Neuroscience Research 122 (2017) 35–44

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Epidural focal brain cooling abolishes neocortical seizures in cats and non-human primates

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ARTICLE INFO

Article history:
Received 27 March 2016
Received in revised form 7 February 2017
Accepted 7 April 2017
Available online 24 April 2017

Keywords:
Epilepsy
Implantable device
Focal brain cooling
Hypothermia
Neuromodulation
Motor cortex
Penicillin G

ABSTRACT

Focal brain cooling (FBC) is under investigation in preclinical trials of intractable epilepsy (IE), including status epilepticus (SE). This method has been studied in rodents as a possible treatment for epileptic disorders, but more evidence from large animal studies is required. To provide evidence that FBC is a safe and effective therapy for IE, we investigated if FBC using a titanium cooling plate can reduce or terminate focal neocortical seizures without having a significant impact on brain tissue. Two cats and two macaque monkeys were chronically implanted with an epidural FBC device over the somatosensory and motor cortex. Penicillin G was delivered via the intracranial cannula for induction of local seizures. Repetitive FBC was performed using a cooling device implanted for a medium-term period (FBC for 30 min at least twice every week; 3 months total) in three of the four animals. The animals exhibited seizures with repetitive epileptiform discharges (EDs) after administration of penicillin G, and these discharges decreased at less than 20 °C cooling with no adverse histological effects. The results of this study suggest that epidural FBC is a safe and effective potential treatment for IE and SE.

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1. Introduction

Intractable epilepsy (IE) is a major public health concern that has an anatomical and electrophysiological basis and may afflict more than 10 million people worldwide. Antiepileptic medication is used as initial treatment for epileptic seizure. However, benzodiazepines, phenytoin, and phenobarbital fail to terminate or inhibit seizures in 30–50% cases, and cases of longer duration become more difficult to treat. For status epilepticus (SE) (Lowenstein and Alldredge, 1993), hypothermia may be useful for control of continuous seizures, reducing the need for high-dose barbiturates, benzodiazepines, and vasopressors (Corry et al., 2008), but also has several associated side effects. Therefore, different approaches are needed to abolish seizure activity and reduce brain injury in this population.

In response to this challenge, several intracranial therapeutic approaches have been developed for treatment of IE or SE that is not amenable to surgery or high dose medication. These include antiepileptic drug-releasing intracortical polymers (Tamargo et al., 2002), hybrid neuroprostheses for transmeningeal pharmacotherapy (Ludvig et al., 2009; Stein et al., 2000), deep brain stimulation (DBS) (Gigante and Goodman, 2011), cortical stimulation such as that with the Responsive Neurostimulation (RNS) (Bezard et al., 1999; Blauwblomme et al., 2011; Gigante and Goodman, 2011), and vagus nerve stimulation (VNS). Among these therapeutic devices, DBS, RNS and VNS apparatuses are in clinical trials or in use, whereas the other methods are in the preclinical phase. In the first VNS study (EO3), 50% of the patients wanted to continue the stimulation treatment after the study period (Boon et al., 1999). Clinical trials of RNS and DBS (RNS trial and SANTE, respectively) have not clearly demonstrated a significant quality-of-life benefit attributable to reduction in seizure frequency during blinded

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http://dx.doi.org/10.1016/j.neures.2017.04.007
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comparison phases (Gigante and Goodman, 2011). However, these approaches show promise for treatment of IE.

Focal brain cooling (FBC) is well established as a method for suppressing epileptic discharges (EDs). Partial support for this effect was obtained in an intraoperative experiment in which partial epileptic activity was suppressed during surface cooling of the brain of epileptic patients through bath application in saline at 4 °C (Karkar et al., 2002). Our previous studies (Imoto et al., 2006; Kida et al., 2012; Oku et al., 2009) and that of others (Yang and Rothman, 2001) have shown that use of a Peltier device can suppress EDs induced by cerebral infusion of kainic acid and penicillin G without causing histological damage in anesthetized rats. In a chronic rat model of partial neocortical epilepsy of the sensory motor cortex, we demonstrated suppression of EDs by focal cortical cooling induced by a Peltier device, and showed that this cooling had no discernible effect on normal cortical functions (Fujii et al., 2012). However, more evidence is required to determine whether FBC can be applied to large animal models and used clinically.

The Peltier device can produce effective cooling through direct contact with the brain. However, application of this device in large animals is highly restricted because fabrication of a brain-like curved shape is difficult with a Peltier device and integration of a fail-safe system is required because the Peltier device consumes a large amount of electrical power and loss of control of the temperature control system can cause brain injury. FBC using a recirculating coolant cooling system has been studied for many years (Brinkman et al., 1985; Lin et al., 1993; Sasaki and Gemba, 1984) and has recently been examined for head injury in focal cerebral cooling using the ChillerPad^{TM} system (King et al., 2010). These studies suggest that the use of cold coolant for focal cortical temperature control gives an adequate cooling performance and provides a therapeutic effect in the injured area. Cook and coworkers have also described an inexpensive and implantable cooling device for FBC that allows cooling of both the brain surface and cerebral sulcus (Cooke et al., 2012). However, 100% ethanol is used as a coolant, which raises a concern regarding leakage of ethanol from the cooling system to the brain surface. In contrast, we have chosen to use direct cooling with cold lactated Ringer's solution using a metal plate with an inner coolant channel, which we believe will be adequate in large animals.

Burton and colleagues developed a transcortical cooling plate made of copper to inhibit hippocampal-kindled seizures in rat, and showed that kindling-induced tonic–clonic seizures could be suppressed with cooling (Burton et al., 2005). Hence, we recently developed a titanium cooling plate to allow FBC directly over an epileptic focus without whole-body cooling (Inoue et al., 2011). This plate provides stable cooling without the temperature limitations associated with cardiac instability or shivering, and for prolonged periods compared with hypothermia. To extend the FBC studies mentioned above, in this study a titanium cooling plate was used in cat and monkey models to investigate the medium-term cooling performance and beneficial effect on seizure reduction, with the goal of examining the therapeutic efficiency of epidural cooling for epileptiform seizure in large animals.

2. Materials and methods

2.1. Animals

A male cat A (weight: 2.6 kg), a female cat B (2.8 kg), and two female Japanese monkeys (*Macaca fuscata*; A: 6.0 kg and B: 5.8 kg) were used in the study. All procedures were performed according to the guidelines of the Committee for Animal Experimentation at the Graduate School of Medicine, Yamaguchi University.

2.2. Surgical procedures in cats and monkeys

Animals underwent overnight fasting prior to the surgical procedures, which were performed under general anesthesia. Preoperative medication for monkeys included ketamine (7.5 mg/kg), medetomidine (0.05 mg/kg), and cefazolin (40 mg/kg), followed by inhalation of sevoflurane anesthesia. Cats were sedated with medetomidine (0.08 mg/kg) and cefazolin (40 mg/kg), followed by inhalation of sevoflurane anesthesia. Electrodes for electrocardiography and pulse oximetry were used, an intravenous catheter was inserted into the femoral vein for fluid supply (lactated Ringer's solution), and the body was warmed with a warming pad and blanket to prevent hypothermia. Using endotracheal intubation, anesthesia was maintained with sevoflurane (1–3%) inhalation in oxygen (60–99%) (A.D.S. 1000 Model: 2000, Sanko, Saitama, Japan). The head was placed in a stereotaxic apparatus (SN-2N; Narishige, Tokyo, Japan) for immobilization during surgery. The cooling plate, ECoG electrodes, thermosensor, and cannula were implanted into the left hemisphere in all animals.

In cat, the skull was exposed, and a craniotomy was drilled over the left frontal-parietal area to expose the somatosensory-motor area. The cats underwent implantation of ECoG electrodes (FUL-501, Unique Medical Co., Tokyo, Japan), a thin thermocouple (IT-23, Physitemp Instruments Inc., Clifton, NJ, USA), a penicillin G injection cannula (CBAS-C30, Instech Laboratories Inc., Plymouth Meeting, PA, USA), and a titanium cooling plate (Fig. 1A). The cannula and thin thermocouple were inserted longitudinally in the subdural space from the caudal toward the rostral after a small perforation of the dura mater was made. The cooling plate was epidurally and tightly attached to the brain surface via the dura mater to cover the primary motor area precisely (superior aspect of the cruciate sulcus). Two Ag electrodes and two epidural screw electrodes were placed on the front end of the cooling plate (inferior aspect of the cruciate sulcus) in the right frontal and left occipital areas for reference and grounding of the animal, respectively. A head piece was mounted on the cooling plate and anchor screws, and fixed with dental cement (Unifast III, GC, Tokyo, Japan).

In monkey, somatosensory evoked potentials (SEPs) were recorded prior to implantation of the cooling plate to position an over the 'hand' representation on the convexity of the pre- and post-central gyri of the cerebral cortex. During motor seizures in monkey, ictal activity may be transmitted to post-central gyri through the tight anatomic projection systems from the brain (Kato et al., 1980). In experimental models of epilepsy, this event has been demonstrated electrophysiologically (Julien and Laxer, 1974) and autoradiographically (Kennedy et al., 1976). Therefore, to ensure suppression of seizures, we used a cooling plate covering both the pre- and post-central gyri of the left hemisphere (Fig. 1B). A craniotomy was performed to expose the somatosensory-motor area such that the central sulcus was positioned at the center of the cranial window. The dura mater of the caudal part of the cranial window was cut (4-mm width) and shape memory alloy electrodes, a fine thermistor (N312W/BR11KA202K, Nikkiso Thermo, Tokyo, Japan), and a penicillin G injection cannula which is the same one as used in cats were slipped into the subdural space from the caudal toward the rostral. The tip of the thermistor and cannula were kept above the motor cortex. The shape memory alloy electrode (1 kΩ ohm at 1 kHz), which is a subdural Ag electrode array guided by a 0.3-mm diameter guidewire for minimally invasive ECoG recording without inhibiting the cooling effect (Yamakawa et al., 2011), was unfurled at the center of the cranial window using the characteristics of shape change due to the temperature of the shape memory alloy. The cooling plate was epidurally attached to the dura mater in close contact with the brain surface and self-tapping screws were fixed to bone around the edge of the opening in the skull. Three additional anchor screws were implanted in the

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