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DIFFERING EFFECTS OF CARBOHYDRATE, FAT AND PROTEIN ON THE RATE OF ETHANOL METABOLISM

JO ROGERS*, JILL SMITH†, G. A. STARMER‡ and J. B. WHITFIELD†§

Departments of *Dietetics and †Clinical Biochemistry, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia; ‡Department of Pharmacology, University of Sydney, NSW 2006, Australia

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Abstract — The rate of metabolism of ethanol in humans has been assessed by intravenous infusion of ethanol/saline under feedback control to maintain a constant blood alcohol concentration. After equilibration, meals consisting predominantly of carbohydrate, fat or protein were eaten and changes in ethanol metabolic rate were found. Carbohydrate caused a significant increase in this rate and fat or protein caused small but non-significant decreases. Infusion of ethanol/saline resulted in a temporary fall in plasma free fatty acid levels and a steady rise in plasma triglycerides. The changes in alcohol metabolism following carbohydrate cannot be accounted for by changes in insulin, free fatty acid or lactate/pyruvate levels.

INTRODUCTION

It has generally been considered that little can be done to increase the rate of removal of alcohol from the circulation, although the rate of absorption of alcohol can be affected by food taken at the same time. Ways of increasing the rate of alcohol (ethanol) metabolism in the short term could be useful in reducing the hazards associated with intoxication, and could also throw light on the nature of the rate-limiting processes in alcohol metabolism.

The effects of food on the blood alcohol curve were studied by Mellanby (1919), and it has since been generally found (Sedman *et al.*, 1976; Jones, 1983) that food slows the absorption of alcohol and reduces the peak blood alcohol and the area under the curve. It has also been claimed that carbohydrates, especially fructose, can increase the elimination rate of alcohol already present in the body, but these results are rather variable (Lundquist and Wolthers, 1958; Levy *et al.*, 1977; Franks *et al.*, 1977; Jones, 1983).

Animal experiments using liver homogenates or slices, or perfused livers, have shown differences in alcohol metabolism between the fasting and fed states (Smith and Newman, 1959). A recent report (Schmidt and Oehmichen, 1984) suggested that eating could affect the rate of disappearance of intravenously (i.v.) administered alcohol in humans, which points to an effect on metabolism. In order to avoid effects on absorption, Schmidt and Oehmichen gave alcohol i.v. to volunteers and studied the rate of decrease of blood alcohol concentration on different occasions when meals were included in or excluded from the protocol. They used meals which contained all three of the main groups of nutrients (albeit in varying proportions) and found an increased alcohol disappearance rate after feeding, but no apparent difference between the effects of carbohydrate-rich or fat- and protein-rich meals.

The aims of our study were to confirm the existence of a feeding effect in human subjects, to determine its time-course and magnitude, and to see if it was specific to any type of nutrient. We have also made measurements of insulin, free fatty acids and lactate/pyruvate ratios on blood samples from the subjects in order to test various hypotheses about the mechanism of any feeding effect, and we have taken the opportunity to assess the metabolic

§Author for correspondence.

changes occurring at a constant blood alcohol level maintained for several hours.

We have found that carbohydrate significantly increases the rate of metabolism of alcohol in fasting human subjects, and fat or protein either have no effect or cause a small decrease.

SUBJECTS AND METHODS

Our subjects were five healthy males aged between 23 and 51, who were neither teetotallers nor excessive alcohol users. They gave informed consent to the experimental protocol, which had been approved by the Ethics Review Committee of Royal Prince Alfred Hospital. Each subject was studied on four occasions.

On each occasion a 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 9 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 five minutes 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 was maintained so that the rate of infusion of alcohol could be equated with the rate of metabolism (assuming that routes of removal other than hepatic metabolism are small and constant). On the first occasion for each subject the study was terminated at 180 min, and on the other three occasions a meal was eaten between 180 and 210 min and the infusion, adjusted according to the breath alcohol results, was continued to 300 min. The three meals (Table 1) were designed to be of equal energy content (2100–2200 kJ) but differed in their composition; the first (high-carbohydrate) contained 90% of energy as carbohydrate, the second (high-fat) contained 87% of energy as fat, and the third (high-protein) contained 82% of energy as protein.

The blood samples, and 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 blood samples were also analysed for plasma glucose and triglycerides by enzymatic methods (American Monitor Corp., Indianapolis, U.S.A.), insulin by radioimmunoassay (Bio-mega Diagnostic Inc., Montreal, Canada), and free fatty acids (NEFA-C kit, WAKO Pure Chemical Industries, Osaka, Japan); and for blood lactate and pyruvate by enzyme methods (Boehringer Mannheim, West Germany).

The mass of alcohol infused in each period, for the last period before the meal and four periods after, was subjected to two-way analysis of variance with subject and time (one pre-meal and four post-meal 30 min periods) as factors and changes in blood alcohol concentration as co-variate, in order to test for effects of each of the meals against fasting. To compare the effects of the three meals at various times the results for each time were taken for two-way analysis of variance with the type of meal (carbohydrate, fat, protein) as one factor and the individual subject as the other.

RESULTS

It was found that between 90 and 150 min infusion (depending on the subject) was needed before the required rate of infusion stabilised; this presumably represents equilibration between the circulation and various extravascular compartments. It was also found that the breath alcohol readings sometimes drifted outside the target range despite the best efforts of the experimenter and, as would be expected, a fall in breath alcohol reading was associated with a lower infusion rate and vice versa. Because of uncertainty about the effective volume of distribution of alcohol in relation to such short-term fluctuations, the values for mass of alcohol infused in each 30 min

Table 1. The composition of the test meals

Carbohydrate-rich	White bread, 60 g with 20 g jam. Stewed apple, 200 g, with 30 ml lemon juice, 15 g sultanas, and 15 g sucrose. 200 ml fresh orange juice. Total carbohydrate 121 g/1933 kJ, total fat 3 g/96 kJ, total protein 8 g/128 kJ.
Fat-rich	Fried fatty bacon, 30 g, with 100 g fresh tomato and 10 g polyunsaturated margarine. 150 ml of unsweetened jelly with 30 ml cream. 200 ml black decaffeinated coffee with 30 ml cream. Total carbohydrate 6 g/104 kJ, total fat 50 g/1865 kJ, total protein 11 g/179 kJ.
Protein-rich	Stewed veal, 400 g uncooked weight, trimmed of fat, with 20 g onion, 100 g tomato, prepared with basil, oregano and salt. Dessert of gelatine, 10 g, egg white 30 g, vanilla flavouring, 150 ml skim milk. Total carbohydrate 12 g/190 kJ, total fat 5 g/200 kJ, total protein 102 g/1729 kJ.

period were adjusted by introducing the difference in blood alcohol over each period as a co-variate. However, these changes were not large; the mean blood alcohol concentration over the relevant periods (120–300 min) in all studies was 17.0 mmol/l. (78 mg/100 ml) and the standard deviation was 1.4 mmol/l. (6.4 mg/100 ml) or 8.1% of the mean. It will be noted that the breath alcohol analysis consistently underestimated the blood alcohol concentrations, but an excellent correlation (r = 0.980) between blood and breath alcohols has previously been shown with this instrument (Perl *et al.*, 1984), and the existence of a small bias in the instrument's readings does not affect its use in maintaining a steady state.

The effects of the different meals on the required alcohol infusion rate are shown in Fig. 1. Carbohydrate caused a significant increase ($P < 0.05$) in the rate, while fat and protein showed either no effects or possibly decreases, which however did not reach statistical significance. Comparing the different meals at each time showed that, as expected, there were no significant differences before the meal; nor was any significant difference found in the 180–210 min period. From 210 to 240, and from 240 to 270 min the differences were significant ($F_{2,8} = 6.45$, $P = 0.022$ and $F_{2,8} = 7.66$, $P = 0.014$ respectively), and the differences were no longer significant in the last (270–300 min) period.

It appears that the carbohydrate effect on alcohol metabolism is greatest around 1 hr after the meal. This was also the time of greatest elevation of plasma glucose (Table 2). Plasma glucose did not increase significantly after the fat or protein meals.

The results for plasma insulin, free fatty acids, and triglycerides and for the blood lactate to pyruvate ratios are given in Tables 3–6.

DISCUSSION

Effects of food on alcohol metabolism

These results confirm that food can have an effect on the rate of metabolism of ethanol, independently of any effects on the rate of absorption. Moreover, this effect appears to be specific for carbohydrate and did not occur after meals which were almost entirely composed of fat or protein. Presumably each of the meals used by Schmidt and Oehmichen (1984) contained some carbohydrate.

Our method, using a continuous infusion under feedback control, allows comparison of pre- and post-treatment utilisation rates within the same subject and the same occasion, and allows determination of the time-course of any effects found. The magnitude of the carbohydrate effect on ethanol metabolism was approximately 60% above fasting, and it occurred at 1–1.5 hr after the meal. The time-course of the effect paralleled changes in plasma glucose and insulin after the carbohydrate meal.

Studies of the effects of glucose and/or insulin on the rate of alcohol metabolism after i.v. infusion were conducted by Stokes and Lasley (1967), who found no change following i.v. glucose and only small and variable in-

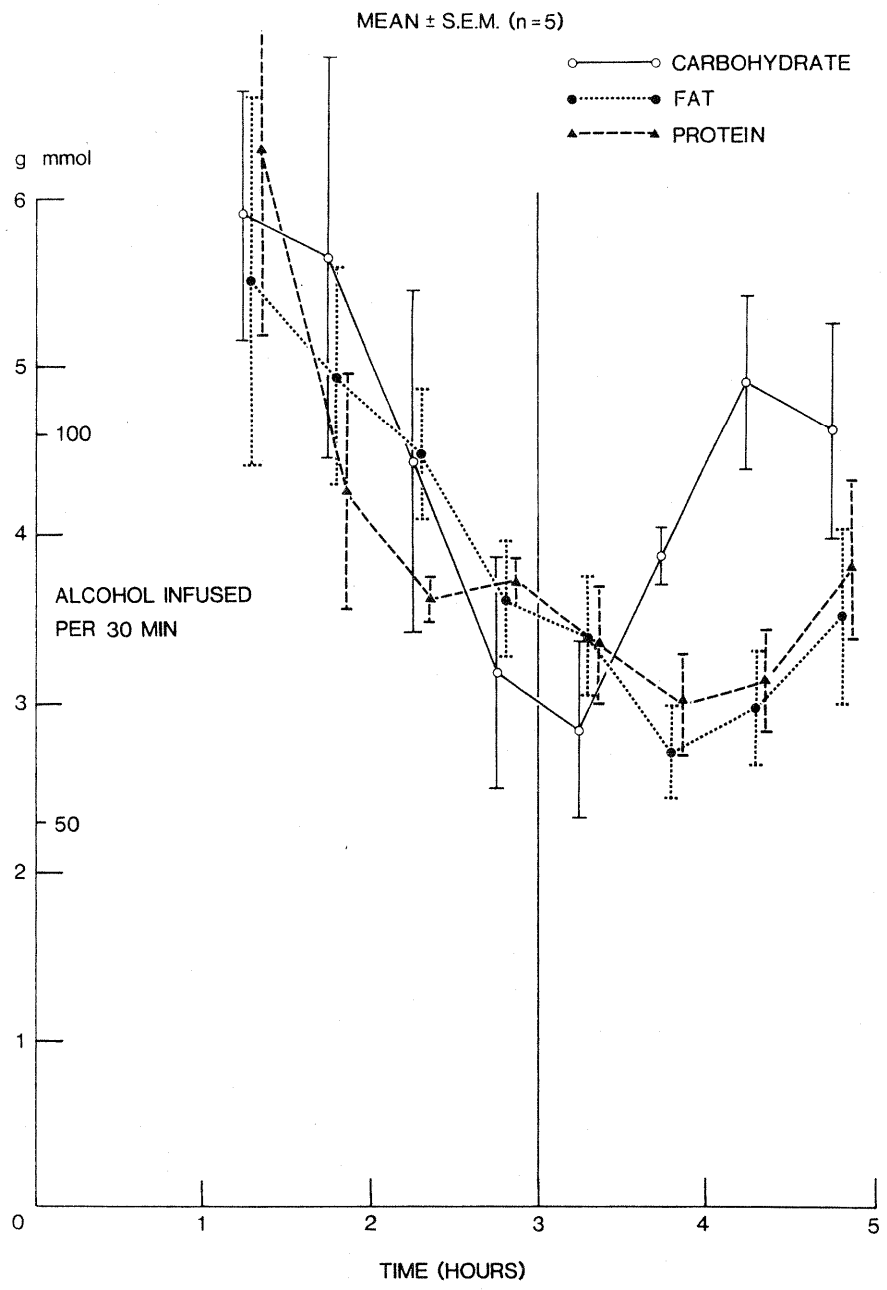

Fig. 1. The amount of alcohol (in g. and mol of absolute alcohol per 30 min) required to maintain a constant blood alcohol concentration of 17 mmol/l., plotted against time for three types of meal; carbohydrate-rich, fat-rich and protein-rich. The meals were eaten at 3 hr after the start of the studies. Error bars show 1 S.E.M. Significant differences between the meals occurred at 4 and at 4.5 hr.

creases after insulin. Their protocol differed from ours in a number of ways and it is difficult to assess which of these differences might be relevant; their subjects were on a high-carbohydrate diet, the alcohol was given over 20–25 min at the beginning of the experiment and the rate of fall was used to assess the rate of metabolism, and the carbohydrate was given i.v. and as glucose or fructose rather than orally.

As mentioned previously, it has been claimed that fructose can increase the rate of alcohol metabolism. Studies in humans have been contradictory; for example Lundquist and

Table 2. Plasma glucose results (mmol/l.) before and after different types of meal

Time	Fasting		Carbohydrate		Fat		Protein	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
0	6.0	0.36	5.8	0.13	5.6	0.20	5.5	0.14
30	5.6	0.13	5.6	0.10	5.7	0.13	5.6	0.17
60	5.3	0.09	5.5	0.10	5.4	0.21	5.5	0.21
90	5.2	0.18	5.7	0.22	5.3	0.20	5.4	0.16
120	5.2	0.09	5.4	0.13	5.2	0.19	5.2	0.19
150	5.1	0.18	5.3	0.09	5.1	0.21	5.2	0.16
180	5.0	0.13	5.4	0.17	5.0	0.13	5.1	0.08
210			7.5	0.59	5.2	0.12	5.1	0.16
240			8.4	0.70	5.1	0.14	5.4	0.17
270			7.8	0.93	5.2	0.15	5.3	0.12
300			7.7	0.82	5.1	0.12	5.3	0.15

Means and their standard errors from five subjects. There was a significant change in mean values over the period 0–180 min ($F_{6,126} = 8.31$, $P < 0.001$). Changes over the period 180–300 min were significant after the carbohydrate meal ($F_{4,16} = 4.12$, $P < 0.05$) but did not reach significance with the fat or protein meals.

Table 3. Plasma insulin results (microunits/ml) before and after different types of meal

Time	Fasting		Carbohydrate		Fat		Protein	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
0	16.2	1.5	18.4	1.9	17.8	1.4	18.4	0.8
30	15.0	1.5	14.8	2.1	13.2	1.2	14.8	1.5
60	12.0	1.4	12.6	1.6	13.0	0.9	17.2	2.6
90	13.2	1.7	15.0	1.4	15.0	0.9	13.6	0.8
120	12.6	1.6	14.6	1.3	14.6	0.8	14.2	1.6
150	13.6	1.9	15.2	2.2	14.8	1.0	14.4	0.8
180	13.6	1.1	16.8	1.0	14.6	0.8	15.0	1.0
210			45.0	7.6	21.8	2.6	22.0	1.9
240			54.8	8.5	18.6	2.1	28.6	4.3
270			59.4	12.3	18.8	1.3	28.6	2.9
300			53.4	11.3	15.2	1.0	22.8	1.1

Means and their standard errors from five subjects. There was a significant change in mean values between 0 and 30 min ($F_{1,31} = 10.53$, $P < 0.01$), and significant changes over the period 180–300 min were associated with each of the meals (carbohydrate $F_{4,16} = 5.02$, $P < 0.01$; fat $F_{4,16} = 3.54$, $P < 0.05$; protein $F_{4,16} = 7.78$, $P < 0.01$).

Wolthers (1958) found an increase in alcohol metabolism after fructose which was greater than that after glucose, while Levy *et al.* (1977) found no difference between glucose and fructose in a double-blind controlled trial of these two carbohydrates in the treatment of intoxication. However, our decision to begin by studying the effects of natural foods rather than purified components means that we cannot rule out an effect of fructose derived from the sucrose in the carbohydrate meal.

Further experiments will be needed to deter-

Table 4. Plasma free fatty acids results (μmol/l.) before and after different types of meal

Time	Fasting		Carbohydrate		Fat		Protein	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
0	345	89	363	64	384	55	293	47
30	272	64	220	38	200	24	197	44
60	262	55	283	55	209	19	202	36
90	345	51	323	57	287	35	255	33
120	357	47	308	58	271	35	256	35
150	316	46	360	77	237	25	304	38
180	313	39	352	78	253	27	310	37
210			304	96	215	21	235	35
240			164	55	216	34	212	55
270			102	30	151	10	163	39
300			103	27	153	10	126	40

Means and their standard errors from five subjects. There was a significant change in mean values between 0 and 30 min ($F_{1,31} = 14.29$, $P < 0.01$), and significant changes over the period 180–300 min were associated with each of the meals (carbohydrate $F_{4,16} = 8.87$, $P < 0.01$; fat $F_{4,16} = 4.42$, $P < 0.05$; protein $F_{4,16} = 17.42$, $P < 0.001$).

Table 5. Plasma triglycerides results (mmol/l.) before and after different types of meals

Time	Fasting		Carbohydrate		Fat		Protein	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
0	0.9	0.2	1.1	0.3	1.1	0.3	1.1	0.2
30	0.7	0.2	0.8	0.3	0.9	0.3	0.9	0.2
60	0.7	0.2	0.9	0.3	0.9	0.3	1.0	0.2
90	0.8	0.2	1.0	0.3	0.9	0.3	1.0	0.2
120	0.8	0.2	1.0	0.4	0.9	0.3	1.1	0.2
150	0.9	0.3	1.0	0.3	0.9	0.3	1.2	0.2
180	1.0	0.3	1.1	0.3	1.0	0.3	1.2	0.2
210			1.3	0.3	1.1	0.3	1.3	0.2
240			1.3	0.4	1.2	0.4	1.4	0.2
270			1.5	0.4	1.3	0.4	1.6	0.2
300			1.5	0.5	1.7	0.5	1.6	0.3

Means and their standard errors from five subjects. There was a significant fall from the fasting value at 30 min ($F_{1,31} = 7.93$, $P < 0.01$) and values rose significantly thereafter regardless of the type of meal ($F_{9,163} = 12.71$, $P < 0.001$).

mine whether the effect we found depends on the route of carbohydrate intake, or the type of carbohydrate, or the preceding diet.

Biochemical changes after alcohol infusion

Our protocol also allows examination of changes in metabolite concentrations resulting from the constant blood alcohol level (before the meals), or from interaction between the alcohol and the different foods (after the meals). This is probably a more appropriate model of drinking behaviour, especially for heavy drinkers, than single-dose studies.

The results in Tables 2–6 show that the alcohol infusion was followed by a steady decrease in plasma glucose and an immediate but small fall in plasma insulin. The free fatty acid levels fell after alcohol infusion com-

Table 6. Blood lactate/pyruvate ratios before and after different types of meal

Time	Fasting		Carbohydrate		Fat		Protein	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
0	13.2	3.0	12.4	2.6	12.3	2.4	13.2	2.4
30	23.4	4.2	35.3	4.7	24.3	3.3	25.2	2.5
60	25.0	3.3	35.7	5.5	27.6	3.0	28.1	2.1
90	26.2	3.7	34.6	5.9	27.6	5.7	27.0	4.7
120	28.0	4.1	32.5	6.0	35.3	10.3	35.3	6.4
150	23.4	2.4	33.9	9.5	45.5	21.3	29.9	4.0
180	29.7	4.8	34.1	4.2	35.9	7.4	29.3	3.2
210			42.2	9.5	30.1	2.5	32.4	3.0
240			45.9	14.4	28.3	4.2	33.1	2.1
270			40.3	11.8	27.4	4.2	40.2	2.0
300			34.9	4.4	29.3	5.2	32.8	5.7

Means and their standard errors from five subjects. The means at 0 and 30 min were significantly different ($F_{1,31} = 36.8$, $P < 0.001$). Changes over the period 180–300 minutes did not reach significance after any of the meals (but see text).

menced, but returned to their pre-alcohol values after about 2 hr. Plasma triglycerides fell slightly initially and then rose gradually over the entire 5 hr of the studies without regard to the type of meal which was eaten.

As expected, there was a sharp increase in the lactate to pyruvate ratio after the alcohol infusion began and despite some variations it appears that the ratio remained on a plateau until the meals were eaten at 180 min.

Possible causes of the carbohydrate effect

While it is generally agreed that the first step in the metabolism of ethanol, its oxidation to acetaldehyde, is rate-limiting (Badawy, 1978), there is less agreement on whether the concentration of the enzyme(s) involved or the availability of substrate (NAD) is more important. Some recent papers indicate that the enzyme concentration is more likely to be critical (Crow *et al.*, 1982; Dawson, 1982; Cornell, 1983) since there is reason to believe that NAD can be regenerated at rates greater than necessary for the observed rate of metabolism of ethanol. Furthermore, there is evidence that some measures can maintain the NAD/NADH ratio at normal levels without increasing the rate of alcohol metabolism while others can accelerate alcohol metabolism without reversing the ethanol-induced alteration in the redox state (Ryle *et al.*, 1985). Nevertheless we have to consider whether the NADH/NAD ratio might change with the change from fasting to the fed state; this is usually assessed from the lactate/pyruvate ratio.

Two other possibilities arise from reports of experiments in rats. Firstly, fatty acids can inhibit ethanol utilisation in rat liver slices (Rawat, 1969) or perfused rat livers (Thurman and Scholz, 1975), so that the carbohydrate meal might suppress circulating and hepatic free fatty acid levels and thereby allow an increase in alcohol metabolism. Secondly, it has been shown that insulin can increase alcohol metabolism in fed rats and absence of insulin brought about by alloxan treatment is associated with low alcohol and aldehyde dehydrogenase activities (Rawat, 1969). An insulin effect on alcohol dehydrogenase activity was also shown in fasting rats (Lakshman *et al.*, 1986). Therefore the effect of the carbohydrate meal might involve insulin, either directly or through its effect on free fatty acid concentrations.

However, examination of the results in Tables 3, 4 and 6 casts serious doubt on all of these explanations. Certainly insulin levels rise after the carbohydrate meal when alcohol metabolism is also rising, but a slight increase in plasma insulin occurs after the fat meal and a substantial one after the protein meal and in neither case is this associated with increased

ethanol metabolism. One would have to postulate a non-linear effect of circulating insulin levels, with effects on alcohol metabolism only above 30 microunits/ml, if the effect is to be mediated through insulin.

Similarly, plasma free fatty acid levels decrease as expected after the carbohydrate meal, but the other meals also cause a lesser decrease without increasing alcohol metabolism.

The lactate to pyruvate ratios (Table 6) increase as expected after alcohol infusion is started, from about 12 to values around 30 at 180 min, just before the meal. The values after fat or protein are rather variable, but the changes after the carbohydrate meal are of interest. It would be expected, if NADH/NAD ratios are relevant, that an increase in lactate/pyruvate would lead to a decrease in alcohol metabolism but in fact the lactate/pyruvate ratios rise after carbohydrate and alcohol metabolism actually increases.

Therefore the proposed mechanisms for this feeding effect are not supported by our findings, and further investigation of this aspect will be needed.

Practical implications

Whatever the mechanism, the food effect on alcohol metabolism exists and it should serve as another reason to avoid drinking on an empty stomach — not only is oral alcohol absorbed more slowly in the fed state, but if the meal contains sufficient carbohydrate it could speed up alcohol metabolism.

In male fasting subjects who are not habitual heavy drinkers the rate of decrease of blood alcohol concentration in the elimination phase has been estimated as 15.5 ± 5.0 mg/100 ml/hr (mean ± S.D.) (Martin *et al.*, 1985). If the 60% increase observed in this study after carbohydrate can be applied to Martin *et al.*'s figures, the mean rate of decrease would rise from about 15 to 25 mg/100 ml/hr. This should result in a decrease in the average time for a person's blood alcohol to fall from, say, 100 to 50 mg/100 ml from 3.2 to 2 hr. This could be a large enough change to be of practical significance. However, most drinks contain some carbohydrate and studies of the dose–response relationship will need to be made before the practical implications of these findings are clear.

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