receptor you could think it was a special case. But the evidence is building for an effect in brain." Indeed, with Worcester colleague Mary Nastuk, Fallon has detected agrin receptors on some spinal cord neurons and on brain "synaptosomes," which are membrane preparations with a high synapse content. "The actors—agrin and its receptor—are there [in brain] now," says Fallon, although he cautions that they haven't yet been shown to contribute to synapse organization in brain.

The finding that agrin works through its own receptor also provides some clues to how the protein brings about the assembly of synaptic structures. Since it doesn't interact directly with the acetylcholine receptor, it apparently exerts its effect through its own intracellular signaling pathway. One clue to what this pathway might include comes from Wallace and Rick Huganir of Johns Hopkins University School of Medicine.

They've found that one of the protein subunits that make up the acetylcholine receptor is rapidly phosphorylated on the amino acid tyrosine when chick muscle fibers are treated with agrin. Such tyrosine phosphorylations are a common way of controlling the activity of proteins, and in this case the phosphorylation appears necessary for the clustering of the receptor. Wallace and Huganir suggest that the tyrosine phosphorylation may be what enables the acetylcholine receptor to bind to the cell skeleton proteins, which are thought to anchor the receptors in place at the neuromuscular junction.

The researchers still have a long way to go to work out how agrin exerts its effects. But if the protein proves to be as important for formation of neuron-neuron synapses as it is for the neuromuscular junction, it's a safe bet that agrin will wind up with a prominent place in the emerging picture of nerve cell communications.

–Jean Marx

Additional Reading

M. J. Ferns and Z. W. Hall, "How Many Agrins Does It Take to Make a Synapse?" *Cell* **70**, 1 (1992).

U. J. McMahan *et al.*, "Agrin Isoforms and Their Role in Synaptogenesis," *Current Opinion in Cell Biology* **4**, 869 (1992).

F. Rupp *et al.*, "Structure and Chromosomal Location of the Mammalian Agrin Gene," *Journal of Neuroscience* **12**, 3535 (1992).

BIOCHEMISTRY

From 'Hunter Magic,' a Pharmacopeia?

Every time Peter Gorman looks at his scars, he remembers the time 6 years ago when, near the Peru-Brazil border, a Matses Indian introduced him to "hunter magic." After burning Gorman's arm with a white-hot stick, his mentor spit onto a stash of dried frog secretion to make a paste and rubbed it into the burns. For 15 minutes, the amateur anthropologist and writer from New York City vomited, defecated, urinated, and drooled while his heart beat furiously and sweat streamed from every pore. "I was hoping and praying that I would die," he recalls. After this wrenching episode, he remembers falling into a day-long listlessness. Finally he woke up feeling transformed. "When you wake...you feel god-like," he says, as if your senses have been sharpened and your strength enhanced.

The magic touch. Before releasing this frog into the forest, a Matses Indian harvests hunter magic.

To the Matses Indians of Peru and several other indigenous groups in western Amazonia, that's exactly how you want to feel before a hunting expedition, and they have perpetuated the practice of "taking frog"—secretions scraped from the skin of the large green frog *Phyllomedusa bicolor*—for generations. Now it seems that the Amazonian potion might work some high-tech magic as well. In the 14 November *Proceedings of the National Academy of Sciences (PNAS)*, bioorganic chemist John Daly of the National Institutes of Health and seven coauthors report finding in the concoction a peptide, 33 amino acids long, that may provide a key to manipulating cellular receptors for the ubiquitous biomolecule adenosine.

The possibility is of more than academic interest. Preliminary animal studies by researchers at the Warner-Lambert Co. have hinted that those receptors, which are distributed throughout the brains of mammals, could offer a target for treating depression, stroke, seizures, and cognitive loss in ailments such as Alzheimer's disease—"it goes on and on," says Daly. As a result, the discovery of a natural compound that interacts with the receptors is catching the attention of Daly's pharmacologist colleagues. "It represents what appears to be a new class of pharmacological mediator," remarks biochemist Michael Zasloff, who recently founded Magainin Pharmaceuticals Inc., which develops drug leads from the vast, barely catalogued library of animal chemical defenses.

The first hints that the frog secretions might contain such a peptide, dubbed adenoregulin in the *PNAS* paper, showed up about a year ago when Daly began experimenting with samples donated by Gorman and Katharine Milton, an anthropologist at the University of California, Berkeley, who, like Gorman, had observed Indian groups in the Amazon jungle taking frog. Daly injected extracts of the frog secretion into a mouse, a common practice for testing whether substances have biological effects. "I saw a profound behavioral depression," Daly recalls, one that resembled what he and others had seen before in mice injected with adenosine and its derivatives.

Daly's team set out to look for the suspected adenosine-like ingredient in the samples of hunter magic. After fractionating extracts to separate the brew's many chemical components, the researchers found one fraction that stood out. Other fractions inhibited the binding of adenosine-receptor agonists—molecules, such as adenosine itself and its analogues, that bind to and activate the receptor. But the adenoregulin-containing fraction enhanced the binding, presumably by subtly altering the receptor's chemical personality to make it more receptive to the agonists. That property makes the compound an exciting pharmacological lead, Daly thinks. After all, he notes, the successful anti-anxiety drug Valium acts on a different class of receptors by much the same mechanism.

If adenoregulin doesn't turn out to be a pharmacological boon, other possibilities may be lurking in the frog potion. As pharmaceutical chemist Vittorio Erspamer at the University of Rome and his co-workers wrote in a 1985 analysis of peptides in *Phyllomedusa* skin, "No other amphibian can compete." Their list totaled about 19 peptides, but the Italian group and other workers including Daly's group have since pushed the number up to several dozen.

Something—maybe a lot of things—in that brew took Gorman and his Matses drug mentors on their pharmacological wild ride. But Milton isn't sure the concoction always lives up to its name, at least among the Mayoruna people she studied. She's never observed its effect on hunting. But she did notice that the Indians tended to perform the ritual on rainy days, when hunting was at best a second string activity. "It seemed more like something to do," she remarks.

–Ivan Amato