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Blood-brain barrier changes in pancreatitis: an electon microscopic study

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The blood-brain barrier (BBB) composed by capillary endothelial cells, pericytes and astrocytes is crucial for the proper working of the central nervous system. The BBB regulates the brain microenvironment, supplies brain cells with nutrients and protects them from toxic materials in the blood. Several diseases, including bacterial and virus infections neurodegenerative diseases and inflammations of different origin can result in lesion of BBB and relatively small changes in its functions may lead to serious neuronal dysfunctions. Acute necrotising pancreatitis may lead to pancreatic encephalopathy. Previous work from our teams demonstrated an elevated BBB permeability in parallel with increased blood cytokine levels in taurocholate induced pancreatitis in rats [1]. A new non-invasive rat pancreatitis model was recently developed and characterised by intraperitoneal injection of the cationic amino acid L-ornithine at the dose of 3 g/kg body weight [2]. Using this in vivo model and our triple co-culture model of the BBB [3] functional and morphological changes were examined. Electron microscopy was used to monitor ultrastructural changes in the cells forming the BBB following L-ornithine treatment.

In the permeability experiments an elevated extravasation of the marker molecules to the brain was determined in rats with pancreatitis. Fragmented glycocalyx, plasma and basal membrane, serious oedema of endothelial cells and glial endfeet, mitochondrial damage and increased number of vesicular elements were observed. Interendothelial tight junctions (TJ) were loosened. Alcian blue used for indication of intact EC function and staining of glycocalyx were found in transcellular vesicles and on /in TJs after 24 h in ornithine-induced pancreatitis (Figure 1), and the dye was also observed in the brain parenchyma.

In case of BBB culture model, the effect of L-ornithine also manifested in increased permeability and decreased resistance and in similar morphological changes as observed in vivo. Deformities of ECs were more profound, including the fragmentation of glycocalyx, spectacularly increased number of caveolae and caveolae-like structures, irregular and open interendothelial junctions and high number of apoptotic bodies (Figure 2).

In conclusion, increased BBB permeability could be observed by both functional and morphological methods in L-ornithine induced pancreatitis in rats, which was at least partially mediated by a direct effect of L-ornithine on brain endothelial cells, as demonstrated by the results obtained on the culture model.

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4. We kindly acknowledge the excellent technical assistence of Győző Goda.

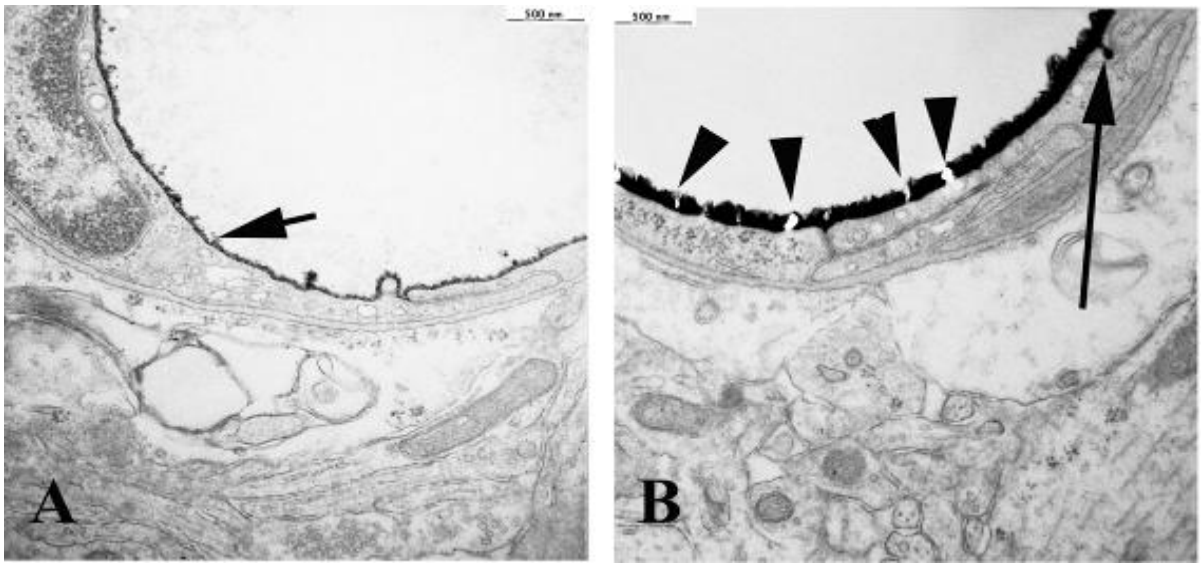

Figure 1. Continuous alcian blue deposit (arrow) covers the luminal plasma membrane of brain capillary endothelial cell in control rat (A). Fragmented glycocalyx (arrowheads) of plasma membrane, caveolae filled with the deposit (arrow) show morphological changes in the endothelial cell of L-ornithine treated (B) rat.

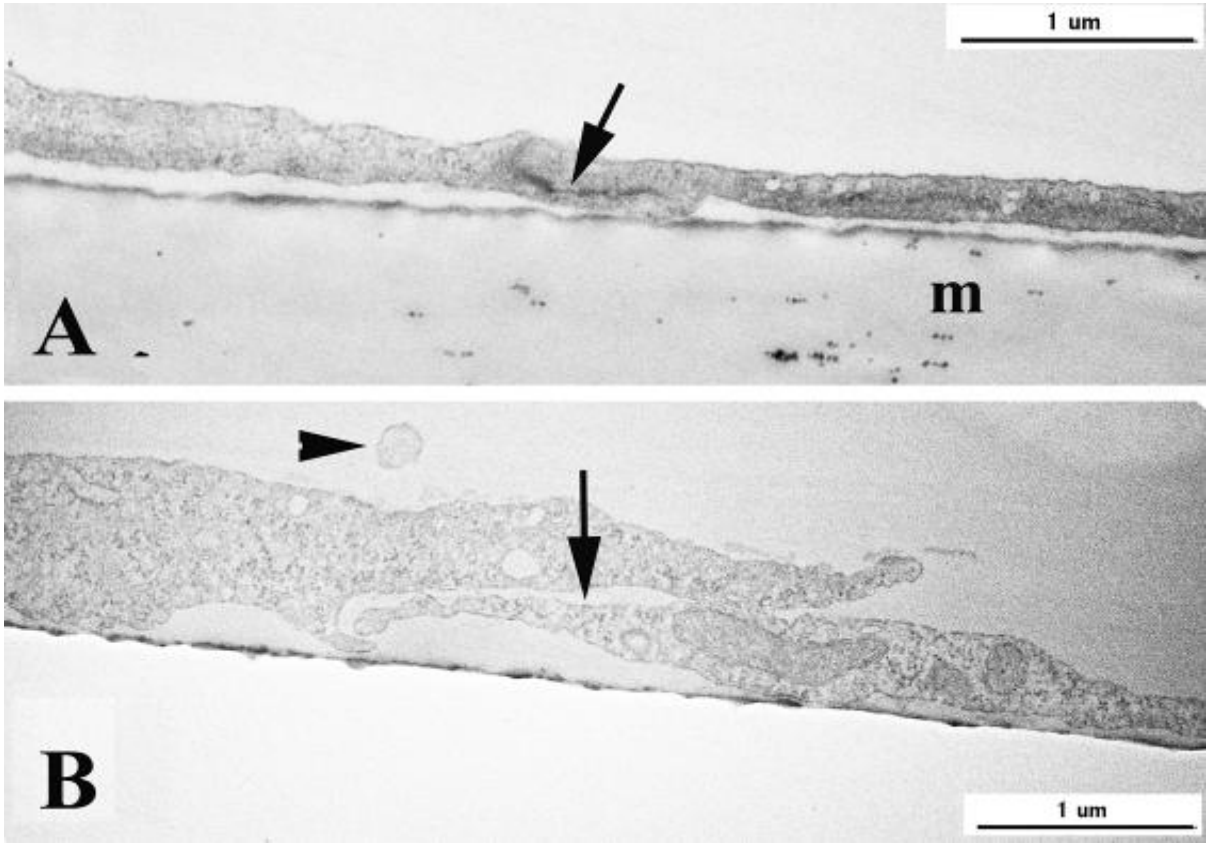

Figure 2. Cultured endothelial cells on plastic membrane (m) show typical tight junction (arrow) in control case, and loosened, almost open interendothelial junction, released vesicle and damaged morphology due to L-ornithine treatment.