Are Abnormalities in Insulin Secretion Responsible for Reactive Hypoglycemia?

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SUMMARY

Seventy patients with reactive hypoglycemia strictly defined by criteria which interpret the low blood glucose value in relationship to clinical and physiologic parameters, were studied to determine if abnormalities in insulin secretion could be demonstrated. These patients were separated into four groups: alimentary (N = 5), diabetic (N = 16), hormonal (N = 5), and idiopathic (N = 44). The findings in these patients were compared to normal control subjects and to weight- and disease-matched patient controls. All of the patients with hormonal and most patients with idiopathic reactive hypoglycemia (thirty-two of forty-four) demonstrated delayed insulin secretion regardless of the control group used for comparison. Diabetic reactive hypoglycemic patients exhibited delayed insulin secretion when compared to normal controls but not when compared to weight-matched diabetic controls. Excessive insulin secretion was consistently found only in the patients with the alimentary variety of reactive hypoglycemia. Using weight- and disease-matched control groups, no abnormalities in insulin secretion could be found to account for the hypoglycemia in the diabetic reactive hypoglycemic patients and some idiopathic reactive hypoglycemic (nine of forty-four) patients. These results help to explain the inconsistent findings of previous investigators and suggest that reactive hypoglycemia is a syndrome having multiple etiologies. DIABETES *23*:589-96, July, 1974.

Abnormalities in insulin secretion, though presumed to be present,[1,2] have not been demonstrated by several investigators[3-7] in reactive hypoglycemia, other than in that seen with maturity-onset diabetes mellitus and the postgastrectomy syndrome. In these conditions hyperinsulinism occurs in the latter,[4,6,8-14] and delayed and excessive insulin secretion occurs in the former.[4-6,10,11] The failure to consistently demonstrate abnormalities in previous studies may be related to patient selection, improper classification and lack of adequate controls. For this study we have defined reactive hypoglycemia on the basis of strict clinical and laboratory criteria.[11] An analysis of insulin-glucose interrelationships in seventy patients with reactive hypoglycemia shows that the majority of patients (forty-five of seventy) have disordered insulin secretion dependent upon the control group used for comparison, while the remainder of the reactive hypoglycemic patients (twenty-five of seventy) have no such abnormality.

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METHODS AND MATERIALS

Seventy patients with reactive hypoglycemia, twenty-two patient controls, twelve disease-matched

controls, and twenty-eight normal control subjects were studied. The patients with reactive hypoglycemia were selected for study on the basis of a previously abnormal five hour oral glucose tolerance test during which the low blood sugar was associated with symptoms present in daily life and suggestive of reactive hypoglycemia. The patient controls were patients referred from the outpatient or neurology clinics with nonspecific symptoms of lethargy, headaches, dizziness and fatigue, who were subsequently found to have no underlying endocrine disease. The disease-matched controls were patients with previous gastrointestinal surgery (vagotomy and pyloroplasty; N = 4 or chemical diabetes; N = 8) who had no symptoms suggestive of reactive hypoglycemia. Obesity was present in seven patient controls and twenty-six hypoglycemic patients and was defined as body weight 15 per cent greater than ideal body weight as given by the Metropolitan Life Insurance Company Statistical Bulletin *40*:1, 1959. The normal controls consisted of healthy young men studied in the U.S. Army Medical Research and Nutrition Laboratory under the conscientious objector program (N = 20),* or were physicians or technician volunteers (N = 8). All normal controls were of ideal body weight and none had evidence of any underlying medical disease or endocrine abnormalities. Each subject consumed a 300 gm. carbohydrate diet for three days prior to the study. A complete history, physical examination and routine laboratory tests, including thyroid function studies, were performed. An oral glucose tolerance test was performed in all individuals using 100 gm. of oral glucose solution (Pal-a-dex). Blood glucose levels were determined every thirty minutes for five hours, and immunoreactive insulin levels were measured every thirty minutes for three hours. Half-hour sampling allowed us to detect twice the number of patients than that which would have been found using hourly sampling. Plasma cortisol samples were measured prior to the administration of glucose, at the blood glucose nadir and at thirty and sixty minutes later. The blood glucose levels were monitored throughout the test with the Ames reflectance meter thus allowing for immediate knowledge as to the configuration of the glucose curve and the blood glucose nadir which enabled us to determine when to draw additional blood samples for cortisol measurements. All blood samples were obtained in a nonstressful manner which permitted frequent sampling through either a slow intravenous saline infusion or through a heparin lock. Samples were drawn so as to avoid saline dilution. It is important in evaluating for reactive hypoglycemia that such a sampling system be utilized as the stress of a difficult venipuncture may activate the patient's hypothalamic-pituitary-adrenal axis and provide ambiguous cortisol information. Delayed insulin secretion is defined as a statistically significant difference in glucose-insulin peak value as compared to normal control subjects.

Plasma glucose levels were measured by an automated enzymatic glucose oxidase method.[15] Immunoreactive insulin was estimated in sixteen patients by a salt precipitation method[16] and in the remainder of the patients by a charcoal absorption method.[17] Plasma corticosteroids as 11-hydroxycorticosteroids were determined by flurometric method.[18]

RESULTS

Normal controls. Results in the normal control subjects are shown in figure 1 and tables 1 and 4. Normal control subjects showed nearly simultaneous glucose and insulin peak secretion at thirty minutes. When the delay between insulin and glucose peaks was considered, taking the mean of all the individual peaks for the group, the mean (± S.E.M.) delay was 8 ± 2.9 minutes. The plasma cortisol throughout the glucose tolerance test showed a diurnal decay and there was no significant elevation in the plasma cortisol following the nadir of the blood glucose.

Patient controls. Results are shown in tables 1, 3 and

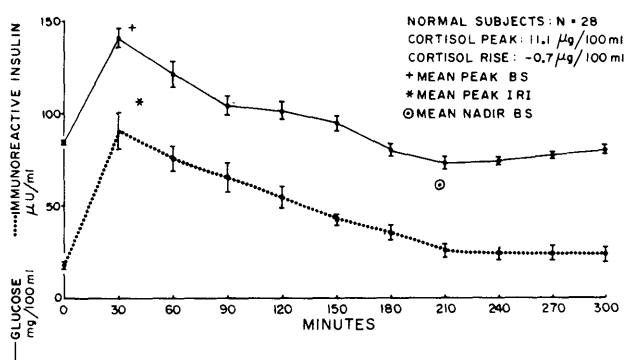

FIG. 1. Glucose-insulin values in normal controls. Each curve represents mean value ± S.E.M.

*The normal subjects volunteered for the study under the provisions of Contract no. DA-49-193-MC-2596 between the University of Colorado and The Commanding General of the U. S. Army Medical Research and Development Command as part of the conscientious objector program. The provisions of the contract make it obligatory to obtain informed consent in general for the subjects' services, and specifically for each definitive study, and precludes the in vivo use of any radioactive substance.

TABLE 1

Comparison of glucose-insulin interrelationships in controls

Group	Number	Peak glucose time mean ± S.E.M. (min.)	Peak insulin time mean ± S.E.M. (min.)	Delay mean ± S.E.M. (min.)	Peak insulin value mean ± S.E.M. (μU./ml.)	Total insulin secretion mean ± S.E.M. (μU-min.)/ml.
Normal controls	28	38 ± 2.5	42 ± 3.3	8 ± 2.9	107 ± 9.5	9,643 ± 807
Patient controls	22	41 ± 3.7	54 ± 4.9	11 ± 4.2	118 ± 16.7	11,212 ± 1,349
nonobese	16	45 ± 4.7	54 ± 6.3	9 ± 4.5	88 ± 12.5	7,703 ± 918
obese	6	30 ± 0.0	50 ± 10.0	15 ± 10.2	179 ± 32.7	17,635 ± 2,573
Alimentary controls	4	53 ± 14.3	60 ± 12.2	8 ± 7.5	141 ± 28.1	10,122 ± 1,718
Diabetic controls	8	71 ± 5.5	98 ± 11.0	26 ± 8.9	162 ± 42.6	13,663 ± 3,605
nonobese	7	72 ± 6.0	94 ± 12.1	21 ± 8.6	178 ± 45.5	14,599 ± 4,020
Hypothyroid (on therapy)	3	50 ± 10.0	40 ± 10.0	0 ± 0.0	190 ± 20.0	6,980 ± 3,139

4. Patient controls similar to normal controls showed a simultaneous peaking of blood glucose and insulin curves. The delay in insulin secretion (11 ± 4.2 min.) was greater in the patient controls, compared to the normal controls, but this difference was not significant. Within this group, nonobese and obese subjects underwent a separate analysis.

Compared to nonobese patient controls, the obese patient controls showed greater peak insulin values ($p < .0025$) and area under the three hour insulin curve ($p < .001$). The patient controls showed no increase in plasma cortisol to the hypoglycemic nadir.

Eight diabetic patient controls (one obese and seven nonobese) demonstrated delayed and excessive insulin secretion characteristic of the diabetic state. All four alimentary control patients were nonobese; they showed hyperinsulinism in response to oral glucose. Likewise, the diabetic and alimentary control patients showed no plasma cortisol rise to the glucose nadir.

Patients with reactive hypoglycemia. Five nonobese patients with alimentary reactive hypoglycemia (vagotomy and pyloroplasty) showed hyperinsulinemia and early hypoglycemia. These results are shown in figure 2 and tables 2 and 3. The peak insulin values and areas of insulin secretion were significantly greater than those seen in normal controls ($p < .0005$ and $p < .0005$, respectively) and nonobese disease-matched controls ($p < .05$ and $p < .05$ respectively). The delay in glucose and insulin peaks was not significantly different among these groups.

Sixteen patients with late diabetic reactive hypoglycemia (thirteen nonobese, three obese) showed mild chemical diabetic glucose tolerance curves (according to the criteria of Fajans and Conn[19]) with a significantly delayed insulin curve (figure 3, tables 2 and 3) as compared to normal control subjects ($p < .0025$), but not when compared to disease-matched diabetic control patients. The peak insulin values and areas of insulin secretion were not significantly different among obese and nonobese diabetic reactive hypoglycemic patients or between nonobese-matched diabetic control patients. However, nonobese diabetic reactive hypoglycemic patients had significantly greater peak insulin levels and areas of insulin secretion than the normal control subjects ($p < .01$ and $p < .005$, respectively). The delay in glucose and insulin peaks was not significant between obese and nonobese diabetic reactive hypoglycemic patients or when compared to disease-matched control patients. Obese diabetic reactive hypoglycemic patients were not statistically compared because of their small number.

Five patients with hormonal hypoglycemia (four

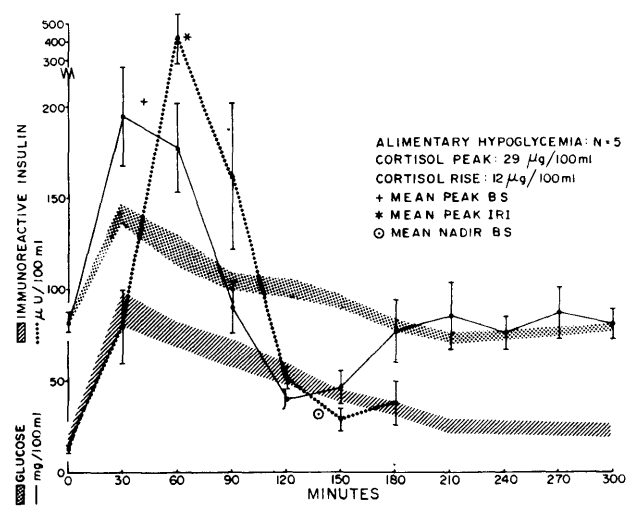

FIG. 2. Glucose-insulin values in alimentary hypoglycemic patients compared to previously shown (figure 1) normal controls. Top hatched area represents mean glucose ± S.E.M. and bottom hatched area mean insulin ± S.E.M. of the normal control group. Mean glucose curve of alimentary patients ± S.E.M. is shown in the solid line and mean insulin curve ± S.E.M. in the broken line.

TABLE 2

Comparison of glucose-insulin interrelationships in reactive hypoglycemic patients

Group	Number	Peak glucose time mean ± S.E.M. (min.)	Peak insulin time mean ± S.E.M. (min.)	Delay mean ± S.E.M. (min.)	Peak insulin value mean ± S.E.M. (μU./ml.)	Total insulin secretion mean ± S.E.M. (μU.-min.)/ml.
Alimentary	5	42 ± 7.3	66 ± 6.0	18 ± 7.3	422 ± 121.8	30,334 ± 4,922
Diabetic	16	79 ± 7.2	111 ± 8.1	32 ± 8.4	204 ± 47.3	18,173 ± 3,632
nonobese	13	76 ± 8.0	106 ± 8.0	30 ± 9.0	213 ± 57.5	18,896 ± 4,418
obese	3	70 ± 10.0	110 ± 20.0	40 ± 26.5	163 ± 48.1	15,035 ± 3,742
Hormonal	5	54 ± 11.2	114 ± 17.5	72 ± 15.3	184 ± 26.0	14,076 ± 1,698
Hypothyroid (off therapy)	3	30 ± 0.0	70 ± 10.0	40 ± 10.0	230 ± 10.0	14,230 ± 2,374
Idiopathic	44	46 ± 2.3	80 ± 4.7	34 ± 4.4	122 ± 11.2	11,286 ± 894
nonobese	32	46 ± 2.7	79 ± 5.3	34 ± 5.0	107 ± 10.5	10,729 ± 994
obese	12	48 ± 4.5	80 ± 10.6	30 ± 9.8	146 ± 25.3	12,771 ± 1,940

hypothyroid and one with Addison's disease) showed late hypoglycemia with a marked delay in insulin secretion (figure 4, tables 2 and 3). This delay was the greatest seen in all groups and was significant when compared to normal control subjects ($p < .0005$). Only one patient was obese in this group. Peak insulin levels and areas of insulin secretion were significantly increased in this group compared to the normal control group ($p < .0025$ and $p < .025$, respectively). Three hormonal deficient hypoglycemic patients with hypothyroidism were studied before (table 2) and after (table 1) adequate thyroid hormone replacement, thus allowing them to serve as their own controls. There was no significant difference in peak insulin values or in the areas of insulin secretion prior to replacement when

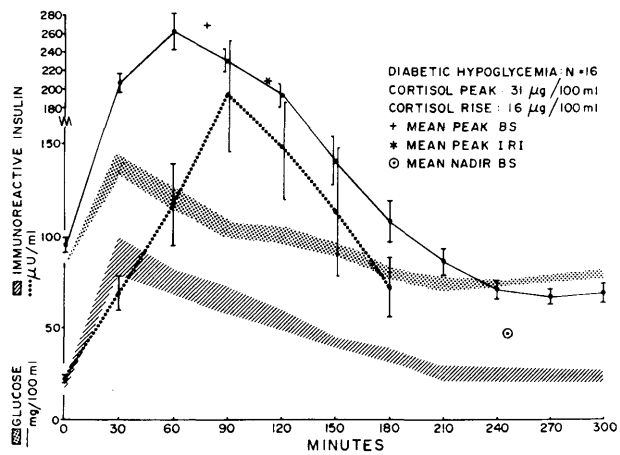

FIG. 3. Glucose-insulin values of diabetic reactive hypoglycemic patients compared to normal controls (data represented in a similar manner to that shown in figure 2).

TABLE 3

Glucose nadir in controls and reactive hypoglycemic patients

Group	Number	Controls: Nadir Blood Glucose mean ± S.E.M. (mg./100 ml.)	Controls: Time-Nadir Blood Glucose mean ± S.E.M. (minutes)
Patient Controls (group)	22	51 ± 2.3	237 ± 7.9
nonobese	16	51 ± 3.0	240 ± 8.7
obese	6	50 ± 3.1	225 ± 20.1
Alimentary Controls	4	57 ± 3.3	173 ± 18.9
Diabetic Controls	8	51 ± 3.8	236 ± 13.2
nonobese	7	48 ± 3.5	244 ± 12.1
Alimentary*	5	32 ± 4.1	138 ± 7.3
Diabetic*	16	48 ± 2.2	246 ± 11.7
nonobese	13	48 ± 2.6	240 ± 13.6
obese	3	48 ± 3.7	270 ± 17.3
Hormonal*	5	34 ± 3.2	222 ± 12.0
Idiopathic*	44	41 ± 1.5	225 ± 5.1
nonobese	32	41 ± 1.6	221 ± 6.5
obese	12	42 ± 3.5	232 ± 8.4

*Reactive hypoglycemic patients.

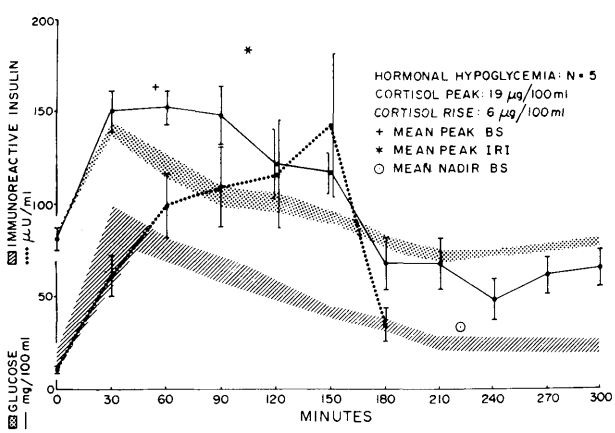

FIG. 4. Glucose-insulin values of hormonal hypoglycemic patients (four hypothyroid, one Addisonian) presented similarly to those in figure 2.

compared to the euthyroid state. However, a delay between glucose peak time and insulin peak time was significantly abnormal; ($p < .025$) in the hypothyroid state as compared to that found following hormonal replacement.

Forty-four patients had idiopathic reactive hypoglycemia (thirty-two nonobese, twelve obese). The glucose-insulin results for these patients are shown in figure 5 and tables 2 and 3. Though the obese idiopathic reactive hypoglycemic patients showed greater peak insulin values and areas of insulin secretion only the insulin peak values were significantly different between obese and nonobese patients ($p < .05$). When peak insulin values and areas of insulin secretion were compared to weight-matched patient controls and normal control subjects there was no significant difference.

The delay in insulin secretion was significant when nonobese idiopathic reactive hypoglycemic patients were compared to nonobese patient controls ($p < .0025$) and normal control subjects ($p < .0005$). Likewise, obese idiopathic reactive hypoglycemic patients had a significant delay in insulin release when compared to obese patient controls ($p < .05$). Twelve of the idiopathic reactive hypoglycemic group (four obese and eight nonobese) had no delay in insulin secretion. Within this subgroup, excessive insulin secretion was not demonstrated except for three nonobese patients whose areas of insulin secretion were significantly increased when compared to normal control subjects and to nonobese patient controls.

In reactive hypoglycemic patients cortisol increases (figures 2 through 5) occurred following the hypoglycemic nadir and symptoms with increases to peak values of 28.7 ± 1.5, 30.9 ± 2.7, 19.3 ± 5.0 and 27.7 ± 1.2 μg. per 100 ml. in alimentary, diabetic, hormonal and idiopathic hypoglycemic groups, respectively. Three of the hormonal patients showed inadequate cortisol responses despite clinically symptomatic hypoglycemia.

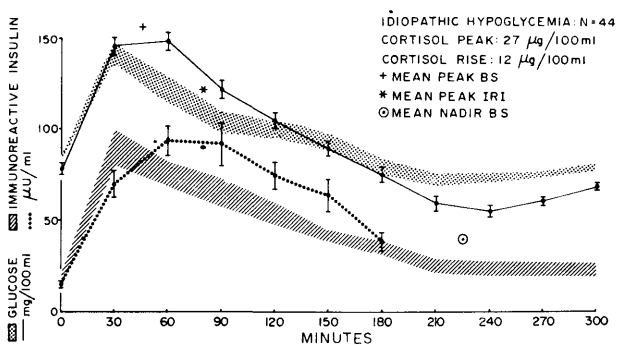

FIG. 5. Glucose-insulin values of idiopathic reactive hypoglycemic patients presented similarly to those in figure 2.

TABLE 4

Cortisol changes to glucose nadir in control subjects

	Fasting Cortisol (μg./100 ml.)	Basic Cortisol* (μg./100 ml.)	30 min. (μg./100 ml.)	60 min. (μg./100 ml.)
Normal control	21.9	11.8	11.1	10.6
Patient controls	21.0	12.0	11.4	11.2
Alimentary controls	16.5	9.3	8.4	7.1
Diabetic controls	18.2	11.7	13.4	11.4

*Basic cortisol is that value obtained at the time of the glucose nadir (mean values given).

DISCUSSION

In 1924, Harris first described the syndrome of reactive hypoglycemia and suggested that abnormalities in insulin secretion may be involved in its etiology.[1] With the recognition that several categories of reactive hypoglycemia exist, Conn and Seltzer, in 1955, postulated that absolute or relative excessive insulin secretion was the most probable cause for idiopathic and alimentary hypoglycemia, while delayed insulin secretion was probably related to the spontaneous hypoglycemia of early adult-onset diabetes mellitus.[2]

Since the development of the radioimmunoassay for the measurement of insulin by Berson and Yalow in 1960, several studies have appeared which have attempted to define the relationship between insulin secretion and the occurrence of hypoglycemia. Most studies in patients with alimentary hypoglycemia have revealed excessive secretion of insulin,[4,6,10-14] although there is a notable exception.[7] Idiopathic hypoglycemia has been found by some to be accompanied by greater than normal insulin secretion,[20,21] but not by others.[3-6] In diabetes mellitus, delayed and excessive insulin secretion has been noted.[4-6,10,11]

In reviewing these studies, it became readily apparent that markedly different criteria were used in selecting patients for study. Some investigators utilized clinical symptoms alone[12,14] in choosing patients for study, while others included patients who had blood glucose levels below a certain arbitrary limit, whether or not they experienced symptoms of hypoglycemia at those times.[4-6,21-23] Furthermore, once selected, patients were tested and included in the study if blood glucose levels dropped below a certain value, regardless

of whether symptoms simulating those of daily life accompanied the low blood glucose levels. Very few investigators utilized objective evidence to verify the pathophysiologic nature of the hypoglycemic symptoms experienced by their patients. Measurements of epinephrine excretion, serum cortisol rises, or elevations in growth hormone have been used only sparingly.[11,20] In addition, because of the different causes of reactive hypoglycemia that have been identified, control groups have for the most part been inadequate in all studies with one exception.[6] Also, the important variable of obesity has not been controlled in several studies.

In the present study, patients were selected if they had symptoms in daily life which suggested hypoglycemia and which were mimicked during an oral glucose tolerance test when the nadir in blood glucose was reached. In addition, a rise in serum cortisol temporarily related to the patient's clinical symptoms and the blood glucose nadir had to occur for the patient to be included in the study. The degree of obesity was calculated; patients who were 15 per cent above ideal body weight underwent separate analysis. Control groups, consisting of normal and patient controls for the idiopathic group, chemically diabetic patients for the diabetic group, and vagotomy and pyloroplasty patients for the alimentary group were utilized in analyzing the data.

Insulin secretion from the normal beta cell occurs within minutes after intravenous glucose[24-26] or other stimuli.[27-30] This prompt and integrated insulin response to a glucose stimulus, as noted by others,[26,31,32] is well demonstrated in our normal control and patient control groups by the close temporal relationship of the insulin to the glucose curve and the nearly simultaneous peaking of both curves.

Patients with alimentary reactive hypoglycemia will give a history of previous gastrointestinal surgery, active peptic ulcer disease or gastrointestinal distress without active ulceration. An occasional patient may be asymptomatic.[9] The altered adequacy of the pylorus and increased gastrointestinal motility allows for rapid gastric glucose emptying and intestinal glucose absorption. This results in excessive glucose-mediated insulin secretion which is potentiated by the gastrointestinal hormones.[29,30,33-36] The present series of nonobese patients showed excessive insulin secretion which was significantly greater than alimentary control patients, nonobese patient controls, and normal control subjects and confirms the findings of hyperinsulinism noted by others.[4,6,8-14] The onset of symptoms and the hypoglycemic nadir occurred earliest in this group. Insulin secretion was delayed as compared to alimentary control patients, patient controls and normal control subjects, but this difference was not significant. The history of gastrointestinal disease, the early onset of hypoglycemia and the excessive insulin discharge are characteristic abnormalities in this group.

In diabetes mellitus there is a delay in insulin secretion in response to oral glucose and in some patients the insulin discharge may be excessive when compared to normal control subjects.[24,37-39] Early in the course of their diabetes some patients respond to this excessive late insulin secretion with symptomatic reactive hypoglycemia. In these individuals there is an inappropriate elevation of serum insulin at a time when blood glucose is falling. Thus, the normal postprandial transitional point of blood glucose becomes abnormally low and the individual experiences the symptoms of hypoglycemic stress.

In the present series, the delayed and excessive insulin secretion characteristic of diabetic reactive hypoglycemia[4-6,10,11] was seen when the diabetic reactive hypoglycemic patients were compared to normal control subjects but not when they were compared to weight-matched diabetic control patients. These data do not explain nor predict why only certain diabetic patients experience hypoglycemia. Perhaps diabetic reactive hypoglycemia with hyperglycemia followed by hypoglycemia represents an abnormal oscillation of the mechanism controlling blood glucose and the defect lies in the response to the glucagon-insulin system or in hepatic gluconeogenesis.

Six of our thirteen nonobese patients with diabetic reactive hypoglycemia had gastrointestinal disease (three with previous gastrointestinal surgery and three with chronic peptic ulcer disease). It may well be that the combination of chemical diabetes mellitus and altered gastrointestinal physiology predisposes some of these patients to late reactive hypoglycemia.

In the hormonal hypoglycemic group the greatest delay in insulin secretion occurred. When the delay between the glucose and insulin peaks in three hypothyroid patients was compared before and after adequate hormonal replacement (tables 1 and 2), there was a return of timely insulin secretion. This would suggest that for adequate functioning of the pancreatic beta cell thyroid hormone and cortisone are required. Altered gastric emptying may play a role, but this may not be a major factor as peak glucose absorption occurred at 54 ± 11.2 minutes, which was not significantly different from the patient or normal control groups.

Patients with idiopathic hypoglycemia demonstrated a delay in peak insulin secretion relative to peak blood glucose levels regardless of the control group used for comparison. Though delayed insulin secretion appeared to be a frequent finding in this group, there were twelve patients who had no such delay. A separate analysis of obese and nonobese idiopathic patients compared to weight-matched normal controls and patient controls showed no significant difference in the amount or peak values of insulin secretion. It is unlikely that all of these idiopathic reactive hypoglycemic patients represent prediabetes, although they may share in common the same defect in timely insulin secretion. Of the idiopathic reactive hypoglycemic patients with delayed insulin secretion, 47 per cent gave a family history of diabetes mellitus and of those with no delay in insulin secretion, 29 per cent had a positive family history for diabetes mellitus.

In the subgroup with no delay in glucose-insulin peak times, there were three nonobese idiopathic reactive hypoglycemic patients who showed significantly excessive insulin secretion in the absence of any clinical evidence of gastrointestinal disease. Thus in nine idiopathic reactive hypoglycemic patients, there were no abnormalities in insulin secretion to account for the hypoglycemia. One would have to postulate other mechanisms as the cause of the hypoglycemia, such as a relative increased insulin sensitivity or failure of timely responsiveness of hepatic gluconeogenic mechanisms early in the fasting state. In support of the latter we have identified several patients in this group with partial hepatic fructose-1,6-diphosphatase deficiency. Further detailed studies of gluconeogenic mechanisms are being conducted in this idiopathic group.

In the majority of individuals with reactive hypoglycemia, as herein described, there is either excessive insulin discharge or delayed insulin secretion depending on the control group used for comparison. We have found that plasma cortisol levels after the hypoglycemia nadir have proved to be a useful laboratory tool in supporting the clinical significance of the low blood glucose levels. The failure of cortisol to rise late in the glucose tolerance test at the time of the physiologic nadir in asymptomatic control subjects has been observed by others.[40] As shown in table 4, patient and normal control subjects show no significant elevation of plasma cortisol as compared to those patients described with reactive hypoglycemia (figures 2 through 5).

If strict attention is paid to clinical circumstances, glucose-insulin interrelationships and counterhormonal regulatory mechanisms, then the significance of the glucose nadir can be interpreted properly. The delay in insulin secretion seen in most of these patients may explain the usefulness of the oral sulfonylureas in treating this disorder.[41]

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