No secondary elevation of extracellular adenosine in malignant edema formation following transient MCA occlusion

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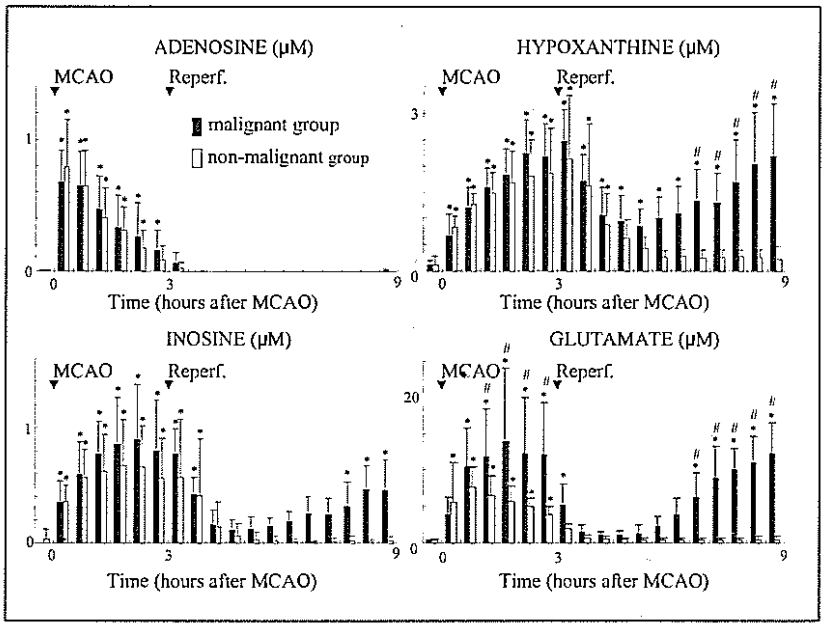
Introduction: Malignant edema is a relevant, serious complication in various clinical situations including large hemispheric stroke. To date, the roles of purine catabolites and amino acids in the course of malignant edema formation remain obscure. We examined the correlation between secondary perfusional disturbance and elevation of extracellular purine catabolites and amino acids in a transient focal ischemia model in cats that is prone to develop malignant edema and thereby secondary ischemia during reperfusion (1).

Methods: In 10 cats, the middle cerebral artery was occluded (MCAO) for 3 hours followed by 6 hours reperfusion. A microdialysis probe was inserted into the core of the MCA territory. Concentrations of purine catabolites and amino acids in dialysates were analyzed by HPLC. Adjacent to the microdialysis probe, a laser Doppler probe measured regional CBF (LDF), a strain-gauge MicroSensor measured intracranial pressure (ICP).



Results: MCAO reduced LDF in all animals below 25% of control. During MCAO, adenosine, inosine, hypoxanthine and glutamate increased significantly ($p<0.05$). Following reperfusion, LDF and extracellular substrates primarily recovered. Later in the reperfusion period, however, five of the 10 cats developed signs of malignant edema formation including drastic rise of ICP, drop of CPP, and finally pupil dilation. This group was defined as the malignant group. The remaining five cats formed the non-malignant group. In the malignant group, inosine, hypoxanthine and glutamate rose significantly ($p<0.05$) during reperfusion, when CPP decreased below 60 mmHg. Surprisingly, adenosine did not rise again during this period of secondary ischemia (see figure), even though it had been elevated during MCAO. In the non-malignant group, secondary elevations of ICP were not pronounced, and CPP did not drop below 60 mmHg. Consequently, none of the measured extracellular substances increased secondarily in the non-malignant group during the reperfusion period.

Conclusion: Secondary elevation of inosine, hypoxanthine and glutamate in the course of malignant MCAO is related to the severe drop of CPP that causes secondary ischemia. Surprisingly, this drop of CPP does not elevate adenosine. We assume that after reperfusion, salvage pathways are able to resynthesize IMP but not AMP because inosine and hypoxanthine as precursors for IMP synthesis have been formed in excess during MCAO but adenosine as the precursor of AMP synthesis is only transiently elevated during MCAO. In consequence, inosine and hypoxanthine would again be formed from IMP during secondary ischemia, whereas adenosine would not be formed, because it origins only from the now missing AMP.

References: [1] Toyota S et al; *Stroke*, **33**:1383-91 (2002)