Journal of Behavioral and Brain Science, 2014, 4, 325-333
Published Online July 2014 in SciRes. http://www.scirp.org/journal/jbbs
http://dx.doi.org/10.4236/jbbs.2014.47033

Retrieval of Pups by Female Rats Undernourished during the Pre- and Neonatal Period

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Received 23 May 2014; revised 6 July 2014; accepted 17 July 2014

Abstract

Early mother-litter bonds alterations elicited by pre- and neonatal undernutrition are a source of long-lasting brain and functional disorders such as exploratory and emotional deficits and maternal unresponsiveness to the newborn. Here, we examined the prolonged effects of gestational and neonatal food restriction on the retrieval of pups and nest building activity by primiparous adult Wistar rats on postnatal days (PDs) 4, 8, and 12. In early undernourished dams, the latency to retrieve the first or the fifth pups in the litter was extended; and nest building activity was significantly reduced. Additionally, early underfed dams retrieved the pups in a rough manner, eliciting distress cries and grasping the pups by unusual body areas. The current findings suggest that pre- and neonatal food restriction may affect the anatomical and functional forebrain structures, modulating the cognitive and motor components underlying maternal responsiveness.

Keywords

Perinatal Undernutrition, Retrieval of Pups, Stressed Dams

1. Introduction

In altricial species the maternal response is fundamental for newborn survival, interactions with the mother and environmental cues in the nest stimulate the normal brain developmental processes and promote subsequent brain plasticity changes that may have a variety of long-term anatomical and functional consequences. Maternal behavior in the rat is initiated by a gradual decrease of progesterone from high levels at mid-gestation and an increase in estradiol and prolactin levels; after birth, maternal responsiveness depends primarily on the pup's de-

How to cite this paper: Felix, J., Regalado, M., Torrero, C. and Salas, M. (2014) Retrieval of Pups by Female Rats Undernourished during the Pre- and Neonatal Period. *Journal of Behavioral and Brain Science*, **4**, 325-333.
http://dx.doi.org/10.4236/jbbs.2014.47033

mands in the context of the nest environment [1]. Previous studies have shown that different paradigms of neonatal undernutrition or malnutrition in the rat produce severe alterations in the maternal response of adult lactating dams, including deficiencies in nest building, licking of pups, nursing time, and retrieval of the young [2]-[5]. Most of these long-term behavioral alterations result from an interference with programming of the hypothalamic-hypophysial axis that results in defects in activating hormonal targets [6]. These behavioral deficiencies of early underfed dams correlate well with their brain alterations in myelination, dendritic arbor growth, and the synaptic organization of the neuronal sensory systems, alterations that seriously interfere with the mother-litter interactions and cause functional deficiencies and brain disorders throughout the lifespan of the progeny [4] [7]-[13].

The maternal circuitry normally acquires neuronal plasticity during gestation and lactation; this unique CNS property involves through hormonal and sensory mechanisms and specific synaptic and functional changes in the medial preoptic area, prefrontal, medial, and dorsolateral cortices; the anterior cingulated gyrus, and the amygdala to improve and adapt the dam's responsiveness to the pup's demands that are essential for their survival and growth [1] [14]-[17].

The current study analyzed the long-term effects of perinatal undernourishment (PU) on the mother-litter bonds: these effects reflect deficient plasticity of the maternal circuitry and include reduced nest building, prolonged retrieval latency, abnormal site of grasping pups for transportation, and pup vocalizations during the maternal retrieval. Our interest in the maternal response components arose from previous studies in which we found that neonatal undernutrition significantly reduces the magnitude of these normal behavioral components [4] [5].

2. Material and Methods

2.1. Subjects

Animals were female Wistar rats (Rattus norvegicus) and the first-litters descendants of a stock originally obtained from Harlan Sprague-Dawley, Indianapolis, USA. The subjects were born and bred in the animal care facility at the Neurobiology Institute, University of Mexico. They were maintained at a temperature of 24˚C ± 2˚C and 50% humidity on a 12 hr/12 hr light/dark cycle (lights on at 0700 hr), with water and food (Purina chow) ad lib. For mating, two males were placed in a plastic cage containing four virgin females (200 - 250 g). Sperm-positive females were placed individually in plastic maternity cages (50 × 30 × 20 cm^3) with grill tops and wood shavings as nesting material one week before parturition. The day of birth was referred to as postnatal day 0; 24 hr later pups were weighed and sexed, and five females and five males from each litter were randomly distributed among dams in order to minimize genetic and nutritional differences that may influence the experimental results. The presence of the bilateral thoracic and abdominal line of nipples and the shorter anogenital distance in the females were used as criteria for sex recognition [18]. Animal care and protocols were approved by local Animal Committees and were consistent with the NRC Guide for the Care and Use of Laboratory Animals [19].

2.2. Nutritional Procedures

2.2.1. Control Group (CG)

The CG animals were 12 female pups obtained from five litters normally nourished by well-fed mothers with free access to food and water during the gestation and lactating periods. After birth, pups were fed and handled by interchanging a pair of normally lactating mothers every 12 hr for 24 days as previously described [20]. The female rats obtained by this procedure were mated and maternally tested as adults.

2.2.2. Underfeed Group (UG)

The UG females (n = 12) came from at least five different litters. The normal chow diet requirement was calculated by measuring the food intake of a group of 6 pregnant control rats (200 - 250 g) every week during a 21-day period. The resulting average food intake for each week was the basal level used to calculate the food-intake percentage of the UG females. Thus, dams were fed from gestational day 6 (G6) to G12 with 50% (7.8 g) of the normal diet (Purina chow), from G13 to G19 with 70% (10.9 g), and then with 100% (15.6 g) of the same diet until parturition to avoid resorption or cannibalism of pups. This protocol was chosen because neurogenesis of the cortical and subcortical maternal circuit and afferent connectivity occur primarily from G16 to G21 [21]. At birth, prenatally underfed female newborns were nursed by two, gestationally underfed dams, in one of which the main galactophorous ducts had been tied subcutaneously. The two lactating dams were interchanged every 12 hr between litters from postnatal days 1 to 23. Both experimental groups were weaned at 25 days of age, after which rats were allowed free access to water and food (Purina chow) (**Figure 1**). The females were maintained in groups of 4 - 6 until reaching 90 - 100 days of age, when they were mated and tested for maternal behavior with their own litter. This cross-fostering procedure ameliorates the effects on the pups of maternal sensory deprivation [20]. No attempts were made to measure food intake in pregnant dams or newborn female rats. Approximately 80% of the total PU subjects included here were undernourished during the light phase of the cycle. To evaluate the effects of the different nutritional paradigms on physical growth, body weights of dams at gestational day 21, and of the pups at PDs 1, 4, 8, and 12 were noted.

2.3. Behavioral Testing

A total of 24 dams (12 control and 12 undernourished) were tested for maternal behavior in their own plastic living cages at 90 days of age. Approximately 3 days before parturition, nulliparous females were placed in translucent plastic maternity cages (20 × 40 × 60 cm^3) and provided with wood shavings as bedding. Twenty-four hours after parturition each litter was culled to 10 pups per mother (5 males and 5 females). Each mother was given three retrieval tests, one each on days 4, 8, and 12 postpartum, in its own living cage including wood shavings, and with its own litter. The tests were performed between 10:00 and 12:00 hr when maternal care is highly expressed [22]-[25]. This test was performed on three days only, to minimize the disruption of mother-infant bonds. The behavioral tests were videotaped (10 min) in a sound-proof chamber next to the main laboratory under continuous dim illumination provided by a red light (60 W). Different litters and pups in a litter were assigned a random number to insure that behavioral measures taken by a rater were blind with respect to their age and treatment, and to the hypothesis of the experiment. Furthermore, the retrieval latency to the first and the fifth pup in the litter by the dam measurements were compared to the counts obtained in at least two other litters per group, randomly chosen by another experimenter. A score of 1 was assigned to gentle pup transportation and 2 to a rough type, and vocalizations were noted.

At the end of the retrieval test, nest building was evaluated as another sign of maternal care. The nest was scored on the basis of its shape and dimensions. A score of 3 was assigned to a round, well-made nest approximately 3 - 4 cm in height; 2, to a partially destroyed oval nest; and 1, to a nearly destroyed nest of amorphous shape.

2.4. Statistics

Experimental data were analyzed with the Systat Statistical Package version 7.0. To compare differences in body weight of dams and pups, maternal retrieval, nest building, ages, and dietary treatments, the following separate statistical analyses were used: 1) body weight scores of pups nursed by control or perinatally underfed dams were compared in a two-way ANOVA, 2 (nutritional regimes), with repeated measures in one factor 4 (ages); 2) separate latencies to retrieve the first and the fifth pup on three postpartum days, and nest building of dams were analyzed by a two-way ANOVA, 2 (nutritional regimes) × 3 (ages) in both cases with repeated measures in the

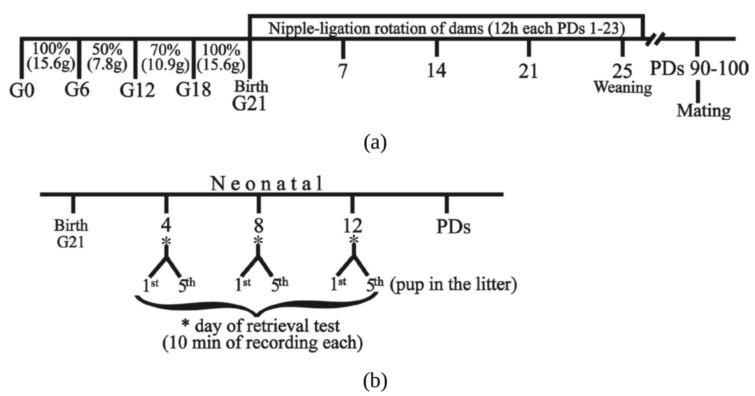

Figure 1. Experimental design for underfeeding and maternal evaluation. (a) Underfeeding method; (b) Maternal behavior (retrieval and nest building).

age factor; 3) to compare the probability of grasping body areas a three-way ANOVA, 2 (nutritional regimes) × 4 (ages) × 6 (body areas) was used; 4) rough transportation of pups by 12 dams per experimental condition at the three ages tested was analyzed with a two-way ANOVA 2 (nutritional regimes) × 3 (ages) with repeated measures in the age factor. Comparisons of scores between the nutritional regimes over time were made using the Fisher LSD post hoc test. The threshold level for significance was set at $p < 0.05$.

3. Results

3.1. Effects on Body Weight

The ANOVA comparisons of the body weight scores between the CG and the UG dams at gestational day 21 yielded a significant effect of diet, $F(1, 22) = 33.72$, $p < 0.0001$. After birth the UG dams weighed significantly less than CG mothers, $F(1, 22) = 28.96$, $p < 0.00002$, with a significant effect of age, $F(3, 66) = 21.38$, $p < 0.00001$, and without interaction between factors. Body weights of dams in both experimental groups at postnatal days (PDs) 1, 4, 8, and 12 showed a slight increase although the values for the UG were significantly lower than those of the CG subjects ($p < 0.01$). The ANOVA comparisons of the pups body weight score between CG and the UG along the ages indicated significant effects of the diet, $F(1, 198) = 6.56$, $p < 0.01$, and the age factor, $F(3, 594) = 583.21$, $p < 0.0001$ without interactions between factors. Furthermore, newborn body weights measured on PDs 1, 4, 8, and 12 were significantly reduced ($p < 0.05$) only on PD 12 (**Table 1**).

3.2. Effects on the Maternal Response

3.2.1. Effects on the Retrieval Latency

The ANOVA comparisons between groups showed that underfed dams were significantly slower in retrieving the first of the pups compared to the UG mothers, $F(1, 44) = 10.61$, $p < 0.003$; this was affected by the retrieval day, $F(2, 44) = 3.74$, $p < 0.03$, but without interactions between factors. The latency to retrieve the fifth pup was also longer in the UG dams, $F(1, 44) = 34.96$, $p < 0.00006$; it was also modified by the retrieval day, $F(2, 44) = 10.94$, $p < 0.0001$, and there was a significant interaction between the diet × age factors, $F(2, 44) = 5.37$, $p < 0.008$. Post hoc comparisons for each day of testing showed significantly prolonged ($p < 0.05$) latencies to retrieve the first on PD 12 and the fifth pup in the litter by the UG mothers only on PDs 8 and 12, respectively (**Figure 2(a)** and **Figure 2(b)**).

The probability of each area of the pup's body being grasped for the experimental dam on PDs 4, 8, and 12 is based on a sample of 24 measurements of mothers carrying pups on each day, and is shown in **Figure 3(a)**. The dams in the CG grasped pups by the nape of the neck, $F(1, 22) = p < 0.0001$ more often than UG dams, and other body areas were rarely chosen; there was also a significant interaction between the diet × age factors, $F(2, 44) = 3.28$, $p < 0.04$. By contrast, UG mothers showed a clear preference for grasping the pups by the anterior or posterior limbs, $F(1, 22) = 106.42$, $p < 0.0001$, and the head, $F(1, 22) = p < 0.0001$, compared to the CG mothers. The ANOVA comparisons did not indicate significant interactions between the factors. The statistical analysis also showed that during the retrieval test of 12 PU dams, the pups emitted more significant distress vocalizations than controls, $F(1, 44) = 39.73$, $p < 0.0002$ on all days of the study. Post hoc comparisons indicated that pups carried by UG dams emitted significantly ($p < 0.05$) more distress vocalizations than those carried by CG dams (**Figure 3(b)**).

3.2.2. Effects on Nest Building

The ANOVA comparisons of the nest scores yielded evidence of deficient nest building activity in the UG dams, $F(1, 44) = 12.20$, $p < 0.002$; with changes on the postpartum days, $F(2, 44) = 5.27$, $p < 0.0.008$ and no interaction between factors. The post hoc comparisons on each day of testing indicated significant reductions ($p < 0.05$) in the nest building parameters only on PDs 4, and 8 (**Figure 4**).

4. Discussion

The current findings indicated that in the PU dams the latency to retrieve the first or the fifth of the pups in the litter was significantly prolonged, and the nest-building response was also reduced. Additionally, these early underfed dams retrieved the pups in a rough manner, eliciting distress cries, they grasped the pups by unusual body areas, and showed more non-maternal tail chasing than controls, suggesting the dams had deficits in pup's recognition, visual discrimination, and transport of newborns [4] [5] [7] [11] [12]. These long-term maternal be

Table 1. Body weight of pups reared by control (CG) and neonatally underfed (UG) dams (n = 100) during development.

Days	Body weight		
	CG	UG	
1	7.10 ± 0.057	6.93 ± 0.091	
4	9.72 ± 0.091	9.75 ± 0.175	
8	15.94 ± 0.873	14.93 ± 0.197	
12	21.21 ± 0.212	19.57 ± 0.363*	
Factor	**df**	**F**	***p***
Diet (A)	1,198	6.563	<0.0110
Age (B)	3,594	583.211	<0.0001
A × B	3,594	2.415	NS

NS. Non significant, $^{*}p < 0.05$, Fisher LSD test.

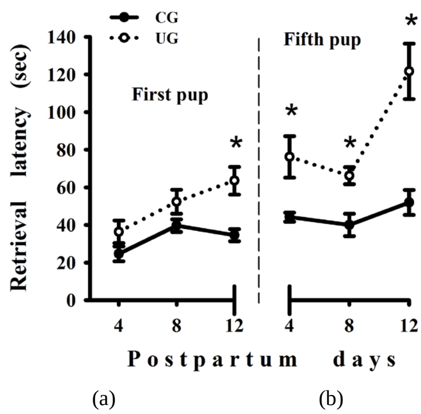

Figure 2. Mean latency (±SEM) in seconds, for retrieval of the first (a) and the fifth pup (b) after placing the mother on an empty nest, exhibited by lactating control (CG) and perinatally undernourished (UG) dams. *Statistically significant differences ($p < 0.05$).

havioral alterations may be related to a number of factors occurring during the gestation including the reduced size, and, abnormal structure and function of the placenta that interferes with the nutrient supply to the fetus, its weight, and physical development [26]-[28]. Additionally, perinatal food restriction of the dams during lactation results in significant decreases in the dendritic density, number of spines, and synaptogenesis in the prefrontal and limbic structures that generate, in adulthood, cognitive attentional deficiencies that impair pup retrieval and the nest building response [13] [29]-[32].

Two other factors that might explain the dam's abnormal pup retrieval and nest-building activity observed here are the role of the PU and alterations in the mother-litter-bonds. Previous studies show that early undernutrition or malnutrition in lactating dams seriously interferes with the mother-litter relationships, as indicated by the reduced maternal, anogenital, and fur licking of the pups, the reduced ventrum somatosensory contacts provided to the pups, and less nursing time spent with the litter which impacts the milk secretion. At the same time, the deficient mother-litter bond also affects the newborn brain growth, behavioral development, and stress all of which have been associated with mental disorders at later stages of life [4] [10] [31]-[33].

The fact that PU dams were affected early in life by the current pre- and neonatal-underfeeding paradigms, provides a test of how a mild chronic stress influenced the development of a circuit of prefrontal cortical structures underlying the attentional processes and maternal care of the progeny. In this regard, it is known that different types of undernutrition, and chronic stress situations underlie impairments in the cognitive perceptual attentional and the executive maternal responsiveness to the young, these include separating pups for 6 hr daily in a

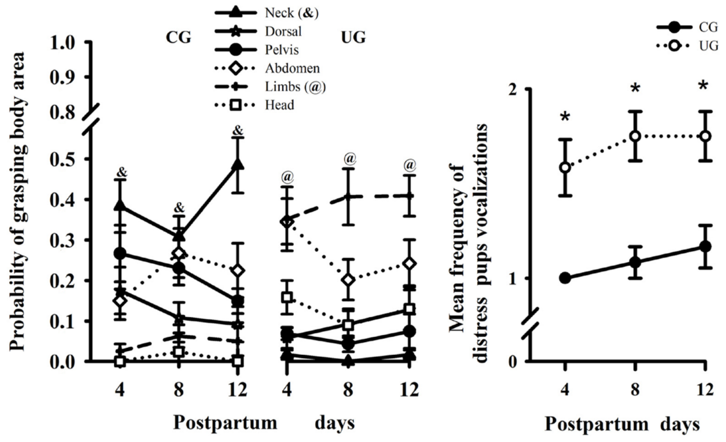

Figure 3. (a) Probability of control (CG) and perinatally undernourished (UG) dams grasping each of the specific body areas of pups during the retrieval test, based on 12 observations per experimental group of dams on each day of the lactating period; (b) Mean number (±SEM) of distress vocalizations emitted by nursed control and undernourished pups during maternal transport at the three different ages. *Statistically significant differences ($p < 0.05$).

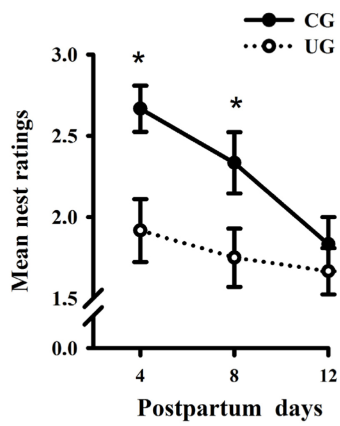

Figure 4. Mean nest-building score (±SEM) yielded from lactating control (CG) and perinatally undernourished (UG) dams. *Statistically significant differences ($p < 0.05$).

wire mesh restrainer for 21 days; placing pregnant dams in cylindrical restrainers for 15 to 45 min daily for 23 days postnatally; 12 hr of daily isolation over a 24-hr day span in an incubator, or cytotoxic lesions that provoked reduced apical or basilar dendritic prolongations, spine density, and perikarya pyramidal measurements of layer II/III in the medial prefrontal cortex, dorsal anterior cingulate, and dorsolateral prefrontal cortex [13] [31]-[34]. The neuronal hypoplasia in the maternal circuitry structures may disrupt the ascending integration of spatiotemporal patterns of coding information needed to regulate the expression of plastic maternal behavior [13]. By contrast when the individual pup's daily separation from the dam is only 1 hr, body and brain weights were not significantly different between the underfed and control groups suggesting a differential brain impact related to the time and the intensity of the stress exposure [35].

On the other hand, the disrupted mother-litter interactions of the PU rats tested for maternal behavior in adulthood may reflect a poor nest environment, insufficient tactile and somatosensory stimulation, and interference with the release of different hormones (GH, T4-T3), growth factors (EGF) and the ornithine decarboxylase (ODC) enzyme, all of which influence protein synthesis in the brain and interfere with its physical, and functional development, leading to defects in maternal behavior [10] [36]-[41]. Finally, the maternal response deficits of early underfed dams may be correlated with functional alterations elicited in neurons during lactation by the low but significant levels of circulating leptin, or with increased plasma levels of glucocorticoids that interfere with the anatomical organization of neurons in the hippocampus and the prefrontal cortices, both of which can impair the behavioral cognitive processes at later ages [42] [43].

5. Conclusion

The maternal behavioral deficiencies of dams with PU described here reflect not only the delay in early sensory development, but also the poor mother-litter bonds formed as adults that negatively impact the physical and brain development of the progeny. Our data also suggest that the maternal circuitry plasticity of PU dams occurred during the gestation and lactation was insufficient for the integration of the physiological cognitive processes such as the maternal behavior.

Acknowledgements

The study was partly supported by DGAPA/UNAM, IN200413. The authors thank Dr. Dorothy Pless for editorial assistance and helpful suggestions.

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