Serotonin Function in Panic and Generalized Anxiety Disorders

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Considerable recent research has increased the understanding of the neurobiologic etiology of anxiety disorders and the mechanism of action of antianxiety drugs. Many neuronal systems have been implicated in anxiety and fear states, especially the noradrenergic, dopaminergic, benzodiazepine, and corticotropin releasing factor (CRF) systems. In addition, there is evidence suggesting that alterations in serotonin function may relate to the development of certain types of anxiety and the therapeutic effectiveness of specific antianxiety drugs. This article will review preclinical studies of the regulation of serotonin activity and clinical investigations of panic disorder (PD) and generalized anxiety disorder (GAD) that impact on the hypothesis that serotonin function is important in the genesis and treatment of anxiety disorders.

PRECLINICAL INVESTIGATIONS
Neuroanatomy of Brain Serotonin Systems

Neuroanatomical studies of the serotonin system indicate a distribution consistent with an important role in behavioral regulation. Numerous investigations using retrograde and anterograde fiber tracing techniques or immunohistochemical methods have shown that the cell bodies of serotoninergic neurons are located in the midbrain raphe nuclei. The neurons in the dorsal and median raphe nuclei give rise...
to major ascending projections to the cerebral cortex, and limbic areas that may relate to anxiety and fear behaviors.\textsuperscript{1,2}

**Serotonin Receptor Subtypes**

A convincing body of evidence suggests that several types of serotonin receptors exist in the mammalian brain, and that they differ in neuroanatomical distribution and functional properties. These receptors have been classified into 5-HT\textsubscript{1A}, 5-HT\textsubscript{2}, and 5-HT\textsubscript{3} receptor "families."

**5-HT\textsubscript{1A} Receptor Family**

The 5-HT\textsubscript{1A} receptor family consists of 5-HT\textsubscript{1A1}, 5-HT\textsubscript{1A2}, and 5-HT\textsubscript{1A3} receptor subtypes that share structural and pharmacologic properties.\textsuperscript{3,10} These receptors share nanomolar affinity for 5-HT and 5-carboxamidotryptamine (5-CT) and micromolar affinity for ketanserin, mesulergine, and ICS-205-930. Another characteristic shared by 5-HT\textsubscript{1A} receptors is their negative linkage to adenylate cyclase.\textsuperscript{10} The molecular biology, pharmacology, and biochemistry of the 5-HT\textsubscript{1A} receptor,\textsuperscript{11,12} initially classified as a 5-HT\textsubscript{1A} receptor subtype, suggests it should be more appropriately placed in the 5-HT\textsubscript{2} "family" of receptors.

Radioisotopes have been developed that label 5-HT\textsubscript{1A} binding sites, such as 3\textsuperscript{H}-OH-DPAT\textsuperscript{3,13}. Autoradiographic studies of human brains indicate that high or very high densities of 5-HT\textsubscript{1A} receptors are located in the hippocampus, raphe nuclei, layers I and II of the cortex, and nuclei of the thalamus and amygdala.\textsuperscript{14} 5-HT\textsubscript{1B} binding sites have not been definitively identified in human brains.\textsuperscript{15} The recently identified 5-HT\textsubscript{1D} receptor site, which displays nanomolar affinity for 5-HT, 5-CT, 5-methoxytryptamine, and metergoline, is most dense in the caudate, substantia nigra, and frontal cortex.\textsuperscript{16}

The physiologic characteristics of 5-HT\textsubscript{1A} receptors have not been studied extensively. An exception is the 5-HT\textsubscript{1A} receptor, which appears to mediate an inhibition of cell firing in the raphe nuclei.\textsuperscript{17} 5-HT\textsubscript{1A} receptor agonists directly hyperpolarize hippocampal CA1 pyramidal cells by opening potassium channels via a pertussis toxin-sensitive G protein.\textsuperscript{18} Conclusive data are not yet available on the physiological properties of 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors.

**5-HT\textsubscript{2} Receptor Family**

The 5-HT\textsubscript{2} receptor family shares nanomolar affinity for 5-HT antagonists, such as ketanserin, mesulergine, metergoline, and D-LSD. These receptors are positively coupled to the phosphoinositide hydrolysis second messenger pathway.\textsuperscript{9,10}

The 5-HT\textsubscript{1C} receptor is included within the 5-HT\textsubscript{2} receptor family because of the shared molecular, pharmacologic, and biochemical characteristics with other members of the 5-HT\textsubscript{2} receptor family. For example, 50% of the amino acid sequence of the 5-HT\textsubscript{2} receptor is identical to the sequence encoding the 5-HT\textsubscript{1C} receptor.\textsuperscript{10,21}

The anatomical distribution of 5-HT\textsubscript{2} receptors in the human brain has been studied by light microscopic autoradiography using ketanserin as a ligand.\textsuperscript{21} Very high concentrations have been localized in layers III and V in several cortical areas, including frontal, parietal, temporal, and occipital lobes, as well as the corpus mammillare of the hypothalamus. The claustrum and nucleus lateralis of the amygdala also have high densities of 5-HT\textsubscript{2} receptors. High densities of 5-HT\textsubscript{1C} receptors are present in the choroid plexus, substantia nigra, globus pallidus and ventral medial hypothalamus.\textsuperscript{21}

Two specific neurophysiologic properties of 5-HT have been attributed to activation of the 5-HT\textsubscript{2} receptor.\textsuperscript{17} Serotonin facilitates the excitatory effects of glutamate in the facial motor nucleus, an effect blocked by 5-HT\textsubscript{2} receptor antagonists. In the cerebral cortex, the depolarizing effects of 5-HT also are antagonized by 5-HT\textsubscript{2} receptor blockers.\textsuperscript{22} Neurophysiologic studies of 5-HT\textsubscript{1C} receptors in specific brain areas have not been reported.

**5-HT\textsubscript{3} Receptor Family**

5-HT\textsubscript{3} receptors were initially well characterized in periphery, but in the past few years it has become apparent that 5-HT\textsubscript{3} receptors are present in the brain. In order to identify the precise location of brain 5-HT\textsubscript{3} receptors, quantitative receptor autoradiography has been employed using a variety of 5-HT\textsubscript{3} receptor ligands.\textsuperscript{23,24} The highest levels of these receptors are found in the area postrema and limbic system. The functional properties of 5-HT\textsubscript{3} receptors have yet to be established, although it may be one of a family of receptors modulating ligand-gated ion channels.\textsuperscript{10}

**5-HT Transporter Complex**

There is now substantial evidence that several ligands of different structures, including (\textsuperscript{3}H)-imipramine and (\textsuperscript{3}H)-paroxetine, bind with high affinity to a recognition site associated with the 5-HT transporter complex. This recognition site, widely distributed in the brain, mediates the inhibition of the sodium-dependent uptake of 5-HT. The available evidence suggests that the binding site is not identical to the transporter recognition site for 5-HT, but, rather, that an allosteric coupling exists between the two sites. Consequently, the (\textsuperscript{3}H)imipramine recognition site may represent a novel type of presynaptic receptor whose function is to modulate 5-HT uptake, and it may play a
role in the antidepressant and anti-
panic mechanisms of action of spe-
cific and potent 5-HT reuptake inhib-
hitors such as fluoxetine and fluvoxamine.25

NEUROANATOMICAL SUBSTRATES FOR
ANXIETY OR FEAR AND THEIR
RELATION TO THE SEROTONIN
HYPOTHESIS OF ANXIETY

A comprehensive discussion of the
neural substrates of anxiety or fear is
beyond the scope of this paper. How-
ever, the following brief outline is
evidence supporting a role for several
brain areas in the development of
anxiety or fear and their association
with serotonin receptors.

From a neuroanatomical perspec-
tive, the amygdala is particularly well
suited to be an important factor in
the mediation of anxiety or fear.
The amygdala receives afferents from
cortical and thalamic extero-
ceptive systems, as well as from sub-
cortical visceral afferent pathways.
Projections from the amygdala go to
autonomic pathways, neurohnu-
moral pathways, and skeletal motor
systems.26-28 Amygdalectomy has
been shown to reduce the response
to threatening stimuli in monkeys,
to increase punished responding in
dogs, and to block the conditioned
Fear induced by the potentiated startle
response.29-32 The presence of
5-HT1A receptors on the amygdala
suggest the anxiolytic properties of
5-HT1A receptor agonists (eg, buspi-
role) may be mediated, in part, at
the amygdala.

The thalamus is another area that
is important in fear responses. Ev-
dence from classically conditioned
emotional responses shows that the
processing of threatening stimuli
involves the relay of sensory signals
to the limbic forebrain directly from
the thalamus and cortex.30 Fear res-
sponses to acoustic stimuli are dis-
rupted by thalamic lesions; res-
sponses depend on the connection
between the thalamus and the
amygdala. A recent study of the
effects of electrical stimulation of the
median and dorsal raphe nuclei
on local cerebral glucose use in the
rat suggest a relationship between
serotonergic activity and thalamus
function. Stimulation of the dorsal
raphe nuclei produced an increase
in glucose use in thalamic nuclei
that subserves a processing of soma-
tosensory, visual, and limbic infor-
mation.31

The hippocampus has been hy-
pothesized to play a key position in
anxiety development. The septohip-
 pocampal system has connections
with limbic structures and cortical
sensorial areas. Lesions increase pun-
ished responses like anxiolytic
drugs.38 However, lesions of this
area have had equivocal effects on
classically conditioned fear and do
not consistently affect the anxiolytic
properties of anxiolytic drugs.36,38
Since high densities of 5-HT1A re-
ceptors are located in the hip-
pocampus, the anxiolytic actions of
5-HT1A agonists may involve the hip-
pocampus.

There is also strong support for
the role of the locus coeruleus-
norepinephrine system in the de-
velopment of anxiety.39,40 The locus
coeeruleus sends projections to
other areas involved in fear or anxi-
ety such as the thalamus, the cere-
bral cortex, the amygdala, the
hippocampus and the hypothalamus.
In addition, the locus coeruleus re-
ceives afferents which suggest a criti-
cal role in alarm responses to both
the external and internal danger
environment.41 For example, altera-
tions in blood pressure, body tem-
perature, and fission of internal
organs such as the bladder, colon
and stomach, all activate the locus
coeeruleus.42

Other evidence supporting the
role for the locus coeruleus in anxi-
ey or fear includes the observation
that drugs which activate the locus
coeeruleus are anxiogenic and drugs
which decrease its function are anxi-
oytic.40,43 Stimulation of the locus
coeeruleus in monkeys produce fear-
like behavior and lesions result in
behavior consistent with reduced
fear responses.41 In freely moving
cats, threatening stimuli results in
a specific activation of the locus coer-
uleus.41

The activity of the locus coeruleus
is highly regulated with benzodiaze-
pine, serotonin, and opiates recep-
tors having inhibitory effects and
VIP, CRF, substance P, and ace-
tyline resulting in activation.
40,43 The ability of serotonin to
decrease locus coeruleus firing sug-
gest that interactions between no-
radrenergic and serotonergic sys-
tems may be relevant to the expres-
sion and treatment of anxiety or
fear and the mechanism of action of
anxiety treatments.

It is probable that the sensory
processing areas of the neocortex
linked with the limbic forebrain are
particularly important in the inter-
pretation of sensory stimuli from
emotionally significant events
such as those involving threat.36
Electrical stimulation of serotonin
raphe nuclei produce well circums-
cribed increases in cortical glucose
use in frontal motor, frontal senso-
rinotor, and frontoparietal soma-
tosensory cortices.38 The presence
of high concentrations of 5-HT4 re-
ceptors and the electrophysiologic
investigations of 5-HT4 receptors in
the cortex suggest this receptor may
be involved in the role of the neo-
cortex in the experience of anxiety
or fear. It is possible that the puta-
tive anxiety effects of 5-HT4 re-
ceptor antagonist drugs (eg, ri-
tanserin) are caused by actions in
the cortex.

LABORATORY ANIMAL BEHAVIORAL
MODELS OF ANXIETY AND FEAR:
RELATIONSHIP TO SEROTONIN
FUNCTION

Most laboratory animal behav-
TABLE 1
Effect of Benzodiazepines and Serotonin Specific Drugs on Two Animal Models of Anxiety

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Conflict Test</th>
<th>Social Interaction Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines (eg, diazepam)</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt; agonists (eg, buspirone)</td>
<td>+ / 0</td>
<td>+ / 0</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt; antagonists (eg, ritanserin)</td>
<td>+ / 0</td>
<td>0</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt; antagonists (eg, olanzapine)</td>
<td>0</td>
<td>+ / 0</td>
</tr>
<tr>
<td>5-HT reuptake inhibitors (eg, fluoxetine, fluvoxamine)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0 No anxiolytic effect
+ Slight anxiolytic effect
++ Moderate anxiolytic effect
+++ Strong anxiolytic effect

Panic and Generalized Anxiety Disorders

ioral models of anxiety have limited validity for human anxiety disorders. The models have been primarily based on the pharmacologic actions of benzodiazepines. Therefore, while useful for detecting benzodiazepine-like activity, they probably are not helpful in identifying anxiolytic (eg, serotonin-specific) drugs with different pharmacologic and therapeutic profiles. The two behavioral models of anxiety most relevant to the relationship between serotonin and anxiety are the conflict and social interaction tests.

Conflict Paradigms

The standard conflict paradigm consists of training laboratory animals in operant tasks with food reward and then introducing short signal periods during which responding for food is rewarded but also punished by a mild electric shock. Animals stop responding during these short periods, exhibiting a so-called punishment-induced suppression. The punishment-induced blockade of ongoing behavior has been shown to be a useful method of identifying benzodiazepine-like anxiolytic agents. Indeed, such drugs are the only group of agents consistently able to increase punished responding. In addition, there is a good correlation between the minimally effective antipunishment drug dose of benzodiazepines in animals and the average daily doses used in the treatment of anxiety. A variety of experimental paradigms have resulted in findings consistent with the hypothesis that depressed serotonin neural transmission is associated with attenuation of punishment-induced inhibition. However, 5-HT<sub>1A</sub> receptor agonists and 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor antagonists have only weak or no effects.

Social Interaction Paradigms

Novel stimuli may increase the general level of fear. Often, but not invariably, one consequence of novelty is an inhibition of behavior. This includes inhibition of food intake in new surroundings, reduction of ambulation or exploratory behavior, and suppression of social interactions between a pair of rats. Benzodiazepines generally release these forms of behavioral inhibition, such as increasing eating or drinking, exploratory behavior, and social interactions in unfamiliar situations. Destruction of serotonergic neurons, like benzodiazepines, preferentially increases social contacts in animals placed in unfamiliar situations. However, 5-HT<sub>1A</sub> receptor agonists, 5-HT<sub>2</sub>, and 5-HT<sub>3</sub> receptor antagonists also are weak or generally inactive in this model (Table 1).

THE EFFECT OF ANTIPANIC AND ANTIGENERALIZED ANXIETY DRUGS ON INDICES OF SEROTONIN FUNCTION

Nonbenzodiazepine Antipanic Drugs

Neurophysiological studies have consistently indicated that a spectrum of drugs with antipanic (and antidepressant) properties increase serotonin neurotransmission with chronic administration. This appears to occur via at least two separate mechanisms. Specific serotonin reuptake inhibitors, such as fluoxetine or fluvoxamine, and monoamine oxidase inhibitors, produce a decreased sensitivity of the serotonin autoreceptor, whereas a spectrum of other drug treatments including norepinephrine reuptake inhibitors, such as desipramine and imipramine, produce postsynaptic serotonin supersensitivity in brain sites including the lateral geniculate, amygdala, facial motor nucleus, cerebral cortex, and hippocampus. This increase in serotonin neurotransmission has not been associated with an increase in the density of serotonin receptors. In contrast, 5-HT<sub>2</sub> receptors are reduced by long-term administration of most antipanic and antidepressant treatments.

Neurophysiological studies indicate that in brain areas where 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors exist, the 5-HT<sub>2</sub> receptor reduces inhibitory and enhances excitatory effects produced by activation of the 5-HT<sub>1</sub> receptor. Of particular relevance is the finding in the prefrontal cortex that 5-HT<sub>2</sub> receptor activation works in opposition to the depressant effects of serotonin on cell firing. Therefore, in the prefrontal cortex, the drug induced decrease in 5-HT<sub>2</sub> receptors may be associated with a potentiation of the effects of serotonin mediated through 5-HT<sub>1</sub> receptors.

Behavioral paradigms of serot
Antigenelized Anxiety Drugs

Benzodiazepine drugs and 5-HT1A receptor agonists, such as buspirone and gepirone, reduce serotonergic neurotransmission when given acutely. There is evidence that tolerance may develop to the 5-HT reducing effects of benzodiazepines with chronic treatment.54-57 There has been one study assessing the effect on serotonin function of longer term 5-HT1A receptor agonist treatment. Gepirone acutely reduces the firing rate of dorsal raphe serotonin neurons followed by a gradual return to normal with 14 days of treatment. The responsiveness of dorsal raphe neurons to LSD, 5-HT, 8-OH-DPAT and gepirone, but not to GABA, is decreased after 14 days of gepirone treatment. A desensitization of the somatodendritic autoreceptor can thus account for the gradual recovery of the firing rate serotonin neurons. This may provide an explanation for the delayed onset of action of drugs such as buspirone and gepirone in GAD. From this data, and from the fact that postsynaptic serotonin receptor function is unchanged by long-term gepirone administration, it has been hypothesized that serotonin neurotransmission is increased by such a treatment. This may result from normal activity of serotonin neurons and normal release of serotonin combined with tonic activation by gepirone and presumably other 5-HT1A agonist drugs of nonsensitive postsynaptic serotonin receptors.

<table>
<thead>
<tr>
<th>Specific 5-HT reuptake inhibitors</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Acute*</th>
<th>Chronic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>5-HT1A agonists (buspirone)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>MAOIs</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Specific 5-HT reuptake inhibitors</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

* Acute (few days or less) and chronic (at least few weeks) refer to duration of drug administration

↑ Decreased
↓ Increased
0 No major effect
? Increased in one study, but replication required

SUMMARY OF PRECLINICAL STUDIES

The neuroanatomical distribution of the serotonin neuronal system is consistent with an important role in the regulation of anxiety or fear behavior. The presence of specific serotonin receptors in brain regions such as the amygdala, thalamus, hippocampus, locus coeruleus, and neocortex, suggest specific sites for serotonin regulation of anxiety. In particular, the high density of 5-HT1A receptors in the amygdala and hippocampus indicate this area may be important in the antianxiety actions of the 5-HT1A agonists such as buspirone and gepirone.59 The high concentration of 5-HT2 receptors in the neocortex raises the possibility that effects in this region may account for the putative anxiolytic properties of 5-HT2 antagonist such as ritanserin.60 The functional interactions between the serotonin system and other neuronal systems, particularly the noradrenergic appear to be important as evidenced by the regulation of locus coeruleus activity by serotonin receptors.

The preclinical studies of behavioral models of anxiety and fear have provided an inconsistent picture of the relationship between serotonin function and different forms of anxiety. The 5-HT1A agonists and 5-HT2 antagonists generally have weak anxiolytic properties in animal models of anxiety. The probability that the different animal models are reflective of different types of anxiety or fear and that serotonin neurons are involved in some, but not all, forms of anxiety contributes to the confusion. Available animal models may be limited in usefulness and generally designed to identify benzodiazepine effects.

The neurobiologic investigations of the mechanism of action of anxiolytics and benzodiazepine-antagonized anxiety drugs suggest that drugs whose anxiolytic effects relate to actions on serotonin function (tricyclics, monoamine oxidase inhibitors [MAOIs], specific serotonin reuptake inhibitors, 5-HT1A agonists) may be increasing serotonin function, a hypothesis tantamount to a reversal of the original hypothesis that the affinity of benzodiazepine drugs to reduce serotonin activity was therapeutically important. The mechanism of action of benzodiazepine drugs which are effective in the treatment of both PD and GAD, is probably due to actions on benzodiazepine-GABA receptors. Most of the current evidence suggests benzodiazepine-induced changes in serotonin function are not their primary anxiolytic mechanism of action.

CLINICAL INVESTIGATION

Studies of Serotonin Function in Patients With Anxiety Disorders

Relatively few clinical investigations of serotonin function in patients with PD have been per-

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formed; no studies of serotonin function in GAD have been published.

Two studies evaluated the effects of 5-HT precursors in patients with panic disorder. In one study, the ability of tryptophan to increase prolactin levels (shown to reflect serotonin function) was no different between patients and healthy subjects. Similar findings have been obtained using another serotonin precursor, 5-hydroxytryptophan. L-5-hydroxytryptophan did not have anxiogenic effects in either PD patients or healthy subjects and produced similar increases in plasma cortisol and β-endorphin in both the patients and healthy subjects.

Another method used to assess the role of serotonin function in the development of panic anxiety has been the measurement of behavioral and biochemical responses to the serotonin receptor agonist, m-chlorophenylpiperazine (mCPP). In a recently reported study, mCPP had anxiogenic effects in both healthy subjects and patients with PD. Panic attacks meeting DSM-III-R criteria occurred following mCPP in approximately 45% of the patients and 30% of the healthy subjects (nonsignificant). Other anxiety ratings did not distinguish the two groups. MCPP resulted in significant but similar increases in cortisol, prolactin and growth hormone in the healthy subjects and patients. This investigation suggested that serotonin neuronal dysfunction may not be of etiologic significance in most patients with panic disorder. However, the observed anxiogenic properties of mCPP indicated that additional studies of the role of serotonin systems in the pathophysiology of human anxiety disorders are needed.

Low oral doses of mCPP (0.25 mg/kg) have been reported to increase anxiety and produce panic attacks in PD patients with or without major depression. In healthy subjects and in patients with major depression but without panic disorder, the drug did not influence anxiety levels. The release of cortisol after mCPP also was augmented in patients with panic disorder. This led to a hypothesis that hypersensitivity of postsynaptic 5-HT receptors may exist in some PD patients.

A small preliminary study recently showed that fenfluramine, which enhances presynaptic serotonin release, produced greater anxiogenic responses and prolactin and cortisol increases in patients with PD than in healthy subjects. Most investigations indicate the

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TABLE 3
Clinical Investigations of Serotonergic Function in Panic Disorder Patients

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Dose</th>
<th>Method of Administration</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presynaptic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan-induced prolactin response</td>
<td>100 mg/kg</td>
<td>Intravenous</td>
<td>Prolactin response similar in patients and healthy subjects: no changes in anxiety</td>
</tr>
<tr>
<td>L-5-hydroxytryptophan neuroendocrine and behavioral responses</td>
<td>60 mg</td>
<td>Oral</td>
<td>Similar increases in cortisol and β-endorphin in patients and healthy subjects: no changes in anxiety</td>
</tr>
<tr>
<td>Fenfluramine-induced neuroendocrine and behavioral responses</td>
<td>60 mg</td>
<td>Oral</td>
<td>Greater increases in cortisol, prolactin, and anxiety in patients</td>
</tr>
<tr>
<td>Postsynaptic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCPP-induced changes in behavior and neuroendocrine function</td>
<td>0.1 mg/kg</td>
<td>Intravenous</td>
<td>Similar increases in cortisol, prolactin, growth hormone, and anxiety in patients and healthy subjects</td>
</tr>
<tr>
<td></td>
<td>0.25 mg/kg</td>
<td>Oral</td>
<td>Greater increases in cortisol and anxiety in patients</td>
</tr>
<tr>
<td>Peripheral Measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet imipramine binding</td>
<td>-</td>
<td>-</td>
<td>Similar in patients and healthy subjects in four of five studies</td>
</tr>
<tr>
<td>Platelet serotonin uptake and peripheral serotonin levels</td>
<td>-</td>
<td>-</td>
<td>One study found increased V_max in patients; one study reported decreased plasma 5-HT in patients; another, no difference in platelet 5-HT</td>
</tr>
</tbody>
</table>
### TABLE 4
**The Efficacy of Serotonin Specific Drugs in Anxiety Disorders**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Panic Disorder</th>
<th>Generalized Anxiety Disorder</th>
<th>Proposed Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT_{1A} agonists</td>
<td>Efficacy*</td>
<td>Replication†</td>
<td>Efficacy*</td>
</tr>
<tr>
<td>(eg, buspirone)</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>5-HT_{2} antagonists</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(eg, ritanserin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT_{3} antagonists</td>
<td>NT</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>(eg, olanzapine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT reuptake inhibitors</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(eg, fluoxetine, fluvoxamine)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Symbols: 0 = ineffective, + = slightly effective, ++ = moderately effective, +++ = very effective, and NT = not tested.
†Replication = extent of which efficacy of agent has been investigated. Symbols: + = only one or two controlled studies conducted; ++ = several controlled investigations; further studies indicated; and +++ = highly replicated and consistent efficacy reported.

platelet imipramine-binding site is normal in PD patients. One study has measured platelet serotonin uptake in patients with panic attacks and found higher Vmax values in the patient group than in the controls while the affinity constant Kd was not significantly different. The authors suggested that there may be a specific abnormality of platelet serotonin uptake in patients with panic attacks and the increased platelet reuptake of serotonin was consistent with a report of lower concentrations of this neurotransmitter in the plasma of PD patients. It should be noted, however, that the great bulk of plasma serotonin is in platelets and this serotonin is believed to originate mainly from chromaffin cells in the gut walls. In another study, platelet serotonin levels were found to be normal in patients with PD compared to healthy subjects (Table 3).

### SEROTONIN-SPECIFIC DRUGS FOR GAD AND PD

#### 5-HT_{1A} Receptor Agonists

The development of the 5-HT_{1A} receptor agonists as anxiolytics represents a new generation of nonbenzodiazepine anxiolytics. Buspirone (Buspar), a prototypical drug of this class of compounds, is an established treatment for GAD.

In controlled comparison studies, buspirone and benzodiazepine drugs (eg, diazepam) are equally effective. However, while benzodiazepines are effective after a single dose, buspirone requires several weeks of administration before clinical effects are apparent. The side effect profile of buspirone has several advantages over benzodiazepines because it does not produce sedation, ataxia, or amnesia and is not associated with withdrawal reactions following abrupt discontinuation.

Evidence is emerging that other drugs of this class, not yet generally available, such as gepirone, ipsapirone, and tandospirone, are similarly effective for GAD. In contrast to its efficacy for GAD, buspirone is not a therapeutic agent for agoraphobic and PD patients.

#### 5-HT_{2} Receptor Antagonists

The ability of a variety of psychotrophic medications to downregulate 5-HT_{2} receptors has led to research designed to identify the antidepressant and anxiolytic properties of compounds that directly antagonize this receptor. Several 5-HT_{2} receptor antagonists are in clinical development with ritanserin being the best studied. In several double-blind active drug and placebo-controlled comparison trials, ritanserin has been demonstrated to be effective in GAD patients. A recent investigation found ritanserin to be ineffective for PD patients.

#### 5-HT_{3} Receptor Antagonists

Ongoing clinical studies are attempting to determine if selective 5-HT_{3} receptor antagonists possess anxiolytic properties. Preliminary results with the relatively high doses of 5-HT_{3} receptor antagonist olanzapine have been disappointing. However, additional studies with lower doses of 5-HT reuptake inhibitors are indicated.

Evidence is accumulating that shows 5-HT reuptake inhibitors fluvoxamine and fluoxetine to be effective in treating PD. As with major depression, it has not been
demonstrated that these agents are superior in efficacy to other antianxiety drug treatments such as imipramine, phenelzine, and alprazolam (Table 4).

Similar to preclinical work, clinical studies have demonstrated that 5-HT reuptake inhibitors markedly increase serotonin function. In addition, a recent investigation has shown that the 5-HT reuptake inhibitor-induced remission from depression is dependent upon the integrity of the serotonin neuronal system. A 90% reduction in plasma tryptophan produced by a tryptophan-free amino acid drink produces a depressive relapse in patients remitted on fluoxetine within 8 hours. It is likely that some of the therapeutic properties of the 5-HT reuptake inhibitors are due to interactions with other transmitter systems. These compounds may decrease noradrenergic function because serotonin is inhibitory to the firing of noradrenergic neurons such as those of the locus coeruleus. In addition, some of the 5-HT inhibitors have shown in laboratory animals to downregulate beta-adrenergic post synaptic receptors.

**BENZODIAZEPINES**

Few clinical studies have assessed the effects of benzodiazepines on serotonin function. Long-term alprazolam treatment has no effect on the tryptophan-induced increase in prolactin, suggesting no net change in serotonin function. In healthy subjects, a single diazepam dose attenuated the prolactin rise produced by tryptophan, suggesting that a reduction in serotonin function occurs following acute but not chronic benzodiazepine treatment. It has been speculated that these benzodiazepine effects, such as sedation, to which tolerance develops, are related to actions on serotonin neurons rather than antianxiety effects.

**CONCLUSION**

This article has reviewed evidence suggesting possible roles for serotonin neurotransmission in the development and treatment of anxiety states. While preclinical studies suggest possible roles for serotonin in anxiety or fear, the specific nature of the involvement has not been defined. This may be related to several factors, including the existence of serotonin receptor subtypes with different functional properties, behavioral models of anxiety that reflect different types of anxiety or fear, and the paucity of studies comparing the acute and chronic effects of anxiolytic drugs.

At present, clinical studies of the pathophysiology of anxiety disorders permit only preliminary observations. The ability of mCPP and fenfluramine to elicit panic anxiety supports the hypothesis that serotonin dysfunction is anxiogenic. However, there is not yet consistent replicated evidence of an abnormality in serotonin function in PD, and very little clinical neurobiological research on GAD.

The demonstration that serotonin reuptake inhibitor drugs are antianxiety is not consistent with the hypothesis of hypersensitive serotonin receptor function in PD because chronic administration of these drugs (e.g., when anxiolytic action occurs) appears to enhance serotonin neurotransmission. The preliminary observation that the 5-HT2 antagonist ritanserin is not antianxiety also fails to support this hypothesis. The function of the spectrum of serotonin receptors, as well as the functional interaction between receptor subtypes, needs to be assessed in anxiety disorder patients.

The net effect of 5-HT1A agonists such as buspirone and gepirone on serotonin function also should be studied in humans. Research must determine whether the ability of these drugs to acutely reduce serotonin firing is translated into reduced or increased serotonin neurotransmission through chronic treatment when therapeutic actions are commencing. Since these are drugs effective for GAD but not for PD, the possibility exists that serotonin dysfunction, particularly involving 5-HT1A receptors, may occur in GAD.

**REFERENCES**


32. Hinckcock JM, Davis M. Lesions of the amygdala, but not of the cerebellum or red nucleus block conditioned fear as measured with the potentiated startle paradigm. Behav Neurosci 1986; 100:11-22.

33. Itaya J, LeDouX JE, Moeley MP, Arneric S, Reis DJ. Intrinsic neurons in the amygdaloid field project to the mediodiagonal geniculate body mediate emotional responses conditioned to acoustic stimuli. Brain Res. 1986; 383:105-121.

34. Kapp BS, Freyberger RC, Gallagher M, Halcot J. Amygdala and central nucleus lesions: effects on heart rate conditioning in the rabbit. Physiol Behav. 1979; 23:1109-1117.


56. Lisney RG, File SE. Changes in regional
concentrations in the rat brain of 5-hydroxytryptamine and 5-hydroxyindo-
leic acid during the development of tolerance to the sedative action of chlor-

57. Nauta DJ, Gower PJ. Diazepam alters brain 5-HTI function in man: implica-

58. Bier P, de Montigny C. Modification of 5-HTI neuron properties by sustained administra-

59. Traber J, Glaser T. 5-HTI receptor-related anxio-

60. Ceulemans BJS, Hoppenbrouwers M-JA, Gelders YG, Revnijens AJM. The influence of ritanserin, a serotonin antago-

61. Charney DS, Heninger GR. Serotonin function in panic disorder: the effects of intravenous tryptophan in healthy sub-
jects and patients with panic disorder before and during alprazolam treat-


63. Kahn R, Asnis C, Wetzler S, Van Praag HM. Neuroendocrine evidence for a se-

64. Kahn R, Wetzler S, Van Praag HM, Asnis GM, Strauman T. Behavioral indica-
tions for serotonin receptor hypersen-


67. Lewis DA, Noves R, Correll W, Claney J. Tricyclic imipramine binding to platelets is decreased in patients with agorapho-


69. Schneider LS, Munjack D, Severson JA, Palmer R. Platelet [3H]imipramine bind-
ing in generalized anxiety disorder, panic disorder and agoraphobia with panic attacks. Biol Psychiatry. 1987; 22:59-
66.


72. Schneider L, Evans L, Rosslee L, et al. Plasma biogenic amine levels in agor-


75. Rickels K, Schweizer E, Cimarossi I, Cag-WG, Chuang H. Long-term treatment of anxiety and risk of withdrawal. Prospecive comparison of clorazepate and bu-
spirone. Arch Gen Psychiatry. 1988; 15:444-


77. Sheehan DV, Raj AR, Sheehan KH, Soto S. The relative efficacy of buspirone, imipramine and placebo in panic disor-


79. Den Boer JA. Serotonin function in panic disorder: a double-blind placebo-

controlled study with fluoxetine and ritanserin. Patients with panic disor-

80. Den Boer JA, Westenberg GM. Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder: a double-blind comparison study with fluoxet-

ine and mirtazapine. Int Clin Psychophar-


82. Delgado PL, Charney DS, Price LH, Agahianian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action: reversal of anti-

depressant-induced remission by rapid depleton of plasma tryptophan. Arch Gen Psychiatry. 1990; 47:411-418.