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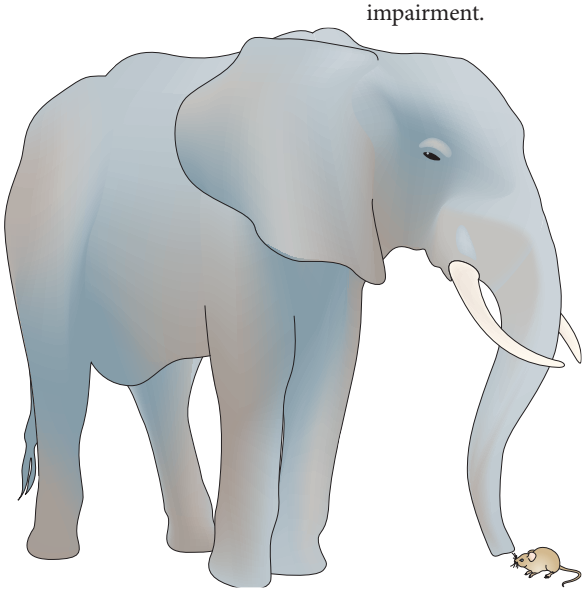
LEARNING AND MEMORY

Small molecule, big hindrance to memory

There is growing evidence of the importance of microRNA-regulated gene expression in the nervous system. These small non-coding RNAs have been implicated in synaptic plasticity and neurogenesis, as well as in neurodegeneration and psychiatric diseases. A new study published in the *EMBO Journal* identifies microRNA-34c as a potential target for the treatment of cognitive impairment.



Fischer and colleagues carried out massive parallel sequencing of small RNA libraries of the mouse hippocampus to determine the complete microRNAome of this key brain structure and major target of diseases such as Alzheimer's disease. They found that 488 microRNAs are expressed in the hippocampus. Of these, 23 are highly expressed and account for 83% of the total microRNA content.

The authors show that microRNA-34c, microRNA-379 and microRNA-181b are highly expressed in the mouse hippocampus but are minimally expressed in whole-brain tissue, suggesting that they might have specific roles in regulating hippocampal function. To further explore this possibility, they examined the gene targets of these microRNAs. MicroRNA-34c showed the highest degree of enrichment in hippocampal genes that have been associated with learning in rodents. Interestingly, microRNA-34c expression was upregulated in 24-month-old mice (which have been shown to have age-associated memory impairment), in APPPS1-21 mice (an Alzheimer's disease mouse model) and in post-mortem tissue from patients with Alzheimer's disease, indicating that the levels of this microRNA could be linked to hippocampal learning impairments.

Using an *in vivo* small RNA transfection system, the authors delivered a microRNA-34c mimic into the hippocampus of mice, 12 hours before carrying out various memory tests. They found that associative learning, object recognition memory and spatial memory were impaired in these animals compared with scrambled microRNA-injected controls. These learning impairments inversely correlated with levels of NAD-dependent deacetylase sirtuin 1 (SIRT1), a microRNA-34c target that is known to be crucial for memory formation. When the interaction between microRNA-34c and SIRT1 was blocked the behavioural effects were reversed. Moreover, injection of seed microRNA-34c inhibitors (which prevent target recognition) rescued the learning impairments observed in APPPS1-21 and aged mice, further highlighting the potential of microRNA-34c for the diagnosis and treatment of diseases associated with cognitive decline.

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ORIGINAL RESEARCH PAPER Zovoilis, A. *et al.* microRNA-34c is a novel target to treat dementias. *EMBO J.* 23 Sep 2011 (doi:10.1038/emboj.2011.327)