Scientists discover blood factors that appear to cause aging in brains of mice

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Memo to mature, health-minded vampires: You might want to consider limiting your treats to victims under age 30.

In a study to be published Sept. 1 in *Nature*, Stanford University School of Medicine scientists have found substances in the blood of old mice that makes young brains act older. These substances, whose levels rise with increasing age, appear to inhibit the brain's ability to produce new nerve cells critical to memory and learning.

The findings raise the question of whether it might be possible to shield the brain from aging by eliminating or mitigating the effects of these apparently detrimental blood-borne substances, or perhaps by identifying other blood-borne substances that exert rejuvenating effects on the brain but whose levels decline with age, said associate professor of neurology and neurological sciences Tony Wyss-Coray, PhD, the study's senior author. Wyss-Coray is also associate director of the Center for Tissue Regeneration, Repair and Restoration at the Veterans Affairs Palo Alto Health Care System.

It was long thought that the adult human brain produces no new nerve cells. But it is now known that in at least two places in mammalian brains, including those of mice and humans, such new cells continue to be formed throughout adulthood. One of these places is the dentate gyrus — part of a key brain region, the hippocampus, where new experiences are locked into memory. As in other tissues, new cells in these brain areas can arise there only because of the presence of stem

cells, which can both replicate themselves and spin off daughter cells that differentiate to become dedicated nerve cells.

The number of stem cells in adult brains diminishes with increasing age, as do certain cognitive capacities, such as spatial memory: An example in humans is remembering where you parked the car — or, if you are a mouse, recalling the whereabouts of an underwater platform you can perch on so you won't have to keep swimming in order to keep your nose above water.

An early step in the Stanford team's study involved connecting the circulatory systems of pairs of old and young mice via a surgical procedure, so that blood from the two mice comingled. "This way, we could examine the effects of old mice's blood on young mice's brains, and vice versa," said Saul Villeda, PhD, a postdoctoral researcher in Wyss-Coray's laboratory, who led the study en route to his doctoral thesis. (The procedure was pioneered by study co-author and neurology and neurological sciences professor Thomas Rando, MD, PhD, who has used it to demonstrate that young blood can rejuvenate old muscle.)

The mixing of old and young blood produced changes in both the young and the old mice's brains. For one thing, the older mouse in these pairs produced more new nerve cells in their dentate gyrus than solo older mice did.

"We saw a threefold increase in the number of new nerve cells being generated in old mice exposed to this 'younger' environment," said Wyss-Coray. In contrast, the young members of old/young mouse pairs exhibited fewer new nerve cells in the dentate gyrus than did young mice untethered to elders.

The investigators then turned to the question of precisely what, in blood, was producing the effect. To rule out the possibility that an exchange of

cells between the young and old mice was responsible, they created circulation-sharing young/old mouse pairs, one of whose members had been genetically engineered so that every one of its cells would glow green when exposed to light. In each case, green cells from the modified mouse turned up in the blood of the other mouse in the pair, as might be expected, but virtually never in the brain of the non-modified mouse. Clearly, some other substances besides cells from each mouse's blood were affecting its partner's brain.

Moreover, when plasma — the cell-free fraction of blood — from old mice was injected into young mice, it wrought the same deleterious changes in their dentate gyrus as if they'd been sharing blood with older mice. And on spatial-navigation tasks, such as finding a high spot to rest on in a water-filled chamber, young mice who had received injections of older mice's plasma performed more poorly than a group that got injections of plasma from younger mice. The "old-blood" mice seemed to learn the desirable location as easily as the "youngbloods" did — but they forgot it more quickly, a sign of impaired hippocampal function.

To identify specific circulating factors associated with aging and tissue degeneration or tissue regeneration, the researchers assayed 66 different immune-signaling proteins found in mice's blood. Six of these factors were elevated in both unpaired old mice and young mice that had been paired with older ones.

At the top of the list was eotaxin, a small protein that attracts a certain type of immune cells to areas where it has been secreted by other types of cells. Highlighting this discovery's possible relevance to humans, tests that Wyss-Coray's team conducted on blood and cerebrospinal fluid samples drawn from healthy people between the ages of 20 and 90 showed a parallel age-related increase in eotaxin. In humans, eotaxin is associated with allergic responses and asthma.

Normal young-adult mice given eotaxin injections exhibited deficient generation of new nerve cells in their dentate gyrus. So did both young mice administered plasma from old mice and young mice whose circulatory systems were joined with those of old mice — an effect that could be countered by injections of another substance that blocks eotaxin's action. Eotaxin injections also impaired performance on spatial-memory tests.

Other blood-borne factors are probably significant players in aging-related declines in cognitive function. One of the six substances identified in the protein screen by Wyss-Coray's group was MCP-1, a chemical that, in mice and humans, attracts immune cells called macrophages. Associate professor of neurosurgery Theo Palmer, PhD, has previously linked inflammation-triggered elevations of MCP-1 levels to reduced stem-cell numbers in the dentate gyrus.

The Wyss-Coray group is now testing eotaxin's potential role in memory loss associated with Alzheimer's disease, and is developing expanded blood-protein assays in a hunt for "rejuvenating" factors in blood that may prove useful in treating dementia and, perhaps, slowing the aging process in older brains.

Provided by Stanford University Medical Center

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