

Effect of oral fructose on ethanol elimination from the bloodstream

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ALCOHOL HAS BEEN IDENTIFIED AS A MAJOR factor contributing to traffic accidents in South Africa, affecting both drivers and pedestrians alike. An agent capable of facilitating ethanol metabolism safely and effectively is of potential value in reducing the frequency of such incidents, and for individuals wishing to reduce their blood alcohol to levels below the legal limit before taking control of a vehicle. Here we show that fructose, at a dose of 1 g/kg, fulfils the criteria for such an agent. When ingested by healthy volunteers who had imbibed ethanol equivalent to 8 standard tots, it reduced the time required to attain a legal blood alcohol level (50 mg%) by approximately 70 min ($n = 9$). When ingested before a dose of alcohol equivalent to a double tot, fructose reduced both the magnitude and duration of the subsequent increase in blood alcohol; mean peak height, area under the curve, and time taken to reach zero were 39%, 32% and 51%, respectively, of that observed in the absence of fructose ($n = 12$). We conclude that, whether taken after imbibing alcoholic beverages or prophylactically before commencing drinking, oral fructose significantly lowers blood alcohol levels and reduces the time required for alcohol to disappear from the bloodstream.

Background

Alcoholic beverages are much enjoyed, in this country as much as in any, and, in moderation, are reported to confer protection against certain diseases, particularly those involving the cardiovascular system. Unfortunately, their abuse can impact negatively on health. One of the main causes of alcohol-associated morbidity and mortality is trauma caused by road traffic accidents,¹ which can be avoided either by total abstinence or by taking to public thoroughfares, as motorist or pedestrian, only when blood alcohol has declined to a safe level. A safe level is currently legally defined in South Africa as less than 50 mg%, although the absolute figure varies between countries.

An agent capable of accelerating the disappearance of alcohol from the blood, or of decreasing peak blood alcohol levels prior to drinking alcoholic beverages, would be of potential use in reducing the blood alcohol of road users to safe levels.

It may also be of value to individuals wishing to travel by road, or engage in any activity involving mechanical equipment, only when no longer under the influence of alcohol, as legally defined. An agent that reportedly has this property is the simple sugar, fructose.

The ability of fructose to enhance ethanol metabolism was first described about 50 years ago.^{2,3} Several studies since then have supported the original observation. The consensus is that fructose, taken in sufficient doses, generally >1 g/kg, will enhance ethanol metabolism by up to 80%.⁴⁻¹¹ Other studies, however, failed to confirm this 'fructose effect',¹²⁻¹⁴ one going as far as to claim that not only is fructose ineffective in reducing blood alcohol levels but results in undesirable biochemical derangements, including metabolic acidosis (due to lactate and ketone bodies) and hyperuricaemia.¹³

In the face of these conflicting data, and the potential value of an agent able to reduce blood alcohol rapidly and effectively, we investigated whether and to what extent fructose reduced blood alcohol levels in intoxicated subjects. Many of the earlier studies were conducted under sophisticated and strictly controlled laboratory conditions, using intravenous infusions of fructose and/or alcohol, and sampling blood from specific sites, such as the hepatic vein.¹⁵ Ours was more in the nature of a field study, in which alcohol and fructose were ingested under conditions applicable to real-life scenarios.

We report here that fructose ingestion significantly accelerated alcohol metabolism, whether given after alcohol to reduce existing high blood levels or provided as prophylaxis before commencing drinking to reduce subsequent blood levels.

Methods

Experimental subjects used were either one of us (PB), staff of the Foundation for Alcohol-Related Research (A-S) or medical student volunteers, from whom fully informed consent was obtained. The protocol adopted for the 'fructose as treatment' experiments was for volunteers to imbibe 8 drinks of their choice (wine or spirits) at midday, over a period of one

hour. They were permitted a light snack during this period. Details of what they ate and drank were noted, to allow duplication on a later occasion. At the end of the one hour drinking session, 30 min was allowed for alcohol absorption, then breath alcohol was measured every 10 min for 4 h, or until it had fallen to zero, whichever occurred sooner. A week later, the experimental procedure was repeated, with the same subjects ingesting the same drinks as before, except that on this occasion 100 g fructose, dissolved in water, was administered 20 min after drinking had ceased.

The protocol adopted for the 'fructose as prophylaxis' experiments was to administer fructose, dissolved in water, at a dose of 1 g/kg, to volunteers prior to ethanol consumption. Ethanol equivalent to a double tot of spirits (50 ml) was then consumed over 5 min. A period of 10 min allowed for the dissipation of residual ethanol vapour from the oral cavity, after which breath alcohol measurements were taken and continued until levels had fallen to zero.

Blood alcohol levels were not quantitated directly, but were extrapolated from measurement of breath alcohol, using a commercially available breathalyser, the ALCO-SENSOR IV (Intoximeters, St Louis, MO). This instrument is widely used by law enforcement personnel. The ALCO-SENSOR was calibrated before use with a Scotty V ethanol breath standard of 82 mg%, as prescribed by the manufacturers.

Results

We initially investigated the effect of fructose used as 'treatment', that is, to lower pre-existing high blood alcohol levels. Nine subjects were rendered inebriated by the ingestion of 8 units of alcohol of their choice, consumed over a period of 1 h. This led, in most cases, to blood ethanol levels exceeding the legal limit of 50 mg% for an appreciable length of time. The subsequent decline in blood alcohol was monitored, either in the presence or absence of ingested fructose, as described above. A typical response is shown in Fig. 1. In general, the presence of fructose resulted in significantly lower blood alcohol levels at all corresponding time points, and shortened the period required for blood alcohol to fall to zero. Interestingly, fructose did not affect the rate of alcohol metabolism, as reflected by a steeper decline of blood alcohol with time. Rather, it decreased the peak level of alcohol achieved, and shortened the lag period, or plateau, observed before alco-

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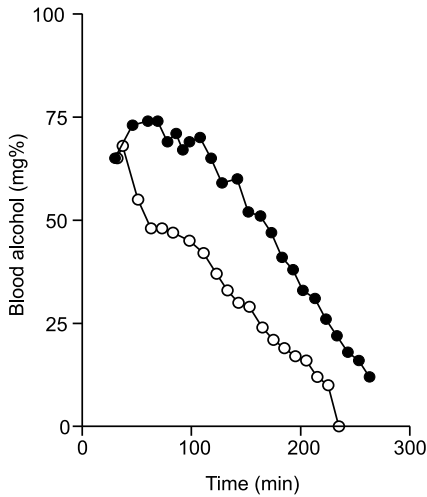


Fig. 1. Effect of fructose given after alcohol. A healthy volunteer consumed eight drinks in the space of an hour. Thirty minutes after alcohol intake ceased, blood alcohol was measured at 10-min intervals (closed circles). On a separate occasion, the experiment was duplicated, except that 100 g fructose was ingested prior to commencing measurements (open circles). The abscissa indicates time elapsed after alcohol intake ceased. This is a representative result drawn from nine subjects so tested.

hol levels began their linear decline. Fructose-induced shortening of the time taken to reach three arbitrarily chosen blood alcohol levels are depicted in Fig. 2; fructose reduced the time taken by a mean of approximately 70 min, essentially inde-

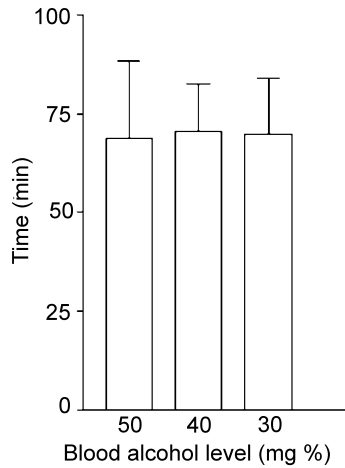


Fig. 2. Extent of fructose-induced blood alcohol reduction. Nine healthy volunteers consumed eight drinks in the space of an hour, waited 30 min, then blood alcohol was measured at 10-min intervals. The experiment was duplicated a week later; on this occasion 100 g fructose was ingested prior to commencing measurements. Bar height indicates the mean shortening by fructose of time taken for blood alcohol levels to fall to values indicated on the abscissa ($n = 9$); 50 mg% is the current legal limit in South Africa. Error bars denote s.e.m.

pendent of the particular blood level chosen. The considerable inter-individual variation is reflected by the large standard error of the mean.

A second approach was to investigate whether fructose, administered prophyl-

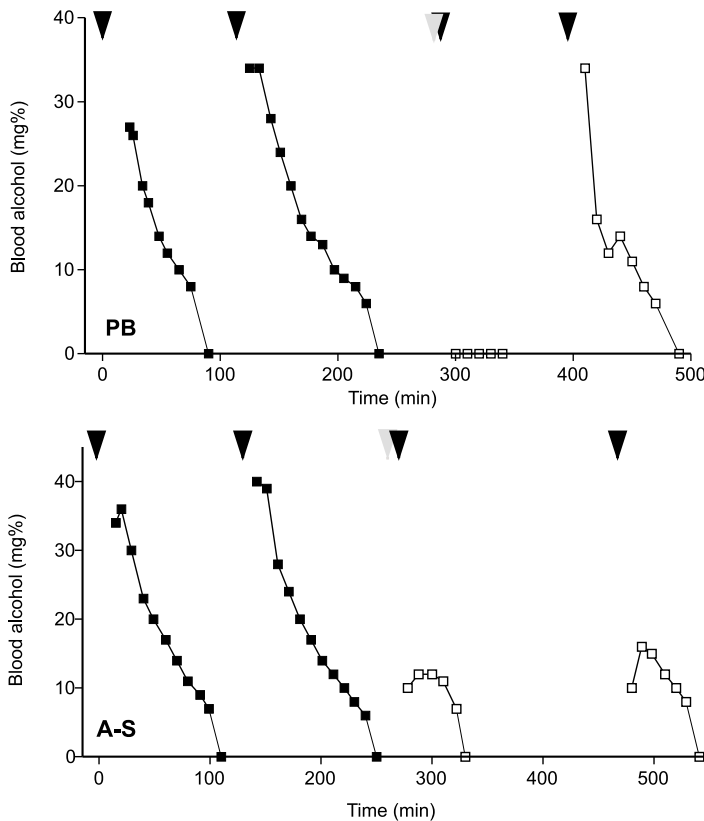


Fig. 3. Effect of fructose given before alcohol. A standard bolus of alcohol (40 ml whisky) was consumed at times depicted by the black arrows. Fructose (1 g/kg) was administered at the time indicated by the grey arrow. Closed and open symbols indicate blood alcohol levels before and after fructose ingestion, respectively. Subjects' initials shown in bottom left-hand corner.

lactically before drinking, could lower blood alcohol levels when a drink was subsequently ingested. The results of a pilot experiment on two individuals are depicted in Fig. 3. After ingestion of 50 ml whisky alone, blood alcohol levels rose to 30–40 mg%, then declined to zero over a period of approximately 2 h. Subsequent ingestion of the same dose yielded essentially similar results. At this point, fructose was administered, and a further 50 ml whisky consumed. This time, however, the increase in blood alcohol was significantly moderated. In one subject (PB), no blood alcohol was detected, while in the other (A-S) a peak level of just over 10 mg% was observed. Interestingly, the moderating effect persisted in subject A-S upon rechallenge with a further 50 ml bolus of whisky 3 h later, whereas in PB, the effect, although initially more profound, was shorter-lived.

To ascertain whether this inter-individual difference in the 'fructose effect' was consistent in a given individual, the experiment depicted in Fig. 3 was repeated in the same subjects a week later (except in this case, only a single pre-fructose drink was taken). As can be seen in Fig. 4, a similar pattern was observed; suppression of blood alcohol levels by fructose was more profound, but shorter-lived, in PB than in A-S. A third subject (NM) displayed an intermediate response.

To generalize these findings to a larger cohort of subjects, six healthy volunteers were challenged with 50 ml spirits and resulting blood alcohol levels were recorded until they reached zero. Subjects then ingested fructose (1 g/kg) and were rechallenged with an identical alcohol dose. In all cases, when given prior to a drink, fructose significantly suppressed subsequent increase in blood alcohol. Data were pooled from all subjects in whom fructose was administered prophylactically ($n = 11$), and its effects on alcohol kinetics expressed quantitatively, including maximum blood alcohol peak height attained, area under the blood alcohol–time curve (AUC), and time taken for blood alcohol to fall to zero. For all parameters, values obtained in the presence of fructose were expressed as a percentage of those observed in its absence, after an identical dose of alcohol. The mean, standard deviation and range of each are depicted in Table 1.

Discussion

Since first described 50 years ago,^{2,3} the efficacy of fructose in lowering blood alcohol levels remains a contentious issue, the literature abounding with

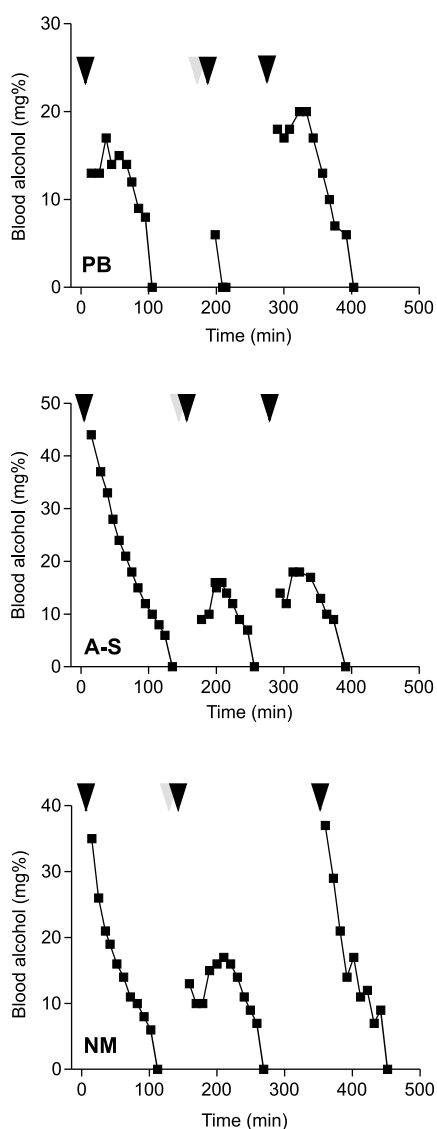


Fig. 4. Within-individual consistency of the alcohol response to pre-loading with fructose. The same subjects reported in Fig. 3 were rechallenged with alcohol (50 ml whisky) before and after ingesting fructose. Black arrows, whisky intake; grey arrow, fructose ingestion.

conflicting reports. From the data presented here, we conclude that oral fructose is indeed effective in lowering blood alcohol levels. When given after the end of a drinking session, it shortened the time taken for blood alcohol to fall to a predetermined level by over an hour. The ability of fructose to reduce the magnitude and duration of blood alcohol increase when taken before a drink was

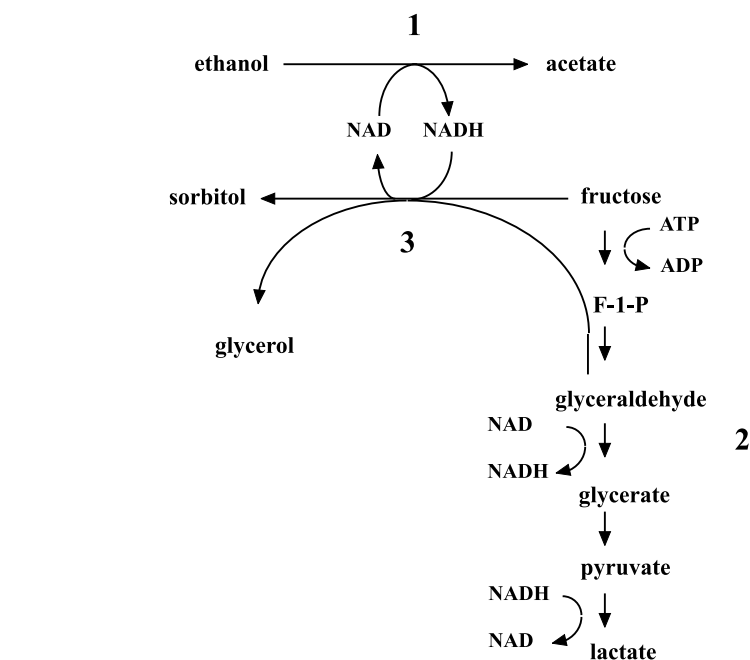


Fig. 5. Interaction of fructose with ethanol metabolism. Reactions occurring in the presence of ethanol alone, fructose alone, and ethanol and fructose together, are indicated by the numbers 1, 2 and 3, respectively. Note that glyceraldehyde, formed from fructose, is a branch point; in the absence of ethanol, it is oxidized to glycerate and lactate via terminal steps of glycolysis, whereas when ethanol is present, limiting amounts of NAD (and excess NADH) cause it to be preferentially reduced to glycerol. F-1-P = fructose-1-phosphate.

even more pronounced. Following an alcohol dose equivalent to a double tot of spirits, mean peak blood alcohol levels were reduced by 61%, zero blood level attained in half the time, and the mean area under the blood alcohol–time curve declined by almost 70%, when compared to an identical dose of alcohol given without fructose.

The biochemical mechanism of this enhancement — the so-called ‘fructose effect’ — remains an enigma. The conventional explanation is that alcohol metabolism generates NADH from NAD in the liver cell, and that the overall rate of alcohol oxidation is limited by the rate of NAD regeneration,⁶ as depicted in Fig. 5. Any substance that accelerates the rate of NADH re-oxidation to NAD in the liver will enhance its ability to metabolize alcohol. Fructose can accept reducing equivalents from NADH either directly, forming sorbitol, or after conversion to its metabolite, glyceraldehyde, to form glycerol. In support of this theory are studies showing greater accumulation of

sorbitol^{9,15} and glycerol¹⁵ after administration of alcohol and fructose together than when either agent is administered alone.

A fructose-induced decline in lactate/pyruvate ratios in blood would be indirect evidence for a decrease in the NADH/NAD ratio. However, Mascord *et al.* performed a study in which subjects were infused with alcohol to maintain a constant blood level.⁴ Infusion rate then accurately reflected rate of alcohol disposal — analogous to euglycaemic clamp studies used to measure the rate of glucose utilization in diabetics. Administration of oral fructose increased the rate of alcohol disposal by 80%, although there was considerable variation, related to the plasma fructose level. Interestingly, the researchers noted an increase (rather than decrease) in blood lactate/pyruvate ratios after fructose, and concluded that accelerated NADH recycling to NAD did not provide an explanation for the fructose effect.

Yamamoto *et al.* showed that fructose enhances hepatic ATP degradation, particularly in the presence of alcohol.¹⁶ This explains the earlier finding of Tygstrup *et al.* that ethanol and fructose together increase hepatic oxygen consumption by 60%.¹⁵ A fall in cellular ATP would presumably activate mitochondrial electron transport, which would in turn expedite NADH oxidation to NAD. Fructose enhances hepatic ATP degradation by temporarily trapping its high energy phosphate as fructose-6-phosphate, and

Table 1. Effects of fructose pre-loading on subsequent blood alcohol kinetics. Data from subjects challenged with alcohol before and after pre-loading with fructose were pooled.

Parameter*	Mean	s.d.	Range
Blood alcohol peak height	39	16	0–67
Area under the blood alcohol-time curve	32	27	0–93
Time taken for blood alcohol to reach zero	51	34	0–113

*The value of each parameter observed in the presence of fructose is expressed as a percentage of that observed in its absence; for example, the mean peak blood alcohol observed after fructose was 39% of that noted in its absence (after an identical dose of alcohol).

other phosphorylated glycolytic intermediates. Boesch *et al.* used ^{31}P magnetic resonance spectroscopy to follow fructose metabolism *in vivo*.¹⁷ They confirmed that fructose metabolism was slowed by alcohol at a point subsequent to its phosphorylation, and suggested aldolase as a possible site of inhibition. Whatever the precise mechanism, it appears that stimulation of alcohol metabolism by fructose is accompanied by reciprocal inhibition of fructose metabolism by alcohol, as manifest by the persistence of fructose-derived phosphorylated intermediates in the liver.

Perhaps the most definitive study on the biochemical mechanism of the fructose effect was undertaken by Tygstrup *et al.*,¹⁵ who infused alcohol and/or fructose into the right atrium of human volunteers, and simultaneously sampled from the hepatic vein and arterial circulation. Although rather invasive, this experiment allowed direct measurement of consumption or production of metabolites by the liver. It was found that fructose almost doubled hepatic ethanol uptake and acetate output, and that fructose and alcohol together (but neither substance alone) increased hepatic oxygen uptake by 60%. The lactate/pyruvate ratio in hepatic venous blood was greatly increased by ethanol and was unaffected by fructose. Fructose alone gave rise to a 20-fold increase in lactate production by the liver, but giving it with ethanol reduced lactate output markedly, leading instead to the appearance of polyols, glycerol and sorbitol, in blood from the hepatic vein. Tygstrup *et al.* interpreted their data as follows: fructose is phosphorylated in the liver, and cleaved to yield glyceraldehyde. In the absence of ethanol, glyceraldehyde is oxidized to glycerate and released from the liver as lactate.

In the presence of ethanol, however, glyceraldehyde is preferentially reduced to glycerol by the excess NADH, and is either released as such or participates in the transport of NADH-derived reducing equivalents into mitochondria as glycerol phosphate. Some fructose accepts reducing equivalents directly, forming sorbitol. All these biochemical reactions serve to regenerate NAD needed for ethanol oxidation to proceed — see Fig. 5.

Another explanation for the 'fructose effect' is that ingestion of sugars in general delays alcohol absorption.¹⁸ This does not, however, account for the specific effect of fructose, which is much more profound than that of other sugars like glucose. Also, it does not explain our

finding of enhanced alcohol clearance even when fructose was ingested 30 min after alcohol intake had ceased, when alcohol absorption was presumably nearly complete.

Our results indicate that fructose decreases the peak alcohol blood level observed and hastens the linear phase of blood alcohol decline, rather than steepening the rate of that decline. A study by Crownover *et al.* showed that the way in which fructose affected the kinetics of alcohol elimination was dependent on the timing of fructose administration.¹¹ When they gave fructose and ethanol together, peak alcohol levels were lower but elimination rate barely affected (it increased by 10%). Thus fructose caused an apparent increase in the volume of distribution of alcohol, a finding that accords with the first set of observations reported here (Fig. 1). When they gave the fructose 1 h post-ethanol, however, peak ethanol values and volume of distribution were unaffected, whereas the slope of ethanol elimination increased by 20–30% and the time needed for ethanol elimination was shortened by 90 min.

None of our subjects suffered serious untoward effects after ingesting large quantities of fructose. At the higher dose of 100 g, some individuals with smaller body mass, particularly the women, experienced some abdominal discomfort and nausea. This largely disappeared when the dose was adjusted to 1 g per kg body mass. Nevertheless, some individuals might find the ingestion of this quantity of intensely sweet material unacceptable. A study by Levy *et al.*,¹³ which dismissed the ability of fructose to enhance ethanol metabolism, claimed that the attendant increases in lactate and urate were contra-indications for its use. These substances were not measured in our study. By contrast, Ylikahri *et al.*¹⁴ reported that although neither fructose nor glucose affected the rate of ethanol elimination, the intensity of intoxication, or the subsequent hangover, fructose did prevent the metabolic derangements seen with alcohol alone, such as the metabolic acidosis (due to lactate and/or ketone bodies) and hypoglycaemia.

In conclusion, our study adds weight to those reports claiming that oral fructose does indeed enhance metabolic clearance of ingested alcohol. In particular, pre-loading with fructose is an effective way of limiting the increase in blood alcohol after imbibing modest doses of alcohol.

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