Playing out possibilities helps rats to make decisions

A new study shows that a specific pattern of activity in one part of the brain occurs when rats in a maze are playing out memories that help them decide which way to go. This demonstrates that rats rely on memories when making decisions.

After a rat travels the different pathways in a maze, spatial trajectories are recorded in the hippocampus. A pattern of brain activity called sharp-wave ripple (SWR) events represents the possible paths that the rat can take from its current location. These SWRs are 'reactivated' when the rat must decide which path to take. In this way, SWRs play an important role in the evaluation of upcoming choices.

Loren M. Frank (Massachusetts Institute of Technology, Cambridge) and colleagues asked how SWR reactivation aided memory-guided spatial decisions in Long-Evans rats (*Neuron* **77**, 1163–1173; 2013). Rats were placed in a W-shaped maze and rewarded for visiting the different arms of the maze in the following order: center, left, center, right, center, left, etc. Frank's team was most interested in SWR activity when the animals were in the center arm, because at that point the animals must remember whether they previously visited the left or right arm in order to know which arm they should visit next to earn the reward. The researchers found that the number of SWRs was greatest when the rats were still—that is, when they were considering their options. These memory reactivation events represented sequences that proceeded away from the animal's current location when the rats chose the correct path.

The researchers measured the brain activity of the rats while they were learning to perform this task and after they had perfected it. They found that there was more SWR reactivation before the rats correctly chose which way to go. The proportion of activated cells could predict whether the rat chose the correct path or the incorrect path. In other words, when the rat remembered the possibilities better, it made better decisions.

Interestingly, the trajectories represented by the SWRs included both the correct choice and the incorrect choice. When the rats had mastered the task (>85% correct trials), there was a bias toward reactivating the representation of the correct pathway. The scientists suggested that perhaps the hippocampus becomes biased toward reactivating the correct action sequence in order to increase the likelihood of the rat carrying out that action sequence.

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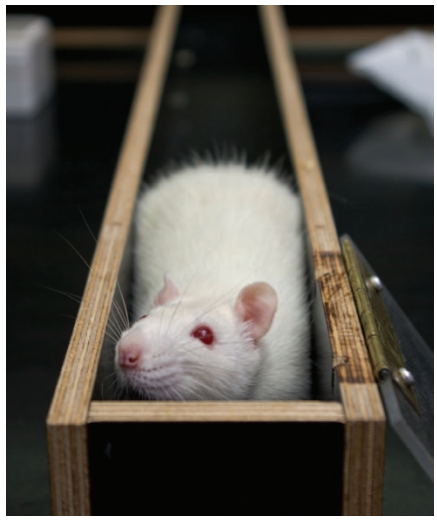

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FOR LUPUS TREATMENT, DRUG DELIVERY MAY BE KEY

Lupus is an autoimmune disorder in which the immune system becomes dysregulated, attacking the body's own cells and tissues and causing inflammation and subsequent damage. Systemic lupus erythematosus (SLE) is the most common and serious form of lupus. There is no cure; treatments instead focus on suppressing the immune response in order to minimize organ damage. Many currently available drugs must be taken continually, and some are quite toxic, leading to a high rate of treatment noncompliance. Immunobiologists continue to search for strategies that can target immunosuppressant drugs to specific immune cells, lowering the dose of medication that is effective.

Scientists at Yale University (New Haven, CT) now report successful treatment of a mouse model of SLE using nanogel technology to deliver relatively low but effective doses of the immunosuppressant mycophenolic acid (MPA), a form of which is already used to treat SLE in humans. MPA-loaded nanogels extended mean survival time by 3 months when administered before the onset of disease and by 2 months when administered to mice that had already developed renal failure (*J. Clin. Invest.* published online 1 March 2013; doi:10.1172/JCI65907). "Three months of a mouse's life is roughly equivalent to more than eight years of a human life, so this is dramatic," Tarek Fahmy, the lead researcher, told *Yale News*. "The potential for human benefit is clear and promising."

Mice treated with MPA-loaded nanogels showed no signs of hematological or organ toxicity, and their white blood cells were not completely depleted, suggesting that nanogel delivery might preserve immune function and reduce the vulnerability to infection that commonly occurs with immunosuppressant therapy.

The nanogel has a biodegradable gel core surrounded by a lipid bilayer, enabling it to encapsulate both hydrophilic and hydrophobic molecules and to stabilize them for delivery. Delivery via nanogel improved distribution of MPA to organs and retention of the drug within the body. Although the nanogels have not yet been tested in human SLE, the nanogel components are approved by the FDA, and similar systems have been tested for delivery of cancer-fighting drugs.

Fahmy says the study is "the first in-depth and comprehensive application of a promising nanotechnology for directed immunosuppressant delivery in a heterogeneous autoimmune disease with limited therapeutic options." His team suggests that nanogel delivery could prove to be a useful therapeutic strategy in other autoimmune conditions as well.

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