Effects of Dexamethasone and Secobarbital on the Pituitary Response to Thyrotropin Releasing Hormone (TRH) in Man: Synergistic Inhibition of Thyrotropin (TSH) Release

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Abstract. The present study was made to investigate the possible effects of dexamethasone and secobarbital on the pituitary responses of prolactin (PRL) and TSH to TRH. Dexamethasone (1 mg) and secobarbital (100 mg) were administered separately or together at 11 p.m. An intravenous injection of 200 μg TRH was given at 9 a.m. the following morning. PRL control levels and release were not modified by prior administration of the drugs. TSH control levels remained unchanged but TSH release was significantly inhibited by the combined pre-treatment; dexamethasone and secobarbital given alone had no effect. The present study supports the view of a direct synergistic effect of both drugs on the pituitary thyrotropes, diminishing their responsiveness to TRH.

Glucocorticoids decrease serum or plasma TSH levels in both man and rat [Wilber and Utiger, 1969; Haigler et al., 1971] and inhibit the TSH-dependent circadian iodine release cycle in man [Nicoloff et al., 1970]. It has been suggested that glucocorticoids act exclusively at the hypothalamic level by an inhibition of TRH secretion [Wilber and Utiger, 1969; Nicoloff et al., 1970; Singer and Nicoloff, 1973]. However, other authors [Polosa et al., 1972; Faglia et al., 1973; Otsuki et al., 1973] have recently presented conclusive data supporting a corticoid-induced inhibition of pituitary TSH release following TRH injection. This inhibitory effect on the pituitary depends strongly upon the schedule of corticoid administration; indeed, in normal subjects, lack of inhibition has been reported with only low doses and brief administration periods of dexamethasone [Besser et al., 1971] or methylprednisolone.

Key Words
TRH
TSH
Barbiturates
Glucocorticoids
Prolactin

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Erratum: Fig. 1 is to be replaced by Fig. 3 and vice versa.
[WOOLF et al., 1973]. A possible synergistic action of barbiturates upon the corticoid inhibition of the pituitary TSH response to TRH was never investigated. On the other hand, no data are available in man on the possible action of glucocorticoids and barbiturates on the PRL release induced by TRH.

The present work was intended to determine the possible influence of low doses of dexamethasone and of secobarbital administered separately or together on the pituitary hormonal release induced by TRH injection.

Materials and Methods

Three groups of 6 normal male volunteers, aged 21 to 39 years, were submitted twice, with an interval of one week or more, to an i.v. injection of 200 μg synthetic Pyroglu-His-Pro-NH₂: TRH (Roche, Belgium). The injection was performed at 9 a.m. (0-min), after an overnight fast. Blood was taken through an indwelling needle at frequent intervals between —30 and +120 min. Randomly paired experiments were performed: one under normal basal conditions, the other after oral administration, at 11 p.m. the previous evening, of 1 mg dexamethasone (group I), 100 mg secobarbital (group II), or the 2 drugs together (group III). Serum corticoids were measured by a competitive protein binding technique including a methylene chloride extraction of serum steroids and a dextran-coated charcoal separation of free and protein bound steroids; total serum corticoids were expressed as equivalents of cortisol [LECLERCQ et al., 1969]. With this technique cortisol levels estimated in serum or in plasma samples are identical [LECLERCQ, unpublished data]. Serum TSH was measured by a double antibody radioimmunoassay [GOLSTEIN and VANHAELST, 1973] and the results were expressed in μU/ml in terms of the Human Research Standard A (National Medical Research Council, Mill-Hill, England). Serum PRL was estimated by a double antibody radioimmunoassay using 125I ovine PRL as tracer and anti-ovine PRL antiseraum [L'HERMITE et al., 1972a]. With this assay, no cross-reaction was found with TSH Research Standard A up to 100 μU/ or synthetic TRH up to 200 μg per assay tube. A pool of PRL-rich human sera was used as laboratory standard for PRL assays. An immunological activity of 1 U was arbitrarily conferred to 1 ml of this pool, equivalent to 2.3 milliampullae of Research Standard 71/167 (National Medical Research Council, Mill-Hill, England).

Statistical analysis was performed using the paired t-test, either on the values obtained at different times of the experiments, on the maximal increments (Δ max) of hormonal levels, or on the secretory areas, i.e. the areas between the basal line of 0-min and the curve drawn from the values measured at different times after 0-min.

Results

In the 3 groups of subjects, basal cortisol values exhibited a progressive decrease from —30 min to +120 min (fig. 1, 2, 3). This decrease
Table I. PRL release in the different groups of subjects without (−) and with (+) drug pre-treatment, represented by the $\Delta$ max of PRL levels (mU/ml) and by the corresponding secretory areas (SA) (area unit = 5 mU-min/ml)

<table>
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<th>Group III</th>
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<td>$\Delta$ max</td>
<td>SA</td>
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<td>4,929</td>
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<tr>
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<td>575</td>
<td>4,805</td>
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<td>114</td>
<td>1,435</td>
<td>106</td>
<td>1,135</td>
<td>123</td>
<td>676</td>
<td>60</td>
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$t_{\Delta \text{max} - vs +} = 0.43$ $t_{\Delta \text{max} - vs +} > 0.50$ $t_{\Delta \text{max} - vs +} = 0.52$ $t_{\Delta \text{max} - vs +} > 0.50$ $t_{\Delta \text{max} - vs +} = 1.46$ $t_{\Delta \text{max} - vs +} > 0.20$ $t_{\Delta \text{max} - vs +} = 1.55$ $t_{\Delta \text{max} - vs +} > 0.10$ $t_{\Delta \text{max} - vs +} = 1.27$ $t_{\Delta \text{max} - vs +} > 0.20$
Synergy of Barbiturates and Glucocorticoids on TRH Action

Fig. 1. Mean values (± SEM) of serum PRL, TSH and cortisol before and after TRH injection (arrow), without (solid line) and with (dotted line) prior administration of 1 mg dexamethasone.

Persisted after secobarbital alone (fig. 2) while after dexamethasone given alone or in association with secobarbital, cortisol secretion was almost completely – and identically – abolished (fig. 1, 3).

Under basal conditions, all the subjects responded to TRH with a rise in serum PRL (fig. 1, 2, 3); this increase was significant from +5 or +10 min until +60 or +80 min depending upon the group of subjects. Pre-treatment did not modify the PRL control levels (i.e. values at -30, -15 and 0 min). Furthermore, drug administration did not significantly change the TRH-induced PRL release, calculated either as to \( \Delta \) max in blood level or as to the secretory area (fig. 1, 2, 3; table I).
Fig. 2. Mean values (± SEM) of serum PRL, TSH and cortisol before and after TRH injection (arrow), without (solid line) and with (dotted line) prior administration of 100 mg secobarbital.

In the basal state, after TRH injection, all the subjects exhibited a rise in serum TSH with a peak between +20 and +50 min (fig. 1, 2, 3). Control TSH values were not modified by drug administration. The same was true for the secretory TSH response to TRH, after dexamethasone alone (fig. 1; table II), as well as after secobarbital alone (fig. 2; table II). Only the pre-treatment with dexamethasone and secobarbital together significantly inhibited the TSH discharge, calculated on the Δ max and on the secretory areas (fig. 3, 4; table II).
Table II. TSH release in the different groups of subjects without (−) and with (+) drug pre-treatment, represented by the Δ max of TSH levels (μU/ml) and by the corresponding secretory areas (SA) (area unit = 0.5 μU-min/ml)

<table>
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<td>691</td>
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<td>510</td>
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- tΔmax vs + = 1.26
- PΔmax vs + > 0.20
- tSA vs + = 0.65
- PSA vs + > 0.50

Synergy of BartJBom and Glucocorticoids on TRH Action
Fig. 3. Mean values (± SEM) of serum PRL, TSH and cortisol before and after TRH injection (arrow), without (solid line) and with (dotted line) prior administration of 1 mg dexamethasone and 100 mg secobarbital.

Discussion

The present data confirm that serum cortisol levels are not influenced by TRH administration [Anderson et al., 1971]; the progressive decrease observed in the basal condition and after secobarbital (group II) is in part due to the classical circadian variations. After dexamethasone administration (groups I and III) cortisol secretion was almost completely abolished throughout the duration of the experiment.

The well-known PRL release after TRH administration [Bowers et al., 1971; Jacobs et al., 1971; L'Hermite et al., 1972b] was found in all
subjects of the present study; neither PRL control levels nor its release were modified by any of the drug pre-treatments. However, it is worthwhile to stress that the administration of 4 mg dexamethasone per day during 2 successive days almost completely abolishes basal serum PRL values (to be published). The level of the hypothalamo-pituitary axis where this inhibitory effect is exerted remains unknown.

The combined administration of dexamethasone and secobarbital (group III) significantly inhibited the TSH release response to TRH, whereas none of these drugs, acting separately (groups I, II), produced any effect. TSH control levels, however, remained unchanged in all the experiments. Neither glucocorticoids [WILBER and UTiger, 1969; NICOLOFF et al., 1970] nor barbiturates [CAVALIERI et al., 1973] alter the plasma binding of thyroid hormones; moreover, the corticoids do not influence the peripheral catabolism of thyroid hormones [WILBER and UTiger, 1969], whereas barbiturates enhance it [CAVALIERI et al., 1973]. Therefore, it is unlikely that their simultaneous administration triggers the feedback mechanism inhibiting the pituitary release of TSH. On the
other hand, because individual patterns of TSH response to TRH (fig. 4) do not suggest an accelerated disappearance of the hormone from blood after the combined pre-treatment, it seems unlikely that this pre-treatment could modify the peripheral distribution or the metabolism of TSH.

Thus the present data favor a direct and synergistic pituitary effect of low doses of dexamethasone and secobarbital, diminishing the responsiveness of thyrotropes to TRH.

With regard to glucocorticoids, the data of the literature are conflicting. Indeed, whereas preliminary studies suggested that the inhibitory effect of glucocorticoids on the hypothalamo-pituitary-thyroid axis was only due to a hypothalamic inhibition of TRH secretion [Wilber and Utiger, 1969; Nicoloff et al., 1970], more recent data have definitely proved that both dexamethasone and cortisol depress the reactivity of pituitary thyrotropes to TRH [Polosa et al., 1972; Faglia et al., 1973; Otsuki et al., 1973]. The administration schedule of glucocorticoids and TRH seems to be very important. Indeed, inhibition was obtained with high doses of corticoids and/or a long administration period. The reduction of one or both parameters led to an absence of effect of the glucocorticoids [Bessier et al., 1971; Woolf et al., 1973] or even to a stimulation of the pituitary TSH secretory response [Otsuki et al., 1973]. On the other hand, an increase in the dose of TRH may overcome the inhibitory effect of corticoids [Otsuki et al., 1973]. Thus, the present data, showing the lack of effect of 1 mg dexamethasone administered alone on the pituitary TSH response to TRH, are in agreement with the studies published thus far.

An inverse modulation of TSH and ACTH secretion by the pituitary, suggested in the rat by Sakiz and Guillemin [1965], seems excluded in the present experiment. Indeed, the inhibition of ACTH secretion, as indicated by the almost complete abolition of cortisol secretion, was identical in groups I and III, whereas only the subjects of group III presented a blunting of the TSH release after TRH. With regard to barbiturates, the present data are suggestive of either a specific inhibitory effect on the pituitary thyrotropes, or a potentiation of the inhibition due to dexamethasone.

Finally, the present results are an additional example of a dissociation of TSH and PRL secretions [L'Hermité et al., 1974] in man submitted to similar experimental conditions. If the synergistic effect of dexamethasone and seconal is exerted on the cells of the anterior pituitary, then the absence of modification of TRH-induced PRL release, contrasting with
the inhibition of TSH secretion, indicates a different sensitivity of lactotropes and thyrotropes to identical pharmacological influences.

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References


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