EFFECTS OF MALNUTRITION AND CORTISOL ADMINISTRATION ON GROWTH AND PHYSICAL DEVELOPMENT

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ABSTRACT

It was observed weekly the growth in terms of weight and length and the ages of appearance of some physical parameters in 4 experimental groups of rats: the offspring of mothers fed either a 20$ (N) or a 10% (M) protein diet during gestation either with a 0,9% NaCl solution (S) or with a dose of 0,5 mg./100 g. body weight hidrocortisone acetate solution (C). Results show that the experimental treatments especially affect the ages of appearance of the physical parameters, which have a greater delay in the NC and MS groups than in the MC group.

Key Words: Protein malnutrition, cortisol, growth, physical development.

RESUMEN

Efectos de la malnutrición y la administración de cortisol sobre el crecimiento y desarrollo físico.- Se observó semanalmente el peso y la longitud así como la edad de aparición de algunas características físicas en 4 grupos de ratas: crías cuyas madres se alimentaron con dieta al 20% (N) o al 10% (M) de proteína durante los períodos de gestación y lactancia, y que fueron inyectadas diariamente durante la gestación con una solución al 0.9% de ClNa (S) o con una dosis de 0,5 mg./100 g. de peso corporal de una solución de acetato de hidrocortisona (C). Los tratamientos experimentales afectan principalmente a las características físicas que muestran una mayor demora en los grupos NC y MS que en el grupo MC.

Palabras clave: Malnutrición proteica, cortisol, crecimiento, desarrollo físico.

Delayed growth and general development have been observed in many reports on the effects of protein malnutrition in early life. For example, significant differences in body weight were always found in malnourished animals as compared with controls, whatever the method used to produce malnutrition and even the age at which it took place (Resnick, Morgane, Hasson y Miller, 1982; Mello, 1987). This deficiency was not homogeneus, the brain being affected in a milder way than the rest of the organs (Dobbing, 1968).

Psicothema, 1991, vol. 3, nº 1, pp. 111-119
ISSN 0214 - 9915 CODEN PSOTEG

The lower growth of the malnourished animals could be explained by several factors such as alterations in the hormones controlling the growth (Phillips, 1986), the decrease of the efficiency food ratio (Marcos, Varela, Muñoz-Martínez y Unzaga, 1986), the placental deficits (Araya, Aguilera, Soto y Masson, 1986), the changes in volume and composition of milk (Grimble y Mansaray, 1987) and in the maternal behavior (Crnic, 1980).

Malnutrition also results in a delayed appearance of certain morphological characteristics such as ear unfolding, incisor eruption, eyes opening and adult hair growth (Smart y Dobbing, 1971; Bush y Leathwood, 1975; Sykes y Cheyne, 1976; Sánchez Turet, González-Sastre y Sabater-Tobella, 1978) which can be considered as maturation indicators. This delays can influence later behavior, for example by limiting perception of environmental stimuli for some time.

Glucocorticoid administration to well-fed pregnant rats seems to have a negative effect on their offspring development. Nevertheless, sometimes they constitute the election therapy, so it would be advisable to study in detail their influence con growth and maturation processes. Thus, their administration in prenatal (Varela, Marcos y Rey de Viñas, 1985) or postnatal (Howard, 1965; Ortega, Rey de Viñas y Varela, 1981) periods decreases body weight. This effect is probably due to a diminished intake (Alario, Gamallo, Beato y Trancho, 1987), to their catabolic action on peripheral tissues, and, in short, to an impaired metabolic —non digestive— management of proteins (Moreiras-Varela y Varela, 1972). Also, pituitary cell cultures after long exposure to glucocorticoids showed an increased production of GH (Ceda, Davis y Hoffman, 1987), like it happened in protein malnourished animals.

The studies on the effect of corticosteroids on morphological characteristics indicate premature eye opening (Salas y Schapiro, 1970; Schapiro, Salas y Vukovich, 1970; Benesova y Pavlik, 1986) and incisor eruption (Benesova y Pavlik, 1986) following the injection of glucocorticoids in the first day of life. In contrast, other observations include delays in nervous system maturation (Howard, 1965; Bohn y Friedrich, 1982).

Some reports lead us to think that cortisol administered to underfed pregnant rats could ameliorate the consequences of protein defficiency through its catabolic action on tissues, producing free amino acids which could be used by the fetus, whose development is of priority under normal conditions. These reports include those of Chandler, Leury, Bird y Bell (1985) that maternal structures can be used under certain circumstances as a substrate for fetal tissue formation; of Naismith y Morgan (1976) that protein given to undernourished gestating rats increase fetal weight and cellularity; of Millward, Garlick y Nnanyelungo (1976) that cortisol administration might be a protecting mechanism against hypoalbuminemia by increasing muscle protein degradation so that it could maintain amino acids for hepatic protein synthesis; of Rao y Ramakrishnan (1986) that hydrocortisone administration during neonatal undernutrition improved the rate of maturation of intestinal structure and enzimes activities and finally those of Marcos et al. (1986) that cortisol had no negative effects on growth of pups from malnourished mothers (protein synthesis was higher than in those non-treated malnourished mothers) in contrast with the catabolic action observed under normal nutrition —this could be explained by a restriction in the passage of cortisol troughout the placenta, as a consequence of the deterioration brought on by malnutrition (Munro, 1980)—.

Based on the previous research, the object of the present study was to observe

how the following three factors influenced weight and length of the pups from birth until the end of the suckling period and on the ages of appearance of ear unfolding, incisor eruption and eye opening: 1) malnutrition, 2) cortisol administration, and 3) both malnutrition and cortisol administration.

METHOD

Animals

Twenty litters of Wistar rats (Charles River stock, obtained from the Centro de Biología Molecular, Universidad Autónoma de Madrid) were used. All the mothers were virgins weighting 150 ± 10 g. They were caged in groups of three, and were randomly assigned to one of two isocaloric diets (20% and 10% casein, composition detailed in table 1). All rats received water and diet ad libitum. Litters for the NS group were obtained from 5 female rats. For the remaining groups it was necessary to use 6 females in each case: in the group NC all them became pregnated, but one litter was eliminated because of mortality of some pups; in the malnourished groups 1 females did not become pregnated.

Mineral mixture contained per 1000 g. of diet: KI, 0,20 mg; CuSO4 -5H2O, 24,72 mg; NaI, 2,341 mg.; MnSO4 -%H2O, 169020 mg.; FeSO4 -7H2O, 199,04 mg.; NaCl, 1,41 mg.; MgCO3, 769.78 mg.; MgSO4, 2,250 mg.; Ca(PO4H2)2, 14760,3 mg.; KH2PO4 3599,2 mg.; CaCO3, 4124 mg.; ZnCO3, 25,26 mg.; KHCO3, 6103, 43 mg.; Cr2 O3, 0,118 mg.; Na2SeO3, 0,240 mg.

Vitamin mixture contained per 1000 g: Choline, 1,111g.; Folic Acid, 1.110 mg.; Niacin, 22,22 mg.; Ca Pantothenate, 8,88 mg.; Riboflavin, 3,33 mg.; Thiamin, 4,44 mg.; Vitamin B6, 6,66 mg.; Vitamin B12, 0,055 mg.; Vitamin A, 1,514 mg.; Vitamin D3, 2,222 mg.; Vitamin K, 0,055 mg.; Vitamin E, 33,3 mg.

	20%	10%
CASEIN	20,13	10,85
METHIONINE	0,20	0,20
CORN OIL	0,50	0,50
OLIVE OIL	4,95	4,95
CELLULOSE	5,00	5,00
STARCH	32,88	37,52
SUGAR	32,88	37,52
MINERAL MIXTURE	3,34	3,34
VITAMIN MIXTURE	0,12	0,12

Table 1. Composition of diets (% of dry substance).

Procedure

After a one week period of adaptation to laboratory and diet, mating was conducted by introducing a male rat into each cage. Once gestation was confirmed either by observation of the vaginal plug or by checking the estrum and the presence of sperm in a vaginal smear, rats were caged singly in standard cages (50 x 25 x 14 cm.). Each

dietary group was then subdivided into two according to the treatment they were to receive exclusively during pregnancy. One group was administered a daily injection (between 10–11 h.) of 0,5 mg./100 g. body weight cortisol acetate solution; the other group received 0,9% NaCl solution. Four experimental group containing 5 litters each were thus obtained:

- NS group: offspring from mothers fed a diet containing 20% protein during pregnancy and lactation, and injected with isocaloric saline solution during gestation.
- NC group: offspring from mothers fed a diet containing 20% protein during pregnancy and lactation, and injected with cortisol acetate solution during gestation.
- MS group: offspring from mothers fed a diet containing 10% protein during gestation and lactation, and injected with isocaloric saline solution during gestation.
- MC group: offspring from mothers fed a diet containing 10% protein during pregnancy and lactation and injected with cortisol acetate solution during gestation.

After delivery (zero day of lactation period) the newborn stayed with the mother until the twentyfirst day, and dietary conditions remained unchanged. On the first day of study, all subjects were marked for identification by staining the back of the ears with coloured inks (in our experience this an efficient nontoxic method).

From the first day after birth to 21 days of age body weight and lenght (measured from the tip of the snout to the base of the tail) were recorded weekly, and the age of appearance of certain morphological characteristics were registered (ear unfolding, incisor eruption and eye opening). During inspection mothers were put into another standard cage with food and water. To prevent heat loss, the cage with litters were placed close to a stove.

The number of individuals in a litter ranged from 9 to 11 in all groups. There was zero mortality in the litters under experiment. Dietary conditions were constant troughout the experimental period, as were environmental conditions, with 12 hour light-dark cycle, temperature of 20 ± 2 °C and relative humidity of about 50%.

Morphological characteristics data were statistically treated by analyses of variance and then by t-test (7D program of the BMDP-Dixon, 1987), and analyses of variance for repeated measures (2V program of the BMDP) and Tukey's method for multiple comparisons were applied to growth data, using litter means to control litter effects (Abbey y Howard, 1973), so n = 5 per group.

RESULTS

Weight

Data were studied by means of an analysis of variance of three factors, nutrition(N) x cortisol treatment (C) x days(D). Significant effects for N [$F(1, 16) = 6{,}16$, $p < 0{,}05$], D [$F(3, 48) = 268{,}06$, $p < 0{,}001$] and N x D [$F(3, 48) = 3{,}51$, $p < 0{,}05$] were found. Tukey's method disclosed significant differences between NS and NC groups on day 7 ($p < 0{,}05$), between NS group and the malnourished groups from day 7 on ($p < 0{,}05$ on day 7, $p < 0{,}01$ from day 14 on), and between NC group and the malnourished groups on day 21)$p < 0{,}01$).

Figure 1 shows the mean group weight for each group on days under study (1, 7, 14 and 21 of postnatal life). The NS group always presented the highest values. Both malnourished groups showed similar values troughout lactation. the NC group values tended to be closer to those of the NS group as days pass (as the suspension of the steroid treatment grows more remote.

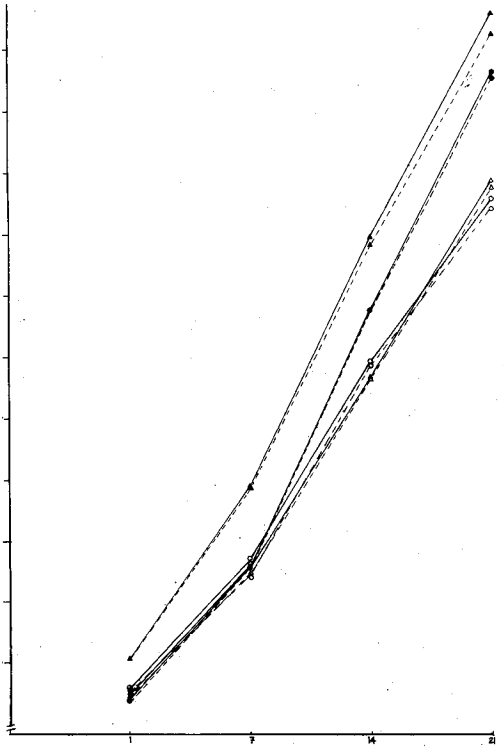

Fig. 1. Weight of the offspring during lactation (▲: NS, ●: NC, Δ: MS, 0: MC). Peso de la descendencia durante la lactancia. ♂ ♀

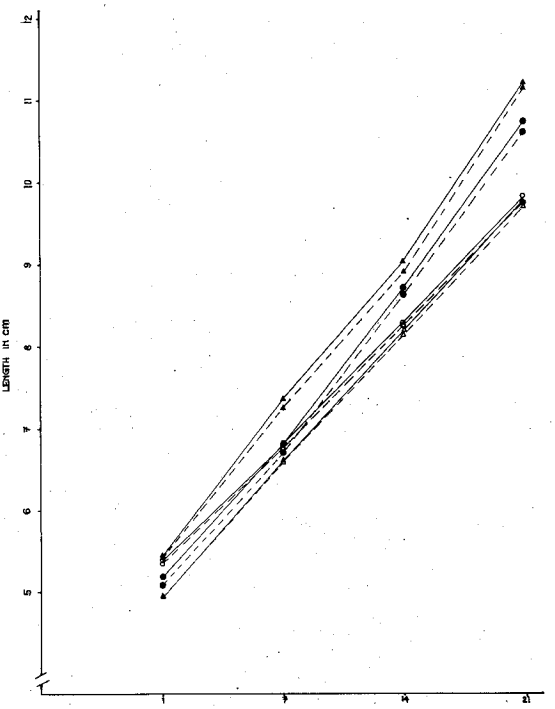

Fig. 2. Length of the offspring during lactation (▲: NS, ●: NC, Δ: MS, 0: MC). Longitud de la descendencia durante la lactancia. ♂ ♀

Length

An analysis of variance of three factors N x C x D showed a significant effect of N [F (1, 16) = 14,50, $p < 0,01$], D [F (3, 48) = 789,99, $p < 0,001$] and N x D [F (3, 48) = 6,83, $p < 0,001$]. Tukey's method disclosed significant differences between NS and NC groups on day 7 ($p < 0,05$), between NS and MS groups on every day under study ($p < 0,01$ in all cases), between NS and MC groups from day 7 on ($p < 0,05$ on day 7, $p < 0,01$ on the remaining days), and between NC and the malnourished groups from day 14 on ($p < 0,05$ on day 14, $p < 0,01$ on day 21).

Figure 2 shows the mean length in every group in the recorded days. Animals show for this variable a tendency similar to that for body weight.

Physical characteristics

Table 2 shows the means and standard deviations of the groups for these variables. Analyses of variance of two factors (N and C) showed a significant effect of N x C on the age of appearance of ear unfolding [F(1, 16) = 13,21, $p < 0,01$], incisor eruption [F(1, 16) = 6,10, $p < 0,05$] and eye opening [F(1, 16) = 14,39, $p < 0,01$]. For ear unfolding t-test disclosed significant differences when compa-

ring the MS group with the NC ($p < 0,01$) and the MC ($p <),05$) groups; comparison between the NS group and the NC group was almost significant ($P = 0,0503$). For incisor eruption only the comparison between NS and NC groups was significant when comparing the NS group with the NC ($p < 0,05$) and the MS($p < 0,01$) groups, and also when comparing the MC group with the NC and the MS groups ($P < 0,05$ in both cases).

NS	NC	MS	MC	
Ear unfolding	3,25 ± 0,49	4,12 ± 0,66	4,64 ± 0,47	3,53 ± 0,75
Incisor eruption	9,12 ± 0,01	10,52 ± 0,46	10,40 ± 1,00	9,78 ± 0.90
Eye opening	14,72 ± 0,56	16,22 ± 0,13	16,59 ± 1,46	114,98 ± 0,95

Table 2. Means and Standard Deviations of the four groups for the morphological characteristics.

DISCUSSION

As it was expected, significant differences in growth existed between the NS and MS groups. Thus, the growth curves show a steeper slope for the MS group than for the NS group, indicating a slower growth in malnutrition states. This is consistent with other authors' observations (Dickerson, Hughes, y McAnulty, 1972; Turner, 1973; Fernández, Marín y Fernández Patterson, 1985). Such reductions could be the result of the decrease in weight gain throughout gestation experienced by malnourished pregnant rats that indicates a lowering of maternal reserves that otherwise could be used for fetal development (Kanarek, Schonfeld y Morgane, 1986; Marcos et al., 1986), of the diminished efficiency in protein management(Millward et al., 1974) as well as the low activity of somatomedins (Shapiro y Pimstone, 1977; Phillips, 1986). In consequence, nutrients and especially proteins are diverted from growth to more important processes, such as nervous system development (Morgane et al., 1978; Rodríguez Pérez, 1988). In this sense, a reduced size is an adaptative mechanism; in fact, the ratio brain weight / body weight is greater in the malnourished animals than in the wellnourished ones(Morgane et al., 1978).

Differences in growth between the NS and NC groups are not significant except for length and body weight on day 7. This could be a Type I error, since significant differences in an isolated intermediate value are not expected to be found. However, it is interesting that all NS animals are above the NC group's mean weight at birth, and that at birth only 27% of NC animals are heavier that the smallest NS animals, whereas towards the end of the experimental period this percentage raises to 96%. This is interpreted as «catching up» as the effect of hormone administered during gestation decreases. Cortisol, like malnutrition, leads to reduce intake and poor metabolic management of protein, thus slowing growth. When treatment is supressed, a normal growth rhythm is recovered (Ortega et al., 1981) «trough a late improving action on protein management efficiency (explained by a higher uptake of dietary nitrogen) seen in animals treated with the hormone» (Moreiras-Varela y Varela, 1972).

Examining Figures 1 and 2, we can

see that values at birth are similar in the NC and MS groups, but later the NC group has higher values. This is explained by recovery from the effects of cortisol during gestation, while the MS group remains under the influence of inadequate nutrition.

Animals in the MC group had weight and length values similar to those in the MS group, with minimal differences between the means. These results would be in accordance with Marcos et al. (1986) in that they also obtained a similar wight for newborns from mothers under the same treatments.

As for the ages of appearance of ear unfolding, incisor eruption and eye opening, which we have considered as maturation indicators, they always appeared earliest in the control (NS) group, while in the MC group earlier than in the MS and NC groups (Table 2).

The delays we observed in the MS group for the studied variables are similar to other authors observations (Zeman, 1967; Smart y Dobbing, 1971; Bush y Leathwood, 1975; etc) who employed different methods to produce undernutrition. Eye opening seems to be more influenced by nutritional defficiency as previously reported (Smart y Dobbing, 1971; Hsueh, Simonson, Chow y Hanson, 1974; Sánchez-Turet et al., 1978), than are the other characteristics. that this and other studies (e.g. Jen, Wehmer y Morofsky, 1978) observed no significantly delayed.

Concerning glucocorticoid administration to animals with a good nutritional status, the few studies we know injected the hormone postnatally and show an advanced age for incisor eruption (Benesova y Pavlik, 1986) and eyes opening (Salas and Schapiro, 1970: Schapiro et al., 1970; Benesova y Pavlik, 1986), which is not in accordance with the observations of delays in brain maturation (Bohn and Friedrich, 1982; Howard, 1965), in the appearance of evoked responses by visual, auditory and sciatic nerve stimulation and auditory startle reflex (Salas and Schapiro et al., 1970), in the development of normal natatory patterns (Schapiro et al., 1970), and with our own results (significant delays kin the age of appearance of all the characteristics when compared with animals at the same dietary level not treated with the hormone).

Lastly, in the MC group morphological characteristics appear not significantly delayed in respect to the NS group, and earlier than in the MS group. This improving effect could be explained by an increased production of maternal aminoacids passing the placentary barrier and used by the fetus to build its own structures, giving priority to those of greater functional importance. Perhaps for this reason we find significant delays for the maturation indicators in the MS animals while their weight and length are similar to those of MC animals.

So, it seems that glucocorticoid administration to well-fed gestant mothers produces a similar picture to malnutrition in the progeny whereas their administration to gestant rats fed on hypoproteic diet ameliorate the effects of malnutrition on the progeny.

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