ALCOHOL, AGGRESSION AND SEROTONIN: METABOLIC ASPECTS

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Abstract — The role of serotonin (5-hydroxytryptamine) in alcohol-induced aggressive behaviour is discussed. Considerable evidence exists in support of an association between aggression and serotonin deficiency and between aggression and alcohol consumption, and it is also known that alcohol consumption exerts major effects on serotonin metabolism. These links are synthesized into the serotonin deficiency hypothesis of alcohol-induced aggressive behaviour, which postulates that individuals susceptible to aggression after alcohol consumption exhibit a marked depletion of their brain serotonin rendering them prone to aggression in response to environmental or psychological stimuli or situations. This hypothesis has already received support from experimental studies in non-aggressive subjects, but remains to be examined in those known to be aggressive after alcohol consumption.

INTRODUCTION

It is clear from the preceding paper (Pihl and LeMarquand, 1998) and indeed most of the other papers in this issue that a strong direct relationship exists between alcohol consumption and aggressive behaviour. That an equally robust, but inverse, relationship exists between aggression and the cerebral indolylamine 5-hydroxytryptamine (5-HT or serotonin) both in experimental animals and in man in general and in relation to alcohol consumption in particular has also been amply demonstrated in a considerable array of experimental and clinical studies (for references, see Pihl and LeMarquand, 1998). As regards the role of serotonin deficiency in alcohol-induced or -related aggressive behaviour in man, most studies have been performed in the USA by the group led by Dr M. Linnoila, but also by other groups (reviewed by LeMarquand et al., 1994a and Pihl and LeMarquand, 1998), and involved a clear demonstration of low concentrations of the 5-HT major metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA) in cerebrospinal fluid (CSF) of subjects with a history of aggressive behaviour related to alcohol abuse and alcoholism, strongly suggesting that aggressive or violent behaviour is associated with a decreased cerebral 5-HT turnover. These studies by Linnoila and other researchers have therefore been instrumental in linking alcohol-induced aggression with a serotonin deficiency and have thus set the stage for the further development of the serotonin deficiency hypothesis of alcohol-induced aggression through mechanistic studies which should aim at identifying the precise metabolic cause of this deficiency. Elucidation of such a mechanism(s) is likely to lead to the primary event underlying the serotonin deficiency of alcohol-related aggression and thus facilitate the development of effective screening, preventative and therapeutic strategies in this important area of general, forensic, and psychological medicine. In this article, the serotonin deficiency hypothesis of alcohol-induced aggressive behaviour will first be outlined. This will then be followed by a brief description of serotonin metabolism and its control, the effects of alcohol on serotonin and related metabolism, and finally a description of experimental and other studies illustrating the importance of metabolic investigations in examining the serotonin status in alcohol-induced aggression.

THE SEROTONIN DEFICIENCY HYPOTHESIS OF ALCOHOL-INDUCED AGGRESSION

The major question facing investigators of serotonin metabolism in the context of the relationship between alcohol consumption and aggressive behaviour is how does alcohol influence serotonin metabolism and function to pre-
ACtication aggressive behaviour? Since aggression is associated with a reduced function and depletion of serotonin (see Pihl and LeMarquand, 1998, and references cited therein), it must be assumed that alcohol-induced aggression involves depletion of serotonin following alcohol intake. Also, since some, but not all, alcohol-consuming subjects exhibit aggressive behaviour following alcohol consumption, it is reasonable to suggest that this 'subgroup' may be particularly vulnerable to a possible serotonin-depleting effect of alcohol consumption. I should like to propose a serotonin deficiency hypothesis of alcohol-induced aggression, and postulate that susceptible subjects have a greater sensitivity or responsiveness to an acute serotonin-lowering effect of alcohol intake. Such a greater sensitivity or responsiveness may represent a serotonin—biosynthetic pathway that may be: (1) of normal activity, but either labile or vulnerable to inhibition by alcohol; (2) borderline at the lower normal level or even lower than normal and therefore more likely to be modulated further by alcohol. In either case, susceptible individuals would be expected to exhibit a greater depletion of brain serotonin following alcohol consumption and could therefore be prone to episodes of aggression in response to minor environmental or psychological provocative stimuli or situations. To test this hypothesis, it is necessary first to establish any likely basal differences (i.e. in the absence of alcohol intake) in serotonin metabolism and function between normal (non-aggressive) control subjects (i.e. those exhibiting no aggressive behaviour following alcohol consumption) and those known to exhibit aggression following alcohol consumption, then to examine the effects of an acute alcohol challenge test on the serotonin—biosynthetic pathway in normal subjects and compare this with the response of subjects susceptible to alcohol-induced aggression. Before describing the few studies performed so far in this area, it may be useful to give a brief account of serotonin metabolism and its modulation by alcohol consumption.

**SEROTONIN METABOLISM AND ITS CONTROL**

Brain 5-HT is synthesized from the amino acid precursor L-tryptophan (Trp) through a two-step process: hydroxylation to 5-hydroxytryptophan by the action of Trp hydroxylase, followed by decarboxylation of 5-hydroxytryptophan to 5-HT by the action of aromatic L-amino acid decarboxylase. 5-HT is broken down mainly to its major oxidative metabolite 5-HIAA by the consecutive actions of monoamine oxidase and aldehyde dehydrogenase. A little serotonin is converted in the brain into the minor reductive metabolite 5-hydroxytryptophol and in the pineal gland into the important physiological mediator melatonin (N-acetyl-5-methoxytryptamine).

Although Trp hydroxylase is the rate-limiting enzyme of the 5-HT—biosynthetic pathway, brain Trp concentration ([Trp]) is physiologically the most important single factor controlling serotonin synthesis. This is because Trp hydroxylase is unsaturated with its Trp substrate (i.e. the physiological concentration of Trp in the brain is well below the \( K_m \) value of the enzyme at which it can hydroxylate Trp at only half its maximal speed) (Fernstrom and Wurtman, 1971; Carlsson and Lindqvist, 1978; Curzon, 1979). It follows therefore that peripheral factors influencing circulating Trp availability to the brain must play important roles in the control of cerebral 5-HT synthesis. These factors include: (1) extent of binding of Trp to circulating albumin and its modulation by the physiological displacers of albumin-bound Trp, namely non-esterified fatty acids (NEFA) (Curzon and Knott, 1974); (2) extent of competition between Trp and five other circulating amino acids (Val, Leu, Ile, Phe, and Tyr), collectively known as the competing amino acids (CAA), for the same cerebral uptake mechanism (Fernstrom and Wurtman, 1971); (3) activity of the major Trp-degrading enzyme, liver Trp pyrroline (Trp 2,3-dioxigenase), the first and rate-limiting enzyme of the quantitatively most important Trp-degradative route, the hepatic kynurenine—nicotinic acid pathway (Badawy, 1977). In human metabolic studies, assessment of the serotonin—biosynthetic status must take into consideration all these three factors, through determination of the concentrations of circulating free (diffusible) Trp, total (free + albumin-bound) Trp, albumin, NEFA, kynurenine (the major Trp-oxidative product of the pyrroline-controlled hepatic—kynurenine pathway) and the [Trp]/[CAA] ratio, which is the most accurate predictor of brain Trp, and hence 5-HT, changes. The following two sections will describe briefly the
effects of alcohol intake on serotonin metabolism in experimental animals and in man respectively; the findings in experimental animals are described here only to illustrate the variety of the ethanol effects and also as models for some of the effects observed in man. Studies of the effects of alcohol on serotonin receptors and related functions, which have previously been reviewed (LeMarquand et al., 1994a,b), will not be described here and do not appear so far to have thrown a significant light on the influence of ethanol on serotonin status.

EFFECTS OF ALCOHOL ON SEROTONIN METABOLISM IN EXPERIMENTAL ANIMALS

Such effects are complex and varied and depend in the first place on whether alcohol has been administered acutely in a single dose or chronically over a long period, and, in the latter case, whether studies have been performed during chronic treatment or subsequent withdrawal. Other important factors determining the ethanol effects on animal brain serotonin metabolism are the dose of ethanol and route of its administration, animal species tested, nutritional status, and methods of assessment of the parameters tested, such as 5-HT turnover. The effects of alcohol on animal brain serotonin have been reviewed in recent years (Badawy, 1988; LeMarquand et al., 1994b) and it is generally accepted that, in the most extensively studied species, the rat, whose Trp and serotonin metabolism resemble most closely that of man, acute ethanol administration exerts a biphasic effect on brain 5-HT synthesis and turnover; an initial enhancement followed by an inhibition (Badawy and Evans, 1976). The initial enhancement is due to a lipolysis-dependent catecholamine-mediated displacement of albumin-bound Trp and a consequent increase in circulating free Trp availability to the brain, whereas the later inhibition of 5-HT synthesis and turnover is due to a decrease in Trp availability to the brain secondary to Trp activation of liver Trp pyrrolase. Rat brain 5-HT synthesis and turnover are also enhanced by chronic ethanol administration (Badawy et al., 1979), but are inhibited during subsequent withdrawal (Badawy et al., 1980; Bano et al., 1996). Here again, the changes in cerebral 5-HT synthesis and turnover are caused by corresponding changes in circulating Trp availability to the brain produced respectively by inhibition and induction of liver Trp pyrrolase activity during chronic treatment with, and subsequent withdrawal of, ethanol respectively. Liver Trp pyrrolase therefore appears to play a major role in the effects of ethanol on brain serotonin synthesis in the rat. As will be seen below, there is evidence suggesting that liver Trp pyrrolase may also be a target of ethanol in man.

EFFECTS OF ALCOHOL ON SEROTONIN METABOLISM IN MAN

The best known effect of alcohol on serotonin metabolism in man is the ability of acute consumption of this drug to divert the metabolism of 5-HT from its main oxidative (that leading to production of 5-HIAA), to its minor reductive (that leading to production of 5-hydroxytryptophol), pathway (Davis et al., 1967). A major application of this diversion is the use of the urinary \[5\text{-hydroxytryptophol}/5\text{-HIAA}\] ratio as a sensitive laboratory marker of current and recent alcohol intake in relation to monitoring alcohol consumption, compliance with treatment during, and relapse after, abstinence (Helander et al., 1994). This diversion is generally thought to occur mainly in the periphery, and to a much lesser extent in the brain. Much less is known about the effects of acute or chronic alcohol intake or subsequent withdrawal on human brain 5-HT metabolism. Although the chronic effects generally determine the serotonin status in chronic alcoholism and hence likely the response of such patients to situations which may lead to aggressive behaviour, it is the acute effects of alcohol intake which may be more important in this context, particularly in non-dependent (normal) subjects. In control subjects, acute ethanol consumption has been shown (Badawy et al., 1995) to decrease circulating Trp availability to the brain, as determined from the \[\text{Trp}/\text{CAA}\] ratio; an effect almost certain to lead to a decrease in brain [Trp] and hence in 5-HT synthesis and turnover. This decrease in the ratio was found to be due to a decrease in [Trp], rather than to an increase in the [CAA]. The decrease in [Trp] was quantitatively the same for both the free (ultrafiltrable) and total (free + albumin-bound) fractions, and was thus not associated with altered Trp binding to
albumin. Such a profile is characteristic of enhancement of liver Trp pyrrolase activity and it is therefore most likely that acute ethanol intake by humans decreases brain serotonin synthesis by activating liver Trp pyrrolase, an effect similar to that described earlier in studies in rats. For ethical reasons, the effects of acute ethanol intake could only be studied in non-abstinent (but not in abstinent) chronic alcoholic subjects. In the former subjects, such studies have started in this laboratory, and preliminary evidence suggests that ethanol is incapable of lowering circulating Trp concentrations in non-abstinent alcoholics; a finding which also suggests that liver Trp pyrrolase activity may be inhibited in non-abstinent chronic alcoholics, as is the case in chronically ethanol-treated rats (Badawy et al., 1979, 1980). Such a possible inhibition in man has been suggested from previous oral Trp loading studies in chronic alcoholic subjects demonstrating decreased urinary excretion of Trp metabolites of the kynurenine pathway within the first 24 h of cessation of alcohol intake (Walsh et al., 1966) and decreased serum kynurenine levels in the immediate post-detoxification phase, in comparison with a month later (Friedman et al., 1988). In this latter study, it was also found that serum kynurenine levels following oral Trp loading remained elevated in alcoholics who were still abstinent at 3 months, but were decreased again in those who relapsed into heavy drinking, thus confirming the pyrrolase-inhibitory effect of chronic alcohol intake and also suggesting that alcoholics may have a higher liver Trp pyrrolase activity when not drinking. Trp availability to the brain was not studied by the above two groups, but it is tempting to suggest that brain 5-HT synthesis will have been altered secondarily to the above modulation of liver Trp pyrrolase activity, and to speculate that chronic alcoholics may have a serotonin defect induced by a high liver Trp pyrrolase activity and that alcohol intake may represent a means of ‘self-medication’ to correct such a serotonin defect through pyrrolase inhibition. Studies in support of these possibilities are in progress, but will not be discussed here, as they fall outside the immediate scope of this article. Studies by other research groups demonstrating the modulation of the serotonin status in chronic alcoholism have also been performed (for review, see LeMarquand et al., 1994a).

EXPERIMENTAL STUDIES IN SUPPORT OF THE SEROTONIN DEFICIENCY HYPOTHESIS OF ALCOHOL-INDUCED AGGRESSION

In the study by Badawy et al. (1995), the decrease in circulating Trp availability to the brain observed in normal (non-aggressive) subjects was of the order of 20% in the [Trp]/[CAA] ratio and 25% in [Trp] after oral intake of a moderate dose of ethanol (0.8 g/kg body wt). As shown in Fig. 1, the maximum decreases in free and total serum [Trp] occurred at 1.5–2 h after intake of this dose of ethanol, and were followed by recovery towards 3 h after intake. This dose of ethanol (equivalent to 2–2.5 pints of normal-strength beer) produced at 1 h an average blood alcohol level (75–78 mg/dl) just below the official legal limit in the UK (80 mg/dl). Such a level is achievable under most normal ‘social drinking’ conditions and it is therefore very likely that, under such conditions, most social drinkers will experience a decrease in the rate of synthesis of their brain serotonin of about 20%. Since such a possible decrease is not accompanied in the majority of social drinkers with aggressive behaviour or a feeling of dysphoria, it could be argued that the brain can maintain its control of mood and impulses in the presence of this moderate inhibition of serotonin synthesis. The serotonin deficiency hypothesis of alcohol-induced aggression postulates that, in susceptible individuals, the decrease in brain serotonin synthesis may well be stronger, perhaps of the order of 40–60%, such that acute serotonin depletion of this order triggers an episode of aggressive behaviour, perhaps accompanied by negative mood, since 5-HT also appears to play a major role in the control of mood and features prominently in the monoamine hypothesis of affective disorders (for review, see van Praag, 1978). A stronger depletion of brain serotonin in susceptible (aggressive) individuals, compared with that observed in controls, could occur under two major sets of physiological conditions: (1) if their serotonin–biosynthetic status is already lower than normal or is in the borderline lower normal range, such that an additional 20% or so depletion after alcohol intake results in an additional (further) depletion; (2) if their metabolic pathways are more sensitive to modulation by alcohol intake (e.g. if their liver Trp pyrrolase is more sensitive to activation by alcohol, or if alcohol additionally
Experimental studies in support of the serotonin deficiency hypothesis of alcohol-induced aggressive behaviour have involved the use of the technique of acute tryptophan depletion (ATD), which causes acute depletion of brain 5-HT secondarily to depletion of circulating Trp following oral intake of an amino acid mixture deficient in Trp. Under these conditions, Trp, and hence serotonin, depletion can be shown to induce a negative mood in normal subjects (Young et al., 1988) and to cause reversal of antidepressant-induced remission in patients with depression (Delgado et al., 1990). By using this technique in healthy volunteers, increased aggressive responding was observed in studies involving physical or psychological provocation (Cleare and Bond, 1995; Pihl et al., 1995; Moeller et al., 1996), but not in those not involving such provocation (Smith et al., 1987; Salomon et al., 1994). Other experimental studies with acute Trp depletion have also demonstrated aggressive behaviour in subjects with high pre-existing hostile or antisocial characteristics (for references, see Pihl and LeMarquand, 1998). As regards alcohol-induced aggression, Pihl et al. (1995) found that lowering brain serotonin through acute Trp depletion resulted in subsequent alcohol intake becoming capable of increasing aggressive behaviour in the Taylor task experimental model, with alcohol and Trp depletion producing independent additive effects. The mechanism of such an additive effect is not understood at present. However, it seems that alcohol intake acts as a provocative stimulus to induce aggressive behaviour in Trp-depleted (serotonin-deficient) subjects. According to the serotonin deficiency hypothesis, it is possible that, under these conditions, alcohol intake may cause a strong depletion of brain serotonin and thus induce aggression. It is tempting to speculate that these psychological or physical provocations may also induce a further serotonin depletion. These possibilities are amenable to laboratory investigation.

GENERAL CONCLUSIONS AND COMMENTS

It is clear from these experimental and preliminary studies that serotonin deficiency may be an important factor in alcohol-induced aggressive
behaviour. Detailed metabolic studies aimed at establishing the serotonin status and associated metabolism, particularly Trp disposition and availability to the brain, in conjunction with experimental, behavioural and clinical investigations of the role of serotonin in alcohol-induced aggressive behaviour are likely to improve our understanding of the biological basis of aggressive behaviour and of the mechanisms governing the role of alcohol intake in induction of such behaviour, thus facilitating laboratory and other means of identification of subjects susceptible to alcohol-induced aggressive behaviour and enabling the development of effective and more rational therapeutic and preventative strategies in this area of medicine. Thus, basal differences in the Trp-metabolic and serotonin status between controls and subjects known to exhibit aggression after alcohol consumption need to be identified, as should likely differences in this status between these two groups of subjects following acute alcohol intake. The possibility that such likely basal or alcohol-induced differences could form the basis of a laboratory screening test for identification of subjects at risk from alcohol-induced aggression should also be explored. Finally the possibility that subjects predisposed to alcohol-induced aggression could benefit from targeting for nutritional and/or pharmacological intervention aimed at correcting a possible Trp—serotonin defect should be a further aim. Further studies along these and related clinical lines aimed at addressing these important issues may therefore be fruitful.

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