MARIO WAGNER

AGEING

Restoration project

Future generations may have less to fear from cognitive decline thanks to microscopic insights into the ageing brain, and interventions from unexpected quarters.

BY ANNABEL MCGILVRAY

Ageing rodents have had a good few years. In the United States, neurologist Tony Wyss-Coray made old mice think that they were young again by giving them plasma donated by students. Thousands of miles away in Austria, neuroscientist Ludwig Aigner achieved a similar feat in elderly rats using a common asthma medication.

These are preliminary results, but both researchers are attempting to rewrite the story on cognitive decline. "It's important to think about the aged brain differently from how we used to think about it," says Aigner, who is head of the Institute of Molecular Regenerative Medicine at Paracelsus Medical University in Salzburg. Rejuvenation might be, as he says, "a sexy term", but it is one that researchers such as Aigner and Wyss-Coray are using seriously in relation to preventing cognitive loss in the healthy ageing brain. Ageing does not have to be a one-way, downhill street. But reversing the direction requires a better understanding of why the brain begins to decline in the first place.

KEEPING NUMBERS UP

In cerebral terms, ageing starts early, long before symptoms manifest. The typical human brain begins to shrink at about age 20; by the time it is 100 years old, the brain has lost 20% of its mass. And this is for a healthy brain. Those affected by neurodegenerative disorders such as Alzheimer's disease dwindle even more.

Ageing involves the gradual deterioration of the myelin sheathing that surrounds some nerves, and which, alongside glial cells, comprises the brain's white matter. There is some loss of neurons, but this — in a revision of the traditional dogma — is not the main driver of the decline. Instead, neurons have reduced function, and the connections between them are weakened.

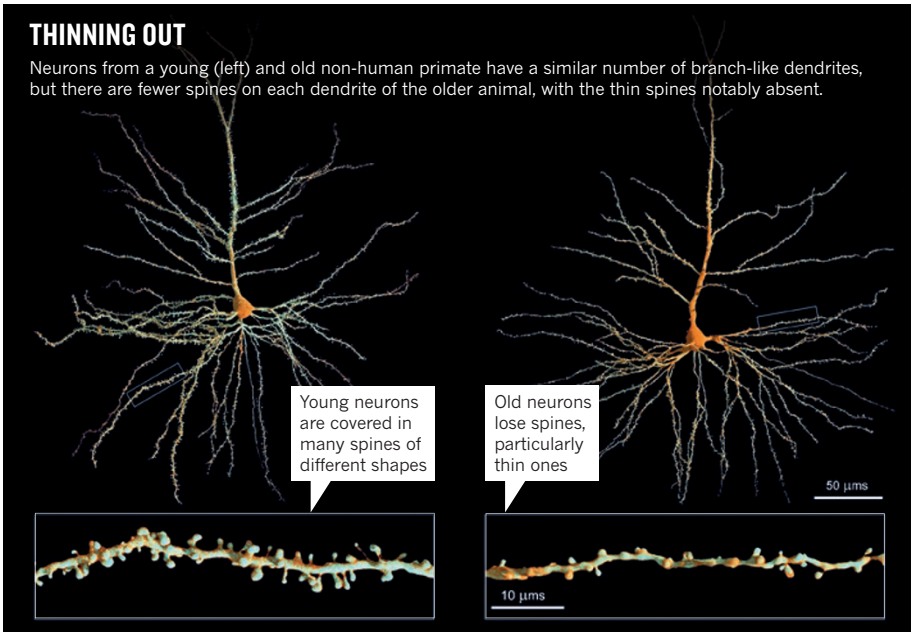
Decline isn't uniform in the brain or across cognitive tasks. Particularly hard hit are the hippocampus, which is crucial for memory formation and short- to mid-term storage, and the prefrontal cortex, which manages decision making and planning. This means that when deterioration occurs, memory of recent events and facts fades quicker than items that have been stored for a long time, such as words and numbers.

"There are a myriad of changes compared to the young brain that cross every level, every cell type," says Wyss-Coray, who is at Stanford University in California. In mice, he says, the changes begin at 6 months, which is equivalent to a 30-year-old human. By the time mice reach an age that corresponds to the 50s and 60s, he says, "there are already striking changes at the cellular level in the brain". These include modifications to the way DNA is expressed, epigenetic alterations that affect which genes are active and marked shifts in the communication between cells. Furthermore, metabolism declines in both white and grey matter as the cell's powerhouses, mitochondria, start to fail.

At Mount Sinai School of Medicine in New York, neuroscientist Mark Baxter and other researchers at the institute are exploring the impact of ageing on synapses — the connections between neurons. His colleagues used electron microscopy to examine changes in the synapses of the hippocampal and prefrontal cortex regions of ageing rhesus monkeys. The monkeys were given tasks that tested working memory, which is associated with the temporal lobe (where the hippocampus is located). The researchers used a delayed-response task in which the monkeys needed to remember one object for a period of time and then select a second non-matching object in order to receive a food reward[1]. The team found that monkeys that had more problems on the memory task tended to have more axon terminals (the ends of neurons which connect to other neurons) with a single or no synapse. "The underlying synaptic structure of those neurons is being degraded," says Baxter.

At the other ends of neurons are dendrites, which connect to axon terminals of other neurons by dendritic spines. Neurons in the prefrontal cortex have three different types of spines: stubby, mushroom-shaped and thin. The latter emerge from, and retract into, the dendrites as required, giving the prefrontal cortex great plasticity. As the brain ages, synapses in this region become dominated by mushroom-shaped connections, which are associated with long-term memory formation, but not with mental flexibility (see 'Thinning out'). Similar to the altered synapses that Baxter's colleagues saw in the monkey's temporal lobes, ageing monkeys with declining working memory have an altered synaptic environment in the prefrontal cortex. "The thin spines are lost," says Baxter.

These structural changes do not rule out therapeutics to treat cognitive decline,



MARK BAXTER/JOHN MORRISON

according to Baxter. "The basic elements of neural computation, the neurons, are still there to work with," he says. One possible way to preserve both the thin dendritic spines in the prefrontal cortex and the multisynapse connections in the hippocampus is to use oestrogen — in women at least. In older female rhesus monkeys, treatment with oestrogen increased the density of the thin spines and correlated with enhanced performance in delayed-response tasks[2]. The researchers experimented with a continuous delivery system and one that mimics the menstrual cycle. So far, they have found that the latter works best in female monkeys, "if you take oestrogen, you want to take it cyclically and not continuously," says Baxter.

A DOSE OF YOUTH

Wyss-Coray began his work with mice and plasma by studying the effects of parabiosis — the joining of two animals so that they share blood — on the ageing brain. He and his colleagues showed that when older mice share circulation with younger mice, the brains of the older mice show dramatic changes[3]. Neuron growth is boosted, and there are improvements in the animals' ability to learn and speed of recall.

The same effect is seen when plasma from young volunteers is transfused into old mice. Once every 3 days for 3 weeks, Wyss-Coray's team gave old mice with cognitive impairment 15 microlitres of plasma (the equivalent of one unit — around 200 ml — for humans) donated by students. The treated mice were able to remember the location of one hole among many that would allow them to shelter from a strong light shining on the testing platform. The untreated mice could only find the hole through trial and error. Is it rejuvenation? "Rejuvenation in mice, definitely," Wyss-Coray says.

Wyss-Coray has now begun a clinical trial of the use of plasma from young donors to treat patients with Alzheimer's disease. The double-blind trial was originally scheduled for completion in October 2015, but it is progressing slowly. There is no lack of willing participants, he says, but recruitment has been difficult owing to participation criteria that exclude certain common medical conditions and medications. Over the course of a month, half the trial participants receive weekly infusions of one unit of plasma from young (under 30 years) male donors; the remainder receive saline solution. The participants are then tested for memory, language, spatial orientation and visual attention.

In the meantime, work is continuing to determine what molecules underpin the parabiosis effect. Wyss-Coray suspects that the answer may come from outside the brain. He and his colleagues, including Aigner, have already identified eotaxin — commonly associated with asthma — as one protein that is present in higher quantities in the plasma of older animals[4]. This research prompted Aigner to look at other asthma signalling proteins — and led to the discovery of the rejuvenating powers of the common asthma drug montelukast.

INFLAMMATORY WORK

Aigner's breakthrough attracted headlines around the world in 2015. His team showed that montelukast improved cognition and boosted neuron growth in old rats[5]. He stops short of saying that the drug completely restores function. "But yes, we can partially rejuvenate the brain."

Montelukast blocks the inflammatory action that a class of proteins called leukotrienes can trigger in the lungs. These proteins also appear in the brain — in which, according to Aigner, the levels of an enzyme involved in the production of leukotrienes increases during ageing. Leukotrienes contribute to neural inflammation, cell death and the unnecessary activation of the brain's immune cells, microglia, which can damage healthy neurons.

By giving rats with age-related cognitive decline montelukast over a six-week period, Aigner's team stopped the inflammatory action of the leukotrienes and improved the animals' cognitive function. Further testing in rats with dementia suggests that the drug causes a complete reversal in disease-related cognitive decline. Aigner is hoping to secure funding for a clinical trial of montelukast in patients with Parkinson's disease.

It is no coincidence that Aigner and Wyss-Coray's potential interventions against the cognitive decline of the healthy brain are similar to the possible treatments of neurodegenerative disorders such as Alzheimer's and Parkinson's. The ageing process in a healthy brain resembles the early stages of pathological deterioration in these types of dementia. Aigner points out that many of the microscopic markers of neurodegenerative disease — synaptic decline, reduced neurogenesis, inflammation and even the notorious amyloid plaques associated with Alzheimer's — are also present in the ageing brain of a healthy person.

Wyss-Coray agrees that current knowledge points to many microscopic similarities between pathological and non-pathological ageing of the brain. At the cellular level, "it's very hard to discriminate normal healthy ageing from disease." He speculates that if everybody were to live to 100 years old, most people would develop dementia. "If you look at a normal healthy control, most of those are on their way to getting a neurodegenerative disease," he says.

The proportion of the world's population aged over 60 is forecast to nearly double to 22% in 2050. Cognitive impairment is already one of the leading causes of admission to residential care; without some form of prevention or rejuvenation, caring for older populations will become much more of a burden.

Neurodegenerative diseases remain the priority, says Baxter, but against a background of an ageing population, neuroscientists recognize the importance of keeping as many people as possible mentally fit. "We want everyone to have excellent cognition as they get older, so they have a good quality of life," he says. "And they're not struggling to remember whether they turned their stove off, or if they took their high-blood-pressure pill that morning." ■

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