Dopamine in the pituitary adaptation to starvation in man

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Summary: To investigate the role of the dopaminergic system in the pituitary adaptation to energy deprivation, the effect of metoclopramide, a dopamine receptor blocker, on prolactin (PRL), TSH, FSH and LH secretion was investigated in 6 healthy men in the fed state and at 36 h starvation. All underwent a further 36 h of starvation on a separate occasion to assess the effect of starvation on the TSH and PRL responses to TRH and the LH and FSH responses to gonadotrophin releasing hormone (GnRH). In all subjects starvation produced the expected reduction in serum T_3 and an average decrease of 53% in the cumulative TSH response to TRH. The basal serum PRL and its response to TRH and metoclopramide remained unchanged with 36 h starvation. The FSH response to GnRH also remained unchanged, but the LH response was significantly greater during starvation. We conclude that factor(s) other than dopamine influence not only thyrotrophic activity but also other aspects of pituitary function during energy deprivation.

Introduction

Starvation is associated with a decrease in serum triiodothyronine (T_3) due to a reduction in T_3 production rate, the metabolic clearance rate remaining unchanged (Carlson *et al.*, 1977; Chopra, 1977). Although the rate of thyroxine (T_4) production is also decreased on starvation, the serum T_4 is maintained by the reduction in the rate of T_4 deiodination to T_3 . Despite the fall in serum T_3 , TSH levels either remain unchanged or decrease on energy restriction (Carlson *et al.*, 1977; Croxson *et al.*, 1977; Pamblad *et al.*, 1977; Vinik *et al.*, 1974, 1975). There is a loss of TSH diurnal variation and a diminished TSH response to thyrotrophin releasing hormone (TRH) within 36 h of fasting (Croxson *et al.*, 1977; Vinik *et al.*, 1974, 1975). This is not due to an increased sensitivity of TSH secretion to the circulating thyroid hormones for the effect of exogenous T_3 in inhibiting TSH secretion is actually diminished within 48 h of starvation (Burger *et al.*, 1980).

In rats, pituitary adaptation does not appear to be an intrinsic response since studies *in vitro* with pituitary slices from starved animals show a preservation of their response to T_4 and T_3 (Chopra *et al.*, 1978). Likewise in man, it appears that starvation lowers pituitary thyrotrophic activity not by an intrinsic pituitary mechanism but by the increased effect of an inhibitory factor(s) which then act on the pituitary,

for if the fall in serum T_3 concentration brought about by starvation is prevented by exogenous T_3 the TSH response to TRH still becomes blunted (Gardner *et al.*, 1979).

The report of Vinik *et al.* (1974) of a reduced prolactin (PRL) response to TRH on fasting might indicate increased dopaminergic activity on the pituitary in the early phases of energy restriction. It is also known that dopamine infusion will diminish not only the PRL response to TRH but also the TSH response (Scanlon *et al.*, 1978). To investigate whether enhanced dopaminergic activity is responsible for this pituitary adaptation to starvation we have studied the effects of a dopamine receptor blocker (metoclopramide) on PRL secretion in healthy men in the 'fed' state and at 36 h of starvation. As LH release can be inhibited by dopamine we have also studied the LH and FSH response to GnRH in the fed and starved states.

Subjects and methods

Six healthy euthyroid males weighing 68.2 ± 3.8 kg (mean $\pm$ s.e.), an average 1.3% above ideal weight (Metropolitan Life Insurance Company, 1960) and aged 28.7 ± 1.5 y underwent 36 h of starvation on two separate occasions. On one occasion the subjects were given 10 mg i.v. metoclopramide (Maxolon^R) after an overnight fast (i.e. 'fed' state) and at 36 h of starvation. On another occasion the subjects underwent combined TRH (200 μ g) and GnRH (100 μ g) test again

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after an overnight fast and at 36 h of starvation. The protocol required the subject to fast initially from food and drink, except water, from midnight during the 'fed' state and at 0800 h undergo one or other of the tests. The subjects then ate normally. After an evening meal the subject starved, except for water, for 36 h when he then underwent the same test again at the same hour.

Blood samples were taken prior to intravenous TRH and GnRH and at 30, 60 and 120 min afterwards. Blood samples for the metoclopramide test were taken at -15 and 0 min before and at 5, 10, 20, 30, 45, 60, 90 and 120 min after injection. All test samples were measured for PRL, TSH, LH and FSH by specific radioimmunoassay (for methods see Kelly *et al.*, 1978). Blood was also taken in the fed state and at 36 h starvation on both occasions and measured by radioimmunoassay (Kelly *et al.*, 1978) for total T_4 and T_3 . Samples for a single subject were measured together in one assay. The mean intra-assay coefficient of variation was 7.7% for TSH, 7.2% for PRL, 9.0% for LH, 6.0% for FSH, 4.8% for T_4 and 3.0% for T_3 .

Fully informed consent was given by each subject and the project was approved by the Royal Postgraduate Medical School and Hammersmith Hospital Ethical Committee. Statistical analysis was by the paired Student's *t* test and significance is considered present if $P < 0.05$. Values are given as mean $\pm$ s.e. The results will be referred to as obtained in the 'fed' state representing overnight fast or in the 'starved' state representing 36 h starvation.

Table 1 Serum total T_4 , T_3 and basal prolactin (mean $\pm$ s.e.) in fed state and at 36 h of starvation during the two separate occasions of starvation

	'Fed' state	'Starved' state
First occasion		
Thyroxine nmol/l	110.0 $\pm$ 8.3	112.0 $\pm$ 12.0
Triiodothyronine nmol/l	2.25 $\pm$ 0.12	1.90 $\pm$ 0.13*
Prolactin μ g/l	7.9 $\pm$ 0.8	7.0 $\pm$ 1.3
Second occasion		
Thyroxine nmol/l	104.5 $\pm$ 6.3	112.7 $\pm$ 7.3
Triiodothyronine nmol/l	2.17 $\pm$ 0.27	1.73 $\pm$ 0.11†
Prolactin μ g/l	5.8 $\pm$ 1.1	6.1 $\pm$ 2.2

Mean $\pm$ s.e. significance of difference between fed and starved states; * $P < 0.01$; † $P < 0.02$.

Results

Starvation for 36 h did not alter the serum T_4 but did produce a significant reduction in serum T_3 on both occasions, falling on average to about 80% of basal (Table 1). Starvation was associated with a significant decrease in the TSH response to TRH at all times studied (Figure 1) with an average cumulative decrease of 53% (fed 15.4 ± 1.8 ; starved 7.3 ± 1.6 mU/l). Basal serum PRL levels and the PRL response to TRH were unaltered by 36 h of starvation (Figure 1). Although the mean incremental PRL responses to meto-

Figure 1 TSH (a) and PRL (b) responses to TRH in the fed state (—) and at 36 h of starvation (...). Mean $\pm$ s.e. ** $P < 0.01$.

Figure 2 Incremental prolactin response to metoclopramide (10 mg) in the fed state (—) and at 36 h of starvation (...). At no single point in time after metoclopramide was the PRL increment significantly higher in the starved state. Mean $\pm$ s.e.

clopramide were higher in the starved state (Figure 2) this failed to reach significance at all the times studied. The 95% confidence limits were -5.5 to 33.3 for peak response. The TSH, FSH and LH responses to metoclopramide were so slight that no significant changes were noted on comparing the values obtained in the fed and starved states (data not shown).

The response of LH to GnRH was significantly greater in the starved state at the 60 min mark (Figure 3). However, serum FSH both basally and in response to GnRH (Figure 3) did not rise significantly with starvation.

Discussion

Our findings that starvation does not alter PRL basally or its response to TRH or metoclopramide would suggest that dopaminergic tone is not increased after 36 h starvation in man. The enhanced LH response to GnRH would also be in keeping with this as dopamine inhibits LH release (Judd *et al.*, 1978). Our findings are, however, in marked contrast to that reported by Vinik *et al.* (1974) who found a reduction

Figure 3 LH (a) and FSH (b) responses to GnRH in the 'fed' state (—) and at 36 h of starvation (...). Mean $\pm$ s.e. * $P < 0.02$.

in the PRL response to 100 µg of TRH in 9 male subjects after a similar period of fasting. Nevertheless, our findings are supported by the report of Burger *et al.* (1980) who also found no change in the PRL response to 200 µg of TRH in both men and women at 48 h of starvation. Possibly the lower dosage of 100 µg of TRH as used by Vinik *et al.* (1974) may account for this disparity of response.

It has been recently suggested that starvation might enhance peripheral dopaminergic activity as dopamine receptor blockade decreased the total ketone body levels in fasted rats (Belsa-Malpica *et al.*, 1981). However, this may not apply to man or necessarily to all peripheral tissues in animals for the following reasons. Firstly, we have found that venous plasma dopamine concentrations in man actually show a slight decline on energy reduction (personal observation). Secondly, the neurotensin response to metoclopramide is blunted in the starved state and, thirdly, metoclopramide, which in the fed state causes an immediate decrease in insulin release, fails to do this if injected at 36 h starvation, suggesting that peripheral dopaminergic action on the islets is reduced

with starvation in man (Wood *et al.*, 1981). In animals, energy reduction also appears to be associated with an actual decrease in brain dopaminergic activity (Biggio *et al.*, 1977). It, therefore, appears that there are other factors besides dopaminergic activity which are involved in the modulation of the thyrotropic-thyroidal axis in starvation and that these factors also affect other aspects of pituitary function. If this factor(s) could be found and its action reversed then it might be possible to prevent the fall in metabolic rate associated with energy restriction and thus enhance the weight loss of obese patients on energy restriction diets.

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