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Cadmium-induced neurotoxicity: impairment of the blood brain barrier

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Cadmium (Cd), an ubiquitous heavy metal, known to be accumulated outside of the blood–brain barrier (1) and to cause neurotoxicity, has also been demonstrated to induce an increase in the blood–brain barrier (BBB) permeability (2). Key components of BBB integrity are primarily the tight junctions (TJs) between adjacent brain microvascular endothelial cells that confers low paracellular permeability, making the barrier to function (3). Cd-dependent BBB alterations are elicited by a caspase-3 activation-dependent pathway (4) that triggers the irreversible open of pannexin-1 (panx-1) (5), a large transmembrane channel that allows an ATP massive spillage (6), imparing the neurovascular unit (NVU) homeostasis (7). In this study, we investigated the Cd cytotoxicity in a rat brain endothelial cell line (RBE4). Results from the cell viability assay showed that Cd caused a remarkable decrease in cell viability in a dose-dependent manner. 10 μM Cd induced caspase 3 activation and an increment in extracellular ATP concentration, indicative for a panx-1 involvement. The increase of BBB permeability was evaluated analyzing zonula occludens-1 (ZO-1) expression levels and its subcellular dislocation. ZO-1 is a protein localized on the plasma membrane in areas of cell-cell contact that acts as a crucial central regulator of the structural organization of the TJs (8). The presence of Cd 10 μM caused a significative reduction of ZO-1 expression levels (as determined by western blot technique) and an altered distribution of this protein (analyzed by immunofluorescence) that appears patchy or faded away from membrane areas. Summarizing, these data offer an initial image of the NVU homeostasis impairment induced by Cd, suggesting Panx-1 as a novel target to counteract its neurotoxicity.

References

[1] Arvidson and Tjalve (1986) Distribution of 109Cd in the nervous system of rats after intravenous injection. Acta Neuropathol 69: 111.
[2] Petty and Lo (2002) Junctional complexes of the blood-brain barrier: permeability changes in neuroinflammation. Prog Neurobiol 68: 311.
[3] Romero (2003) Changes in cytoskeletal and tight junctional proteins correlate with decreased permeability induced by dexamethasone in cultured rat brain endothelial cells. Neurosci Lett 344: 112.
[4] Jung (2007) Cadmium induces apoptotic cell death through p38 MAPK in brain microvessel endothelial cells. Eur J Pharmacol 578: 11.
[5] Engelhardt (2015) Effects on channel properties and induction of cell death induced by c-terminal truncations of pannexin1 depend on domain length. J Membr Biol 248: 285.
[6] Bao (2004) Pannexin membrane channels are mechanosensitive conduits for ATP. FEBS Lett 572: 65.
[7] Kaneko (2015) Contribution of pannexin 1 and connexin 43 hemichannels to extracellular calcium-dependent transport dynamics in human blood-brain barrier endothelial cells. J Pharmacol Exp Ther 353: 192.
[8] Fanning (1998) The tight junction protein ZO-1 establishes a link between the transmembrane protein occludin and the actin cytoskeleton. J Biol Chem 273: 29745.

Keywords

Cadmium; BBB permeability; pannexin-1.