The Therapeutic Potential of Focal Cooling for Neocortical Epilepsy

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Summary: The therapy of the focal cortical epilepsies remains unsatisfactory. Close to a third of patients fail to gain adequate control with antiepileptic drugs and a portion of those who do, experience unacceptable side effects. Moreover, the favorable response rate after surgical resection, approximately 60%, is not nearly as high as the response rate of complex partial seizures caused by mesial temporal sclerosis. The suppressive effect of cooling on neuronal activity has been recognized for over a century. Therefore, we have begun to explore the possible application of cooling as a therapy for focal cortical seizures. In initial brain slice experiments, we found that cooling to 20° C could rapidly terminate paroxysmal activity. Then we developed an *in vivo* model of focal seizures using a local

injection of the convulsant 4-aminopyridine and found that cooling the injected area to less than 24° C with a thermoelectric Peltier device aborted seizures within a few seconds. Other laboratories have independently confirmed our initial observations. More recent experiments from our laboratory have shown that cooling, *per se*, is not associated with significant cortical damage, even at surface temperatures as low as 5° C. Advances in the fabrication of extremely thin thermoelectric devices, less than a few hundred microns thick, has raised the possibility of incorporating an implantable cooling unit into a closed loop seizure detection and treatment system. **Key Words:** 4-aminopyridine, cooling, hypothermia, Peltier device, thermoelectric cooler (TEC).

INTRODUCTION

The end of the twentieth century produced remarkable advances in the understanding and treatment of many of the epilepsies. Scientific speculation that some genetic epilepsies were caused by mutations in ion and voltage-gated channels was validated by a series of landmark genetic discoveries. New anticonvulsants, several with highly favorable therapeutic indices, were introduced. Sensitive magnetic resonance and positron-emitting based imaging tests that revealed the focal cause of many complicated, symptomatic epilepsies emerged and evolved very rapidly. Finally, the once radical therapeutic option of surgical resection entered the epilepsy mainstream.

Despite this progress, many patients with epilepsy have been left behind. The focal extratemporal epilepsies have remained especially problematic. Accounting for up to half of patients with poorly controlled seizures, focal and multifocal seizures arising from the neocortex have

proven extremely refractory to both conventional anti-convulsant therapy and the newer surgical approaches. Even with guidance from modern imaging techniques that allow functional anatomic correlation of seizure onset with surface rendering of the neocortex, the surgical treatment of extratemporal epilepsy results in seizure freedom in 36 to 76% of patients.¹ There are at least three reasons why surgical management of neocortical epilepsy is so difficult. First, conventional neurophysiological techniques frequently have a difficult time localizing a patient's seizures. Second, identification of specific neurological function(s) residing in the seizure onset zone, which is essential for an accurate prediction of adverse effects of resection, can be very difficult. Third the expectation that resection will leave a permanent neurological deficit precludes surgery altogether.

ALTERNATIVES TO PERMANENT RESECTION FOR NEOCORTICAL EPILEPSY

A variety of invasive but nondestructive strategies have recently been used or proposed to reduce the frequency and severity of neocortical seizures. For the past 15 years, vagal nerve stimulation has been used for a

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subset of children and adults with refractory epilepsy.² While clinical studies have validated its efficacy, the overall reduction in seizure frequency with vagal nerve stimulation was 28% in one randomized control trial.³ Although this represents an improvement in seizure control for some patients, the improvement in quality of life is insubstantial for many patients. There is some experimental evidence that trigeminal nerve stimulation might provide better seizure control, but as yet, there have been no human studies of this modality. Transcranial magnetic stimulation for epilepsy has been described in several publications. The initial reports were optimistic, but subsequent controlled prospective trials have not shown significant reduction in seizure frequency.⁴ *In vitro* brain slice studies have shown that direct application of a constant or DC electrical field can diminish neuronal excitability and experimental seizure discharges, but this technique has not been tried yet in experimental seizure models in live animals.⁵

There is limited experience with several variations of intermittent electrical stimulation for human epilepsy. Recent publications have identified subsets of patients who benefited from intermittent hippocampal or thalamic stimulation.^{6,7} These results are still too premature to allow definite conclusions, but a large, prospective trial of anterior thalamic nuclear stimulation is close to completion. The most sophisticated intervention currently in clinical trials is a totally implantable, closed-loop feedback system for seizure detection and cortical stimulation to terminate focal seizures. Using the same electrodes for recording and stimulation, along with a custom designed seizure detection algorithm, this device has been able to abruptly terminate seizures by delivering a burst of stimulation lasting approximately a tenth of a second.⁸ The use of this device is being tested at this time in prospective clinical trials at several North American epilepsy centers.

COOLING AND THE BRAIN

An extremely attractive, nondestructive strategy for terminating and possibly preventing focal seizures would be focal cooling. There is extensive neurophysiological literature documenting that cooling reduces synaptic transmission in the mammalian brain, and it should be possible to use new engineering technology to deliver very focal cooling. The first descriptions of the central neurological effects of focal cooling come from articles written by Stefani⁹ and Deganello¹⁰ at the end of the nineteenth century. A decade later, the German physiologist Trendelenburg began a systematic study of local hypothermia, investigating its effects on both brainstem autonomic reflexes and the neocortex.¹¹ While lacking any cellular insights, all three investigators concluded that cooling reduced neurological function at the system

level. Throughout the rest of the 20th century, physiologists continued to use local cooling to investigate cortical and subcortical localization of specific brain functions.

Information about the neurobiological effects of cooling advanced for the last 50 years. Using intracellular recording at the frog neuromuscular junction, Katz and Miledi¹² showed that cooling prolonged the latency of end plate potentials, likely by desynchronizing acetylcholine release from presynaptic terminals. More recent experiments in mammalian tissue culture and brain slices have shown that cooling affects neurotransmission by both pre- and postsynaptic mechanisms.¹³ Cooling can augment the magnitude of neuronal action potentials and inhibits the sodium-potassium adenosine triphosphatase. Although the initial adenosine triphosphatase inhibition and concomitant cell depolarization may elicit transient hyperexcitability, cooling eventually reduces neuronal excitability. Our own recent observations indicate that hypothermia rapidly reduces transmitter release from presynaptic vesicles and suggest that this may be a dominant effect of rapid cooling on central neuronal excitability.¹⁴

The potential clinical utility of cooling for neurological disease has been discussed for half a century. Fay¹⁵ began an extensive investigation of brain cooling in 1938. He suggested that either systemic hypothermia or local cooling of the brain with cooled fluid circulating through a sealed metal capsule might be an efficacious treatment for head trauma and intractable pain. He also believed that reducing brain temperature might inhibit tumor growth and tried intracranial cooling for inoperable gliomas. More recent controlled studies have reported benefits of cooling patients after acute head trauma or asphyxia. Interestingly, the temperature reduction in these recent clinical reports is generally no more than 4° C, which would not be expected to have a very large effect on synaptic transmission. This is also a much smaller drop than the cooling required to terminate experimental seizures.

Physicians have been aware of a causal relationship between elevated temperature and seizures since Hippocrates. Moreover, numerous *in vitro* and *in vivo* experimental epilepsy studies have consistently demonstrated that cooling reduces paroxysmal bursting and can diminish or stop seizure activity. There are encouraging clinical reports suggesting the utility of brain cooling for human seizures as well. At least three separate clinical investigations have documented the efficacy of cooling in the therapy of patients with intractable status epilepticus or chronic, recurrent seizures. The initial article showed that externally cooling (31–36° C) six patients with refractory status epilepticus stopped seizures in five.¹⁶ The second article described 25 patients, ranging in age from 8 to 46, who had frequent major motor

FIG. 1. Photographs of thermoelectric or Peltier devices. A: Commercially available Peltier devices. Peltier on left is filled with epoxy so that it is impermeable to body fluids. Device on right shows the individual semiconductors connecting the two ceramic wafers. B: Peltier device fabricated by thin film technology on surface of conventional device. The new devices can be less than 0.2-mm thick.

seizures poorly controlled on chronic anticonvulsant therapy.¹⁷ While under general anesthesia, they were placed in an enclosed chamber and chilled to 29° C with cold air. At that point, bilateral frontal burr holes were opened and the subarachnoid space or ventricles were irrigated with iced saline, which reduced cortical surface temperature below 24° C in 21 of the patients. A total volume of 500 to 20,000 cc of saline was infused into the patients after they slowly recovered from anesthesia. Of the 15 patients followed-up for 1 year, 11 showed a marked reduction in seizure frequency, including 4 who had been seizure free. The third article documented resolution of intractable status epilepticus by vascular cooling to 31 to 35° C in 4 patients whose seizures persisted, despite aggressive intravenous drug therapy that included continuous midazolam or pentobarbital infusion.¹⁸

Two more recent descriptions of direct cooling of human brain during operative neurosurgical mapping have confirmed that acutely lowering cortical temperature will terminate paroxysmal discharges.^{19,20} In these cases, focal spikes abruptly stopped when iced saline was applied to the neocortex in the operating room. Both sets of studies have encouraged the development of more convenient methods of brain cooling for epilepsy.

COOLING METHODOLOGY

It would be impossible to design a practical cooling device for epilepsy therapy based on circulating cold water or conventional refrigeration methodology. However, improvements in thermoelectric devices and the necessary supporting technology have allowed us to re-evaluate cooling as a therapy for some forms of epilepsy. Thermoelectric devices exploit Peltier's 1834 observation that a temperature gradient develops at the junction between two dissimilar conductors when an electric current is applied across them. The discovery in the 1920s that synthetic semiconductors were superior to metals as thermoelectric elements hastened progress in this field.

The development of modern semiconductors, typically alloys of bismuth, tellurium, selenium, and antimony, has made possible the fabrication of small, light thermo-

electric modules or Peltier devices, only a few mm in length and width and 1.5-mm thick (FIG. 1A). In these modules, pairs of N- and P-type semiconductors are connected between two ceramic plates so that they are electrically in series and thermally in parallel. The newest thermoelectric devices are fabricated with thin film technology developed for the microelectronics industry and are less than 200 μ m thick. They have up to 10 times the heat pumping capability of conventional devices, making them ideal for medical devices (FIG. 1B).

Thermoelectric devices are capable of generating temperature differentials of 70° C, but for these differentials to result in cooling, heat must be efficiently removed from the hot side. For most of our work, we have attached the hot side of the device to a copper rod, which both removes heat and acts as a convenient holder for a manipulator.

RESULTS WITH EXPERIMENTAL EPILEPSY

In 1999, we became aware of the attractive features of commercially available thermoelectric devices and began experiments to determine whether they could terminate acute seizures. Initially, we induced seizures in rat hippocampal brain slices by perfusing them with 4-aminopyridine, a blocker of voltage-gated potassium channels, and a well-established convulsant. We positioned the slices on the surface of a thermoelectric device that had been machined into a clear plastic chamber. In this configuration, we were able to rapidly cool the slices at the onset of electrographic ictal-like behavior. We found that cooling to 20° C quickly terminated this paroxysmal activity and also reversibly inhibited evoked field potentials.²¹

These positive *in vitro* results encouraged us to attempt to suppress ictal activity *in vivo*. We found that we could reliably induce focal seizures in halothane-anesthetized rats with a 4-aminopyridine solution. The drug was inserted 0.5 mm below the pial surface of the motor cortex using a micropipette. The animals developed recurrent focal seizures within 20 minutes and continued to have electrographic seizures for approximately 2 hours. Untreated seizures lasted between 60 and 80 seconds.

When we allowed a thermoelectric device to directly contact the neocortex immediately above the injection site and activated cooling to 20° C at seizure onset,

seizure duration was reduced to approximately 7 seconds (FIG. 2).²²

This rapid effect must be due to the local cooling, because the thermoelectric device did not influence seizure duration if it was not in direct contact with the cortical surface. In this preparation, there was a progressive decrease in seizure duration below 26° C, but no difference between 22 and 20° C.²³ We have not yet tried temperatures below 20° C. It is possible that our preparation leads us to overestimate the degree of cooling required for seizure termination, because another group has shown that paroxysmal discharges in a slice model of epilepsy were eliminated by rapid temperature reductions of only 1° C.²⁴

After completing our initial cooling experiments, we developed a frequency-based seizure detection algorithm for the 4-aminopyridine seizures, which allowed us to use a closed-loop system to abort seizures. To minimize false positives, we set a relatively high threshold before cooling was activated. In these circumstances, our closed-loop system was as effective in terminating seizures as manual activation. Had we decided to accept more false positives, we could have initiated more rapid cooling and further reduced seizure duration.²³

We have investigated other important aspects of cooling for focal seizures. Using a small thermocouple inserted into a 30-gauge needle, we mapped the cortex below our thermoelectric device and showed that cooling extends only approximately 4 mm below the surface. Thus, its effect should be localized to just a small region of neocortex below the pia.

Recent work has explored the possibility of brain damage induced by local cooling. Thus far, we have not seen any evidence that cooling as low as 5° C for 2 hours produces neuronal loss or activates apoptotic pathways.²⁵ While there is minimal gliosis close to the region of cortical contact with the Peltier, it is similar to the response provoked by any foreign body and cannot be attributed to cooling. Interestingly, when brain slices obtained from transgenic mice expressing the green fluorescent protein (GFP) were cooled to 5° C, there was transient, but completely reversible blebbing of dendrite shafts and loss of spines (FIG. 3). This is probably secondary to ion pump inhibition, because other investiga-

FIG. 2. Cortical cooling significantly reduces the duration of seizures. A: Cooling shortens the duration of the entire group of cooled seizures, as well as the first cooled seizure in each animal. A and B: Different from C and D ($p < 0.001$; Tukey test). B: Control, uncooled seizure durations decreased during a 2-hour observation period, but were still significantly longer than cooled seizures (see text). C: Control seizures were longer than first through sixth cooled seizure groups ($p < 0.001$; Tukey test). However, the durations of the first through sixth cooled seizure groups were not significantly different from each other. (Reprinted from Yang X-F, Rothman SM, *Annals of Neurology* 2001;49:724.²²)

FIG. 3. Effect of cooling on dendritic spines in mouse hippocampal slices, imaged with 2-photon microscopy. A: Control slice from mouse expressing GFP has multiple spines readily identified in a single section from a Z-stack (arrows, A1). After 60 and 120 minutes (A2 and A3, respectively) at 32° C, the same spines are still evident. B: Cooling the perfusate to 5° C reversibly alters dendritic anatomy. Spines are easily seen in control slice (arrows, B1). After 30 minutes, there is beading of the dendritic shaft (arrowheads), but some spines are still present (B2). After 15 minutes of rewarming to 32° C, the beading has disappeared and the spines that were initially present are evident again (B3). Calibration bar in B3 is for entire figure, 5 μ m.

tors have made similar observations after treating brain slices with Na^+/K^+ -adenosine triphosphatase inhibitors.

We have also failed to observe any neuronal loss in cat neocortex, after 7 to 10 months of intermittent cooling during neurophysiological experiments.²⁵ These results make us optimistic that the effect of cooling will be exquisitely focal and well tolerated.

A series of more recent experiments have replicated and extended our observations that cooling attenuates experimental epilepsy. In kindled rat hippocampal seizures, cooling between 23 and 26° C, with saline flowing through thin copper tubing next to the dorsal hippocampus, reduced both seizure severity and after discharge duration.²⁶ Another laboratory using Peltier devices almost identical to those used in our work, has shown that cortical excitability triggered by local injection of kainic acid is reduced by focal cooling.²⁷ This group then showed that they could cool deep into the rat hippocampus by attaching an insulated needle to a Peltier device held away from the brain surface.²⁸

A limited set of unpublished observations on a single monkey have verified that our thermoelectric device is capable of inhibiting function in the primate neocortex. When our thermoelectric device was placed in direct contact with the pia on the surface of the hand region of the pre-central gyrus, there was a consistent, reversible impairment in skilled finger movements associated with a reduction in surface temperature. This indicates that the small thermoelectric devices have sufficient power to

cool primate cortex. Of note, even with cooling to 10° C, the impairment was not instantaneous and did not completely paralyze hand movements.

To move ahead with the design of a fully implantable cooling device for human focal epilepsy, we have begun to address the problem of heat dissipation from the hot side of thermoelectric devices. Although a copper rod has worked well for experiments in anesthetized or immobilized animals, a more compact device will be required to transfer heat from a clinical device. There is extensive literature describing heat pipes, which are hollow, evacuated, wicked tubes that rapidly equilibrate temperature by allowing a liquid to alternately evaporate and recondense under reduced atmospheric pressure. Our engineering colleagues have designed a thin, bendable, laminar heat pipe composed of outer layers of copper foil and an inner layer of sintered copper columns sandwiched between two layers of sintered copper.²⁹ The pipe contains water at low pressure, which vaporizes at the warm end, condenses at the cool end, and is wicked back to the warm end, thereby transferring heat. The mechanical properties of this heat pipe indicate that it should be capable of diffusing sufficient heat from a thermoelectric device in contact with the cortex to maintain a cold side temperature of 20° C without heating the adjacent brain above 38° C. We envision positioning a similar heat pipe between the hot side of a thermoelectric device and dura, skull, or scalp, so that heat can be efficiently transferred to one of these highly vascular compartments.

THE PATH TO CLINICAL COOLING?

The most critical question at this time is the degree of cooling required to terminate or prevent *human* focal seizures, and rodents are unlikely to inform us about this question. There is no rodent model of chronic focal epilepsy that reliably reproduces the human condition and the 4-AP model, which we have used in our studies, is much more severe than even the most refractory human epilepsy. The rats typically have 60- to 80-s seizures every 2 to 3 min, which is an unrealistically high frequency for almost all human epilepsies. Therefore, it seems likely that rodent focal seizures require a much larger temperature reduction than human seizures. This information is critical because the required degree of cooling will govern the current required to power the thermoelectric device. Moreover, the degree of cooling will determine the amount of heat that has to be dissipated to the vasculature or dura through the heat pipe.

We believe that the most efficient way to sort this out will entail fabricating a cooling device that uses cold saline rather than a thermoelectric device. The device would combine a conventional silastic grid used for invasive monitoring and a bladder through which cold saline flows. After preliminary testing in a large animal to verify safety and cooling ability, the device could be temporarily implanted in focal seizure patients during monitoring, prior to surgical resection. It would permit determination of the degree of cooling required to stop seizures without having to cope with heat dissipation. Once the cooling parameters have been better defined, it will be possible to rationally design an implantable device using thermoelectric technology.

There are several clear obstacles and objections that need to be addressed before focal cooling can be used to treat human epilepsy. First, the convolutions of the human brain keep approximately two-thirds of the neocortex buried in sulci and inaccessible to surface cooling. However, it should still be possible to cool portions of the substantial area of exposed cortex that are responsible for seizure generation. In addition, cooling the lip of cortical sulci may block the spread of seizures arising within the sulci, a suspected mechanism of seizure generalization. It should even be feasible to connect thin, flexible heat pipes to thermoelectric devices to cool structures deeper in the brain.

Second, cooling may be as disruptive to normal brain function as some seizures. We are optimistic that there may be a temperature range that separates seizure control from disruption of normal cortical function. The results of Bakken and colleagues³⁰ that cooling below 10° C over eloquent cortex did not produce a complete anomia or nonfluent aphasia support this hope.

Third, although we are concerned that the current requirements for present commercial thermoelectric de-

vices exceed an ampere, the short-duty cycle may allow these devices to operate for long periods without recharge or replacement. Moreover, improvements in battery life and thin-film, thermoelectric design should make it possible to generate more efficient devices soon.

Fourth, while there is presently no fully validated algorithm for seizure detection or prediction, other sections of this monograph suggest that these remain attainable goals.

Variations of these algorithms are currently undergoing trials in devices using either an external or implanted detection system linked to electrical stimulation. There is nothing about these systems that would preclude replacing stimulation with cooling as the efferent arm of the device.

Full implementation of cooling as a clinical therapy will still require further research. However, given the steady neurobiological progress for the last 5 years and the rapid advances in all aspects of the engineering relevant to our work, it would be reasonable to anticipate some investigational application of cooling for epilepsy therapy by the end of the decade.

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