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Research Article

EFFECT OF GROWTH HORMONE ON PLASMA FATTY ACIDS *

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Administration of growth hormone to animals has been found to reduce fat stores (1, 2), to increase liver fat (3, 4) and to cause ketosis (5) and a depression of respiratory quotient (6, 7). The increase in mobilization and metabolism of fat implied by these findings has been thought to contribute either in an auxiliary or in an essential way to the anabolic stimulus induced by growth hormone.

The recent work of Dole (8) and of Gordon and Cherkes (9, 10), indicating a relationship between the concentration of plasma unesterified fatty acids and adipokinesis, suggested another approach to the study of the effects of growth hormone on fat mobilization and offered a means of studying the effect in man.

METHODS AND MATERIALS

Plasma fatty acids were extracted and titrated according to the method of Dole (8). The term "fatty acids" as used in this paper is synonymous with nonesterified acids (NEFA) and unesterified fatty acids (UFA).

Purified preparations of human, simian and porcine growth hormone were made by the glacial acetic acid extraction method (11, 12). "Partially purified porcine growth hormone (acetic fraction)" refers to material extracted in the same way and treated with oxidized cellulose to remove corticotropin and intermedin, but not carried through the final precipitations.

Human and porcine corticotropin were prepared by the oxycel method of Astwood, Raben, Payne and Grady (13).

Purified bovine growth hormone (NIH-BGH-1) and ovine lactogenic hormone (NIH-SP-1) were gifts from the Endocrinology Study Section, National Institutes of Health. These and Thyrotropar® (bovine thyrotropin) were prepared by Armour and Company.

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RESULTS

Studies in dogs

Plasma fatty acid values were elevated by fasting and depressed by the administration of food, glucose, or insulin, as previously noted by others (9, 10). In both normal and diabetic dogs the morning fasting value was increased 100 per cent or more in each dog after an injection of 80 to 100 mg. of partially purified porcine growth hormone (acetic fraction) administered the preceding afternoon. The results of 22 determinations in three normal dogs and 15 determinations in three diabetic dogs are shown in Figure 1.

Although growth hormone raised the fasting value of fatty acids, it did not prevent the fall that occurred with infusions of glucose or glucose and insulin. Despite the administration of 80 mg. of acetic fraction both 18 hours before and again at the start of an intravenous infusion, injection of glucose at a rate of 1 Gm. per Kg. per hour into

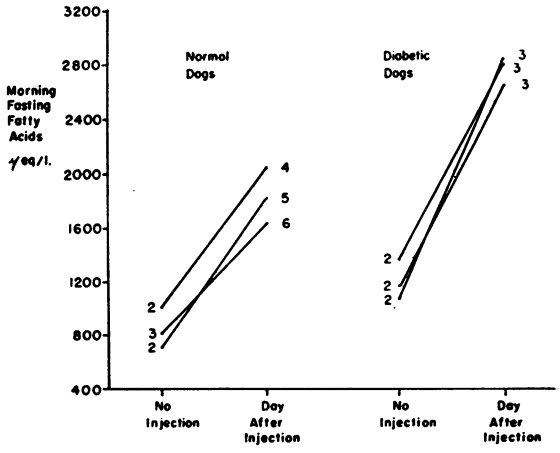

FIG. 1. FASTING VALUES OF PLASMA FATTY ACIDS IN NORMAL AND DIABETIC DOGS WITH AND WITHOUT GROWTH HORMONE

Eighty to 100 mg. of acetic fraction was administered 18 hours earlier. Each point is the average of the indicated number of determinations.

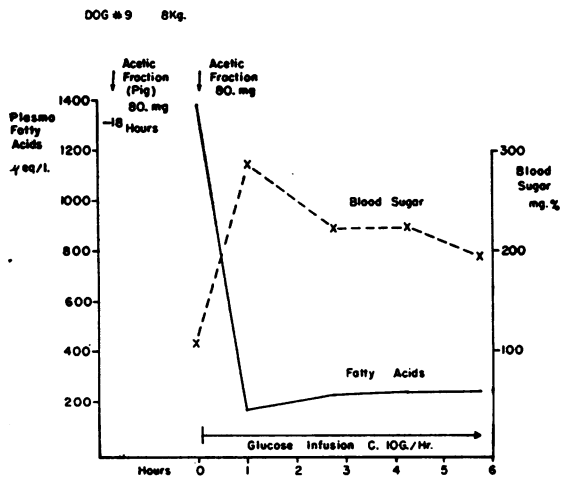

FIG. 2. THE EFFECT OF GLUCOSE ON FATTY ACID VALUES IN A DOG PRETREATED WITH GROWTH HORMONE

a dog anesthetized with sodium pentobarbital produced a fall in fatty acids from 1,400 to 180 μEq. per L. in one hour and the value remained low during the six hour infusion (Figure 2). A fall in concentration of variable magnitude was observed without glucose in dogs anesthetized with pentobarbital, but the depressant effect of glucose was much greater than that obtained with anesthesia alone.

In a similar experiment, but with insulin as well as glucose in the infusion medium, the value again fell despite prior growth hormone administration, but large doses of epinephrine, 0.2 mg. and 0.25 mg. given 10 minutes apart intravenously, caused a rapid rise in fatty acids despite the continued infusion. Fatty acids rose from 250 μEq. per L. to 1,220 μEq. per L. 30 minutes after the first injection. Growth hormone differed from epinephrine, which had previously been shown to elevate fatty acids (8, 9), in producing a slower response and a more sustained rise after a single injection and in the complete suppression of its effect by glucose.

Alloxan diabetic dogs were more sensitive than normal dogs to the effect of growth hormone. The difference in sensitivity was more apparent when sampling was performed seven hours after the daily meal rather than after a 24 hour fast. Growth hormone administered four hours before the determination greatly increased the values in diabetic dogs but affected normal dogs only slightly. In this experiment growth hormone elevated the values before a spontaneous postabsorptive rise occurred, suggesting that food suppresses the growth hormone effect less effectively in the diabetic dog.

The diabetic dogs responded to the smallest doses of purified growth hormone preparations used, 0.03 mg. per Kg. Fatty acid values in dogs were increased with purified preparations of porcine, bovine, human and simian growth hormone in contrast to the values in man which were affected only by the human and simian materials. The responsiveness of dogs to human growth hormone appeared to diminish over some weeks with repeated injections, whereas human subjects showed no loss in sensitivity over much longer periods.

Studies in man

The fasting value of plasma fatty acids in man was increased within four hours by the injection of human growth hormone. Fasting samples were obtained between 8:00 and 10:00 a.m.; the test substance was then administered intramuscularly and another blood sample was obtained four hours after the injection.

In the first group of 11 tests in five subjects, the average plasma fatty acid value rose from 555 μEq. per L. to 1,107 μEq. per L. following administration of 3 to 8 mg. of human growth hormone. In an equal number of trials without hormone, the average values were 642 μEq. per L. initially and 628 μEq. per L. four hours later. The individual

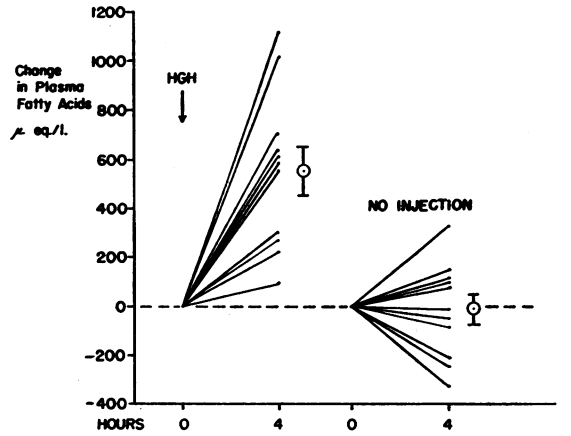

FIG. 3. EFFECT OF 3 TO 8 MG. OF HUMAN GROWTH HORMONE ON FASTING PLASMA FATTY ACID VALUES IN HUMAN SUBJECTS

responses are shown in Figure 3. The time of maximal effect was not established but was probably longer than four hours. Four mg. of human growth hormone raised the value for at least 24 hours in hypopituitary subjects, but usually for less than this period in normal subjects.

Three subjects, two normal adult males and an elderly hypopituitary male, were tested repeatedly over a six month period. The four hour change in fatty acids exceeded 400 μEq. per L. in 16 or 18 trials with hormone and in none of 14 trials without hormone (Figure 4). The minimal effective dose in the normal subjects was approximately 1.0 and 2.0 mg., while the hypopituitary subject had a substantial response from 0.5 mg., the smallest dose used. Other hypopituitary subjects were also found to be more sensitive than normal individuals, and some normal subjects required larger doses for a definite effect than the subjects of Figure 4.

As in the dog, glucose and food abolished the fatty acid response to growth hormone. Figure 5 illustrates a study in a 73 year old hypopituitary male in whom two control (2:00 p.m.) fasting values were 427 and 366 μEq. per L. on two different days. Injection of 4.0 mg. of human growth hormone at 10:00 a.m. produced a 2:00 p.m. value of 1,457 μEq. per L. When breakfast was allowed and 125 Gm. of glucose was ingested (50 Gm. at 9:30 a.m.; 50 Gm. at 12:15 p.m.; 25 Gm. at 1:30 p.m.), the 2:00 p.m. value was lowered to 130 μEq. per L. despite the injection of the same amount of growth hormone.

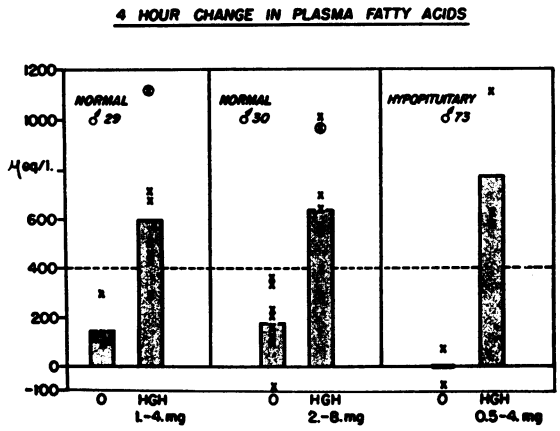

FIG. 4. CHANGE IN FATTY ACID VALUES IN TWO NORMAL AND ONE HYPOPITUITARY SUBJECT TESTED REPEATEDLY OVER SIX MONTHS

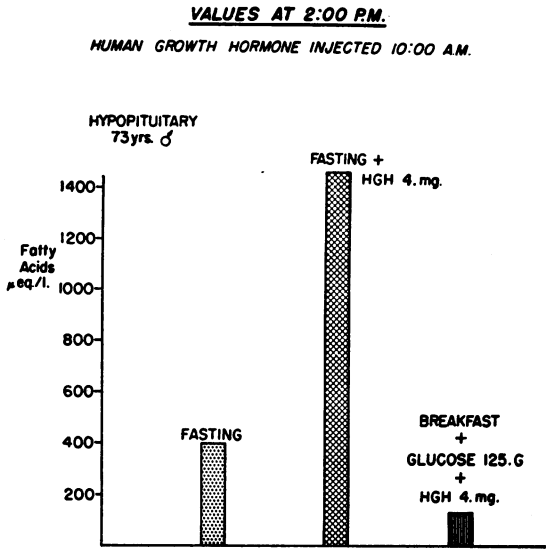

FIG. 5. INHIBITION OF THE PLASMA FATTY ACID RESPONSE TO HUMAN GROWTH HORMONE WITH FOOD AND GLUCOSE

Simian growth hormone was also active in man but porcine and bovine preparations were inert. All values four hours after 3 to 8 mg. of human growth hormone and after 4 to 20 mg. of simian growth hormone exceeded 1,000 μEq. per L. and all values on control days or after other pituitary preparations were below this figure (Figure 6). These included values after 20 to 30 mg. of porcine and 30 mg. of bovine growth hormone, 10 units of Thyrotropar®, 25 mg. of lactogenic hormone, and 50 to 400 clinical units of porcine and human corticotropin.

Larger effects might have been expected with corticotropin which was shown by Rosenberg (14) to increase liver fat in the mouse, and by White

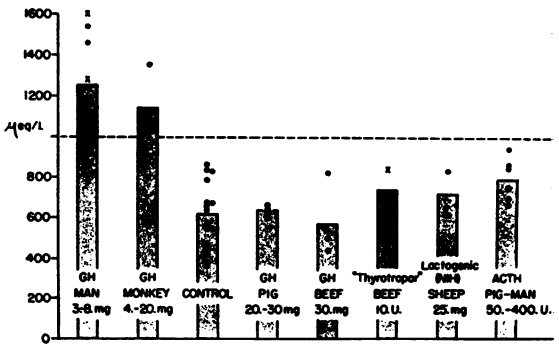

FIG. 6. PLASMA FATTY ACID VALUES IN THE THREE SUBJECTS OF FIGURE 4 FOUR HOURS AFTER TEST SUBSTANCES AND ON CONTROL DAYS

and Engel (15) and by Astwood (16) to stimulate fatty acid release from rat adipose tissue when added *in vitro*. The small response to corticotropin was apparently not due to adrenal stimulation, since cortisone neither lowered the fatty acid value nor inhibited the response to growth hormone.

In the subjects tested repeatedly over a six month period no loss in responsiveness to human growth hormone was observed and the material was invariably well tolerated. Most subjects noted no subjective effects, but three reported an increased libido and an obese woman on a 400 calorie diet reported a diminution in appetite when receiving human growth hormone (5.0 mg. per day). Blood sugar values were not affected in these tests.

DISCUSSION

The small doses of human growth hormone needed to elevate plasma fatty acids suggest a physiological role for this hormone in fat mobilization as well as in growth. Indeed, if corrected for body weight, the dose necessary for fatty acid elevation may be smaller than that required for growth, although little information is as yet available as to the amount needed for growth in man (17).

The suppression of the adipokinetic effect by food provides a mechanism of control not requiring changes in growth hormone secretion. Growth hormone could control, at least in part, the rate of fat mobilization in the postabsorptive state and yet be present at all times to direct the available energy whether from food or fat depots, towards protein synthesis and protein sparing. A pattern such as this would make unnecessary rapid fluctuation in hormone level in response to rapidly changing conditions. The long survival of injected growth hormone (18) makes it indeed unlikely that rapid changes in available hormone can occur.

The decrease in fatty acids after glucose in a hypopituitary subject, as also noted in this study, suggested to Dole, Bierman and Roberts (19) that the control of the release of fatty acids was independent of the pituitary. It is now seen that growth hormone accelerates fat mobilization beyond the rate induced by fasting in the absence of the pituitary.

Human growth hormone prepared by the acetic acid extraction method is virtually free of other known anterior and posterior lobe hormones, and thus its adipokinetic effect must be due to growth hormone or to a yet unidentified factor present in the preparation. The specificity of the human response to human and simian preparations noted in this study is compatible with other evidence of growth hormone behavior in man. Porcine and bovine preparations have appeared active only occasionally in many metabolic balance and growth studies. Human preparations have been regularly active and simian hormone, though less extensively tested, has appeared to be active in metabolic balance studies (20–24). The fatty acid response may indeed provide a rapid test for the effectiveness of growth hormone preparations in man (25).

SUMMARY

Fasting values of plasma unesterified fatty acids were raised in man by human and simian growth hormone and in the dog by human, simian, porcine and bovine growth hormone. Glucose, glucose and insulin, and food suppressed the effect of growth hormone on fatty acids. It was inferred that growth hormone influences the rate of fat mobilization in the postabsorptive period.

ACKNOWLEDGMENT

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CORRECTION

In the paper by Scheinberg and Morell entitled "Exchange of Ceruloplasmin Copper with Ionic Cu^{64} with Reference to Wilson's Disease," in volume 36, pages 1193–1201, line 3 of page 1193 should read ". . . 15 to 30 mg. per 100 ml." In addition, columns 6 and 8 of Table IV on page 1197 are in error. The values given should read as follows:

.....Ceruloplasmin $\Delta O.D._{610}^{5cm} \div 0.34$	.....Enzymatic activity
mg./ml.	ΔO.D./min.
0.548	0.0546
0.380	0.0459
0.494	0.0399
0.576	0.0510
0.424	0.0408
0.448	0.0393