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Impact of cocaine, HIV and aging on calcium regulation of cortical neurons

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Cocaine is a highly-addictive psychostimulant that affects cognition. Despite combination antiretroviral therapy (cART), mild forms of HIV-Associated Neurocognitive Disorders (HAND) are still prevalent and are expected to increase with the aging HIV^+ population. HIV-infected cocaine abusers display more severe progression of HAND than non-abusing HIV/AIDS patients. The medial prefrontal cortex (mPFC) is a regulator of addiction and neurocognition and is altered profoundly by chronic cocaine/HIV exposure *in vivo*. Mechanisms underlying mPFC neuronal dysregulation by cocaine/HAND are not fully understood, especially during aging but dysregulated neuronal Ca^{2+} homeostasis may play a critical role. Our studies focus on the effects of chronic cocaine, HIV and aging on voltage-gated Ca^{2+} channel (VGCC) function in mPFC pyramidal neurons, using cocaine-exposure and/or the HIV-1 transgenic (Tg) rat model. We perform electrophysiology (whole-cell patch-clamping) in brain slices to assess neuronal excitability and Ca^{2+} influx via VGCCs (represented by Ca^{2+} spikes) as well as biochemical studies (Western blotting) to evaluate changes in VGCC protein levels. We found that (1) Firing of mPFC pyramidal neurons is abnormally-increased and associated with excessive Ca^{2+} influx (which is toxic) via VGCCs in adolescent (~7 weeks-old) cocaine-exposed rats or HIV-1 Tg rats; (2) Similar neuronal/VGCC dysregulation occurs in young adult cocaine-exposed and/or HIV-1 Tg rats (6 month-old; 6mo), but some dysfunctions are significantly greater following combined exposure and (3) mPFC hyper-excitability remains in older (12 mo) HIV-1 Tg rats but with different mechanisms (unaltered voltage-sensitive Ca^{2+} influx associated with reduced L-channel protein levels). These findings reveal that mPFC excitability is altered by chronic cocaine, HIV and aging through different mechanisms. Besides Ca^{2+} dysregulation, our parallel studies also suggest that dysfunctional K^+ channels also play a role in cocaine/HIV-induced mPFC hyperactivity. Together, our studies demonstrate that chronic exposure to cocaine/HIV *in vivo* significantly alters Ca^{2+} homeostasis in mPFC neurons, which could be exacerbated during aging.

Biography

Xiu-Ti Hu has his expertise in drug addiction and neuro-HIV research, which focuses on elucidating mechanisms that underlie neuronal dysfunction in the mesocorticolimbic dopamine system. He has published 58 peer-reviewed scientific articles and 10 invited book chapters.

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