0031-6997/91/4304-0509$03.00/0
PHARMACOLOGICAL REVIEWS

Vol. 43, No. 4
Printed in U.S.A.

II. Critical Issues in Defining the Role of Serotonin in Psychiatric Disorders

LARRY J. SIEVER,* RENÉ S. KAHN, BRIAN A. LAWLOR, ROBERT L. TRESTMAN, TIMOTHY L. LAWRENCE, AND EMIL F. COCCARO

Department of Psychiatry of the Bronx Veterans Affairs Medical Center of the Mount Sinai School of Medicine, Bronx, New York

I. Introduction

THE serotonergic system has been implicated in a variety of central nervous system-mediated processes including activity, sleep, mood, feeding behavior, sexual activity, neuroendocrine function, and cognitive function. It is not surprising, then, that it has been a focus of interest for investigators of the pathogenesis of a variety of psychiatric disorders. The serotonergic system has been investigated in the major affective disorders, anxiety disorders, schizophrenia, impulse disorders, personality disorders, and AD. †Findings implicating altered serotonergic function have been reported for each of

* Address for reprints: Department of Psychiatry of the Bronx Veterans Affairs Medical Center of the Mount Sinai School of Medicine, 130 West Kingsbridge, Bronx, NY 10469.

†Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; CSF, cerebrospinal fluid; 5-HTP, 5-hydroxytryptophan; 5-HT, 5-hydroxytryptamine, serotonin; DA, dopamine; *m*-CPP, *m*-chlorophenylpiperazine; MHPG, methoxy-4-hydroxyphenylglycol; OCD, obsessive-compulsive disorder; GABA, τ-aminobutyric acid; LC, locus coeruleus; AD, Alzheimer's disease; nbM, nucleus basalis of Meynert.

these disorders. Agents that enhance or modulate serotonergic function have also been utilized as pharmacological treatments, either clinically or experimentally, for each of these disorders as well.

Varieties of indices have been used to explore serotonergic function in the psychiatric disorders including metabolites such as 5-HIAA in CSF; response to psychopharmacological challenges that perturb serotonergic activity such as fenfluramine, tryptophan, or 5-HTP; serotonin uptake and imipramine binding and receptor sites on platelets; postmortem brain studies of metabolites and receptors; and effects of serotonin precursors and pharmacological agents altering serotonergic activity.

5-HT is considered to be a modulatory neurotransmitter with generally inhibitory effects; (Gorzalka et al., 1990 as reviewed elsewhere (Meltzer and Lowy, 1987; Vogt, 1982). It plays a role in the regulation of a variety of psychobiological domains. Lesions of the serotonergic system result in disinhibited aggression in animals and in lack of extinction of punished behaviors (Soubrie, 1989). These effects suggest that 5-HT normally serves to suppress excessive aggression, as well as other motoric behaviors that might result in aversive consequences. 5-HT also has inhibitory effects on sexual behaviors, apparently partially mediated by actions on gonadal hormones (McEwen and Parsons, 1982; Richardson, 1990), and analgesic effects, inhibiting perception of pain. General inhibitory effects of 5-HT are consistent with findings that inhibition of 5-HT synthesis may cause insomnia, whereas enhancement of its activity may improve sleep (Hartmann, 1983; Wauquier et al., 1985). This amine also has inhibitory effects on appetite and may produce elevations of mood (Curzon, 1990; Meltzer and Lowy, 1987). It also has a modulatory influence on temperature (Aulakh et al., 1988). Many of these psychobiological functions are disturbed in the psychiatric disorders, an observation consistent with the possibility that 5-HT may play a role in a variety of psychiatric disorders.

II. Critical Issues in Defining Serotonergic Dysfunction in Human Studies

Although previous paradigms of 5-HT function have centered around hypotheses of global increases or decreases in serotonergic activity in specific psychiatric disorders, it is increasingly apparent that such formulations may be simplistic. It has been proposed, for example, that both decreased serotonergic activity (Murphy et al., 1978) and increased serotonergic activity are associated with depression (Ogren et al., 1979). As our neurobiological sophistication increases, it is becoming apparent that there may be differences between different components of the serotonergic system in these disorders rather than merely global changes in level of function. Thus, presynaptic versus postsynaptic alterations must be considered. Even at postsynaptic sites, the presence of specific 5-HT receptor subtypes with different pharmacological and behavioral effects demand that consideration be given to differential alterations of specific subtypes of these receptors. Patterns of alteration of these components of the serotonergic system would be expected to be quite different if, for example, there was a relative failure of the serotonergic system to develop or innervate the brain (a relative hypotrophy) in contrast to a dynamic alteration in the components of the system. In the first case, decreases of all components in the system, including presynaptic and postsynaptic receptor sites, would be expected, whereas in the latter case some components, e.g., presynaptic activity, might be decreased; others, e.g., postsynaptic activity, might be increased. Although the majority of serotonergic neurons arise from the median raphe nucleus, their innervation covers a wide expanse of cortex and limbic structures. Regional differences in activity at specific terminal fields of the serotonergic system might have important implications for differences in behavior. Preclinical research increasingly highlights the degree of neurotransmitter interactions in the central nervous system and of the relationship of 5-HT function to norepinephrine, DA, and acetylcholine. The range of effects that 5-HT has on central nervous system function also makes it unlikely that a disturbance in 5-HT function would necessarily specifically result in a single psychiatric disorder. The possibility of dimensional versus categorical correlates, then, of 5-HT dysfunction must be considered in linking biochemical indices to behavioral traits. These issues will be discussed in greater length and reviewed in relation to recent results of studies implicating serotonergic dysfunction in the affective and personality disorders, as well as briefly in other psychiatric disorders, with consideration of their potential implications for developing future diagnostic and therapeutic agents.

III. Overview of Neuropsychiatric Disorders in which Serotonin Is Implicated

Historically, 5-HT was initially investigated primarily in affective disorders. Studies of metabolites of 5-HT, such as 5-HIAA, in various bodily fluids suggested that depressed patients might have reduced serotonergic activity. Subsequent investigations suggested that those individuals with reduced serotonergic activity might specifically constitute a group who had attempted suicide (Asberg et al., 1987; Meltzer and Lowy, 1987). These findings prompted investigation of the serotonergic system in the impulse disorders and, more specifically, the impulsive personality disorders. These studies will be reviewed in more depth in the next section.

The effectiveness of serotonergic agents on anxiety disorders such as OCD and even other anxiety disorders stimulated investigation of alterations in serotonergic function in these disorders. As will be reviewed later, there is evidence of altered serotonergic function in several of the anxiety disorders as well. The current efficacy

of clozapine, a 5-HT_2 receptor antagonist, has stimulated studies of serotonergic function in schizophrenia, an area that was also of interest in early studies of schizophrenia. Finally, there has been increasing emphasis on the role of 5-HT in AD as well. The role of 5-HT in each of these disorders will be reviewed, with specific emphasis on the affective and personality disorders.

IV. Studies of Serotonin Function in Affective and Personality Disorders

A. Cerebrospinal Fluid 5-Hydroxyindoleacetic Acid

The 5-HT metabolite, 5-HIAA, has been found to be reduced in numbers of studies of medication-free depressed patients. Recent reanalysis of a large sample of depressed patients and controls suggested that this reduction in CSF 5-HIAA was due to the presence of a subgroup of depressed patients (Gibbons and Davis, 1986) in a bimodal distribution. Although concentrations of 5-HT metabolites in CSF have not been consistently correlated with depressive symptoms, reduced CSF 5-HIAA has been suggested to occur in a subgroup of suicide-attempting patients with depression (Asberg et al., 1987; Asberg et al., 1976; Agren, 1980; Banki et al., 1981; Banki and Arato, 1983). Indeed, suicide attempts are associated with reduced CSF 5-HIAA in psychiatric diagnoses other than depression (Brown et al., 1979, 1982; Van Praag, 1983; Ninan et al., 1984), raising the possibility that the serotonergic abnormality was more associated with suicide attempts than depression per se. There appears to be a relative consistency in reductions of CSF 5-HIAA across behavioral states, although modest increases of 5-HIAA may result with recovery (Traskman-Bendz et al., 1984).

Reduced concentrations of CSF 5-HIAA have also been correlated with physical aggression directed toward others. Military subjects with a variety of personality disorders demonstrated diminished CSF 5-HIAA concentrations associated with high aggression scores and premature discharge from the military. Correlations were also found with a history of suicide attempt in these patients as well (Brown et al., 1979). In a second study, CSF 5-HIAA was negatively correlated with a life history of physical aggression and psychopathic deviance as assessed by the Minnesota Multiphasic Personality Inventory (Brown et al., 1982).

A specific association of reduced CSF 5-HIAA concentrations and impulsive aggressive behavior, particularly violent aggression, has been reported in subjects selected for violent offenses. Those subjects committing impulsive violence, who are more likely to have antisocial or explosive personality disorder diagnoses, had CSF 5-HIAA concentrations that were lower than those who committed premeditated violent acts, who usually have paranoid or "anxious cluster" personality disorders diagnoses (Linnoila, 1983). This distinction between planned and impulsive violence has been supported by studies of professional killers, violent offenders who killed someone close to them (Lidberg et al., 1985), and impulsive arsonists (Virkkunen et al., 1987). Other correlations between externally directed aggression and CSF 5-HIAA or impulsivity and CSF 5-HIAA have been reported in normal volunteers (Roy et al., 1988; Traskman-Bendz et al., 1986).

Correlations with history of aggression, as well as the propensity for suicide attempts, might suggest that CSF 5-HIAA represents a partially state-independent index. Indeed, there appear to be both trait and state components to CSF 5-HIAA concentrations because these concentrations may correlate when measured at two points in time in normal volunteers and in depressed patients, but CSF 5-HIAA concentrations may increase during recovery in depressed patients with initially low concentrations (Traskman-Bendz et al., 1984). A study of patients with euthymic bipolar disorder treated with lithium reported normal CSF levels of 5-HIAA (Berrettini et al., 1985). However, other studies suggest that reduced 5-HT metabolism may be observed in patients with euthymia and that persistence of these reductions from the ill to recovered state predict increased risk for future depressions (Van Praag and DeHaan, 1979). Some data suggest that reduced concentrations of CSF 5-HIAA may predict treatment response to the 5-HT precursor 5-HTP and that such treatment diminishes the likelihood of subsequent depression (Van Praag and DeHaan, 1980; Van Praag et al., 1972). Other studies have found that low CSF 5-HIAA predicted clinical response to tricyclics such as imipramine (Maas et al., 1982; Aberg-Wistedt et al., 1982).

In summary, although a number of studies have suggested that depressed patients may have low CSF 5-HIAA, these findings are not consistent and the decrease in CSF 5-HIAA concentration does not consistently correlate with the severity of the depression. On the other hand, reductions in CSF 5-HIAA correlate with suicide attempts in patients with personality disorders and depressed patients. Reductions in CSF 5-HIAA have correlated with outwardly directed aggression, particularly impulsive, violent aggression, in patients with personality disorders and criminal offenders, usually with antisocial or explosive personality disorder diagnoses; such a correlation has not been clearly documented in patients with affective disorders. Thus, decreases in 5-HT, as reflected in reduced CSF 5-HIAA concentrations, may be more closely related to self- or other-oriented aggression than to the state of depression.

B. Plasma Tryptophan

Plasma tryptophan levels are an index of the tryptophan available to be converted into 5-HT in the central nervous system and thus may be an overall measure of central 5-HT activity. Reduced plasma tryptophan levels have been observed in numerous studies of depressed patients (Meltzer and Lowy, 1987). Interestingly, de-

creases in plasma levels of tryptophan have also been associated with a history of aggressive or suicidal behavior in alcoholics (Branchey et al., 1984). These and other studies, reviewed elsewhere (Coccaro et al., 1990b), suggest that reduced serotonergic function, perhaps partially stemming from reduced serotonergic availability, may be associated with aggressive behavior across several diagnostic categories.

C. Platelet-Imipramine Binding

Decreases in the binding of imipramine to platelets have been reported in numerous studies of depressed patients as reviewed elsewhere (Meltzer and Lowy, 1987). Interestingly, the reductions in imipramine binding may be specifically associated with a family history of depression (Lewis and McChesney, 1985). Because this site is allosterically related to the 5-HT uptake site (Briley et al., 1980), it might be considered to be a marker of presynaptic serotonergic neurons. One study has suggested that reductions of imipramine-binding sites may be associated with aggression in adolescents with a diagnosis of conduct disorder (Stoff et al., 1987). Because newer studies suggest that paroxetine may be the more appropriate ligand for these binding sites (Mellerup et al., 1983; D'Haenen et al., 1988), additional studies of patients with personality disorders are needed to assess the relationship with aggression that has been established using central metabolite and challenge studies of 5-HT.

D. Serotonin Uptake in Platelets

The platelet, like central 5-HT neurons, has 5-HT uptake sites that may be assayed in depressed patients. Decreased V_{max}, that is, a decrease in the number of uptake sites, has been reported in both unmedicated depressed patients (Coppen et al., 1978; Meltzer et al., 1981) and manic patients (Meltzer et al., 1981), a finding that may persist even after recovery in unipolar depressed patients (Meltzer and Lowy, 1987). This finding does not appear to be an artifact of drug treatment. It is not clear whether it represents a primary abnormality, which would tend to result in more 5-HT in the synapse or as a compensatory response to reduced serotonergic activity (Meltzer and Lowy, 1987). Studies of 5-HT uptake have not been performed in patients with impulsive personality disorders.

E. Neuroendocrine Responses to Serotonergic Precursors

Pharmacological challenge with precursors, releasing agents, reuptake markers, and direct 5-HT agonists can assess the perturbation of central serotonergic systems and may provide a reflection of the net function of the system. A diminished prolactin response to L-tryptophan at an intravenous dose of 100 mg/kg has been reported in unmedicated depressed patients compared with controls (Heninger et al., 1984). Other studies suggest the possibility that this response might have been due to differences in plasma tryptophan levels (Koyama and Meltzer, 1986).

In contrast, the cortisol response to the serotonergic precursor, D,L-5-HTP, administered orally in a 200-mg dose has been reported to be increased in both unmedicated depressed and manic patients (Meltzer et al., 1984). The differences in response to these two different precursors may have to do with differences in serotonergic control of cortisol versus prolactin. For example, the 5-HT_2 receptor may be particularly involved in mediating the prolactin response to 5-HTP (Meltzer and Lowy, 1987). Alternatively, hypertrophy or increased activity of the hypothalamopituitary axis may account for the increased cortisol secretion. Mixed results obtained regarding the possible role of 5-HT_{1A} receptors in prolactin secretion have been reported (Coccaro et al., 1990a; Lesch et al., 1989).

Although tryptophan alone is not considered as effective as tricyclic antidepressant medications (Murphy et al., 1978), tryptophan does have antidepressant effects and potentiates the action of tricyclic or monoamine oxidase inhibitor medications (Meltzer and Lowy, 1987; Baldessarini, 1984). L-5-HTP has antidepressant efficacy and also may prevent depression (Van Praag, 1984; Van Praag and DeHaan, 1980).

Analogously, specialized amino acid diets that deplete tryptophan may worsen depression in patients with symptoms (Delgado et al., 1989). Tryptophan depletion has not been used in patients with impulsive personality disorders, although depressed patients receiving a tryptophan depletion diet are reported to be somewhat amotivational and irritable.

F. Neuroendocrine Responses to Fenfluramine

Reduced prolactin responses to fenfluramine relative to controls have been reported in patients with major depression disorders (Siever et al., 1984) and specifically in depressed patients without concomitant history of panic attack compared with depressed patients with either panic or dysthymic disorders (Lopez-Ibor et al., 1988). In contrast, differences between major depressive disorder in outpatients and normal controls did not reach significance in another study (Asnis et al., 1988). Inspection of the data in all of these studies indicates a considerable overlap of the magnitude of the prolactin response to fenfluramine between depressed patients and controls. Reductions in the response to fenfluramine may not be associated with complicated or milder depression in outpatients. However, the specific characteristics of depression associated with reduced prolactin response to fenfluramine cannot be determined from these studies.

In studies designed to investigate the relationship of reduced prolactin responses to fenfluramine in depression, impulsivity/aggression, and suicide attempts in patients with affective and personality disorders, reduced prolactin responses to fenfluramine were again found in drug-free, acutely depressed patients compared with

matched normal controls (Coccaro et al., 1989b). However, only about 40% of these patients showed significantly blunted responses to fenfluramine. Additionally, a similar proportion of depressed patients in remission, who had not received antidepressants and other medications for at least 2 weeks, also had a reduced prolactin response to fenfluramine (Coccaro et al., 1989b). In a subset of six patients studied across two states, those with blunted responses tended to continue to have blunted responses across states, although there was an apparent trend for responses to increase slightly with recovery. These findings could not be attributed to differences in age, weight, plasma concentrations of fenfluramine, basal concentrations of prolactin, time without antidepressant medications, season of the year, or any other demographic variables. Furthermore, there was no correlation with the severity of depressive symptoms in this sample.

A comparably designed study of prolactin responses to fenfluramine in a mixed sample of patients with personality disorders also suggested blunted prolactin responses to fenfluramine. As described before, these responses could not be attributed to any of the potential artifacts such as age, weight, etc. that were also found to be noncontributory in patients with major affective disorders. A history of suicide attempts was associated with reduced prolactin responses to fenfluramine in the cohorts with affective and personality disorders. However, the degree of reduction in prolactin response showed no correlation with severity of depression or with history of, or concomitant depression in, the cohort with personality disorders (Coccaro et al., 1989b).

These studies parallel those of CSF 5-HIAA by suggesting that reductions of serotonergic function may be associated more specifically with suicide attempts than with degree of depressive symptomatology. Further evaluation of patients with personality disorders indicated that those who met criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* edition 3, for borderline personality disorder had a reduced prolactin response to fenfluramine compared with other patients with personality disorders who did not meet criteria for borderline personality disorder. In contrast, no other specific axis II disorder that could be meaningfully evaluated in this sample showed an association with reduced prolactin responses to fenfluramine. Furthermore, those criteria particularly associated with impulsivity/aggression, such as impulsive acts, self-damaging acts, and angry outbursts, were specifically associated with a reduced prolactin response, whereas other borderline criteria were not. Cumulatively, these results suggest that the reduced prolactin responses to fenfluramine might be related to impulsive aggression (Coccaro et al., 1989b).

A more direct test of this hypothesis would be to examine correlationally the relationship between prolactin response to fenfluramine and indices of impulsivity/aggression across all patients with personality disorders. Indeed, significant correlations between the prolactin response to fenfluramine and two subscales of the Buss-Durkee Hostility Inventory, the "assault" and "irritability" subscales, and one subscale of the Barratt impulsivity scales, "motor impulsivity," were observed. Reduced prolactin responses to fenfluramine also were correlated with the Brown-Goodwin Lifetime Inventory of Aggression. These scales were also highly intercorrelated. However, no significant correlations were observed with other measures of pathology including items less related to irritability/impulsivity/aggression in the Barrett and Buss-Durkee scales as well as inventories of anxieties, sensation seeking, and other forms of psychopathology. These data cumulatively suggest a strong and specific association between the reduced prolactin responses to fenfluramine and impulsive aggression.

Differences in the prolactin response to fenfluramine between persons who attempt suicides and those who do not and between persons who abuse alcohol compared with those who do not were eliminated when a factor of impulsivity/aggression was covaried in these comparisons, whereas the converse was not the issue (Coccaro et al., 1989b), suggesting that a factor of impulsivity/aggression may underlie the observed findings. However, other studies of drug abusers have found a positive correlation between the prolactin response to fenfluramine and impulsivity (Fishbein et al., 1989).

In contrast to the findings in patients with personality disorders, no relationship between impulsivity/aggression, as indexed by the above scales, was found with the prolactin responses to fenfluramine in depressed patients in remission. However, the association with suicide attempts and reduced prolactin responses to fenfluramine was observed in the depressed patients in remission as part of the combined depressed patient cohort comparable to the correlation between suicide attempts and blunted prolactin responses in the patients with personality disorders. Thus, it appeared that internally directed aggression, i.e., suicide attempts, was common to patients with both affective and personality disorders, whereas externally oriented aggression, i.e., fights, impulsivity, volatility, and irritability, was only associated with reductions in serotonergic activity in the patients with personality disorders. These results suggest that other systems, which are likely to differ in their function between patients with affective and personality disorders, may account for differences in the direction of expression of aggression.

G. Neuroendocrine Responses to Direct Serotonin Receptor Agonists

Although neuroendocrine responses to precursors or releasing agents may give an indication of "net" serotonergic activity, recent interest has shifted to the evaluation of 5-HT receptor responses. *m*-CPP is a direct 5-HT receptor agonist that acts on 5-HT_{1C}, 5-HT_2, and 5-

HT_3 receptors. Its administration results in increases in prolactin, cortisol, and growth hormone. Studies of *m*-CPP in depressed patients have not yielded consistent differences from normal controls (Kahn et al., 1990b). A preliminary study of the relationship of the prolactin response to *m*-CPP revealed similar significant correlations in a negative direction between the prolactin response and measures of irritability/aggression (Coccaro et al., 1989a).

Interestingly, prolactin responses to *m*-CPP were highly correlated with prolactin responses to fenfluramine when *m*-CPP plasma concentrations were considered as a covariant in the correlation. However, prolactin responses to fenfluramine were not correlated with CSF 5-HIAA in an overlapping cohort of patients (Coccaro et al., 1989b). These results suggest that at least part of the variations in serotonergic activity related to impulsivity/aggression may be postsynaptic.

H. Neuroendocrine Responses to Buspirone

Buspirone is a relatively selective 5-HT_{1A} agonist that stimulates the release of prolactin and cortisol (Meltzer and Lowy, 1987). A prolactin response to buspirone can be blocked by metergoline, which antagonizes both 5-HT_1 and 5-HT_2 receptors (Coccaro et al., 1990a). The prolactin, but not the cortisol, response to buspirone is blocked by 20 mg of pindolol, a β-adrenergic and 5-HT_{1A} antagonist (Coccaro et al., 1990a). In this preliminary study, in one subject, higher doses of pindolol were associated with increased prolactin responses, suggesting the possibility of paradoxical agonist effects of pindolol on prolactin secretion at higher doses. Although buspirone may have DA antagonist properties, a blockade of the prolactin response to buspirone by pindolol suggests that it may be substantially mediated by 5-HT_{1A} receptors. However, ipsapirone, a 5-HT_{1A} agonist with less dopaminergic antagonism, apparently does not cause the release of prolactin, at least in one study of normal subjects (Lesch et al., 1989).

In a pilot study of patients with personality disorders, prolactin responses to buspirone were negatively correlated with indices of impulsivity/aggression, including the "irritability" and "assaultiveness" scales of the Buss-Durkee scales (Coccaro et al., 1990b). These studies lend further support to the inverse relationship between serotonergic activity and aggression and are consistent with the possibility that these effects may be partially mediated by postsynaptic 5-HT_{1A} receptors.

I. Relationship to Indices of Noradrenergic Function

The results of studies of both CSF 5-HIAA and prolactin responses to fenfluramine suggest that these indices of reduced serotonergic functions are associated with suicide attempts in patients with both personality and affective disorders and with externally directed aggression, e.g., fights, irritable behavior, in patients with personality disorders. However, the inverse association between reduced indices of serotonergic activity and externally directed aggression has not been observed in patients with affective disorders. For example, the prolactin response to fenfluramine negatively correlates with self-directed aggression, i.e., suicide attempts, but not with scales reflecting externally reflected irritability/aggression in depressed patients in remission (Coccaro et al., 1989b). These results raise the possibility that other biological systems, which may mediate the directionality of expressed aggression, may differ between patients with affective and personality disorders.

One possible system that may differ between the groups is the noradrenergic system. The LC, the major noradrenergic nucleus, mediates the organism's response to novel, and especially threatening, stimuli in the environment. Increased activity of the LC is associated with higher levels of arousal, whereas reduced activity of the noradrenergic system is associated with vegetative, restitutive functions (Foote et al., 1983). Thus, the noradrenergic system may be seen as mediating the responsiveness and sensitivity of an individual to his or her environment. Evidence suggests that the noradrenergic system may be inefficient and dysregulated in major depressive disorder, particularly endogenous depression (Siever and Davis, 1985; Weiss et al., 1982). Deficient noradrenergic function may contribute to the vegetative symptoms, lack of goal directed behavior, and lack of responsiveness to environmental change seen in endogenous or "autonomous" major depressive disorder. It is thus conceivable that the diminished responsiveness of the noradrenergic system and the associated deficit in environmental responsiveness associated with depression may diminish the external expression of aggressive behavior in patients with major, particularly melancholic, depressive disorders.

Conversely, increased noradrenergic activity has been associated with increased environmental responsiveness, as indicated by novelty- or sensation-seeking behavior, risk-seeking behavior (e.g., gambling), and extroversion (Roy et al., 1988, 1989). For example, increased concentrations of MHPG have been associated with pathological gamblers (Roy et al., 1988). Levels of CSF MHPG, plasma MHPG, and the sum of urinary metabolites of norepinephrine are correlated with measures of extroversion on the Eysenck Personality Inventory (Roy et al., 1989). Sensation seeking on the Zuckerman Sensation Seeking Scale and urinary levels of MHPG have been correlated in normal volunteers (Buchsbaum et al., 1981). These results suggest that increased activity of the noradrenergic system may be associated with impulsive/aggressive behavior and raise the possibility that increased responsiveness of the noradrenergic system coupled with decreased responsiveness of the serotonergic system would be most likely to predispose to aggressive behavior. Preliminary studies in our laboratories suggest that increased growth hormone responses to clonidine, a

noradrenergic agonist, are associated with measures of impulsivity and aggression in patients with personality disorders (Lawrence et al., 1991). Because the growth hormone response to norepinephrine assesses the responsiveness of postsynaptic adrenergic receptors, it might be hypothesized that increased responsiveness of these receptors may be associated with greater noradrenergic-mediated responses to environmental stimuli. In the study, no correlation was found with the prolactin response to fenfluramine, suggesting that these noradrenergic and serotonergic indices are independent. The interaction of these two systems in predisposing to impulsive aggression is currently being explored.

J. Intercorrelations between Serotonergic Indices

In the studies of patients with affective and personality disorders cited above, high correlations were observed between prolactin responses to fenfluramine and prolactin responses to *m*-CPP, suggesting a common postsynaptic mechanism (Coccaro et al., unpublished data). In contrast, the prolactin response to fenfluramine did not correlate with measures of the platelet imipramine binding or CSF concentrations of 5-HIAA. In fact, a modest negative correlation was found between the prolactin response to fenfluramine and concentrations of CSF 5-HIAA, again suggesting that the neuroendocrine challenge paradigm may more substantially assess postsynaptic receptor responsiveness.

V. Implications of 5-Hydroxyindoleacetic Acid Studies of Patients with Affective and Personality Disorders

A. Presynaptic versus Postsynaptic Indices

These studies suggest that pre- and postsynaptic indices of serotonergic function may differ in their behavioral correlates. Thus, various indices of serotonergic activity need not be considered equivalent. For example, imipramine binding and CSF 5-HIAA concentration in patients with personality disorders are not correlated with measures of impulsive aggression, whereas postsynaptic indices including prolactin responses to fenfluramine, *m*-CPP, and buspirone are correlated. Because CSF 5-HIAA concentrations have been associated with externally oriented aggression in other studies, it may be that, in this population of patients with personality disorders, individual differences in postsynaptic indices of serotonergic function may contribute substantially to variations in predisposition to aggression as well as presynaptic components of 5-HT function. These studies would imply that the neuroendocrine response to serotonergic challenge may be mediated as much by postsynaptic receptors as by presynaptic serotonergic availability.

B. 5-Hydroxyindoleacetic Acid Receptor Subtypes

It is known that the 5-HT receptor system consists of several different receptor subtypes including the 5-HT_{1A}, 5-HT_{1D}, 5-HT_2, and 5-HT_3 receptors. Although the functional effects of these receptors are not fully understood, the receptors are found in different brain locations and are coupled to different second messenger systems. For example, 5-HT_{1A} receptors are found in human frontal cortex and hippocampus (Hoyer et al., 1986) and activate adenylate cyclase (Hoyer, 1988); 5-HT_2 receptors are also located in the hippocampus and frontal cortex but are linked to phosphatidyl inositol turnover (Hoyer et al., 1986; Hoyer, 1988). Available neuroendocrine probes may target more than one receptor. For example, *m*-CPP binds to 5-HT_{1A}, 5-HT_{1D}, and 5-HT_2 (Hamik and Peroutka, 1980) and 5-HT_{1C} (Hoyer, 1988) receptors. Some studies suggest that its effects may be particularly mediated by 5-HT_{1C} receptors. Buspirone, on the other hand, is a 5-HT_{1A} partial agonist with few effects in other serotonergic subtypes. In these studies, responses to *m*-CPP and buspirone, as well as to the broad-spectrum serotonergic agent, fenfluramine, were associated with impulsivity/aggression, raising the possibility that the correlation may be partially attributable to variations in 5-HT_{1A} receptor responsiveness. However, the prolactin response to ipsapirone has not been identified in normal subjects (Lesch et al., 1989), a result apparently discrepant from those previously described. Ultimately, more extensive studies of serotonergic agents, such as fenfluramine, *m*-CPP, and tryptophan, with selective antagonists may be required to disentangle the meaning of specific neuroendocrine responses to serotonergic agents.

C. Hypotrophy versus Dysregulation

Alterations in the serotonergic system could be conceived of as reflecting different roots of pathogenesis. For example, a genetic or acquired deficiency in the development of the serotonergic neuronal system would predict reductions in a variety of indices of 5-HT activity, including CSF 5-HIAA, imipramine binding, and indices of serotonergic receptor activity. In contrast, an abnormality of a single serotonergic receptor subtype might actually result in increases in presynaptic 5-HT activity and secondary down-regulation of other subtypes. Another possibility is that the serotonergic receptors are not properly regulated in relation to changing concentrations of presynaptic 5-HT. In this case, correlations in the negative direction between pre- and postsynaptic elements could be expected. Although too few data are available to confidently speculate on the origin of serotonergic alterations in patients with personality and affective disorders, the decreased postsynaptic indices of serotonergic responsiveness in the face of normal to reduced presynaptic activity suggests a generalized failure in the development of the serotonergic system or intrinsic defects in the postsynaptic receptor. More definitive characterization of the relationship of pre- and postsynaptic indices will be required to disentangle these possibilities.

D. Regional Differences

The serotonergic system has widespread innervations throughout the cortex, limbic system, and basal ganglia, as well as the hypothalamus. It is quite conceivable that deficits in one brain area may not be matched by parallel deficits in other serotonergically innervated brain regions. This differential deficit might be particularly expected if alterations in single-receptor subsystems with their specific receptor fields were altered in a given psychiatric disorder. Ultimately, imaging studies will be required to resolve these issues. However, there are correlations between hypothalamic responses to serotonergic challenges, such as fenfluramine, and behavioral responses (Coccaro et al., 1989b). Thus, serotonergic agents may be indicated for a particular symptomatic cluster in several psychiatric disorders. 5-HT reuptake blockers (e.g., fluoxetine) have been implicated as effective in affective, obsessive-compulsive, and impulsivity disorders. However, differences between expression of the serotonergic dysfunction in different categories secondary to interaction with other disturbed neurotransmitter systems might be targeted by combinations with other more specific agents.

Correlations between hypothalamic and behavioral responses to serotonergic challenge suggest that, in patients with personality and affective disorders, the abnormalities are not confined to a single brain region.

E. Neurotransmitter Interaction

The differing relationships between the serotonergic system and externally oriented impulsive/aggression in patients with personality disorders and depressed patients in remission raises the possibility of other neurotransmitter systems modulating the direction of the expression of impulsive aggression. Because the noradrenergic system is a behavioral arousal system that may modulate the extent to which an organism "tunes in" to the environment, increased activity might be expected to be associated with excessively responsive or irritable responses to the environment, which, when coupled with a reduced serotonergic function or disinhibition of normally suppressed aggressive behaviors, would result in irritable aggression. These considerations call for paradigms of neurotransmitter dysfunction in psychiatric disorders that take into account interactions between neurotransmitter systems. The interaction of these specific neurotransmitter systems would then be considered as contributing to the specific clinical systems of a particular disorder or even to symptoms that cross a range of diagnostic categories. In this case, animal models support the hypothesis that the noradrenergic and serotonergic neurotransmitter systems interactively contribute to impulsivity and aggression.

5-HT-mediated aggression is diminished in animals whose noradrenergic system has been impaired (Soubrie, 1989), and reduced levels of arousal, expected with low noradrenergic activity, will interfere with the expression of 5-HT-mediated aggression (Chamberlain et al., 1987). The serotonergic and noradrenergic systems are closely related anatomically and functionally, and changes of activity in one system may contribute to alterations in the regulation of the other (Janowsky et al., 1982). Thus, serotonergic dysfunction cannot be understood in relation to psychiatric disorders when it is not considered in the context of other related neurotransmitter systems, such as the noradrenergic, dopaminergic, or cholinergic systems.

F. Dimensional versus Categorical Correlations

The results of studies of patients with affective and personality disorders suggest that a dimensional correlative serotonergic dysfunction may be more appropriate and useful than the attempt to fit 5-HT dysfunction into categorical distinctions. Thus, although reduced prolactin responses of fenfluramine were associated particularly with borderline personality disorder compared with other personality disorders, they were specifically related to the criteria for aggressive and impulsive behavior (Coccaro et al., 1989b). History of suicide attempts correlated with prolactin responses to fenfluramine across both diagnostic categories, affective and personality disorders. Again, serotonergic dysfunction was not associated with a particular disorder but with a dimension of unmodulated aggression, with differences in the direction of this expression in patients with personality and affective disorders. Such a dimensional approach involving neurotransmitter interactions may appear to be more complex but yet remains testable and provides more realistic models of psychopathology with implications for drug development.

VI. Serotonin Function in Other Psychiatric Disorders

A. Serotonin in Anxiety Disorder

In comparison with studies of 5-HT in depression, the role of 5-HT in anxiety has received considerably less attention. Most of the data supporting a connection between 5-HT and anxiety is based on animal studies. 5-HT research in human subjects has only recently begun in contrast to the extensive research on the role of noradrenergic mechanisms in anxiety. Nonetheless, a substantial body of work in animals and some exciting recent findings in humans warrants a closer examination of the 5-HT/anxiety relationship. The most consistent finding emerging from animal anxiety studies is that diminishing 5-HT function results in decreased anxiety. A few studies have found that increasing 5-HT function may result in anxiety. Unfortunately, the results of the different studies vary because of methodological deficiencies and inconsistencies, including differences in research design, assessment of anxiety, and pharmacological agents used (Kahn et al., 1988a).

A variety of methods have been used to assess different aspects of 5-HT function in human anxiety studies. These have included studies in which 5-HT metabolism was measured, challenge studies with 5-HT agonists, and treatment studies with agents altering 5-HT availability. Although measurement of the 5-HT metabolite, 5-HIAA, in CSF is perhaps the most informative method for assessing central 5-HT metabolism, it has been done in only a few anxiety studies. Another method, the so-called challenge paradigm, is particularly well suited to assessment of central 5-HT receptor sensitivity. Treatment studies of anxiety disorders with drugs selective for 5-HT systems have also been useful in exploring the relationship between 5-HT and anxiety in humans (Van Praag et al., 1987). A possible role for 5-HT has been studied in OCD, panic disorder, and generalized anxiety disorder.

Evidence from challenge and treatment studies suggest that 5-HT is involved in OCD, although the nature of this involvement is unclear. Suggestive evidence for a 5-HT role in OCD comes from the increasing number of studies of successful treatment of OCD with indirect 5-HT agonists. Several placebo-controlled studies involving clomipramine (a 5-HT reuptake inhibitor) demonstrated both antiobsessional and anticompulsive effects (Kahn et al., 1988b). In contrast, other tricyclic antidepressants with fewer or no effects on 5-HT reuptake, such as desmethylimipramine (Zohar and Insel, 1987) and nortriptyline (Thoren et al., 1980) and amitriptyline (Ananth et al., 1981), have been found ineffective in treating OCD. Because two studies found a relationship between clinical improvement and clomipramine levels but not the levels of its noradrenergic metabolite, desmethylclomipramine (Stern et al., 1980; Insel et al., 1983), clomipramine's therapeutic effects are most likely related to its 5-HT agonistic properties and not to its noradrenergic properties.

Challenge studies with the 5-HT agonist *m*-CPP in OCD have provided conflicting results. In one study (Zohar et al., 1987), *m*-CPP administration to patients with OCD resulted in increased anxiety and obsessions, suggesting the presence of 5-HT receptor hypersensitivity. Yet, the cortisol response was blunted and the prolactin response no different from normals, indicating that 5-HT receptor hypersensitivity was not involved in 5-HT-mediated hormonal responses. On rechallenge with *m*-CPP following 3½ months of clomipramine treatment, anxiety and obsessions were not induced (Zohar et al., 1988), suggesting that down-regulation of 5-HT receptors had occurred. Charney et al. (1988) failed to find exacerbation of OCD symptoms with either *m*-CPP (0.1 mg/kg, intravenously) or tryptophan challenge (7 g, intravenously). On the other hand, that study reported blunted prolactin but normal cortisol responses in female patients with OCD. Although the present data indicate a role for 5-HT in OCD, its exact nature is far from clear.

A number of treatment studies using 5-HT agents in patients with panic disorder suggest that indirect 5-HT agonists are effective antipanic agents. A unique phenomenon found in treatment studies involving indirect 5-HT agonists is the so called "biphasic response," in which improvement in symptoms follows an initial period of symptom exacerbation. Further evidence that indirect 5-HT agonists may increase anxiety in patients with panic disorder is provided by the *m*-CPP challenge test. *m*-CPP given intravenously (0.1 mg/kg) induced anxiety and panic in patients with panic disorder and in normal controls (Charney et al., 1987). This effect appears to be related to dose and route of administration, because other researchers, using *m*-CPP in an oral dose of 0.5 mg/kg, did not report anxiety induction in normal subjects (Mueller et al., 1985, 1986; Zohar et al., 1987; Kahn et al., 1990b). *m*-CPP, when used at an even lower oral dose (0.25 mg/kg), was found to increase anxiety and panic in patients with panic disorder but not in normal controls (Kahn et al., 1988b,c).

Hormonal responses to *m*-CPP also appear to indicate that patients with panic disorder have hypersensitive 5-HT receptors. Whereas a low oral dose of *m*-CPP (0.25 mg/kg) induced augmented cortisol release only in patients with panic disorder (Kahn et al., 1988c), higher doses (e.g., 0.1 mg/kg *m*-CPP, intravenously) resulted in increased cortisol levels in patients and controls (Charney et al., 1987). The 5-HT-releasing agent, fenfluramine, also induces anxiety and panic as well as augmented cortisol and prolactin release in (female) patients with panic disorder, in contrast to normal controls and patients with major depression (Tagrum and Marshall, 1990). Den Boer and Westenberg (1990), however, using 5-HTP as a challenge agent, found similar cortisol release in patients with panic disorder and normal controls. Because the majority of the normal subjects and nine of the 20 patients vomited during the test, the interpretation of their results is difficult. The cortisol release is likely to have been stress induced rather than the result of 5-HTP-induced adrenocorticotrophic hormone release. In one study, in which the 5-HT precursor, tryptophan, was used to challenge 5-HT receptors, normal prolactin responses were found in patients with panic disorder (Charney and Heninger, 1986). Interestingly, the fact that fenfluramine and *m*-CPP, but not tryptophan, induce augmented behavioral responses in patients with panic disorder, may suggest that the 5-HT deficit in these patients is presynaptically located (Kahn and Van Praag, 1988, 1990).

Evidence that 5-HT function may be involved in generalized anxiety disorder has been obtained from several treatment studies in which agents selective for 5-HT systems were used. Two new drugs, buspirone and ritanserin, both having pronounced effects on 5-HT systems, have been shown to be effective in patients with generalized anxiety disorder. In most investigations, buspirone

benzodiazepines has proven to be as anxiolytic as the benzodiazepines. Buspirone appears to exert its effects through the 5-HT_{1A} receptor for which it has a high affinity. It also binds to DA_2 sites, but the latter is probably less clinically significant because its binding is 16-fold weaker (Peroutka, 1985). Buspirone has been noted to have agonistic and antagonistic effects on 5-HT_{1A} receptors, but its net effect is probably to decrease 5-HT function because administration of buspirone decreases raphe cell activity (Van der Maelen and Wilderman, 1984).

Preliminary results involving the selective 5-HT_{1C}/5-HT_2 antagonist ritanserin show it also to be effective in generalized anxiety disorder (Leysen et al., 1986). Administered for 2 weeks in a 10-mg/day dose in a placebo-controlled study (n = 83), it was found to be more effective than placebo and as effective as lorazepam (Ceulemans et al., 1985b) in a group of patients with generalized anxiety disorder. In another study (n = 191) in which ritanserin (10 mg/day) was compared to placebo and diazepam (10 mg/day), ritanserin (after 3 weeks of treatment) was found to be more effective than diazepam or placebo (Ceulemans et al., 1985c). Its therapeutic effect may be dose related because a lower (5 mg/day) dose of ritanserin appeared to be ineffective (Ceulemans et al., 1985b).

In conclusion, it appears that 5-HT receptor abnormalities are present in patients with prominent anxiety symptoms. Which of the multiple 5-HT receptor systems is involved, however, is not known. In OCD, there appears to be evidence of both *decreased* (blunted cortisol release to *m*-CPP) and *increased* (increased obsessions to *m*-CPP) 5-HT receptor sensitivity. This could be explained by hypothesizing differential abnormalities in some of the 5-HT subreceptors. In panic disorder, behavioral and cortisol responses (to *m*-CPP and fenfluramine) suggest postsynaptic 5-HT receptor hypersensitivity, but the normal prolactin responses to *m*-CPP suggest that other 5-HT receptors (i.e., those mediating prolactin response to *m*-CPP) are normal in panic disorder. Finally, in generalized anxiety disorder, both 5-HT_2 antagonists and 5-HT_{1A} partial agonists are effective, suggesting that decreasing 5-HT function, either by blocking the postsynaptic receptor (5-HT_2 antagonist) or decreasing release (5-HT_{1A} partial agonist), reduces anxiety in humans. Interestingly, whereas 5-HT reuptake inhibitors are effective in panic disorder, 5-HT_2 antagonists (Westenberg and Den Boer, 1989) and 5-HT_{1A} partial agonists (Sheehan et al., 1989) may not be. Efficacy of drugs that combine 5-HT_{1A} agonism and 5-HT_2 antagonism has not been tested in patients with anxiety disorders. Finally, the use of 5-HT_3 antagonists, effective in animal anxiety models, in human anxiety is another area of great therapeutic and scientific promise.

The pathogenesis of anxiety is unlikely, however, to be limited to 5-HT receptor abnormalities. For instance, increased noradrenergic function has been proposed as a pathogenic factor in panic attacks (Redmond and Huang, 1979; Charney and Redmond, 1983) and others have postulated a benzodiazepine-GABA hypothesis of anxiety production (Paul et al., 1981). According to the hypothesis, benzodiazepines exert their anxiolytic effect by activating GABA's inhibitory effects on neuronal excitability (through the facilitation of a cellular influx of Cl^- ions, resulting in increased neuronal polarity) (Costa et al., 1975). Evidence in support of the hypothesis comes from studies in which administration of benzodiazepine receptor antagonists induce anxiety-like behavior in monkeys (Ninan et al., 1982) and in humans (Dorow et al., 1983).

How might one reconcile the role of 5-HT in the pathogenesis of anxiety with the evidence of noradrenergic and GABAergic involvement? Several possible explanations may be considered. For example, certain anxiety states might be related to a predominant dysfunction of one neurotransmitter system, and other anxiety states may be related to disturbances in another neurotransmitter system. Alternatively, because 5-HT and noradrenergic systems have extensive connecting pathways, a disturbance in one may cause secondary or complementary effects in the other. 5-HT neurons, for example, project from the dorsal raphe to the LC (the main nucleus of noradrenergic-containing neurons) as shown by autoradiographic (Descarries and Leger, 1978), immunocytochemical (Pickel et al., 1978), and histochemical methods (Leger et al., 1979). Destruction of the mesencephalic part of the raphe system reportedly caused an increase in noradrenergic turnover within the LC (Pujol et al., 1978). Furthermore, stimulation of dorsal raphe nuclei blocked the increase in LC firing typically observed after administration of noxious stimuli. Moreover, this inhibitory effect of dorsal raphe stimulation on the LC is abolished or diminished by pretreatment with *p*-chlorophenylalanine, 5,7-dihydroxytryptamine and methysergide (Segal, 1979). Also, direct application of 5-HT on the LC suppressed its firing (Segal, 1979). Conversely, increased noradrenergic function caused increased 5-HT activity in the raphe nuclei (Baraban and Aghajanian, 1980; Marwaha and Aghajanian, 1982).

Based on these 5-HT/noradrenergic interactions, one possible conclusion is that norepinephrine's anxiogenic effects are mediated through enhancement of 5-HT function. GABA's role in anxiety should also be viewed in the context of its interaction with other neurotransmitters. For example, recent evidence indicates that the GABA and 5-HT systems are highly intertwined, both anatomically and functionally: (*a*) certain neurons of the raphe nuclei contain both 5-HT and GABA (Belin et al., 1983; Nanopoulos et al., 1982); (*b*) systemic administration of GABA agonists decreases 5-HT synthesis and 5-HT transmission (probably by inhibition of raphe neuronal activity) (Nishikawa and Scatton, 1983, 1985a); (*c*)

local infusion of GABA in the raphe nuclei caused decreased 5-HT activity in their projection area (Nishikawa and Scatton, 1985b); (*d*) GABA agonists and antagonists injected in the median raphe, respectively, caused decreased and increased 5-HT turnover (Forchetti and Meek, 1981); and (*e*) in vivo voltammetry showed that GABA inhibited striatal 5-HT transmission (Scatton et al., 1984).

B. Serotonin in Schizophrenia

There is growing evidence that blockade of 5-HT_2 receptors alleviates schizophrenic symptomatology and that 5-HT systems are involved in its pathogenesis. Ritanserin, a selective 5-HT_{1C}/5-HT_2 antagonist, either alone or in combination with a neuroleptic, reduces negative symptoms in patients with schizophrenia (Ceulemans et al., 1985c; Gelders et al., 1986). Mixed 5-HT_2/DA_2 antagonists, with an in vivo binding affinity for DA_2 20-fold more potent than for 5-HT_2 receptors, show reduction of negative symptoms (Ceulemans et al., 1985a; Mesotten et al., 1988; Gelders et al., 1988). Finally, the mixed 5-HT_1/5-HT_2 antagonist, cyproheptidine, was effective in alleviating both positive and negative symptoms in an open pilot study (Silver et al., 1989).

These beneficial effects of 5-HT receptor blockade in schizophrenia may suggest that 5-HT receptor function is altered in some schizophrenic patients. 5-HT receptor function has not been tested in medication-free schizophrenic patients. One study in which 6 to 10 mg of tryptophan was used intravenously as a challenge of 5-HT receptors found augmented prolactin release in medicated patients (Cowen et al., 1985). Hoshino et al. (1985), administering 3 mg/kg of the 5-HT precursor, 5-HTP, found inconsistent changes in prolactin and growth hormone release in patients receiving haloperidol. Postmortem studies examining 5-HT_2 receptors in schizophrenia are tainted by prior medication use. The results have been inconsistent, some investigators finding decreased binding of the 5-HT_2 ligands, [^{3}H]lysergic acid (Bennet et al., 1979) or [^{3}H]ketanserin (Mita et al., 1986), but others finding no differences as compared with normal brains (Whitaker et al., 1981; Reynolds et al., 1983). The most consistent finding suggesting abnormal 5-HT function in schizophrenia is that a subgroup of schizophrenic patients has lower CSF concentrations of 5-HIAA. These patients are generally have cortical atrophy and/or ventricular enlargement (Nyback et al., 1983; Potkin et al., 1983; Losonczy et al., 1986) or a history of suicide attempts (Van Praag, 1983; Banki et al., 1984). Because it has not been studied, one can only speculate whether the decreased 5-HT metabolism found in this subgroup is secondary to increased 5-HT receptor sensitivity.

Recently, interest in a possible role for 5-HT in the pathogenesis of schizophrenia has been boosted by the finding that clozapine, the only compound proven to be effective in patients with schizophrenia refractory to treatment (Kane et al., 1988), is a potent 5-HT_2 antagonist. Clozapine is also more efficacious than conventional neuroleptics in schizophrenic patients nonrefractory to treatment (Claghorn et al., 1987; Fischer-Cornelssen and Ferner, 1976; Shopsin et al., 1979; Leon, 1979; Van Praag et al., 1976). Interestingly, clozapine's superiority may be unrelated to any effect on DA systems. Its binding affinity to DA_2 receptors is 10-fold weaker than that of chlorpromazine (Creese et al., 1976; Peroutka and Snyder, 1980; Richelson, 1984), but in the studies comparing clozapine to chlorpromazine, clozapine was more effective than chlorpromazine, generally using half its dose (Kane et al., 1988; Claghorn et al., 1987; Fischer-Cornelssen and Ferner, 1976; Shopsin et al., 1979; Leon, 1979). Second, it has been consistently found that chronic administration of clozapine (3 weeks to 1 year) does not increase [^{3}H]spiroperidol binding in brain (Seeger et al., 1982; Lee and Tang, 1984; Rupniak et al., 1984, 1985; Jenner et al., 1985; Cohen and Lipinski, 1986), implying that it does not increase DA_2 receptor sensitivity.

Furthermore, in contrast to haloperidol, clozapine alters 5-HT_2 receptor sensitivity after chronic administration. After 4 to 10 weeks, clozapine decreased 5-HT_2 receptor density in the cortex of rats (Lee and Tang, 1984) This effect is also seen with other 5-HT_2 antagonists, such as the selective 5-HT_2 antagonist, ritanserin, and the mixed 5-HT_2/DA_2 antagonist, setoperone (Leysen et al., 1986). In contrast, haloperidol does not alter 5-HT_2 receptor sensitivity in animals (Andree et al., 1986). Behavioral studies in animals suggest that clozapine is a potent 5-HT antagonist. Injection of clozapine in median raphe nuclei blocks lysergic acid-induced hypermotility as effectively as 5-HT antagonists (Fink et al., 1983). Clozapine can also block the interoceptive cue of quipazine, a 5-HT agonist (Friedman et al., 1984). Finally, in contrast to chlorpromazine and haloperidol, clozapine blocks the temperature and cortisol increase induced by the selective 5-HT_2 agonist, MK-212 (but not the cortisol increase induced by the selective 5-HT_{1A} agonist 8-hydroxy-N,N-dipropyl-2-aminotetralin) (Nash et al., 1988).

Several studies are presently underway to test 5-HT receptor sensitivity in patients with schizophrenia, using *m*-CPP as a probe. Preliminary evidence provide suggestions of increased and decreased 5-HT receptor sensitivity in schizophrenia. Linking these receptor abnormalities to treatment response to atypical neuroleptics will be one of the more interesting avenues of research in schizophrenia in future years.

C. Serotonin in Alzheimer's Disease

Recent evidence suggests that there are significant abnormalities in the 5-HT system in AD (Bowen et al., 1983; Cross et al., 1984; Palmer et al., 1987). Abnormalities in 5-HT transmission, and in the functional interaction between an altered 5-HT system and other neu-

rotransmitter systems affected by the disease process, may lead to the clinical expression of symptoms in this illness and may be important in the consideration of symptomatic pharmacotherapeutic strategies for patients with AD.

Postmortem studies have demonstrated significant losses of 5-HT_1 and 5-HT_2 receptors in AD cortex, hippocampus, and amygdala (Cross et al., 1984; Bowen et al., 1983). To date there have been no studies of the status of the 5-HT_3 receptor subtype in the AD brain. There appears to be some regional specificity in this 5-HT receptor decrease and some selectivity in the receptor subtype that is affected by the AD process. For example, the loss in 5-HT_1 receptors is primarily in 5-HT_{1A} receptors from the frontal cortex (Middlemiss et al., 1986). In contrast, the 5-HT_2 receptor loss occurs primarily in the temporal cortex, hippocampus, and amygdala. Whereas the 5-HT_1 receptor loss appears to be age related in persons with AD, the 5-HT_2 receptor decrease is found in both older and younger persons with AD (Cross et al., 1986). The decrement in 5-HT_2 receptors is greater than for the 5-HT_1 subtype and may even be selective for AD, because significant 5-HT_2 receptor losses have not been described in other dementing illnesses, such as Parkinson's dementia, despite the presence of cognitive impairment (Perry et al., 1984). Although the exact localization of the 5-HT_2 receptor site is uncertain, its association with somatostatin-containing immunoreactivity (Cross et al., 1984) suggests that it is located on intrinsic cortical neurons.

Patients with AD show increased behavioral responsivity compared to controls following acute challenge with the selective 5-HT agonist, *m*-CPP (Lawlor et al., 1989b). This may indicate a functionally hyperresponsive 5-HT_1/5-HT_2 system due to intrinsic damage to the serotonergic system with compensatory up-regulation of the remaining postsynaptic receptors (Leysen et al., 1986), similar to the denervation supersensitivity in animals following lesioning of the 5-HT system (Trulson et al., 1978). Modulation of such a hyperresponsive 5-HT system with 5-HT selective antagonists, reuptake inhibitors, or direct agonists may, therefore, represent a rational pharmacotherapy for certain behavioral symptoms in this illness.

1. Functional interactions between serotonergic and dopaminergic systems. In addition to the cortical 5-HT receptor loss in AD, there are significant decreases in large neurons in the dorsal raphe nucleus (Yamamoto and Hirano 1985), which contains the main serotonergic projections from the brainstem to the cortex and striatum. In fact, these projections constitute one of the main ascending pathways from the brainstem to the DA-containing cells of the striatum and, as such, may play an important role in the control of motor movement. Electrophysiological data from animals indicate that the 5-HT input to the striatum, caudate, and putamen is predominantly inhibitory (Dray et al., 1976; Park et al., 1982). The strong relationship between CSF homovanillic acid and 5-HIAA in human studies indicates that there is also an important functional interaction between these two neurotransmitter systems in humans (for review, see Agren et al., 1986). Manipulation of 5-HT function can alter brain DA concentrations in animals and may explain the recent reports of extrapyramidal side effects in patients receiving fluoxetine (Bouchard et al., 1989; Tate, 1989) and the clinical experience of worsened motoric symptoms in patients with Parkinson disease being treated with fluoxetine for depression.

In AD, there is relatively greater damage to the 5-HT system than to the DA system. With the loss of this predominantly inhibitory input of the 5-HT system, a relatively "hyperdopaminergic" state may be assumed, and although highly speculative, this may explain the development of certain noncognitive symptoms such as motor agitation and pacing via striatal dysfunction and the emergence of psychosis via increased frontolimbic activity. The relative damage to the 5-HT system in any particular patient with AD could, therefore, explain the differential presentation of symptoms in patients with the same neuropathological finding, i.e., plaques and tangles.

2. Serotonergic-cholinergic interactions. There is a rich preclinical literature suggesting that the cholinergic and serotonergic systems have many important functional interactions in the brain. 5-HT receptor stimulation with *m*-CPP, a 5-HT agonist, or fenfluramine, a 5-HT-releasing agent, significantly reduce acetylcholine release (Vizi et al., 1981). Acetylcholine release from cortical and hippocampal cholinergic nerve terminals is generally inhibited by the 5-HT system (Bianchi et al., 1986; Muramatsu et al., 1988), possibly via 5-HT_{1B} receptors in the hippocampus (Maura and Raiteri, 1986). This inhibitory action on acetylcholine release in the hippocampus may be important in memory processing and could explain how direct 5-HT agonist stimulation with *m*-CPP resulted in memory impairment in recent studies in human populations (Lawlor et al., 1989a,b). Interestingly, 5-HT_2 receptor sites (which are selectively reduced in patients with AD) appear to be located on cholinergic nerve terminals in the rat cortex, suggesting that further work on 5-HT-cholinergic interactions, and its possible significance in AD, may be warranted (Quirion et al., 1985).

Animal models that possess some of the neurochemical abnormalities present in AD have been developed to test the potential usefulness of different pharmacological agents. One such animal model is the nbM model. The nbM contains the main cortical cholinergic projections. Lesions of this nucleus result in significant (30 to 50%) depletions in cortical markers of cholinergic activity such as choline acetyltransferase and acetylcholinesterase. These lesions are neurochemically specific and do not affect other neurotransmitter systems. Furthermore,

these lesions are stable over time and show little post-lesion recovery of cholinergic activity or behavioral deficit. Animals with such a lesion show profound learning and memory deficits in most behavioral paradigms, including tests of passive avoidance.

The memory impairment produced by nbM lesions induced with ibotenic acid can be reversed pharmacologically with physostigmine (Haroutunian et al., 1986, 1989), showing that drugs that enhance central cholinergic activity can overcome the behavioral deficits produced by a cholinergic lesion. However, in the same model, when the noradrenergic or serotonergic system is also lesioned chemically, increasing central cholinergic activity with cholinergic agents does not completely reverse the effects of the nbM lesion. Specifically, administration of the serotonergic depleting agent *p*-chloroamphetamine to nbM-lesioned rats produces a more profound passive avoidance memory deficit than does nbM lesions alone and, when combined with the nbM lesion, blocked the memory-enhancing effects of a wide range of doses of physostigmine and oxotremorine (Haroutunian et al., 1989). This would suggest that an intact 5-HT neuronal system, in addition to normal cholinergic function, is necessary for normal memory processes, emphasizing the importance of the functional interaction between 5-HT and cholinergic systems in memory processing. It also emphasizes how abnormalities in both of these systems may contribute to the expression of memory loss in patients with AD.

3. Summary. In summary, the abnormalities in serotonergic function, and the net effect of the derangement caused by the AD process in the functional interaction between 5-HT and other neurotransmitter systems, notably DA and acetylcholine, may be important in the clinical expression of symptoms in patients with AD. The development of selective agonists and antagonists for the various 5-HT receptor subtypes may allow us to tease apart the contribution of particular 5-HT receptor changes to the presence of clinical symptoms in this illness and give us direction in the development of 5-H-selective agents to modify symptoms in this debilitating illness. Clearly, further studies are warranted to explore the functional significance of altered neurotransmitter interactions in the Alzheimer disease process.

VII. Pharmacological Implications

The critical issues reviewed in this paper will have important implications for pharmacological development of serotonergic medications. Although traditionally medications affecting the serotonergic system have enhanced presynaptic activity by, for example, reuptake blockade, postsynaptic effects of these medications need to be considered carefully as well. Reduced responsiveness of postsynaptic receptors may diminish the effectiveness of reuptake blockers in the serotonergic system. If the subtype of receptor that is impaired is clearly identified, then specific receptor agonists might be used. Although such clear identification has not been made for affective and personality disorders, the possibility that 5-HT_{1A} agonists might be usedfor the control of aggressive behavior should be considered; indeed, promising results have been obtained along those lines (Olivier et al., 1989). If dysregulation of both presynaptic and postsynaptic elements contribute to the deficit, mood stabilizing serotonergic agents, such as lithium, might be considered as appropriate agents for controlled therapeutic trials.

A drug action on multiple receptor subtypes must be considered. There are some suggestions in the evidence presented that 5-HT_2 or 5-HT_{1C} receptors might be supersensitive in anxiety disorders, and possibly 5-HT_{1A} receptors may be diminished in responsiveness in relation to impulsivity/aggression. It is conceivable in some syndromes characterized by anxious depressions that the combination of 5-HT_2 antagonists, such as ritanseran, and 5-HT_{1A} receptor agonists or broad serotonergic reuptake blockers may compensate for an imbalance between 5-HT_2 and 5-HT_{1A} receptors. The possibility of multiple receptor subtype imbalance in psychiatric disorders must now be considered during the development of more effective treatments for these disorders.

To the extent that the serotonergic system may be seen as dysregulated between presynaptic and postsynaptic components, serotonergic antidepressants may act as "reregulators" in normalizing serotonergic activity. Thus, for example, increased serotonergic function induced by serotonergic reuptake blockers may down-regulate supersensitive postsynaptic receptors in OCDs (Winslow and Insel, 1990). By stabilizing firing of the serotonergic system (DeMontigny and Blier, 1984) and maintaining intersynaptic serotonergic concentrations, the serotonergic system may be better "buffered," explaining why serotonergic reuptake blockers may be effective for a variety of psychiatric disorders with different specific serotonergic dysfunction patterns.

The drugs that target specific receptor subtype fields might induce regionally specific effects. For example, 5-HT_{1A} agonists that reduce presynaptic serotonergic firing, as well as inhibit firing of hippocampal pyramidal cells, may be useful in the anxiety disorders by reducing serotonergic impulse flow to these limbic areas that have been hypothesized to be central to the modulation of anxiety (Murphy, 1990).

An agent or combination of agents rationally tailored to target the dysfunctional interaction of more than one neurotransmitter system may be required to develop effective treatment. For example, the reduction of aggression may require interventions that both reduce noradrenergic receptor responsiveness and enhance serotonergic function. Thus, serotonergic reuptake blockers may promote down-regulation of adrenergic receptors (Janowski et al., 1982), possibly accounting for the reported beneficial effects of serotonergic reuptake blockers, such as fluoxetine, in impulsive aggression (Coccaro et al.,

1990b). Specific efforts to directly target both systems may produce more efficacious drugs for these symptoms.

Finally, the possibility that specific serotonergic agents may be beneficial across diagnostic categories for specific dimensions of behavior, i.e., anxiety, impulsive/aggression, must be considered.

VIII. Conclusions

It is clear that the serotonergic system subserves a broad domain of function in the central nervous system that may be considered modulatory. It may serve to suppress punished behaviors and modulate responses to the environment. Thus, its impairment might be expected to have a broad parade of behavioral effects, the expression of which may depend on the biological context in which it occurs. New drug development must consider the range of altered patterns of serotonergic activity that may exist in the psychiatric disorders, their interaction with other transmitter system abnormalities, and their association with possible dimensions of symptomatology that cut across dimensional diagnostic categories.

REFERENCES

ABERG-WISTEDT, A., ROSS, S. B., JOSTELL, K. G., AND SJÖQVIST, B.: A double-blind study of zimelidine, a serotonin uptake inhibitor, and desipramine, a noradrenaline uptake inhibitor, in endogenous depression. II. Biochemical findings. Acta Psychiatr. Scand. **66:** 66–82, 1982.

AGREN, H.: Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolites in the cerebrospinal fluid: suicide patterns. Psychiatry Res. **3:** 225–236, 1980.

AGREN, H., MEFFORD, I. N., RUDORFER, M. V., LINNOILA, M., AND POTTER, W. Z.: Interacting neurotransmitter systems. A non-experimental approach to 5-HIAA-HVA correlation in human CSF. J. Psychiatr. Res. **20:** 175–193, 1986.

ANANTH, J., PECKNOLD, J. C., AND VAN DER STEEN, N.: Double-blind comparative study of clomipramine and amitryptiline in obsessive compulsive neurosis. Prog. Neuropsychopharmacol. **5:** 257–264, 1981.

ANDREE, T. H., MIKUNI, M., TONG, C. Y., KOENIG, J. I., AND MELTZER, H. Y.: Differential effect of subchronic treatment with various neuroleptic agents on serotonin S2 receptors in rat cerebral cortex. J. Neurochem. **46:** 191–197, 1986.

ASBERG, M., SCHALLING, D., TRASKMAN-BENDZ, L., AND WAGNER, A.: Psychobiology of suicide, impulsivity, and related phenomena. *In* Psychopharmacology: Third Generation of Progress, ed. by H. Y. Meltzer, pp. 655–668, Raven Press, New York, 1987.

ASBERG, M. TRASKMAN, L., AND THOREN, P.: 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch. Gen. Psychiatry **33:** 1193–1197, 1976.

ASNIS, G. M., EISENBERG, J., VAN PRAAG, H. M., LEMUZ, C. Z., HARKAVY-FRIEDMAN, J. M., AND MILLER, A. H.: The neuroendocrine response to fenfluramine in depressives and controls. Biol. Psychiatry **24:** 117–120, 1988.

AULAKH, C. S., WOZNIAK, K. M., HAAS, M., HILL, J. L., ZOHAR, J., AND MURPHY, D. L.: Food intake, neuroendocrine and temperature effects of 8-OHDPAT in the rat. Eur. J. Pharmacol. **146:** 253–259, 1988.

BALDESSARINI, R. J.: Treatment of depression by altering monoamine metabolism: precursors and metabolic inhibitors. Psychopharmacol. Bull. **20:** 224–239, 1984.

BANKI, C. M., AND ARATO, M.: Amine metabolites and neuroendocrine responses related to depression and suicide. J. Affective Dis. **5:** 223–232, 1983.

BANKI, C. M., ARATO, M., PAPP, Z., AND KURCZ, M.: Cerebrospinal fluid amine metabolites and neuroendocrine changes in psychoses and suicide. *In* Cathecholamines, Neuropharmacology and Central Nervous Systems—Therapeutic Aspects, ed. by E. Usdin, A. Carlsson, and A. Dahlstrom, pp. 153–159, Alan R. Liss Inc., New York, 1984.

BANKI, C. M., MOLNAR, G., AND VOJNIK, M.: Cerebrospinal fluid amine metabolites, tryptophan and clinical parameters in depression: psychopathological symptoms. J. Affective Dis. **3:** 1991.

BARABAN, F. M., AND AGHAJANIAN, G. K.: Suppression of firing activity of 5-HT neurons in the dorsal raphe by alpha-adrenoceptor antagonist. Neuropharmacology **19:** 355–363, 1980.

BELIN, M. F., NANOPOULOS, D., DIDIER, M., AGUERA, M., STEINBUSCH, H., VERHOFSTAD, A., MAITRE, M., AND PUJOL, F.: Immunohistochemical evidence for the presence of gamma-aminobutyric acid and serotonin in one nerve cell. A study on the raphe nuclei of the rat using antibodies to glutamate decarboxylase and serotonin. Brain Res. **275:** 329–339, 1983.

BENNET, J. P., ENNA, S. J., BYLUND, D., GILLIN, J. C., AND SNYDER, S. H.: Neurotransmitter receptors in frontal cortex of schizophrenics. Arch. Gen. Psychiatry **36:** 927–934, 1979.

BERRETTINI, W. H., NURNBERGER, J. I., SCHEININ, M., SEPPALA, T., LINNOILA, M., NARROW, W., SIMMONS-ALLING, S., AND GERSHON, E. S.: Cerebrospinal fluid and plasma monoamines and their metabolites in euthymic bipolar patients. Biol. Psychiatry **20:** 257–269, 1985.

BIANCHI, C., SINISCALCHI, A., AND BEANI, L.: The influence of 5-hydroxytryptamine on the release of acetylcholine from guinea-pig brain *ex vivo* and *in vitro*. Neuropharmacology **25:** 1043–1049, 1986.

BLUNDELL, J. E.: Serotonin and appetite. Neuropharmacology **23:** 1537–1551, 1984.

BOUCHARD, R. H., POURCHER, P., AND VINCENT P.: Fluoxetine and extrapyramidal symptoms. Am. J. Psychiatry **146:** 10, 1352–1353, 1989.

BOWEN, D. M., ALLEN, S. J., BENTON, J. S., GOODHARDT, M. J., HAAN, E. A., PALMER, A. M., SIMS, N. R., SMITH, C. C. T., SPILLANE, J. A., ESIRI, M. M., NEARY D., SNOWDEN, S., WILCOCK, G. K., AND DAVISON, A. N.: Biochemical assessment of serotonergic and cholinergic dysfunction and cerebral atrophy and Alzheimer's disease. J. Neurochem. **41:** 266–272, 1983.

BRANCHEY, L., BRANCHEY, M., SHAW, S., AND LIEBER, C. S.: Depression, suicide, and aggression in alcoholics and their relationship to plasma amino acids. Psychiatry Res. **12:** 219–226, 1984.

BRILEY, M. S., LANGER, S. Z., RAISMAN, R., SECHTER, D., AND ZARIFRAN, E.: Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. Science (Wash. DC) **209:** 303–305, 1980.

BROWN, G. L., EBERT, M. H., GOYER, P. F., JIMERSON, D. C., KLEIN, W. J., BUNNEY, W. E., AND GOODWIN, F. K.: Aggression, suicide, and serotonin: relationships to CSF amine metabolites. Am. J. Psychiatry **139:** 741–746, 1982.

BROWN, G. L., GOODWIN, F. K., AND BALLENGER, J. C.: Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res. **A:** 131–139, 1979.

BUCHSBAUM, M., GOODWIN, F., AND MUSCETTOLA, G.: Urinary MHPG, stress response, personality factors, and somatosensory evoked potentials in normal subjects and patients with affective disorders. Neuropsychobiology **7:** 212–224, 1981.

CEULEMANS, D. L. S., GELDERS, Y. G., HOPPENBROUWERS, M.-L. J. A., REYNTJENS, A. J. M., AND JANSSEN, P. A. J.: Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone. Psychopharmacology **85:** 329–332, 1985a.

CEULEMANS, D. L. S., HOPPENBROUWERS, M. L. J. A., GELDERS, Y. G., AND REYNTJENS, A. J. M.: The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Pharmacopsychiatry **18:** 303–305, 1985b.

CEULEMANS, D. L. S., HOPPENBROUWERS, M. L., GELDERS, Y., REYNTJENS, A. J. M., AND JANSSEN, P.: The effect of benzodiazepine withdrawal on the therapeutic efficacy of a serotonin antagonist in anxiety disorders. Presented at the IVth World Congress of Biological Psychiatry, Philadelphia, PA, 1985c.

CHAMBERLAIN, G., ERVIN, F. R., PIHL, R. O., AND YOUNG, S. N.: The effect of raising or lowering tryptophan levels on aggression in vervet monkeys. Pharmacol. Biochem. Behav. **28:** 503–510, 1987.

CHARNEY, D. S., GOODMAN, W. K., PRICE, L. H., WOODS, S. W., RASMUSSEN, S. A., AND HENINGER, G. R.: Serotonin function in obsessive-complusive disorder: a comparison of the effects of tryptophan and *m*-chloophenylpiperazine in patients and healthy subjects. Arch. Gen. Psychiatry **45:** 177–185, 1988.

CHARNEY, D. S., AND HENINGER, G. R.: Serotonin function in panic disorders. The effect of intravenous tryptophan in healthy subjects and patients with panic disorder before and during alprazolam treatment. Arch. Gen. Psychiatry **43:** 1059–1065, 1986.

CHARNEY, D. S., AND REDMOND, D. E., JR.: Neurobiological mechanisms in human anxiety. Evidence supporting central noradrenergic hyperactivity. Neuropharmacology **22:** 1531–1536, 1983.

CHARNEY, D. S., WOODS, S. W., GOODMAN, W. K., AND HENINGER, G. R.: Serotonin function in anxiety. II. Effects of the serotonin agonist *m*-CPP in panic disorder patients and healthy subjects. Psychopharmacology **92:** 14–24, 1987.

CLAGHORN, J., HONIGFELD, G., ABUZZAHAB, F. S., WANG, R., STEINBOOK, R., TUASON, V., AND KLERMAN, G.: The risk and benefits of clozapine versus chlorpromazine. J. Clin. Psychopharmacol. **7:** 377–384, 1987.

COCCARO, E. F., ASTILL, J. L., HERBERT, J. L., AND SCHUT, A. G.: Fluoxetine treatment of impulsive aggression in DSM-III-R personality disorder patients. J. Clin. Psychopharmacol. **10:** 373–375, 1990a.

COCCARO, E. F., GABRIEL, S., MAHON, T., MACALUSO, J., AND SIEVER, L. J.: Preliminary evidence of a serotonin (5-HT-1-like) component to the prolactin response to buspirone challenge in humans. Arch. Gen. Psychiatry **47:** 594–595, 1990b.

COCCARO, E. F., SIEVER, L. J., KAVOUSSI, R., RINALDI, P., MORRISON D., AND HOWARD L.: 5-HT postsynaptic function in aggression. *In* New Research Abstracts of the American Psychiatric Association, American Psychiatric Press, Washington, D.C., May, 1989a.

COCCARO, E. F., SIEVER, L. J., KLAR, H., MAURER, G., COCHRANE, K., COOPER, T. B., MOHS, R. C., AND DAVIS, K. L.: Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. Arch. Gen. Psychiatry **46:** 587–599, 1989b.

COHEN, B. M., AND LIPINSKI, J. F.: *In vivo* potencies of antipsychotic drugs in blocking alpha-1 noradrenergic and dopaminergic D2 receptors: implications for drug mechanisms of action. Life Sci. **39:** 2571–2580, 1986.

COPPEN, A., SWADE, C., AND WOOD, K.: Platelet 5-hydroxytryptamine accumulation in depressive illness. Clin. Chem. Acta **87:** 165–168, 1978.

COSTA, E., GUIDOTTI, A., AND MAO, C. C.: New concepts on the mechanism of action of benzodiazepines. Life Sci. **17:** 167–186, 1975.

COWEN, P. J., GADHVI, H., GODSEN, B., AND KOLAKOWSKA, T.: Responses of prolactin and growth hormone to *l*-tryptophan infusion: effects in normal subjects and schizophrenic patients receiving neuroleptics. Psychopharmacology **86:** 164–169, 1985.

CREESE, I., BURT, D. R., AND SNYDER, S. H.: Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science (Wash. DC) **192:** 481–483, 1976.

CROSS, A. J., CROW, T. J., FERRIER, I. N., AND JOHNSON, J. A.: The selectivity of the reduction of S2 receptors in Alzheimer-type dementia. Neurobiol. Aging **7:** 3–7, 1986.

CROSS, A. J., CROW, T. J., FERRIER, I. N., JOHNSON, J. A., BLOOM, S. R., AND CORSELLIS, J. A. N.: Serotonin receptor changes in dementia of the Alzheimer type. J. Neurochem. **43:** 1574–1581, 1984.

CURZON, G.: Serotonin and appetite. In the neuropharmacology of serotonin. Ann. NY Acad. Sci. **600:** 521–531, 1990.

DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., LANDIS, H., AND HENINGER, G. R.: Neuroendocrine and behavioral effects of dietary tryptophan restriction in healthy subjects. Life Sci. **45:** 2323–2332, 1989.

DEMONTIGNY, C., AND BLIER, P.: Effects of antidepressant treatments on 5-HT neurotransmission: electrophysiological and clinical studies. Adv. Biol. Psychiatry **39:** 223–239, 1984.

DEN BOER, J. A., AND WESTENBURG, H. G. M.: Behavioral, neuroendocrine and biochemical effects of 5-hydroxytryptophan administration in panic disorder. Psychiatry Res. **31:** 267–278, 1990.

DESCARRIES, L., AND LEGER, L.: Serotonin nerve terminals in the locus coeruleus of the adult rat. *In* Interactions between Putative Neurotransmitters in the Brain, ed. by S. Garattini, J. F. Pujol, and R. Samanin, pp 355–367, Raven Press, New York, 1978.

D'HAENEN, H., DEWAELE, M., AND LEYSEN, J. E.: Platelet ^{3}H-paroxetine binding in depressed patients. Psychiatry Res. **26:** 11–17, 1988.

DOROW, R., HOROWSKI, R., PASCHELKE, G., AND AMIN, M.: Severe anxiety induced by FG 7142, a beta-carboline ligand for benzodiazepine receptors. Lancet **1:** 98–99, 1983.

DRAY, A. L., GOYNE, T. J., OAKLEY, R. N., AND TANNER, T.: Evidence for the existence of a raphe projection to the substantia nigra in the rat. Brain Res. **113:** 45–57, 1976.

FINK, H., MORGENSTERN, R., AND OELSSNER, W.: Clozapine-a serotonin antagonist? Pharmacol. Biochem. Behav. **20:** 513–517, 1983.

FISCHER-CORNELSSEN, K. A., AND FERNER, U. J.: An example of European multicenter trials: multispectral analysis of clozapine. Psycopharmacol. Bull. **12:** 34–39, 1976.

FISHBEIN, D. H., LOZOVSKY, D., AND JAFFE, J. H.: Impulsivity, aggression, and neuroendocrine responses to serotonergic stimulation in substance abusers. Biol. Psychiatry **25:** 1049–1066, 1989.

FOOTE, S. L., BLOOM, F. E., AND ASTON-JONES, G.: Nucleus locus coeruleus: new evidence of anatomical and physiologic specificity. Physiol. Rev., **63:** 844–914, 1983.

FORCHETTI, C. M., AND MEEK, J. L.: Evidence for a tonic GABAergic control of serotonin neurons in the median raphe nucleus. Brain Res. **206:** 208–212, 1981.

FRIEDMAN, R. L., SANDERS-BUSH, E., AND BARRETT, R. L.: Clozapine blocks disruptive and discriminative stimulus effects of quipazine. Eur. J. Pharmacol. **106:** 191–193, 1984.

GELDERS, Y., BUSSCHE, G. V., REYNTJKENS, A., AND JANSSEN, P. A. J.: Serotonin S2 receptor blockers in the treatment of chronic schizophrenic. Clin. Neuropharmacol. **9:** 325–327, 1986.

GELDERS, Y., HEYLEN, S., VANDEN BUSSCHE, G., REYNTJENS, A., AND JANSSEN, P. A. J.: Risperidone, a novel antipsychotic with thymostenic properties. Psychopharmacology **96** (suppl.)**:** 100, 1988.

GIBBONS, R. D., AND DAVIS, J. M.: Consistent evidence for a biological subtype of depression characterized by low CSF 5-HIAA monoamine levels. Acta Psychiatr. Scand. **74:** 8–12, 1986.

GORZALKA, B. B., MENDELSON, S. D., AND WATSON, N. V: Serotonin receptor subtypes and sexual behavior. *In* The Neuropharmacology of Serotonin, ed. by P. M. Whitaker-Azmitia and S. J. Peroutka, Annals of the NY Academy of Science, Washington, D.C., 1990.

HAMIK, A., AND PEROUTKA, S. J.: 1-*m*-Chlorophenyl piperazine (*m*CPP) interactions with neurotransmitter receptors in the human brain. Biol. Psychiatry **25:** 569–575, 1980.

HAROUTUNIAN, V., KANOF, P. D., TSUBOYAMA, G. K., CAMPBELL, G. A., AND DAVIS, K. L.: Animal models of Alzheimer's disease: behavior, pharmacology, transplants. Can. J. Neurol. Sci. **13:** 385–393, 1986.

HAROUTUNIAN, V., SANTUCCI, A. C., AND DAVIS, K. L.: Animal models of multiple neurotransmitter dysfunction in Alzheimer's disease: cholinergic/noradrenergic, cholinergic/serotonergic, cholinergic/somatostatinergic interactions. *In* Proceedings of 28th Annual Meeting of American College of Neuropsychopharmacology, Maui, Hawaii, Dec. 10–15, 1989.

HARTMANN, E.: Effects of L-tryptophan on sleepiness and on sleep. J. Psychiatr. Res. **17:** 107–113, 1983.

HENINGER, G. R., CHARNEY, D. S., AND STERNBERG, D. E.: Serotonergic function in depression. Arch. Gen. Psychiatry **41:** 398–402, 1984.

HOSHINO, Y., KANEKO, M., KUMASHIRO, H., AND TACHIBANA, R.: Endocrinological function in schizophrenic patients under haloperidol treatment: plasma prolactin, growth hormone and serotonin levels after *l*-5-HTP loading. Folia Psychiatr. Neurol. Jpn. **39:** 25–31, 1985.

HOYER, D.: Functional correlates of serotonin 5-HT1 recognition sites. J. Receptor Res. **8:** 59–81, 1988.

HOYER, D, PAZOS, A., PROBST, A., AND PALACIOUS, J. M.: Serotonin receptors in the human brain. 1. Characterization and autoradiographic localization of 5-HT$_{1A}$ recognition sites. Apparent absence of 5-HT$_{1B}$ recognition sites. Brain Res. **376:** 85–96, 1986.

INSEL, T. R., MURPHY, D. L., COHEN, R. M., ALTERMAN, I., KILTS, C., AND LINNOILA, M.: Obsessive compulsive disorder: a double blind trial of clomipramine and clorgyline. Arch. Gen. Psychiatry **40:** 605–612, 1983.

JANOWSKY, A., OKADA, F., MANIER, D. H., APPLEGATE, C. D., SULSER, F., AND STERANKA, L. R.: Role of serotonergic input in the regulation of the β-adrenergic receptor-coupled adenylate cyclase system. Science (Wash. DC). **218:** 900–901, 1982.

JENNER, P., RUPNIAK, N. M., AND MARSDEN, C. D.: Differential alteration of striatal D1 and D2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Psychopharmacology **2** (suppl.)**:** 174–181, 1985.

KAHN, R. S., ASNIS, G. M., WETZLER, S., AND VAN PRAAG, H. M.: Neuroendocrine evidence for 5-HT receptor hypersensitivity abnormalities in patients with panic disorder. Psychopharmacology **96:** 360–364, 1988a.

KAHN, R. S., AND VAN PRAAG, H. M.: A serotonin hypothesis of panic disorder. Hum. Psychopharmacol. **3:** 285–288, 1988.

KAHN, R. S., AND VAN PRAAG, H. M.: Panic disorder: a presynaptic serotonin defect? Psychiatry Res. **31:** 209–210, 1990.

KAHN, R. S., VAN PRAAG, H. M., WETZLER, S., ASNIS, G. M., AND BARR, G.: Serotonin and anxiety revisited. Biol. Psychiatry **23:** 189–208, 1988b.

KAHN, R. S., WETZLER, S., ASNIS, G. M., PAPOLOS, D., AND VAN PRAAG, H. M.: Serotonin receptor sensitivity in major depression. Biol. Psychiatry **28:** 358–362, 1990a.

KAHN, R. S., WETZLER, S., ASNIS, G. M., AND VAN PRAAG, H. M.: The effects of *m*-chlorophenylpiperazine in normal subjects: a dose-response study. Psychopharmacology **100:** 339–344, 1990b.

KAHN, R. S., WETZLER, S., VAN PRAAG, H. M., ASNIS, G. M., AND STRAUMAN, T.: Behavioral indications for serotonin receptor hypersensitivity in panic disorder. Psychiatry Res. **25:** 101–104, 1988c.

KANE, J., HONIGFELD, G., SINGER, J., AND MELTZER, H.: Clozapine for the treatment-resistant schizophrenic. Arch. Gen. Psychiatry **45:** 789–796, 1988.

KOYAMA, T., AND MELTZER, H. Y.: A biochemical and neuroendocrine study of the serotonergic system in depression. *In* New Results in Depression Research, ed. by H. Hippius, pp. 169–188, Springer-Verlag, Berlin, 1986.

LAWLOR, B. A., SUNDERLAND, T., MELLOW, A. M., HILL, J. L., MOLCHAN, S. E., AND MURPHY, D. L.: Hyperresponsivity to the serotonin agonist *m*-chlorophenylpiperazine in Alzheimer's disease: a controlled study. Arch. Gen. Psychiatry **46:** 542–549, 1989a.

LAWLOR, B. A., SUNDERLAND, T., MELLOW, A. M., HILL, J. L., NEWHOUSE P. A., AND MURPHY, D. L.: A preliminary study of the effects of intravenous *m*-chlorophenylpiperazine, a serotonin agonist, in elderly subjects. Biol. Psychiatry **25:** 679–686, 1989b.

LAWRENCE, T., COCCARO, E. F., TRESTMAN, R. L., BERNSTEIN, D., MITROPOULOU, V., AND SIEVER, L. J.: Noradrenergic activity in impulsivity/aggression. *In* New Research Abstracts of American Psychiatric Press, Washington, D.C., the 144th Annual American Psychiatric Association Meeting, American Psychiatric Press, Washington, D.C., May, 1991.

LEE, T., AND TANG, S. W.: Lozapine and clozapine decrease serotonin (S2) but do not elevate dopamine (D2) receptor numbers in the rat brain. Psychiatry Res. **12:** 277–285, 1984.

LEGER, L., WIKLUND, L., DESCARRIES, L., AND PERSSON, M.: Description of an indolaminergic cell component in the cat locus coeruleus: a fluorescence histochemical and radioautographic study. Brain Res. **168:** 43–56, 1979.

LEON, C. A.: Therapeutic effects of clozapine: a 4-year follow-up of a controlled clinical trial. Acta Psychiatr. Scand. **59:** 471–480, 1979.

LESCH, K-P., RUPPRECHT, R., POTEN, B., MULLER, U., SOHNLE, K., FRITZE, J., AND SCHULTE, H. M.: Endocrine response to 5-hydroxytryptamine-1a receptor activation by ipsapirone in humans. Biol. Psychiatry **26:** 203–205, 1989.

LEWIS, D. A., AND MCCHESNEY, C.: Tritiated imipramine binding distinguishes among subtypes of depression. Arch. Gen. Psychiatry **42:** 485–488, 1985.

LEYSEN, J. E., VAN GOMPEL, P., GOMMEREN, W., WOESTENBORGHS, R., AND JANSSEN, P. A. J.: Down regulation of serotonin S2 receptor sites in rat brain by chronic treatment with the serotonin S2 antagonists: ritanserin and setoperone. Psychopharmacology **88:** 434–444, 1986.

LIDBERG, L., TUCK, J. R., ASBERG, M., SCALIA-TOMBA, G. P., AND BERTILSSON, L.: Homicide, suicide and CSF 5-HIAA, Acta Psychiatr. Scand. **71:** 230–236, 1985.

LINNOILA, M., VIRKKUNEN, M., SCHEINEN, M., NUUTILA, A., RIMON, R., AND GOODWIN, F. K.: Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci. **33:** 2609–2614, 1983.

LOPEZ-IBOR, J. J., SAIZ-RUIZ, J., AND MORAL IGLESIAS, L.: The fenfluramine challenge test in the affective spectrum: a possible marker of endogeneity and severity. Pharmacopsychiatry **21:** 9–14, 1988.

LOSONCZY, M. F., SONG, I. S., MOHS, R. C., DAVIDSON, M., DAVIS, B. M., AND

DAVIS, K. L.: Correlates of lateral ventricular size in chronic schizophrenia. II. Biological measures. Am. J. Psychiatry **143:** 1113–1118, 1986.

MAAS, J. W., KOCSIS, J. H., BOWDEN, C. L., DAVIS, J. M., REDMOND, D. E., HANIN, I., AND ROBINS, E.: Pre-treatment neurotransmitter metabolites and response to imipramine or amitriptyline treatment. Psychol. Med. **12:** 37–43, 1982.

MARWAHA, J., AND AGHAJANIAN, G. K.: Relative potencies of alpha-1 and alpha-2 antagonists in the locus coeruleus, dorsal raphe and dorsal lateral geniculate nuclei: an electrophysiological study. J. Pharmacol. Exp. Ther. **222:** 287–293, 1982.

MAURA, G., AND RAITERI, M.: Cholinergic terminals in rat hippocampus possess 5-HT1B receptors mediating inhibition of acetylcholine release. Eur. J. Pharmacol. **129:** 333–337, 1986.

MCEWEN, B. S., AND PARSONS, B.: Gonadal steroid action on the brain: neurochemistry and neuropharmacology. Annu. Rev. Pharmacol. Toxicol. **22:** 555–598, 1982.

MELLERUP, E. T., PLENGE, P., AND ENGELSTOF, T.: High affinity binding of [^{3}H]imipramine to human platelet membranes. Eur. J. Pharmacol. **96:** 303–309, 1983.

MELTZER, H. Y., ARORA, R. C., BABER, R., AND TRICOU, B. J.: Serotonin uptake in blood platelets of psychiatric patients. Arch. Gen. Psychiatry **38:** 1322–1326, 1981.

MELTZER, H. Y., AND LOWY, M. T.: The serotonin hypothesis of depression. *In* Psychopharmacology: The Third Generation of Progress, ed. by H. Y. Meltzer, pp. 513–526, Raven Press, New York, 1987.

MELTZER, H. Y., PERLINE, R., TRICOU, B. J., LOWY, M. T., AND ROBERTSON, A.: Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorder. II. Relation to suicide, psychosis, and depressive symptoms. Arch. Gen. Psychiatry **41:** 379–387, 1984.

MESOTTEN, F., PIETQUIN, M., WELLENS, L., HEYLEN, S., GELDERS, Y., AND VANDENBUSSCHE, G.: Therapeutic effect and safety of increasing doses of risperidone in psychotic patients. Psychopharmacology **96** (suppl.)**:** 238, 1988.

MIDDLEMISS, D. N., PALMER, A. M., EDEL, N., AND BOWEN, D. M. BINDING OF THE NOVEL SEROTONIN AGONIST 8-HYDROXY-2(DI-*N*-propylamino)tetralin in normal and Alzheimer brain. J. Neurochem. **46:** 993–996, 1986.

MITA, T., HANADA, S., NISHINO, N., KUNO, T., NAKAI, H., YAMADORI, T., MIZOI, Y., AND TANAKA, C.: Decreased serotonin S2 and increased dopamine D2 receptors in chronic schizophrenics. Biol. Psychiatry **21:** 1407–1414, 1986.

MUELLER, E. A., MURPHY, D. L., AND SUNDERLAND, T.: Further studies of the putative serotonin agonist, *m*-chlorophenylpiperazine: evidence for a serotonin receptor mediated mechanism of action in humans. Psychopharmacology **89:** 388–391, 1986.

MUELLER, E. A., SUNDERLAND, T., AND MURPHY, D. L.: Neuroendocrine effects of *m*-CPP, a serotonin agonist, in humans. J. Clin. Endocrinol. Metab. **61:** 1179–1184, 1985.

MURAMATSU, M., TAMAKI-OHASHI, J., USUKI, C., ARAKI, H., AND AIHARA, H.: Serotonin-2 receptor-mediated regulation of release of acetylcholine by minaprine in cholinergic nerve terminal of hippocampus of rat. Neuropharmacology **27:** 603–609, 1988.

MURPHY, D. L.: Neuropsychiatric disorders and the multiple human brain serotonin receptor subtypes and subsystems. Neuropsychopharmacology **3:** 457–471, 1990.

MURPHY, D. L., CAMPBELL, I., AND COSTA, J. L.: Current status of indoleamine hypothesis of the affective disorders. *In* Psychopharmacology: A Generation of Progress, ed. by M. A. Lipton, A. DiMascio, and K. F. Killam, pp. 1235–1248, Raven Press, New York, 1978.

NANOPOULOS, D, BELIN, M. F., MAITRE, M, VINCENDON, G, AND PUJOL, F.: Immunocytochemical evidence for the existence of GABAergic neurons in the nucleus raphe dorsalis, possible existence of neurons containing serotonin and GABA. Brain Res. **232:** 375–389, 1982.

NASH, J. F., MELTZER, H. Y., AND GUDELSKY, G. A.: Antagonism of serotonin receptor mediated neuroendocrine and temperature responses by atypical neuroleptics in the rat. Eur. J. Pharmacol. **151:** 463–469, 1988.

NINAN, P. T., INSEL, T. M., COHEN, R. M., COOK, J. M., SKOLNICK, P., AND PAUL, S. M.: Benzodiazepine receptor-mediated experimental "anxiety" in primates. Science (Wash. DC) **218:** 1332–1334, 1982.

NINAN, P. T., VAN KAMMEN, D. P., SCHEININ, M., LINNOILA, M., BUNNEY, W. E., AND GOODWIN, F. K.: Cerebrospinal fluid 5-HIAA in suicidal schizophrenic patients. Am. J. Psychiatry **141:** 566–569, 1984.

NISHIKAWA, T., AND SCATTON, B.: Evidence for a GABAergic inhibitory influence on serotonergic neurons originating from the dorsal raphe. Brain Res. **279:** 325–329, 1983.

NISHIKAWA, T., AND SCATTON, B.: Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphe pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Brain Res. **331:** 81–90, 1985a.

NISHIKAWA, T., AND SCATTON, B.: Inhibitory influence of GABA on central serotonergic transmission. Raphe nuclei as the neuroanatomical site of the GABAergic inhibition of cerebral serotonergic neurons. Brain Res. **331:** 91–103, 1985b.

NYBACK, H., BERGGREN, B. M., HINDMARSCH, T., SEDVALL, C., AND WIESEL, F. A.: Cerebroventricular size and cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy volunteers. Psychiatry Res. **9:** 301–308, 1983.

OGREN, S. O., FUXE, K., AGNOTI, L. F., GUSTAFSSON, J. A., JONSSON, G., AND HOLM, A. C.: Reevaluation of the indoleamine hypothesis of depression: evidence for a reduction of functional activity of central 5-HT systems by antidepressant drugs. J. Neural Transm. **46:** 85–103, 1979.

OLIVIER, B., MOS, J., VAN DER HEYDEN, J., AND HARTOG, J.: Serotonergic modulation of social interactions in isolated male mice. Psychopharmacology **97:** 154–156, 1989.

PALMER, A. M., FRANCIS, P. T., AND BENTON, J. S.: Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J. Neurochem. **48:** 8–15, 1987.

PALMER, A. M., STRATMAN, G. C., PROCTER, A. W., AND BOWEN, D. M.: Possible neurotransmitter basis of behavioral changes in Alzheimer's disease. Ann. Neurol. **23:** 616–620, 1988.

PARK, M. R., GONZALES-VEGAS, J. A., AND KITALI, S. T.: Serotonergic excitation from dorsal raphe stimulation recorded intracelluarly from rat caudate-putamen. Brain Res. **243:** 49–58, 1982.

PAUL, S. M., MARANGOS, P. J., AND SKOLNICK, P.: The benzodiazepine- GABA-chloride ionophore receptor complex: common site of minor tranquilizer action. Biol. Psychiatry **16:** 213–229, 1981.

PEROUTKA, S. J.: Selective interaction of novel anxiolytics with 5-HT1a receptors. Biol. Psychiatry **20:** 971–979, 1985.

PEROUTKA, S. J.: Serotonin receptors. *In* Psychopharmacology: Third Generation of Progress, ed by H. Y. Meltzer, pp. 303–311, Raven Press, New York, 1987.

PEROUTKA, S. J., AND SNYDER, S. H.: Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic, and histamine receptors to clinical potence. Am. J. Psychiatry **137:** 1518–1522, 1980.

PERRY, E. K., PERRY, R. H., CANDY, J. M., FAIRBAIRN, A. F., BLESSED, G., DICK, D. J., AND TOMLINSON, B. E.: Cortical serotonin S-2 receptor binding abnormalities in patients with Alzheimer's disease: comparisons with Parkinson's disease. Neurosci. Lett. **51:** 353–357, 1984.

PICKEL, V. M., TONG, H. J., AND REIS, D. J.: Immunocytochemical evidence for serotonergic innervation of noradrenergic neurons in nucleus locus coeruleus. *In* Interactions between Putative Neurotransmitters in the Brain, ed. by S Garattini, J. F. Pujol, and R. Samanin, pp. 369–382, Raven Press, New York, 1978.

POTKIN, S. G., WEINBERGER, D. R., LINNOILA, M., AND WYATT, R. J.: Low CSF 5-hydroxyindoleacetic acid in schizophrenic patients with enlarged cerebral ventricles. Am. J. Psychiatry **140:** 21–25, 1983.

PUJOL, J. F., KEANE, P., MCRAE, A., LEWIS, B. D., AND RENAUD, B.: Biochemical evidence for serotonergic control of the locus ceruleus. *In* Interactions between Putative Neurotransmitters in the Brain, ed by S. Garattini, J. F. Pujol, and R. Samanin, pp. 401–410, Raven Press, New York, 1978.

QUIRION, R., RICHARD, J., AND DAM, T. V.: Evidence for the existence of serotonin type-2 receptors on cholinergic terminals in rat cortex. Brain Res. **333:** 345–349, 1985.

REDMOND, D. E., JR., AND HUANG, Y. H.: Current concepts. II. New evidence for a locus coeruleus-norepinephrine connection with anxiety. Life Sci. **25:** 2149–2162, 1979.

REYNOLDS, G. P., ROSSOR, M. N., AND IVERSEN, J. L.: Preliminary studies of human cortical 5-HT2 receptors and their involvement in schizophrenia and neuroleptic drug action. J. Neural Transm. **18** (suppl)**:** 273–277, 1983.

RICHARDS, B. P.: Serotonin and nociception. In the Neuropharmacology of serotonin. Ann. NY Acad. Sci. **600:** 511–520, 1990.

RICHELSON, E.: Neuroleptic affinities for human brain receptors and their use in predicting adverse effects. J. Clin. Psychiatry **45:** 331–336, 1984.

ROBERTS, M. H. T.: 5-Hydroxytryptamine and antinociception. Neuropharmacology **23:** 1529–1536, 1984.

ROY, A., ADINOFF, B., AND LINNOILA, M.: Acting out hostility in normal volunteers: negative correlation with levels of 5HIAA in cerebrospinal fluid. Psychiatry Res. **24:** 187–194, 1988.

ROY, A., DEJONG J., AND LINNOILA M.: Extraversion in pathological gamblers: correlates with indexes of noradrenergic function. Arch. Gen. Psychiatry **46:** 679–681, 1989.

RUPNIAK, N. M., HALL, M. D., MANN, S., FLEMINGER, S., KILPATRICK, G., JENNER, P., AND MARSDEN, C. D.: Chronic treatment with clozapine, unlike haloperidol, does not induce changes in striatal D2 receptor function in the rat. Biochem. Pharmacol. **43:** 2755–2763, 1985.

RUPNIAK, N. M., KILPATRICK, G., HALL, M. D., JENNER, P., AND MARSDEN, C. D.: Differential alterations in striatal dopamine receptor sensitivity induced by repeated administration of clinically equivalent doses of haloperidol, sulpiride or clozapine in rats. Psychopharmacology **84:** 512–519, 1984.

SALLANON, M., JANIN, M., BUDA, C., AND JOUVET, M.: Serotoninergic mechanisms and sleep rebound. Brain Res. **268:** 95–104, 1983.

SCATTON, B., SERRANO, A., RIVOT, J. P., AND NISHIKAWA, T.: Inhibitory GABAergic influence on striatal serotonergic transmission exerted in the dorsal raphe as revealed by *in vivo* voltammetry. Brain Res. **305:** 343–352, 1984.

SEEGER, T. F., THAL, L., AND GARDNER, E. L.: Behavioral and biochemical aspects of neuroleptic induced dopaminergic supersensitivity: studies with chronic clozapine and haloperidol. Psychopharmacology **80** (suppl.)**:** 182–187, 1982.

SEGAL, M.: Serotonergic innervation of the locus coeruleus from the dorsal raphe and its action on responses to noxious stimuli. J. Physiol. **286:** 401–415, 1979.

SHEEHAN, D. V., RAJ, A. B., SHEEHAN, K. H., AND SOTO, S.: The relative efficacy of buspirone, imipramine and placebo in panic disorder: a preliminary report. Pharmacol. Biochem. Behav. **29:** 815–817, 1988.

SHOPSIN, B., KLEIN, H., AARONSON, M., AND COLLORA, M.: Clozapine, chlor-

promazine and placebo in newly hospitalized acutely schizophrenic patients. Arch. Gen. Psychiatry **36:** 657–664, 1979.

SIEVER, L. J., AND DAVIS, K. L.: Overview: Toward a dysregulation hypothesis of depression. Am. J. Psychiatry **142:** 1017–1031, 1985.

SIEVER, L. J., MURPHY, D. L., SLATER, S., DE LA VEGA, E., AND LIPPER, S.: Plasma prolactin changes following fenfluramine in depressed patients compared to controls: an evaluation of central serotonergic responsivity in depression. Life Sci. **34:** 1029–1039, 1984.

SILVER, H., BLACKER, M., WELLER, M. P. I., AND LERER, B.: Treatment of chronic schizophrenia with cyproheptadine. Biol. Psychiatry **25:** 502–504, 1989.

SOUBRIE, P.: Reconciling the role of central serotonin neurons in human and animal behavior. Behav. Brain Sci. **9:** 319–364, 1989.

STERN, R. S., MARKS, I. M., AND MAWSON, D.: Clomipramine and exposure for compulsive rituals: plasma levels, side effects, and outcome. Br. J. Psychiatry **136:** 161–166, 1980.

STOFF, D. M., POLLACK, L., AND VITIELLO, B.: Reduction of [^{3}H]-imipramine binding sites on platelets of conduct-disordered children. Neuropsychopharmacology **1:** 55–62, 1987.

TAGRUM, S. D., AND MARSHALL, L. E.: Fenfluramine provocation of anxiety in patients with panic disorder. Psychiatry Res. **28:** 95–306, 1990.

TATE, J. L.: Extrapyramidal side effects in a patient taking haloperidol and fluoxetine. Am. J. Psychiatry **146:** 394–395, 1989.

TAYLOR, D. P., EISON, M. S., RIBLET, L. A., AND VAN DER MAELEN, C. P.: Pharmacological and clinical effects of buspirone. Pharmacol. Biochem. Behav. **23:** 687, 1985.

THOREN, P., ASBERG, M., CRONHOLM, B., JORNESTEDT, L., AND TRASKMAN, L.: Clomipramine treatment of obsessive compulsive disorder. I. A controlled clinical trial. Arch. Gen. Psychiatry **37:** 1281–1289, 1980.

TRASKMAN-BENDZ, L., ASBERG, M., BERTILSSON, L., AND THOREN, P.: CSF monoamine metabolites of depressed patients during illness and after recovery. Acta Psychiatr. Scand. **69:** 333–342, 1984.

TRASKMAN-BENDZ, L., ASBERG, M., AND SCHALLING, D.: Serotonergic function and suicidal behavior in personality disorders. Ann. NY Acad. Sci. **487:** 168–174, 1986.

TRULSON, M. E., AND JACOBS, B. L.: Behavorial evidence for denervation supersensivity after destruction of central serotonergic nerve terminals. Ann. NY Acad. Sci. **305:** 497–509. 1978.

VAN DER MAELEN, C. P., AND WILDEMAN, R. C.: Ioniophoretic and systemic administration of the non-benzodiazepine anxiolytic drug busprone causes inhibition of serotonergic dorsal raphe neurons in rats. Fed. Proc. **43:** 947, 1984.

VAN PRAAG, H. M.: CSF 5HIAA and suicide in non-depressed schizophrenics. Lancet **2:** 977–978, 1983.

VAN PRAAG, H. M.: Studies in the mechanism of action of serotonin precursors in depression. Psychopharmacol. Bull. **20:** 599–602, 1984.

VAN PRAAG, H. M.: (Auto)aggression and CSF 5-HIAA in depression and schizophrenia. Psychopharmacol. Bull. **22:** 669–673, 1986.

VAN PRAAG, H. M., AND DE HAAN, S.: Central serotonin metabolism and frequency of depression. Psychiatry Res. **1:** 219–224, 1979.

VAN PRAAG, H. M., AND DE HAAN, S.: Depression vulnerability and 5-HTP prophylaxis. Psychiatry Res. **3:** 75–83, 1980.

VAN PRAAG, H. M., KORF, J., AND DOLS, L. C. W.: Clozapine versus perphenazine: the value of the biochemical mode of action of neuroleptics in predicting their therapeutic efficacy. Br. J. Psychiatry **129:** 547–555, 1976.

VAN PRAAG, H. M., KORF, J., DOLS, L. C. W., AND SCHUT, T.: A pilot study of the predictive value of the probenecid test in application of 5-hydroxytryptophan as antidepressant. Psychopharmacologia **25:** 14–21, 1972.

VAN PRAAG, H. M., LEMUS, C. Z., AND KAHN, R. S.: Hormonal probes of central serotonergic activity: do they really exist? Biol. Psychiatry **22:** 86–98, 1987.

VIRKKUNEN, M., NUUTILA, A., GOODWIN, F. K., AND LINNOILA, M.: Cerebrospinal fluid metabolite levels in male arsonists. Arch. Gen. Psychiatry **44:** 241–247, 1987.

VIZI, E. S., HARSING, L. G., AND ZSILLA, G.: Evidence for a neuromodulatory role of serotonin in acetylcholine release from striatal interneurons. Brain Res. **212:** 89–99, 1981.

VOGT, M.: Some functional aspects of central serotonergic neurones. *In* Biology of Serotonergic Transmission, ed. by N. Osborne, pp. 299–315, Chichester, England, John Wiley, 1982.

WAUQUIER, A., GAILLARD, J. M., MONTI, J. M., AND RADULOVCLI: Sleep, Neurotransmitters, and Neuromodulators, New York, Raven Press, 1985.

WEISS, J. M., BAILEY, W. H., AND GOODMAN, P. A.: A model for neurochemical study of depression. *In* Behavioral Models and the Analysis of Drug Action, ed. by A. Levy and M. V. Spiegelstein, pp. 195–223, Amsterdam, Elsevier, 1982.

WESTENBERG, H. G., AND DEN BOER, J. A.: Serotonin-influencing drugs in the treatment of panic disorder. Psychopathology **22:** 68–77, 1989.

WHITAKER, P. M., CROW, T. J., AND FERRIER, I. N.: Tritiated LSD binding in frontal cortex in schizophrenia. Arch. Gen. Psychiatry **38:** 278–280, 1981.

WINSLOW, J. T., AND INSEL, T. R.: Neurobiology of obsessive compulsive disorder: a possible role for serotonin. J. Clin. Psychiatry **51** (suppl.)**:** 27–31, 1990.

YAMAMOTO, T., AND HIRANO, H.: Nucleus raphe dorsalis in Alzheimer's disease: neurofibrillary tangles and loss of large neurons. Ann. Neurol. **17:** 573–577, 1985.

ZOHAR, J., AND INSEL, T. H. R.: Obsessive compulsive disorder: psychobiological approaches to diagnosis, treatment and pathophysiology. Biol. Psychiatry **22:** 667–687, 1987.

ZOHAR, J., INSEL, T. R., ZOHAR-KADOUCH, R. C., HILL, J. L., AND MURPHY, D. L.: Serotonergic responsivity in obsessive-compulsive disorder: effects of chronic clomipramine treatment. Arch. Gen. Psychiatry **45:** 167–172, 1988.

ZOHAR, J., MUELLER, E. A., INSEL, T. R., ZOHAR-KADOUCH, R. C., AND MURPHY, D. L.: Serotonergic responsivity in obsessive compulsive disorder: comparison of patients and healthy controls. Arch. Gen. Psychiatry **44:** 946–951, 1987.