7 Abstract

The present study comprised the analysis of blood-brain barrier capillary gene expression profiles of 13 weeks old SHRSP and SHR. The aim of this study was to identify disturbed signal transduction pathways and genes that showed an altered expression pattern prior to the onset of neurological symptoms, and that may be involved in the pathogenesis of stroke in the SHRSP.

A total of eight cDNAs were isolated and shown to have a differential expression pattern in the blood-brain barrier of SHRSP and SHR.

Two of the cDNAs that were expressed stronger in the SHRSP (BM247 and BM259) did not show any homology to known genes in public databases. BM247 carries a FCH-domaine and could be involved in the rearrangement of the actin cytoskeleton. Since alterations of the cytoskeleton influence the integrity and permeability of the *tight junctions* BM247 could be responsible for the observed morphological alterations of the *tight junctions* in SHRSP.

The second unknown clone, BM259, does not show any known features that could provide more detailed information about the possible function of the protein.

The clone BM269, which was also more strongly expressed in the SHRSP, could be identified as the sulfonylurea receptor SUR2B and represents the regulatory subunit of ATP-sensitive potassium channels. In how far the increased expression of the SUR2B transcript is connected to the altered potassium metabolism in these animals remains to be tested.

Cystatin-ß, Ubiquitin B and Galectin-9 also showed an increased expression in the SHRSP. All three genes play a role in intracellular protein degradation. Although a higher lysosomal activity after the onset of stroke in the SHRSP is reported there exist no findings whether lysosomal processes are increased before the onset of stroke in these animals.

Cyclophilin A belongs to the family of immunophilins and represents the receptor for the immune suppressor cyclosporine. Moreover, CyPA is involved in the peroxide metabolism of the cell. Increased concentrations of peroxide in the capillaries of SHRSP could be responsible for the altered expression of CyPA in these animals.

RGS5 is involved in the regulation of G-protein mediated signal processes and represents the only gene downregulated in the SHRSP. In the brain RGS5 is expressed predominantly in the endothelial cells of the blood-brain barrier capillaries and in the fenestrated endothelial cells of the choroid plexus. The expression of RGS5 is influenced by the specific activity of PTX-sensitive heterotrimeric G-proteins. Furthermore, PKC and the renin-angiotensin-system are also involved in the regulation of the RGS5 expression. Investigations with a

RGS5-GFP fusion construct showed a cytoplasmic and nuclear distribution pattern of RGS5 in human endothelial cells. After stimulation of the cells with cAMP a translocation of the fusion protein to the membrane and into the nucleus could be observed. Since cAMP increases the integrity of the barrier and therefore the permeability of endothelial cells these findings may suggest, that RGS5 interacts with *tight junction* associated proteins.