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Tat modulates DAT

Mirella Bucci

HIV-associated neurocognitive disorders (HANDs) are a set of neurological disorders including HIV encephalopathy and HIV dementia, which are associated with HIV-1 infection, and specifically with the HIV Tat protein, which is present in the brain of HIV-1-infected patients. Tat is thought to inhibit neuronal communication by acting directly on neurotransmitter transporters such as the human dopamine transporter, hDAT. hDAT transports dopamine from the presynaptic cleft into presynaptic neurons during neurotransmission. Curiously, cocaine blocks this clearance of dopamine by acting directly on hDAT, so HANDs are further exacerbated in HIV-1-positive patients who abuse cocaine. To probe the mechanism of Tat action on hDAT, Yuan et al. used a hDAT homology model to dock Tat onto the transporter and performed MD simulations to probe the conformational state of hDAT bound to Tat. They found that of the three known conformational states of hDAT, Tat binds only the outward-open structure with favorable binding energies. The authors predicted that Tat binding would block the entry pathway of the dopamine substrate, thereby inhibiting dopamine clearance from the presynaptic cleft. As well, the authors were able to identify key intramolecular interactions between Tat and key hDAT residues, including a cation- π interaction involving Y470 of hDAT and two hydrogen-bonding interactions involving hDAT residues Y88 and K92. These interactions persisted throughout the MD simulations. To obtain experimental evidence for the mode of binding predicted by the computational experiments, the authors monitored the effect of Tat on dopamine uptake by hDAT bearing mutations of the key residues they defined. This mutational analysis verified the role of the aromatic ring of hDAT Y470 and therefore the existence of a cation- π interaction with Tat and the role of hydrogen bonding at Y88 and K92. These results suggest a mechanism for how infection by HIV-1 leads to HANDs.