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DOCKING OF SUBSTRATES AND INHIBITORS INTO THE SUBSTRATE BINDING SITE OF TWO SEROTONIN TRANSPORTER MODELS

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The serotonin transporter (SERT) belongs to the neurotransmitter:sodium symporter (NSS) family. Located in the membranes of presynaptic neurons, the transporter removes serotonin (5-HT) from the synaptic cleft, thus reducing the number of neurotransmitters available for interaction with postsynaptic receptors. The transporter is targeted by two of the main classes of antidepressant drugs – the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs) – and is also targeted by psychostimulants such as cocaine, MDMA (ecstasy) and d-amphetamine.

The 3D structure of SERT has not yet been determined. However, the first 3D structure of a NSS family member, the *Aquifex aeolicus* leucine transporter (LeuT) is available both in an occluded conformation [1] as well as in an outward-facing conformation [2]. Based on a comprehensive alignment of NSS [3], two different homology models of SERT representing two different conformational states were generated using the ICM program package and the two LeuT crystal structures [1,2] as templates and serotonin and (S)-citalopram (an SSRI) were docked into the binding pockets detected in both models. Our results indicate that the LeuT crystal structures are reliable templates for homology modelling of SERT and subsequent docking of substrates and inhibitors. The docking indicates that D98 is a key amino acid for binding of both serotonin and (S)-citalopram. Transmembrane helices 1, 3, 6, and 8 were involved in interactions with the docked compounds in both SERT homology models.

Acknowledgements

This study was partly supported by the grant PNRF-103-Al-1/07 through the Norwegian Financial Mechanism and the Norwegian Research Foundation.

References

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