Alcohol & Alcoholism, Vol. 24, No. 3, pp. 189–191, 1989
Printed in Great Britain

0309–1635/89 $3.00 + 0.00
Pergamon Press plc
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RAPID COMMUNICATION

EFFECT OF DIET ON [LACTATE]/[PYRUVATE] RATIOS DURING ALCOHOL METABOLISM IN MAN

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(*First received* 5 *January* 1989; *accepted for publication* 9 *February* 1989)

Abstract — Ten subjects received alcohol by intravenous infusion on two occasions, after five-day periods on high- or low-carbohydrate diets. Blood [lactate]/[pyruvate] ratios were significantly higher during fasting alcohol metabolism after the low-carbohydrate, high-fat diet. The carbohydrate/fat balance in the diet may affect cytoplasmic-mitochondrial NADH transfer. Dietary composition may modify the metabolic changes caused by alcohol.

INTRODUCTION

A number of diverse effects of alcohol are thought to be mediated by changes in the redox state of hepatocytes during alcohol metabolism. For example, the effects of alcohol on gluconeogenesis, fat synthesis and lactate removal after exercise are thought to be due to changes in the [NADH]/[NAD^+] ratio (Krebs, 1968). It was also proposed that alterations to steroid hormone metabolism occur through this mechanism (Andersson *et al.*, 1986).

The [NADH]/[NAD^+] ratio in the cytoplasm is reflected by the [lactate]/[pyruvate] ratio because of the high activity of lactate dehydrogenase, and this in turn changes the [lactate]/[pyruvate] ratio in the blood. NADH is reoxidised in the mitochondria through the action of substrate shuttles which effectively transfer NADH inwards and NAD^+ outwards, and the shuttle activity might be a limiting factor in alcohol metabolism because NADH concentration may limit the activity of alcohol dehydrogenase (ADH) (for review, see Badawy, 1978). However, this view is not universally accepted (Dawson, 1982; Crow *et al.*, 1983).

For all these reasons, the [lactate]/[pyruvate] ratio has been the focus of a great deal of interest. In the present work, we found that the [lactate]/[pyruvate] ratio in the blood during alcohol metabolism can be affected by the diet and this raises questions about the relationship between this ratio and the maximum rate of alcohol metabolism. It also suggests that some of the immediate metabolic effects of alcohol, thought to be mediated through changes in the [NADH]/[NAD^+] ratio, could be affected by the dietary state of the subject.

SUBJECTS AND METHODS

The subjects were ten healthy men aged between 19 and 45 years. They gave informed consent to the study, which was approved by the Ethics Review Committee of Royal Prince Alfred Hospital. Each subject was studied on two occasions, at least two weeks apart. They all drank alcohol socially, in quantities ranging from 50 to 250 g per week, but they abstained from alcohol for five days before each of the two alcohol metabolism studies. During those five-day periods, they took diets designed to be of equal energy and protein content, but differing in fat and carbohydrate content. The first diet (high-carbohydrate) contained 65%

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of energy as carbohydrate, 20% as fat and 15% as protein, and the second (low-carbohydrate) 20% of energy as carbohydrate, 65% as fat and 15% as protein. In each case the energy content was 10.5 megajoules per day. On the sixth day, the fasting subjects arrived at the laboratory at about 8.00 hr and were given an intravenous infusion of 6% ethanol in physiological saline at a rate sufficient to raise their blood alcohol concentrations (as estimated by breath analysis) to 0.065 g/dl, equivalent to plasma concentrations of 20 mmol/l. The blood alcohol concentrations rose over the first 60 min of the experiment and were maintained at the target level thereafter. The rate of alcohol infusion was adjusted to maintain a constant blood alcohol concentration by breath analysis at 5-min intervals and the rate of alcohol metabolism was estimated as the rate of infusion required to maintain a steady state, as previously described (Rogers *et al.*, 1987). The subjects continued to fast for 210 min from the beginning of the alcohol infusion, which is the time period considered in this report. Blood samples were taken before the infusion and every 30 min thereafter, and a portion of each was immediately deproteinized and subsequently analysed for lactate and pyruvate by standard enzymatic methods. Plasma alcohol concentrations were checked by gas chromatography.

RESULTS

The mean [lactate]/[pyruvate] ratios during alcohol infusion under the two dietary conditions are shown in Fig. 1. There were essentially no differences in [lactate]/[pyruvate] ratio between the two diets before or at 30 min after the start of alcohol infusion. There was a difference at 60 min but this did not reach statistical significance. During the phase of constant circulating alcohol concentrations (90–210 min) the difference in [lactate]/[pyruvate] ratios between the diets was highly significant ($F_{1,85}$ = 26.46, $P < 0.001$) and the differences at each time had P values between 0.10 and 0.02. During this period there was a significant upward trend in [lactate]/[pyruvate] ratio on both diets (high-carbohydrate r = 0.36, P = 0.01; low-carbohydrate r = 0.46, P = 0.001).

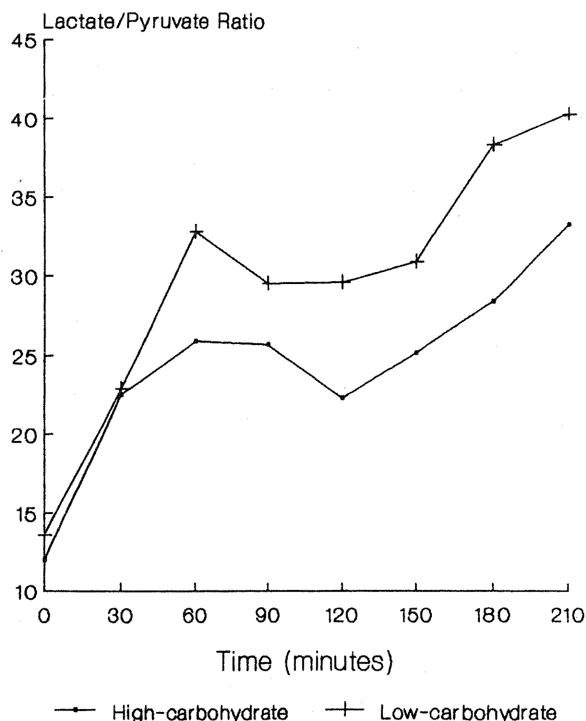

Fig. 1. Mean [lactate]/[pyruvate] ratios during alcohol infusion in ten fasting subjects after five days on high- or low-carbohydrate diets.

Before alcohol infusion, both the blood pyruvate and lactate concentrations were higher in the high-carbohydrate diet treatment; high-carbohydrate diet 0.073 ± 0.010 and 0.874 ± 0.136 respectively, vs low-carbohydrate diet 0.050 ± 0.005 and 0.673 ± 0.077 respectively (all values means ± S.E.M., in mmol/l). The initial blood pyruvate concentration was significantly higher on the high-carbohydrate diet (t = 3.11, $P < 0.05$) but the lactate concentration was not (t = 1.89, NS). During the phase of constant blood alcohol concentrations (90–210 min), the mean blood lactate was significantly lower on the high-carbohydrate diet ($F_{1,85}$ = 14.39, $P < 0.001$) and the mean blood pyruvate was significantly higher ($F_{1,85}$ = 7.53, $P < 0.01$), so that both components contributed to the lower calculated [lactate]/[pyruvate] ratio observed with the high-carbohydrate diet.

The fasting rates of alcohol metabolism did not differ significantly between the two dietary conditions; means were 108 mg/kg/hr on the high-carbohydrate diet and 99 mg/kg/hr on the low-carbohydrate diet.

DISCUSSION

These results have implications in two areas; the nature of the rate-limiting step in alcohol metabolism through the ADH pathway, and the effects of alcohol on other metabolic processes in the liver.

If it is accepted that the blood [lactate]/[pyruvate] ratio reflects the liver cell cytoplasmic [NADH]/[NAD$^+$] ratio, then the differences in this ratio which we found must reflect differences in production and/or removal of NADH in the cytoplasm. The pre-alcohol [lactate]/[pyruvate] ratios were the same on the two diets, and the rate of alcohol metabolism was only slightly different. Therefore a higher [NADH]/[NAD$^+$] ratio results from alcohol metabolism when the subject has been on a low-carbohydrate diet, but this does not change the rate of alcohol metabolism, and the same rate of cytoplasmic-mitochondrial NADH transfer is occurring. This is difficult to reconcile with the concept that the shuttle mechanisms are working at maximum capacity during alcohol metabolism and constitute the rate-limiting process.

The concept that differing cytoplasmic NADH concentrations are associated with the same rate of NADH transfer reactions under different circumstances suggests differing enzyme concentrations, and fits well with the finding of Crow *et al.* (1983) that NADH concentrations in the hepatocytes of rats metabolizing alcohol are considerably below the K_m of malate dehydrogenase and therefore higher NADH concentrations will increase the rate of NADH oxidation to equal its rate of generation. The possible reasons for differences in NADH transfer capacity are unknown at present, but could relate to differences in enzyme levels induced by the two diets. The metabolism of carbohydrate through glycolysis results in the net formation of NADH in the cytosol, while fatty acid oxidation takes place within the mitochondria and so less substrate shuttle activity should be required. If this is so, then it is the use of carbohydrate as the main source of energy (determined by the carbohydrate content of the diet) which will affect the [NADH]/[NAD$^+$] ratio rather than a direct effect of the lipid content of the diets.

It should be pointed out that these results were obtained in fasting subjects, and it is possible that an acute carbohydrate load may also affect the [lactate]/[pyruvate] ratio (Rogers *et al.*, 1987). The acute effect of carbohydrate on the [lactate]/[pyruvate] ratio under various dietary conditions will be the subject of further studies.

Our findings imply that, because alcohol produces greater changes in the [NADH]/[NAD$^+$] ratio when given to people on a high-fat, low-carbohydrate diet, such a diet could lead to a greater susceptibility to adverse metabolic effects of alcohol. These could include inhibition of gluconeogenesis, increased triacylglycerol (triglyceride) synthesis, delayed lactate removal after exercise and abnormal steroid hormone metabolism. However, in considering practical implications it must be remembered that when alcohol utilization is high a considerable proportion of its metabolism may occur through non-ADH pathways, which do not result in net production of NADH because of the consumption of NADPH. How far differences in the dietary intakes of heavy drinkers or alcoholics account for differences in the long-term effects of alcohol remains to be seen.

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