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Blood Glucose and Body Temperature Alterations Induced by Ethanol in Rats Submitted to Different Levels of Food Deprivation[1]

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OLIVEIRA DE SOUZA, M. L. AND J. MASUR. *Blood glucose and body temperature alterations induced by ethanol in rats submitted to different levels of food deprivation.* PHARMAC. BIOCHEM. BEHAV. 15(4)551–554, 1981.—The effects of 1.0, 3.0 and 5.0 g/kg of ethanol on blood glucose levels and body temperature were examined in rats submitted to either acute food deprivation (24 or 48 hr), chronic starvation, or to both chronic plus acute food deprivation. The results show that: (a) 3.0 and 5.0 g/kg produced either an increase or a decrease of glucose levels depending on the state of fasting; (b) rats not deprived of food presented hyperglycemia while being hypothermic; (c) a marked hypothermia was present when no substantial alterations in glycemia were observed; and (d) in cases where hypoglycemia and hypothermia occurred, the fall in body temperature paralleled or preceded the decrease in glucose levels.

Ethanol Body temperature Glycemia Starvation Food deprivation

THE influence of ethanol on the blood glucose concentration is seemingly contradictory, with results varying from hypo to hyperglycemia [10]. The confounding variable appears to be the underlying nutritional state of the organism. Fasting, leading to the depletion of hepatic glucogen stores, facilitates a hypoglycemic effect of ethanol as this drug promotes inhibition of gluconeogenesis [1, 8, 9, 14]. Within this framework, Freinkel *et al.* [4] reported that marked hypoglycemia could be induced only after 72 hr of fasting. Similarly, Mendelson *et al.* [12] suggested fasting was a necessary concomitant for the ethanol-induced hypoglycemia, because they found no alterations in glycemia in 10 subjects with good dietary condition ingesting large amounts of whisky over a 24 day period.

The first purpose of the present report is to analyze ethanol-induced alterations in blood glucose through a dose-dependent study in rats submitted to either acute food deprivation (24 or 48 hr), chronic starvation, or to both chronic plus acute food deprivation.

On the other hand, hypoglycemia has been suggested to underlie ethanol-induced hypothermia [6]. However, there is a paucity of experimental data on this correlation, and information is lacking on the alterations of glycemia and body temperature when different doses of ethanol are administered under different nutritional conditions. To provide data on this issue is the second aim of this report.

METHOD

Animals

Male Wistar rats from our own colony were used. After weaning, at 25 days of age, they were housed in wooden cages measuring 49×39×20 cm and kept at a room temperature of 23±2°C on a 12 hr light-dark cycle.

Drugs

Ethanol for analysis (Merck Lab) diluted with saline to a strength of 20% (w/v) was used.

Blood Glucose Determinations

Blood glucose was measured by the Dextrometer/Dextrostix system, a digital version of the Dextrostix-Eyetone method [13].

Procedure

One group of animals were fed Purina Chow ad lib (nor-

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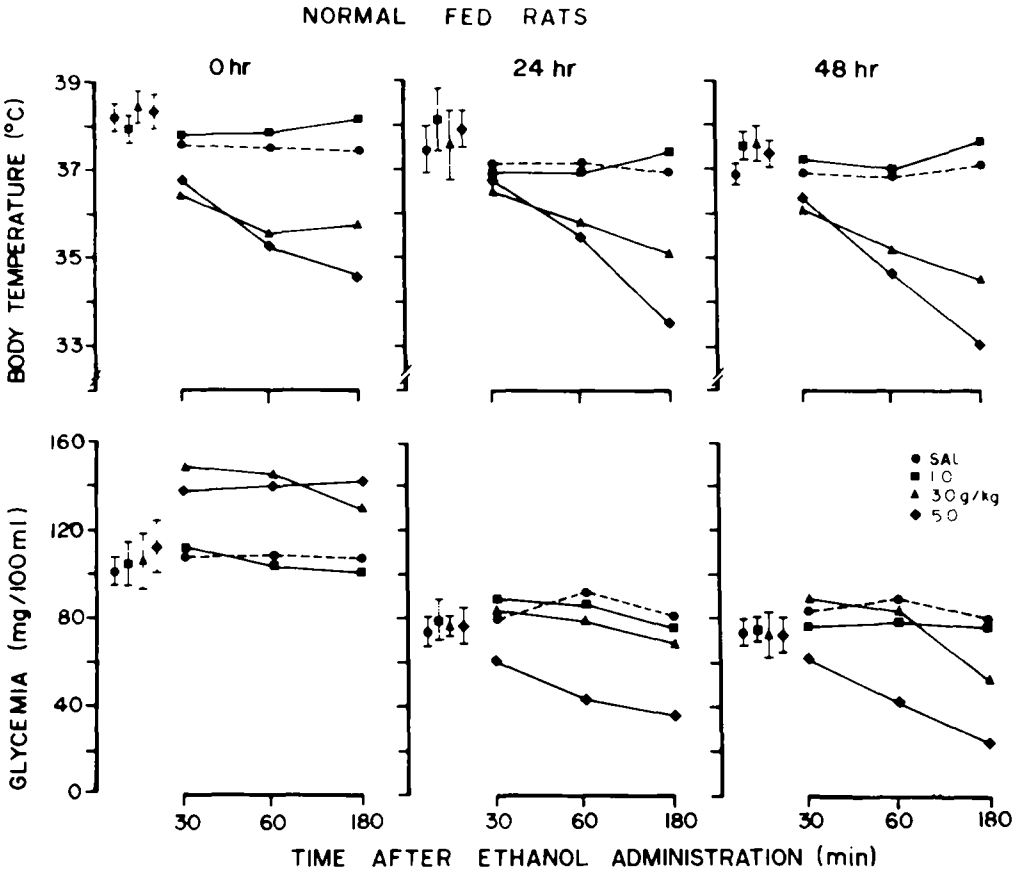

FIG. 1. Mean body temperature and blood glucose levels of normal fed rats under different acute food deprivation conditions after saline or ethanol injections. The isolated points indicate the basal values, immediately before injections. Vertical bars represent 0.95 confidence limits. Standard deviations of the postinjection values varied from 2.4 to 32.3% of the mean for glucose and from 0.5 to 2.3% for temperature.

mal fed group) and the second group was submitted to chronic starvation (chronically starved group). Beginning from weaning the chronically starved group received daily, at 9:00 a.m., 60% by weight of food pellets ingested by the normal fed animals on the previous day. The body weight of the chronically starved group was assessed weekly and was near 75% of the normal rats, whose values were 333±31 g (mean±SD) on the experimental day. After 90 days of such treatment both the normal fed and the starved groups were divided into sub-groups: 0, 24 or 48 hr total food deprivation, before the injections of either 1.0, 3.0 or 5.0 g/kg ethanol or control saline. For each sub-group 6 animals were used.

On the experimental days, the animals were placed in plastic restraining cages and the colonic temperature was taken with clinical thermometers at the following times: 0 (before ethanol or saline) and 30, 60 and 180 min after drug administration through intraperitoneal route (IP). The thermometer was introduced approximately 4 cm into the rectum for 60 sec. The temperature recording was immediately followed by withdrawing a drop of blood from the tail for the assessment of glucose levels. The 1.0, 3.0 and 5.0 g/kg doses of ethanol were chosen based on a pilot study which showed that they produced, respectively, motor impairment, loss of the righting reflex, and mortality of near 50% of the animals. Room temperature during testing was maintained at 23–24°C. Measures were always performed beginning at 1:00 p.m.

Statistical Analysis

The values of blood glucose and body temperature after injections were compared with the values at time 0, considering 0.95 confidence limits for small samples according to Hardyck and Petrinovich [7].

RESULTS

The effects of the different doses of ethanol on blood glucose levels and body temperature of normal fed rats, after different periods of acute total food deprivation are represented in Fig. 1.

The doses of 3.0 and 5.0 g/kg induced marked hypothermia in all groups of animals. The same doses also altered the glycemia; however the direction of change was dependent on the level of acute food deprivation. Thus, while non-deprived rats (0 hr) showed an increase in glucose levels, the 24 or 48 hr deprived animals showed a decrease. The

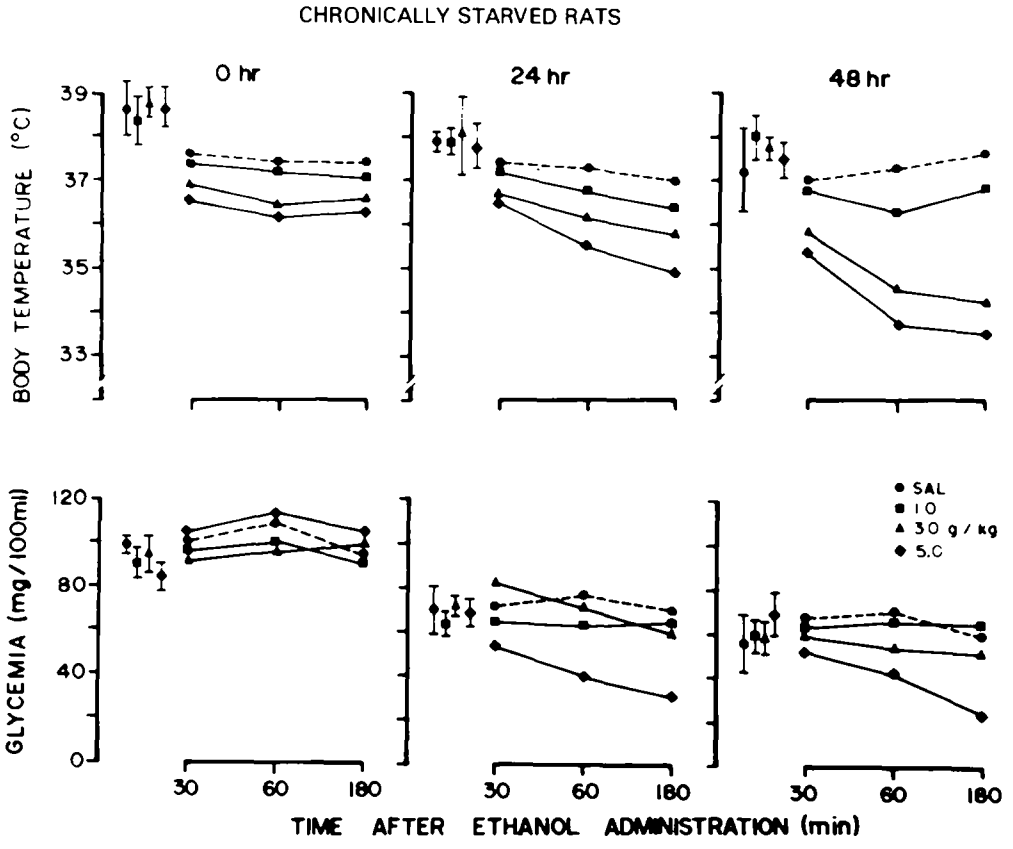

FIG. 2. Mean body temperature and blood glucose levels of chronically starved rats after different periods of total food deprivation, after saline or ethanol injections. Standard deviations of the postinjection values varied from 4.0 to 31.5% of the mean for glucose and from 0.5 to 3.3% for temperature. To be read as in Fig. 1.

ethanol-induced thermic and glycemic alterations obeyed a dose-dependent relationship. Thus, 1.0 g/kg did not alter both parameters and 5.0 g/kg induced the larger alterations; 3.0 g/kg also clearly decreased body temperature although less markedly than 5.0 g/kg. The hypoglycemic effect of 3.0 g/kg was only detected in the 48 hr group, 180 min after ethanol. It is pertinent to note that in the rats subjected to 48 hr food deprivation and given 3.0 g/kg of ethanol the hypothermia preceded the hypoglycemic effect; hypothermia was detected 30 min after ethanol administration while hypoglycemia was only observed at 180 min. Further inspection of Fig. 1 also shows an interesting relationship between the level of food deprivation and glycemic alterations induced by 3.0 g/kg: hyperglycemia, no effect, and hypoglycemia was observed in the 0, 24 and 48 hr groups, respectively.

The effects of ethanol in the chronically starved group subjected to different levels of acute food deprivation are represented in Fig. 2. The results were basically the same as described for the normal fed group, being smaller, however, in the magnitude of the alterations. The highest doses of ethanol induced a clear hypothermia in all groups and the larger the period of total food deprivation the larger the effect. Concerning glucose levels no substantial alteration was observed in the 0 hr group, except a slight hyperglycemia in the rats that received 5.0 g/kg ethanol. The same dose induced a clear decrease in glycemia in the 24 and 48 hr groups while 1.0 and 3.0 g/kg induced no substantial alterations. Again, as occurred with the normal fed rats, hypothermia was observed even when no alterations in blood glucose levels were detected.

DISCUSSION

Concerning the first purpose of the present report, that is, the analysis of the ethanol-induced alterations in blood glucose in rats subjected to different schedules of food deprivation, the data obtained show that: (a) 3.0 and 5.0 g/kg of ethanol produced either an increase or a decrease of glucose levels depending on the state of fasting and (b) in chronically starved rats the effects were less pronounced than in the normal fed animals.

The mechanisms by which ethanol induces hyperglycemia, as suggested by other authors, are an increase in the breakdown of liver glycogen by an increased sympathetic response, and/or a decrease in peripheral utilization of glucose. The hypoglycemia observed in the 24 or 48 hr starved rats would result from the ethanol-induced inhibition of gluconeogenesis, as this is the primary mechanism respon-

sible for hepatic glucose output in a food deprivation condition [10,15].

The apparent decrease in sensitivity of chronically starved rats to the glycemic and thermic actions of ethanol may have a relationship with recent findings showing that chronic starvation in rats decreases the depressant effect of pentobarbital, haloperidol and ethanol [11]. For ethanol a tentative explanation was provided by the authors, considering a possible bias in the calculation of the dose used. Thus, when a constant dose of ethanol in grams per kilogram is administered, the fatter individual will yield a higher blood concentration due to the difference in adipose tissue.

The second aim of the present report was to determine to what extent alcohol induced alterations in body temperature and glycemia are causally correlated. Haight and Katinge [6] suggest that the depletion of blood glucose levels contributes to the ethanol induced fall in temperature. However, at least in rats, this causality does not necessarily hold, as our results show that: (a) rats not deprived of food presented hyperglycemia while being hypothermic, (b) a marked hypothermia was present when no substantial alterations in glycemia were observed, and (c) in cases where both hypoglycemia and hypothermia occurred, the fall in body temperature paralleled or preceded the decrease in glucose levels. It could be tentatively suggested that, in rats, the fall in body temperature induced by ethanol could lead to a carbohydrate mobilization for heat production. In non food deprived animals this could result in hyperglycemia, as observed in the present experiment. The results with 3.0 g/kg ethanol, when a marked hypothermia in the 24 hr deprived rats occurred (Fig. 1) without a substantial alteration in glycemia, could be explained on the basis that, parallel to the increase in mobilization of carbohydrates, there is also the inhibition of neoglucogenesis induced by ethanol, cancelling each other. Increasing the starvation to 48 hr, the same dose produced hypoglycemia, probably due to the enhancement of the importance of neoglucogenesis. With 5.0 g/kg ethanol the inhibitory effect of neoglucogenesis would prevail, resulting in the marked hypoglycemia observed in the 24 and 48 hr starved rats. This hypothesis presupposes that, in the absence of the inhibitory effect on neoglucogenesis, the animals would, even if food deprived, show an increase in glucose levels. In this respect we have observed that in 48 hr food deprived rats, in spite of a marked hypothermia, there is an increase in blood glucose levels (near 50%) following administration of 10 mg/kg chlorpromazine (unpublished observations). As chlorpromazine has no known effects on neoglucogenesis, this seems to support our contention.

An interesting way of further investigating the nature of the link between ethanol-induced thermic and glycemic alterations in rats would be by overcoming hypothermia through an increase in the environmental temperature. Keeping the animal's body temperature constant by raising ambient temperature following administration of drugs that normally cause hypothermia may be useful to separate the effects of the drug itself from those effects induced by an alteration in body temperature [5]. Another possibility would be to observe whether the development of tolerance to the hypothermic effect of ethanol, described in the literature [2,3], would prevent blood glucose alterations. Such experiments are now underway.

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