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Central Serotonin and Impulsive Aggression

EMIL F. COCCARO

The role of central serotonergic (5-HT) system dysfunction in the regulation of aggression in both animals and man has been investigated for more than the past two decades. Evidence for reduced central 5-HT in the mediation of aggression comes from both behavioural and correlative studies. Functional reduction and augmentation of 5-HT activity is respectively associated with increased and decreased aggression in various animal models of aggression. While similar studies in man have not been performed, strong and consistent associations between indices reflecting reduced pre-synaptic 5-HT activity and aggression have been reported. Evidence of post-synaptic receptor upregulation in the brains of suicide victims has also been reported leaving the functional status 5-HT activity in such patients an open question. However, reduced neuroendocrine (i.e. prolactin) responses to fenfluramine, a 5-HT uptake inhibitor/releaser, which activates both pre- and post-synaptic sides of the 5-HT synapse, strongly suggest that overall central 5-HT activity is reduced in mood and/or personality disorder patients with history of suicidal and/or impulsive aggressive behaviour. Preliminary data with the 5-HT receptor agonist *m*-chlorophenylpiperazine further suggest that reduced activity of post-synaptic 5-HT receptors may be an important correlate of impulsive aggressive behaviour. Pharmacological agents with potent 5-HT pre- and/or post-synaptic augmenting effects should be tested clinically to determine their efficacy in the treatment of impulsive aggressive behaviour in psychiatric patients.

The role of the central serotonergic (5-HT) system in behavioural disorders has been a focus of research for more than two decades (for reviews, see Åsberg *et al*, 1987; Meltzer & Lowy, 1987). Through its widespread projections to the cortex and various limbic structures, the 5-HT system is involved in the regulation of a wide variety of physiologic and affective functions, including sleep, appetite, noiciception, cognition, mood, sexual, and other motoric activity (Vogt, 1982). Hence, dysfunction within this system is likely to contribute to the aetiology of any of the various psychiatric disorders that prominently feature abnormalities in these functions (e.g. major affective, anxiety, eating, and personality disorders; Coccaro and Murphy, in press).

Recently, there is recognition that abnormalities within the central 5-HT system may be manifest across diagnostic groups along specific dimensions of behaviour. In particular, evidence that abnormalities of central 5-HT function are associated with impulsive (self- [i.e. suicidal] or other-directed) aggressive behaviour among patients from different diagnostic groups suggests that impulsive aggression may be the most common behavioural correlate of central 5-HT system dysfunction (Åsberg *et al*, 1987). Accordingly, this review will focus on work that reflects the role of the central 5-HT system in the expression of impulsive aggressive behaviour.

Animal studies

Evidence that 5-HT has played a central role in aggressive behaviour has existed in the literature since 1959. At that time 5-HT was first reported to reduce isolation-induced aggression in mice (Yen *et al*, 1959). Subsequently, a wealth of data from animal studies has been published supporting the hypothesis that central 5-HT is integrally involved in the regulation of aggressive behaviour (Soubrie, 1986).

In addition to isolation-induced aggression (a model in which aggressive behavour has been shown repeatedly to correlate inversely with central 5-HT activity (Garattini *et al*, 1969; Valzelli & Bernasconi, 1979), shock-induced fighting (Kantak *et al*, 1981; Sewell *et al*, 1982), muricidal behaviour (Waldbillig, 1979; Katz, 1980) and filicidal behaviour (i.e. pup killing; Copenhaver *et al*, 1978) are each increased and decreased by neurochemical manipulations which, respectively, decrease and increase central 5-HT activity.

Evidence exists that reduced central 5-HT activity is more closely associated with a tendency toward aggressive behaviour, rather than the frank expression of aggression itself. For example, previous exposure of rats to mice prevents the muricidal response to manipulations which reduce central 5-HT activity (Marks *et al*, 1977; Vergnes *et al*, 1977). Those findings suggest that in the absence of sufficient arousal, reduced central 5-HT activity may not be associated with aggression. In a recent study of tryptophan-depleted non-human primates, no aggressive behaviour occurred in the absence of conditions which heightened arousal of the subject (e.g. by insertion of a nasogastric tube; Chamberlain *et al*, 1987). Thus, reduced central 5-HT activity may be more specifically associated with a lowered threshold for aggressive responses to noxious

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stimuli than with unprovoked aggressive behaviour itself.

Human studies: post-mortem

Pre-synaptic indices

Studies analysing a post-mortem index of pre-synaptic 5-HT function have examined concentrations of 5-HT and/or its metabolite 5-HIAA, or the binding of tritiated imipramine to brain tissue taken from individuals who had committed suicide (Åsberg *et al*, 1987). While it is not generally known if these subjects displayed clinically significant impulsive aggressive behaviour prior to death, some of the individuals had committed suicide by violent means and may have been generally aggressive during their lives.

Small but statistically significant reductions in 5-HT and/or 5-HIAA concentration have been reported in one or more brain areas in six of eleven reports published to date. Reductions in these metabolites have been reported for the brain stem or other brain regions in all six reports (Shaw *et al*, 1967; Bourne *et al*, 1968; Pare *et al*, 1969; Lloyd *et al*, 1974; Beskow *et al*, 1976; Korpi *et al*, 1986) but for the frontal cortex in only one (Beskow *et al*, 1976). Accordingly, while there may be regional differences in 5-HT system abnormalities in the brains of suicide victims, pre-synaptic 5-HT activity in at least the brain stem may be reduced in these individuals.

Similarly, reductions in the maximal binding of tritiated imipramine (^{3}H-IMI: B_{max}) to brain tissue in various brain regions of suicide victims have been reported in four of six studies pubished to date (Stanley *et al*, 1982; Crow *et al*, 1984; Paul *et al*, 1984; Gross-Isseroff *et al*, 1989); no differences were reported in one (Owen *et al*, 1986) while an increase in ^{3}H-IMI: B_{max} was reported in another (Meyerson *et al*, 1982). ^{3}H-IMI is thought to bind to a pre-synaptic 5-HT receptor site associated with the 5-HT transporter (Langer *et al*, 1987) and may reflect some aspect of pre-synaptic 5-HT function. These observations are compatible with those of the monoamine metabolite studies reviewed above and suggest that there may be a structural abnormality in pre-synaptic 5-HT function (e.g. loss of 5-HT-transporter sites; loss of pre-synaptic 5-HT terminals) in individuals displaying serious suicidal behaviour.

Post-synaptic indices

In contrast to those observations, putative indices of increased post-synaptic 5-HT function from brain tissue of suicide victims have been reported. Greater binding of radioligands for the 5-HT_2 post-synaptic receptor have been reported as increased in the frontal cortex of suicide victims in four of eight studies published (Arora and Meltzer, 1989; Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et al*, 1986); one of the four remaining negative studies noted a small, statistically non-significant increase in 5-HT_2 binding sites (Cheetham *et al*, 1988).

This observation is thought to reflect a compensatory response of the post-synaptic 5-HT_2 receptor to diminished pre-synaptic activity or innervation. Empirical support for this hypothesis is limited, although an inverse, statistically non-significant ($r = -0.42$, $P > 0.20$) relationship between ^{3}H-IMI and 5-HT_2 receptor binding sites in the frontal cortex of violent suicide victims has been reported (Stanley & Mann, 1983).

Possibly, increased 5-HT_2 receptor binding does not represent a compensatory response to diminished pre-synaptic 5-HT activity in impulsive aggressive and suicidal individuals. Support for this hypothesis includes the observation that depletion of pre-synaptic 5-HT is accompanied neither by an increase in 5-HT_2 receptor number (Seeman *et al*, 1980; Blackshear *et al*, 1981; Quik & Azmitia, 1983) nor by an increase in receptor-mediated biochemical responses to 5-HT stimulation (Conn & Sanders-Bush, 1986).

Alternately, if 5-HT_2 receptor upregulation is associated with an increase in 5-HT_2 subsystem activity, it is possible a decrease in 5-HT_1 subsystem activity could result. Recent evidence of reciprocal relationships between 5-HT_2 and 5-HT_1 receptor-mediated functions (Gudelsky *et al*, 1986), together with data demonstrating simultaneous decreases and increases, respectively, in 5-HT_2 and 5-HT_1-mediated behavioural responses during antidepressant treatment (Pericic & Manev, 1988), provide preliminary support for this conjecture. Pre-clinical data have suggested a role in the mediation of behavioural inhibition for 5-HT_1 rather than 5-HT_2 receptor subsystems (McMillen *et al*, 1987). Hence, if 5-HT_2 receptor upregulation is a compensatory phenomenon, it is possible that it is secondary to reduced activity within the 5-HT_1 system, rather than reduced 5-HT activity within the synapses served by 5-HT_2 receptors. Further research with 5-HT receptor-subtype-specific probes will be necessary to resolve these issues.

Human studies: ante-mortem

Pre-synaptic indices

Åsberg *et al* (1987) have reviewed evidence supporting the hypothesis that putative pre-synaptic 5-HT indices are reduced in suicidal behaviour. Reduced cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (CSF 5-HIAA) have also been reported in most clinical studies of

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patients (regardless of psychiatric diagnosis) who have attempted suicide prior to study. These data strongly support the notion that vulnerability to commit a suicidal act is related to reduced pre-synaptic 5-HT activity. However, as suicidal behaviour is often related to aggressive behaviour in general (Brown *et al*, 1982; Berglund, 1984), these data also raise the possibility that low concentrations of 5-HIAA in cerebrospinal fluid are inversely related to vulnerability to respond aggressively to adverse stimuli.

To date, at least 13 studies investigating the relationship between pre-synaptic indices of 5-HT function in aggressive behaviour have been reported. Nine utilise levels of 5-HIAA in cerebrospinal fluid as a central 5-HT index (Table I) and four utilise whole blood 5-HT, plasma tryptophan (the 5-HT precursor), or ^{3}H-IMI binding to the platelet as a peripheral 5-HT index (Table II).

Nearly all studies show that concentrations of CSF 5-HIAA are inversely related to clinician- or self-reported ratings of aggression (Brown *et al*, 1979, 1982; Linnoila *et al*, 1983a; Lidberg *et al*, 1985); irritability and hostility (Rydin *et al*, 1982; Brown & Goodwin, 1984; van Praag, 1986; Roy *et al*, 1988), or criminal activity (Linnoila *et al*, 1983a; Lidberg *et al*, 1985; van Praag, 1983; Virkkunen *et al*, 1987) (Table I). CSF 5-HIAA has also been found to correlate inversely with self-rated behavioural difficulties during childhood (Brown *et al*, 1985), raising the possibility that reduced 5-HT activity during childhood and adolescence may have also been associated with behavioural difficulties during that time.

Even peripheral indices of 5-HT function may correlate with aggressive behaviours in some clinical populations. Three of four studies examining a peripheral index of 5-HT function (Table II) have demonstrated an inverse relationship with clinician-rated measures of aggression, reflected either as a measure of current behaviour (Greenburg & Coleman, 1976; Stoff *et al*, 1987) or as the historic occurrence of a serious aggressive act (e.g. leading to incarceration; Branchey *et al*, 1984). While a positive correlation between whole blood 5-HT and conduct disorder ratings in adolescent males was reported in the most recent study Pliszka *et al*, 1988), there is preliminary evidence that whole blood 5-HT varies inversely with other central indices of 5-HT function (McBride *et al*, 1989). Further investigation into the pathophysiologic significance of such findings is necessary. Whether (and how) these indices mirror processes occurring in the relevant areas of the brain, as proposed for platelet ^{3}H-IMI binding, or represent peripheral factors that play a role in regulating the disposition of 5-HT in the brain, as proposed for the plasma tryptophan/amino acid ratio, remains to be determined.

Post-synaptic indices

While there are no data available examining the relationship between an index of post-synaptic 5-HT function and impulsive aggression in clinical samples, a positive relationship between the cortisol response to 5-HTP challenge and history of suicidal behaviour in 40 depressed and manic patients has been reported (Meltzer *et al*, 1984). This finding, like that of increased 5-HT$_2$ receptor binding in the brains of suicide victims reviewed above, has been interpreted as reflecting post-synaptic receptor upregulation in response to diminished pre-synaptic 5-HT (Meltzer *et al*, 1984). However, while the cortisol response to 5-HTP challenge has been shown to reflect activation at 5-HT synapses in general (Petraglia *et al*, 1984) these responses do not appear to reflect activity at 5-HT$_2$ post-synaptic receptors specifically (Facchinetti *et al*, 1987). Further investigation with more selective and specific post-synaptic 5-HT receptor probes will be necessary to resolve the functional state of the post-synaptic 5-HT receptors in these largely bipolar patients.

Integrated pre-synaptic and post-synaptic indices

Evidence of reduced pre-synaptic 5-HT activity and increased 5-HT receptor binding or neuroendocrine responsiveness to 5-HTP challenge in aggressive and suicidal patients points to a reduction in overall 5-HT activity in those patients. In this model, increased indices of post-synaptic 5-HT receptor activity (Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et al*, 1986) represent a compensatory response to reduction in pre-synaptic 5-HT activity. Presumably, the compensatory mechanisms at the post-synaptic site are insufficient, and overall 5-HT activity is reduced. However, because no study to date has employed a methodology capable of assessing simultaneous pre- and post-synaptic 5-HT activity, the actual state of overall 5-HT function in patients with impulsive aggression or histories of suicide attempt is unknown. To address this issue, Coccaro *et al* (1989) examined the prolactin (PRL) response to fenfluramine in patients with mood and/or personality disorders.

Fenfluramine increases 5-HT system activity at 5-HT synapses by releasing endogenous stores of 5-HT and by blocking its reuptake into the pre-synaptic terminal (Rowland & Carlton, 1986). The burst of released 5-HT by acute challenge with fenfluramine then stimulates the post-synaptic 5-HT receptor and leads to a variety of post-synaptically mediated events which, in the hypothalamic-pituitary axis, lead to the release of anterior pituitary hormones such as prolactin (Quattrone *et al*, 1983; Lewis & Sherman, 1985). Fenfluramine-induced release of prolactin is antagonised by 5-HT

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TABLE I

Clinical psychobiologic studies regarding indices of central 5-HT function and impulsive aggressive behaviour

Study	*Patient group*	*5-HT index*	*Result**
Brown *et al* (1979)	24 male naval recruits DSM-II personality disorder	CSF 5-HIAA	Inverse correlation with life history of aggressive events ($r = -0.78$)
Brown *et al* (1982)	12 male naval recruits with DSM-III borderline personality disorder (BPD)	CSF 5-HIAA	Inverse correlation with MMPI-Pd scale ($r = -0.77$); trivariate relationship with low CSF 5-HIAA and life history of aggression and suicide attempt
Rydin *et al* (1982)	14 pairs of depressed and/or suicidal patients (6 male/ 8 female pairs) with low and normal CSF 5-HIAA matched for age and body height	CSF 5-HIAA	Low CSF 5-HIAA patients had higher Rorschach ratings for variables related to hostility and anxiety
Linnoila *et al* (1983)	36 male violent offenders with history of alcoholism and DSM-III personality disorder	CSF 5-HIAA	Violent offenders with 'impulsive' personality disorders had lower CSF 5-HIAA than those with a 'non-impulsive' personality disorder; CSF 5-HIAA was lower in patients with history of suicide attempt
Lidberg *et al* (1985)	16 male homicide offenders (5 subjects who had killed a sexual partner; 11 subjects who had killed someone other than a sexual partner)	CSF 5-HIAA	Subjects committing homicide against sexual partner had lower CSF 5-HIAA than those who killed a person other than a sexual partner
Brown *et al* (1985)	12 male naval recruits from Brown *et al* (1979, 1982)	CSF 5-HIAA	Inverse correlation with self-reported behavioural problems during childhood
van Praag (1983)	50 patients with depression; 25 with low CSF 5-HIAA, 25 with normal CSF 5-HIAA	CSF 5-HIAA (Post-probenecid)	Greater frequency of suicide attempt, outward directed hostility and contact with the police in low CSF 5-HIAA group
Virkkunen *et al* (1987)	20 male arsonists	CSF 5-HIAA	Reduced CSF 5-HIAA in 'impulsive' arsonists; inverse correlation with criminal acts other than arson ($r = -0.46$)
Roy *et al* (1988)	17 healthy (10 male/7 female) nonpatient volunteers	CSF 5-HIAA	Inverse correlation with 'acting out' hostility ($r = -0.53$)
Coccaro *et al* (1989)	20 male patients with DSM-III Axis II personality disorder	Prolactin (PRL) response to fenfluramine challenge (60 mg,p.o.): PRL[FEN]	Inverse correlation with 'impulsive aggression' ($r = -0.77$). Affect of this dimension upon PRL[FEN] found to account for the reduced PRL[FEN] responses seen among patients with BPD and histories of suicide attempt and episodic alcohol abuse

* Probability values for reported correlation coefficients are 0.05 (i.e. $P<0.05$) or lower.

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TABLE II

Clinical psychobiologic studies regarding indices of peripheral 5-HT function and impulsive aggressive behaviour

Study	*Patient group*	*5-HT index*	*Result**
Greenberg & Coleman (1976)	30 mentally retarded patients with hyperactivity and aggressive behaviour	Whole blood 5-HT	Inverse relationship with hyperactivity and aggression observed
Pliszka *et al* (1988)	44 adolescent males; 27 at a juvenile detention centre; 17 at a community mental health clinic	Whole blood 5-HT	Positive correlation with conduct ratings ($r = 0.53$) in sample ($n = 43$)
Branchey *et al* (1984)	43 male alcoholics	Plasma tryptophan/ neutral amino acid ratio	Tryptophan AA ratio low in alcoholics with history of aggression compared to alcoholics without this history
Stoff *et al* (1987)	17 (14 male/3 female) pre-pubertal children with DSM-III conduct disorder; 15 age/sex matched control children	Platelet ^{3}H-IMI binding (B_{max})	Conduct disorder children low compared to an age-matched group of normal children. Inverse correlation with the aggressive ($r = -0.48$) and externalizing ($r = -0.42$) factors of a parent-evaluated assessment in entire sample

* Probability values for reported correlation coefficients are 0.05 (i.e. $P<0.05$) or lower.

receptor blockers (Quattrone *et al*, 1983; Lewis & Sherman, 1985). It may be augmented after long-term destruction of pre-synaptic 5-HT terminals in animal studies (Kuhn *et al*, 1981), indicating that this measure can reflect, to some degree, the sensitivity of the post-synaptic 5-HT receptor. However, because the initial site of action of fenfluramine is pre-synaptic, and can be abolished by acute lesions of pre-synaptic 5-HT terminals (Quattrone *et al*, 1979), PRL responses to fenfluramine are interpreted generally as reflecting the 'net' result of pre- and post-synaptic activation of the 5-HT system in the hypothalamic–pituitary axis (Siever *et al*, 1984; Coccaro *et al*, 1989).

Studies of the fenfluramine challenge in patients with major affective disorder and/or personality disorders (Coccaro *et al*, 1989) reveal that such patients exhibit reduced prolactin responses to fenfluramine compared with normal controls. In patients with a history of suicide attempt, prolactin responses to fenfluramine were reduced in comparison with the patients without this history or to normal controls. However, only those patients with DSM-III axis II personality disorder displayed an inverse correlation between the prolactin response to fenfluramine and 'irritable' impulsive aggression (Fig. 1); neither patients with major affective disorders or normal controls showed any relationship

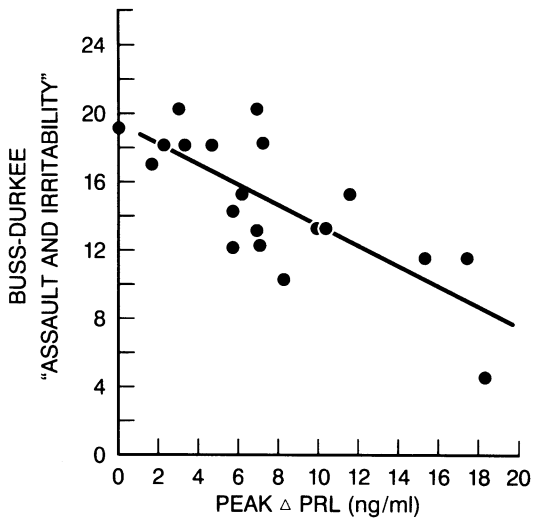


FIG. 1 Correlation between peak delta PRL responses to fenfluramine and the sum score of the self-rated Buss-Durkee 'Assault' and 'Irritability' subscales (from the Buss-Durkee Hostility Inventory; Buss & Durkee, 1957) in 20 male patients with DSM-III personality disorders; $n = 20$, $r = -0.77$, $P = 0.0002$. (Data from Coccaro *et al*, 1989.)

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between outwardly directed impulsive aggression and this index of overall 5-HT function. Additionally, patients with histories of bipolarity did not manifest an inverse relationship between history of suicide attempt (i.e. inwardly directed aggression) and prolactin responses to fenfluramine. In the subset with personality disorder, the inverse relationship between prolactin responses to fenfluramine and impulsive aggression appeared to account for reduced prolactin responses to fenfluramine observed among three subgroups of patients: those meeting DSM-III criteria for borderline personality disorder; those defined as having a history of suicide attempt(s); and those with a history of episodic alcohol abuse. Accordingly, the most powerful correlate of overall 5-HT function in these groups appeared to be a history of impulsive aggressive behaviour.

While the prolactin response to fenfluramine cannot specifically locate the pre- and post-synaptic site of this abnormality, preliminary data reveal a similar inverse relationship between prolactin responses to the direct post-synaptic 5-HT receptor agonist, *m*-chlorophenylpiperazine (Mueller *et al*, 1985, 1986), and impulsive aggression in five of the subjects included in our fenfluramine challenge study ($r = -0.87$, $P<0.05$; Coccaro *et al*, unpublished data). This suggests that post-synaptic 5-HT receptor sensitivity may be reduced in such patients and that this abnormality may contribute to the reduced prolactin responses to fenfluramine observed in these patients. However, because the endogenous 5-HT released by fenfluramine may stimulate any number of 5-HT receptor subtypes, it is not known if the diminished PRL responses to fenfluramine are reflecting diminished post-synaptic receptor sensitivity of the 5-HT_1 (a,b,c,d), 5-HT_2, or 5-HT_3 receptor subtype. Further investigation with more selective and specific post-synaptic 5-HT receptor probes will be necessary to uncover which of the many 5-HT receptor subtypes may be subsensitive in these patients.

A psychobiological model of 5-HT function in impulsive aggression: a rationale for the understanding and treatment of impulsive aggression

Overall, the picture that emerges from these data is that reduced indices of 5-HT function correlate most specifically with 'irritable' impulsive aggression, rather than premeditated aggression or violence. The observation that violent subjects (Linnoila *et al*, 1983a) and/or homicidal offenders (Lidberg *et al*, 1985) who commit premeditated acts of aggression toward others have relatively normal concentrations of CSF 5-HIAA suggests that violence by itself is not necessarily associated with reduced 5-HT function. Moreover, most studies of patients with low CSF 5-HIAA find increases in irritability (Brown & Goodwin, 1984) or hostility (Rydin *et al*, 1982; van Praag, 1986; Roy *et al*, 1988) if not histories of actual impulsive (outwardly directed) aggressive acts. This clinical picture is compatible with that observed in animal studies that characterise the central hyposerotonergic state by hyperirritability, hyperexcitability, and hypersensitivity (Valzelli, 1981).

An understanding of how reduced 5-HT function relates to non-premeditated suicidal behaviour follows directly from these observations. Reduced function in the relevant central 5-HT pathways renders the affected individual vulnerable to responding to noxious stimuli in an exaggerated fashion. Hence, the individual strikes out at the source of the noxious stimuli (i.e. arousal), be it the self (e.g. in dysphoric-depressive states) or another stimulus in the environment (e.g. an angry-hostile assault) at a lower threshold. Accordingly impulsive aggressive behaviour may be considered to be the net result of inhibiting (mediated by 5-HT) and activating neuronal systems (mediated by other neurotransmitter systems, such as norepinephrine or dopamine (Depue & Spoont, 1986)).

Such a multineurotransmitter-based model of impulsive aggression may help to explain the apparent lack of relationship between suicidal behaviour and 5-HT function in bipolar patients in studies with fenfluramine challenge (Coccaro *et al*, 1989) or CSF 5-HIAA (Ågren, 1983; Roy-Byrne *et al*, 1983; Berrettini *et al*, 1986). Is it possible that differences exist among subject populations (e.g. bipolar versus nonbipolar) in the functioning of neuronal systems involved in the expression of impulsive aggressive behaviour? Indices of pre-synaptic noradrenergic function are reduced in bipolar patients (see Siever, 1987, for review). Hence, this deficit could impair the neuronal systems involved in activation so that neither inwardly nor outwardly directed aggression could occur. A report of non-aggressive behaviour in rats with low 5-HT levels and an accompanying noradrenergic system deficit offers some experimental support for this hypothesis (Hodge & Butcher, 1975).

A similar explanation may be given in unipolar depressed patients where an inverse relationship has been observed between prolactin responses to fenfluramine and history of suicide attempt but not with impulsive aggression (Coccaro *et al*, 1989). As reduced post-synaptic $alpha_2$ noradrenergic receptor sensitivity has been noted in depressed patients (Siever, 1987), it is possible that diminished post-synaptic noradrenergic receptor sensitivity may generally buffer the behavioural activation-inhibition system, blunting stimulus-linked

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activation except in times of great distress (e.g. during a severe major depressive episode). During such an episode, the individual may act upon his or her impulse against the source of distress (e.g. the worthless and/or guilt-ridden self) and attempt suicide. Despite reduced post-synaptic noradrenergic receptor sensitivity in depressed patients, evidence of noradrenergic dysregulation with wide fluctuations of pre-synaptic output has been described in depressed (particularly unipolar) patients (Siever, 1987), providing support for this hypothesis.

Clinical psychopharmacology of impulsive aggression

Psychopharmacologic agents generally used in the treatment of impulsive aggression include lithium carbonate, the non-selective beta-adrenergic antagonists, neuroleptics, and carbamazepine. Unfortunately, while these agents are often prescribed, there is limited data from double-blind clinical studies to support their use in the treatment of impulsive aggression. The best available data from double-blind, placebo-controlled studies support the use of lithium carbonate in the therapy of impulsive aggression in antisocial adults (e.g. prison inmates; Sheard *et al*, 1976), conduct-disordered adolescents (Campbell *et al*, 1984), and mentally handicapped subjects (Worrell *et al*, 1975; Tyrer *et al*, 1984). Numerous case studies and open trials, but fewer double-blinded studies, have also suggested the efficacy of high-dose beta-adrenergic antagonists in controlling aggression (Sorgi *et al*, 1986), particularly in organically compromised individuals (Elliot, 1977; Yudofsky *et al*, 1981) or schizophrenia (Sorgi *et al*, 1986). Two placebo-controlled double-blinded studies have cited the efficacy of neuroleptic agents over placebo in the treatment of suicidal and/or impulsive aggressive behaviour in adults (Montgomery & Montgomery, 1982) and children (Campbell *et al*, 1984). In the first, depot flupenthixol was found to be effective in reducing suicide attempts in a population of patients with recurrent suicide attempts and impulsive aggressive behaviour (Montgomery & Montgomery 1982). In the second study, low-dose haloperidol was found to be efficacious (though less well tolerated than lithium) in reducing aggressivity in hospitalised conduct-disordered children (Campbell *et al*, 1984). Other placebo-controlled studies of neuroleptic treatment in personality disorder patients demonstrate modest efficacy in clinician- and self-rated hostility or belligerence with low-dose haloperidol (Soloff *et al*, 1986) or a tendency toward reduced self-rated hostility with low-dose thiothixine (Goldberg *et al*, 1986). Finally, one small double-blinded, placebo-controlled cross-over study demonstrated the efficacy of carbamazepine in reducing episodes of behavioural dyscontrol and aggression in female patients with borderline personality disorder (Cowdry & Gardner, 1988).

The pharmacologic non-specificity of these agents, however, cannot allow the testing of a 5-HT hypothesis of impulsive aggression in man. While serotonin-enhancing effects of lithium carbonate have been demonstrated (Bunney & Garland-Bunney, 1987), lithium may also diminish catecholaminergic function (Linnoila *et al*, 1983b, c). Because increased noradrenergic and/or dopaminergic system function is associated with aggressive behaviour in animals (Senault, 1970; Hodge & Butcher, 1975) and in clinical studies (Brown *et al*, 1979), it is not known if lithium's anti-aggressive effects are due to increased serotonergic function or to decreased catecholaminergic function.

The same possibility exists for the non-selective beta-blockers and for carbamazepine. In addition to blocking the activity of endogenous norepinephrine at beta-receptors, non-selective beta-blockers (e.g. propranolol, pindolol) bind to 5-HT_1 receptors and appear to have 5-HT_1 agonist properties (Hjorth & Carlsson, 1986) at dosages in the range of those used in the treatment of aggressive behaviour. This raises the possibility that 5-HT_1 agonist effects of the non-selective beta-blockers may contribute to the clinical efficacy of these agents. However, recent reports that lipophobic beta-blockers (which do not readily cross the blood–brain barrier; e.g. nadolol) are also efficacious in the treatment of aggression (Sorgi *et al*, 1988), suggest that these agents may not work through a central 5-HT mechanism.

Similarly, carbamazepine has been shown to have effects on both 5-HT and catecholaminergic systems. Carbamazepine has been shown to increase levels of plasma tryptophan (Pratt *et al*, 1984; which may then be taken up by brain 5-HT neurons and converted to 5-HT) and to diminish dopaminergic function in some studies (Waldmeier *et al*, 1984; Post *et al*, 1985). However, the observation that carbamazepine is inactive in animal models of aggression (Koella *et al*, 1975) thought to reflect central serotonergic mechanisms (Soubrie, 1986; Depue & Spoont, 1986) suggests that carbamazepine's anti-aggressive activity may not be due to an enhancement of central 5-HT.

The efficacy of neuroleptics in aggression would appear to be due to their antidopaminergic (at low to high doses) and sedative effects (at high doses). However, the observation that neuroleptics have moderate binding affinity for 5-HT_2 receptors (Ortmann *et al*, 1982), that 5-HT_2 receptor agonists and antagonists downregulate 5-HT_2 receptors (Leyson *et al*, 1986), and that increased 5-HT_2 receptor number may be associated with violent suicidal behaviour (Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et*

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al, 1986) raises the possibility that neuroleptics, too, may have a serotonergic mode of action in the treatment of impulsive aggression. Observations suggesting that haloperiodol (Soloff *et al*, 1986) may be more efficacious than thiothixine (Goldberg *et al*, 1986) in this regard, and those demonstrating that haloperiodol is more potent than thiothixine at 5-HT_2 receptor binding (Ortmann *et al*, 1982), provides some support for this conjecture. Accordingly, studies comparing a neuroleptic with potent 5-HT_2 antagonistic properties (e.g. clozapine; Lee & Tang, 1984; Wilmot & Szczepanik, 1989) against one without these properties (e.g. thiothixine; Ortmann *et al*, 1982), in the treatment of impulsive aggression, would be of interest.

Presently, there are at least two 5-HT specific agents available for such clinical trials. These agents include the atypical antidepressant, fluoxetine, a potent and specific 5-HT uptake inhibitor (Stark *et al*, 1985), and the atypical anxiolytic, buspirone, which has high affinity for the 5-HT_{1a} receptor (Hoyer, 1988). These agents, and others in their class, have shown activity in animal models of aggression (Berzsenyi *et al*, 1983; Olivier *et al*, 1984; Molina *et al*, 1986; McMillen *et al*, 1988) and thus support a rationale for their use in clinical trials. There is one report of tryptophan's efficacy in the treatment of aggressive schizophrenics (Morand *et al*, 1983), though high-dose tryptophan may have effects on catecholaminergic systems as well (i.e. by competing with tyrosine, the precursor of the catecholamines, for uptake into the brain; Møller, 1980). Other 5-HT specific agents currently under development, and potentially available for similar efficacy trials, include the 5-HT specific uptake inhibitors sertraline and fluvoxamine, and the 5-HT_{1a} and 5-$HT_{1a,b}$ agonists gepirone and eltoprozine, respectively. Clinical trials with each of these agents will be necessary in order to more fully understand the clinical psychopharmacology of 5-HT agents in the treatment of suicidal and/or impulsive aggressive behaviours.

Future directions

A reduction in central 5-HT function appears to be associated with a tendency toward suicidal and impulsive aggressive behaviour in both animal and clinical studies. However, while selective 5-HT agents are becoming available for clinical trials, future investigations will need to focus on the specific neuropharmacologic nature of these central 5-HT abnormalities so that pharmacotherapy can be more rationally targeted to the treatment of impulsive aggression as it appears in clinical populations.

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E. F. Coccaro MD, *Director, Clinical Neuroscience Research Unit, Department of Psychiatry, Eastern Pennsylvania Psychiatric Institute, Medical College of Pennsylvania, Philadelphia*

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