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SIMVASTATIN AND NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY: EFFECT OF A PROPHYLACTIC AND DELAYED TREATMENT AND INVOLVEMENT OF APOPTOTIC PATHWAYS

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Background and Purpose- Previous studies from this laboratory have shown that a prophylactic administration of simvastatin (Sim) provides protection against brain damage and its long-lasting behavioural consequences in a neonatal model of cerebral ischemia (Balduini et al., 2001). The aim of the present study was two fold: 1) to investigate the effect of Sim administration during and after the ischemic insult, and 2) to gather some information on the mechanism whereby Sim affords neuroprotection.
Methods- On postnatal day (PN) 7 newborn male rats were subjected to legation of the right common carotid artery followed by 3 hours of hypoxia (hypoxia-ischemia, HI), as previously described (Balduini et al., 2000, 2001). The experiment included the following groups of animals: vehicle-treated sham-operated controls, HI damaged animals, and three different groups of animals treated with activated Sim (20 mg/kg) and daily injected from PN1 to PN7 (HI-Sim 1-7), from PN4 to PN11 (HI-Sim 4-11) or from PN7 to PN14 (HI-Sim 7-14). The neuroprotective effect of Sim was evaluated after the rats reached adulthood using a T-maze, a circular water maze and histological analysis. Biochemical experiments were performed in different groups of HI and HI-Sim 1-7 animals. Rats were sacrificed 6 hours, 24 hours, and 5 days after HI and the expression of several apoptotic markers was examined in the cerebral cortex and hippocampus.
Results. HI rats show behavioural asymmetry (Balduini et al., 2000) and when tested in a T-maze preferentially chose the right arm, i.e. the arm ipsilateral to the damaged side (right/left ratio: control 1.29 ± 0.21; HI 4.14 ± 0.69, $P< 0.05$). The right/left ratio of HI-Sim 1-7 and HI-Sim 4-11 animals was significantly lower compared to the ischemic group (1.69 ± 0.39 and 2.11 ± 1.0, respectively; $P < 0.05$) whereas no changes were found for the HI-Sim 7-14 group (2.4 ± 0.95). Learning abilities were tested in a circular water maze using a training-to-criterion test using two different positions of the pedestal. Groups differed significantly in the number of sessions required to find the submerged pedestal in both the first and the second position. However, only HI and HI-Sim 7-14 groups differed significantly from controls. Consistently, it was found that brain damage was significantly attenuated.
In the cerebral cortex, HI itself did not produce any change in expression of Bcl-2 and Bax. Treatment with Sim did not have any effect on Bax but slightly increased Bcl-2 expression. Caspase-3 was significantly increased after HI. In HI-Sim 1-7 animals, however, caspase-3 expression resulted significantly lower compared to HI rats. A similar pattern was observed in the hippocampus.
Conclusions- These findings indicate that prophylactic - but not delayed - administration of Sim improves functional and histological outcomes in a neonatal model of ischemic stroke. The alteration of the expression of proteins involved in the apoptotic process may play a role in the neuroprotective effect of Sim.

References

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