FOCAL BRAIN COOLING FOR THE TREATMENT OF EPILEPSY: LABORATORY AND CLINICAL INVESTIGATION

HIROSHI FUJIOKA (1,4), MASAMI FUJII (1,4), HIROYASU KOIZUMI (1,4), SADAHIRO NOMURA (1,4), HIROCHIKI IMOTO (1,4), TAKAO INOUE (1, 4), TAKASHI SAITO (2), TAKESHI YAMAKAWA (3,4), MICHIYASU SUZUKI (1,4)

(1) Department of Neurosurgery, Graduate School of Medicine, Yamaguchi University
(2) Applied Medical Engineering Science, Graduate School of Medicine, Yamaguchi University
(3) Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology
(4) Consortium of Advanced Epilepsy Treatment (CADET)

ABSTRACT - Although focal brain cooling has distinct power on suppressing epileptic seizures, the technological and physiological feasibility for therapeutic application still remains unknown. This paper addressed the issue of technical feasibility though the development of an implantable, thermolectrically-driven cooling device. Chronic application of the device on the seizure focus in rats significantly suppressed seizure frequencies at 20°C that were associated with the improvement of neurological functions in comparison to those of non-cooling groups. Further, we intraoperatively applied the cooling device on the irritated epileptic foci of the intractably epileptic patients (n=6). The results potentially supported the therapeutic feasibility of hypothermal devices for the treatment of epilepsy.

Key Words: epilepsy, seizure, focal brain cooling, thermal neuromodulation, medical device, closed-loop system

1. INTRODUCTION

Epileptic patients are estimated to be about 1% in worldwide population. Since about one third of epileptic patients are resistant with any anti-epileptic drugs, and due to limited neurosurgical indications, much attention has been given to implantable, device-based therapies (Stacey and Litt 2008). Currently proposed are devices for electrical stimulation, magnetic stimulation, localized drug delivery, and focal brain cooling (Stacey and Litt 2008). Of these, only electrical stimulation devices (such as vagus nerve stimulation) have been clinically used, but the therapeutic effect is by no means satisfactory (Milby et al. 2009).

Although focal brain cooling has been one of the potential and promising candidates of device-based therapies due to its distinct suppressive power on epileptic discharges (Sartorius et al. 1998, Hill et al. 2000, Karkar et al. 2002, Imoto et al. 2006, Tanaka et al. 2008, Fujioka et al. 2008) and epileptic seizures (Ommaya and Baldwin 1963, Vastola et al. 1969, Sourek and Travnicek 1970, Burton et al. 2005), the therapeutic feasibility still remains unelucidated. The issue needs to be addressed from physiological and technological aspects, but this paper does not go into details of the physiological aspect.

From technological point of view, an implantable cooling device must be equipped with safety, portability, cooling power, and precise temperature control. A majority of previous studies on focal cooling employed the circulatory cooling type (Lomber and Payne 2000, Burton et al. 2005, Clark and Colbourne 2007), wherein focal area of the brain is cooled by circulating a cold medium (about 0°C) in metallic tubes. The method will be useful for bed-side application in the form that the device is transiently applied in craniotomized patients. However, it will not be practical for implantation in free-moving conditions (see Rothman et al. 2005) due to the bulkiness and lack in precise temperature control. Moreover, it is unrealistic to insulate extremely low temperature of metallic tubes (about 0°C) in the non-targeted area of brain or the body.

Given the above background, this paper addressed what kinds of cooling devices are suitable for therapeutic instrumentation. Among various cooling technologies (circulatory cooling, gas cooling, heat pipes, etc), thermoelectric devices have been one of the promising candidates (Rothman and Yang 2003,
Rothman et al. 2005, Imoto et al. 2006, Tanaka et al. 2008, Fujioka et al. 2008), but the severe drawback is the heat from the device. Due to homeostasis, excessive heat in the body is dynamically regulated through dissipation from veins or skin, but the physiologically affordable ranges of temperatures are essentially limited. Thus, heat from a given thermoelectric device must be forcibly dissipated, which can be formulated by the following differential equation (1):

\[
C_\text{dt} = Q_\text{dt} - U(t - t_a)F_\text{dt}
\]  

(1).

Here, \(C\): heat capacitance (kcal°C), \(t\): temperature (°C), \(Q\): amount of heat generation (kcal/h), \(\tau\): elapsed time (h), \(U\): coefficient of overall heat transmission, \(t_a\): ambient temperature (°C), \(F\): surface area (m²). Solving the equation (1) under the condition that \(t = t_i\) when \(\tau = 0\) gives the general expression:

\[
t = \frac{Q}{K + t_a} - \left(\frac{Q}{K} - \left(t_i - t_a\right)\right) \exp\left(-\frac{K}{C}\tau\right)
\]  

(2)

where \(t_i\) is an initial temperature (°C). Here we propose a heat processing system that forcibly cools the heat from the thermoelectric device (Fig. 1). Although complete implantation of a heat processing system is impractical at the current stage, this kind of transcutaneous application of a medical device has been FDA-approved and adopted in left ventricular assist devices (Wilson et al. 2009). With this system, we investigated the technological feasibility in epileptic rats and epileptic humans.

![Fig. 1: A schematic figure for human application (left) and an overview of the hypothermal system.](image)

### 2. LABORATORY INVESTIGATION

Animal experiments were performed by protocols approved by the Institutional Animal Care at Yamaguchi University School of Medicine. A PID-controlled thermoelectric device (6.0×6.0 mm; Imax 1.8A, \(V_{\text{max}} 2.5V\), \(Q_{\text{max}} 2.4W\); Ferrotec Corp. Japan), which was originally developed in our lab (Imoto et al. 2006, Tanaka et al. 2008, Oku et al. 2009, Fujioka et al. 2010), was further modified for portability, and ipsilaterally applied on the SI-MI area of first anesthetized male Sprague-Dawley rats as a drug (bicuculline)-induced focal epileptic model, and subsequently anesthetized/free-moving male spontaneously epileptic rats (NERS, Noda et al. 1998). The EEG (~7Ch), ECG, cortical temperatures, cerebral blood flow (CBF), and extracellular fluids (glutamate and lactate) were monitored. The cooling system was completely automated (cf. Fig. 2); following the automatic detection of anticipating epileptic discharges through real-time analyses by a commercially available software (SciWorks, USA), the cortex was instantly cooled or rewarmed by a cooling device.

Heat from the cooling device was transferred by a copper-made heat sink (6×6 mm with a thickness of 4mm for rats; see Imoto et al. 2006, Tanaka et al. 2008) that was attached with the hot side of the chip. The heat sink, with two water channels inside, was connected to a portable heat processing module via medical catheters (TYGON, R-3603, USA). The module (110×47×140 mm, total weight of 685 grams) composed of a reservoir filled with Ringer’s solution (85 ml) set to 20°C by a thermoelectric chip (29.8×29.8 mm; Imax 4.0A, \(V_{\text{max}} 9.8V\), \(Q_{\text{max}} 21W\); Ferrotec Corp. Japan) with an air-cooling fan, and a DC-driven pump.
(flow rate of 50ml/min). Power to the cooling system was supplied with an AC-power or with a rechargeable DC-power with a parallel connection of 8 batteries (Eneloop, 1.25V/battery, Sanyo, Japan).

Fig. 2: An overview of the thermoelectrically-driven cooling system for animals (left). The right figure shows chronic application of the system in an epileptic rat (right). A detachable heat processing system (in a black pouch) was transcutaneously applied on the back of the rat.

Fig. 3: Rat brain temperatures and mean temperatures of the reservoir in a heat processing system. The implanted system reliably cooled the cortex to a target temperature of 15 °C, while temperatures of the reservoir were within physiologically affordable ranges. The cortex of anesthetized (acute) and free-moving (chronic) rats was cooled to 15 °C.

The implanted system reliably cooled the cortex within ±0.05°C from set temperatures (37.0–10.0°C) without overshooting (Fig. 3). Epileptic seizures in anesthetized NERs as well as drug-induced Sprague-Dawley rats were instantly suppressed by cooling at about 25°C. Cooling was also effective in the awake, free-moving NERs, where the onset of seizures as well as partial and generalized seizures in progress were significantly suppressed at 20°C. The suppressive effect of cooling continued throughout the entire cooling period. Implantation for 1 month caused no behavioral, cardiologic, or histological damage, except for some partial gliosis in the contact area. Excessive cooling (< 15°C) caused a significant dysfunction of the sensori-motor systems as revealed by the behavioral scores (p < 0.01; Hunter et al. 2000), which corresponded with a decrease in the receptive fields (Dunnett post hoc tests; p < 0.05, see Fujioka et al. 2004 for methods). The cerebral blood flow significantly decreased during cooling at 10°C, but thereafter it returned to normal soon after rewarming (Dunnett post hoc tests; p < 0.05). Microdialysis analyses revealed no significant difference in glutamate or lactate levels between rapid or slow cooling and rewarming.

We subsequently investigated the efficacy of a closed-loop system. To this end, automatic detection and prediction programs were made using temporal frequency analyses and applied in free-moving NERs. We tentatively classified the power bands of interictal ECoG into δ (0.5-4Hz), θ (4-8Hz), α (8-12Hz), β (12-
30Hz), and $\gamma$ (30-45Hz) ranges, and investigated which power bands were susceptible before and during ictal stages. The results showed that $\beta$ and $\gamma$ band ranges were selectively increased just before the onset of seizures (Fig. 4 right). Thus, power bands ten times above those of the interictal stages were set as a threshold. The results showed that prediction was possible 3.05±3.38 sec before the ictal events (maximally 30 sec before the event). However, reliable prediction proved to be difficult due to various noises and inter-individual variability of targeted bands.

Together, the results of the animal studies showed, for the first time, the potential feasibility of therapeutic application of the cooling system.

**Fig. 4:** Ictal ECoG of a NER before, during, and after 10°C cooling (left). Distinct reduction of epileptic discharges was confirmed during cooling. The right graphs show changes of power spectrum before and after the onset of epileptic seizures in NERs (n=5)

### 3. CLINICAL INVESTIGATION

Intraoperative cooling was subsequently performed by protocols approved by the Ethics Committee at Yamaguchi University. Patient criteria were intractably epileptic patients with an indication of neurosurgical treatment for focal resection of neocortex, and informed consent to participate in the study was obtained in all of the patients (n=6). The cooling device was further modified for clinical use (29.8×29.8 mm for humans; $I_{\text{max}}$ 4.0A, $V_{\text{max}}$ 9.8V, $Q_{\text{max}}$ 21W; Ferrotec Corp. Japan) without changing the aforementioned heat processing module. Assuming the lowest affordable temperature as 15°C from animal studies, intraoperative cooling was performed on an epileptic focus on cortex in intractably epileptic patients. The foci were transiently irritated (i.e., purposefully enhanced interictal epileptiform discharges to identify epileptic foci) by 2.5% sevoflurane.

Cooling to 15°C induced, in addition to the significant reduction of epileptic discharge amplitudes (Fig. 5), coupling of cerebral blood flow and metabolism with a significant reduction in the glutamate level. Histological investigation showed no particular cooling-associated changes in the resected cortices.

**Fig. 5:** Intraoperative application of a cooling device on the cortical focus in an intractably epileptic patient (left and middle). A microdialysis probe was inserted into an epileptogenic cortex. ECoG during cooling at the epileptic focus clearly indicated cooling-induced reduction of epileptic discharges in the same way as those in animal studies. Temporal frequency analyses showed that cooling was effective on suppressing both fast and slow wave components.
4. DISCUSSION

This study clearly showed, for the first time, the potential feasibility of a device-based hypothermal therapy on epilepsy. The suppressive effects of focal brain cooling were powerful, instantaneous and continuous, indicating the absolute advantage over any other epileptic therapies. Given the substantial number of intractable epileptic patients, the potential demand for the therapy will be undoubtedly high. Presumably good indication of focal brain cooling will be for patients with an identified epileptogenic focus on cortex, especially on the eloquent cortex (such as motor or language areas), where surgical resection will induce severe functional damages.

From technological point of view, there are many issues to be solved for therapeutic application. Firstly, the cooling device must be much smaller and thinner (from our rough estimation, thickness should be less than 8mm to be implanted in the human brain) without sacrificing cooling power. Secondly, a fail-safe system must be incorporated in the system for any possible emergent situations. Thirdly, prediction analytic methods must be developed. Our preliminary attempt to use one of the representative analyses in a closed-loop system worked to some degree but was impractical. Indeed, it has been reported that even state-of-the-art techniques for prediction analyses have certain limitation for clinical use primarily in terms of lack of reliability (Lehnertz et al. 2007). Given the fact that the suppressive effect continues so long as cooling is performed, on-demand cooling will suffice (for example, if an epileptic patient wants to drive a car, all he/she has to do is to manually activate the cooling system before driving). Nonetheless, it is desirable to incorporate automatic prediction analyses in the system in terms of energy conservation. Finally, legislative hurdles must be conquered for medical instrumentation, which are especially true with implantable devices.

Despite many hurdles to overcome, focal brain cooling is certainly the only method that reliably and instantly suppresses epileptic seizures. Furthermore, focal brain cooling has potential availability not only for epilepsy but for central nervous diseases. This is because of the unique property of focal brain cooling through modulating synaptic transmission, which we term, “thermal neuromodulation”. Thus, substantial development is suggested for the treatment of central nervous diseases that are associated with hyperexcitability of neurons, such as cerebrovascular disease (Clark et al. 2007), neurotrauma, pain (Fujioka et al. 2010).

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