Role of Perivascular Pool of Aquaporin-4 in Cerebral Edema following Experimental Cardiac Arrest

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BACKGROUND AND HYPOTHESES

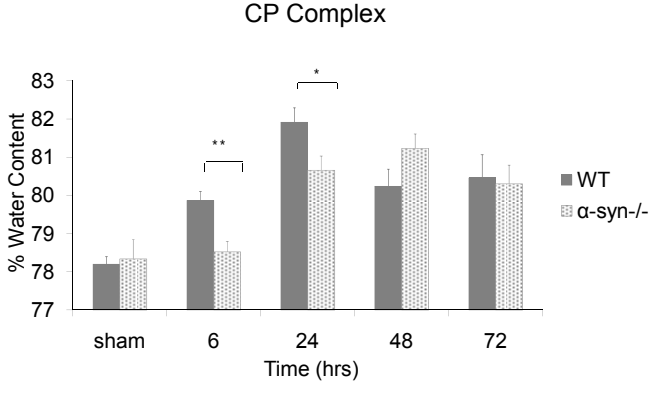
- Cerebral edema occurs commonly following cardiac arrest (CA) and is a significant cause of mortality and morbidity.
- The mechanism of edema formation after CA remain poorly understood.
- Aquaporin-4 (AQP4), a water channel concentrated in perivascular and subpial membrane domains of brain astrocytes, has been demonstrated to play an important role in the evolution of brain edema following ischemia.
- We hypothesized that perivascular pool of AQP4 plays a significant role in edema formation after CA and cardiopulmonary resuscitation (CPR) by utilizing animals 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.

METHODS

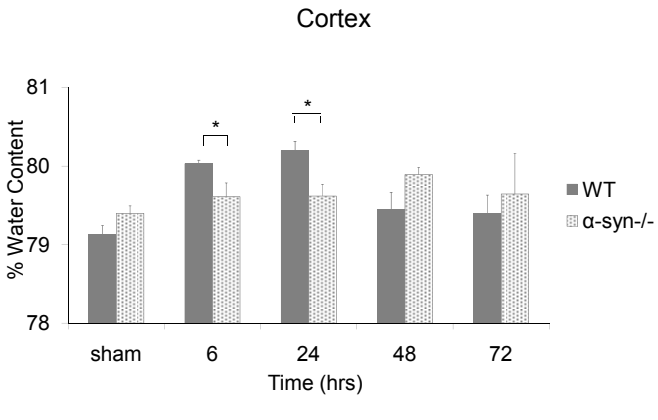
- *Animal Model:* Adult male wild type mice (WT; C57Bl/6) and mice homozygous (20-25 g) for targeted disruption of the gene encoding α-syntrophin (α-Syn$^{-/-}$) that lack the perivascular AQP4 pool but retain the endothelial pool of this protein.
- CA (8 min) was induced under isoflurane anesthesia (~2%) by intravenous (IV) injection of KCl (0.5 M) with head heating (38.8 ± 0.2˚C).
- CPR was initiated by chest compressions (300/min), simultaneous IV administration of epinephrine (0.3 mg/kg), and ventilation with 100% oxygen.
- CPR was discontinued after return of spontaneous circulation. After 30 min of observation, catheters were removed and the animals moved to recovery room.
- Regional cerebral edema (cortex, caudoputamen (CP) complex) was assessed by wet-to-dry weight ratio at various time points (6, 24, 48, 72 hr). Surgical shams served as controls.
- Histopathological analysis was performed 72 hr following CA/CPR with H&E staining in CA1 and Neu-N staining in CP complex.

RESULTS

- Physiological variables, epinephrine dose and duration of CPR were not different in various experimental groups in WT and α-Syn$^{-/-}$ mice.



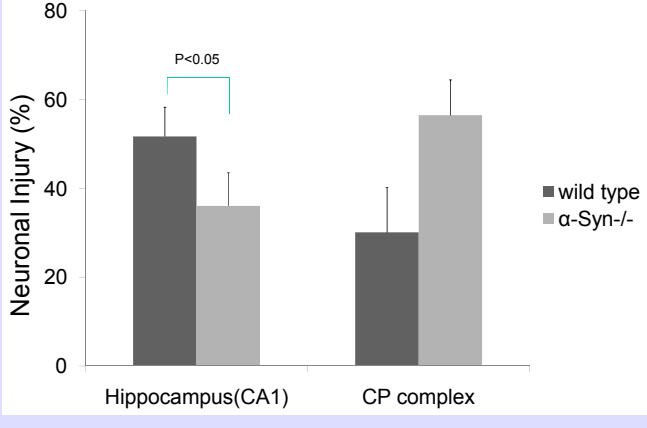
Water content of CP complex: following CA/CPR: Cerebral edema at 6 and 24 hr following CA was attanuated in α-syn$^{-/-}$ mice. *P < 0.05 **P < 0.01 by unpaired t-test.



Water Content in cortex following CA/CPR: Cerebral edema at 6 and 24 hr following CA was attenuated in α-syn$^{-/-}$ mice. *p < 0.05 by unpaired t-test.

	WT	α-syn$^{-/-}$	P value
sham	328 ± 6	325 ± 3	0.62
6 hr	322 ± 4	330 ± 4	0.27
24 hr	316 ± 1	320 ± 3	0.10

There were no differences in serum osmolalities between surgical shams, or WT and α-syn$^{-/-}$ mice at 6 and 24 hr following CA/CPR (unpaired t-test).



Histopathological evaluation 72 hr following CA/CPR in hippocampus and CP complex with both WT and α-syn$^{-/-}$. In α-syn$^{-/-}$ mice, neuronal injury was significantly attenuated in the CA1 region but not in CP complex (p=0.22). * p < 0.05 by Mann-Whitney U-test.

CONCLUSIONS

- Following CA/CPR, targeted deletion of perivascular pool of AQP4:
  - Significantly delays the peak of cerebral edema.
  - Reduces hippocampal neuronal death.

ACKNOWLWDGEMENTS

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