

# Brain Serotonin Neurotransmission: An Overview and Update With an Emphasis on Serotonin Subsystem Heterogeneity, Multiple Receptors, Interactions With Other Neurotransmitter Systems, and Consequent Implications for Understanding the Actions of Serotonergic Drugs

Dennis L. Murphy, M.D.; Anne M. Andrews, Ph.D.; Christine H. Wichems, Ph.D.;  
Qian Li, Ph.D.; Michihisa Tohda, Ph.D.; and Benjamin Greenberg, M.D., Ph.D.

Knowledge about serotonergic neurotransmission has been expanding rapidly. Recent research has delineated 15 molecularly different serotonin receptors and multiple, discrete neuronal and nonneuronal (including endocrine) pathways and mechanisms that mediate the many functions of serotonin. Nonetheless, gaps remain regarding aspects of the anatomy and physiology of serotonin in its roles as a neurotransmitter, a neuromodulator, and a hormone. Few serotonin receptor-selective drugs are available for clinical use. A group of selective serotonin reuptake inhibitors (SSRIs) remain the agents with greatest therapeutic utility, although the mechanisms underlying their delayed efficacy, which clearly result from adaptive consequences following repeated administration rather than early uptake inhibition of serotonin by itself, are incompletely understood and appear to involve changes in signal transduction and gene expression in serotonergic and other neurotransmitter systems.

(*J Clin Psychiatry* 1998;59[suppl 15]:4-12)

A wealth of evidence strongly implicates the involvement of serotonin (5-HT) in many centrally and peripherally mediated physiological functions (Table 1; for review see reference 1). In some phylogenetically ancient organisms with relatively simple nervous systems, there is direct evidence for a specific role for serotonergic transmission in behaviors such as sexual, feeding, and aggressive behavior. In more complex organisms, experimental techniques such as electrophysiologic recording, microdialysis, and other neurochemical assessments have provided evidence implicating serotonin in centrally mediated functions. These techniques are especially valuable when used together with pharmacologic agents that selectively alter serotonin synthesis, release, metabolism, or uptake, or agents that have direct effects on specific serotonin receptors or their signal transduction mechanisms.

Additional evidence has been elicited by using lesions produced by surgical or other physical procedures that tar-

get the different 5-HT-synthesizing mesencephalic raphe nuclei, or the different 5-HT brain pathways or by using selective serotonin neurotoxins like 5,7-dihydroxytryptamine or 2'-NH<sub>2</sub>-MPTP, which target specific 5-HT projection fields.<sup>2,3</sup> More recently, transgenic methodology has led to the "knockout" or "knockdown" of individual molecular components of the serotonergic system, including different serotonin receptors, the serotonin transporter, and the 2 serotonin metabolizing enzymes, monoamine oxidase type A (MAO-A) and type B (MAO-B).

In some neuropsychiatric disorders, an etiologic role for altered 5-HT function has been suggested. Evidence for this hypothesized serotonergic neurotransmission dysfunction comes mainly from quantified observations rather than controlled experiments. Some evidence has been obtained from clinical trials of agents whose primary or only known direct mechanism of action is on serotonin neurotransmission, e.g., the demonstrated efficacy of selective serotonin reuptake inhibitors (SSRIs) in many major neuropsychiatric disorders (Table 2). This evidence, however, indicates only that therapeutic benefit results from an intervention in serotonergic neurotransmission; it cannot be used as primary evidence for serotonergic dysfunction in the pathophysiology of these disorders.

The primary objective of this overview is to highlight the heterogeneous and complex nature of serotonin neurotransmission in terms of both structure and function. This heterogeneity is implicitly recognized by the loose design-

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*From the Laboratory of Clinical Science, National Institute of Mental Health Intramural Research Program, Bethesda, Md.*

*Presented at the closed roundtable symposium "Optimizing Clinical Use of SSRIs: Theory and Practice," which was held December 6, 1997, in San Francisco, Calif., and supported by an unrestricted educational grant from Forest Laboratories.*

*Reprint requests to: Dennis L. Murphy, M.D., Laboratory of Clinical Science, NIMH Intramural Research Program, NIH Clinical Center, 10/3D41, Bethesda, MD 20892-1264.*

**Table 1. Physiologic Functions Influenced by Serotonin**

Aggression/impulse control
Anxiety/affect
Appetite/satiety
Cardiovascular functions
Circadian rhythms/sleep
Cognitive functions
Endocrine regulation
Gastrointestinal functions
Motor activity
Pain
Reproductive functions
Sensory functions

**Table 2. The Widening Spectrum of Therapeutic Efficacy for the Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants**

Demonstrated Efficacy	Suggested Efficacy
Depression (acute/continuation and maintenance treatment)	Autistic disorder
Obsessive-compulsive disorder	Anorexia nervosa
Panic disorder/agoraphobia	Ethanol consumption
Social phobia	Trichotillomania
Bulimia/binges (acute treatment and relapse prevention)	Onychophagia
Obesity (acute treatment, not maintenance or relapse prevention)	Migraine
Generalized anxiety disorder	
Premenstrual syndrome	
Chronic pain syndrome	

**Table 3. Characteristics of CNS Serotonin Subsystems**

15 different molecularly-identified 5-HT receptors with different pharmacologic properties identified for most receptors
Different projection pathways for 5-HT cell bodies in dorsal, medial, and caudal raphe nuclei
Different cellular location of 5-HT terminals with different effects on cellular function in some well-studied areas (e.g., hippocampus, cortex, basal ganglia, cerebellum)
Different cotransmitters or comodulator neuropeptides in some 5-HT terminals, particularly in the caudal raphe nuclei
Different actions of 5-HT as a classic neurotransmitter via synaptic connections, or as a neuromodulator or neurohormone, often with longer-lasting effects

**Table 4. Examples of Serotonin Receptor-Mediated Interactions With Other Neurotransmitter Systems**

Neurotransmitter System	Effect	Serotonin Receptor
Dopamine	Inhibit release	5-HT <sub>1A</sub>
	Increase release	5-HT <sub>3</sub>
Acetylcholine	Increase release	5-HT <sub>1A</sub>
	Inhibit release	5-HT <sub>3</sub>
Glutamate	Inhibit release	5-HT <sub>1A</sub>
	Potiation	5-HT <sub>2</sub>
Norepinephrine	Inhibit release	5-HT <sub>1</sub>
Cholecystokinin	Increase release	5-HT <sub>3</sub>

nations of different central serotonin “subsystems” or “neuronal networks” in recent literature. Heterogeneity is particularly evident in the existence of 15 different receptors upon which serotonin exerts its initial presynaptic or

postsynaptic actions. In different phyla, species, and locations, 5-HT can act as a classical neurotransmitter via actions on presynaptic and postsynaptic receptors. It can, alternatively or additionally, act as a neuromodulator or neurohormone, with less localized effects, and variably longer durations of action (Table 3).

The most pragmatic conclusion is that changes in global brain serotonin neurotransmission such as that produced by lesions or drugs that affect release or reuptake of 5-HT, or genetically engineered or spontaneous genetically based alterations in 5-HT reuptake,<sup>4</sup> will lead to a multitude of effects, both immediate and delayed. Some of these effects will depend upon the functional status of other neurotransmitter systems with which 5-HT interacts via different 5-HT receptors, including some with opposite effects on 1 or more of these other neurotransmitter systems (Table 4). Of course, repeated drug administration or the delayed, adaptive consequences of lesions or other enduring changes (e.g., knockouts of individual molecular components of 5-HT neurons) may lead to supersensitivity, tolerance, trophic changes, or other alterations in 5-HT-modulated CNS or peripheral functions.<sup>5-7</sup>

### WHY IS BRAIN SEROTONIN NEUROTRANSMISSION SO COMPLEX AND WHY ARE THERE 15 DIFFERENT SEROTONIN RECEPTORS IN VERTEBRATE BRAIN?

5-HT neurons in brain and other tissues use only 1 synthesis pathway, that from L-tryptophan to 5-hydroxytryptophan via tryptophan hydroxylase and then to 5-HT via L-amino acid decarboxylase. Likewise, a single molecule whose structure is highly homologous across species, the 5-HT transporter (5-HTT), is primarily responsible for terminating the action of 5-HT in brain and many other tissues via reuptake of released 5-HT. Metabolic degradation of 5-HT is primarily by MAO-A, although the closely related enzyme, MAO-B, is present in some serotonin-containing cells in brain, as well as in blood platelets, and can deaminate 5-HT when 5-HT is present at high concentrations.

As listed in Table 5, 15 molecularly-identified serotonin receptors are found in vertebrates. This far exceeds the number of receptors known for any other transmitter system. 5-HT receptors have been grouped into 7 families. The largest of these are the 5-HT<sub>1</sub> receptors (5-HT<sub>1A</sub>, B, D $\alpha$ , D $\beta$ , E, F), which are predominantly coupled to the G proteins, G<sub>i</sub> or G<sub>o</sub>, and generally act to inhibit cyclic AMP formation (G<sub>i</sub>) or open potassium channels (G<sub>o</sub>). 5-HT<sub>2A</sub>, B, C receptors are coupled to G<sub>q</sub> or G<sub>11</sub> and increase phosphatidylinositol (IP<sub>3</sub>) hydrolysis, diacylglycerol and cyclic GMP (cyclic guanosine monophosphate). The 5-HT<sub>3</sub> receptor is the only 5-HT receptor which is an ion channel, and thus, is the only subtype that does not share the general structural backbone of 7 or 8 transmembrane do-

mains, or the coupling to G proteins found for all other known 5-HT receptors. 5-HT<sub>4</sub>, 5-HT<sub>5 $\alpha$</sub> , 5-HT<sub>5 $\beta$</sub> , 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> have been more recently identified, and while less is known about these receptors, most are coupled to G<sub>s</sub> and act to increase cyclic AMP formation, although the signal transducing mechanisms of the 5-HT<sub>5</sub> receptors remain unknown.

One speculative rationale for this large number of receptors is that 5-HT has apparently been used as a neurotransmitter or neuromodulator dating back to very primitive organisms,<sup>8</sup> and thus, the multiplicity of these receptors could represent evolutionary mechanisms that over time permitted serotonin to modulate multiple functions. 5-HT can be found in all phyla that possess nervous systems, including invertebrates such as coelenterates, flatworms, nematodes (e.g., *C. elegans*), mollusks (e.g., aplysia), leeches, crustaceans (lobster, crayfish), and echinoderms (sea urchins, starfish).<sup>9</sup> In these organisms, 5-HT subserves sensory, motor, and cardiovascular functions, including those contributing to more complex behaviors, such as feeding, egg laying, defensive and aggressive behavior, and learning. In only a few instances have serotonin receptors from these organisms been molecularly identified and their homology compared with vertebrate 5-HT receptors. Several 5-HT receptors with homology to human 5-HT<sub>1A</sub> and 5-HT receptors are found in drosophila, however, and have been molecularly characterized.<sup>10,11</sup>

Some examples of the anatomical and physiologic complexity of serotonergic transmission are discussed in several following sections of this article. The basis for this complexity has been attributed to phylogenetic ancestry, multiple mechanisms of actions, and also the possible need for integration of the many physiologic functions subserved by 5-HT.<sup>12,13</sup>

## MULTIPLE SEROTONIN RECEPTORS AND PHARMACOLOGIC EFFECTS

For a long time, the pharmacology of serotonin neurotransmission has been complicated by the moderate-to-marked homology within and sometimes across receptor subtypes (except 5-HT<sub>3</sub> receptors, which have almost no structural homology to the other 5-HT receptors). Some older ligands with high affinity for almost all serotonin receptor subtypes (e.g., lysergic acid diethylamide, 5-CT, and metergoline) have provided the first clues used to identify some of the more recently discovered receptors (some discovered as "orphan" cloned receptors) as being serotonin receptors, e.g., 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors.<sup>13-16</sup>

Among some of the "classic" 5-HT receptor subtype agents, 8-OH-DPAT appeared to have highly selective affinity for 5-HT<sub>1A</sub> receptors sites and considerably lesser affinity for other 5-HT<sub>1</sub> sites, as well as 5-HT<sub>2</sub> sites. It constituted an example of 1 of the few agents with selective pharmacologic agonist effects on the 5-HT<sub>1A</sub> receptor

**Table 5. 15 Molecularly Identified Serotonin Receptors and Their Signal Transduction Mechanisms\***

Receptor	Effector	Signal Transduction
5-HT <sub>1A,B,D<math>\alpha</math>,D<math>\beta</math>,E,F</sub>	G <sub>i/o</sub>	↓Cyclic AMP, ↑K <sup>+</sup> channel
5-HT <sub>2A,B,C</sub>	G <sub>q/11</sub>	IP-3, DAG, cyclic GMP
5-HT <sub>3</sub>	...	Ligand-gated ion channel; IP-3
5-HT <sub>4</sub>	G <sub>s</sub>	↑Cyclic AMP
5-HT <sub>5<math>\alpha</math>,5<math>\beta</math></sub>		Unknown
5-HT <sub>6</sub>	G <sub>s</sub>	↑Cyclic AMP
5-HT <sub>7</sub>	G <sub>s</sub>	↑Cyclic AMP

\*Other former names and identities: 5-HT<sub>2A</sub> = 5-HT<sub>2</sub>, 5-HT<sub>2B</sub>; 5-HT<sub>2C</sub> = 5-HT<sub>1C</sub>; 5-HT<sub>3</sub> = M; 5-HT<sub>F</sub> = 5-HT<sub>1EB</sub>; also briefly designated 5-HT<sub>6</sub>. Abbreviations: AMP = adenosine monophosphate; DAG = diacylglycerol, GMP = cyclic guanosine monophosphate, IP-3 = phosphatidyl inositol.

across a wide range of physiologic functions regulated by 5-HT, including temperature, food intake, motor activity, and neuroendocrine functions. Recently it has become known that 8-OH-DPAT also has appreciable affinity for 5-HT<sub>7</sub> receptors.<sup>16</sup> Since, however, at present the pharmacology and function of the 5-HT<sub>7</sub> receptor remain undefined, it is not clear if any effects of 8-OH-DPAT previously related to 5-HT<sub>1A</sub> actions may actually represent 5-HT<sub>7</sub>-mediated actions.

Among agents acting at 5-HT<sub>2</sub> receptors, 1-(2,5-dimethoxy-4-phenyl)-2-aminopropane (DOI) and its congeners, DOB and DOM, have substantially greater affinity for 5-HT<sub>2</sub> sites than for any other sites (including 5-HT<sub>4,5,6,7</sub>). The agonist effects of DOI at 5-HT<sub>2A</sub> versus 5-HT<sub>2C</sub> receptors were difficult to separate, despite the fact that the 5-HT<sub>2A</sub> antagonist ketanserin (in vivo) and, more clearly, spiperone (in vitro only, because of its strong dopamine antagonist properties) were shown to possess greater 5-HT<sub>2A</sub> antagonist than 5-HT<sub>2C</sub> antagonist effects. Nonetheless, differences in the physiologic alterations produced via 5-HT<sub>2A</sub> versus 5-HT<sub>2C</sub> receptors became apparent only in paradigms that employed repeated administration of DOI versus *m*-chlorophenylpiperazine (*m*-CPP), a relatively selective 5-HT<sub>2C</sub> agonist, in investigations in rats.<sup>17,18</sup> Recently, antagonists with greater affinity for 5-HT<sub>2A</sub> vs. 5-HT<sub>2C</sub> (e.g., MDL-100,907; SB-206553) have been synthesized, and reports of their selective efficacy on functions thought to be mediated by 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> receptors are emerging, although, as yet, are incomplete.<sup>19,20</sup>

Among agents acting at 5-HT<sub>3</sub> receptors, highly selective antagonists, including granisetron, ondansetron, and tropisetron have been identified.<sup>21</sup> In contrast, few high affinity, high potency 5-HT<sub>3</sub> agonists have been found, although 2-methyl-5-HT and *m*-chlorylbiquanide exhibit some selectivity at 5-HT<sub>3</sub> sites.

The pharmacology of 5-HT<sub>4</sub> receptors has been aided by the identification of some selective agonists (ML-10302, RS-67506, and BIMU-8) and antagonists (SB-204070, GR-113808, and RS-39604). The pharmacology of the 5-HT<sub>7</sub> subtype is developing rapidly, but that

of the 2 5-HT<sub>5</sub> variants and the 5-HT<sub>6</sub> receptor subtype remain largely unknown at this time.<sup>13,16,22-24</sup>

With regard to 5-HT receptor pharmacology, one general issue needs to be emphasized. While many characteristics of molecules involved in serotonergic transmission are conserved across vertebrate species, this conservation cannot be assumed a priori. Some examples include the following: The human and rat 5-HT<sub>1B</sub> receptors share 97% sequence homology, yet their responses to pharmacologic agents differ greatly.<sup>25</sup> The human (and guinea pig) 5-HT<sub>1D</sub> receptors are 5-HT terminal autoreceptors, and this same function is subserved in rodents by 5-HT<sub>1B</sub> receptors. The pharmacology of 5-HT<sub>1D/1B</sub> receptor is very similar across primate and rodent species.<sup>25-31</sup>

5-HT<sub>1A</sub> presynaptic receptors subserve an autoreceptor function at somatodendritic sites located in the raphe area in both rodents and primates. The same 5-HT<sub>1A</sub> receptor molecule also subserves postsynaptic functions throughout the brain. All of the other serotonin receptors are located postsynaptically, although as noted below, some are found at some distance from serotonin-releasing terminals, especially in peripheral tissues, and thus have more in common with hormone receptors.<sup>13,32</sup>

#### **SOME EXAMPLES OF THE COMPLEXITY OF SEROTONERGIC INNERVATION IN SPECIFIC BRAIN REGIONS**

Rostral projections from the dorsal, median, and adjacent raphe nuclei have long been known to innervate various brain regions differentially. For example, the median raphe nucleus preferentially innervates the cingulate cortex, septal nuclei, and the hippocampus, whereas the dorsal raphe nucleus preferentially innervates the substantia nigra, striatum, amygdala, and nucleus accumbens.<sup>33,34</sup>

#### **Serotonin Neurotransmission in the Hippocampus**

The hippocampus is a clearly demarcated forebrain structure that is richly innervated by serotonergic, noradrenergic, and other neurotransmitter systems. It has long been regarded as a component of the limbic system, contributing to the appraisal and expression of both emotional behaviors and learning, particularly the learning of emotionally-related events.<sup>35</sup>

Different axonal pathways have been identified from the dorsal and median raphe 5-HT neurons to the hippocampus.<sup>33,34</sup> 5-HT neuronal cell bodies from the dorsal raphe nucleus project to the hippocampus via the fimbria-fornix and fasciculus cinguli pathways. Those 5-HT axons in the fimbria-fornix pathway are distributed to the hippocampal CA<sub>1</sub> and CA<sub>3</sub> layers and the molecular layer of the dentate gyrus of the hippocampus. These axons are very fine, with small varicosities, and are highly susceptible to damage by serotonin neurotoxins.<sup>32,36</sup> In contrast, axons from 5-HT neuronal cell bodies in the median raphe

nucleus reach the dentate gyrus, Ammon's horn, and subiculum regions of the hippocampus via the fasciculus cinguli pathway. These axons are thicker and have larger varicosities and greater resistance to damage by serotonin neurotoxins.

One illustration of how these separate anatomical fiber projections are accompanied by functional differences comes from studies of 5-HT<sub>1A</sub> receptor-mediated release of 5-HT in the hippocampus. The 5-HT<sub>1A</sub> agonist, 8-OH-DPAT, given systemically, has long been known to reduce 5-HT release in the hippocampus and other brain areas, such as the striatum and cortex, when measured via microdialysis cannulae placed in these brain areas. Electrophysiologic and other data identified the site of action of 8-OH-DPAT to be somatodendritic autoreceptors in the raphe nuclei area, and this was verified by the finding that 8-OH-DPAT, when administered directly into the microdialysis cannulae in the hippocampus, had no effect on 5-HT release.<sup>37</sup> However, injection of 8-OH-DPAT directly into the median raphe nucleus reduced 5-HT release in the hippocampus, while, interestingly, 5-HT release in the striatum was unchanged. In contrast, local injections of 8-OH-DPAT directly into the dorsal raphe nucleus did not reduce 5-HT release in the hippocampus, but did so in the striatum.<sup>37,38</sup>

#### **Serotonin Neurotransmission in the Cerebellum**

In comparison to other brain regions, 5-HT innervation of the cerebellum is sparse. Yet, recent investigations have revealed that this innervation is specifically organized along the same pattern as that of other more well-studied cerebellar neuronal networks. For example, the depolarization-induced release of glutamate from parallel/climbing fiber presynaptic terminals is inhibited by activation of 5-HT<sub>1D</sub> receptors.<sup>39,40</sup> Postsynaptic responses elicited by *N*-methyl-D-aspartate (NMDA) antagonists are inhibited by 5-HT via actions at 5-HT<sub>1A</sub> receptors<sup>40</sup> and also 5-HT<sub>2C</sub> receptors.<sup>41</sup>

Thus, a complex and well-organized serotonergic modulation of glutaminergic transmission via 3 5-HT receptors can be found in the cerebellum. Marcoli and co-workers<sup>41</sup> suggest that these interactions may play a role in the cerebral control of movement, including that associated with movement disorders such as cerebellar ataxia. This hypothesis is supported by recent data indicating some efficacy for 5-HT<sub>1A</sub> agents in clinical studies of cerebellar ataxia,<sup>42,43</sup> and another study demonstrating a relatively high density of 5-HT<sub>2C</sub> receptors in the cerebellum.<sup>44</sup>

#### **SEROTONIN-MEDIATED FUNCTIONS OUTSIDE THE BRAIN**

This review is primarily focused on brain serotonin neurotransmission, and is principally directed toward scientists and physicians with neuropsychiatric interests.

Brief mention needs to be made, nonetheless, of the function of serotonin in the periphery, first described in 1954.<sup>45</sup> Some of these functions, in fact, are directly mediated by the caudal raphe nuclei, which project into the cranial nerves and down the spinal cord. Other functions are found in cells that are embryonically associated with the neural crest, from which the raphe nuclei also differentiate, e.g., thyroid parafollicular cells.<sup>46</sup> Still other cells that transport, store, and release 5-HT by using the identical 5-HT transporter and MAO-B molecules as those found in brain have different embryologic origins, e.g., blood platelets and lung epithelial cells.<sup>47-49</sup> As a cautionary note, however, serotonin function has sometimes been studied in cultured cell lines, e.g., neuroblastoma cells. Many of these cell lines are of uncertain origin, and may exhibit ectopic gene expression. Thus, while they provide convenient models for studies, they may not contain normally present regulatory proteins or complete intracellular signaling elements; hence, studies in such systems could produce misleading conclusions.

The first identified physiologic function of serotonin was as a vasoconstricting substance.<sup>50</sup> It may not be a coincidence that the most recent and one of the most serious medical complications associated with an agent with a primary serotonergic mechanism of action was reported in 1997 when pulmonary hypertension and surprisingly common cardiac valve damage was discovered in obese individuals treated with fenfluramine—leading to the Federal Drug Administration (FDA) mandate to recall this drug.<sup>51,52</sup> It needs to be noted that several substituted amphetamines including fenfluramine and 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) have long been considered as potentially neurotoxic.<sup>53-56</sup> These agents act via the 5-HT transporter to release stored 5-HT. Other drugs like the SSRIs, which act by blocking reuptake of 5-HT, but which do not produce 5-HT release, have not been associated with neurotoxicity. In fact, in some models, SSRIs including fluoxetine and citalopram have been shown to prevent neurotoxicity, including apoptosis, produced by MDMA and fenfluramine.<sup>57,58</sup>

Serotonin has long been known to be present in most peripheral organs where it mediates, in part, the neural and local control of their functions.<sup>59</sup> High concentrations of 5-HT are present in the gut both as part of an enteric nervous system and in nonneural endocrine system cells (enterochromaffin cells).<sup>45,60,61</sup> 5-HT regulates many gastrointestinal functions, from peristalsis<sup>62,63</sup> to pancreatic secretion.<sup>64-67</sup> The cardiovascular system, including blood vessels, are now known to possess at least 4 different 5-HT receptors.<sup>68-70</sup> When they are examined comprehensively, some organs, such as the lumbar dorsal root ganglia and the cervical sympathetic ganglia, have been reported to have 6 and 7 different 5-HT receptors, respectively.<sup>71</sup>

The fundamental conclusion regarding incompletely studied serotonin subsystems in the periphery is that drugs

given to influence brain serotonin for therapeutic aims in neuropsychiatric disorders may also act in the periphery. Such actions may contribute to or complicate their effects in ways not yet completely understood.

## SEROTONIN NEUROTRANSMISSION AND CLINICAL NEUROPHARMACOLOGY

Despite the existence of 15 molecularly-identified serotonin receptors, most of which have been identified in human brain or cultured human cells, only a few 5-HT receptor subtype selective agents are available as pharmacologic therapeutic agents, and only for limited indications. Ondansetron and granisetron (5-HT<sub>3</sub> antagonists) are available for the treatment of emesis associated with anticancer chemotherapy. Sumatriptan (a 5-HT<sub>1D</sub> ligand) is available for the treatment of migraine headaches. One 5-HT<sub>1A</sub> partial agonist, buspirone, is available for the treatment of anxiety disorders.

While nonselective inhibitors of MAO-A/B are available as antidepressants, moclobemide, a more recently developed selective MAO-A inhibitor, is available in many countries, but not in the United States. No drugs acting on the serotonin synthesis pathway are available. L-tryptophan had been available as a nonprescription dietary supplement, but there are few data that increased oral L-tryptophan (at least in combination with a normal diet, or without coadministration with other drugs) leads to any increase in serotonin-mediated functions.

Thus, despite the intricacies of multiple serotonin subsystems served by 15 different serotonin receptors, SSRIs, such as fluoxetine, paroxetine, sertraline, and citalopram, remain the most widely-used class of serotonin-selective agents of therapeutic benefit available (Table 2). Their mechanisms of action are complex and may vary across different disorders (for reviews, see references 72-74). The SSRIs differ with respect to many properties, including 5-HT transporter affinity, pharmacokinetic properties (including absorption, duration of action, presence of active metabolites and interactions via drug metabolizing enzymes with other drugs), as well as other properties, such as additional direct effects on serotonin receptors in the case of some SSRIs and their metabolites,<sup>75-77</sup> and effects on other neurotransmitter systems.<sup>78-84</sup>

## CHANGES IN SEROTONIN-RELATED FUNCTIONS FOLLOWING TRANSGENIC DELETIONS OR ALTERATIONS OF MOLECULAR COMPONENTS OF THE SEROTONERGIC NEUROTRANSMITTER SUBSYSTEMS

The newest evidence demonstrating contributions of serotonergic transmission to physiology and behavior, particularly in the complex nervous system of vertebrates, is the use of transgenic methodology to delete single mo-

lecular components of the 5-HT neurotransmitter system. This has been accomplished for several 5-HT receptors and the 5-HT transporter. These models are in the early stages of study, but have provided both expected and unexpected additional knowledge of 5-HT-mediated functions.<sup>85-90</sup>

### 5-HT<sub>2C</sub>-Deficient Mice

These mice were generated by introducing a nonsense mutation into exon 5 of the gene encoding the 5-HT<sub>2C</sub> receptor, thereby placing a stop codon within the fifth putative transmembrane segment and eliminating the carboxy terminal half of the protein. These mice do not exhibit apparent developmental defects and are fertile. Their most obvious phenotypic difference is manifested by the occurrence of spontaneous seizures and a markedly greater susceptibility to sound-induced seizures.<sup>91,92</sup> These mice are also overweight and do not respond to *m*-CPP, an appetite-suppressant agent in rodents and humans whose principal effects long have been thought to be mediated by 5-HT<sub>2C</sub> receptors.<sup>91,93-95</sup>

### 5-HT<sub>1B</sub>-Deficient Mice

These mice also appeared developmentally normal. However, they were unresponsive to the locomotor enhancing effects of the 5-HT<sub>1A/1B</sub> agonist, RU-24969, and also demonstrated reduced sensitivity to selective 5-HT<sub>1B</sub> autoreceptor agonists.<sup>14,96</sup> Because a number of agents that are thought to act via 5-HT<sub>1B</sub>-mediated actions have anti-aggressive activity, aggressive behavior was investigated in these mice. After a period of isolation, mice lacking 5-HT<sub>1B</sub> receptors were found to show increased aggression in a standard resident-intruder paradigm of rodent aggression.<sup>14</sup>

### Other Transgenic Mice Models

Mice with a disrupted MAO-A gene were found to lack MAO-A enzyme activity and to have markedly elevated (up to 9-fold higher) brain serotonin concentrations during early development.<sup>97</sup> These mice displayed evidence of increased spontaneous aggression as well as increased aggression in the resident-intruder paradigm. They also exhibited altered mating behaviors and altered open-field behavior (more time in the center of the field).<sup>97-99</sup> While the latter change could be interpreted as an indication of a reduction in anxiety or fear-related behaviors, neuroanatomical evidence of alterations in the barrel fields of the somatosensory cortex raised the question of whether cognitive or sensory alterations might contribute to this behavioral difference. Of note, treating neonatal mice lacking MAO-A with the serotonin synthesis inhibitor, para-chlorophenylalanine (PCPA), partially restored the capacity to form cortical barrels.<sup>97,98</sup>

Increased aggressive behavior and decreased fear responses were also observed in mice deficient in

$\alpha$ -calcium-calmodulin kinase II ( $\alpha$ -CAMKII), a facilitator of presynaptic neurotransmitter release.<sup>100</sup> While alterations in 5-HT release were found in electrophysiologic studies of brain slices from these mice, further studies are required to evaluate a possible connection between serotonergic neurotransmission changes and the behavioral abnormalities they display.<sup>101</sup>

Further study also is needed of the deficit in fear conditioning observed when  $\alpha$ -CAMKII was transgenically expressed at high levels in the lateral amygdala and the striatum, but not in other forebrain areas.<sup>102</sup> Increased aggression, which was completely normalized by administration of 2 selective inhibitors of serotonin reuptake, zimelidine or clomipramine, also has been observed in a different transgenic model, mice overexpressing human growth factor.<sup>103,104</sup>

Preliminary data indicate that mice lacking the 5-HT transporter have apparently normal early development patterns, with intact feeding and mating behaviors.<sup>105</sup> However, these mice exhibit gene dose-dependent reductions in responses to serotonergic agents, including MDMA ("ecstasy") and 8-OH-DPAT.<sup>105-107</sup> While there is some evidence that serotonin regulates neural crest migration in rodents, and that excess serotonin, including that produced by SSRI administration, might lead to dysmorphogenesis,<sup>108,109</sup> the apparent physiologic and anatomical normality of these mice is in agreement with teratogenic surveys of pregnant humans exposed to SSRIs which indicated a lack or minimal risk of developmental problems.<sup>110-112</sup> These data raise the question of whether serotonergic neurotransmission, with all of its heterogeneity, is adaptively redundant, and that normal or near-normal function can be maintained despite a marked reduction or even total absence of a key component of this system, the 5-HTT, for example. This is in decided contrast with results from a similar knockout of the mouse dopamine transporter.<sup>113</sup> However, the possibility of localized, highly specialized alterations in somatosensory-related neuroanatomy and possibly function such as that found in some studies in rodents exposed to excess 5-HT or to SSRIs requires further investigation.<sup>97,98,114</sup>

## CONCLUSIONS

Unraveling the complexity of brain serotonergic transmission in attempts to link structure and function has proved to be a daunting task. The existence of different projection fields from the 2 rostral nuclei (dorsal raphe vs. median raphe), which use different pathways through the brain dually or singly to innervate some regions or specific neurons, has been demonstrated in vertebrate brain. The existence of 15 different serotonin receptors, some of which have opposite effects on other neurotransmitter system neurons (including dopamine, acetylcholine, and glutamate neurons), also has been demonstrated. Understand-

ing the mechanism of action of selective serotonergic agents that primarily target 1 serotonin receptor, e.g., the 5-HT<sub>3</sub> receptor, remains a reasonable goal.

The situation with drugs like the SSRIs, however, is far more complicated. These drugs, as well as serotonin-releasing drugs like fenfluramine, initially act by increasing synaptic and other extracellular serotonin concentrations that, theoretically, could affect all 15 serotonin receptors. The therapeutic effects of the SSRIs may require 3 to 6 weeks of continued administration in depressed patients and as long as 10 to 12 weeks in patients with obsessive-compulsive disorder. These therapeutic effects are likely to depend upon adaptive events involving changes in the multiple 5-HT receptors, their signal transducing mechanisms, expression of genes for these receptors or other components of the system (5-HT synthetic enzymes, the 5-HT transporter), or trophic effects.<sup>115–118</sup> Similar adaptive events may occur in the other neurotransmitter or neuromodulator systems that interact with the serotonin systems. Thus, while even partial understanding of the final mechanisms involved in the therapeutic effects of drugs like the SSRI antidepressants continues to be elusive, the search for these mechanisms has been enhanced by powerful new research strategies.

*Drug names:* buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), dopamine (Dopastat, Intropin), fenfluramine (Pondimin), fluoxetine (Prozac), granisetron (Kytril), L-tryptophan (Trofan and others), ondansetron (Zotran), paroxetine (Paxil), sertraline (Zoloft), spiperone (Spiropitan), sumatriptan (Imitrex).

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