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MEETING ABSTRACT

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Claudins and claudin mimetics: tight junction proteins in normal and ischemic blood–brain barrier

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The blood–brain barrier (BBB) limits drug delivery to the brain. BBB's role in stroke and BBB modulation are not understood. The BBB-forming endothelium, paracellularly sealed by tight junction (TJ) proteins, ensures brain homeostasis and metabolite exchange. As far as known, claudin-5 (Cldn5) dominates the TJs and the paracellular tightening of the BBB. Contribution of other TJ proteins is unclear. We therefore elucidated the structure and function of TJs upon stroke and administration of claudin mimetics. Mice were analysed for BBB permeability (small/large molecules), expression (mRNA/protein) and morphology of the TJs *in vitro* after hypoxia (cell models, capillaries) and *in vivo* without and after transient middle cerebral artery occludion (MRI, electron microscopy, immunohistochemistry, BBB opening, infarct/oedema area). To manipulate cerebral TJs, claudin mimetics (peptides, small molecules) were designed/screened. We discovered that Cldn3 tightened the BBB for small molecules, limited endothelial endocytosis and transcytosis of proteins, complemented TJ morphology, prevented inflammatory processes, and regulated TJ proteins (Cldn1, Cldn5, occludin). Acute hypoxia of isolated mouse brain capillaries did not affect the BBB-specific TJ marker Cldn5 in presence of Cldn3. In Cldn3 deficiency, Cldn5 declined at the TJs. In postischemic infarction, Cldn3 accounted for increased infarct volume due to increased swelling of the affected brain. The claudin modulators increased permeability through cell-culture models of cerebral barriers (bEnd, MDCK-Cldn5) and through the BBB of intact mice. Cldns 5, 3 and 1 contribute to the intactness of the BBB under physiological and pathological conditions, protect the BBB in stroke but prevent detumescence of the injured area, hence worsening infarct outcome. Thus, modulation of Cldns paracellularly tightening the BBB might help to improve stroke recovery as well as cerebral drug delivery.

Keywords: blood–brain barrier – cell contacts – tight junction proteins – drug delivery – stroke

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