PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 146, 972–974 (1974)

Suppression of Isoproterenol-Induced Hyperglycemia by Ethanol (38230)

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Ethanol can produce profound hypoglycemia in underfed or starved humans and laboratory animals (1, 2). This derangement of metabolism by ethanol has been shown to be the consequence of inhibition of hepatic gluconeogenesis (3, 4). Ethanol inhibits the hepatic conversion of lactate, alanine and glycerol into glucose purportedly by increasing the ratio of [free NADH]/[free NAD^+] in the liver (5, 6).

Interestingly, it has been suggested that 70–90% of glucose released by the liver of fasted rats arises from circulating glycerol (7). In comparison to larger animals glycogen stores are small in rats in relation to the rate of glucose turnover. Therefore, it seems likely that gluconeogenesis may be of major importance for maintaining plasma glucose levels in the fasting rat, even during short periods of food deprivation (8).

It has been proposed that the hyperglycemic activity of isoproterenol in the fasted rat may be the consequence of glycogenolysis in muscle with the subsequent conversion of lactate to glucose in the liver (9). This hypothesis was put forth to explain the evidence that isoproterenol produces a hyperglycemic response in fasted rats, which have increased hepatic gluconeogenesis but not in fed rats, which have reduced hepatic gluconeogenesis (9). In addition, catecholamines can stimulate the conversion of lactate to glucose in the perfused liver (10).

In the present study, fasted rats were treated acutely with ethanol and then challenged with an injection of isoproterenol, epinephrine or saline. In these experiments we sought to determine if a proven inhibitor of gluconeogenesis, ethanol, could selectively interfere with the hyperglycemic activity of either catecholamine.

Materials and Methods. Male Holtzman rats weighing between 250–370 g were fasted for 24 hr before the experiment. Animals were divided into 5 groups and treated as follows:

Groups 1 and 2 received an injection of saline, 1 ml/100 g, 1 hr before the injection of either l-isoproterenol, 1 mg/kg, base, or l-epinephrine, 0.3 mg/kg, base. Groups 3, 4 and 5 received an injection of ethanol (15% v/v), 1 ml/100 g, one hour before the injection of saline, l-isoproterenol or l-epinephrine in the concentration indicated above. The quantity of diluted ethanol solution injected is equivalent to 1.5 ml/kg or 1.19 g/kg of absolute ethyl alcohol. All drugs were administered by the intraperitoneal route. Sampling of blood was accomplished by cutting the tip of the tail. Blood samples were taken before and after pretreatment with saline or ethanol and at ½, 1, 2 and 3 hr after the administration of isoproterenol, epinephrine or saline.

Blood glucose levels were determined by using the Hoffman method (1) as adapted to the Technicon Autoanalyzer.

Stock solutions (1 mg/ml) of the catecholamines were prepared daily in acidified saline (pH = 4.5) to prevent oxidation and appropriate dilutions were made to the desired concentrations with physiological saline. Drug concentrations were calculated and expressed in terms of the mg of base per unit vol.

Results. Figure 1 illustrates the changes in blood glucose induced by l-isoproterenol

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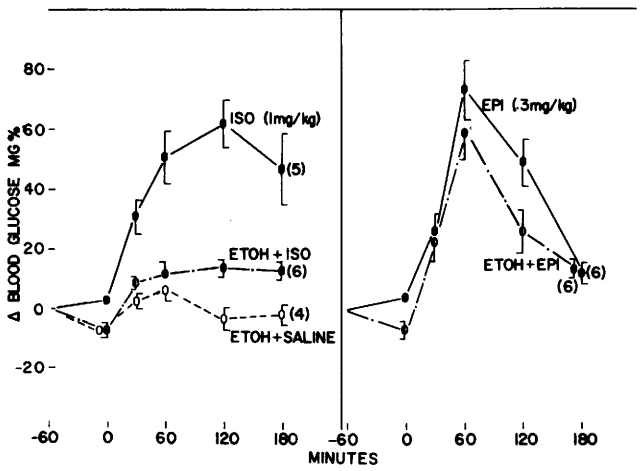

FIG. 1. The effect of acute administration of ethanol on isoproterenol– and epinephrine–induced hyperglycemias. Each point represents the mean change in blood glucose (±S.E.) as determined from the number of animals shown in parentheses.

(left panel) and l-epinephrine (right panel) in fasted rats pretreated with saline or ethanol. Also shown is the change in blood glucose levels produced by ethanol and saline. A control blood sample was taken just before the injection of ethanol or saline; another sample was taken 1 hr after the injection of ethanol or saline, just prior to the injection of the catecholamines. The changes in blood glucose after the injection of the catecholamines were calculated as changes from the control blood sample. The doses of catecholamines selected were those producing similar peak increases in blood glucose levels. However, the maximum increase in blood glucose occurred with isoproterenol at 2 hr, and with epinephrine at 1 hr postinjection.

Our work agrees with earlier reports which have shown that ethanol, in doses lower than 3 g/kg, produces no significant change in blood glucose levels in rats (12, 13). It is noteworthy that pretreatment with ethanol suppressed markedly the hyperglycemic response to isoproterenol whereas the response to epinephrine was not changed appreciably.

Discussion. The ability of catecholamines to produce elevations in blood glucose in laboratory animals and in man is well established. There are at least three mechanisms by which these agents can produce this effect in the intact animal: (1) by promoting glycogenolysis in the liver (14); (2) by stimulating gluconeogenesis (10); (3) by decreasing peripheral utilization of glucose by several mechanisms including the inhibition of insulin secretion (15). A pertinent question to be answered concerns the relative contribution of each of the mechanisms listed above to the total hyperglycemic effect elicited by each of the individual catecholamines.

It is well established that epinephrine is a more potent hyperglycemic agent than isoproterenol in the rat (16). Epinephrine is much more active than isoproterenol in depleting liver glycogen in the rat, whereas isoproterenol is considerably more active than epinephrine in producing glycogenolysis in the skeletal muscles of the rat (17). The mechanism(s) for production of hyperglycemia by isoproterenol in the fasted rat is suggested to involve mainly hepatic gluconeogenesis. This presumption is based largely upon: (a) the demonstrated ability of catecholamines, particularly isoproterenol, to release lactate from muscle which can then be converted by the liver into glucose (18), and (b) the failure of isoproterenol to produce significant reductions in liver glucogen content in the fasted rat during the period of elevation of blood glucose levels (17). Theoretically, isoproterenol should be more active than epinephrine in stimulating the conversion of lactate to glu-

cose in the fasted rat by virtue of its stronger activity in promoting glycogenolysis in muscle (17, 19). The increased availability of lactate can, by itself, accelerate gluconeogenesis by the liver (17). If this mode of elevating blood glucose levels by isoproterenol in the fasted rat could be firmly established, then this would provide an intact animal model for drug-stimulated gluconeogenesis upon which other inhibitors of gluconeogenesis could be tested.

It has been demonstrated that ethanol, in the dose-range of 0.7–3.0 g/kg, does not overtly affect blood glucose levels, hepatic glycogen content or catecholamine output in the fasted rat (12, 13). The acute administration of low to moderate doses of ethanol had no effect on basal plasma insulin levels (2) but inhibited cyclic AMP-induced insulin release (20). Preliminary and unpublished data from this laboratory indicate that pretreatment with ethanol does not enhance the insulinogenic action of isoproterenol but that ethanol pretreatment may, in fact, suppress the elevation of plasma insulin levels produced by isoproterenol in the rat. Interestingly, concentrations of ethanol as low as 10–20 mg/100 ml can inhibit gluconeogenesis *in vivo* (21).

The data reported in this paper suggests that, in the fasted rat, ethanol interferes selectively with the mechanisms, including gluconeogenesis, involved in the production of hyperglycemia by isoproterenol, but that these mechanisms are of little importance in epinephrine-induced hyperglycemia.

It is concluded, therefore, that the marked inhibition of isoproterenol-induced hyperglycemia by ethanol in the fasted rat may be interpreted to be the consequence of suppression of gluconeogenesis. A nonspecific depression of hepatic glucose output by ethanol can be discounted as a possible mechanism because the response to epinephrine was relatively unimpaired.

Summary. Ethanol inhibited markedly the hyperglycemic response to isoproterenol in the fasted rat, whereas the hyperglycemic response to epinephrine was not changed significantly. Since ethanol is a potent inhibitor of gluconeogenesis, these data give support to the suggestion that isoproterenol produces its hyperglycemic effect in the fasted rat by mechanisms involving gluconeogenesis. Furthermore, this work suggests that isoproterenol-induced hyperglycemia in the fasted rat may provide an animal model for testing other inhibitors of gluconeogenesis.

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Received Jan. 30, 1974. P.S.E.B.M., 1974, Vol. 146.