Pancreatic α-Cell Function in Idiopathic Reactive Hypoglycemia

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Idiopathic reactive hypoglycemia (IRH) is a well-documented but overdiagnosed syndrome. The presence of transient hypoglycemia and enhanced insulin secretion and/or increased insulin sensitivity before the onset of IRH is well documented. However, the data regarding glucagon secretion are sparse. Therefore, this study assessed glucagon and insulin responses to (1) oral ingestion of 100 g glucose oral glucose tolerance test (OGTT) and (2) a 100-g protein meal after an overnight fast in a randomized sequence at intervals of 7 to 10 days in five subjects with previously well-documented IRH and six normal subjects. Basal plasma glucose and insulin levels were not significantly different in both groups. However, basal glucagon was significantly higher ($P < .025$) in IRH subjects (347 ± 83 ng/L) compared with normals (135 ± 20 ng/L). In IRH subjects during the OGTT, hypoglycemia (2.7 ± 0.11 mmol/L) occurred at 150 ± 16 minutes and was preceded by a markedly higher ($P < .01$) peak glucose concentration (11.7 ± 0.6 mmol/L) at 36 ± 6 minutes in comparison to normals (8.8 ± 0.4 mmol/L), indicating the presence of impaired glucose tolerance in these subjects. Similarly, the plasma insulin increase was significantly higher ($P < .01$) but delayed in IRH subjects compared with normals. In contrast, glucagon suppression was not significantly different in both groups, although glucagon failed to increase following hypoglycemia in IRH. During a protein meal, plasma glucose declined in both groups, with a significantly ($P < .05$) greater decrease in IRH subjects (−0.8 ± 0.2 mmol/L) compared with normals (0.5 ± 0.1 mmol/L). However, the glucagon increase was significantly ($P < .01$) blunted in IRH subjects (61% ± 15%) in comparison to normals (152% ± 39%). Thus, basal hyperglucagonemia with normal glucose concentration may suggest the presence of a hyposensitivity of the glucagon receptor in IRH. Moreover, the lack of appropriate suppression during the OGTT despite marked hyperglycemia, the lack of an increase at the onset of hypoglycemia, and the inhibited response to a protein meal in IRH subjects compared with normals denote altered glucagon secretion in IRH. Therefore, it is likely that glucagon receptor downregulation and impaired glucagon sensitivity and secretion may contribute to postprandial hypoglycemia in IRH.

IDIOPATHIC REACTIVE (postprandial) hypoglycemia (IRH) is an uncommon disorder manifesting hypoglycemic symptoms such as palpitation, sweating, anxiety, tremor, headache, confusion, weakness, dizziness, and blurred vision, usually occurring 1 to 4 hours after a meal.[1-5] The existence of this disorder has been questioned by some.[6-9] Nevertheless, many other investigators not only continue to confirm its presence but also attempt to assess the mechanism of hypoglycemia in this syndrome.[10-14] Most of these studies have attributed the hypoglycemia to hyperinsulinemia occurring following marked hyperglycemia and enhanced insulin sensitivity in this syndrome.[1,10,13,15,16] However, the role of glucagon in this syndrome has not been well examined.[17-19] Therefore, this study assessed pancreatic α-cell function in subjects presenting with this disorder.

MATERIALS AND METHODS

Five subjects, three men and three women aged 26 to 45 years, participated in the study after informed consent was obtained. The diagnosis of IRH was established by (1) a history of several hypoglycemic events suggested by the presence of known symptoms of hypoglycemia usually occurring 1 to 4 hours after a mixed meal, some of which were documented by a blood glucose level less than 3.0 mmol/L as determined by home blood glucose monitoring systems, and (2) documentation of venous plasma glucose less than 50 mg/dL (<2.7 mmol/L) when symptoms of hypoglycemia occurred during a 5-hour oral glucose tolerance test (OGTT) with 75 g glucose.[1-4,10-16] None of the subjects with IRH had peptic ulcer disease, altered gastrointestinal motility, ie, diarrhea, previous gastrointestinal surgery, or any other disorders, including hyperthyroidism and type II diabetes mellitus, that are known to induce reactive hypoglycemia[4,5,9,11,12,14,20-23] at the time of or at any time before enrollment onto this study protocol. Thus, only after a thorough evaluation were all subjects deemed to manifest IRH. As controls, six aged-matched (24 to 42 years) healthy volunteers, three men and three women, participated in the study. None of the healthy subjects demonstrated either impaired glucose tolerance or diabetes mellitus by the criteria established by the National Diabetes Data Group.[24] Neither did any participant in the study have a family history of diabetes mellitus. All subjects were within 10% of ideal body weight and were free of any acute or chronic disorder at the time of study as documented by a thorough history and a normal physical examination, complete blood cell counts, entire clinical chemistries, and liver function tests. Neither did they consume any medications at the time of study.

The studies were performed in a randomized sequence with intervals of 7 to 10 days. All participating subjects were asked to consume a regular diet containing at least 150 g carbohydrate for at least 3 consecutive days before each study. On the fourth day, they presented to the endocrinology laboratory between 8 and 9 AM after an overnight fast. An OGTT was performed in all subjects using 100 g oral glucose solution (Glucola). The protein meal study was performed in all subjects using 100 g cherry-flavored, predigested, preformed protein liquid, a mixture of amino acids with less than 1% fat content and no carbohydrate content (Proamino Liquid; United Nutrition, Narberth, PA). Blood samples (8 mL) were collected for glucose, insulin, and glucagon determinations before oral ingestion of either glucose or the protein meal and again at 15, 30, 60, 90, 120, 150, and 180 minutes during both studies. Each blood sample was divided into three portions. A 5-mL aliquot was placed in a cooled heparinized tube and promptly

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centrifuged at 4°C, and plasma was extracted. One milliliter of plasma was frozen and stored at −20°C for determination of insulin at a later date. The remaining plasma was used for measurement of glucose levels on the same day. Three milliliters of blood was placed in a chilled tube containing EDTA (1.5 mg/mL) and 3,000 U Trasylol. The blood specimens were immediately centrifuged at 4°C. The plasma was extracted and frozen at −20°C for determination of glucagon at a later date.

Plasma glucose was determined by a commercial kit using the glucose oxidase method (Worthington Diagnostics, Worthington, NJ). Plasma insulin was assessed by a commercial kit (Immunex, San Diego, CA) using a well-established radioimmunoassay (RIA) technique. Plasma glucagon was also estimated by RIA using a 34K glucagon antibody (Cambridge Medical Technology, Billerica, MS). This antibody is specific for determination of bioactive glucagon as previously reported.[21,25,26] Interassay and intraassay coefficients of variation for all determinations were between 5% and 11% in our laboratory. All data are reported as the mean ± SEM. Statistical analyses were performed with Student's *t* test and ANOVA. Glucose responses were expressed as an absolute change (Δ), ie, the difference between the peak or nadir concentration and the basal level. Insulin and glucagon responses were expressed as an absolute change (Δ) and as a percent change [(absolute change/basal level) × 100].

RESULTS

Fasting plasma glucose and insulin levels were not significantly different in either group. However, basal glucagon was significantly higher in subjects with IRH compared with normal subjects (Table 1). During the OGTT, hypoglycemia (<2.7 mmol/L) occurred at 150 ± 16 minutes and was preceded by marked hyperglycemia (11.7 ± 0.6 mmol/L) at 36 ± 6 minutes in IRH. Furthermore, this peak glucose concentration was significantly higher ($P < .01$) in IRH subjects compared with normal subjects (8.8 ± 0.4 mmol/L). Simultaneously, the nadir glucose concentration was significantly lower ($P < .01$) in IRH subjects (2.7 ± .04 mmol/L) compared with normal subjects (5.5 ± 0.3 mmol/L). Plasma insulin increased promptly in both groups, with a significantly higher increase in subjects with IRH as expressed by both the absolute response (Fig 1) and the percent change, 2,177% ± 414% in IRH subjects and 1,100% ± 198% in normal subjects. However, the greater insulin peak in IRH subjects was significantly delayed (75 ± 6 minutes; range, 60 to 90) in comparison to normal subjects (47 ± 5 minutes; range, 30 to 60). Plasma glucagon declined progressively in normal subjects, with an absolute decrease of 40 ± 17 ng/L and a percent decline of 29% ± 12%. In contrast, a paradoxical increase in plasma glucagon was noted during the first 30 minutes before a later suppression in IRH, as documented by an absolute decrease of 127 ± 46 ng/L and a percent decline of 36% ± 14% (Fig 1). However, this greater absolute decrease in IRH occurred in the face of a markedly higher basal plasma glucagon concentration. Finally, the glucagon nadir occurred significantly earlier ($P < .001$) in subjects with IRH (62 ± 10 minutes) compared with normal subjects (148 ± 25 minutes). Furthermore, there was no significant alteration in plasma glucagon concentration at the onset of hypoglycemia in subjects with IRH (prehypoglycemia, 344 ± 67 ng/L; with hypoglycemia, 348 ± 78 ng/L). During the protein meal (Fig 2), plasma glucose levels declined in both groups, with a significantly greater decrease ($P < .05$) in subjects with IRH (0.8 ± 0.2 mmol/L) in comparison to normal subjects (0.5 ± 0.1 mmol/L). Plasma insulin increased promptly in both groups, and the responses were not significantly different ($P < .05$) when

Table 1. Fasting Plasma Glucose, Insulin, and Glucagon Levels in Five Subjects With IRH and Six Normal Subjects

Group	Age (yr)	Body Weight (kg)	Fasting Plasma Glucose (mmol/L)*	Fasting Plasma Insulin (mU/L)*	Fasting Plasma Glucagon (ng/L)*
IRH	37 ± 6	59 ± 8	4.9 ± 0.2	7 ± 2	347 ± 83†
Normal	34 ± 5	62 ± 7	5.2 ± 0.1	6 ± 1	135 ± 20

*The average of 2 values in individual subjects, 1 during the OGTT and the other during the protein meal study, was used for calculation.
†$P < .025$, IRH *v* normal.

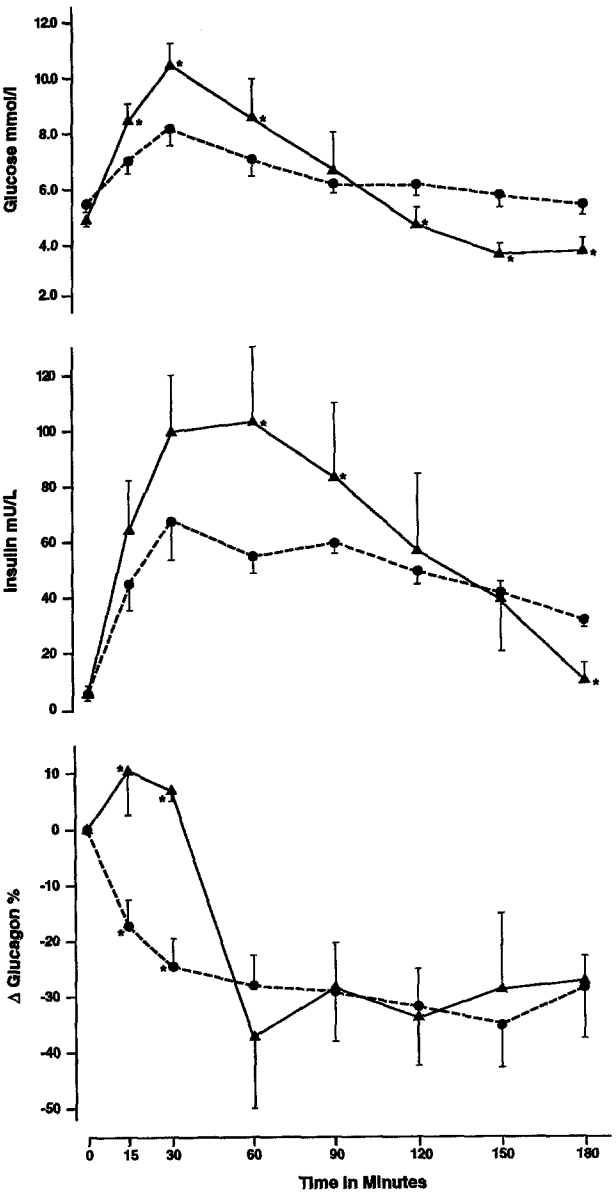

Fig 1. Glucose, insulin, and glucagon responses to oral ingestion of 100 g glucose (OGTT) in 5 subjects with IRH (▲) and 6 normal subjects (●). *$P < .01$ *v* normal.

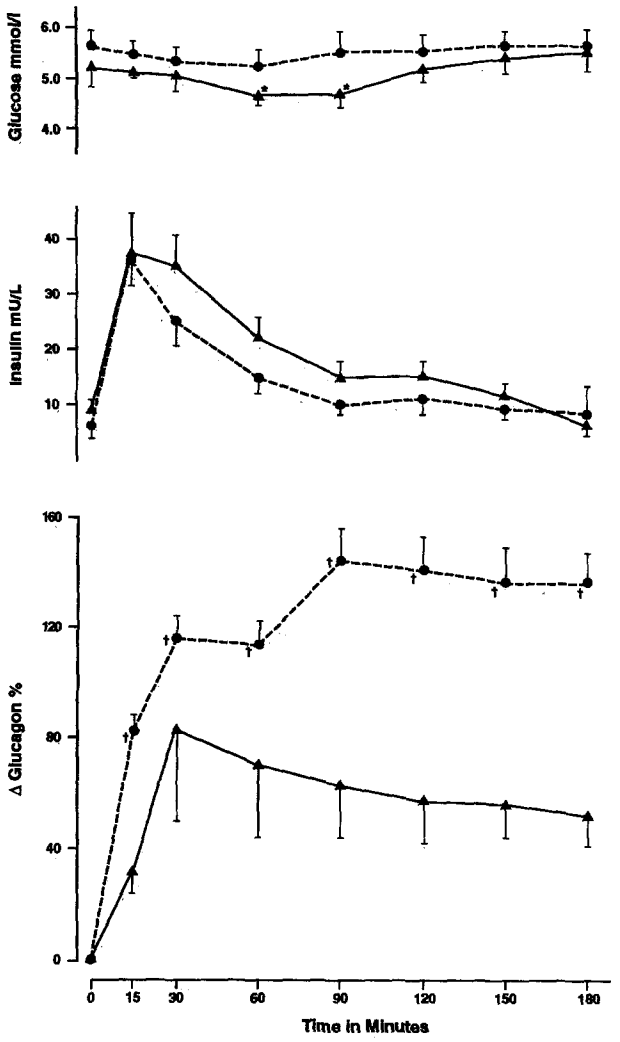

Fig 2. Glucose, insulin, and glucagon responses to oral ingestion of a protein meal in 5 subjects with IRH (▲) and 6 normal subjects (●). *$P < .05$ v normal. †$P < .01$ v IRH.

expressed either as an absolute increase (Fig 1) or as a percent increment (308% ± 63% in IRH and 333% ± 58% in normal subjects). In contrast, the plasma glucagon response was significantly ($P < .01$) blunted if expressed as a percent increase in subjects with IRH (61% ± 15%) compared with normal subjects (152% ± 39%). However, the absolute increase in plasma glucagon was almost identical in IRH subjects (215 ± 52 ng/L) compared with normal subjects (205 ± 50), albeit in the presence of a significantly higher basal glucagon concentration (Table 1).

DISCUSSION

IRH, although questioned in some quarters, does seem to exist in many subjects.[1-5,10-17,19,20,24-29] Furthermore, it appears to cause a marked disturbance in the daily activities of some of these subjects because of less than tolerable clinical manifestations. The management of this condition consists of ingestion of frequent small meals with high protein and low refined-carbohydrate content. Additionally, several drugs such as calcium-channel blockers, anticholinergic agents, or somatostatin have been used successfully in treating patients when dietary manipulation has failed to prevent hypoglycemic episodes.[1,5,27-30] These therapeutic options are based on decreasing peak glucose and insulin concentrations, since hyperinsulinemia is implicated as one of the major factors in induction of hypoglycemia in this disorder. However, a prompt glucagon increase caused by a high-protein meal may also account for the prevention of hypoglycemia with a high-protein, low-carbohydrate diet, although pancreatic α-cell function has not been well studied in this syndrome.[17-19] Therefore, this study examined the influence of oral glucose ingestion and a protein meal on glucagon secretion to assess pancreatic α-cell function in this syndrome, since the influence of carbohydrate ingestion or a protein meal in the regulation of glucagon secretion is well established.[21,25,26] Glucose responses during both studies were expressed only as absolute changes from the basal levels because fasting concentrations were not significantly different in either group. However, glucagon and insulin responses during both studies were expressed as percent changes from the basal levels because basal glucagon levels were markedly and significantly higher in subjects with IRH in comparison to normal subjects. Also, we believe it is inappropriate to compare absolute responses between two groups with markedly different concentrations, ie, a change of 30 U from a basal level of 100 U, a 30% response, is distinctly different from the same absolute change of 30 U with a basal level of 300 U, a 10% response. Therefore, percent changes from the basal level appear more meaningful for comparison between two groups when basal levels are grossly different. Finally, absolute changes in plasma insulin and glucagon concentrations were also documented to maintain uniformity and to assess their relationships with glucose responses.

This study confirms the induction of hypoglycemia following ingestion of glucose in subjects with IRH. Moreover, it also documents the initial hyperglycemia indicating the presence of impaired glucose tolerance and markedly elevated plasma insulin before the induction of hypoglycemia that occurred in every individual subject with IRH but at different times (90 to 150 minutes). The variability in the time of occurrence of hypoglycemia may be responsible for the lack of documentation of hypoglycemia (<2.7 mmol/L) at any one period as a group (Fig 1), since only mean glucose concentrations at each period are depicted. However, the greater insulin peak noted in subjects with IRH was delayed in comparsion to that in normal subjects, and a similar finding was noted in subjects with reactive hypoglycemia induced by other disorders, with the exception of type II diabetes mellitus, as described in several previous studies.[2,4,9,11,15,20,21,23,30] However, percent glucagon suppression similar to that noted in normal subjects despite a greater degree of hyperglycemia and a lack of a significant increase at the onset of hypoglycemia indicate altered pancreatic α-cell function in IRH. We believe that the absolute decline in glucagon levels in IRH, although significantly higher than in normal subjects, was not appropriate in the presence of markedly higher postprandial plasma glucose levels indicative of impaired glucose tolerance and basal hyperglucagonemia. A similar abnormality of glucagon secretion has been reported in several other states manifesting impaired glucose toler-

ance.[21,25,31,32] Furthermore, a possible initial paradoxical increase within 30 minutes in response to glucose ingestion followed by a relatively earlier decline compared with that in normal subjects may also suggest a further aberration of glucagon secretion in IRH.

Our observation in IRH regarding alterations in plasma glucose and insulin concentrations is consistent with previous data in the literature.[1-3,10,13,15,28-30] However, data regarding glucagon secretion are sparse and conflicting.[17-19] The impaired suppression of glucagon following glucose ingestion noted in our study was reported in a previous study.[18] Similarly, the lack of an increase following the reactive hypoglycemia during the OGTT was also described in previous studies.[17-19] The lack of a normal glucagon increase following a protein meal was noted in our study was also documented in one study during an alanine infusion.[17] However, another study[19] reported a "normal" glucagon increase from the basal level on insulin-induced hypoglycemia and alanine administration, although without depicting actual data in normal subjects. Moreover, this study also reported variable glucagon responses in individual subjects with IRH. We believe that glucagon secretagogues do induce glucagon stimulation in subjects with IRH, as noted in the previous study.[19] However, the glucagon responses seem to be significantly impaired in comparison to those in normal subjects. Finally, the basal hyperglucagonemia and the initial paradoxical increase following glucose ingestion were not previously documented. Thus, it is apparent from both studies, ie, the OGTT and the protein meal, that pancreatic α-cell function is altered in IRH.

The high basal glucagon concentration in the presence of euglycemia may suggest hyposensitivity and/or downregulation of the glucagon receptor, as described previously in hepatic cirrhosis.[31,32] Alternatively, euglycemia in the presence of hyperglucagonemia may suggest increased non–insulin-mediated glucose uptake by tissues, although this possibility remains to be assessed. Finally, the onset of reactive hypoglycemia during the OGTT and the larger decrease in glucose after a protein meal may also be attributed to impaired glucagon secretion in subjects with IRH. Therefore, we believe that the IRH syndrome does exist and may be attributed to both glucagon receptor downregulation and/or hyposensitivity and impaired glucagon secretion. Moreover, the desensitization of glucagon secretion noted in IRH may be comparable to the desensitization of insulin secretion documented in non–insulin-dependent diabetes mellitus. Finally, this syndrome may resemble the other extreme end of the spectrum opposite to non–insulin-dependent diabetes mellitus, in which both insulin sensitivity and secretion are also impaired.

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REFERENCES

1. Pears J, Jung RT, Browning MCK, et al: Reactive hypoglycemia in association with disordered islet function and abnormal hepatic glucose-6-phosphatase activity: Response to diazoxide. Diabet Med 8:268-271, 1991

2. Hadji-Georgopoulos A, Schmidt MI, Margolis S, et al: Elevated hypoglycemic index and late hyperinsulinism in symptomatic postprandial hypoglycemia. J Clin Endocrinol Metab 50:371-376, 1980

3. Hadji-Georgopoulos A, Schmidt MI, Elahi D, et al: Increased gastric inhibitory polypeptide levels in patients with symptomatic postprandial hypoglycemia. J Clin Endocrinol Metab 56:648-652, 1983

4. Lefebvre PJ: Statement of "post-prandial" or "reactive" hypoglycemia. Diabetologia 31:68, 1988

5. Berlin I, Grimali A, Landault C, et al: Suspected postprandial hypoglycemia is associated with B-adrenergic hypersensitivity and emotional distress. J Clin Endocrinol Metab 79:1428-1433, 1994

6. Charles MA, Hofeldt F, Shackelford A, et al: Comparison of oral glucose tolerance tests and mixed meals in patients with apparent idiopathic postabsorptive hypoglycemia. Absence of hypoglycemia after meals. Diabetes 30:465-470, 1981

7. Yager J, Young RT: Non-hypoglycemia is an epidemic condition. N Engl J Med 291:907-908, 1974

8. Cahill GF, Soeldner JS: A non-editorial on non-hypoglycemia. N Engl J Med 291:905-906, 1974

9. Service FJ: Hypoglycemic disorders. N Engl J Med 332:1144-1152, 1995

10. Hofeldt FD, Lufkin EG, Haglar L, et al: Are abnormalities in insulin secretion responsible for reactive hypoglycemia? Diabetes 23:589-593, 1974

11. Lev-Ran A, Anderson RW: The diagnosis of postprandial hypoglycemia. Diabetes 30:996-999, 1981

12. Betteridge DJ: Reactive hypoglycemia. Br Med J 295:286-287, 1987

13. Tamburrano G, Leonetti F, Sbraccia P, et al: Increased insulin sensitivity in patients with idiopathic reactive hypoglycemia. J Clin Endocrinol Metab 69:885-890, 1989

14. Hoefeldt FD: Reactive hypoglycemia. Metabolism 24:1193-1208, 1975

15. Goldman J: Pathogenesis of functional or idiopathic hypoglycemia: Hyperresponsiveness to insulin and increased receptor effector coupling, in Andreani D, DePirro R, Lauro R, et al (eds): Current Views on Insulin Receptor. San Diego, CA, Academic, 1981, pp 499-505

16. Goldman J: Idiopathic reactive hypoglycemia: A syndrome of hyperresponsiveness to insulin. Clin Res 27:655A, 1979 (abstr)

17. Foa PP, Dunbar JC, Klein SP, et al: Reactive hypoglycemia and A-cell ("pancreatic") glucagon deficiency in the adult. JAMA 244:2281-2285, 1980

18. Leonetti F, Morviducci L, Giaccari A, et al: Idiopathic reactive hypoglycemia: A role for glucagon? J Endocrinol Invest 15:273-278, 1992

19. Block MB, Lufkin EG, Hoefeldt FD, et al: The response of glucagon-like immunoreactivity to reactive hypoglycemia. Mil Med 141:32-37, 1977

20. Hoefeldt FD: Reactive hypoglycemia. Endocrinol Metab Clin North Am 185-201, 1989

21. Kabadi UM, Eisenstein AB: Glucose intolerance in hyperthyroidism: Role of glucagon. J Clin Endocrinol Metab 50:392-396, 1980

22. Leonetti F, Sbraccia P, Giaccari A, et al: Study of insulin sensitivity by glucose clamp technique in subjects with reactive hypoglycemia, in Andreani D, Marks V, Lefebvre PJ (eds): Hypoglycemia, Serono Symposia Publications, vol 38. New York, NY, Raven, 1987, pp 245-247

23. Cryer PE: Glucose homeostasis and hypoglycemia, in Wilson JD, Foster DW (eds): Williams' Textbook of Endocrinology (ed 7). Philadelphia, PA, Saunders, 1985, pp 989-1017

24. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 12:1039-1057, 1979

25. Kabadi UM, Eisenstein AB: Impaired pancreatic-cell response in hyperthyroidism. J Clin Endocrinol Metab 51:478-482, 1980

26. Kabadi UM: Dose-kinetics of pancreatic- and B-cell responses to a protein meal in normal subjects. Metabolism 40:236-240, 1991

27. Sanke T, Nanjo K, Kondo M, et al: Effect of calcium antagonists on reactive hypoglycemia associated with hyperinsulinemia. Metabolism 35:924-927, 1986

28. Service FJ, Nelson RL, Rubenstein AH, et al: Direct effect of insulin on secretion of insulin, glucagon, and gastric inhibitory polypeptide during maintenance of normoglycemia. J Clin Endocrinol Metab 47:488-493, 1978

29. Baschieri L, Antonelli A, del Guerra P, et al: Somatostatin effect in postprandial hypoglycemia. Metabolism 38:568-571, 1989

30. Permutt MA, Keller D, Santiago J: Cholinergic blockage in reactive hypoglycemia. Diabetes 26:121-127, 1977

31. Sherwin RS, Foster M, Becoff J, et al: Hyperglucagonemia in cirrhosis: Altered secretion and sensitivity to glucagon. Gastroenterology 74:1224-1228, 1978

32. Kabadi U: Hepatic regulation of pancreatic-cell function. Metabolism 42:535-543, 1993