Growth hormone and prolactin response to bromocriptine in patients with Huntington's chorea

R. J. CHALMERS, R. H. JOHNSON, H. J. KEOGH,
AND R. N. NANDA

From Glasgow University Department of Neurology, Institute of Neurological Sciences,
Southern General Hospital, Glasgow

SUMMARY The growth hormone (hGH) and prolactin (hPRL) responses to oral bromocriptine were studied in two groups of patients with Huntington's chorea and in seven healthy control subjects. The patients included six patients who had previously been treated with phenothiazines and six patients who had not received phenothiazine treatment. All medication was stopped 72 hours before the investigation which involved taking blood samples for up to 210 minutes after taking bromocriptine (2.5 mg). Plasma samples were analysed for hGH and hPRL. There was no significant difference in basal hGH concentrations between the patients and control subjects. The hGH response to bromocriptine varied in the individual patients but the concentrations were significantly lower in the patients compared with the controls between 160 and 210 minutes. The basal concentrations of hPRL were also not different, apart from the findings of elevated hPRL concentrations in three patients previously treated with phenothiazines. The patients and control subjects showed a consistent fall in hPRL concentrations after taking bromocriptine. The lower peak hGH response to bromocriptine found in the patients suggests that there may be an alteration of dopaminergic neurones mediating hGH release.

Huntington's chorea is an inherited degenerative disorder of the nervous system. There is evidence of biochemical abnormalities in patients with the disorder. This includes the finding of low levels of γ aminobutyric acid (GABA) and its synthesising enzyme (glutamic acid decarboxylase). Dopamine levels are normal but dopamine receptor activity may be disturbed (Barbeau, 1973; Perry *et al.*, 1973; Bird and Iversen, 1974; Stahl and Swanson, 1974; Bird *et al.*, 1976). Patients with Huntington's chorea often show weight loss and excessive sweating (Bruyn, 1968), and this may be related to altered hypothalamic function. It has recently been reported that the growth hormone (hGH) response to insulin induced hypoglycaemia in patients with the disorder showed an earlier elevation than controls (Keogh *et al.*, 1976; Phillipson and Bird, 1976), and it was suggested that this may be due to increased sensitivity of dopamine receptors in the hypothalamus mediating hGH release.

Bromocriptine is a specific dopamine receptor agonist which produces an elevation of hGH and depresses prolactin (hPRL) concentrations in normal subjects (del Pozo *et al.*, 1972; Cammani *et al.*, 1976). We, therefore, decided to investigate the hGH response to bromocriptine in patients with Huntington's chorea to determine if there was any evidence for altered sensitivity of dopamine receptors mediating hGH release.

Subjects and methods

Twelve unrelated patients with chorea and a positive family history of Huntington's chorea were studied. The first group were inpatients in Hartwood Hospital, Lanarkshire under the care of Dr J. Bolt. They were all receiving a variety of drugs including phenothiazines. Six patients, two males and four females aged 43-53 years (mean 47 years), were studied. The second group consisted of five outpatients and one inpatient from Hartwood Hospital who had not received treatment with phenothiazines. The six patients comprised two males and four females aged 47-68 years (mean 59 years). Seven healthy control

Address for reprint requests: R. J. Chalmers, Lecturer in Nutrition, The Queen's College, Glasgow, 2 Park Drive, Glasgow, Scotland.

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subjects, four males and three females aged 23–55 years (mean 44 years), were also studied. Consent was obtained after the purpose and procedure had been explained to the patients and their relatives. The control subjects all agreed to take part in the investigation.

Drug medication was stopped 72 hours before the investigation which was carried out in the morning after an overnight fast. The half life of hGH is relatively short (20–30 min), and we, therefore, decided to take blood samples at 10 min intervals during the period of the hGH response. Blood samples (10 ml) were taken from a cannula in an antecubital vein before and at 30, 60, 90, 120, 130, 140, 150, 160, 170, 180, and 210 minutes after an oral dose of bromocriptine (2.5 mg). Blood samples were collected in heparinised tubes for later separation of plasma. The plasma samples were analysed by a radioimmunoassay technique (Sorin, Gruppo Radiochimica, Italy) for hGH (Morgan, 1966) and hPRL (Reuter *et al.*, 1976). The growth hormone concentrations are expressed in terms of the World Health Organisation First International Reference Preparation of Growth Hormone, 66/217 1 mg=2 IU. The radioimmunoassay kits were supplied by Eurotope Laboratory Services, London. Significance of difference was examined with the Mann-Whitney nonparametric U test for small samples (Mann and Whitney, 1947).

Results

Details of the recent medication for the six in-patients who had received phenothiazines before the investigation is given in Table 1.

PLASMA GROWTH HORMONE (hGH) (TABLE 2)

Patients treated with phenothiazines There was no significant difference between the basal hGH concentrations of the patients and controls before

taking bromocriptine. All the controls showed an increase in hGH concentrations after bromocriptine but the response of the patients was significantly lower than the controls at 160, 170, 180, and 210 minutes. Four of the patients showed an increase in hGH concentrations after bromocriptine but only three showed a peak hGH response greater than 10 mu/l and the remaining two patients failed to show a response.

Patients not treated with phenothiazines There was no significant difference in the resting hGH concentrations before bromocriptine between the patients and controls. Only three of the patients showed a rise in hGH concentrations after taking bromocriptine and only one had a peak greater than 10 mu/l. The hGH concentrations of the patients were significantly lower than the corresponding values for the controls at 150, 160, 170, 180, and 210 minutes.

PLASMA PROLACTIN (hPRL) (TABLE 3)

Patients treated with phenothiazines Basal hPRL concentrations were markedly elevated (>1000 mu/l) in the two patients who failed to show an hGH response and raised (900 mu/l) in another patient. Basal hPRL concentrations in the remaining four patients were within the range of the corresponding values for the controls (60–440 mu/l). Both the patients and the control subjects showed a consistent fall from basal hPRL concentrations after bromocriptine.

Patients not treated with phenothiazines There was no significant difference in hPRL concentrations between patients and controls either before or after taking bromocriptine. Four of the five patients showed a consistent fall from resting hPRL concentrations after taking bromocriptine.

Discussion

Biochemical assay of corpus striatum obtained post mortem from patients who have suffered from Huntington's chorea shows a reduction of GABA and glutamic acid decarboxylase—the enzyme which synthesises GABA—and normal levels of dopamine (Perry *et al.*, 1973; Bird and Iversen, 1974; Stahl and Swanson, 1974). There is evidence for a relationship between GABA and dopamine-releasing neurones as elevation of brain GABA levels by inhibition of GABA transaminase alters dopamine turnover (Shoulson *et al.*, 1976). The development of the hyperkinetic condition characteristic of the disorder may be related to a change in the interrelationship between dopamine and GABA-containing neurones. Although dopamine levels are normal, dopamine receptors may

Table 1 Details of six patients with Huntington's chorea and medication received during treatment

Patient	Sex	Age (yr)	Medication
DG	M	53	Chlorpromazine
MN	M	43	Benzhexol Chlorpromazine
AR	F	47	Orphenadrine Trifluoperazine Thioridazine
AMcL	F	45	Diazepam, Fluphenazine Benzhexol, Nitrazepam
AMcK	M	44	Trifluoperazine, Codeine Dichloralphenazone
MB	F	48	Chlorpromazine Thiopropazate

Table 2 Plasma growth hormone concentration in milli-units/l (mu/l) before and after the administration of bromocriptine (2.5 mg) in 12 patients with Huntington's chorea (six receiving and six not receiving phenothiazines) and in seven normal control subjects

Patient numbers	Time (min)	0	30	60	90	120	130	140	150	160	170	180	210
Treated with phenothiazine													
016665		2.0	3.0	3.0	2.8	4.0	4.0	7.0	10.0	15.0*	—	—	—
012367		1.6	2.4	1.4	1.2	2.6	4.8	4.2	3.8	3.8	6.0	6.0	6.2
016867		16.4	10.0	4.8	9.6	10.6	20.4	27.0	24.4	13.4	12.0	12.0	7.8
011267		1.6	1.4	1.0	1.4	1.0	0.4	0.6	1.0	1.4	2.8	2.6	3.2
016389		1.0	1.0	0.6	0.4	3.8	7.8	10.0	12.8	10.4	9.0	6.6	4.0
011377		2.4	1.2	1.0	1.0	0.8	0.8	1.2	0.8	2.0	1.4	3.6	1.6
Mean		4.2	3.2	2.0	2.7	3.8	6.4	8.3	8.8	7.7	6.2	6.2	4.6
SEM ±		2.5	1.4	0.7	1.4	1.5	3.0	4.0	3.7	2.5	2.0	1.6	1.1
Not treated with phenothiazine													
013511		1.2	0.6	0.4	0.4	14.0	14.0	14.0	1.2	10.4	4.2	6.6	8.0
808794		1.8	0.8	0.8	4.0	2.6	2.4	1.8	1.4	1.2	1.0	1.0	0.8
806513		6.2	2.8	3.6	6.8	5.2	7.4	6.4	7.4	9.0	5.0	5.8	7.0
227498		7.0	3.4	3.4	3.0	3.4	2.6	2.4	2.4	2.4	2.6	3.2	3.2
244298		0.4	0.2	0.6	3.0	7.0	6.2	4.0	2.4	2.4	2.2	2.2	2.2
823307		1.0	1.2	0.6	0.6	7.0	9.0	7.4	5.2	5.4	6.0	3.4	4.4
Mean		2.9	1.5	1.6	3.0	6.5	6.9	6.0	3.3	5.1	3.5	3.7	4.3
SEM ±		1.2	0.5	0.6	1.0	1.7	1.8	1.8	1.0	1.6	0.8	0.9	1.1
Control subjects													
Mean		6.1	6.6	4.7	4.4	7.7	9.5	12.0	14.0	15.2	17.4	15.1	12.1
SEM ±		3.0	3.2	1.8	2.7	3.0	3.7	3.4	3.1	2.7	2.1	2.4	4.9
Significance of difference between patients and control subjects													
Treated with phenothiazine		NS	NS	NS	NS	NS	NS	NS	NS	P < 0.05	P < 0.005	P < 0.01	P < 0.05
Not treated with phenothiazine		NS	NS	NS	NS	NS	NS	NS	P < 0.01	P < 0.01	P < 0.002	P < 0.002	P < 0.05

*Investigation discontinued after 160 minutes.

be hypersensitive (Barbeau, 1961, 1973; Bird *et al.*, 1976). If there is hypersensitivity of dopamine receptors, we might expect to find increased responsiveness of dopamine receptors mediating hGH release, and this might be the basis for the earlier release of hGH reported in Huntington's chorea (Keogh *et al.*, 1976; Phillipson and Bird, 1976).

We did not find any significant elevation of basal hGH levels in our patients as has been reported by Phillipson and Bird (1976). The control subjects all showed a rise in hGH concentrations after taking bromocriptine and our results are consistent with other published findings (Tolis *et al.*, 1975; Cammani *et al.*, 1976). In the patients with Huntington's chorea the majority showed a reduced hGH response compared with controls. However, Parkes *et al.* (1976) failed to find an hGH response to 2.5 mg of bromocriptine in patients with Parkinson's disease although they did find a response to higher doses. It is possible that the dose of bromocriptine used in our study was too low but we were unwilling to increase the dose as higher doses are known to increase chorea (Kartzinel, 1976). We do not know if the lower

peak hGH response to bromocriptine found in patients with Huntington's chorea is due to an alteration of growth hormone release mechanisms. The finding of a lower peak hGH response to bromocriptine in our patients suggests that the earlier hGH response reported to follow insulin-induced hypoglycaemia in patients with the disorder is not due to increased sensitivity of dopamine receptors mediating hGH release.

In the investigation of patients who had previously received phenothiazines the failure to detect a consistent hGH response may have been because only 72 hours had been allowed between withdrawal of drug treatment and the investigation. Phenothiazines are known to block dopamine receptors (Anden *et al.*, 1964), to impair hGH responses (Sherman *et al.*, 1971), and to increase hPRL concentrations (Beumont *et al.*, 1974; Meltzer *et al.*, 1976), and this may explain why the two patients with the greatest increase in basal hPRL concentrations failed to show an hGH response. Klawans (1970) has proposed that dopamine receptor hypersensitivity may follow withdrawal of phenothiazine treatment but there was no evidence of a hypersensitive hGH response

Table 3 Plasma prolactin concentrations in $\mu\text{l/l}$ before and after the administration of bromocriptine (2.5 mg) in 12 patients with Huntington's chorea (six receiving and six not receiving phenothiazines) and in seven normal control subjects

Patient numbers	Time (min)	0	30	60	90	120	130	140	150	160	170	180	210
Treated with phenothiazine													
016665		900	840	770	650	440	600	240	300	280*	—	—	—
012367		280	230	280	220	220	160	160	100	100	70	70	120
016867		180	200	70	36	40	60	80	80	60	40	40	40
011267		1800	1800	1800	1640	1580	1380	1240	1160	1240	1000	1000	1000
016389		60	80	80	40	40	40	60	20	60	80	80	80
011377		1020	820	640	760	600	400	420	500	400	370	320	260
	Mean	707	662	607	558	487	440	367	360	357	312	302	300
	SEM $\pm$	271	264	266	250	237	208	183	176	185	182	406	179
Not treated with phenothiazine													
013511		310	180	200	160	310	310	310	260	180	200	200	170
808794		220	160	120	140	140	120	100	140	100	140	80	100
806513		220	200	200	180	180	160	160	180	160	160	160	120
227498		240	200	160	120	120	160	120	120	120	160	100	100
244298		200	200	120	200	380	340	320	240	260	260	240	200
823307		360	320	260	200	200	180	180	180	160	160	180	160
	Mean	242	210	177	167	222	212	198	187	163	180	160	142
	SEM $\pm$	35	23	22	13	42	37	39	22	23	18	25	17
Control subjects													
	Mean	184	161	161	142	140	120	121	168	140	145	141	142
	SEM $\pm$	48	38	46	37	40	32	34	60	53	49	49	40
Significance of difference between patients and control subjects	Treated with phenothiazine	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
	Not treated with phenothiazine	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

*Investigation discontinued after 160 minutes.

after withdrawal of phenothiazine treatment in our study. In the investigation on patients who had not received phenothiazines most of the patients showed a depression of hPRL concentrations after taking bromocriptine.

The results presented here demonstrate that the hGH response to bromocriptine is significantly reduced in patients with Huntington's chorea and suggest that there may be an alteration of dopaminergic neurones mediating hGH release. The lower peak hGH response may be related to decreased sensitivity of dopamine receptors or to reduced levels of dopamine at the postsynaptic receptor as the action of bromocriptine is dependent on intact catecholamine synthesis and storage mechanisms (Johnson *et al.*, 1976). These suggestions merit further investigation as neuroendocrine studies may give useful information about hypothalamic neurone function in Huntington's chorea.

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