Role of Insulin and Glucagon in Obesity

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SUMMARY

To investigate the hormonal balance in obesity with respect to insulin and glucagon secretion and to assess their effect at the substrate level, we compared ten obese subjects with an equal number of normal weight controls. No subject was diabetic by USPHS criteria.

Aminogenic hormonal secretion was measured after arginine was given intravenously at a rate of 1 gm./min. for thirty minutes. Changes in the hormonally sensitive substrates, glucose and free fatty acids, were examined in relation to the hormonal secretion.

Our obese population was characterized by increased insulin and decreased glucagon secretion. At the substrate level, these hormonal differences were reflected in changes of serum glucose but not in free fatty acids. DIABETES *23*:657-61, August, 1974.

Obesity is a pathologic condition characterized by excessive body tissues, predominantly adipose tissue. The role of various hormones in producing and/or maintaining the obese state has not been resolved. Two hormones which influence the disposal of foodstuffs into tissue formation are insulin and glucagon.[1] Insulin is an anabolic hormone, enhancing the synthesis of triglycerides from glycerol and free fatty acids, and glycogen from glucose. In the experimental animal, obesity has been produced and maintained with exogenous insulin administration.[2] In man, obesity is characterized by hyperinsulinism,[3] but its role in the pathogenesis of this disorder is not known. In contrast to insulin, glucagon is catabolic, enhancing the conversion of adipocyte triglycerides into free fatty acids and hepatic glycogen to glucose. To date, its role in obesity and level of secretion is unresolved since it has been reported to be reduced, by Wise et al.[4] and elevated, by Kalkhoff.[5] Since insulin is anabolic and glucagon is catabolic, it has been suggested[6] that the relative secretion of these two hormones may determine the net metabolic state of the individual. Until the level of glucagon secretion in obesity is resolved, its net hormonal metabolic state will be in doubt.

Although the plasma concentration of a hormone can be measured, it may not reflect the biologic effect of this hormone at the tissue level. Since insulin and glucagon influence many metabolic systems, more than one parameter may need to be examined to assess net metabolic effect. Glucose and free fatty acids are two substrates influenced by these hormones. Insulin reduces the plasma levels of these substrates in contrast to their elevation caused by glucagon. If obesity is an abnormal metabolic state from an hormonal standpoint, tissue effects of this imbalance might be reflected in changes of these substrates. On the other hand, if tissue response to these hormones is altered in obesity, the hormonal imbalance might not be reflected at the substrate level. The investigation reported here was designed to answer the following two questions: Is obesity characterized by increased or reduced aminogenic glucagon secretion? What effects do the net insulin and glucagon secretions have on regulation of the hormonally sensitive substrates —glucose and free fatty acids?

METHODS

Ten obese subjects averaging 236 ± 20 per cent above ideal body weight by the Metropolitan Life Insurance Tables[7] were chosen from a larger obese population on the basis of a normal[8] glucose tolerance test after a standard 100 gm. oral glucose load (USPHS criteria). The control group consisted of ten healthy controls also nondiabetic by the same criteria. All subjects were instructed to continue their usual weight-maintaining dietary habits. After a twelve-hour overnight fast, all subjects rested supine for

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thirty minutes prior to testing and remained supine until completion of the experiment. Arginine (Argene) in a 5 per cent isotonic solution was given intravenously at a rate of 1 gm./min. for thirty minutes to stimulate hormonal secretion. Frequent blood samples were drawn from the contralateral arm via an indwelling no. 19 scalp vein needle kept patent with a slow drip of isotonic saline. All samples were assayed for insulin, glucagon, alpha amino nitrogen, glucose and free fatty acids by methods previously described.[9] The glucagon-specific antisera has been generated in our laboratory and previously characterized.[10]

RESULTS

The upper one third of figure 1 demonstrates the rise of serum alpha amino nitrogen which occurs in both groups during arginine infusion. This assay measures free amino acids in serum and includes arginine. A similar rise in both groups was observed through twenty minutes after which time a small but statistically nonsignificant reduction in serum alpha amino nitrogen levels occurred in the obese subjects. Table 1 gives the actual values and standard error of the means for this curve.

Table 2 summarizes the serum insulin response of both the obese and control populations. These data are graphically depicted in the upper half of figure 2 and demonstrate that at all time periods measured, the obese population has significantly higher levels of serum insulin in both the basal and stimulated states.

The lower half of table 2 summarizes the plasma glucagon levels assayed with our previously described glucagon-specific antisera.[10] Fasting glucagon concentrations are in good agreement with previously published values using the antibody 30K obtained from Unger.[4,5] However, the rise in plasma glucagon concentration following arginine infusion is two- to threefold greater than has been reported by others using the Unger 30K antibody. The obese population demonstrated no significant difference in glucagon concentration in the basal state compared with controls. However, with arginine stimulation, the plasma glucagon levels in the obese subjects did not attain the same levels as were seen in controls. This difference was significant ($p < 0.05$) at 20, 30 and 40 minutes.

Table 1 summarizes the changes in glucose and free fatty acids with arginine infusion, which are graphically depicted in the lower two thirds of figure 1. The obese group is characterized by both elevated fasting glucose and free fatty acid levels as compared to the controls. With aminogenic stimulation, a delay in the rise of glucose was observed in the obese group as compared to control. At twenty minutes, this difference was significant at the $p < 0.05$ level. The elevated levels of free fatty acids present in the obese population are maintained throughout the infusion, but almost identical absolute decreases in their concentration occur in both groups with arginine infusion.

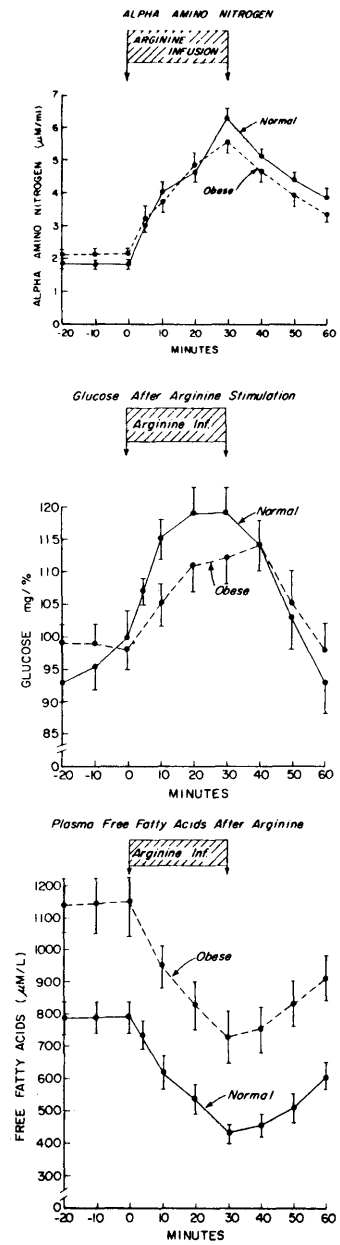

FIG. 1. Effect of arginine infusion on the concentrations of serum alpha amino nitrogen (top), glucose (middle), and free fatty acid (lower) in normal weight and obese patients.

TABLE 1

Substrates After Arginine Stimulation

α Amino Nitrogen (μM/ml.)

Time (Min.)	−5	(Arg.) ↓ +10	+20	+30	+40	+60
Control	1.8 ± 0.1	4.0 ± 0.3	4.6 ± 0.3	6.3 ± 0.3	5.1 ± 0.2	3.8 ± 0.3
Obese	2.1 ± 0.2	3.7 ± 0.3	4.8 ± 0.4	5.5 ± 0.3	4.6 ± 0.3	3.3 ± 0.2
P values	NS	NS	NS	NS	NS	

Glucose (mg.%)

Time (Min.)	−5	(Arg.) ↓ +10	+20	+30	+40	+60
Control	100 ± 4	115 ± 3	119 ± 4	119 ± 4	114 ± 4	93 ± 5
Obese	98 ± 3	105 ± 3	111 ± 4	112 ± 4	114 ± 4	98 ± 4
P values	NS	NS	< 0.05	NS	NS	NS

FFA (μM/L.)

Time (Min.)	−5	(Arg.) ↓ +10	+20	+30	+40	+60
Control	797 ± 57	624 ± 50	539 ± 40	427 ± 25	454 ± 36	605 ± 39
Obese	1,145 ± 85	946 ± 68	829 ± 68	723 ± 78	755 ± 73	914 ± 75
P values	< .01	< .01	< .01	< .01	< .01	< .01

DISCUSSION

To date, two reports have appeared concerning glucagon secretion in obesity. Wise et al.[4] found decreased secretion using alanine as the aminogenic stimulus at a dose of 0.15 gm./kg. body weight infused as a bolus over two to four minutes. At this dosage, plasma alanine in his nondiabetic obese group rose to approximately twice the plasma levels in the normal weight controls. In contrast, Kalkhoff et al.[5] reported elevated glucagon secretion in obesity using arginine stimulation at a dose of 1 gm./min. for thirty minutes in all subjects. Whether plasma arginine levels reached or exceeded control group levels in the obese subjects was not reported. In our study, we used the same format as Kalkhoff and found that alpha amino nitrogen levels were similar in both groups; therefore, the reduced glucagon secretion observed in the obese population cannot reflect inadequate aminogenic stimulus.

Several factors might explain the different levels of glucagon secretion in our obese group as compared to that of Kalkhoff. Although subjects in both groups were given weight-maintaining diets three days prior to testing, the quantity of carbohydrate ingested may have differed significantly. Since a diet high in car-

TABLE 2

Plasma Insulin and Glucagon Concentrations After Arginine Stimulation

Insulin (μU./ml.)

Time (Min.)	−5	(Arg.) ↓ +10	+20	+30	+40	+60
Control	10 ± 1	27 ± 3	40 ± 5	51 ± 8	41 ± 6	21 ± 4
Obese	35 ± 5	78 ± 9	131 ± 22	141 ± 23	115 ± 17	46 ± 8
P values	< .01	< .01	< .01	< .01	< .01	< .01

Glucagon (pg./ml.)

Time (Min.)	−5	(Arg.) ↓ +10	+20	+30	+40	+60
Control	87 ± 26	523 ± 67	749 ± 124	990 ± 155	715 ± 133	256 ± 99
Obese	69 ± 26	323 ± 131	411 ± 129	512 ± 96	300 ± 72	100 ± 33
P values	NS	NS	< .05	< .05	< .05	NS

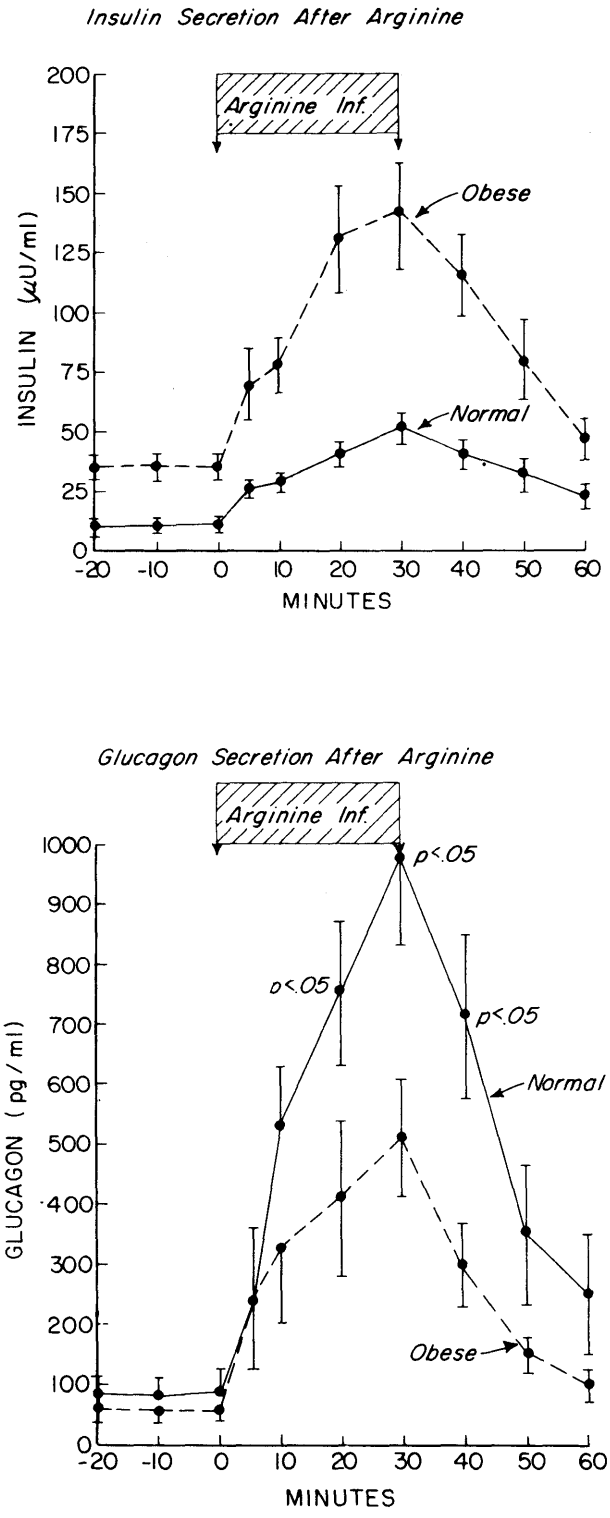

FIG. 2. Effect of arginine infusion on the concentrations of serum insulin (top) and glucagon (lower) in normal weight and obese patients.

bohydrate is known to suppress glucagon,[11] a high carbohydrate intake in our obese group might lead to reduced glucagon secretion. Other differing variables in their study and ours may include growth hormone secretion, degree of obesity, age, sex and basal free fatty acid concentrations.

Different investigators have reported elevated,[12] normal[13] and reduced[14] free fatty acid levels in obesity suggesting that much variation exists in this population. However, our obese population is characterized by elevated basal FFA concentration, suggesting the possibility of a contribution of FFA metabolism to hormone regulation. Experimental changes in plasma free fatty acid levels in man have demonstrated that a reduction results in both a decreased basal insulin and a reduced insulin response to insulinotropic agents.[15] In contrast, an experimental increase in free fatty acids results in an enhanced immunoreactive insulin response to glucose stimulation.[15] These data have been interpreted to suggest that free fatty acids are important regulators of insulin secretion in man. Luyckx et al.[16] have shown that glucagon secretion in the dog is stimulated when plasma free fatty acids are reduced with nicotinic acid. Conversely, Madison et al.[17] have reported that an increase in plasma free fatty acids obtained by simultaneous infusion of triglyceride and heparin in the dog causes an immediate fall in glucagon and elevation of insulin. Thus, the elevated plasma FFA concentration in our obese patients may contribute to the simultaneous suppression of glucagon secretion and stimulation of insulin secretion. Since this potential regulatory process has not been previously reported in man, further data must be obtained before final conclusions can be made. Since neither Wise et al. nor Kalkhoff et al. reported the free fatty acid levels in their obese population, a direct comparison with our data is not possible.

Our data indicate that obesity is characterized by increased insulin and decreased glucagon secretion. From a hormonal standpoint, this would suggest that an anabolic state exists compared to a control population under similar aminogenic stimulation. However, since insulin resistance is also characteristic of obesity,[18] extrapolation of hormonal effects from plasma hormone concentration may not be possible. The two substrates, glucose and free fatty acids, are regulated in vivo to a large extent by insulin and glucagon secretion.[19] Insulin reduces the plasma level of both these substrates in contrast to the elevation caused by glucagon. If obesity is characterized by a derangement in insulin and glucagon secretion, one might expect to see this derangement reflected in the

changes that occur in the hormonally sensitive substrates—glucose and free fatty acids.

A difference between the two groups was observed with glucose but not with free fatty acids. After aminogenic stimulation, the obese population's glucose rose more slowly and obtained a lower absolute value. This difference was not observed with free fatty acids since similar absolute decreases were observed in both groups. Within the limits of our experimental design, we conclude from these data that the abnormal plasma levels of insulin and glucose in obesity may be reflected in glucose but not in free fatty acid metabolism. A possible role of growth hormone in these events has not been excluded by this study.

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