptic networks deficiencies subserving social play in mammal species, emerged from peripheral and central lesions associated to early malnutrition or perinatal food restriction. Thus, morphometric rapid and

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Golgi-Cox staining neuronal deficiencies and the reduced Fos-I activation of cortical and subcortical structures were associated with lower motivation and neuronal communication associated with early food restriction Finally, under these conditions, the juvenile play development model in the rat may be a useful tool to analyze, during a sensitive stage in life, the impacts of a series of noxious developmental factors disrupting the mechanisms for gathering early experience and cognition.

6. Conflict of interest

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

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