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Anxiety and Alcoholism: A Serotonin Link

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The augmentation of serotonin (5-HT) neurotransmission attenuates alcohol consumption, whereas depletion enhances use. A number of serotonin-specific pharmacological probes appear to be effective in reducing the voluntary consumption of alcohol. The 5-HT_{1A} receptor agonist buspirone is an anxiolytic which has been shown to diminish the desire to consume alcohol in anxious alcoholic patients. Thus, serotonin may represent a common denominator for a spectrum of behavioural disorders including anxiety and alcoholism. Novel serotonin drugs, such as the azapirones, may usefully supplement conventional treatment strategies for substance abuse.

Alcoholism represents a major public health problem: an estimated 11–16% of the US population exhibits a lifetime prevalence of alcohol abuse or dependence (Robins *et al*, 1984), with an annual cost of about $117 billion (Department of Health and Human Services, 1987). A number of studies have demonstrated an association between alcoholism and anxiety (Smail *et al*, 1984; Weiss & Rosenberg, 1985). Alcoholism may also predispose to a variety of other psychiatric disorders, while conversely, some psychiatric disturbances may contribute to the development of alcoholism and further exacerbate the primary disorder (Solomon, 1982).

Prevalence studies indicate that 30–44% of alcoholics display anxious or mixed anxious/depressive symptoms (Weissman *et al*, 1980; Powell *et al*, 1982); psychometric studies and studies with the Minnesota Multiphasic Personality Inventory (Barnes, 1979; Morey & Blashfield, 1981) also suggest higher levels of anxious features among alcoholics than non-alcoholics. Unfortunately, the reponse profile to the treatment of anxiety symptoms in alcohol-dependent patients has infrequently been investigated. However, observations in the literature suggest that anxious patients may not uncommonly use alcohol to obtain an anxiolytic effect (Quitkin *et al*, 1972; Curlee & Stern, 1973).

There is increasing evidence that the voluntary use of alcohol may be modulated by one or more central neurotransmitters (Naranjo *et al*, 1986); brain serotonin may be one such mediator (Rockman *et al*, 1979; Daoust *et al*, 1985). While diminished serotonin neurotransmission may not mark any single neuropsychiatric disorder, it has been associated with a clinical continuum that includes anxiety (Gardner, 1986; Kahn *et al*, 1988) and alcoholism (Holman & Snape, 1985; Murphy *et al*, 1982). Accordingly, trials of selective serotonergic compounds have now been conducted in both disorders. The well known risk factors associated with benzodiazepine anxiolytics in this population indicate a need for well designed studies of possible alternative treatments.

Anxiety and alcohol

The idea that people suffering from anxiety have a proclivity to consume alcohol to relieve their symptoms dates back to anquity. Hippocrates' prescription was, "Wine drunk with an equal quantity of water puts away anxiety and terrors" (1886), while Westphal observed that "the use of beer or wine allowed the [agoraphobic] patient to pass through the feared locality with comfort" (see Marks, 1987). Early theorists (e.g. Jellinek, 1954) suggested that alcohol's anxiolytic effects may reinforce drinking; Conger (1956) proposed that alcohol lessens the fear which motivates avoidance, that is, reduces tension. Sher (1986) concluded that although drinking in response to stress is a complex phenomenon, alcohol does reduce the perception of stress. Consistent with a self-medication hypothesis, studies of various anxiety disorders have reported that the experience of anxiety typically antedates the misuse of alcohol in, for example, phobias (Quitkin *et al*, 1972; Smail *et al*, 1984), panic or obsessive–compulsive disorders (Powell *et al*, 1982; Ross *et al*, 1988), or in generalised anxiety disorders (Powell *et al*, 1982).

The co-prevalence of alcoholism and the anxiety disorders has been emphasised in many publications (for an excellent review see Kushner *et al* (1990)). Surveys of the out-patient treatment of alcoholics suggest that up to a quarter of patients manifest comorbid anxiety, with an even greater number in in-patient samples. Selective investigation of anxiety disorders in ambulatory settings has indicated that the highest co-prevalence (20%) of alcoholism is with the phobias (Amies *et al*, 1983; Thyer *et al*, 1986; Noyes *et al*, 1986); in generalised anxiety disorder

it is 10% (Thyer *et al*, 1986), and in panic disorder it is 1.2% (Bibb & Chambless, 1986; Thyer *et al*, 1986; Noyes *et al*, 1986). Karno *et al* (1988) reported that the comorbidity of alcoholism with obsessive–compulsive disorder in the community was 24%, that is, twice as common as in non-obsessive–compulsive controls.

Serotonin and alcoholism

Animal models

Alcohol intake is regulated by a complex interaction of neurobiological and systemic factors (Naranjo *et al*, 1986); investigations have linked brain serotonin levels with an alcohol preference across a variety of animal species (Collins, 1979). Murphy *et al* (1982) reported that the level of serotonin is reduced in some regions of the brain in alcohol-naive rats bred for an alcohol preference. Examination of the striatal synapse in rats suggests that the acute effects of alcohol are characterised by increased release and turnover of serotonin in the striatum (Tytell & Myers, 1973; Holman & Snape, 1985; Murphy *et al*, 1988). Chronic administration of alcohol has been associated with decreased serotonergic turnover and receptor stimulation (Morinan, 1987). However, within the striatum, and perhaps mediating compulsive craving (Modell *et al*, 1990), serotonin metabolism is reported to be enhanced after chronic exposure to alcohol (Kempf *et al*, 1985) – an observation also characterising an extended post-withdrawal period (Sjoquist *et al*, 1982).

Numerous studies in which serotonin neurotransmission was manipulated are reported to have shown an influence on ethanol consumption; for instance, direct administration of serotonin (50–100 mg intravenously) attenuated ethanol use (Hill, 1974). Levy *et al* (1989) reported that bilateral micro-injections of serotonin into the nucleus accumbens induced a dose-dependent reduction in ethanol intake among rats. Similar outcomes were found with administration of parenteral tryptophan (Zabik *et al*, 1985), reuptake blockers such as zimelidine (Lawrin *et al*, 1983), and post-synaptic receptor agonists such as MK 212 (Lawrin *et al*, 1983) and quipazine (Zabik *et al*, 1985). Conversely, the chemical destruction of serotonergic neurones by dihydroxytryptamine increased alcohol consumption (Richardson & Novakowski, 1978).

Human studies

5-HIAA in cerebrospinal fluid

Ballenger *et al* (1979) proposed that alcoholic subjects have lower baseline levels of 5-hydroxyindolacetic acid (5-HIAA) in cerebrospinal fluid (CSF). These are transiently elevated on acute alcohol consumption but, with continued use, further depletion characterises non-consuming periods and aggravates the cycle. Thus, it could be hypothesised that the alcoholic who repeatedly drinks may be attempting to modify a relative deficiency of serotonin.

Analyses of CSF by Roy *et al* (1987) have found low 5-HIAA levels in association with poor impulse control, alcoholism, depression, and also in suicide victims. Reduced levels of 5-HIAA characterises active, detoxified, and abstinent alcoholics, making it a possible trait marker (Ballenger *et al*, 1979). Takahashi *et al* (1974) analysed samples of CSF and found no difference in levels of 5-HIAA between matched controls and 30 alcoholic subjects after one week of abstinence. However, when the alcoholic sample was divided, based on the presence or absence of withdrawal symptoms, the former subgroup manifested significantly lower levels. Repeat lumbar puncture four weeks later confirmed this reduction. Banki (1978, 1981) reported a negative correlation between the number of abstinent days and levels of 5-HIAA in CSF. In a comparison of depressed probands with or without a positive family history for alcoholism, Rosenthal *et al* (1980) reported significantly lower concentrations of 5-HIAA in CSF in the subgroup with a positive family history. Linnoila *et al* (1987) reported that subjects with alcoholic fathers manifested both lower mean cerebrospinal 5-HIAA concentrations and more impulse-orientated behaviour than matched subjects without alcoholic fathers.

Peripheral serotonergic models

Reduced concentration (Banki, 1978) and uptake (Kent *et al*, 1985) of serotonin in platelets have been reported in alcoholic subjects. The formation of the 5-HT_2 receptor-linked second messenger inositol-1,4,5 triphosphate has also been shown to be significantly impaired in platelets from alcoholics versus matched controls. Neiman *et al* (1987) studied seven alcoholic men admitted for detoxification, who showed low initial uptake of serotonin into platelets, although this normalised with abstinence. It is possible that this may reflect an alcohol-induced alteration of the lipid microenvironment of the membrane-bound serotonin receptor (Sun & Sun, 1985) and serve as a state marker for alcoholism (Boismare *et al*, 1987). Friedman *et al* (1988) studied serotonin metabolism in 35 in-patient alcoholics: this group converted significantly more tryptophan than serotonin to kynurenine. This offers another possible explanation for a serotonergic deficiency.

Anxiety and serotonin

The biological basis of anxiety involves multiple neurotransmitter systems and it has been proposed that serotonin is implicated in a psychopathological continuum that includes anxiety (van Praag *et al*, 1987). Gray (1982) has put forward the view that anxiety is mediated through a "behavioural-inhibition system" involving serotonin-containing septohippocampal projections. Murphy & Pigott (1990) reviewed the human studies that supported a role for serotonin in anxiety. Examples include the observation that drugs which enhance the effects of serotonin (e.g. reuptake blockers) are effective in obsessive–compulsive (Thoren *et al*, 1980) and possibly panic (Kahn *et al*, 1987) disorders, while serotonin receptor antagonists may be clinically effective in generalised anxiety (Leysen *et al*, 1985; Peroutka *et al*, 1989). Kahn *et al* (1988) considered the evidence that a reduction in serotonin neurotransmission attenuates anxiety. In concordance, both benzodiazepines and the newer azapirone anxiolytics reduce the firing rates of serotonin-containing neurones (Blier & deMontigny, 1987).

Pharmacological treatment of alcoholism by drugs interacting with serotonin mechanisms

As we increasingly understand the molecular effects of alcohol, a rational pharmacotherapy appears possible. A new generation of therapeutic agents with serotonin-selective profiles represents such an opportunity. There is evidence to suggest that drugs which selectively interact with serotonin mechanisms can diminish both alcohol consumption and preference (Sellers & Naranjo, 1986). The effective drugs include the serotonin precursors (e.g. L-tryptophan), reuptake inhibitors (e.g. citalopram), releasing agents (e.g. fenfluramine), post-synaptic agonists (e.g. quipazine), and 5-HT_{1A} receptor partial agonists (e.g. buspirone).

The serotonin system is highly complex by virtue of its numerous receptor subtypes (Peroutka *et al*, 1989). The 5-HT_{1A} receptors are found at both pre- and post-synaptic sites; within animal models they mediate the intake of preferred solutions (Gatto *et al*, 1989). Repeated micro-injections of the 5-HT_{1A} partial agonist buspirone into the brains of rats have decreased the voluntary intake of alcohol by test animals (Privette *et al*, 1987). However, the degree of this effect was site-specific, the greatest effect being observed when administration was in the substantia nigra, nucleus accumbens/pre-optic area, or the medial lemniscus/zona incerta. In several studies, fluoxetine (a serotonin uptake blocker) (Gorelik, 1986; McBride *et al*, 1988; Haraguchi *et al*, 1989) or the 5-HT_{1B} receptor agonist trifluoromethylphenylpiperazine also diminished voluntary alcohol consumption (McBride *et al*, 1988), although a 5-HT_{1A} receptor agonist (8-hydroxy-dipropylamino-tetralin) did not. In another study, the administration of the 5-HT_{1A} receptor antagonist spiroxatrine with fluoxetine reduced alcohol consumption to a greater extent than fluoxetine alone (Murphy *et al*, 1989). This effect has been postulated to occur pre-synaptically, as the prior administration of 5-HT_1 and 5-HT_2 receptor antagonists did not block a reduction in alcohol use following the administration of a reuptake blocker of serotonin (Rockman *et al*, 1982; Murphy *et al*, 1985). Linnoila *et al* (1987) reported that intraperitoneally administered fluoxetine or fluvoxamine (another serotonin uptake blocker) attenuated the anxiolytic effects of an alcohol challenge in Swiss-strain mice; Rockman *et al* (1979) administered another serotonin reuptake blocker, zimelidine, to rats, with a similar result.

Azapirones: mechanisms in anxiety and alcoholism

The azapirones, including buspirone, are active in models that predict both anxiolytic and antidepressant activity; these compounds alter serotonergic neurotransmission, principally at the 5-HT_{1A} receptor. The brain areas most enriched with these sites are the dentate gyrus, hippocampus, and septal nuclei (Pazos & Palacios, 1985). The 5-HT_{1A} binding sites have been identified both pre- and post-synaptically. Azapirones act both as full serotonin receptor agonists (pre-synaptically) and as partial agonists (post-synaptically). Thus, in anxiety states, where a regional serotonergic excess is thought to exist, azapirone acting at pre-synaptic sites reduces serotonergic release, while post-synaptically competing with serotonin for a finite number of receptors. Conversely, on the assumption that alcoholism is a serotonergic-deficiency disorder, azapirones would bestow a regionally specific post-synaptic agonism in the relative absence of serotonin. With chronic administration, pre-synaptic desensitisation would also permit these neurones to fire more often. Thus, the azapirones' unique pharmacological activities may normalise serotonergic transmission in brain regions which show either an excess (anxiety) or deficit (alcoholism).

Clinical trials

Three relevant trials have been reported up to now. Firstly, Olivera *et al* (1990) studied 60 individuals

with dual diagnoses of chronic anxiety and substance dependence according to DSM-III-R criteria, in an open trial of buspirone. At a relatively small daily dose (mean 15.8 mg), a significant reduction was reported in scores on the Hamilton Rating Scale for Anxiety (HRSA) and the Zung Anxiety Scale. At this dose buspirone was well tolerated by the subjects in the study.

Secondly, Bruno (1989) employed buspirone (mean dose 20 mg per day) in an eight-week double-blind trial in 50 alcoholic out-patients with a variety of other psychiatric diagnoses; the treatment discontinuation rate was significantly lower in the buspirone group. A visual-analogue measure demonstrated reduced craving in the buspirone group, and this was associated with reductions in scores on the HRSA and the Hamilton Rating Scale for Depression (HRSD).

Thirdly, Tollefson *et al* (1990) reported a randomised placebo-controlled double-blind investigation of buspirone in 51 ambulatory patients with concurrent generalised anxiety disorder and alcohol abuse/dependency, confirmed by the Structured Clinical Interview for Diagnosis. Of the 51 patients, 42 (22 in the buspirone group and 20 in the placebo group) completed at least four weeks of treatment. Fourteen subjects completed the entire 24 weeks of study; ten of these had been assigned to buspirone and four to placebo (a statistically significant difference, $P < 0.05$). The most frequent reason for leaving the study was that the patient's condition had worsened or not improved: 3 buspirone and 12 placebo patients withdrew for this reason. This difference favoured the active treatment, and was also significant ($P < 0.05$). The mean final total daily dose was 42.25 mg. The mean reduction in score on the HRSA significantly favoured buspirone over placebo at week 12 and thereafter to the end-point visit: 16 out of 22 buspirone versus only 6 out of 20 placebo patients were considered to have achieved a full response, and this overall group difference was also statistically significant. A similar analysis of secondary mood symptoms revealed a non-significant trend towards greater improvement on the HRSD for the buspirone recipients.

Serotonin reuptake blockers

Following an alternative strategy, several investigators have employed a series of serotonin reuptake blockers in alcoholism. Naranjo *et al* (1986) conducted a double-blind, randomised cross-over study of zimelidine (200 mg/day); zimelidine decreased alcohol use, with a corresponding increase in abstinent days, in non-depressed alcoholic men. A similar group of subjects received citalopram or placebo in a four-week double-blind cross-over trial, with a similar outcome. Other reuptake blockers of serotonin, including indalpine, sertraline, and clomipramine, have also reportedly reduced the voluntary intake of alcohol (LeBourhis *et al*, 1981; Daoust *et al*, 1985; Gill *et al*, 1988).

A neurophysiological link to craving?

Modell *et al* (1990) reviewed a substantial body of literature which suggested that basal ganglia/limbic-striatal/thalamocortical circuits may be involved in alcohol craving. This model proposes that craving may be analogous to obsessive-compulsive symptoms. The therapeutic profile of several potent serotonin reuptake blockers in both obsessive-compulsive disorder and alcoholism underscores this possible neurophysiological link. The reduced intake of alcohol with specific reuptake blockers could be mediated by increased synaptic levels of serotonin, secondary to a dampening of terminal autoreceptor affinity, while the resulting increased serotonin activity within frontal optico-thalamic pathways would inhibit compulsive drives. An alternative mechanism may be the induction of post-synaptic 5-HT_2 receptor subsensitivity; a consequent decrease in serotonin neurotransmission in the striatoaccumbens has been proposed in explaining the efficacy of these compounds in obsessive-compulsive disorder (Zohar *et al*, 1988).

Discussion

Alcoholism and anxiety frequently coexist and may be interactive. Evidence suggests that a spectrum of behaviour disorders, including anxiety and alcoholism, are influenced by serotonin systems. Both pre-clinical and clinical trials with a variety of serotonin-selective pharmacological probes have reliably demonstrated this association.

Building on serotonin as a common denominator in anxiety and alcoholism, it has been found in subjects with both diagnoses that buspirone is an effective anxiolytic that also reduces associated dysphoria (Tollefson *et al*, 1990). Whether anxiolysis directly reduces the associated characteristics of alcohol abuse (e.g. craving) has not yet been unequivocally shown. However, in the same study, assignment to buspirone was associated with a significantly greater improvement in both the subjective and the doctor's clinical global impressions of both anxiety and alcohol problems than was the case with placebo.

The evidence reviewed above seems to provide the foundation for the possible incorporation of

novel and selective serotonergic compounds into the pharmacological treatment of alcoholism. Their favourable side-effect profile and the absence of associated mood-altering or reinforcing properties argue for continued investigation. An evolution may be anticipated towards eventual specific treatment strategies, matched to specific comorbid symptom complexes within the overall population of alcoholics. Pharmacotherapy, however, is likely to remain only part of a comprehensive and broadly based treatment programme.

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