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Meeting abstract



# Mutations in the amino-terminus impair amphetamine-induced efflux by inducing inward-facing conformations of the serotonin transporter

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## Background

The serotonin transporter (SERT) is responsible for the rapid termination of neurotransmission by removing serotonin from the synaptic cleft. We have explored the functional significance of a highly conserved threonine residue, at position 81, located within the amino-terminus of SERT.

## Methods and results

Our findings indicate that, although the mutated transporters are normally targeted to the plasma membrane, they exhibit marked functional defects, such as: (i) a dramatic decrease in amphetamine-induced efflux (despite retaining normal amphetamine-induced currents), (ii) a 3-fold reduction in transporter turnover numbers (indicating impaired substrate translocation) and (iii) a 4-fold decrease in inhibitor affinity (due to a declined on-rate and an enhanced off-rate). The latter suggests that the mutated SERTs have a preference for inward-facing transporter conformations, as further supported by our molecular dynamics simulation experiments. By studying several H-bond and hydrophobic interactions of the wild-type T81, compared to its mutations to alanine or aspartate, structural changes were detected in the juxtamembrane N-terminus region of SERT. The computer models demonstrate a degradation of N-terminus interactions with IL2 and IL3 (which are likely involved in the transition between inward- and outward-facing SERT conformations) and a shift of the C-terminus away from the N-terminus upon mutation. Moreover, truncation of the first 64 residues of the amino-terminus results in functional defects comparable to the sole mutation of T81.

## Conclusion

Hence, alterations in the amino-terminus region of SERT induce inward-facing transporter states, causing hindrance to conformational changes required for amphetamine-stimulated release, without simultaneously obstructing the transporter's ability to operate in its channel or uptake mode of action.