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Epinephrine: selective inhibition of the acute insulin response to glucose

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Epinephrine: Selective Inhibition of the Acute Insulin Response to Glucose

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ABSTRACT An epinephrine infusion of 6 μg/min decreased the rapid insulin response to a 5 g glucose pulse by 96% ($P < 0.001$) compared with the preinfusion control. In contrast when an identical epinephrine infusion was superimposed on a prolonged glucose infusion, elevated steady-state insulin levels did not decrease, but increased from 26.9 ±6 (mean ±SD, μU/ml) to 56.8 ±15 μU/ml ($P < 0.05$) in parallel with the epinephrine-induced hyperglycemia. Thus epinephrine inhibition of insulin secretion was observed during acute but not chronic glucose stimulation. To evaluate further the insulin responses during a prolonged glucose infusion, a 5 g glucose pulse was given before and 60 min later during a concomitant epinephrine infusion. Although the acute insulin response to the first glucose pulse was observed during the elevated steady-state glucose and insulin levels associated with the glucose infusion, epinephrine again inhibited the acute insulin response to the subsequent 5 g glucose pulse by 91% ($P < 0.01$). Thus epinephrine appears to inhibit selectively the rapid insulin response to glucose but not to influence insulin output stimulated by prolonged hyperglycemia. These observations provide further evidence for a model of insulin secretion which includes a small storage pool available for immediate release to a glucose challenge and a more slowly responding pool regulating insulin secretion in the basal and steady state.

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INTRODUCTION

Epinephrine is a well known inhibitor of insulin responses to glucose, glucagon, and tolbutamide (1). The inhibition of insulin release is mediated by stimulation of the alpha adrenergic receptor, since simultaneous infusion of an alpha adrenergic antagonist, phentolamine, reverses this blockade (2).

Since these reports, several groups of investigators have provided evidence that glucose-stimulated insulin secretion is multiphasic, (3, 4) or multicompartmental (5). Recently a simple two-pool model for insulin secretion in man has been proposed (5). The first functional pool is a small storage pool of insulin which rapidly responds to changes in the plasma glucose level. This pool is refilled by a second pool which responds more slowly. Secretion from the second slower pool is reflected in the basal insulin levels after an overnight fast and in steady-state insulin levels measured during a prolonged glucose infusion.

Studies in patients with pheochromocytoma have indicated that basal insulin levels were higher but insulin responses were blunted to glucose (6). This pattern of insulin responses was reversed after removal of the tumor (6, 7). These observations suggested that epinephrine inhibited insulin responses to glucose stimulation only from an acutely releasable pool. To test this hypothesis the following studies were undertaken.

METHODS

Three groups comprising a total of 17 white male volunteers between the ages of 21 and 29 were hospitalized for study on the Clinical Research Center of University Hospital. All subjects were within 15% of ideal body weight according to Metropolitan Life Insurance tables and had no family history of diabetes. Before the study all subjects

were encouraged to eat a weight maintaining calorically balanced diet.

The six subjects in group I were studied at bed rest beginning at 8 a.m. after a 12 hr fast. Two small butterfly cannulas were inserted in an antecubital vein and in a superficial vein on the dorsum of the contralateral hand respectively, and were maintained patent by a slow drip of 0.85% NaCl. During the subsequent 60 min control period, 4 blood samples for basal insulin and glucose determinations were obtained at 15 min intervals, after which 5 g glucose as 50% dextrose in water was injected intravenously over a period of 10 sec (pulse). 60 min later, an epinephrine infusion, 6 μg/min, was begun and continued for the following 120 min. After the first 60 min of epinephrine infusion, a second 5 g glucose pulse was administered.

At approximately 6 p.m. before the day of study, the six subjects in group II were placed in bed and, after insertion of a plastic cannula in a forearm vein, a 300 mg/min glucose infusion was started. On the following morning at 8 a.m., after the insertion of the two cannulas was accomplished (vide supra) and after a 60 min control period, an epinephrine infusion 6 μg/min was superimposed on the glucose infusion and both infusions continued for the next 120 min.

The experimental protocol for the five subjects in group III was identical to that of group II with the following exceptions. After the 60 min control period, a 5 g glucose pulse was administered. 60 min later, an epinephrine infusion, 6 μg/min, was superimposed on the continuing glucose infusion and both infusions were continued for the subsequent 120 min. After the first 60 min of the epinephrine infusion, a second 5 g glucose pulse was given.

Basal glucose and insulin levels (4 blood samples at 15 min intervals after a 12 hr overnight fast) were obtained from all subjects in groups II and III within 3 days after the studies were completed. Previous basal insulin levels were available in almost all of the subjects and showed variation of approximately ±1 μU/ml. In groups I and III, blood samples for glucose and insulin after all glucose pulses were obtained at the following times: 3, 4, 5, 7, 10, 15, 30, 45, and 60 min by the method previously described (5). After the start of the epinephrine infusion in group II, blood samples for glucose and insulin levels were obtained at 15 min intervals for 120 min; in groups I and III, at 15 min intervals for the first 60 min. Serum insulin

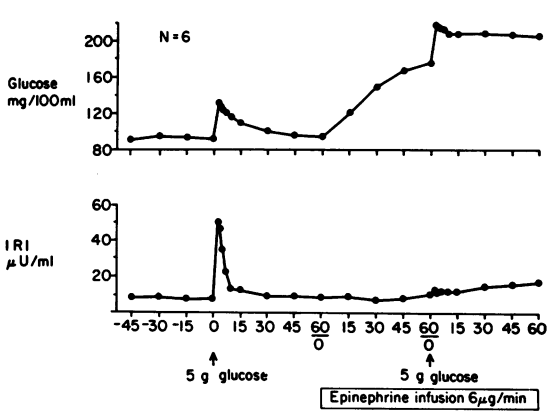

FIGURE 1 Mean glucose and insulin levels in response to a 5 g glucose before and during epinephrine infusion.

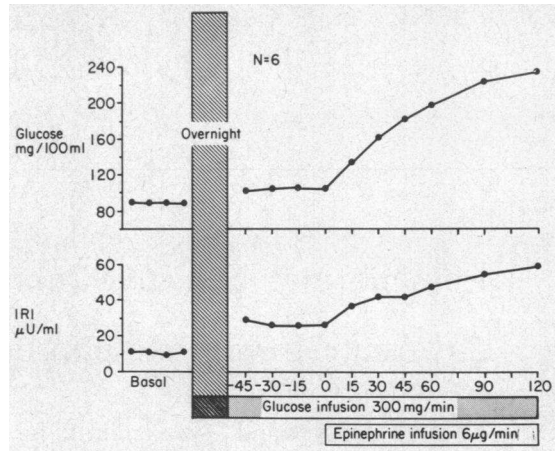

FIGURE 2 Mean steady-state glucose and insulin levels during prolonged glucose infusion before and during concomitant epinephrine infusion.

was measured as immunoreactive insulin (IRI) by the method of Morgan and Lazarow (8) and plasma glucose was measured by the AutoAnalyzer ferricyanide technique. The estimate of the acute insulin response was made from the mean of the incremental change (Δ) in plasma insulin from 3 through 5 min after a glucose pulse (3–5′ Δ IRI, μU/ml). The glucose disappearance rate (Kg) was measured by the decline in plasma glucose levels between 10 and 30 min after glucose pulse by the method of least squares (9). Statistical analysis of data within each group was done by paired "t" test; between any two groups by Students "*t*" test (10).

RESULTS

Effect of epinephrine on the acute insulin response to a 5 g glucose pulse. The 5 g glucose pulse raised plasma glucose levels, with peak levels being observed within 3–5 min (Fig. 1). The acute insulin response also occurred between 3 and 5 min after the glucose pulse and returned to prestimulated levels (Fig. 1). After 60 min of the epinephrine infusion, plasma glucose levels were higher compared to preinfusion control ($P < 0.001$, Table I) but no significant change was observed in plasma insulin levels (Table I Fig. 1). During the epinephrine infusion the acute insulin response to the 5 g glucose pulse was diminished by 96% ±9 (mean ±SD, $P < 0.001$, Table I).

The effect of epinephrine on steady-state glucose and insulin levels. After a 12–14 hr overnight glucose infusion, steady-state glucose levels rose in all subjects of group II ($P < 0.001$) and steady-state insulin levels were increased compared with the respective basal values ($P < 0.01$, Table I). When a concomitant epinephrine infusion was begun, insulin levels increased in parallel with the rising plasma glucose levels induced by epinephrine (Fig. 2). Insulin levels (Table I) were significantly increased at 60 min ($P < 0.05$) and 120 min ($P < 0.001$) of the epinephrine infusion.

TABLE I

Glucose and Insulin Levels before and during Epinephrine Infusion

			Preepinephrine			During epinephrine			
			5g glucose pulse					5g glucose pulse	
	Basal		3–5′Δ	3–5′Δ		60 min		3–5′Δ	3–5′Δ
	Glucose*	IRI*	Glucose	IRI	Kg	Glucose	IRI	Glucose	IRI
	mg/100 ml	*μU/ml*	*mg/100 ml*	*μU/ml*	*%/min*	*mg/100 ml*	*μU/ml*	*mg/100 ml*	*μU/ml*
Group I: 5 g glucose pulses before and during epinephrine infusion									
1	88	12	33	38.7	−1.66	196	14	35	3
2	94.3	7.8	46.1	38.9	−1.77	168	8	39.7	1
3	89.3	6.5	35.7	36.8	−1.73	181	4	41	0
4	98	8.5	24.3	16.8	−1.47	207	11	40.3	0
5	88.8	10.8	29.9	54.2	−1.62	156	18	40.1	3.3
6	96.8	6.8	39.2	26.9	−1.52	142	8	37.8	1.7
Mean	92.5	8.7	34.7	35.4	−1.63	175	10.5	39.8	1.5
SD	4	2	8	13	.2	25	5	2	1

Group II: glucose infusion before and during epinephrine infusion

			Glucose infusion					
					Epinephrine infusion			
	Basal		Steady state		60 min		120 min	
	Glucose*	IRI*	Glucose*	IRI*	Glucose	IRI	Glucose	IRI
	mg/100 ml	*μU/ml*	*mg/100 ml*	*μU/ml*	*mg/100 ml*	*μU/ml*	*mg/100 ml*	*μU/ml*
1	99	9	117	28.5	181	62	215	76
2	86.8	9.8	121	26.5	256	32	300	52
3	87.3	13.5	105	23.5	171	76	207	72
4	96.5	12	121	22	201	46	248	60
5	84.8	11	112	38.8	161	50	169	62
6	83	8	108	22.3	213	21	268	31
Mean	89.6	10.6	114	26.9	197	47.8	235	58.8
SD	7	2	7	6	35	20	47	16

Group III: glucose infusion; 5 g glucose pulses before and during epinephrine infusion

			Glucose infusion								
					Preepinephrine			During epinephrine			
					5 g glucose pulse					5 g glucose pulse	
	Basal		Steady state		3–5′Δ	3–5′Δ		60 min		3–5′Δ	3–5′Δ
	Glucose*	IRI*	Glucose*	IRI*	Glucose	IRI	Kg	Glucose	IRI	Glucose	IRI
	mg/100 ml	*μU/ml*	*mg/100 ml*	*μU/ml*	*mg/100 ml*	*μU/ml*	*%/min*	*mg/100 ml*	*μU/ml*	*mg/100 ml*	*μU/ml*
1	88.3	6.3	111	18.8	39	16.9	−1.26	155	24	40	2.5
2	100	7	112	18.8	46.7	13.5	−1.58	220	24	46	0.3
3	88.8	7	106	20.3	39.7	13	−1.83	198	47	41	11.3
4	93.3	9.8	109	21	41	11	−2.08	190	38	43.3	−1
5	107	12	105	23.5	49.3	10.5	−1.40	221	29	44	−1.5
Mean	95.5	8.4	109	20.5	43.1	13	−1.63	197	32.4	42.9	1.6
SD	8	2	3	2	5	2	.3	27	10	2	6

* Mean of four samples.

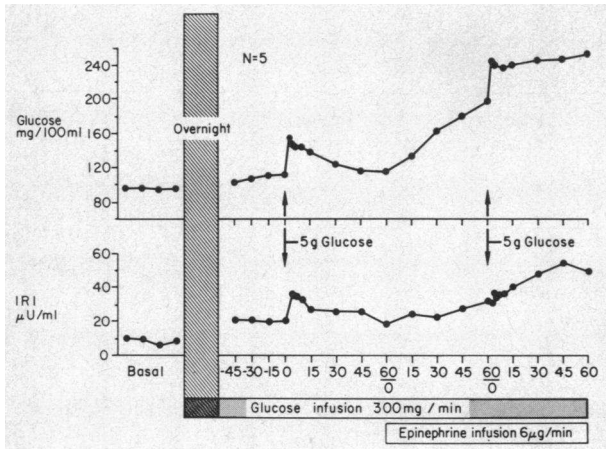

FIGURE 3 Mean glucose and insulin levels during prolonged glucose infusion and to a 5 g glucose pulse before and during concomitant epinephrine infusion.

The effect of epinephrine on the acute insulin response to a 5 g glucose pulse during a glucose infusion. Similar to the results of the studies in group II, after an overnight glucose infusion, both steady-state glucose and insulin levels (Table I) were increased in all group III subjects compared to their respective basal values ($P < 0.05$). No significant differences in basal or steady-state glucose or insulin levels were found between subjects of groups II and III. 60 min of concomitant epinephrine infusion increased plasma levels of both glucose ($P < 0.01$) and insulin ($P < 0.01$), (Table I). However, the acute insulin response to a 5 g glucose pulse during the epinephrine infusion was markedly diminished (91% ±45, $P < 0.01$) compared with the response to the preinfusion glucose pulse (Table I, Fig. 3).

DISCUSSION

These studies confirm a previous report that epinephrine inhibits glucose stimulated insulin responses (1). However, if glucose-stimulated insulin responses were a simple function of the glucose concentration, the elevated steady-state insulin response observed during the stimulus of a prolonged glucose infusion, should be similarly inhibited by the concommitant infusion of epinephrine. In contrast to the expected fall, steady-state insulin levels increased in parallel with the rising glucose level during the epinephrine infusion. Although no inhibition of basal and steady-state insulin levels was noted during the epinephrine infusion, the possibility exists that at a higher infusion rate, such an effect might be seen. However, when a 6 μg/min epinephrine infusion was increased to 12 μg/min (unpublished observations), no decline in basal insulin levels was noted.

Further separation of these different patterns of insulin response was observed when glucose pulses were administered during the prolonged glucose infusion before and during a simultaneous epinephrine infusion in group III subjects. Although similar parallel increases in steady-state insulin levels occurred during epinephrine, the acute insulin responses to the glucose pulse were still markedly inhibited. A possible explanation for the inhibition of rapid insulin responses during epinephrine infusion is that hyperglycemia may inhibit the insulin response to a glucose pulse. Previous studies employing prolonged glucose infusions resulted in elevated glucose levels that overlapped with the present observations; however, despite this degree of hyperglycemia glucose pulses elicited the same or greater rapid insulin responses or compared with preinfusion control (5). Furthermore, other studies demonstrated a prompt insulin response after a simultaneous infusion of glucose and epinephrine was discontinued while plasma glucose concentrations were essentially unchanged (1) and were comparable with the levels seen in the present study. These lines of evidence indicate that inhibition of the early insulin response during epinephrine infusion is not due to the effect of hyperglycemia. Thus the results of the present study suggest that the inhibition of insulin responses is selective for one type of insulin response to glucose and provides further supporting evidence for the previously proposed two pool model for insulin secretion (5).

These observations may provide an explanation for insulin levels observed in patients with pheochromocytoma. Some patients with pheochromocytoma have both elevated basal glucose and insulin levels (6, 7) similar to values in normal subjects during a prolonged glucose infusion (5). However, the acute insulin responses to glucose and tolbutamide are blunted (6), consistent with inhibition of the storage pool output. After surgical removal of the tumor, basal insulin and glucose levels are lower, and insulin responses are similar to normal subjects (6, 7). Chronic adrenergic blockade in patients with pheochromocytoma has also reduced basal insulin levels, lowered glucose levels, and improved insulin responses and glucose disappearance rates in some patients (6).

Since steady-state insulin levels are higher and acute insulin responses are lower in pheochromocytoma patients, a two pool system for glucose-induced insulin release in which adrenergic inhibition affects secretion only from the small storage pool, but not basal or steady-state insulin output during prolonged hyperglycemia would provide an explanation for such findings. One physiological role of such a system may be to protect normal individuals from ketoacidosis during periods of great stress such as burns, severe congestive heart fail-

ure, and myocardial infarction. Although these states have been associated with increased catechol output (11–13) and severe inhibition of acute insulin release (14–16), the maintenance of normal or elevated basal insulin levels appears adequate to suppress lipolysis and may account for the rarity of ketoacidosis in these conditions.

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