Twenty-four hour plasma levels of growth hormone and prolactin in Huntington's disease

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SUMMARY Since hypothalamic neural degeneration is thought to occur in individuals with Huntington's disease, anterior pituitary hormone secretion which is in part regulated by the hypothalamus, was postulated to be altered in patients with this disease. To test this proposal, nine females with Huntington's disease were matched with controls to participate in a 24-hour basal level study of growth hormone and prolactin concentration in plasma. Patients who were free from all centrally active medication for at least six months and normal volunteers had blood sampled at 30-minute intervals over 24 hours in a minimal stress environment. The results demonstrated that plasma levels of growth hormone were elevated throughout the 24-hour time period in Huntington's disease individuals. Despite the elevation, the mean growth hormone curve of the Huntington's disease group retained characteristics similar to the control curve throughout the 24-hour time. Basal 24-hour plasma prolactin concentrations in Huntington's disease patients showed no difference from those in control individuals.

Huntington's disease is an autosomal dominant neurological disorder characterised by ganglion cell degeneration throughout the brain. The well known pathological changes in basal ganglia and, to a lesser extent, in cerebral cortex have been associated with the involuntary movements and cognitive deterioration which occur in the illness.¹ Neuronal loss and degenerative changes associated with selective biochemical abnormalities have also been reported to involve the hypothalamus.²⁻⁴ These observations suggest that alterations in hypothalamic-modulated function may occur in Huntington's disease. Since the hypothalamus influences the release of hormones from the anterior pituitary, characteristic abnormalities in the secretion of growth hormone (GH), and prolactin (PRL), might be expected.

Numerous previous investigations have attempted to evaluate basal growth hormone and prolactin plasma levels in patients with Huntington's disease (reviewed in ref 5). However, these studies have often drawn conflicting conclusions about whether

plasma GH and PRL values are increased, decreased, or remain within the normal range in Huntington's disease individuals. GH and PRL are both episodically released in a periodic pattern; thus, single or even multiple closely spaced measurements can be insufficient to fully describe basal levels. Because implications important to our understanding of the pathophysiology of Huntington's disease might be drawn from alterations in anterior pituitary hormone control, plasma GH and PRL levels were studied with a 30-minute repeated sampling technique over a 24-hour period in Huntington's disease subjects.

Methods

Nine females with Huntington's disease and an equal number of normal controls were hospitalised for study. Six of the Huntington's disease patients had the classical adult-onset form of this disorder; the three remaining individuals had the rigid-akinetic variant. All had a positive family history. Mean ($\pm$ SD) age of the Huntington's disease group was 43 ± 12 years and of controls was 45 ± 14 years. Five of the nine Huntington's disease subjects had never been treated with antipsychotic drugs; furthermore, none of the patients or controls received any regularly prescribed centrally active drugs for at least six months prior to admission to this study. Menstruating women were tested

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during the luteal phase of their cycle. All study subjects gave their informed consent before participating in this investigation.

The 24-hour sampling procedure began by the placement of an indwelling heparinised intravenous catheter in the forearm. Following a 45–60 minute stabilisation period, blood sampling began (5 ml/sample) and was repeated at 30 minute intervals for 24 hours. Immediately after collection, specimens were placed on ice; plasma was separated from whole blood within one hour and frozen at -70°C until assay. At night, the sleep of each subject was monitored by electroencephalography to document the duration of total sleep and the proportion of slow wave sleep. All subjects were maintained on regular hospital diet given on a fixed schedule (0800 h, 1230 h, 1700 h) and allowed only to ambulate quietly within the confines of their own rooms.

A double antibody radioimmunoassay was used to measure levels of GH and PRL in plasma. Materials from the Hormone Distribution Program of the National Insti-

Table

	Growth hormone (ng/ml)	
	Huntington's disease	Controls
24 Hour mean	4.5 ± 0.4	2.3 ± 0.35
Daytime (0800 h–1530 h)	3.5 ± 0.36	1.9 ± 0.15
Evening (1600 h–2330 h)	4.4 ± 0.40	2.8 ± 0.5
Night (2400 h–0730 h)	5.5 ± 0.7	3.5 ± 0.59
	Prolactin (ng/ml)	
	Huntington's disease	Controls
24 Hour mean	17.0 ± 2.0	13.9 ± 1.8
Daytime (0800 h–1530 h)	11.4 ± 0.5	9.1 ± 0.71
Evening (1600 h–2330 h)	13.9 ± 0.4	10.0 ± 0.34
Night (2400 h–0730 h)	25.6 ± 1.6	22.6 ± 1.6

Fig 1 (a) Plasma levels of GH (ng/ml) in nine Huntington's disease females (●) and in nine female controls (○) over 24 hours of continuous sampling. Significantly greater GH values obtained in the Huntington's disease population ($p < 0.005$). (b) Plasma levels of PRL (ng/ml) in nine Huntington's disease females (●) and nine matched controls (○) over a 24 hour sampling period. No significant differences obtained between the two groups, even though the Huntington's disease curve generally remained above the curve for controls.

tute of Arthritis, Diabetes, and Digestive and Kidney Diseases were used with the accompanying assay methodology. All the samples from a single patient and that patient's matched control were analysed in a single assay. The within-assay and between-assay error of the HGH radioimmunoassay were 5.1% and 13.5% respectively. Plasma levels of cortisol were determined with a double antibody radioimmunoassay procedure using the RIANEN Assay System (New England Nuclear, 084, 085). The results were analysed using a factorial or split-plot analysis of variance (ANOVA) with repeated measures. Two group comparisons were made with specialised Dunnett's multiple-comparison test.⁶ A time series analysis was done on the 24-hour GH data using a frequency domain approach.

Results

Plasma GH concentrations over the entire 24-hour period were significantly higher in Huntington's disease patients than in the control subjects ($F = 10.8$; $df = 1, 16$; $p < 0.005$) (fig 1a) as tested with the repeated measures ANOVA statistic; specific times of significant elevation were 0300 h, 0930 h, 2000 h, and 2400 h. In addition, the mean GH level in the Huntington's disease subjects during the 24-hour period was elevated as compared with controls (table). Similarly, mean GH values during certain subportions of the 24 hour period, daytime (0800 h–1530 h), evening (1600 h–2330 h), and night (2400 h–0730 h) were increased. Despite these changes, the pattern of secretory episodes in the Huntington's disease group remained indistinguishable from those found in the control individuals; in a time series analysis, the Huntington's disease curve did not differ from the normal in average spectral density.

Plasma levels of PRL were consistently higher in the Huntington's disease subjects than in controls; however, the difference did not attain statistical significance ($F = 1.35$; $df = 1, 16$; $p < 0.26$) (fig 1b). Similarly, neither mean PRL values during the 24-

hour period, nor daytime/evening/night mean levels were significantly different between groups (table).

Sleep EEG recordings (mean $\pm$ SD) showed a reduced amount of total sleep in patients compared with control individuals (332 ± 29 min and 394 ± 13 min respectively), but a similar duration of slow wave sleep (78 ± 14.5 min and 92.7 ± 18.5 min respectively).

The possible effect of stress as a factor contributing to elevations in the plasma content of GH or PRL was evaluated by comparing mean AM plasma cortisol levels (sampled at 0730 h, 0800 h, 0830 h) and mean PM plasma cortisol levels (sampled at 2200 h, 2230 h, 2300 h) between the Huntington's disease patients and normal control groups. The mean ($\pm$ SD) morning and evening plasma cortisol levels (ng/ml) in the Huntington's disease patients was 205 ± 10 and 99 ± 14 , respectively, and in the control subjects was 151 ± 13 and 60 ± 15 , respectively. The differences between Huntington's disease and normal subjects for either morning or evening samples failed to reach statistical significance.

The possibility that the involuntary movements in some of the Huntington's disease patients influenced plasma GH and PRL concentrations was evaluated by comparing results from three of the nine-member Huntington's disease cohort who had the non-choreatic, rigid-akinetic form of this disorder. Mean ($\pm$ SD) 24 hour levels of GH (4.03 ± 0.28 ng/ml) or PRL (16 ± 1.7 ng/ml) in these individuals did not differ significantly from the values found in the remaining six patients with the classical, choreatic form of Huntington's disease. Moreover, the plasma GH elevations in the Huntington's disease group continued during the evening and night in both choreatic and nonchoreatic subjects when normal sleep patterns were demonstrated by EEG but no involuntary movements could be observed.

Discussion

The present data may help clarify the conflicting reports on basal levels of plasma GH and PRL in Huntington's disease. Prior studies have found basal GH levels either elevated⁷⁻⁹ or unchanged¹⁰⁻¹² from controls, and basal PRL levels either depressed,¹³ elevated,^{11, 14} or unchanged.^{9, 15-17} The results of this study indicate that the basal plasma levels of GH are significantly increased in Huntington's disease subjects while basal PRL levels remain within the normal range. The GH findings in the Huntington's disease population could reflect either an increase in GH secretion from the anterior pituitary, or an alteration in its metabolism. Histopathologic changes already identified in the hypothalamus of Huntington's disease individuals provide the anatomical basis for

Durso, Tamminga, Ruggeri, Denaro, Kuo, Chase

postulating an alteration in the regulation of GH secretion to account for the abnormality. Since PRL levels remained normal, the present results do not support previous conclusions¹¹⁻¹³ that a generalised abnormality in the dopamine system, which contributes to the regulation of both GH and PRL, occurs in Huntington's disease.

The potential neural basis of the observed GH abnormality could be a disorder of either of the two hypothalamic factors regulating pituitary GH synthesis and release. Growth Hormone Releasing Factor (GRF) physically stimulates GH secretion;¹⁸ while Somatotropin-Release-Inhibiting Factor, somatostatin, tonically inhibits GH release.¹⁹ Because somatostatin appears to mediate tonic and inhibitory control of GH,²⁰ a loss of this peptide could disinhibit GH secretion, thus elevating plasma GH. If the somatostatin effect is diminished in Huntington's disease, due to a loss of inputs to the hypothalamic somatostatin system, to a degeneration of somatostatin-containing neurons, or to a hyporesponsivity of relevant somatostatin receptors, resultant plasma GH levels would be increased. Indeed, levels of somatostatin in spinal fluid of Huntington's disease subjects have been reported to be substantially reduced.²¹ However, diminished somatostatin levels in suprachiasmatic areas of hypothalamus have not been confirmed.²² Further evaluation of the somatostatin system in Huntington's disease may therefore be of interest.

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