SPECIFIC INHIBITION BY SOMATOSTATIN OF GROWTH HORMONE RELEASE AFTER HYPOGLYCAEMIA IN NORMAL MAN

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SUMMARY

In normal man, synthetic linear somatostatin (growth hormone-release inhibiting hormone) inhibits the growth hormone response to insulin induced hypoglycaemia, but has no influence on plasma levels of cortisol, prolactin, TSH and FSH.

INTRODUCTION

Brazeau et al. (1973) and Burgus et al. (1973) showed that a cyclic tetradecapeptide isolated from sheep hypothalamus, and subsequently synthesized in the linear form, inhibited secretion in vitro of immunoreactive rat and human growth hormones; this synthetic compound also inhibited in vivo the release of growth hormone in rats. Therefore, Brazeau et al. (1973) suggested that this peptide could be a physiological growth hormone-release inhibiting hormone (GH-RIH), and proposed to name it ‘somatostatin’.

In the present study, we investigated the effect of synthetic somatostatin on immunoreactive growth hormone response to insulin induced hypoglycaemia in normal man. We also studied the possible influence of this peptide on the secretion of several other pituitary hormones during the same experiments.

SUBJECTS AND METHODS

Six normal males were investigated. One was 15 years old, the other five were aged 23–33 years. All studies were started between 8 and 9 a.m., after an overnight fast. Two indwelling plastic needles were inserted into forearm veins; one for blood sampling, the other for drug administration. A fresh solution of synthetic linear somatostatin in saline, 250 µg/ml, was prepared immediately before each experiment. At 0 min, 0.12 U/kg of insulin ‘Actrapid’ Novo were injected rapidly through one of the indwelling needles; this needle was then washed with saline, and 250 µg of somatostatin were injected by the same way over

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30 sec. Thereafter, 500 μg of somatostatin in 150 ml saline were infused intravenously over a period of 60 min. Control studies were performed in the same subjects at intervals of 1 week to 2 months, using the same protocol except that no somatostatin was administered. All subjects developed clinical signs of hypoglycaemia, but no additional side-effect, attributable to somatostatin, was observed.

Blood samples were obtained at frequent intervals from −60 to 180 min of the tests. Blood sugar was determined with a Technicon AutoAnalyzer (Hoffman, 1937). Plasma cortisol was estimated by a competitive protein-binding radioassay (Leclercq et al., 1969). Plasma levels of growth hormone (GH) (Virasoro et al., 1971), thyrotropin releasing hormone (TRH) (Odell et al., 1967; Golstein & Vanhaelst, 1974) and follicle stimulating hormone (FSH) (Odell & Hescox, 1971) were measured by radioimmunological methods. Plasma prolactin was determined using a homologous ovine radioimmunoassay (L’Hermite et al., 1972; Nokin et al., 1972). Plasma levels of prolactin were evaluated by reference to a serum pool, rich in prolactin, which was arbitrarily considered to contain 1 unit of immunoreactive prolactin per ml. It was subsequently found that 1 mU of this standard preparation corresponds to 2.3 milli-ampoules of the standard prolactin preparation 71/167 of the Medical Research Council, Great Britain.

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**RESULTS**

Results are summarized in Fig. 1. Individual data for GH are shown in Table 1. Statistical significance was calculated using the 't' test with pairing.
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Fig. 1. Mean values of blood sugar, and of plasma GH, cortisol, prolactin, TSH and FSH during somatostatin (○) and control (●) experiments. Vertical bars denote standard errors of the mean.
Blood sugar fell markedly after the injection of insulin, to reach in all cases minimum levels lower than 35 mg/100 ml. Mean minimum levels were observed at 25 min in both series of experiments. Absolute minimum values were significantly lower in the somatostatin studies than in the control experiments ($P<0.02$), but the magnitude of the fall was similar in both series ($P>0.60$).

No significant change occurred in TSH and FSH levels during somatostatin experiments. The patterns of cortisol and prolactin responses to hypoglycaemia were not modified by the concomitant administration of somatostatin. Except in two subjects who presented a slight elevation during the basal period of one of their tests, plasma levels of GH remained fairly constant up to 25 min in both series of experiments. Thereafter, a steep increase of GH values occurred in control studies, whereas in five of six subjects no noticeable elevation was observed until the end of the infusion (60 min) in somatostatin experiments; thus, at 30 and 60 min, GH values in control studies were significantly higher than in somatostatin experiments ($P<0.05$ and $<0.01$ respectively). After the somatostatin infusion was stopped, plasma levels of GH rose rapidly in all subjects.

**DISCUSSION**

The present study shows that intravenous administration of synthetic linear somatostatin to normal adult males generally suppresses the growth hormone response to insulin induced hypoglycaemia. This inhibitory effect rapidly disappears when somatostatin administration is stopped. It is not clear why somatostatin had no effect in one of our six subjects; it is tempting (but premature) to speculate that this could be due to his youth (15 years).

It appears that somatostatin is usually a powerful inhibitor of growth hormone response to a most potent and constant pharmacological stimulus acting at the hypothalamic level (Roth et al., 1963). At the dosage used, this action seems to be specific, since the normal cortisol and prolactin responses to hypoglycaemia were unaffected; moreover, circulating levels of TSH and of FSH, which are not consistently modified by hypoglycaemia (Franchimont & Legros, 1970; Copinschi et al., 1972), remained unchanged during somatostatin administration.

The present data extend to normal man the observations previously made in vitro on human and animal pituitary cells and in vivo in animals (Brazeau et al., 1973; Lovinger et al., 1973; Vale et al., 1973). They confirm the results of Hall et al. (1973), who used the cyclic form of the peptide; moreover, Siler et al. (1973) recorded the suppression by linear somatostatin of the growth hormone response to arginine and L-dopa in normal man, and Hansen et al. (1973) reported the inhibition by cyclic somatostatin of the plasma growth hormone rise induced by exercise in normal and diabetic subjects. Therefore, it appears that both linear and cyclic forms of somatostatin inhibit growth hormone secretion in man.

Although these data do not unequivocally demonstrate that this tetradecapeptide plays a physiological role in man, they add further support to this hypothesis.

**ACKNOWLEDGMENTS**

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REFERENCES


