Summary

Aneurismal subarachnoid hemorrhage (SAK) is a cerebrovascular accident with high mortality. It carries both short and long term consequences. Mechanisms of neurologic damage after SAK include intracranial hypertension, early and delayed brain vasoconstriction, as well as inflammatory response are involved. Vasoconstriction is a crucial phenomenon in both early and delayed phases and nitric oxide (NO) plays the key role.

Aim of the study was to test following hypotheses in animal model: 1. Subarachnoid hemorrhage causes decrease of brain perfusion by mechanism of intracranial hypertension and early vasoconstriction, 2. Both administration of vasodilator – NO donor, and elimination of intracranial hypertension can reverse the early hypoperfusion, 3. SAH leads to generation of free radicals, 4. Administration of antioxidant (melatonin) can attenuate the free radical damage.

Methods: Adult male Wistar rats were used for the experiments. SAH was induced by injection of arterial blood into prechiasmatic cistern. Perfusion of brain cortex was measured by Laser Speckle Contrast Analysis (LASCA).

In the first experiment, SAH was induced and sodium nitroprusside (SNP, 10 μg / 5 μl) was administered into the lateral ventricle in 2 phases according to the dynamics of perfusion changes: (1) all animals received SNP 3 mins after SAH induction, (2) after reaching plateau of perfusion, in occurrence of "peak – plateau" pattern. Control animals received only vehicle (V) of SNP.

In the second experiment, we tested the effect of decompressive craniectomy (DC) on perfusion, in order to distinguish between the influence of intracranial hypertension and vasoconstriction on the early hypoperfusion after SAH. The animals underwent extensive bilateral fronto-temporo-parietal craniectomy and durotomy. Cerebral vascular resistance (CPP divided by change of brain perfusion in per cent of baseline values, R = CPP / Δ perfusion) was counted as a measure of cerebral vasoconstriction.

In the third experiment, we measured levels of free radicals in both SAH and sham groups using the EPR/ESR method. Then we evaluated the effect of melatonin on long-time neurologic deficit. Melatonin (100 mg / kg *i.p.*) was administered 1 hour before SAH induction or sham procedure. Neurologic deficit was evaluated by behavioral tests. At the end, a blinded evaluator counted the number of dead neurons in slices of hippocampal hilus.

Results: Approximately one half of SNP-treated animals developed serious systemic hypotension and significant decrease of brain perfusion; perfusion in the other animals did not differ from control group. Second dose of SNP slightly increased the brain perfusion; nevertheless, this increase was insignificant compared to animals without pharmacointervention.

Despite DC significantly decreased ICP and reduced immediate mortality, it did not improve the early hypoperfusion after SAH. DC itself increased cerebral vascular resistance and decreased brain perfusion, compared to non-DC groups.

EPR/ESR method showed increase of hydroxyl and nitroxyl radicals in both, SAH and sham-operated, groups. The administration of melatonin significantly decreased the amount of dead neurons in hippocampus; nevertheless, we observed no significant difference between groups in either sensorimotor tests or in test of learning and memory in Morris Water Maze.

Conclusions: Perfusion impairment after SAH is caused mainly by intracranial hypertension and decrease of cerebral perfusion pressure. Decompressive craniectomy eliminated the intracranial hypertension and decreased the immediate mortality of experimental animals; on the other hand, it did not improve the cortical perfusion and increased cerebral vascular resistance. Intra-cerebroventricular administration of sodium nitroprusside improved the brain perfusion only minimally, besides, it had serious side effects (hypotension) that worsened the perfusion. Preemptive administration of melatonin decreased the amount of dead neurons in hippocampus; nevertheless no beneficial effect in neurobehavioral tests was detected.