Body weight recovery in intrauterine growth-retarded rats treated with growth hormone

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Summary

The aim of this work was to analyze the action of growth hormone (GH) on postnatal body weight recovery in intrauterine growth-retarded (IUGR) rats. Wistar rats were assigned to three groups: 1) control; 2) IUGR and 3) sham-operated. Uterine vessels of dams in the IUGR group were partially bent on the 14th day of pregnancy. At weaning, some IUGR pups were randomly selected and injected with GH (3 mg/kg/day), up to the 60th day. A standard diet *ad libitum* was available to mothers and offspring. The animals were weighed and food intake was recorded weekly. The weight gained velocity and relative food intake (RFI) was calculated. IUGR animals showed significant lower body weights than the control group. GH treatment allowed body weight recovery in IUGR rats. In females, body weight increased 14 days before males, and the former had greater RFI values. In conclusion, our results indicated differences in sexual responses to GH treatment. There is a need for more research on the mechanisms involved in that sexual difference.

Key words: Body growth; Growth hormone; IUGR; Sexual dimorphism.

Introduction

Intrauterine growth retardation (IUGR) constitutes a major clinical problem and it is the result of one of three general pathologic mechanisms: (1) chromosomal/genetic defects, (2) fetal infection/toxicity, or (3) compromised substrate delivery to the fetus [1, 2]. The obstruction of uterine vessels is an extreme example of uteroplacental insufficiency, which produces severe alterations of the fetal physiology [3]. This experimental model is widely used because it allows the effects of isolated variables such as age, sex, nutrition, etiology, etc., to be studied [4-6]. In the rat, a progressive and significant increase of both blood flow to uterine tissue and fetal body weight occurs during the third/third of pregnancy. Fetal mass increases from 0.1 g to 6.5 g during this period [7].

During fetal growth there are high levels of growth hormone (GH), and the GH receptors are widely distributed [8]. Although some reports suggest an active role of GH in normal fetal development [9], the relevance of GH on prenatal growth has not been fully elucidated. The first postnatal therapeutic trials using human pituitary GH on fetal growth restriction, did not show positive results, probably due to the small dose used and the low availability of drug [10, 11]. The disposability of recombinant human GH led to the re-examination of the paradigm [12]. Studies by Albertsson-Wikland and Stanhope *et al.* [13, 14] – among others – found growth acceleration and an improvement in adult stature in IUGR children treated with GH. However, GH actions on body weight are not clear yet. The aim of the present work was to evaluate the effect of growth hormone (GH) on postnatal body weight recovery in intrauterine growth-retarded rats.

Material and methods

Wistar rats had been brought up at the Centro de Investigaciones en Genética Básica y Aplicada (CIGEBA-UNLP). Forty females (200-250 g body weight) were mated overnight with ten adult males. The beginning of pregnancy was assumed by the presence of spermatozoa in the vaginal smear. Pregnant rats were housed in individual steel boxes and fed on stock diet *ad libitum*. Three groups were formed: 1) control (C); 2) IUGR; 3) sham operated (Sh).

IUGR was induced by the technique reported by Oyhenart *et al.* [6]. A lower midline laparotomy was performed on the 14th day of pregnancy. A light-ether anesthesia was given during surgery. The uterine vessels near the lower end of each uterine horn were partially bent and fastened with a 3-0 silk suture. Pregnancy was allowed to proceed until delivery. The procedure applied to the sham-operated dams was similar to that used for the IUGR group. The uterine vessels, however, were not obstructed in order to isolate the effects of surgery from those of vessel bending. At delivery, IUGR and sham-operated pups (4 males and 4 females) were cross-fostered to control dams.

At weaning (21 days old), IUGR pups were randomly selected from each litter and injected subcutaneously over 39 days with GH (Genotropin 3 mg/kg/day) (IUGR+GH group). This treatment lasted up to day 60, when the rats reached early adulthood. Pups from sham-operated dams were injected with

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hormonal diluent in the same dose as the hormone. Body weight (BW) was recorded weekly on a Mettler H80 scale (0.1 mg precision), from birth to the end of the experiment (84 days old). The growth velocity for body weight (WV) was calculated by subtracting successive records (g/week).

A standard diet *ad libitum* was available to mothers and offspring. Daily food intake (FI) was recorded and Relative Food Intake index (RFI) calculated as follows: RFI= 100 (FI/BW) (mg/g).

The one-sample Kolmogorov-Smirnov test was applied to examine the frequency distributions of data. Since the variables were not normally distributed, data were logarithmically transformed in order to achieve normal distributions. A multifactor analysis of variance (ANOVA) test was performed and – in significant cases – sex/treatment comparisons were determined by the Fisher least square differences (LSD). The differences in growth velocity were tested by Wilcoxon statistics. Comparisons were designed to test the following factors: IUGR, IUGR plus GH, and surgery plus hormonal diluent.

For graphical purposes, the sexual comparison of RFI mean values were standardized by percentual differences between means (PDM). PDM = 100*[(mean RFI in females–mean RFI in males)/mean RFI in males. This procedure has been frequently employed since the PDM is not affected by the magnitude of the variables or the sense of the difference [6].

Results

Means and standard deviations are shown in Table 1. Multivariate analyses showed a significant effect of age, age-sex, and age-treatment in all the variables. The interaction age-sex-treatment was also significant (Table 2). In the between-subject analysis, the treatment and sex were statistically significant in body weight, food intake and RFI. There was no interaction between factors (Table 3).

In the control-sham operated pup comparison, the post-hoc LSD test showed significant differences at 35, and 70-84 days old in males, and at seven days old in females. Due to these differences, the sham-operated pups were taken as controls (Table 4).

The comparison between sham-operated and IUGR males indicated significant differences at all ages, while in females differences were observed at 1-42, 63 and 77-84 days old. In all cases differences in the sham-operated rats were greater than the IUGRs. Sham-operated males compared to IUGR+GH males indicated significant differences from birth to 42 and 63 days old. Females had significant differences up to 35 days old. On the other

Table 1. — *Means (M) and standard deviations (SD) values for body weight and food intake.*

Age (days)	Control		Sham-operated		IUGR		IUGR+GH	
	Weight	Food intake	Weight	Food intake	Weight	Food intake	Weight	Food intake
Males	M SD	M SD	M SD	M SD	M SD	M SD	M SD	M SD
1	6.9 ± 0.3	-	6.9 ± 0.2	-	5.7 ± 0.7	-	6.0 ± 0.6	-
7	11.1 ± 0.7	-	10.2 ± 0.7	-	10.0 ± 1.3	-	9.4 ± 1.5	-
14	20.5 ± 3.3	-	21.7 ± 3.5	-	18.0 ± 3.2	-	17.4 ± 3.3	-
21	33.5 ± 5.3	-	32.5 ± 3.4	-	28.3 ± 4.4	-	26.0 ± 5.5	-
28	57.3 ± 6.6	7.5 ± 1.0	57.0 ± 8.8	6.7 ± 1.1	52.6 ± 6.1	6.6 ± 1.0	48.4 ± 6.7	5.3 ± 1.3
35	96.0 ± 8.0	12.7 ± 1.4	86.1 ± 11.5	10.1 ± 1.7	78.8 ± 9.3	9.6 ± 2.0	84.0 ± 15.2	9.2 ± 1.0
42	129.9 ± 9.5	15.8 ± 2.7	128.8 ± 14.1	14.6 ± 2.8	113.3 ± 12.8	14.59 ± 4.0	113.0 ± 17.0	12.6 ± 3.0
49	161.6 ± 13.2	17.6 ± 1.5	165.6 ± 21.0	17.1 ± 3.1	150.8 ± 12.9	15.9 ± 5.2	159.0 ± 15.9	15.3 ± 3.4
56	202.6 ± 13.9	20.1 ± 2.2	204.7 ± 21.4	20.1 ± 3.9	185.0 ± 14.4	17.9 ± 2.0	193. 3 ± 18.6	17.5 ± 2.7
63	230.8 ± 20.0	19.3 ± 2.5	238.5 ± 22. 0	19.5 ± 0.6	207.5 ± 14.2	18.6 ± 3.5	220.1 ± 17.4	20.2 ± 4.7
70	253.5 ± 24.8	20.7 ± 3.3	269.7 ± 25.5	21.6 ± 1.2	235.9 ± 19.9	19.7 ± 4.1	251.4 ± 17.9	21.3 ± 4.2
77	278.8 ± 23.4	19.7 ± 3.6	294.4 ± 19.3	20.9 ± 1.5	263.5 ± 30.0	20.9 ± 2.1	275.3 ± 19.3	21.7 ± 3.6
84	302.5 ± 22.5	20.6 ± 2.2	319.9 ± 21.4	22.6 ± 2.5	273.9 ± 17.6	20.0 ± 2.6	296.5 ± 18.5	18.8 ± 3.6
Females								
1	6.4 ± 0.2	-	6.8 ± 0.1	-	5.3 ± 0.9	-	5.4 ± 0.5	-
7	11.8 ± 1.9	-	10.3 ± 0.9	-	9.6 ± 1.3	-	8.8 ± 1.8	-
14	20.7 ± 2.5	-	20.0 ± 2.8	-	17.7 ± 3.6	-	16.1 ± 3.3	-
21	34.6 ± 4.8	-	31.8 ± 4.4	-	28.1 ± 4.1	-	25.9 ± 3.0	-
28	56.7 ± 6.5	8.4 ± 1.0	52.8 ± 5.2	6.5 ± 1.0	50.6 ± 6.7	6.6 ± 0.8	46.8 ± 7.1	6.4 ± 0.8
35	87.4 ± 10.8	11.8 ± 2.0	83.2 ± 10.3	10.3 ± 1.0	78.5 ± 9.4	9.8 ± 1.0	79.8 ± 10.9	10.5 ± 2.5
42	113.9 ± 10.0	15.0 ± 3.7	112.9 ± 10.1	14.3 ± 2.6	105.7 ± 9.5	13.0 ± 2.6	111.8 ± 9.6	12.4 ± 3.0
49	134.7 ± 14.3	15.4 ± 3.2	133.3 ± 12.6	14.7 ± 1.1	125.1 ± 9.0	14.2 ± 0.9	138.8 ± 12.4	13.2 ± 2.4
56	157.4 ± 12.3	17.2 ± 3.2	155.4 ± 15.5	15.4 ± 2.5	146.9 ± 10.0	14.3 ± 1.3	161.4 ± 14.2	13.9 ± 3.3
63	174.3 ± 12.2	17.3 ± 3.2	173.9 ± 19.2	14.4 ± 1.0	162.3 ± 10.5	15.4 ± 1.5	175.1 ± 9.7	15.5 ± 1.8
70	187.3 ± 15.2	18.1 ± 2.9	186.8 ± 19.2	17.6 ± 1.5	175.8 ± 11.9	14.3 ± 1.1	192.4 ± 13.3	16.2 ± 2.5
77	198.9 ± 18.4	17.6 ± 3.2	201.3 ± 18.4	16.0 ± 1.2	184.4 ± 12.0	15.9 ± 1.4	202.4 ± 14.7	16.9 ± 2.3
84	212.2 ± 19.6	17.4 ± 2.3	215.1 ± 24.5	17.1 ± 2.4	195.5 ± 12.9	16.8 ± 2.0	214.2 ± 12.1	20.8 ± 4.0

IUGR: Intrauterine growth-retarded
IUGR+GH: Intrauterine growth-retarded-plus GH injections

hand, the comparison between IUGR and IUGR+GH rats showed significant differences from 63 (males) and 49 days of age (females) onwards. Both male and female GH-treated rats had greater body weight than those from the IUGR group (Table 4 and Figure 1).

Weight growth velocity in IUGR males and females decelerated at weaning. However it was recovered in both IUGR and IUGR+GH rats. In treated animals, velocity remained higher up to day 35. From this age onwards, both groups had different growth patterns, and a new acceleration was observed in GH treated rats (Figure 2).

The three highest peaks of WV (PWV) were seen in IUGR+GH males compared to IUGR males at 35, 49, and 70 days old. The IUGR+GH females showed higher WV compared to IUGR females (35-49 and 70 days old). The highest WV was observed at 84 days old in IUGR+GH males and females (Figure 2). In males the Wilcoxon test showed significant differences between sham-operated-IUGR and IUGR-IUGR+GH males, while in females all comparisons were significant (Table 5).

The RFI values showed no sexual differences between IUGR animals. At variance, significant differences were seen in IUGR rats treated with GH, reaching 28%, 13%, and 42% (35, 77 and 84 days old, respectively) (Figure 3).

Table 2. — *Multivariate coefficients for body weight and food intake.*

Variable	Lambda de Wilk's	F
Body Weight		
Age	0.007	2666.17**
Age-sex	0.132	123.65**
Age-treatment	0.419	6.35**
Age-sex-treatment	0.638	3.05**
Food Intake		
Age	0.019	974.92**
Age-sex	0.358	33.58**
Age-treatment	0.455	5.67**
Age-sex-treatment	0.598	3.52**

**p < 0.01

Table 3. — *Effects of the treatment, sex, and their interactions.*

Variable	Factor Treatment	Factor Sex	Interaction
Body Weight	20.61**	370.14**	1.69
Food Intake	7.96**	74.84**	1.26
Relative Food Intake	5.17**	19.90**	0.18

**p < 0.01

Discussion

Several experimental studies have reported that reduction in the uteroplacental blood flow impaired growth and development in fetuses [3, 5, 6, 16, 17]. Our results support such assumption since body weight at birth was strongly affected by the restricted intrauterine blood supply. In fact, body weight is one of the most important indicators of fetal intrauterine growth retardation. Finally one-third of the variation in birthweight is determined by genetic variables and two-thirds by environmental factors [15].

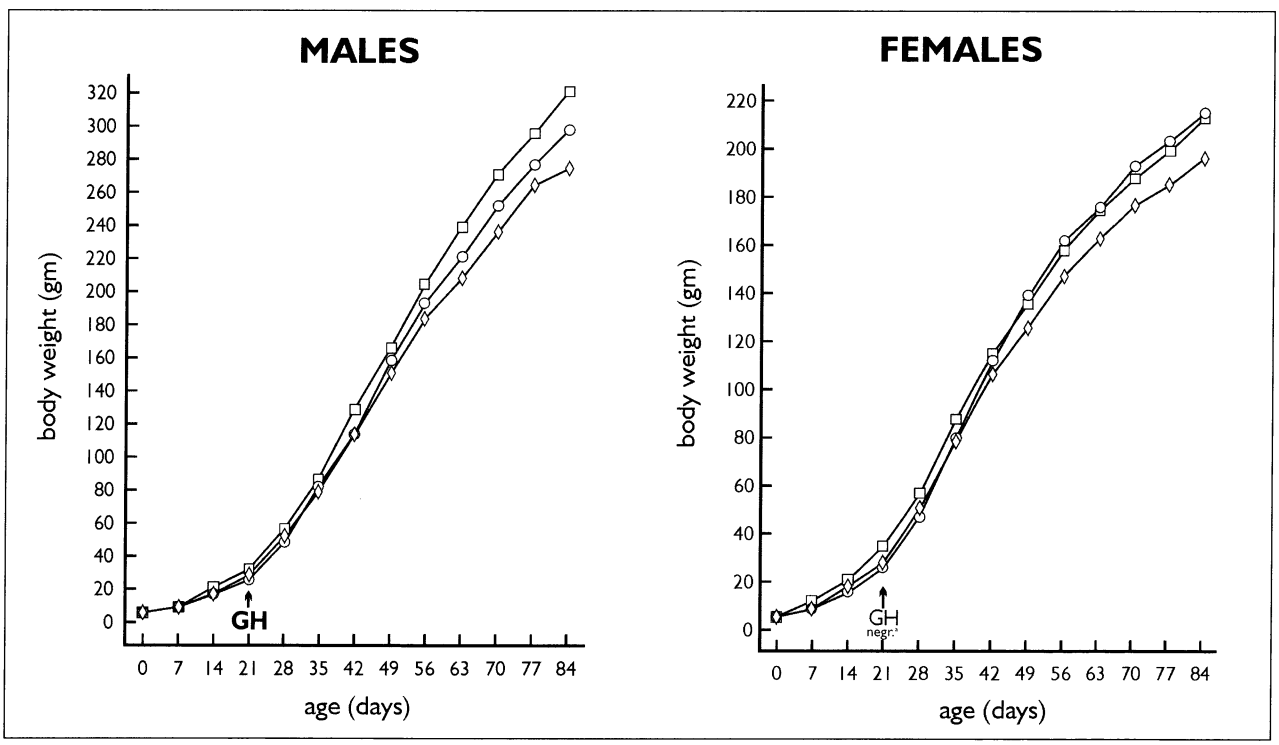

Figure 1. — Body weight gain (g) in males and females.
Square: Control, Diamond: Intrauterine growth-retarded, Circle: Intrauterine growth-retarded plus growth hormone treatment.

Table 4. — *Differences between treatments in body weight.*

Age (days)	Comparisons C-SH	SH-IUGR	SH-IUGR+GH	IUGR-IUGR+GH
Males	F	F	F	F
1	0.0	1.1**	0.8**	0.3
7	0.9	1.1*	1.7**	0.6
14	1.1	2.5*	3.1**	0.6
21	1.0	5.2**	7.5**	2.3
28	0.3	4.7*	8.9**	4.1
35	9.9*	17.2**	12.0**	5.2
42	1.1	16.7**	16.9**	0.3
49	4.1	10.8*	2.6	8.2
56	2.1	17.6**	9.3	8.3
63	7.7	23.3**	10.8*	-12.6*
70	-16.1*	17.6**	2.1	-15.5*
77	-15.6*	15.3*	3.5	11.8
84	-17.4*	28.6**	6.0	-22.6**
Females				
1	0.3	1.1**	1.0**	0.1
7	1.5**	2.2**	3.0**	0.8
14	0.7	3.0**	4.6**	1.6
21	2.8	6.5**	8.7**	2.2
28	3.9	6.0**	9.9**	3.9
35	4.3	8.9*	7.6*	2.9
42	0.9	8.2*	2.1	6.1
49	1.4	9.5	4.2	-13.7**
56	2.0	10.5	3.9	-14.4**
63	0.5	12.1*	0.7	-12.8*
70	0.5	11.5	5.1	-16.6**
77	2.3	14.5*	3.5	-18.0**
84	2.9	16.7*	2.0	-18.7**

* $p < 0.05$
** $p < 0.01$
C: Control
SH: Sham-operated
IUGR: Intrauterine growth-retarded
IUGR+GH: Intrauterine growth-retarded-plus GH injections

Table 5. — *Differences in body growth velocity.*

Comparison	Z-value
Males	
SH - IUGR	1.9*
SH - IUGR+GH	0.8
IUGR - IUGR+GH	2.6**
Females	
SH - IUGR	2.6**
SH – IUGR+GH	2.6**
IUGR – IUGR+GH	2.6**

* $p < 0.05$
** $p < 0.01$
SH: Sham-operated
IUGR: Intrauterine growth-retarded
IUGR+GH: Intrauterine growth-retarded plus GH injections

About 10-30% of the small-for-gestational age newborns (SGA) fail to catch up on growth [18]. The catch-up growth rate in SGA is highly dependent on the etiology [19], family social environment, rate of catch-up growth during early life and the incidence of growth faltering between six and 18 months of age [20]. However, the mechanisms that contribute to postnatal growth failure followed by IUGR rats are poorly understood. When the postnatal nutritional rehabilitation of IUGR animals was assessed, body weight had not been recovered showing that nutrition is not enough to promote the catch-up growth in body weight.

Bauer *et al.* [9] suggested that postnatal growth is determined by the interaction between the genetic potential of the organism and the environment, with the GH axis being a very important mediator. Previous studies demonstrated that nutritional deprivation in the pregnant rat leads to changes in the offspring somatothropic axis

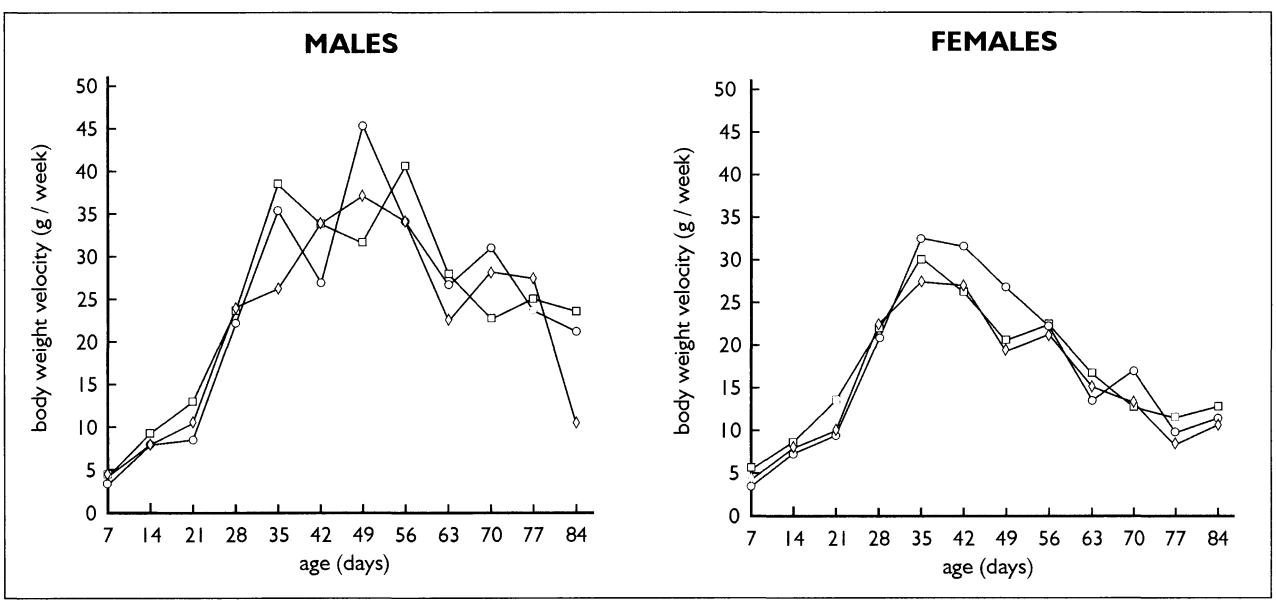

Figure 2. — Body weight velocity (g/week) in males and females.
Diamond: Intrauterine growth-retarded, Circle: Intrauterine growth-retarded plus growth hormone treatment.

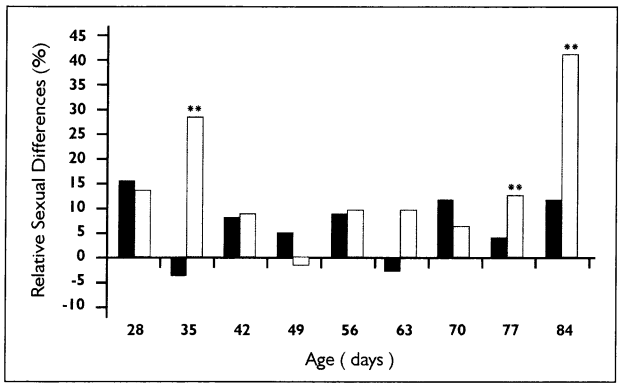

Figure 3. — Percentual sexual differences between means (PDM) in IUGR (black bars) and IUGR+GH (hatched bars). ** $p < 0.01$.

[21-24]. Similarly, Chisari *et al.* [25] found a clear metabolic-neuroendocrine dysfunction in pups of undernourished mothers. In that sense, several studies reported that malnourished rats, lambs and pigs responded to GH treatment [6, 26-30]. Coincidentally, we found that GH was active in body weight recovery in IUGR rats. However, it increased 14 days earlier in females than in males. Furthermore, the growth hormone therapy was capable of increasing growth velocity from the 35th day onwards. A sexual dimorphic growth pattern could be established with females growing less and presenting spurts of lower amplitude and smaller duration than males.

These findings may be associated with food intake since the GH-treated females ate more than males compared to the IUGR males. Although we cannot establish the relationship between GH and feeding, these results would indicate that no single mechanism could completely explain the food intake in IUGR rats treated with GH during nutritional rehabilitation.

It can be concluded that GH stimulates the catch-up growth in body weight. However this process occurs in females earlier than in males. Some mechanisms other than the differences in food intake may be involved in such sexual dimorphism and need a more exhaustive study.

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