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Title: Substrate selectivity profiling of the human monoamine transporters

Abstract in Englisch

The serotonin, dopamine and norepinephrine transporter proteins (SERT, DAT, NET, respectively) are collectively named as the monoamine transporters (MATs) and are involved in a variety of psychiatric disorders such as depression, addiction and attention-deficit hyperactivity disorder (ADHD). This has made them a central topic in life sciences research during the last decades. The selectivity of MAT substrates has been thoroughly studied during this thesis, using computational and biochemical methods. The binding modes and selectivity of exogenous compounds have not been studied extensively before this study. Cathinones are compounds gaining increased popularity in the party scene and are also transported by the MATs.

Their uptake inhibitory activity on the MATs was exploited in order to better understand the selectivity phenomenon. Molecular docking of a set of these cathinones into a homology model of SERT validated their binding mode in the substrate binding site and indicated that their chemical scaffold overlap. Additionally, their binding activity was rationalized based on the interaction between the chemical substituents and protein residues that surround them. Further validation was obtained by Hansch analysis. This approach indicated that a polarizable or lipophilic para-substituent increases SERT affinity, whereas a bulky nitrogen substituent would be unfavorable. Different datasets indicated that a lack of substituents on the aromatic ring rendered the compounds DAT-over-SERT selective.

Therefore, a molecular dynamics (MD) and thermodynamic integration (TI) study was conducted, which indicated the substrate binding site to be the major recognition site for these compounds. The DAT-over-SERT selectivity was ascribed to: 1. more favorable aromatic stacking interactions which were more favorable in DAT presumably, due to a less bulky Val152 compared to Ile172 in SERT that would disrupt such an interaction. 2. More attractive electrostatic interactions caused by a slightly tighter DAT binding pocket with a smaller number of waters on average entering the binding site, as compared to SERT. The hypotheses were validated by uptake inhibitory assays on mutants of the transporters.