Investigation of the interaction between 5-HT$_3$R and its modulators: progress in understanding the agonist binding site

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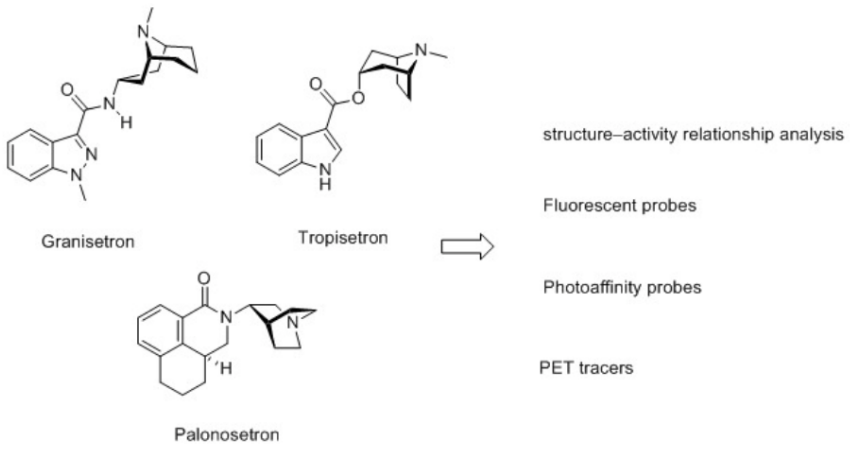
The serotoninergic system plays an essential role in the brain. Nerve cells that use serotonin as neurotransmitter are among the most branched and cross-linked. They are responsible for the modulation of several processes of the CNS. Therefore, the serotoninergic system is the target for the therapy of different diseases like depression, pain, schizophrenia and chemotherapy induced nausea and vomiting. Additionally, several drugs of abuse, like LSD, DMT, Mescalin and Psilocybin are acting directly on this system.

After serotonin (5-hydroxytryptamine, 5-HT) is released into the synaptic cleft, the natural agonist binds to different receptors. Seven classes of receptors have been described too date, most of them are GPCRs (5-HT$_{1\text{-}2,4\text{-}7}$R), only the 5-HT$_3$R is an ion channel belonging to the Cys-loop superfamily of transmembrane receptors. The 5-HT$_3$R is assembled from 5 subunit positioned around the central pore. It is permeable to sodium, potassium and calcium. Recently, the crystal structure of the mouse 5-HT$_3$R was solved and reported using x-ray analysis.[1] This structure was stabilized by nanobodies, deeply binding into the orthosteric binding site, that leaves unanswered questions in the understanding of the pharmacology of the receptor.

Since few years our research focused on the study of the structure and pharmacology of 5-HT$_3$R. We report here our most recent results. Different approaches were applied. Starting from FDA approved antagonists we synthesised several probes (fluorescent,[2] photoaffinity[3] and PET[4]) and their behaviour was investigated. Most of them show very high binding affinity (low nM or even pM) and could be used as tools in microscopy, PET and proteomic analyses. Furthermore we established a stable *h*5-HT$_3$R expressing cell line and a purification protocol to yield the receptor in a high purity.



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