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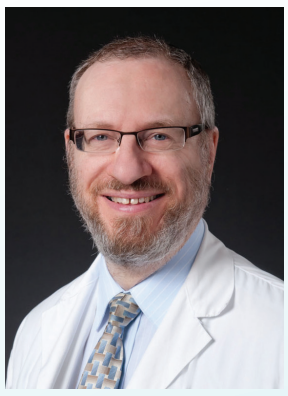
PAPER OF THE MONTH • SEPTEMBER 2012



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The Journal of Neuroscience

Schizophrenia-Like Features in Transgenic Mice Overexpressing Human HO-1 in the Astrocytic Compartment

Wei Song, Hillel Zukor, Shih-Hsiung Lin, Jacob Hascalovici, Adrienne Liberman, Ayda Tavitian, Jeannie Mui, Hojatollah Vali, Xin-Kang Tong, Sanjeev K. Bhardwaj, Lalit K. Srivastava, Edith Hamel, and Hyman M. Schipper

Delineation of key molecules that act epigenetically to transduce diverse stressors into established patterns of disease would facilitate the advent of preventive and disease-modifying therapeutics for a host of neurological disorders. Herein, we demonstrate that selective overexpression of the stress protein heme oxygenase-1 (HO-1) in astrocytes of novel GFAP.HMOX1 transgenic mice results in subcortical oxidative stress and mitochondrial damage/autophagy; diminished neuronal reelin content (males); induction of Nurr1 and Pitx3 with attendant suppression of their targeting miRNAs, 145 and 133b; increased tyrosine hydroxylase and αsynuclein expression with downregulation of the targeting miR-7b of the latter; augmented dopamine and serotonin levels in basal ganglia; reduced D1 receptor binding in nucleus accumbens; axodendritic pathology and altered hippocampal cytoarchitectonics; impaired neurovascular coupling; attenuated prepulse inhibition (males); and hyperkinetic behavior. The GFAP.HMOX1 neurophenotype bears resemblances to human schizophrenia and other neurodevelopmental conditions and implicates glial HO-1 as a prime transducer of inimical (endogenous and environmental) influences on the development of monoaminergic circuitry. Containment of the glial HO-1 response to noxious stimuli at strategic points of the life cycle may afford novel opportunities for the effective management of human neurodevelopmental and neurodegenerative conditions.

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