EFFECT OF ORAL GLUCOSE ON THE RATE OF METABOLISM OF ETHANOL IN HUMANS

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Abstract — We have tested whether the effect of carbohydrate on the rate of alcohol metabolism can be reproduced by glucose alone. Ten male subjects were given ethanol by intravenous infusion until a steady state was established and 100 g glucose in solution was then taken orally. The rate of alcohol metabolism, measured as the rate of infusion required to maintain a constant breath alcohol reading, increased significantly after glucose but there were differences between the subjects. The presence or absence of a change in the rate of alcohol metabolism after glucose was associated with the subject's fasting rate and with their glucose tolerance.

INTRODUCTION

The rate of metabolism of alcohol has been shown to be modified by fasting and feeding in rats (Dontcheff, 1937; Smith and Newman, 1959; Lumeng *et al.*, 1979) and in humans (Schmidt and Oehmichen, 1984). We have found that carbohydrate-rich, but not fat- or protein-rich, meals increase the rate of metabolism by around 60%, which might be enough to be of practical importance in reducing the time spent intoxicated after drinking (Rogers *et al.*, 1987).

The literature contains many papers on the effects of carbohydrate on alcohol pharmacokinetics but in many of these studies both the alcohol and the carbohydrate were taken orally (e.g. Sedman *et al.*, 1976), emphasising the effects on absorption rather than metabolism. Nevertheless, there is widespread support for the belief that fructose in particular can speed up alcohol metabolism. Since in our previous study the carbohydrate meal contained an undefined mixture of carbohydrates (starch, sucrose and some glucose and fructose), we have proceeded to test the effect of glucose alone on the rate of alcohol metabolism.

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SUBJECTS AND METHODS

Ten male subjects, aged between 20 and 51 yr, participated in this study. The subjects were recruited from university or hospital staff and students; they were in good health, not taking any medication, and their estimates of their alcohol intakes ranged from 20 to 150 g of alcohol per week. The protocol had been approved by the Ethics Review committee of Royal Prince Alfred Hospital and subjects gave informed consent. The study design was essentially the same as that previously described (Rogers *et al.*, 1987) except that a solution containing 100 g of glucose in 285 ml of carbonated, flavoured beverage (Glucaid, Histolabs, Pennant Hills, NSW, Australia) was taken instead of the meals.

Briefly, a constant blood alcohol level was maintained by intravenous infusion of ethanol; after an initial loading period the rate of infusion was adjusted to maintain breath alcohol readings of 0.065 g/100 ml. With this steady-state design the rate of infusion required can be equated with the rate of metabolism of alcohol, assuming that losses in urine, sweat and breath are small and constant.

On each occasion the subject fasted from 9 p.m. the previous day and an infusion of ethanol (Dehydrated Alcohol B.P., David Bull

Laboratories, Mulgrave, Victoria, Australia) 6% w/v in 0.9% NaCl (Abbott Australasia, Sydney, Australia), into an arm vein was commenced between 8 and 10 a.m. Blood was taken from the other arm before the infusion started and at 30 min intervals thereafter, and breath alcohol was determined with an Alcotest 7010 (Drager, Lübeck, West Germany) before the infusion and every 5 min thereafter. The rate of infusion was controlled by an IMED 960 volumetric infusion pump (IMED, Abingdon, U.K.) and after an initial period to raise the blood alcohol to the desired level the rate was adjusted after each breath analysis in order to maintain the reading between 0.062 and 0.068 g/100 ml. After saturation of the body with alcohol, a steady state with respect to blood alcohol levels was maintained for the duration of the experiment. The glucose solution was given at 180, 210 or 240 min depending on the time taken for the subject to reach a steady state and the experiment was continued for at least a further 150 min.

Samples from the bags of infusion fluid were analysed for alcohol by gas chromatography. The volume of fluid infused in each 30 min period was recorded and the mass of ethanol infused in the 30 min was calculated. The mass of ethanol was expressed as mg/kg body weight/hr for each subject.

The blood samples were analysed for plasma glucose by the glucose oxidase method (American Monitor Corp., Indianapolis, U.S.A.), and for insulin by radioimmunoassay (Bio-Mega Diagnostic Inc., Montreal, Canada).

The mass of alcohol infused in each period, for the last period before the glucose load and five periods after, was subjected to two-way analysis of variance with subject and time (one pre-meal and five post-meal 30 min periods) as factors, in order to test for effects of the glucose solution. The rates in the periods after the glucose were each compared with the fasting rate, using paired *t*-tests and the Newman–Keuls *post hoc* test statistic. Statistical tests were performed using SPSS or SPSS-X.

RESULTS

Taking the subjects as a group, there was a significant change in the rate of alcohol meta-

bolism after the 100 g glucose load ($F_{5.45} = 6.23$, $P < 0.001$). The effect occurred between 30 and 90 min after the glucose and *t*-tests showed significant ($P < 0.05$) differences from the pre-glucose rates in the 30–60 and 60–90 min periods. If the Newman–Keuls test, which adjusts for the possibility of apparently significant differences occurring by chance when multiple comparisons are made, was used then only the 60–90 min rate was significantly different from fasting.

It was noticeable that not all subjects responded to the glucose load to the same degree; some showed a doubling of the rate while others showed changes of less than 10%. The individual results are shown in Fig. 1.

Inspection of the results suggested that those subjects with a higher initial (pre-glucose) rate of alcohol metabolism tended to show only a small increase after glucose, while those with lower initial rates showed an increase to or even exceeding the basal rates found in the non-responding subjects. The percentage increase in alcohol metabolic rate was calculated for each subject by taking the highest post-glucose half-hourly rate and comparing it with the rate in the half hour before the glucose (Table 1).

As expected, plasma glucose and insulin levels rose after the glucose load in all subjects. Inspection of the individual results suggested that plasma glucose levels after the load were higher in the subjects who did not increase their rate of alcohol metabolism. To test this hypothesis the ten subjects were divided into two groups; four 'non-responders' whose rate of alcohol metabolism increased by less than 10%, and six 'responders' whose rate increased by more than 30%. The mean glucose and insulin results for these two groups are shown in Fig. 2. Two-way analysis of variance with time and group (responders/non-responders) as factors showed that the glucose concentrations after 100 g of glucose were significantly higher in the non-responding group ($F_{1.44} = 5.17$, $P = 0.028$) but that insulin levels (while lower in the non-responders) did not differ significantly between the groups. However, when insulin results were subjected to analysis of covariance with the same two factors but adding glucose levels as covariate, insulin levels were signifi-
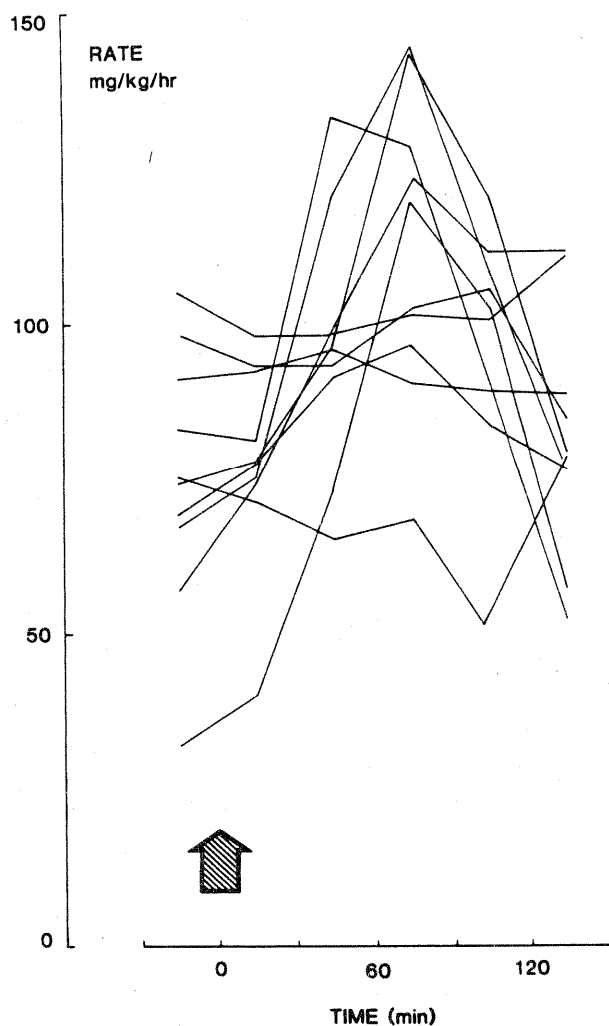
Fig. 1. Timecourse of individual subjects' changes in alcohol metabolism after 100 g of glucose. Abscissa: time after glucose in min; ordinate: rate of alcohol infusion required to maintain a constant breath alcohol reading, in mg/kg body weight/hr.

Table 1. Fasting and maximum post-glucose rates of alcohol metabolism in the ten subjects. The subjects are ranked in order of their fasting rates

Subject	Fasting rate (mg/kg/hr)	Maximum post-glucose rate (mg/kg/hr)	% increase
D	105	110	5
O	98	105	7
F	91	96	5
G	83	133	60
J	75	78	4
A	74	143	93
S	69	96	39
P	67	144	115
H	57	123	116
W	32	119	272

cantly lower in the non-responding group ($F_{1.43} = 11.51$, $P = 0.001$). Therefore the group of subjects who did not increase their alcohol metabolism in response to glucose had a slight but statistically significant impairment in glucose tolerance, and lower insulin levels for a given plasma glucose, than the other group.

DISCUSSION

Our results demonstrate that glucose can increase the rate of alcohol metabolism in fasting humans. The increase can be substantial in some subjects and these results are rather different from those found by previous workers whose experimental designs may have been less sensitive to changes in rate of metabolism. While our previous results (Rogers et al., 1987) could possibly have been ascribed to the presence of sucrose in the carbohydrate meal, which would have given rise to fructose, we can now see that the carbohydrate effect is not restricted to fructose.

Experiments with oral alcohol and oral glucose have usually shown a reduction in peak blood alcohol levels, blood alcohol levels in the post-absorptive phase or total area under the curve when the alcohol is accompanied by glucose (Sedman et al., 1976). These results could be due to effects on absorption, a possibility which intravenous administration of alcohol avoids. However, Stokes and Lasley (1967) gave alcohol intravenously to 33 subjects (patients in a psychiatric institution, some of whom were chronic alcoholics) without finding any change in the rate of fall of blood alcohol concentration after glucose. This may be a consequence of their experimental design; the alcohol was given over 20–25 min at the start of the study only, and the rate of fall was monitored over the next 60–90 min. We have found that even when alcohol is given intravenously equilibration takes 120–150 min, and the blood alcohol curves of Stokes and Lasley may have been more influenced by distribution of the alcohol through the body than by its metab-
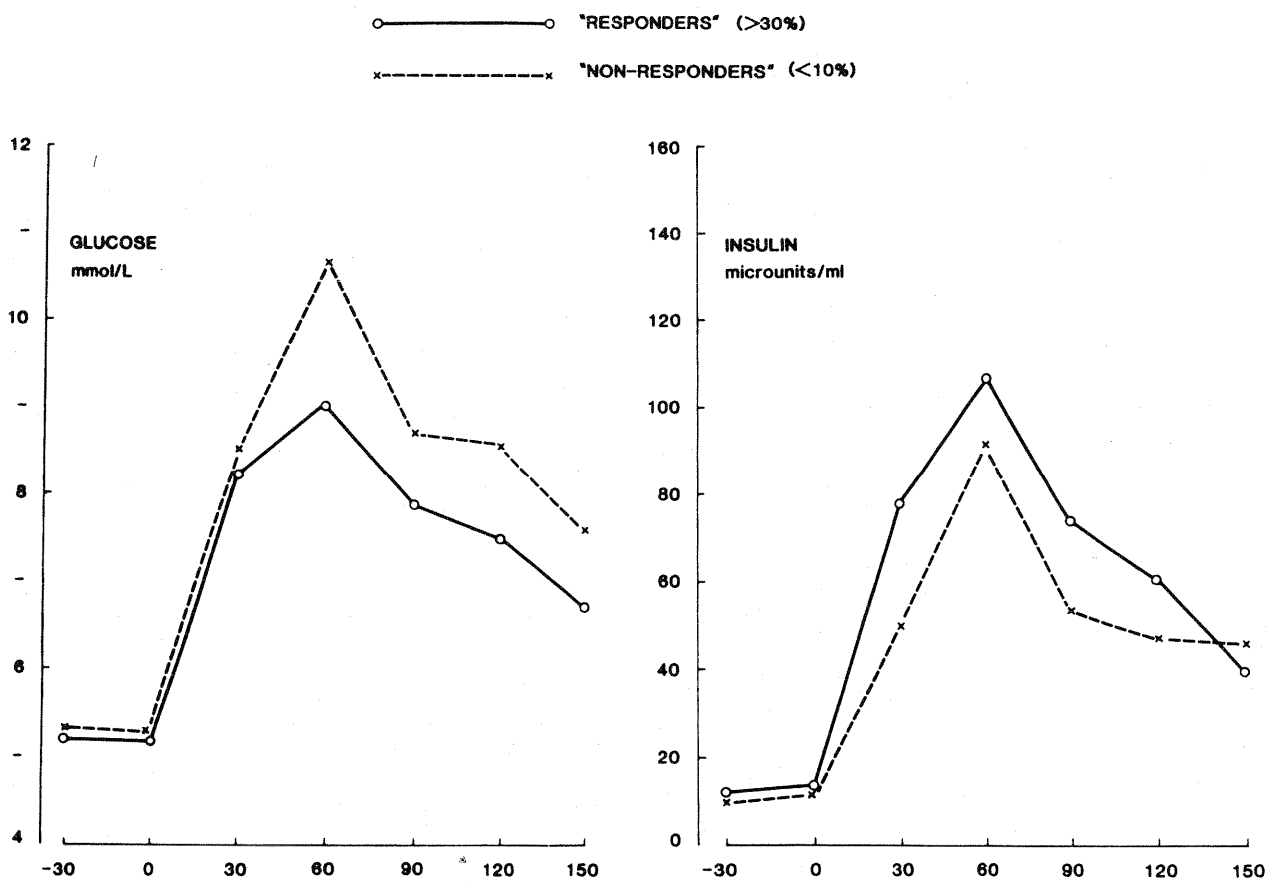
Fig. 2. Mean plasma glucose and insulin values in the two groups of subjects. 'Responders' showed an increase in alcohol metabolism of greater than 30% after glucose, 'Non-responders' showed an increase of less than 10%.

olism. Incidentally, they found no effect from fructose either.

A recent report (Schmidt et al., 1987) has compared the effects of oral and intravenous glucose on the rate of alcohol metabolism in four subjects. While either 50 g or 200 g of oral glucose produced an approximately 20% increase in the rate, intravenous glucose (25 g or 50 g) made little difference. It is not clear whether this difference in results was due to the dose or the route of administration. The change in the rate of alcohol metabolism after oral glucose was less than we have found, possibly because it was measured as an average rate of fall of blood alcohol concentration over several hours whereas our design allows measurement of the rate in consecutive half-hour periods.

Studies in vitro using rat liver slices (Forsander and Himberg, 1969) have shown an

acceleration of alcohol metabolism in the presence of added glucose. However, extrapolation to the in vivo situation may not always be valid because of the role of extrahepatic tissues in the further metabolism of acetate, the possible influence of insulin levels (Rawat, 1969), and the fact that their results showed the greatest effect between 0 and 3 mmol/l. added glucose. Studies in intact rats by Jones (1983) showed that fructose, glucose, or a mixture of sugars each had a major effect after oral administration but there was also accelerated metabolism after intraperitoneal administration of alcohol and any of the sugars when compared with alcohol and saline.

Most, but not all, studies on fructose have shown an increased rate of alcohol metabolism compared with control. One of the exceptions (Levy et al., 1977) was a double-blind study in which glucose was used as the control. A re-

cent report (Crownover et al., 1986) demonstrates the important influence of experimental design on the results obtained after fructose.

Our results suggest that there is a carbohydrate effect rather than, or in addition to, a specific fructose effect and this means that the commonly accepted mechanism of the fructose effect must be questioned. Fructose, but not glucose, may give rise to glyceraldehyde and the conversion of glyceraldehyde to glycerol, using NADH, has been thought to account for the acceleration of alcohol metabolism in the presence of fructose (Tygstrup et al., 1965). Since glucose can produce a similar effect on the rate of alcohol metabolism, this and other explanations which have been put forward for the fructose effect in the past (e.g. Damgaard et al., 1972) need to be re-examined.

Differences between people in the response of alcohol metabolism to carbohydrate have been noted in the past. Marks (1978) reviewed the published experiments on fructose and commented on an inverse relationship between the rate of decrease of blood alcohol concentration (a measure of the rate of metabolism in the single-dose design) and the percentage increase in that rate after fructose. Our 'alcohol-clamp' design has shown the same relationship for glucose (Table 1). The degree of response seems to be linked in some way to glucose tolerance, as the 'non-responders' had significantly higher plasma glucose values after the glucose load and also a diminished insulin response to glucose. Possible reasons for differences between the two groups include obesity, previous experience with alcohol, or diet. Each subjects' body mass index was calculated, and they were asked about their customary alcohol intake and diet, but no differences between the two groups could be demonstrated.

In our previous experiments (Rogers et al., 1987) the carbohydrate meal was calculated to contain 120 g of total carbohydrate. A comparison of the results found with mixed carbohydrate in that study and the present 100 g glucose load is shown in Fig. 3. Taking into account the 20% difference in dose, and the fact that four of the ten subjects in the glucose study showed no increase in alcohol metabolism, it seems that the mixed carbohydrates and
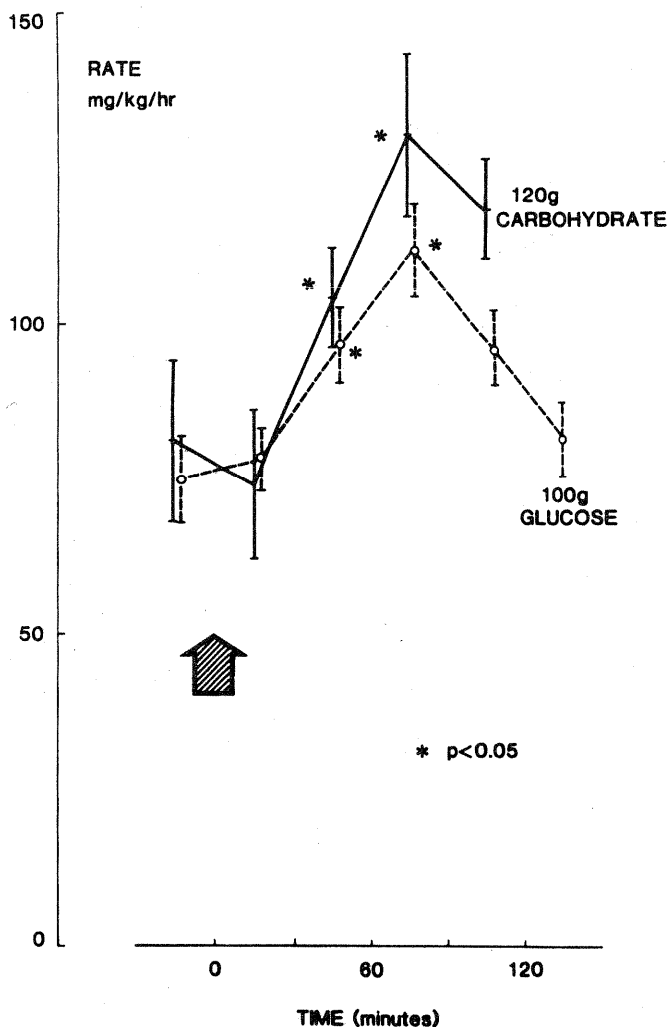

Fig. 3. Comparison between the effects of 100 g of glucose and 120 g of mixed carbohydrates on the rate of alcohol metabolism. Abscissa: time after carbohydrate meal or glucose load in min; ordinate: rate of alcohol infusion required to maintain a constant breath alcohol reading, in mg/kg body weight/hr.
*Significant difference from fasting rate ($P < 0.05$) by paired t-test (but see text).

glucose give about the same effect per g, or per mole of monosaccharide. The exact nature of the dose–response curve, and the minimum effective dose of carbohydrate, remain to be determined.

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