When more is not more

Boosting the function of a learning protein jams the brain with too much information, according to Ype Elgersma (Erasmus MC, Rotterdam, Netherlands), Alcino Silva (University of California, Los Angeles, CA), and colleagues. The result is a cautionary tale for those seeking to develop learning drugs.

The team created mice lacking two inhibitory phosphorylation sites on αCaMKII. Wild-type αCaMKII is displaced from synapses in part by the phosphorylation, but the mutant protein has an enhanced affinity for synapses. This lowers the threshold for establishing long-term potentiation (LTP)—a synapse-strengthening event associated with learning—probably because it now takes less calcium rushing into the synapse to reach the necessary level of αCaMKII activity.

Initial water-maze learning by the mice was normal. But the mutant mice, unlike wild type, did not improve on their early learning. Silva believes that the mice solidify all early information—both correct and incorrect—as permanent memories that are difficult to erase.

"A weak signal to these animals is a strong signal," says Silva. "Initially that may be good. But later it may be more difficult to filter out the earlier mistakes. "The problem with bringing in a lot of garbage," says Silva, "is that it is really hard to fine-tune."

Consistent with this view, retraining the mutant mice does not work well. The fixed mice continue to respond to the original training, and ignore the new maze target.

Fine detail is also missing in another task. The mutants can learn to associate an upcoming shock with a particular cage. But when presented with two similar but different cages, the mutant mice freeze in fear in both cages, whereas wild-type mice freeze only in the cage that is identical to the cage where the shock was originally administered.

Thus, as a memory booster, this method backfires. In contrast, overexpression of CREB has been shown to enhance learning. But in these experiments the animals were in a uniform environment and had to learn specific, isolated tasks. Silva thinks that CREB boosters would not work in the complexities of a human environment because the brain would overload. "They may work for sporadic use [such as against Alzheimer’s disease], but they won’t work in the long term," he says. "More is not more. This is not about getting more plasticity; it’s about getting circuits that store more information."

Reference: Elgersma, Y., et al. 2002. Neuron. 36:493–505.

Cells spin into view

Ohad Medalia, Wolfgang Baumeister, and colleagues (Max Planck Institute for Biochemistry, Martinsried, Germany) have shown that a three-dimensional version of electron microscopy (EM), called cryoelectron tomography (cryo-ET), can be applied to whole intact cells. Their eventual aim, says Medalia, is "to get pseudo-atomic maps of the cytoplasm."

Standard EM methods yield two-dimensional projections. Thus, researchers such as Gary Borisy (Northwestern University, Chicago, IL) have studied systems that approximate two dimensionality, such as the flattened lamellipodia at the front of a moving cell. But, says Borisy, "there is no substitute for three-dimensional data. Even in the systems we have analyzed I would love to have three-dimensional data."

The tomogram provides these data by rotating the sample between sampling runs. After each rotation the sample must be refocused and realigned—a process that the German group automated to minimize beam damage to the specimen. The sample itself was prepared by quick freezing. This eliminates fixation artifacts and leaves membrane systems intact.

The group observed linkages of actin filaments both to the membrane and, at a wide variety of angles, to each other. Assigning these linkages to specific actin-binding proteins will require either immunological labeling (via microinjection of gold-conjugated antibodies) or pattern recognition of the linking proteins. The 2.5-MD proteasome was sufficiently hefty and distinctive to be recognized by the group, but identifying diminutive actin-binding proteins will be a far greater challenge.

To meet that challenge, the Baumeister laboratory has recently shipped in a new microscope cooled by liquid helium rather than liquid nitrogen. The lower temperature should allow longer exposures to electrons with less damage, thus giving the laboratory a shot at increasing resolution from the current 5–6 nm to a projected 2 nm. "In two years we will know if this is the answer," says Medalia.

But even with the existing resolution there is plenty to do. Borisy, for one, wants to know how lamellipodia keep themselves flat by restricting upwards growth of actin filaments. "This [current study] is to show that indeed this technique works," says Medalia. "Now it will spread and people can do as much as their imagination allows."

Reference: Medalia, O., et al. 2002. Science. 298:1209–1213.