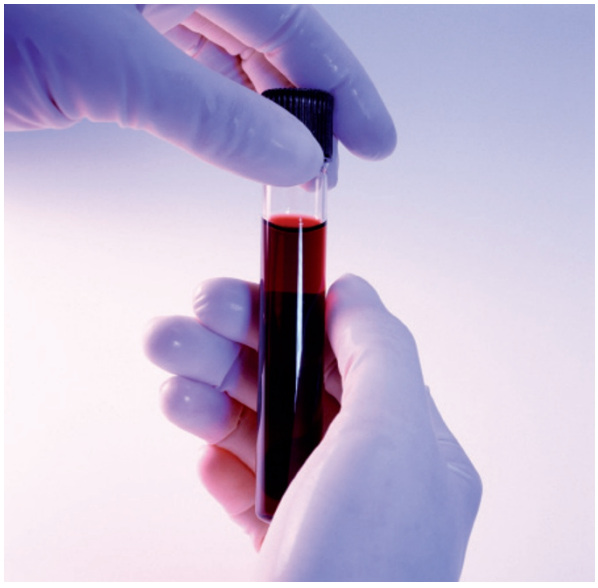
AGEING

Ageing, it's in the blood

Ageing is associated with a decrease in neurogenesis in specific brain regions and with cognitive impairment. A study now published in *Nature* shows that these age-linked phenomena may, in part, result from age-related changes in blood-borne factors.

Adult neurogenesis has been linked to several cognitive functions, including learning and memory, and primarily occurs in the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricle. These so-called neurogenic niches are characterized by pervasive blood supplies, possibly allowing 'interaction' between the systemic environment and these brain regions through the entrance of factors from the blood into the CNS. Given this potential route of communication, Wyss-Coray and colleagues explored whether ageing-associated changes in systemic factors underlie the age-related deficits in neurogenesis and cognition.

> "young adult mice that received CCL11 systemically showed learning and memory deficits"



The authors focused on the dentate gyrus and first characterized age-related changes that are linked to this region in mice. They confirmed that, compared with young mice, old mice had a reduced number of doublecortin (DCX)-positive neurons in the dentate gyrus, indicating a decrease in neurogenesis, and exhibited impaired hippocampus-dependent learning in contextual fear conditioning and radial arm water maze (RAWM) paradigms.

To investigate whether systemic factors elicit age-related changes in the dentate gyrus, the authors surgically connected mice to create isochronic (young–young and old–old) and heterochronic (young–old) pairs of animals, and showed that paired animals had a shared vasculature. Interestingly, young heterochronic mice had cellular changes (including decreased DCX immunoreactivity) that were indicative of decreased neurogenesis in the dentate gyrus, whereas old heterochronic mice had signs of increased neurogenesis, suggesting that in heterochronic pairs, factors in the blood can affect this neurogenic niche.

The authors went on to show that injecting young unpaired mice with plasma from old unpaired animals also reduced the number of hippocampal DCX-positive neurons in young mice; these animals also showed learning and memory defects in the aforementioned behavioural paradigms. Thus, soluble factors in the blood of aged mice can inhibit neurogenesis and impair cognition.

Using standardized multiplex sandwich enzyme-linked immunosorbant assays, Wyss-Coray and colleagues identified six proteins, including CC-chemokine ligand 11 (CCL11; also known as eotaxin), that were elevated in plasma from both old unpaired mice and young heterochronic mice. They focused their attention on CCL11 and, strikingly, they found that levels of this chemokine were increased in plasma and cerebrospinal fluid from aged humans as well as plasma from aged mice.

Systemic administration of CCL11 in young adult mice increased the plasma concentration of this protein and led to a marked decrease in DCX-positive neurons in the dentate gyrus. Thus, a rise in the systemic level of this chemokine shows similar effects to ageing on neurogenesis. Moreover, injection of anti-CCL11 neutralizing antibodies directly into the dentate gyrus of mice that had received systemic CCL11 rescued DCX-positive neuronal number in this brain region, suggesting that systemic CCL11 can have a direct effect in the CNS.

Lastly, the authors examined the cognitive effects resulting from a rise in systemic CCL11. Consistent with the results of the earlier behavioural experiments, young adult mice that received CCL11 systemically showed learning and memory deficits in both the contextual fear conditioning and RAWM paradigms.

This study shows that ageing-induced molecular changes — particularly a rise in CCL11 levels — in the blood are at least partly responsible for the reduction in neurogenesis and the impairment in cognitive function that are observed with ageing in mice. The authors suggest that broader proteomic screens might also identify systemic factors that have 'pro-neurogenic' effects and might inhibit cognitive decline.

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ORIGINAL RESEARCH PAPER Villeda, S. A. *et al.* The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* **477**, 90–94 (2011)