SHORT COMMUNICATION

Plasma growth hormone concentrations in Huntington's chorea

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Summary

1. Growth hormone secretion was assessed in nine control subjects and nine patients with Huntington's chorea.

2. Early-morning fasting plasma samples from patients with Huntington's chorea contained abnormally high concentrations of growth hormone.

3. The suppression of growth hormone after oral glucose in choreic patients, unlike the control subjects, occurred at irregular intervals after the glucose was given and was followed, again at irregular intervals, by an exaggerated rebound phase.

4. The response to intravenous insulin was not markedly abnormal in choreic patients. However, there was a significant increase in the rate of rise of growth hormone concentration in the first half an hour after the insulin injection when compared with control subjects.

Key words: glucose, growth hormone, Huntington's chorea, insulin.

Introduction

The neuropathological findings reported by Vogt & Vogt (1952) in the hypothalamus of patients dying with Huntington's chorea have received little attention. More recent work (Bruyn, 1973) has demonstrated the existence of distinct lesions in areas of the hypothalamus, which, in the rat, may be concerned in the regulation of secretion of growth hormone (Martin, 1971). Since the secretion of growth hormone in response to hypoglycaemia is mediated via the hypothalamus (Abrams, Parker, Blanco, Reichlin & Doughaday, 1966) we decided to investigate the responsiveness of the hypothalamic mechanisms controlling the secretion by subjecting patients with Huntington's chorea to a glucose tolerance test and an insulin provocation test.

Materials and methods

Nine patients with Huntington's chorea and nine age- and sex-matched control subjects were subjected to a glucose tolerance test (100 g orally) and an insulin provocation test (0·1 i.u./kg intravenously). All subjects were fully informed of the aims, procedures and risks of the investigations and their consent was obtained before proceeding with the study. Subjects in both groups were taking their usual diets before the tests. The glucose test was always administered the day before the insulin test. None of the subjects was taking any drugs, with the exception of three control subjects (treated with dihydrocodeine, ethinyloestradiol and clonidine) and these did not take any drugs on the day of the tests. None of the subjects was obese (i.e. greater than 15% over the ideal body weight). The mean weight of the control group was 66 kg and that of the patients with Huntington's chorea was 56 kg. None of the control subjects had a history of metabolic or endocrine abnormality. The mean age of the chorea group was 43 years and that of the control group 41 years. After an overnight period of fasting by the subjects, an indwelling cannula was
inserted into a forearm vein and connected to a slowly running sodium chloride (saline; 0.154 mmol/l) infusion. After a further 30 min, three baseline blood samples were withdrawn at 30, 15 and 0 min before either glucose or insulin was given. Blood was then kept after collection until the end of the test, at 4°C, and centrifuged for 10 min at room temperature. Plasma was then separated and stored at −20°C until analysed for growth hormone by the method of Hartog, Gaafar, Meisser & Frazer (1964). Values are reported as munits/l. Although three base-line blood samples were drawn from control subjects for other studies only one of these was analysed for growth hormone. Glucose was estimated on whole blood with a Technicon Autoanalyzer Mk. 2, the standard neocuproine method (AA 11-02) being used. Results are given as mean values ± SEM. Statistical significance was calculated by Student's t-test, unless otherwise stated.

Results

Growth hormone

As shown in Fig. 1, the fasting concentration of growth hormone at zero time (26.7 ± 7.4 munits/l) was significantly greater than that in control subjects (1.6 ± 0.3 munits/l; P < 0.01). The response to glucose appeared abnormal in that there was no mean reduction in secretion of growth hormone during the hyperglycaemic phase. However, if the results of individual patients were studied a different pattern emerged: in seven out of the nine patients the high resting hormone secretion was indeed followed by suppression at some period during hyperglycaemia. This suppression did not appear in the mean values since the timing of the suppression varied from patient to patient. Similarly, in all of the choreic patients except one, there was an exaggerated rebound in the plasma growth hormone concentration at various time-intervals after glucose, the hormone concentrations returning to the high resting values and in two cases well above their high resting base-line values. This feature is, again, not readily observed in the mean values. The base-line concentration of growth hormone before insulin was significantly greater in the patients with Huntington's chorea (8.2 ± 2.7 munits/l) than in the control group (3.1 ± 1.1 munits/l; P < 0.05). However, within the choreic group, the fasting concentration of growth hormone at 0 min in the glucose test (26.7 ± 7.4 munits/l) was significantly greater than at 0 min in the insulin test (8.2 ± 2.7 munits/l; P < 0.05). In the group of patients with Huntington's chorea, the response to insulin differed from that of the control group only in one respect. The concentration of growth hormone 30 min after insulin was significantly greater in the patients with Huntington's chorea (45.6 ± 23.0 munits/l) than in the control group (45.6 ± 23.0 munits/l; P < 0.05, by Mann–Whitney test). During the first half hour after insulin, therefore, there was a much greater rate of increase in concentration of growth hormone in the choreic group than in the control group. However, the peak height of secretion of growth hormone did not differ significantly in the two groups. Only in one choreic patient was there a normal response in the glucose tolerance test ('normality' being defined as occurring when all the individual hormone values for a given patient lie within the limit of the highest values of the control group at their respective time-points). (The limits for our control group were at 3.0, 2.5, 2.5 and 5.3 munits/l at 0, 1, 2 and 2½ h respectively.) There was no apparent correlation between the degree of the abnormalities seen and the duration of disease or of the age of the patient in either test.

Blood glucose

Glucose tolerance test. Fasting, peak and 2 h glucose concentrations were 4.3 ± 0.1, 7.3 ± 0.7, 6.6 ± 0.6 mmol/l in the choreic group, and 4.1 ± 0.1,
Discussion

While this work was in progress, a report was published by Podolsky & Leopold (1974) which showed abnormalities in secretion of growth hormone in patients with Huntington's chorea after an oral glucose load. The main difference between their results and ours was in the fasting hormone concentrations, which we found to be increased in choreic patients compared with the control group whereas they found no difference. Otherwise, the values throughout the rest of their glucose tolerance test were comparable with ours. There is no obvious explanation for the difference in fasting growth hormone concentrations, although there are various possible reasons.

Anxiety is known to be a stimulus for the release of growth hormone. Degrees of anxiety between different patients are hard to measure, but this factor may explain the tendency towards higher fasting hormone concentrations on the first day, when compared with the second-day results in patients with Huntington's chorea. On the other hand, one might expect the anxiety provoked by the experimental arrangements to affect control subjects as well as choreic patients. Their growth hormone concentrations, however, were not affected.

A second factor, known to stimulate release of growth hormone, is exercise. This, however, does not seem likely, as it has been shown (Hansen, 1970) that only very severe exercise stimulates release of growth hormone in normal subjects, and the degree of choreic movement in our subjects could not be said to constitute severe muscular exercise. It has been demonstrated (Passa, Gaville & Canivet, 1974) that moderate exercise, at a level which does not cause release of growth hormone in normal subjects, can stimulate release in diabetic patients. Since we did not find any evidence of abnormal glucose tolerance in our group of choreic patients, this explanation cannot account for our results.

Thus it seems probable that either neuropathological or functional changes within the hypothalamic systems controlling release of growth hormone are responsible for our results. The changes reported by Bruyn (1973) involved the lateral hypothalamic nucleus and the ventromedial hypothalamic nucleus. Although stimulation of the latter area causes alterations in secretion of growth hormone in the rat (Martin, 1971), these results should be treated with caution, as there appears to be considerable species variation in the mechanisms controlling the secretion.

The possible role of functional changes in the hypothalamus should also be outlined. It is known that release of growth hormone in man is stimulated by dopaminergic mechanisms (Lal, de la Vega, Sourkes & Friesen, 1973), and it has been proposed that choreic movements result from supersensitivity of central dopamine receptors (Klawans, 1970). It is tempting therefore to link the growth hormone responses with a dopaminergic abnormality. Since, however, no changes have yet been found in dopamine concentrations in brains from choreic patients post mortem, either in the basal ganglia or in the hypothalamus (Bird, 1976), this suggestion must remain speculative.

Serotoninergic mechanisms appear to play a role in the regulation of growth hormone secretion in the rat (Smythe & Lazarus, 1973). However, the significance of serotonin in the regulation of this hormone in man is controversial (Imura, Nakai & Yoshimi, 1973; Müller, Brambilla, Cavagnini, Peracchi & Panerai, 1974). Nevertheless, there are widespread metabolic disturbances in patients with Huntington's chorea, involving plasma free fatty acids, free tryptophan and the branched-chain amino acids (O. T. Phillipson and E. D. Bird, unpublished work). Central serotoninergic mechanisms are known to be sensitive to alterations in these factors in the rat (Curzon, Friedel, Kantamaneni, Greenwood & Lader, 1974; Fernstrom & Wurtman, 1972; Biggio, Fadda, Fanni, Tagliamonte & Gessa, 1974) and in man (Pérez-Cruet, Chase & Murphy, 1974). Therefore serotonin may play a role in the production of the abnormalities in growth hormone secretion described in this paper. Clearly, further studies in this area are needed.

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References


