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Effect of glucagon infusion on blood glucose, plasma immunoreactive insulin, growth hormone and adenosine 3'5'-monophosphate in obese children

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The behaviour of plasma glucose, immunoreactive insulin, growth hormone and adenosine 3',5'-monophosphate (cAMP) in response to glucagon infusion was investigated in obese and control children. Hyperinsulinaemia and low growth hormone levels were found in the obese group. Hyperinsulinaemia did not prevent the glucagon-induced cAMP release in obese children. The plasma cAMP concentration decreased after the first hour of glucagon infusion in both groups. The decline of cAMP concentration was more rapid in the obese group than in the controls, resulting in a significantly lower plasma cAMP level at the end of the glucagon load.

Adenosine 3',5'-monophosphate plays a principal role in mammalian tissue as an intracellular mediator of the actions of a number of hormones [21]. Some of the nucleotides escape from the cells into the extracellular space including plasma [4, 7, 16] and cerebrospinal fluid [4, 7]. It is excreted by the kidney and a rise in plasma concentration is normally associated with an increased urinary excretion [1, 7]. Glucagon and insulin play an important role in the control of hepatocellular cAMP, the former stimulates and the latter inhibits its production reflected by an increased plasma level [13, 15, 17, 23]. From this we would expect an increased hepatic release of cAMP in diabetes both in the basal condition and during exogenous glucagon stimulation. Liljenquist et al. [18], however, did not observe such changes in diabetic patients. Broadus et al. [5] followed urinary cAMP excretion during glucose and insulin tolerance test in normal subjects: while there was only a slight increase in the hypoglycaemic phase of the glucose load, a twofold rise occurred in response to the insulin-induced hypoglycaemia.

In view of the suggested interaction of glucagon and insulin on hepatic cAMP production on the one hand, and the well-established hyperinsulinism [3, 9–11, 20] and low growth

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hormone level [8, 19, 26, 27] in obesity on the other hand, it appeared of interest to investigate the behaviour of plasma cAMP in relation to the metabolic and hormonal status as well as its changes in response to glucagon infusion. Since glucagon induces cAMP, insulin and growth hormone release, we considered it a suitable means to explore how and to what extent does obesity alter the metabolic and hormonal effects of glucagon.

Subjects and Methods

Ten obese (relative body weight above 120%), non-diabetic, and six nonobese children were investigated. The anthropometric measurements of the obese and control children are summarized in Table I.

Skinfold measurements were made by Harpenden caliper according to Durnin and Rahaman [12]. Body fat and lean body mass were calculated according to Brook [6].

Glucagon (Lilly) was administered intravenously (6 μg/kg/hour) for three hours after an overnight fast. Blood samples were obtained from an indwelling venous line and assayed for blood glucose, plasma cAMP, immunoreactive insulin (IRI) and growth hormone (GH).

IRI, cAMP and CH were determined with double antibody radioimmunoassay method, using the radioimmunoassay kit supplied by The Radiochemical Centre (Amersham) for insulin and cAMP and by Biodata for GH. Blood glucose was measured by the glucose oxidase method according to Sigiura and Hirano [24].

Results

All patients responded to glucagon infusion by elevation of blood glucose in the first 60 minutes which then began to fall and approached the basal value in the third hour (Fig. 1). The course of the glucose curve was similar in the obese and control group of children.

The basal value and the glucagon-induced rise of IRI in the first hour

Table I

Anthropometric measurements of the obese and control children

	Control		Obese	
	Mean	SE	Mean	SE
Age, year	10.6	0.63	10.7	0.45
Height, cm	142.7	3.01	148.4	2.63
Weight, Kp	32.9	2.23	60.8	3.3
Triceps skinfold, mm	10.0	0.7	28.9	1.03
Biceps skinfold, mm	5.6	0.37	15.6	0.87
Subscapular skinfold, mm	8.3	0.66	31.5	1.08
Suprailiacal skinfold, mm	9.4	0.83	27.7	1.58
Body fat, per cent	20.01	1.29	40.5	0.77
Lean body mass, Kp	26.2	1.58	37.1	2.03
Ideal body weight, per cent	89.9	2.5	148.9	3.77

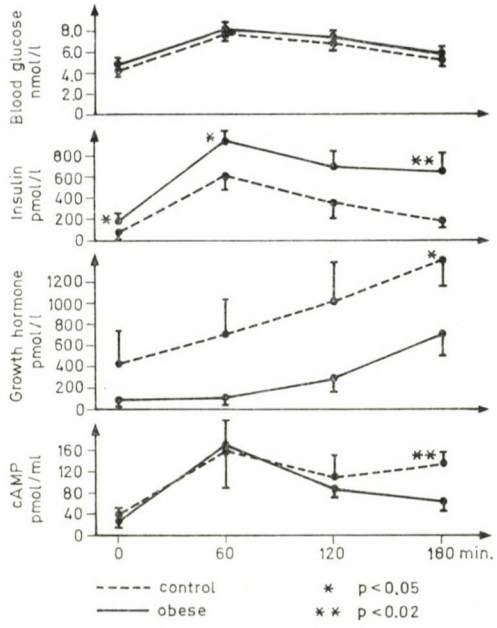

FIG. 1. Blood glucose, plasma IRI, GH, and cAMP response to glucagon load, in obese and control children

of the glucagon infusion was significantly higher in the obese group as compared to the controls (Fig. 1). IRI gradually decreased from the 2nd hour in the control patients reaching the starting level during the third hour, while it remained at a high level in the obese children throughout the whole infusion period.

Glucagon administration induced an elevation of plasma GH in both obese and control children, which reached the level of significance by the end of the 3-hour infusion period. As it can be seen in Fig. 1, plasma GH was higher in the control children throughout the intravenous glucagon load, but, only the 180 minute value was significantly different from that of obese children.

Since only hourly measurements were made we do not know when the peak of the plasma cAMP occurred in response to glucagon, but it was still elevated at the end of the first hour. Thereafter the plasma cAMP level decreased in both groups. The decline was more rapid in obese children and as a result, the plasma cAMP concentration was significantly lower at the end of the test period.

DISCUSSION

In accordance with previous findings, the present study has also shown that obesity is characterized by hyperinsulinaemia and a low growth hormone level. The finding

that the increased plasma insulin level is not associated with a low basal plasma cAMP concentration is in accordance with the observation of ROBINSON et al. [22] that insulin administration is not capable of reducing hepatic cAMP below the baseline level.

Glucagon infusion induced cAMP and insulin release in both the obese and the control children. The response of cAMP at the end of the first hour of infusion was similar in magnitude, from which it can be concluded that the simultaneous increase in plasma insulin did not suppress the glucagon-stimulated cAMP release.

As a result of the more rapid decline of cAMP concentration in obese children, a significantly higher plasma cAMP level was observed in the controls at the end of glucagon infusion. This difference could possibly be explained by the persistent hyperinsulinaemia in obese children. Still, in view of the observation that in non-insulin-secreting diabetes a decline of cAMP occurs during glucagon infusion [18], the role of hyperinsulinaemia becomes uncertain.

An alternative explanation may be the decreased GH response to glucagon in obese children. An acute administration of GH failed to affect urinary cAMP excretion [25], since it exerts its action through protein synthesis [14]. Fain et al. [14] suggested that the effect of GH on cAMP production may be only demonstrated in conjunction with another agent known to stimulate cAMP production. In the present study the increased gH secretion and the continuously infused glucagon together may have slowed down the decline of plasma cAMP concentration in control children. This explanation appears to be supported by the observation of August and Hung [2] according to which in growth hormone deficient children the impaired cAMP response to glucagon improved after growth hormone treatment.

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