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Seeking Smart Drugs

COVER STORY | Federal and biotech labs research a new generation of drug therapy that improves memory and concentration without side effects | By Eugene Russo

Image: Anne MacNamara

Cognition--memory, perception, and attention--is a prerequisite to success, an essential for a normal life. When it becomes impaired through illness or accident, a person's life is turned upside down. Existing memory enhancement drugs treat maladies that rob memory, but they are relatively ineffective and have significant side effects. Some researchers, realizing the huge market that an aging, memory-slipping population can generate, are working to modify some drugs currently on the market and to generate others that improve memory, sharpen perception, and focus attention. Goals include increasing hippocampal levels of cycle AMP, and targeting ion channels and intracellular cascades.

These hopeful cognition improvers are not household names. "The major pharmaceutical companies have been a little reluctant to venture into this arena," says **Steven H. Ferris**, executive director of New York University's Silberstein Aging and Dementia Research Center. "The small startup companies have nothing to lose. And frankly, whoever breaks through is going to be very successful. You can imagine what the market size is."

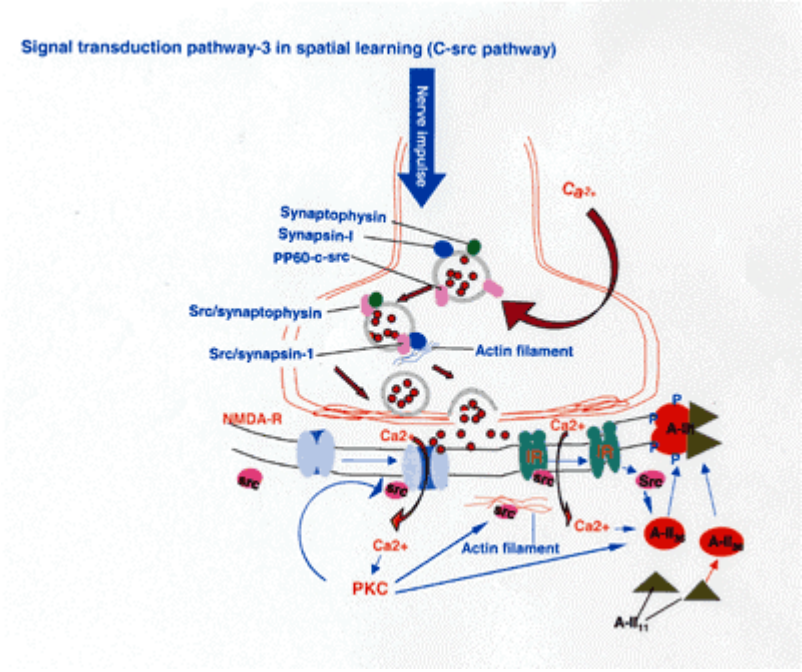
THE SCIENCE OF COGNITIVE ENHANCEMENT For now, memory enhancement research is primarily geared toward neurodegenerative diseases. The few currently approved drugs are acetylcholinesterase inhibitors. Based on research in the 1960s and 1970s, these drugs work by boosting the effectiveness of the neurotransmitter acetylcholine. Oftentimes patients with Alzheimer disease have inadequate amounts of acetylcholine in the synapses between neurons. Acetylcholinesterase inhibitors increase the effectiveness of the neurotransmitters by inhibiting the enzyme that breaks down acetylcholine. Generally, however, these drugs have only modest effects in patients with Alzheimer disease. "The cholinergic approach is not sustained and not dramatic," says **Rene A. Etcheberrigaray**, laboratory director for NeuroLogic, in Rockville, Md. "The reason is very simple: It's not linked to an early pathophysiological event."

A new generation of enhancers is promising to be more specific and more powerful. Companies such as Memory Pharmaceuticals and NeuroLogic are seeking to uncover compounds that will alleviate an array of diseases by targeting the basic molecular underpinnings of memory formation. Researchers have shown that aged rodent models can demonstrate memory deficits, specifically within pathways involved in long-term memory consolidation, which may be akin to that in humans. Theoretically, the animals provide a good way to test compounds that restore the ability to form new memories. Nobel laureate **Eric Kandel**, who helped illustrate how changes in synaptic function underlie learning and memory, cofounded Memory Pharmaceuticals in 1998. Its mission: generate treatments for chronic learning and memory deficits associated with conditions like Parkinson disease, vascular dementia, and Alzheimer disease.

One major strategy is to increase hippocampal levels of cyclic AMP, a second messenger that carries signals from the cell surface to proteins within the cell. Memory president and chief scientific officer **Axel Unterbeck** calls cAMP the "cellular driver of gene expression associated with long-term memory consolidation." By inhibiting the intracellular enzyme phosphodiesterase, which is known to break down cAMP, he and his colleagues have boosted these cAMP levels in rodents and demonstrated memory improvement, he says. Other memory targets include G-protein-coupled receptors, neuron-governing ion channels, and mechanisms of neurotransmitter release. "Our strategy is to go upstream of nuclear events," explains Unterbeck. "We don't interfere with protein-DNA interactions, which is very difficult to do. But we go upstream on a second messenger level, and also [a] cell surface receptor level."

NeuroLogic focuses on somewhat different molecular cascades, based largely on the memory research of **Daniel L. Alkon**, scientific director of Johns Hopkins University's Blanchette Rockefeller Neurosciences Institute, a NeuroLogic collaborator. Targets include not only ion channels but intracellular cascades consisting of enzymes like protein kinase C or carbonic anhydrase, a synaptic plasticity mediator. Etcheberrigaray says that NeuroLogic is looking for targets that permit neurons to be either more receptive to stimuli or more susceptible to the associations that constitute memory. "This is a highly reductionist approach," says Etcheberrigaray, "and then we have to prove it back to the animal."

Image: Courtesy of Weiqin Zhao Daniel L. Alkon



PATHWAYS TO LEARNING: C-src protein kinase-associated signaling pathways are activated during spatial learning. C-src kinase interacts with both pre- and postsynaptic proteins to regulate synaptic neurotransmission. It also interacts with insulin receptor and regulates phosphorylation of annexin-II leading to polymerization of annexin-II on the synaptic membranes.

Lacking the super-screening power of Big Pharma, companies such as NeuroLogic and Memory are interested in using or modifying existing, approved drugs for their own needs--a cancer-treating compound, for example, may have many of the properties suitable for memory enhancement. "It's a very powerful way to eliminate lots of risk," says Unterbeck. As with all treatments targeting the brain, cognitive enhancers must somehow get past the blood-brain barrier to reach their targets. Optimizing drug delivery is a constant challenge.

Both companies claim to have strong preclinical results, and at least one drug manufacturer is paying attention: In late July, Memory Pharmaceuticals announced a potential $150 million deal with pharmaceutical giant F. Hoffmann-La Roche of Basel, Switzerland. If these companies successfully create a new generation of safe, effective enhancers, might healthy persons seek to reap the benefits as well?

ENHANCING NORMAL COGNITION Thirty years ago, cholinesterase inhibitors were tested in normal individuals. But bad side effects, including nausea, vomiting, and diarrhea, made them acceptable only for patients with disease, though side effects have since lessened somewhat. One more recent study demonstrated the significant, positive effects of cholinesterase inhibitors, specifically one called donepezil, in normal, middle-aged private airplane pilots.[1] This drug is frequently prescribed for patients with Alzheimer disease. In a randomized, double-blind, placebo-controlled study, investigators compared the flight simulator performance of nine normal pilots on placebo with that of nine normal pilots on donepezil. After 30 days of

treatment, the latter group performed better on a set of complex simulator tasks. Senior investigator **Peter J. Whitehouse**, professor of neurology, Case Western Reserve University, says his group now plans to do tests with galantamine in normal persons; galantamine is the most recently approved drug for treating Alzheimer disease.

One group in particular is quite interested in finding ways to improve cognition: the US military. Research projects in drug enhancement are underway at the Defense Advance Research Projects Agency, the research and development organization for the Department of Defense. "Every uniform service, as far as I know back in history, has tried to do everything they could reasonably do to enhance performance to make our guys a little better than their guys or a lot better than their guys," says **Dennis K. McBride**, former head of the Navy's operational medicine research and development unit and the current president of the Potomac Institute for Policy Studies in Arlington, Va.

McBride cites three major reasons the military seeks to understand human performance: better selection techniques to get the best people for a given position; better ways of training to improve performance; and better ergonomics to make more efficient the interaction between humans and machinery. Pharmaceutical enhancement would be aimed at lengthy performance enhancement--perhaps to assist a special-operations soldier staking out an embassy for 48 sleepless hours. Says McBride: "It's not necessarily about improving his performance, but maintaining a level ... he wouldn't be able to maintain otherwise without the drugs."

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1. J.A. Yesavage et al., "Donepezil and flight simulator performance: Effects on retention of complex skills," *Neurology*, 59:123-5, July 9, 2002.