Experimental epileptic discharge can be transmitted between 2 brains in rats

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ABSTRACT

الأهداف: تحديد ما إذا كان يمكن توصيل شحنات الصرع إلى خارج الدماغ وفقاً لمبدأ مانعة الصواعق.

الطريقة: أجريت هذه الدراسة في جامعة وسط الجنوب – مستشفى الشانياه – الصين، خلال الفترة مابين 2005م وحتى 2008م. تم زرع أقطاب كهربائية في ثمانين فأر (سبراغ دوالي) في منطقتي الفص الأمامي (intra frontal lobe) وداخل الحصين (intra-hippocampus). تم تقسيم الفئران عشوائياً إلى ثلاثة مجموعات: مجموعة (A) والتي تم تحفيزها بواسطة حقنها بالبنسيلين في منطقة الحصين، مجموعة (B) تم تحفيزها بواسطة سلك نحاسي موصل بقطب الحصين الموجود في المجموعة (A)، مجموعة (C) وهي مجموعة المراقبة و تضم الفئران الغير محفزة (control group)، حيث قيمت التغيرات السلوكية والنشاطات صرعية الشكل بواسطة راسين قريد(Racine Grade) والتخطيط الكهربائي للدماغ (ECoG).

النتائج: أظهرت نتائج مخطط كهربائية الدماغ (ECoG) تطابق مع النوبات المرضية والنوبات الإليكتروجرافية، ليس فقط في الفئران المحقونة في المجموعة (A) وإنما أيضاً في مجموعة الفئران المتصلة (B)، وعلى الرغم من ذلك لم تكن هناك أي نوبات مرئية أو تغيرات مرضية في مخطط كهربية الدماغ في المجموعة (C).

خاتمة: من الممكن تصريف شحنات الصرع إلي خارج الدماغ، الأمر الذي قد يفتح مجالات جديدة لعلاج الصرع.

Objectives: To identify whether epileptic discharges can be conducted out of the brain according to the principle of a lightning rod.

Methods: This experimental study was conducted at Central South University, Xiangya Hospital, Hunan, China between 2005 and 2008. Eighty Sprague-Dawley rats were implanted with intra hippocampus and intra frontal lobe electrodes, and randomized to 3 groups: (A) a group that was kindled via stimulation of intra-hippocampus injection of penicillin, (B) a group that was stimulated via a copper wire connected to the intra-hippocampus electrodes of group A, (C) a group composed of non-stimulated, control rats. The behavioral changes and epileptiform activity were assessed by both Racine Grade and electrocorticogram (ECoG).

Results: The intrahippocampal ECoG recordings were coincident with clinical seizures, electrographic seizures occurred not only in the injected hippocampus group A rats, but also in the connected group B rats. However, there were no visible seizures or ECoG burst at any time in group C rats.

Conclusion: Epileptic discharge can be conducted out of the brain, which may open new therapeutic approaches for epilepsy.

Neurosciences 2009; Vol. 14 (2): 128-130

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Received 11th December 2008. Accepted 9th February 2009.

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Epilepsy is one of the most common neurological disorders characterized by recurring, not instigated seizures. In patients with epilepsy, seizures can be well regulated with suitable medication. However, epidemiological data show that 20-30% of patients with newly diagnosed epilepsy are resistant to all forms of medical therapy. These individuals are often severely disabled by their condition, and have an unsatisfactory quality of life.[1,2] Further, epilepsy is associated with an increased risk of psychiatric disturbances, the most common being depression,[3-5] anxiety disorders,[6] cognitive disturbances,[7] and other mood disorders.[8] Treatment of intractable epileptic patients is increasingly becoming a medical and social problem. Even if most of these patients benefit from surgical resection, many would still need new therapies.[9] Brain stimulation has been proposed as an alternative to drug therapy. Stimulation might also have the advantages of reversibility and adjustability in patients who would otherwise be thought of as candidates for surgery.[10] The idea of brain

stimulation is not new. Stimulation for uncontrolled epilepsy with electrodes implanted in the brain itself has been carried out for many years; the initial claims for therapeutic success have not been confirmed by subsequent controlled studies so far. The best structures to stimulate and the most effective stimuli to use are unknown.[11] In 2001, Katariwala et al[12] reported 6 patients with medically intractable partial epilepsy. The latter underwent seizure localization with intracranial EEG using intracerebral or subdural electrodes. No surgical resection was performed, but all had seizure remission ranging from 11 months to 15 years. The authors supposed that electrode implantation in the brain-reduced seizures through interruption of seizure propagation pathways. Based on these findings, we proposed that intractable epilepsy could be controlled if the epileptic discharges were conducted out of the brain. Thus, the aim of this research paper was to identify whether epileptic discharge could be conducted out of the brain.

Methods. This experimental study was conducted at Central South University, Xiangya Medical College, Xiangya Hospital, Hunan, China from 2005-2008, under the supervision and approval of the Central South University Ethics Committee. All experiments were carried out in accordance and adherence to local guidelines for the care and use of laboratory animals and in accordance and adherence to the guidelines of the European Community Council for experimental animal care. Eighty Sprague-Dawley rats were randomized to 3 groups [A (n 27), B (n 27) and C (n 26)] and purchased at a body weight of 250-300 g. The rats were housed under a 12:12 hour light-dark cycle (light exposure 7:00 hours) with a room temperature of 23±2°C. Animals were given free access to food and water and every effort was made to minimize suffering. All rats were adapted to laboratory and housing conditions for at least 5 days before being used in the experiments. All experiments were performed between 10:00 and 14:00 hours. The epileptic focus was produced by penicillin injection. For the penicillin injection and electrode implantation, group A rats were anesthetized with chloral hydrate (360 mg/kg, intraperitoneally), placed in a stereotaxic apparatus, and 4000 IU penicillin unilaterally injected into the right dorsal hippocampus (approximately 2 mm lateral from the midline suture, 3 mm rostral to the lambda, and 3.5 mm below the brain surface). After injection, the microsyringe was withdrawn and electrodes were positioned at the same stereotaxic location used for drug injection in the right dorsal hippocampus, and in the right frontal lobe. Group B and C rats were implanted with electrodes positioned at the same stereotaxic location used for group A rats. Electrodes in the right frontal lobe served as recording-electrodes. To examine whether epileptic discharge was transmitted from the rat's brain in group A to group B, a small copper wire with on off switch was used to connect the 2 microelectrodes between the 2 groups (A-B). The epileptic activity was analyzed by electrocorticogram (ECoG) from the right frontal lobe for all groups. The latent period of ECoG burst was calculated from injection of penicillin to epileptic burst in group A, and from switch on to epileptic burst in group B. Observations were carried out during the same time periods and intervals for group C. The behavior changes were carefully assessed by Racine Stages,[13] considering only convulsive (motor) seizures for scoring: stage I, mouth and facial movement; stage II, head nodding; stage III, forelimb clonus; stage IV, rearing with forelimb clonus; and stage V, rearing and falling with forelimb clonus (generalized motor convulsions). The latent period of clinical seizure was assessed from injection of penicillin to clinical seizure in group A and from switch turn to clinical seizure in group B, and during the same time periods and intervals for group C.

Results. Intra hippocampus injection of penicillin induced epileptiform activity in the group A experimental animals (**Figure 1**). Also epileptiform activity was induced in group B rats after switch turn (**Figure 2**). The mean time latencies were determined as 7.6±5.2 minutes in group A, and 14.3±6.5 minutes in group B rats. No epileptic ECoG bursts were recorded at any time in group C (**Figure 3**), and before switch turn in group B rats (**Figure 4**). After penicillin injection

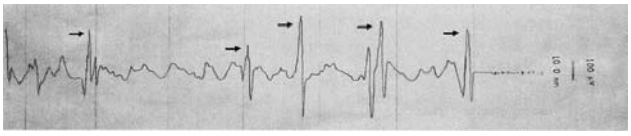

Figure 1 - The ECoG changes after injection of penicillin in group A rats.

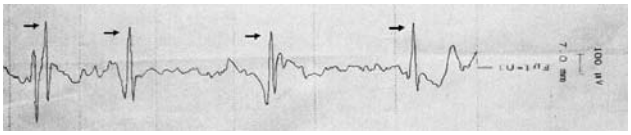

Figure 2 - The ECoG changes after switch turn in group B rats.

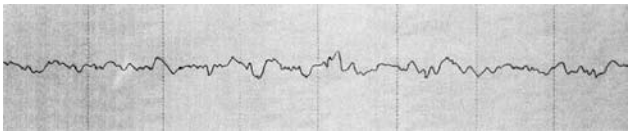

Figure 3 - The ECoG character in group C rats.

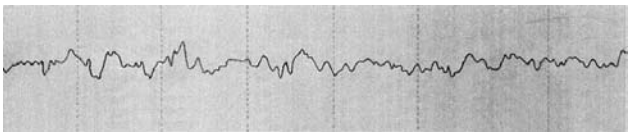

Figure 4 - The ECoG before switch turn in group B rats.

and switch turn between A and B groups, differences were apparent for the Racine stages and latency of the behavioral effects. Before switch turn, Racine stages for group A animals were IV-V with mean time latencies of 11.8±8.5 minutes, but no visible seizure found in group C or group B. After switch turn, Racine stages for group A rats were II-IV, while in group B rats, Racine stages were III-IV with mean time latencies of 16.7±10.2 minutes. Turning off the switch between groups A and B consistently caused Racine stages to increase from II-IV to IV-V for group A rats. Seizures symptoms continued for 12 hours after operation and were recorded by ECoG 24 hours after operation.

Discussion. Epilepsy is a chronic disorder that adversely affects social, vocational, and psychological function. The common features of all types of epilepsy are the synchronized, and uncontrolled discharges of nerve cell assemblies.[14,15] Penicillin-induced experimental epilepsy is a classical method to produce epileptic activity and broadly used by various researchers.[16] In the present study, 4000 IU of penicillin was injected in the right dorsal hippocampus, and significantly produced epileptic activity. This effect was demonstrated via both behavioral observations (Racine stages IV-V) and the electrophysiological recording method.

It is still unknown whether epileptic discharges originating from one brain can be transmitted out to another brain. We plotted an experimental plan to prove this. The results showed that clinical seizure and epileptic ECoG bursts were found in group B after turning on the switch between group A and B, and there were no visible changes observed in group C. It is strongly supported that epileptic discharge originating from the rat's brain in group A was transmitted to the rat's brain in group B. It could be hypothesized that conducting epileptic discharge out of rats' brain may have an antiepileptic effect. Furthermore, in this paper, epileptic discharges were conducted out of the brain according to the principle of a lightning rod. Benjamin Franklin was involved not only with the nature of electricity, but also with its possible medical utility.[17] Benjamin Franklin demonstrated the effectiveness of lightning rods in preventing or greatly reducing the damage from direct lightning strikes, and the proposed theory on the operation of the lightning rod is lightning diversion. We used the same principle of lightning rods to conduct epileptic discharge out of rats' brain. A number of studies have indicated that the electrophysiological mechanism of epilepsy is the nature of synchronized and uncontrolled discharges of nerve cells.[6,7] When epileptic discharge occurred, the electrical current can be recorded not only in vitro,[18] but also in vivo.[19] Implantation of intracranial electrodes could reduce seizures, possibly through interruption of seizure propagation pathways.[12]

In conclusion, according to our findings, propagation pathways of epileptic discharge have been changed; at least part of the epileptic discharge was transmitted from one brain to another. Further research is warranted to establish whether conduction of an epileptic discharge out of a patient's brain could provide a new therapeutical basis for epilepsy. The significant limitation of this study relates to its scope. The extent to which therapeutic application in the human setting could be construed needs to be researched further.

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