Protein Precision in the Brain

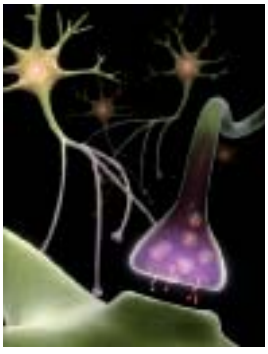
TWO CAUSES OF AUTISM ARISE FROM OPPOSITE CELLULAR MECHANISMS.

To function normally, the brain needs to maintain a precise level of synaptic protein synthesis—too much or too little can cause problems, according to research by HHMI investigator Mark F. Bear and his lab team. Their findings provide insight into two forms of autism with overlapping symptoms.

A decade ago, Bear and his colleagues at the Massachusetts Institute of Technology discovered that fragile X mental retardation protein (FMRP) counterbalances a neurotransmitter receptor called mGluR5. Normally, FMRP keeps mGluR5 from turning on protein synthesis at the synapse between neurons. But in fragile X syndrome, FMRP is missing so protein synthesis proceeds unchecked. This increase in protein synthesis in brain cells, Bear has shown, accounts for multiple symptoms in animal models of fragile X. Drugs that block mGluR5 are now in clinical trials to treat autism and intellectual disability in fragile X patients.

Bear wanted to see if the same drugs could be used to treat another disease—tuberous sclerosis complex—that causes autism and learning delays and is also linked to genes that regulate synaptic protein synthesis. The disease is caused by mutations in tuberous sclerosis complex protein 1 or 2 (Tsc1 or Tsc2). Inactivation of either of these proteins results in an increase in the activity of mTOR, a protein involved in RNA translation. Scientists hypothesized that a boost in mTOR levels might increase synaptic protein production via the same pathway as mGluR5.

Using a mouse model of tuberous sclerosis, Bear's team looked at how mutations in Tsc2 affect protein synthesis at the synapse. To their surprise, synthesis decreased in neurons with the Tsc2 mutations—the opposite of what happens in fragile X. Interestingly, mice engineered to carry mutations in both the *Tsc2* and *Fmr1* genes generate just the right amount of synaptic protein. The team published its findings online November 23, 2011, in *Nature*.



Too much or too little protein production at the synapse between neurons can cause autism and intellectual disability.

A drug that blocks mTOR—called rapamycin—is already in clinical trials to treat tuberous sclerosis, and Bear's new study offers an explanation of how the drug works to reverse some problems caused by the disease. Next, he hopes to more fully understand how the pathway controls synaptic protein synthesis. ■ –NICOLE KRESGE

IN BRIEF

which parts of the brain these taste receptors activate.

Charles S. Zuker and his colleagues injected neurons with a dye that made them light up when activated. Using high-powered microscopes, the scientists could watch hundreds of nerve cells in the brain at once. They discovered that when a mouse is given something bitter to taste, many neurons in a small, specific area light up. Salty foods activate a separate area a few millimeters away. As they reported in the September 2, 2011, issue of *Science*, each basic taste corresponded to a different hotspot in the brain.

Now, that he's created a "gustotopic map," Zuker is studying how taste combines with other sensory inputs, such as smell and texture, and the internal state—hunger and expectation, for example—to choreograph flavor, taste memories, and taste behaviors.

THE DEET DEFENSE AGAINST MOSQUITOES

Campers often find relief from mosquito attacks by dousing themselves in DEET-laden bug sprays. But until recently, no one knew how this bug-repelling compound worked. A new study suggests that DEET confuses insects by jamming their odor receptors.

Insects smell with their antennae, which contain neurons with odor receptors. Each receptor consists of two components: a protein called Orco and a variable protein that confers odor selectivity. HHMI investigator Leslie Vosshall, a neurobiologist at Rockefeller University, previously determined that DEET prevents some of these odor receptors from functioning properly.

In her latest work, published October 27, 2011, in *Nature*, Vosshall and her team reported that DEET alters the way different neurons respond to an odor. For example a compound called 1-octen-3-ol normally inhibits a neuron with a receptor containing the variable protein or59b and activates a neighboring neuron that contains or85a. In the presence of DEET, 1-octen-3-ol has the opposite effects on the same two neurons—it activates the or59b-containing neuron and suppresses the activity of the neurons containing or85a. A mutation in the or59b receptor makes the neuron insensitive to DEET, which shows that DEET is acting directly on the odor receptor protein.

"It completely scrambles the code," says Vosshall, explaining that her team's data indicate that insects do detect odors in the presence of DEET—they just can't figure out what they are.

TURNING ON FETAL HEMOGLOBIN

A single mutation in the adult hemoglobin gene can cause normally flexible, disk-like red blood cells to assume rigid, crescent shapes and clog the small blood vessels. The resulting condition, sickle cell anemia, is marked by fatigue, severe pain, and organ damage, including strokes. All the features of sickle cell disease can be alleviated by elevating levels of fetal hemoglobin, but finding an effective way to do this has eluded scientists, until now.

Several years ago, HHMI investigator Stuart H. Orkin of Children's Hospital Boston discovered that BCL11A, a transcription factor that binds to DNA and regulates gene expression, can halt fetal hemoglobin production. In the November 18, 2011, issue of *Science*, Orkin and his team revealed that suppressing BCL11A can reactivate fetal hemoglobin production in adult mice, effectively reversing sickle cell disease.

BCL11A is probably one of many molecules involved in controlling fetal hemoglobin production, but Orkin's results indicate that it's an essential player in the process.

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