

## serotonin Pharmacology

### Editorial

The pharmacology of serotonin (5-hydroxytryptamine or 5-HT) in the gut has been the centre of intense interest and research for several decades. In the gut, 5-HT is an important mucosal signalling molecule targeting enterocytes, smooth muscle cells, and enteric neurones. Its biological function is complex and multifaceted, modulating mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction. Serotonin is primarily found in the enteric nervous system located in the gastrointestinal tract (GI tract). However, it is also produced in the central nervous system (CNS), specifically in the Raphe nuclei located in the brainstem, Merkel cells located in the skin and taste receptor cells in the tongue. Additionally, serotonin is stored in blood platelets and is released during agitation and vasoconstriction, where it then acts as an agonist to other platelets. Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the GI tract, where it regulates intestinal movements. About 8% is found in platelets and 1%-2% in the CNS. The serotonin is secreted lumenally and basolaterally, which leads to increased serotonin uptake by circulating platelets and activation after stimulation, which gives increased stimulation of myenteric neurons and gastrointestinal motility. The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions. These include the regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning. Several classes of antidepressants, such as the SSRIs and the SNRIs among others, interfere with the normal reabsorption of serotonin after it is done with the transmission of the signal, therefore augmenting the neurotransmitter levels in the synapses. Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it can serve as a vasoconstrictor or a vasodilator while regulating hemostasis and blood clotting. In high concentrations, serotonin acts as a vasoconstrictor by contracting endothelial smooth muscle directly or by potentiating the effects of other vasoconstrictors (e.g. angiotensin II, norepinephrine). The vasoconstrictive property is mostly seen in pathologic states affecting the endothelium – such as atherosclerosis or chronic hypertension. In physiologic states, vasodilation occurs through the serotonin mediated release of nitric oxide from endothelial cells. Additionally, it inhibits the release of norepinephrine from adrenergic nerves.[16] Serotonin is also a growth factor for some types of cells, which may

give it a role in wound healing. Invertebrate receptors for the neurotransmitter serotonin (5-HT) have been identified in numerous species from diverse phyla, including Arthropoda, Mollusca, Nematoda and Platyhelminthes. For many receptors, cloning and characterization in heterologous systems have contributed data on molecular structure and function across both closely and distantly related species. This article provides an overview of heterologously expressed receptors, and considers evolutionary relationships among them, classification based on these relationships and nomenclature that reflects classification. In addition, transduction pathways and pharmacological profiles are compared across receptor subtypes and species. Previous work has shown that transduction mechanisms are well conserved within receptor subtypes, but responses to drugs are complex. A few ligands display specificity for different receptors within a single species; however, none acts with high specificity in receptors across different species. Two non-selective vertebrate ligands, the agonist 5-methoxytryptamine and antagonist methiothepin, are active in most receptor subtypes in multiple species and hence bind very generally to invertebrate 5-HT receptors. Future challenges for the field include determining how pharmacological profiles are affected by differences in species and receptor subtype, and how function in heterologous receptors can be used to better understand 5-HT activity in intact organisms. Diverse neuropsychiatric disorders present dysfunctional memory and no effective treatment exists for them; likely as result of the absence of neural markers associated to memory. Neurotransmitter systems and signaling pathways have been implicated in memory and dysfunctional memory; however, their role is poorly understood. Hence, neural markers and cerebral functions and dysfunctions are revised. To our knowledge no previous systematic works have been published addressing these issues. The interactions among behavioral tasks, control groups and molecular changes and/or pharmacological effects are mentioned. Neurotransmitter receptors and signaling pathways, during normal and abnormally functioning memory with an emphasis on the behavioral aspects of memory are revised. With focus on serotonin, since as it is a well characterized neurotransmitter, with multiple pharmacological tools, and well characterized downstream signaling in mammals' species. 5-HT<sub>1A</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors as well as SERT (serotonin transporter) seem to be useful neural markers and/or therapeutic targets. Certainly, if the mentioned evidence is replicated, then the translatability from preclinical and clinical studies to neural changes might be confirmed. Hypothesis and theories might provide appropriate limits and perspectives of evidence.