

Plasma Insulin Levels During Reactive Hypoglycemia

Karl E. Sussman, M.D., Leo Stimmler, M.B., and Harold Birenboim, M.D., Denver

SUMMARY

The plasma insulin response to an oral glucose load was studied in fourteen patients with reactive hypoglycemia—based on blood glucose values of 45 mg./100 ml. or below following 100 gm. of glucose. In reactive hypoglycemia, no single mechanism involving insulin secretion could explain the development of low blood glucose values. Six patients with reactive hypoglycemia demonstrated elevated plasma insulin values in association with normal blood glucose levels. In five patients the results of glucose tolerance tests suggested mild diabetes mellitus, and plasma insulin levels were increased. Three patients with reactive hypoglycemia had essentially normal glucose tolerance tests and no abnormality in plasma insulin response was noted. *DIABETES* 15:1-4, January, 1966.

The spontaneous occurrence of hypoglycemia in patients was described by Harris in 1924.¹ It has been observed that spontaneous hypoglycemia may be due to numerous causes. Approximately 70 per cent of these patients have reactive or functional hypoglycemia, that is, hypoglycemia following ingestion of glucose or foods rich in glucose.² Most other patients have had liver disease, insulin secreting tumors, starvation and excessive ethyl alcohol ingestion to account for their hypoglycemia.

In reactive hypoglycemia, the precise mechanism responsible for the low blood glucose values remains unknown. It has been postulated that either insulin secretion from the pancreas is excessive or that the discharge of insulin from the pancreas is delayed, thereby producing late hypoglycemia.^{2,3} The present study represents an initial attempt to calibrate the plasma insulin responses observed in reactive hypoglycemia, in particular the changes in insulin levels induced by oral carbohydrate administration.

METHODS

Fourteen patients having clinical signs and symptoms

From the Departments of Medicine and Pediatrics, University of Colorado School of Medicine, Denver, Colorado.

suggesting hypoglycemia were studied (see Appendix). The patients were admitted to the Clinical Research Center of the University of Colorado Medical Center. They were maintained on a diet of 1800 calories with 180 gm. of carbohydrate. All subjects were fasted for a period of ten hours before performance of the various studies noted.

In the oral glucose tolerance test 100 gm. of glucose was administered. A slow intravenous saline infusion permitted the obtaining of blood samples at frequent intervals. In the initial pilot studies, blood glucose and plasma insulin levels were measured at every half hour for two hours, thereafter at every hour up to six hours. Subsequently, it was found necessary to perform these determinations at more frequent intervals. The method was altered to determine blood glucose and plasma insulin levels approximately every ten minutes during the first hour, every fifteen minutes during the second hour and every half hour thereafter up to six hours. The patients with reactive hypoglycemia in this report not only had subjective manifestations of hypoglycemia but also a blood glucose value of 45 mg./100 ml. or less in an oral glucose tolerance test.

Plasma insulin levels were determined by the immunoassay technic described by Morgan and Lazarow⁴ using porcine insulin labeled with iodine-125. Blood glucose was measured by the glucose oxidase method.⁵ Table 1 lists the blood glucose and plasma insulin levels

TABLE 1

Blood glucose and plasma insulin response to oral glucose administration (100 gm.) in twenty normal subjects

Time (min.)	Blood glucose (mg./100 ml.) Mean \pm 1 S.D.	Plasma insulin (μ U./ml.) Mean \pm 1 S.D.	Range
FAST	75.4 \pm 9.3	24.2 \pm 15.1	0—55
15	93.9 \pm 17.1	44.0 \pm 26.7	15—110
30	113.0 \pm 22.2	51.0 \pm 28.2	5—110
45	114.9 \pm 18.1	58.8 \pm 30.7	20—110
60	111.6 \pm 17.6	60.3 \pm 32.2	15—150
90	105.7 \pm 24.2	73.7 \pm 50.4	0—180
120	92.7 \pm 14.8	51.0 \pm 27.2	0—105
150	94.0 \pm 12.7	70.0 \pm 23.6	35—95
180	87.3 \pm 19.6	37.0 \pm 11.7	15—60
240	76.0 \pm 9.1	36.3 \pm 18.7	0—65

obtained in this laboratory in twenty normal subjects after the oral administration of 100 gm. of glucose. The normal subjects did not have symptoms of reactive hypoglycemia and the lowest blood glucose value observed in an oral glucose tolerance test was 55 mg./100 ml.

Studies were undertaken in an attempt to rule out a possible insulin secreting tumor or the presence of significant hepatic disease. In the intravenous tolbutamide test, a fasting blood glucose was measured as well as at 20 min., 30 min., 1 hr., 2 hrs. and 3 hrs. later.⁶ All subjects were fasted for a period of 48 to 72 hrs. in an attempt to induce hypoglycemia. Liver function tests (bilirubin, alkaline phosphatase, SGOT, SGPT) were performed in the patients in this study.

RESULTS

Three general types of response to oral glucose as judged by blood sugar and insulin levels were observed:

(1) Normal glucose tolerance curve with reactive hypoglycemia and prompt but elevated insulin levels. Typical data from a subject in this group are shown in figure 1 and table 2.

(2) A diabetic blood glucose curve as shown in figure 2 and table 2—this patient was shaky, nervous, confused and perspired profusely in 4 hrs. and was

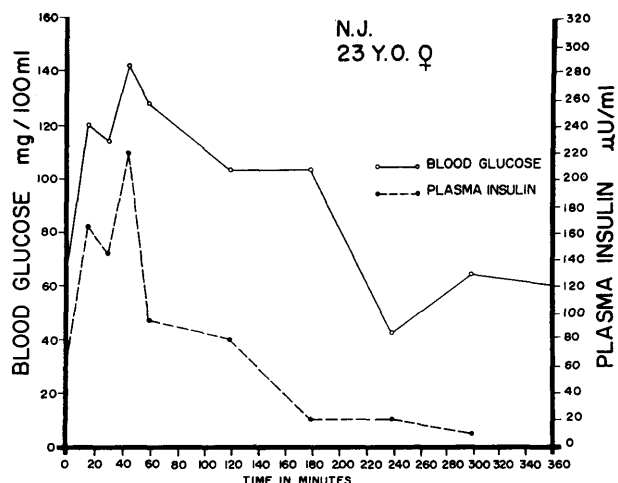


FIG. 1. Oral glucose tolerance test with plasma insulin levels (patient representative of Group 1).

found to have a blood glucose of 43 mg./100 ml. The four other patients in this group had diabetic oral glucose tolerance tests with peak blood glucose levels of 186, 234, 200 and 194 mg./100 ml.

(3) A normal blood glucose curve with reactive hypoglycemia accompanied by essentially normal insulin levels. A typical patient is shown in figure 3 and table 2.

Table 2 lists the clinical features, the degree of hypo-

TABLE 2
Blood glucose, plasma insulin response to oral glucose administration in patients with reactive hypoglycemia

Group	Age	Sex	Lowest blood glucose (mg./100 ml.)	Time of low glucose value (min.)	Peak insulin response (μU./ml.)	Time of peak insulin response (min.)	Glucose tolerance	Family history of diabetes
Group 1								
E.S.	39	F	36†	120	390	30	Normal	Positive
G.F.	39	M	36†	210	355	60	Normal	Negative
M.H.	48	M	33†	210	215	60	Normal	Positive
N.J.	23	F	43†	240	220	45	Normal	Negative
P.S.	29	F	45†	270	360	320	Normal	Negative
K.B.	27	F	31†	240	535	60	Normal	Negative
Group 2								
A.V.	35	F	43†	240	484-625	30-120	Diabetic	Negative
A.V.*	36	F	38†	240	240	75	Normal	Negative
A.D.	48	M	36†	180	305	15	Diabetic	Negative
E.G.	70	F	43†	240	245	30	Diabetic	Negative
A.M.	48	F	42	270	260	90	Diabetic	Negative
C.K.	73	M	42†	240	240	120	Diabetic	Negative
Group 3								
M.B.	23	M	25†	165	165	45	Normal	Negative
M.B.*	23	M	40†	150	180	50	Normal	Negative
M.T.	28	F	41†	210	150	15	Normal	Negative
L.M.	51	M	43†	270	130	75	Normal	Negative
L.M.*	51	M	45	240	110	120	Normal	Negative

*Repeat oral glucose tolerance test in the same patient.
†Symptoms of reactive hypoglycemia present during test.

DISCUSSION

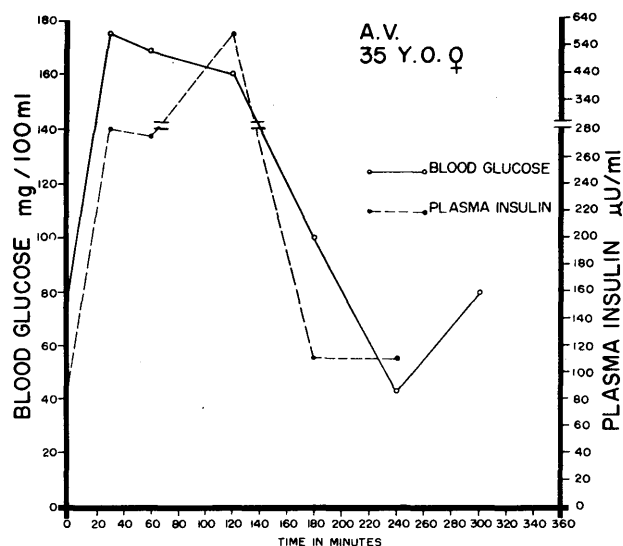


FIG. 2. Oral glucose tolerance test with plasma insulin levels (patient representative of Group 2).

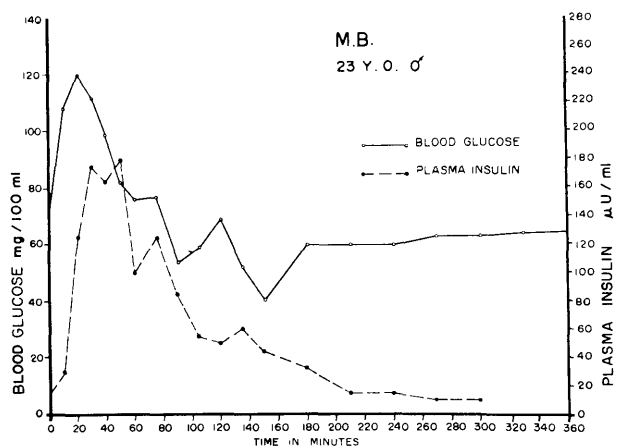


FIG. 3. Oral glucose tolerance test with plasma insulin levels (patient representative of Group 3).

glycemia and the peak insulin response which was observed after oral glucose administration to patients with reactive hypoglycemia. The age range of the patients in this study extends from 23 to 73 yrs. with a mean of 41.5 yrs. There are eight females and six males. As previously noted, in order for a patient to be in this series the blood glucose value had to decrease to 45 mg./100 ml. or less during an oral glucose tolerance test.

Tests of hepatic function were normal in the patients studied. Fasting for 48 to 72 hrs. was well tolerated, with the blood glucose values following the fast ranging from 55 mg./100 ml. to 102 mg./100 ml. Intravenous tolbutamide tests failed to produce sustained periods of hypoglycemia.

It is apparent from these studies that there is no single explanation for the occurrence of low blood glucose values in patients with reactive hypoglycemia.

There is a group of patients who manifest an abnormal increase in plasma insulin in response to essentially normal blood glucose values. It has been postulated that the islets in these patients are histologically normal, but yet there occurs excessive insulin secretion in response to normal stimulation.

A second group of patients appears to be in an early stage of diabetes mellitus. Their curves after glucose tolerance tests are all modestly elevated and with this they manifest increased plasma insulin values. In the initial observations made by Harris¹ with regards to spontaneous hypoglycemia, two patients with diabetes mellitus were presented. It has been repeatedly stated that the presence of reactive hypoglycemia may represent one of the earliest manifestations of diabetes mellitus.⁷⁻⁹ Within this group are two patients, C.K. and A.M., who not only manifest elevated plasma insulin levels but the time of peak insulin response is delayed. Seltzer, Fajans and Conn³ in reviewing reactive hypoglycemia, postulated that in some patients there appeared to be a diminished speed of mobilization of insulin in response to a glucose load. These authors suggested that the initial hyperglycemia which the patients manifested as a consequence of delayed secretion of insulin created a supernormal stimulus to the islets to subsequently release insulin, thereby producing delayed hypoglycemia.

There are patients who demonstrate significant degrees of hypoglycemia in whom the glucose tolerance test appears to be otherwise normal, and no distinct abnormality in plasma insulin levels can be demonstrated. Groen in studies using bioassay procedures for the measurement of plasma insulin has also found normal insulin levels in reactive hypoglycemia.¹⁰ With this particular group, it does not seem that one can implicate insulin secretion per se as a cause of the hypoglycemia. It is assumed, on the basis of the normal hepatic function tests, that these patients have the capacity to synthesize glycogen and to release glucose normally. Although not specifically evaluated in this study, it is presumed that the rate of glucose utilization is normal. At present an attempt is being made to elucidate possible mechanisms of hypoglycemia in this group.

The classification of reactive hypoglycemia on the basis of changes in plasma insulin and blood glucose is arbitrary at best. The data presented would seem to

indicate there are various explanations why patients become hypoglycemic following a glucose load. However, it is conceivable that these do not represent distinctly different clinical entities but that there may be some interrelationship in the abnormalities noted. The present direction of this study is to continue this evaluation for an extended period of time to determine the ultimate course and prognosis for these subjects.

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APPENDIX

- E.G.—70 yrs., female, has had sudden attacks of weakness and fatigue relieved by rest or by drinking carbonated beverages. Usually these episodes occur in the midafternoon.
- A.M.—48 yrs., female, had no symptoms to suggest reactive hypoglycemia. She complained of occasional periods of mid-epigastric pain. Gastrointestinal series was negative. Glucose tolerance test revealed a blood glucose of 30 mg./100 ml. at 2.5 hrs. at which time, the patient complained of shakiness, sweating and weakness.
- L.M.—51 yrs., male, noted spells in which he would see black spots in front of him, then would lose consciousness for varying periods of time. He would recover spontaneously. These episodes would occur between 3:00 and 4:00 p.m.
- A.D.—46 yrs., male, admitted with episodic bizarre behavior and occasional grand mal seizures. Episodes subside after eating food. Glucose tolerance test revealed reactive hypoglycemia.
- G.F.—39 yrs., male, on occasion noted extreme fatigability, nervousness and increased perspiration. Most of these episodes have occurred some 2 to 3 hrs. after eating. He is able to get relief by drinking carbonated beverages or eating candy.
- K.B.—27 yrs., registered nurse, had episodes of weakness, lightheadedness and shakiness. These are not related to physical activity, time of the day or to ingestion of particular foods. She would eat doughnuts and cake and obtain relief sometimes.
- N.J.—23 yrs., female, laboratory technician, was to serve as a normal subject for another study. During the course of an oral glucose tolerance test, the patient started to perspire

profusely, became weak and nervous. There is nothing in her previous history to suggest reactive hypoglycemia.

- E.S.—38 yrs., female. For past 2 yrs. has had episodes of lightheadedness, increased perspiration and mild confusion. She was seen by the Neurology Service and a standard oral glucose tolerance test revealed a blood glucose of 50 mg./100 ml. at 2 hrs.
- M.B.—23 yrs., male, medical student, at 9:30 a.m., became anxious, irritable, weak and noted that his right upper extremity felt numb. This episode lasted 10 min. and the patient recovered spontaneously.
- C.K.—73 yrs., male, had periods occurring in the morning in which he would fall asleep and become unresponsive. On one occasion, he felt extremely weak and shaky. There is no history of relief after the ingestion of food.
- M.H.—45 yrs., male, has had spells of "passing out," seven to eight occasions during the past 5 yrs. These have occurred without any aura or warning and he has recovered spontaneously.
- P.S.—29 yrs., obese female, had episodes of weakness and intense hunger occurring before lunch and supper. At these times she would get relief from eating some form of carbohydrate.
- A.V.—36 yrs., female, had long-term history of psychiatric difficulty. Grand mal seizures necessitated repeated hospitalization. On repeated occasions she would experience attacks of acute anxiety, weakness and nervousness from which she was able to obtain relief by food ingestion.
- M.T.—28 yrs., female, thin, had had a few episodes of syncope occurring primarily before noon. She has obtained relief by lying down or eating food.

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