

# The Serotonin System

## Part I: Clinical Significance

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### ABSTRACT

The serotonin (5-hydroxytryptamine, 5-HT) system has been implicated in the pathogenesis of a variety of psychiatric conditions, including: depression, anxiety, eating disorders and aggressive behaviour. This paper reviews the current literature concerning synthesis, distribution and clinical significance of serotonin and the 5-HT family of receptors. There are at least eight known and named receptors within the central nervous system. The aim of much research is to elucidate the connection between these receptors and various psychiatric dysfunctions. The receptors can be broadly divided into four subtypes: the 5-HT<sub>1</sub> receptors (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>1D</sub>), the 5-HT<sub>2</sub> receptors (5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub>), the 5-HT<sub>3</sub> receptor(s) and the 5-HT<sub>4</sub> receptor. Each receptor type and subtype apparently governs unique biochemical secondary messenger systems; thus, by understanding their function and clinical significance, more highly refined pharmacologic probes may be designed which will allow for effective, specific treatment without the side effect profile associated with traditionally available medications. Coincidentally, by studying receptor physiology, valuable information about psychopathological adaptation is also learned. Such information will assist greatly in future diagnosis and treatment.

**Key Words:** 5-hydroxytryptamine, pharmacology, psychiatry, serotonin

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### RÉSUMÉ

Le système de la sérotonine (5-hydroxytryptamine, 5-HT) intervient dans la pathogénèse de divers troubles psychiatriques, notamment la dépression, l'anxiété, les troubles du comportement alimentaire et le comportement agressif. Les auteurs passent en revue la documentation existante sur la synthèse, la distribution et l'importance clinique de la sérotonine et des récepteurs 5-HT. Le système nerveux central compte au moins huit récepteurs de ce genre. Le but de la recherche était d'éclaircir les liens entre ces récepteurs et divers problèmes psychiatriques. Les récepteurs peuvent être dans une large mesure divisés en quatre sous-types: les récepteurs 5-HT<sub>1</sub> (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> et 5-HT<sub>1D</sub>), les récepteurs 5-HT<sub>2</sub> (5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> et 5-HT<sub>2C</sub>), le(s) récepteur(s) 5-HT<sub>3</sub> et le récepteur 5-HT<sub>4</sub>. Chaque récepteur et ses sous-types semblent ne gouverner qu'un seul ensemble de médiateurs biochimiques secondaires. En précisant leur rôle et leur importance clinique, il serait donc possible de mettre au point de meilleures sondes pharmacologiques pour soigner efficacement et spécifiquement les problèmes concernés, sans déclencher la série d'effets secondaires qui résulte habituellement de l'emploi des médicaments usuels. Par ailleurs, en étudiant la physiologie des récepteurs, on recueillera des renseignements fort utiles sur l'adaptation psychopathologique. Ces renseignements pourraient fortement contribuer au diagnostic et au traitement des maladies concernées dans l'avenir.

**Mots clés:** 5-hydroxytryptamine, pharmacologie, psychiatrie, sérotonine

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In the past decade, there has been an increased interest in the use of agents which specifically affect serotonin. It is thought that the serotonergic system may directly or indirectly mediate the therapeutic effects of a wide variety of drugs, including anxiolytics, anti-hypertensives,<sup>1</sup> antidepressants,<sup>2,3</sup> and migraine prophylaxis agents.<sup>4</sup> Success with medications which act specifically upon this system has been encouraging. It has also allowed the use of pharmacologic

probes as a means for understanding a diverse range of psychiatric dysfunctions.<sup>5</sup>

Molecular biologic, radioligand binding and electrophysiologic scanning techniques have increased our understanding of the physiology and functioning of the serotonin system.<sup>6</sup> Research has focused on the unique interaction of serotonin and its receptors in an effort to identify the potential clinical significance. Recently, evidence has accumulated which sug-

gests the existence of a multiplicity of serotonin receptors. Each of these receptors provides a target which can "be pharmacologically manipulated to alter serotonergic function in unique ways to achieve specific clinical effects".<sup>7</sup>

### Serotonin Biochemistry

Serotonin is synthesized from the dietary essential amino acid L-tryptophan (L-TRP) found in many diverse food sources. L-tryptophan is converted into 5-hydroxytrypta-

mine (5-HT, serotonin) through a rate-limiting enzymatic step involving tryptophan hydroxylase. Over 90% of the body's supply of 5-HT is found in the enterochromaffin cells of the gastro-intestinal (GI) tract. Of the remaining 10%, one-half is located within platelet cells, the other half is localized within specific neurons (centred in the raphe nuclei) of the Central Nervous System.

The catabolism of 5-HT requires monoamine oxidase and aldehyde dehydrogenase. The final metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) has been the source of considerable speculation. It is thought to reflect fairly accurately central supplies of serotonin (though this has not been proven), therefore, 5-HIAA may be an important endogenous marker for certain psychiatric dysfunctions.<sup>8</sup> For example, post-mortem studies of people who have committed suicide using particularly violent means have suggested there is a correlation between such aggressivity and decreased concentrations of 5-HIAA in the cerebrospinal fluid. Though not conclusive, such studies do suggest a role for the serotonin system in the expression of such behaviour.

### Receptor Physiology

The 5-HT family of receptors, as described earlier, is generally subdivided into three or four main classes, based on similar neuroanatomical distribution, radioligand affinities, structural similarities and functional significance. The best-studied of these receptors, the 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, have subdivisions, and recent studies suggest the number of these types and subtypes of receptors will continue to expand.

Serotonin appears to exert different effects at different receptor sites. Some receptors, located presynaptically, are inhibitory: when

stimulated by serotonin, they are involved in a negative feedback loop causing a decrease in the subsequent release of serotonin at the synapse. Other receptors, located postsynaptically, have the exact opposite effect, stimulating further release of serotonin. A predictable model for serotonin and its receptor interactions is therefore difficult to devise. This also demonstrates the importance of characterizing each of the receptors carefully and trying to target the receptor desired so that precise, desired clinical outcomes can be achieved without unnecessary, and potentially counterproductive, stimulation of other serotonin receptor subtypes.

**5-HT<sub>1A</sub>:** The highest concentration of this receptor appears to be in the dentate gyrus of the hippocampus, and in the raphe nuclei. The activity of this receptor has been linked to inhibition of adenylate cyclase. It is thought that 5-HT<sub>1A</sub> stimulation may be partly responsible for mediating an inhibitory effect on serotonin release.

Several selective pre-synaptic 5-HT<sub>1A</sub> agonists exist, such as buspirone (which also acts as a partial agonist post-synaptically). Buspirone, and other azapirones have been used as pharmacologic probes to improve our understanding of the functional significance of this receptor site. The 5-HT<sub>1A</sub> receptor appears to be important in the expression of generalized anxiety disorders and panic disorders, a theory supported by the finding that selective and partial agonists have anxiolytic effects equivalent to that of diazepam.<sup>9</sup> In panic disorder, one study suggested that imipramine may be superior to buspirone.<sup>10</sup> In another, no statistically significant advantage over placebo was reported,<sup>11</sup> though further trials are progressing.

Recently, with the emergence of

co-morbidity diagnoses such as Mixed Anxiety-Depressive Disorder (MADD), there has been speculation that 5-HT<sub>1A</sub> receptors are involved in the development of depressive symptomatology. 5-HT<sub>1A</sub> agonists may, therefore, be useful anti-depressants. Animal studies have demonstrated that long-term treatment with antidepressants induces a reduction of 5-HT<sub>1A</sub> receptors, and this effect has been also demonstrated with buspirone.<sup>12</sup> Studies in humans have also supported an antidepressant role for 5-HT<sub>1A</sub> agonists.<sup>13</sup>

Buspirone is the only commercially available 5-HT<sub>1A</sub> partial agonist. Its official indication is for anxiety, though phase III trials are under way to determine efficacy in depression. Other 5-HT<sub>1A</sub> agonists, gepirone and ipsapirone are also undergoing studies for dual indications.

Other possible clinical applications for 5-HT<sub>1A</sub> active agents have also been reported. At least one study has demonstrated that 5-HT<sub>1A</sub> activation may decrease alcohol consumption and improve short-term memory disorders, especially those noted in patients suffering from Parkinson's disease.<sup>14</sup> Reports using 5-HT<sub>1A</sub> agonists in the treatment of eating disorders and appetite control have suggested a potential role for these agents in the future. Other possible applications include therapy for pre-menstrual syndrome, obsessive-compulsive disorders, and smoking cessation.

**5-HT<sub>1B</sub>:** This subtype of receptor appears to be species specific, found in rat and mouse brain, but not in human brain. Similar to the 5-HT<sub>1A</sub> receptor, there appears to be a negative coupling to adenylate cyclase, so that stimulation of this receptor inhibits further release of serotonin. There may be a role for this receptor in the expression of anxiety in rodents.

**5-HT<sub>1D</sub>:** This receptor subtype was first characterized in 1987. It is negatively coupled to denylate cyclase, and may act as the serotonin system's autoreceptor. There is widespread distribution of the 5-HT<sub>1D</sub> receptor throughout the brain, with special clusters located at or on cerebral blood vessels. Sumatriptan, a potent and selective 5-HT<sub>1D</sub> agonist causes vasoconstriction of cerebral arteries, and has been reported to be extremely effective in the acute treatment of migraine, though not in migraine prophylaxis.

### The 5-HT<sub>2</sub> Receptors

**5-HT<sub>1C</sub>:** As the name implies, the 5-HT<sub>1C</sub> receptor was initially characterized as a 5-HT<sub>1</sub> receptor subtype. Subsequent study with radioligand binding techniques have demonstrated more similarities between 5-HT<sub>1C</sub> and the 5-HT<sub>2</sub> family of receptors, and so, it has been re-classified. There is a high density of 5-HT<sub>1C</sub> receptors in the choroid plexus, hippocampus, basal ganglia and spinal cord. Unfortunately, no specific 5-HT<sub>1C</sub> active agents exist, so very little is known about the function of this receptor. It may modulate production or absorption of cerebrospinal fluid, but the clinical significance of this is at present unknown.

**5-HT<sub>2A</sub> and 5-HT<sub>2B</sub>:** Only recently has work focused on differentiating these two receptors; it appears that the 5-HT<sub>2B</sub> receptor is the classic serotonin receptor, though the differences between 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> are slight. These receptors appear to play an important role in the pathophysiology of psychiatric dysfunction, though their specific role has yet to be identified.

They do appear to play a role in depression, though that role is unclear. Traditional antidepressants decrease the number of 5-HT<sub>2</sub> receptors, but electroconvul-

sive therapy, another effective treatment actually increases this number. Double blind studies indicate that mianserin, a 5-HT<sub>2</sub> antagonist has been equally effective in the treatment of depression as imipramine, amitriptyline, and trazodone and only slightly less effective than fluoxetine.<sup>15</sup>

The 5-HT<sub>2</sub> antagonists, methysergide, pizotiline and cyproheptadine, have been used and studied extensively in migraine prophylaxis. It is thought that 5-HT<sub>2</sub> antagonists inhibit metabolism of phosphatidylinositol and arachidonic acid pathways which lead to sterile inflammatory reactions of brain vasculature. This inhibition is prophylactic and accounts for the lack of efficacy observed with these agents in the treatment of acute migraine situations.

Cyproheptadine, in particular, has been studied as a method of inducing weight gain, especially in non-bulimic anorexic patients. Another 5-HT antagonist, ketanserin, has been studied as an anti-hypertensive and in treatment of peripheral vascular disease, thrombotic episodes and cardiopulmonary emergency.

### The 5-HT<sub>3</sub> Receptors

These receptors were first described in the GI tract (90% of body supplies of serotonin are found in the enterochromaffin cells of the GI tract). They have been also identified centrally, and appear to be involved in dopamine-mediated hyperreactivity in rats. The 5-HT<sub>3</sub> antagonists, ondansetron, granisetron and zacopride are unique and potent inhibitors of 5-HT<sub>3</sub> and are effective anti-emetics. These drugs may also exert effects on vagal afferent neurons which would, in part, explain their efficacy as anti-emetics.

The existence of highly specific pharmacologic probes for the 5-HT system has allowed us to gain

an insight into the serotonergic basis for various psychiatric dysfunctions. As our knowledge becomes refined, we can target these receptors more precisely and accurately, thereby treating patients with a minimum amount of side effects.<sup>16</sup> The efficacy of novel serotonin-specific agents will undoubtedly lead to improved quality of life for patients and a new understanding about the pathophysiology of psychiatric disease. ☒

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#### Appendix A: The Serotonin System

Receptor	Functional Significance	Agonists	Antagonists	Clinical Significance
<b>5-HT<sub>1</sub> Receptors:</b>				
5-HT <sub>1A</sub>	Inhibition of Adenylate Cycl.	Buspirone Gepirone Ipsapirone		Depression Anxiety Disorders Panic Disorders Regulation of appetite ?Alcoholism?
5-HT <sub>1B</sub>	Inhibition of Adenylate Cycl.	None	None	Species specific — found in rodents — Anxiety?
5-HT <sub>1D</sub>	Inhibition of Adenylate Cycl.	Sumatriptan	None	Migraine Treatment
<b>5-HT<sub>2</sub> Receptors:</b>				
5-HT <sub>1C</sub>	Phosphatidylinositol Turnover	Mianserin Methysergide		Unknown
5-HT <sub>2A/B</sub>	Unknown		Mianserin Ritanserin Methysergide Cyproheptadine Pizotifen	Migraine Prophylaxis Depression Eating Disorders
5-HT <sub>3</sub>	Unknown	None	Ondansetron Granisetron	Chemotherapy Induced Emesis ?Anxiety?