High-Dose Intranasal Insulin During CPR Improves Neurological Outcomes In A Rat Model Of Asphyxial Cardiac Arrest

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No conflicts of interest

AHA's Strategically Focused Research Networks (SFRN) : Arrhythmias and Sudden Cardiac Death
How is Insulin Neuroprotective?

Intravenous insulin causes dose-dependent brain AKT phosphorylation

*Sanderson Neurol Res 2013*

High-dose intravenous insulin (20 U/kg) is neuroprotective in rat model of transient global brain ischemia

*Sanderson J Neurochem 2008*
Why Trans-nasal Delivery?

- Bypasses Blood Brain Barrier
- Rapid CNS delivery
- Negligible systemic effects
- Simple non-invasive administration
- Feasibility of initiating during CPR

**Human Clinical trials of Intranasal insulin:**
- Alzheimer’s disease (NCT02462161)
- Ischemic stroke (NCT02810392)
- Parkinson’s disease (NCT02064166)
Hypothesis

High-dose intranasal insulin (HD-IN-I) administered during CPR improves neurologic outcomes in a rat model of asphyxial cardiac arrest.
Experimental Design

Target Engagement Study
- Asphyxial cardiac arrest (8min)
  - Tran-nasal placebo (n=6)
  - Tran-nasal insulin (1.9U/g brain wet weight) (n=6)
  - Sham (n=3)

  Euthanasia & brain collection @ 30-minutes post-ROSC

  Western blot (Hippocampus)

  Phosphorylated Akt

  Phosphorylated Insulin Receptor

Outcome Study
- Asphyxial cardiac arrest (8min) Block randomized blinded study
  - Tran-nasal placebo (n=14)
  - Tran-nasal insulin (1.9U/g brain wet weight) (n=14)
  - Sham (n=14)

  Behavioral testing
  - Day7-10: Rotarod & Barnes maze
  - Day9-10: Passive avoidance

  10-day survival
  Euthanize, brain removal, histology

Treatment
Insulin or placebo delivered in a total volume of 40 microliters (20 microliters into each nostril) at the onset of CPR.
Target Engagement Study

p<0.05 Intranasal insulin vs Placebo & Sham (1W-ANOVA; Tukey Posthoc). Data expressed as mean ± SD

* p<0.05 Intranasal insulin vs Placebo & Sham (1W-ANOVA; Tukey Posthoc). Data expressed as mean ± SD
**Outcome Study: ROSC and Survival**

### ROSC Rates

- Placebo: 100% (14/14)
- Insulin: 71% (10/14)
- 43% (6/14)

Chi-Square: $P = 0.55$

### Survival Curve

- Sham: 100% (14/14)
- Insulin: 71% (10/14)
- Placebo: 43% (6/14)

Log-Rank: $P = 0.12$; Insulin vs Placebo
Outcome Study: Serum Glucose

P > 0.05; 2W ANOVA with RM
Data expressed as mean ± SD
Outcome Study: Rotarod

Latency to fall off the rotarod (seconds)

- Sham
- Placebo
- Insulin

* p<0.05 Intranasal insulin vs Placebo. 2W ANOVA with RM
Data expressed as mean ± SD
Barnes Maze

Latency to enter into escape box (seconds)

* p<0.05 Intranasal insulin vs Placebo. 2W ANOVA with RM

Data expressed as mean ± SD
Passive Avoidance

Latency to enter into dark chamber (seconds)

- Sham
- Placebo
- Insulin

* p<0.05 Intranasal insulin vs Placebo. 2W ANOVA with RM
Data expressed as mean ± SD
Limitations

• Young healthy rats with no co-morbidities

• Sex as biological variable was not evaluated

• Dose-response, therapeutic window, duration of therapy not tested

• Synergistic/additive effect with hypothermia not tested

• Single severity of injury tested
Summary

**Study Findings**

High Dose Intranasal Insulin during CPR resulted in:

- Hippocampal Akt phosphorylation within 30 minutes of post-ROSC
- Improved behavioral function

**Future Directions**

- Brain distribution studies
- Dose optimization
- Therapeutic window
- Effectiveness in large animal models
- Maximum tolerated dose in humans
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Hippocampal CA1 Pyramidal Layer Histology

CA1 Pyramidal Neuron Counts

- Sham
- Placebo
- Insulin

* Significant difference
Evidence for trans-nasal insulin in brain

- **p** = 0.074

- **p**_{AUC 0-120} = 0.6

- **z-values**

- Amygdala fALFF change

- Placebo, Insulin 40U, Insulin 80U, Insulin 160U

- Plasma glucose (mmol/l)

- 0 U, 40 U, 80 U, 160 U

- Time after spray application (minutes)