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Allosteric modulatory effects on HIV-1 Tat protein-induced inhibition of human dopamine transporter function

The inducible HIV-1 Tat Transgenic (iTat) mouse model recapitulates many aspects of neurocognitive impairments observed in HIV infected individuals. Tat and cocaine synergistically increase synaptic Dopamine (DA) levels by directly inhibiting DA Transporter (DAT) activity, ultimately leading to dopaminergic neuron damage. This study determined allosteric modulatory effects of SRI-30827 on HIV-1 Tat protein-mediated regulation of human DAT and Cocaine Condition Place Preference (CPP) in iTat mice. Results show that SRI-30827 attenuated Tat-induced inhibition of [3H]DA uptake and [3H]WIN35,428 binding in PC12 cells expressing human DAT. After a 7-d doxycycline (Dox) treatment, HPLC analysis revealed that DA content in the Prefrontal Cortex (PFC) and Nucleus accumbens (NAc) of iTat-Tg mice were increased by 92% and 37%, respectively, compared to control mice. Consistently, DA/DOPAC in the PFC and NAc of iTat-Tg mice was increased by 44% and 26%, respectively. We performed the patch clamp recording to measure Medium Spine Neurons (MSN) firing in brain NAc slices of iTat mice in the presence of DA and cocaine. Results show that that action potential frequency of NAc shell MSN was significantly increased in iTat mice compared to control mice. Further, action potential frequency of NAc shell neurons was decreased in response to 5 μ M cocaine and further decreased when cocaine and 5 μ M were applied together, which were completely attenuated in iTat mice. Finally, we found that ICV infusion of SRI-30827, a novel allosteric modulator, partially attenuated the potentiated cocaine-CPP in iTat mice. These findings suggest the hypothesis that Tat potentiates cocaine rewarding effect and allosteric modulator has potential for treatment of Tat-induced drug reward.

Biography

J Zhu research aims toward finding solutions to a newly recognized challenge in treatment for HIV-associated neurocognitive disorders (HANDs). About one-half of HIV-1-positive individuals suffer from HAND, which dramatically affects memory, learning, decision-making, planning and overall quality of life. Cocaine has been shown to exacerbate the severity of HAND. HAND is associated with HIV-1 viral proteins, which are present in the brain of HIV-1-infected patients. HIV-1 transactivator of transcription (Tat) protein—an HIV regulatory protein is thought to inhibit neuronal communication by acting directly on the human dopamine transporter, a membrane protein in the brain responsible for pumping the dopamine back into the cytosol and terminating dopamine signaling during neurotransmission. Dr. Zhu's project is to investigate how cocaine and Tat work to create binders that derail neuronal communication in the brain. The ultimate goal is to develop neuroprotective drugs and help HIV patients recover their neurological function.

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