Abstract


BACKGROUND AND PURPOSE

The blood-brain barrier (BBB) restricts drug penetration to the brain preventing effective treatment of patients suffering from brain tumours. Intra-arterial injection of short-chain alkylglycerols (AGs) opens the BBB and increases delivery of molecules to rodent brain parenchyma in vivo. The mechanism underlying AG-mediated modification of BBB permeability is still unknown.

Here, we have tested the effects of AGs on barrier properties of cultured brain microvascular endothelial cells.

EXPERIMENTAL APPROACH

The effects of two AGs, 1-O-pentylglycerol and 2-O-hexyl diglycerol were examined using an in vitro BBB model consisting of primary cultures of rat brain endothelial cells, co-cultured with rat cerebral glial cells. Integrity of the paracellular, tight junction-based, permeation route was analysed by functional assays, immunostaining for junctional proteins, freeze-fracture electron microscopy, and analysis of claudin-claudin trans-interactions.

KEY RESULTS

AG treatment (5 min) reversibly reduced transendothelial electrical resistance and increased BBB permeability for fluorescein accompanied by changes in cell morphology and immunostaining for claudin-5 and β-catenin. These short-term changes were not accompanied by alterations of inter-endothelial tight junction strand complexity or the trans-interaction of claudin-5.

CONCLUSION AND IMPLICATIONS

AG-mediated increase in brain endothelial paracellular permeability was short, reversible and did not affect tight junction strand complexity. Redistribution of junctional proteins and alterations in the cell shape indicate the involvement of the cytoskeleton in the action of AGs. These data confirm the results from in vivo studies in rodents characterizing AGs as adjuvants that transiently open the BBB.