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Calbindin- and parvalbumin-positive neurons and microglia display sexual dimorphism in long-term responses to methamphetamine and HIV-associated brain injury

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Methamphetamine (METH) use is a frequent comorbidity of infection with human immunodeficiency virus type-1 (HIV-1) and exacerbates HIV-associated neurocognitive disorders (HAND). However, the combined pathological mechanisms of METH and HIV-1 are incompletely understood. Transgenic mice expressing the HIV-1 envelope protein gp120 in the brain (gp120tg) share characteristic neuropathological features and gene expression patterns with neurocognitively impaired HIV/AIDS patients. We previously exposed gp120tg mice to an escalating METH binge regimen for 25 days and analyzed the animals 7 months later, at about 12 months of age. Both, HIVgp120 and METH compromised neurites, synapses and behavioral performance (Hoefler et al., Exp. Neurol. 2015). In this study, we analyzed calbindin (Calb)- and parvalbumin (PV)-positive neurons and glial cells. Calb and PV revealed sex-dependent differences in cerebral cortex and hippocampus with regard to the number of neurons, the quantity of the cell marker's expression, and the response to gp120 and/or METH exposure (RNA & protein). Similarly, pronounced sexual dimorphism was observed in microglia, including in the response to METH. In contrast, astrocytosis indicated only in cerebral cortex a sex-dependent difference associated with gp120 expression but not in response to METH. In summary, METH exposure and viral gp120 compromise learning and memory function and induce neuropathology in both sexes. While injury to MAP-2 and synaptophysin-positive neurites and presynaptic terminals, respectively, does not reveal sexual dimorphism, Calb- and PV-positive interneurons and microglia display significant sex- and brain region-specific differences in the long-term effects of METH exposure and HIVgp120 expression.