Primate model brings new hope for stroke treatment

Despite much promising animal research on protecting the brain after stroke, no treatments have yet proven to be effective in humans. This disconnect has contributed to both a lack of confidence in the relevance of animal models for certain types of medical research and a growing concern that stroke-related brain damage may not be avoidable in higher-order mammals such as humans. To bridge this gap, a team of researchers led by Michael Tymianski (Toronto Western Hospital Research Institute, Ontario, Canada) has developed a primate model of stroke by occluding the middle cerebral artery in cynomolgus macaques (*Macaca fascicularis*). Because primates share behavioral, genetic and anatomical characteristics with humans, success in treating stroke in primates should be a more reliable predictor of success in humans.

Tymianski's group used the macaque model to test the efficacy of an experimental stroke treatment that has shown promise in rat studies and found that the treatment reduced infarct size and improved outcomes in the macaques (*Nature* **483**, 213–217; 2012). The scientists state that these findings "defeat the current pessimistic belief by demonstrating that pharmacological neuroprotection of the high-order brain of gyrencephalic primates is unequivocally possible." Furthermore, they suggest that "[u]nless there exist fundamental, as yet unknown, relevant differences between such primates and humans, neuroprotection in humans… should also be feasible."

The treatment tested by Tymianski's team inhibits interactions between post-synaptic density protein 95 (PSD-95) and neurotoxic signaling pathways, protecting the brain against stroke-related damage. In the macaque study, experimental stroke was induced for 90 minutes, and either PSD-95 inhibitor or a placebo was administered 60 minutes later. The size of the infarct, or ischemic tissue resulting from the stroke, was assessed by magnetic resonance imaging.

Infarcts in macaques that received PSD-95 inhibitor were ~40% smaller both 24 h and 30 d after stroke than infarcts in macaques that received placebo. When final infarct sizes were normalized to initial sizes to account for variations among individuals, infarct sizes were reduced by 55% at 24 h and 70% at 30 d by treatment with PSD-95 inhibitor. Macaques that received PSD-95 inhibitor also performed better on physical and behavioral tests and had better stroke scores than did macaques that received placebo.

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PSD-95 inhibitor has already been tested in a clinical trial to treat ruptured brain aneurysms and shown to be effective in lessening ischemic brain damage and improving neurological scores, making it the first stroke therapy that has demonstrated benefits in humans after testing in primate models.

Monica Harrington

CREATING FALSE MEMORIES IN MICE

Scientists have been searching for ways to better understand how memories are formed in the brain and to potentially weaken harmful or distorted memories in order to treat conditions such as schizophrenia and post-traumatic stress disorder. Understanding how the activity of the brain leads to fearful representations of the world may explain what goes wrong in these disorders.

Memories can be triggered experimentally by stimulating various regions of the brain. Mark Mayford and researchers at The Scripps Research Institute in La Jolla, CA, in collaboration with scientists at the University of Oregon in Eugene, have developed a new method of triggering memories by creating transgenic mice with a genetic 'on/off switch.'

These transgenic mice were first put into a box, activating a group of neurons involved in forming a memory of the box. The researchers next put each mouse into a different box and injected it with a drug to turn on the neurons involved in forming the memory of the first box. This induced the mice to involuntarily remember the first box while in the second box. They then gave the mice a small shock. Normally, the shock would condition the mouse to fear its current environment, the second box, but instead, the mouse was conditioned to fear a combination of the two contexts. Only when the mouse had been injected with the drug to induce the memory of the first context and was present in the second context did it exhibit a fear response (*Science* **335**, 1513–1516; 2012).

In a similar study, a team of scientists led by Susumu Tonegawa (Massachusetts Institute of Technology, Cambridge) used a new technology called optogenetics to genetically engineer mice so that when a memory was formed, the neurons involved became responsive to light. In this experiment, a mouse was placed in a box and given a shock. The mouse was then put in a different box, and pulses of light were delivered through optic fibers implanted in the mouse's brain in order to activate the neurons involved in forming the memory of the first box. In response to the activated memory of the box where it had been shocked, the mouse froze even though it was in a totally different context (*Nature* doi:10.1038/nature11028; published online 22 March 2012).

These experiments demonstrate that artificial perceptions produced when memory-associated neurons are activated can seem just as real as the actual environment. In the future, researchers hope to find ways to deactivate these neurons in order to disrupt harmful thought processes.

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