LEARNING AND MEMORY

Restoring balance in diabetes

Although most people are aware of the risks to cardiovascular and general health that result from diabetes, its consequences for brain function are perhaps less well appreciated. However, the nervous system is by no means spared the negative influence of the disease, and diabetes has been linked to impairments in cognitive function in both patients and animal models. Mattson and colleagues now show that elevated levels of corticosterone contribute to these deficits.

In humans with diabetes and in animal models of the disease, the hypothalamo–pituitary–adrenal axis is often hyperactive, resulting in abnormally high levels of the adrenal steroid cortisol (corticosterone in rodents). Elevated corticosterone levels have adverse effects on cognition in other circumstances, such as stress, and so the authors reasoned that they might also mediate the effects of diabetes on learning. To test this idea, they normalized the levels of corticosterone in two animal models of diabetes — streptozocin-treated rats, which model the insulin-dependent form of the disease, and obese mice that carry a mutation in the leptin receptor (*db*/*db* mice), which model insulin-resistant diabetes — by removing the adrenal glands and treating the animals with low levels of corticosterone, and examined the animals' performance in learning and memory tasks.

Normalizing corticosterone levels in this way reversed the learning deficits that are usually seen in diabetic animals in hippocampus-dependent tests of both spatial learning (water maze) and recognition memory (novel-object preference). To confirm the central role of corticosterone in mediating these effects, the authors treated a separate group of adrenalectomized animals with high levels of corticosterone and showed that this resulted in learning and memory impairments that were equivalent to those that are seen in sham-operated diabetic animals.

Both synaptic strengthening and increased proliferation of neural precursors in the hippocampus are associated with learning processes and are altered in diabetic animals. The authors therefore went on to examine the effect that normalizing corticosterone levels had on these processes. They revealed that restoring corticosterone levels to normal prevented the impairments in long-term potentiation that are observed at perforant-path–dentate-gyrus (DG) synapses in sham-operated animals. Furthermore, the reduced proliferation in the DG that is observed in sham-operated diabetic animals was also prevented by the treatment. This suggests that elevated corticosterone levels affect multiple learning mechanisms in the hippocampus.

Given the rising prevalence of diabetes in Western society, the discovery of approaches to treat its cognitive symptoms would be welcomed. Although more work is required to determine whether the effects seen here in rodents can be replicated in humans with diabetes, this study suggests that restoring cortisol levels to normal might prevent some of the cognitive impairments that are associated with the disease.

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