

Title: The role of human dopamine transporter in NeuroAIDS

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About one-half of HIV-1-positive individuals suffer from HIV-associated neurocognitive disorders (HAND), which dramatically affects memory, learning, decision-making, planning and overall quality of life. HAND remains highly prevalent in HIV infected individuals and represents a special group of neuropathological disorders, which are associated with HIV-1 viral proteins, such as transactivator of transcription (Tat) protein. For a long time, the idea of the HIV virus crossing the blood-brain barrier was not even considered, but it's now clear that HIV-1 viral proteins are released in the brain where they disrupt normal brain functions. Cocaine abuse increases the incidence of HAND and exacerbates its severity by enhancing viral replication. Perturbation of dopaminergic transmission has been implicated as a risk determinant of HAND. The presynaptic dopamine (DA) transporter (DAT) is essential for DA homeostasis and dopaminergic modulation of the brain function including cognition. Tat and cocaine synergistically elevate synaptic DA levels by acting directly on human DAT (hDAT), ultimately leading to dysregulation of DA transmission. Through integrated computational modeling and experimental validation, key residues have been identified in hDAT that play a role in Tat-induced inhibition of DAT and induce transporter conformational transitions. This review presents current information regarding neurological changes in DAT-mediated dopaminergic system associated with HIV infection, DAT-mediated adaptive responses to Tat as well as allosteric modulatory effects of novel compounds on hDAT. Understanding the molecular mechanisms by which Tat induces DAT-mediated dysregulation of DA system is of great clinical interest for identifying new targets for an early therapeutic intervention for HAND.

Biography

Dr. Zhu received his PhD from the Fukui Medical University, Fukui, Japan and completed his postdoctoral studies from Univeristy of Kentucky, College of Pharmacy, USA. Currently, he is a tenured Associate Professor at the Department of Drug Discovery and Biomedical Sciences, College of Pharmacy, University of South carolina. He has published more than 50 peer-reviewed articles and has been serving as an reviewer of multiple national and international journals and grant application for US National Institutes of Health. Zhu's lab is interested in dopaminergic transmission, particular in regulation of dopamine transporter (DAT) function by psychostimulants and HIV-1 viral proteins.

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