Innovations

Total recall
Helicon Therapeutics, Inc.

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Tim Tully and Jerry Yin have made flies with photographic memories, and with the backing of a major pharmaceutical company they hope to transfer some of that capability to humans. Whether or not they are the first to succeed, it seems almost inevitable that society will soon face the question of whether more — be it hair (Propecia), weight-loss (Fen-phen), sex (Viagra), or now memories — is always better.

Building a better fly

Helicon Therapeutics, Inc. is a collaborative venture between Tully and Yin (Cold Spring Harbor Laboratory, Cold Spring Harbor, New York), OSI Pharmaceuticals, Inc. (Uniondale, New York) and Roche Holding Ltd. (Basel, Switzerland). "It's essentially a virtual company," says CEO Walter Lovenberg.

Its focus is the cAMP-responsive element-binding protein (CREB); its inspiration is the work of Seymour Benzer and the isolation of *dunce*, the original *Drosophila melanogaster* learning mutant. *Dunce*, which encodes a cAMP phosphodiesterase, and its successor *rutabaga*, a calcium/calmodulin-dependent adenyl cyclase, led to CREB.

But Tully and Yin's first task was to define fly memory stages. They exposed flies to one odor while they were given repeated shocks, and another odor in the absence of shocks. Trained flies were then asked to choose between the two odors in a simple T-maze.

A single training session resulted in a low level of short-lived memory. Ten consecutive training sessions improved the memory somewhat, but it was still short-lived. Only with ten spaced training sessions did the flies retain their lesson for over seven days, a long time for a fly.

It was with CREB that Tully and Yin hit the jackpot. In experiments published in 1994 and 1995, they first knocked out fly long-term memory by expressing a repressor form of CREB, and then created photographic memory — long-term memories after only a single training session — by expressing an activator form of CREB.

This was not just a fly phenomenon. Eric Kandel (Columbia University, New York) had reduced the gill withdrawal reflex of the sea slug *Aplysia* to a cellular model involving only a single sensory neuron and a single motor neuron. Serotonin, normally supplied by an interneuron, could mimic the effect of training, which strengthens the synapse and therefore enhances the next response of the gill to a noxious chemical. Cyclic AMP and CREB were implicated in this process.

Knockouts in mice, although imperfect because of multiple genes and splice forms, strongly suggested that various forms of memory in mice needed CREB. This was confirmed in rats using antisense oligonucleotides.

The current model for long-term memory in flies involves a calcium influx activating Rutabaga protein to produce cAMP, which frees protein kinase A from its inhibitor so it can phosphorylate CREB. Phosphorylated CREB binds to CREB-dependent genes, and the products of these genes ultimately change synaptic structure.

The first step

> *Prof Nemur says if it werks good and its perminent they will make other pepul like me smart also. Maybe pepul all over the werld. **

The first field of attack for memory-enhancing drugs is Alzheimer's disease. The approved drugs include the acetylcholinesterase inhibitors Cognex (tacrine hydrochloride; Parke-Davis), Aricept (donezepil; Eisai Company and Pfizer) and Exelon (ENA-713; Novartis; approved only in Europe). These drugs have limited efficacy, at best effecting only a short-lived increase in acetylcholine-based transmission.

The approach of Cortex Pharmaceuticals, Inc. (Irvine, California) is more closely tied to mechanisms of memory formation. Based on the work of Gary Lynch (University of California, Irvine), Cortex is targeting the AMPA receptor, one of many glutamate receptors. The AMPA receptor is involved in long-term potentiation (LTP), the long-term strengthening of synapses that is thought to be involved in vertebrate learning and memory. Depolarization of the membrane by the AMPA receptor opens the NMDA receptor, which allows calcium entry and LTP.

The first of Cortex's 'ampakines' is in phase I/IIa trials for Alzheimer's and schizophrenia. Lynch claims that drug specificity should be good. "On its own [the drug] doesn't create neurotransmission," he says. "We increase synaptic transmission, but only where it normally occurs." As a result there appears to be little if any effect on the disposition of the trial participants. "They don't feel a buzz; they don't feel activated," says Lynch.

Early results look promising, according to Lynch. "There seems to be a small effect in young people," he says. "But when you have a deficit the drug is more effective."

The Helicon approach

For a company formed in 1997, Helicon has not been wasting time. OSI has used cell lines with CREB promoters linked to luciferase reporters to test Roche's collection of ~200,000 neuro-biased chemicals for induction of CREB activator function. Lovenberg reports that there has been a healthy hit rate. The best leads will be tested in flies and mice at Cold Spring Harbor, using a 48-chamber automated system for the flies.

*Italicized quotations are from "Flowers for Algernon" © 1966 Daniel Keyes (renewed 1994), published by Harcourt Brace & Co.

Meanwhile, Kandel has recently formed Memory Pharmaceuticals to exploit his CREB-related work. At press time the company spokesperson, CEO Axel Unterbeck, was refusing interviews from both *Chemistry & Biology* and the TV newsmagazine 20/20, citing lack of time.

Thus is seems likely that a CREB activating drug will be found. The next question is what it will do. There are many forms of long-term memory, depending on the learning paradigm. Mark Mayford (University of California, San Diego) does not see this as a problem. "It's really at the anatomical level that these distinctions occur," he says. "By tapping into this molecular pathway you should tap into almost all forms of learning."

CREB has its detractors, however. "The very fact that they call CREB the master switch should be cause for concern," says Lynch. Contrasting CREB to the ampakine approach of only increasing existing activity, he says: "It may do things you don't want done." CREB is also involved in a host of signal-transduction events outside the brain. Helicon is therefore investigating DNA chip technologies to find targets of CREB transcriptional activation that are involved specifically in memory formation.

Why do we need a smart drug?

If your smart you can have lots of frends to talk to and you never get lonley by yourself all the time.

Alzheimer's is a common excuse for memory drug development, but that idea is not without its flaws — Alzheimer's is a disease of nerve degeneration, not defective CREB functioning. "Our rationale is that a drug that would enhance memory might enhance the functioning of the neurons that are surviving," says Lovenberg. "Clearly it will not be a curative treatment, but hopefully the neurons that remain will work better." Mayford calls this "unlikely."

But Alzheimer's is far from the only memory disorder, and James McGaugh of the University of California, Irvine, would welcome therapies for other indications. "These diseases are devastating," he says. "You lose who you are — you are your memories. It would be a blessing to have [memory] drugs."

The ultimate back-up plan involves the largest potential market: everyone. "You would only get [a memory drug] approved for marketing for a defined clinical indication — you wouldn't get it approved for kids taking tests," says Lovenberg. "On the other hand, there are a wide variety of situations where a memory drug could be used. The defense department appears to be interested in this approach. Being able to train the military over a very short period of time before a mission would be of great interest to them."

The most interest lies in reversing age-related memory loss; in short, solving the 'where are my keys?' problem. "Not much is known about what underlies these changes. The major change is sludginess — things just get slower," says McGaugh. "Anything that improves the strength of memory will improve the speed of recall." It seems likely that only memory of what occurred while the subject was taking the drugs will be improved.

Few anticipate that any decent memory drug will be controlled by anyone, including the US Food and Drug Administration (FDA). "Given the situation in the US, where physicians cannot be controlled and the elderly population is eager to improve their condition of health, I think there will be pressure [to prescribe off-indication]," says Cortex's Lynch. According to McGaugh, "This could be the Viagra for intellectual functioning."

Complications

"The more intelligent you become the more problems you'll have, Charlie."

"It's a classical double-edged sword. [A memory drug is] needed very badly, but it's open to abuse," says McGaugh. "If someone takes it before an entrance exam, could a medical school make it a condition of entry that they keep taking it? Or could the medical school sue for fraud? You can imagine that an employer would make a condition of employment that you use these drugs."

McGaugh says some of these concerns are not new. "Valium is the most widely prescribed drug for anxiety disorders, but do you need it because you are a little nervous about giving a speech? This is drug abuse in the social sense."

Of course, there is always the possibility that a memory drug will backfire. "This may help you form associations better, but if you do that for a long enough period you might run into problems," says Mayford. "Once there's too much information you may slow things down, so that something that took ten seconds now takes half an hour."

Then there is the problem of whether superior memory equals intelligence, which may be what the general public is really after. Observes Lovenberg: "From casual observation, I have known several individuals with basically photographic memory. I went to graduate school with a student like this. I thought, 'This person will knock the world dead.' But he was a total failure in research. Perhaps he wasn't creative enough, or he had his brain cluttered with too many things."

"If you instilled in somebody the capacity to remember everything they heard and saw they might have defects in their ability to reason or recall," says Lovenberg. "I am sure you could have too much of a good thing. But in many situations, improving the storage in long-term memory, if it's not overdone, could be very positive."

What's right? Ironic that all my intelligence doesn't help me solve a problem like this.

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