such complicating factors as variable absorption or distribution.

Two important features emerge from this study. Firstly, our findings confirm observations¹⁰⁻¹¹ of an age-related decline in microsomal oxidation rates in man. Secondly, they show that in a population exhibiting this decline acetylation does not change with age. Thus, there are pharmacokinetic grounds in the elderly for reducing the dose of drugs that are metabolised by oxidation, but this does not seem to apply to drugs metabolised by acetylation. Indeed, in so far as the latter pathway is concerned, not only was there no observed difference in acetylator phenotype in the two groups but there was also no apparent difference within the phenotypes, or in antimodes between the populations. These findings do not therefore support the hypothesis that heterozygotes for acetylation have a survival advantage to old age. Nor do they support the hypothesis that there is a general decline of liver function with advancing age in man.¹⁸

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Growth hormone, insulin, and prolactin secretion in anorexia nervosa and obesity during bromocriptine treatment

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Summary

We studied secretion of growth hormone (GH), insulin, and prolactin in eight women with anorexia nervosa and nine women with refractory obesity before and during treatment with bromocriptine, 10 mg/day.

In the anorexic patients the raised plasma GH concentrations occurring during an oral glucose tolerance test fell significantly while on bromocriptine treatment, but there was no change in plasma insulin or blood glucose concentrations. In the obese patients, however, plasma GH concentrations remained low during the oral glucose tolerance test, and were not modified by bromocriptine. Blood glucose and plasma insulin concentrations were also unchanged. Plasma GH and plasma 11-hydroxycorticosteroid responses to insulin-induced hypoglycaemia were unaffected. Serum prolactin concentrations which were raised in five anorexic patients and mar-

ginally raised in two obese subjects, fell significantly in both groups during treatment. We observed no consistent weight changes in either group.

Introduction

Bromocriptine raises the blood concentration of growth hormone (GH) in normal subjects,¹ while depressing the raised concentrations of GH in patients with acromegaly.²⁻³ Most patients with anorexia nervosa have raised fasting concentrations of GH that fail to decrease during an oral glucose tolerance test, and may indeed show a paradoxical rise as in some cases of acromegaly.⁴ In obesity, however, plasma GH concentrations are low⁵ and do not show the post-absorptive peak seen in normal subjects.⁶ These anomalous GH responses prompted us to study the effect of bromocriptine on GH and insulin secretion in patients with anorexia nervosa and refractory obesity.

Serum prolactin concentrations have been reported to be normal⁷⁻⁸ or increased⁹ in patients with anorexia nervosa, but there is no information about prolactin concentrations in obese people. We therefore also investigated the effect of bromocriptine on serum prolactin concentrations in both conditions. We monitored the weights of both groups of patients closely since some overweight patients with galactorrhoea have been shown to revert to their normal weight while on treatment with bromocriptine.¹⁰

Patients and methods

We studied eight women with typical anorexia nervosa. Six of them were under our care for the first time, and two (cases 1 and 2) had

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already undergone treatment in the department of psychiatry for six weeks (table I). None of the patients was receiving or had received any drugs at the time of the initial investigation or for at least four weeks beforehand. Nine women patients, each of whom exceeded her standard weight by more than 25%, formed the obese group.

Despite continuous supervision of diet the weights of these patients had remained unchanged for at least a year (table II). The nature of the investigation was fully explained to each patient and all those approached agreed to participate. We took a dietary history from patients (tables I and II), but did not try to modify their diet during treatment with bromocriptine.

Patients were admitted to the metabolic unit, and after an overnight fast a butterfly needle (Abbott) was inserted into a forearm vein 30 minutes before taking a baseline sample; the needle was kept patent with heparinised saline. An oral glucose load of 50 g was then given

and blood was taken into heparinised tubes at 30-minute intervals for five hours. Plasma was separated immediately and stored at -20°C for assay later. In the obese patients only, after a further overnight fast and when a baseline blood sample had been obtained, each patient was given soluble insulin (0.15 U/kg) intravenously. Further samples of blood were taken after 10, 20, 30, 45, 60, 90, and 120 minutes. Blood glucose was estimated by the Technicon autoanalyser using a glucose-oxidase method.¹¹ Plasma 11-hydroxycorticosteroid concentrations (11-OHCS) were measured by fluorometry.¹² Plasma GH¹³ and insulin¹⁴ concentrations and serum prolactin¹⁵ concentrations were estimated by specific radioimmunoassay.

Treatment was then started with bromocriptine, initially 2.5 mg once daily with food, increasing by 2.5 mg/day at intervals of three days to a maximum of 10 mg/day in four divided doses. The anorexic patients remained in hospital and were studied two weeks after they had been established on a daily dose of 10 mg of bromocriptine. The obese patients were readmitted and the investigations repeated after they had been treated as outpatients for four weeks. Thereafter they remained on treatment with bromocriptine for three months and were seen at intervals of two weeks or less; they were weighed at each visit and we asked them about any possible side effects from the drug.

Results

ANOREXIA NERVOSA

Figure 1 shows the GH values during the oral glucose tolerance test for each patient before and during treatment with bromocriptine. For each patient the concentrations of GH during treatment were lower than before, and the higher the concentrations before treatment the greater the fall. During treatment with bromocriptine, plasma GH concentrations were significantly lower from one to four hours after the oral glucose tolerance test. There was no change in blood glucose or plasma insulin concentrations during the test (fig 2). Prolactin concentrations were raised initially in five out of the eight patients, and fell during treatment in the whole group ($P < 0.05$; table I and fig 3).

FIG 1—Plasma growth hormone concentrations during an oral glucose tolerance test in eight women patients with anorexia nervosa before (dashed line) and during (solid line) treatment with bromocriptine 10 mg/day .

TABLE I—Clinical details of eight women patients with anorexia nervosa, including weight change during study and serum prolactin concentrations before and during treatment with bromocriptine. Daily energy intake was estimated from patients' histories

Patient	Age (years)	Height (cm)	Weight (kg)	% Standard weight	Weight change (kg)	Duration of illness (years)	Energy intake (MJ/day)	Serum prolactin ($\mu\text{g/l}$)	
								Before treatment	During treatment
1	17	163	41.4	74	Nil	0.25	0.4	12	<2.5
2	22	153	33.2	60	Nil	5	NA	90	<2.5
3	20	167	43.4	72.5	+0.8	1.5	4.6	20	4
4	22	160	37.5	68.3	+2.5	2.75	6.9	20	<2.5
5	36	167	36.2	56	-2.1	4	3.1	17	4
6	15	162	45.8	88	-0.4	1	4.3	15	<2.5
7	21	161	46	76	+2.9	1.5	NA	21	3
8	24	162	31.4	55	+2.4	0.5	3.5	11	3.2
								$26 \pm 9^*$	$3 \pm 0.2^*$

*Mean values $\pm$ SE of mean.

NA = Not available.

Conversion: SI to traditional units—Serum prolactin $1\text{ }\mu\text{g/l} = 1\text{ ng/ml}$ (reference range $3\text{--}16\text{ }\mu\text{g/l}$); energy intake $1\text{ MJ} \approx 239.2\text{ kcal}$.

TABLE II—Clinical details of nine women patients with refractory obesity who were treated with bromocriptine. Weight change was estimated after three months' treatment

Patient	Age (years)	Weight (kg)	% Standard weight	Weight change (kg)	Estimated energy intake (MJ/day)	Serum prolactin ($\mu\text{g/l}$)	
						Before treatment	During treatment
1	30	90.9	180	Nil	10.8	14	3.5
2	45	124	208	+2.3	9.9	9.2	9.3
3	33	94.5	148	+1.8	5.9	11	13
4	44	82.7	142	-2.4	11.3	5.2	<2.5
5	41	132	215	+2.5	5.6	18	5
6	35	80.5	146	+0.7	6.5	20	18
7	36	95.9	150	-1.0	8.2	9.2	3
8	38	96.1	163	+0.2	6.2	8.5	5.6
9	36	107.3	190	+1.0	8.3	13	5.4
						$12 \pm 1.6^*$	$7.3 \pm 1.7^*$

*Mean values $\pm$ SE of mean.

Conversion: SI to traditional units—Serum prolactin $1\text{ }\mu\text{g/l} = 1\text{ ng/ml}$ (reference range $3\text{--}16\text{ }\mu\text{g/l}$); energy intake $1\text{ MJ} \approx 239.2\text{ kcal}$.

FIG 2—Mean ($\pm$ SE of mean) blood glucose and plasma insulin concentrations during oral glucose tolerance test in eight women patients with anorexia nervosa before (dashed line) and during (solid line) treatment with bromocriptine.
Conversion: SI to traditional units—Blood glucose 1 mmol/l $\approx$ 18 mg/100 ml.

FIG 3—Mean ($\pm$ SE of mean) serum prolactin concentrations in eight female patients with anorexia nervosa and nine female patients with refractory obesity before and during treatment with bromocriptine 10 mg/day.

One patient complained of slight nausea on starting treatment, but this soon disappeared. During treatment changes in weight were trivial and inconsistent (table I).

OBESITY

Figure 4 shows the mean values for plasma GH during the oral glucose tolerance test both before and during treatment with bromocriptine. In contrast to the anorexic patients we found no significant changes, the GH concentrations remaining suppressed throughout the study. The blood glucose and plasma insulin concentrations were also unaffected by bromocriptine either in individual patients or in the group as a whole (fig 4). The GH response to insulin-induced hypoglycaemia was unaltered by treatment with bromocriptine (fig 5), adequate hypoglycaemia (blood glucose < 2 mmol/l (36 mg/100 ml)) being obtained in each case. Similarly, the plasma 11-OHCS response to hypoglycaemia was unaffected by bromocriptine (fig 5). Prolactin concentrations were normal in seven patients and marginally raised in two; the concentrations fell significantly during treatment in the group as a whole ($P < 0.02$; table II and fig 3).

After treatment with bromocriptine for three months, weight changes in the obese ranged from -2.4 to 2.5 kg. Only two patients lost any weight (table II). All nine patients experienced some side effects, mainly nausea; in six patients this disappeared on continuing treatment. In two other patients the nausea persisted on increasing the dose above 5 mg/day and another patient complained of light-headedness that continued after increasing the dose to 10 mg. One patient complained of persistent yawning on a dose of 5 mg/day, but this disappeared with continuing treatment.

Discussion

In anorexia nervosa, as in acromegaly, bromocriptine reduced the raised GH concentrations occurring during the oral glucose tolerance test. This suggests that the hypothalamopituitary

FIG 4—Mean ($\pm$ SE of mean) plasma growth hormone, blood glucose, and plasma insulin concentrations during an oral glucose tolerance test in nine women patients with refractory obesity before (dashed line) and during (solid line) treatment with bromocriptine 10 mg/day.

FIG 5—Mean ($\pm$ SE of mean) plasma growth hormone and 11-hydroxycorticosteroid (11-OHCS) concentrations during an insulin tolerance test in nine women patients with refractory obesity before (dashed line) and during (solid line) treatment with bromocriptine.

Conversion: SI to traditional units—Plasma 11-hydroxycorticosteroid 1 nmol/l $\approx$ 0.04 μ g/100 ml.

pathways that stimulate or suppress GH release in these two conditions may be alike, and may therefore be similarly modified by bromocriptine. Alternatively, a main site of action of bromocriptine may be the pituitary, where the cells may respond to the drug in the same way in anorexia nervosa as in the adenoma of the patient with acromegaly. In the obese patients bromocriptine did not alter the response to the oral glucose tolerance test, GH concentrations being neither raised nor lowered. Any initial GH release after bromocriptine might be short-lived, and might not occur with continuous administration.

The failure of bromocriptine to modify the GH response to insulin-induced hypoglycaemia is in keeping with the suggestion that this response is largely serotonergic, as it is partially inhibited by serotonin antagonists.¹⁶ Similar serotonergic mechanisms have been shown in the corticotrophin response to insulin hypoglycaemia,¹⁷ and the rise in plasma 11-OHCS was also unaltered during bromocriptine treatment.

Prolactin concentrations were reduced during treatment in both groups of patients, the anorexic patients as a group having a higher concentration before treatment than the obese patients. The dose of 10 mg bromocriptine daily was not only ineffective in reducing the weight of patients with refractory obesity, but the side effects were also more troublesome than those experienced by the patients with anorexia nervosa.

Although no significant weight changes occurred in the anorexic patients over a period of two weeks' treatment, the effect of bromocriptine on GH release suggests that the drug merits further consideration in this disorder. Amenorrhoea in anorexia nervosa, which precedes weight loss in many patients,⁴ might be related to hyperprolactinaemia. Such an association, together with the known effect of bromocriptine on hyperprolactinaemia, would justify further study in this type of patient,

particularly if patients could be identified as anorexic before their abnormal eating habits and behaviour had become firmly established. Our findings, however, do not justify further use of the drug in obesity.

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Circulating immune complexes after repeated halothane anaesthesia

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Summary

A patient developed hepatitis after receiving three halothane anaesthetics in 22 days. Twenty-four hours after the onset of jaundice she developed an acute serum sickness syndrome with polyarthralgia, proteinuria, and transient impairment of renal function. Serum concentrations of complement components C1q, C4, and

C3 were substantially reduced, and immune complexes capable of activating the complement system via the classical pathway were present in the serum and synovial fluid. A metabolite of halothane was associated with these complexes. Fourteen months after exposure to halothane her lymphocytes were stimulated in vitro by this metabolite. The conditions under which stimulation occurred were unusual—namely, a 7S fraction of the serum, presumably IgG, was necessary. Our results provide strong evidence that halothane may be immunogenic and that its immunogenicity is dependent on the non-covalent binding of one of its metabolites to plasma proteins.

Introduction

Although the incidence of jaundice after halothane anaesthesia is believed to be low,¹ there is continuing controversy whether a direct association exists between repeated exposure to halothane and postoperative hepatic necrosis.² The mechanisms producing liver damage are not known, although it is widely held to be the result of a delayed hypersensitivity response to halothane or one of its metabolites.

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