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Tight junctions of the blood-brain barrier: composition and regulation in health and disease

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Tight junctions are the structure responsible for the restriction of paracellular permeability and the resistance of the blood-brain barrier endothelial cells. Those tight junctions are composed of transmembrane proteins such as occludin, the claudins and JAM and ESAM and cytoplasmic proteins like zonula occludens proteins, cingulin and 7H6. Tight junctions are very dynamic structures. Several signaling pathways like G-proteins, kinases, calcium and cAMP levels as well as proteases and cytokines have been found to modulate the tightness of the enothelial barrier cells. Endothelial blood-brain barrier tight junctions differ from epithelial tight junctions by their distinctive morphology and molecular properties and in particular regarding their sensitivity to microenvironmental changes during either development and adulthood. Astrocytes are believed to be a prerequisite for barrier formation within the brain capillary endothelial cells during developoment; however, the mechanism of glio-vascular signaling is completely unknown so far. There is growing evidence that also a specific composition of the vascular basement membrane is important for the maintenance of the blood-brain barrier integrity. Especially the heparan sulfate proteoglycan agrin seems to play an important role in this regard as it has been shown in studies describing blood-brain barrier development and pathological conditions with a disturbed blood-brain barrier like brain tumors and Alzheimer's disease. In other pathological conditions like hypertension the signaling at the blood-brain barrier seems to be disturbed as it seems also to be the case in multiple sclerosis. This disturbed signaling leads in the case of hypertension to an increased vulnerability of the blood-brain barrier towards insults and in multiple sclerosis to leukocyte extravasation.