

MEETING ABSTRACT

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# The high-affinity binding site for tricyclic antidepressants resides in the outer vestibule of the serotonin transporter

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## Background

The structure of the bacterial leucine transporter LeuT<sub>Aa</sub> has been used as a model for mammalian Na<sup>+</sup>/Cl<sup>-</sup>-dependent transporters, in particular the serotonin transporter (SERT). The crystal structure of LeuT<sub>Aa</sub> liganded to tricyclic antidepressants predicts simultaneous binding of inhibitor and substrate. This is incompatible with the mutually competitive inhibition of substrates and inhibitors of SERT.

## Methods

We explored the binding modes of tricyclic antidepressants by homology modeling and docking studies. Two approaches were used subsequently to differentiate between three clusters of potential docking poses: (i) a diagnostic SERT<sup>Y95F</sup> mutation, which greatly reduced the affinity for [<sup>3</sup>H]imipramine but did not affect substrate binding, and (ii) competition binding experiments in the presence and absence of carbamazepine (i.e. a tricyclic imipramine analog with a short side chain that competes with [<sup>3</sup>H]imipramine binding to SERT).

## Results

Binding of releasers (*para*-chloroamphetamine, methylene-dioxy-methamphetamine/ecstasy) and of carbamazepine were mutually exclusive, but Dixon plots generated in the presence of carbamazepine yielded intersecting lines for serotonin, MPP<sup>+</sup>, paroxetine and ibogaine.

## Conclusions

These observations are consistent with a model, where (i) the tricyclic ring is docked into the outer vestibule and the dimethyl-aminopropyl side chain points to the substrate binding site, (ii) binding of amphetamines creates a structural change in the inner and outer vestibule that precludes docking of the tricyclic ring, (iii) simultaneous binding of ibogaine (which binds to the inward-facing conformation) and of carbamazepine is indicative of a second binding site in the inner vestibule, consistent with the pseudo-symmetric fold of monoamine transporters. This may be the second low-affinity binding site for antidepressants.

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