Regulation of lipolysis during the neonatal period. Importance of thyrotropin.

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Research Article

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Regulation of Lipolysis during the Neonatal Period

Importance of Thyrotropin

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Abstract

We investigated the lipolytic effect of several hormones on isolated human adipocytes obtained at different donor ages. In neonates, noradrenaline and adrenaline had an insignificant lipolytic effect (70% over basal). In this age group only thyrotropin (TSH) had a significant effect in physiological concentrations, and the maximal lipolytic effect (700% over basal) was the same as that of isoprenaline. The lipolytic effect of TSH was the same in premature 4–10-wk-old infants with a gestational age of 27–33 wk as in neonates, but fat cells from infants 4–10 wk old, born at term, showed a significantly lower effect. In children and adults, the lipolytic effect of TSH gradually decreased further and was present only in unphysiological concentrations. The catecholamine-induced lipolysis was pronounced and was similar in children and adults (350% over basal). TSH is the dominating lipolytic hormone in vitro during the neonatal period. Thus, the peak elevation of circulating TSH, which is seen immediately after birth, may be essential to lipolysis during this part of life.

Introduction

Shortly after birth and before lactation is established, the infant uses the energy sources that develop during gestation. Since carbohydrate reserves are used up rapidly, lipids mobilized via lipolysis in fat cells are the major energy substrates during this first phase of life (1).

Few data are available about the regulation of lipolysis during the neonatal period. This is mainly because of the obvious problem of obtaining enough adipose tissue for the measurement of lipolysis with conventional methods. Animal studies are of limited value since the hormonal regulation of lipolysis differs markedly between various species. In adult man, only catecholamines have a marked and acute lipolytic effect via beta adrenoceptors (2). PTH also stimulates lipolysis in adult man (3), although the physiological significance is doubtful since only a small effect is obtained with unphysiologically high doses. However, in most other species several other hormones, such as glucagon, ACTH, and thyrotropin (TSH), have pronounced lipolytic activity. Furthermore, in contrast to most species, including the rat, catecholamines have a dual effect on human adipocyte lipolysis since alpha-2-adrenoceptors on human fat cells reduce the lipolytic effect of the catecholamines (4, 5). The regulation of lipolysis in growing subjects seems to differ from that in adults. The effect of catecholamines on lipolysis during the first year of life was recently investigated (7) using a sensitive bioluminescence assay of glycerol (6), which makes possible the measurement of lipolysis in small tissue samples. During the first two months of life the lipolytic effect of catecholamines on isolated adipocytes was poor, mainly because of enhanced alpha-2-adrenoceptor-mediated antilipolytic activity. These results raised the question of whether other hormones have any lipolytic activity during infancy. Furthermore, to the best of our knowledge, the regulation of lipolysis during the neonatal period has not yet been investigated.

In the present study, we investigated the ability of catecholamines, PTH, and several hormones that are lipolytic in other species, to stimulate lipolysis in isolated human fat cells. These cells were obtained at different donor ages, including the neonatal period.

Methods

Subjects. 10 neonates, 6 h–4 wk old (2±1 wk; mean±SE), four premature infants 4–10 wk old (6.8±2) with a gestational age of 27–33 wk (31.2±2), nine infants 4–10 wk old (7.0±2) but born at term (mean gestational age 39.3±1 wk), seven children 3–7 yr old (4.5±0.5 yr), 10 young adults 20–35 yr old (26±3), and eight middle-aged adults 36–50 yr old (42±2) were investigated. Five neonates were operated on for patent ductus arteriosus, two for gastrointestinal malformations, two for inguinal hernias, and one for diaphragmatic hernia. Two of the premature infants were operated on for patent ductus arteriosus. The other infants, the children, and the adults were all operated on for inguinal hernias. They were otherwise healthy and of normal weight. The gestational age was estimated from early measurements of the biparietal diameter of the fetus (8) and confirmed at birth using Finnström's development scale (9). Anesthesia was induced with thiopental sodium and maintained with fentanyl and a mixture of oxygen and nitrous oxide. Pancurone was given as a muscle-relaxing agent.

The study was approved by the Ethics Committee of the Karolinska Institute.

Isolation of adipocytes and determination of lipolysis. A small piece (30–300 mg) of adipose tissue was removed from the surgical incision at the start of the operations. Isolated adipocytes (10) were prepared within 45 min after collection. Previous methodological studies have shown that this lag period has no influence on lipolysis in infants or in adults (data not shown). The adipocytes were incubated in duplicate for 2 h at 37°C in Krebs-Ringer phosphate buffer (pH 7.4) containing 40 g/liter BSA, 0.1 g/liter ascorbic acid, and 1 g/liter glucose, with air as the gas phase. To some of the incubations we added 1 U/ml of adenosine deaminase (ADA),[1] which effectively removes endogenous aden-

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1. *Abbreviations used in this paper:* ADA, adenosine deaminase; hCG, human chorionic gonadotropin.

osine. The final fat cell concentration was 1% (vol/vol). At the end of the incubation an aliquot of the medium was removed for analysis of the glycerol release, which was used as an index of lipolysis and was determined by a sensitive kinetic bioluminescence assay (6). The diameters of the isolated fat cells were measured during direct microscopy, and mean fat cell volume and surface area were calculated as described (11, 12).

Expression of the results. Lipolysis was expressed per unit of cell surface area, making it possible to compare lipolysis in fat cells of different sizes. Changes in lipolysis, which merely reflect variations in fat cell size, are avoided by this expression (see reference 7 for a detailed discussion). The concentration of hormone that produced ED_{50} was calculated graphically from the individual dose-response curves.

Chemicals. Propranolol, isoprenaline, and the hormones were obtained from Sigma Chemical Co. (St. Louis, MO). We used the following hormone concentration ranges: human ACTH, 0.01–4 U/ml; adrenaline and noradrenaline, 10^{-12}–10^{-5} mol/liter; porcine glucagon, 0.05–5 μg/ml; human chorionic gonadotropin (hCG), 0.1–100 U/ml; bovine luteinizing hormone (LH), 0.01–100 U/ml; human 1–84 PTH, 10^{-16}–10^{-5} mol/liter; porcine secretin, 0.01–1 μg/ml, and bovine or human TSH, 1–5 × 10^6 μU/ml.

TSH antiserum was obtained from Milab (Malmö, Sweden). This rabbit antiserum was generated against highly purified TSH, and the cross-reactivity against other pituitary hormones was < 0.2%. The estimated binding capacity was 250 μU of TSH per milliliter of serum. Collagenase was prepared from *Clostridium histolyticum* and was of Sigma type 1. Dialyzed BSA (Fraction V) came from the Armour Pharmaceutical Company (Eastbourne, England), and ADA from Boehringer-Mannheim GmBH (Mannheim, FRG). The same batches of hormones, collagenase, and albumin were used in all experiments.

Statistics. The values presented are the means and the SEM. The *t* test, analysis of variance in combination with Duncan's new multiple range test, and linear regression analysis were used when appropriate.

Results

Fat cell size, basal, and isoprenaline-induced lipolysis. The mean fat cell volume (pl, ±SE) per group was 50±20 in neonates, 73±19 in preterm infants, 155±28 in infants born at term, 252±46 in children, 390±73 in younger adults, and 589±60 in middle-aged adults. This relationship between age and fat cell size confirms the results of many previous studies (13).

Basal lipolysis did not differ among the groups. The latter values (μmol glycerol/μm^2 per 2 h × 10^{-11}) were 1.3±0.3, 1.1±0.2, 1.4±0.3, 0.9±0.3, 1.1±0.2, and 1.6±0.3 in the neonatal, preterm infant, term infant, child, young adult, and middle-aged groups, respectively. The maximal rates of glycerol release induced with the synthetic β-adrenergic agonist isoprenaline (10^{-9}–10^{-6} mol/liter) were also similar in the four age groups: 6.9±1.2, 7.4±1.5, 7.4±1.4, 7.1±1.5, 7.7±0.9, and 7.5±1.5 μmol/μm^2 per 2 h × 10^{-11}, respectively. Thus, in agreement with a previous report (3), basal lipolysis and β-adrenoceptor-mediated lipolysis were not influenced by age.

Hormone-induced lipolysis. Table I shows the results with differing concentrations of various potentially lipolytic hormones. Of these, ACTH, glucagon, LH, and secretin had no lipolytic effect in any of the subjects, although all of them have marked lipolytic effects in other species (14). hCG had a poor and inconstant lipolytic effect (< 50% increase over basal) in some of the neonates and infants when we used extremely high hCG concentrations. In contrast, PTH had a weak effect in all groups and TSH had a markedly lipolytic effect on fat cells from neonates, infants, and children. The effect of TSH was less marked but significant in both of the adult groups. The lipolytic effect of the catecholamines, noradrenaline, and adrenaline was almost undetectable in the neonates. In the other groups of subjects, catecholamines had a lipolytic effect.

Table I. Effects of Potentially Lipolytic Hormones on Glycerol Release from Isolated Human Fat Cells

Hormones	Age groups				
	A	*B*	*C*	*D*	*E*
ACTH	0	0	0	0	0
Adrenaline	(+)	+	++	++	++
Glucagon	0	0	0	0	0
hCG	0	0	0	0	0
LH	0	0	0	0	0
Noradrenaline	(+)	+	++	++	++
PTH	(+)	(+)	(+)	(+)	(+)
Secretin	0	0	0	0	0
TSH	+++	+++	+++	++	+

The subjects were divided into five groups: (A) neonates; (B) infants; (C) children; (D) young adults; and (E) middle-aged adults. The symbols denote the lipolytic effect of the maximal effective hormone concentration. 0, no effect; +++, marked effect.

In Fig. 1, the dose-response relationship for the hormones with lipolytic effect in humans (catecholamines, TSH, PTH) is presented. In the neonatal group, the lipolytic effect of noradrenaline was not significant at any hormone concentration, and a mean maximal increase of 70% over the basal value was obtained. In the children and the two adult groups, noradrenaline had a marked and dose-dependent lipolytic effect. The dose-response curves for noradrenaline were almost identical in these age groups and showed a 3.5-fold stimulation of lipolysis at the maximal effective concentration. TSH showed the opposite pattern. In the neonatal group, the lipolytic effect was marked in the physiological concentration range of the hormone. The maximal response to TSH (sevenfold stimulation) was in the same order of magnitude as that with isoprenaline. In the children, the mean dose-response curve for TSH showed a shift to the right. No significant lipolytic effect was found with physiological concentrations, but the maximal lipolytic effect was similar to that in the neonates. The adults showed a further reduction in the lipolytic effect of TSH. Both the sensitivity and the maximal response decreased gradually with age in adult life.

The lipolytic effect of PTH was weak. The PTH dose-response curves were superimposable in all groups and the mean maximal effect was only an 80% stimulation of the basal lipolysis rate.

The age-dependent changes in TSH sensitivity were further investigated in infants (Fig. 2). When the infants were 4–10 wk old, the adipocytes had already lost almost all of their sensitivity to TSH in the physiological concentration range of the hormone. On the other hand, adipocytes obtained from premature infants 4–10 wk old showed the same lipolytic activity of TSH as the neonates. Thus, infants with a "postconceptional" age of 37–41 wk showed the same lipolytic effect of TSH regardless of the time of birth.

The mean ED_{50} values for the age groups studied are summarized in Fig. 3 and, for illustrative purposes, are presented on a logarithmic scale. The ED_{50} gradually increased with age,

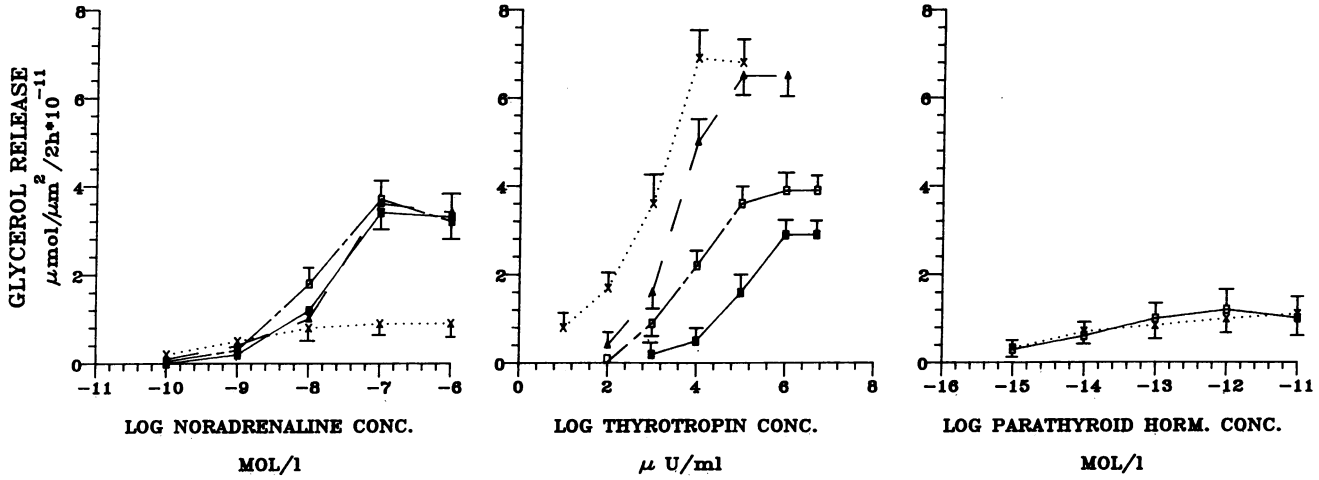

Figure 1. Dose-response curves for hormones with a lipolytic effect in man. Human adipocytes were incubated with increasing concentrations of noradrenaline, TSH, and PTH. The glycerol release to the medium was determined. The basal glycerol release was subtracted from the hormone-induced values and the net glycerol release is shown. The values are means±SE. ×, neonates; ▲, children; □, young adults; ■, middle-aged adults.

except with regard to the neonates and the preterm infants. Furthermore, the correlation between the individual ED_{50} values and age (lin-lin) was significant both for the children aged 0–7 yr taken separately ($r = 0.61$, $P < 0.01$) and for the whole material ($r = 0.76$, $P < 0.001$).

Effects of TSH antiserum and propranolol on TSH-induced lipolysis. To study the specificity of TSH-induced lipolysis, fat cells from infants were incubated with TSH or isoprenaline in combination with TSH antibodies or the beta adrenergic blocking agent propranolol (Fig. 4). The antibodies depressed TSH-induced lipolysis in a dose-dependent manner, but did not affect lipolysis induced with isoprenaline. In contrast, propranolol depressed the isoprenaline-induced lipolysis rate, but had no effect on the TSH-induced lipolysis rate. In all age groups, human TSH proved as effective as the presently used bovine TSH preparation (uncharted experiments). Taken together, these data strongly suggest that the lipolytic effect is specific for TSH and is not due to contamination, and that the lipolytic effect of TSH is induced via a receptor other than the beta adrenoceptor.

Effect of the addition of ADA on hormone-induced lipolysis. In experiments with fat cells from neonates, infants, children, and adults, hormone-induced lipolysis was investigated in both the presence and the absence of 1 U/liter of ADA, since it has been reported that endogenous adenosine in human fat cell suspensions may have a marked effect on lipolysis (15). However, no differences in sensitivity or maximal response were found (data not shown). This agrees with previous studies on infants and adults in our laboratory (7).

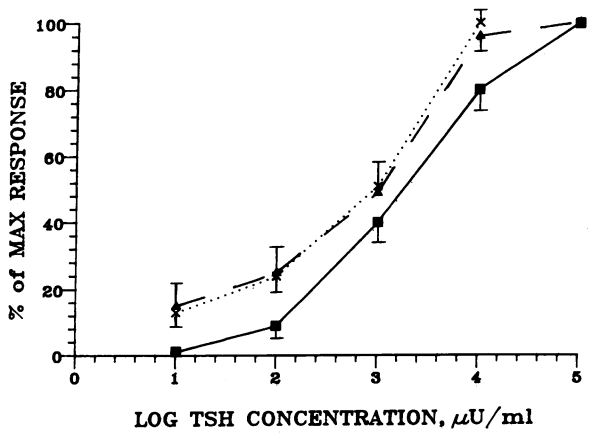

Figure 2. Alterations in TSH sensitivity during the first months of life. Adipocytes from neonates, infants born at term with a mean age of 7 wk, and premature infants with the same mean age but with a mean gestational age of 31 wk were incubated with indicated concentrations of TSH. The values are means±SE. ×, neonates; ▲, prematurely born infants; ■, infants born at term.

Discussion

The mobilization of lipids during the neonatal period is essential to the maintenance of human life, since lactation is not well established until 2–3 d after birth. During this phase of life, there is a rapid change from glucose to lipids as the major energy source, since only limited amounts of stored carbohydrates are available (1). These lipids in humans are predominantly of white adipose tissue origin. In contrast to many other mammals, only 3–6% of the total amount of the adipose tissue in the human neonate is brown fat (16, 17). 2–3 d after birth the respiratory quotient decreases to 0.7–0.75 (18), indicating that oxidation of FFA from adipose tissue is the major source of energy. There is no correlation between the circulating levels of catecholamines and lipolytic products during delivery (19) and the first hours of life (20). Serum levels of glycerol and FFA are low during delivery, but increase markedly during the first hours of life (21). The catecholamine levels, however, are extremely high during delivery and decrease thereafter (19, 20, 22). From these in vivo findings, as well as from the present and previous (7) in vitro results, it seems reasonable to infer that catecholamines have only a limited effect on lipolysis during the neonatal period.

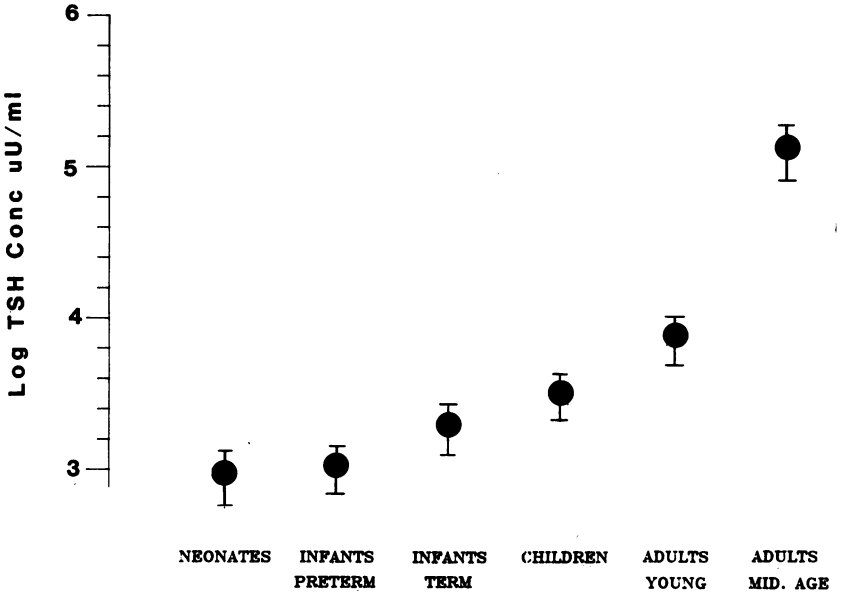

Figure 3. Concentrations of TSH giving half-maximal stimulation of lipolysis (ED_{50}) in various age groups. The experiments in Fig. *1* and *2* were used to calculate the ED_{50} values from each individual dose-response curve. The differences between the age groups are statistically significant with the exception of the difference between neonates and preterm infants and between term infants and children.

The TSH levels are low in the umbilical cord, but it is well established in humans that birth induces a fast excretion of TSH, which results in peak serum values of 50–100 μU/ml (i.e., a TSH concentration ~ 50 times above the normal serum values) 10 min after birth (23, 24). The present results demonstrate that these TSH levels can induce lipolysis in adipocytes from neonates. Furthermore, TSH was the only hormone with a marked lipolytic effect on adipocytes from neonates, and physiological TSH doses were significantly more effective than any noradrenaline concentration. The TSH-induced lipolysis was blocked by TSH antiserum. Human and bovine TSH had the same lipolytic effect, whereas other pituitary hormones were without effect. This indicates that the lipolytic effect of TSH is specific and not due to any contamination of pituitary peptides. This is further supported by the fact that no endogenous substance was previously known to have the same lipolytic effect as isoprenaline in humans. The weak and inconstant effect of hCG may be due to interaction with TSH receptors (25). Therefore, our data are consistent with the conclusion that TSH is the major lipolytic hormone in white fat cells immediately after birth, provided that the in vitro findings are representative of the situation in vivo. Whether human brown adipocytes are regulated in a similar or different way is unknown.

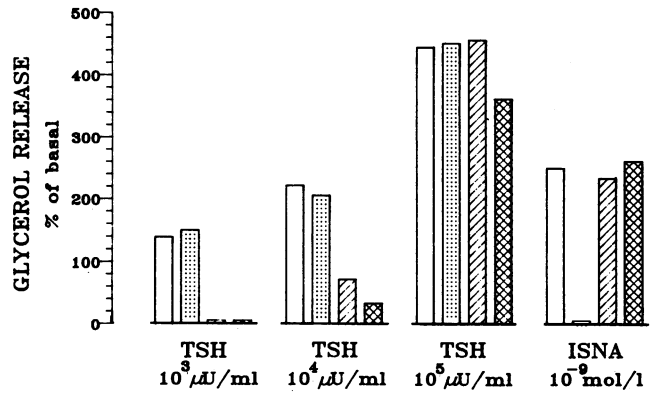

Figure 4. Effects of TSH antibodies and propranolol on TSH- and isoprenaline-induced lipolysis. Adipocytes from infants were incubated with indicated concentrations of TSH or the β-adrenoceptor agonist isoprenaline (ISNA). The effect of TSH antibody serum (75 and 37.5 μl serum/ml incubation medium, respectively) with an estimated binding capacity of 250 μU/μl serum or the beta adrenoceptor blocking agent propranolol (10^{-5} mol/liter) were studied. Neither antibody serum nor propranolol had any effect on lipolysis when added alone. *Open bars,* agonist alone; *dotted bars,* agonist + propranolol; *hatched bars,* agonist + low TSH antibody concentration; *cross-hatched bars,* agonist + high TSH antibody concentration. One representative experiment on a 3-mo-old infant is presented. Three different experiments were performed. Values are means of duplicate incubations.

The role of TSH as a lipolysis regulator seems to be a short-term one. The TSH dose-response curves were already shifted to the right at 1–2 mo, and completely shifted to an unphysiological concentration range at 3–7 yr when a full expression of the lipolytic effect of noradrenaline also was found. Moreover, in healthy infants the high TSH serum levels decline rapidly during the first three to five days of life (24), and the lipolytic effect of noradrenaline increases in isolated fat cells from 2–6-mo-old infants compared with 0–2-mo-old infants (7). This further indicates that TSH plays a dominant lipolytic role among hormones only during the period immediately after birth. During early infancy, this role is taken over by catecholamines. The lipolytic effect of TSH is gradually reduced both in terms of sensitivity and responsiveness (maximal effect). During adult life it is present only in extremely high hormone concentrations.

The lipolytic effects of TSH and catecholamines are mediated by the cAMP system through a chain of events that is initiated by hormone-receptor interactions and terminated by the activation of hormone-sensitive lipase (4). The present results cannot be explained by the influence of age on the final steps in lipolysis activation (i.e., protein kinase/hormone-sensitive lipase), since the lipolytic effects of isoprenaline reported in this and a previous study (7) were similar at all ages. As mentioned in the introduction, the poor lipolytic effect of cate-

cholamines during the first months of life seems to be secondary to an enhancement of the alpha-2-adrenoceptor-mediated antilipolytic effect of the hormones (7). Although not investigated in neonates, it is probably the same mechanism that deprives catecholamines of their lipolytic effect during this period of life.

Regarding the alterations in TSH-induced lipolysis, the rapid decrease in TSH sensitivity that was observed when adipocytes from 2-mo-old full-term infants were investigated was not found in premature infants of the same age. These data indicate that neither the change from intra- to extrauterine metabolism nor birth itself are of major importance for the decrease in TSH sensitivity. On the contrary, it is probable that the decreased TSH sensitivity is due merely to the development and aging of the fat cell itself. Furthermore, it is possible that the TSH surge during the first hours of life induces some downregulation of the TSH effect on lipolysis.

The molecular mechanisms behind the decrease in the lipolytic effect of TSH are not known. However, the dose-response curves shifted first to the right with increasing age, without any decrease in maximal response; a decrease in maximal response, combined with a further decrease in the sensitivity to the hormone, then occurred. This suggests that the alteration in TSH-induced lipolysis occurs early in the cascade of events that finally leads to the activation of the hormone-sensitive lipase. This may include changes at the TSH receptor level or in the linking of the TSH receptors and the guanosine triphosphate–sensitive coupling proteins. The methods for studying these phenomena require large amounts of samples and were not feasible in the present study. For ethical reasons it was possible only to remove very small amounts of adipose tissue from the neonates and the infants.

In summary, the present results suggest that TSH, beyond the regulation of thyroid gland activity, plays a hitherto unknown vital role as a lipolytic hormone at birth in man. This role is replaced rapidly by the catecholamines during infancy.

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