Stimulating neurons to grow

Deep brain stimulation (DBS) is an established treatment for neurological disorders such as Parkinson's disease. The technique uses a surgically implanted electrode to deliver electrical stimulation directly into a specific area of the brain, such as the motor cortex, in order to increase neural activity in the targeted region. Researchers have recently begun exploring other applications for DBS, such as the treatment of cognitive and mood disorders. Though the treatment has been effective in treating certain disorders, studies explaining how the treatment works have been scarce.

A team of researchers led by Paul W. Frankland and colleagues at The Hospital for Sick Children in Toronto, Canada, have sought to uncover the mechanisms that allow DBS to translate into neurological changes (*J. Neurosci.* **31**, 13469–13484; 2011). They hypothesized that DBS might influence cognitive ability if applied to the hippocampus, the center of learning and memory in the brain. In a set of mice, DBS was used to stimulate to the entorhinal cortex, a region of the brain that provides direct input into memory-related circuitry in the hippocampus.

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They found that stimulation of the entorhinal cortex led to increased production of new neurons in the hippocampus, demonstrating that the effects of DBS may spread farther than the targeted brain region. Furthermore, these new neurons were quickly integrated into existing memory circuits, suggesting that they might functionally contribute to memory processes.

The scientists tested whether this neuronal growth spurt led to an enhancement in the mice's memory ability. Based on the location of the new cells, they investigated whether spatial memory ability would be enhanced in the stimulated mice. They found that mice who had received DBS were significantly better at navigating to a designated target than those that had not received the treatment. This suggests not only that DBS stimulates growth of new neurons in the brain, but also that these new neurons can translate into enhanced cognitive abilities.

The results of this study show that DBS can enhance cognitive abilities by increasing the production of new neurons in the brain. The treatment, which has already been used in thousands of human patients, may therefore provide therapeutic benefits. Frankland told the Society for Neuroscience, "These new findings have important clinical implications as they inform potential treatments for humans with memory disorders."

Kara Rosania

SIRTUINS UNDER SCRUTINY

The protein called silent information regulator 2 (Sir2) was first discovered in budding yeast, *Saccharomyces cerevisiae*. It belongs to a highly conserved family of proteins christened sirtuins, which are found in almost all organisms and are involved in responses to stressors, such as heat and starvation. In 1999, Sir2 was reported to increase lifespan in yeast cells (*Genes Dev.* **13**, 12570–2580). Then in 2001, scientists reported a link between overexpression of the gene *sir-2* and longevity in the nematode *Caenorhabditis elegans* (*Nature* **410**, 227–230). A few years later, a second group of researchers noted a similar association of *Sir2* with longevity in *Drosophila melanogaster* fruit flies (*Proc. Natl. Acad. Sci. USA* **101**, 15998–16003; 2004). Furthermore, it was suggested that activation of Sir2 could be the mechanism underlying the lifespan-lengthening effects of calorie restriction, a well-documented phenomenon in many organisms, including mammals.

The gathering body of work focused a great deal of attention on sirtuins as the fabled 'fountain of youth.' Research groups began looking for evidence that sirtuins' longevity effects extended to mammals, such as mice, and began looking for ways to activate sirtuins and, they hoped, extend lifespan.

But trouble was brewing in sirtuin research, as contradictory and inconclusive results began to accumulate, and questions began to surface about the genetic background of the experimental animals and the controls used in the original experiments.

Researchers from the Institute of Healthy Ageing at University College London (UK), led by David Gems and Linda Partridge, in collaboration with several other laboratories, decided to take a closer look, re-examining the effects of Sir2 on longevity in *C. elegans* and *D. melanogaster*. They found that standardizing the genetic backgrounds of the experimental animals and using appropriate experimental controls eliminated the increased longevity in the sirtuin mutants of both species (*Nature* **477**, 482–485; 2011). The authors stress that their findings "underscore the importance of controlling for genetic background and for the mutagenic effects of transgene insertions in studies of genetic effects of lifespan."

The report won't be the last to address the question of sirtuins and longevity. Members of the laboratories that contributed the original reports acknowledge some flaws in those experiments but provide new results that confirm an effect (though smaller than that originally reported, at least for *C. elegans*) of Sir2 on longevity.

Speaking with *Nature News*, Gems agreed that sirtuin research should not be abandoned: "They are very interesting proteins…and have very interesting metabolic effects."

Monica Harrington