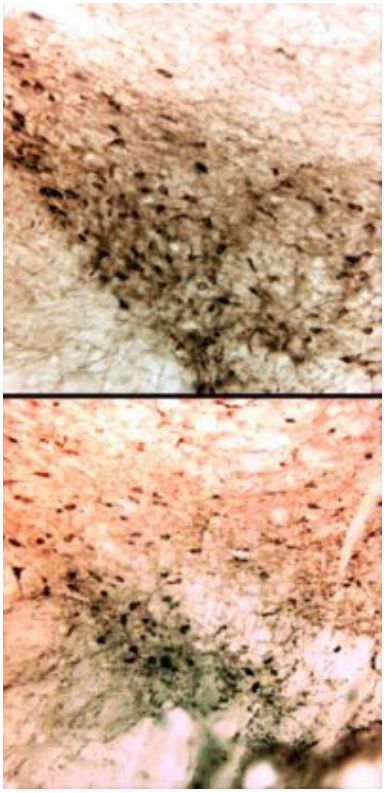
New drug may help rescue the aging brain



Age on the brain. An experimental drug, S18986, seems to counteract numerous symptoms of aging in rats. Animals given the drug daily for four months were active, with better memories and less inflammation in their brains. Dopamine-producing neurons in the forebrain of an 18-month-old drugged rat (top) are far more active than those in a normal rat of the same age.

As people age, their brains pay the price — inflammation goes up, levels of certain neurotransmitters go down, and the result is a plethora of ailments ranging from memory impairment and depression to Alzheimer's and Parkinson's. But in a long-term study with implications to treat these and other conditions, researchers have found that an experimental drug, taken chronically, has the ability to stem the effects of aging in the rat brain.

The drug, temporarily designated S18986, interacts with AMPA (short for α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid, or ampakine) receptors in the brain. These receptors transmit excitatory signals in the brain, and researchers were interested in experimental AMPA-receptor drugs (such as S18986) for their neuroprotective abilities and for the way they temporarily boost memory.

But rather than investigating the compound's short-term effects, Alfred E. Mirsky Professor Bruce McEwen and his lab members made a far longer commitment: The scientists studied the drug's impacts on middle-aged to elderly rats and found that, when administered daily over four consecutive months, it appeared to improve memory and slow brain aging.

"Nobody had ever looked at the long-term effects of these ampakines on the aging brain," says McEwen, head of Rockefeller's Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology. Short-term studies, he notes, had shown that the drug appears to improve aspects of memory, likely by temporarily ramping up AMPA receptors in the hippocampus — the brain's memory and learning center. But McEwen, research assistant Erik Bloss and postdocs Elizabeth Waters and Richard Hunter found that, over the course of four months, S18986 changed the entire profile of the older rodents' brains.

When compared to control animals that had received only sugar water, the drugged rats were not only more

active and better at memory tests, but their brains showed physical signs of slowed aging. Neurons in the forebrain that produce acetylcholine, a neurotransmitter known to play a role in learning and memory, had 37 percent less decline. Dopamine-producing neurons, which are responsible for sustaining activity and motivation levels, slowed their decline by 43 percent. Levels of inflammation in the brain were also significantly lower. “Every marker we chose to look at seemed to indicate there was some preservation of function during aging with chronic treatment,” Hunter says. The drug appears to slow aging’s effects throughout the entire brain.

Dopamine is a motivation- and movement-related neurotransmitter in the brain, and its presence is necessary for maintaining normal activity levels — it’s the chemical that helps you get up off the couch and socialize or exercise. A severe loss of dopamine production causes Parkinson’s disease, “so this drug has the potential, perhaps, to block the progression of the disease,” Hunter says.

Not only that, but it could be helpful for much less severe conditions, too. As people age, it’s often harder for them to feel motivated to socialize or even eat, leading to depression and making latent conditions worse. “So maybe this drug isn’t going to be the one that prevents Parkinson’s,” Waters says, “but maybe it’s going to improve the quality of life as you age, so that up until the very end of your life you can sustain that quality and sustain a higher activity level.”

With such a variety of impacts on neurotransmitters, S18986 holds enormous potential. But so far, it’s only potential. The researchers hope to dig deeper to find out precisely how the drug works. “There’s a lot to be done,” Hunter says, “and this shows that there’s broad potential for these compounds.”

Citation: *Experimental Neurology* 210(1):109–117 (March, 2008)

Source: Rockefeller University