Effect of Acute Glucose Infusion on Plasma Concentrations of Human Growth Hormone (HGH).* (32345)

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It has been demonstrated(1,2) that oral glucose administration caused a temporary suppression of plasma Human Growth Hormone (HGH) level, followed by its elevation at 4-6 hours. This "secondary rise" of plasma HGH following glucose administration has been considered due to a stimulation caused by the rapid fall of blood sugar level. However, Hunter, Clarke and Duncan(3) recently pointed out that the stimulus to the increase of HGH was neither the amount nor rapidity of the fall of blood sugar, but was related to the reduction of its level below a threshold value, which was shown to be lower than the fasting blood glucose level.

We attempted to study this relationship in 18 normal subjects, by serial measurements of HGH after glucose infusion performed for periods of 3, 10, 20 and 30 minutes, and report the results obtained.

Materials and methods. All 18 subjects were healthy male students, their ages ranging from 21 to 24 years old. They were non-obese, and had no family history of diabetes mellitus. All had fasted overnight for 13-15 hours. Upon arrival at the hospital next morning, subjects had bed rest for at least 30 minutes before starting glucose infusion. Bed rest was taken throughout the study. Continuous intravenous infusion of glucose was performed for periods of 3, 10, 20 and 30 minutes as indicated in Table I. Blood was drawn from antecubital vein by heparinized syringe before and at appropriate intervals, timed from the start of the infusion. Plasma was obtained by immediate centrifugation and samples were stored at —20C till the time of measurement.

Plasma HGH concentrations were determined by the method of Glick, Roth, Yalow and Berson(4). Our current assay is capable to detect 0.25 mμg/ml of Raben HGH preparation. Plasma glucose and non-esterified fatty acids (NEFA) were measured by glucose oxidase method(5) and Dole's method (6).

Results. Results are shown in Table I. All cases showed rapid fall of blood glucose following the cessation of glucose infusion. Plasma NEFA, which are not recorded in the Table, showed a sharp decrease followed by a gradual increase in all cases.

In the group of 3-minutes' infusion (cases 1-8), the reduction of blood glucose below the fasting level (hypoglycemic phase) was reached in all cases except for case 5 by 60-90 minutes. A definite rise of plasma HGH was defined as an increase exceeding 3 mμg/ml, and this was observed in 3 cases (cases 6-8) at 180 minutes. In the group of 10, 20 and 30-minutes infusion (cases 9-18), the hypoglycemic phase was reached in all cases except for case 11 by 60-120 minutes. A definite rise of plasma HGH was observed in all cases by 90-180 minutes.

Discussion. Our results showed that in 5 of 8 cases of 3 minutes' infusion, no rise of plasma HGH occurred. Of these 5 cases, a hypoglycemic phase occurred following infusion in 4 cases (cases 1-4), and the blood glucose levels of cases 1-3 at this phase were 42, 49 and 60 mg/ml, which appear to be below the threshold value shown by Hunter *et al*(3). Only 3 cases of 3 minutes' infusion showed the rise of plasma HGH at 180 minutes, whereas all 10 cases of 10, 20 and 30 minutes' infusion showed the rise. From the Table, it is clear that the time of HGH rise after the period of falling blood glucose is variable.

From these results, it appears that the falling blood glucose *per se* is not a direct stimulus, and that the reduction of blood glucose below the fasting level is not necessarily a stimulatory factor of HGH secretion. It appears that the high concentration of

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TABLE I. Plasma Glucose and HGH Concentrations Following Glucose Infusion.

No. of cases	Infusion period (min)	% of glucose solution infused	Total glucose infused (g)	Time from start of infusion: 0 min	10 min	20 min	30 min	60 min	90 min	120 min	180 min	240 min
1	3	50	25	65* <.25†	234 <.25	176 <.25	94 <.25	42 <.25	61 <.25	61 <.25	78 <.25	
2	3	50	25	71 3.6	240 3.0	172 2.3	151 4.0	96 3.4	49 5.0	53 3.7	58 1.6	71 3.2
3	3	50	25	77 <.25	219 <.25	175 <.25	145 <.25	99 <.25	73 <.25	60 <.25	83 1.0	93 <.25
4	3	50	25	75 .5	253 <.25	242 <.25	170 .8	71 .5	84 1.0	84 1.8	94 .8	
5	3	50	25	46 .8	156 .6	140 <.25	106 .3	52 .3	58 .3	69 .3	74 1.9	66 1.9
6	3	50	25	82 <.25	207 1.2	161 1.2	139 .9	86 2.0	63 <.25	69 <.25	79 6.5	90 2.8
7	3	50	25	75 <.25	260 <.25	222 <.25	168 <.25	102 <.25	63 .5	53 3.0	64 23.1	76 14.0
8	3	50	25	86 <.25	246 <.25	184 <.25	94 <.25	59 <.25	74 <.25	63 <.25	67 3.6	74 9.0
9	10	50	25	67 4.0	286 <.25	205 —	154 .8	67 <.25	49 <.25	44 5.0	64 4.0	80 5.2
10	10	50	25	75 <.25	213 <.25	190 <.25	126 <.25	56 <.25	59 <.25	70 <.25	81 4.0	
11	10	50	25	64 —	156 8.2	216 2.0	167 3.0	76 1.0	75 .4	88 30.0	95 30.0	
12	10	50	25	75 3.7	287 6.4	188 4.8	162 7.4	75 8.1	69 —	71 11.6	90 17.0	98 15.6
13	20	50	25	86 6.4	178 5.1	191 6.4	170 7.0	87 1.5	73 7.7	77 7.0	86 15.8	85 40.8
14	20	50	25	85 6.3	206 6.3	246 7.6	166 6.3	82 3.3	68 6.2	72 20.0	76 —	95 15.9
15	20	10	30	82 —	222 <.25	143 <.25	105 <.25	65 <.25	60 23.0	64 10.6	67 <.25	71 <.25
16	20	10	30	74 1.5	120 3.0	170 1.0	156 1.0	70 2.5	49 1.0	47 15.0	76 10.0	
17	30	10	50	86 <.25	— —	332 .3	362 .4	187 <.25	118 .4	54 1.2	86 5.0	
18	30	10	50	73 <.25	— —	254 .8	416 <.25	322 <.25	251 <.25	60 .5	70 5.5	

* Left number shows plasma glucose (mg/dl.).

† Right number shows plasma HGH (mμg/ml).

The rise of plasma HGH is indicated by an underline.

blood glucose must be maintained for a certain period before its reduction to stimulate HGH secretion.

Our observation is difficult to interpret, but raises some questions on the regulatory manner of HGH secretion mediated by glucose metabolism. If the stimulation of HGH secretion occurs by intracellular glucose deprivation(1-3) in the hypothalamus(2,7) as proposed, glucose infused for a short period in most cases is unable to induce enough metabolic shift in the hypothalamic cells to stimulate HGH secretion, in spite of other definite responses such as plasma NEFA change. An alternative explanation may be that the direct stimulant of HGH secretion is not the extracellular or intracellular glucose itself, but the metabolites or other substances related to glucose metabolism, which are different quantitatively or qualitatively in the conditions of short and long continuous glucose infusion. Since plasma NEFA change was similar in all cases, it is apparent that there is no correlation between the rise of plasma HGH and the value of plasma NEFA. In these respects, our results may support the observation of Quabbe *et al*(8), who showed the absence of correlation between plasma HGH rise and blood glucose or plasma NEFA level during a 24-hour fast in normal subjects.

Summary. Serial plasma HGH concentrations were measured, in 18 normal subjects, following continuous intravenous glucose infusion performed for periods of 3, 10, 20 and 30 minutes. In 5 of 8 cases infused for 3 minutes, no rise of plasma HGH was observed in spite of the rapid fall of blood glucose with (4 cases) or without (1 case) its reduction below the fasting level. The 3 other cases infused for 3 minutes and all 10 cases of 10, 20 and 30 minutes' infusion showed definite rise of plasma HGH at 90-180 minutes following the infusion. From the results obtained, it appears that the falling blood glucose *per se* is not a direct stimulus, and the reduction of blood glucose below the fasting level is not necessarily a stimulus to HGH secretion.

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Role of Protein Component of Endotoxin in Modification of Host Reactivity.* (32346)

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The bacterial endotoxins are characterized as lipopolysaccharides(1,2). Boivin-type preparations of endotoxins contain significant amounts of protein which may be largely removed by phenol-water partition(3) yielding purified and potent Westphal-type endotoxins of low protein nitrogen content. Ribi and co-workers(4) have succeeded in preparing a potent protein-free endotoxin having the usual range of toxic and protective properties and containing only 0.2% nitrogen, accounted for by hexose-amine content. This lack of dependence of biological activity upon protein content or presence has led to

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