Chronic, low dosage methamphetamine modifies memory performance compromised by exposure to HIV-1 Tat protein

Marcus Kaul¹,²,³, Ricky Maung¹,³, Daniel Ojeda-Juárez¹,³, Paloma Sanchez-Pavon³, Ana B. Sanchez²,³, Amanda Roberts⁴, TMARC Group²

¹Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521, USA; ²Translational Methamphetamine AIDS Research Center (TMARC), Department of Psychiatry, University of California San Diego, San Diego, CA 92093, USA; ³Center for Infectious and Inflammatory Disease, Sanford Burnham Prebys Discovery Medical Institute, La Jolla, CA 92037, USA; ⁴The Scripps Research Institute, Department of Molecular and Integrative Neuroscience, 10550 North Torrey Pines Road, MB6, La Jolla, CA 92037, USA

In order to model a chronic, low-dose methamphetamine (METH) use regimen in the context of infection of the brain with human immunodeficiency virus type-1 (HIV-1), we subjected transgenic mice that express a tetracycline-inducible viral regulatory protein Tat in the brain (iTat mice) at 4 months of age to the following 12-week METH regimen: Week 1, starting at 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 1 x 2.5 mg/kg/day (Mon–Fri = 20+ days per month). In addition to METH the mice received i.p. Dox (100 mg/kg) for induction of Tat expression during week four of the regimen. The mouse cohort included rtTA-positive TRE-Tat-negative control animals, which cannot express Tat upon Dox injection, and comprised each about 50 % females and males. Following a four months abstinence period and thus at 11-12 months of age, treated iTat-tg mice underwent behavioral assessment followed by euthanasia and collection of brain tissues. The behavioral tests included optomotor test of vision (OPT), locomotor activity (LM), novel object recognition (NO) and Barnes maze test (BM; 4 day acquisition + probe trial). The NO and BM paradigms revealed that expression of Tat and exposure to METH each compromised behavioral performance. However, the combination of METH and Tat resulted in a gradual amelioration of the Tat effect in the NO paradigm and a virtually normal performance in the probe trial of the BM. However, METH and Tat exposure were associated with alterations in expression of genes related to neurotransmission. The observation that METH can improve performance in memory tasks otherwise compromised by HIV infection may provide a potential explanation of why some HIV patients continue to use the psychostimulant despite an overall increased risk of neurocognitive deterioration.

Supported by NIH, MH087332, MH104131, MH105330 and DA026306 P5 (to M.K.)