Evidence for existence of two types of massive obesity

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Summary and conclusions

The responses of growth hormone, cortisol, and prolactin to symptomatic hypoglycaemia during an intravenous insulin tolerance test were measured in 20 massively obese subjects and six lean volunteers. In 11 subjects, who had been obese since early childhood, an impaired growth-hormone response and an absent prolactin response were found. In the nine other obese subjects, however, the growth-hormone and prolactin responses were not significantly impaired. Seven of these subjects had become obese either as a teenager or during adult life.

These findings suggest the existence of two types of human obesity similar to those found in rodent models. In one the disorder of hypothalamic function may be due to a basic, possibly genetic abnormality, while in the other it is acquired.

Introduction

We previously reported¹ an absent prolactin and impaired growth-hormone and cortisol response to insulin-induced hypoglycaemia in a group of massively obese women. We concluded that this was evidence for a change in hypothalamic function in these women, all of whom had been obese since early childhood. We questioned whether a similar abnormal hypothalamopituitary response would occur in massively obese subjects who had become obese in adult life, because in rodent models different patterns of prolactin and growth-hormone secretion are seen depending on the aetiology of the obesity. We now report the results of our extended study of 20 massively obese subjects, of whom 13 had been obese since early childhood and seven had become obese as either teenagers or adults.

Patients, methods, and results

Details of the subjects and controls studied are shown in table I. The obese subjects, whose thyroid function was normal, were studied in hospital while receiving a weight-maintaining diet, and informed consent was obtained for the investigation. Two of these subjects, who were not known to be diabetic, gave abnormal results to oral glucose tolerance tests. No subject was taking any medication. An intravenous insulin tolerance test (0.15 units soluble insulin/kg) was performed in the morning after an overnight fast; subjects were rested for at least 30 minutes after the insertion of an intravenous cannula, through which the blood samples were drawn. Blood was taken before and then at 30-minute intervals for two hours after the injection of insulin. Blood glucose concentrations fell to less than 40% of the fasting value after insulin, and this fall was accompanied by symptoms in all subjects. Each sample was immediately centrifuged and the plasma frozen and stored at -20°C until assay.

Prolactin, growth hormone, and cortisol concentrations were measured by specific radioimmunoassays. The standard used in the prolactin assay was IRP 75/504, and in the growth-hormone assay IRP 66/217. Reagents for the prolactin and cortisol assays were

provided by the matched reagents programme of the human reproduction unit of the World Health Organisation. Tables I and II show the results of the study and the significance of differences between the groups, the subjects being grouped according to their prolactin response to hypoglycaemia.

Discussion

We previously reported¹ impaired growth-hormone and cortisol responses and an absent prolactin response to insulin-induced hypoglycaemia in nine massively obese women. Further studies yielded a woman and a man who showed no prolactin response to symptomatic hypoglycaemia. In all of these 11 subjects the obesity had developed at an early age. Our investigations of late-onset obesity have now provided evidence for a separate type of obesity. In subjects who became obese as teenagers or adults the growth-hormone response to hypoglycaemia was not significantly impaired and the prolactin and cortisol responses were normal. A similar pattern of response was also seen, however, in two obese subjects who had been obese as children. No physical features differentiated the two groups.

The existence of two types of human obesity was suggested by Ball *et al.*,² who found that some obese people regain their growth-hormone response to insulin-induced hypoglycaemia after losing weight whereas others continue to have an impaired response despite remaining at a lower weight for six months. Jung *et al.*³ recently described a basic abnormality of thermogenesis in obese women with a strong family history of obesity. This abnormality remains even when these women have lost weight. Interestingly, a similar defect of thermogenesis occurs in the genetically obese ob/ob mouse.

In obese mice with hypothalamic disorders the pattern of prolactin and growth-hormone response depends on the type of obesity. In the ob/ob mouse plasma prolactin and growth-hormone concentrations are low before the onset of obesity, and in the adult ob/ob mouse the prolactin response to stimulation with the dopamine receptor antagonist perphenazine is impaired.⁴ Conversely, mice made obese by aurothioglucose injections or overfeeding show an exaggerated prolactin response to perphenazine, which returns to normal on weight reduction.⁵ Furthermore, the plasma concentration of growth hormone, which is reduced when these mice are obese, also becomes normal after weight loss. A direct extrapolation from rodent obesity to human obesity is not warranted. Nevertheless, the finding that in obese mice the patterns of prolactin and growth-hormone responses depend on the type of obesity may be relevant to obesity in man.

We conclude from our findings that a disorder of hypothalamic function is present in massive obesity. The different patterns of prolactin response to insulin-induced hypoglycaemia suggest two types of human obesity. In type 1 (in which the subjects show no prolactin response to hypoglycaemia) the disorder of hypothalamic function may be due to a basic, possibly genetic abnormality. All of our 11 subjects in this group had been obese since early childhood. In type 2 (in which the subjects show a normal prolactin response to hypoglycaemia) the hypothalamic disorder is acquired and may be the result of chronic dietary excess; weight loss would be expected to result in complete normalisation of hypothalamic function. Seven of our nine subjects in this group had become obese either as teenagers or as adults.

The biochemical difference between these two types of obesity is clear: there is no overlap between the prolactin

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TABLE I—Clinical details and response to insulin tolerance test in obese subjects (classified according to prolactin response to hypoglycaemia) and controls

Case No	Age (years)	Age at obesity	Weight (% of ideal body weight)*	Family history of obesity	Blood glucose (mmol/l)		Prolactin		Growth hormone		Cortisol	
					Fasting	Minimum during ITT	Basal (mU/l)	Total integrated response	Basal (mU/l)	Total integrated response	Basal (nmol/l)	Total integrated response
Non-responders												
1	34	Childhood	200	+	5.0	1.5	270	-4	1.0	130	340	+166
2	36	"	200	+ +	7.0	2.0	230	-303	2.2	427	580	-95
3†	44	"	220	+ +	4.2	1.4	<60	0	2.1	4694	340	+322
4	49	"	230	+	4.3	1.5	200	-105	3.2	2391	430	+132
5	27	"	280	+	3.8	1.0	1100	-100	3.6	1664	540	+59
6	35	"	240	+	3.8	1.4	270	-49	2.2	2464	590	-1
7	32	"	200	+	6.4	1.5	360	-148	1.3	169	550	-44
8	30	"	240	+	9.8	2.2	220	30	2.4	1250	400	-54
9	27	"	220	+	4.3	0.7	200	-65	1.5	3653	660	+16
10	30	"	230	+	4.7	1.0	140	-179	2.7	744	530	+62
11	27	"	240	+	3.7	1.5	280	22	2.3	1324	310	0
Mean	33.7		227		5.2	1.4	302	-82	2.2	1719	479	+51
Responders												
12	32	Childhood	280	+	5.2	1.4	<50	+5300	2.0	2025	360	+188
13	46	Teenager	200	+	4.4	1.0	140	+398	3.0	2077	350	+121
14	34	Adult	200	-	4.8	0.8	440	+1024	2.0	3600	440	+261
15	34	Teenager	260	+	4.2	1.3	300	+364	2.7	227	410	+76
16	30	"	220	+	4.2	1.0	670	+378	2.3	3668	580	+46
17	38	Childhood	200	+ +	5.0	1.0	300	+1812	2.0	5410	540	+67
18	46	Adult	200	-	4.9	1.0	330	+1313	2.1	4694	360	+362
19	20	Teenager	200	-	4.2	1.0	500	+322	2.5	3852	610	-14
20	26	"	260	+ +	3.5	1.4	240	+400	2.0	3965	340	+129
Mean	34.0		220		4.5	1.1	330	+1256	2.3	3279	443	+137
Controls												
21	28		100				200	+625	4.5	12 339	400	+136
22	27		95				250	+304	3.3	5045	400	+154
23	24		105				250	+1368	2.3	3169	310	+155
24	22		100				580	+970	0.9	669	230	+341
25	18		100				190	+478	5.2	5912	670	+14
26	21		100				450	+1409	3.2	18 377	220	+862
Mean	23.3		100				320	+859	3.2	7585	370	+277

*Ideal body weight = Midpoint of weight range for medium frame size, Metropolitan Life Insurance Co tables.

† = One parent obese. ++ = Both parents obese. - = No family history.

‡ Only male subject studied.

ITT = Insulin tolerance test.

Conversion: SI to traditional units—Blood glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Plasma cortisol: 1 nmol/l $\approx$ 0.036 μ g/100 ml.TABLE II—Significance of differences between groups (*P* values),* subjects being grouped according to prolactin response to hypoglycaemia

	Prolactin	Growth hormone	Cortisol
Responders <i>v</i> controls	>0.1	>0.1	>0.1
Non-responders <i>v</i> controls	<0.01	<0.05	<0.1
Non-responders <i>v</i> responders	<0.01	<0.05	<0.1

*Determined by Wilcoxon non-parametric test.

responses (table I). The difference in age of onset is less clear-cut, however, since two patients apparently obese since early childhood had normal prolactin responses and it is uncertain whether their obesity may be considered to have a genetic basis.

We shall investigate the hypothesis that two types of human obesity exist in the same group of subjects after they have lost a substantial amount of weight.

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ONE HUNDRED YEARS AGO A recent case, on which an inquest was held by Dr Hardwicke, shows clearly the necessity for the provision at all our police-stations of a system of ambulance conveyance to the nearest hospital, for persons found either sick, injured, or insensible. The poor fellow was a cabman, who had fallen backwards while lifting a heavy box on to his cab. He was conveyed by a policeman in his cab to the hospital, and on the way fell twice into the bottom of the cab; and on arrival, was found to be dead. Police-constable 303 C deposed that, whilst going along to the hospital in the cab, the deceased coughed once or twice, and slipped down from the seat to the bottom of the cab, and he could not raise him without opening the door of the cab. In answer to questions as to why he did not procure a police-ambulance instead of letting a man in such a case lie in a heap at the bottom of a cab, he said they had not one at Marl-

borough Street, and he did not know if there was one at Marylebone Lane, but there was one at the Vine Street Station. Mr E Fardon, resident medical officer of the hospital, said, on the deceased's arrival, he was dead. He had made a *post mortem* examination. There were no injuries to the back of the head, although the membranes of the brain were congested. The lungs were congested, and there was slight bronchitis, and there was disease of the mitral valves. The immediate cause of death was congestion of the brain, accelerated by the fall and the way in which deceased was brought to the hospital. The system of "help to the wounded" by our police needs reorganising; the practice of treating insensible people as "drunk and incapable," and of conveying men with fracture of the skull or in swooning from failure of the circulation, upright in a cab, is often little short of murderous. (*British Medical Journal*, 1880.)