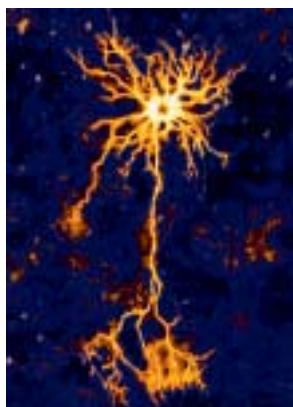


Fixing Fragile X

KNOCKING OUT A SINGLE GENE IN NEURONS ELIMINATES SYMPTOMS OF FRAGILE X SYNDROME IN MICE.

By probing the network of genes and proteins active at the junctions between neurons in the brain, HHMI researchers have unearthed a new strategy for treating fragile X syndrome—the most common inherited form of mental retardation.

Mark Bear, an HHMI investigator at the Massachusetts Institute of Technology, studies how the connections between neurons are strengthened or weakened as new pieces of information are retained



The connections between neurons in the brain hold a surprising clue to fragile X syndrome.

in the brain, and other memories fade. He previously found that a neurotransmitter receptor called mGluR5 plays a role in weakening neural connections, by increasing the amount of proteins made at the synapses between neurons.

Most recently, Bear discovered that fragile X mental retardation protein (FMRP), which is mutated in fragile X syndrome, counterbalances mGluR5. “The fragile X protein is normally putting a brake on the protein synthesis stimulated by mGluR5,”

explains Bear. This means that in fragile X syndrome, FMRP is not around so the protein synthesis goes unchecked.

Bear and his colleagues, in a study published in the December 20, 2007, issue of *Neuron*, showed that getting rid of one copy of mGluR5 in fragile X-affected mice eliminates the seizures and memory impairments that such mice typically exhibit.

The researchers bred mice with fragile X syndrome—characterized by developmental delay, structural changes in the brain, and epilepsy—with mice engineered to produce half the normal level of mGluR5. Their offspring showed few symptoms of fragile X, despite the mutation in FMRP they had inherited.

Since mGluR5 and FMRP do not directly interact, but influence neural protein synthesis in opposite directions, the results suggest that it is the increased protein synthesis in fragile X patients that leads to the syndrome. The brains of fragile X-affected mice typically have an excess of particularly weak neural connections. Bear hypothesizes that the excess protein synthesis could be leading to this high density of connections.

“Now we have a lot of work ahead of us to figure out which proteins are producing the pathology,” says Bear, who is also now studying whether blocking mGluR5 receptors in humans can counter fragile X syndrome. ■ —SARAH C.P. WILLIAMS

IN BRIEF

people without mental retardation found no instances of the deletion. The results appeared online in *Nature Genetics* on February 17, 2008.

In most of the affected cases, the large segments of DNA were deleted spontaneously, not inherited. “These kinds of events are happening all the time when sperm and egg are being generated,” says Eichler. “We think everyone has some areas of the genome that are duplicated or deleted but it doesn’t always cause disease.”

The missing chromosome segment spans six genes, and the scientists hope to pinpoint which of those deleted genes is linked to the epilepsy commonly seen in the patients.

While this missing segment explains only 3 in 1,000 cases of mental retardation, Eichler says other spontaneous deletions and duplications of large chunks of chromosomes could explain more.

“Collectively all of these rare sites probably account for 10 percent of mental retardations,” he says.

NUCLEAR NEIGHBORHOODS CONTROL GENE EXPRESSION

By forcing bits of genetic material to the edge of the nucleus, scientists have shown that placement of genes within the nucleus

can affect whether the gene is expressed as a protein.

HHMI investigator Harinder Singh, University of Chicago, was studying how B and T cells of the immune system assemble their receptor genes using the same machinery but never mix up their parts—the proteins that stud the surface of B cells are never expressed in T cells, for example. He and his colleagues noticed that in T cells, the genes encoding B cell receptor proteins were positioned at the edge of the nucleus.

To study the significance of this placement, the researchers designed a molecular tool to tether genes at the nuclear edge. They found that genes bound there were not expressed. Moreover, in research that appeared February 13, 2008, online in *Nature*, they identified membrane proteins that could connect unneeded genes to the nuclear envelope.

Singh says their results suggest that location in the nucleus could be as important as location in the rest of the cell—where compartments process and sort proteins in a specific order.

“We should be thinking of genes in the nucleus as having to be moved and sorted too,” he says. “There’s a degree of organization in the nucleus that we haven’t paid much attention to.”

STRUCTURE OF SPASTIN ENZYME REVEALS HOW IT SLURPS UP MICROTUBULES

HHMI researchers have pieced together the structure of spastin, a protein that remodels networks of microtubules, which transport molecules inside cells. When spastin malfunctions, as it does in hereditary spastic paraplegias, people experience progressive weakness and stiffness. Understanding spastin’s control of microtubules could lead to treatments for these disorders.

Ronald D. Vale of the University of California, San Francisco, has now confirmed the suspicion that spastin is a ring composed of six identical subunits. The details of spastin’s structure appeared in *Nature* on January 17, 2008. By complementing the x-ray techniques used to determine this structure with further tests, Vale and his colleagues shed light on how the protein works.

“Spastin appears to grab a loose tail region of the microtubule and mechanically ratchet it through the pore,” says Vale, who described it as “a kind of noodle-slurping mechanism.”

This breaking apart of microtubules is probably necessary to the constant remodeling inside cells, says Vale. When this