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Chronic, low dose methamphetamine and HIV-1 Tat protein lead to neuronal injury, astrocyte activation and gene expression patterns displaying sexual dimorphism

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We studied the impact of methamphetamine (METH) on HIV infection of the brain. Therefore, we subjected transgenic mice that express a tetracycline-inducible HIV Tat protein in the brain (iTat-tg mice) at 4 months of age to a 12-week METH regimen: Starting week 1 with 0.5 mg/kg s.c., 1 x day, step-wise increase by 0.5 mg/kg with each injection over 5 days (Mon–Fri), followed by 11 weeks of 1 x 2.5 mg/kg/day. During week 4, all mice received Doxycyclin (Dox, 100 mg/kg, i.p.) for induction of Tat expression. The cohort included rtTA-positive TRE-Tat-negative control animals and was sex- and age-matched. Four months after the last METH exposure, at 11-12 months of age, all mice underwent behavioral testing before collection of brain tissue for analysis of neuropathology and gene expression. METH and Tat affected recognition but not spatial memory in a sex-dependent fashion. METH and Tat each damaged presynaptic terminals in cortex and hippocampus but METH+Tat did not significantly affect male cortex. MAP-2+ neurites were significantly altered only in females. Astrocyte activation was increased by METH+Tat only in males. An increase of microglial cell numbers due to Tat was observed in both sexes but in response to METH and METH+Tat only in male cortex compared to Tat-negative saline controls. RNA-seq revealed sex-dependent expression patterns due to Tat, METH and METH+Tat exposure and also in Tat-negative saline controls. Sexual dimorphic expression patterns include gene networks of neurotransmission, immunity, inflammation and cell stress. Supported by NIH R01DA052209, R01MH087332 and P50DA026306 (P5) to M.K.