Application of Focal Cerebral Cooling for the Treatment of Intractable Epilepsy

Masami FUJII*††, Hiroshi FUJIOKA*††, Takayuki OKU*, Nobuhiro TANAKA*, Hirochika IMOTO*††, Yuichi MARUTA*††, Sadahiro NOMURA*††, Koji KAJIWARA*, Takashi SAITO**, Toshitaka YAMAKAWA†††, Takeshi YAMAKAWA**††, and Michiyasu SUZUKI*††

*Department of Neurosurgery, and **Applied Medical Engineering Science, Graduate School of Medicine Yamaguchi University, Ube, Yamaguchi; ***Department of Electrical and Electronics Engineering, Faculty of Engineering, Shizuoka University, Hamamatsu, Shizuoka; †Kyushu Institute of Technology, Graduate School of Life Science and Systems Engineering, Kitakyushu, Fukuoka; ††Consortium of Advanced Epilepsy Treatment (CADET)

Abstract

Epilepsy is usually treated with medication, but adequate seizure control is still not achieved in over 30% of epilepsy patients, even with the best available agents. Surgical treatment is also performed for such patients, but is not always successful. Focal cooling of the brain using a thermoelectric device has recently been evaluated as an alternative to epilepsy surgery. Brain cooling was first proposed approximately 50 years ago as an effective method for suppressing epileptic discharges (EDs). Recent studies indicate that focal cooling of the brain to a cortical surface temperature of 20°C to 25°C terminates EDs without inducing irreversible neurophysiological dysfunctions or neuronal damage in the brain tissue. Several mechanisms have been proposed for the antiepileptic effects of focal cooling, including reduction in neurotransmitter release, alternation of activation-inactivation kinetics in voltage-gated ion channels, and the slowing of catabolic processes. Developments in the implantable cooling device with closed-loop cooling systems for seizure detection and focal cooling have been promoted in the field of neuromodulation, but several aspects remain uncharacterized concerning the hardware. Recent advances in precision devices have enabled the optimization of the implantable local cooling system, which may become clinically applicable in the near future.

Key words: intractable epilepsy, focal cooling, thermoelectric device, neuromodulation, neuropathology

Introduction

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. Epilepsy is usually treated with medication, but even the best agents do not provide seizure control in over 30% of epilepsy patients.8) Surgical treatment is also performed for such patients, but is not always successful. Furthermore, if the epileptogenic foci are located in critical areas such as the motor and speech cortices, then surgical resection is impractical.

Several clinical trials have recently assessed various methods for treating refractory epilepsy. Vagal nerve stimulation has been used for the past decade.20) Electrical stimulation of the brain has been proposed to replace surgical resection using the anterior nucleus of the thalamus or the hippocampus as the stimulation target. However, clinical studies have not achieved satisfactory results.2,31,32) Clinical trials of an implantable, responsive, closed-loop stimulation system are currently in progress.12) This device can terminate seizures by delivering a burst of stimulation after detecting seizures with an electroencephalography (EEG) algorithm through an implanted electrode.33) Although the efficacy was demonstrated in a feasibility trial, further clinical investigation and optimization are required.

Another attractive and nondestructive approach
for the treatment of patients with epilepsy is focal cooling of the brain. Brain cooling was proposed approximately 50 years ago as an effective method for suppressing epileptic discharges (EDs), and has recently been revived with technological and medical engineering advances. Our institutions have obtained valuable results for the practical use as a new therapy for patients with intractable epilepsy.

This review describes the effect of focal cooling on seizures, the influence of focal cooling on the normal brain, the mechanisms of seizure termination due to cooling, and the practicality of an implantable cooling system based on our findings and published data.

**History of Brain Cooling as a Therapy for Epilepsy**

The effect of brain cooling on neurological diseases has been discussed for over 50 years. The therapeutic value of focal cooling was first summarized in the 1940s. Focal cooling was used to treat patients with head traumas, cancer, and pain, and emphasized the utility of local cooling.

The effect of cooling on epilepsy was first demonstrated as systemic hypothermia suppressing EDs in the primate temporal lobe. Thereafter, local cooling with the gas method was shown to suppress EDs in human. Ventricular irrigation with cold Ringer’s solution was also found to suppress seizures.

Other initial studies indicated that systemic hypothermia (30–32°C) suppressed seizures in patients with refractory epilepsy. Despite these initial studies indicating that brain cooling has the potential to terminate seizure activity, brain cooling has not yet been optimized for clinical use because of the difficulty in improving the cooling systems. Initial cooling methodologies such as local refrigeration with gas and cold water or ventricular irrigation had many problems for clinical use. These methodologies increase the chance for infection, and are difficult to use over longer periods or permanently. Severe systematic hypothermia can suppress seizures, but has fatal complications including infection, cardiac arrhythmia, and blood coagulation disturbances.

Focal brain cooling has recently gained more attention, although many studies were completed several decades ago. Irrigation of the brain surface with cold Ringer’s solution rapidly halts the focal seizure activity induced by direct cortical stimulation mapping. Focal cooling of the neocortex with thermoelectric (Peltier) devices terminates EDs. Such an implantable focal-cooling device can be combined with a seizure detection system. Encouraged by these studies, our group has begun to examine the practicality of focal brain cooling as a therapy for patients with intractable epilepsy.

**Focal-Cooling Device for Animal Experiments**

A Peltier chip is the basis of the thermoelectric device in recent studies. The chip is only 4.0 mm in length and width, and 2.0 mm in thickness (Fig. 1A). The chip consists of two conductors, which are connected in parallel (Fig. 1B). Passing an electric current between the conductors causes cooling of one conductor and heating of the other because of the electronic refrigeration phenomenon (the Peltier effect). A heat sink is attached to the chip to help dissipate the heat generated (Fig. 1C). This heat sink is constructed of aluminum with an internal water channel. Two silicone tubes are connected to the heat sink to circulate water through the channel. The temperature of the circulating water is maintained at 37°C by a temperature-controlled bath to achieve compatibility with an implantable system.

**Effect of Focal Brain Cooling on EDs**

I. Neocortical seizure model

Experiments were performed on adult male Sprague-Dawley rats under halothane anesthesia. Craniotomy was performed to expose the sensori-
motor cortex, then a cooling device was placed on the surface of the cortex. Kainic acid (KA) was injected into the cortex just beneath the cooled area to provoke EDs (Fig. 2A). The EDs, which appeared within 20 minutes after KA injection, began to decrease in amplitude immediately after the start of cooling and continued to decrease as the temperature of the cortex was lowered. Reduction of the temperature of the cortical surface to 30°C, 28°C, and 25°C caused the frequency of EDs to decrease as the temperature of the cortex was lowered, with final disappearance at 25°C during the cooling period (Fig. 2B).14)

Previously, focal cooling of neocortex rapidly terminated EDs in rats with 4-aminopyridine-induced epilepsy.38) Our results are in good accordance with previous reports, which concluded that the optimum temperature of the cortical surface for terminating seizures is approximately 20°C to 25°C.34,38]

II. Hippocampal seizure model

We also investigated the inhibitory effect of selective hippocampal cooling on hippocampal seizures in rats.27) The cooling needle, which was attached to the Peltier chip, a thermocouple, and a needle electrode for EEG recording were inserted into the right hippocampus. KA was injected into the left hippocampus to provoke EDs. Changes in EDs transmitted from the left hippocampus were observed before and during the cooling period in the right hippocampus. The temperature at the needle tip fell below 20°C within 1 minute and was maintained at the same level until the end of the cooling process. The amplitude of the EDs was suppressed to 68.1 ± 4.8% of the pre-cooling value and remained low thereafter (Fig. 3). These results are consistent with previous findings.6,13,18)

Influence of Focal Cooling on Brain Tissue

Focal brain cooling has a suppressive effect on EDs or a protective effect on brain tissue.5) However, the exact influence of brain cooling on brain tissue remained unclear. Therefore, we investigated the neuropathological consequences of focal cooling and changes in threshold temperature, which cause irreversible histological change in the neocortices of rats.19) We concluded that focal cortical cooling at −5°C for 1 hour causes irreversible histological changes, which are coincident with the cryoinjury in the cooled cortex. However, focal brain cooling above 0°C for 1 hour did not cause motor dysfunction or histological damage (Fig. 4). Cooling of the rat brain to 5°C every 2 minutes for 30 seconds for a total duration of 2 hours, and cooling of the cat brain to 3°C for 1–2 hours every day for 7–10 months indicated that the neuropathological consequences of focal brain cooling to 3–5°C were insignificant.36) These data support our results, and we showed that
Influence of Focal Cooling on Neurophysiological Functions

Several studies have described the effects of cooling on the electrophysiology of the normal brain. Cooling of cortical tissue to temperatures between 0°C and 20°C disrupts local synaptic activity without causing permanent injury to the brain tissue. The motor response is preserved after cold saline is applied for the termination of EDs caused by cortical stimulation mapping. Focal cooling of the somatosensory cortex in rats by 20°C for 5 minutes induces recognizable changes of the somatosensory evoked potential, which are fully reversible after warming up the tissue. These studies suggest that reversible neurophysiological dysfunctions are induced at a threshold temperature of approximately 20°C.

Antiepileptic Mechanisms of Focal Brain Cooling

The exact mechanisms for the antiepileptic effects of focal cooling remain poorly characterized, although several possible mechanisms have been proposed, including reduction in neurotransmitter release, alternation of activation-inactivation kinetics in voltage-gated ion channels, and slowing of catabolic processes. A 2-photon microscopy technique demonstrated that a major neurophysiological effect of cooling in the brain is reduction in presynaptic neurotransmitter release. Furthermore, examination of rat hippocampal slices demonstrated that moderate cooling (21°C) induced a reversible block in the network synchrony, which was required to generate EDs, without any blockage of the synaptic transmissions.

Effect of Focal Cooling on EDs in Humans

The focal brain cooling method was assessed in patients with intractable epilepsy after receiving the approval of our University Ethics Committee and informed consent from the patients and family. During surgery, cooling was performed in the human cortex at the location of the recorded EDs, which was the target of resection. Electrocorticograms and the temperature just beneath the cooling site were recorded before and during the cooling process. The EDs diminished during the cooling process when the temperature of the brain surface reached less than 25°C (Fig. 5).

Development of Implantable Cooling Devices for the Treatment of Intractable Epilepsy

Our and other previous studies have demonstrated the termination of EDs by focal brain cooling, and indicate the therapeutic potential of focal brain cool-
ing for patients with intractable epilepsy as an alternative to invasive surgery. However, several problems remain in the hardware and must be resolved before this system can be clinically used on a larger scale in the future. First, no optimal fluid has been developed as the circulating fluid for heat dissipation. Second, the cooling device should be placed close to the epileptic focus, so multiple implantations of the cooling device and miniaturization of the device may be necessary. Such miniaturization of the device to include subdural electrodes and the development of the ED-detection system may allow cooling of the exact sites responsible for seizure generation immediately after the detection of EDs. Third, the sizes of the ancillary devices such as the electric power supply, EEG detection system, and thermometer should also be minimized in the future. Precision devices and micro-electromechanical system technology have made remarkable advances that should enable the development of micropumps, micro-batteries, and micro-charging systems. With the continued development of such equipment, implantable local cooling systems may become available in the near future.

Conclusions

Focal cooling of the brain is a promising new therapeutic option for the treatment of patients with intractable epilepsy as an alternative to epilepsy surgery. Recent advances in precision devices may allow the application of an implantable local cooling system for the treatment of epilepsy in the near future.

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Address reprint requests to: Masami Fujii, M.D., Department of Neurosurgery, Yamaguchi University School of Medicine, 1–1–1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan.
e-mail: masfujii@yamaguchi-u.ac.jp

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