This Week in The Journal

Spatial Alternation Relies on More than Working Memory

David B. Kastner, Anna K. Gillespie, Peter Dayan, and Loren M. Frank

(see pages 7319–7325)

Many behavioral tasks have been developed to identify brain areas, genes, and molecular pathways involved in cognitive processes and neurological conditions. For example, the open-field test is used to investigate contributors to anxiety, the Morris water maze tests spatial learning, and spatial alternation tasks measure working memory. But performance on these tasks requires multiple nervous system functions. Some of these, such as locomotion, vision, and motivation, are well recognized, and their contributions to impaired task performance under specific experimental conditions are usually assessed. Yet other cognitive processes might make contributions as well. For example, Kastner et al. have identified two cognitive components that influence spatial alternation.

Spatial alternation tasks typically use mazes with three connected arms. To receive rewards, animals starting in the central arm must proceed to the left or right arm, return to the center alley, and then visit the third arm. The animals must use working memory to remember which outer arm they visited most recently. To determine whether working memory is sufficient to explain rats' behavior on this task, Kastner et al. created a reinforcement-learning-based computational model incorporating working memory, and they compared the model's performance with that of rats.

Even when the model was given perfect memory, it did not learn the task as quickly as rats. Moreover, the pattern of errors made by the model differed from that made by rats. Rats learned to go to the middle arm after visiting an outer arm more quickly than they learned to go to the appropriate outer arm after visiting the middle arm; in contrast, the model learned the middle-to-outer rule more quickly than the outer-to-middle rule. But when the model was augmented to include preferences for particular arms and for transitions

between arms, and when it was initialized to reflect an estimate of prior starting biases, its performance more closely matched the pattern and rate of learning in rats.

These results suggest that performance on the spatial alternation task is determined by other cognitive factors in addition to working memory. The work identifies a set of preferences that can explain the pattern of errors rats make, but future work will be needed to determine which factors actually influence learning in animals.

After ischemia (right), astrocytes in wild-type mice (top) become activated, as indicated by an increase in volume (indicated by color: blue, 200 μm^3 ; red, 1000 μm^3) relative to the uninjured state (left). Astrocyte activation is blunted when aromatase is knocked out in forebrain neurons (bottom). See Lu et al. for details.

Estradiol Frees Astrocytes to Protect Neurons after Ischemia

Yujiao Lu, Gangadhara R. Sareddy, Jing Wang, Quanguang Zhang, Fu-Lei Tang, et al.

(see pages 7363–7382)

Estradiol is produced in both male and female brains, where it regulates synaptic plasticity and influences learning, memory, and other brain functions. It also promotes neuronal survival. Knocking down aromatase, the enzyme that synthesizes estradiol, exacerbates brain damage after ischemia. Although aromatase is expressed almost exclusively by neurons in healthy brains, it is also expressed in glia after ischemic injury. Therefore, the extent to which neuronal and glial aromatase and estradiol contribute to neuroprotection has been unclear. To find out, Lu et al. examined the effects of global cerebral ischemia in male and female

mice in which aromatase was knocked out selectively in forebrain neurons.

In control mice, briefly stopping blood flow to the brain caused neuronal death in the hippocampus and impaired spatial memory. Ischemia also induced activation of hippocampal astrocytes and increased levels of astrocyte-derived neuroprotective proteins, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and the glutamate transporter GLT-1, which takes up synaptic glutamate and thus limits excitotoxicity. Aromatase expression also increased in astrocytes after ischemia, leading to higher hippocampal estradiol levels. Astrocytic activation likely depended on ischemia-induced downregulation of fibroblast growth factor 2 (FGF2) and its receptor FGFR3, which normally inhibit glial activation.

In mice lacking forebrain neuronal aromatase, however, FGF2 levels increased after ischemia, and astrocyte activation, production of neuroprotective factors, and aromatase expression were significantly lower, whereas ischemia-induced neuronal death and memory impairment were higher than in control mice. Notably, blocking FGFR3 function in knock-out mice restored ischemia-induced astrocyte activation and protein expression and reduced neuron death and memory impairment. Moreover, infusion of estradiol after ischemia reduced hippocampal FGF2 and FGFR3 levels and restored astrocyte activation, protein expression, and neuronal survival.

These data suggest that estradiol produced by neuronal aromatase inhibits expression of FGF2 after ischemia, thus removing FGF2-mediated suppression of astrogliosis. This allows astrocytes to assume a neuroprotective role, secreting BDNF and IGF-1, increasing glutamate uptake, and further elevating hippocampal estradiol levels. Some combination of these effects reduces neuronal death and thus minimizes the loss of cognitive function. Given that knockout of neuronal aromatase prevents upregulation of glial aromatase, future work should determine whether glial-derived estradiol is required for astrocyte activation and neural protection.

This Week in The Journal was written by Teresa Esch, Ph.D.
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