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FOOD RESTRICTION INDUCED THYROID CHANGES AND THEIR REVERSAL AFTER REFEEDING IN FEMALE RATS AND THEIR PUPS

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In the present study, two groups of pregnant female rats were submitted to food restriction (24 h fast versus 24 h diet intake) from the 14th day of pregnancy until either the 14th day (group B) or the 4th day after parturition (group C). All pups and their mothers were sacrificed on day 14 after delivery. The body weight of the 14-day-old pups (group B) was 46% less than the controls (group A). Free thyroxine and free triiodothyronine levels in the plasma were reduced by 44 and 16% in pups and by 20 and 36% in their mothers, respectively. These reductions were correlated with a decrease in thyroid iodine content of the pups (–50%) and their mothers (–24%). Radioiodine uptake (^{131}I) by the thyroid gland of pups was significantly increased by 27%. Plasma TSH levels were decreased by 38% in pups and by 44% in dams. Morphological changes in thyroid glands were observed in energy restricted dams and in their pups. Some of follicles in pups were empty. Moroever in dams, we noted the presence of peripheral resorbed vacuoles, sign of thyroid hyperactivity. After a refeeding (group C) period of ten days, total recovery occurred in plasma thyroid hormone levels (FT_4 and FT_3) and in thyroid iodine contents of pups in spite of a partial recovery of body weights and plasma TSH levels. In dams, a partial recovery occurred in plasma thyroid hormone levels in spite of total recovery in thyroid iodine contents, while plasma TSH levels exceeded control values. A significant amelioration in thyroid histological aspects was observed in pups and their dams.

Keywords: Food restriction – refeeding – adult rats – nursing pups – thyroid hormones

INTRODUCTION

Various factors such as iodine deficiency [32, 37], antithyroid drugs [1, 40], dietary goitrigens [8, 15] , ionizing radiations [48], pollution [4, 22] and malnutrition [30, 40] can induce thyroid dysfunction.

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Malnutrition, provoked by food restriction, is also associated with a number of endocrine disturbances, including hypoinsulinemia [3, 25] and insulin-like growth factor-1 (IGF-I) deficiency [10]. Moreover, a reduction of milk yield in food-restricted rats as reported by Flint and Vernon [13] is accompanied by a catabolic state, as judged by lipid mobilization from adipose tissue and by low concentrations of serum IGF-1, triiodothyronine and thyroxine. Some of these effects may be attributed to body weight reduction.

Body weight regulation is determined in early stages of pregnancy and lactation. It could be mediated by changes in the serum concentrations of several weight regulatory hormones such as leptin [41, 42], MSH [45] and thyroid hormones which play key role in development and strengthen GH effects on growth [27, 49].

We know that the uptake of iodide is an essential step in thyroid hormone synthesis. Its transport process is mediated by the Na^+/I^- symporter (NIS). Alterations of the structure and/or the expression of the NIS gene are implicated in various thyroid disorders such as; congenital hypothyroidism [24], autoimmunity [2], treatment of cancer [23] and iodine deficiency [46]. So, NIS plays a key role in thyroid pathophysiology. Moreover, NIS was shown to be the mediator of I^- transport in lactating mammary gland [43]. The mammary gland sodium iodine symporter (mg-NIS) transcriptional activity could be regulated by leptin, hormone product of the ob gene synthetized in adipose tissue. It is possible that the marked decrease in circulating leptin after energy restriction, observed by Kume and his collaborators [19], reduced milk production, thus explaining low iodine secretion into the milk at the beginning of lactation period.

Several studies suggested that malnutrition in growing rats [29] caused changes in thyroid economy that are different from those described in adult rats [35, 38]. Several experimental models were designed to evaluate thyroid function in young malnourished pups during gestation and/or lactation periods. In our knowledge, there is no study of malnutrition which evaluates changes in thyroid function of the offspring during late pregnancy and early postnatal periods. Moreover, it is not known if these changes are reversible after the reestablishment of a normal diet.

The aim of the current study is to investigate thyroid changes in suckling rats and their mothers submitted to food restriction during late pregnancy and early postnatal periods and their reversal after refeeding.

MATERIALS AND METHODS

Adult Wistar rats, used throughout the experiment, were purchased from Central Pharmacy (SIPHAT, Tunisia). They were kept in an air conditioned room (temperature 22 ± 3 °C, relative humidity 40%) under a 12 hour light/dark cycles. Commercial diet (SICO, Sfax, Tunisia) and tap water were available *ad libitum.*

The standard diet contained 0.720 ± 0.012 µg of iodine/g of diet. Iodine content of diet was determined, after acid mineralization, using the catalytic method of Sandell and Kolthoff [36].

After one week of acclimatization to the laboratory conditions, male and female rats were caged by pairs in each cage. Pregnant female rats were inspected daily by the presence of the vaginal plug, which indicated day zero of pregnancy. Eighteen pregnant rats were divided on day 14 of pregnancy into three groups of six animals each: a control group (A) that had free access to standard diet and two energy restricted groups with 24 h fast versus 24 h dietary intake until either day 14 for the first group (B) or day 4 after delivery for the second group (C). Rats of the last group were allowed daily, for the next ten days, free access to tap water and standard diet. Each pregnant rat was placed in an individual cage during the experimental period. Pregnant rats were allowed to deliver spontaneously three weeks after coitus. Within 24 hours of birth, the number of pups born, their sex and weight were recorded. Excess pups were removed, so that only 8 pups were kept per dam (4 males and 4 females, if it was possible) because it has been shown that this procedure maximizes lactation performance [12]. The day of birth was considered as postnatal day zero.

From birth, food and drink consumptions by control rats were measured daily during 14 days. In energy restricted dams, food intake was recorded (1 day/2) during the same period. So quantities of iodine ingested by mothers of each group were calculated. Differences between energy restricted (group B) and the controls (group A) were significant, $p < 0.01$ (20.468 ± 2.696 vs 23.321 ± 2.011 µg/day/mother).

To determine radioactive iodide (I^{131}) uptake by thyroid gland, pups ($n = 12$) from each group have received on day 13 after delivery a single intraperitoneal injection of 0.9% saline solution containing 0.5 µCi of I^{131} (Cis Bio, France). Sixteen hours later, 14-day-old pups were killed by an intra-abdominal lethal dose of chloral hydrate, and thyroid glands were removed. Their radioactivity was quickly determined with a gamma Counter (Wallac type 1261 multigamma) and expressed as the percentage of the injected dose. It has been demonstrated by Zeghal and her collaborators [50] that uptake of radioiodide (I^{131}) by thyroid gland was maximal 16 hours after its administration to young rats.

Thyroid glands were removed from pups ($n = 12$) and dams ($n = 5$). They were weighed and preserved at –20 °C until analysis for their iodine content, after alkaline mineralization, by the method of Sandell and Kolthoff [36].

Other thyroid samples destined for light microscopy, were dissected together with a piece of trachea, fixed in Bouin solution, embedded in paraffin and serially sectioned at 5 µm. They were stained with hematoxylin-eosin [14].

Body weights of pups and dams were measured and blood samples were taken by brachial artery of pups and by aortic puncture of their mothers. After centrifugation at 2200 g, plasma samples were withdrawn and stored at –20 °C until analysis of FT_4, FT_3 and TSH levels. FT_3 and FT_4 levels in plasma were determined by radioimmunoassay using commercial kits (Immunotech, France. ref: 1363, 1579, respectively). Plasma TSH levels were measured by RIA using a specific rat TSH kit supplied by IBL-Germany (ref. AHR 001).

Statistical analysis was performed using Stat View (SAS Institute Inc: Berkeley, USA). All values were expressed as means ± standard deviation. For comparison

data in control group (A), energy restricted group (B) and refeeding group (C), one-way ANOVA test was used. Statistical significance was considered for P values < 0.05.

RESULTS

Compared with the control group, fourteen-day-old rats, whose mothers have been submitted to energy restriction until day 14 after delivery, showed a 46% decrease in body weight and a 35% decrease in thyroid weight Table 1.

Table 1
Body and thyroid weights of 14-day-old rats and of their mothers: Controls (A) and rats submitted to energy restriction (1 day/2) from day 14 of pregnancy until either the 14th day (B) or the 4th day (C) after parturition

Parameters	Controls (A)	Fasted (B)	Refed (C)
Body weight (g)			
Offspring (n = 48)	23.149 ± 0.782	12.588 ± 0.615 ***	20.826 ± 1.556 $^{+++}$ ***
Mothers (n = 6)	189.587 ± 1.598	171.167 ± 6.585 ns	188.601 ± 4.336 ns
Thyroid weight			
Offspring (n = 24)	2.578 ± 0.418	1.686 ± 0.424 ***	2.827 ± 0.595 $^{+++}$
Mothers (n = 5)	12.195 ± 0.761	11.335 ± 0.744 ns	11.431 ± 0.677 ns

Fasted (B) vs. Controls (A): *** $p < 0.001$
Refed (C) vs. Fasted (B): $^{+++}$ $p < 0.001$
Refed (C) vs. Controls (A): *** $p < 0.001$
Number of determinations is indicated between brackets
ns: no significant difference

Free thyroid hormone levels in plasma were significantly reduced by 44% (FT4) and by 16% (FT_3) (Fig. 1). Thyroid iodine content of pups was decreased by 50% and radioiodide uptake (I^{131}) by thyroid gland was increased by 27% (Fig. 2). In their mothers, plasma thyroid hormone levels (FT_4, FT_3) and thyroid iodine contents were reduced by 20, 36 and 24%, respectively (Figs 1 and 2). Their body and thyroid weights were slightly reduced (Table 1). The decrease in thyroid weight could be correlated with a reduction of plasma TSH levels by 44% ($p < 0.001$) in dams and by 38% ($p < 0.01$) in their offspring (Fig. 1).

Initiation of refeeding period for ten days to energy restricted dams with a regular diet, similar to that of the control group, resulted in a partial recovery in body weight of pups. However, complete recovery occurred in thyroid weights, in plasma FT_4 and

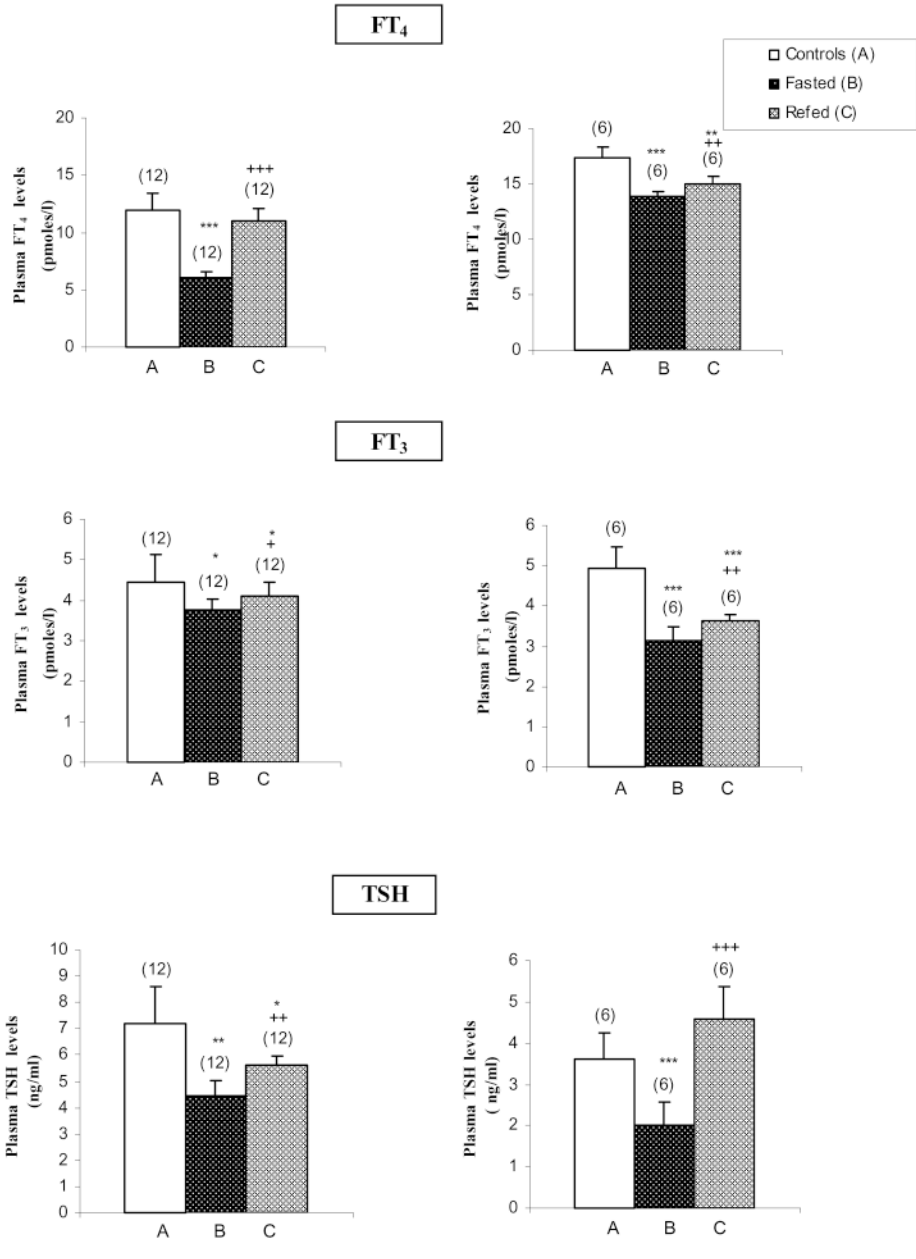

Fig. 1. Plasma FT_4, FT_3 and TSH levels of 14-day-old rats and their mothers: controls (A) and submitted to energy restriction (1 day/2) from day 14 of pregnancy until either the 14th day (B) or the 4th day (C) after parturition. Fasted (B) vs. Controls (A): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Refed (C) vs. Fasted (B): $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$. Refed (C) vs. Controls (A): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Number of determinations is represented above columns

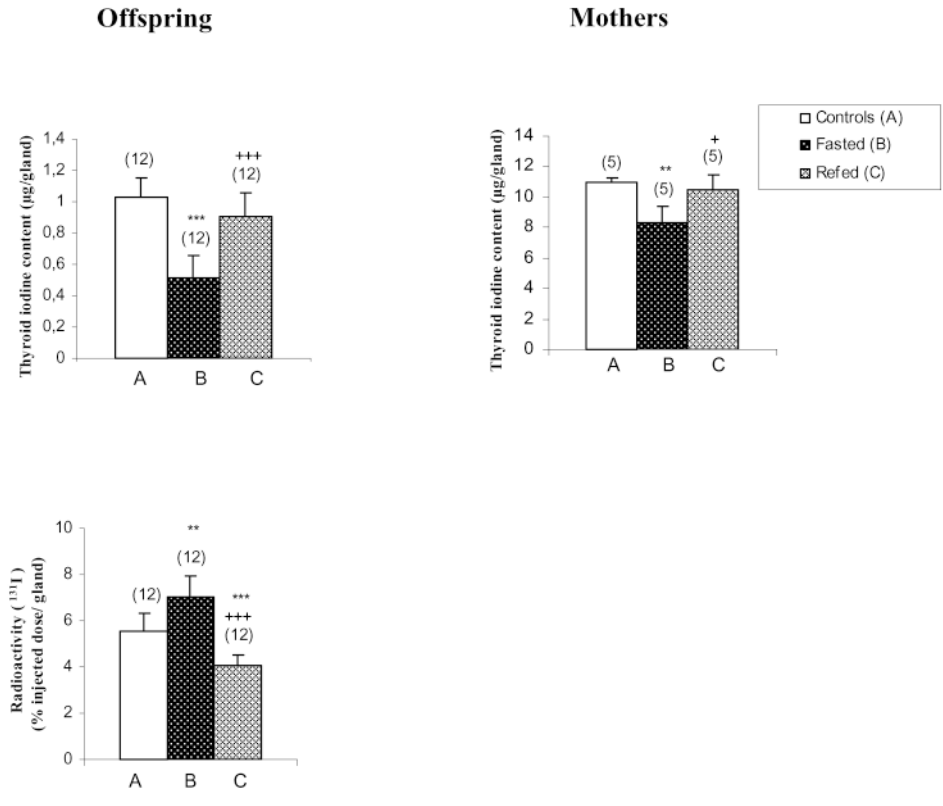

Fig. 2. Thyroid iodine contents of 14-day-old rats and their mothers. Radioiodide uptake (^{131}I) by thyroid gland of 14-day-old rats controls (A) and submitted to energy restriction (1 day/2) from day 14 of pregnancy until either the 14th (B) or the 4th (C) day after parturition. Fasted (B) vs. Controls (A): ** $p < 0.01$; *** $p < 0.001$. Refed (C) vs. Fasted (B): $^{+}p < 0.05$; $^{+++}p < 0.001$. Refed (C) vs. Controls (A): *** $p < 0.001$. Number of determinations is represented above columns

FT_3 levels and in thyroid iodine contents in spite of a partial recovery of plasma TSH levels. In dams, partial recovery occurred in plasma FT_4 and FT_3 levels, in spite of total recovery of thyroid iodine contents and thyroid weights. While plasma TSH rates exceeded control values.

The biochemical modifications observed in pups and dams were correlated with histological structural of thyroid glands. In fact, in pups of group B, thyroid follicles presented a reduction in colloid space. Some of them were empty (Fig. $3B_1$). Ten days after refeeding dams of group C daily with standard diet, a partial recovery of thyroid histological character was obtained in their pups (Fig. $3C_1$). In control rats and comparatively to energy restricted pups, we have noted follicles of various sizes containing abundant colloid (Fig. $3A_1$). Moreover, in energy restricted dams, thyroid follicles presented cuboidal epithelial cells which surrounded vesicular cavities con-

taining some vesicles of resorption (Fig. $3B_2$). After refeeding dams during ten days, significant improvement in thyroid histological pictures was observed (Fig. $3C_2$) but it did not reach those of controls (Fig. $3A_2$).

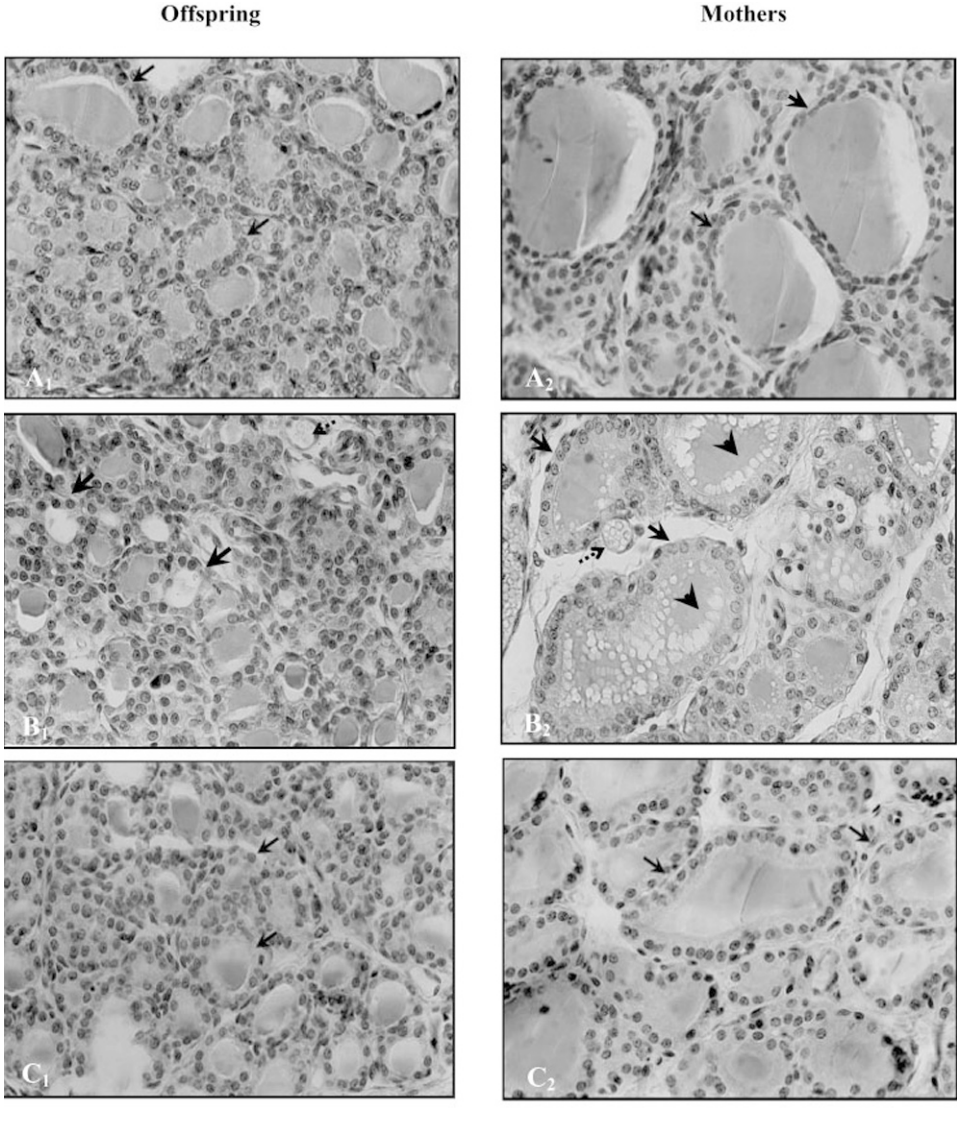

Fig. 3. Histological thyroid sections of 14-day-old rats and their mothers: controls (A_1, A_2) fasted (B_1, B_2) and refed (C_1, C_2). Optic microscopy: HE (×400). ➔ Arrows indicate thyroid follicles. ⋯➔ Arrows indicate blood vessels. ➤ Arrows indicate vacuoles of resorption

DISCUSSION

In our study, malnutrition of dams (group B) induced by energy restriction during 21 days, involved an important decrease of body and thyroid weights in their offspring. The reduction of body weight in 14-day-old rats could be explained either by an impaired thyroid status and/or by a decrease of milk yield [13]. Our results showed a significant decrease in plasma thyroid hormones, which confirmed previous data of Oberkettor and Rasmussen [26]. Moroever, food restriction involved also an important decrease in thyroid iodine content, which may be explained by a great iodine deficiency. The uptake of iodine by the thyroid gland became insufficient and the pool of intrathyroidal iodine decreased. A low total iodide pool may impose a reduction of thyroid iodine content and a critical limitation on hormonal synthesis since the iodine was necessary for thyroid hormone biosynthesis. A decrease in plasma thyroid hormone levels of nursing pups (group B) could be explained by inhibition of sodium iodide coupled symport transport abolishing prolactin (Prl) effects on iodide accumulation and incorporation in the mammary gland [33]. The biochemical changes were in agreement with histological structures of the hypothyroid animals. Histological changes, seen in the thyroid gland of rats submitted to energy restriction (group B), were characterized by an increase of vacuolization and a decrease of colloid space, which reflected a reduction of thyroid hormone synthesis as reported by our results. Since, iodine was the precursor of thyroid hormone production, thyroid iodine content was also reduced. According to Fish and his collaborators [11], the amount of iodine available in the gland was inversely related to the degree of I^{131} uptake by thyroid gland. In fact, we have obtained 1.27-fold increase of radioiodine uptake by thyroid gland in energy restricted pups of group B compared to controls. Our results confirmed previous findings of Zeghal and her collaborators [50], who had found, compared to controls, an increase of radioiodide uptake by thyroid gland in 14-day-old rats whose mothers have been treated by perchlorate, an antithyroid drug. In energy restricted dams, histopathological changes, seen in thyroid gland of food restricted dams (group B), were characterized by follicular cell hyperplasia, resorbed peripheral vacuoles suggestive for enhanced thyroid activity.

In previous studies, it has been suggested that a decrease in NIS expression might play a role in the escape from the acute Wolff-Chaikoff effect [9]. Many reports have demonstrated that thyrotropin (TSH), together with thyroid gland iodine content regulated the transport of iodide into the gland, so TSH stimulated expression of the NIS gene, increased iodide uptake by thyrocytes [31] and provoked an hypertrophy of thyroid gland. In energy restricted dams, we have obtained atrophy of thyroid gland associated with a reduction of plasma TSH levels. Our results were in agreement with previous studies, which demonstrated that food restriction as well as food deprivation reduced circulating levels of TSH [6, 34] and TSH β mRNA levels in the pituitary system [21]. Moreover, the pituitary feedback system appears to be altered in energy restricted rats and their pups, since T_4 and not T_3 is the main regulator of TSH secretion. However, this feedback was impaired in energy restricted lactating rats and their pups as low serum FT_4 did not increase serum TSH concentration.

Another mechanism to explain the disturbance in thyroid status and TSH levels was the decrease in leptin levels. In fact, previous studies have reported that leptin concentration was decreased in food-restricted rats during lactation [44]. Most studies concerning leptin action on thyroid axis favoured the concept that leptin acted primarily on the hypothalamus, stimulating directly or indirectly TRH production and release [16, 18, 20]. Recently, Ortiga-Carvalho and his collaborators [28] showed a direct inhibitory effect of leptin on TSH release by *in vitro* pituitary explants, suggesting that leptin may act as an autocrine/paracrine factor at the pituitary level, which stimulates the secretion of thyroid hormone through a direct mechanism involving the thyroid leptin receptor. A decrease in thyroid weight of energy restricted dams and their pups (group B), obtained in our experiment, could be interpreted as the result of the hypothalamic pituitary axis dysfunction as it has been reported by De Groot and his collaborators [7]. Moroever, according to Van Haastern et al. [47], hypothyroid conditions induced by fasting coincided with suppressed production and release of the TRH in the hypothalamic paraventricular nucleus and median eminence. The thyroid gland atrophy was known to occur when the effects of TSH on thyroid cells were either reduced or completely lacking. This pathological state was generally characterized by a decrease in thyroid cell volume [5]. On the other hand, the decrease in thyroid cell volume could be due to a reduction of follicular cell number during the involution by inhibition of cell proliferation, cell death by necrosis or by apoptosis. The fast recovery of pups' thyroid function (group C), only ten days after refeeding dams with a control diet, was remarkable. At this time the pups from group (C) showed a compensatory increase in thyroid iodine content and in thyroid hormone production. These results were positively correlated with milk FT_3 levels ($r^2 = 0.619$; $p \leq 0.01$) (unpublished results). This could be explained by the increased activity of type I deiodinase in the mammary gland which converted T_4 to T_3, promoting local production of T_3 that may be secreted in milk [17]. A slight increase of plasma TSH levels could explain a total recovery of thyroid weights.

In refed dams (group C), for a period of ten days, reversibility of thyroid function occurred with a partial return to control values of thyroid iodine content and a slight increase in thyroid hormone production. While plasma TSH levels exceeded control values. Higher plasma TSH rates suggested an adaptative mechanism of dams to increase the supply of iodine to the offspring through the milk for sufficient production of thyroid hormones, which were essential for development of the newborn's nervous system.

In conclusion, this study has shown that food restriction provoked thyroid dysfunction in female rats and their nursing pups which could be largely reversed by refeeding dams for a period of ten days. This reversibility evidently involved the return to the normal function of the thyroid gland in which the phenomena of proliferation and cell death must be involved.

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