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Neurovascular unit breakdown in EAE cerebral cortex

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Experimental autoimmune encephalomyelitis (EAE) is an experimental induced autoimmune disease of the central nervous system (CNS) that mimics the main histopathological and clinical aspects of multiple sclerosis (MS), as the breakdown of the brain neurovascular unit (NVU) barrier. Although transendothelial migration of activated leucocytes and release of inflammatory cytokines/chemokines are believed to represent the onset of the blood-brain barrier (BBB) breakdown in MS, a definitive comprehension of mechanisms leading to NVU/BBB injury is lacking. Histopathological studies have shown that vascular changes take place not only within MS lesions but also in normal appearing white matter (WM), and that BBB dysfunction may precede leukocyte infiltration. Moreover, there are evidences that intracortical MS lesions are not associated with leucocyte infiltration. On the basis of these data, we analysed the expression of markers of NVU cell (endothelial cells, pericytes, perivascular glial cells) and basal lamina (claudin-5, caveolin-1, type IV collagen) as well as of leucocytes (CD45) in cerebral cortex and subcortical white matter of EAE and control mice, by immunofluorescence confocal microscopy. EAE was induced by immunization with $MOG_{35–55}$ supplemented with Mycobacterium tuberculosis and pertussis toxin. The results demonstrated numerous monocytes/macrophages in leptomeningeal tissue, Virchow-Robin spaces and WM; the amount of perivascular monocytes/macrophages was lesser in the cortex layers. The cortical vessels showed a decreased expression and an altered distribution of the junctional protein claudin-5: the endothelial cell contacts appeared thinner, and frequently the junction linear tracts were discontinuous or formed by rows of puncta; in some microvessels the claudin-5 immunoreactivity was punctuated and diffused throughout in the endothelial cytoplasms. The EAE brain endothelial cells showed an increment of caveolin-1 immunoreactivity compared with healthy samples. These results indicate that NVU/BBB is modified in EAE brain and that the changes are, at least in part, unrelated to inflammation and demyelinated lesions.