New horizons for newborn brain protection: boosting endogenous neuroprotective mechanisms after neonatal asphyxia

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Perinatal hypoxia-ischemia (HI) affects infant brain development, leading to various severe disorders that can be manifested long after the HI episode. Although the brain can partially compensate for injury, there are still no clinical therapies or drugs specifically designed to boost the self-repair processes. Currently, the standard of care in neonates with hypoxic–ischemic encephalopathy, is therapeutic hypothermia (TH) . Our previous research showed that body temperature during hypoxia affects oxidative stress, antioxidant protection, and the activation of adaptive systems in the brain. Although TH is clearly beneficial in preventing death, it does not provide complete neuroprotection. Current cooling protocols are near optimal, but still the new therapies to support TH are needed to improve long-term outcomes. One promising agent is cannabidiol (CBD), the main non-psychoactive component of *Cannabis sativa*. CBD has a broad spectrum of therapeutic properties, including neuroprotective effects, by attenuating oxidative stress, excitotoxicity, and inflammation - the "deadly triad" which leads to hypoxia-induced brain damage. Recently we found that CBD has strong neuroprotective effects in neonatal mice following global hypoxia. It prevented antioxidant depletion and reduced lipid peroxidation. For the first time, we also demonstrated that CBD upregulated the concentration of hypoxia-inducible factor-1 alpha (HIF-1α), which plays a key role in regulating cellular adaptation to hypoxia and oxidative stress. Our preliminary research also showed that CBD affects the expression of neurogenesis markers, including brain-derived neurotrophic factor (BDNF). Both, BDNF signaling and cannabinoid systems play crucial regulatory roles in neurogenesis under pathological conditions. Understanding the interaction between these two system will contribute to the development of new therapeutic strategies for brain repair and regeneration after HI. Cannabinoid-based therapy may constitute a novel therapeutic strategy for the brain repair.