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Alcohol and Violence and The Possible Role of Serotonin

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ABSTRACT

There is undisputed evidence linking alcohol consumption and violence and other forms of aggressive behaviour, and also linking aggression with dysfunction of the brain indolylamine serotonin (5-hydroxytryptamine or 5-HT). Alcohol consumption

also causes major disturbances in the metabolism of brain serotonin. In particular, acute alcohol intake depletes brain serotonin levels in normal (non-alcohol-dependent) subjects. On the basis of the above statements, it is suggested that, at the biological level, alcohol may induce aggressive behaviour in susceptible individuals, at least in part, by inducing a strong depletion of brain serotonin levels. In this article, evidence supporting these interrelationships and interactions will be summarised and discussed, the alcohol-serotonin-aggression hypothesis will be reiterated, and potential intervention strategies will be proposed.

INTRODUCTION: ALCOHOL AND VIOLENCE

It is now well established that alcohol consumption is a significant presence in over half of all cases of violence, including homicide and physical and sexual assaults (Murdoch *et al.*, 1990). That alcohol is a major factor in violence and other forms of aggressive behaviour is an undisputed fact, judging from the voluminous literature

attesting to this link in both real-life situations (Shupe, 1954; Wolfgang and Strohm, 1956; Voss and Hepburn, 1968; Amir, 1971; Nicol *et al.*, 1973; Virkkunen, 1974; Mayfield, 1976; Gerson and Preston, 1979; Leonard *et al.*, 1985; Hore, 1988; Murdoch *et al.*, 1990; Pernanen, 1991; Rossow, 1996; Bushman, 1997; Zhang *et al.*, 1997; Graham *et al.*, 1997, 1998, 2000; Brismar and Bergman, 1998; Scott *et al.*, 1999; Wells *et al.*, 2000) and in experimental studies on aggression (Cherek *et al.*, 1985; Pihl and Zacchia, 1986; Lindman *et al.*, 1987; Chermack and Taylor, 1995; Giancola and Zeichner, 1995*a,b*; Zeichner *et al.*, 1995; Meier *et al.*, 1996; Bjork and Dougherty, 1998; Hoaken *et al.*, 1998*a,b*; Pihl and LeMarquand, 1998; Moeller *et al.*, 1998; Cheong and Nagoshi, 1999; Dougherty *et al.*, 1999; Hoaken and Pihl, 2000).

However, despite this overwhelming evidence, the important role of alcohol in violence and other forms of aggressive behaviour is, as pointed out by Pihl and LeMarquand (1998), often ignored in legal and social circles. These latter authors have eloquently proposed four explanations for this position. (1) There is a widely-held belief that the alcohol-aggression relationship is a purely artefactual one, arising from the influence of the environment within which alcohol is consumed at social gatherings. (2) Alcohol is thought to provide the excuse for violence (see further below), though of course this, in itself, implicates alcohol as a direct cause of violence. (3) In the socio-politico-legal world, biological explanations are embarrassingly incompatible with entrenched philosophies. (4) As alcohol diffuses in almost all organs and tissues of the body, the question often asked by those less knowledgeable about the pharmacology of alcohol is why should the brain be especially targeted for blame? However, while we all recognise that aggressive behaviour has multiple contributing factors, there is also no doubt that the

pharmacological effects of alcohol (as a drug) play an important role in the alcohol-aggression relationship. Thus, a meta-analysis of experimental aggression studies has shown this relationship to be causal and not simply correlational (Bushman and Cooper, 1990). The effects of alcohol, in common with other pharmacological characteristics, are: (1) dose-dependent and, in particular, related to the rising or falling limbs of the blood-alcohol concentration profile; (2) subject-specific; (3) related to brain chemical processes. However convincing the pharmacological evidence is, there is no doubt that other (non-pharmacological) factors are involved in the alcohol-aggression relationship. Many theories have been put forward to explain such a relationship, the most prominent of which are the: (1) disinhibition theory; (2) deviance/disavowal theory; (3) embolden hypothesis; (4) expectancy theory. A recent discussion of these theories (Zhang *et al.*, 2002 and references cited therein) suggests that all have supporting evidence to varying degrees, depending on the depth of their investigations, and that, at least in relation to theories (2) and (3), aggression-related alcohol expectancies may play an important role in the link between alcohol and violence. Though outside the immediate scope of the present discussion, some of these theories will be discussed briefly in the context of the potential biological basis of the above relationship. The present review will consider briefly biological aspects of alcohol-related aggression, with particular emphasis on the potential role of serotonin. This is not meant to be an exhaustive or critical review of the alcohol-serotonin-aggression literature, but, rather, intended to emphasize to the non-expert an aspect of the alcohol-aggression link to which little attention has so far been paid in medico-legal circles. It is hoped that, with the growing acceptance in legal circles of the role of genetics and related biological mechanisms delineated through recent advances in scientific research in biochemistry and molecular biology, the biological

effects of alcohol will soon be accepted as important correlates, if not determinants, in cases involving alcohol-related aggression and other forms of violence.

POTENTIAL BIOLOGICAL CORRELATES AND/OR DETERMINANTS OF AGGRESSION

A number of biological factors have been implicated in aggression. These include: (1) genetic predisposition (Vernon *et al.*, 1999; Hudziak *et al.*, 2000); (2) high serum testosterone levels (Sanchez-Martin *et al.*, 2000; Soler *et al.*, 2000); (3) low serum cholesterol levels (Muldoon *et al.*, 1990; Kaplan *et al.*, 1994; Modai *et al.*, 1995 and references cited therein; Mufti *et al.*, 1998); (4) low blood glucose nadir in the glucose-tolerance test (Virkkunen and Närvänen, 1987 and references cited therein); (5) low brain serotonin levels (for references, see below). Although, except for serotonin, which is the most extensively studied among these factors, a discussion of these potential mediators of aggression is outside the immediate scope of this paper, it is important to state here that the precise role(s) of the above biological factors in aggression and other forms of violence is currently not clearly understood. In particular, whether these mechanisms play a primary role or are secondary epiphenomena in the process of aggression remains to be investigated.

SEROTONIN AND AGGRESSION

As is the case for the alcohol-aggression relationship, there is equally overwhelming evidence in support of a serotonin-aggression link. This evidence has come from: (1) studies with experimental animals; (2) studies of real life situations involving violence; (3) human physiological studies (those using hormone challenge and receptor function tests); (4) other human studies on experimentally-induced

aggressive behaviour. The following is a brief and selective summary of these studies.

Animal studies

It has been known for sometime that aggressive behaviour can be induced by lowering brain serotonin levels by a variety of mechanisms, including dietary restriction of the serotonin precursor tryptophan (Trp), inhibition of serotonin synthesis by administration of the Trp hydroxylase inhibitor *p*-chlorophenylalanine, or destruction of serotonin neurons by administration of the serotonin neurotoxin 5,7-dihydroxytryptamine (for reviews, see Pucilowski and Kostowski, 1980; Valzelli, 1984; Eichelman, 1990). More recently, genetic differences in serotonin function in animals have been utilized to demonstrate differences in their aggressive behaviour. Thus, following provocation, mice lacking the serotonin 5-HT_{1B} receptor have been shown (Saudou *et al.*, 1994) to be more aggressive than control mice. Of other animal models of aggression, the non-human primate has been the most extensively studied; its aggressive and impulsive behaviours have been shown to be associated with low brain serotonin turnover (for reviews and references, see Pihl and LeMarquand, 1998; Higley and Bennett, 1999).

Serotonin and real-life violence

Much evidence exists to implicate serotonin dysfunction, usually expressed as low cerebrospinal fluid (CSF) levels of the major serotonin metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA), in violence and other form of aggressive behaviour. Thus, low CSF [5-HIAA] has been shown to be present in aggressive subjects with personality disorder (Bioulac *et al.*, 1978, 1980; Brown *et al.*, 1979, 1982), and in homicidal offenders (Lidberg *et al.*, 1984, 1985). CSF 5-HIAA has also been reported to be low in “normal” subjects who self-reported high aggression (Roy *et al.*,

1988) and to be correlated negatively with aggression in children and adolescents with disruptive behaviours (Kruesi *et al.*, 1990). The work of the group of the late Dr Markku Linnoila has been instrumental in establishing the role of impulse disorder in the close association between low CSF 5-HIAA levels and aggressive behaviour in violent offenders, fire-setters, serious suicide attempters, and impulsive subjects with paternal alcoholism (for reviews and references, see Pihl and LeMarquand, 1998; Higley and Bennett, 1999). A critical appraisal by Tuinier *et al.* (1995) of the evidence supports the serotonin-aggression relationship, especially among relatively young, white, personality disordered males with criminal records.

The association between serotonin dysfunction and aggression and violence is not limited to instances where the latter acts are directed against others, but extends to self-inflicted aggression, namely suicide (see, e.g., Asberg *et al.*, 1976; Brown *et al.*, 1982; van Praag, 1983; Maes *et al.*, 1995). Furthermore, more recently, genetic studies have demonstrated an association between violent suicide and a low activity allele of the serotonin transporter gene (Courtet *et al.*, 2001). Earlier, a mutation in the gene encoding the “A” form of monoamine oxidase, the enzyme that prefers serotonin for its degradative function, was demonstrated by Brunner *et al.* (1993).

Human physiological studies

There have been more positive than negative studies demonstrating blunted responses in hormone challenge tests of serotonin function in impulsive/aggressive subjects, e.g. prolactin or cortisol release following administration of the serotonin-receptor-modulating agents fenfluramine and *m*-chorophenylpiperazine, suggesting that aggression is associated with impaired serotonin postsynaptic receptor function. Similar conclusions can be drawn from studies demonstrating impaired binding of

serotonin receptor ligands to the blood platelet 5-HT receptors, and of lower densities of these receptors (for references, see Pihl and LeMarquand, 1998).

Serotonin and experimentally-induced aggressive behaviour in humans

There is also considerable evidence from experimental studies in support of the serotonin-aggression relationship. One interesting experimental strategy involves acute tryptophan (Trp) depletion (ATD) (Young *et al.*, 1988), in which brain serotonin levels are decreased after intake of an amino acid mixture deficient in Trp, but rich certain other amino acids known to compete with Trp for entry into the brain (mainly valine, leucine, isoleucine, phenylalanine and tyrosine, known collectively as the competing amino acids or CAA). Brain serotonin synthesis is controlled mainly by brain [Trp] and in human studies, where the latter cannot be measured directly, the serum or plasma [Trp]/[CAA] ratio is the most accurate predictor of changes in brain Trp, and hence 5-HT (for a discussion of these and related biochemical aspects, see Badawy, 2002). Experimental studies using the ATD technique have demonstrated increased aggressive responding following provocation, using the Taylor reaction time aggression task (Cleare and Bond, 1995; Pihl *et al.*, 1995), or the point-subtraction aggression test (Moeller *et al.*, 1996). Other experimental studies with ATD have also demonstrated aggressive behaviour in subjects with high pre-existing hostile or antisocial characteristics (Cleare and Bond, 1995; Finn *et al.*, 1998).

Basis of the serotonin-aggression relationship

Taken together, the above accounts strongly suggest that aggressive behaviour is very closely associated with a subnormal brain serotonin status. The mechanism(s) by which decreased serotonin function may lead to aggressive behaviour is less clearly understood or explored, although potential explanations have been proposed. Thus, Pihl and LeMarquand (1998) suggested “disinhibition” as a potential

mechanism by which lowered serotonin function may lead to aggressive behaviour under certain conditions (e.g. provocation). This is a very plausible explanation, given the well-accepted notion that this amine exerts a major controlling influence over impulsive behaviour, and is supported by the observation (LeMarquand *et al.*, 1998) that ATD increases behavioural disinhibition. A second, equally plausible, explanation proposed by Pihl and LeMarquand (1998), given the role of serotonin in cognition (for review, see Meneses, 1999), is that serotonin dysfunction interferes with cognition, disrupting appraisal of aggression-provoking situations.

SEROTONIN DEPLETION BY ALCOHOL AS A POTENTIAL MECHANISM OF ALCOHOL-INDUCED AGGRESSION

The major question in investigating serotonin metabolism in the context of the alcohol-aggression relationship is how does alcohol influence serotonin metabolism and function to precipitate aggressive behaviour? As aggression is associated with a reduced function and depletion of serotonin, could alcohol-induced aggression involve depletion of serotonin? In this section, evidence will be presented that acute alcohol consumption lowers brain serotonin levels; an effect that may provide the necessary link for the above relationship.

In normal human subjects, acute ethanol consumption has been shown (Badawy *et al.*, 1995) to decrease circulating Trp availability to the brain, as determined from the [Trp]/[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]. A decrease in circulating Trp in non-alcoholic subjects has previously been demonstrated by Siegel *et al.* (1964) and Eriksson *et al.* (1983). In our more detailed study (Badawy *et al.*, 1995), we found that the decrease was quantitatively the same for both the free

(ultrafiltrable) and total (free + albumin-bound) Trp fractions, and was thus not associated with altered Trp binding to albumin. Such a profile is characteristic of enhancement of activity of the major Trp-degrading enzyme, liver Trp pyrrolase. 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 extensive review, see Badawy, 2002). In our human study, 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). The maximum decreases in free and total serum [Trp] occurred at 1.5-2h 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 not only achievable, but is more often exceeded, 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 at least 20%. Since this level of serotonin depletion 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 under these conditions. Our hypothesis postulates that, in susceptible individuals, the decrease in brain serotonin synthesis may well be stronger, perhaps of the order of 40-60%, thus triggering an episode of aggressive behaviour, perhaps accompanied by dysphoria. 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, an additional 20% or so depletion after alcohol intake could result 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 also affects other determinants of serotonin synthesis, this could lead to a combined greater rate of depletion. These possibilities require experimental assessment in subjects in whom alcohol induces aggressive behaviour. Other experimental studies examining the alcohol-aggression-serotonin relationship will now be described.

MECHANISMS OF THE SEROTONIN INVOLVEMENT IN ALCOHOL-INDUCED AGGRESSION

The question of how serotonin could mediate alcohol-induced aggressive behaviour is currently being appraised. Pihl and LeMarquand (1998) have proposed a model, which postulates that alcohol-induced aggression is caused by alcohol: (1) potentiating behaviour in two ways; direct facilitation of aggression and promotion of approach behaviour, despite any potential threat; (2) overcoming anxiety (Pohorecky, 1991), which is considered a major inhibitor of aggressive behaviour; (3) disrupting executive cognitive function (Hoaken *et al.*, 1998a; Giancola, 2000), in particular working memory, which involves assessment of risky situations. Earlier, 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. Either alcohol intake acts as a provocative stimulus to induce aggressive behaviour in Trp-depleted (serotonin-deficient) subjects, or that, as

suggested above, under these conditions, alcohol intake may cause a further (additive) decrease in brain serotonin, causing a pronounced depletion resulting in aggression. It is also tempting to speculate that psychological or physical provocations may also induce a further serotonin depletion in alcohol-drinking subjects of sufficient extent to precipitate aggressive behaviour.

CONCLUSIONS AND COMMENS

From the above accounts, it may be concluded that there is strong evidence that alcohol consumption induces aggressive behaviour in susceptible individuals and that depletion of the brain chemical serotonin may be an important determinant of this effect. Further studies are needed to establish more firmly this serotonin involvement and its mechanism(s). If serotonin depletion is established as a major determinant of alcohol-induced aggressive behaviour, further studies could be performed to establish a laboratory screening test for this depletion and for intervention at the population level through a variety of strategies. For example, aggressive subjects with serotonin deficiency could be targeted for dietary-induced enhancement of their serotonin status, through eating high carbohydrate, low protein diets, as the former is known (Madras *et al.*, 1973) to increase, whereas the latter is known (Møller, 1985) to decrease, Trp entry into the brain and hence serotonin synthesis. Targeting aggressive individuals for dietary intervention has recently been explored by Gesch *et al.* (2002), who showed in a placebo-controlled randomised trial that dietary supplementation with vitamins, minerals and essential fatty acids led young adult prisoners to commit significantly fewer antisocial behaviours. It is tempting to speculate that these dietary supplements could have acted, at least in part, through modulation of serotonin metabolism, a possibility that requires investigation. Exercise also increases brain serotonin (Newsholme *et al.*, 1991) and this could form the basis of another strategy.

Still further, susceptible subjects could be given serotonin-enhancing drugs to correct their potential serotonin defect. I believe that these potential biologically-based strategies, which are amenable to investigation at the population level, may provide an opportunity of tackling alcohol-related violence, in conjunction with psychosocial intervention strategies, as part of a comprehensive public health programme.

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