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Okayama University research: Antibodies prolong seizure latency in epileptic mice

(Okayama, 22 May) **Researchers at Okayama University describe in *Scientifc Reports* the effect of a particular type of monoclonal antibody on epilepsy in mice. Findings include the prevention of disrupted brain–blood barrier function, the inhibition of inflammations, and prolonged epilepsy seizure latency.**

Epilepsy is a category of neurological disorders characterized by recurrent seizures. The causes of epilepsy are largely unknown, but it has been established that high mobility group box 1 (HMBG1) protein expression may be linked to epilepsy-related inflammations. A team of researchers led by Masahiro Nishibori from Okayama University has now investigated the HMBG1–epilepsy connection in detail, and found that administering anti-HMBG1 monoclonal antibodies (mAb) prolongs the latency of epileptic seizures – an important finding in the on-going quest for understanding and curing epilepsy.

Since an increased production of HMBG1 has been observed earlier in human and rat epileptic brain, Nishibori and colleagues tested the hypothesis that HMBG1 plays a role in epileptogenesis and, specifically, in disruptions of the functioning of the blood–brain barrier. The latter is a semipermeable membrane in the brain separating blood from other, extracellular fluid.

The researchers did experiments with mice treated with pilocarpine, a model commonly used for the study of epilepsy. Pilocarpine is a molecule normally used as a medicine (for e.g. relaxing increased pressure in the eye), but when injected systematically with a high dose in mice, it could initiate seizure and then cause status epilepticus. Nishibori and colleagues confirmed this disruption: pilocarpine-injected mice undergo a translocation of HMGB1 from the cerebrum (the principal part of the brain located at the front of the skull) to the blood, affecting the permeability of blood-brain barrier. They also proved that administering of exogenous HMGB1 could exacerbate the blood-brain barrier disruption.

The scientists then looked at the effect of intravenously introducing anti-HMGB1 mAb to the pilocarpine mouse model. They found that such treatment leads to the inhibition of HMGB1 translocation and the protection of blood–brain barrier permeability. This in turn resulted in prolonged seizure latency. Nishibori and colleagues therefore conclude that “anti-HMGB1 therapy may provide a novel strategy for controlling the epileptogenesis”.

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Background

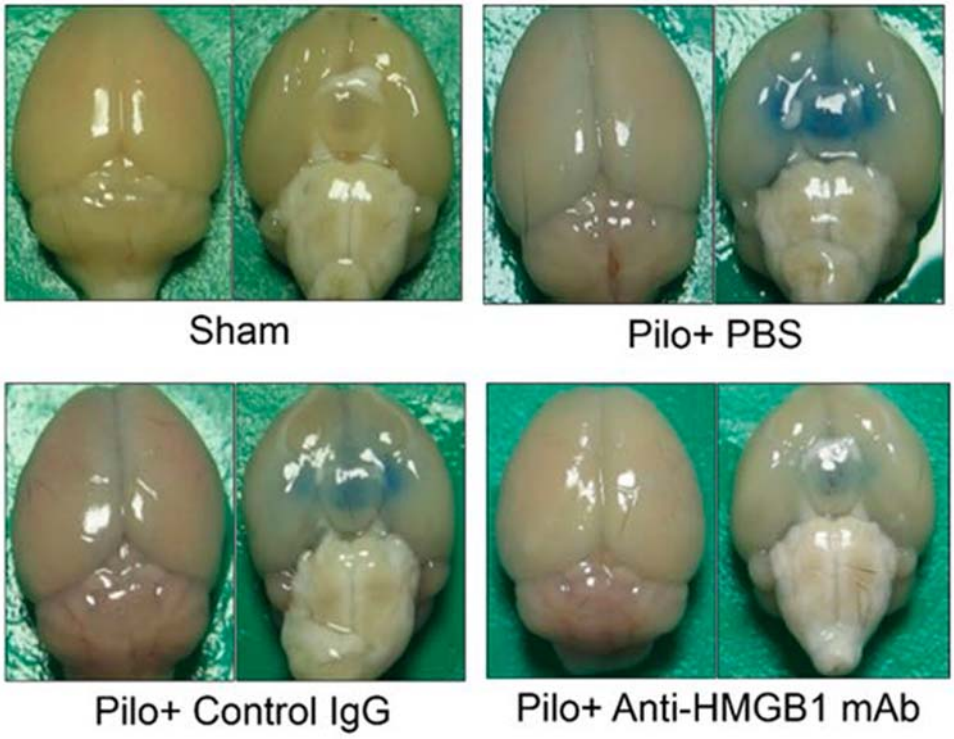
Pilocarpine

Pilocarpine is an organic molecule often used as a medicine, e.g. for treating dry mouth (xerostomia) or decreased the pressure of the fluid in the eye (intraocular pressure). When injected in rodents, such as rats and mice, it could causes status epilepticus. Pilocarpine-injected mice are therefore good models for studying the physiology and treatment of epilepsy. Specifically, pilocarpine-induced epilepsy has been reported to be a very good model for human temporal lobe epilepsy, a form of epilepsy affecting at least 20% of patients suffering from recurrent seizures.

HMGB1 and antibodies

High mobility group box 1 (HMGB1), sometimes referred to as amphoterin, is a protein produced by almost all kinds of cells. Excessive release of HMGB1 is believed to be associated with brain injury and dysfunction. Masahiro Nishibori from Okayama University and colleagues investigated how exactly the protein is involved in the development of epileptogenesis — what role it plays in the disrupted functioning of the brain–blood barrier and the induction of inflammatory processes.

Realizing the importance of HMGB1 in the context of epilepsy, the researchers tried, with success, to inhibit its effects by intravenous HMGB1 antibodies. Antibodies, also known as immunoglobulins, are molecules that are able to identify and 'capture' molecules considered harmful (e.g.HMGB1 molecules).



Caption

Epilepsy is related to disrupted functioning of the brain–blood barrier. Its permeability was tested for pilocarpine-injected mice by monitoring the leakage of Evans blue dye, with and without administered HMGB1 monoclonal antibodies.

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Reference

Li Fu, Keyue Liu, Hidenori Wake, Kiyoshi Teshigawara, Tadashi Yoshino, Hideo Takahashi, Shuji Mori & Masahiro Nishibori. Therapeutic effects of anti-HMGB1 monoclonal antibody on pilocarpine-induced status epilepticus in mice. *Scientific Reports*, April 26, 2017. DOI:10.1038/s41598-017-01325-y
https://www.nature.com/articles/s41598-017-01325-y

Reference (Okayama University e-Bulletin & OU-MRU) : Professor Nishibori's team

e-Bulletin Vol.2 : The invention of an antibody drug for the treatment of brain infarction
OU-MRU Vol.27 : Keeping cells in shape to fight sepsis

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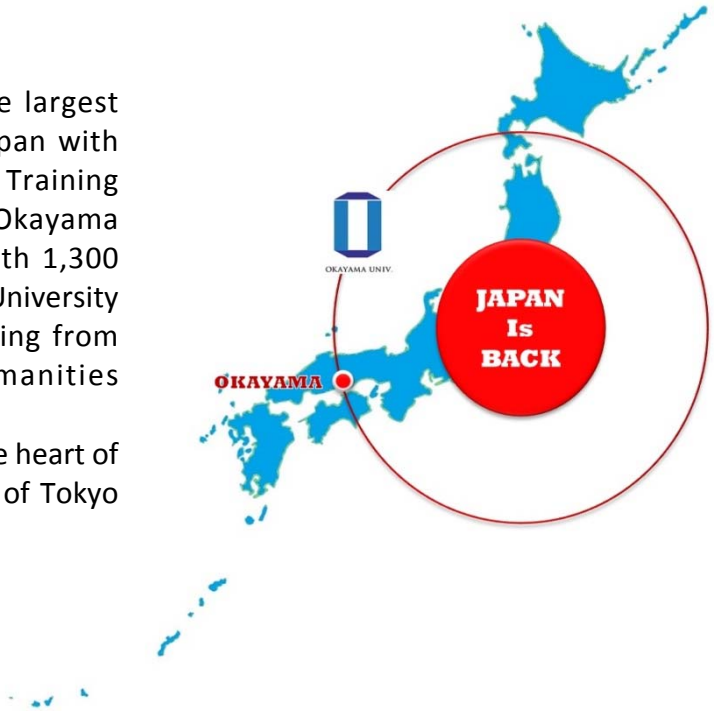
About Okayama University

Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 14,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.
Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.



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