Successful treatment of mitochondrial dysfunction after vasospasm in translational animal model

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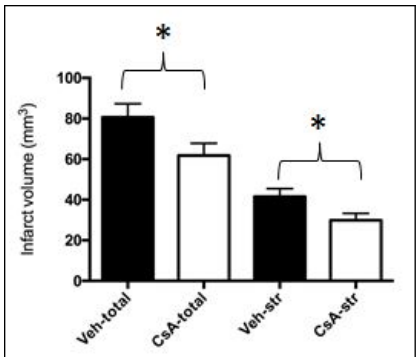
Introduction

A wide range of acute cerebral pathologies are associated with mitochondrial dysfunction. Amongst these is subarachnoid haemorrhage (SAH), where metabolic alterations in the vasospasm phase contribute to morbidity and mortality. Earlier studies have described a specific microdialytic pattern, and thus a potential clinical diagnostic method, for this metabolic state. There are currently no documented treatments for mitochondrial dysfunction in clinical use, but several compounds have shown great potential.



Total and striatal infarction sizes in CsA treatment group and vehicle controls. *=p<0.05.

Methods

We modified an earlier described endothelin-1 (ET-1) rat model of vasospasm to create a translational setting in which to evaluate pharmacological interventions in post-ischemic mitochondrial dysfunction. Using cerebral microdialysis in awake, freely moving rats we measured dynamics in glucose, lactate, pyruvate and Lactate/pyruvate-ratio (LPR) whilst inducing transient ischemia and randomizing animals to acute phase i.v. treatment with Cyclosporin A (CsA) as lipid emulsion (provided by NeuroVive Pharmaceutical AB Lund, Sweden) or vehicle. Metabolite concentrations were measured in 15 minute intervalls and results analysed statistically using mixed effect model (STATA 14.2). Rat brains were sectioned and stained. Infarct sizes were quantified (n=31) using the Cavalieri-principle and differences in the treatment groups analyzed with parametric t test after confirming normal distribution in the samples.

Conclusions

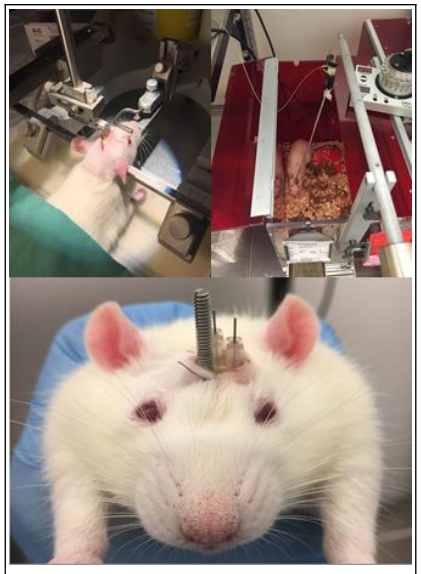
Dysfunctional post-ischemic cerebral metabolism is amenable to medical treatment. High dosage CsA (15mg/kg i.v.) ameliorates post-ischemic LPR in the acute phase. The metabolic results are corroborated by infarction size estimations, with a considerable difference in favour of the treatment group. The model described is translational in several aspects including diagnostic equipment, physiological settings and pharmaceutical admnistration and may be used as a model for testing other pharmacological interventions directed toward post-ischemic metabolic disturbances.

Results

The biochemical pattern observed in this model corresponds to earlier desxcribed patterns of post-ischemic mitochondrial dysfunction with a prolonged phase of supranormal LPR with concomitant normal or supranormal pyruvate.

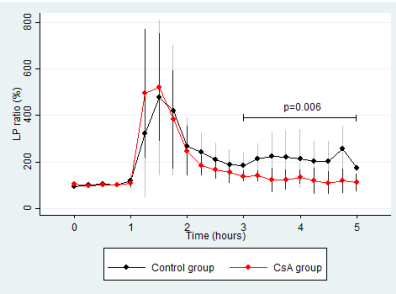
LPR in the CsA treatment group (n=10) were significantly lower after reperfusion (mean 66.6% point, Mixed effect model P=0.006) compared to the vehicle treated controls (n=8) in the 2 hour measurement period, with the CsA treatment group nearing base-line levels.

Total and striatal Infarct volumes were smaller in the CsA treatment group (n=17) then the vehicle group (n=14) with a mean reduction percentage of 25-28% with the most convincing statistical significans in striatal infarction volumes (two tailed t test Str p=0.0326, Tot p=0.0459).

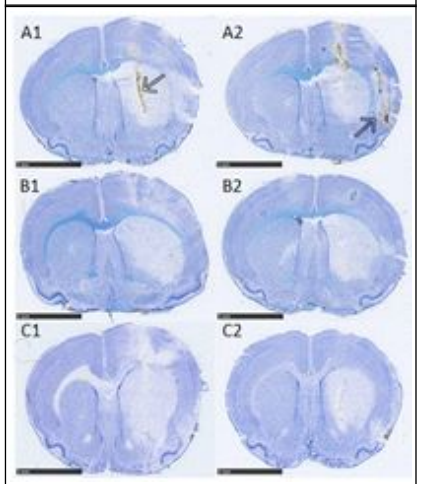


Stereotaxic implantations, experimental setup with sviwel and fraction collector and cranial implant collection close-up.

LP-ratio Treatment vs placebo



Mixed effect model analysis of Lactate/pyruvate-ratio in the CsA group (n=10) vs Placebo (n=8). Ischemia induced at 1 hour, directly followed by treatment. The average difference in LP-ratio after 3 hours was 66,6% points.



Representative infarctions in treated animals (right column) vs controls (left column). Arrows indicating microdialysis and ET-1 probes