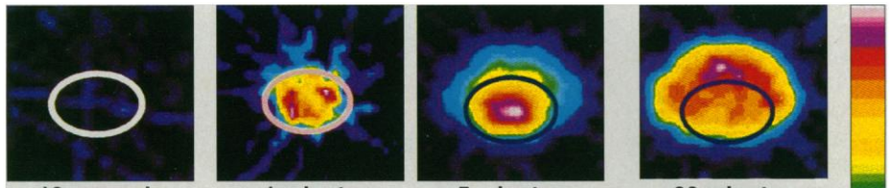
Will a New Type of Drug Make Memory-Making Easier?

For 2 years, Gary Lynch and his colleagues have been watching rats in their labs—under the influence of a new class of drugs—learn remarkably quickly to navigate new mazes. As they watched, the researchers also wondered: Do the new drugs give rats extraordinary memory, or do they simply make the rats exceptionally alert? The distinction is crucial, because if the former turns out to be true, Lynch, a neuroscientist at the University of California, Irvine, and his colleagues have reached a long-sought goal—developing drugs that have profound effects on the molecules that transmit memories.



A memorable effect? Drugs called Ampakines are taken up by a rat brain one minute after injection, shown here by positron emission tomography. Highest concentrations are indicated by colors at top of scale *(right)*—but don't indicate whether the drug affects cognition.

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But it's far from certain that they've reached that goal. The drugs in question are called Ampakines and bind to neurotransmitter receptor molecules on neurons in the brain. The molecules are called DL-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or AMPA receptors. And Lynch's results, some of which were published in January in the *Proceedings of the National Academy of Sciences* (another paper is due out next month) have aroused both interest and criticism. The interest stems from neuroscientists' desire to find compounds that can improve memory in a meaningful way. "This type of memory-enhancing drug could be very beneficial" for people in the early stages of Alzheimer's disease and other forms of dementia, says Steven Younkin, an Alzheimer's disease researcher at Case Western Reserve University in Cleveland. Other memory-enhancing drugs on the market which affect either AMPA receptors or the excitatory neurotransmitter acetylcholine have had little impact in treating memory disorders.

The criticism, however, stems from worries that Ampakines too have their limits. Younkin hastens to add that Ampakines "are not going to cure Alzheimer's," as they won't affect the neural degeneration that is the hallmark of the disease. Beyond that, critics say there's a chance the drugs won't have much of an effect on memory and learning at all: Ampakines' mode of action in the brain appears analogous to that of caffeine, which does affect learning, but only to a small degree. "And you wouldn't expect much from giving caffeine to an Alzheimer's patient," says one neuroscientist.

It wasn't the clinical uses of Ampakines, however, that originally sparked the interest of Lynch and a number of other researchers who have investigated them, such as Ursula Staubli and Joseph LeDoux of New York University (NYU) and Princeton University's Tracy Shors. The drugs first intrigued Lynch as a tool for exploring the biochemical changes that take place during learning and memory. Researchers have long believed that the key to such changes lies in what happens at synapses, where the communication between neurons takes place.

The prevailing theory of memory creation, long-term potentiation (LTP), holds that the brain encodes memories by strengthening chemical connections between certain neurons; one neuron becomes sensitized so that it responds more easily to subsequent signals from a neighboring neuron. Evidence for this theory comes in part from researchers' success at disrupting LTP by using drugs or by deleting important genes (*Science*, 10 July 1992, p. 162). But scientists have had less success on the flip side, failing to find ways to dramatically boost these chemical changes.

But in 1990 a team of Japanese researchers led by Isao Ito of the Chugai Pharmaceutical Co. published a paper in the *Journal of Physiology* showing that in brain tissue samples from rats, a drug called aniracetam boosted the excitatory signals given off by AMPA receptors, which are common throughout the brain and thereby widely believed to play a major role in learning and memory. Ordinarily, AMPA receptors bind to the neurotransmitter glutamate, which prompts them to open a channel into the cell on the far side of the synapse, allowing sodium ions to flow into it. These charge-carrying ions then create an electrical current. If this electrical stimulation is great enough, it enhances the opening of another channel by neighboring molecules called NMDA receptors, the effect of which is the long-term modification of the synapse found in LTP.

By increasing the excitatory signal from AMPA receptors, aniracetam immediately became a candidate for boosting LTP in learning. Lynch, who was working at the time to find drugs that increased glutamate release in hopes of boosting LTP, read this paper with intense interest. "That was the first evidence that you could modulate the [AMPA] receptor pharmacologically," Lynch says. "We jumped into that [line of research] right away."

Lynch and several colleagues at the University of Pennsylvania found that aniracetam triggers the increased signal by binding to the AMPA receptor in addition to glutamate, where it holds the sodium channel open longer (*Science*, 11 October 1991, p. 288). At the same time, researchers realized aniracetam was far from ideal as a drug. Its effect on AMPA receptors was weak, and most of the drug never made it to the brain anyway, because enzymes and acids in the stomach and blood broke it down. So in 1991, Lynch teamed up with UC Santa Barbara synthetic chemist Gary Rogers to make new versions of the drug that were more potent and metabolically stable. When these compounds were tested in rats, the investigators found they were not broken down, and they traveled from the stomach to AMPA receptors in the brain in minutes.

The drugs also improved the rate at which the animals learned new tasks. Staubli, now at NYU's Center for Neural Science, showed in the January *PNAS* paper that rats that received injections of one version of the drug performed markedly better on a variety of learning tasks than did undrugged rats. In one task, called a radial maze test, rats received a food reward when they walked down each of the eight arms of a star-shaped maze. The rats were removed from the maze after visiting just four arms. When they were returned 8 hours later, the animals had to identify the four unvisited arms, which held the remaining food.

When rats received injections of the drug prior to their first entry into the maze, they made few mistakes, such as visiting an arm twice. Yet their undrugged counterparts made twice as many mistakes and went down a lot of blind alleys. Preliminary results from scientists at other labs, including Shors at Princeton and LeDoux and Michael Rogan at NYU, have also shown that Ampakines speed up rats' learning on classical and fear-conditioning tasks.

The enhanced performance of the drugged rats in the star-shaped maze after 8 hours is particularly interesting, says Lynch, because "the drug is long gone by that time."

Positron emission tomography scans of rats that received radiolabeled Ampakines show that the drug is active at AMPA receptors for only 90 minutes. That means the animals "must have formed a stronger memory trace," says Lynch, which he chalks up to the drugs' ability to boost LTP.

Despite these results, some researchers doubt that Ampakines will affect memory and learning in people any more than does an extra cup of coffee. Charles Stevens, an LTP researcher at the Salk Institute in La Jolla, California, notes that Ampakines seem to be stimulating stronger synaptic currents as does caffeine, although by a different molecular route. And while caffeine and drugs with similar actions do boost learning, there are well-known limits to their effects. "Increasing synaptic strength is a simplistic way to increase memory," Stevens says. "There's no reason to think it will have a greater effect than that of caffeine."

"This possibility keeps us up nights," says Robert Schehr, a neurobiology consultant with Cortex, a biotechnology start-up hoping to commercialize the drugs. (Lynch was a founder and now owns Cortex stock.) Caffeine and other drugs that boost arousal, however, typically cause behavioral changes in the animals such as restlessness or jitters. "We don't see that with these drugs," says Schehr. But he adds that it's difficult to gauge the arousal level of animals, and a more definitive answer may come from the more sophisticated monitoring in human toxicology trials, slated to be conducted next month in Germany by Cortex and a German pharmacologic testing company. And in Staubli's upcoming *PNAS* paper, she reports that she implanted electrodes in the hippocampus of rats to induce LTP with an electrical pulse. In rats given Ampakines, LTP was easier to induce than in undrugged rats.

Stevens has other concerns as well. He's worried about the possibility of side effects, because Ampakines affect receptors prevalent throughout the brain. The drugs could, for instance, affect neurons in the brainstem, which could alter balance or the cardiovascular system. Lynch admits this may be so, but adds that "I worry about this less and less as time goes on because we're just not seeing" these side effects.

Others in the neurobiology community seem to have adopted a wait-and-see attitude towards Ampakines. Samuel Barondes, director of the Center for Neurobiology and Psychiatry at UC San Francisco, says the animal behavior is consistent with the notion that learning is being affected. But he's skeptical that any agent that works on one step in the complex, multistage process of memory making will prove clinically valuable. Whether Barondes and others are eventually swayed, and whether the clinical trials produce positive results, will determine whether Ampakines become a memorable drug—or just another blind alley, soon to be forgotten.

–Robert F. Service

PALEONTOLOGY

New African Dinosaurs Give An Old World a Novel Look

Last September, a caravan of six Land Rovers wound its way across 500 miles of Saharan desert, following sand-blown tracks from oasis to oasis in Algeria and Niger. The University of Chicago paleontologist leading the caravan, Paul Sereno, had traced this route before, on a 1990 survey with a British Museum expedition, and knew it would lead his team to a site dubbed "the dinosaurs' graveyard" 50 years ago by a French priest and paleontologist. But Sereno was after an even richer mortuary. Just 20 kilometers beyond the priest's site, Sereno had spotted a massive row of sauropod vertebrae poking above the sands and hinting at the wealth of bones that lay below. On last fall's foray, these hints were borne out. Almost every fossil Sereno and his team picked up was from a new, unknown species. "You can't find a dinosaur there that's been found before," he says.

On page 267 of this issue, Sereno and his colleagues report on two of those finds—previously unknown species of a carnivore and an herbivore—that lived about 130 million years ago. Paleontologists are hailing these discoveries as important new sources of information because, for creatures that supposedly dominated the entire planet, dinosaurs have been extremely difficult to find in Africa, particularly dinosaurs that lived during the Early Cretaceous, from 145 to 100 million years ago. "Africa at that time has been the most lost world of the dinosaurs," says Dale Russell, a dinosaur researcher at the Canadian Museum of Nature. "So Sereno's discoveries provide us with some badly needed diagnostic material." Adds Lou Jacobs, a paleontologist at Southern Methodist University in Dallas, Texas, who has discovered dinosaur fossils in Malawi: "These are good, fine skeletons from brand-new dinosaurs, and they suggest a diversity for that area [sub-Saharan Africa] that we didn't know about before. Finally, we've got some pieces of the puzzle coming in."

As researchers begin to assemble pieces of that puzzle, however, the image they see is rather unexpected. Sereno's finds are upsetting accepted notions about the relationships among dinosaurs at the end of the Jurassic, about 150 million years ago, when the supercontinent of Pangaea was beginning to break apart into the continents we know today. Some dinosaur experts had expected to find strong connections between African and South American species, suggesting that dinosaurs in the Early Cretaceous were divided into distinct northern and southern hemisphere populations. Sereno's finds, however, suggest a close connection between the African and North American dinosaurs, implying that Africa maintained a connection with the north far longer than previously believed. His hypothesis intrigues other paleontologists who are eagerly looking forward to putting it to the test.

The site that's triggering this excitement is called "In Abaka" in the language of the local Touareg inhabitants of the region. So Sereno and his colleagues have named the carnivore, which is the most complete of the specimens, *Afrovenator abakensis*, or "hunter from In Abaka, Africa." *Afrovenator*, with its sickle-clawed three-fingered hands and 2-inch-long, bladelike teeth, closely resembles the western North American *Allosaurus*, which thrived in the Late Jurassic, about 160 million years ago. The herbivore is a broad-toothed sauropod (a long-necked giant such as the brontosaurus); Sereno has not named this species, as the team did not find a complete skull. But the skeleton looks like *Cama-*

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African desert dinos. Paleontologist Didier B. Dutheil sits near a partially excavated dinosaur skeleton in Niger.