Hypertonic Saline Attenuates Cerebral Edema following Cardiac Arrest: Role of Aquaporin-4

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BACKGROUND AND PURPOSE

- Cerebral edema is a significant cause of morbidity and mortality following cardiac arrest (CA) and cardiopulmonary resuscitation (CPR).
- The mechanisms of edema formation following CA/CPR have not been completely elucidated.
- Water channel aquaporin-4 (AQP4) has been implicated in the pathogenesis of cerebral edema in a variety of brain injury paradigms including focal cerebral ischemia.
- The perivascular pool of AQP4 has been shown to play a critical role in brain water influx and efflux in ischemia-evoked cerebral edema.
- Hypertonic saline (HS) is used as an osmotherapeutic agent for cerebral edema in a variety of brain injury paradigms.
- Few studies have investigated mechanisms of osmotherapy with HS as it pertains to anatomical domains of AQP4. We have previously shown that the perivascular pool of AQP4 mediates the effect of osmotherapy in stroke-evoked cerebral edema.

HYPOTHESES

- Osmotherapy with HS attenuates regional cerebral edema following experimental CA/CPR.
- The perivascular pool of AQP4 is selectively involved in the egress of water from the brain with osmotherapy.

METHODS

- *Experimental CA/CPR Animal Model:* Adult male (20-26g) wild type mice (WT) and mice with targeted disruption of the gene encoding α-syntrophin (α-Syn$^{-/-}$) that lack the perivascular AQP4 pool but retain the endothelial pool of this protein.
- Mice were anesthetized with 2% isoflurane, the jugular vein was cannulated, the trachea was intubated and mechanically ventilated.
- CA was induced by intravenous (IV) KCl for 8 min
- Temperature control; Cranial temperature 38.8 ± 0.2ºC
- Body temperature 37ºC → 28ºC
- CPR was initiated with IV epinephrine (8 µg), ventilation with 100% oxygen and chest compressions (rate 300/min).
- Sham-operated mice in both strains served as controls.

- *Experimental Groups:* WT and α-Syn$^{-/-}$ mice were treated with either continuous IV infusion of 0.9% saline (NS), 3% HS, 5% HS or 7.5% HS (1 ml/kg/hr) for 24 hr.

- *Measurements:* Serum osmolality and regional brain water content by wet-to-dry ratio were determined at the end of the experiment.

RESULTS

Summary of physiologic variables in **WT** mice (Mean ± SEM)

	sham NS	CPR NS	sham 3%	CPR 3%	sham 5%	CPR 5%	sham 7.5%	CPR 7.5%
Body weight (g)	24.5±0.4	24.1±0.6	24.2±0.5	24.9±0.4	24.5±0.5	24.7±0.4	24.7±0.5	24.3±0.4
CPR duration (sec)		61±6		60±5		60±7		61±8
Epinephrine (µg)		8.8±0.2		8.7±0.2		8.8±0.2		8.9±0.2
Surviving animals, n(%)	8(100%)	12(80%)	8(100%)	11(85%)	7(100%)	10 (83%)	9 (100%)	10 (77%)
Sodium (mmol/L)	145±1	146±1	147±1	147±1	152±1*	152±1*	155±2*	156±3*
Osmolality (mOsm/L)	317±2	314±1	317±1	318±2	325±2¶	326±2¶	347±9¶	345±6¶

*P < 0.05 vs. NS and 3% treatment groups; ¶P < 0.05 vs. all other treatment groups

Summary of physiologic variables in **α-syn$^{-/-}$** mice (Mean ± SEM)

	sham NS	CPR NS	sham 7.5%	CPR 7.5%
Body weight (g)	24.5±0.4	24.1±0.6	24.7±0.5	24.3±0.4
CPR duration (sec)		65±5		64±6
Epinephrine (µg)		8.9±0.2		9.0±0.2
Surviving animals, n (%)	8 (100%)	10 (71%)	8 (100%)	10 (71%)
Sodium (mmol/L)	145±1	146±1	154±2*	157±4*
Osmolality (mOsm/L)	316±3	316±4	340±5*	352±7*

*P < 0.05 vs. NS treatment groups

Survival rates were similar following CA/CPR among experimental groups. Treatment with HS elevated serum osmolality in a dose-dependent manner.

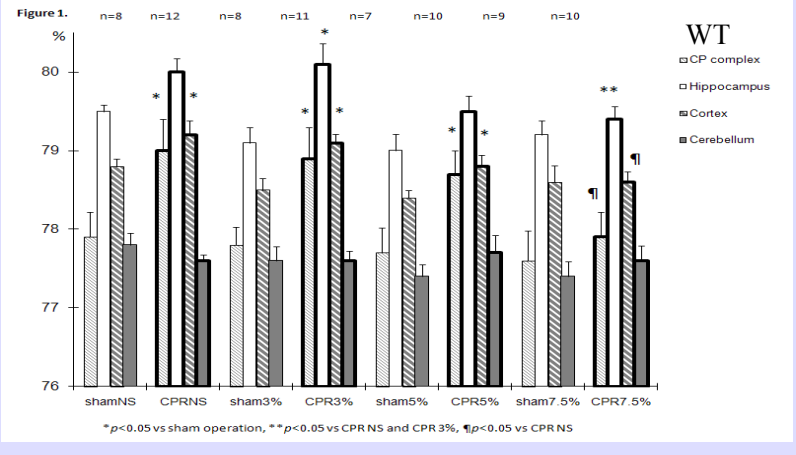

Figure 1: In WT mice, water content was significantly increased in the caudoputamen (CP) complex and cortex in animals treated with NS, 3% HS and 5% HS compared to sham-operated animals. While 3% HS and 5% HS treatment did not attenuate water content as compared with NS-treatment, 7.5% HS treatment significantly attenuated regional water content in the cortex (7.5% HS: 79.4 ± 0.2%; NS: 80 ± 0.2%), CP complex (7.5% HS: 77.9 ± 0.3%; NS: 79.0 ± 0.4%) and hippocampus (7.5% HS: 78.6 ± 0.1%; 79.2 ± 0.2%).

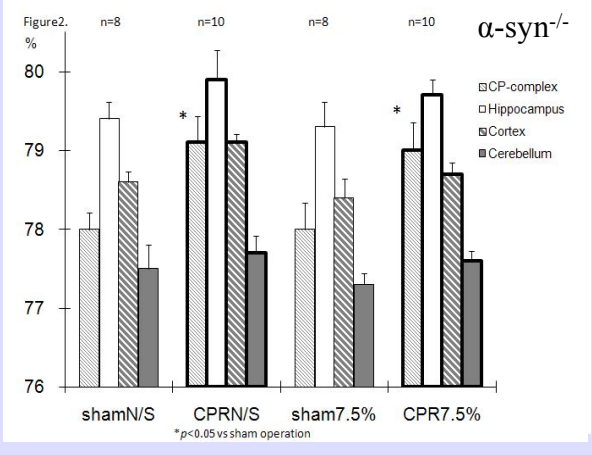

Figure 2: In α-syn$^{-/-}$ mice, 7.5% HS treatment did not attenuate regional brain water content compared to NS treatment

CONCLUSIONS

- Continuous HS infusion maintained to achieve serum osmolality ~ 350 mOSm/L is optimal for the treatment of cerebral edema following CA.
- HS treatment had no effect on the brain water content in α-Syn$^{-/-}$ mice.
- The perivascular pool of AQP4 mediates the effect of osmotherapy in post-ischemic cerebral edema following CA.

ACKNOWLWDGEMENTS

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