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Arteriogenesis in the rat brain: Development and characterization of a stroke model and investigation of granulocyte-macrophage colony-stimulating factor induced arteriogenesis

In Germany stroke is one of the most often causes of death. Therapy of stroke is carried out mainly symptomatic as treatment with antithrombotic medicaments often causes bleedings. Surgical methods such as carotid endarterectomy or percutaneous transluminal balloon angioplasty are very complex and include some certain risks.
Therapeutic accelerated arteriogenesis provides a prophylactic treatment of stroke. In the model of three-vessel occlusion (3-VO) arteriogenesis, the fast adaptive growth of pre-exisisting collateral arteries, in the brain was investigated. By occlusion of one carotid and both vertebral arteries blood flow is redistributed through the posterior cerebral artery that grows about 39 % in diameter within one week. By the stimulating treatment with granulocyte-macrophage colony-stimulating factor (GM-CSF) the growth within one week is accelerated to 72 %. Moreover cerebrovascular reactivity which is nearly completely suppressed immediately after 3-VO recovers to 97 %.

The work shows the development of an animal model of hemodynamic stroke on basis of a persisting 3-VO. In that model the arteriogenic influence of GM-CSF on hemodynamic stroke should be investigated.

For developing an animal model of hemodynamic stroke blood pressure was lowered by bleeding down to 50 - 20 mmHg for 15 - 30 minutes one week after 3-VO. The threshold value for evoking an ipsilateral ATP deficit measured by ATP specific bioluminescence was hypotension of 20 mmHg for 15 minutes. In that model rats treated with GM-CSF ($40\mu g \cdot kg^{-1} \cdot d^{-1}$) were compared with rats treated with Ringer's solution. By one week treatment with GM-CSF infarct volume defined as cerebral decline of ATP below $0.5\mu Mol \cdot g^{-1}$ significantly decreased from 48.8 ± 44.2 % to 15.8 ± 17.4 % ($p < 0.05$). Autoradiographically measured ipsilateral cerebral blood flow (CBF) in cortex supplied by the middle and posterior cerebral arteries, caudate-putamen and hippocampus in rats treated with Ringer's solution was significant lower than in rats without hypotension. By treatment with GM-CSF a strong decline of CBF during hypotension compared to GM-CSF treated rats without hypotension was prevented. The positive effect of GM-CSF treatment on the metabolic situation and CBF during hypotension is attributed to accelerated arteriogenesis with fast recovery of cerebrovascular reactivity.

The developed model reflects the situation in patients with arterial stenosis under sudden decline of blood pressure, such as during the early morning. Transferred to clinic the showed pro-arteriogenic treatment of hemodynamic stroke with GM-CSF may be a new concept of prophylactic treatment of patients with high risk to suffer from stroke.