Hormone Fuel Interrelationships During Alcohol Hypoglycemia in Man[1] (36817)

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The hepatic oxidation of alcohol may cause hypoglycemia by increasing the $NADH_2$/NAD ratio and, as a result, impair the transformation of the major gluconeogenic precursors, glycerol, lactate and amino acids, into glucose (1). Since serum insulin levels do not increase during alcohol hypoglycemia, it has been presumed that the observed decline in circulating glucose concentrations reflects the inhibitory effect of alcohol on hepatic glucose production. The dissociation previously shown between circulating glucose levels and rates of glucose utilization during alcohol hypoglycemia in dogs (2) has suggested that factors unrelated to gluconeogenesis may influence the rate of decline of glucose.

In order to determine whether compensatory changes in insulin levels also might influence the rate of glucose utilization and to further assess the metabolic and hormonal responses to alcohol hypoglycemia in man, immunoreactive insulin (IRI), growth hormone (GH), and plasma free fatty acid (FFA), glycerol and acetoacetate levels were measured during 6 hour ethanol infusions.

Methods. Six healthy nonobese (less than 110% of ideal body weight according to Metropolitan Life Insurance tables) nondiabetic adult male subjects (ages 35–50 yr) with previously determined carbohydrate tolerance were admitted to a metabolic ward and placed on a 3-day fast. None had significant antecedent medical disease; all had stable weights and normal dietary intake for at least 1 yr prior to study. On the morning of the fourth hospital day all subjects received 6-hr ethanol infusions (236 mg/min) according to the method of Freinkel *et al.* (3). Three blood samples were obtained from an indwelling needle in an antecubital vein prior to start of the alcohol infusion and at 30-min intervals thereafter. Serum immunoreactive insulin (IRI), glucose, free fatty acids (FFA) and glycerol concentrations were measured as previously described (4). Growth hormone (GH) levels also were determined by radioimmunoassay (5), and acetoacetate concentrations by an enzymatic method (6). Basal levels in each patient were expressed as the mean value of three separate preinfusion samples obtained 10 minutes apart. The paired t test was employed to compare the preinfusion basal level of each substance in each patient with measurements obtained at each subsequent sampling interval.

Results. During the first hour of alcohol infusion, IRI and glucose levels fell in parallel and subsequently stabilized at reduced levels (Fig. 1). FFA fell slightly despite the early decline in IRI, but rose after 1 hr and remained elevated throughout the duration of the infusion. Glycerol levels tended to parallel changes in FFA. Acetoacetate concentrations increased after the second hour and remained elevated subsequently. No significant change in growth hormone was noted although a slight increase was observed at 30 min when glucose and IRI levels were declining.

Discussion. The relative infrequency of clinical hypoglycemia in poorly nourished alcoholics has suggested that compensatory mechanisms must provide significant protection against the devastating effects of glucose deprivation on the central nervous system. Results of this study indicate that the primary inhibition of gluconeogenesis and decrease in hepatic glucose production calls forth several counter-regulatory processes which

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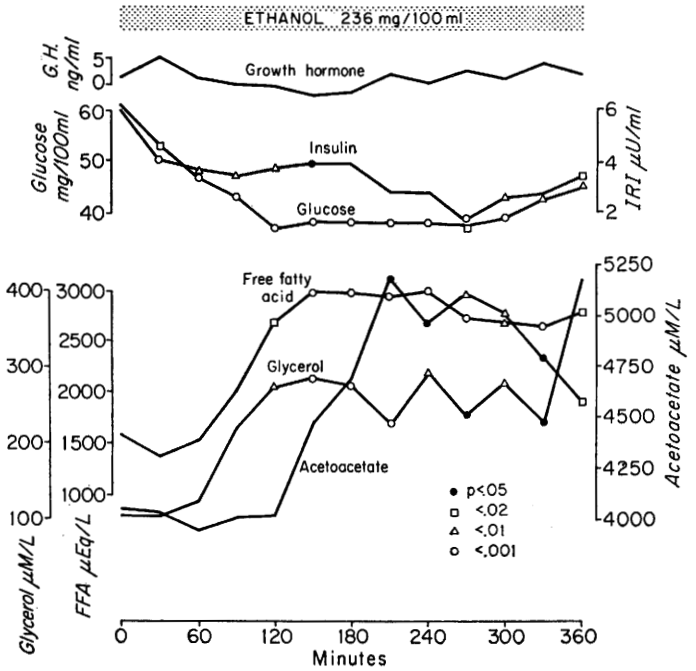

FIG. 1. Mean changes in immunoreactive insulin (IRI), growth hormone (GH), glucose and other substrates in six male subjects during alcohol hypoglycemia.

serve both to limit glucose utilization by insulin-sensitive peripheral tissues, and increase the availability of other metabolic substrates.

Probably of central importance is the fact that while glucose production is reduced significantly in most alcoholics owing to the altered redox state created by alcohol oxidation, inhibition of gluconeogenesis is not complete. The stabilization of both glucose and IRI levels at reduced levels in the present study suggests that a new steady state is reached at a decreased rate of hepatic glucose production.

Past observations that both plasma (7) and urinary catecholamines (8) increase during hypoglycemia and studies showing that insulin secretion is under autonomic control (9) suggest that the sympathetic nervous system may mediate the counter-regulatory responses following alcohol as in other clinical forms of hypoglycemia. It is therefore possible that the changes observed in IRI and GH as circulating glucose levels began to decline may result from inhibition of basal IRI secretion and stimulation of GH release, processes which have been shown to be adrenergically mediated (10, 11).

While the early elevation of FFA and glycerol and the subsequent increase in acetoacetate concentrations could solely reflect accelerated lipolysis resulting from the decline in IRI and early increase in GH, it is possible that these changes may also result from sustained adrenergic activation.

Summary. Basal serum immunoreactive insulin (IRI) levels fell promptly and in parallel with the decline observed in circulating glucose levels when alcohol was administered intravenously to fasting man. Hypoglycemia and the decrease in basal insulin secretion were associated with an initial transient increment in growth hormone levels and sustained lipolysis manifested by increased free fatty acid, glycerol and acetoacetate concentrations. These findings may result from activation of the sympathetic nervous system which is known to be operative in other hypoglycemic states.

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