The Glucose Receptor

A DEFECTIVE MECHANISM IN DIABETES MELLITUS DISTINCT FROM THE BETA ADRENERGIC RECEPTOR

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ABSTRACT Acute serum insulin responses in 10 normal subjects after rapid intravenous injection of glucose (5 g) or isoproterenol (2 μg) were of similar magnitude and timing (glucose: 431±349%; mean Δ3–5′ insulin (IRI)±SD, per cent basal and isoproterenol: 359±216%; mean Δ2–4′ IRI±SD, per cent basal). To elucidate the relationship of glucose-induced insulin secretion to pancreatic beta adrenergic receptors and the implications of this relationship with regards to abnormal insulin secretion in diabetes mellitus, two questions were studied. (*a*) To determine whether glucose-induced insulin secretion is dependent upon beta adrenergic activity, the effect of beta adrenergic blockade with intravenous propranolol (0.08 mg/min) upon acute insulin responses to isoproterenol and glucose were compared in normal subjects. (*b*) To determine whether acute insulin responses to beta adrenergic stimulation were intact in diabetes mellitus, the effect of isoproterenol upon serum insulin levels was studied in diabetic subjects. Beta adrenergic blockade in the normal subjects obliterated acute insulin responses to isoproterenol (before: 361±270%, during: −31±15%; $n = 6$, $P < 0.001$) but did not significantly affect responses to glucose (before: 311±270%; during: 284±206%; $n = 5$). The mean acute insulin response after isoproterenol in the diabetic group was significantly elevated over basal levels (152±74%; $n = 10, P < 0.001$) but the response after glucose was not (−11±11%). These data suggest that insulin responses to glucose in normal subjects are mediated by specific pancreatic glucose receptors which are independent from beta adrenergic receptors and that abnormal glucose-induced insulin secretion in diabetics is due to defects within glucose receptors and not beta adrenergic receptors as has been previously hypothesized.

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INTRODUCTION

Defects in pancreatic adenyl cyclase and cyclic AMP activity have been hypothesized to explain the failure of diabetic subjects to secrete insulin normally after glucose challenge and suspicion has specifically been cast upon the beta adrenergic receptor (1, 2), a hypothetical entity whose function is believed to depend upon adenyl cyclase and cyclic AMP. However, two questions which are critical in elucidating the relationship of glucose-induced insulin secretion to pancreatic beta adrenergic receptors and the implications of this relationship with regard to abnormal insulin secretion in diabetes mellitus have been left unanswered. (*a*) In normal subjects, does the insulin response to glucose depend upon beta adrenergic activity? (*b*) In diabetic subjects, are insulin responses to beta adrenergic stimulation intact despite abnormal responses to glucose? These questions were studied (*a*) by investigating the effect of beta adrenergic blockade in normal subjects upon glucose-stimulated acute insulin responeses, i.e., the response measurable in peripheral blood within 5 min after intravenous stimulation, and (*b*) by comparing acute insulin responses after glucose and beta adrenergic stimulation in normal and diabetic subjects.

METHODS

There were two groups of subjects: (*a*) normal subjects of varying degrees of obesity with no personal or family history of diabetes mellitus who responded to a request for volunteers posted on hospital bulletin boards, and (*b*) ambulatory diabetic subjects of varying degrees of adiposity who were noninsulin-dependent and had received no oral

hypoglycemic agents for at least 5 days before testing. All studies were conducted after a 12 h fast and at bed rest between the hours of 8 a.m. and 1 p.m. Intravenous 0.85% sodium choloride infusions were begun in both arms 1 h before administration of the various test agents. All blood samples were drawn through three-way stopcocks to avoid additional vena punctures during the infusions. After an initial 1 h basal period, glucose stimulation was provided by 5 g of intravenous glucose and 60 min later beta adrenergic stimulation was provided by 2 μg of isoproterenol, both stimuli given intravenously in less than 3 s; in some instances this order of injecting glucose and isoproterenol was reversed. Immediately thereafter beta adrenergic blockade was produced by intravenous propranolol, 5 mg in less than 3 s followed immediately by 0.08 mg/min infusion. Blood samples were drawn at 45, 30, 15, and 0 min before the stimulating agents were given. Plasma insulin levels were measured in blood samples drawn at 3, 4, 5, 7, 10, 15, 30, 45, and 60 min after glucose; 2, 3, 4, 5, 7, 10, 15, and 30 min after isoproterenol; and 15, 30, 45, and 60 min after the beginning of the propanolol infusions. After isoproterenol, the mean of the 2, 3, and 4 min insulin values for each individual was subtracted from the mean of the individual's four control values and termed the acute insulin response (mean 2–4 Δ IRI).[1] After glucose the mean of the 3, 4, and 5 min insulin values were used in the same fashion (mean 3–5′ Δ IRI). The calculations for the responses to isoproterenol began with the 2 min value because the peak response was generally 1 min earlier than that seen with glucose. The insulin values for each individual were expressed as per cent of the mean of the individual's four control values when the data was combined in the normal and diabetic groups because of previous publications (3) demonstrating a linear relationship between basal insulin level and the magnitude of response after glucose stimulation. After collection, heparinized blood samples for glucose were kept at 4°C until the end of the study, then centrifuged at 4°C, and the plasma was frozen for future analysis by the AutoAnalyzer-ferrocyanide method (4). Blood samples for insulin were allowed to clot at room temperature and then were centrifuged, and the serum was frozen for future analysis by the double antibody immunoprecipitation technique modified from Morgan and Lazarow (5). This assay has an intraassay coefficient of variation of 10% and an interassay coefficient of variation of 20%. All samples from one subject were analyzed in the same assay. Statistical comparisons were performed by paired *t* test, and correlation coefficients were derived by the Pearson Product Moment method.

[1] *Abbreviation used in this paper:* IRI, insulin.

TABLE I

Fasting Plasma Glucose and Serum Insulin Values in Normal and Diabetic Subjects

	Glucose	Insulin
	mg/100 ml	*μU/ml*
Normal subjects		
K. M.	90	11
N. G.	92	7
E. B.	95	7
A. R.	95	8
J. L.	98	23
S. Y.	99	8
G. C.	102	56
W. B.	105	12
A. E.	107	44
L. H.	110	11
Diabetic subjects		
Y. F.	158	43
W. K.	185	21
H. B.	204	11
E. W.	229	27
R. J.	236	8
S. R.	242	3
V. B.	264	11
E. L.	271	17
C. R.	298	16
O. L.	305	15

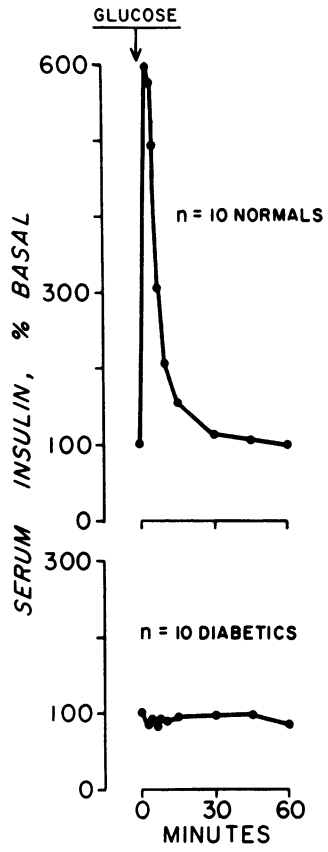

FIGURE 1 Effect of intravenous glucose (5 g) given in less than 3 s upon serum insulin levels in normal and diabetic subjects.

RESULTS

Acute insulin responses in normal subjects after intravenous glucose and isoproterenol. All normal subjects had fasting plasma glucose levels < 111 mg/100 ml (Table I) and varied with respect to age (26± 4 yr, mean ±SD), obesity (124±29%, per cent ideal body

TABLE II

Plasma Insulin (μU/ml) and Serum Glucose (mg/100 ml) Levels after Intravenous Glucose (5 g bolus) Given at 0 time before and at the end of the First Hour of an Intravenous Infusion of Propranolol (0.08 mg/min) in normal Subjects

											Propranolol													
Time, min...	0*	3	4	5	7	10	15	30	45	60	0	15	30	45	60	0‡	3	4	5	7	10	15	30	45	60
Subjects' insulin levels																									
A. R.	8	28	24	24	16	13	8	8	12	8		7	6	6	6		18	30	22	14	9	7	7	6	6
S. Y.	8	75	84	67	41	22	15	14	12	7		7	10	7	6		69	64	50	29	14	8	6	2	4
G. C.	56	189	180	159	152	108	82	50	42	42		37	41	40	34		136	163	147	68	31	27	36	33	39
W. B.	12	27	21	19	14	16	12	10	11	11		8	5	5	7		16	24	16	10	9	10	12	6	4
A. E.	44	161	135	94	74	67	69	48	45	44		48	36	38	39		195	161	101	72	64	42	33	29	38
K. M.	11	24	44	54	49	30	22	16	12	11															
N. G.	7	70	76	54	32	18	12	8	6	9															
E. B.	7	67	44	31	19	12	9	8	9	8															
J. L.	23	320	336	280	160	108	72	22	16	18															
L. H.	11	36	36	27	18	16	15	12	12	14															
Subjects' glucose levels																									
A. R.	95	130	126	122	119	118	114	104	95	91		100	99	96	98		140	134	134	128	120	116	104	98	99
S. Y.	99	143	130	130	127	124	114	104	99	94		97	100	100	96		142	133	131	127	122	116	108	103	102
G. C.	102	133	129	126	123	119	114	103	99	96		97	96	94	90		154	136	132	125	122	115	102	98	98
W. B.	105	151	144	142	138	126	122	114	108	104		100	100	98	100		140	136	140	126	124	120	108	102	98
A. E.	107	144	132	128	124	122	118	110	106	105		101	100	100	100		134	125	124	119	115	112	101	98	95
K. M.	90	—	150	130	123	119	112	101	96	95															
N. G.	92	138	125	119	115	112	108	97	96	98															
E. B.	95	132	127	125	121	119	112	103	97	94															
J. L.	98	120	120	118	115	110	103	91	93	94															
L. H.	110	141	146	135	134	130	125	116	108	105															
Insulin, % basal $n = 5$																									
Mean		444	431	359	254	183	138	111	114	91		83	79	72	72		381	406	305	181	113	83	80	55	63
±SD		282	351	273	155	56	38	19	34	10		18	30	19	12		292	231	187	108	49	21	14	19	21
Insulin, % basal $n = 10$																									
Mean		611	606	496	330	223	164	114	107	100															
±SD		418	146	114	63	34	21	9	10	6															

* Mean of 4 samples before first glucose bolus.
‡ Glucose bolus.

weight,[2] mean ±SD) and basal insulin level (19±16, μU/ml, mean ±SD). All 10 subjects had immediate insulin responses after 5 g of intravenous glucose (Table II, Fig. 1). Serum insulin levels were maximal for the group by 3 min and base-line levels were reestablished by 30 min. The mean acute response for the group (431±349%, mean Δ 3–5′ IRI, per cent basal, mean ±SD) was significantly greater than control levels ($P < 0.01$). There was a similar insulin response after 2 μg of intravenous isoproterenol (Table III, Fig. 2). Serum insulin levels were maximal for the group by 2 min and base-line levels were reestablished by 15 min. The mean acute response for the group (359±216%) was significantly greater than control values ($P < 0.001$). The insulin response to isoproterenol was compared in six of these subjects before and during beta adrenergic blockade with intravenous propranolol. In 6/6 subjects the isoproterenol-stimulated response was completely obliterated by propranolol (before: 361±143%; during: −31±15%; $P < 0.001$). In contrast, the glucose-stimulated response in 5/5 subjects tested was not significantly diminished when compared before (311±270%) and during (284±206%) beta blockade with the identical dose of intravenous propranolol (Table II, Fig. 3).

Acute insulin responses in diabetic subjects after intravenous glucose and isoproterenol. All diabetic subjects had fasting plasma glucose levels > 157 mg/ml (Table I) and varied with respect to age (46±9 yr, mean ±SD), obesity (123±27%, per cent ideal body weight, mean ±SD) and basal insulin level (17±11, μU/ml, mean ±SD). Obesity and basal insulin level were similar in the normal and diabetic groups, but the diabetic group was significantly older ($P < 0.001$). All 10 subjects had no significant increase in insulin level acutely in any individual after 5 g of intravenous glucose (Table IV, Fig. 1); the mean response for the group was −11±11%. In striking contrast, all the dia-

[2] Metropolitan Life Insurance tables, Metropolitan Life Insurance Company, New York.

TABLE III

Plasma Insulin (μU/ml) and Serum Glucose (mg/100 ml) Levels after Intravenous Isoproterenol (2 μg bolus) Given before and at the end of the First Hour of an Intravenous Infusion of Propranolol (0.08 mg/min) in Normal Subjects

										Propranolol												Responses to isoproterenol	
Time, min...	0*	2	3	4	5	7	10	15	30	0	15	30	45	60	0‡	2	3	4	5	7	10	15	30	$\bar{x}$ Δ2-4′ IRI	$\bar{x}$ Δ2-4′ IRI % basal
Subjects' insulin levels																									
A. R.	8	33	31	38	25	12	9	7	10	7	6	6	6		6	5	2	6	4	4	6	6		26	325
S. Y.	8	63	42	35	23	15	10	9	6	7	10	7	6		7	5	10	6	8	6	6	4		39	484
G. C.	56	154	166	120	138	88	71	68	48	37	41	40	34		34	34	26	32	34	52	80	88		91	162
W. B.	12	84	67	46	25	18	12	12	9	8	5	5	7		8	10	10	10	8	5	8	1		54	447
A. E.	44	140	155	107	91	63	50	49	43	48	36	38	39		40	38	30	34	39	36	26	—		90	204
K. M.	11	61	76	76	64	45	25	15	—	6	5	4	4		4	5	3	6	2	1	6	2		60	545
N. G.	7	46	44	28	21	14	10	10	10															32	857
E. B.	7	20	14	12	12	8	6	6	8															8	141
J. L.	23	88	80	75	59	38	22	18	20															58	252
L. H.	11	42	36	20	20	15	11	11	13															22	200
Mean ±SD																								48±28	359±216
Subjects' glucose levels																									
A. R.	95	96	96	97	95	95	94	90	95	100	99	96	98		98	98	94	95	96	98	99	100			
S. Y.	99	96	96	96	94	94	92	91	94	97	100	100	96		98	96	98	98	94	96	94	94			
G. C.	102	100	101	102	101	99	99	96	91	97	96	94	90		90	90	90	92	91	92	94	94			
W. B.	105	102	103	104	104	103	102	98	100	100	100	98	100		98	96	97	95	96	95	95	94			
A. E.	107	106	107	108	107	106	105	104	104	101	100	100	100		97	98	98	96	98	96	96	98			
K. M.	90	98	98	96	96	94	92	92	—	96	94	93	94		93	93	94	94	90	93	96	90			
N. G.	92	93	94	98	97	98	97	95	94																
E. B.	95	94	93	92	94	91	90	89	87																
J. L.	98	95	94	96	95	95	94	94	94																
L. H.	110	104	106	104	106	104	101	104	101																
Insulin, % basal																									
n = 6																									
Mean		508	468	407	307	200	134	112	92	81	76	68	67		76	71	70	74	74	68	88	59			
±SD		190	136	159	129	95	42	15	19	17	28	20	16		13	13	38	10	21	22	31	63			
n = 10																									
Mean		476	431	352	275	181	123	108	93																
±SD		62	53	54	39	28	14	7	12																

* Mean of 4 samples before first isoproterenol bolus.
‡ Isoproterenol bolus.

betic subjects had an acute insulin response after intravenous isoproterenol (Table IV, Fig. 4). Serum insulin levels were maximal for the group by 2 min, and base-line levels were reestablished by 15 min. The mean acute response for the group (152±74%) was significantly greater than control values ($P < 0.001$). Although the mean acute insulin response to isoproterenol, expressed as per cent basal, for the diabetic group was significantly less than that seen for the normal group ($P < 0.02$), no appreciable differences in the normal and diabetic responses could be visualized when the absolute acute insulin response for each individual was plotted as a function of his basal insulin level (Fig. 5). There was no significant correlation between acute insulin response after isoproterenol and fasting plasma glucose in either the normal ($r = -0.52$) or diabetic ($r = -0.02$) groups. Plasma glucose levels were unaffected by the isoproterenol injections in both the normal and diabetic groups, and in both groups individual plasma

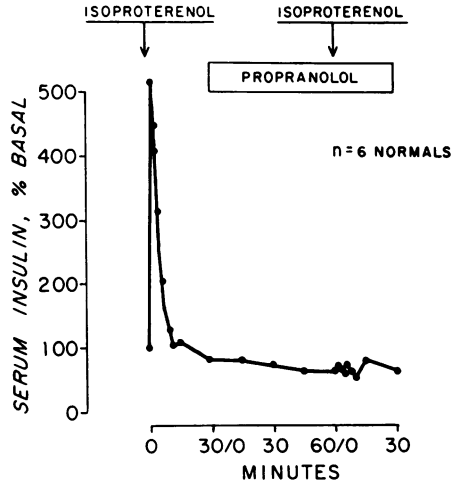

FIGURE 2 Effect of intravenous isoproterenol (2 μg) given in less than 3 s before and during intravenous propranolol infusion (0.08 mg/min) upon serum insulin levels in normal subjects.

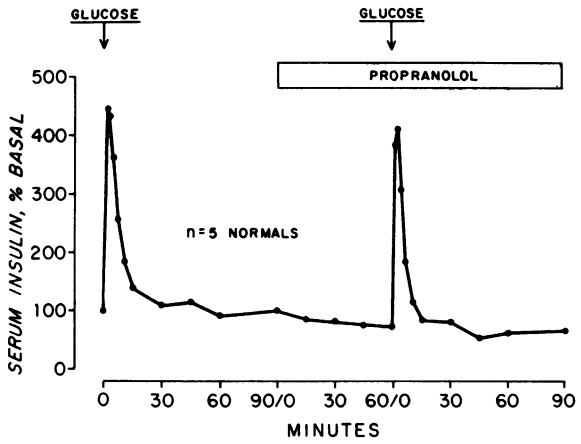

FIGURE 3 Effect of intravenous glucose (5 g) given in less than 3 s before and during intravenous propranolol infusion (0.08 mg/min) upon serum insulin levels in normal subjects.

glucose levels before glucose and isoproterenol injections varied less than 4±3% (mean ±SD).

DISCUSSION

A strong argument for the existence of separate and distinct receptors within the pancreatic islet for glucose and beta adrenergic agonists can be advanced by virtue of the differential effect of beta adrenergic blockade upon the acute insulin responses to glucose and isoproterenol in the normal subjects. In the doses used, both stimuli induced acute insulin responses of similar magnitude within minutes of intravenous injection. Yet, although the responses were comparable with regard to magnitude and timing, the response to glucose stimulation was not affected by a level of beta adrenergic blockade which obliterated the response to isoproterenol stimulation. Thus, in a situation where the hypothetical pancreatic beta adrenergic receptors were unresponsive, it was possible to stimulate a normal response with glucose. The conclusion thus seems warranted that the glucose-stimulated response was independent of the beta adrenergic receptor. Consequently, the need arises to postulate a separate and functionally distinct glucose receptor. Data supporting the existence of glucoreceptors has been previously published by Matschinsky, Landgraf, Ellerman, and Kotler-Brajtburg (6) and has been recently reviewed.

An argument can be marshalled against a concept of discrete and independent receptors through use of data published by Cerasi, Effendic, and Luft (1) who de-

TABLE IV

Plasma Insulin (μU/ml) and Serum Glucose (mg/100 ml) Levels after Intravenous Glucose (5 g bolus) and Intravenous Isoproterenol (2 μg bolus) in Diabetic Subjects

												Responses to isoproterenol									
Time, min...	0*	3	4	5	7	10	15	30	45	60	0‡	2	3	4	5	7	10	15	30	$\bar{x}$ Δ2-4′ IRI	$\bar{x}$ Δ2-4′ IRI % basal
Subjects' insulin levels																					
Y. F.	43	48	41	40	48	48	62	80	41	45		150	150	129	87	72	47	40	55	100	233
W. K.	42	43	33	38	43	44	41	57	52	38	21§	32	36	33	29	26	28	24	20	13	62
H. B.	11	11	9	10	9	9	11	11	—	—		34	34	37	28	19	13	13	11	24	218
E. W.	27	28	30	27	19	26	30	26	28	26		88	95	55	48	47	33	26	32	52	193
R. J.	8	6	8	6	8	7	9	7	7	7		14	11	10	10	10	11	10	8	4	50
S. R.	3	2	2	3	2	2	2	1	2	1		12	10	6	6	2	3	5	2	6	200
V. B.	11	8	8	8	9	7	8	12	10	11		17	18	20	20	16	14	12	11	7	64
E. L.	17	14	13	11	12	14	13	15	11	12		33	33	23	23	22	14	16	14	13	77
C. R.	16	15	15	14	16	11	12	20	31	20		54	55	41	24	22	18	16	18	34	213
O. L.	15	10	16	14	12	17	18	12	19	16		42	54	44	34	22	17	18	11	32	213
Mean ±SD																				29±29	152±74
Subjects' glucose levels																					
Y. F.	153	194	194	190	185	184	179	167	158	153		155	155	156	156	154	154	157	153		
W. K.	128	148	146	146	148	141	141	133	125	120	185§	180	180	180	182	178	178	177	176		
H. B.	188*	215	218	218	214	210	213	202	—	—		198	198	202	200	204	202	196	188		
E. W.	229	268	264	262	256	254	246	236	232	225		217	217	217	217	218	214	216	210		
R. J.	209	267	268	256	260	252	246	230	218	216		225	219	224	228	224	229	226	210		
S. R.	234	278	272	272	270	269	258	266	253	249		236	241	242	240	242	234	239	234		
V. B.	264	462	310	288	280	286	267	280	282	272		262	262	254	264	260	260	258	253		
E. L.	262	300	302	294	300	292	286	280	268	264		256	264	260	260	260	234	256	262		
C. R.	284	337	373	328	318	313	305	307	302	285		295	282	292	288	297	293	290	284		
O. L.	300	356	350	348	340	340	324	324	296	300		296	304	304	304	300	292	300	300		
Insulin, % basal																					
Mean		87	88	87	87	88	98	104	106	91		205	263	211	172	133	109	108	93		
±SD		6	5	4	5	6	8	13	39	26		35	35	28	18	13	7	9	8		

* Mean of 4 samples before glucose bolus.
‡ Isoproterenol bolus.
§ Performed on a different day.

scribed attenuation of insulin responses after glucose during propranolol infusion. However, in their studies glucose was administered as a 500 mg/kg priming dose followed by 20 mg/kg per min infusion for 1 h—thus, both dose and duration of infusion were not comparable to those used in the present study. Moreover, the significance of the results reported by Cerasi et al. (1) is open to question since propranolol inhibited the acute insulin response to glucose in only three of the six subjects studied. These authors have recently published (7) an extension of this study in 16 normal subjects showing that the described inhibition upon insulin secretion, while statistically significant, varied markedly with some subjects showing no inhibition. On the other hand, it might be argued that the dose of propranolol used in the present study was too small to inhibit a theoretical beta adrenergically-mediated response to 5 g of glucose. However, this is not likely since the dose of propranolol used in this study was sufficient to obliterate the insulin response to isoproterenol, a response comparable to that after glucose in both magnitude and timing.

A comparison of the insulin responses after glucose and isoproterenol in the diabetic subjects provides further evidence that the glucose receptor is functionally independent of the beta adrenergic receptor. The observation that none of the diabetic subjects had an acute insulin response after glucose, but all of them had responses after isoproterenol, supports the contention that separate receptors were involved. Interestingly, the diabetic group had a significantly smaller mean acute insulin response after isoproterenol than that seen in the normal group, suggesting that the diabetic pancreas has a diminished ability to respond to beta adrenergic stimulation. It is unlikely that severity of hyperglycemia or quality of therapeutic control is the explanation for this finding since no significant correlation was found between the acute insulin response to isoproterenol and fasting plasma glucose level among individuals in either the normal or the diabetic groups. On the other hand, the

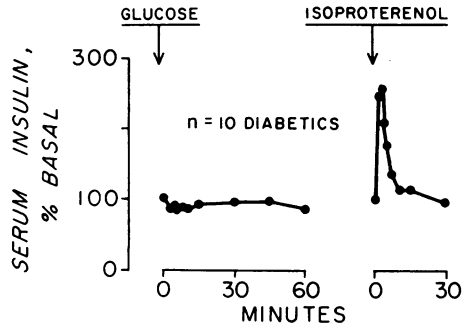

FIGURE 4 Effects of intravenous glucose (5 g) and intravenous isoproterenol (2 μg) given in less than 3 s upon serum insulin level in diabetic subjects.

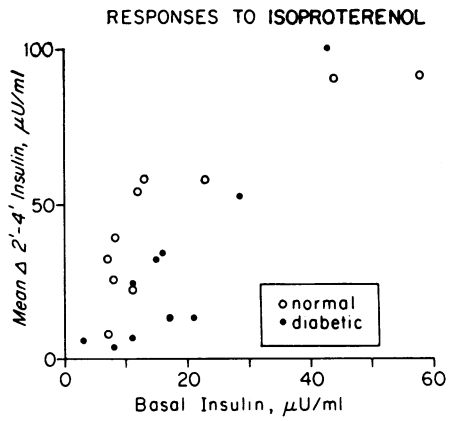

FIGURE 5 Comparison of mean acute insulin responses related to basal insulin level after intravenous isoproterenol (2 μg) in normal and diabetic subjects.

observed difference in mean group responses to isoproterenol may actually be misleading since the normal and diabetic subjects were not of comparable ages and moreover could not be readily distinguished from one another when individual responses were plotted as a function of basal insulin level (Fig. 5). The possibility that responses to beta adrenergic stimulation are not significantly different in normal and diabetic subjects is supported by a recent publication by Deckert, Lauridsen, Madsen, and Deckert (8) reporting comparable elevation of insulin levels in normal and diabetic subjects during prolonged intravenous infusion of the beta agonist isoprenaline. In any event, even if the diabetic pancreas should have a diminished sensitivity to beta adrenergic stimulation, this could not be the explanation for absent insulin responses to glucose since in normal subjects beta blockade at a level which obliterated responses to isoproterenol did not affect responses to glucose.

The pathophysiologic relevance of these observations to human disease lies in their clear implication that hypotheses which invoke defects within the beta adrenergic receptor or pancreatic adenyl cyclase and cyclic AMP activity in diabetic subjects to explain defective insulin secretion after glucose stimulation are open to question and may be erroneous. In this regard, the concept advanced herein that the cause of this abnormal response may lie in a defective glucose receptor within the diabetic islet is supported by previous observations that glucagon and secretin have both been reported to induce insulin secretion in diabetic subjects (9, 10).

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