Monoamine ligands binding to the dopamine, norepinephrine and serotonin transporters : through ionic interactions or sodium chelation ?

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Re-uptake of neurotransmitters by dopamine, norepinephrine, and serotonin transporters during neuronal transmission requires a sodium gradient. An “ionic mode” of binding proposes that aspartate anchors the ligand's positive charge, but ignores the direct role of sodium in ligand binding seen in the only representative structure, the prokaryotic leucine transporter LeuT. Here, we built structural models of human DAT, NET and SERT using the LeuT structure. The ligand and sodium binding sites are highly conserved. We examined the possibilities for ligand binding given the available experimental evidence, including examples of catechol-cation chelates in X-ray structures of protein and other complexes. We conclude that a “chelation mode” of binding with direct interaction between the catechol hydroxyls and sodium is a valid alternative, with consequences for pharmaceutical design. In the modeled serotonin transporter complexes, Y95 is placed where it could select for serotonin through hydrogen bonding to the indole nitrogen.

For more information, please see:
"Coordination of Na+ by monoamine ligands in dopamine, norepinephrine and serotonin transporters". Xhaard, Henri; Backström, Vera; Denessiouk, Konstantin; Johnson, Mark. *Journal of Chemical Information and Modeling*. In press.
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