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► **To cite this version:**

G. Cabello, Chantal Wrutniak. Thyroid hormone and growth: relationships with growth hormone effects and regulation. *Reproduction Nutrition Development*, 1989, 29 (4), pp.387-402. hal-00899073

**HAL Id: hal-00899073**

**<https://hal.science/hal-00899073>**

Submitted on 11 May 2020

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## Thyroid hormone and growth : relationships with growth hormone effects and regulation

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(received 28 November 1988, accepted 5 September 1989)

**Summary** — For some years, research in the field of growth endocrinology has been mainly focused on growth hormone (GH). However, it appears that GH does not always control growth rate. For instance, it does not clearly influence intra-uterine growth : moreover, although the results of GRF or GH administration appear convincing in rats, pigs or heifers, this is not the case in chickens and lambs. In addition, GH does not always clearly stimulate somatomedin production, particularly during food restriction and fetal life, and in hypothyroid animals or sex-linked dwarf chickens. In such situations, this phenomenon is associated with a reduced T3 production, suggesting a significant influence of thyroid function on GH action, and more generally, on body growth. In fact, numerous data demonstrate that thyroid hormone is strongly involved in the regulation of body growth. In species with low maturity at birth, such as the rat. T4 and T3 affect postnatal growth eleven days earlier than the appearance of GH influence. In contrast to GH, thyroid hormone significantly influences fetal growth in sheep. Moreover, the body growth rate is clearly stimulated by T3 in dwarf animals. In addition to its complex metabolic effects involved in the general mechanisms of body growth, thyroid hormone stimulates the production of growth factors, particularly EGF and NGF. Moreover, it affects GH and somatomedin production and also their tissue activity. All these results strongly suggest that it would be difficult to study GH regulation and physiological effects without taking thyroid function into account.

**body growth — thyroid hormone — GH — GRF — IGF**

**Résumé** — **Hormones thyroïdiennes et croissance. Interactions avec l'axe somatotrope.**

*Depuis plusieurs années, les recherches concernant l'endocrinologie de la croissance sont particulièrement orientées sur l'hormone de croissance (GH). Il semble cependant que le GH ne contrôle pas la croissance dans toutes les situations. Ainsi, elle ne semble pas influencer la croissance intra-utérine; de plus, si les résultats de l'administration de GRF ou de GH sont convaincants chez le rat, le porc ou le bovin, ils s'avèrent plus décevants chez le poulet ou le mouton. D'autre part, la GH n'induit pas toujours une stimulation de la production de somatomédines, notamment pendant la vie intra-utérine, au cours de la restriction alimentaire, ainsi que chez les animaux hypothyroïdiens et chez les poulets nains (nanisme lié au sexe). Dans toutes ces situations particulières, la déficience de stimulation des somatomédines par la GH est associée à une production réduite de T3, ce qui suggère une influence significative de la fonction thyroïdienne sur les effets de la GH, et plus généralement sur la croissance. En fait, de nombreux résultats*

*démontrent que les hormones thyroïdiennes sont impliquées dans la régulation de la croissance corporelle. Chez les espèces à faible maturité à la naissance telles que le rat, la T4 et la T3 influencent la croissance postnatale bien avant que la GH ait un effet significatif. De plus, contrairement à la GH, les hormones thyroïdiennes affectent la croissance foetale chez le mouton. D'autre part, la croissance corporelle est significativement stimulée par la T3 chez les animaux nains. En plus de leurs effets métaboliques complexes qui participent aux mécanismes généraux de la croissance corporelle, les hormones thyroïdiennes stimulent la production de facteurs de croissance tels que le NGF ou l'EGF. Elles influencent également la production de GH et de somatomédines, ainsi que leurs activités tissulaires. Tous ces résultats suggèrent qu'il serait difficile d'étudier la régulation de l'axe somatotrope et ses conséquences physiologiques, en particulier sur la croissance, sans tenir compte de la fonction thyroïdienne.*

### **croissance corporelle — hormone thyroïdienne — GH — GRF — IGF**

## **INTRODUCTION**

Despite intensive work, the endocrine regulation of growth is still poorly understood. Pathological conditions such as acromegalia, growth hormone (GH) deficiency and cretinism have shown the importance of GH and thyroid function. However, from embryonic life onward, all hormonal regulations are probably implicated at different levels and at different periods in the control of growth. The hierarchy of endocrine influences in this field has not been established, and studies of situations in which growth has stopped or has slowed down could provide some valuable information.

For some years, research in the field of growth endocrinology has been focused mainly on growth hormone, raising an important question : is the stimulation of GH and somatomedin production sufficient to increase body growth ? Numerous data do not agree with such a concept.

In this paper, we will first present some experimental facts suggesting that growth hormone cannot be considered alone in growth regulation, particularly in situations where T3 production is impaired. Secondly, we will discuss some significant data

indicating the important role of thyroid function in this field. Lastly, mechanisms mediating the influence of thyroid hormones on growth will be reviewed, with special reference to the relationships between thyroid function and GH regulation.

## **GROWTH HORMONE DOES NOT ALWAYS CONTROL GROWTH RATE**

Numerous observations have been reported suggesting that GH does not always have as decisive a role as expected in growth control.

### ***Fetal GH does not clearly influence intra-uterine growth***

The first argument is that growth hormone does not clearly control fetal body growth. In all animals studied such as mice (Eguchi, 1961) and rats (Jost, 1977), lack of circulating GH, induced by decapitation, did not affect fetal growth. Moreover, the influence of pituitary destruction upon

body growth is not detectable before the 25th day of extra-uterine life in rats (Walker *et al.*, 1950), and is even more delayed in rabbits (Vézinet, 1968).

In the fetal lamb, the situation needs some clarification. It is generally assumed that hypophysectomy, performed between days 100 and 112 of pregnancy in sheep fetuses, does not reduce the birthweight of lambs (Jones *et al.*, 1985; Parkes, 1985). However, in similar experimental conditions, we have observed that fetal pituitary destruction was associated with a 30% reduction of the birthweight (Wrutniak *et al.*, 1985). Hypophysectomy, like thyroidectomy, results in very low plasma thyroid hormone levels in lamb fetuses, and thyroidectomy induces a similar reduction of the birthweight (Hopkins & Thorburn, 1972; Bhakthavathsalan *et al.*, 1981) without suppression of the levels of other pituitary hormones or other hormones influenced by the pituitary. Therefore, in our opinion, the effect of hypophysectomy recorded in our work could be due to a thyroid hormone deficiency. However, in this hypothesis, the observation by other researchers that fetal pituitary destruction fails to affect intra-uterine growth, is not clear and needs further study.

It could be assumed that the influence of fetal GH on intra-uterine growth may be masked by a significant production of placental GH. Such a placental factor was identified in pregnant women by Franckenne *et al.* (1987). However, no evidence was provided that this GH could reach the fetus. Moreover, such a possibility does agree with the observation that rat and rabbit body growth is not sensitive to pituitary destruction before days 25 and 100 of extra-uterine life (Vézinet, 1968; Walker *et al.*, 1950).

### ***The varying effects of growth hormone releasing factor (GRF) or GH administration on postnatal growth***

GRF administration is a convenient means of increasing plasma GH levels : after a single injection, hp GRF (1-44) NH<sub>2</sub>, or hp GRF (1-29) NH<sub>2</sub> are equipotent in stimulating GH secretion in heifers or pigs (Petitclerc *et al.*, 1987). However, the mode of administration is important : Kensinger *et al.* (1987) have shown that the administration of the same amount/day of GRF is more effective in raising GH levels in lambs when performed using four to eight daily injections, than using only two injections or continuous infusion. Moreover, in steers, Moseley *et al.* (1984) have shown that the pulsatile administration of GRF is able to increase GH secretion without desensitization for at least 5 days. Therefore, bearing the mode of GRF administration in mind, the effects of GH and GRF administration upon body growth should be considered together.

GRF administration could be effective in improving body growth in rats. Pulsatile injections of GRF every 3 h for 12 days, increased the body growth of the young by  $\approx 30\%$  (Clark & Robinson, 1985). On the other hand, Wehrenberg (1986) reported that the growth rate of rats was significantly decreased by chronic treatment with GRF antisera. However, continuous infusion (Clark & Robinson, 1985), or GRF administration twice a day (Dubreuil & Morisset, 1986), was without effect despite a significant rise in plasma GH levels. This suggests, as in other species, the significance of the mode of GRF administration.

GH has had a marked effect in pigs. Treatment with exogenous pituitary porcine GH (Boyd *et al.*, 1986; Campbell *et al.*, 1988; Chung *et al.*, 1985; Etherton

*et al.*, 1986; 1987), or recombinant porcine GH (Evock *et al.*, 1988), increases pig growth performance. Despite differences between studies, GH seems to increase the average daily gain from 10% to 20%, and to improve feeding efficiency from 15% to 35%.

In Belgian white blue heifers, subcutaneous GH injections, once a day for 8 weeks, increased weight gain by 21% and also feeding efficiency (Fabry *et al.*, 1985; 1987). Moreover, Closset *et al.* (1986) reported that immunization against somatostatin was associated with an 11% improvement of body growth in young bulls of the same breed.

However, more negative than positive results have been reported in other animals. In chickens, Bowen *et al.* (1987) failed to observe a significant effect of chicken GH administration in three different lines. Leung *et al.* (1986) observed a slight positive influence of homologous GH, or human GRF, administration on body growth, but this effect was very transient. Moreover, the results of Baile *et al.* (1985) did not show evidence of any effect of GRF administration despite a substantial rise in plasma GH levels.

Similarly in sheep, only Wagner & Veenhuizen (1978) reported a significant influence of GH administration which was not recorded by Wheatley *et al.* (1966) or Muir *et al.* (1983). In addition, Pastoureau *et al.* (1988) did not observe an improved growth rate in hypotrophic or normal lambs receiving two daily injections of GRF. In this species, Bass *et al.* (1987) observed only a small growth response to somatostatin immunization.

### ***Growth hormone does not always stimulate somatomedin production***

Although growth hormone exerts direct metabolic effects, its major influence on

growth is mediated by an increase in cell production of somatomedins. However, GH does not always stimulate somatomedin production. Although caution must be used in the interpretation of some results which do not take into consideration the pulsatile mode of GH secretion, it is generally agreed that such a phenomenon is apparent in at least four situations: food restriction, fetal life, sex-linked dwarfism and hypothyroidism. A better knowledge of the hormonal status encountered in these particular situations could provide interesting ways to study endocrine influences required for an optimal effect of GH on body growth.

Food restriction is associated with a rise in plasma GH levels in numerous species such as the ewe and its fetus (Koritnik *et al.*, 1981), the chicken (Falconner *et al.*, 1981) and man (Grant *et al.*, 1973), whereas, somatomedin activity, or somatomedin-C/IGF1, are significantly decreased in plasma (chicken: Falconner *et al.*, 1981; man: Grant *et al.*, 1973; rat: Maes *et al.*, 1986). This phenomenon could be explained by a reduction in the number of GH receptors, at least in the rat (Baxter *et al.*, 1981; Postel-Vinay *et al.*, 1982; Maes *et al.*, 1986).

A similar dissociation between GH and somatomedin-C/IGF1 is apparent during intra-uterine life. After the 100th day of pregnancy, the plasma level of GH is about 10 times higher in the ovine fetus than in its mother (Basset *et al.*, 1970; Bassett & Gluckman, 1986; Lowe *et al.*, 1986) and the secretion of this hormone is characterized by a markedly exaggerated pulsatile release (Gluckman, 1985); however, the plasma concentrations of IGF1 are very low (Gluckman & Butler, 1985). Moreover, as decapitation did not influence plasma IGF1 levels (Gluckman, 1985), IGF1 production is not obviously dependent on GH regulation. The

situation is the same in human fetuses, where plasma IGF1 levels are similar to those observed in adults with total GH deficiency (Lassare *et al.*, 1986). At birth, the level of GH in neonates is about ten times higher than in adults, whereas, concentrations of somatomedin-C are five times lower (Nagashima *et al.*, 1986). As in sheep, fetal IGF1 production does not seem to be regulated by GH secretion (Sara & Carlsson-Skwirut, 1986).

In sex-linked dwarf chickens, plasma GH levels are also higher than in normal animals (Hoshino & Yamamoto, 1977; Hoshino *et al.*, 1982; Scanes *et al.*, 1983; Huybrechts *et al.*, 1987), but the levels of somatomedin C are lower (Hoshino *et al.*, 1982; Huybrechts *et al.*, 1985; 1987). This could be explained by a reduction in growth hormone receptor binding (Leung *et al.*, 1987).

Hypothyroidism is associated with a comparable situation. If, in hypothyroid rats, plasma GH and IGF levels are significantly lowered, GH administration does not restore IGF1 concentrations (Burstein *et al.*, 1979). Similarly, plasma levels of somatomedin-C are decreased in hypothyroid chickens despite normal GH concentrations (Decuypère *et al.*, 1987).

### ***T3 deficiency in situations in which GH does not increase somatomedin production***

In the preceding situations in which GH apparently does not increase somatomedin-C/IGF1 production, T3 deficiency simultaneously occurred.

In all animals studied, food restriction was associated with a considerable reduction of plasma T3 levels, such as in man (Burman *et al.*, 1979; Marugo *et al.*, 1984; Suda *et al.* 1978), calves (Blum &

Kunz, 1981; Tveit & Larsen, 1983) and adult (Blum *et al.*, 1980) or newborn sheep (Wrutniak & Cabello, 1987a). This decrease in T3 production could be explained not only by a lowered TSH secretion (Burger *et al.*, 1981; Hugues *et al.*, 1984; Röjdmärk & Nygren, 1983; Tveit & Almlid, 1980; Wrutniak & Cabello, 1987a), but also by an inhibition of the peripheral conversion of T4 into T3 (Balsam & Ingbar, 1979; Chopra, 1980; Gavin & Moeller, 1983).

In the ovine fetus, plasma T3 levels are very low during the major part of the pregnancy, in parallel with a reduced T3 thyroid secretion (Klein *et al.*, 1980), and a marked inactivity of cellular 5'-deiodinases (Wu *et al.*, 1986). They progressively rose only after the 130 th day of gestation (Klein *et al.*, 1978; Wrutniak *et al.*, 1985). Similarly, in the human fetus, T3 levels remain undetectable until the 30 th week of pregnancy and rise during the last 10 weeks. At birth, they are three times lower than those measured in the mother (Fisher *et al.*, 1977).

As in the other situations, Scanes *et al.* (1983), May & Marks (1983), Marsh *et al.* (1984) and Lauterio *et al.* (1986) have reported that plasma T3 levels decreased in sex-linked dwarf chickens. Moreover, Hoshino *et al.* (1986) have observed that, despite a large increase in plasma T4 levels after TRH administration, plasma T3 levels did not rise in these animals, suggesting a depressed T4 to T3 conversion. As in chickens growth hormone could induce stimulation of 5'-deiodinases (Kühn *et al.*, 1986a, b); the diminished hepatic growth hormone binding reported in such animals (Leung *et al.*, 1987) could be partly involved in this depression.

Therefore, in addition to hypothyroidism, the situations in which growth hormone does not increase somato-

medin-C/IGF1 production are associated with T3 deficiency. Although this set of data must not be considered as a direct proof, it could suggest the existence of relationships between thyroid function and physiological effects of GH. In particular, as is stressed in a following chapter, T3 could affect IGF1 production, and therefore, the stimulation of this production by GH. Such a phenomenon could partly explain the subsequently presented effects of thyroid hormones on body growth.

### **THYROID HORMONE STRONGLY INFLUENCES BODY GROWTH**

A great number of clinical or experimental observations underline the importance of thyroid function in the regulation of body growth.

#### ***Dwarfism resulting from congenital hypothyroidism***

Like GH deficiency, congenital hypothyroidism, and particularly cretinism, is often associated with dwarfism. In contrast to mental retardation, this growth deficiency could be easily reversed by thyroxine administration (Utiger, 1979).

#### ***Thyroid hormone influences the fetal growth***

In species with low maturity at birth, the fetal growth is apparently independent of thyroid function, as in the rabbit (Jost *et al.*, 1958) or the rat (Cooke *et al.*, 1984;

Jost, 1969; Jost & Picon, 1970). However, no conclusion could be drawn from these results, as this endocrine function is immature during intra-uterine life. Plasma T3 levels are undetectable and T4 concentrations are slightly higher than the limit of detection of the radio-immunological assay near birth (Wrutniak & Cabello, 1983). However, at least in the rat, iodinated hormones considerably affect postnatal growth after 12th - 14th days of life (at this age, plasma T3 levels have reached a maximum value), 11 days earlier than the appearance of the influence of GH (Bakke *et al.*, 1976; Cooke *et al.*, 1984; Kikuyama *et al.*, 1974).

In species with a long gestation period, thyroid hormone influences fetal growth. In monkeys, radiothyroidectomy performed at mid-gestation (80 days) induced a slight but significant decrease in fetal weight ( $\approx 10\%$ ), measured 70 days later (Holt *et al.*, 1973; Kerr *et al.*, 1972). Similarly, in the fetal lamb, a thyroid hormone deficiency, linked to poor maternal iodine intake, was associated with a 20% reduction in the birthweight (Setchell *et al.*, 1960). This growth retardation was  $> 30\%$ , after a thyroidectomy performed around the 100th day of pregnancy (Bhakhavathsalan *et al.*, 1981; Erenberg *et al.*, 1973; Hopkins & Thorburn, 1972). The only exception could be the human newborn in whom it is generally assumed that moderate congenital hypothyroidism does not appear to influence the intra-uterine growth.

Therefore, in contrast to GH, thyroid hormones could be involved in fetal growth regulation, at least in late gestation in big mammals. In small mammals, which are less mature at birth, this influence seems to appear only after birth when thyroid function is well developed (this occurs at an earlier stage than that

recorded for the onset of the influence of GH).

### ***Thyroid hormone improves body growth in dwarf animals***

Fouchereau-Péron *et al.* (1981) have shown that in the dwarf mouse, growth could be stimulated by T3 and/or GH administration. However, the activation induced by GH was significantly lower than that observed after T3 administration. Moreover the effects of T3 + GH were not greater than the influence of T3 alone. As pituitary function is significantly impaired in dwarf mice, these data are in agreement with the results published by Scanes *et al.* (1986b) showing that T3, but not GH, was able to restore the growth of hypophysectomized chickens.

In sex-linked dwarf chickens, Bowen *et al.* (1987) have observed that T3 supplementation could increase growth. According to these authors, the same treatment decreased growth in the corresponding normal and dwarf (autosomal dwarfing gene) strains, characterized by normal plasma T3 levels, a result which agrees with the well-known adverse effects of thyroid hormone excess upon body growth.

Similarly, intra-uterine growth retarded lambs displayed T4 and T3 deficiencies during at least the first month of life (Wrutniak & Cabello, 1987b; 1988). The administration of T3, three times a week, improved the growth rate of these animals by 25% during the first month of life (Cabello & Wrutniak, unpublished results).

### **SOME MECHANISMS OF ACTION OF THYROID HORMONES ON BODY GROWTH**

The purpose of this paper is not to review the complex metabolic effects of thyroid hormone included in the general mechanisms of body growth, such as the stimulation of protein synthesis in muscle (Brown, 1966; Goldberg, 1978) or influence on energy management (Van Hardeveld, 1986). In order to obtain valuable information on this topic, readers should refer to general reviews such as those of Ramsden (1977) or Van Hardeveld (1986). We have focused our attention on two aspects of thyroid hormone activity, the influence on growth factor production and the relationship to the regulation of the GH axis.

#### ***Thyroid hormone stimulates growth factor production***

Although no significant influence of growth factors, such as nerve growth factor (NGF) or epidermal growth factor could be observed on *in vivo* growth rate, their potent mitogenic activity (Hollenberg, 1979) suggests a strong implication in the cellular mechanisms of growth and differentiation.

Numerous studies have shown that T4 increases NGF concentrations in the sub-mandillary gland (Aloe & Levy-Montaicini, 1980; Lakshmanan *et al.*, 1984; Walker *et al.*, 1981a) and in the brain (Walker *et al.*, 1979; 1981b) of the neonatal or adult mouse. Moreover, Wion *et al.* (1985),



using mouse L- cells, reported that T3 and T4 were able to increase the cell level of NGF mRNA, suggesting that this influence is exerted by the control of NGF gene expression.

Similarly, in the same animal, thyroid hormone induces increased levels of EGF in the submandillary gland (Fisher *et al.*, 1982; Gresik *et al.*, 1981; Hosai *et al.*, 1981; Walker *et al.*, 1981a), the ocular tissue (Lakshmanan *et al.*, 1985) or the skin (Hoath *et al.*, 1983) during neonatal or adult life.

In addition, Hinkle & Kinsella (1986) have shown that T3 stimulated the production of an autocrine growth factor in pituitary tumor cells; this factor, with an apparent molecular weight of 50,000, could be different from the growth factors identified today.

### ***T3 influences growth hormone and somatomedin production, and also their tissue activities***

Numerous studies have shown that thyroid hormone, especially T3, influences the production and the physiological effects of GH.

### ***T3 increases GH synthesis and secretion in mammals***

Today it is well-established that T3 influences synthesis and secretion of growth hormone on the basis of *in vivo* and *in vitro* studies.

*In vivo*, Wakabayashi *et al.* (1985) and Katakami *et al.* (1986) have shown that in thyroidectomized rats the amount of hypothalamic GRF was depressed, as was the sensitivity of pituitary somatotroph cells assessed by cyclic AMP and

GH accumulation after GRF stimulation. Similarly, rats treated by an antithyroid drug showed lowered pituitary and plasma GH concentrations, and a reduced response of these levels to GRF administration (Burstein *et al.*, 1979; Dieguez *et al.*, 1986; Kikuyama *et al.*, 1974; Walker & Dussault, 1980). The same data have been reported in rats developing a hypothyroid state consecutive to the administration of large doses of thyroxine (Pascual-Leone *et al.*, 1976).

Several types of producing GH pituitary cell lines (GH1, GH3, GC) are convenient for studying the *in vitro* effects of thyroid hormone on GH production. In these cells, it has been shown that physiological amounts of T3 ( $\approx 2.5\text{nM}$ ) are able to stimulate the transcription of the GH gene, and also GH mRNA and GH accumulation (Dobner *et al.*, 1981; Evans *et al.*, 1982; Martial *et al.*, 1977; Seo *et al.*, 1977; Spindler *et al.*, 1982). Moreover, the stimulation of gene transcription is dose-dependent and occurs without a latency period (Yaffe & Samuels, 1984). In fact, Casanova *et al.* (1985) have shown that this effect was mediated by the T3 nuclear receptor bound to a 5'-regulatory element of the GH gene.

However, in contrast to these results obtained in mammals or in mammals cells, it appears that thyroid hormone, and particularly T3, decreases both basal and TRH or GRF-induced GH secretion in chickens (Harvey, 1983; Scanes *et al.*, 1986a; Scanes & Harvey, 1989). This discrepancy needs further clarification in the species studied.

### ***T3 could influence the number of cell GH receptors***

As GH administration did not restore IGF levels in hypothyroid animals (Burstein *et*

*al.*, 1979), thyroid hormone could act at levels other than GH production sites in order to influence body growth. One of these sites of action could be the synthesis of GH receptors.

In the dwarf mouse, T3 administration over 4 weeks increased GH binding to hepatocytes four-fold (Fouchereau-Péron *et al.* 1981). However, Chernašek *et al.* (1982) reported that membranes of hepatocytes from thyroidectomized rats were able to bind higher amounts of GH than those from control animals, a result which was somewhat contradictory to the data of Fouchereau-Péron *et al.* (1981). Therefore, this aspect of thyroid hormone action needs clarification.

### **T3 increases somatomedin production**

Whatever the mechanisms involved, T3 seems to increase somatomedin cell production. Thus, *in vivo*, in the dwarf mouse or in the hypophysectomized rat, T4 or T3 + GH administration respectively increased or restored plasma levels of somatomedins (Holder & Wallis, 1977; Schalch *et al.*, 1979). On the other hand, in chickens, Decuypère *et al.* (1987) have shown that MMI-induced hypothyroidism strongly reduced plasma somatomedin-C levels without influence on GH concentrations. *In vitro*, Binoux *et al.* (1985) observed that T3 stimulates insulin-like growth factor production by fetal hypothalamic cells. Taking into account all these results, it appears that T3 could increase autocrine or paracrine, as endocrine stimulation of growth by somatomedins.

### **T3 influences the tissue activity of somatomedins**

This hypothesis, drawn from the work of Froesch *et al.* (1976) indicating that T3 is needed for a maximum stimulation of chick cartilage by somatomedins, needs further confirmation.

## **CONCLUSIONS**

In this paper, we have shown that the so-called growth hormone does not always exert a positive influence upon IGF1 production and therefore upon general body growth. Moreover, it appears that its somatic effects are strongly dependent on thyroid status and particularly on T3 production. Therefore, it seems difficult to study GH regulation and physiological effects without taking into account this endocrine function.

In addition, we have stressed that T3 at least could be considered as a potent hormone affecting body growth, with not only specific effects, but also as a hormone able to potentiate GH and IGF1 activity. Thus it is quite surprising that, as in the case of GH, systematic studies of modifications of T3 production have not been performed in order to stimulate growth performance in domestic animals. This could be due to the fact that thyroid hormone excess is as unfavourable as thyroid hormone deficiency, and that it is today very difficult to induce slight modifications in T3 production. This suggests that the study of accurate

adjustments of T3 production could be an interesting field of research for improving body growth. In this purpose, two methods could be investigated :

The study of the regulation of type I and type II deiodinases involved in cellular T4 to T3 conversion, which are as yet poorly understood, could be a promising area for research. The half-life of these enzymes is short (about 30 min according to Leonard & Visser, 1986) and in the future it is possible to imagine accurate manipulation of their activity. The recent cloning of one of these deiodinases (Boado *et al.*, 1988) is an important step in this direction.

The identification of a factor inducing a short-term specific secretion of T3 by the thyroid gland (Cabello & Wrutniak, 1988) could be another way to accurately adjust T3 production.

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