

Neuroscience Colloquium 2007/08

Location: Virchow-Lecture-Room, Anatomy, CCM **Date:** Tuesday, 6:15 p.m.

13 November 2007

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"Blood brain barrier injury in neuroinflammation: Molecular mechanisms and therapeutic interventions"

The blood-brain barrier (BBB) is the specialized system of brain microvascular endothelial cells (BMVEC) that shields the brain from toxic substances in the blood, supplies brain tissues with the nutrients and filters harmful compounds from the brain back to the bloodstream. The close interaction between BMVEC and other components of the neurovascular unit (astrocytes, pericytes, neurons and basement membrane) ensures proper function of the central nervous system (CNS). Transport across the BBB is strictly limited through both physical (tight junctions, TJ) and metabolic barriers (enzymes, diverse transport systems). Neuroinflammation (like multiple sclerosis and HIV-1 encephalitis, HIVE) results in BBB injury (down regulation of transport systems and TJ disruption). Brain tissues of patients affected by HIVE demonstrate infiltration of monocytes and diminished TJ expression on BMVEC. Our previous work indicated that activation of small dimeric G-proteins (Rho GTPases, such as RhoA and Rac1) played a central role in alterations of BMVEC TJ in HIVE. RhoA inhibition prevented migration of HIV-1 infected monocytes, TJ changes and diminished permeability of the BBB. We identified soluble factors that disrupt the barrier and increased monocyte migration across the BBB. Secretion of these factors by HIV-1 infected/activated macrophages on the brain side of the barrier could explain widespread BBB injury seen in the areas devoid of monocyte infiltration. Thus, pro-inflammatory molecules secreted by HIV-1 infected/activated macrophages and BMVEC-monocyte interactions and are two major factors contributing to BBB abnormalities. In order to prevent BBB injury, we identified several intracellular signaling pathways including peroxisome proliferator-activated receptor gamma (PPAR γ) and glycogen synthase kinase (GSK)-3 β . Our recent findings indicated that **PPAR γ stimulation** and **GSK-3 β inhibition** prevented activation of Rho GTPases in BMVEC and monocytes, decreased monocyte migration through the BBB, preserve TJ integrity and production of inflammatory molecules by activated macrophages maintaining BBB structural integrity. *In vitro* findings were confirmed in animal model for HIVE. Currently, we analyze effects of neuroinflammation on BBB transporter systems.

Organized by the Neuroscience Research Center (NWFZ) – Dietmar Schmitz
With support from

SFB 665 "Developmental Disturbances in the Nervous System" ,

GRK 1258/1 "The Impact of Inflammation on Nervous System Function" &

GRK 1123 "Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation"