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Focal Brain Cooling: Revisiting a Potential Therapeutic Option for Intractable Epilepsy

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Abstract Seizure control is not achieved in approximately one-third of patients with epilepsy, even with the best available medications. Surgical treatment can be performed for these patients, however this is also not always successful. Under these circumstances, the potential for seizure suppression by focal brain cooling has gained attention. Brain cooling was first proposed about 50 years ago, and has come into the spotlight in recent years with advances in technology. Recent studies indicate that focal cooling of the brain to a cortical surface temperature of 20 to 25°C terminates epileptic discharges without inducing irreversible neurophysiological dysfunction or neuronal damage. These results have promoted development of implantable focal cooling devices, but some aspects of the hardware in these devices require optimization. However, advances in precision machining have enabled optimization of an implantable focal cooling system, and this suggests that brain cooling therapy may become a reality in the near future.

Key words: epilepsy, focal brain cooling, seizure, device, neuromodulation

Introduction

Epilepsy is usually treated with medication, but approximately one-third of epilepsy patients do not attain seizure control, even with the best medications.¹ Surgical treatment is also used, but is not always successful. Furthermore, surgical resection is impossible if the epileptogenic focus is in critical areas such as the motor and speech cortices. Under these circumstances, several clinical trials of neuromodulation technology for treating refractory epilepsy have recently been performed. Vagal nerve stimulation has been used for the past decade² and electrical stimulation of the brain has been proposed as an alternative to surgical resection. The anterior nucleus of the thalamus or hippocampus has been chosen as a stimulation target. Clinical pilot stimulation studies have been performed, but the results remain unsatisfactory.³⁻⁵ A unique clinical study

with an implantable, responsive, closed-loop stimulation system is currently in progress.⁶ This device can terminate seizures by delivering a burst of stimulation after detecting a seizure with an electroencephalogram (EEG) algorithm through an implanted electrode.⁷ The preliminary efficacy of this method was demonstrated in a feasibility trial, but further clinical investigation and optimization are required.

Focal cooling of the brain is another attractive and nondestructive approach for treatment of patients with epilepsy. Brain cooling was first proposed about 50 years ago as an effective method for suppressing epileptic discharges (EDs),^{8,9} and has recently been revived with advances in technology and medical engineering.^{10,11} At our institution, we have obtained interesting results in practical use of brain cooling as a new therapy, which we refer to as “thermal neuromodulation”, for patients with intractable epilepsy.^{12,13} In

this review, we discuss the historical background of focal cooling, the influence of focal cooling on epileptic seizure and the normal brain, the mechanisms of seizure termination due to focal cooling, and the practicality of use of an implantable cooling system based on our experimental data and results published in the literature.

Historical background

The therapeutic value of focal cooling initially gained attention in the 1950s. At that time, local cooling of the nervous system was achieved in animal models using perivascular methods.^{14,15} Local cooling was also used to treat patients with head trauma, cancer, and pain, and the findings emphasized the utility of this method.¹⁶ The effect of cooling on epilepsy was first demonstrated by suppression of EDs in the primate temporal lobe using systemic hypothermia.⁸ Thereafter, local cooling with the gas method was shown to suppress EDs in human.⁹ Ventricular irrigation with cold Ringer's solution was also found to suppress seizures.¹⁷ Another early study indicated that systemic hypothermia suppressed seizures in patients with refractory epilepsy.¹⁸

Despite these initial studies indicating that brain cooling has the potential to terminate seizure activity, the method was not optimized for clinical use because of the difficulty in improving the cooling system. Initial cooling methodologies such as local refrigeration with gas and cold water or ventricular irrigation had many problems for clinical use. These methodologies increased the chance for infection and are difficult to use over long periods or permanently. Severe systematic hypothermia can suppress seizures,^{18,19} but also has fatal complications including infection, cardiac arrhythmia, and blood coagulation disturbances.²⁰

Focal brain cooling has recently gained attention because of advances in technology. In recent studies, evidence for an anticonvulsant effect of focal cooling has been obtained in neocortical and hippocampal epilepsy models^{10,11,21-23} and in humans.^{24,25} Clinically, Sartorius et al. found that focal seizure activity induced by direct cortical stimulation mapping was rapidly halted by irrigation

of the brain surface with cold Ringer's solution.²⁶ In recent studies, including our work, a thermoelectric device has been used because of its small size and strong cooling effect.^{10-13,27} This kind of focal-cooling device is implantable and can be combined with a seizure detection system.²⁸ Use of this technology has caused new interest in focal brain cooling as a therapy for patients with intractable epilepsy.

Inhibitory effect of focal cooling on epileptic seizure

We investigated the effect of focal brain cooling on EDs in rat neocortical and hippocampal seizure models.^{12,13} A Peltier chip was used as the basis of the thermoelectric device. This chip consists of two conductors, which are connected in parallel. Passing an electric current between the conductors causes cooling of one conductor and heating of the other because of the electronic refrigeration phenomenon (Peltier effect). A heat sink made of aluminum with a water channel is attached to the chip to help dissipate the heat generated. Two silicone tubes are connected to the heat sink to circulate water through the channel.¹²

A neocortical seizure model was made in adult male Sprague-Dawley rats. After craniotomy, a cooling device was placed on the surface of the sensorimotor cortex. Kainic acid (KA) was injected into the cortex just beneath the cooled area to provoke EDs. 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 of EDs at 25°C during the cooling period.¹² Rapid termination of EDs by focal cooling of the neocortex has previously been shown in rats with 4-aminopyridine-induced epilepsy.¹¹ Our results are also consistent with reports showing that the optimum temperature of the cortical surface for terminating seizures is approximately 20 to 25°C.^{11,27}

We also investigated the inhibitory effect of selective hippocampal cooling on KA-induced hippocampal seizures in rats.¹³ Control of the temperature of the cooling site at 20°C caused significant suppression of the amplitude of the EDs. These results are also con-

sistent with previous findings.²¹⁻²³

Influence of focal cooling on brain tissue and neurophysiological function

Focal brain cooling has an inhibitory effect on EDs and a protective effect on brain tissue.²⁹ However, the mechanisms underlying the influence of focal cooling on brain tissue and neurophysiological function have not been investigated in detail. Therefore, we examined the pathological and neurophysiological consequences of focal cooling in the neocortices of rats.³⁰ Pathologically, focal cortical cooling at -5°C for 1 hour caused irreversible histological changes that were consistent with cryoinjury. However, focal brain cooling above 0°C for 1 hour did not cause histological damage of the cortex. Yang et al. found that 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 had insignificant pathological consequences.³¹ These findings agree with our results, and we also showed that irreversible neuronal damage was not caused by focal brain cooling above 0°C for 1 hour.³⁰

Several studies have described the effects of cooling on the electrophysiology of the normal brain. Cooling of cortical tissue to temperatures between 0 and 20°C disrupts local synaptic activity without causing permanent injury to brain tissue.³² The motor response is preserved after cold saline is applied for termination of EDs caused by cortical stimulation mapping.²⁴ Focal cooling of the somatosensory cortex in rats at 20°C for 5 minutes induces recognizable changes of somatosensory evoked potentials, but these are fully reversible after warming the tissue.³³ These studies suggest that reversible neurophysiological dysfunction is induced at a threshold temperature of approximately 20°C .

Mechanisms of seizure termination

Focal brain cooling is generally thought to reduce transmitter release,³⁴ alter the kinetics of voltage-gated ion channels,^{21,35} and cause network desynchronization.³⁶ The precise antiepileptic mechanisms remain to be determined, but it is generally recognized that suppression of synaptic transmission is

involved in reduction of seizures.

In our study, EDs were selectively inhibited, but motor function was preserved when the cortical surface was cooled to $20\text{-}25^{\circ}\text{C}$.³⁰ An explanation of this phenomenon is needed. An *in vitro* study showed that synaptic transmission begins to decrease below 20°C .³⁵ In a case in which the temperature is $<20^{\circ}\text{C}$ at 1 mm under the cortical surface, but $>20^{\circ}\text{C}$ at a depth of 2 mm, it is reasonable to assume that synaptic transmissions and EDs in the shallow cortex (layer II/III) are selectively suppressed because of the spread through neurons in the shallow layer with horizontal connections to the ipsilateral or contralateral cortex. Selective suppression of synaptic transmission due to a cooling-induced thermogradient in the cortex may have contributed to the vulnerability of somatosensory processing, as indicated by the reduction of receptive fields during cooling. Since the motor cortex lies deep in the sensorimotor cortex (layer V), selective transmission failure may have occurred during surface cooling.³⁷

Practicality of use of an implantable cooling system

Our previous studies and those of others have demonstrated termination of EDs by focal brain cooling and indicate the therapeutic potential of this method for patients with intractable epilepsy, as an alternative to invasive surgery. Focal brain cooling may be applied for patients with an epileptic focus on the eloquent cortex (i.e., motor or language area). In our institute, we have initiated development of an implantable focal cooling system including a cooling component, an automatic electrocorticogram (ECoG) analytical system, a heat processing system, a rechargeable battery, and a fail-safe system (Fig. 1). However, several hardware issues remain to be resolved before this system can be used clinically on a large scale. First, an optimal fluid is required for use as the circulating fluid for heat dissipation. Second, the cooling device with Peltier chips requires large amounts of electricity, and development of electricity supply technology for the device is required. Third, miniaturization of the cooling device may be necessary. Smaller ancillary devices such as the electric power sup-

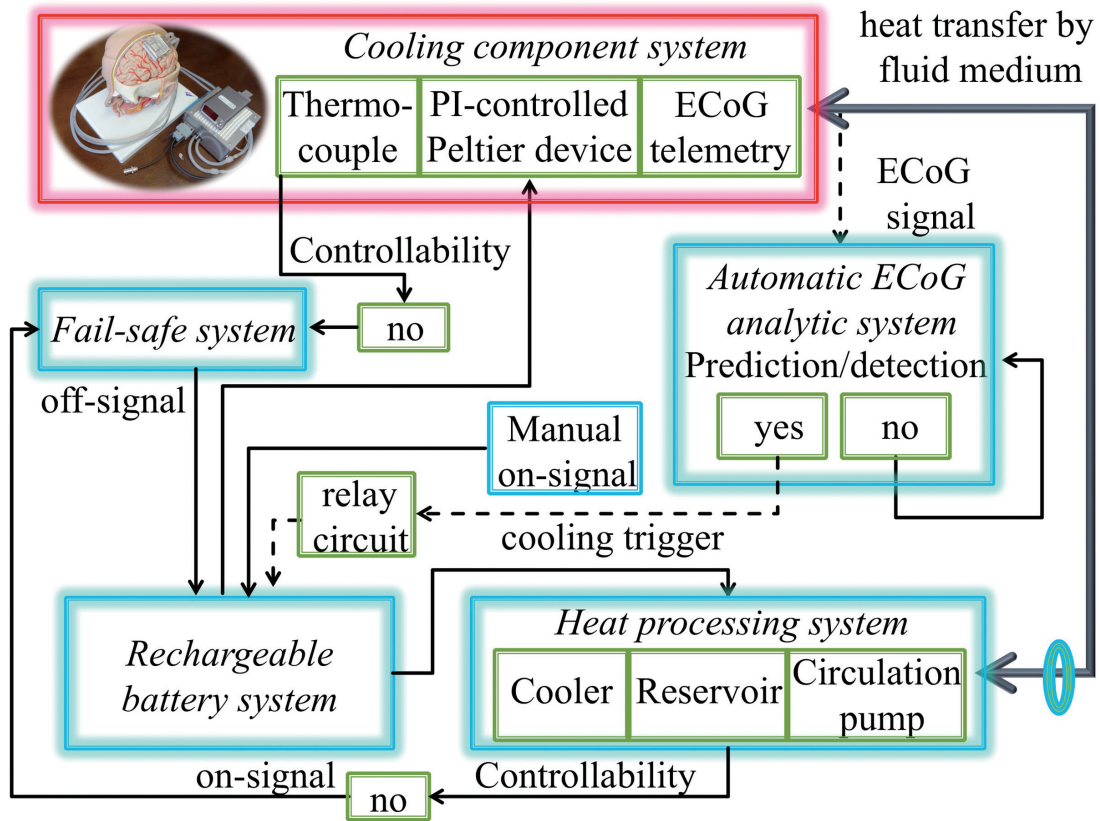


Fig. 1 Flow chart of an implantable focal brain cooling system for intractable epilepsy. ECoG; electroencephalogram.

ply, EEG detection system, and thermometer are also required. However, precision devices and micro-electromechanical technology have made remarkable advances that are likely to facilitate development of micropumps, micro-batteries, and microcharging systems. The continuing development of this equipment suggests that an implantable local cooling system may become available in the near future.

Proposal for "thermal neuromodulation"

In this review, we discussed brain cooling for treatment of intractable epilepsy. However, clinical demand for a focal-cooling device will not be limited to the epileptic field; other potential applications include treatment of cerebrovascular diseases in post-stroke rehabilitation,^{38,39} neurotrauma,³⁸ and pain,⁴⁰ all of which depend on "thermal modulation" of neuronal excitability. Therefore, thermal neuromodulation has considerable potential as a new therapy for serious neurological dis-

orders.

Conclusion

Focal brain cooling terminates EDs and modulates seizures. These findings have promoted development of implantable focal cooling devices with a closed-loop system (seizure detection and focal cooling) for use in neuromodulation. However, several hardware components of these devices require optimization before clinical use can be considered.

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Conflict of Interest

The author states no conflict of interest.

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