The Effect of Glucagon, Phenmetrazine and Epinephrine on Hunger, Food Intake and Plasma Nonesterified Fatty Acids

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Experimental data suggest that some humoral substance may exist which signals the hypothalamic "centers" responsible for feeding behavior and thus takes part in the control of food intake. Since hunger is predictably relieved by the ingestion of food, investigations to identify this substance have centered upon the study of the products of digestion. The general hypothesis is that between feedings the supply of some substance becomes depleted and its concentration in the blood lowered; therefore, hunger ensues. It has been assumed that when a meal is eaten, the absorption of this substance raises its level in the blood, and satiety results. In this context, the blood glucose and the blood glucose arteriovenous difference have been investigated extensively by a variety of methods.[1–3] However, work from this laboratory[4] has raised serious doubt that either the blood glucose or the blood glucose arteriovenous difference directly mediates the control of hunger. Observations on the role of fatty substances[5] and amino acids[6] in this connection have been inconclusive.

In the course of our investigations, we have noted that the pancreatic hormone, glucagon, exerts a powerful depressing effect on the appetite of healthy men and that this effect is temporally unrelated to its effect on blood glucose. However, glucagon also has marked effects on fat metabolism,[7] one of which is a biphasic effect on the plasma nonesterified fatty acids. After an initial fall, the nonesterified fatty acid level begins to rise ninety minutes after glucagon injection and continues to rise for several hours. This rising nonesterified fatty acid level coincides temporally with the appetite-depressing effect of glucagon. The present studies were undertaken to determine whether or not the appetite-depressing effect of glucagon is related to its effect on plasma nonesterified fatty acids. As a part of these studies, the effects of glucagon on nonesterified fatty acid levels and hunger were compared with those of phenmetrazine* and epinephrine. Phenmetrazine was used as an appetite depressant known to have no great effect on nonesterified fatty acids, and epinephrine was used because it reliably raises plasma nonesterified fatty acid levels. Glucose was administered orally on one occasion to produce a rapid fall in the nonesterified fatty acid level.

METHODS

Ninety-four experiments were carried out on four healthy young men. They came to the laboratory twice weekly at 5 P.M. following a four hour fast. Upon arrival, and at thirty minute intervals thereafter, they were asked to complete a multiple choice questionnaire to assess their degree of hunger. In one series of experiments, subjects were given either 1 mg. glucagon intramuscularly or placebo upon arrival and either 25 mg. phenmetrazine orally or placebo one hour later. A test meal was served at

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* As Preludin,® Geigy Pharmaceuticals, Yonkers, New York.

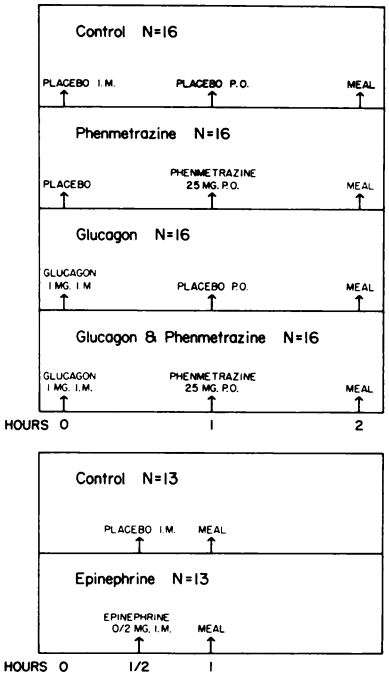

FIG. 1. Medications schedule.

two hours. In another series of experiments, either 0.2 mg. epinephrine was administered intramuscularly or placebo was given a half hour before a test meal. Choice of medication was determined randomly, and administration was double blind. The medication schedule is summarized in Figure 1. Blood was drawn on arrival and every thirty minutes thereafter for determination of plasma nonesterified fatty acid levels by the method of Dole.[8] Subjects were comfortably seated, reading, studying or talking during the experiment. Test meals consisted of cold roast beef, potato salad, cole slaw, bread and butter, milk and cookies. A total of 2,600 calories was offered at each meal. Subjects were allowed to eat as much as they wanted. They were told that this was a "metabolic experiment" and were not aware that their food intake was a major endpoint of the study. Meals and physical surroundings were similar at each session.

RESULTS

Plasma Nonesterified Fatty Acids

The effect of test substances on plasma nonesterified fatty acids is summarized in Figure 2. Mean control values are shown. There was a slow slight rise from the initial value of 926.3 ± 15.1 μg. per L.* to the two hour value of 979 ± 17.9 μg. per L. This is consistent with increased fat mobilization during fasting. There is no significant difference in the curve following phenmetrazine administration. Administration of 1 mg. glucagon caused a pronounced decrease in plasma nonesterified fatty acids, the fasting mean of 986.6 ± 13.8 μg. per L. dropping to 699.9 ± 13.1 at thirty minutes, 504.8 ± 10.6 at one hour and to 497.5 ± 10.9 at one and a half hours. By two hours, levels had risen to 624.3 ± 13.4. Figure 2 also demonstrates the anticipated effect of glucagon in the first hour with a fall from an initial mean of 912.8 ± 12.1 to a one hour mean of 469.3 ± 11.8. Phenmetrazine, when given after glucagon, produced an effect not significantly different from that of glucagon alone. In the second series of experiments, the administration of 0.2 μg. epinephrine caused a rise in plasma nonesterified fatty acids from an initial mean level of 885 to 1,818.2 μg. per L. thirty minutes following injection.

* Variation is expressed as the standard error of the mean (S.E.M.).

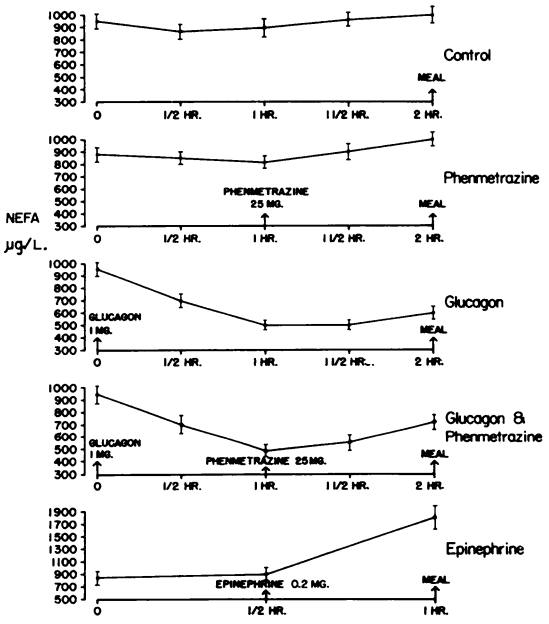

FIG. 2. Effect of several test substances on the nonesterified fatty acid levels of men.

Effect on Hunger

The effect of test drugs on hunger is summarized in Figure 3. All subjects reported themselves "very hungry" or "hungry" at the beginning of the experiment. A "decrease in hunger" meant that subjects, initially hungry, reported that they were either "not hungry" or "slightly nauseated" when the meal was served. Decrease in hunger was reported in two of twenty-nine control experiments, one of sixteen experiments with phenmetrazine, nine of sixteen experiments with glucagon, ten of sixteen experiments with glucagon and phenmetrazine and two of thirteen experiments with epinephrine.

Effect on Food Intake

Depression of food intake is defined as consumption of a number of calories 2 standard deviations below the mean control food intake of that subject. Results are summarized in Figure 4. Depression of food intake occurred in two of twenty-nine control experiments, two of sixteen experiments with phenmetrazine, five of sixteen experiments with glucagon, five of sixteen experiments with glucagon and phenmetrazine and in two of thirteen experiments with epinephrine.

COMMENTS

The effect of glucagon on hunger, whether or not phenmetrazine was given, was pronounced and was greater than that noted in control

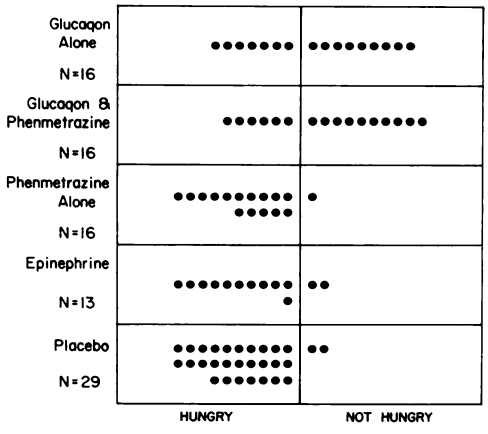

FIG. 3. Effect of treatment with glucagon, phenmetrazine, epinephrine and placebo on hunger.

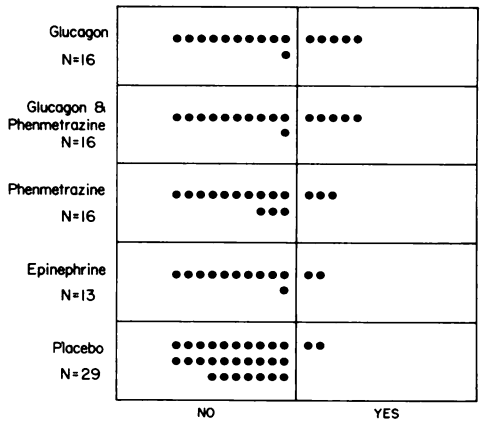

FIG. 4. Effect of treatment with glucagon, phenmetrazine, epinephrine and placebo on food intake. Yes = depression of intake; No = no depression of intake.

experiments ($p < 0.001$), in experiments with phenmetrazine ($p < 0.001$) and in experiments with epinephrine ($p < 0.001$). The effect of glucagon on food intake, whether or not phenmetrazine was given, was significantly different from that in placebo experiments ($p < 0.05$). However, there was no significant difference between the effect of glucagon on food intake and that of either phenmetrazine alone or of epinephrine. Phenmetrazine and epinephrine seemed to have no significant effect upon either hunger or food intake under the conditions of these experiments.

The mean number of calories consumed at each meal was 2,275; this is a large single meal. After the experiment, subjects said that, not knowing the purpose of the experiment, they had "saved up" for these biweekly sessions, eating little breakfast or lunch on experimental days. They came to the laboratory prepared to eat huge amounts of food even though they might not be hungry. For example, one subject reported himself as "slightly nauseated" and proceeded to consume 2,600 calories. These results emphasize the importance of observing more than one aspect of the subjects' response in studies of hunger. The subjects' determination to eat may also explain why phenmetrazine, a clinically useful appetite depressant,[9] failed to exert much effect on food intake in these experiments. Yet, on a significant number of occasions,

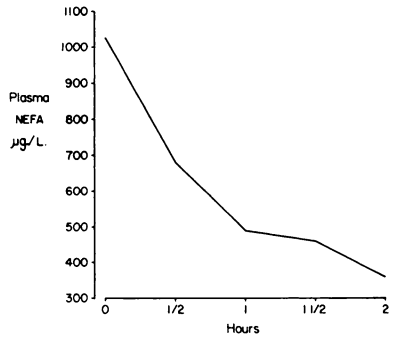

FIG. 5. Effect on plasma nonesterified fatty acid levels of 100 gm. glucose administered orally. The values are the means for four subjects.

glucagon exerted an effect sufficiently powerful to break through the subjects' determination to eat.

No fluctuation of plasma nonesterified fatty acid levels *per se* could be predictably associated with appetite depression. After 0.2 µg. epinephrine was given, which produced a sharp rise in nonesterified fatty acid levels, no consistent effect on food intake was observed. A sharp rise in the nonesterified fatty acid level did not appear to be associated with depression of food intake.

Epinephrine produced high plasma nonesterified fatty acid levels but had little effect upon either food intake or hunger. It is, therefore, unlikely that a high plasma nonesterified fatty acid level *per se* affected hunger or food intake.

A rapidly falling plasma nonesterified fatty acid level was observed soon after glucagon administration in these subjects. In previous work[4] we found that the effect of glucagon on hunger and food intake is not observed thirty minutes after injection when nonesterified fatty acid levels are falling rapidly, but at two hours after injection when they have returned to their former levels.

Low plasma nonesterified fatty acid levels may be produced by the ingestion of large amounts of carbohydrate.[8] Response of these four subjects to the administration of 100 gm. glucose is shown in Figure 5. We have found in previous experiments that this amount of glucose does not affect hunger or food intake either thirty minutes or two hours after its ingestion.[4] It is, therefore, unlikely that low plasma nonesterified fatty acid levels *per se* had any effect upon hunger or food intake.

Thus, in these experiments no association could be made between the appetite-depressing effect of glucagon and its effect on plasma nonesterified fatty acids. Previous work[4] showed that the effect of glucagon on blood sugar is not temporally correlated with its effect on hunger and food intake. The present studies confirm the appetite-depressing effect of glucagon, which was effective in a situation in which phenmetrazine had little effect. No distinct relation between the known metabolic effects of glucagon and its effect on hunger was found. Other work from this laboratory strongly suggests that the effect of glucagon on hunger may be related to its effect on the stomach.[16] Whether or not this is a direct or centrally mediated effect is not yet clear.

SUMMARY AND CONCLUSION

Ninety-four experiments were carried out in four healthy young men to determine the effects of glucagon, epinephrine and phenmetrazine on their plasma nonesterified fatty acid levels, hunger and food intake.

Glucagon caused an initial fall in nonesterified fatty acid levels and then a rise. Epinephrine caused a rise, and phenmetrazine had no significant effect. Glucagon, whether given with phenmetrazine or alone, had a significant depressing effect on hunger when compared with epinephrine, phenmetrazine and placebo. Under the conditions of these experiments, epinephrine and phenmetrazine had an effect not significantly different from placebo. Glucagon had a significant depressing effect on food intake when compared with placebo. No other substance significantly depressed food intake. The potent anorexigenic effect of glucagon did not appear to be the result of any fluctuation of plasma nonesterified fatty acid levels *per se*. The effect of glucagon on appetite could not be specifically correlated with any of its known metabolic effects.

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