Counter-Regulation of Basal Insulin Secretion During Alcohol Hypoglycemia in Diabetic and Normal Subjects

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SUMMARY

To determine (1) whether differences in insulin levels, and (2) the presence of diabetes mellitus influenced the hypoglycemic response to alcohol, immunoreactive insulin (IRI) and glucose levels were measured during alcohol infusion in twenty obese and thin subjects with normal and mildly abnormal carbohydrate tolerance after a preparatory three-day fast. Despite small differences in the rates of decline of glucose, IRI fell promptly, and were indistinguishable when the subjects were grouped according to both glucose tolerance and weight. These findings indicate that the regulation of basal IRI in response to a falling glucose level during ethanol hypoglycemia appears to be intact in both obesity and mild diabetes. DIABETES *21*:65-70, February, 1972.

On the basis of extensive study in both man and animals, it is now accepted that alcohol hypoglycemia results from the hepatic oxidation of alcohol. The degradative metabolism of alcohol utilizes oxidized pyridine nucleotide (NAD), a substance of critical importance in the maintenance of gluconeogenesis. It is this resulting increase in the ratio of $NADH_2$ to NAD (reduced/oxidized nicotinamide adenine dinucleotide) generated in the liver cell during alcohol oxidation that appears to be causally linked with suppression of hepatic gluconeogenesis, and consequent decline in circulating glucose levels.[1-4]

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The lack of any observable increase in circulating insulin levels during ethanol hypoglycemia[5] has suggested that the decline observed in glucose concentration was not mediated by insulin and instead reflected inhibition of hepatic gluconeogenesis. The recent report from Madison's laboratory[6] indicating that peripheral glucose utilization in fasted dogs decreases during ethanol administration independent of changes in glucose levels suggests that other factors also may influence the disappearance rate of circulating glucose during alcohol hypoglycemia in man.

In order to determine whether compensatory changes in insulin secretion might be one previously unrecognized factor which influences the hypoglycemic response to alcohol, insulin and glucose levels were measured during alcohol infusion in obese and nonobese diabetic and nondiabetic human subjects.

METHODS

Twenty thin and obese nondiabetic and diabetic subjects with carbohydrate tolerance determined by previously described criteria[7] were hospitalized for study on a metabolic ward. All obese subjects weighed in excess of 125 per cent and thin subjects less than 112 per cent of their ideal body weight according to Metropolitan Life Insurance Company tables. Three-hour (100 gm.) glucose tolerance tests were performed in all subjects after receiving weight-maintaining diets which contained 300 gm. of carbohydrate daily for three days. Glucose responses were classified as either diabetic or nondiabetic, as previously described.[8] Those diabetic subjects receiving oral hypoglycemic agents discontinued medication at least one week prior to hospitalization.

After a three-day fast, all subjects received six-hour ethanol infusions (236 mg./min.) according to the method of Freinkel.[5] Serum immunoreactive insulin (IRI) levels were measured by a previously described

TABLE 1

Basal measurements and alterations in plasma glucose and serum immunoreactive insulin levels during ethanol infusion in thin and obese diabetic and nondiabetic subjects

Group	Weight kg.	% ideal	Pre-fast	Glucose concentrations (mg./100 ml.) Post-fast	During ethanol infusion (min.) 30	60	90	120	150	180	210	240	270	300	330	360
Thin nondiabetic																
I-1	65.8	96	99	78	70	67	63	60	61	60	59	60	60	61	61	63
I-2	75.4	112	87	76	68	60	54	51	50	49	49	49	49	49	49	51
I-3	72	105	91	77	67	61	56	49	46	47	47	46	46	47	49	51
I-4	80	106	67	29	29	26	22	18	19	20	19	20	19	20	20	21
I-5	75.2	105	62	54	44	38	30	28	27	27	23	24	24	26	—	—
I-6	90.0	108	98	66	57	47	39	32	35	34	35	35	34	37	—	—
I-7	95.5	100	75	55	45	38	35	23	29	30	33	30	31	36	38	39
Mean ± S.E.M.				61±7	53±6	47±6	42±6	38±6	38±6	38±6	38±6	38±6	38±6	39±6	43±6	45±8
Obese nondiabetic																
II-1	116	160	97	65	65	61	57	54	54	53	52	52	53	52	53	50
II-2	106.3	141	100	77	70	66	63	59	54	52	51	51	49	49	50	50
II-3	97.6	135	95	76	72	69	66	62	60	57	56	55	55	55	56	56
II-4	112.3	160	99	79	78	75	74	71	69	68	68	67	67	65	66	64
II-5	145	146	100	84	78	78	77	74	76	75	76	74	70	71	71	71
II-6	154	160	90	62	58	57	55	54	53	52	48	48	48	50	49	45
Mean ± S.E.M.				74±4	70±3	68±4	65±4	62±4	61±4	60±4	59±5	58±5	57±4	51±4	58±4	56±4
Thin diabetic																
III-1	87.4	98	104	68	65	60	55	49	50	50	50	49	50	50	49	48
III-2	66.8	103	102	64	59	56	53	50	48	46	46	46	47	46	47	48
III-3	77	108	175	68	67	65	57	59	58	55	52	50	51	51	50	50
Mean ± S.E.M.				67±2	64±4	60±5	55±2	53±6	52±5	50±4	49±3	48±2	49±2	49±3	47±2	49±1
Obese diabetic																
IV-1	131	172	150	69	68	66	66	64	65	60	57	57	55	49	51	50
IV-2	120	151	151	94	89	88	86	81	77	74	70	67	67	68	66	65
IV-3	85	133	99	84	78	71	69	64	61	60	59	58	59	61	62	62
IV-4	116.2	166	256	151	145	137	135	129	123	118	116	113	110	110	108	96
Mean ± S.E.M.				100±36	95±34	90±32	89±32	84±31	81±28	78±27	76±27	74±27	73±25	72±27	72±25	68±20

Group	Weight kg.	% ideal	Pre-fast	Basal immunoreactive insulin (μU./ml.) Post-fast	During ethanol infusion (min.) 30	60	90	120	150	180	210	240	270	300	330	360
Thin nondiabetic																
I-1	65.8	96	17	9	5	7	6	5	4	7	4	5	9	4	1	5
I-2	75.4	112	15	6	5	5	4	5	7	3	1	7	1	4	1	5
I-3	72	105	12	8	3	2	2	1	1	1	1	1	1	1	1	1
I-4	80	106	16	6	4	4	6	3	3	4	3	0	0	0	1	2
I-5	75.2	105	15	5	3	3	3	3	4	6	4	4	3	3	—	—
I-6	90.0	108	15	5	4	2	2	4	4	3	4	2	3	3	—	—
I-7	95.5	100	12	6	4	2	3	6	5	2	2	2	2	3	6	4
Mean ± S.E.M.				6.4±.6	4.0±.3	3.6±.8	3.7±.7	3.9±.8	3.9±.8	3.7±.8	2.7±.6	3.0±1.0	2.7±1.2	2.6±.6	2.0±1.1	3.4±.9
Obese nondiabetic																
II-1	116	160	32	8	4	4	2	3	7	4	4	1	9	12	1	1
II-2	106.3	141	38	18	17	7	7	6	5	5	4	5	6	5	6	4
II-3	97.6	135	26	9	8	7	6	5	4	5	3	2	2	3	3	3
II-4	112.3	160	60	24	11	15	12	19	14	11	11	8	8	8	7	9
II-5	145	146	36	14	12	12	11	8	9	10	8	7	6	5	7	6
II-6	154	160	28	14	13	15	12	15	12	11	14	10	11	11	10	10
Mean ± S.E.M.				14.5±3	10.8±2	10±2	8±1.8	9.3±2.8	8.5±1.8	7.6± 1.5	7.3± 1.9	5.5± 1.6	7.0± 1.4	7.3± 1.6	5.7± 1.4	5.5± 1.6
Thin diabetic																
III-1	87.4	98	9	4	3	3	2	1	1	1	1	1	1	2	2	1
III-2	66.8	103	20	13	6	5	5	5	3	7	6	6	7	5	4	3
III-3	77	108	26	7	7	6	7	5	6	3	4	3	3	2	2	1
Mean ± S.E.M.				8±5	5±2	5±2	5±3	4±2	3±3	4±3	4±3	3±3	4±3	3±2	3±1	2±1
Obese diabetic																
IV-1	131	172	66	21	14	18	17	14	8	14	12	9	14	19	12	10
IV-2	120	151	76	22	14	25	19	19	—	18	18	14	17	14	12	13
IV-3	85	133	15	10	3	3	1	1	1	2	2	1	1	2	1	1
IV-4	116.2	166	88	31	21	20	22	22	23	23	22	24	23	22	20	20
Mean ± S.E.M.				21±9	13±7	17±9	15±9	14±10	11±10	14±9	13±9	12±10	14±9	14±9	11±8	11±8

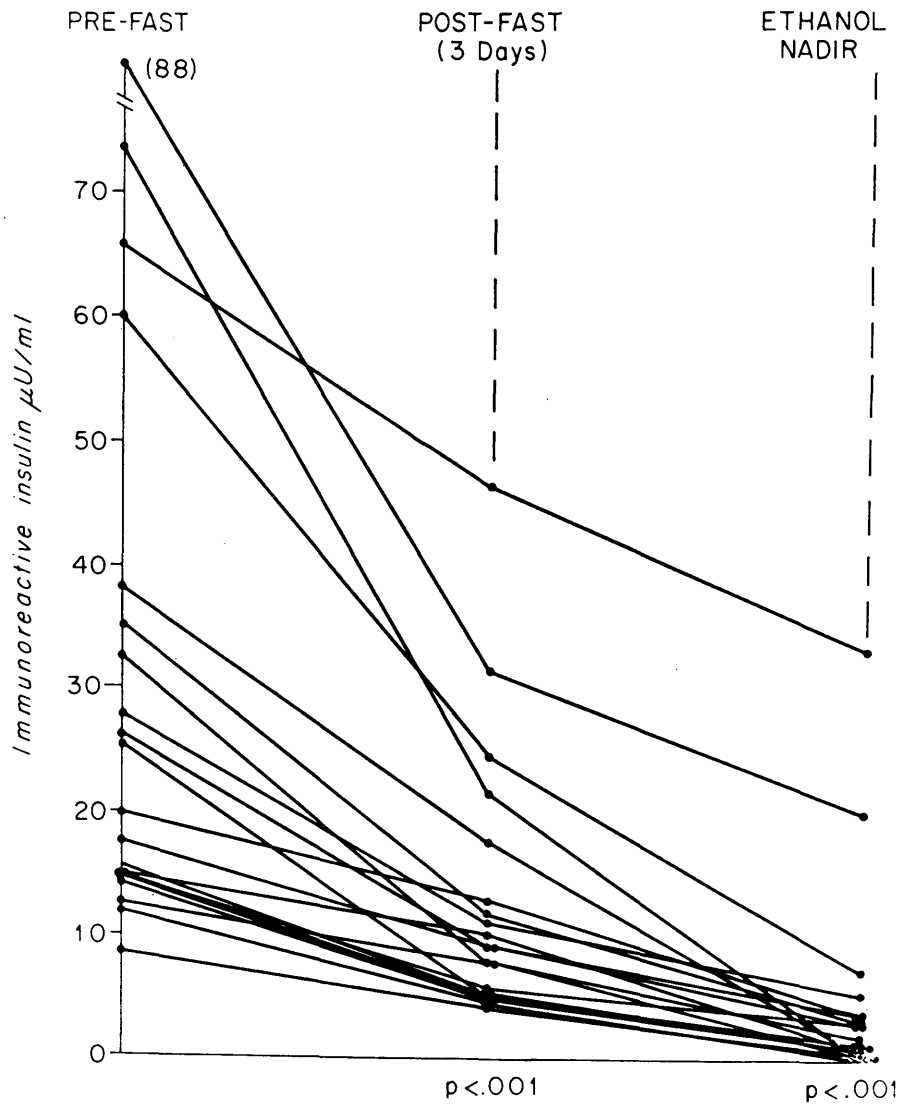

FIGURE 1

Steady-state immunoreactive insulin levels (IRI) in twenty obese and thin subjects with normal and abnormal carbohydrate tolerance before and after a three-day fast and the nadir observed during six-hour ethanol infusions.

method,[7] and glucose by the AutoAnalyzer ferricyanide method, and these values compared before and after the preparatory three-day fast and during the period of ethanol infusion. This assay has a between-assay coefficient of variation of 20 per cent down to 5 μU./ml., and a 10 per cent coefficient of variation within one assay. All samples from one subject were always assayed together. Between 2 and 5 μU./ml. the assay has a 25 per cent coefficient of variation. Values below 2 μU./ml. cannot be reliably distinguished from 0. See table 1.

RESULTS

Prior to the three-day fast, steady state (basal) IRI in this group of subjects correlated closely with obesity ($r = +.80$, $p < .001$), as previously described.[7] Following the brief fast, IRI levels fell in all subjects and continued to correlate with obesity ($r = +.72$, $p < .001$). The close correlation between pre-fast basal IRI and the absolute decline noted after the three-day fast ($r = +.98$, $p < .001$) indicated that obese subjects with the higher pre-fast basal IRI tended to demonstrate the greatest fall in IRI following the fast. During ethanol infusion a further decline was observed (figure 1).

Despite small differences in the rates of fall of glucose concentrations during the infusion period, IRI declined promptly and the rates of fall were indistinguishable when these subjects were grouped according to either body weight or glucose tolerance (figure 2, 3). In no group was any relationship demonstrable between the fall in glucose and IRI. These observations indicate

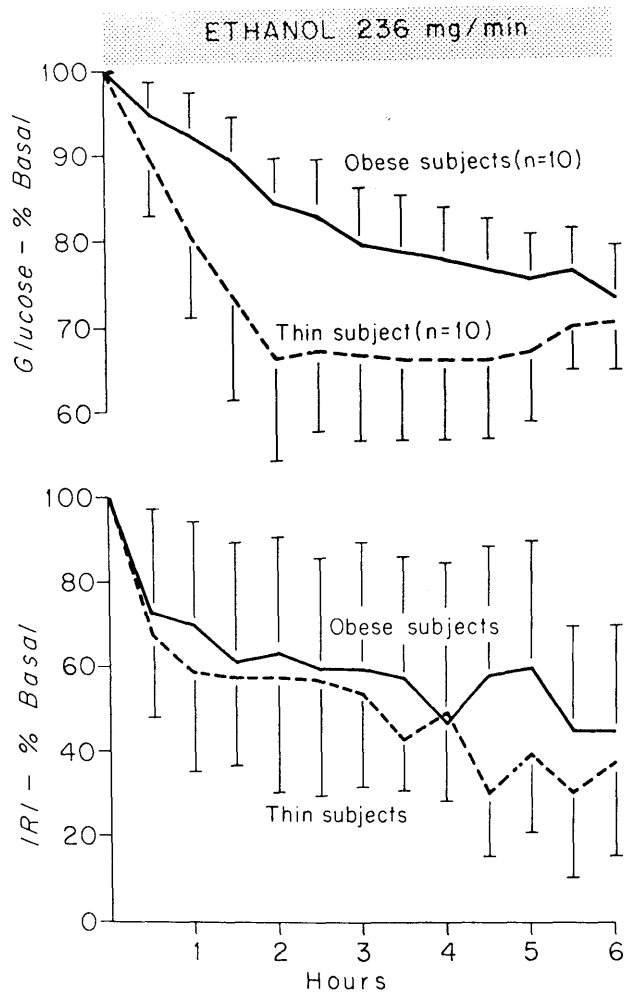

FIG. 2. Mean (± 1 S.D.) changes in plasma glucose and serum immunoreactive insulin (IRI) levels expressed as percentages of preinfusion basal level during six-hour alcohol infusions in ten obese and ten thin subjects.

that the regulation of basal IRI in response to a falling glucose level during ethanol hypoglycemia appears to be intact in both obesity and diabetes.

To determine whether this fall in IRI during ethanol infusion resulted from a direct effect of ethanol on pancreatic insulin secretion independent of changes in hepatic glucose production, two thin nondiabetic male subjects were infused with ethanol and glucose simultaneously for two hours after receiving continuous overnight (ten-hour) glucose infusions (300 mg./min.) in order to completely suppress hepatic gluconeogenesis. As previously reported,[5] no alteration in IRI or glucose (figure 4) was observed, suggesting that ethanol did not directly inhibit insulin secretion.

DISCUSSION

While a variety of drugs such as estrogen-containing contraceptives, and glucocorticoids and abnormal metabolic states such as obesity, uremia, acromegaly, and Cushing's syndrome have been shown to elevate basal insulin levels,[8] presumably through alterations in peripheral insulin resistance, only weight reduction[9] and fasting[10] have been shown to decrease basal insulin secretion. The present observations obtained during alcohol administration indicate that hypoglycemia also may inhibit insulin secretion in man in the non-stimulated or basal state as has been shown earlier in in vitro studies.[12] It is of interest that the decrement observed in

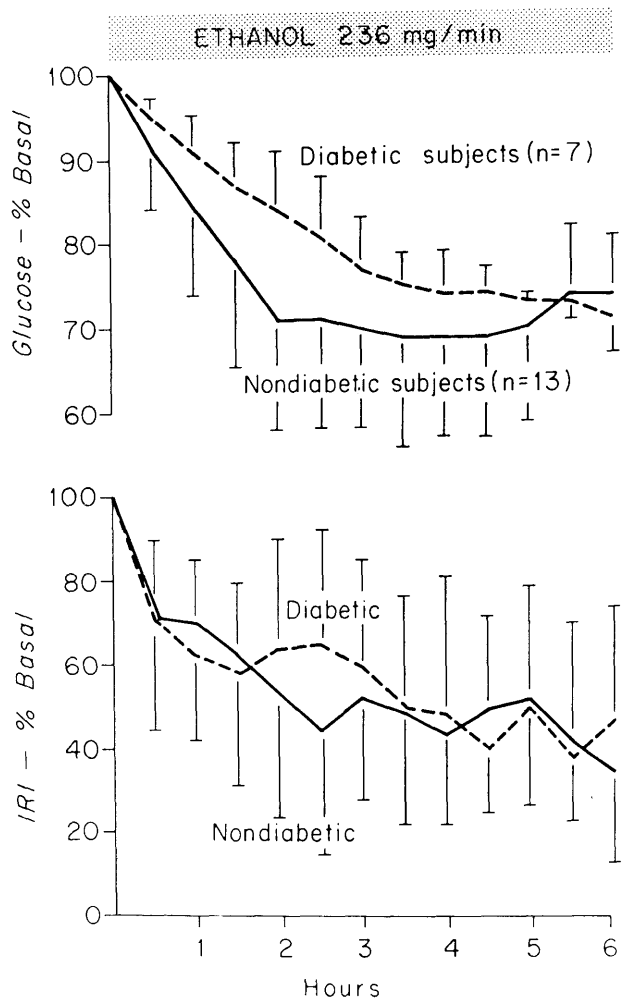

FIG. 3. Mean (± 1 S.D.) changes in plasma glucose and serum immunoreactive insulin (IRI) levels expressed as percentages of basal preinfusion level during six-hour alcohol infusions in seven diabetic and thirteen nondiabetic subjects.

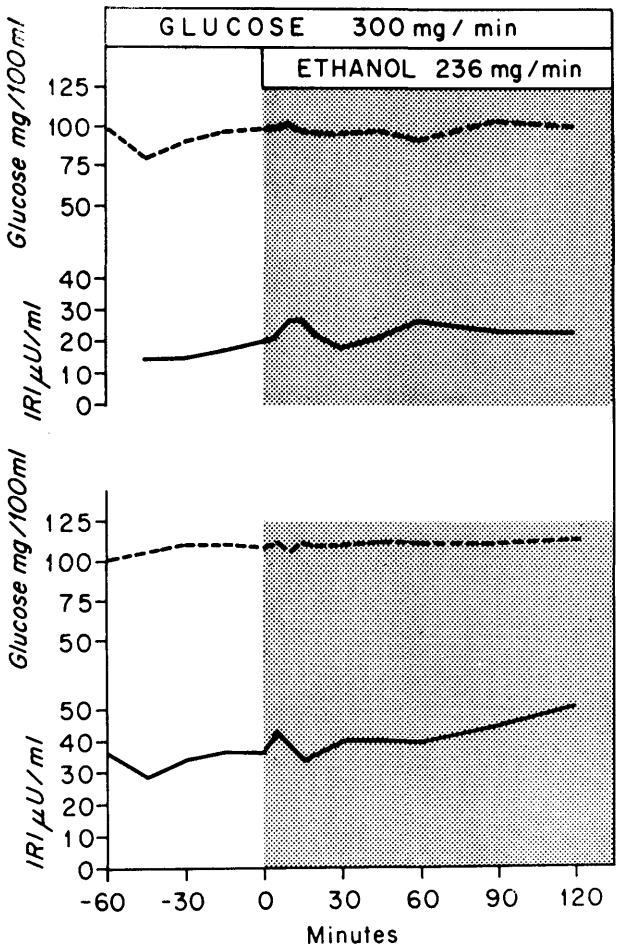

FIG. 4. Changes in plasma glucose and immunoreactive insulin (IRI) levels in two thin nondiabetic subjects during simultaneous infusion with glucose and insulin following overnight glucose infusion.

basal IRI following the preparatory three-day fast correlated closely with the pre-fast IRI level. This relationship between basal IRI and the response observed appears to represent another example of the "law of initial value" which has been shown in a variety of biologic systems.[13]

The lack of any discernible alteration in either glucose or IRI levels in the subjects infused simultaneously with glucose and ethanol makes it unlikely that the observed fall in IRI during ethanol infusion alone resulted from a direct action of alcohol on the pancreatic islet. The prompt fall in IRI noted in all groups despite differences in rates of decline of glucose suggests that a falling glucose concentration may represent a negative stimulus on the intracellular insulin pool from which steady-state IRI presumably are derived.[8] These findings indicate further that during alcohol hypoglycemia glucose concentration may be influenced both by compensatory changes in IRI as well as by a decrease in hepatic glucose production.

By decreasing peripheral glucose utilization in the presence of falling blood glucose levels, this decline in IRI would appear to represent an important homeostatic counter-regulatory mechanism to protect against hypoglycemia. A similar response in insulin levels may explain the decrease in glucose utilization reported by Madison in dogs during alcohol hypoglycemia.[6] This phenomenon also might explain the relative infrequency of clinical hypoglycemia in the poorly nourished alcoholic population. Additional as yet unidentified factors related to the primary alteration in hepatic gluconeogenesis also may influence the rate of glucose disappearance during alcohol hypoglycemia.

While the obese subjects in this study demonstrated the previously shown delayed decline in glucose levels during ethanol infusion,[11] their prompt decline in IRI was identical to that observed in the nonobese subjects. This observation suggests that relatively small changes in glucose levels may activate this counter-regulatory control of basal insulin secretion. Since catecholamines in the past have been shown to have no inhibitory effects on basal insulin release from a functionally discrete beta-cell pool which responds to prolonged hyperglycemia,[8] it seemed unlikely that the sympathetic nervous system might mediate this response. Recent findings,[14] however, indicate that epinephrine produces a rapid, transient, 50 per cent decrease in basal IRI; therefore sympathetic mechanisms may contribute to the rather rapid declines in IRI observed in some subjects in this study shortly after the start of the alcohol infusion when blood glucose levels declined only slightly.

The lack of any discernible impairment in this counter-regulatory IRI response in both diabetic and obese subjects indicates that the sensitivity of the beta-cell to the negative stimulus of hypoglycemia and/or sympathetic activity is intact in diabetes. The preservation and integrity of this regulatory mechanism of basal insulin secretion in diabetes is not an unexpected finding, since, in one current theory of a two-pool model for insulin secretion in man, basal and steady-state levels[8] appear to be normal in diabetic subjects.

ACKNOWLEDGMENT

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