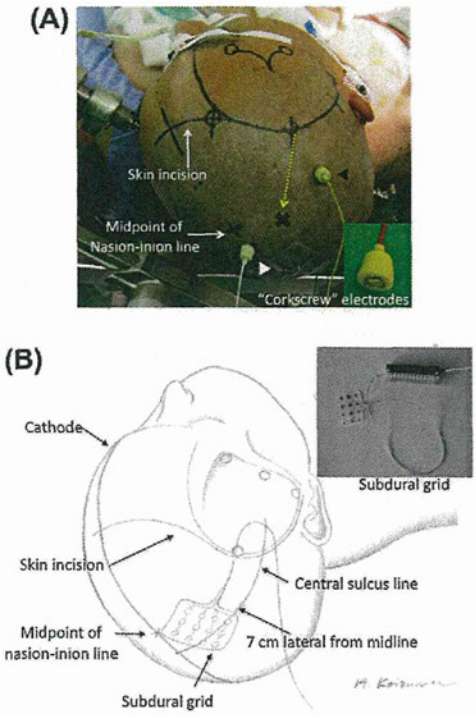

Fig. 1. Neurophysiological MEP monitoring methods. Intraoperative photograph (A) and schematic drawing (B) showing the placement of the subdural grid for electrical stimulation during pterional craniotomy. A: "Corkscrew" electrodes placed at Cz′ (white arrowhead) and C3 of the international 10–20 system (black arrowhead). A yellow dotted line and a bold "×" mark (C2 of the international 10–20 system) indicate the direction of grid insertion. B: the ideal position of the subdural grid is indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

landmarks ('Corkscrew' electrodes) on the scalp (Fig. 1A). Ideally, the optimal contact was located 2–2.5 cm lateral from the midline on the motor cortex for recording constant MEP responses (Fig. 1B). A strip electrode was also available for use when damage of well-developed bridging veins was likely from angiograms, but we generally used a grid electrode because an optimal contact was easily selected by a multi-channel somatosensory evoked potential (SEP) recording with a single insertion trial. In cases of bifrontal craniotomy for ACA distal aneurysms or frontal lobe tumours, a subdural strip (six contacts) was placed bilaterally and parallel to the sagittal sinus 2 cm lateral from the midline as the grid crossed the surface of the motor cortex. In cases where the motor cortex was exposed in the range of craniotomy, a strip or grid electrode was placed directly over the motor cortex on the convex side.

2.2.2. Stimulation and recording conditions

The contact in the subdural grid or strip providing the highest MEP amplitude was chosen for the optimal site of the anode. The subdermal needle electrode was placed at the Fpz (International 10–20 System) for the cathode. Anodal-electrical monopolar stimulation was performed for eliciting LE-MEPs with DCS, with short trains of five stimuli consisting of rectangular pulses with an individual pulse width of 0.5 or 1.0 milliseconds (ms) and an interstimulus time interval of 2 ms. Compound muscle action potentials were recorded using sterilised needle electrodes inserted into the soleus or anterior tibial muscles or abductor hallucis muscles (the abductor hallucis muscle was commonly used as a recording site). A bandpass filter was set from 30 to 3000 Hz.

Intra-operatively, the stimulus intensities of DCS were maintained at 2 mA above the threshold level of the MEP without exceeding 30 mA (Neuloh et al., 2004). An amplitude decrease of 50% or more in three or more consecutive MEP recordings was taken as a warning criterion, even when increasing the stimulus intensities by 20% or more (Fujiki et al., 2006; Neuloh et al., 2004; Neuloh and Schramm, 2004b). These MEPs were recorded using Viking Select and Endeavor monitoring systems (Nicolet Instruments, Biomedical Division, Madison, WI, USA).

2.3. Anaesthesia

Anaesthesia was induced with a bolus of propofol (1 mg kg^{-1}) and remifentanyl (0.5 μg kg^{-1}), and maintained with propofol (6 mg kg^{-1} h^{-1}) and remifentanyl (0.1–0.2 μg kg^{-1} min^{-1}). A short-acting muscle relaxant was administered as a bolus for intubation purposes only.

3. Results

The stimulus parameters and results of LE-MEP monitoring are listed in Table 1. MEP monitoring was consistently performed in all patients. The applied stimulus intensities ranged from 12.5 to 30.0 mA. A pulse width of 1.0 ms was selected in the first three cases for obtaining constant LE-MEP waveforms. Thereafter, the pulse width was reduced to 0.5 ms to avoid excitotoxicity because in our experience, LE-MEPs could be constantly recorded with a shorter pulse width.

Significant MEP changes were observed in five patients (23%) during the surgical procedures. These changes occurred after the temporary occlusion of an artery supplying blood flow to the motor cortex of the lower extremity and the MEPs had recovered almost to the control level by dural closure. Postoperatively, although *de novo* motor weakness was found in the first postoperative examination in two patients (cases #1 and #18), permanent motor deficit did not occur in these patients. The initial Medical Research Council (MRC) Scale scores for muscle strength and deficit duration to full recovery of these patients (cases #1 and #18) were as follows: case #1, left extremity: 2/5, for 42 days; case #18, right extremity: 3/5, left extremity: 2+/5, for 26 days. Of the five patients who had MEP changes, one (case #1) developed lacunar infarction in the right basal ganglia. The other four patients did not develop new lesions based on postoperative neuroimaging with magnetic resonance imaging (MRI) or computed tomography (CT). There were two true positives, three false positives, 16 true negatives and one false negative for transient early postoperative motor deficits (Table 1). These data gave a sensitivity of 66.7% (2/3 cases), a specificity of 84.2% (16/19 cases), a positive predictive value (PPV) of 40.0% (2/5 cases) and a negative predictive value (NPV) of 94.1% (16/17 cases).

No significant MEP changes were observed during surgery, but a transient motor weakness was observed postoperatively in a patient with falx meningioma (case #7). Motor weakness was found in the first postoperative examination and the initial MRC Scale score was 3+/5 in the right extremity, with a deficit duration to full recovery of 8 days. Body movements, which could interfere with microsurgical dissection, were not induced by DCS. Minor and controllable bleeding from the bridging vein occurred in one patient during placement of a grid electrode. No other adverse events were observed in the manipulation of LE-MEP monitoring.

4. Illustrative cases

A 59-year-old female patient (case #8) was admitted with symptoms of a severe headache and vomiting. Neuroimaging

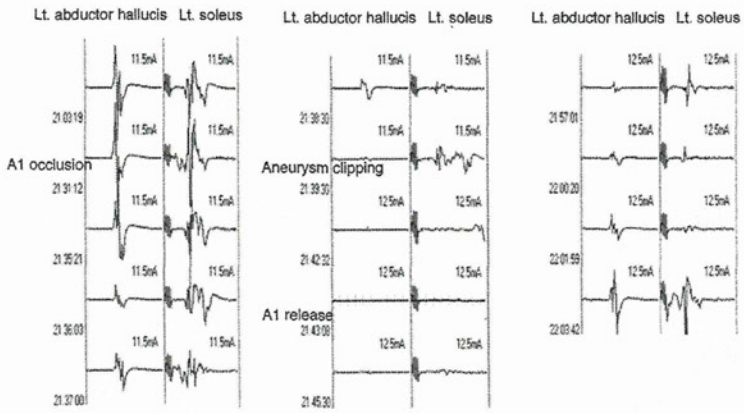

Fig. 2. The waveforms of MEPs recorded from the left soleus and the adductor hallucis are indicated. The MEP decreased in amplitude and disappeared after the proximal right-ACA (A1) was occluded. Although the MEPs disappeared for 8 min, they recovered after permanent clipping of the aneurysm and release of the A1 occlusion.

revealed subarachnoid haemorrhage (SAH) and an AcomA aneurysm. Right pterional craniotomy and neck clipping of the aneurysm were immediately performed. Preparation for MEP monitoring was performed as described above and MEPs were recorded during the microscopic procedure. The amplitudes of the MEPs recorded from the left soleus and abductor hallucis muscle gradually decreased and then the MEPs disappeared after temporary occlusion of the proximal ACA. After permanent clipping was applied, the ACA was reperfused. Although the MEP waveforms disappeared for 8 min, they had recovered to the control level by the time of dural closure (Fig. 2). Postoperatively, no motor deficits were identified.

A 72-year-old male patient (case #18) was admitted with a symptom of impaired orientation. Neuroimaging revealed an azygos ACA and a huge ACA aneurysm that was partially thrombosed (Fig. 3A–D). The patient underwent bifrontal craniotomy and neck clipping of the aneurysm. Subdural strips (1 × 6 contacts) were placed through the craniotomy bilaterally and parallel to the sagittal sinus from 2 cm lateral to the midline (Fig. 4A and B). Before applying permanent clips for the aneurysm, the proximal portion of the ACA (azygos ACA) was temporarily occluded. MEP waveforms disappeared 20 min after occlusion. However, 22 min after releasing the temporary clip, the MEP waveforms had recovered to 75% of the previous amplitude (Fig. 4C). Although the patient temporarily had motor weakness in both lower extremities, the motor deficit had fully resolved at 26 days postoperatively.

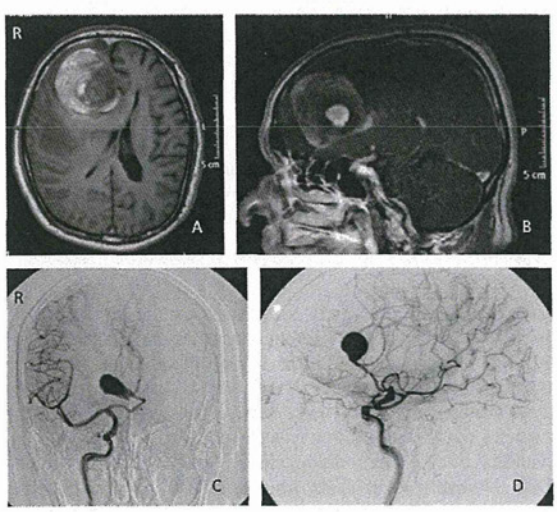

Fig. 3. Axial (A) and Gd-enhanced sagittal (B) T1-weighted MR images of a patient (case 18) with a thrombosed aneurysm of the ACA. Anterior (C) and lateral (D) views of digital subtraction angiography showing an azygos ACA and a thrombosed aneurysm.

A 56-year-old male patient (case #6) presented with focal seizures of the right fingers. The patient was diagnosed with a parasagittal meningioma of the left peri-rolandic area (Fig. 5A and B) and underwent surgery. Because the motor cortex was exposed in craniotomy, a subdural grid was placed directly on the motor cortex to cover the entire precentral gyrus on the convex side (Fig. 5C). The central sulcus was identified using a neuronavigation system (Stealth Station, Medtronics Inc., Minneapolis, MN, USA) and SEP recording. MEP waveforms were consistently recorded from the muscles of the upper or lower extremity by stimulating a contact on the hand area or on the motor cortex closest to the midline, respectively. The meningioma was safely removed while confirming no reduction in the MEP amplitudes of the upper and lower extremities during the excision (Fig. 5D).

5. Discussion

In the present study, we demonstrated consistent recording of LE-MEPs by applying DCS using a subdural electrode placed over the motor cortex on the convex side close to the midline. Szelényi et al. found that MEP waveforms from the lower-limb muscles could be recorded in only 55% of patients undergoing surgery for aneurysms in the ACA territory (Szelényi et al., 2005). Furthermore, there have been no detailed descriptions of methodology for LE-MEP monitoring using DCS for accurate monitoring. It is commonly believed that because the leg area of the motor cortex is hidden in the sagittal plane, it is difficult to monitor LE-MEPs. However, LE-MEPs were consistently recorded in the present series by identifying the optimal stimulation site on the primary motor cortex on the convex side, even in a pterional approach. Our study also indicates that LE-MEPs can be consistently recorded without placing an electrode for stimulation in the sagittal plane after dissecting the interhemispheric fissure.

It is necessary to explain why LE-MEPs could be recorded by stimulation of the convex side of the motor cortex close to the midline. As the leg area of the motor cortex is located in the interhemispheric

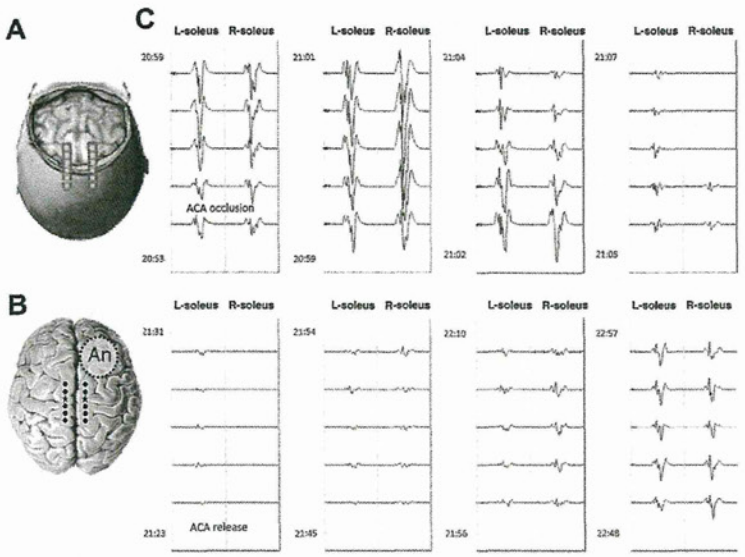

Fig. 4. Location of stimulus electrodes and MEP waveforms during surgery. Location of subdural strips with six contacts inserted from a cranial window (A). The stimulation sites are indicated by asterisks (B). The location of the aneurysm is indicated by An and a dashed circle-line. MEP waveforms disappeared 20 min after application of the temporary clip to the azygos ACA (C). However, the waveforms recovered to the control level 22 min after releasing the temporary occlusion.

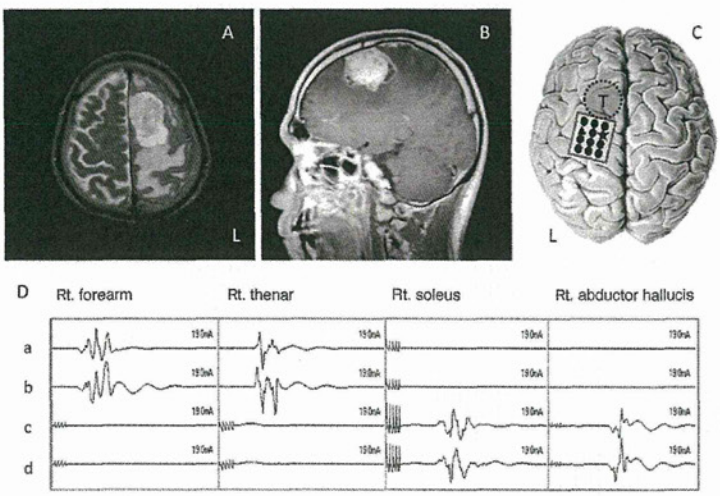

Fig. 5. Axial T2-weighted MR image (A) and sagittal Gd-enhanced T1-weighted MR image (B) of a patient (case 6) with a parasagittal meningioma. A 4 × 3 grid was placed directly on the motor cortex to cover the entire precentral gyrus (C). The stimulation sites for the lower and upper limb MEPs are indicated by an asterisk and a triangle, respectively. The location of the tumor is indicated by a T and a dashed circle. MEPs (D) were successfully recorded from the muscles of the upper (a and b) or lower (c and d) extremities, respectively.

fissure, we believe that the LE-MEP responses are elicited by stimulation of subcortical fibres from the leg cortex, rather than the pure leg motor cortex. In our experience, it was difficult to record LE-MEPs by bipolar stimulation between the two contacts over the motor cortex on the convex side. The most consistent recording was obtained by anodal–monopolar stimulation of the motor cortex with a frontal cathode at Fpz. Kombos et al. pointed out that because the current spreads transversely to the surface of the cortex with bipolar stimulation and longitudinally with monopolar stimulation, the effect of bipolar stimulation is on the level of the cortex, but monopolar stimulation spreads to the subcortical area and pyramidal tract (Kombos et al., 2001). Furthermore, for these reasons, bipolar cortical stimulation is recommended for intra-operative mapping of cortical functions such as speech (Kombos et al., 1999), and monopolar stimulation is recommended for monitoring of subcortical motor pathways (Kombos et al., 2009). According to previous studies and our own experience, the direction of the current spread significantly influences the elicitation of LE-MEPs, and the validity of our methodology for LE-MEP monitoring can be proved. However, when using monopolar DCS, a strong current may spread in the deep subcortical layer. Therefore, it is important to recognise that 'false-negative' results may occur due to direct cortical injury in the interhemispheric fissure and leave the efferent subcortical pathway intact, although direct damage of the leg motor

cortex only is unlikely in standard pterional and bifrontal craniotomy.

Based on the results that significant MEP changes were observed in five patients when the proximal arteries were temporarily occluded during aneurysmal clipping, we showed that the MEP responded sensitively to the insufficiency of arterial blood flow in the motor pathway of the lower extremity. Postoperatively, although two of these patients had transient weaknesses of the lower extremity, permanent motor deficit was not observed in any of the patients. Transient and mild motor weakness was observed postoperatively in a patient with falx meningioma (case #7), although significant MEP changes were not observed. We believe that damage to the supplementary motor area due to surgical manipulation may have induced transient motor weakness without significant MEP changes because the tumour was located over the interhemispheric premotor area. These findings indicated that the preservation of the MEP waveforms sensitively reflects the avoidance of permanent motor deficits of the lower extremity.

Transcranial electric stimulation (TES) has also been applied for LE-MEP monitoring in other studies, especially in the field of spine surgery (Chen et al., 2007; Deletis and Sala, 2008; Deletis et al., 2009; Kelleher et al., 2008; Langeloo et al., 2007; Rothwell et al., 1994; Szelényi et al., 2005). Among these studies, LE-MEP monitoring during supratentorial surgery was found to have a success rate of only 66% (Chen et al., 2007). Furthermore, TES has several disadvantages in comparison to the DCS method, including a lack of reproducibility of the MEP waveforms, which can lead to false-positive judgements. This uncertainty of waveforms is caused by an increase in the distance between the scalp stimulation site and the motor cortex because of the gradual dilatation of the space between the brain and the dura mater during supratentorial surgery. Therefore, higher-intensity stimulation is applied towards the end of surgery. However, care must be taken in interpreting MEP waveforms elicited by high-intensity TES, as this stimulation can activate the corticospinal tract as deeply as the pyramidal decussation (Rothwell et al., 1994), and this may cause false-negative results in supratentorial surgery. By contrast, in DCS, when the subdural space is dilated and electrical conduction into the brain is reduced, close contact of the electrode and the cortex can be obtained by inserting compressing materials such as neurosurgical sponges in the subdural space. Another disadvantage of TES is possible patient movement induced by excessive muscle contractions caused by high-intensity stimulation. Therefore, DCS using a subdural electrode is more favourable than TES in LE-MEP monitoring during supratentorial surgery.

SEP monitoring was previously considered to be a surrogate technique to avoid postoperative motor dysfunction of the lower limbs (Holland, 1998; Min et al., 2001; Neuloh and Schramm, 2004a; Sako et al., 1998). However, there is a serious problem with recording, which is referred to as a 'false negative' in SEP monitoring (Sako et al., 1998). Holland et al. reported the occurrence of stroke despite normal SEP recordings during aneurysm surgery (Holland, 1998). Min et al. described a false-negative rate of 11% for SEP in aneurysm surgery (Min et al., 2001). Therefore, SEP monitoring alone may be insufficient for intra-operative monitoring of the motor function of the lower limbs due to a lack of accuracy.

Exposure or dissection of the interhemispheric fissure for placing the subdural electrode on the leg motor cortex is not possible in a pterional or bifrontal approach. Therefore, we performed LE-MEP monitoring by placing the subdural electrode on the motor cortex of the convex side close to the midline. This is a unique and safer method. Adverse events associated with MEP monitoring are rare (MacDonald, 2002; Szelényi et al., 2005), with incidences of seizures of 0.85% for TES and 1% for DCS (Szelényi et al., 2005). Subdural bleeding from bridging veins occurred in 2% of patients during placement of a subdural electrode (Szelényi et al., 2005). Although no significant adverse events were experienced in the current series, careful and gentle insertion is required to place the electrodes and avoid vein injury. Attention must also be paid to the stimulus intensity and frequency during surgery to avoid body movements and seizures.

6. Conclusion

We herein describe a useful method for monitoring LE-MEPs during supratentorial surgery using anodal–monopolar DCS with a frontal cathode. LE-MEPs were consistently recorded by DCS using a subdural electrode placed over the convex side of the motor cortex close to the midline. This monitoring technique can also be applied to standard pterional craniotomy.

Acknowledgements

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FULL-LENGTH ORIGINAL RESEARCH

Cooling of the epileptic focus suppresses seizures with minimal influence on neurologic functions

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Summary

Purpose: **Focal brain cooling is effective for suppression of epileptic seizures, but it is unclear if seizures can be suppressed without a substantial influence on normal neurologic function. To address the issue, a thermoelectrically driven cooling system was developed and applied in free-moving rat models of focal seizure and epilepsy.**

Methods: **Focal seizures limited to the unilateral forelimb were induced by local application of a penicillin G solution or cobalt powder to the unilateral sensorimotor cortex. A proportional integration and differentiation (PID)–controlled, thermoelectrically driven cooling device (weight of 11 g) and bipolar electrodes were chronically implanted on the eloquent area (on the epileptic focus) and the effects of cooling (20, 15, and 10°C) on electrocorticography, seizure frequency, and neurologic changes were investigated.**

Key Findings: **Cooling was associated with a distinct reduction of the epileptic discharges. In both models, cooling of epileptic foci significantly improved both seizure frequency and neurologic functions from 20°C down to 15°C. Cooling to 10°C also suppressed seizures, but with no further improvement in neurologic function. Subsequent investigation of sensorimotor function revealed significant deterioration in foot-fault tests and the receptive field size at 15°C.**

Significance: **Despite the beneficial effects in ictal rats, sensorimotor functions deteriorated at 15°C, thereby suggesting a lower limit for the therapeutic temperature. These results provide important evidence of a therapeutic effect of temperatures from 20 to 15°C using an implantable, hypothermal device for focal epilepsy.**

KEY WORDS: **Epilepsy, Implantable device, Focal brain cooling, Therapeutic temperatures.**

Focal or selective brain cooling is a candidate treatment for epilepsy (Stacey & Litt, 2008; Rothman, 2009). The first clinical application was performed almost 50 years ago and demonstrated clear suppression of epileptic seizures in patients with intractable epilepsy (Ommaya & Baldwin, 1963). A number of subsequent studies have confirmed the strong suppressive effect of cooling on epileptic discharges (Vastola et al., 1969; Reynolds et al., 1975; Sartorius & Berger, 1998; Hill et al., 2000; Yang & Rothman, 2001; Karkar et al., 2002, Imoto et al., 2006; Yang et al., 2006; Tanaka et al., 2008) and epileptic seizures (Sourek & Travnicek, 1970; Burton et al., 2005).

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Despite the long history of investigation, the clinical feasibility of focal brain cooling remains unclear. One of the crucial but unresolved issues is to clarify whether "therapeutic temperatures" really exist, since focal brain cooling can suppress epileptic seizures, but is also associated with suppression of synaptic transmission. Indeed, a series of in vivo experiments have shown cooling-induced deterioration of various neurologic functions, including visual function in cats (Lomber et al., 1996; Lomber & Payne, 2004), auditory function in cats (Malhotra et al., 2004), and motor function in monkeys (Sasaki & Gemba, 1984; Brinkman et al., 1985). The cooling temperatures of the cortical surface in these experiments were not explicitly described, but neurologic deterioration was presumably induced by excessive suppression of synaptic transmission. Therefore, to address the issue of clinical feasibility, it is necessary to clarify whether seizure suppression can be achieved with a minimal influence on neurologic function.

This issue was preliminarily investigated by Karkar et al. (2002) wherein bath application of 4°C saline on the cortex in a patient with epilepsy did not influence the amplitudes of motor-evoked potentials. Another study of cooling showed that network synchronization in hippocampal slices was terminated without blocking normal synaptic transmission (Javedan et al., 2002). Although these results are promising, they do not provide direct evidence. Therefore, we addressed the effect of cooling on seizure and neurologic functions in awake, free-moving rats using an implantable cooling system, with a focus on the eloquent cortex.

Methods

Cooling system

A cooling device originally developed in our laboratory (Imoto et al., 2006; Oku et al., 2009; Fujioka et al., 2010) was used in the study. This device includes a cooling component and a heat-processing component. The cooling component (about 11 g in weight) consists of a proportional integration and differentiation (PID)–controlled thermoelectric chip (6.0 × 6.0 mm; maximum current (I max) 1.8A, maxmum voltage (V max) 2.5V, maximum power (Q max) 2.4W; Ferrotec Corp., Tokyo, Japan). The cooling side of the thermoelectric chip is attached to a pure silver plate (thickness of 1 mm) for direct cooling of the cortex. To avoid contact injuries with the brain, a fine thermocouple (Physitemp 23T, Clifton, NJ, U.S.A.) is embedded in the silver plate (Fig. 1A). The thermoelectric chip is controlled by a PID controller (Yamatake Corp., Tokyo, Japan). Each PID value was selected by automatic tuning of the controller to minimize overshooting or undershooting of a target temperature. The temperatures of the brain surface were cooled to 20, 15, and 10°C. Heat from the thermoelectric chip was transferred via a copper-made heat sink (6 × 6 mm with a thickness of 4 mm; see Imoto et al., 2006; Tanaka et al., 2008; Fujioka et al., 2010). The heat sink, with two water channels inside, was connected to the heat processing component via medical catheters (TYGON, R-3603, Saint-Gobain Performance Plastics, Akron, OH, U.S.A.) filled with Ringer's lactate. The

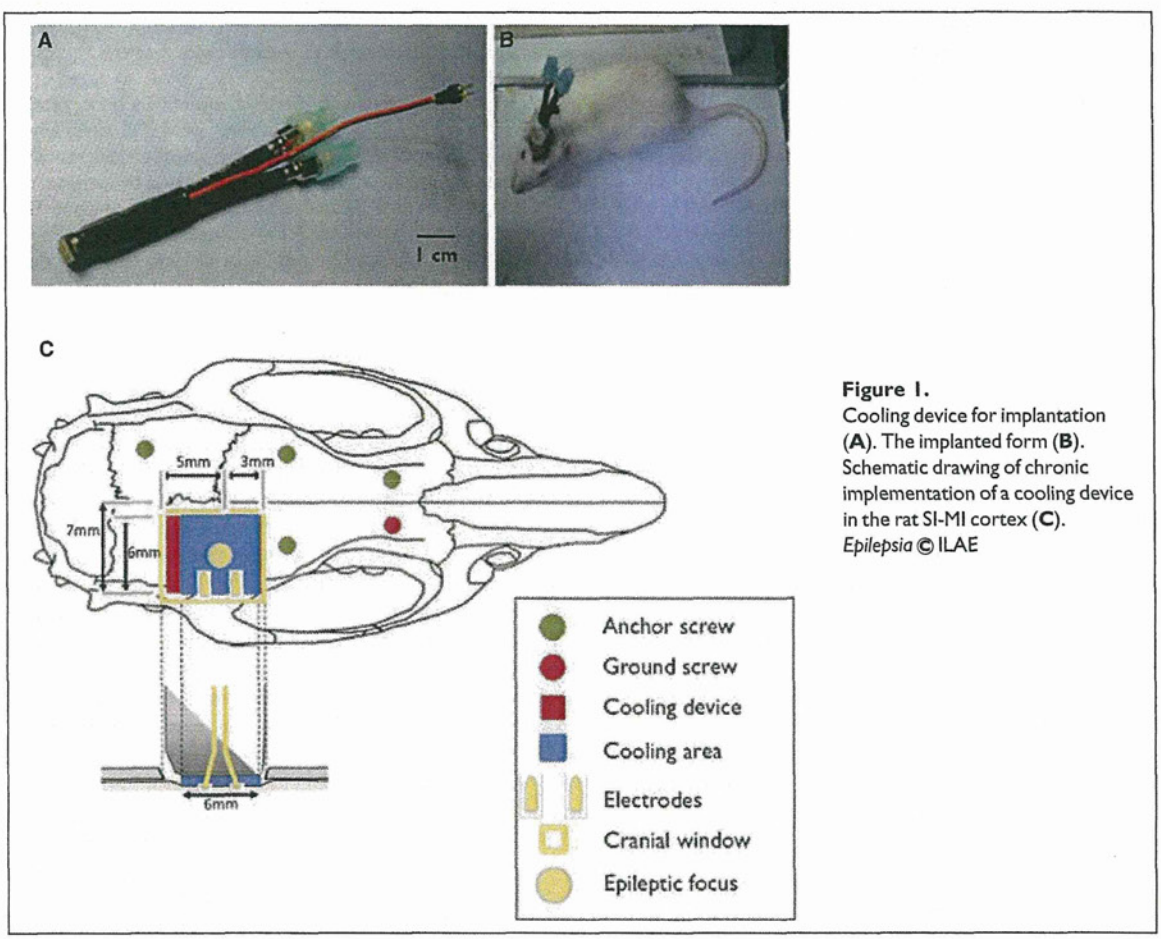

Figure 1.
Cooling device for implantation (**A**). The implanted form (**B**). Schematic drawing of chronic implementation of a cooling device in the rat SI-MI cortex (**C**).
Epilepsia © ILAE

heat-processing component includes a helium-gas cooler (TwinBird Corp., Tsubame, Japan) and a direct current (DC)-driven pump (flow rate of 200 ml/min), which circulates Ringer's solution at a controlled temperature of 20°C. Cooling was started manually in the current study.

Focal seizure and epilepsy models

Animal experiments were performed using protocols approved by the Yamaguchi University School of Medicine Institutional Animal Care Committee. Male Wistar rats (Chiyoda Kaihatsu Co. Ltd., Tokyo, Japan) (450 ± 50 g) housed in a temperature-controlled room (23.0 ± 2.0°C) were used in the study (n = 29 in total). Following induction of anesthesia by 4% sevoflurane, atropine (0.01 mg/kg) was injected subcutaneously and a mixture of ketamine (40 mg/kg, i.m.) and xylazine (4 mg/kg, i.m.) was administered for maintenance of anesthesia. The rectal temperature was maintained at 37 ± 0.2°C using a heating pad. The skull of the rat was fixed using a stereotactic apparatus (Narishige, Tokyo, Japan) and the skin on the skull was cut following injection of lidocaine (2%). A craniotomy was made with a dental drill over the ipsilateral sensorimotor (SI-MI) area (1.5–7.5 mm lateral, 3.0 mm anterior, and 4.0 mm posterior to the bregma). The cooling device was implanted and fixed in place with medical resin (Unifast II; GC Corp., Tokyo, Japan). The cooling component (6.0 × 6.0 mm) cools the entire somatotopic representation center, except for the tongue and lips, in rats (Fig. 1B,C) (Hall & Lindholm, 1974).

We used a focal seizure model (n = 12) and a focal epilepsy model (n = 6) for induction of focal seizures limited to the unilateral forepaw area. Rats with seizures outside the forepaw area were excluded from the study. Focal seizures were induced by intracortical infusion of a 4% NaCl solution of penicillin G (PG) using a syringe pump (0.3 μl/min at a concentration of 200 IU/μl, up to 1,200 IU) until continuous seizures were stably but minimally induced. Intracortical infusion was performed using a fine needle (28 gauge) with a tip length of 0.8 mm, which was attached to the center of the cooling component. The needle was stereotactically implanted on the eloquent area (i.e., the forepaw area of the sensorimotor [SI-MI] cortex at a depth of 0.8, 1.0 mm anterior, and 3.6 mm lateral to the bregma) using medical resin. Once seizures were induced, experiments were performed within 30 min. The frequency of seizures was stable over this time window. To investigate the effect of cooling when the seizure focus extends out of the forelimb area, >1,200 IU (up to 2,200 IU) of PG solution was also applied (n = 3).

Focal epilepsy was induced by direct application of cobalt powder on the same area of the cortex (Dow et al., 1962). Following a small craniotomy made with a dental drill, cobalt powder (8 mg; Sigma-Aldrich Co. LLC., Tokyo, Japan) was applied on the dura over the eloquent cortex. A sterilized cotton sheet was placed and the skin was sutured. Following a recovery period of 3 days, the rat was reanesthetized and the cooling device was implanted using dental resin at the center of the forepaw area, which became an epileptic focus. Cooling experiments were performed at 9 ± 2 days after implantation.

Neurologic assessments

The effect of cooling on the frequency of seizures before and during cooling was evaluated by the number of involuntary lifts of the forepaw from the floor in 3 min for both the focal seizure and epilepsy models. All tests were recorded by video camera (60 frames/s) and forepaw lifting was evaluated blindly by at least two of four researchers. Comprehensive neurologic functions before and during cooling were assessed on a 21-point neurologic scale, which was originally developed for assessment of a cerebral ischemia model in rodents (Hunter et al., 2000). This scale comprises a battery of 10 items: assessment of paw placement, righting reflex, ability to grip a horizontal bar, time on an inclined platform, rotation, visual forepaw reaching, circling, contralateral reflex, motility, and general condition. This kind of scale is commonly used in behavior assessments of rats (McGill et al., 2005). The assessment was performed three times within 30 min in the current study.

Sensorimotor functions of the limbs were investigated in foot-fault tests and according to the receptive field size in the forepaw area. Foot-fault tests were evaluated using the following formula: (foot faults *per* limb/steps *per* limb) × 100 (Soblosky et al., 1996). The rat was placed gently on an elevated grid and the number of slips into the grid (i.e., foot faults) in 25 paired steps was calculated. The trial was performed three times and mean scores were calculated. Sensory function was evaluated by measuring the receptive field (RF) size of the forepaw area contralateral to the cooling cortex (layer iv; depth 450–800 μm) under the ketamine anesthesia described above (n = 5) (Fujioka et al., 2004). Tactile stimuli were applied on the forepaw areas of the skin (40 points) with von Frey hair-type probes (calculated force of 0.6 g) before and during cooling. The number of reaction fields was counted and defined as the RF size. All behavioral experiments were performed at cooling temperatures of 20, 15, and 10°C. All tests were also recorded by video camera (60 frames/s) and were evaluated blindly by at least two of four researchers.

Electrocorticography

An electrocorticography (ECoG, 1 Ch) over the epileptic focus in all rats was differentially recorded using a pair of needle-type electrodes (impedance 500 kOhm at 500 Hz) attached to the bottom of the cooling device (Fig. 1C). Data were amplified and recorded in Powerlab (ADInstruments, Colorado Springs, CO, U.S.A.) with a sampling rate of 2 kHz (low-cut filter 5 Hz, high-cut filter 100 Hz).

Electrocardiography (ECG)

Before implantation of the device, the skin of the right chest was incised in the supine position and a telemetry system (PhysioTel, DSI, St. Paul, MN, U.S.A.) was implanted in normal rats (n = 4) and in normal sham rats with a cooling device implanted in the brain (n = 4). Two-lead ECG was sampled at 2 kHz with a duration of 1 min and recorded in a PC via a Powerlab instrument (ADInstruments).

Histology

Following the experiments, the rats were sacrificed and hematoxylin and eosin (H&E) staining was performed (5-μm sections).

Statistics

Statistical analyses were performed by paired Student *t*-tests, Dunnett post hoc tests, or Steel-Dwass tests using the R software package (see the homepage; http://www.R-project.org.). $p < 0.05$ was considered to be statistically significant. Analysis of variance (ANOVA) was performed to evaluate the significance of differences between the means of all groups. A Dunnett test or Steel–Dwass post hoc test for multiple comparisons was used to compare groups with parametric or nonparametric data and unequal sample size or sample variance. Data are shown as the mean ± standard deviation (SD) in Student *t*-tests and Dunnett tests, and as the mean ± standard error of the mean (SEM) in the Steel–Dwass test.

RESULTS

Temperature gradient of the cooling area

The temperature gradient under the cooling device was evaluated thermographically on an agar surface warmed to 37°C. This surface was cooled to 20°C with the cooling device (6 × 6 mm). The cooling effect was limited to the contact area and did not reach the perimeter (Fig. 2).

Effects of cooling on focal seizures

Device implantation

The implanted device (Fig. 1A–C) did not influence ordinary behaviors in sham rats, such as eating, moving, grooming, or sleeping. ECG did not show any cooling-associated changes in rate rhythms (194 ± 6.32 in normal rats vs. 198.5 ± 14.73 in normal sham rats, $p = 0.65$ by Student *t*-test) and did not induce arrhythmia before, during, or after cooling. Although cooling to a target temperature was achieved without overshooting or undershooting, such precise temperature control was generally obtained at the cost of time. The times to reach the target temperatures of 20, 15, and 10°C were 9 ± 0.2, 12 ± 0.4, and 20 ± 0.4 s, respectively (mean ± SD, each n = 4).

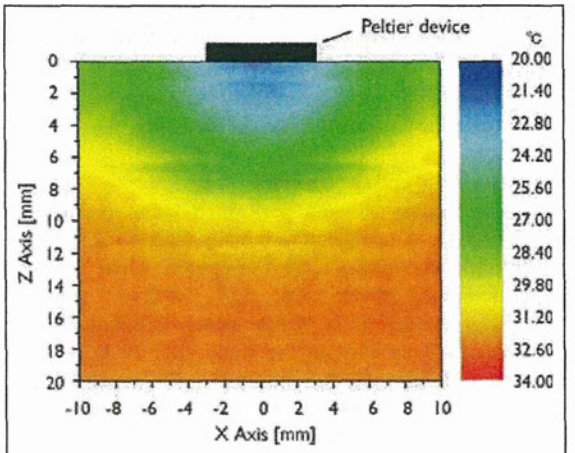

Figure 2.
Temperature gradient under the cooling device. The temperature of the cortical surface was controlled at 20°C. Note that the cooling effect was limited to the contact area and did not reach the perimeter.
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Focal seizure model

Intracortical application of a PG solution reliably induced focal seizures limited to the unilateral forelimb area. Cooling of the seizure focus immediately and significantly reduced the frequency of seizures per minute at surface brain temperatures of 20°C (48.7%, $p < 0.0001$), 15°C (11.8%, $p < 0.0001$), and 10°C (0%, $p < 0.0001$), in comparison to the noncooling ictal group (100%, n = 6, Fig. 3A). The reduction of the seizure frequency was coincident with the suppression of epileptic discharges (EDs) in the ECoG (Fig. 4A,D). The effect of cooling-induced seizure suppression was continuous and was not diminished as long as cooling was performed. There was no apparent difference in the extent of suppression between rapid and slow cooling to a target temperature.

The significant reduction of the seizure frequency was also associated with improvement of neurologic scores within the range of 20–15°C. Induction of seizures caused a significant deterioration of neurologic scores (15.6 ± 0.43, $p = 0.023$). These scores were improved to 18.33 ± 0.21 at 20°C ($p = 0.027$) and 19.5 ± 0.22 at 15°C ($p = 0.029$), compared to those of the noncooling group (Fig. 3B). These effects disappeared soon after cessation of cooling. Cooling to 10°C also achieved a seizure-free condition, but neurologic scores remained low (15.93 ± 0.21, $p = 0.979$). Additional injection of a PG solution (>1,200 IU) induced seizures outside the forelimb area, which made it impossible to inhibit seizures in the forelimb area, as well as in areas outside the forelimb (Fig. 4B,E).

Implantation of the device for 1 month with 1 h cooling per day did not result in detrimental changes in H&E

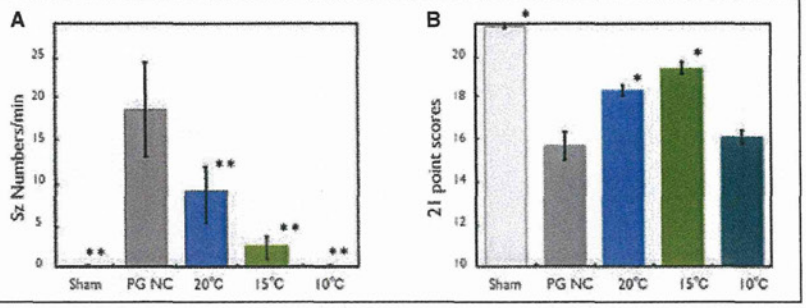

Figure 3.
Frequency of seizures (**A**) and neurologic scores (**B**) as a function of temperature at the seizure foci. PG, penicillin G; NC, noncooling. Error bars: SD in **A**, SEM in **B**. *$p < 0.05$. **$p < 0.01$ versus noncooling groups (n = 6).
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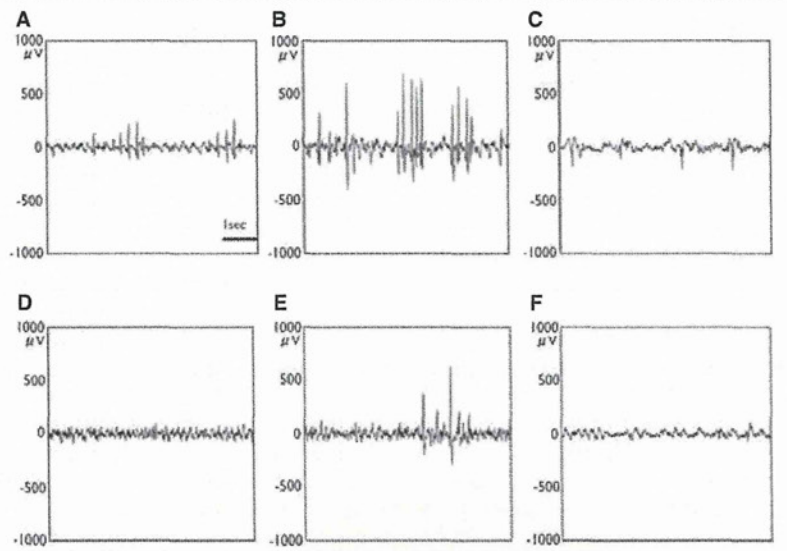

Figure 4.
Epileptic discharges (EDs) before (**A–C**) and during cooling at 15°C (**D–F**) at the seizure focus in penicillin G (PG)–treated (**A,B,D,E**) and cobalt-treated (**C, F**) rats. Suppression of EDs was associated with amelioration of seizure frequency when a seizure focus was in a cooled area—before (**A**) and during (**D**) cooling at 15°C. When the seizure focus extended outside the cooled area due to excess application of PG, EDs were not completely terminated at temperatures down to 15°C (**B, E**). Suppression of EDs also occurred during cooling in a cobalt-treated rat (**C, F**).
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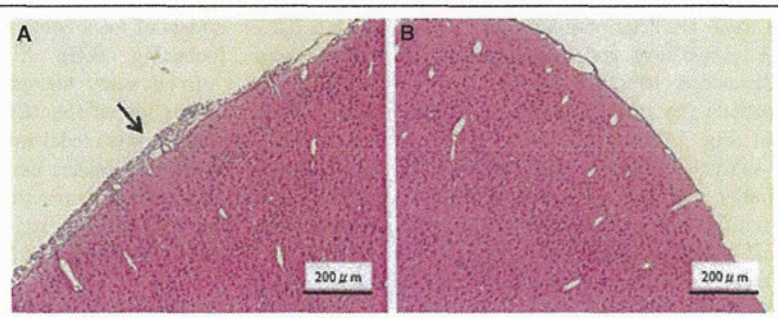

Figure 5.
Following implantation of the device for 1 month, partial fibrosis was observed in the subarachnoid of the cortex, but was limited to the area under the device (shown by an arrow). No histologic changes were observed in the contralateral homologous area.
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staining (n = 5), except for partial fibrosis of the subarachnoid region under the device (Fig. 5).

Focal epilepsy model

Cobalt-induced epileptic seizures limited to the unilateral forelimb area were sufficiently severe and continuous to be suggestive of a state of epilepsia partialis continua. The number of seizures per minute in the cobalt model was double that in the PG model. Seizure frequency was reduced in association with improvement of neurologic scores in a cooling range of 20–15°C and was coincident with suppression of EDs during cooling (Fig. 4C,F). The frequency of seizures per minute was reduced by 54.4% at 20°C ($p < 0.0001$), 3.9% at 15°C ($p < 0.0001$), and 0% at 10°C ($p < 0.0001$) (Fig. 6A). The significantly lower neurologic scores under noncooling, ictal conditions (14.5 ± 0.34,

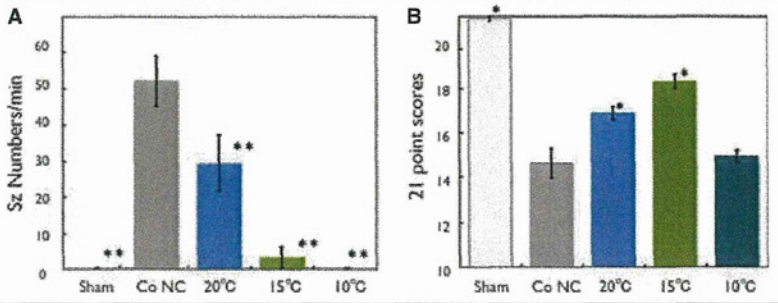

Figure 6.
Frequency of seizures (**A**) and neurologic scores (**B**) as a function of temperatures. Co, cobalt; NC, noncooling. Error bars: SD in **A**, SEM in **B**. *$p < 0.05$. **$p < 0.01$ for ictal rats (n = 6) versus noncooling groups (n = 6).
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p = 0.023) were improved by 16.88 ± 0.28 at 20°C (p = 0.027) and 18.38 ± 0.2 at 15°C (p = 0.029, Fig. 6B), in comparison with the noncooling group (n = 6). As in the PG model, cooling to 10°C did not improve the neurologic scores (14.88 ± 0.41, p = 0.979, Fig. 6B). The therapeutic effect was not diminished as long as cooling was performed.

Histology in cobalt-treated rats shows bowl-shaped necrotic changes (Dow et al., 1962), which were limited to the shallow cortex in our study. There were no other particular cooling-associated changes.

Effects of cooling on neurologic functions

Because neurologic improvement was limited in the cooling ranges of 20–15°C, we hypothesized that cooling below 15°C induced excessive blockage of synaptic transmission. Therefore, we investigated the effects of cooling on normal neurologic functions in sham rats. Apparent neurologic deficits in ordinary behaviors (walking, eating, grooming, and so on) were not observed by cooling to 15°C. Neurologic functions (n = 6) were robust with cooling to 20°C (20.9 ± 0.06, 99.8%, vs. sham group, p = 0.92), but a trend for deterioration began at 15°C (20.6 ± 0.20, 98.1%, p = 0.089), and these changes reached statistical significance at 10°C (18.2 ± 0.21, 86.7%, p = 0.012), in comparison to the noncooling group (20.95 ± 0.05, 100%) (Fig. 7A).

A subsequent investigation of sensorimotor functions invariably revealed significant deterioration at 15°C. In foot-fault tests (n = 6), cooling to 20°C did not induce substantial changes (% error of 1.1 ± 1.31%, p = 0.957), but the findings reached statistical significance at 15°C (3.34 ± 0.73%, p = 0.018) and 10°C (18 ± 3.45%, $p < 0.0001$, Fig. 7B). In anesthetized sham rats (n = 5), RFs of the forepaw under the cooling area began to diminish at 20°C (84.1%, p = 0.099) and reached statistical significance at 15°C (30.6%, $p < 0.0001$) and 10°C (1.2%, $p < 0.0001$), in comparison to the noncooling group (100%) (Fig. 7C).

Discussion

This study provided important evidence for a therapeutic effect of low temperature on focal seizure and epilepsy in an animal model. The results build on findings in previous studies (Yang & Rothman, 2001; Rothman et al., 2005; Yang et al., 2006; Rothman, 2009). Temperatures from 20°C down to 15°C significantly suppressed seizures and were associated with improvement of neurologic function. The effect was powerful, instantaneous, and continuous, which suggests advantages over other existing epileptic therapies.

Limitations and feasibility of focal brain cooling for epilepsy treatment

An indication of focal brain cooling for focal epilepsy requires accurate identification of epileptic foci of a size that is well within the cooling area. These conditions were produced in two animal models. The PG model of focal seizure allows adjustment of the size and extent of seizures (Elger & Speckmann, 1983). Therapeutic effects were obtained when the focal seizure was within the cooling area. However, application of PG >1,200 IU caused the focal seizures to no longer be limited to the forelimb, but to extend over the hind limb and body. In such cases, the suppressive effects of focal cooling were limited, even in the epileptic focus (Fig. 4B,E).

In our study, the epileptic focus in the cobalt model was clearly identifiable (Chang et al., 2004). The epileptic seizures in this model were more severe than those in the PG model, but seizure control was as prominent as that in the PG model. Therapeutic temperatures were also identified in the cobalt model, suggesting the feasibility of focal brain cooling as therapy for focal epilepsy.

Factors influencing the therapeutic cooling temperature

The results of the study show that therapeutic temperatures are not uniquely defined, but are changed by factors such as seizure severity and the size of the focus. Other factors that can influence the therapeutic temperatures include antiepileptic drugs (AEDs) and neuroplasticity. We did not use AEDs in the study, but the assumed synergistic effects of AEDs during cooling (Sourek & Travnicek, 1970) may increase the upper limit of the therapeutic temperature. Another important aspect of focal brain cooling is the involvement of functional compensation, presumably due to

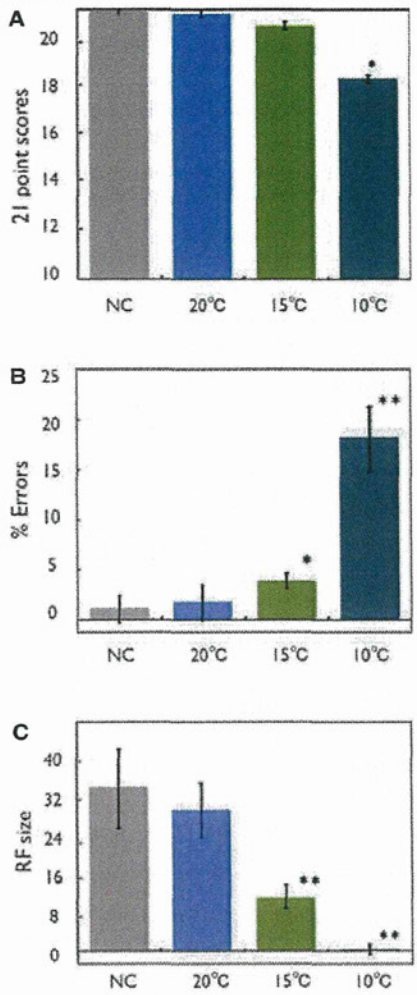

Figure 7.
Temperature-dependent changes in neurologic scores (**A**, n = 7), foot-fault tests (% errors; **B**, n = 6) and sizes of receptive fields (RFs; **C**, n = 5). Error bars: SD. *p < 0.05. **p < 0.01 versus noncooling groups.
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behavioral adaptation or neuronal plasticity. This property has been reported in a series of studies in normal monkeys, wherein cooling-induced functional deficits began to be ameliorated over a time course of months (Sasaki & Gemba, 1984; Brinkman et al., 1985). Identification and evaluation of these factors are important issues that remain to be addressed.

Determination of the therapeutic cooling temperature

Our data showed that cooling to 15°C reliably suppressed focal seizures and improved neurologic function (21-point scores), but a detailed investigation of sensorimotor functions (foot-fault tests and receptive field size) in normal sham rats revealed significant deterioration. Clinicians who place an emphasis on seizure suppression may prefer lower therapeutic temperatures at the cost of functional deterioration, whereas those who wish to avoid neurologic dysfunction may prefer higher therapeutic temperatures. Therefore, determining the therapeutic temperature in patients with epilepsy will depend not only on objective criteria but also on subjective criteria that maximize the quality of life.

Mechanism of seizure suppression by focal brain cooling

Focal brain cooling is generally considered to induce reduction of transmitter release (Eilers & Bickler, 1996), kinetic alteration of voltage-gated ion channels (Traynelis & Dingledine, 1988; Hill et al., 2000; Volgushev et al., 2000), and network desynchronization (Javedan et al., 2002). Although the precise antiepileptic mechanisms remain to be determined, it is generally recognized that suppression of synaptic transmission is involved in reduction of seizures. An in vitro study showed that synaptic transmission begins to decrease below 20°C (Volgushev et al., 2000). In a case in which the temperature is <20°C at 1 mm under the cortical surface, but >20°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 (Nolte, 2009). Selective suppression of synaptic transmission due to a cooling-induced thermogradient in the cortex may contribute to the vulnerability of somatosensory processing, as indicated by the reduction of RFs during cooling. Because the neurons that form a pyramidal tract (layer V) lie deep in the sensorimotor cortex, selective transmission failure may have occurred during surface cooling.

Histologic assessment

Pathologic changes due to cooling were not observed in the PG and cobalt models. Although partial fibrosis under the cooling device did occur, this was probably not caused by cooling, given the histologic tolerance to focal brain cooling even down to 5°C (Yang et al., 2006; Oku et al., 2009). Rather, it is likely that this histologic change was caused by direct contact with the cooling part of the device (i.e., pure silver) because inflammation of the contact area cannot be avoided under free-moving conditions.

Clinical advantages and requirements of the cooling device

Temperature control is of crucial importance in therapeutic applications, given that the range of therapeutic temperatures is narrow and that a small deviation from this range may lead to neurologic dysfunction. Furthermore, varying brain temperatures in the ictal stage may further complicate temperature control. In this regard, thermoelectronic

devices have an advantage over traditional circulatory-cooling devices, since the thermoelectronic devices are small but have sufficient cooling power and precise temperature control. An alternative approach using systemic hypothermia has been used in refractory status epilepticus (Corry et al., 2008), but clinical use of this method is limited by adverse effects and limitations on the cooling temperature (31–35°C) and period.

Clinical demand for an implantable cooling device will not be limited to the epileptic field. Other potential applications include treatment for cerebrovascular diseases, including poststroke rehabilitation (Clark & Colbourne, 2007), neurotrauma (Clark & Colbourne, 2007), and pain (Fujioka et al., 2010), all of which will depend on thermal modulation of neuronal excitability.

Application of the cooling device for treatment of epilepsy

Focal brain cooling may be applied therapeutically for patients who have an epileptic focus on the eloquent cortex (i.e., motor or language area) or those who cannot be treated with AEDs. Cooling may also be used as a diagnostic tool in intracranial ECoG monitoring of patients with potential neurosurgical indications, but in whom the focus cannot be clearly defined. In such cases, the final surgical indication would be decided by preliminary application of cooling to the focus. There are several physiologic and technical issues to be solved before the device can be applied in intractable epilepsy. However, this study is an important step toward medical use of an implantable hypothermal device for treatment of focal epilepsy and other neurologic disorders.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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症例 ◆ Case Report

難治性複雑部分発作を呈した島回部 psammomatous meningioma の1手術例*

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Insular Psammomatous Meningioma Presenting Intractable Complex Partial Seizures

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Key words:
insular cortex,
psammomatous meningioma,
complex partial seizure,
intractable epilepsy

We describe a 30-year-old female with intractable symptomatic epilepsy caused by an insular calcified mass, which was histologically proved as psammomatous meningioma. Seizures were described as consciousness impairment, motionless stare and automatism. After total removal of the tumor with a neuronavigation system and motor evoked potential (MEP) monitoring, seizures completely disappeared without neurological deficit. We emphasize that insular meningioma presents complex partial seizures which mimic medial temporal lobe epilepsy and seizures are controlled by total resection of the tumor.

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I. はじめに

てんかん症例において，発作が島回部より起始する場合，多彩な臨床症状を呈するために症候のみでの焦点診断は困難なことが多い．特に複雑部分発作が発作症状の主体である場合には，側頭葉てんかんとの鑑別に苦慮する場合がある[9]．今回われわれは，側頭葉てんかんと同様な複雑部分発作を呈した島回部に主座をおく髄膜腫（deep sylvian meningioma）の1例を経験したので，文献的考察を加え報告する．

II. 症　例

〈患　者〉 30歳　女性

主　訴　意識減損を伴う無目的な行動

既往歴・家族歴　特記すべきことなし

現病歴　27歳時，妊娠30週頃から意識減損にはじまり，無動凝視，自動症（口部自動症，無目的な行動・発言）を呈する複雑部分発作が出現するようになった．妊娠36週に前医に紹介となったが，本人の希望により抗てんかん薬の内服は行われなかった．男児を出産後も発作を認めていたが，授乳のために抗てんかん薬の内服は行われな

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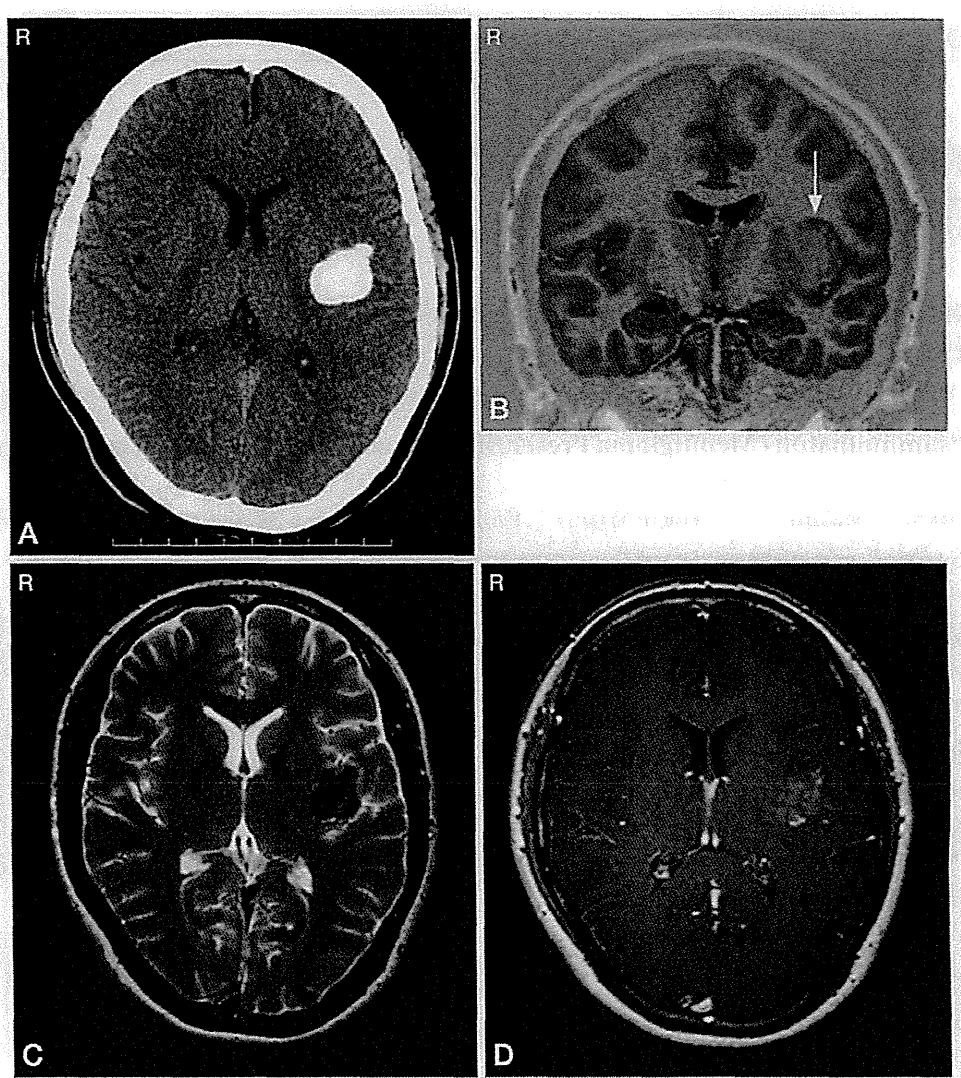

Fig. 1 Computed tomography (CT) and magnetic resonance image (MRI) on admission. A: CT, B: T1-weighted image, C: T2-weighted image, D: Gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) enhanced T1-weighted image. CT shows a calcified mass in the deep sylvian fissure (A), and MRIs show the lesion slightly enhanced by Gd (D), however, there is no apparent edema around the lesion (C). The lesion (arrow) is close to the left hippocampus (B).

かった．しかし発作頻度が次第に増加したため，出産1年後より投薬加療が行われた．当初はゾニサミド，バルプロ酸で加療が開始され，発作が消失しないために各種抗てんかん薬が使用され，最終的には1日量としてカルバマゼピン400 mg，クロバザム10 mg，ラモトリジン100 mgの併用が行われたが，発作は残存した．前医初診時より画像上左島回部に石灰化病変を認めており，発作が難治に経過するためにてんかん焦点との関与が疑われ，同病変の精査および外科的治療目的で当科に紹介となった．

初診時所見　意識清明，神経学的に異常を認めなかった．発作型は前述のごとく，自動症，無動凝視，意識減損を主体とした複雑部分発作であった．入浴中や調理中にも発作があり，手指に切創を来すことがあった．発作の頻度は週に1～2回であり，1回の発作は約2分間持続し，発作後のもうろう状態は約5分程度であった．

検査所見　CTでは左島回部に石灰化腫瘤を認め，周囲の浮腫は認めなかった．MRIでもCTと同様の所見で，ほぼ全体が石灰化した腫瘤性病変を認め，内部は一部が不均一に淡く造影されるものの，全体的にはほぼ造影効果を認めなかった（Fig. 1）．病変部は島回のやや尾側に位置し，海馬と近接していた．海馬に萎縮や層構造異常などの明らかな異常は指摘できなかった．Tractographyを施行すると病変部は錐体路から離れており（Fig. 2），またFDG-PET（^{18}F-fluorodeoxy glucose-positron emission tomography）では病変部のFDG集積は周囲と比較して極めて低く，また両側内側側頭葉のFDG集積低下は明らかではなかった（Fig. 3）．脳血管撮影を施行したが，腫瘍濃染像などの明らかな異常血管は認められなかった．また同時に施行したプロポフォール（7 mg, 1 mg/mL）を用いたワダテストでは，記憶，言語とも左側が優位半球であった．神経心理学的検査ではWechsler Adult Intelligence Scale, a revised form（WAIS-R）は言語性知能（VIQ）118，動作性知能（PIQ）106，全検査知能（FSIQ）114であった．記憶検査（Wechsler Memory Scale, a revised form：WMS-R）は言語性記憶121，視覚性記憶111，一般記憶121，注意/集中力105，遅延再生121であった．

発作間欠期頭皮上脳波では明らかなてんかん性異常波を捉えることはできなかった．1週間の脳波ビデオ同時モニタリングでは，前述と同様に意識減損，無動凝視，自動症を呈する発作が認められたが，発作時脳波所見からは症状と同期したてんかん性異常放電の起始特定には至らなかった．

治療経過　発作型からは発作焦点として側頭葉が最も考えやすい所見であったが，①過去に，島回を発作焦点とする場合にも複雑部分発作を呈する報告があること[1]，②本症例においても病変から海馬までの距離が近いため，発作型も側頭葉てんかん類似の症状を呈していると考えて矛盾はないこと，③画像所見としてCT，MRIにて明らかに左島回に病変があること，④PETでの側頭葉集積低下が認められないことより，側頭葉よりも島回部の石灰化病変周囲にてんかん原性域が存在する可能性が高いと考え，左島回病変の摘出術を施行した．

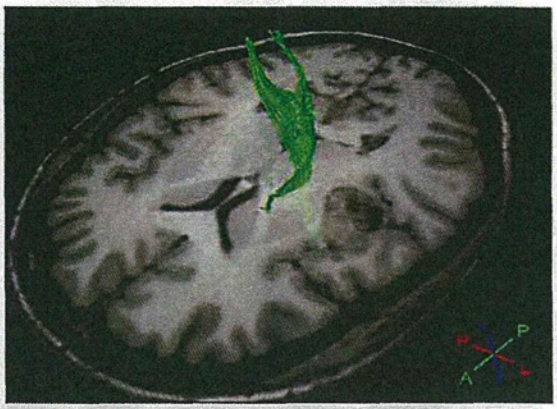

Fig. 2　Magnetic resonance image (MRI)-tractography; Pyramidal tract is displaced from the tumor.

左前頭側頭開頭を行い，まずナビゲーション装置（Medtronic Sofamor Danek社製）を用いて病変部をマーキングした．また術中操作による運動麻痺を回避するため，電気刺激用の硬膜下電極（12極グリッド，ユニークメディカル社製）を中心溝近傍に留置し，上肢（母指球筋）筋電図導出の運動誘発電位（motor evoked potential：MEP）モニタリングを行いながら手術を行った．病変の摘出が可能となるようにナビゲーションに従ってシルビウス裂を大きく開放し，島回を広く露出した．まず島回上で皮質脳波を記録すると，同病変およびその前頭側の島回にて棘波が観察された．病変と正常脳との境界は明瞭であり，癒着は認められなかったが，画像所見のごとく石灰化が主体の非常に固い病変であったため，適宜内減圧を行いながら摘出を行った．最終的に石灰化病変を全摘出し，さらに棘波がみられた島回部皮質を約1 cmの範囲で摘出した．摘出後の皮質脳波では棘波の消失が確認された．

術後は発作を認めず，術中MEP所見に変化はなく，術後一過性に右上肢軽度脱力を来したものの軽快し，退院した．術後1年が経過し，内服を中止したが，てんかん発作は消失（Engel分類class Ⅰ），また明らかな神経脱落症状なく家事，仕事を行っている．高次脳機能に関してもWAIS-R（術前/術後）はVIQ 118/115，PIQ 106/110，FSIQ 114/114，WMS-R（術前/術後）は言語性記憶121/129，

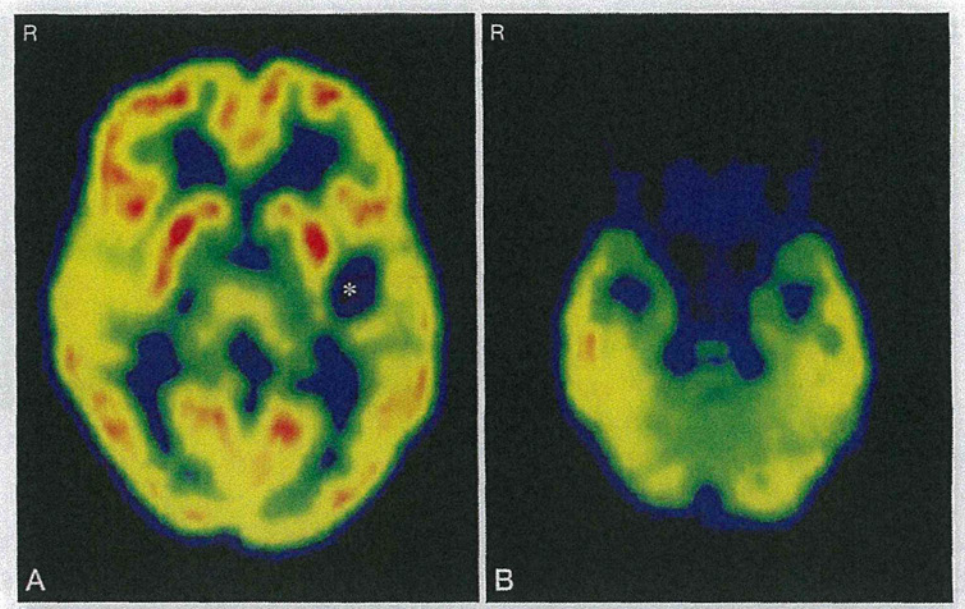

Fig. 3 ^{18}F-fluorodeoxy glucose-positron emission tomography (FDG-PET) showing the hypometabolic area in the calcified mass (white asterisk) (A) and no hypometabolic area in the mesial temporal lobe (B).

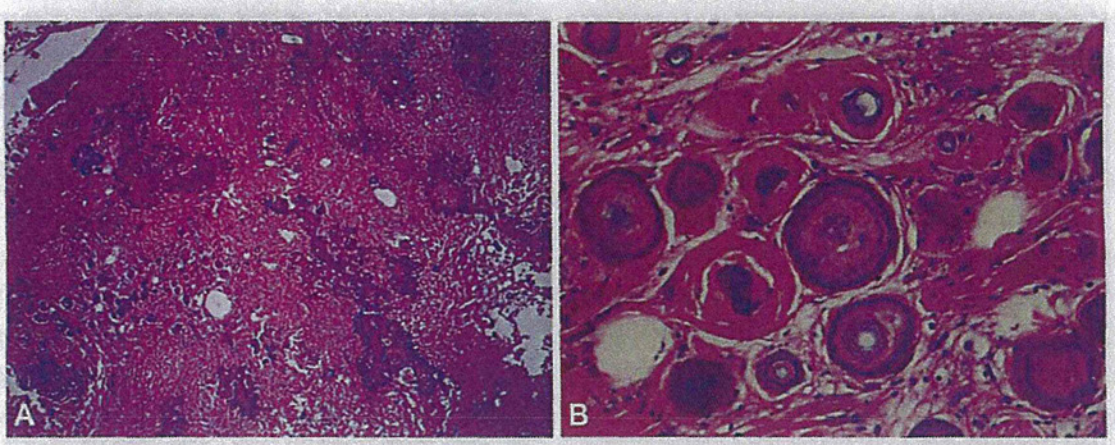

Fig. 4 Photomicrography showing multiple psammoma body. The tumor is diagnosed as psammomatous meningioma [hematoxylin and eosin stain, ×4 (A), ×20 (B)].

視覚性記憶 111/114，一般記憶 121/129，注意/集中力 105/121，遅延再生 121/128 であり，術前後に著変はない．また術後の脳波も正常範囲内である．

病理所見　石灰化病変は病理学的には psammoma body を多く認め，またその間にはいわゆる whorl formation を呈する細胞の集簇を認めた．悪性所見は認めず，psammomatous meningioma と診断した（**Fig. 4**）．切除した島回部皮質には明らかな異常は認められなかった．

III. 考　察

島回部起始のてんかん発作症候に関しては，脳神経外科領域ではあまり詳細に検討されていない．Isnard らの島回部領域を発作焦点とするてんかん 5 例の詳細な研究によれば，発作は喉頭圧迫感，口および顔面の異常感覚，嘔気/嘔吐，唾液過多，上腹部不快感からはじまり，異常感覚の拡大，構語障害，けいれんに至ることが典型的特徴

Table Reported cases of insular meningioma presenting complex partial seizure

Author (Year)	Age, Sex	Tissue type	Seizure type
Mori et al (1977)	23 yrs, M	transitional	LOC, generalized convulsion, psychomotor seizure
Saito et al (1979)	31 yrs, F	psammomatous	LOC, howling, scrabbling
Hirao et al (1986)	34 yrs, F	fibroblastic	LOC
Matsumoto et al (1995)	62 yrs, F	psammomatous	LOC
Mitsuyama et al (2000)	1 yr, M	fibrous	LOC, convulsion
Kumar et al (2009)	6 yrs, M	WHO grade I	laugher with bizarre movements of hands, transient loss of contact with surroundings, lip smacking

(Abbreviation) LOC: loss of consciousness

とされている[9]．この報告で全例において異常感覚が出現したとされるのは，てんかん性異常波が中心後回の感覚皮質（特に舌，咽頭，顔面部分）に伝播したためと考えられる．また島回部の発作波が側頭葉や辺縁系に広がれば，側頭葉てんかん類似の複雑部分発作，前頭葉に広がれば，顔面を中心とした運動症状を呈するとされている．われわれの症例では腫瘍の前側頭寄りの皮質から発作波が起始し，辺縁系および側頭葉に伝播し，複雑部分発作を呈したことが推測される．

本症例と同様な島回部髄膜腫の過去の報告において，てんかん発作を呈したものは渉猟し得た限りでは18例[1-5,7,8,10-17,19,20]であった．複雑部分発作を思わせる症例は，意識消失とのみ記載があるものを含め，6例[8,11,12,14,16,19]である（Table）．さらに自動症の記載があるものは，1例[11]にすぎず，発作症候が十分検討されていないのが現状と考えられる．てんかん発作で発症した島回部髄膜腫では，われわれの症例のようにてんかん症候学を十分検討した上で，発作消失を目指した手術戦略が必要と考えられる．

さらに，島回部に病変を有することで生じた難治性てんかんの報告は，海綿状血管腫やlow grade gliomaなどの疾患でも見受けられるが，やはり詳細な発作症候が記載されているものは少ない．比較的詳細に発作症候を記載したものを見てみると，Duffauらは，難治性症候性てんかんを呈した島回部のlow grade glioma 11例を報告しており，1例で口部自動症を認め，また前兆として既視感が4例にみられたとしている[6]．またRoperらは，2例の島回部low grade gliomaのうち，1例は上腹部不快感を思わせる「のどに蝶がいる」という前兆を認めたと報告している[18]．von Leheらは，24例の自験例を詳細に検討しており，内訳は脳腫瘍13例，海綿状血管腫2例，皮質形成異常6例，gliosis 3例であり，最も多い初発症状は内臓感覚異常や感情的な症状であるが，他の症状がない意識消失（複雑部分発作と考えられる）が3例（13%）存在したとしており[21]，われわれの症例と同様の発作伝播形態が考えられる．

今回てんかんの焦点診断に難渋した理由の1つとして，頭皮上脳波ではまったく異常が捉えられなかったことが挙げられる．一般に，病変がある程度深部に存在する場合には，頭皮上脳波，脳磁図では明らかな異常を捉えられない可能性がある．Roperらもシルビウス裂内深部にてんかん原生域が存在する場合，頭皮上の脳波記録により異常波を検出することが困難と述べている[18]．脳波異常が検出できない場合，今回の症例のように他のmodalityの組み合わせにより焦点診断を行う必要があると考えられる．仮に，他のmodalityを組み合わせても焦点診断に悩む場合には，侵襲的な検査にはなるが，積極的に頭蓋内電極留置によるモニタリングを考慮すべきであろう[18]．

われわれの基本的な方針は，術中脳波で棘波などのてんかん性異常波が出現する部位は可及的に切除することとしているため，今回も棘波の出現する島回の一部切除を行った．しかし限局性病変

によるてんかん症例では，病変部の切除で発作消失が得られると報告されている[2,3,11]．またvon Leheらは島回部のlesionectomyでは合併症のリスクを最小限にするため，島皮質の切除は2～3 mmにとどめることを推奨している[21]．これらを考慮すると，今回の症例も主には髄膜腫の全摘出により発作を消失させることができたと考えられ，島回の切除は必ずしも必要ではなかったかもしれない．

島回部腫瘍の摘出に際しては，中大脳動脈およびその穿通枝を損傷しないことが重要である．そのため繊細な手術手技が求められるが，それ以外に術前にMRI-tractographyにより，錐体路の走行を確認しておくことや，術中ナビゲーションを用いた操作位置の確認およびMEP記録による運動機能の評価を行いながら手術操作を進めることが重要と考えられる．またてんかん発症の島回部腫瘍では術中皮質脳波記録を用いることも有用と考えられる．

IV. 結　語

側頭葉てんかんに類似する難治性複雑部分発作を呈した島回部psammomatous meningiomaにおいて，腫瘍の全摘出により発作が消失した1例を報告した．てんかん発作を呈する島回部腫瘍の摘出手術に際しては，術前に発作症候を含め複数の検査手法を用いて発作焦点部位を推定し，術中は運動機能をモニタリングしながら，安全かつ発作消失を目指した手術戦略を立てることが重要である．

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