Focal Brain Cooling as an Alternative Therapy for Intractable Epilepsy

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Incidence of epilepsy is about 1%. About 30% of epileptic patients are resistant with drug therapies.

Neurosurgical resection would be the first choice, but it is not always available.

Alternative therapies will be:

1. Vagus nerve stimulation (commercially available)
2. Cerebral stimulation (electrical or magnetic stim.)
3. Focal brain cooling
History of Focal Brain Cooling

Pioneering research on a focal cerebral cooling since 1960’s~:

- **Bedside application for intractably epileptic patients** (Ommaya et al. 1963)
- **Intraoperative application for epileptic patients** (Pasztor et al. 1969)
- **Bedside application for humans & animals** (Vastola et al. 1969)

Now over 40 years have passed since then, but….

Figure 1: an ideal closed-loop cooling system that is implantable in the brain and body of an intractable epileptic patients.
Cooling System (I)

Essential Components:

1. Cooling Device
2. Heat Dissipation
3. Thermal Controller
4. On-line EEG Analyses
5. Power Supply
Cooling System (II)

-Cooling Device: PID-controlled Peltier chip with a heat sink
   (6.0 × 6.0 mm or 30 × 30 mm)

-Cooling Area of Brain: SI-MI (sensori-motor) area

-Model Animals:
   Focal seizure: Wistar rats through microinjection of BMI or kainic acid
   Generalized seizure: spontaneously epileptic rats (NERs) or drug-induced rats

-Cooling Temperatures: 20, 15, 10 °C

-EEG Detection System: PCA or TFA

-Seizure Scoring:
   Racine’s scoring (0: no behavioral changes, 1: immobility, facial myoclonus, 2: head nodding, 3: forelimb clonus, 4: rearing, 5: jumping, 6: severe tonic-clonic seizures)

-Behavior Scoring:
   Modified neurological severity scoring (NSS: Shapira et al. 1988),
   Motor functional scoring by Oda et al. (Oda et al. 2005).
Thermo-Gradients

Depth

Cooling at 20°C and 5°C:
- 1mm: 23.3°C, 8.5°C
- 2mm: 24.0°C, 11.5°C
- 3mm: 25.4°C, 18.0°C

Cf. Inhibition of action potentials at 10°C (Volgushev et al. 2000)
Cooling and Physiology (I)

-Sensory function: remains normal down to 20 °C.
-Motor function (locomotion, motor coordination): remains normal down to 15 °C.

Cooling below 15 °C caused a significant dysfunction of the sensory systems (significant decrease in a modified NSS scores (p<0.01), which corresponded with a significant decrease in the receptive fields on the forepaw areas (p<0.05)).
Cooling and Physiology (II)

Cooling down to 20 (~15 °C) is physiologically affordable.
Overview of Epileptic Models

-Focal (partial, local) seizures:
  1. Simple focal seizures (BMI, kainic acid)
  2. Complex focal seizures
  3. Secondarily generalized seizures
     (kindling, kainic acid; in progress)

-Generalized seizures:
  1. Absence seizures (SER, GAER; in progress)
  2. Myoclonic seizures (NER; in progress)
  3. Generalized tonic-clonic seizures
     (NER, SER, BMI, kainic acid)

-Unclassified seizures:
Simple focal seizures (BMI or kainic acid) are invariably suppressed by focal cooling at 20°C. The suppressive effect was observed both in anesthetized and free-moving rats.
The video shows that focal cooling at 20°C on the right sensori-motor cortex suppressed the spontaneous generalized tonic-clonic seizures in an anesthetized NER. Interestingly, the cooling on the ipsilateral cortex was sufficient to terminate the GTC seizures.
Racine’s scoring: from GTC (6 points) to immobility (1 point).
GTC Seizures (chronic)

Successful prediction

False detection
Implantation of the cooling device for 1 month caused no behavioral, cardiologic, or histological damage, except for some partial gliosis (shown by an arrow).
Clinical Investigation (I)

Patient with tuberous sclerosis
(Male, 33yrs.)

Patient with parietal lobe epi.
(Female, 58yrs.)

Peltier device

EEG (µV)

Surface Temp (°C)

CBF (ml/100g/min)
Clinical Investigation (II)

Glutamate (mmol/L)

Case 1

Case 2

Case 3

Lactate (mmol/L)
Discussion: Non-linearity

Hysteresis Effect

21.4 ° (acute)  30.4 ° (acute)
20.3 ° (chronic) 29.9 ° (chronic)

*P<0.05
Focal cerebral cooling through 2mm diameter probe.

A 2 mm diameter probe was enough to suppress GTC seizures. The suppression was associated with the reduction of the epileptic discharges on the bilateral cortices (SI-MI, SI, and visual cortices) and the hippocampi.
Hypothesis

What is the mechanisms of seizure suppression through focal brain cooling?

- Suppression of neuronal transmission may not provide a sufficient explanation.

- Strong nonlinear characters as observed in experiments suggest that nonlinear dynamics must be involved (correlation dimension suggested chaos).

- Mathematical formulation (such as chaos theory, bifurcation theory) and/or large scale neuronal network simulation will be the key to understand seizure dynamics.

Figure: cusp catastrophe
Conclusion

-Our experimental and clinical studies suggested that cooling at 20 °C is enough to suppress focal seizures without causing detrimental effects on normal physiological functions.

-But it is unclear regarding in what ways some GTC seizures are suppressed by focal cerebral cooling. Non-linear analyses may be a key for understanding the mechanisms.

-Clinical application of closed-loop system is not sufficient at the current stage. More powerful analytical methods or alternative ways will advance the realization of cooling system.
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