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C095 - Progesterone downscale oxidative stress and boosts antioxidant defense capacity in rat model of permanent common carotid artery occlusion

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Potent neurosteroid progesterone (P₄) strongly influences functional recovery in various models of neurological diseases. However, its protective antioxidative potential is not well established in stance of chronic cerebral hypoperfusion (CCH) that induces ischemic milieu in the brain. CCH results in a cascade of events leading to uncontrolled generation of 4-hydroxynonenal (HNE), a hallmark of oxidative stress that can be abolished by mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD). Post-ischemic brain regeneration requires preservation of cerebral blood flow that could be achieved by production of vasodilator nitric oxide (NO), synthesized by endothelial NO synthase (eNOS) whose actions are regulated by phosphorylation at various sites. Decreased phosphorylation of eNOS at Thr⁴⁹⁵ during antioxidative response, promotes its activity and NO production, contributing to neuroprotection. Given the scarcity of data about P₄ antioxidative actions in prefrontal cortex during CCH, current study assessed the level of HNE and NO, as well as MnSOD activity and the extent of eNOS phosphorylation at Thr⁴⁹⁵ in rats subjected to sham operation and injected with vehicle (commercial flax oil) or animals with permanent occlusion of common carotid arteries and treated either with vehicle or P₄ (1.7 mg/kg/day) for 7 days. Results indicate that P₄ decreases CCH-induced HNE generation and MnSOD activity, diminishes inactivation of eNOS and increases production of protective NO. In conclusion, P₄ might downscale oxidative stress and boost antioxidant defense capacity in CCH model, pointing investigated parameters as potential targets of P₄ neuroprotective actions. Financially supported by MNTPR RS, grants 173044 and 41014.