Mapping Hypothalamic Glial Responses in Chronic Hypoxia-Induced Pulmonary Hypertension: The Arcuate Nucleus

Background: Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure and right ventricular failure, with high mortality and limited therapeutic options. Sympathetic nervous system overactivity is present in PH and is associated with disease severity and adverse clinical outcomes.[1] Our group has previously shown that neuroinflammation in the paraventricular nucleus of the hypothalamus (PVN) is associated with sustained increases in sympathetic drive in PH.[2] The hypothalamic arcuate nucleus (ArcN) provides afferent input to the PVN and contributes to autonomic regulation.[3] Preliminary data from our group indicate that presynaptic markers of inhibitory synapses are not different between control and hypoxic conditions. However, the effects of PH on neuroinflammatory responses within the ArcN remain poorly understood. Because the ArcN is exposed to circulating factors through its proximity to the median eminence, we hypothesized that chronic hypoxia-induced PH increases microglial and astrocytic activation within the ArcN.

Methods: C57BL/6 wild type mice (WT) were exposed to normoxic conditions (n = 5) or chronic hypoxia (10% O_2; n = 6) to induce PH. Brain sections containing the ArcN were immunostained for ionized calcium-binding adaptor molecule 1 (Iba1) and glial fibrillary acidic protein (GFAP) to assess microglial and astrocytic responses, respectively. Fluorescence microscopy was used to image the ArcN, and integrated fluorescence density was quantified for Iba1 and GFAP immunoreactivity. Glial fluorescence intensity was compared between normoxic and hypoxic groups and evaluated in relation to right ventricular systolic pressure (RVSP).

Results: Preliminary analyses revealed no statistically significant differences in ArcN Iba1 or GFAP integrated fluorescence density between normoxic and hypoxic animals. Both markers demonstrated modest increases in mean fluorescence density in hypoxic animals, although substantial inter-animal variability was observed. Associations between RVSP and Iba1 or GFAP fluorescence density were weak and did not demonstrate significant relationships. Additional experiments and analyses are ongoing to further characterize cellular responses and synaptic density within the ArcN during chronic hypoxia-induced PH.

Conclusions: These preliminary findings indicate no significant changes in microglial or astrocytic immunoreactivity within the ArcN following chronic hypoxia despite development of PH. Further investigation is needed to determine whether chronic hypoxia-induced PH produces more selective cellular or regional alterations within the ArcN and to clarify the potential contribution of this hypothalamic region to altered autonomic regulation in PH.

References

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