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LINE-1 on the Move: A Report on Regional Differences in Brain LINE-1 Activity after Chronic Methamphetamine Administration

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Methamphetamine (METH) is a widely abused psychostimulant which causes a broad range of neurobehavioral abnormalities when abused chronically, particularly at high doses. These abnormalities are related to METH neurotoxicity in the striatum, prefrontal cortex and hippocampus. Transposable elements are repetitive DNA sequences that can induce epigenetic alterations in the genome. Activation of transposable Long INterspersed Element 1 (LINE-1) is associated with several neurological diseases as well as with drug abuse. However, there is very limited data on the effects of high-dose METH on the activity of LINE-1 in adult brain. Employing 2-month-old male Sprague-Dawley rats, pyrosequencing, and real-time quantitative PCR, we tested the hypothesis that LINE-1 activity in the striatum, dentate gyrus, and prefrontal cortex was increased in chronic METH-treated rats compared to saline controls. This study demonstrates that chronic administration of neurotoxic METH doses results in significantly increased expression of LINE-1-encoded ORF-1 (Open Reading Frame 1 mRNA) in rat striatum at 24h after the last dose of the drug and decreased ORF-1 expression on the 7th day of METH withdrawal, with the dentate gyrus developing tolerance to these METH effects and prefrontal cortex showing unaffected LINE-1 activity at both time points (as assessed by multiple unpaired two-tailed *t*-tests followed by the Holm-Sidak method to adjust for the probability of Type I errors in multiple comparisons). The results indicate that LINE-1 activation might be a new factor mediating neurotoxic effects of chronic METH in the striatum and, therefore, a new drug target against METH-induced psychomotor abnormalities in chronic METH users.