

An Original and Suitable Induction Method of Repeated Hypoxic Stress by Hydralazine to Investigate the Integrity of an in Vitro Contact Co-Culture Blood Brain Barrier Model

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Abstract : Several neurological disorders are linked to repeated hypoxia. The impact of such repeated hypoxic stress, on endothelial cells function of the blood-brain barrier (BBB) is little studied in the literature. Indeed, the study of hypoxic stress in cellular pathways is complex using hypoxia exposure because HIF 1 α (factor induced by hypoxia) has a short half life. Our study presents an innovative induction method of repeated hypoxic stress, more reproducible, which allows us to study its impacts on an in vitro contact co-culture BBB model. Repeated hypoxic stress was induced by hydralazine (a mimetic agent of hypoxia pathway) during two hours and repeated during 24 hours. Then, BBB integrity was assessed by permeability measurements (transendothelial electrical resistance and membrane permeability), tight junction protein expressions (cell-ELISA and confocal microscopy) and by studying expression and activity of efflux transporters. First, this study showed that repeated hypoxic stress leads to a BBB's dysfunction illustrated by a significant increase in permeability. This loss of membrane integrity was linked to a significant decrease of tight junctions' protein expressions, facilitating a possible transfer of potential cytotoxic compounds in the brain. Secondly, we demonstrated that brain microvascular endothelial cells had set-up defence mechanism. These endothelial cells significantly increased the activity of their efflux transporters which was associated with a significant increase in their expression. In conclusion, repeated hypoxic stress lead to a loss of BBB integrity with a decrease of tight junction proteins. In contrast, endothelial cells increased the expression of their efflux transporters to fight against cytotoxic compounds brain crossing. Unfortunately, enhanced efflux activity could also lead to reducing pharmacological drugs delivering to the brain in such hypoxic conditions.

Keywords : BBB model, efflux transporters, repeated hypoxic stress, tight junction proteins

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