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Cold Atmospheric Plasma in the Realm of Neuroscience and Regenerative Medicine: Analyzing the Role of Reactive Oxygen and Nitrogen Species and Molecular Signaling Pathways in Neural Differentiation, Proliferation, and Neuroprotection

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ABSTRACT

Introduction: Cold atmospheric plasma (CAP), a novel physicochemical source generated at atmospheric pressure, is fundamental to regenerative medicine due to its capacity to control neural stem cell (NSC) fate. This review analyzes CAP's influence on neural differentiation, proliferation, and protection, fundamentally mediated by reactive oxygen and nitrogen species.

Materials and Methods: This review synthesizes findings from in vitro (e.g., N2a cells) and in vivo (e.g., Tg(Huc:GFP) zebrafish embryos, rat SCI) models. The core mechanism involves a precise physicochemical-to-biological cascade. CAP produces extracellular nitric oxide, which acts as an upstream messenger, targeting mitochondria, leading to the production of $\cdot O_2-$. This radical converts to cytosolic H_2O_2, which selectively activates the Trk/Ras/ERK signaling pathway, critical for neural differentiation.

Results and Discussion: CAP induces selective neuronal differentiation of NSCs with high efficiency (~75%). It promotes neuronal proliferation and axonal elongation in SH-SY5Y cells, partly through increased expression of tau and activation of the Wnt3a/*ß*-catenin pathway. In neuroprotection, CAP mitigates cellular damage from hypoxia/ischemia and glutamate excitotoxicity by enhancing cellular antioxidant defenses (e.g., Nrf2). In vivo studies confirm CAP reduces neuronal apoptosis and key inflammatory cytokines (TNF-*α*/IL-1*ß*) after SCI.

Conclusion: CAP is a promising, dose-dependent therapeutic strategy, governed by the hermetic effect. Precise calibration of plasma parameters is essential for successful clinical translation.

Keywords: Cold atmospheric plasma, Neural stem cells, Nitric oxide, Reactive oxygen and nitrogen species

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