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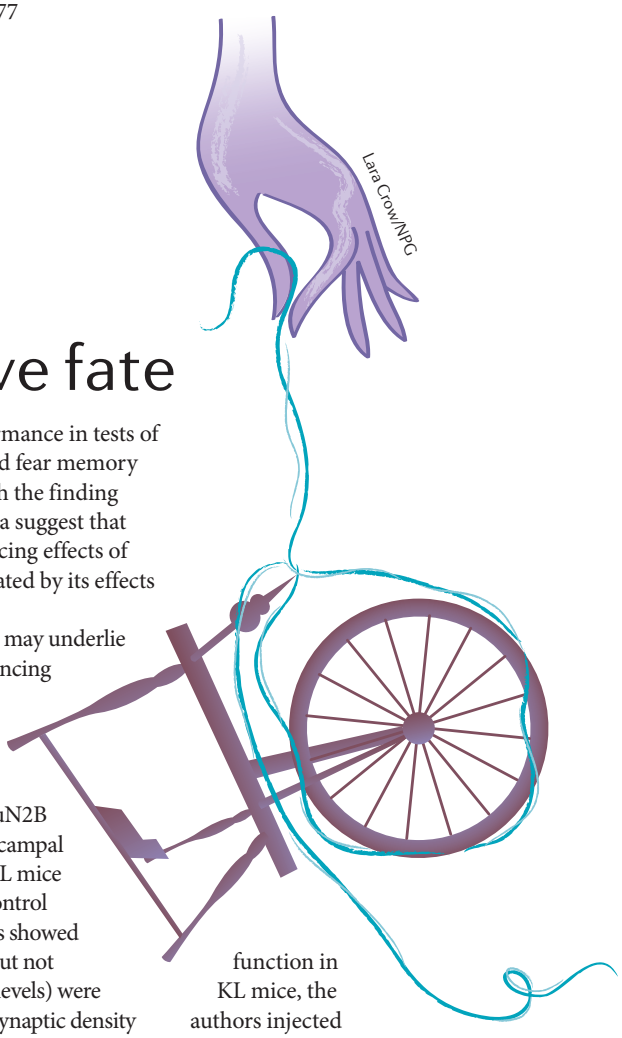

COGNITION

Klotho spins cognitive fate

Cognitive functioning declines with age, and Dubal and colleagues investigated whether Klotho (encoded by *KL*), a protein that is known to regulate ageing, modulates cognition. In a study published in *Cell Reports*, they showed that Klotho indeed improves cognition — but independently of any effects on ageing — probably through a mechanism that involves the NMDA receptor (NMDAR) subunit GluN2B.

Previous studies in mice and nematodes showed that Klotho overexpression promotes longevity and, conversely, that reducing Klotho expression shortens lifespan and induces an aged phenotype. Moreover, a variant *KL* allele known as KL-VS that increases Klotho secretion *in vitro* is associated with longevity in humans. Inspired by these findings, the authors set out to investigate whether Klotho plays a part in cognitive decline during ageing.

In three separate human population cohorts, carriers of the KL-VS allele scored higher than non-carriers in several cognitive tests that probed executive function, language, visuospatial processing and different types of learning and memory. Interestingly, this effect was independent of the subjects' age.

To further investigate the role of Klotho in cognition, the authors used transgenic mice that overexpress this protein (KL mice). These mice had higher survival than wild-type mice at all ages. Both older (10–12-month-old) and young (4–7-month-old) KL mice performed better than wild-type mice in the Morris water maze, which assesses hippocampus-dependent spatial learning and memory. Further behavioural assessments in young animals revealed that KL mice showed better performance in tests of working memory and fear memory as well. Together with the finding in humans, these data suggest that the cognition-enhancing effects of Klotho are not mediated by its effects on ageing.

What mechanism may underlie these cognition-enhancing effects? The authors showed that protein (but not mRNA) levels of the NMDAR subunit GluN2B were higher in hippocampal homogenates from KL mice than in those from control mice. Further analysis showed that GluN2B levels (but not GluN2A or GluN2C levels) were increased at the postsynaptic density of synapses in the hippocampus and frontal cortex of KL mice compared with control mice. The link between improved cognition and increased GluN2B levels in KL mice is in accordance with earlier findings that increased and decreased expression of this subunit in rodents enhanced and impaired cognition, respectively.

The authors next showed that hippocampal expression of the immediate-early gene product FOS — which is induced by NMDAR activation — after the Morris water maze test was higher in KL mice than in control mice. Moreover, hippocampal slices from KL mice had enhanced long-term potentiation at input synapses onto granule cells, which is known to be mediated by NMDARs. These results indicated that the Klotho-induced increase in GluN2B levels in KL mice had functional consequences.

To establish whether blocking GluN2B could prevent Klotho-induced improvements in cognitive function in KL mice, the authors injected young mice intraperitoneally with a low-dose GluN2B antagonist or vehicle before fear-conditioning training. The antagonist had no effect on fear memory in control mice, but it prevented the memory-enhancement that characterizes KL mice. Similarly, two different GluN2B antagonists prevented the improvement in working memory shown by middle-aged and young KL mice (compared with control mice) in a Y-maze test.

These results show that Klotho improves cognition —independently of age — by regulating synaptic NMDARs. Although the mechanisms underlying this regulation remain a topic for future research, this study suggests that Klotho may be a potential target for therapies aimed at cognitive enhancement.

Leonie Welberg

> "The [GluN2B] antagonist had no effect on fear memory in control mice, but it prevented the memory-enhancement that characterizes KL mice"

ORIGINAL RESEARCH PAPER Dubal, D. B. *et al.* Life extension factor klotho enhances cognition. *Cell Rep.* **7**, 1065–1076 (2014)