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Dissection of an allosteric mechanism on the serotonin transporter: a cross-species study.

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Abstract

The serotonin transporter (SERT), which belongs to a family of sodium/chloride-dependent transporters, is the major pharmacological target in the treatment of several clinical disorders, including depression and anxiety. Interaction with a low-affinity allosteric site on SERT modulates the ligand affinity at the high-affinity binding site. Serotonin (5-hydroxytryptamine) and certain SERT inhibitors possess affinity for both sites. In the present study, we report the characterization of a severely attenuated allosteric mechanism at the recently cloned chicken serotonin transporter (gSERT). A cross-species chimera study was performed, followed by species scanning mutagenesis. Residues important for the allosteric mechanism were mapped to the C-terminal part of SERT containing the transmembrane domains 10 to 12. We identified nine residues located in four distinct amino acid segments. The contribution of each segment and individual residues was investigated. Consequently, a gSERT mutant with a restored allosteric mechanism, as well as a human SERT (hSERT) mutant with a severely attenuated allosteric mechanism, was generated. The nine residues confer a functional allosteric mechanism for different combinations of ligands, suggesting that they contribute to a general allosteric mechanism at SERT. The finding of an allosteric mechanism at SERT is likely to be of physiological importance, in that serotonin was also found to act as an allosteric effector at duloxetine, RTI-55 and (S)-citalopram. Furthermore, the allosteric potency of 5-HT was found to be conserved for both hSERT and gSERT.

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