Alcohol Metabolism and Its Effects

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INTRODUCTION

There is wide variation in the rate of elimination of alcohol from the body. As well as the obvious effects of such variation on the duration of intoxication, alcohol metabolism leads to the generation of possibly harmful metabolites whose steady-state concentrations depend on the rate of alcohol metabolism. Variation in alcohol metabolism is therefore of interest not only for its own sake but because of its potential consequences.

Factors affecting alcohol metabolism may be grouped into genetic, physiological, and pathological categories. Current views in each of these areas are reviewed, and the results of some experimental studies in alcohol metabolism are discussed. These reveal that alcohol metabolism can be increased by a wider range of compounds than previously thought, and that changes in concentration of metabolites in response to changes in the rate of alcohol metabolism are not predictable from simple models of the process.

Harmful alcohol consumption, and alcohol dependence, are problems which have major medical, social and personal consequences. It has become clear over the past few years that some people are particularly at risk because of inherited factors which influence alcohol use, alcohol dependence and, probably, alcohol-related organ damage. At present there is great interest in determining what these heritable factors are (even though genetic influences are far from being the only ones) using recently developed methods of pedigree analysis and the techniques of molecular biology.

One obvious area where variation between people could influence vulnerability to alcohol abuse and its consequences is in the metabolism of alcohol itself. Therefore it is appropriate to review current knowledge of normal and abnormal alcohol metabolism, before describing some experimental studies, in order to see how far two questions can be answered:

— Firstly, how can the known in-vitro properties of alcohol-metabolising enzymes account for observed features of in-vivo alcohol metabolism, and
— Secondly, can the in-vitro properties of alcohol-metabolising systems account for variation in alcohol use and in the occurrence of alcohol abuse and its consequences?

After briefly reviewing the alcohol metabolism pathway, and the characteristics of its enzymes, it will be necessary to consider how far alcohol metabolism varies between individual subjects, what the possible implications of such variation might be, and what is known about the factors which accelerate or retard alcohol metabolism.

ALCOHOL METABOLISM

The metabolism of alcohol is considered to be well understood but there may still be significant gaps in our knowledge about the functioning of this system. In particular, the factors which determine the rate of conversion of alcohol through these pathways are still not entirely understood.

It is helpful to consider alcohol metabolism firstly in the usual way, by following the pathway of the carbon skeleton of the molecule, and then by considering the various possible fates of the hydrogen atoms transferred in the first and second steps of alcohol metabolism.

Figure 1 shows the compounds and enzymes involved in the metabolism of the carbon skeleton of ethanol. As far as the formation of acetyl CoA, this is a linear pathway which has as its role (at least in humans) the elimination of ethanol and more rarely of other alcohols. The limiting step in the conversion of ethanol to acetaldehyde since the subsequent stages are catalysed by enzymes which are present in high enough concentration to match the alcohol dehydrogenase (ADH) activity.

It is not clear whether the limitation is imposed by the number of ADH molecules and their intrinsic turnover capabilities or by the metabolic environment in which the ADH molecules have to operate. Certainly the pH within the hepatocytes is quite different from the in-vitro optimum of most ADH's, and it has been suggested that substrate, cofactor or product concentrations also reduce the actual in-vivo enzyme activity. Nevertheless, it is clear from the fundamental principles of enzyme action that even if the metabolic environment is such as to hold the reaction velocity below the V_{max} the rate of reaction is still a direct function of the amount of enzyme present.

Comparisons have been made in rats of the actual in-vivo rate of alcohol metabolism and the ADH content of the rats' livers, corrected for the pH, substrate and product concentrations thought to occur in-vivo. Figure 2 shows reported results for animals subjected to three different conditions: fed, fasted and maintained on a reduced food intake for a number of days. Under each of these conditions the in-vivo rate of alcohol metabolism and the capacity calculated from in-vitro enzyme activity were close to each other and the actual rate was slightly below the theoretical maximum.

Each of the first two steps of alcohol metabolism result in the formation of NADH from NAD$^+$ partly in the cytoplasm (by ADH and by the cytoplasmic form of aldehyde dehydrogenase, ALDH-1) and partly in the mitochondria (by mitochondrial aldehyde dehydrogenase, ALDH-2). Figure 3 shows

[Figure 1. Alcohol metabolism; reactions of the carbon skeleton.

these and other reactions involving NAD⁺ and NADP⁺ which are relevant to consideration of alcohol metabolism.

Since the ADH reaction requires the conversion of NAD⁺ to NADH, either insufficient NAD⁺ or too much NADH could reduce the rate of reaction. Because NAD⁺ is present in the liver cytoplasm at concentrations around 500 μmol/L, while NADH concentrations are around 1 μmol/L, alcohol metabolism will change NAD⁺ concentrations proportionately much more than NADH concentrations to, say, 499 and 2 μmol/L, respectively. The enzyme cannot 'run out of' NAD⁺, but it might be inhibited by NADH.

Further NADH metabolism requires its transfer from the cytoplasm to the mitochondria, but NADH itself is not readily transferable. Instead, other substrates such as oxaloacetate are reduced in the cytoplasm, the product (such as malate) is transferred to the mitochondria, and a re-oxidation of malate converts mitochondrial NAD⁺ to NADH. Once in the mitochondria, the NADH is recycled to NAD⁺ through participation in oxidative phosphorylation. It has been both suggested⁴ and denied⁵ that the activity of these shuttle mechanisms may determine the sustainable rate of alcohol metabolism.

Changes in the ratio of NADH to NAD⁺ within liver cells can be monitored by measuring the ratios of other redox pairs in equilibrium with them. The high activity of lactate dehydrogenase in the cytoplasm and of β-hydroxybutyrate dehydrogenase in the mitochondria means that the peripheral blood lactate/pyruvate ratio and β-hydroxybutyrate/acetoacetate ratio reflect the cytoplasmic and mitochondrial NADH/NAD⁺ ratios, respectively.

In humans or experimental animals exposed to large amounts of alcohol, an additional alcohol-metabolising system may be induced. Like ADH, it converts ethanol to acetaldehyde but is located in the microsomal sub-cellular fraction, has a lesser affinity (higher Kₘ for ethanol, and uses NADP⁺ and molecular oxygen instead of NAD⁺. This is generally known as the microsomal ethanol-oxidising system or MEOS.

One of the main reasons for favouring the theory that NADH concentrations limit ADH activity is the fact that this can explain the action of fructose in increasing the rate of alcohol metabolism in vivo. Very few ways of accelerating alcohol metabolism are known but many papers have demonstrated that fructose can do this. The metabolism of fructose leads to the formation of glyceraldehyde and its conversion to glyceral results in the formation of NAD⁺ from NADH in the cytoplasm. The consequent decrease in NADH concentration could allow ADH to work more effectively. Other theories about the mode of action of fructose have been put forward but all depend on a central role for NADH in limiting alcohol metabolism.

**IN-VIVO ALCOHOL METABOLISM**

Figure 4 shows the changes in blood alcohol concentration with time after oral intake of various amounts of alcohol by a single subject. Several distinct phases of alcohol absorption, distribution, and elimination can be distinguished. The rate of fall in blood alcohol concentration is linear or near-linear for a considerable period, and this rate is commonly accepted as being independent of alcohol concentration or dose over the range encountered in non-alcoholic subjects. The model can be improved slightly by including some concentration dependence due to the ethanol concentration not being infinitely greater than the ADH Kₘ for ethanol, but for practical purposes the rate of alcohol metabolism can be measured by fitting a linear term to observed concentration/time data.

At low concentrations of ethanol the rate of alcohol metabolism is seen to decrease; this is almost certainly due to the concentrations approaching the ADH Kₘ, but this has not been directly shown in humans. Different subjects have ADH's with differing Kₘ's, and it should be possible to compare the in-vivo and in-vitro aspects of alcohol metabolism in this respect also.

**VARIATION IN ALCOHOL METABOLISM**

If variation in alcohol metabolism is to account for important aspects of alcohol problems, it is necessary to consider how much variation there is and what causes it. Just as one can determine the range of values for plasma cholesterol, investigate how extreme values may be associated with increased risk of disease, and study the factors which influence an individual's value, one can apply the same processes to aspects of alcohol metabolism.

Figure 5 is a frequency distribution showing the calculated rates of alcohol metabolism in approximately 400 young adult, normal subjects, from a study conducted some ten years ago. It is evident that there is quite a degree of variation — fivefold or more — between the extremes. This degree of variation in rate between subjects is corroborated by other data sets.

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Figure 4. Blood alcohol curves after varying doses of alcohol (from reference 10).

It is not yet known what the long-term consequences of being at the higher or lower end of this spectrum are, but two sorts of short-term consequences can be identified. Firstly, the faster alcohol is metabolised the shorter the duration of intoxication from a given amount of alcohol. Therefore, someone who metabolises alcohol faster will be less likely to cause a traffic accident, less likely to be involved in other accidents, fights or homicide, and less likely to incur the social consequences of intoxication; unless of course people who metabolise alcohol faster drink more in order to maintain the desired effect.

However, the rate of alcohol metabolism will also affect the rate of generation of the acetaldehyde, acetate and other metabolites of alcohol, which must in turn be removed at an equal rate. The consequence is illustrated in Figures 6 and 7. Figure 6 shows both the well-known effect of substrate concentration on the rate of an enzyme reaction and the converse; that if a certain rate of reaction is to be sustained in order to maintain the flow of substrate through several steps of a pathway, then the concentrations of the intermediate substrates will rise until they are high enough to drive the next reaction at the required rate. A hydraulic analogy is shown in Figure 7; if water runs into a tank at a fast rate then the level will rise until hydrostatic pressure forces it out of the outlet at an equal rate but, if the rate of flow of water is less, then the water level in the tank does not need to rise as high to maintain the steady state.

Therefore the faster alcohol metabolism proceeds, the higher the concentration of compounds such as acetaldehyde, acetate, NADH and possibly free radicals. Since each of these may have undesirable effects increased alcohol metabolism may be harmful, especially if it is combined with prolonged consumption to sustain some desired level of alcohol effect.

Average plasma concentrations during alcohol metabolism are approximately 1 mmol/L for acetate and 1 μmol/L or less for acetaldehyde. Hepatic concentrations are undoubtedly somewhat higher, but exact values for humans are not available. Changes in lactate/pyruvate ratios suggest that the hepatocyte cytoplasmic NADH concentrations double or triple, to perhaps 3 μmol/L. In molar terms, the concentration of alcohol in the plasma and in the liver will be around 10-20 mmol/L after moderate alcohol intake.

The K_m values for ADH's, ALDH's and acetyl CoA synthase are shown in Table 1. For the substrates other than ethanol, the K_m values are comparable with, or considerably greater than, the substrate concentrations. Steady state parameters will be determined by both the amount and the K_m of the enzymes.

Table 1. Substrate affinities and substrate concentrations during alcohol metabolism.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>K_m mmol/L</th>
<th>[S] mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>Ethanol</td>
<td>0.05-5</td>
<td>10-50</td>
</tr>
<tr>
<td>MEOS</td>
<td>Ethanol</td>
<td>10-15</td>
<td></td>
</tr>
<tr>
<td>ALDH-1</td>
<td>Acetaldehyde</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>ALDH-2</td>
<td>Acetaldehyde</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Acetyl CoA</td>
<td>Acetaldehyde</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>synthase</td>
<td>Acetate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Frequency distribution for rates of alcohol metabolism in 412 normal subjects (from reference 11).
Whereas ethanol concentrations are well above the $K_m$ values for most forms of ADH, the $K_m$ for the microsomal ethanol oxidising system (MEOS) is around 15 mmol/L and, in those subjects with substantial induction of this system, alcohol metabolism and product concentrations should increase with increasing concentration. Whether this actually occurs in humans is not clear; only a few subjects have been studied and the results are equivocal.\(^{14,19}\)

Some of the expected effects can be demonstrated from literature reports, while others have not been directly observed. No studies of metabolite levels during alcohol metabolism in large numbers of subjects appear to exist, so it cannot be ascertained how far such variation would reflect differences in alcohol metabolic rate, and hence the rate of generation of metabolites, or differences in removal. Where differences in metabolite levels have been documented between normal subjects and alcoholics they are usually secondary to damage or to enzyme induction caused by alcohol, rather than primary differences.

One exception to this generalisation is the ALDH deficiency found in many Asian populations.\(^{20}\) An abnormal form of the mitochondrial ALDH causes high levels of acetaldehyde during alcohol metabolism (see below) and unpleasant symptoms (the alcohol flush reaction). People affected by such reactions tend to avoid alcohol and are therefore protected from alcoholism. Similar reactions are far less common among Europeans but a few subjects with ALDH deficiency have been reported\(^{31}\) and a few percent of Europeans report reactions to alcohol from so far unknown causes.

The metabolites of ethanol may have undesirable effects; acetaldehyde through modification of proteins and (or) generation of false neurotransmitters; acetate by effects on the heart; and NADH by effects on fatty acid synthesis and triglyceride deposition in the liver and on gluconeogenesis, for example. Therefore, a faster rate of alcohol metabolism could have adverse effects.

**CAUSES OF VARIATION**

The causes of variation in alcohol metabolism may be classified into three groups: genetic, pathological and physiological. Since little is known about causes of variation in metabolite concentrations the main focus must be on the rate of alcohol metabolism.

**Genetic Factors**

Starting at the whole-organism level, it has been shown that a significant part of the variation in rate of alcohol metabolism in normal subjects is of genetic origin. This does not necessarily mean that there are differences between different races. In fact, most studies have found that such differences are small or non-existent after allowing for differences in body size or composition. Differences between people within the same general racial group, however, do have a genetic component. The evidence for this is based on a number of twin studies, the largest of which was referred to above and is the source of the histogram in Figure 5. By comparing the similarity of members of monozygotic ('identical') and dizygotic pairs, Martin et al.\(^{31}\) were able to establish that the heritability of rate of alcohol metabolism is around 50%.
Table 2. Kinetic properties of physiologically relevant ADH enzymes (homodimers) and their known genetic variants. Typical intracellular concentrations during alcohol metabolism are ethanol, 10 mmol/L; NAD, 500 μmol/L; and NADH, 1 μmol/L.

<table>
<thead>
<tr>
<th>Type</th>
<th>Km ETH</th>
<th>Km NAD</th>
<th>Ki NADH</th>
<th>V-max</th>
<th>pH opt</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>4.2</td>
<td>13</td>
<td>0.4</td>
<td>27</td>
<td>10.5</td>
</tr>
<tr>
<td>2-1</td>
<td>0.05</td>
<td>7.4</td>
<td>0.2</td>
<td>9.2</td>
<td>8.5</td>
</tr>
<tr>
<td>2-2</td>
<td>0.94</td>
<td>180</td>
<td>9.7</td>
<td>400</td>
<td>7.0</td>
</tr>
<tr>
<td>2-3</td>
<td>34</td>
<td>530</td>
<td>0.7</td>
<td>400</td>
<td>10.5</td>
</tr>
<tr>
<td>3-1</td>
<td>1.0</td>
<td>7.9</td>
<td>0.7</td>
<td>400</td>
<td>10.5</td>
</tr>
<tr>
<td>3-2</td>
<td>0.6</td>
<td>8.7</td>
<td>0.7</td>
<td>400</td>
<td>10.5</td>
</tr>
</tbody>
</table>

The non-genetic factors appear to vary from occasion to occasion because when some of these subjects were tested a second time the repeatability (that is, the proportion of the total observed variance due to factors constant for an individual) was very similar to the heritability (which is the proportion of the total observed variance due to genetic factors). There is therefore a need to identify non-genetic, variable influences on alcohol metabolism.

The obvious question about genetic influences on alcohol metabolism is whether they can be accounted for by known polymorphisms of alcohol dehydrogenase. ADH is made up of dimeric combinations of alpha, beta and gamma subunits coded by ADH1, ADH2 and ADH3. Variation in ADH2 and ADH3 is well described and the properties of the variants are shown in Table 2. Although many people have written about variation in alcohol metabolism and assumed that the ADH2 and ADH3 variants can account for its genetic component, this is by no means established and is in fact quite unlikely.

In the first place, the kinetic differences between ADH2-1, 2-2 and 2-3 are much greater than the differences found in-vivo on the rather small number of subjects who have been tested both by ADH typing and alcohol administration. Secondly, the gene frequency of ADH2-1 in Europeans is around 0.95 and so the rare ADH2-2 and 2-3 could not account for the heritability found in twin studies with European subjects. Thirdly, although ADH2-2 is common in Asians and ADH2-3 is reasonably prevalent in Africans, racial differences in rate of alcohol metabolism are not large and may in fact be non-existent when corrections are made for body mass and composition (see above).

Therefore other sources of genetic variation must be sought, either in the ADH structural genes, in genes controlling ADH expression, or in genes which influence the metabolic environment in which ADH works. This takes the argument back to the question of whether alcohol metabolism in-vivo is limited by the amount of ADH or by factors controlling substrate and product concentrations such as the activity of NADH shuttles.

In previous discussion it was pointed out that the amount of ADH in rats' livers was close to that required to account for in-vivo alcohol-metabolising capacity. Not surprisingly, there is little comparable data for humans but a number of reports demonstrate a range of ADH activities in human livers between different subjects. There is up to ten-fold difference between the extremes of the range, although some of this may represent sampling error because of the small amount of tissue obtained. This variation may represent some form of control of ADH expression; little is known of such mechanisms but a regulatory sequence near the ADH genes has recently been described.

**Genetic Variation in Metabolite Levels:**

**ALDH Deficiency**

The existence of an inactive, or low-activity, form of mitochondrial aldehyde dehydrogenase (ALDH2-2) in many people of Asian descent was referred to earlier. This inherited condition leads to high acetaldehyde levels during alcohol metabolism, which causes the alcohol flush reaction. For reasons which are not well understood but which presumably involve interaction between the subunits in the ALDH tetramer, the enzyme activity is low in homozygotes and heterozygotes; the condition is inherited as a dominant characteristic.

Figure 8 shows results of a comparison of blood acetaldehyde concentrations after alcohol was taken by groups of Japanese subjects of known ALDH2 genotypes. The blood alcohol curves were essentially identical in subjects homozygous for the active enzyme (ALDH2-1), heterozygous subjects, and a single subject homozygous for the inactive enzyme (ALDH2-2). In particular, the rates of alcohol metabolism and, hence, of acetaldehyde generation were the same but the concentrations of acetaldehyde were much greater when the enzyme deficiency was present — as would be expected. However, there is another unexpected and important feature of the acetaldehyde concentrations; although the rate of alcohol metabolism is constant over several hours the concentration of acetaldehyde in the blood of the ALDH2-deficient subjects peaked at about one hour after the alcohol and then fell to a much lower level. This has also been found in another study of ALDH2 deficient subjects and in non-deficient volunteers given the ALDH inhibitor calcium carbimide. Since we assume that the rate of formation of acetaldehyde is constant throughout, its rate of removal must increase after about an hour but there is no known mechanism for such an increase.

**Pathological Causes of Variation in Alcohol Metabolism**

It has been known for many years that alcoholics can metabolise alcohol faster than other people. Indeed, the amount of alcohol consumed in a day by many alcoholics could not be eliminated before the next day's drinking began unless there was an increased capacity to metabolise it. One of many studies on the rate of alcohol metabolism in alcoholics was carried out by Ugarte et al., who found that alcoholics who had been drinking up to the time of testing had an
average rate twice that of control subjects. Alcoholics absti-
nent for various times reverted to normal rates, the process
taking two to four weeks.

Another study on alcoholics and controls showed not only mea-
sured in-vivo alcohol metabolism but also measured ADH and
MEOS in liver biopsy samples. The ADH activity was not
increased in the alcoholics but the MEOS activity was and this
is in accordance with many studies in rats and other experi-
mental animals.

Induction of MEOS may not be a complete explanation of
the increased rate of alcohol metabolism in alcoholics. Enlar-
gement of the liver, which is common in alcoholics, would
allow an increased rate through the normal pathway if the
ADH concentration per gram of tissue remains normal, as was
found by Mezey and Tobin. Secondly, because the micro-
osomal system has a much higher K_i for ethanol than ADH, the
rate of alcohol metabolism should be greater at higher con-
centrations in people with substantial MEOS induction.

This concentration-rate dependence has not been thor-
oughly tested in humans. One study of a single subject
showed a greater rate of fall in blood alcohol at higher concen-
trations after four weeks consuming 4 g/kg/day (about 300 g
ethanol/day), but not during abstinence or after two weeks of
this high consumption. Another study of eight alcoholics
drinkers showed that alcohol oxidation was accelerated by the
single linear rate of fall of blood alcohol was compatible with
the observed results in six of the subjects, but the authors
commented that "statistical uncertainty gives room for up to
50% elimination via a high K_i pathway".

The question of how far microsomal ethanol metabolism
occurs in human, heavy drinkers and alcoholics is important
because of its different expected effects on NADH concen-
trations and free radical generation from the ADH pathway but
this has not been sufficiently studied.

Pathological conditions other than alcoholism do not
appear to have major effects on alcohol metabolism. Liver
disease does not generally change the rate, although subjects
with cirrhosis do have decreased ADH activity. Experimental
diseases in rats has been variably found to decrease ethanol
oxidation rate and hepatic ADH activity or to increase hepatic ADH activity. These effects may be strain-specific.

Information on human diabetes is sparse. Glycogen storage
disease Type I was found to have a dramatic effect on alcohol
metabolism in three children, increasing it about fourfold
compared to controls. However, the subjects had enlarged
livers and so it is not clear whether the cause of their increased
alcohol metabolism was biochemical or anatomical.

METABOLITE CONCENTRATIONS IN ALCOHOLICS

Three factors operating in alcoholicics will tend to change
the steady-state concentrations of metabolites during alcohol
metabolism: a greater rate of production, changes in ALDH
activity, and the operation of the microsomal pathway.

Acetaldehyde concentrations have been found to be
higher in alcoholics than in controls in several studies;
although some such findings pre-date the development of
reliable acetaldehyde methods the increase seems to be real.

The estimation of acetaldehyde has been subject to
many technical difficulties, and estimates of the circulating
acetaldehyde concentrations have fallen as techniques have
improved, but current values are probably reliable. As well as
increased rates of production of acetaldehyde from alcohol,
alcoholics have decreased concentrations of ALDH. The
quantitative importance of cytosolic ALDH in humans is not
clear, but it probably plays a significant part in acetaldehyde
metabolism despite its higher K_M because the conversion of
alcohol to acetaldehyde occurs in the cytoplasm. A few sub-
jects with a deficiency of cytosolic ALDH have been de-
cribed who experience reactions to alcohol similar to those
caused by mitochondrial ALDH deficiency and this suggests
a significant role for cytosolic ALDH.

The decrease in cytosolic ALDH appears to be secondary
to excessive alcohol consumption but it could also form part
of the vicious cycle leading to liver damage. Since acetalde-
yde is a reactive compound, it can react with free amino
groups on proteins and this may give rise to immunologically
mediated tissue damage. In this way high acetaldehyde levels
could be both a result and a cause of liver damage in alcohol-
ics, but this is only a hypothesis at present.

Acetate concentration would be expected to be higher
when alcohol metabolism is faster and indeed alcoholics
show higher concentrations than controls. This has even
been suggested as a test to distinguish between occasional
drinkers and alcoholics. Acetate is not an obviously reactive
or toxic compound and it has been used for many years in
haemodialysis fluids. However it has been suggested that it
has undesirable effects

Little is known about the hepatic concentrations of NADH
during alcohol metabolism in alcoholic humans or about
changes in [lactate]/[pyruvate] ratios. Two opposing processes
make it difficult to predict the direction of any difference
because increased rates of the ADH and ALDH reactions will
lead to more NADH being produced but the microsomal
system which is probably more active in alcoholics, uses
NADPH and produces NADP+. If the NADP+ and NAD+ systems
interchange hydrogen, then MEOS activity would lead to a lower NADH concentration in the liver. The NADH
concentrations are potentially important because of their
effects on gluconeogenesis and fatty acid synthesis but there
seems to be little information available on the actual outcome
of the two opposing trends in human alcoholics.

PHYSIOLOGICAL INFLUENCES ON ALCOHOL METABOLISM

Despite many studies, there is only one well-recognised
way of increasing the rate of alcohol metabolism in the short
term. This is by ingestion of fructose. Search of the very
extensive literature on alcohol metabolism does reveal infor-
mation suggesting that food, and possibly diet, can alter alco-
hol metabolism but many studies are difficult to interpret
because the effects of food on alcohol absorption interfere
with studies of metabolism. In 1985, however, a report
appeared showing that a meal could increase the rate of
elimination of alcohol given intravenously. Such an effect
would have to be on metabolism rather than absorption,
but its potential mechanism was unknown. Although it has been
possible to confirm the existence of such a food effect, and to
define what types of food can bring it about, the way in which
it occurs is still unknown.

The Effects of Feeding on the Rate of Alcohol Metabolism

In order to confirm the existence of the food effect and to test
different foods, a system for investigation of the rate of
alcohol metabolism was devised. Because it was known that
there is wide variation in the rate of alcohol metabolism
between different subjects, and even within the same subject
on different occasions (see above), the greatest power to detect
change would be provided by a design in which rates could
be compared before and after food (or some other challenge)
within a single occasion. This was achieved by continuous
intravenous infusion of alcohol (in saline solution) with main-
tenance of a constant blood alcohol concentration by feed-
back from breathalyser readings. Once a steady state is
reached, after the distribution of alcohol through the body, the
rate of infusion of alcohol required will be determined by the
rate of metabolism, and changes in metabolism can be fol-
lowed by recording the infusion rate.

Despite being labour-intensive, this design proved to have
a number of advantages. Firstly, the time-course and extent of
changes in alcohol metabolism can be observed, this is diffi-
cult with the more usual single-dose design. Secondly, each
subject and occasion has both pre-treatment and post-
treatment observations, giving greater statistical power. Thirdly, changes in alcohol metabolite concentrations can be measured, both over time in the fasting state and in response to induced changes in the rate of alcohol metabolism.

The first series of experiments involved comparing the effects of carbohydrate, fat and protein meals on the rate of alcohol metabolism. The rate of infusion of alcohol was plotted against time, and initially the rate was high as the alcohol was distributed through the body. After some 2.5 to 3 hours the rate of infusion required became constant, and the mean rate of alcohol infusion required is very close to the mean rate of alcohol metabolism reported in many other published papers.

After 3 hours the subjects ate one of the meals, with results which can be seen in Figure 9. After the fat or protein meals there was no significant change in the rate of alcohol metabolism, but after the carbohydrate meal the rate increased significantly. It therefore appears that the food effect is specific to carbohydrate but, because the meal had been designed to be palatable and contained a variety of carbohydrates, it was not possible to tell whether the effect was due to fructose or to other carbohydrates.

Comparison of the Effects of Glucose and Fructose

If the effect of the carbohydrate meal was due to its fructose content, then administration of glucose in equivalent amounts should have no effect on the rate of alcohol metabolism. If, on the other hand, all carbohydrates have the same effect both glucose and fructose would bring about the same increase in alcohol metabolism. Further experiments with other subjects were done to test these single carbohydrates, with ten subjects taking glucose and ten others taking fructose under the same experimental design as before.

The results are shown in Figure 10. Both glucose and fructose produced a significant increase in the rate of alcohol metabolism but the fructose effect was considerably greater.

Therefore the carbohydrate effect is not restricted to fructose but neither is it uniform across all carbohydrates. This effect of glucose on the rate of alcohol metabolism has also been demonstrated by others. The response to these carbohydrates was not the same in all subjects: some subjects showed little or no response while others showed a major increase in alcohol metabolism.

The reasons for the differences between subjects in their degree of response to carbohydrate are uncertain. With the glucose load, there was an inverse relationship between the pre-glucose rate of alcohol metabolism and the size of the increase afterwards. There was no obvious connection with habitual alcohol intake, diet or obesity but there was a relationship with glucose tolerance. Subjects who showed little or no response to alcohol metabolism to glucose had significantly higher plasma glucose values. Despite this greater stimulus to insulin release they had lower insulin values.

With the response to the fructose load, subjects with a smaller increase in alcohol metabolism had lower plasma fructose values and delayed plasma glucose and insulin curves. The differences between subjects in response to fructose may therefore be due in part to differences in intestinal absorption.

Effects of Varying Alcohol Metabolism on Metabolite Concentrations

The use of fructose or glucose allows us to study the effects of increased alcohol metabolism on the steady-state concentrations of alcohol metabolites; as discussed above the concentrations should rise in step with the faster alcohol metabolism and then decline as the carbohydrate effect wears off. This has been done for two metabolites: acetate, as measured in the plasma, and NADH measured indirectly by changes in the blood lactate/pyruvate ratio.

Effects of Glucose and Fructose on Acetate

Acetate was measured enzymatically on plasma samples from the subjects in the glucose and fructose studies. As explained above, and as predicted from comparison of acetate concentrations in alcoholic and control subjects metabolising alcohol, the acetate concentration was expected to
increase in parallel with the increased rate of flow of substrate through the alcohol metabolism pathway.

The results after fructose were generally in line with this expectation, but the stimulus to alcohol metabolism provided by glucose did not have the same effect. In the group as a whole, and in both the responding and non-responding subjects, acetate concentrations remained steady after glucose, at the same levels as were seen during fasting alcohol metabolism. Logic therefore requires that acetate disposal must have increased in direct proportion to its production from alcohol, and also that glucose did not increase acetate metabolism in those subjects in which it did not increase alcohol metabolism. The mechanisms which could lead to such a balanced effect are unknown.

The Lactate/Pyruvate Ratio and the Mechanism of Action of Fructose

As outlined earlier, theories of the mechanism of fructose augmentation of alcohol metabolism depend on NADH concentrations limiting ADH activity, with fructose lowering the hepatocyte cytoplasmic NADH concentration in some way.

If this was so, fructose metabolism would tend to decrease the NADH concentration below its maximum sustainable level and the rate of alcohol metabolism (and of NADH generation) would increase until the NADH concentration was again limiting ADH activity. NADH concentration would not rise beyond its pre-fructose value.

If on the other hand the concentration of NADH simply reflects its rate of generation, as is thought to occur for acetate in alcoholics, then an increase in the rate of alcoholic metabolism would lead to an increase in NADH concentration and therefore to an increase in the blood lactate/pyruvate ratio. The behaviour of the lactate/pyruvate ratio after fructose provides a test of these two hypotheses. Although many studies of the effects of fructose on alcohol have been published, only one appears to have included lactate/pyruvate ratio measurements. In that study the mean ratio fell slightly after fructose but no test of significance was reported and the authors expressed doubt about the reliability of the ratio results.

The results of our study are summarised in Figure 11. The lactate/pyruvate ratio rose from pre-alcohol values after the alcohol infusions commenced and remained at a constant value during the period of fasting alcohol metabolism. This is consistent with increased NADH generation from alcohol during this phase, with the increased concentration increasing cytoplasmic-mitochondrial transfer and a new steady state being established. After the subjects took fructose, and their rate of alcohol metabolism increased, the lactate/pyruvate ratio (and, by inference, the hepatic cytosolic NADH concentration) rose further. There were significant differences from the pre-fructose value at 30, 60, 90 and 120 min after fructose. This shows that the NADH concentration does not limit alcohol metabolism (a conclusion which several other studies support) and that the mechanism of action of fructose is not the one which has been previously accepted.

CONCLUSIONS

Two questions were posed earlier and these related to the correspondence between in-vitro and in-vivo features of alcohol metabolism, and to possible connections between alcohol metabolism and alcohol-related disease.

It appears that there are still some quite fundamental questions about in-vivo phenomena of alcohol metabolism which are unanswered. Some of the experiments described make it difficult to fully accept either of the competing theories on the limitation of the rate of alcohol metabolism; if the amount of ADH is limiting then how do carbohydrates increase alcohol metabolism in the comparatively short time-scale observed? The rise and fall in the rate within two to three hours makes it unlikely that synthesis of ADH is the mechanism. But if on the other hand it is the metabolic environment which determines the activity of ADH, what changes are occurring to lift the activity by 50-100% in some subjects, to levels above the apparent capacity of the amount of enzyme as measured in vitro? Changes in NADH concentration do not seem able to afford an acceptable explanation.

Related to this issue is the mechanism of the carbohydrate effect: how do fructose and glucose exert their effects? Why do they have major effects in some subjects and none in others?

Further down the metabolic pathway, other questions remain. Why does blood acetaldehyde fall (from its initial peak) during alcohol metabolism in ALDH-deficient subjects? Why is alcohol elimination faster in alcoholics? How does administration of acetate increase the metabolism of alcohol?

The second question related to alcohol-metabolising systems and alcohol abuse is variation in alcohol metabolism significant in determining variation in alcohol use, susceptibility to intoxication, alcohol dependence and alcohol-related disease?

With the exception of aversive experiences which make it unlikely that some people will ever expose themselves to hazardous amounts of alcohol (the ‘alcohol flush reaction’), there is little evidence for any link between alcohol metabolism and alcohol use, abuse and dependence. In the case of the physiological consequences of alcohol abuse, however, the situation is likely to be different. The effects of alcohol metabolism (and variation in the rate of alcohol metabolism) on the concentrations of many compounds in the liver and, secondly, the fact that the liver is the main site of alcohol metabolism and also an organ most frequently damaged by alcohol abuse, make it more likely that variations in alcohol metabolism under the variation in susceptibility to disease caused by alcohol.

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REFERENCES


