A molecular investigation into the mechanisms of ischaemia-mediated breakdown of human blood-brain barrier

Disruption of blood-brain barrier (BBB) during cerebral ischaemia leads to the formation of brain oedema, with underlying mechanisms remain largely unknown. We hypothesise that the excessive release of inflammatory cytokines IL-1β and TNF-α during an ischaemic injury may impair the BBB function through a chain of interrelated mechanisms initiated by overproduction of reactive oxygen species (ROS) in brain microvascular endothelial cells (BMEC) via pro-oxidant enzyme NADPH oxidase. ROS then not only promote apoptosis of the main cellular components of the neurovascular unit i.e. BMEC, astrocytes and pericytes but also phosphorylates myosin light chain (MLC) to promote cytoskeletal reorganisation and paracellular leakage. Ischaemia-mediated activation of matrix metalloproteinases (MMPs) may also add to barrier damage via dissolution of the BBB basement membrane. The validity of these hypotheses will be tested using a sophisticated *in vitro* model of BBB consisting of human BMEC, astrocytes and pericytes. The findings generated will provide a better understanding for the ischaemia-induced BBB damage and pave the way for future collaborative studies aiming to test the therapeutic capacity of the most prominent mechanisms to emerge in preventing and/or reversing brain oedema that develop subsequent to ischaemic strokes.

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Fee band: High cost laboratory-based research

Project availability: International students only