Effects of alcohol on tryptophan metabolism

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Introduction

Tryptophan is the most extensively studied amino acid in relation to alcohol and alcoholism. This is probably most likely because it is the precursor of the cerebral indoleamine 5-hydroxytryptamine (5-HT), which is believed to be involved in neurotransmission and the regulation of mood and possibly also certain other behaviours. In this short account, both experimental and clinical studies will be reviewed and further work in relation to a number of important clinical aspects of alcoholism will be suggested, but first, it may be useful briefly to review the major factors controlling tryptophan metabolism itself. The most recent detailed review of the biochemistry of tryptophan in health and disease is by Bender (1983).

Tryptophan metabolism

Tryptophan circulates in blood mainly bound to proteins and, as is the case with other physiologically active protein-bound substances, it is the free fraction that is thought to be available for tissue uptake. Tryptophan is catabolized in mammals by at least four known pathways (Fig. 1). Both the decarboxylase- and aminotransferase-catalysed pathways are of little quantitative importance (see Young et al., 1978; Stanley et al., 1984). Similarly, the 5-HT biosynthetic pathway in brain, and to a lesser extent in the gut, is also of minor quantitative significance. The cerebral pathway is, however, of considerable physiological and pharmacological importance, because of the possible involvement of 5-HT in neurotransmission, mood regulation and possibly also other cerebral functions. By contrast with these three minor pathways, the hepatic kynurenine-nicotinic acid pathway is the major route of tryptophan degradation and cofactor activation by haem. Major functions of the tryptophan pyrrolase include the control of tryptophan degradation and cofactor activation by haem.

The hepatic kynurenine pathway is controlled by the activity of the first enzyme, the cytosolic haemoprotein tryptophan pyrrolase (tryptophan 2,3-dioxygenase. EC 1.13.11.11), the functions and regulation of which have previously been reviewed (Badawy, 1977, 1979, 1984). Briefly, tryptophan pyrrolase activity can be regulated by at least three major mechanisms: hormonal induction by glucocorticoids, substrate activation and stabilization by tryptophan and cofactor activation by haem. Major functions of the pyrrolase include the control of tryptophan degradation and hence, among other things, its availability for a number of physiological processes, notably hepatic NAD\(^+\) and cerebral 5-HT synthesis, and also the utilization of liver haem. Recent evidence (Salter et al., 1986) suggests that the flux of tryptophan through the hepatic kynurenine pathway is controlled largely by tryptophan pyrrolase activity and to a lesser extent by transport across the plasma membrane, with no control being exerted by subsequent enzymes, such as kynureninase or kynurenine hydroxylase.

The cerebral 5-HT biosynthetic pathway is also controlled by the activity of the first enzyme, tryptophan hydroxylase, but because this enzyme exists partially unsaturated with its tryptophan substrate, it is believed that cerebral 5-HT synthesis is determined mainly by brain tryptophan concentration (see Fernstrom & Wurtman, 1971; Carlson & Lindqvist, 1978; Curzon, 1979). It follows, therefore, that peripheral factors controlling tryptophan availability to the brain must play important roles in cerebral 5-HT synthesis. These peripheral factors include: (1) tryptophan binding to circulating proteins; (2) the extent of competition between tryptophan and the other five amino acids (Leu, Ile, Val, Phc and Tyr) known to share the same cerebral uptake mechanism; and (3) the activity of the major tryptophan-degrading enzyme, liver tryptophan pyrrolase.

Effects of ethanol on tryptophan metabolism

Very little is known about the possible effects of ethanol on tryptophan decarboxylation or transamination or its conversion in the pineal to melatonin. Thus ethanol inhibits in vitro the hepatic oxidation of tryptamine to indol-3-ylacetic acid (Asaad et al., 1974), whereas after its chronic consumption, but not during subsequent withdrawal, it decreases rat pineal melatonin synthesis by some as yet unidentified mechanism (Moss et al., 1986). By contrast, much more is known about the effects of ethanol on tryptophan metabolism by the kynurenine and 5-HT pathways (for reviews of various aspects, see Badawy & Evans, 1974b; Hunt & Majchrowicz, 1979; Nutt & Badawy, 1986). It should, however, be emphasized here that most of the previous work has led to contradictory conclusions and this can largely be explained on the basis of differences in species and/or strains of animals used, doses of ethanol and routes of administration after, its administration or consumption and choice of appropriate control treatments and of methods of assessment of some aspects of metabolism, e.g. 5-HT turnover rate.

Acute effects in animals. When some of these issues were addressed, it was found (Badawy & Evans, 1976b) that, in the rat, whose tryptophan metabolism resembles more closely that of man, acute ethanol administration exerts a biphasic effect on cerebral 5-HT synthesis, consisting of an initial enhancement followed by an inhibition, caused by an appropriate alteration in tryptophan availability to the brain. The initial increase in this availability is caused by a lipolysis-dependent non-esterified-fatty-acid-mediated displacement of serum-protein-bound tryptophan resulting in an elevation of the circulating free amino acid concentration, whereas the subsequent decrease in tryptophan availability to the brain is due to increased hepatic degradation of the amino acid by tryptophan pyrrolase, the activity of which is enhanced by a substrate-type mechanism following the above increase in circulating free tryptophan concentration. These results suggest that the rate of tryptophan hydroxylation in brain in vivo should be enhanced, then inhibited, by ethanol. This has not been examined, except at 50–60 min after ethanol administration, when no change could be demonstrated (Carlsson & Lindqvist, 1973; Engel & Rydelberg, 1985) at such a relatively early time interval.

The mechanism(s) by which acute alcohol administration enhances rat liver tryptophan pyrrolase activity has been the subject of controversy. Thus, whereas we consistently obtained evidence for a substrate-type enhancement in fed (Badawy & Evans, 1973a,b, 1975, 1976b, 1977) andstarved rats (A. A.-B. Badawy, C. J. Morgan & N. R. Davis, 1988).
unpublished work), Rouach et al. (1980) demonstrated a tryptophan-like effect of ethanol only in starved rats, and the group of Morland (Stowell et al., 1983; Morland et al., 1985) obtained evidence for a hormonal induction mechanism in starved rats, but failed to demonstrate activation after oral administration to fed animals. Some of these differences could be explained on methodological and/or metabolic grounds, whereas others require further experimental scrutiny.

Although acute ethanol administration enhances liver pyrrolase activity in rats, its effect in mice is strain-dependent (Badawy & Evans, 1976b) and is absent in species, such as the guinea-pig and golden hamster, known to lack permanently the free apoenzyme form (Badawy & Evans, 1974a, 1976a).

Acute effects in man. Most of the available information concerns the shift in 5-HT metabolism from the major oxidative to the minor reductive (that leading to the formation of 5-hydroxytryptophol) pathway demonstrated by Davis & Walsh (1971) and reviewed by Hunt & Majchrzack (1979), and more recently, the effects of ethanol on circulating tryptophan concentrations. Eriksson et al. (1983) reported that acute ethanol consumption by normal male volunteers lowers plasma tryptophan concentration and also those of most other circulating amino acids. Under somewhat different experimental conditions, we (Badawy et al., 1987, 1988) found that acute ethanol consumption by fasting (12 h) normal male volunteers decreases circulating free and total tryptophan concentrations, without altering its binding to serum protein. This may be explained by ethanol enhancing hepatic tryptophan pyrrolase activity. The mechanism of such a possible enhancement is unlikely to be glucocorticoid or substrate mediated, because of the absence of any increases in concentrations of circulating cortisol and tryptophan. Co-factor activation (by haem) is therefore a more likely possibility. We also found that tryptophan availability to the brain, as determined from the ratios of the concentrations of free or total tryptophan to the sum of those of the five other competitors, was decreased by ethanol, in comparison with ratios in control subjects. This strongly suggests that acute ethanol consumption may, by decreasing tryptophan availability to the brain, inhibit cerebral 5-HT synthesis and possibly also turnover.

Chronic and withdrawal effects in animals. As stated above, the contradictory literature concerning the effects of chronic administration and subsequent withdrawal of ethanol on tryptophan and 5-HT metabolism can be explained largely on methodological grounds (see Badawy et al., 1979, 1980, and references cited therein). Inhibition of rat liver tryptophan pyrrolase activity by chronic ethanol administration was first reported from this laboratory (Badawy & Evans, 1973a,b) and subsequently confirmed by Morland (1974), but not by Brachey & Lieber (1982), who observed a moderate enhancement. Both these latter two groups of investigators administered ethanol in a liquid diet, whereas we provided it in drinking water. Subsequent studies have revealed that this inhibition is produced by NAD(P)H secondarily to the metabolism of ethanol by NAD+−dependent alcohol dehydrogenase (Badawy & Evans, 1975, 1979; Evans & Badawy, 1977; Punjani et al., 1979), and causes an increase in tryptophan availability to the brain, leading to an enhanced 5-HT synthesis (Badawy et al., 1979; Punjani et al., 1979; Badawy et al., 1980). It is noteworthy that chronic ethanol administration to guinea-pigs or golden hamsters does not inhibit pyrrolase activity, but causes a moderate enhancement (Badawy & Evans, 1975). By contrast with the above chronic effects, we found (Badawy & Evans, 1973a,b, 1975; Badawy et al., 1980) that in rats ethanol withdrawal causes an enhancement of liver tryptophan pyrrolase activity leading to a decrease in the availability of circulating tryptophan to the brain with a consequent inhibition of cerebral 5-HT synthesis. The pyrrolase enhancement during withdrawal appears to be of the hormonal-type and this is further suggested by the observed correlation with the elevation of circulating corticosterone concentration.

Chronic and withdrawal effects in man. Relatively more work has been done on tryptophan and 5-HT metabolism in chronic alcoholics, as compared with acute studies in normal subjects. As regards the hepatic kynurenine−nicotinic acid pathway, Walsh et al. (1966) found that some, but not all, chronic alcoholics, examined within 24 h of cessation of alcohol intake, excrete decreased amounts of kynurenine metabolites in urine, and Payne et al. (1974) also suggested from dietary tryptophan and nicotinic acid correlation studies that alcoholics exhibit abnormalities in tryptophan metabolism that may be of a metabolic or genetic nature. Studies involving the urinary excretion of the major 5-HT metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA) have led to contradictory findings, with a decrease (Olson et al., 1960), an increase (Borg et al., 1983) and no change (Murphy et al., 1962) having all been reported. Also it was recently shown (Thomson & McMillen, 1987) that chronic abstinent alcoholics exhibit decreased ratios of urinary concentrations of 5-HIAA to those of indol-3-ylacetic acid or
anthranilic acid (the latter two being metabolites of the
decarboxylation and kynurenine pathways, respectively),
thus suggesting that alcoholics have a defective 5-HT path-
way. More consistent findings have been obtained by
measuring cerebrospinal fluid 5-HIAA concentrations,
which is decreased in chronic alcoholics who have been
abstinent for 4–12 weeks, as compared with controls or alco-
holics both in the immediate post-intoxication phase of 2
days and subsequently (Ballenger et al., 1979; Borg et al.,
1983, 1985). Abstinent alcoholics also appear to have lower
plasma tryptophan concentrations and ratios to other
competitors and this can be correlated to the presence of
aggressive behaviour (Branchey et al., 1984), hallucinations
(Branchey et al., 1985) or epilepsy (Marion et al., 1985).
Whether chronic ethanol consumption itself influences circu-
lating tryptophan and/or CSF 5-HIAA concentration
remains to be determined. Recently, Diehl et al. (1986)
found that chronic alcoholics generally have decreased plasma
concentrations of tryptophan, the five other competitors and
most other amino acids and suggested that this may be due to
nutritional deficiencies. It will clearly be important to assess
the role of such deficiencies in relation to any possible
specific effects of alcoholism itself on tryptophan availability
to the brain.

General conclusions and comments

The above account has demonstrated that tryptophan
metabolism and disposition are influenced by acute and
chronic ethanol consumption and subsequent withdrawal.
5-HT is thought to regulate mood and certain other behav-
iours and a disturbance in its cerebral metabolism and func-
tion has been implicated in conditions, such as aggression,
anger and depression, known to be clinical and/or
behavioural features of alcoholism and alcohol abuse.
Another important functional aspect of 5-HT is its possible
involvement in alcohol preference and/or predisposition to
alcohol consumption (for recent review, see Narango et al.,
1986) and, hence, dependence. The human data, however
scanty, and the experimental findings reviewed here may be
of considerable importance in relation to these aspects and it
is therefore hoped that further work addressing these and
related issues will be fruitful.

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