Prenatal undernutrition decreases the sensitivity of the hypothalamo-pituitary-adrenal axis in rat, as revealed by subcutaneous and intra-paraventricular dexamethasone challenges

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Abstract

Prenatal undernutrition is known to disturb the hypothalamo-pituitary-adrenal (HPA) axis, possibly through the programming of decreased expression of hypothalamic and pituitary glucocorticoid receptors. To test this hypothesis, we examined the corticosterone response to moderate subcutaneous (100 μg/kg) and intra-paraventricular (50 pmol, bilaterally) dexamethasone (DEX) challenges in normal eutrophic and prenatally undernourished young rats. Undernutrition was induced during fetal life by restricting the diet of pregnant mothers to 10 g daily, while mothers of eutrophic rats received the same diet ad libitum. At day 40 of postnatal life (i) undernourished rats showed increased plasma corticosterone concentration compared to normals; and (ii) subcutaneous and intra-paraventricular administrations of DEX led to reduced corticosterone levels in normal and undernourished animals, the effect of DEX (administered either peripherally or centrally) being significantly lower in the latter group. Results suggest that the low sensitivity of the HPA axis to DEX as well as the increased plasma corticosterone observed in prenatally undernourished rats could be due to the already reported glucocorticoid receptor underexpression found in the hypothalamus and pituitary of in utero undernourished animals, but alternative explanations involving central noradrenergic adaptive changes could also be possible.

Keywords: Prenatal undernutrition; Hypothalamo-pituitary-adrenal axis; Corticosterone; Dexamethasone; Paraventricular nucleus

Epidemiological studies point out an association between low birth weight and arterial hypertension, coronary disease and type 2 diabetes during adult life, suggesting that these dysfunctions are programmed during fetal life [1]. One of the main factors determining fetal growth is the nutritional status of the mother, in such a way that periods of malnutrition during pregnancy will lead to growth retardation during prenatal life as well as to elevated blood pressure at later postnatal ages [1]. This notion is supported by studies in animals showing that pregnant rats submitted to different forms of protein or protein–calorie restriction gave birth pups that developed hypertension during postnatal life in spite of they were nutritionally rehabilitated during lactation [11,24,39].

Such effect of maternal undernutrition in offspring could be related to disturbances in the fetal hormonal environment, particularly in the activity of the hypothalamo-pituitary-adrenal (HPA) axis. In fact, there is evidence that both maternal protein [12] and maternal food [13] restrictions to pregnant rats result in lower placental 11β-hydroxy-steroid dehydrogenase type 2 (11βHSD2) activity, the enzyme that converts physiological glucocorticoids to inactive 11-keto products, thus resulting in overexposure of the fetus to maternal glucocorticoids. Deficiency in placental 11βHSD2 has also been reported in babies with reduced body weight at birth [37]. Overexposure to maternal glucocorticoids caused by prenatal undernutrition has been found to reduce glucocorticoid receptor expression in

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the hippocampus [13], hypothalamus [2] and pituitary [8] of the offspring, which are important sites of feed-back control upon the HPA axis. Hypothetically, reduced glucocorticoid receptor expression in these sites would result in decreased negative feed-back control by glucocorticoids and thereby in increased HPA activity. This possibility is supported by studies reporting higher expression of hypothalamic corticotropin-releasing hormone (CRH) as well as greater plasma levels of adrenocorticotropin hormone (ACTH) and corticosterone/cortisol in rats and lambs that underwent different forms of prenatal undernutrition [7,19,22,26,34]. Epidemiologic studies have also associated low birth weight of babies, an index of intrauterine undernutrition, with increased basal plasma cortisol levels when adults [25].

In spite of the synthetic glucocorticoid dexamethasone (DEX) has been widely used for in vitro and in vivo studies of the glucocorticoid effects on a number of different cellular and physiological responses, the DEX suppression test has not still been employed for determining the status of the negative feed-back control of the HPA axis in subjects that experienced undernutrition during fetal life. In this regard, several studies in rat have demonstrated a pituitary rather than a central site of action in the suppression of HPA axis if moderate amounts of DEX are administered [4,5], since the expression of the efflux transporter P-glycoprotein hampers the penetration of DEX into the brain [16] and, on the other hand a moderate dose of DEX results in suppression of endogenous corticosterone secretion [10]. Therefore, central administration of DEX into the paraventricular nucleus (PVN) would be necessary to study DEX-induced suppression of HPA axis at the hypothalamic level. In the present investigation we examined the corticosterone response to moderate subcutaneous and intra-PVN DEX challenges in normal eutrophic and prenatally undernourished young rats in order to test at both, the pituitary and hypothalamic levels respectively, changes in sensitivity of the negative feed-back control of the HPA axis that would be programmed by undernutrition during fetal life.

The experimental protocol and animal management were in accordance with the NIH Guide for the Care and Use of Laboratory Animals [18]. The experiments were carried out on male and female Wistar rats, born from mothers subjected during pregnancy to one of the following nutritional conditions: (i) normal pregnant rats, with free access to a 21% protein standard laboratory diet (Champion, Santiago, Chile); (ii) undernourished pregnant rats, with restricted access (10 g daily) to the standard laboratory diet throughout pregnancy; this amount of food is about 40% of that consumed by normal pregnant rats [34], and was given two times daily (5 g at 09:00 h and 5 g at 19:00 h) in order to minimize anxiety for feeding in food restricted pregnant dams. To prevent undernutrition of pups during postnatal life, prenatally undernourished pups were at birth fostered to well-nourished dams giving birth on that day, according to rearing procedures already described [17]; pups born from well-nourished mothers were also fostered to well-nourished dams, in order to equalize among groups other factors that may depend on the rearing conditions (i.e. stress due to cross-fostering). During the lactation period all litters were adjusted to eight pups per dam, and all dams continued to receive the standard laboratory diet ad libitum. After weaning at 22 days of age, all pups were housed eight per cage and fed on the standard laboratory diet, under controlled laboratory conditions (a 12-h light/dark cycle with lights on at 09:00 h). During the light cycle, light intensity was maintained at 300 lx as measured at the level of the cage floor. The body weight of pregnant mothers and the body weight of pups were measured daily.

All experimental groups were composed by six rats (three males and three females) arising from different litters. On day 40 of postnatal life, at 19:00–20:00 h, six normal and six prenatally undernourished rats were s.c. injected with a single low dose of 100 μg/kg DEX-21-phosphate (Sigma–Aldrich, St. Louis, MO) dissolved in 0.9% (w/v) NaCl to induce a decrease in plasmatic corticosterone. Another six normal and six prenatally undernourished rats receiving the same volume of s.c. saline served as controls. Other groups of six normal and six prenatally undernourished rats were used to study the effect of intra-PVN microinjection of DEX on plasma corticosterone. Six additional normal and six additional prenatally undernourished rats microinjected with saline into the PVN served as controls. In order to microinjecting DEX or saline, animals were anesthetized with sodium pentobarbital (45 mg/kg body weight) and placed in a stereotaxic apparatus for rats (Narishige ST-7, Narishige Scientific Instrument Lab., Tokyo, Japan). The horizontal zero plane of the stereotaxic apparatus was tangent to the upper incisor bar and 5 mm above the interaural line. The skull was exposed and two 2.0-mm diameter holes, centered at 0.5 mm lateral to the midline and 0.6 mm rostral to the bregma point, were drilled in the right and left parietal bones for approaching both PVNs at coordinates A, 6.4; L, 0.5; V, −1.6 (in mm) [21]. DEX-21-phosphate (Sigma–Aldrich, St. Louis, MO) was bilaterally injected (50 pmol DEX/0.2 μl saline) using a 10-μl Hamilton syringe directed at each PVN. This dose was taken from studies using centrally microinjected DEX in other brain nuclei, such as the nucleus tractus solitarius, to produce modification in cardiovascular parameters [20,38]. Similar saline volumes were microinjected into the PVNs of control animals. The injections were performed gradually over a period of 2 min. Afterwards, rats were kept one animal per cage until the next morning.

Fourteen hours after the DEX challenge (s.c. or intra-PVN), rats were killed rapidly by decapitation between 09:00 and 10:00 h in a room separate from that in which the other animals are kept. Trunk blood was collected in heparinized Eppendorf tubes and immediately centrifuged (1700 × *g*, 10 min, 4 °C) and plasma stored at −20 °C. Plasma corticosterone was measured using a RIA based on ^{125}I-labelled rat corticosterone that was performed according to the manufacturer's instructions (Diagnostic Products Corporation, Los Angeles, CA, USA). This Coat-a-Count rat corticosterone kit is a solid-phase RIA, in which rat ^{125}I-corticosterone competes for antibody sites with corticosterone in the sample during a fixed time (120 min). The antibody is coated on the wall of a polypropylene tube. Decanting the supernatant is sufficient to terminate the competition and to isolate the antibody-bound fraction of the radiolabelled corticosterone. Counting the tube in a gamma counter (Riastar

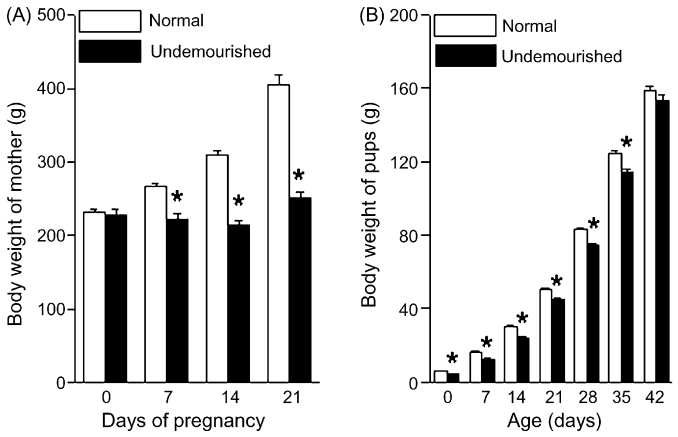

Fig. 1. (A) Time-course of body weight of pregnant rats submitted to ad libitum (normal group) or restricted (10 g/day, undernourished group) dietary paradigms. Values are means ± S.E.M. at days 0, 7, 14 and 21 of pregnancy. $N = 8$ dams per group. Asterisks indicate significant differences in body weight between normal and undernourished rats ($P < 0.001$, Student's t-test). (B) Time-course of body weight during the postnatal life of normal and prenatally undernourished pups. Values are means ± S.E.M. at 0, 7, 14, 21, 28, 35 and 42 days of age. $N = 32$ pups per group. Asterisks indicate significant differences in body weight between normal and undernourished groups (*$P < 0.001$, unpaired two-tailed Student's t-test).

Packard, CT, USA) then yields a number that converts by way of a calibration curve to a measure of the corticosterone present in the sample. Intra and interassay coefficients of variation were approximately 5%. Corticosterone concentration was expressed as ng/ml plasma.

To determine the changes induced by the undernutrition regimen during pregnancy on body weight of pregnant mothers as well as on body weight of pups, values obtained from undernourished animals were expressed as means ± S.E.M. and compared to the corresponding values found in normal animals using unpaired two-tailed Student's t-test.). To analyze the effect DEX or saline (drug treatment) on plasma corticosterone of normal eutrophic and prenatally undernourished rats (nutritional condition), a two-way ANOVA followed by the Bonferroni *post hoc* test was used (Prism 3.00, GraphPad Software Inc., San Diego, CA, USA).

Fig. 1A shows that at days 7, 14 and 21 of pregnancy, the mean body weight of undernourished dams was significantly lower than that of normal dams ($P < 0.001$). Fig. 1B shows that throughout the postnatal life (from day 0 until day 35) prenatally undernourished pups exhibited a significant body weight deficit compared to normal pups ($P < 0.001$).

Table 1 shows that at day 40 of postnatal age plasma corticosterone was significantly higher ($P < 0.001$) in undernourished rats compared to plasma corticosterone levels found in normal rats. Table 1 also shows that either s.c. DEX or intra-PVN microinjected DEX significantly decreased the plasmatic concentration of corticosterone in both normal and undernourished animals ($P < 0.001$). In this respect, two-way ANOVA showed a significant effect of the drug treatments (s.c. and intra-PVN DEX versus s.c. and intra-PVN saline) as well as a significant effect of the nutritional condition (undernourished versus normal eutrophic controls). Besides, the significant drug x nutrition

Table 1
Effect of systemical (100 μg/kg s.c.) and intra-PVN (50 pmol, bilaterally) administration of DEX on plasma corticosterone (ng/ml) of 40-day old normal and prenatally undernourished rats. Saline groups of same age served as controls

	Normal	Undernourished
Saline s.c.	93.4 ± 6.9	143.7 ± 11.2[a]
DEX s.c.	6.1 ± 2.9**	88.8 ± 7.1**,[a]
Saline intra-PVN	102.7 ± 7.2	147.6 ± 11.2[b]
DEX intra-PVN	34.8 ± 4.1**	117.5 ± 9.9*,[a]

Values are means ± S.E.M. $N = 6$ for all groups. For s.c. DEX, two-way ANOVA indicates significant effects of the drug treatment (F ANOVA = 76.29; P ANOVA < 0.0001), the nutritional condition (F ANOVA = 87.21; P ANOVA < 0.0001), and the drug × nutrition interaction (F ANOVA = 4.53; P ANOVA = 0.0460). **$P < 0.001$, when comparing DEX treated vs. saline treated animals; [a]$P < 0.001$, when comparing undernourished vs. normal animals (Bonferroni multiple comparisons post-hoc test). For intra-PVN DEX, two-way ANOVA indicates significant effects of the drug treatment (F ANOVA = 55.74; P ANOVA < 0.0001), the nutritional condition (F ANOVA = 32.88; P ANOVA < 0.0001), and the drug x nutrition interaction (F ANOVA = 4.89; P ANOVA = 0.0388). *$P < 0.05$, **$P < 0.001$, when comparing DEX treated vs. saline treated animals; [a]$P < 0.001$, [b]$P < 0.01$, when comparing undernourished vs. normal animals (Bonferroni multiple comparisons post-hoc test).

interaction (P ANOVA < 0.05) revealed that the effectiveness of s.c. and intra-PVN administration of DEX to reduce plasma corticosterone was different in undernourished rats compared to eutrophic controls. This can be better observed in Fig. 2, showing significantly lower decreases (in percentage) of corticosterone in undernourished animals than in normal rats after s.c. and intra-PVN DEX challenges. Thus, in spite of both s.c. and intra-PVN administrations of DEX reduced corticosterone levels in normal and undernourished animals, the effect of DEX (administered either peripherally or centrally) was significantly lower in the latter group.

Reduction of food intake during pregnancy resulted in a lower maternal weight gain as well as in significant body weight

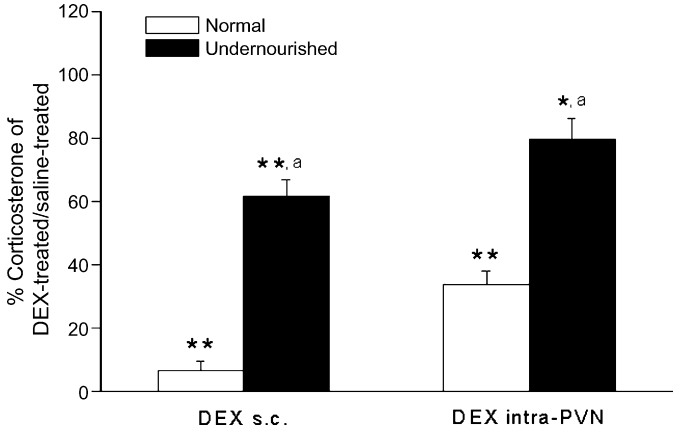

Fig. 2. Decreases in plasma corticosterone in normal and undernourished rats after systemical (DEX s.c.) and intra-PVN (DEX intra-PVN) administration of DEX. Ordinates: % corticosterone of DEX-treated respect to saline-treated rats. Values are means ± S.E.M. Data were initially analyzed by two-way ANOVA (for F ratios and P ANOVA see legend to Table 1). *$P < 0.05$, **$P < 0.001$, vs. the 100% corticosterone level of saline treated rats; [a]$P < 0.001$, as compared with the respective normal group (Bonferroni multiple comparisons post hoc test).

deficits of pups during the lactation period, which is indicative of fetal growth retardation. Fostering of the pups at birth to well-nourished dams led to body weight recovery of the offspring on week sixth of postnatal life. Similar results have been obtained by others [32].

On day 40 of age, undernourished rats had enhanced level of plasma corticosterone measured during the light phase. This is in line with previous reports showing that maternal food restriction during gestation [33] or maternal food restriction during gestation and lactation [29] resulted in high basal plasma levels of corticosterone in adult rat offspring, suggesting a long-lasting maternal undernutrition programming of glucocorticoid secretion in the progeny. In agreement with animal studies, low human birth weight, as an approximation for undernutrition in utero, is associated with increased urinary glucocorticoid secretion in children [3] and increased plasma levels of glucocorticoids in adult men [25].

As expected, the s.c. DEX challenge significantly decreased the basal (trough) plasmatic concentration of corticosterone in both normal and undernourished animals. In this respect, significant effects on plasma corticosterone have been observed as long as 24 h after a single low dose of DEX in rats [14]. As previously mentioned, studies in rat have demonstrated a pituitary rather than a central site of action in the suppression of HPA axis when moderate amounts of systemically DEX are administered [4,5], because the expression of the efflux transporter P-glycoprotein hampers the penetration of DEX into the brain [16] and, on the other hand a moderate dose of DEX results in suppression of endogenous corticosterone secretion [10]. Microinjection of DEX into the PVN also led to decreased concentration of plasma corticosterone in both normal and undernourished rats, the effect being measured 14 h after intra-PVN administration of DEX. This suggests that the reduction of plasma corticosterone resulted from glucocorticoid receptor-dependent genomic mechanisms that blunted CRH surge in PVN neurons, thereby decreasing the activity of the HPA axis.

Interestingly, irrespective the route of administration utilized, the effectiveness of DEX to reduce plasma corticosterone was lower in undernourished rats compared to eutrophic controls. This is probably the result of decreased glucocorticoid feedback control of the HPA axis programmed during prenatal life. As discussed elsewhere [30], fetal growth restriction leads to a reduction of the glucocorticoid negative feedback by means of a series of sequential events, including decreased activity of placental 11βHSD2 [12,13] which results in decreased glucocorticoid receptor expression during fetal life in regions concerned with the regulation of the HPA axis, such as the hypothalamus [2] and the pituitary [8]. Consistent with this interpretation, lower decreases of plasma corticosterone in undernourished animals than in normal rats after s.c. and intra-PVN DEX challenges were observed in the present study. This suggests that reduction in the number of glucocorticoid receptors in the hypothalamus and the pituitary of prenatally undernourished animals would constitute, at first sight, a sufficient condition to explain the decreased sensitivity of the HPA axis to DEX challenge, and consequently, higher plasma levels of corticosterone in these animals. Other possibility is that the corticosterone increase observed in undernourished rats arose from adrenal hypertrophy [9]. However, this alternative seems unlikely since the increase in adrenal weights these authors observed in prenatally undernourished rats amounted at most 10%, while in the present study, plasma corticosterone increase in undernourished animals reached around 50%. Another likely explanation for the decreased sensitivity of the HPA axis to DEX we observed in prenatally undernourished rats could be based on the fact that the PVN in these animals is overstimulated by central noradrenergic afferents coming from the locus coeruleus and other noradrenergic nuclei [23]. In conditions of PVN overstimulation by central noradrenergic mechanisms, the negative feedback exerted by DEX on PVN and/or pituitary glucocorticoid receptors could possibly be functionally compensated by the hyperactive status of the HPA axis, and a higher release of corticosterone by adrenal glands of undernourished animals could be expected. In this respect, increased number and expression of α_{2C} adrenoceptors has been already observed in the neocortex of prenatally undernourished rats [31,36] together with increased noradrenaline turnover [15] and release [34,35], but changes in expression of hypothalamic noradrenergic receptors induced by undernutrition, especially the α_1 subtype mediating excitatory input in PVN neurons [6,27,28], have not still been reported. It is apparent then, that complex alterations involving more receptors than the glucocorticoid subtype seems to be induced by prenatal undernutrition, as part of the adaptive changes by which fetal undernutrition could set up the sensitivity of the HPA axis during adult life. Further studies on molecular/cellular modifications occurring in PVN neurons would be helpful for a better understanding of the mechanisms by which maternal undernutrition leads to fetal programming of HPA hyperactivity.

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