MPTP-induced deficits in striatal synaptic plasticity are prevented by glial cell line-derived neurotrophic factor expressed via an adeno-associated viral vector

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摘要

Abstract

This study determined the consequences of dopamine denervation of the striatum on synaptic plasticity and prevention of these changes with gene therapy using an adeno-associated viral vector (AAV) expressing glial cell line-derived neurotrophic factor (GDNF). C57BL6/J mice were injected with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP); long-term depression (LTD) or potentiation (LTP) were measured in vitro. Fast-scan cyclic voltammetry measured electrically released dopamine from a functionally relevant pool in these same striatal slices. After MPTP, dopamine release and uptake were greatly diminished, and LTP and LTD were blocked in the striatal slices. The loss of plasticity resulted directly from the loss of dopamine since its application rescued synaptic plasticity. Striatal GDNF expression via AAV, before MPTP, significantly protected against the loss of dopamine and prevented the blockade of corticostriatal LTP. These data demonstrate that dopamine plays a role in supporting several forms of striatal plasticity and that GDNF expression via AAV prevents the loss of dopamine and striatal plasticity caused by MPTP. We propose that impairment of striatal plasticity after dopamine denervation plays a role in the symptomology of Parkinson’ s disease and that AAV expression of neurotrophic factors represents a tenable approach to protecting against or slowing these neurobiological deficits.—Chen, Y-H., Harvey, B. K., Hoffman, A. F., Wang, Y., Chiang, Y-H., Lupica, C. R. MPTP-induced deficits in striatal synaptic plasticity are prevented by glial cell line-derived neurotrophic factor expressed via an adeno-associated viral vector.