Long lasting effects of neonatal dexamethasone treatment on spatial learning and hippocampal synaptic plasticity. Involvement of the NMDA receptor complex

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Major concern has emerged about the possible adverse neurodevelopmental effects of neonatal dexamethasone (DEX) treatment of preterm human infants for the prevention of chronic lung disease. In rats, we have shown previously that neonatal treatment with DEX impaired social behavior, immune- and neuroendocrine functioning in adulthood. We also studied the effects of neonatal DEX treatment on spatial leaning and memory, and hippocampal synaptic plasticity at the electrophysiological and molecular levels in adult rats. Spatial learning in reference and working memory versions of the Morris Maze was impaired in DEX treated rats. In hippocampal slices of DEX rats, long-term depression was facilitated and long-term potentiation impaired. Paired pulse facilitation was normal, suggesting a postsynaptic defect as the cause of the learning and plasticity deficits. Western blot analysis of hippocampal post-synaptic densities (PSD) revealed a reduction in NR2B subunit protein, while the abundance of the other major NMDA receptor subunits, AMPA receptor subunits, scaffolding proteins and αCaMKII were not affected. This selective reduction in NR2B likely resulted from altered receptor assembly rather than subunit expression, since the abundance of NR2B in the homogenate and crude synaptosomal fractions was unaltered. In addition, activity of αCaMKII, a protein kinase associated with the NMDA receptor complex, was increased in PSD of DEX rats. The results indicate that neonatal treatment with DEX causes alterations in composition and function of the hippocampal NMDA receptor complex, likely explaining the deficits in synaptic plasticity and spatial learning. Importantly, these adverse effects of DEX treatment on cognition, but also on social behavior and neuroendocrine functioning, were also present in old –16 months of age rats, indicating the adverse effects of neonatal DEX treatment persists throughout he entire life of DEX rats. Clearly, these data warrant investigation of potentially lasting, adverse effects of treatment of premature human neonates with DEX.

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