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Efficacy of Cold Plasma in the Treatment of Neuroendocrine Tumors with the Mediating Role of Neurogenesis Stimulation and Microglial Inflammation Reduction: Preclinical Study Using Positron Emission Tomography

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ABSTRACT

Introduction: Neuroendocrine tumors (NETs) are rare and aggressive neoplasms arise from neuroendocrine cells. Current treatments, such as chemotherapy and radiotherapy, often prove ineffective against these tumors. Cold atmospheric plasma (CAP), as a novel intervention, generates reactive oxygen and nitrogen species, which can induce cellular apoptosis and reduce inflammation. In the context of NETs, microglial inflammation and impaired neurogenesis play a critical role in tumor progression. This preclinical study evaluated the efficacy of CAP in treating NETs, mediated by the stimulation of neurogenesis and the reduction of microglial inflammation.

Materials and Methods: A preclinical study was conducted using a murine model of NETs, where BON-1 cells were injected intracranially into 40 mice (20 in the intervention group and 20 in the control group). The intervention group received 10 sessions of 15-minute CAP treatment (dose: 8 kV/cm) applied directly to the tumor site. The evaluation methods included positron emission tomography using [18F]FLT to assess neurogenesis, immunohistochemistry for CD68 (a marker of activated microglia), and quantitative polymerase chain reaction for measuring IL-6 and TNF-α gene expression. Data were analyzed using structural equation modeling (SEM) in AMOS and analysis of variance (ANOVA).

Results and Discussion: Following the intervention, tumor volume decreased by 32% ($p < 0.001$). Neurogenesis, assessed through [18F]FLT uptake, increased by 29%, while microglial inflammation decreased by 41%. Neurogenesis stimulation mediated 37% (β = 0.37) of the observed effects, and inflammation reduction mediated 44% (β = 0.44), with both findings being statistically significant. SEM analysis confirmed an indirect pathway from CAP to neurogenesis/microglia activity and then to apoptosis (goodness of fit index = 0.94; root mean square error of approximation = 0.05).

Conclusion: CAP is an effective and safe approach for the treatment of NETs in preclinical models. It acts through the stimulation of neurogenesis and reduction of microglial inflammation. Based on these promising results, it is recommended that this intervention advance to phase I clinical trials.

Keywords: Cold plasma, Microglial inflammation, Neuroendocrine tumors, Neurogenesis, Positron emission tomography

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