© European Journal of Endocrinology 1994, 131: 302–6

# Interleukin 6 effects on the pituitary–thyroid axis in the rat

Luigi Bartalena, Lucia Grasso, Sandra Brogioni and Enio Martino

*Istituto di Endocrinologia, University of Pisa, Tirrenia-Pisa, Italy*

Bartalena L, Grasso L, Brogioni S, Martino E. Interleukin 6 effects on the pituitary–thyroid axis in the rat. Eur J Endocrinol 1994;131:302–6. ISSN 0804–4643

It has been postulated recently that cytokines, and in particular interleukin 1 (IL-1) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$), may have a role in the pathogenesis of the changes of serum thyroid hormone concentrations that are encountered in patients with non-thyroidal illness (NTI). Many of the IL-1 and TNF-$\alpha$ effects are believed to be mediated by the induction of IL-6 synthesis, which might, therefore, represent an important mediator of thyroid hormone changes in NTI. To address this problem, male Wistar rats were injected subcutaneously with 2.5 $\mu$g of recombinant human IL-6 (rhIL-6, in 500 $\mu$l of saline solution), with 2.5 $\mu$g of rhIL-6 preincubated with 100 $\mu$l of anti-IL-6 neutralizing antibody or with saline solution alone (control group). Administration of rhIL-6 resulted in a significant decrease of thyroxine ($T_4$) from 82 ± 4 nmol/l (mean± SEM) to a nadir of 33 ± 3 nmol/l ($p < 0.0001$) after 48 h, and of triiodothyronine ($T_3$) from 1.6 ± 0.1 to 0.8 ± 0.1 nmol/l after 48 h ($p < 0.0001$). A slight decrease in serum $T_4$ and $T_3$ concentrations also was observed in the control group, but the lowest values ($T_4$, 66 ± 3 nmol/l; $T_3$, 1.2 ± 0.1 nmol/l) were significantly higher ($p < 0.0001$) than in IL-6-treated rats. The IL-6-induced changes could be prevented by preincubation of rhIL-6 with its neutralizing antibody. Slight but not significant changes occurred in serum reverse $T_3$ ($rT_3$) concentration, so that the $T_4/rT_3$ ratio remained substantially unchanged after rhIL-6 injection, whereas the $T_4/T_3$ ratio decreased significantly from 53.6 to 39.9 ($p < 0.02$) in IL-6-treated rats. The effects of IL-6 on thyrotropin (TSH) were investigated after rendering the rats hypothyroid by methimazole administration for 3 weeks. Serum TSH decreased from 19.0 ± 6.8 to 13.3 ± 3.8 $\mu$g/l after 48 h ($p < 0.01$) in IL-6-treated rats, while it increased from 17.2 ± 2.8 to 25.8 ± 4.0 $\mu$g/l ($p < 0.01$) in the control group. These results show that a single injection of rhIL-6 causes a decrease in serum $T_4$, $T_3$ and TSH concentrations in the rat, without affecting serum $rT_3$ levels. This is compatible with a predominantly central effect of the cytokine. The apparent lack of inhibition of 5′-deiodinating activity, a key feature of NTI, suggests that IL-6, if involved, is only one of the factors responsible for the changes of thyroid hormone secretion and metabolism observed in NTI.

*Luigi Bartalena, Istituto di Endocrinologia, University of Pisa, Viale del Tirreno 64, 56018 Tirrenia-Pisa, Italy*

Changes in serum concentrations of thyroid hormones, which occur in non-thyroidal illnesses (NTI) and define the so-called "Euthyroid Sick Syndrome" (ESS), are well characterized and include a decrease in serum triiodothyronine ($T_3$), an increase in serum reverse $T_3$ ($rT_3$) and, in most severe forms, a decrease in serum thyroxine ($T_4$) concentrations (1). The pathogenesis of these abnormalities is far less understood, but circumstantial evidence has been provided that cytokines, and especially interleukin 1 (IL-1) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$), might be factors involved in their regulation (1). Recently, the elevated serum IL-6 concentration found in NTI has been correlated with the abnormalities of thyroid function tests found in ESS, suggesting also that this cytokine might participate in the pathogenesis of these changes (2, 3).

The role of IL-6 in generating abnormalities of thyroid function in vivo in the animal is controversial, because preliminary reports have provided evidence that thyroid function tests are affected by IL-6 in rats (4) but not in mice (5). Thus, the present study was undertaken to evaluate further the effects of IL-6 administration on the pituitary–thyroid axis in the rat.

## Materials and methods

### *Animals*

Adult (6-week-old) male Wistar rats weighing 150–200 g were housed, four per cage, in plexiglass cages in an artificially lighted and temperature-controlled room (lights on at 07.00 h, lights off at 19.00 h), and fed rat chow and tap water ad libitum for 2 weeks prior to the experiments.

### *Test materials*

Recombinant human IL-6 (rhIL-6) expressed in *Escherichia coli* and goat anti-rhIL-6 neutralizing antiserum were obtained from R&D Systems (Berkeley, USA). The

anti-rhIL-6 antibody had no cross-reactivity with IL-1 or TNF-$\alpha$.

### *In vivo experimental procedure*

On the day of the experiment, rats were weighed and anesthesized by ether. In a preliminary experiment, rats were subdivided into four groups of six rats, receiving subcutaneously either saline solution alone, rhIL-6 in three different doses (1, 2.5 or 5 $\mu$g dissolved in 500 $\mu$l of saline solution) or normal goat serum (100 $\mu$l added with 400 $\mu$l of saline solution). Blood was drawn from the tail, under slight anesthesia, prior to injection and 4 and 24 h after. In three subsequent experiments, rats were divided into three groups of eight rats: the first group was administered a single subcutaneous injection of rhIL-6 (2.5 $\mu$g in 500 $\mu$l of saline solution); the second group received rhIL-6 preincubated for 1 h at room temperature with 100 $\mu$l of undiluted goat anti-IL-6 neutralizing antiserum; the third group was constituted by control rats injected with saline (500 $\mu$l). Blood was drawn, as described above, prior to injection and 4, 24, 48 and 72 h after. Serum was stored at −20°C until assayed.

In three subsequent experiments, hypothyroidism was induced in two additional groups of eight rats by the addition of methimazole to the drinking water (1.5 g/l) 3 weeks prior to the experiment. Rats received either rhIL-6 (2.5 $\mu$mg in 500 $\mu$l of saline) or saline alone. Blood was drawn prior to the experiment and 24 and 48 h after.

### *Assays*

Radioimmunoassay (RIA) kits were used for the determination of serum total $T_4$ and $T_3$ (Byk Gulden, Milan, Italy) and $rT_3$ (Ares Serono, MIlan, Italy); the latter assay had a sensitivity of 0.019 nmol/l. Serum TSH concentration was determined by RIA using the material kindly provided by the National Hormone and Pituitary Program, National Institutes of Health, Bethesda, USA, as described previously (6).

### *Statistical analysis*

Values were expressed as means ± SEM. Undetectable $rT_3$ values were given, for statistical purposes, an arbitrary value equal to one half of the least detectable value. Variations within groups were analyzed by one-way ANOVA for repeated measures and by Student–Newman–Keuls test for multiple comparisons. Differences between different groups were analyzed by Student's *t*-test for unpaired data.

## Results

In preliminary experiments, the subcutaneous injection of 1 $\mu$g of rhIL-6 was associated with a slight, but not significant, reduction in serum $T_4$ and $T_3$ concentrations, while the administration of 2.5 and 5 $\mu$g caused a significant decrease in hormone levels. As rats given 5 $\mu$g showed a pronounced reduction of the body weight, a dose of 2.5 $\mu$g of rhIL-6 was selected for further experiments. The injection of normal goat serum did not produce variations of serum $T_4$ and $T_3$ levels different from those observed in control rats injected with saline.

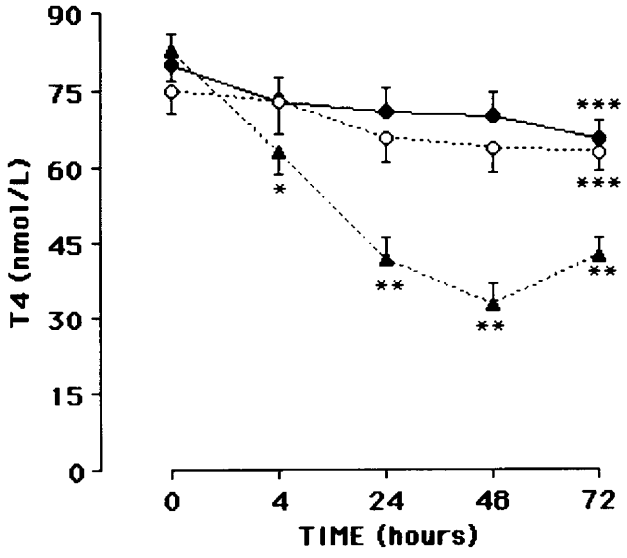


*Fig. 1.* Changes in serum $T_4$ concentrations (mean ± SEM of three experiments) in rats given subcutaneously recombinant human interleukin 6 (2.5 $\mu$g of rhIL-6 in 500 $\mu$l of saline solution) (▲), rhIL-6 preincubated with 100 $\mu$l of anti-IL-6 neutralizing antibody (○) or saline solution alone (●). *$p < 0.001$ vs baseline: **$p < 0.0001$ vs baseline: ***$p < 0.01$ vs baseline.

In a subsequent experiment, rats were treated with 2.5 $\mu$g of rhIL-6, with 2.5 $\mu$g of rhIL-6 preincubated with 100 $\mu$l of anti-IL-6 neutralizing antibody or with saline solution alone. Throughout the experiment, the food intake did not differ in the three groups; accordingly, a similar decrease in body weight was observed in control rats (from 211 ± 10 to 195 ± 8 g), IL-6-treated rats (from 205 ± 8 to 196 ± 10 g) and rats treated with IL-6 preincubated with the neutralizing antibody (from 197 ± 6 to 190 ± 7 g), with no differences among groups. As shown in Fig. 1, a single subcutaneous injection of 2.5 $\mu$g of rhIL-6 caused a significant decrease in serum $T_4$ from 82 ± 4 to 62 ± 3 nmol/l after 4 h ($p < 0.001$), 41 ± 3 nmol/l after 24 h ($p < 0.0001$) and 33 ± 3 nmol/l after 48 h ($p < 0.0001$); at 72 h values were slightly, although not significantly, higher than after 48 h (43 ± 3 nmol/l). A slight, but significant, decrease was observed also in the control group (saline alone) from 80 ± 3 to 66 ± 3 nmol/l ($p < 0.01$) after 72 h. Baseline serum $T_4$ values did not differ in IL-6-treated and in control rats, whereas values after 4, 24, 48 and 72 h were

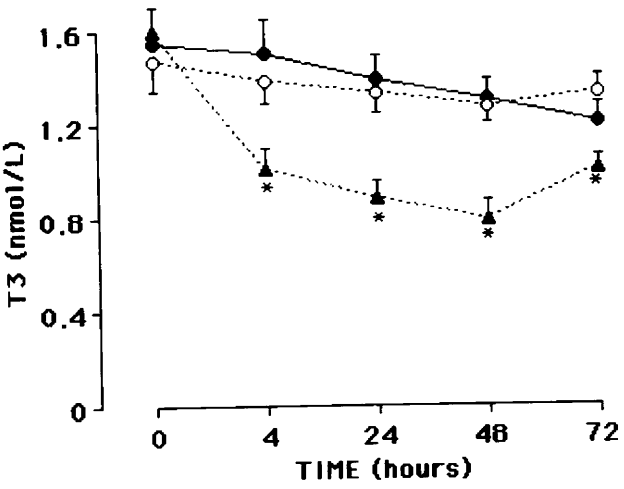


*Fig. 2.* Changes in serum $T_3$ concentrations (mean ± SEM of three experiments) in rats given subcutaneously recombinant human interleukin 6 (2.5 μg of rhIL-6 in 500 μl of saline solution) (▲), rhIL-6-preincubated with 100 μl of anti-IL-6 neutralizing antibody (○) or saline solution alone (●). *$p < 0.0001$ vs baseline.

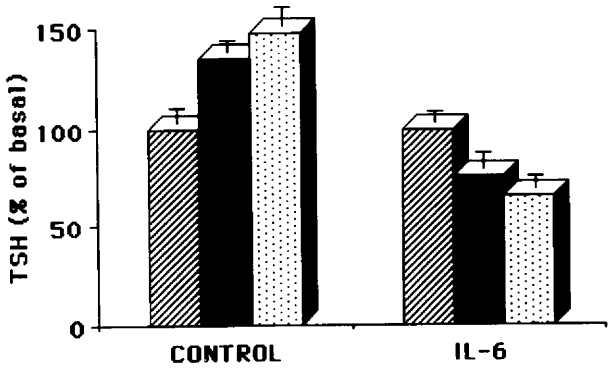


*Fig. 3.* Changes in TSH level in hypothyroid rats treated with interleukin 6 (2.5 μg of IL-6 subcutaneously) and in control rats. Data are expressed as percentage variations of baseline values (+SEM): (□) *baseline;* (■) 24-h value; (□) 48-h value.

significantly lower ($p < 0.0001$) in rats receiving rhIL-6. As illustrated in Fig. 1, the effect of rhIL-6 could be prevented by preincubating the cytokine with 100 μl of anti-IL-6 neutralizing antibody: in this group of rats, serum $T_4$ decreased from 75 ± 5 to 64 ± 2 nmol/l after 48 h ($p < 0.01$), with no significant differences with respect to the control group.

As shown in Fig. 2, a similar decrease, after rhIL-6 administration, was observed for serum $T_3$ concentration from 1.6 ± 0.1 to 0.8 ± 0.1 nmol/l ($p < 0.0001$) after 48 h. The control group also showed a slight, but not significant, decrease in serum $T_3$ levels, from 1.5 ± 0.1 to 1.2 ± 0.05 nmol/l after 72 h (p = NS). As for $T_4$, the IL-6 effect on $T_3$ could be abolished by preincubating the cytokine with its neutralizing antibody (Fig. 2).

Slight, but not significant, variations in serum $rT_3$ concentration were found in either group (from 0.048 to 0.044 nmol/l in control group, from 0.045 to 0.035 nmol/l in IL-6-treated rats, and from 0.044 to 0.042 nmol/l in the group treated with the neutralized cytokine). Two rats in each group had undetectable serum $rT_3$ levels, which remained undetectable throughout the experiment. Accordingly, the $T_4/rT_3$ ratio showed only marginal and not significant changes throughout the experiment, with no differences between control and IL-6-treated rats (Table 1). At variance, the $T_4/T_3$ ratio decreased significantly from 53.6 to 39.9 ($p < 0.02$) in IL-6-treated rats but not in control rats or in rats treated with the neutralized cytokine (Table 1).

*Table 1.* Effect of subcutaneous injection of recombinant human interleukin 6 (rhIL-6, 2.5 μg) on $T_4/rT_3$ and $T_4/T_3$ ratios.

| | $T_4/rT_3$ | | $T_4/T_3$ | |
|---|---|---|---|---|
| Group | Basal | 48 h | Basal | 48 h |
| rhIL-6 | 1741 ± 295 | 1492 ± 238 | 53.9 ± 3.3 | 39.9 ± 3.9* |
| rhIL-6 + Ab[a] | 1670 ± 218 | 1501 ± 204 | 55.5 ± 3.1 | 54.4 ± 2.8 |
| Controls | 1683 ± 223 | 1499 ± 126 | 54.5 ± 3.9 | 54.9 ± 3.4 |

[a] Recombinant rhIL-6 was preincubated for 1 h at room temperature with 100 μl of undiluted neutralizing anti-IL-6 antibody (Ab).
*$p < 0.02$ vs basal.

Euthyroid rats had low-normal or undetectable serum TSH values, which did not allow detection of small changes. Therefore, to investigate the effects of IL-6 on TSH secretion, rats were made hypothyroid by adding methimazole to the drinking water for 3 weeks prior to injection with either rhIL-6 or saline. Hypothyroidism was confirmed by the very low or undetectable serum $T_4$ and $T_3$ concentrations. In the control group, serum TSH increased from 17.2 ± 2.8 to 25.8 ± 4.0 μg/l after 48 h ($p < 0.001$), whereas in IL-6-treated rats the hormone concentration decreased from 19.0 ± 4.8 to 13.3 ± 3.8 μg/l ($p < 0.01$). Thus, in control rats a 50% increase in serum TSH concentration was observed during the 48-h experiment, while in the IL-6 group a 30% decrease occurred (Fig. 3). Baseline serum TSH levels did not differ, but values at 48 h were significantly lower in IL-6-treated rats ($p < 0.0001$).

## Discussion

Interleukin 6 is a pleiotropic cytokine involved in B-cell terminal differentiation and activation of T cells (7), stimulation of acute-phase proteins (7) and regulation of hormone transport proteins (8, 9). It is synthesized by different cells, including thyroid cells (10–12). Increased serum IL-6 concentrations have been found in patients with thyroidal destructive processes, such as subacute thyroiditis (13), some forms of amiodarone-induced thyrotoxicosis (14) and after percutaneous

ethanol injection into hot nodules (15). Under these circumstances, the increased IL-6 concentration in serum is the expression of thyroid cell damage.

Serum IL-6 levels are increased also in patients with NTI (16–21), and appear to correlate with changes of serum thyroid hormone concentration (2, 3). Furthermore, administration of IL-6 to patients with metastatic renal carcinoma has been associated with a reduction in serum $T_3$ and TSH concentrations and an increase in serum $rT_3$ levels (22). Thus, IL-6 might represent a possible mediator of ESS.

Our results in vivo in the rat showed that a single rhIL-6 injection is followed by a decrease in serum $T_4$, $T_3$ and TSH concentrations. These data are in keeping with preliminary results by Onoda et al. (4) in the rat, but in disagreement with negative effects of IL-6 in mice (5). It is possible that these discrepancies may be attributed to the different animal species. Our study demonstrated that IL-6 affects TSH secretion (at least in hypothyroid animals), but the mechanism responsible for this action is unclear. Onoda et al. (4) failed to show any substantial change in pituitary TSH content and TSH-$\beta$ mRNA abundance, or in the hypothalamic TSH-releasing hormone content. It might, therefore, be that the inhibitory effect of IL-6 is indirect, carried out through other IL-6-stimulated mediators, such as ACTH and adrenal steroids (23). Interestingly, IL-6 has been reported to stimulate in vitro the release of other anterior pituitary hormones, including prolactin, growth hormone and luteinizing hormone (24). Whatever the mechanism(s), the inhibition of TSH secretion by IL-6 is in agreement with the notion that in NTI, despite the reduction in serum thyroid hormone concentration, serum TSH is often inappropriately low/normal (with a reduction or abolishment of its nocturnal peak), thus depicting a condition of central hypothyroidism (25–28).

The reduction in serum $T_4$ and $T_3$ concentrations might be the consequence of the decreased thyroid stimulation by TSH and/or of a direct effect of IL-6 on the thyroid. While the first possibility is likely in view of the cytokine effect on TSH, the second mechanism could not be demonstrated directly in our animal model. However, it is worth mentioning that IL-6 seems to have direct effects at the thyroid level, where it has been reported to block TSH-induced thyroid hormone release and thyroid peroxidase gene expression (29). It is, therefore, conceivable that the reduction in thyroid hormone release induced by IL-6 in vivo may be mediated partly by an IL-6-induced reduction in TSH release, but also may result from a direct action of the cytokine at the thyroid level. It should, however, be mentioned that IL-6 failed to influence thyroglobulin production by cultures of human thyrocytes (30).

Interestingly, IL-6 administration was associated neither with an increase in serum $rT_3$ concentrations nor with a significant decrease in the $T_4/rT_3$ ratio. This is in agreement with the report by Hermus et al. (31), who found serum $rT_3$ levels below the limit of detection of the assay throughout IL-1$\beta$ infusion. At variance, the $T_4/T_3$ ratio decreased significantly after IL-6 injection. These data, taken together, suggest that type I deiodinase activity is not reduced by IL-6 administration in the rat. In this regard, it is worth noting that IL-1 and TNF-$\alpha$ have been reported to increase 5′-deiodinating activity in the mouse liver (32, 33).

Both central (i.e. a reduced TSH secretion) and peripheral (i.e. a reduced peripheral monodeiodination of $T_4$) mechanisms intervene in the pathogenesis of ESS (see Ref. 1 for a review). Interest in the role of cytokines in NTI has focused mostly on TNF-$\alpha$ and IL-1, and multiple effects of these cytokines have been described both at the hypothalamic–pituitary level and at the thyroid level (31–36), which might be mediated partially by induction of IL-6 synthesis and release (7). However, while our results showed that IL-6 does inhibit TSH (at least in hypothyroid animals) and thyroid hormone secretion, they apparently failed to demonstrate any impairment of 5′-deiodinating activity, which is a key feature of ESS. It is likely, therefore, that IL-6, if involved, is only one of the (largely unknown) factors responsible for the changes of thyroid hormone secretion and metabolism seen in NTI.

*Acknowledgments.* The authors want to thank Professor Aldo Pinchera for his continuous encouragement and advice. The study was supported in part by grants from the Italian Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST, 40%–60%) "Progetto Finalizzato Invecchiamento" INV 94/11/445 and from the National Research Council (CNR, target project "Prevention and Control of Disease Factor (FATMA)", grant no. 9300689PF41), Rome, Italy.

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Received January 27th, 1994
Accepted May 16th, 1994