Brief Notes and Comments

Effect of Insulin on the Exaggerated Glucagon Response to Arginine Stimulation in Diabetes Mellitus

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SUMMARY

The effect of insulin on the glucagon response to intravenous arginine was studied in eight juvenile-type and six adult-onset diabetics. In the juvenile-type diabetics, concomitant administration of insulin significantly blunted the glucagon response from a mean maximal rise of 310 ± 54 pg./ml. to only 184 ± 39 pg./ml. ($p < 0.01$), about the same as in nondiabetics. In the adult-onset patients, however, insulin had no effect, the mean maximal rise being 250 ± 50 pg./ml. without insulin and 307 ± 71 pg./ml. with insulin (N.S.).

This study demonstrates that in juvenile-type diabetics concomitant administration of supraphysiologic quantities of insulin can reduce the exaggerated glucagon response to intravenous arginine to normal, whereas in the adult-type group, it has no apparent effect. DIABETES *25*:227-29, March, 1976.

Hyperglucagonemia has been reported in all forms of experimental[1-4] and spontaneous diabetes mellitus.[5-7] In human diabetes of both juvenile-onset and adult-onset types, the glucagon response to amino acid stimulation is greater than in nondiabetics.[6,8] However, it is not clear whether these abnormalities in man simply represent the consequences of the concomitant insulin deficiency or reflect an independent and perhaps even primary disturbance of A-cell function. While in both the juvenile-type and adult-onset type of diabetes, the intravenous administration of physiologic amounts of insulin plus glucose results in a substantial decline in plasma glucagon,[9] there is evidence in adult-type diabetics suggesting that the exaggerated glucagon response to stimulation may be independent of the plasma insulin level.[10,11] These studies were, therefore, designed to determine if the glucagon hyperresponsiveness to arginine in juvenile-type and adult-type human diabetics is improved by the concomitant administration of insulin.

METHODS

Eight patients with juvenile-type diabetes mellitus and six with adult-onset diabetes were studied. Of the juvenile-type group, two were males and six were females; their ages ranged from 18 to 38 years and averaged 23 years. Weights ranged from 40 to 63 kg. and averaged 57 kg. None were obese as determined by the standards of the Metropolitan Life Insurance Company. All required insulin therapy.

Of the six adult-type patients, five were female. Their ages ranged from 38 to 58 years and averaged 48 years. Their weights ranged from 63 to 102 kg. and averaged 85 kg. Four of the six were obese. Four were being treated with sulfonylureas and two with insulin.

All patients were studied as outpatients after an overnight fast. Insulin or other medications were omitted on the morning of the test. Those patients receiving two daily injections of insulin omitted their evening dose on the night prior to the test. All experiments were carried out with informed consent of the patient.

Patients were studied in random order on separate days within one week; on one day, arginine was administered alone and on the other day arginine and insulin were administered together. After a 20-minute rest period, arginine hydrochloride ("R-Gene," Cutter Laboratories, Berkeley, California) was infused for 40 minutes. Monocomponent insulin* was administered intravenously with an initial rapid

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injection of 0.1 U./kg. followed by 0.06 U./kg. over the subsequent 40 minutes. Blood samples were obtained through a 19-gauge butterfly needle in the antecubital vein. Specimens were collected in chilled tubes containing 12 mg. EDTA and 1 ml. of Trasylol (500 Kallikrein Inhibitor U./ml. of blood), and centrifuged promptly at 4° C. The plasma was separated and stored at 20° C. until the time of hormone assay.

Glucagon was assayed by a recent modification[12] of the previously described radioimmunoassay using antiserum 30K.[13] Insulin was measured by the Herbert modification[14] of the method of Yalow and Berson[15] in patients without circulating insulin antibodies. Glucose was measured by means of the glucose oxidase method using the Technicon SMAC.

For comparison within groups, the Student *t*-test for paired groups was used. The *t*-test for two groups was employed for comparisons between groups. The baseline values employed represented the mean of three preinfusion samples.

RESULTS

Effect of Insulin on Arginine-stimulated Glucagon Response in Juvenile-type Diabetics

In eight juvenile diabetics, glucagon increased during the arginine infusion from a baseline average of 119 pg./ml. ± 17 (S.E.M.) to a peak value at 30 minutes of 396 ± 61 pg./ml. ($p < 0.001$) (figure 1). Glucose rose from 250 ± 25 mg./dl. during the baseline period to a peak of 293 ± 19 mg./dl. at 40 minutes ($p < 0.01$). When insulin was added to the arginine infusion, glucagon rose significantly ($p < 0.001$) from 111 ± 19 pg./ml. to a peak at 30 minutes of only 292 ± 53 pg./ml, significantly less than in the absence of added insulin at 20 ($p < 0.01$) and 30 ($p < 0.001$) minutes. The mean maximal glucagon increment was 310 ± 54 pg./ml. without insulin, and only 184 ± 39 pg./ml. with insulin ($p < 0.01$), which is about the same as in nondiabetic patients.†

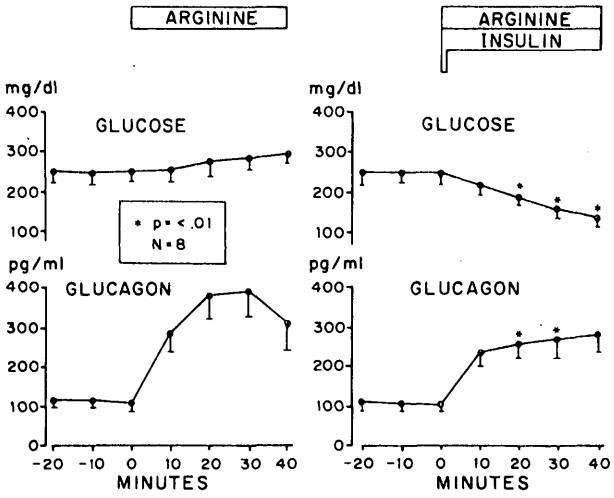

FIG. 1. The glucagon response of eight juvenile-type diabetics to 0.5 gm. per minute of arginine hydrochloride with or without the concomitant administration of insulin.

When insulin was given glucose declined from 254 ± 27 mg./dl. to 142 ± 22 mg./dl. at 40 minutes, significantly lower than in the absence of insulin at 20, 30, and 40 minutes ($p < 0.01$). A lower plasma glucose tends to exaggerate rather than reduce the glucagon response to arginine.

Effect of Insulin on the Arginine-stimulated Glucagon Response in Adult-onset Diabetics

In a group of six adult-type diabetics, arginine raised plasma glucagon from 143 ± 11 pg./ml. to a 30-minute peak of 383 ± 54 pg./ml. ($p < 0.01$) (figure 2). Plasma insulin, measured in the four patients without insulin antibodies, rose from 11 ± 3 μU./ml. to a 40-minute peak of 27 ± 10 μU./ml. Plasma glucose increased from 219 ± 33 mg./dl. to a 40-minute high of 248 ± 34 mg./dl.

When insulin was infused with arginine, raising plasma insulin to a peak of 1,125 ± 178 μU./ml. at 10 minutes, mean plasma glucagon rose from 148 ± 13 pg./ml. to a peak of 450 ± 75 pg./ml. at 40 minutes and did not differ significantly at any point from the levels observed with arginine alone. Without insulin, the mean maximal glucagon increment was 250 ± 50 pg./ml. and with insulin was 307 ± 71 pg./ml. (N.S.). In five of the six patients, the glucagon rise was higher when insulin was administered.

When insulin was given, mean plasma glucose declined from 221 ± 45 mg./dl. to a nadir of 172 ± 50 mg./dl., but only at the 40-minute point did it differ significantly ($p < 0.05$) from the glucose levels observed without insulin. The mean maximal decline in glucose was 50 ± 12 mg./dl. in the adult-type patients given arginine plus insulin, significantly less than the mean maximal decline of 112 ± 20 mg./dl. in the juvenile-type diabetics given arginine plus insulin ($p < 0.05$).

DISCUSSION

This study indicates that, in juvenile-type diabetics, the exaggerated glucagon response to intravenous

†Böttger, I. and Unger, R.H.: Unpublished observations.

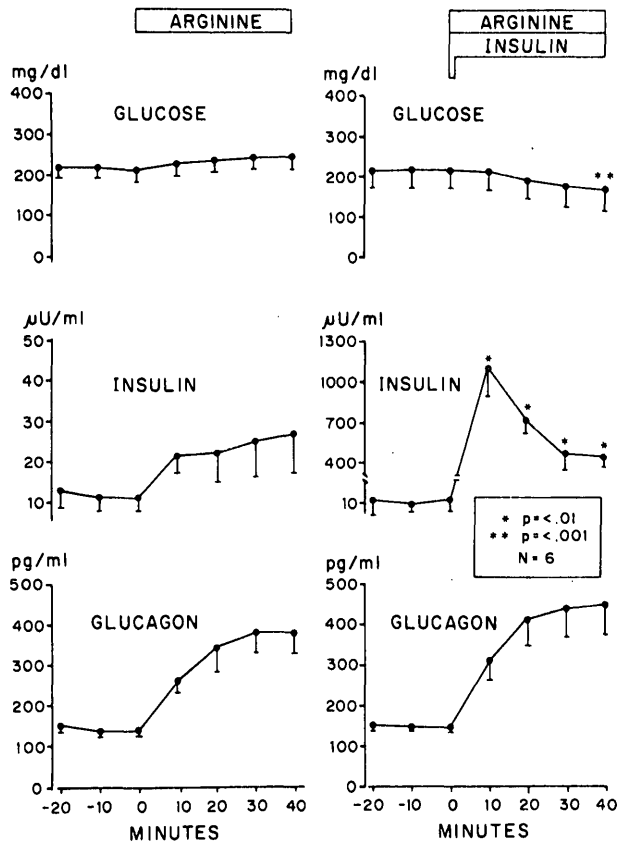

FIG. 2. The glucagon response of six adult-type diabetics to 0.5 gm. per minute of arginine hydrochloride with or without the concomitant administration of insulin.

arginine can be normalized by the concomitant administration of supraphysiologic quantities of insulin while, in adult-type diabetics, insulin does not reduce the glucagon response. This apparent insensitivity of the stimulated A-cell in most adult-type diabetics to even supraphysiologic quantities of insulin is in accord with the earlier demonstration that the infusion of insulin does not correct the abnormal glucagon response of such patients to a carbohydrate meal,[10] and with the fact that the glucagon response to arginine is as great in hyperinsulinemic as in hypoinsulinemic adult-type diabetic Pima Indians.[11]

Whatever the cause of the A-cell defect in adult diabetics, a clear-cut difference from the A-cell function of juvenile-type diabetics is apparent. Whether the persistent hyperglucagonemia in the latter patients contributes to their reduced glucose sensitivity to insulin remains to be determined.

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