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Research article

Differential effects of T_4 and T_3 on TRH- and GRF-induced GH secretion in the domestic fowl

S Harvey [1]*, E Decuypere [2], VM Darras [3], L Berghman [4]

[1] *Department of Physiology, University of Alberta, Edmonton, Canada T6G 2H7;*
[2] *Laboratory for Physiology of Domestic Animals, Katholieke Universiteite Leuven;*
[3] *Laboratory for Comparative Endocrinology, Katholieke Universiteite Leuven;*
[4] *Neuroendocrinology and Immunological Biotechnology, Katholieke Universiteite Leuven, B-3030 Leuven, Belgium*

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Summary — The *in vivo* growth hormone (GH) response of immature domestic fowl to thyrotrophin-releasing hormone (TRH) and GH-releasing factor (GRF) was suppressed in birds fed diets supplemented (1 ppm) with triiodothyronine (T_3) or given bolus intraperitoneal (ip) injections (100 µg/kg for 10 d) of T_3. Supplementation (ppm) of the diet with T_4 had no effect on secretagogue- induced GH release. Exogenous T_3 or T_4 suppressed basal, TRH- and GRF-induced GH release 2 h after daily ip administration (100 µg/kg for 10 d). 24 h after the last injection, only T_3 was effective in inhibiting basal and stimulated GH secretion *in vivo*. The systemic administration of T_3 was followed 2 h and 24 h later by a downregulation of pituitary TRH binding sites. T_4 administration had no effect on pituitary TRH binding. When chicken pituitary glands were incubated *in vitro*, basal GH release was unaffected by the addition of 10^{-9}–10^{-5} M T_3 or T_4 to the incubation media. The *in vitro* GH response to TRH (10^{-6} M) or GRF (10^{-6} M) challenge was, however, suppressed in a dose-related manner by T_3 but was unaffected by the coincubation of T_4. These results demonstrate inhibitory effects of T_3 and T_4 on basal and secretagogue-induced GH secretion in fowl. T_4 is less active than T_3 and probably exerts some of its effects *via* T_3-independent mechanisms.

chicken / GH / T_3 / T_4 / TRH / GRF

Résumé — Effets différents de T_4 et T_3 sur la secrétion de GH induite par TRH ou GRF chez le poulet. *La secrétion de l'hormone de croissance (GH) est stimulée par une injection de TRH ou de GRF. L'intensité de cette stimulation est réduite chez les poulets immatures alimentés avec une ration supplémentée en triiodothyronine (T_3; 1 ppm) ou recevant des injections intrapéritonéales (ip) quotidiennes de T_3 (100 µg/kg/j pendant 10 jours). Le supplément de thyroxine dans la ration (T_4; 1 ppm) n'a pas d'effet sur la secrétion de GH induite par les neuropeptides. Les taux de base de GH ainsi que la réponse à TRH ou GRF sont diminués 2 h après l'administration ip quotidienne de T_3 ou T_4 (100 µg/kg pendant 10 jours). Vingt-quatre h après la dernière injection, la réduction du taux de base ou du taux stimulé de GH n'est plus observée que pour T_3. L'administration systémique de T_3 est suivie, 2 h et 24 h plus tard, par une réduction importante (downregulation) des récepteurs hypophysaires de TRH alors que l'administration de T_4 est sans effet sur ces mêmes récepteurs. L'incubation* in vitro *d'hypophyses de poulets en présence de 10^{-9}–10^{-5} M de T_3 ou T_4, ne modifie pas la*

* Correspondence and reprints

sécrétion de base de GH. Par contre, la réponse in vitro *de GH induite par TRH (10^{-6} M) ou par GRF (10^{-8}) est supprimée par T_3 d'une façon reliée à la dose de T_3 mais elle ne l'est pas par T_4. Ces résultats démontrent les effets inhibiteurs de T_3 et T_4 sur la secrétion de base de GH et sur la secrétion de GH induite par les neuroleptiques chez le poulet. T_4 est moins active que T_3 et exerce probablement certains de ses effets par des mécanismes indépendants de T_3.*

poulet / GH / hormones thyroïdiennes / TRH / GRF

INTRODUCTION

Thyroid status modulates growth hormone (GH) secretion in birds. Basal circulating GH concentrations are elevated in birds fed or injected with goitrogens (Leung *et al,* 1985a; Scanes *et al,* 1986a; Harvey *et al,* 1988), genetically deficient in triiodothyronine (T_3) (Scanes *et al,* 1983, 1986a; Harvey *et al,* 1984; Huybrechts *et al,* 1985), suffering from autoimmune thyroiditis (Scanes *et al,* 1976), or which have been surgically thyroidectomized (Harvey *et al,* 1983, 1988). In contrast, exogenous T_3 suppresses basal and thyrotrophin releasing hormone (TRH)-induced GH secretion in euthyroid (Harvey, 1983; Marsh *et al,* 1984a; Scanes and Harvey, 1989) and hypothyroid (Leung *et al,* 1984; Scanes *et al,* 1986a) birds. Similarly, thyroxine (T_4), which can be monodeiodinated by peripheral tissues to T_3 (Lam and Harvey, 1986; Decuypere and Kühn, 1988), can also inhibit basal and TRH-induced GH secretion, although it is less effective than T_3 (Harvey, 1983; Leung *et al,* 1984; Scanes *et al,* 1986a) or even ineffective in some experiments (Marsh *et al,* 1984b; Lauterio and Scanes, 1988; Lazarus and Scanes, 1988).

Since GH increases circulating T_3 concentrations by stimulation of peripheral 5'-monodeiodination (Kühn *et al,* 1987, 1988), T_3 and T_4 may, therefore, provide feedback regulation in the control of GH release (Harvey, 1990a). GH secretion is regulated primarily by hypothalamic releasing factors, of which TRH and a putative GH releasing factor (GRF) stimulate GH release (Harvey, 1990a). The possibility that T_4 may inhibit GRF-induced GH secretion *in vivo* and *in vitro* has therefore been assessed in the present study and compared with the effects of T_3.

MATERIALS AND METHODS

Experiment 1

One-d-old domestic fowl of a broiler strain (Hybro, from Euribrid) were reared from hatch until 7 wk of age and were fed a commercial diet, supplemented with either T_3 or T_4, at concentrations of 1 ppm (Decuypere *et al,* 1987). For comparative purposes, another group was fed a diet supplemented (0.1%) with the goitrogen methimazole (MMI, 2-mercapto-5-methylimidazole, Janssens Pharmaceuticals). A fourth group of controls was fed unsupplemented diet. At 3 and 7 wk of age, birds from each group were intravenously injected with TRH (1 μg/kg) and at 5 wk with human pancreatic GRF_{1-44} NH_2 (10 μg/kg). The peptides were obtained from Peninsula Laboratories (Belmont, CA) and were used at doses maximally effective in stimulating GH release in fowl (Harvey and Scanes, 1984). A control group was injected with the 0.9% NaCl vehicle (1 ml/kg). Heparinized venous blood samples were collected by venipuncture from the brachial vein before and at intervals after the injection of test substances. Following centrifugation and separation, the plasma was stored at –20 °C prior to GH analysis by a homologous radioimmunoassay (Berghman *et al,* 1989) which used a murine monoclonal antibody directed against

affinity-purified chicken GH. This antibody does not cross-react with other pituitary hormones and the assay has a sensivity of 2 ng/ml and an intrassay coefficient of variation of 4%.

Experiment 2

Six-wk-old white Leghorn cockerels were injected ip with T_3 (100 μg/kg), T_4 (100 μg/kg) or with MMI (50 mg/kg), once a day for 10 d. Controls were injected with 0.9% NaCl (1 ml/kg). Two h or 24 h after the last intraperitoneal injection, birds from each group were injected iv with either TRH (1 μg/kg), GRF (10 μg/kg) or the 0.9% NaCl vehicle. Heparinized venous blood samples were collected before and 10 min after injections of the secretagogues, at the time of maximal GH responses (Harvey and Scanes, 1984). Plasma GH concentrations were determined by a homologous radioimmunoassay (Harvey and Scanes, 1977) which used a polyclonal antibody raised in a rabbit against chicken GH isolated by gel filtration and ion-exchange chromatography. This antibody is specific for chicken GH and the assay has a sensitivity of <0.5 ng/ml and an intrassay coefficient or variation of <5.0%. Further birds from each group were killed 2 h or 24 h after the last ip injection of T_3, T_4 or MMI and their anterior pituitary glands rapidly dissected out and collected on ice-cold 20 mM phosphate buffer, pH 7.0. The caudal lobes containing the GH-secreting cells (Malamed *et al,* 1985), were separated and plasma membranes isolated after homogenization in phosphate buffer (pH 7.4), and after centrifugation and ultracentrifugation (Harvey and Baidwan, 1989). The specific binding of TRH to these membranes was determined with [^{3}H]3-methyl-histidine^{2}TRH ([^{3}H]MeTRH; 80 Ci/mmol, New England Nuclear, Missisauga, Ontario) as radioligand, as previously described (Harvey and Baidwan, 1989). Briefly, the plasma membranes (at a concentration of 50 mg wet wt of pituitary tissue/ml; 5 mg/tube) were incubated with [^{3}H] Me-TRH for 60 min at 4 °C, alone or in the presence of 10 μM Me-TRH to determine non-specific binding. Bound and free radioactivity was separated by filtration through Whatman GF/B filters, and then counted in a liquid scintillation cocktail in a beta counter.

Experiment 3

Heads from freshly-killed broiler fowl were obtained from a local slaughterhouse and the anterior pituitary glands were collected on ice-cold medium 199 (M199; Gibco Laboratories, Grand Island, NY). The glands were then bisected and following a 60-min preincubation period the hemipituitaries were incubated for 4 h at 39 °C in a shaking water bath in freshly gassed (95% O_2/5% CO_2) M199 containing test substances, as detailed elsewhere (Hall *et al,* 1985). Contralateral hemipituitary glands were incubated in the absence or presence of 10^{-6} M TRH or 10^{-6} M GRF to stimulate GH release (Hall et al, 1985; Perez *et al,* 1987), in control media or media containing 10^{-5}–10^{-9} M T_3 or T_4. Following incubation, the media were aspirated and stored at −20 °C prior to GH analysis (Harvey and Scanes, 1977).

Statistical differences in the results were determined by analysis of variance or Student's *t*-test where appropriate.

RESULTS

Experiment 1

Basal plasma GH concentrations were unaffected by the addition of 1 ppm T_3 or T_4 to the diet, but were elevated ($P < 0.001$) at 3, 5 and 7 wk of age by 0.1% MMI fig 1; data for wk 3 not shown). At 7 wk of age and in all groups, the administration of TRH was followed 10 min later by increased ($P < 0.01$) GH concentrations. The GH response to TRH in the birds fed 1 ppm T_3 was, however, significantly ($P < 0.05$) reduced in comparison with the corresponding untreated controls. Dietary T_4 supplementation did not impair the GH response to TRH, which was augmented and prolonged by MMI feeding. Similar effects of T_3, T_4 and MMI on TRH-induced GH secretion were also observed at 3 wk of age

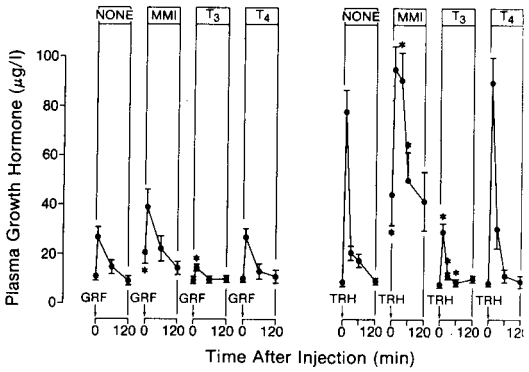

Fig 1. Growth hormone (GH) concentrations in the plasma of control domestic fowl and birds given dietary supplements of methimazole (MMI, 0.1%), triiodothyronine (T_3, 1 ppm) or thyroxine (T_4, 1 ppm) from hatch. The birds were given a bolus intravenous injection of growth hormone releasing factor (GRF, 10 μg/kg) at 5 wk of age and an intravenous injection of thyrotrophin-releasing factor (TRH, 1 μg/kg) at 7 wk of age. Means ± SEM (n = 10). The asterisks indicate values significantly different ($P < 0.05$) from those of controls.

(data not shown). At 5 wk of age, the administration of GRF induced ($P < 0.01$) GH release in the controls and in birds fed 0.1% MMI or 1 ppm T_4 (fig 1). In each case, the GH response to GRF was of comparable magnitude. Dietary supplementation with 1 ppm T_3 completely suppressed GH response to GRF challenge.

The administration of the 0.9% NaCl vehicle to each treatment group at all ages had no significant effect on circulating GH concentrations (data not shown).

Experiment 2

In birds injected for 10 d with MMI, the basal circulating GH concentrations 2 h and 24 h after the last injection were higher ($P < 0.01$) than those in the vehicle-injected controls (fig 2). In contrast, the basal GH concentration was decreased 2 h ($P < 0.001$) and 24 h ($P < 0.05$) after the last injection of T_3, whereas resting GH concentrations were reduced ($P < 0.001$) 2 h but not 24 h after the last injection of T_4. The administration of TRH or GRF increased ($P < 0.05$) the circulating GH concentrations in each group. The magnitude of the GH response to TRH or GRF challenge in birds injected with MMI 2 h or 24 h previously was greater ($P < 0.05$) than that in controls. In contrast, the GH response to TRH and GRF was consistently decreased ($P < 0.01$) 2 h and 24 h after T_3 administra-

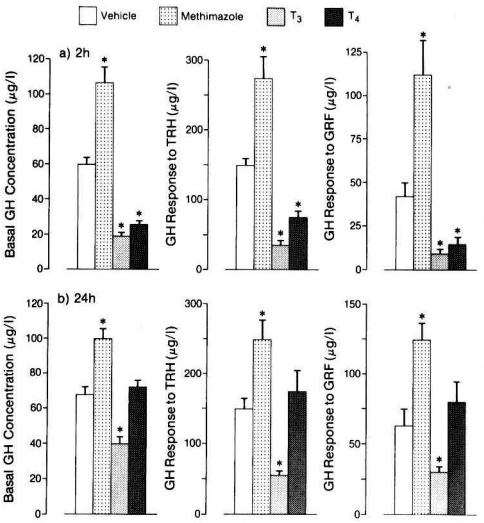

Fig 2. Growth hormone (GH) concentrations in the plasma of immature domestic fowl intraperitoneally (ip) injected with methimazole (50 mg/kg), triiodothyronine (T_3, 100 μg/kg), thyroxine (T_4, 100 μg/kg) or with the 0.9% NaCl vehicle (1 ml/kg) once a day for 10 d. The data indicate the basal GH concentrations 2 and 24 h after the last ip injection and the GH response (measured 10 min later) to intravenous thyrotrophin-releasing hormone (TRH, 1 μg/kg) or growth hormone releasing factor (GRF, 10 μg/kg) challenge. Means ± SEM (n = 10). The asterisks indicate values significantly different ($P < 0.05$ at least) from controls.

tion. However, while the GH response to TRH or GRF was reduced 2 h after the last injection of T_4, it was similar to that in the controls 24 h afterwards.

In each group, the injection of 0.9% NaCl instead of TRH or GRF had no significant effect on circulating GH concentrations (data not shown).

Two h and 24 h after the last injection of MMI, the relative specific binding of [^{3}H]MeTRH to the pituitary caudal lobe was greater ($P < 0.05$) than that in the controls (fig 3). The binding of [^{3}H]MeTRH was suppressed ($P < 0.01$) 2 h and 24 h after T_3 administration, but was unaffected by exogenous T_4.

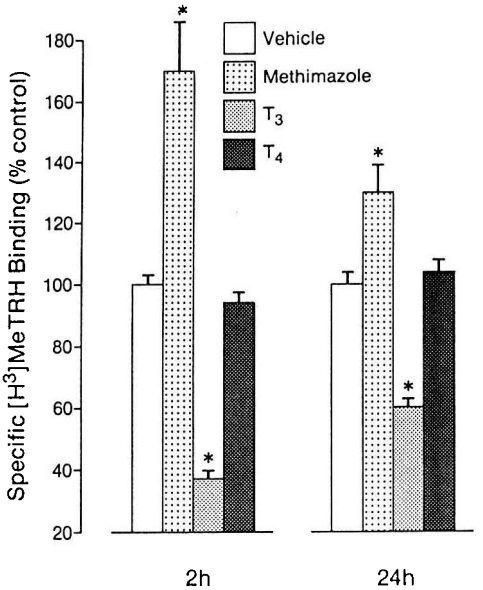

Fig 3. Specific binding of [^{3}H]3-methylhistidine2TRH ([^{3}H]MeTRH) to the caudal lobe membranes of birds killed 2 h or 24 h after treatment with methimazole (50 mg/kg per day for 10 d), triiodothyronine (T_3, 100 μg/kg for 10 days) or thyroxine (T_4, 100 μg/kg). Means ± SEM (n = 8). The asterisks indicate values significantly different ($P < 0.05$) from those in the corresponding controls. Total binding of the tracer to pituitary membranes from both control groups was 1 550 ± 48 cpm, whereas non-specific binding was 169 ± 8 cpm.

Experiment 3

Basal GH release from chicken hemipituitary glands *in vitro* was not affected by the addition of 10^{-9}-10^{-5} M T_3 or T_4 to the incubation media (data not shown). In the presence of 10^{-6} M TRH or 10^{-6} M GRF, GH release was significantly increased ($P < 0.001$ in both cases) (fig 4). The coincubation of TRH with 10^{-8}–10^{-5} M T_3 suppressed the GH response in a dose-related manner. At a concentration of 10^{-5} M, the GH response to TRH stimulation was completely suppressed by exogenous T_3. T_3 at concentrations of 10^{-7}–10^{-5} M also suppressed ($P < 0.01$) the GH response to GRF. In contrast, the addition of 10^{-9}–10^{-5} M T_4 to the incubation media had no significant effect on TRH- or GRF-induced GH secretion.

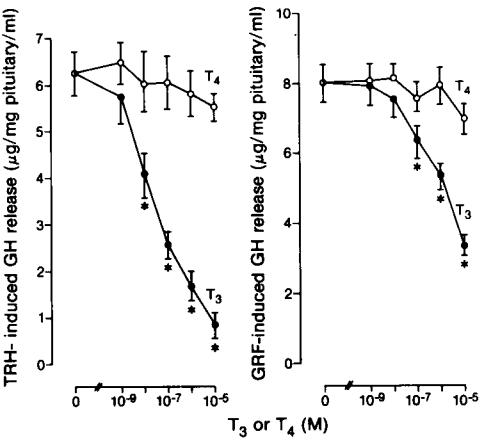

Fig 4. Release of growth hormone (GH) from chicken pituitary glands in response to thyrotrophin-releasing hormone (TRH, 10^{-6} M) or growth hormone releasing factor (GRF, 10^{-6} M), in the presence or absence of 10^{-5}-10^{-9} M triiodothyronine (T_3) or 10^{-5}-10^{-9} M thyroxine (T_4). Means ± SEM (n = 10). The asterisks indicate values significantly different ($P < 0.05$) from those in corresponding controls. The basal release of GH in the absence of thyroid hormones, TRH or GRF was 0.85 ± 0.09 μg/mg pituitary/ml.

DISCUSSION AND CONCLUSION

These results provide further evidence that the hypothalamo–pituitary–thyroid axis plays a role in the regulation of GH secretion in domestic fowl. In the present study, T_3 suppressed basal and TRH-induced GH secretion, in agreement with a number of previous studies (Harvey, 1990a). Although dietary T_3 failed to inhibit basal GH secretion in this study, other studies using the same dose of T_3 (1 ppm) did report a suppression of basal GH concentrations (Scanes *et al,* 1986a; Lauterio and Scanes, 1988). This difference may therefore be due to strain differences in the sensitivity of the birds to exogenous T_3 and may also indicate that basal and stimulated GH secretion are mediated by different mechanisms, or that they have different thresholds for T_3 inhibition.

In the present study, T_3 not only suppressed TRH-induced GH secretion, but also impaired the *in vivo* GH response to GRF. This latter finding is consistent with *in vivo* studies on anaesthetized chickens (Scanes and Harvey, 1989) and *in vitro* studies on perfused chicken pituitary cells (Scanes *et al,* 1986b), and indicates a pituitary site of T_3 action. This finding is, however, in marked contrast to mammalian studies, in which T_3 potentiates GRF-induced GH release (Vale *et al,* 1983; Dieguez *et al,* 1985) and increases GH synthesis by direct effects on gene transcription (Spindler *et al,* 1982; Samuels *et al,* 1988).

While T_3 may act at a level subsequent to TRH or GRF binding to its membrane receptor to inhibit GH secretion, the present results indicate that T_3 is able to reduce TRH binding to the caudal lobe, which is predominately composed of somatotroph cells and is devoid of thyrotroph and lactotroph cells (Mikami and Takahashi, 1987). Such an effect would likely impair the *in vivo* and *in vitro* GH response to TRH challenge, by analogy with the inhibitory effect of thyroid hormones on TRH receptors and thyrotropin secretion in mammalian pituitary glands (see Harvey and Baidwan, 1990). Moreover, since the *in vivo* GH response to GRF is potentiated by TRH (Harvey and Scanes, 1985; Leung *et al,* 1985b; Buonomo and Baile, 1986; Scanes and Harvey, 1986; Taylor *et al,* 1986), the blunting of the GH secretory response to GRF stimulation in T_3-treated birds could also be partly due to a down-regulation of TRH receptors and possibly to inhibition of TRH release *in vivo* (Hinkle and Goh, 1982; Mori and Yamada, 1987; De los Frailes *et al,* 1988; Dyess *et al,* 1988). Since TRH may stimulate GH secretion in birds by action at extrapituitary sites, it is less potent *in vitro* than *in vivo* (Harvey, 1990b). Thus while TRH is a more effective GH secretagoque than GRF *in vivo* it is approximately equipotent with GRF *in vitro*, as observed in the present study.

Although T_3 is derived from T_4 by monodeiodination in peripheral tissues, including the pituitary gland (Lam, 1986), T_4 had no effect on GH release from pituitary tissue *in vitro* and had no long-term effect on *in vivo* GH secretion. The failure of dietary T_4 to suppress stimulated GH secretion probably reflects its lower biological potency and the dosage used, since dietary T_4 supplements that increase circulating T_3 concentrations suppress GH secretion (Leung *et al,* 1984). The ability of the injected dose of T_4 to acutely inhibit basal and secretagogue-induced GH release, in agreement with other studies (Harvey, 1983; Harvey *et al,* 1988), in the absence of long-lasting effects, is consistent with this view.

However, the inhibition of GH secretion induced by T_4 is probably not simply due to its conversion to T_3. This conclusion is

based on the inability of T_4 to directly suppress *in vitro* GH secretion, even at high (10^{-5} M) dose levels. The acute suppression of basal GH concentrations in T_4 treated birds *in vivo* also occurred without inducing a down-regulation of TRH binding sites, as would be expected if the effect was due to T_4 to T_3 conversion. Basal GH secretion is similarly transiently suppressed by exogenous T_4 in birds in which peripheral and intrapituitary T_4 to T_3 conversion is blocked by iopanoic acid (Harvey *et al,* 1990), further suggesting T_3-independent effects of T_4 on GH secretion. Moreover, while T_4 is rapidly converted to T_3 in hypothyroid birds, it is mainly converted to reverse T_3 (rT_3) in euthyroid birds (Decuypere *et al,* 1987; Decuypere and Kühn, 1988), possibly to prevent the accumulation of toxic T_3 concentrations. The activity of intrathyroidal type III deiodinase, responsible for the conversion of T_4 to T_3, is greater in birds than in mammals (Decuypere and Kühn, 1988), and since rT_3 antagonizes the effects of T_3 (Lynch *et al,* 1985; Han *et al,* 1986), the inhibitory effects of T_4 on GH secretion are unlikely to be mediated by T_3.

In summary, these results show differential effects of T_4 and T_3 on GH secretion in fowl and suggest they act at different sites in the hypothalamo-pituitary axis.

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