BMC Pharmacology

MEETING ABSTRACT Open Access

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

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From 16th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Vienna, Austria. 25-27 November 2010

Background

The structure of the bacterial leucine transporter $LeuT_{Aa}$ has been used as a model for mammalian Na^+/Cl^--dependent transporters, in particular the serotonin transporter (SERT). The crystal structure of $LeuT_{Aa}$ 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 $SERT^{Y95F}$ mutation, which greatly reduced the affinity for [^{3}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 [^{3}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^+, 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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Published: 16 November 2010

doi:10.1186/1471-2210-10-S1-A21
Cite this article as: Sarker *et al.*: The high-affinity binding site for tricyclic antidepressants resides in the outer vestibule of the serotonin transporter. *BMC Pharmacology* 2010 **10**(Suppl 1):A21.

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