Vol. 21, Suppl. 1 © 2001 The International Society for Cerebral Blood Flow and Metabolism
Published by Lippincott Williams & Wilkins, Inc., Philadelphia

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Malignant edema formation following transient MCA occlusion: decrease of cerebral perfusion pressure causes secondary elevation of glutamate

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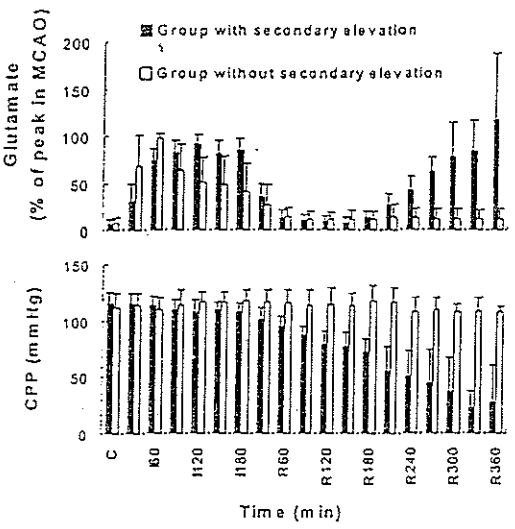
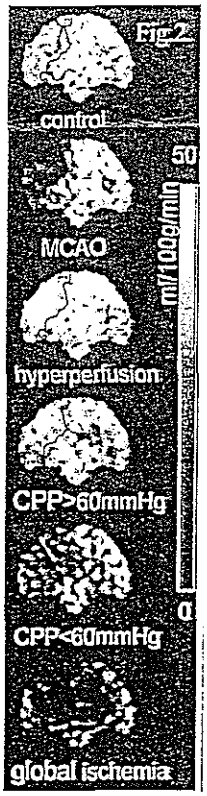
Introduction: Malignant, space-occupying brain edema is a relevant, serious complication in various clinical situations including large hemispheric stroke. In the search for intensive monitoring tools that permit early identification of such fatal outcome, microdialysis has recently been introduced in patient care. Furthermore, to date, the role of neuroactive substances in malignant edema remains obscure. We therefore examined the correlation between secondary perfusional disturbance assessed by monitoring cerebral perfusion pressure (CPP) and secondary elevation of glutamate and other neuroactive substrates in a reperfusion injury model in cats that was produced by 3 hours middle cerebral artery occlusion followed by 6 hours reperfusion.

Fig.1



Methods: In halothane anesthetized cats (n=8), the left middle cerebral artery was occluded (MCAO) for 3 hours followed by 6 hours reperfusion. Microdialysis probes were inserted into the core of the MCA territory in the left cerebral cortex. Concentrations of amino acids in dialysate were analyzed by HPLC. Adjacent to microdialysis probes, a laser Doppler probe measured regional CBF (LDF-CBF), a strain-gauge MicroSensor measured ICP, and a thermocouple measured regional brain temperature. After completion of the preparation, the skull was sealed. In a complementary experiment, the course of regional changes of brain perfusion in relation to glutamate alterations was assessed by positron emission tomography (PET). In this experiment, CBF was repeatedly measured using ^{15}O-H_2O (bolus i.v. injection) on a CTI/Siemens ECAT EXACT HR PET scanner.



Results: MCAO reduced LDF-CBF in all animals below 25% of control, and increased extracellular glutamate about 20 times. Upon reperfusion, LDF-CBF and glutamate primarily recovered. In 4 of 8 cats, secondary elevation of glutamate was apparent during the reperfusion period (see Fig.1). In this "secondary elevation group", glutamate started to rise when CPP decreased below 60 mmHg (see Fig.1). Almost at the same time, symptoms of transtentorial herniation were recognized. Minimal values of CPP in the animals of this group were below 50 mmHg, and brains showed midline-shift and neuronal necrosis even in the contralateral hemisphere. Sequential PET measurements (see Fig.2) revealed that in the reperfusion period, a phase of hyperperfusion was followed by global ischemia progressing from the formerly ischemic focus into the contralateral hemisphere when CPP fell below 60 mmHg.

Conclusion: Secondary amino acid elevation in the reperfusion period is caused by a drastic decrease of CPP in the final stage of malignant edema formation. Since the progression into this global type of ischemia starts in the core of the ischemic focus, microdialysis determinations in this region seem most predictive regarding the fatal course. In order to avoid excitotoxic glutamate elevation, CPP should be kept at least over 60 mmHg.