

Effect of maternal food restriction during gestation on early development of F1 and F2 offspring in the rat-like hamster (*Cricetulus triton*)

Hong Liang^{a,b}, Wenhua Xiong^{a,b}, Zhibin Zhang^{a,*}

^aState Key Laboratory of Integrated Management of Pest Insects and Rodents in Agriculture, Institute of Zoology, Chinese Academy of Sciences, 25 Beisihuanxi Road, Haidian District, Beijing 100080, PR China

^bGraduate School of the Chinese Academy of Sciences, Beijing 100039, PR China

Received 8 August 2006; received in revised form 31 October 2006; accepted 29 November 2006

Abstract

Maternal food restriction (FR) may have strong and long-term effects on body weight, brain and behavior development of offspring. However, it is still not well understood whether such an effect is carried over to the next generation. Our objective was to examine the differences of maternal behavior, body growth, cranial growth and early development of F1 and F2 offspring of rat-like hamsters between a FR group and a control group. Results show that FR has a significant influence on maternal gathering behavior. The body weight of F1 offspring was significantly lower in the food-restricted group compared with that of the control animals, while the body weight of food-restricted F2 offspring was not significantly different from that of the control group. The physical development and neurodevelopment of food-restricted F1 and F2 offspring were significantly delayed compared to the controls. These results suggest that FR in female rat-like hamsters affected negatively the body growth of F1 offspring, and the physical and neurodevelopment of both F1 and F2 offspring. The effect of maternal FR on F2 offspring was smaller than that on F1 offspring. These factors may, in turn, play an important role in the population regulation of this species.

© 2007 Elsevier GmbH. All rights reserved.

Keywords: Maternal effect; Growth; Malnutrition; Transgenerational effect; Developmental plasticity

Introduction

Fluctuation of food supply experienced during ontogeny may bear considerable corollaries for the later life history of a species (Gebhardt-Henrich and Richner, 1998). Several studies demonstrated that maternal malnutrition may result in strong and long-lasting effects on offspring body weight (Albon et al., 1987; Kruuk et al., 1999), morphology, brain and behavior (Levitsky et al., 1975; De Oliveira, 1985; Riul et al., 1999; Almeida and Araújo, 2001). Some studies have

shown that the effects of different uterine environments on progeny may last well into sexual maturity (Cowley et al., 1989; Atchley et al., 1991). Rats with prenatal food restriction (FR) have a significantly lower birth weight than controls (Abel, 1990). Huck et al. (1987) reported that maternal FR resulted in significantly lower body weight of F1 male hamsters (*Mesocricetus auratus*) from birth through day 25 when compared to control animals with normal food supply, while the difference of body weight of F1 female hamsters between FR and controls was not significant. Although effects of maternal FR on first-generation offspring (F1) birth mass or size were well investigated for a few species (Clutton-Brock et al., 1982), the effect of maternal FR

*Corresponding author.

E-mail address: zhangzb@ioz.ac.cn (Z. Zhang).

on second-generation offspring (F2) is little known (Mech et al., 1991).

The rat-like hamster (*Cricetulus triton*) is one of dominant rodent species in the North China Plain. Population abundance varies greatly among seasons and years; there is a prolonged low density after each population crash of this species (Zhang et al., 1998). The effect of maternal FR might be an important factor in the population regulation of this species (Liang et al., 2004). This paper addresses the effect of maternal FR during gestation on behavior, body growth and early development of F1 and F2 offspring of the rat-like hamster. We hypothesize that maternal FR may have transgenerational effects into the second generation (F2). We test this idea by exposing gravid hamsters to FR and measuring body growth as well as morphological and neurological development of first- (F1) and second-generation (F2) offspring.

Materials and methods

Animals and diets

The parental generation was captured in farmlands in Hebei Province, North China Plain. Forty-three females, on average weighing 148.9 ± 24.3 g, were mated. The day on which sperm was identified in vaginal smears was designated day 1 of pregnancy. Individual pregnant females were housed in plastic cages (40 cm \times 25 cm \times 15 cm) with wood shavings as bedding, maintained on a 16L:8D light cycle (lights on at 21:00 h) at approximately 23 °C. Tap water was available ad libitum. Food restriction (calorie and protein restriction) was only applied during the pregnancy of the maternal FR group animals. The food-restricted animals ($n = 21$) were presented with 70% of the mean daily intake of ad-lib-fed animals ($n = 22$). Rat chow (Keaoxieli, Beijing, China) was provided as described by Liang et al. (2004).

All animals delivered on day 18. Starting at the day of parturition, now designated day 1 of lactation, litters were weighted and sexed every 5 days until 90 days of age. Food (rat chow) and tap water were provided ad libitum in both groups after parturition. F1 were removed from their mothers at 25 days of age and were housed individually in polycarbonate cages. Rat chow and water were available ad libitum within both groups.

When the F1 daughters of the FR mothers and the control animals were 90 days old, 20 daughters were selected randomly from each group (all animals' ages were within 1 week of each other). Each control and FR daughter was paired with an F1 male chosen randomly from its own group (no sibling mate). On the day each

litter was born, the litter (F2) was weighted and sexed, as they were every 5 days until 90 days of age. All F2 offspring received the normal unrestricted diet throughout their development.

Maternal behavior testing

Maternal behavior of subjects towards offspring was examined using nursing and gathering indices, which were assessed by examining the cage of each subject twice daily from parturition to weaning to determine whether, at the time of inspection: (a) all pups were gathered in the nest and (b) the dam was in a nursing posture over the pups and the pups were attached to the dam's nipples. Each dam was awarded scores for each inspection during which her pups were gathered in the nest or the dam was nursing her young (Clark and Galef, 1986).

Physical and behavioral observations

The physical development of the offspring was examined from day 1. One pup from each litter was individually identified, and the parameters of eyes opening, adult locomotion, digit separation, unfolding of the external ear, turning over oneself, sparse hair on the dorsum and incisors' eruption were monitored according to Kim et al. (2004) and Salvatori et al. (2004), with the days required for the appearance of these landmarks being recorded until all measured pups were positive for the developmental parameters. Then, the mean day of appearance of these parameters was calculated for all groups separately.

Neurodevelopmental reflex assessments

Smart and Dobbing (1971) established the time at which neurodevelopmental reflexes are expected to appear in healthy rat pups (Table 1) and this has been successfully used to assess the effect of diet on neurodevelopment in rat pups by Saste et al. (1998) and Kim et al. (2004). From postnatal day 2 through 25, the listed reflex tests (Table 1) were assessed daily in the same pups as a physical development test. During testing, pups were removed from dams and were kept in a 37 °C chamber. Testing was conducted by one of the two investigators. In the case of testing for cliff avoidance and negative geotaxis appearance, a time limit criterion of 30 s was employed by investigators.

Craniofacial skeleton measurements

At 90 days of age, 20 F1 and 20 F2 offspring of each group were sacrificed and the craniofacial skeletons were anatomized. The connective tissue was cleaned and the

Table 1. Description of reflex tests used to assess the effect of diet on neurodevelopment in rat pups

Reflex	Eliciting stimuli	Response	Reflex appearance in reference rats (days postpartum)
Righting reflex	Pup placed on back on flat surface	Turns onto ventral surface	4.2 ± 1.2
Cliff avoidance	Pup put on edge of board with nose and force feet just over edge	Withdrawal of head and both forefeet from edge	6.0 ± 1.3
Negative geotaxis	Pup placed head downwards on a 20° slope	Turns to face up the slope	8.6 ± 3.6
Auditory startle	Snap of mousetrap closing	Sudden, brief extension of hind limbs	11.6 ± 0.5
Vibrissa placing	Pup held by tail, vibrissa just touching vertical surface	Lifts head and extends forelegs in direction of bench	11.8 ± 1.0
Free-fall righting	Pup dropped, back downwards, from 2 ft onto cotton wool pad	Turns in mid-air to land on all fours	14.2 ± 0.9
Visual placing	Pup held from edge of bench by tail without vibrissa touching	Lifts head and extends forelegs in direction of bench	19.7 ± 0.5

Adapted from Smart and Dobbing (1971), and Saste et al. (1998).

following measurements were taken by vernier caliper: neurocranial length (NI) from nasion to opisthocranium, neurocranial width (Nw) from euryon to euryon, neurocranial height (Nh) from the sphenoccipital synchondrosis to vertex, facial length (FI) from nasion to rhinion, facial width (Fw) from zygion to zygion and facial height (Fh) from palate (just in front of the first molars) to nasion. Volumetric neurocranial (VNI), volumetric facial (VFI) and neurofacial (NFI) indices were calculated as follows:

$$VNI = \sqrt[3]{NI \cdot Nw \cdot Nh},$$

$$VFI = \sqrt[3]{FI \cdot Fw \cdot Fh},$$

$$NFI = VNI/VFI.$$

We defined the craniofacial skeleton measurements following Cesani et al. (2003). VNI and VFI represent the geometric mean of the three main dimensions, reflecting the size variation of neurocranium and face, respectively; NFI measures the shape in terms of neurocranial volume per unit of facial variation (Cesani et al., 2003).

Statistical analyses

Statistical analyses were performed using the SPSS 13.0 statistical package. The trends of maternal behavior were analyzed with a mixed model with days of lactation and feeding treatment as fixed effects and maternal number as random effect. Body weight of F1 and F2 offspring was tested by using repeated measures and multivariate analyses of general linear model (GLM), with weight as dependent variable, day of measurement as repeated factor, and feeding treatment and gender as fixed effects. The craniofacial morphology data were analyzed with multivariate analyses of GLM using feeding treatment and gender as fixed factors. Compar-

isons of physical development and neurodevelopment were made using multivariate analyses of GLM with feeding regime as the fixed factor.

Results

Figs. 1a and b show the differences of maternal gathering and nursing behavior of females between the FR and control groups. Maternal gathering and nursing behaviors decrease with the increase of time during lactation ($F_{24,700} = 15.913$, $P = 0$; $F_{24,700} = 7.546$, $P = 0$). The gathering behavior of FR mothers is significantly reduced as compared to that of control mothers ($F_{1,700} = 4.248$, $P = 0.040$). The differences in nursing behavior between FR and control dams were not statistically significant ($F_{1,700} = 2.976$, $P > 0.05$).

Repeated measures GLM show that the body weight of FR F1 offspring is significantly smaller than that of the control group ($F = 4.96$, $df = 1$, $P < 0.05$). Neither a difference of body weight between male and female pups ($F = 0.1430$, $df = 1$, $P > 0.05$) nor a significant interactive effect between feeding treatment and gender factors is found ($F = 4.009$, $df = 1$, $P > 0.05$). Multivariate analysis shows that the body weight of FR F1 offspring is significantly smaller than that of the control group on day 1 ($F = 4.773$, $df = 1$, $P < 0.05$), day 2 ($F = 5.483$, $df = 1$, $P < 0.05$), day 3 ($F = 4.478$, $df = 1$, $P < 0.05$) and day 20 ($F = 4.151$, $df = 1$, $P < 0.05$) (Fig. 2).

Repeated measures GLM show that there is no significant effect of maternal FR on the body growth of F2 offspring ($F = 1.084$, $df = 1$, $P > 0.05$). The difference in body weight between males and females of F2 offspring is not significant ($F = 2.200$, $df = 1$, $P > 0.05$). There is no interactive effect between the feeding treatment and gender factors ($F = 0.113$, $df = 1$, $P > 0.05$).

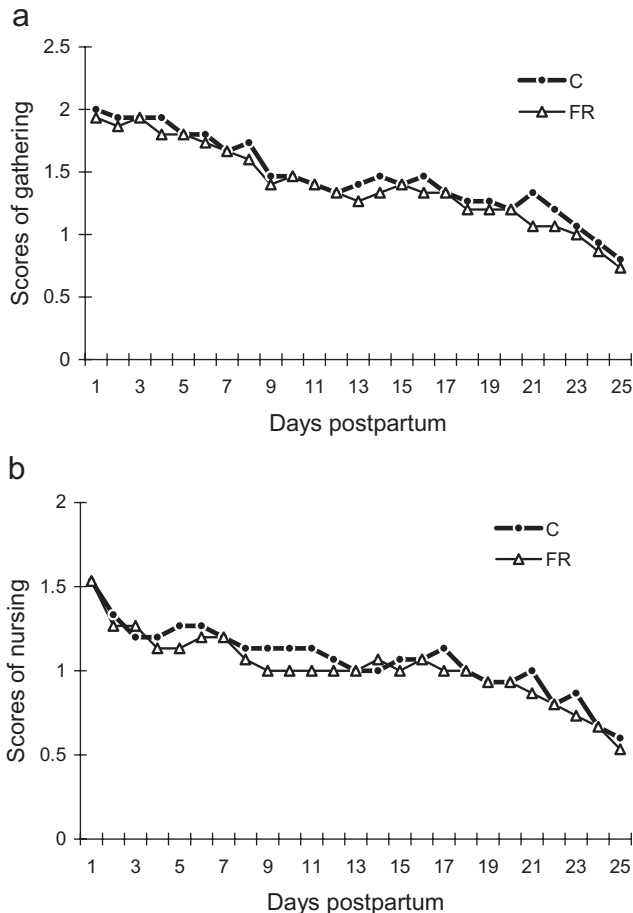


Fig. 1. Effect of food restriction during gestation on mean gathering (a) and nursing (b) scores of mothers in the rat-like hamster *C. triton*. FR, food restriction group; C, control group.

As shown in Fig. 3a, the eyes of FR F1 offspring open 1.4 days later on average than those of the control offspring ($F = 5.062$, $df = 1$, $P < 0.05$). Separation of digits happens after 7.82 days in control F1 offspring, which is significantly earlier than in the FR group (8.34 days) ($F = 6.149$, $df = 1$, $P < 0.05$). The difference in the time necessary for ear unfolding between FR F1 offspring and control offspring is also significant ($F = 9.083$, $df = 1$, $P < 0.01$). At 2.79 days of age, control F1 offspring began to have sparse hair on the dorsum, while in FR F1 offspring the time was delayed to 3.26 days ($F = 4.84$, $df = 1$, $P < 0.05$). The difference in the onset of incisor eruption between control and FR F1 offspring is not significant. Both the incidence of turning over oneself and of adult locomotion are significantly earlier in control F1 offspring than in FR offspring (turning over oneself, $F = 6.662$, $df = 1$, $P < 0.05$; adult locomotion, $F = 21.616$, $df = 1$, $P < 0.01$).

As shown in Fig. 3b, the eyes of FR F2 offspring open 1.8 days later on average than those of the control group

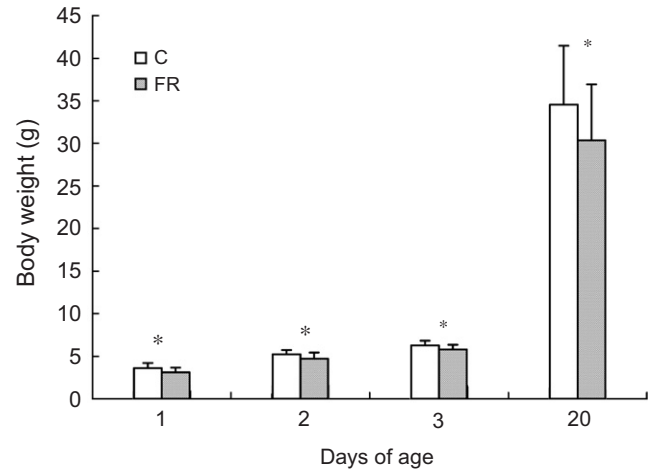


Fig. 2. Effect of maternal food restriction during gestation on body weight of F1 offspring in the rat-like hamster *C. triton* (mean + positive SE; * $P < 0.05$).

($F = 6.976$, $df = 1$, $P < 0.05$). Control F2 offspring can turn over themselves at an age of 2.3 days, whereas FR F2 offspring do not turn over themselves until an age of 2.8 days ($F = 6.869$, $df = 1$, $P < 0.05$). The time differences regarding digit separation, ear unfolding, sparse hair on the dorsum, incisors eruption and adult locomotion of F2 offspring are not significant between the control and FR groups.

The neurodevelopment of F1 offspring is significantly delayed by maternal FR (Table 2). The postnatal day of appearance of the righting reflex ($F = 12.316$, $df = 1$, $P < 0.01$), negative geotaxis ($F = 47.900$, $df = 1$, $P < 0.01$), auditory startle ($F = 6.533$, $df = 1$, $P < 0.01$) and visual placing ($F = 10.060$, $df = 1$, $P < 0.01$) of F1 FR group offspring is significantly later than that of the control group, whereas the time of appearance of the reflexes of cliff avoidance, vibrissa placing and free-fall righting of F1 offspring is not significantly different between the FR and control groups (Table 2).

The neurodevelopment is also significantly delayed in FR F2 offspring. The reflexes of negative geotaxis ($F = 6.359$, $df = 1$, $P < 0.05$), auditory startle ($F = 3.333$, $df = 1$, $P < 0.05$) and visual placing ($F = 4.665$, $df = 1$, $P < 0.05$) of FR F2 offspring appear significantly later than those of the control group. The righting reflex, cliff avoidance, vibrissa placing and free-fall righting reflex of F2 offspring are not significantly different between the control and FR groups (Table 2).

The differences in VNI, VFI and NFI of the F1 and F2 offspring (control and FR group) are all not significant. A multivariate test shows that there is no inter-correlation between treatment and gender factors. This result indicates that maternal FR neither resulted in smaller skulls nor evoked changes of skull shape in F1 and F2 offspring at the age of 90 days (Fig. 4).

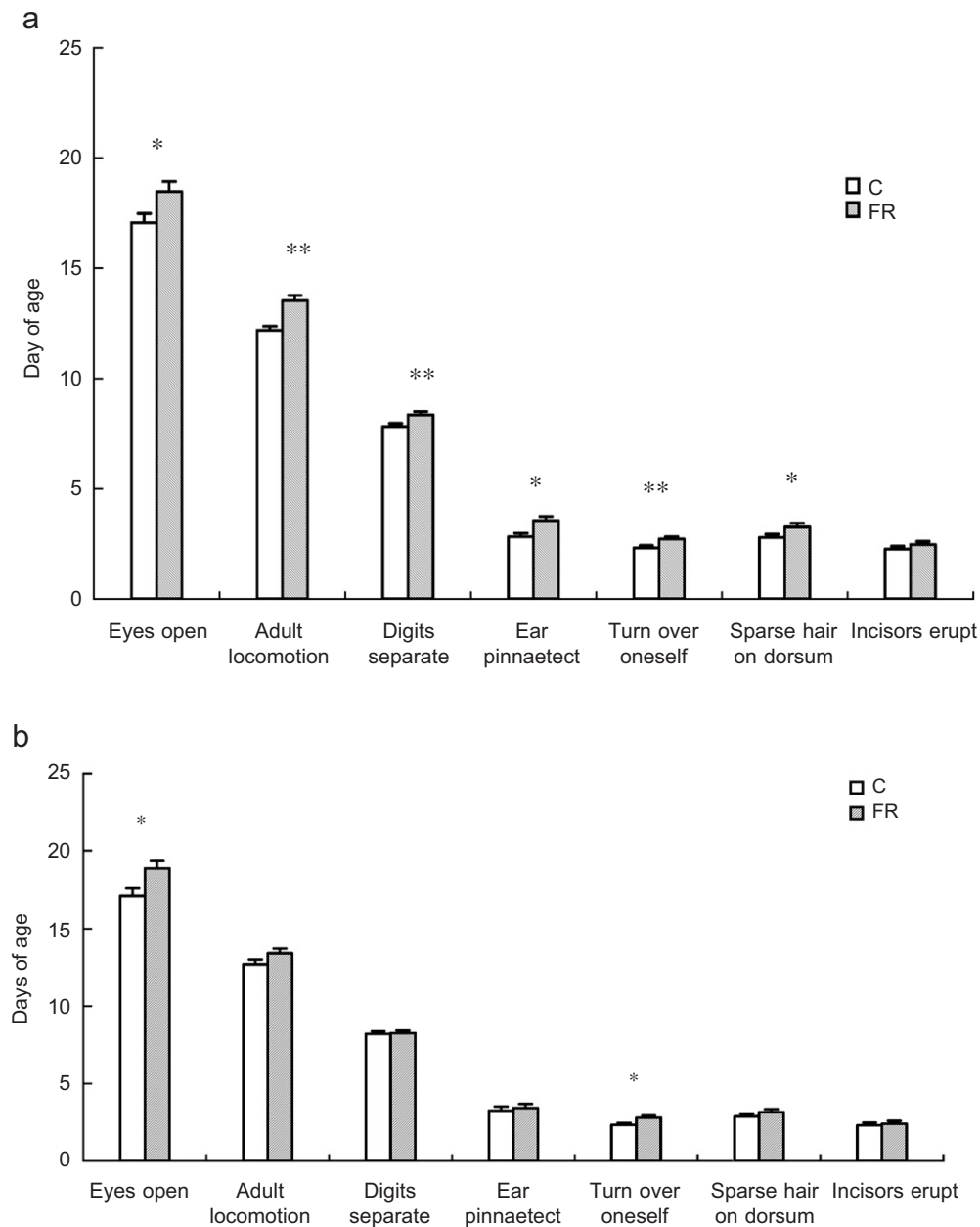


Fig. 3. Effect of maternal food restriction during gestation on the physical and behavior development of (a) F1 and (b) F2 offspring in the rat-like hamster *C. triton* (mean + positive SE; * $P < 0.05$, ** $P < 0.01$).

Discussion

Dietary restriction takes many forms, such as protein or calorie restriction (Miller and German, 1999; Almeida and Araújo, 2001; Drickamer and Meikle, 1988), and animal models of malnutrition differ primarily in the severity and timing of the deficiency. Different dietary restrictions may have different results. It is notable that our results are achieved by calorie and protein restriction.

Studies of maternal FR on successive generation offspring are rare. Stewart et al. (1975, 1980) maintained rats on a protein-restricted diet for 12 generations,

documenting the effects of protein restriction on behavior, life-history traits and growth. Huck et al. (1987) demonstrated that female hamsters maintained on a restricted diet during the first 50 days of life showed long-term consequences regarding body weight and sex ratios of F1 and F2 offspring. Lobe et al. (2006) tested the differences of skeletal growth in rats caused by life-long protein malnutrition and found that the consequences of protein malnutrition could affect more than one generation. The second generation's growth trajectories resembled the longer and slower growth of the first malnourished generation. Our results demonstrated

Table 2. Effect of maternal food restriction (FR) during gestation on the neurodevelopment of F1 and F2 offspring in the rat-like hamster *C. triton*

Reflex	F1 offspring		F2 offspring	
	Control	FR	Control	FR
Righting reflex	2.19±0.33	2.70±0.46**	2.16±0.07	2.34±0.09
Cliff avoidance	5.88±1.15	6.53±0.89	5.98±0.27	6.48±0.19
Vibrissa placing	11.23±1.07	11.12±1.05	11.19±0.26	11.12±0.24
Negative geotaxis	11.07±1.32	14.30±1.24**	12.36±0.34	13.66±0.38*
Auditory startle	15.3±0.46	16.23±0.82**	15.43±0.16	16.10±0.21*
Free-fall righting	14.57±1.05	15.05±1.09	14.53±0.26	15.05±0.28
Visual placing	16.37±0.90	17.87±1.60**	16.63±0.32	17.60±0.32*

Mean±SE, * $P<0.05$, ** $P<0.01$.

that maternal 70% FR during pregnancy negatively affected the early development of F1 and F2 offspring of rat-like hamsters. The successive negative effect across generations of the rat-like hamster is probably caused by poor development of the F1 generation. In previous studies, the organs and hormone levels of the F1 offspring of the FR group were significantly smaller or lower than those of the control ones (Liang et al., 2004; Liang and Zhang, 2006). It is obvious that the F2 individuals of FR F1 offspring will be poorly developed.

Early malnutrition changes the behavior of mother and offspring as well as mother–pup interactions during the lactation period. It was suggested that behavioral differences in adulthood might result from changes in the social behavior of juvenile rats induced by early protein malnutrition (Almeida and Araújo, 2001). Massaro et al. (1974) showed that malnourished mothers spend more time in the nest area with enhanced maternal behavior in contrast to the control mothers that are more frequently observed in non-maternal behavior. The changes in mother–pup interaction produced by protein malnutrition during the lactation period of rats may be due to retardation in the neuromotor development and a higher dependence of the offspring on their mothers. These changes may represent an important means of energy saving and heat maintenance in malnourished offspring (Riul et al., 1999). Similar results were achieved for rats by Levitsky et al. (1975) and De Oliveira (1985). However, Moses et al. (1998) reported that offspring of food-restricted mothers was attached to their mothers' teats as often as offspring of food-enriched mothers in bushy-tailed woodrats (*Neotoma cinerea*). Our study indicated that the gathering behavior of FR dams was significantly reduced as compared to that of control dams, which might be the reason of the retarded physical development and neurodevelopment of FR offspring. In contrast, the nursing behavior of FR dams was not significantly different from that of controls.

Maternal malnutrition can result in a lower brain weight at birth (Resnick and Morgane, 1984) and several morphological and neurochemical alterations in the central nervous system in offspring (Almeida et al., 1996; Galler et al., 1996). The neurocranium houses the brain and its growth is influenced primarily by brain expansion. The craniofacial skeleton is critically affected by protein malnutrition (Miller and German, 1999), and the viscerocranium appears more susceptible to environmental factors than the neurocranium (Pucciarelli, 1981; Cesani et al., 2003). But in this study, the differences in neurocranium and face size of F1 and F2 offspring between FR and control groups were all not significant. This result differs from those in the literature, which suggest a much stronger effect of malnutrition on skull size (Miller and German 1999; Cesani et al., 2003). Lobe et al. (2006) also reported that there is a significant impact of life-long protein malnutrition on the craniofacial skeleton in rat. A possible explanation of this discrepancy is that the skull growth of the rat-like hamster might be not very sensitive to FR of mothers during pregnancy.

The time of appearance of specific neurodevelopment reflexes in rats has been established (Smart and Dobbins, 1971), and early malnutrition is known to affect the neurodevelopment. According to Altman and Sudarshan (1975), three peripheral systems may be involved in the regulation of postural adjustments, including the vestibular, exteroceptive and proprioceptive systems. The vestibular system functions at birth although vestibular reactions are hampered by immaturity of the motor system. The righting reflex and geotaxis responses of young hamsters reflect both motor development and activity guided by the vestibular system (Salvatori et al., 2004). In our study, maternal FR delayed the development of these two reflexes in F1 and F2 offspring. The auditory startle reflex has often been used as a neurobiological test for studying neural mechanisms of sensorimotor reactivity and plasticity at the brainstem level (Pellet, 1990). The reflex of auditory

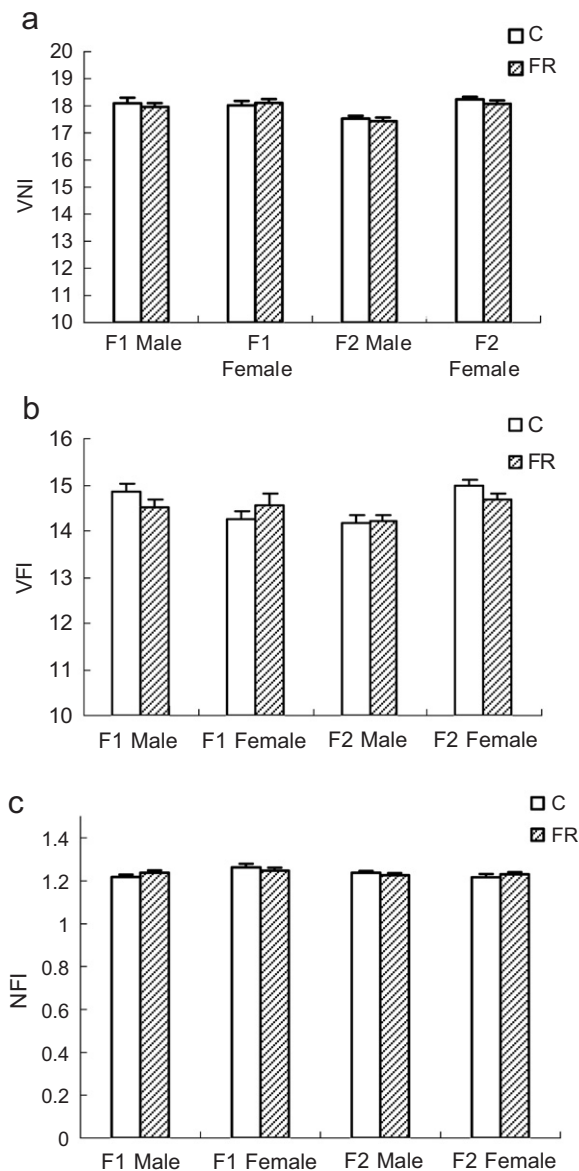


Fig. 4. Effect of maternal food restriction during gestation on neurocranial (a, VNI), facial (b, VFI) and neurofacial (c, NFI) indices of the craniofacial skeleton of F1 and F2 offspring in the rat-like hamster *C. triton* (mean + positive SE). FR, food restriction group; C, control group.

startle of both FR F1 and F2 offspring of hamsters was significantly retarded as compared to that of the control group. In general, our results demonstrated that the brain development and behavior of both F1 and F2 FR offspring were significantly delayed by maternal FR during gestation.

Eye opening is the sign of maturation of sensory perceptual mechanisms. Eye opening is delayed in offspring born to mothers food-restricted during lactation in woodrats (*N. cinerea*) (Moses et al., 1998). Adult locomotion and turning over oneself are the signs of maturation of neuromotor coordination. Krishna and

Ramakrishna (1984) reported the delayed onset of neuromotor coordination in prenatally pyridoxine-deficient rats. In the present study, some physical development parameters of F1 and F2 offspring were delayed in the FR group, indicating the impairment of physical and behavior development by maternal FR.

The effect of maternal FR on infant body weight remains controversial. The growth impairment of offspring malnourished early in life is well documented in many studies (e.g. Rocha and Mello, 1994; Riul et al., 1999). In rats, the fetal and placental weight is reduced by 25% by FR during the pregnancy of dams, and during FR the fetal rat cannot utilize maternal nutrient stores to prevent growth retardation (Lederman and Rosso, 1981). The birth weight of red deer is strongly influenced by a mother's nutritional status during gestation (Albon et al., 1987; Kruuk et al., 1999). However, some reports demonstrated that there was no difference in the mean birth or weaning body weights of offspring of food-deprived and control mothers in wild house mice (*Mus musculus*) (Drickamer and Meikle, 1988; Meikle and Westberg, 2001). Mech et al. (1991) demonstrated that the body mass of single male white-tailed deer (*Odocoileus virginianus*) fawns is related directly to the nutrition of their grandmothers. Huck et al. (1987) showed that the F1 offspring descended from food-restricted female hamsters were significantly smaller on days 5–25 than the control group. Our results suggest that maternal FR delayed the body growth of F1 offspring, whereas the body weight of F2 offspring did not vary significantly between the control and FR groups.

In mammalian species, maternal effects influence growth traits, particularly pre-weaning, and are investigated as a potential general cause of population cycles in small mammals (Boonstra and Hochachka, 1997). The food hypothesis suggests that fluctuations in quantity (Lack, 1954) or quality (Agrell et al., 1995) of food resources produce changes in the demographic rates which then cause density fluctuations. Natural populations of rat-like hamsters in the North China Plain oscillate strongly in abundance, and in peak phases hamsters often face food shortages during breeding seasons (Zhang et al., 1998). In this study, we found that maternal FR had significant effects on the growth and development of F1 and F2 offspring of rat-like hamsters, which supports our idea that food shortage during high population-density periods might, through transgenerational effects, affect the density after a population crash (Liang et al., 2004).

Acknowledgments

This study was supported by the CAS Innovation Program (KSCX2-SW-103), the CAS Innovation Re-

search International Partnership Project and a grant of the National Natural Science Foundation of China (30370232). All animal procedures were approved by the Institutional Animal Care and Use Committee of the Institute of Zoology, Chinese Academy of Sciences.

References

- Abel, E.L., 1990. Effects of paternal and maternal undernutrition on growth of offspring in rats. *Growth Dev. Aging* 54, 125–129.
- Agrell, J., Erlinge, S., Nelson, J., Nilsson, C., Persson, I., 1995. Delayed density dependence in voles. *Proc. R. Soc. London B* 262, 65–70.
- Albon, S.D., Clutton-Brock, T.H., Guinness, F., 1987. Early development and population dynamics in red deer. II. Density-independent effects and cohort variation. *J. Anim. Ecol.* 56, 69–81.
- Almeida, S.S., Araújo, M., 2001. Postnatal protein malnutrition affects play behavior and other social interactions in juvenile rats. *Physiol. Behav.* 74, 45–51.
- Almeida, S.S., Tonkiss, J., Galler, J.R., 1996. Prenatal protein malnutrition affects the social interactions of juvenile rats. *Physiol. Behav.* 60, 197–201.
- Altman, J., Sudarshan, K., 1975. Postnatal development of locomotion in the laboratory rat. *Anim. Behav.* 23, 896–920.
- Atchley, W.R., Logsdon, T., Cowley, D.E., Eisen, E.J., 1991. Uterine effects, epigenetics, and postnatal skeletal development in the mouse. *Evolution* 45, 891–909.
- Boonstra, R., Hochachka, W.M., 1997. Maternal effects and additive genetic inheritance in the collared lemming *Dicrostonyx groenlandicus*. *Evol. Ecol.* 11, 169–182.
- Cesani, M.F., Orden, B., Zucchi, M., Muñe, M.C., Oyhenart, E.E., Pucciarelli, H.M., 2003. Effect of undernutrition on the cranial growth of the rat. *Cells Tissues Organs* 174, 129–135.
- Clark, M.M., Galef Jr., B.G., 1986. Postnatal effects on reproduction and maternal care in early- and late-maturing gerbils. *Physiol. Behav.* 36, 997–1003.
- Clutton-Brock, T.H., Guinness, F.E., Albon, S.D., 1982. *Red Deer – Behavior and Ecology of Two Sexes*, Wildlife Behavior and Ecology Series. University of Chicago Press, Chicago.
- Cowley, D.E., Pomp, D., Atchley, W.R., Eisen, E.J., Hawkins-Brown, D., 1989. The impact of maternal uterine genotype on postnatal growth and adult body size in mice. *Genetics* 122, 193–203.
- De Oliveira, L.M., 1985. Malnutrition and environment: interaction effects upon animal behavior. *Rev. Chil. Nutr. Chile* 13, 99–108.
- Drickamer, L.C., Meikle, D.B., 1988. Food deprivation affects reproduction in adult female mice (*Mus musculus*) and the age of puberty for their female progeny. *Acta. Biol. Hung.* 39, 361–375.
- Galler, J.R., Shumsky, J.S., Morgane, P.J., 1996. Malnutrition and brain development. In: Walker, W.A., Watkins, J.B. (Eds.), *Nutrition in Pediatrics*, second ed. Decker Europe Inc., Neuilly-sur-Seine, France, pp. 194–210.
- Gebhardt-Henrich, S., Richner, H., 1998. Causes of growth variation and its consequences for fitness. In: Starck, J.M., Ricklefs, R.E. (Eds.), *Avian Growth and Development*. Oxford University Press, New York, pp. 324–339.
- Huck, U.W., Labov, J.B., Lisk, R.D., 1987. Food-restricting first generation juvenile female hamsters (*Mesocricetus auratus*) affects sex ratio and growth of third generation offspring. *Biol. Reprod.* 37, 612–617.
- Kim, J.C., Shin, D.H., Kim, S.H., Oh, K.S., Jung, Y.H., Kwon, H.J., Yun, H.I., Shin, H.C., Chung, M.K., 2004. Peri- and postnatal developmental toxicity of the fluor-quinolone antibacterial DW-116 in rats. *Food Chem. Toxicol.* 42, 389–395.
- Krishna, A.P., Ramakrishna, T., 1984. Effect of pyridoxine deficiency on the exploratory behavior of rats. *Int. J. Psychophysiol.* 2, 39–43.
- Kruuk, L.E.B., Clutton-Brock, T.H., Rose, K.E., Guinness, F.E., 1999. Early determinants of lifetime reproductive success differ between the sexes in red deer. *Proc. R. Soc. London B* 266, 1655–1661.
- Lack, D., 1954. *The Natural Regulation of Animal Numbers*. Oxford University Press, Oxford.
- Lederman, S.A., Rosso, P., 1981. Effects of obesity, food restriction and pregnancy on fetal and maternal weight and on body composition in rats. *J. Nutr.* 111, 2162–2171.
- Levitsky, D.A., Massaro, T.F., Barnes, R.H., 1975. Maternal malnutrition and the neonatal environment. *Fed. Proc.* 34, 1583–1586.
- Liang, H., Zhang, Z.B., 2006. Food restriction affects reproduction and survival of F1 and F2 offspring of rat-like hamster (*Cricetulus triton*). *Physiol. Behav.* 87, 607–613.
- Liang, H., Zhang, J.J., Zhang, Z.B., 2004. Food restriction in pregnant rat-like hamsters (*Cricetulus triton*) affects endocrine, immune function and odor attractiveness of male offspring. *Physiol. Behav.* 82, 453–458.
- Lobe, S.L., Bernstein, M.C., German, R.Z., 2006. Life-long protein malnutrition in the rat (*Rattus norvegicus*) results in altered patterns of craniofacial growth and smaller individuals. *J. Anat.* 208, 795–812.
- Massaro, T.F., Levitsky, D.A., Barnes, R.H., 1974. Protein malnutrition in the rat: its effects on maternal behavior and pup development. *Dev. Psychobiol.* 7, 551–561.
- Mech, L.D., Nelson, M.E., McRoberts, R.E., 1991. Effects of maternal and grandmaternal nutrition on deer mass and vulnerability to wolf predation. *J. Mammal.* 72, 146–151.
- Meikle, D., Westberg, M., 2001. Maternal nutrition and reproduction of daughters in wild house mice (*Mus musculus*). *Reproduction* 122, 437–442.
- Miller, J.P., German, R.Z., 1999. Protein malnutrition affects the growth trajectories of the craniofacial skeleton in Rats. *J. Nutr.* 129, 2061–2069.
- Moses, R.A., Boutin, S., Teferi, T., 1998. Sex-biased mortality in woodrats occurs in the absence of parental intervention. *Anim. Behav.* 55, 563–571.
- Pellet, J., 1990. Neural organization in the brainstem circuit mediating the primary acoustic head startle: an electrophysiological study in the rat. *Physiol. Behav.* 48, 727–739.

- Pucciarelli, H.M., 1981. Growth of the functional components of the rat skull and its alteration by nutritional effects. *Am. J. Phys. Anthropol.* 56, 33–41.
- Resnick, O., Morgane, P.J., 1984. Generational effect of protein malnutrition in the rat. *Brain Res.* 317, 219–227.
- Riul, T.R., Carvalho, A.F., Almeida, P.S., De Oliveira, L.M., Almeida, S.S., 1999. Ethological analysis of mother-pup interactions and other behavioral reactions in rats: effects of malnutrition and tactile stimulation of the pups. *Braz. J. Med. Biol. Res.* 32, 975–983.
- Rocha, J.B.T., Mello, C.F., 1994. Handling during suckling alters rat behavior but does not reverse the deleterious effects of undernutrition on naltrexone-induced inhibition of exploratory behavior. *J. Vit. Nutr. Res.* 64, 152–156.
- Salvatori, F., Talassi, C.B., Salzgeber, S.A., Spinosa, H.S., Bernardi, M.M., 2004. Embryotoxic and long-term effects of cadmium exposure during embryogenesis in rats. *Neurotoxicol. Teratol.* 26, 673–680.
- Saste, M.D., Carver, J.D., Stockard, J.E., Benford, V.J., Chen, L.T., Phelps, C.P., 1998. Maternal diet fatty acid composition affects neurodevelopment in rat pups. *J. Nutr.* 128, 740–743.
- Smart, J., Dobbing, J., 1971. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. *Brain Res.* 28, 85–95.
- Stewart, R., Preece, R., Sheppard, H., 1975. Twelve generations of marginal protein deficiency. *Br. J. Nutr.* 33, 233–253.
- Stewart, R., Sheppard, H., Preece, R., Waterlow, J., 1980. The effect of rehabilitation at different stages of development of rats marginally malnourished for ten to twelve generations. *Br. J. Nutr.* 43, 403–412.
- Zhang, Z.B., Yang, H.F., Wang, S.Q., Wang, F.S., Hao, S.S., Cao, X.P., Zhang, J.X., Xu, Y.X., 1998. The ecology and sustainable management of the rat-like hamster. In: Zhang, Z.B., Wang, Z.W. (Eds.), *Ecology and Management of Rodent Pests in Agriculture*. Ocean Press, Beijing, pp. 1–19 (in Chinese).