
SEROTONIN AND AGGRESSION AND THE ALCOHOL-AGGRESSION RELATIONSHIP

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Abstract — The consumption of an intoxicating dose of alcohol increases the likelihood of violent behaviour. Three possible mechanisms involving potentiation, inhibition, and disorganization of behaviour are presented. The manner in which these three effects may be mediated by serotonergic activity is briefly discussed. A more extensive review of the serotonin-aggression relationship is then presented.

ALCOHOL AND AGGRESSION: INTRODUCTION

The consumption of alcoholic drinks, typically in large quantities, occurs prior to and in close temporal proximity to most forms of violence. One literature review, for example, notes the involvement of alcohol in more than half of all murders, assaults, and rapes (Murdoch et al., 1990). In attempting to explain this relationship, it is important to emphasize that alcohol is a drug. This self-evident fact often, somehow, seems to get lost when constructing explanations for the alcohol-aggression relationship. Four beliefs/arguments seem to lie beneath this obfuscation. First, there is the position that the relationship is artefactual. This view holds that the high correlations between alcohol and violent behaviour represent a temporal artefact or a second-order correlation. For example, it is the case that a great deal of mayhem occurs in and around areas where alcohol is served, and at times of social gatherings, (typically Friday and Saturday evenings). In addition, in longitudinal studies (White et al., 1993), it has been shown that individuals who are prone to be aggressive also drink heavily, although laboratory studies of predisposition are of mixed support (Bailey and Taylor, 1991; Pihl et al., 1997). Pointedly, meta-analyses of controlled human laboratory studies conclude that the alcohol-aggression relationship is causal and not simply correlational (Bushman and Cooper, 1990). These same analyses also discount the second argument that alcohol simply provides the excuse for aggression. That psychological expectations in the response to a drug are important is indisputable. Certainly, any aggressive act has multiple contributing factors, and expectations are not inconsequential as cultural variations in the aggressive response attest (MacAndrew and Edgerton, 1969). However, this conclusion does not obviate the fact that a powerful pharmacological agent is also involved. A third impediment to searching for pharmacological effects rests in the social/political/legal realms where biological explanations are embarrassingly incompatible with entrenched philosophies. Patently, the tortured rationales required to maintain the concept of individual responsibility given an explanation of drug-induced behaviour change is clearly an effort society would prefer to avoid. The important principle of mens rea or the will or intent to commit an act appears quite soluble in alcohol — a reality generally denied in law. The fourth position is based on the notion that alcohol’s effects on brain is general, bathing all tissues and systems equally, so that the determination of any particular mechanism is fundamentally impossible. Increasingly, this position is being proven incorrect. There exists a surfeit of studies which show that alcohol effects are dose specific,

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particular to the rising or falling limb of the blood-alcohol curve, specific to particular individuals, and operative on important neurotransmitter systems. In a more general sense, alcohol's effect can be stimulating, anxiolytic, and be cognitively disruptive, all of which directly impact the likelihood of aggressive behaviour. Each of these points is briefly detailed below.

ALCOHOL EFFECTS AND AN INCREASED LIKELIHOOD OF AGGRESSION

Figure 1 is a schematic representation of a number of alcohol's effects which operate to potentiate, inhibit, and disorganize behaviour. Regarding potentiation, the effect appears twofold. First, alcohol appears to facilitate the response to cues of reward, which promotes approach behaviour even in the face of what might be considered threatening. It thus allows for a breaking of the conservative rules of self-survival and results in the production and exploration of the unexpected. In the extreme, this lack of sensitivity to threat and punishment manifested by extreme approach behaviour would result in dangerous intra- and interpersonal behaviour. Alcohol operates on this dopaminergic-based system of reward like other stimulants, e.g. cocaine and amphetamine (Gessa et al., 1985), and its action appears most pronounced at moderate doses and on the rising limb of the blood-alcohol curve. Significantly, sensitivity to this effect has been found in selective rodent strains and in humans at high risk for developing alcoholism (Pihl and Peterson, 1995). The second potentiating effect is the direct energizing of a basic natural response, aggression. Aggression as a behaviour is most frequent in 2-year-olds and decreases dramatically thereafter. This suggests that this behaviour is a fundamental default response which can be directly potentiated or increased by stimulation.

Anxiety is hypothesized to be a major inhibitor
of aggressive behaviour (Fig. 1). If the socialized individual expects to be punished for being aggressive and/or has learned to empathize with the victim, situations potentially eliciting aggression should also provoke inhibitory cues, i.e. anxiety. Alcohol in sufficient dosage and particularly for some individuals is anxiolytic. This has been demonstrated in studies of tension reduction (see Pohorecky, 1991 for review) and in stress response dampening (see Pihl and Peterson, 1995). Thus, as illustrated in Fig. 1, alcohol is seen as disinhibiting the learned inhibition of aggression. This view may also explain why victims of violence are also likely to be intoxicated (Murdoch et al., 1990).

Finally, alcohol has been shown to have a disruptive effect on higher-order cognitive functioning. Particularly impacted is working memory. Conceptualized broadly, working memory is temporal: including past, present, and future considerations. For example, working memory allows for the ability to consider the future consequences of one’s behaviour. Peterson et al. (1990) have demonstrated that the cognitive measures which assess these types of abilities are specifically altered by intoxicating dosages of alcohol. Further, it has been shown that individuals who display deficits on these tests are more aggressive when sober (Lau et al., 1995) and engage in more fighting behaviour when intoxicated (P. Conrod et al., unpublished work).

**SEROTONIN’S ROLE IN THE POTENTIATION, DISINHIBITION AND DISORGANIZING EFFECTS OF ALCOHOL**

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT), analogized as the brain’s orchestral maestro, seems important in mediating these processes implicated in the effects of alcohol on aggression. For example, serotonin inhibits behaviour in the presence of threat or cues of punishment (Soubrie, 1986) and is also involved in the release of striatal dopamine and increased locomotor activity (Kriem et al., 1996). As alcohol functions to disinhibit behaviour (e.g. producing aggression), it may be influencing the serotonergic system to produce such effects. In general, alcohol acutely facilitates serotonergic levels in animals (LeMarquand et al., 1998) which might be expected to inhibit behaviour. However, the temporal effects of alcohol on the serotonergic system are far from fully elucidated, particularly in humans. Initial facilitation of serotonergic functioning following alcohol ingestion seems subsequently to be followed by a decline, increasing the propensity for disinhibited behaviour (LeMarquand et al., 1994a,b). In a state of depleted serotonergic functioning, anxiety no longer inhibits behaviour, despite maintaining its emotional intensity (Spoont, 1992). Repeated alcohol administration may lower serotonergic functioning to the point where anxiety, even if felt, will no longer function to inhibit aggressive behaviour.

Finally, there is evidence that lowered serotonergic functioning interferes with cognitive function. In one study, normal participants who consumed an amino acid mixture devoid of tryptophan, the amino acid precursor of 5-HT, performed more poorly on memory and learning tests than those who received a mixture with tryptophan (Park et al., 1994). Again, alcohol may be leading to transient deficits in serotonergic functioning, interfering with cognitive processes related to aggressive behaviour. These hypotheses depend on further elucidating the temporal effects of alcohol on central serotonergic functioning. The remainder of this paper focuses on 5-HT’s role in aggressive behaviour.

**SEROTONIN AND AGGRESSION: ANIMAL STUDIES**

Comprehensive reviews of the animal literature clearly demonstrate that aggressive behaviour in rodents can be elicited by experimentally manipulating 5-HT (see Pucilowski and Kostowski, 1980). Recently, mouse strains genetically altered and bred for specific neurochemical characteristics have been used to explore the 5-HT/aggression link. Mice bred to be lacking the 5-HT1B receptor (the rodent homologue of the human 5-HT1D receptor) have been found to be more aggressive following provocation compared to controls (Saudou et al., 1994). Primate studies also have added to the evidence that low 5-HT is associated with aggression and impulsivity, and increased 5-HT function with prosocial behaviour. Cerebrospinal fluid (CSF) 5-HIAA is negatively associated with spontaneous aggression (Higley et al., 1992, 1996a; Doudet et al., 1995), risk-taking.
(Mehlman et al., 1994), and excessive mortality (Higley et al., 1996b), and positively correlated with prosocial behaviour, age of emigration (Mehlman et al., 1995) and social dominance rank (Higley et al., 1992) in male as well as female (Higley et al., 1996c) rhesus monkeys. Interestingly, Raleigh et al. (1984) have reported elevated whole blood serotonin in dominant male adult vervet monkeys that fell subsequent to a reduction in their position in the social hierarchy. Also in male vervets, a mixture of amino acids devoid of tryptophan has been shown to increase competitive aggression (Chamberlain et al., 1987).

Studies also support Soubrie's (1986) contention that 5-HT is related generally to disinhibition. Dexfenfluramine, a 5-HT releaser, decreases impulsivity (i.e. reduces the choice of an immediate small reward in favour of a delayed larger reward) in rats. Low doses of 8-OH-DPAT, a 5-HT1A agonist, increase impulsivity, whereas higher doses decrease it (Poulos et al., 1998), mirroring its effects on alcohol consumption (Tomkins et al., 1994). This suggests that low doses of 8-OH-DPAT act on presynaptic 5-HT1A autoreceptors, resulting in decreased 5-HT function and increased impulsivity, while higher doses act on postsynaptic 5-HT1A receptors, resulting in the converse.

SEROTONIN AND AGGRESSION: HUMAN STUDIES

Correlational studies

In general, there is abundant evidence that low 5-HT is related to aggression. Low CSF 5-HIAA has been repeatedly associated with aggression in a number of clinical groups. Personality-disordered individuals with a history of aggressive/impulsive behaviour (Brown et al., 1979, 1982), aggressive/impulsive individuals with borderline personality disorder (BPD) without major affective disorder (Brown et al., 1982), incarcerated personality-disordered individuals with XYY (Bioulac et al., 1978, 1980), homicidal offenders who had killed a sexual partner (Lidberg et al., 1985) or their own child (Lidberg et al., 1984), depressed individuals (Rydin et al., 1982), alcoholic males (Limson et al., 1991), and normal volunteers (Roy et al., 1988) who self-report high aggression have low CSF 5-HIAA levels. CSF 5-HIAA has also been negatively correlated with aggression in children and adolescents with disruptive behaviour disorders (characterized by hyperactive, impulsive and aggressive behaviours (Kruesi et al., 1990). Further, CSF 5-HIAA significantly predicted severity of physical aggression at 2-year follow-up (Kruesi et al., 1992).

Clinical studies also suggest that it may be impulsive aggression that is related to low 5-HT functioning. Impulsive violent offenders (Linnoila et al., 1983; Virkkunen and Linnoila, 1993; Virkkunen et al., 1994a) and fireseters (Virkkunen et al., 1987) have low 5-HIAA. In this sample, a low blood glucose nadir following oral glucose challenge and low CSF 5-HIAA predict recidivism (Virkkunen et al., 1989a). Also, those individuals with histories of serious suicide attempts have been shown to have lower CSF 5-HIAA and MHPG levels (Virkkunen et al., 1989b), as have impulsive individuals with alcoholic fathers (Linnoila et al., 1989; Virkkunen et al., 1996). Low CSF-5-HIAA is also associated with self-reported irritability and impaired impulse control in alcoholic violent offenders (Virkkunen et al., 1994b). Additionally in one study, the L allele of the tryptophan hydroxylase gene was associated with low CSF-5-HIAA in these impulsive alcoholic violent offenders but not in non-impulsive alcoholic violent offenders or controls, suggesting a possible reduced capacity to hydroxylate tryptophan to 5-hydroxytryptophan, and ultimately to produce 5-HT (Nielsen et al., 1994). However, there have been failures in replicating this finding (Abbar et al., 1995; Nielsen et al., 1996).

As a whole, methodological problems exist in the studies investigating the CSF 5-HIAA—aggression—impulsivity relationship. For example, impulsivity, derived from police records and/or self-reported life histories, has been operationalized as a criminal act committed without provocation or premeditation and without the possibility of economic gain, with the victim(s) unknown to the offender (Virkkunen et al., 1989a). This definition fails to demonstrate impulsivity as a stable personality characteristic, and suffers from the possibility of falsification on the part of an individual to avoid more severe punishment (Tuinier et al., 1995). Nevertheless, eight of the 22 published studies judged to be methodologically rigorous demonstrated the
5-HT-aggression relationship, particularly for relatively young, white, personality-disordered males with histories of criminal acts (Tuinier et al., 1995).

Aggressive behaviour expressed towards the self (suicide) has similarly been associated with low CSF 5-HIAA, regardless of diagnosis (Asberg et al., 1976; Brown et al., 1982; van Praag, 1983; Traskman-Bendz et al., 1986; Tuinier et al., 1995). This relationship holds true particularly for violent suicide (Asberg et al., 1976). Annual variability in plasma L-tryptophan and the ratio of L-tryptophan to amino acids competing for brain uptake has been negatively associated with violent suicides in Belgium (Maes et al., 1995). These data suggest again that it may be aggression (whether outwardly or inwardly directed) characterized by its violent severity and impulsive quality that is related to low 5-HT functioning. Recently, a mutation in gene coding resulting in deficient monoamine oxidase (MAO)-A activity has been associated with aggression and impulsive behaviour in a large kindred with several males characterized with borderline mental retardation and abnormal behaviour (arson, attempted rape, exhibitionism) (Brunner et al., 1993).

Indeed, neuroendocrine evidence demonstrates on the whole that aggression–impulsivity is associated with blunted hormonal responses to 5-HT agonists relative to controls, suggesting lower receptor numbers or impaired functioning. Blunted hormonal response (prolactin, cortisol) to 5-HT agonist (fenfluramine, d-fenfluramine, m-CPP) challenges have been noted in individuals with past histories of suicide attempts, impulse control disorders (bulimia, substance dependence, pathological gambling), and BPD, and narcissistic personality disorder (Lopez-Ibor et al., 1991), murders with antisocial personality (ASP) (O’Keane et al., 1992), BPD patients with histories of impulsive and aggressive behaviour (Siever et al., 1987), and men with ASP (Moss et al., 1990) have been noted. Blunted prolactin responses to fenfluramine challenge were related to a past history of suicide attempts in patients with impulsive aggression in patients only with personality disorders (Coccaro et al., 1989). Further study revealed that reduced prolactin responses to fenfluramine in these patients were associated with an increased morbid risk of impulsive personality traits (and marginally to familial alcoholism) in their first-degree relatives (Coccaro et al., 1994). Blunted prolactin responses to fenfluramine were also inversely correlated to a laboratory measure of aggression in personality-disordered males (Coccaro et al., 1996a). Also, there have been a number of negative studies (Fishbein et al., 1989; Weltzler et al., 1991; Coccaro, 1992; Stoff et al., 1992; Halperin et al., 1994); again, however the weight of this evidence suggests the 5-HT-aggression relationship may be mediated by low postsynaptic receptor functioning.

Platelet receptor binding studies assess the density ($B_{\text{max}}$) and affinity ($K_d$) of platelet receptors using various 5-HT ligands. Lending further support to the hypothesis, significantly lower ketanserin binding to platelet 5-HT$_2$ receptors has been found in adolescent violent delinquents compared to controls (Blumensohn et al., 1995). Similarly, the density of platelet 5-HT$_2$A receptors was found to be lower in boys with parents with histories of incarceration or substance abuse compared to family history-negative boys (Pine et al., 1996). These findings seem to reflect decreased central 5-HT$_2$ postsynaptic receptor function.

Platelet 5-HT uptake studies are consistent in their finding of a negative association between 5-HT uptake and aggression–impulsivity. Conduct-disordered children have been shown to have a reduced number of platelet $H^3$-imipramine maximal binding sites (i.e. low $B_{\text{max}}$), which was inversely correlated with aggressive and externalizing factors on a parent assessment (Stoff et al., 1987). Platelet 5-HT uptake and aggressive behaviour have also been found to be negatively associated in both schizophrenic and conduct-disordered adolescents (Modai et al., 1989). The $B_{\text{max}}$ of platelet $H^3$paroxetine binding has been shown to be inversely correlated with total self-report aggression and the tendency to respond to provocation with physical attacks in individuals with personality disorders relative to controls (Coccarro et al., 1996b). The $B_{\text{max}}$ for platelet $H^3$imipramine binding has also been shown to be lower in highly aggressive mentally retarded adults and suicide attempters compared to controls (Marazziti et al., 1993). Further, in another study, male outpatients with 'episodic aggression' had a lower mean 5-HT uptake compared to male non-aggressive controls; 5-HT uptake was negatively
correlated with impulsivity measures (Brown et al., 1989). Coccaro et al. (1996a,b) have posited that reduced 5-HT uptake might lead to increased synaptic availability, reduced sensitivity of terminal 5-HT autoreceptors, a greater release of 5-HT per neuronal impulse, and a subsensitivity of postsynaptic 5-HT receptors, with the net effect being reduced 5-HT neurotransmission.

The majority of studies investigating the 5-HT–aggression link are correlational; they suggest an inverse correlation between serotonergic functioning and aggression. Moreover, evidence is beginning to accumulate suggesting that it is impulsive aggression that is particularly associated with impaired 5-HT functioning.

**Experimental investigations**

The acute tryptophan depletion (ATD) paradigm theoretically allows one to observe the behavioural consequences of decreased central nervous system 5-HT functioning. Depletion of plasma tryptophan in humans is achieved through the oral administration of a mixture of amino acids devoid of tryptophan (Young et al., 1988). Brain 5-HT metabolism can be significantly influenced by changes in the availability of its precursor tryptophan in the blood (Fernstrom and Wurtman, 1974). In rats, an amino acid diet devoid of tryptophan significantly reduces brain tryptophan, 5-HT, and 5-HIAA levels (Biggio et al., 1974; Gessa et al., 1974; Moja et al., 1989). In vervet monkeys, an amino acid load devoid of tryptophan lowers plasma tryptophan by 50–60%, CSF tryptophan by 61% and 5-HIAA by 34%, with no changes in CSF HVA or MHPG, the respective metabolites of dopamine and noradrenaline (Young et al., 1989). A recent positron emission tomography study found reductions in the rate of brain serotonin synthesis following ATD by a factor of approximately 9.5 in males and 40 in females (Nishizawa et al., 1997).

Increased aggressive responding in healthy males following ATD has been found in studies characterized by an element of physical provocation (Cleare and Bond, 1995; Pihl et al., 1995) using variants of the Taylor reaction time competition aggression task. Studies lacking such provocation (Smith et al., 1987; Salomon et al., 1994) have not demonstrated an effect of ATD on aggressivity. This may relate to the notion that behavioural arousal (in this case produced via physical provocation) is necessary to facilitate differences in central 5-HT function following ATD and thus observable behaviour changes (Young et al., 1988). It should be noted that one study using the point-subtraction aggression paradigm, involving the loss of points exchangeable for money as a provocation, also demonstrated an effect of ATD on aggression (Moeller et al., 1996).

Studies that show an effect of ATD on aggression on the Taylor task have compared ATD individuals to an augmented tryptophan condition (Cleare and Bond, 1995; Pihl et al., 1995), which increases plasma total tryptophan 1100% over baseline levels. A recent study that did not find an ATD-induced increase in aggression used a balanced tryptophan comparison group, which raised plasma total tryptophan 49% over baseline levels. It may be (LeMarquand et al., unpublished work) necessary to compare an ATD group to a control group given an augmented tryptophan mixture to note increased aggression in the Taylor task; this comparison may maximize the differential in serotonergic functioning between the two groups.

Finn et al. (1997) found that normal males high in pre-existing hostile or antisocial traits demonstrated increases in hostility and anxiety (respectively) following ATD. Thus, individuals possessing traits related to low 5-HT activity (high antisocial) may be more susceptible to ATD-induced behavioural changes (Finn et al., 1997). Cleare and Bond (1995) selected young men either high or low on the Buss–Durkee Hostility Inventory, and found increased subjective and behavioural aggressivity after ATD in the high trait aggressive group only.

We are aware of only one other experimental study investigating the 5-HT–aggression relationship. Both aggressive and non-aggressive responding on a point-subtraction aggression paradigm was reduced following the 5-HT1A/1B agonist eltoprazine in healthy males, an effect attributed to the sedative effects of the compound (Cherek et al., 1995).

These preliminary experimental studies investigating the link between 5-HT and aggression provide tentative support for the notion that lowering central 5-HT functioning facilitates aggression. Further work is needed specifically addressing the mechanism(s) through which low-
ered 5-HT may be facilitating aggression. Lowered 5-HT function may produce disinhibition, increasing the potential for aggressive behaviour under certain other conditions. A recent study demonstrated that ATD increased behavioural disinhibition, as assessed by commission errors on a go/no-go learning task, in young men at high risk for alcoholism (LeMarquand et al., 1997). Alternatively, lowered 5-HT function might interfere with cognition, disrupting the appraisal of a potential aggression-provoking situation. It would also be interesting to use 5-HT agonists experimentally to lower aggressive behaviour in individuals with aggressive dispositions.

ALCOHOL, AGGRESSION, AND SEROTONIN

A review of animal studies suggests that acute alcohol intake transiently increases central 5-HT functioning, while chronic intake decreases it (LeMarquand et al., 1994b). Chronic alcohol intake may lead to a state of lowered central 5-HT functioning characterized by a propensity toward disinhibited behaviour, thus increasing the potential for aggressive behaviour. Lowered 5-HT may also increase the likelihood of further alcohol intake (LeMarquand et al., 1994a). Alcohol alone facilitates aggressive behaviour (Bushman and Cooper, 1990); the combination of lowered 5-HT functioning and alcohol intake might be expected to produce additive or interactive effects on aggressive behaviour. This was tested in a recent study (Pihl et al., 1995) combining the technique of ATD and alcohol administration. Healthy males chose higher shock intensities for their non-existent opponents following ATD than did those who received augmented tryptophan mixture (T+) in a modified Taylor task under low provocation, with a trend for such under high provocation. ATD men also tended to administer longer shocks compared to the balanced amino acid group, who in turn administered longer shocks than the T+ group under both low and high provocation. Alcohol significantly increased shock intensities and durations under both low and high provocation, and increased reaction times during the competition task. The alcohol and tryptophan manipulations produced independent, additive effects, with no interaction observed (Pihl et al., 1995). These results are presented in Fig. 2.

This study highlights a way in which the alcohol, aggression, and serotonin relationship can be investigated. Future studies might focus on the effects of ATD and alcohol in individuals with aggressive dispositions. Such a population may be initially predisposed toward disinhibited behaviour by virtue of a lowered baseline 5-HT functioning; ATD and alcohol may interact to increase aggression in these individuals.

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