Alterations of Postsynaptic Density Proteins in the Hippocampus of Rat OffspringFrom the Morphine-Addicted Mother: Beneficial Effect of Dextromethorphan

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摘要

Abstract

Infants passively exposed to morphine or heroin through their addicted mothers usually develop characteristic withdrawal syndrome of morphine after birth. In such early life, the central nervous system exhibits significant plasticity and can be altered by various prenatal influences, including prenatal morphine exposure. Here we studied the effects of prenatal morphine exposure on postsynaptic density protein 95 (PSD-95), an important cytoskeletal specialization involved in the anchoring of the NMDAR and neuronal nitric oxide synthase (nNOS), of the hippocampal CA1 subregion from young offspring at postnatal day 14 (P14). We also evaluated the therapeutic efficacy of dextromethorphan, a widely used antitussive drug with noncompetitive antagonistic effects on NMDARs, for such offspring. The results revealed that prenatal morphine exposure caused a maximal decrease in PSD-95 expression at P14 followed by an age-dependent improvement. In addition, prenatal morphine exposure reduced not only the expression of nNOS and the phosphorylation of cAMP responsive element-binding protein at serine 133 (CREB(Serine-133)), but also the magnitude of long-term depression (LTD) at P14. Subsequently, the morphine-treated offspring exhibited impaired

performance in long-term learning and memory at later ages (P28-29). Prenatal coadministration of dextromethorphan with morphine during pregnancy and throughout lactation could significantly attenuate the adverse effects as described above. Collectively, the study demonstrates that maternal exposure to morphine decreases the magnitude of PSD-95, nNOS, the phosphorylation of CREB(Serine-133), and LTD expression in hippocampal CA1 subregion of young offspring (e.g., P14). Such alterations within the developing brain may play a role for subsequent neurological impairments (e.g., impaired performance of long-term learning and memory). The results raise a possibility that postsynaptic density proteins could serve an important role, at least in part, for the neurobiological pathogenesis in offspring from the morphine-addicted mother and provide tentative therapeutic strategy.