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5-HYDROXYTRYPTAMINE AND DEPRESSION: A MODEL FOR THE INTERACTION OF NORMAL VARIANCE WITH PATHOLOGY

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1 Theories linking 5-hydroxytryptamine (5-HT) with depression are briefly reviewed. The various experimental strategies adopted to investigate this relationship, examination of autopsy data, CSF metabolite data, 5-HT re-uptake patterns in human blood platelets and imipramine binding studies in human platelets, are discussed.

2 Recent studies of 5-hydroxyindole acetic acid (5-HIAA) levels in cerebrospinal fluid have revealed a linkage between low 5-HIAA levels and suicide, aggression and impulsivity. Decreases in the number of imipramine binding sites have also been found in brains of suicide victims.

3 The available data lead to the conclusion that decreased 5-hydroxytryptaminergic function may be associated with an increased risk of depression, suicide, and some types of aggression.

Introduction: Evolution of the amine hypothesis of affective disorders

The drugs we are discussing today alter the activity of a neurotransmitter system that has been implicated in affective disorder for nearly two decades. Theories linking 5-hydroxytryptamine (5-HT) with depression and mania have persisted in one form or another with remarkable tenacity.

The initial suggestion that there may be a relationship between the functional state of a neurotransmitter like 5-HT and the clinical state of depression resulted from the clinical observation that the drug reserpine, widely used to treat hypertension in the 1950s, produced symptoms of depression in many patients. Laboratory experiments at that time were finding that reserpine depleted nerve endings of their stores of the monoamines in brain: 5-HT, dopamine, and noradrenaline (Carlsson *et al.*, 1957; Shore & Brodie, 1957). Somewhat later it was discovered that tricyclic antidepressants (TCAs) enhance monoamine functions, at least in part through inhibition of re-uptake—the process by which the neuron takes back the released neurotransmitter from the synapse (Glowinski & Axelrod, 1964). Clinical and laboratory findings thus converged to suggest the amine hypothesis of affective disorder (Bunney & Davis, 1965; Schildkraut, 1965; Prange, 1973). In its simplest form, this hypothesis states that depression is associated with a functional deficit of one or more brain neurotransmitter amines at specific central synapses, and that conversely mania is associated with a functional excess. In one formulation, depression and mania are specifically linked to alterations in 5-HT metabolism (Coppen, 1967; Lapin & Oxenkrug, 1969).

A more sophisticated reformulation of the hypothesis (Prange *et al.*, 1974) postulated a 'permissive' role for 5-HT- inadequate 5-HT function permitted instability in the central nervous system, making it more vulnerable to perturbations. Here the state changes associated with mania and depression were attributed to other neurotransmitter disturbances. Van Praag (1983) has recently reviewed his own and others' data providing evidence for the low 5-HT vulnerability hypothesis.

Evolution of this more modest view paralleled a number of methodological advances, including gas chromatography with mass spectrometry for more precisely measuring the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) in CSF, and perfection of statistical techniques for the assessment of heterogeneity. It became clear that when groups of clinically similar patients with major depression were examined, there was a wide distribution in measures of amine metabolites.

Today, evidence is mounting that altered 5-HT function contributes to a range of behaviours that reaches beyond the boundaries of affective disorder. Variability in brain 5-HT across several clinically defined populations as well as groups without major psychiatric diagnoses may correlate with a range of 'normal' levels of aggressiveness-impulsivity as well as with related behavioural extremes labelled 'pathologic', including suicide. This new broadened view of 5-HT behavioural relationships will be developed later.

This emerging hypothesis evolved from studies of the relationship between 5-HT and depression. The bodies of data that bear on 5-HT and depression can be grouped into indirect findings (inferences from

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research with animals) and direct findings from human clinical research.

Among the former indirect data are studies of the effects of drugs on 5-HT in animal brain, such as the original biochemical discoveries about MAO inhibitors, tricyclics and reserpine, and more recent experiments with chemical precursors of 5-HT (tryptophan and 5-hydroxytryptophan), lithium, and other substances of clinical interest. Such indirect approaches have traditionally suffered from a lack of specificity of drug effect. The earlier drugs typically acted non-selectively on catecholamines and other systems as well as on 5-HT, confounding efforts to isolate specific relationships. As is evidenced by the papers in this symposium, considerable progress has been made in the development of more specific pharmacological agents selective for central 5-hydroxytryptaminergic systems. These drugs are both an outgrowth of the research on depression and a powerful tool for further refinement of the emerging hypothesis alluded to earlier.

Among the direct approaches in humans, evidence clusters around five major biochemical strategies: 1. autopsy data on 5-HT and its metabolites in brains of suicidal and/or depressed patients; 2. 5-HT metabolites in cerebrospinal fluid (5-HIAA); 3. 5-HT uptake in human blood platelets as a model for neurons; 4. imipramine binding and 5-HT uptake in neurons and platelets and 5. neuroendocrine measures of 5-HT activity. In this paper we will briefly review the first four of these strategies.

A theme that emerges from examination of several biochemical systems, particularly CSF levels of 5-HIAA, is that these measures may provide relatively stable, perhaps genetically influenced characteristics, which in either the normal or pathological range of values may be related to important behavioural predispositions.

Depression

Autopsy data

The bulk of studies based on post-mortem examinations of the brains of suicidal depressed patients have found low levels of 5-HT and/or its metabolite (Table 1). While the earlier studies involved coarse measures of brain areas, some of the more recent work has pinpointed the most pronounced changes in regions rich in 5-hydroxytryptaminergic neurons. These neurons, centered in the brainstem and median and dorsal raphe nuclei of the midbrain, project axons to other points in the brainstem, spinal cord, and forebrain. Neurons in the raphe system project not only directly into ventricular CSF, but downward into the spinal cord and presumably account for the bulk of the brain's contribution to the 5-HT metabolite 5-HIAA in CSF (Valzelli, 1981). This fact of anatomy has proven fortuitous for the feasibility of CSF metabolite studies, since 5-HIAA has been found most decreased in raphe system areas that communicate with the ventricles (Lloyd *et al.*, 1974).

CSF metabolite data

Table 2 (a & b) summarizes results of two kinds of CSF 5-HIAA studies in depression. The first part of the table lists those studies comparing baseline 5-HIAA levels with controls, while the second part lists those which assessed 5-HIAA levels after administration of probenecid, a drug that inhibits active transport of 5-HIAA and related metabolites out of the CSF, thereby permitting an indirect reflection of a process more analogous to transmitter 'turnover'.

Among the baseline studies, about half link low 5-HIAA with depression (Ashcroft *et al.*, 1966; Dencker *et al.*, 1966; van Praag & Korf, 1971a;

Table 1 Amines and metabolites in the brains of suicide victims

Study	*Brain areas*	*Finding*	
Shaw *et al.* (1967)	Lower brainstem	5-HT low	
Bourne *et al.* (1968)	Lower brainstem	5-HT normal 5-HIAA low NA normal	
Pare *et al.* (1969)	Lower brainstem	5-HT low NA normal DA normal	
Lloyd *et al.* (1974)	Various brain regions including six raphe nuclei	5-HT Low in Nuc-dorsalis Cent-inferior	Raphe
Gottfries *et al.* (1976)	Various brain areas	5-HT normal 5-HIAA normal NA normal	

5-HT = 5-hydroxytryptamine; 5-HIAA = 5-hydroxyindoleacetic acid; NA = noradrenaline and DA = dopamine. Reproduced from Goodwin & Post (1975) with permission.

Table 2a 5-HT metabolism in affective illness—5-HIAA[a] in CSF: baseline values

Investigators	*Controls*[b]	*Depressed*[b]	*Manic*[b]
Fotherby *et al.* (1963)	11.5 ± 4.1[c] (11)	12.2 ± 8.2[c] (11)	—
Dencker *et al.* (1966)	—	—	Low (6)
Ashcroft *et al.* (1966)	19.1 ± 4.4[c] (21)	11.1 ± 3.9[c,d] (24)	18.7 ± 5.4[c] (4)
Bowers *et al.* (1969)	39.5 ± 13.1[c] (8)	34.0 ± 11.5[c] (8)	32.0 ± 10.3[c] (8)
Van Praag & Korf (1971b)	40 ± 24 (11)	17 ± 17[d] (14)	—
Papeschi & McClure (1971)	28 ± 3 (10)	22 ± 2 (12)	—
Coppen *et al.* (1972)	42.3 ± 14[c] (2) - -	19.8 ± 8.5[c,d] (31) 19.9 ± 7.2[d,e] (8)	19.7 ± 6.8[c] (18) —
Roos (1972)	29 ± 7[c] (26)	31 ± 8[c] (17)	36 ± 9[c] (19)
Mendels *et al.* (1972)	—	12.9 ± 6.0 (2)	17.1 ± 14.6 (4)
McLeod & McLeod (1972)	32.6 ± 11.4 (12)	20.5 ± 12.1[d] (25)	—
Goodwin *et al.* (1973)	27.3 ± 1.6 (29)	25.5 ± 1.3 (58)	28.7 ± 2.5 (16)
Sjöström (1973)	29 ± 1 (39)	30 ± 1 (23)	33 ± 2 (15)
Brodie *et al.* (1973)	—	Nonsignificant	—
Ashcroft & Glen (1974)	16 ± 8[c] (30)	18 ± 8[c] (9, bipolar) 10 ± 4[d] (11, unipolar)	15 ± 6[c] (11) —
Takahashi *et al.* (1974)	30.4 ± 2.1 (30)	20.1 ± 1.8[d] (30)	—
Subrahmanyam (1975)	40.6 ± 4.2 (12) —	26.2 ± 4.2 (24) 34.6 ± 4.8[e] (24)	— —
Banki (1977)	27.5 ± 1.2 (32)	14.6 ± 1.7[d] (16)	13.9 ± 2.9 (10)
Vestergaard *et al.* (1978)	28 ± 28 (22)	29 ± 12 (28)	40 ± 16 (4)
Goodwin & Post, unpublished data, 1978	—	22.6 ± 1.1 (70)	28.5 ± 2.7 (23)

[a] (5-HIAA) = 5-hydroxyindoleacetic acid. [b] Values are means ± s.e. mean (in ng/ml) with the numbers of patients in parentheses. [c] s.d. [d] Significantly lower. [e] Values for improved depressed patients.

Table 2b 5-HT metabolism in affective illness—5-HIAA[a] in CSF: probenecid-induced accumulations

Investigators	*Controls*[b]	*Depressed*[b]	*Manic*[b]
Roos & Sjöström (1969)	46 ± 13[c] (11)	38 ± 11[c] (17)	43 ± 13[c] (19)
Van Praag *et al.* (1970)	74 ± 26 (11)	39 ± 25[d] (14)	—
Korf & van Praag (1971)	67 ± 25 (15)	40 ± 27[d] (15)	—
Sjöström & Roos (1972)	(66% increase) (12)	(27%[d] increase) (24)	(20% increase) (21)
Sjöström (1973)	52 ± 4 (21)	37 ± 4[d] (11)	40 ± 4 (10)
Goodwin *et al.* (1973)	—	132 ± 7 (26)	133 ± 12 (8)
Van Praag *et al.* (1973)	110 ± 46.7 (12)	76 ± 43.2[d] (28)	—
Bowers (1976)	—	106 ± 14 (12)	120 ± 11 (10)
Banki (1977)	67 ± 3.0 (30)	40 ± 2.1[d] (30)	—
Berger *et al.* (1979)	—	Nonsignificant	—
Goodwin & Post unpublished data, 1978	—	143 ± 54.0[c] (70)	164.6 ± 57.7[c] (24)

[a] (5-HIAA) 5-hydroxyindoleacetic acid. [b] Values are means ± s.e. mean (in ng/ml) with the numbers of patients in parentheses. [c] s.d. [d] Significantly lower.

Coppen *et al.*, 1972; McLeod & McLeod, 1972; Subrahmanyan, 1975; Asberg *et al.*, 1976a), while about half fail to find significant differences (Fotherby *et al.*, 1963; Bowers *et al.*, 1969; Papeschi & McClure, 1972; Ashcroft *et al.*, 1973; Brodie *et al.*, 1973; Goodwin *et al.*, 1973; Jori *et al.*, 1975; Berger *et al.*, 1980). Low 5-HIAA accumulations after probenecid have also been reported (van Praag *et al.*, 1970; van Praag & Korf, 1971a; Sjöström, 1972, 1973; van Praag, 1977b; Goodwin *et al.*, 1977a, b), but again other studies find no significant difference between depressed patients and controls (Jori *et al.*, 1975; Berger *et al.*, 1980). The methodological problems associated with studies of this kind have been reviewed extensively elsewhere (Post & Goodwin, 1974).

Yet some of the CSF metabolite studies do contain clues to 5-HT's likely role. Asberg *et al.* (1976b) (Figure 1) found a bimodal distribution of CSF 5-HIAA among depressed patients in a baseline-controlled study and Goodwin and colleagues (1977a, b) (Figure 2) and van Praag (1983) found a similar trend toward bimodal distributions in studies using probenecid (Figure 3).

Another group of findings (Coppen *et al.*, 1972; van Praag, 1980; Post *et al.*, 1980) show no increase in CSF 5-HIAA following improvement in depression suggesting stability of 5-HT regardless of illness state or phase (Figure 4). Sedvall and colleagues (1980) reported that identical and fraternal twins have highly correlated 5-HIAA levels, indicating that this stability may be on a genetic, or at least familial, basis. These two types of findings are consistent with the idea that low 5-HIAA may be a relatively stable, state-independent or trait marker for patients with a predisposition to low 5-hydroxytryptaminergic function. Sedvall's group also determined that normals with depressed relatives tended to be in the lower end of the 5-HIAA distribution, a finding analogous to that of van Praag & de Haan (1979) who reported that normals in the low range for CSF 5-HIAA tended to have an increased incidence of depression in their families. Van Praag has reported that depressed patients with low 5-HIAA levels respond more favourably than those with higher levels to the 5-HT precursor 5-hydroxytryptophan (5-HTP), to the relatively 5-HT selective tricyclic chlorimipramine and to the two drug treatments in combination (van Praag, 1979, 1980). He finds that these medications which

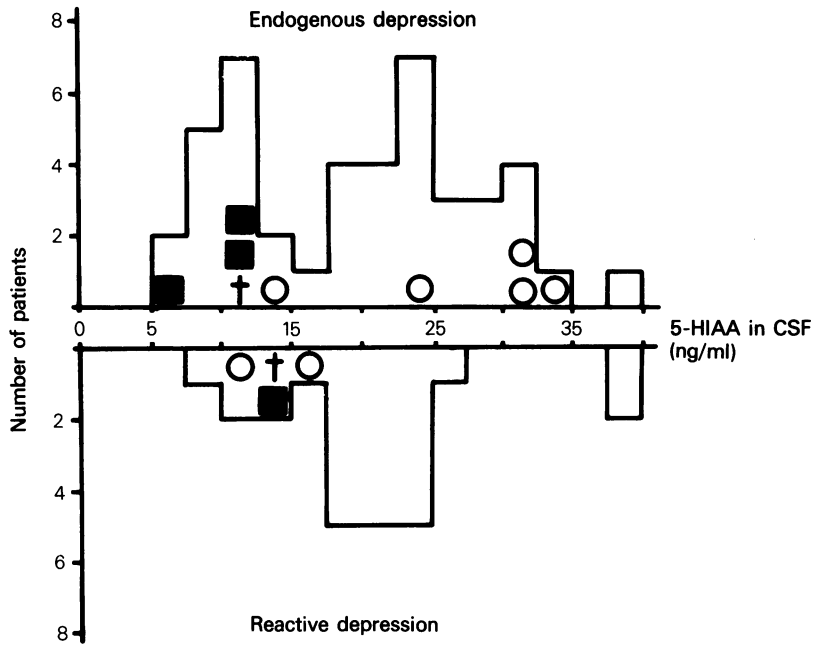

Figure 1 Levels of 5-HIAA in the cerebrospinal fluid (CSF) of depressed patients (from Asberg *et al.*, personal communication). ■ violent suicide attempt, O drug overdose, † suicide.

potentiate the 5-HT system are effective in the long-term prophylactic treatment of affective disorder, 5-HTP apparently by increasing the amount of 5-HT and chlorimipramine by inhibiting its re-uptake.

Since lithium is the principal prophylactic agent used in affective disorder, a brief digression on possible 5-hydroxytryptaminergic processes in its mechanism of action seems in order. One can interpret indirect evidence from animal studies as supporting the hypothesis that lithium stabilizes the 5-hydroxytryptaminergic system in brain (Knapp & Mandell, 1976; Jimerson *et al.*, 1976). When chronically administered in animals, Knapp & Manell (1976) suggested lithium treatment leads to adaptive changes, constricting the range within which 5-HT levels or

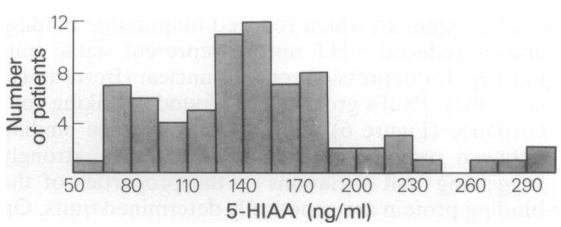

Figure 2 Frequency distribution of 5-HIAA in the CSF of depressed patients (from Goodwin *et al.* 1977a). n = 73, mean ± s.e. mean 145 ± 6.2.

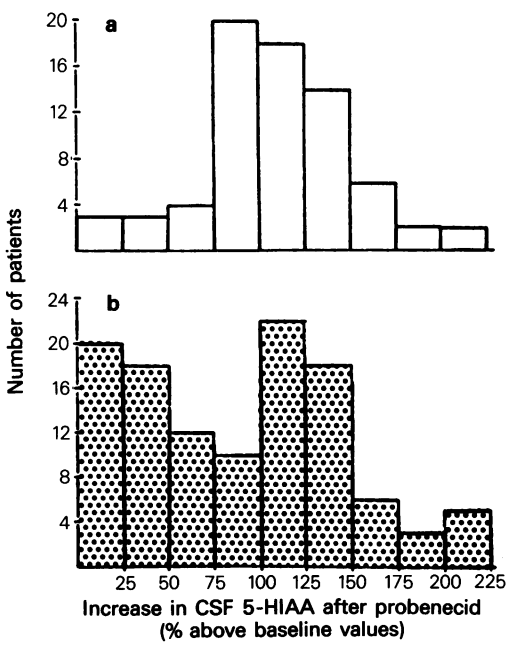

Figure 3 Probenecid-induced accumulation of 5-HIAA in CSF (from van Praag, 1983)—**a** control group, **b** depressed group.

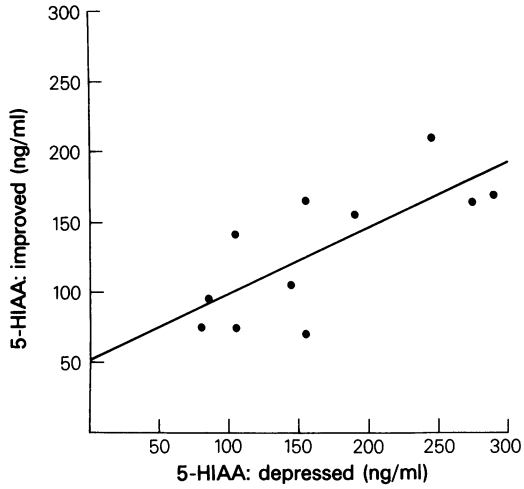

Figure 4 Consistency of CSF accumulation of 5-HIAA in the depressed and improved clinical state (from Post *et al.*, 1980). $r = 0.74$, $P < 0.01$.

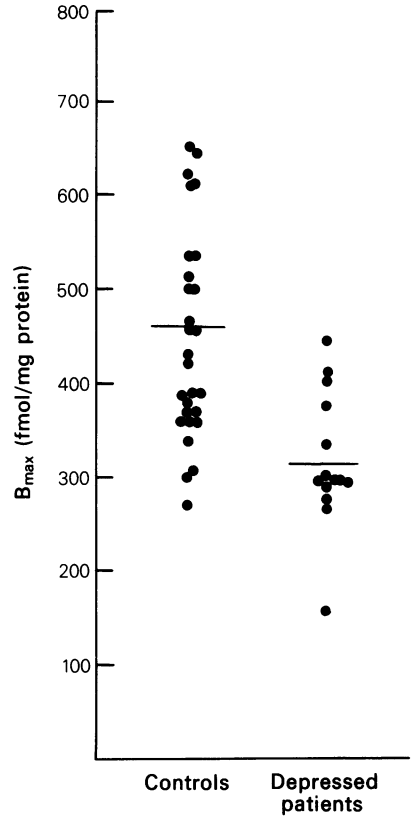

Figure 5 Comparison of maximal binding capacity (B_{max}) of tritiated imipramine in platelets from depressed patients and controls. Values (mean + s.e. mean) were 450 ± 23 fmol/mg protein for controls and 318 ± 19.8 fmol/mg protein for depressed patients ($P < 0.01$ by Student's *t*-test). From Paul *et al.* (1981).

turnover can fluctuate. This likely involves a combination of pre- and post-synaptic mechanisms: 1. an increase in the uptake of tryptophan, the 5-HT precursor, into the nerve ending, resulting in increased 5-HT synthesis; and 2. a decrease in the activity of the enzyme tryptophan hydroxylase, and consequent reduction in the ultimate capacity of the 5-hydroxytryptaminergic system to increase synthesis.

Platelet 5-HT uptake deficiency in depression

Blood platelets take up 5-HT by a process similar to that found in brain (Stahl & Meltzer, 1978) and offer an accessible model for studying presynaptic uptake, storage and release mechanisms in neurons. Meltzer and colleagues (1981) recently confirmed earlier reports (Tuomisto *et al.*, 1979; Coppen *et al.*, 1978) that 5-HT uptake by platelets is significantly reduced among patients with certain types of affective disorder, particularly bipolar illness. Increased 5-HT uptake in platelets of depressed patients following treatment with the tricyclic nortriptyline correlated positively with clinical improvement in Meltzer's study.

Imipramine binding: link to 5-HT uptake in depression

A parallel set of studies (Figure 5) has recently determined that platelets of depressed patients are similarly deficient in high affinity binding sites for the tricyclic antidepressant imipramine (Briley *et al.*, 1980; Paul *et al.*, 1981). Moreover, there is strong evidence that the imipramine binding site in brain and platelet membranes is functionally and structurally associated with the 5-HT uptake or transport complex (Langer *et al.*, 1980a, b; Paul *et al.*, 1981). Although the high affinity imipramine binding site is not the 5-HT recognition site of the transporter, it is clear that the imipramine binding site mediates the inhibition of 5-HT uptake by tricyclic antidepressants as well as by many unrelated uptake blockers (Rehavi *et al.*, 1981, 1983) and is probably an allosteric regulator of 5-HT uptake.

The extent to which reduced imipramine binding and/or reduced 5-HT uptake represent stable trait markers for depression remains unclear (Berrettini *et al.*, 1982). Paul's group (1983) found a striking concordance (Figure 6) in platelet imipramine binding between pairs of healthy identical twins, strongly suggesting that variations in the properties of the binding protein are genetically determined traits. On the other hand, 5-HT uptake was found to be a more complex process, influenced by non-genetic factors. Nevertheless, decreased platelet uptake of 5-HT and

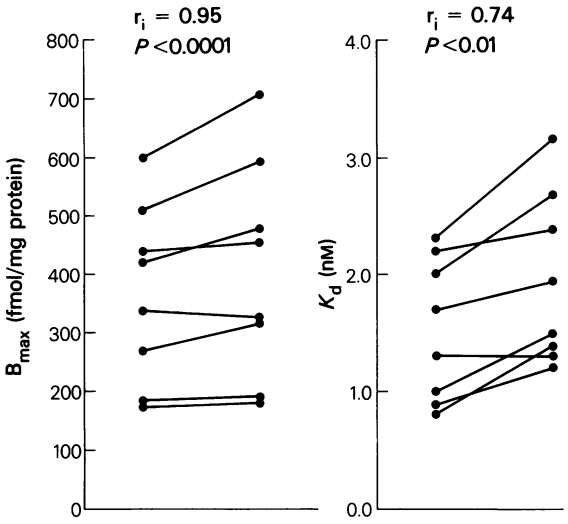

Figure 6 Platelet imipramine binding between pairs of healthy identical twins (from Paul *et al.*, 1983).

[^{3}H]-labelled imipramine binding suggests an alteration in the regulation of 5-HT transport in depressed patients. Interestingly, rats conditioned according to the 'learned helplessness' paradigm, which has been used as a model of depression, showed a decrease in imipramine binding in brain which persisted for as long as 4 days after the experience of inescapable shock stress, but normalized by day 10 (Petty & Sherman, 1982).

Suicide, aggression and impulsivity

CSF metabolite data

We will now turn to the newer CSF data linking low 5-HIAA with suicide, aggression, and impulsivity. In Marie Asberg's bimodal distribution of CSF 5-HIAA among depressed patients (Figure 1), those who made violent suicide attempts, including two who were successful, are in the lower group. In another sample of 46 depressed paients hospitalized for suicide attempts, Asberg's group found that all six patients who killed themselves within 1 year were among the patients in the low mode of the distribution of CSF 5-HIAA values. For patients identified by 5-HIAA levels below the median this represented an astounding 20% 1 year mortality rate (Träskman *et al.*, 1981). The key question is: Is low 5-HIAA characteristic of suicide only in primary depression, or does it relate to suicide in general?

Recent studies at the National Institute of Mental Health of several non-affective disorder groups would suggest the latter. Brown and colleagues (1979a, b) in a sample of Navy enlisted men with personality disorders found that low 5-HIAA (and increased methoxyhydroxyphenylglycol) correlated significantly with both a history of aggressiveness-impulsiveness and suicidal behaviour and high aggression scores on standardized tests. A similar pattern of low 5-HIAA and suicidality (Figure 7) emerged in studies of patients with borderline personality disorders (Brown *et al.*, 1982a, b) and schizophrenia (Ninan *et al.*, in preparation).

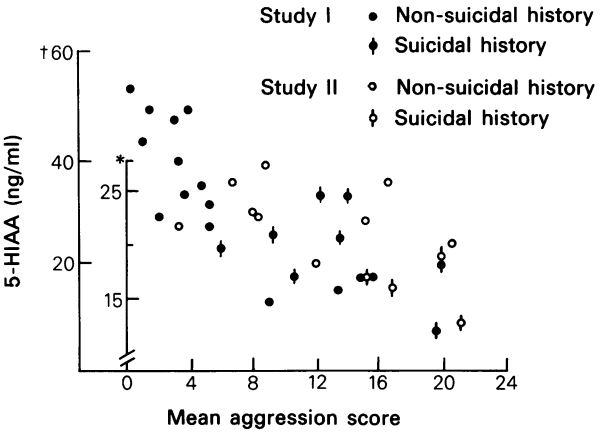

Figure 7 The trivariant relationship between aggression, suicidal history and CSF 5-HIAA in young male subjects with mixed personality disorders. Study I ($r = -0.78$; $P < 0.01$) and Study II ($r = -0.53$; $P < 0.08$). From Brown *et al.* (1982a, b) 5-HIAA levels were measured by fluorimetry in Study I (†) and GC-MS in Study II (*).

The association of low 5-HIAA with impulsivity and aggression may also be extended to persons who commit homicides due to uncontrollable violence (Asberg *et al.*, Linnoila *et al.*, personal communications); low 5-HIAA levels distinguish such psychopathic murderers from paranoid murderers (Figure 8). This is consistent with the finding that criminals jailed for violence who have the 47 XYY chromosomal syndrome show low 5-HIAA turnover after probenecid (Bioulac *et al.*, 1980).

While other neurotransmitter changes have been associated with aggression in animals, decreased central 5-hydroxytryptaminergic function is found most consistently across many species. As in the recent clinical studies, aggression in animals has been linked to decreased 5-hydroxytryptaminergic and/or increased catecholaminergic functioning rather than simply to one system malfunctioning independently (Hodge & Butcher, 1974, 1975). Indeed, different types of animal aggression appear to be connected with different neurotransmitter changes. For instance,

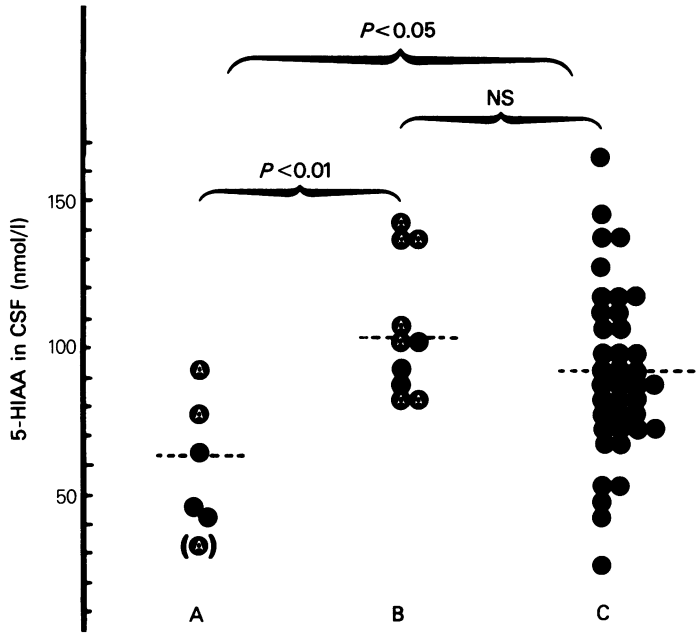

Figure 8 Levels of 5-HIAA in CSF of violent criminals and non-criminal controls (from Asberg *et al.*, personal communication). Group A murderers: victim a sexual partner, or rival; group B murderers: other victims; group C healthy non-criminal control subjects. Ⓐ alcoholic.

muricidal behaviour has been linked to reduced 5-HT metabolism while stress- or shock-induced aggression seems related to the noradrenaline system (Eichelman, 1979; Eichelman & Thoa, 1973). Lithium, which alters 5-HT metabolism, has reduced the frequency of violent episodes among groups of prisoners with a history of such episodes (Sheard, 1971, 1975; Turpin *et al.*, 1973).

5-hydroxytryptaminergic neurons of the raphe and reticular systems have an inhibitory effect on post-synaptic neurons (Aghajanian *et al.*, 1975) and may have a modulatory role relating to sleep, sexual and aggressive behaviour, and responsiveness to pain and other sensory stimuli. Perhaps diminished 5-hydroxytryptaminergic system functioning produces a state of disinhibition associated with vulnerability to self-destructive and/or aggressive impulses.

Imipramine binding

Two recent studies (Stanley *et al.*, 1982; Paul *et al.*, 1983) have found a significant reduction in the number of [^{3}H]-imipramine binding sites (30–40%) in brains of suicide victims, a reduction similar to that observed in the platelets from depressed patients. In the study by Paul *et al.* (1983), no decrease in high-affinity [^{3}H]-desipramine binding (a stable marker for noradrenaline uptake sites) was observed in the same tissue, indicating a selective decrease in 5-HT transport only. Thus, there is an interesting convergence of data suggesting low platelet imipramine binding in depression, low brain imipramine binding in animal models of depression, and low binding in the brains of patients who committed suicide.

Among possible interpretations: decreased imipramine binding could reflect functional changes in the regulation of 5-HT uptake, a functional decrease in a specific protein within the 5-HT neuron, or a more general degeneration of 5-HT terminals. It would be premature to attempt a definitive evaluation of these data at this early stage, but the consistency of the finding of decreased 5-hydroxytrypaminergic metabolism in one or another brain site in suicide victims is noteworthy in light of the new finding of decreased imipramine binding in brain.

Autopsy data re-interpreted

Those autopsy studies which found a relationship between low 5-HT and depression might now warrant some re-interpretation in light of the most recent findings about subgroups. The depressed populations studied are more likely to reflect a preponderance of the subgroup of patients who are suicide-prone, those most likely to die and be identified as depressed and be admitted to hospitals because of increased suicide

Table 3 Human studies—aggression, suicide and CSF amine metabolites

Study	*Subject description*	*Aggression history*			*Suicidal history*		
		5-HIAA	*MHPG*	*HVA*	*5-HIAA*	*MHPG*	*HVA*
Asberg *et al.* (1976a, b)	Depressed, violent and non-violent suicide	—	—	—	↓	—	—
Brown *et al.* (1979a, b)	Non-borderline, mixed personality disorders without affective disorder	↓	↑	NC	↓	↑	NC
Bioulac *et al.* (1978, 1980)	47, XYY personality disorders	a ↓	—	NC	—	—	—
Agren (1980a, b)	Depressed; unipolar and and bipolar	—	—	—	↓	↓	NC
Oreland *et al.* (1981) & Traskman *et al.* (1981)	Depressed and non-depressed personality disorders	—	—	—	↓	NC	NC
Leckman *et al.* (1981)	Affective and schizophrenic disorders	—	—	—	↓ b	—	NC
Brown *et al.* (1982a, b)	Borderline personality disorders with transient psychotic, affective symptoms	↓	NC	NC	↓	NC	NC

(a) Post-probenecid 5-HT turnover
(b) Suicidal ideation, psychotics only
Reproduced from Brown *et al.* (1982) with permission.

risk. Hence the findings of low 5-HT in a subgroup of depressives may be related to the intersection of depression and suicidality.

Conclusions and comments

A common theme in all studies is a trend toward increased precision in the delineation of biochemical and clinical findings.

Cerebrospinal fluid 5-HIAA is not low in all depressed patients, but those in the low end of the continuum or in the low subgroup may have differential symptom pictures and behavioural vulnerabilities, including suicide and pharmacological responsivity. The four different biochemical approaches we have discussed all converge around the same hypothesis: that decreased 5-hydroxytryptaminergic function may be associated with an increased risk of depression, suicide, and some types of aggression. The earlier autopsy studies dovetail with the metabolite data (Table 3) when they are re-interpreted to reflect suicide rather than depression in general. The platelet and imipramine binding studies point in this same direction.

Of course, questions remain about the sources of variance and the biochemical specificity of findings in each of these areas. In the metabolite data, one might still ask whether we are looking at low levels of 5-HT itself or perhaps an alteration in the transport mechanism for its 5-HIAA metabolite. If the latter, one would expect to see low levels of the metabolite of dopamine, homovanillic acid, which is transported by the same system, associated with these clinical variables. Alternatively, low 5-HIAA could reflect an enzyme deficiency such as MAO, since MAO is required to convert 5-HT into 5-HIAA.

From a clinical point of view, the thrust of the evidence would support the notion that variations in 5-HIAA, platelet imipramine binding and 5-HT uptake may be linked to depression and/or suicidality. It is against this backdrop that the importance of 5-HT selective drugs, both for research and treatment, comes into sharp relief. We can use such compounds along with drugs specifically affecting other neurotransmitters, to clarify further and validate the subgroup concept by assessing the degree of selectivity of responses in the low 5-HT subgroup. Might the low 5-HIAA patients also respond to agents that specifically affect other neurotransmitter systems, including dopamine and noradrenaline? Clinically, it would be important to assess whether 5-HT specific drugs offer any better pharmacological treatment not only for depression, but also for suicidality and perhaps other types of aggressivity. As we mentioned earlier, depressed patients with suicide potential are one of the

highest risk groups of patients. Further research is necessary to replicate and extend the finding suggesting that these individuals can be identified using CSF and platelet methodologies to assess 5-hydroxytryptaminergic function.

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