Effects of dexamethasone on the hypothalamic-pituitary-thyroid axis in rats

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Abstract. Effects of dexamethasone on the hypothalamic-pituitary-thyroid axis in rats were studied. Rats given saline (group A), 25 μg of dexamethasone/100 g body weight (group B) or 500 μg of dexamethasone/100 g body weight (group C) were serially decapitated and brain tissues and blood were obtained. TRH contents in the hypothalamus, plasma concentrations of TRH, TSH, T₄, T₃ and reverse T₃ were measured by specific radioimmunoassay. TRH contents in the hypothalamus were significantly increased at 3 h in group B after dexamethasone treatment. In group C, however, they significantly increased for 1 to 3 h, but then decreased with the minimum at 20 h. TRH plasma levels significantly increased with the maximum at 4 h in group B and at 24 h in group C. TSH plasma levels were significantly decreased initially and then significantly increased with the maximum at 5 h in group B and at 24 h in group C. TSH responsiveness to TRH was significantly decreased at 1 to 3 h in group B, but in group C it was significantly decreased initially and then significantly increased. T₃ plasma levels significantly decreased at 1 to 3 h in group B and at 1 to 18 h in group C. Reverse T₃ plasma levels were significantly increased with the maximum at 3 h in group B and at 6 h in group C.

The results demonstrate that dexamethasone may act on multiple sites of the hypothalamic-pituitary-thyroid axis in rats and that its effect depends on the dose used or the time interval after dexamethasone treatment.

There are several reports concerning the effects of glucocorticoid on the hypothalamic-pituitary-thyroid axis in rats or human (Migeon et al. 1952; Ingbar & Freinkel 1956; Guillemín 1967; Wilber & Utiger 1969; Fortier et al. 1970; Nicoloff et al. 1970; Brown & Hedge 1973, 1974, 1980; Chopra et al. 1975; Ranta 1975, 1976; Scwinn et al. 1976; Pamenter & Hedge 1980). An inverse relationship between thyroid stimulating hormone (TSH) and adrenocorticotrophin has been reported (Guillemín 1967), but these findings have not been confirmed (Fortier et al. 1970; Brown & Hedge 1973). It has been reported that dexamethasone has potentiating and inhibitory effects both on the suprahypophyseal region and pituitary in rats (Brown & Hedge 1973). It has also been reported that in dexamethasone-treated rats the cold-induced TSH response was suppressed and TSH responsiveness to thyrotrophin releasing hormone (TRH) was potentiated (Ranta 1976). Glucocorticoid also has a direct suppressive effect on TSH secretion (Sowers et al. 1977). In the human, administration of a large dose of dexamethasone lowered 3,3',5-triiodothyronine (T₃) and elevated 3,3',5'-triiodothyronine, reverse T₃ (rT₃) in serum Chopra et al. 1975).

These contradictory findings may be attributed to different experimental conditions such as the glucocorticoid dose and the time interval after treatment. Therefore we studied the effects of dexamethasone on the hypothalamic-pituitary-thyroid axis in the rat, using two doses of dexamethasone and various intervals after dexamethasone treatment.

Materials and Methods

Male rats (Wistar strain) weighing 200–220 g and housed in temperature and humidity controlled quarters lighted...
from 6 a.m. to 6 p.m. were allowed laboratory chow and water ad libitum. The rats were injected ip with 0.5 ml of saline (group A), 25 μg of dexamethasone/100 g body weight (group B) or 500 μg of dexamethasone/100 g body weight (group C) without anaesthesia at various times of day and night. Rats were sacrificed between 1 and 3 p.m. After saline alone or dexamethasone administration rats were serially decapitated by a guillotine without anaesthesia, trunk blood was collected in heparinized tubes kept on ice and brain tissues were obtained by the method previously described (Mitsuma et al. 1974). After saline or dexamethasone 1 μg of synthetic TRH (Tanabe Co. Ltd., Japan) was injected iv without anaesthesia. Exactly 10 min later the rats were decapi-

![Graph showing effect of dexamethasone on TRH content in the hypothalamus and TRH plasma levels.](image)

**Fig. 1.**

Effect of dexamethasone on TRH content on the hypothalamus and TRH plasma levels. Values are expressed as the mean ± se in each group of 7 rats. ●—● saline, ○—○ 25 μg of dexamethasone/100 g body weight, ●—● 500 μg of dexamethasone/100 g body weight. US: under the limit of sensitivity. Differences from the saline-treated group are shown by * P < 0.001, ** P < 0.05.
tated by a guillotine without anaesthesia and trunk blood was collected in heparinized tubes kept on ice. TRH, thyroxine (T₄), T₃ and rT₃ concentrations in plasma or tissue were measured by specific radioimmunoassay (Mitsuma et al. 1972, 1976; Mitsuma 1978). TSH concentrations in plasma were measured by NIAMDD rat TSH radioimmunoassay kit.

Mean and standard errors of samples were calculated for each group. Student's t-test was used to evaluate the difference between group A, B and C.

Fig. 2.
Effect of dexamethasone on TSH plasma levels and TSH responsiveness to TRH. Values are expressed as the mean ± se in each group of 7 rats. ▲—▲ saline, ○—○ 25 µg of dexamethasone/100 g body weight, ●—● 500 µg of dexamethasone/100 g body weight. △ TSH are expressed as the increment of TSH plasma levels at 10 min after TRH administration. Differences from the saline-treated group are shown by * P < 0.001, ** P < 0.05.
Results

TRH content of the hypothalamus
TRH content of the hypothalamus was significantly increased at 3 h and then returned to the pre-treatment levels in group B (Fig. 1). In group C they were significantly increased at 3 h, but then significantly decreased with the minimum at 20 h (Fig. 1).

TRH plasma levels
In group B TRH plasma levels were significantly increased at 4 h and then returned to the pre-treatment levels (Fig. 1). In group C they were significantly increased with the maximum at 20 h (Fig. 1).

TSH plasma levels
In group B TSH plasma levels were significantly decreased with the minimum at 2 h, followed by an increase with the maximum at 5 h (Fig. 1). In group C TSH levels in plasma were significantly decreased with the minimum at 6 h, followed by an increase with the maximum at 24 h (Fig. 1).

TSH responsiveness to TRH
TSH responsiveness to TRH was examined as TSH plasma levels increments 10 min after TRH administration. In group B TSH responsiveness to TRH was significantly decreased with the minimum at 3 h, but then returned to the pre-treatment levels (Fig. 2). In group C TSH responsiveness to TRH was significantly decreased with the minimum at 3 h, followed by an increase with the maximum at 24 h (Fig. 2).

T₄ plasma levels
T₄ plasma levels did not change during the experiment.

T₃ plasma levels
T₃ plasma levels were significantly decreased from 1 to 2 h in group B and 3 to 18 h in group C (Fig. 3).

rT₃ plasma levels
In group B rT₃ plasma levels were significantly increased with the maximum at 2 h and then returned to the pre-treatment levels. In group C rT₃ plasma levels were significantly increased with the maximum at 6 h and then returned to pre-treatment levels (Fig. 3).

Discussion
This experiment shows that effects of dexamethasone on the hypothalamic-pituitary-thyroid axis in rats depend on the dexamethasone dose and the time interval after dexamethasone treatment.

The modifying effects of dexamethasone on the hypothalamic-pituitary-thyroid axis in rats might be due to: 1) modification of TRH release, synthesis or degradation, 2) modification of TSH release, synthesis or degradation, 3) altered sensitivity of thyrotroph to TRH, 4) altered sensitivity of thyroid gland to TSH, 5) altered thyroid hormone secretion, 6) altered distribution or degradation of thyroid hormones.

TRH contents in the hypothalamus were significantly increased at 3 h, but then significantly decreased in group C after dexamethasone treatment. In group B they were significantly increased at 1 to 3 h, but returned to the pre-treatment levels. It has been reported that TRH contents in the hypothalamus did not change 24 h after 20 μg of dexamethasone/100 g body weight in rats (Kardon et al. 1977). This discrepancy could be attributed to differences in the experimental conditions. TRH plasma levels were significantly increased with the maximum at 4 h in group B and at 24 h in group C. The dexamethasone concentration used in this experiment did not affect the inactivation of TRH immunoreactivity by plasma or brain tissues (Mitsuma & Nogimori, unpubl. data). TRH concentrations in plasma or hypothalamus may be expressed as a balance of TRH synthesis, release or degradation. Therefore, it seems likely that dexamethasone has a direct effect on the hypothalamus, possibly initially inhibiting and then stimulating TRH release.

TSH plasma levels were significantly decreased initially and then increased in group B and C after dexamethasone treatment, but peak levels and times were different in each group. It has been reported that TSH levels in serum have a diurnal rhythm (Fukuda et al. 1975). The rats were decapitated at 1 to 3 p.m. in this experiment, so the effect of diurnal TSH variation in serum could be excluded. TSH responsiveness to TRH was significantly decreased initially and then increased in group C after dexamethasone treatment. In group B TSH responsiveness to TRH was significantly decreased initially, but then returned to the pre-treatment levels after dexamethasone treatment. These data confirm a study in which TSH respon-
Effect of dexamethasone on T4, T3 and rT3 plasma levels. Values are expressed as the mean ± SE in each group of 7 rats. ▲—▲ saline, ○—○ 25 μg of dexamethasone/100 g body weight, •—• 500 μg of dexamethasone/100 g body weight. Differences from the saline-treated group are shown by * P < 0.001, ** P < 0.05.
siveness to TRH was inhibited at 3 h and enhanced at 12 h after dexamethasone treatment (Ranta 1975). Thus, dexamethasone may directly affect the pituitary by triggering TSH release or altering the thyrotroph sensitivity to TRH.

The modifying effect of dexamethasone on plasma thyroid hormone concentrations showed that T₃ plasma levels were significantly decreased initially with elevation of rT₃ plasma levels, but then followed by a return to the pre-treatment levels. These data confirm a previous study in the human (Chopra et al. 1975). These changes might be due to a dexamethasone-altered peripheral metabolism of thyroid hormones.

The findings suggest that dexamethasone may act on multiple sites of the hypothalamic-pituitary-thyroid axis in rats, and that its effect depends on the dose used and time interval after dexamethasone treatment.

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References

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