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Persistent paradoxical effects on striatal and limbic a-synuclein and tyrosine hydroxylase following methamphetamine withdrawal

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Methamphetamine (METH) produces a variety of epigenetic effects in the brain, which are seminal to establish long-lasting alterations in neuronal activity. A number of studies were carried out aimed at rough assessment of the amount of either histone acetylation and methylation or direct DNA methylation, without a selective analysis of specific genes. In the present study we wish to assess whether METH-induced epigenetic alterations may specifically engage the expression of a-synuclein, which is a key protein in neurodegeneration and synaptic plasticity. In this way, a potential long-term alteration of brain circuitries may produce a variation in the threshold for neurotoxicity, sensitization, addiction and neurodegeneration. Thus, the occurrence of long-term changes in the expression of the protein were analyzed in parallel with persistent changes in a specific marker of integrity of meso-striatal/meso-limbic pathway, which is the expression of tyrosine hydroxylase (TH) both in the mesencephalon and within dorsal striatum. The integrity of dopamine (DA) projection was assessed at the level of the olfactory tubercle, the *nucleus accumbens* and *fundus striati*.

Prolonged exposure to small doses of METH, produces nigro-striatal toxicity, when assessed at short time intervals following prolonged exposure. However, at prolonged time intervals a paradoxical increase progressively occurred in TH immunostaining within limbic regions. Such an increase exceeds at large the amount of TH expressed in controls. This occurs concomitantly with an overexpression of the primary transcript as well as the protein alpha synuclein within the same brain regions and dorsal striatum. This increase is persistent at prolonged time interval of METH withdrawal.

The increase in the primary a-synuclein transcript is due to hypomethylation of specific CPG islands placed in the SNCA gene promoter which ranged roughly ten-fold of controls, it was steady, and it persisted at least 21 days following METH withdrawal. Thus, such an apparent synucleinopathy induced by METH indeed was associated with increased mesolimbic DA innervation, which equally surpasses several folds the amount which was measured in controls and persists at least for three weeks. The increase in SNCA is not associated with an increase of SNCA copy number. Nonetheless, the amount of the native protein, which is detected by ultrastructural stoichiometry, exceeds the increase reported following genetic SNCA multiplications (ten-fold of controls).

These findings are discussed in the light of METH-induced phenotype changes which accompany toxicity, sensitization, addiction and neurodegeneration.

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