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MODULATION OF THE CATABOLIC ACTIVITY OF GLUCAGON BY ENDOGENOUS INSULIN SECRETION IN OBESE MAN *

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Obesity is an anabolic state characterized by storage of foodstuffs in excess of anticipated needs. Whether this metabolic state is a consequence of an hormonal derangement which results in increased fat synthesis, abnormal storage, or decreased lipolysis is unresolved. Glucagon is a catabolic hormone in non-obese man which has been reported to both augment lipolysis and ketogenesis [5] and to reduce plasma triglyceride concentration [1]. Recently we have observed [18] that the lipolytic response to glucagon is decreased in obese subjects when compared to the response in normal weight man. In addition, the ketogenic response to glucagon is also decreased in obesity [18] compared to the response in normal subjects following bolus glucagon injection [16]. These observations suggest that 'resistance' to the lipolytic and ketogenic actions of glucagon are characteristic of the obese state.

Recent support for the concept that the molar ratio of glucagon to insulin (and not the absolute concentration of either hormone) determines the net metabolic response to these hormones has been reported [12]. If this concept is valid in obese man, then the characteristic hyperinsulinism of obesity may be responsible for the 'resistance' to the lipolytic and ketogenic actions of glucagon. The present study was undertaken to explore the following two questions concerning the 'resistance' to glucagon in obesity:

1) Is the glucagon to insulin relationship important in determining the catabolic response to obesity?

2) Is the catabolic 'resistance' to glucagon administration in obesity relative or absolute; *i.e.*, can it be corrected with a larger dosage of glucagon?

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To resolve these two questions, 5 obese non-diabetic subjects were administered glucagon at a dosage of 1.0 μg/kg and 2.0 μg/kg body weight. As an assessment of net metabolic response, changes in plasma free fatty acids, β-hydroxybutyrate, glucose, triglycerides, and insulin were observed at frequent intervals following hormone injection. These responses in obese man were compared to the responses, previously published, in non-obese normal subjects [15].

MATERIALS AND METHODS

The obese group consisted of 5 healthy subjects selected from our obesity clinic on the basis of a normal glucose tolerance test by UGDP criteria [7], moderate obesity (180 ± 20% ideal body weight by the Metropolitan Life Insurance Tables [19]), and a willingness to cooperate in the study. All had multiple unsuccessful attempts at weight loss. The control group also consisted of 5 healthy subjects recruited from the hospital personnel on the basis of a normal glucose tolerance test, normal weight (± 5% ideal body weight), and general good health. The clinical characteristics of each group are tabulated in tab 1.

subjects	age (years)	sex	height (cm)	weight (kg)	% of ideal body weight
controls					
D. S.	30	m	177.8	74.8	105
P. E.	38	m	177.8	72.6	100
R. D.	31	m	180.3	77.1	105
S. M.	25	f	167.6	54.4	100
K. A.	24	f	175.3	61.2	100
obese					
P. Y.	24	f	162.6	90.7	166
A. K.	39	f	177.8	119.8	181
C. Q.	25	f	162.6	101.6	187
E. W.	34	f	165.1	109.8	194
P. M.	21	f	160.0	94.8	182

Table 1 - Clinical characteristics of control and obese populations.

For 3 days prior to testing, both groups consumed at least 300 g/*die* of carbohydrate. All tests were conducted at 07^{00} in the post-absorptive state after a 12-h overnight fast. Each subject assumed the supine position throughout the test period. Glucagon was obtained from Eli Lilly & Co. (Indianapolis, Ind., U.S.A.) in vials containing 1.0 mg of hormone which was then diluted with 250 ml of isotonic saline to obtain a final concentration of 4 μg/ml. Minimal insulin (20 μU/ml by radioimmunoassay) was present in this final dilution. Pharmacological dosages of glucagon, 1.0 μg/kg (low dose) and 2.0 μg/kg (high dose) were utilized one week apart for the glucagon tolerance tests because previous studies [16] had demonstrated a brisk ketogenic and lipolytic response to these concentrations in normal weight non-diabetic man.

The solutions were drawn into a plastic syringe and injected over a 10-sec period. To avoid loss of glucagon by non-specific adherence, the syringe was rinsed and reinjected three times with venous blood obtained retrograde from the patient's vein immediately after hormone injection. An # 18 gauge scalp vein needle was placed in the antecubital vein

of the contralateral arm and patency was maintained by a slow drip of isotonic saline. All blood samples were withdrawn from this scalp vein needle after discarding the initial 3 ml of blood. Samples were withdrawn at the following times: 0 (just prior to injection), 2, 5, 10, 15, and 20 min post-injection of glucagon and assayed for β-hydroxybutyrate (BOH), glucose, free fatty acids (FFA), insulin, and glucagon, as previously described [16].

Statistics were done utilizing Student's *t*-test for paired samples when the response in the obese group at the low dose was compared to the response following high dose glucagon [2]. When the response of the obese group was compared to the response of the control population, the *t*-test for non-paired samples was employed [2]. Basal values for the obese and normal control groups are reported as the mean ± SEM calculated from two separate observations for each subject. The response of hormones and substrates following bolus glucagon was calculated as the plasma concentration minus the basal plasma concentration obtained just prior to hormone injection.

RESULTS

Hormones (mean ± SEM)

Plasma glucagon concentration — Mean fasting plasma glucagon concentration was statistically indistinguishable in the obese (67 ± 15 pg/ml) as compared to the normal weight population (91 ± 20 pg/ml) ($p > 0.05$). Following bolus glucagon injection, plasma glucagon concentration exceeded 1,000 pg/ml in both obese and normal groups throughout the first 10 min of the study. Subsequently, in the low dose study (1.0 μg/kg) plasma glucagon concentration was approximately twice as great in the obese group (15 min: 817 ± 95 pg/ml; 20 min: 440 ± 92 pg/ml) as in the control group (15 min: 463 ± 83 pg/ml; 20 min: 193 ± 16 pg/ml) ($p < 0.01$). This observation suggests that the administration of glucagon at a dosage of 1.0 μg/kg may actually provide a greater glucagon challenge to obese subjects than normal weight subjects. However, at the higher dosage of glucagon (2.0 μg/kg) this difference in glucagon challenge was not observed since the mean plasma glucagon concentration at 20 min post-injection was statistically indistinguishable in the obese group (744 ± 135 pg/ml) as compared to the control population (756 ± 68 pg/ml) ($p > 0.2$).

groups	dosage of glucagon administered (μg/kg)	plasma insulin concentration (μU/ml) min 0	2	5	10	15	20	integrated insulin response (μU/ml-min)	glucagon: insulin relationship dose of glucagon (μg/kg) / integrated insulin (μU/ml-min)
control	1.0	10±2	28±5	23±4	18±3	17±3	16±3	367±69	2.72
control	2.0	15±4	55±13	43±12	32±8	32±7	25±4	728±58	2.75
p-value		n.s.	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	n.s.
obese	1.0	21±3	94±21	84±23	80±22	65±13	65±13	1,435±328	0.70
obese	2.0	18±3	99±23	88±25	75±20	65±15	59±15	1,462±327	1.38
p-value		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	<0.01

Table 2 - Mean plasma insulin concentrations following i.v. glucagon administration.

Plasma insulin concentration (tab. 2) — The mean plasma concentration of insulin in the basal state was greater in the obese subjects (20 ± 2 μU/ml) than in the normal weight controls (11 ± 1 μU/ml) ($p < 0.01$). Following glucagon injection, all subjects demonstrated an immediate rise in plasma insulin which became maximal at 2 min post-injection (tab. 2). In the normal weight population, the integrated insulin concentration (728 ± 58 μU/ml-min) following the 2.0 μg/kg dosage was significantly greater than the integrated insulin concentration (367 ± 69 μU/ml-min) following the 1.0 μg/kg dosage ($p < 0.01$). This augmented response to the high dose glucagon contrasted with the response in the obese population. In this group, the large increase in glucagon-stimulated insulin secretion was similar (low dose: 1,435 ± 328 μU/ml-min; high dose: 1,462 ± 327 μU/ml-min) at both the low and high glucagon dosages ($p > 0.2$).

Glucagon : insulin relationship (tab. 2) — During the first 10 min following bolus glucagon injection, plasma glucagon concentration exceeded the upper limits of our assay. Thus, we were unable to calculate the integrated area below the plasma glucagon concentration decay curve for our subjects. We have thus chosen to express the relationship of glucagon to insulin as

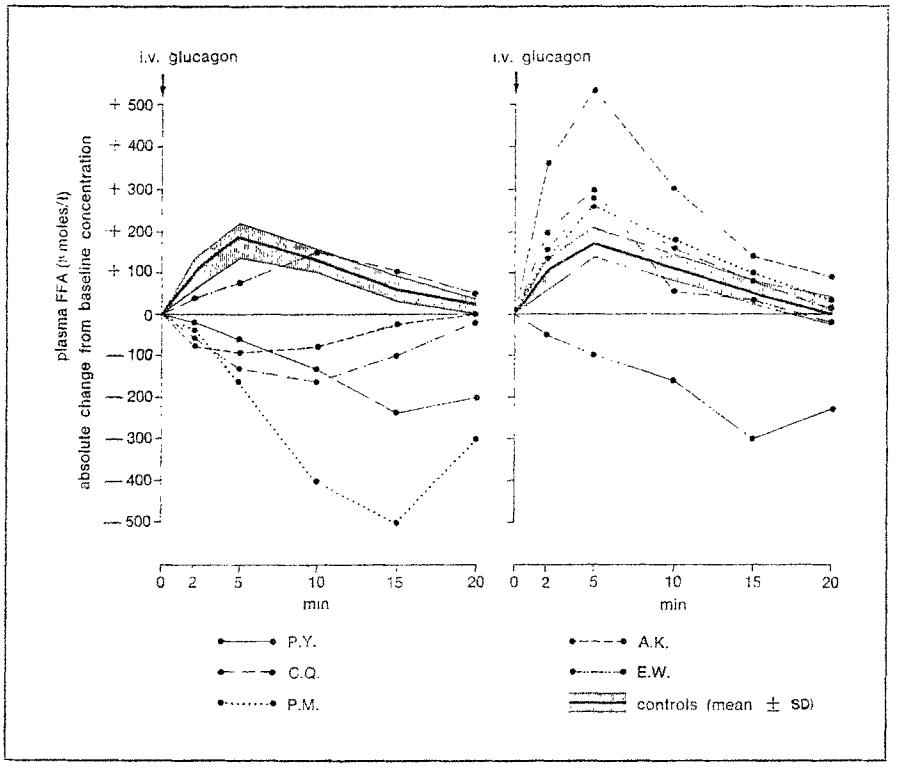

Fig. 1 - Change in free fatty acids with bolus glucagon administration. Glucagon was administered in the dosages of 1.0 μg/kg (left panel) and 2.0 μg/kg (right panel) to 5 normal subjects (plotted as the mean ± SD) and to 5 obese subjects (plotted individually).

the ratio of the administered glucagon dosage to the integrated insulin secretory response. In the normal weight group, the glucagon to insulin relationship (G : I) was not altered when the glucagon challenge was increased from 1.0 μg/kg (G : I = 2.72) to 2.0 μg/kg (G : I = 2.75) since the insulin secretory response also increased (tab. 2). In contrast, in the obese group, the glucagon to insulin relationship approximately doubled when the high dose glucagon dosage was employed. In this group, the doubling of the glucagon dosage was not accompanied by an increase in integrated insulin secretion, and thus a 2-fold increase in the net glucagon: insulin relationship (low dose G : I = 0.70; high dose G : I = 1.38) ($p < 0.01$) occurred.

Substrates

Free fatty acids (FFA) (fig. 1) — The basal FFA concentration was significantly greater in the obese population (813 ± 71 mEq/l) than in the normal weight controls (625 ± 19 mEq/l) ($p < 0.01$). However, this elevated FFA concentration in obese subjects was not maintained after glucagon

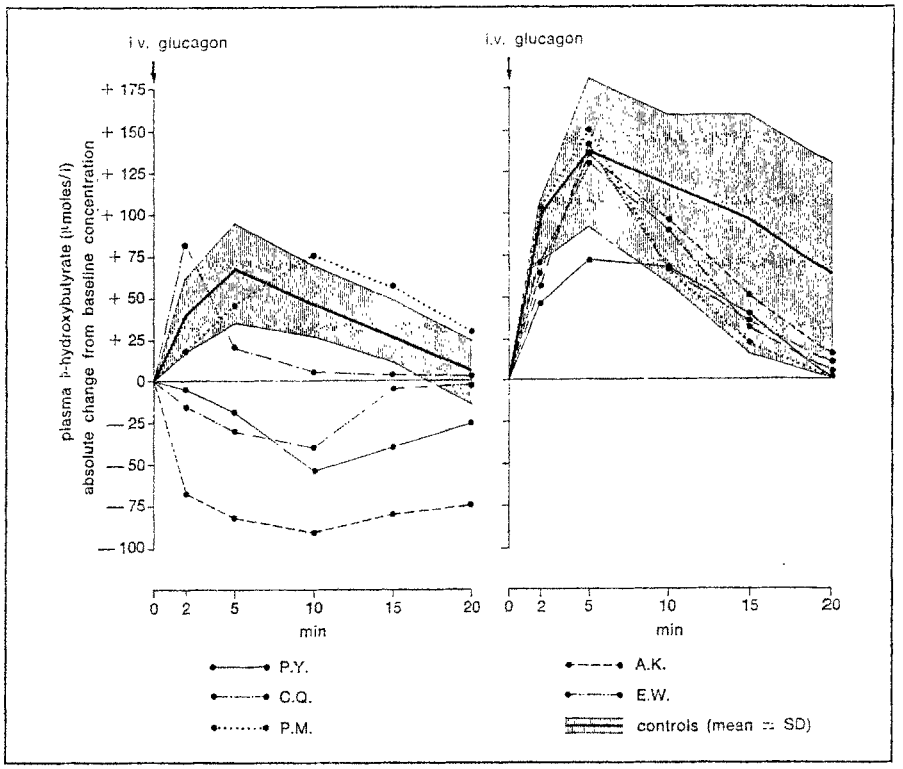

Fig. 2 - Change in β-hydroxybutyrate with bolus glucagon administration. Glucagon was administered in the dosages of 1.0 μg/kg (left panel) and 2.0 μg/kg (right panel) to 5 normal subjects (plotted as the mean ± SD) and to 5 obese subjects (plotted individually).

injection. In marked contrast to the consistent rise in FFA concentration in all normal weight subjects after 1.0 μg/kg bolus injection, 4 of the 5 obese subjects actually exhibited a decline in plasma FFA concentration (fig. 1). If the mean change from basal concentration of FFA in the obese group (-75 ± 37 mEq/l) is compared to the response in control subjects ($+156 \pm 42$ mEq/l) at 5 min post-glucagon injection, a highly significant difference was observed ($p < 0.01$).

In contrast to the antilipolytic response to low dose glucagon, at the higher glucagon dosage of 2.0 μg/kg (as depicted in the right half of fig. 1) the abnormal response in the obese subjects was corrected. Although great variability was observed in the obese patients' response to this high dosage, the values in 4 of the 5 obese subjects exceeded 1.0 SD above the normal response by 5 min post-glucagon injection.

β-hydroxybutyrate (fig. 2) — Basal BOH concentration in the obese group (240 ± 27 μmoles/l) was significantly greater than the basal concentration in control subjects (133 ± 9 μmoles/l) ($p < 0.01$). In contrast to the uniform increase in BOH after glucagon injection in all normal controls in both the low and high dose study, 3 of the 5 obese subjects

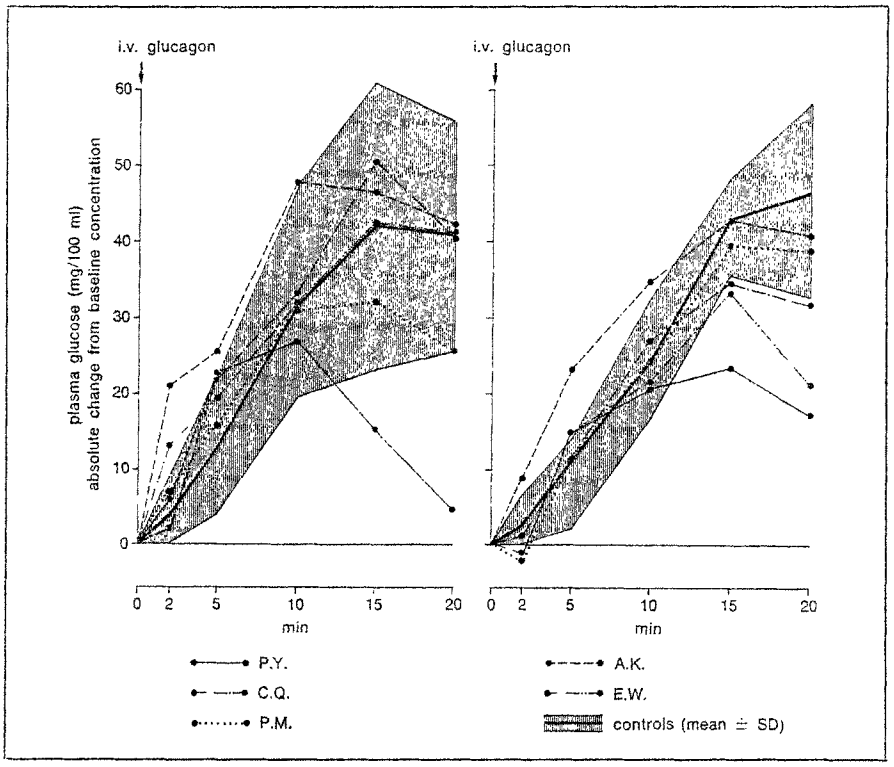

Fig. 3 - Change in glucose with bolus glucagon administration. Glucagon was administered in the dosages of 1.0 μg/kg (left panel) and 2.0 μg/kg (right panel) to 5 normal subjects (plotted as the mean ± SD) and to 5 obese subjects (plotted individually).

exhibited a decrease in ketone body concentration following low dose glucagon injection. Thus, at 5 min post-glucagon injection, when the mean peak concentration was reached in the control group (86 ± 10 μmoles/l), the mean BOH concentration in the obese population was significantly decreased (-13 ± 21 μmoles/l) ($p < 0.01$). This variable but abnormally reduced ketogenic response to low dose glucagon was corrected by administration of the larger dose of glucagon as shown in the right panel of fig. 2. With the greater glucagon dosage of 2.0 μg/kg, all subjects (obese and control) exhibited a similar increase in BOH concentration (obese mean = 126 ± 14 μmoles/l) *vs* control mean = 136 ± 29 μmoles/l) ($p > 0.2$) at 5 min post-injection with the mean plasma concentration of the obese population remaining within $\pm$ 1.0 SD of the normal population mean throughout the 20 min of observation.

Glucose (fig. 3)

Mean plasma glucose in obese fasting subjects (101 ± 2 mg/100 ml) was statistically indistinguishable from the mean in normal weight controls (99 ± 3 mg/100 ml) ($p > 0.2$). After glucagon administration, a rise in plasma glucose above baseline concentration occurred in all obese and control subjects (fig. 1). Though the rise in plasma glucose above baseline was variable in both the obese and control groups, at 10 min post-injection, the mean increase in the obese population (low dose 34 ± 6 mg/100 ml; high dose 27 ± 6 mg/100 ml) was indistinguishable from the glucose rise in the normal group (low dose 24 ± 5 mg/100 ml; high dose 33 ± 5 mg/100 ml) ($p > 0.05$).

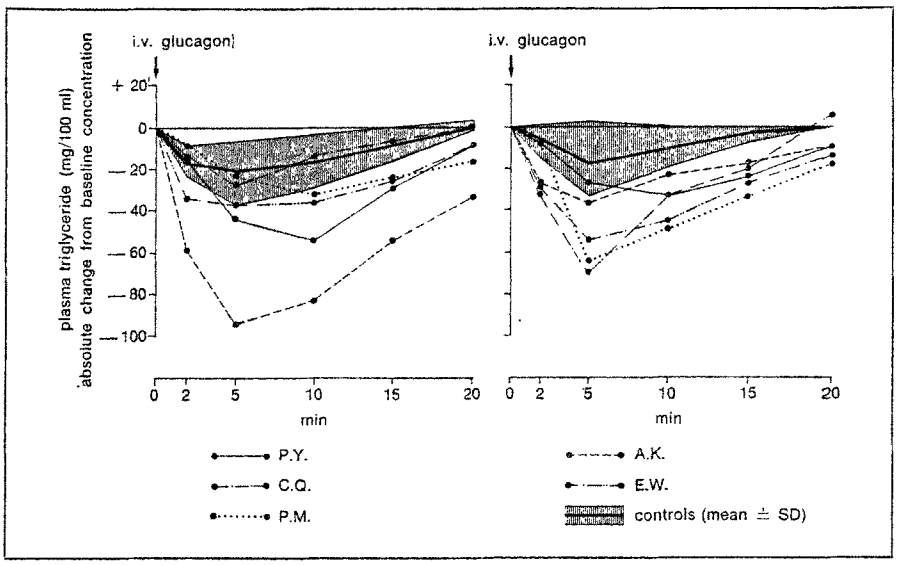

Fig. 4 - Change in triglyceride with bolus glucagon administration. Glucagon was administered in the dosages of 1.0 μg/kg (left panel) and 2.0 μg/kg (right panel) to 5 normal subjects (plotted as the mean ± SD) and to 5 obese subjects (plotted individually).

Plasma triglyceride concentration (mg/100 ml) (mean ± SEM) (fig. 4)

Mean basal plasma triglyceride (TG) concentration was significantly greater in the obese population (180 ± 19 mg/100 ml) than the basal TG concentration in the control population (105 ± 8 mg/100 ml) ($p < 0.01$). Following bolus glucagon injection in the low dose study, all obese subjects exhibited a significantly greater decline (− 46 ± 13 mg/100 ml) at 5 min post-injection than the mean decline in the control population (− 10 ± 9 mg/100 ml) ($p < 0.01$). A similar response was observed at the higher glucagon dosage of 2.0 μg/kg in which the mean decline in the obese population at 5 min post-injection (− 51 ± 8 mg/100 ml) was statistically greater than the mean decline in the control group (− 12 ± 8 mg/100 ml) ($p < 0.01$). Thus, the obese patients exhibited an exaggerated hypolipemic response to both the low and high dosage of glucagon when compared to the modest hypolipemic response in normal weight subjects.

DISCUSSION

Our results suggest that obesity is characterized by an abnormal catabolic response to exogenous glucagon administration. This abnormality is manifested by a glucagon-induced reduction in plasma FFA and BOH concentration and contrast to the normal lipolytic and ketogenic response observed in controls. When a higher dose of glucagon was administered, these abnormal responses were corrected, suggesting a relative rather than absolute 'resistance' to the hormone. In addition, the correction of these abnormal responses was accompanied by a change in the relationship of glucagon administered to insulin secreted in favor of increased glucagon relative to insulin. These findings suggest that the insulin hypersecretion of obesity may produce a resistance to at least two of the catabolic actions of glucagon. If endogenous insulin secretion blunts the lipolytic and ketogenic response to glucagon, then the response to other lipolytic hormones, which do not possess insulinogenic activity, might be exaggerated. Norepinephrine is such a lipolytic hormone which differs from glucagon in that this catecholamine suppresses endogenous insulin secretion [13]. While a dose response investigation of these catabolic effects has not been examined for norepinephrine, the data of WILLMS et al.[20] provide some insight into these events. These investigators observed that following 30 min of norepinephrine infusion (0.08 mg/kg/min), obese non-diabetic subjects exhibited a 2.5-fold increase in both plasma FFA (basal: 0.792 ± 0.212 μmoles/l; 30 min: 2.001 ± 0.471 μmoles/l) and total ketone bodies (basal: 394 μmoles/l; 30 min: 1,013 μmoles/l). During this time, no statistically significant increase in plasma immunoreactive insulin was observed (basal: 23.9 ± 7.3 μU/ml; 30 min: 26.2 ± 5.1 μU/ml). Moreover, the data demonstrated that the non-diabetic obese subjects responded to the infusion with a significantly greater lipolytic response than normal weight controls. This enhanced lipolytic response to norepinephrine contrasts with our observations in which 4 out of 5 obese subjects had an actual reduction in plasma FFA concentration in response to low dose bolus glucagon injection. Since catecholamines suppress and glucagon stimulates endogenous insulin secretion, these contrasting observations in lipolysis may

reflect the differing secondary hormonal events induced by these hormones.

The ketogenic response in 3 out of 5 obese subjects was abnormal as evidenced by a decline in plasma ketone body concentration within 2 min post-glucagon injection. The mechanism of this decline is not resolved but the simultaneous decrease in FFA substrate undoubtedly was contributory. This substrate product relationship for FFA and hepatic ketogenesis has been demonstrated both *in vitro* [6] and *in vivo* [9]. However, that a decline in plasma FFA is not the only determinant of the ketogenic response is supported by subject P. M. (1.0 mg/kg) and subject P. Y. (2.0 mg/kg) (fig. 2), both of whom demonstrated a rise in plasma ketone bodies in spite of a simultaneous decline in plasma FFA concentration. This observation supports the concept that glucagon has ketogenic activity in man unrelated to its lipolytic activity as has been suggested in diabetic [17] and non-diabetic man [16]. A decline in plasma ketone bodies in response to other lipolytic hormones has not been reported in obesity. Thus, in response to 30 min of norepinephrine infusion, obese non-diabetic patients exhibited twice as great an increase in mean plasma ketone bodies (1,209 μmoles/l) as observed in the normal weight control subjects (642 μmoles/l) [20].

The mechanism responsible for the 'resistance' to the catabolic actions (lipolysis and ketogenesis) of glucagon in obesity are not resolved by this study. It may relate to the hypersecretion of insulin following bolus glucagon injection. However, obesity is also characterized by insulin resistance [14] which may negate much of the antilipolytic and antiketogenic activity of insulin. Another possible mechanism to explain the resistance to the lipolytic and ketogenic actions of glucagon in obesity would be a reduction of glucagon receptors on appropriate target organ cells as has been reported for insulin receptors [11]. Although no *in vivo* data in man are available, MANGANIELLO and VAUGHAN [10] reported that with increase in age and weight in the rat, a selective loss of glucagon receptors occurs in the fat cell membrane relative to those for epinephrine and corticotropin. Whatever the mechanism for the resistance, it may contribute to the anabolic state characteristic of obesity.

Glucagon is a potent glucogenic hormone in man. All obese subjects demonstrated an immediate increase in glucose concentration following hormone injection. At the dosages of glucagon employed, no difference in plasma glucose response was observed either between the obese group and controls or between the high and low dose injections. This observation suggests that 'resistance' to the hyperglycemic action of glucagon is not present at the dosages employed in this study. At lower dosages, this 'resistance' may be present as suggested by the delayed rise in glucose in obese subjects following endogenous glucagon secretion [15].

Glucagon has been reported to be hypolipemic when injected into hyperlipemic man [1]. The mechanism of this hypolipemic effect is unresolved but may involve both inhibition of hepatic production and enhanced peripheral utilization. HEIMBERG et al.[6] have demonstrated, in liver perfusion experiments, that glucagon inhibits TG secretion at physiological concentrations of FFA substrate. Glucagon may also decrease plasma TG concentration by enhancing peripheral utilization, either by augmenting the transfer of lipids to blood platelets [4] or by other mechanisms not yet elucidated. In any event, our obese subjects demonstrated a significantly

greater decline in plasma TG than controls at both high and low dose glucagon injection. This observation suggests that the hypolipemic action of glucagon is not impaired in obesity.

The dosages of glucagon utilized in this study must be considered to be in the pharmacological range since during the first 10 min following glucagon injection plasma glucagon concentration exceeded 1,000 pg/ml in most subjects. However, under pathophysiological conditions, plasma glucagon concentrations of 3,000 pg/ml have been reported [8]. In addition, portal vein glucagon concentrations may be 10 times peripheral levels [3]. Therefore, the plasma glucagon concentrations obtained in this study may actually be similar to portal vein concentrations under certain pathophysiological conditions. In any case, the results of this study suggest that further investigation of the catabolic activity of glucagon in obesity may provide new insights into the pathophysiology of this disease.

SUMMARY

The response to exogenous glucagon administration was examined in 5 moderately obese subjects (180 ± 20% ideal body weight) and 5 normal weight controls. Changes in the plasma concentration of glucagon, insulin, glucose, free fatty acids, and β-hydroxybutyrate were observed after both a 1.0 μg/kg or 2.0 μg/kg bolus i.v. glucagon injection. At the lowest dose of glucagon (1.0 μg/kg) the obese group exhibited a markedly altered tissue response. In contrast to the uniform increase in free fatty acid and β-hydroxybutyrate concentration in all normal weight subjects, 4 of the 5 and 3 of the 5 obese subjects respectively demonstrated a decline in the plasma concentration of these two hormonally sensitive substrates. This 'resistance' to the catabolic action of glucagon was overcome at a higher dosage of glucagon (2.0 μg/kg) and was accompanied by a simultaneous increase in the ratio of glucagon administered to the insulin secreted. Our study demonstrates a relative resistance to two of the catabolic actions of glucagon in obesity. Although the mechanism of this resistance is not resolved by this study, the hyperinsulinism present in all our obese subjects may be a contributory factor.

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