COGNITIVE IMPAIRMENT

Rescuing age-related memory loss

Forgetfulness, distractibility and impaired executive function are manifestations of the normal ageing process in both humans and monkeys, and can be observed as early as in middle age. This decline in working memory is associated with prefrontal cortex (PFC) dysfunction, but the underlying molecular basis was unknown until now. Arnsten and colleagues, reporting in *Nature*, show from *in vivo* recordings that PFC neurons in aged monkeys have weaker connections and fire less robustly than in younger animals. Furthermore, this condition can be rescued by modulating the neurochemical environment.

Monkeys are emerging as an important model for studying the normal ageing process, as they exhibit many of the cognitive changes observed in humans and do not develop Alzheimer's-like diseases, which would interfere with these age-related changes. In this study, the authors recorded the responses of PFC neurons in young adult, middle-aged and aged monkeys during a working memory task. They used the oculomotor delayed-response task to measure the monkeys' ability to remember a spatial location following a brief delay period. The neurons were classified according to whether they fired during the presentation of the cue, during the delay period (when the spatial position is being remembered) or both. Interestingly, the authors found an age-dependent decrease in the firing of neurons during the delay period, which is required for working memory, but not in the firing rate of neurons that respond specifically to the cue. These findings reveal the physiological basis of age-related memory decline and indicate that ageing does not affect all neurons equally.

Previous studies have shown that elevated cyclic AMP (cAMP) signalling can reduce the firing rate of PFC neurons by opening hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and KCNQ potassium channels. To test whether this is the mechanism underlying the decrease in working memory-related firing observed in aged monkeys, the authors applied minute quantities of drugs that inhibit cAMP signalling (guanfacine or Rp-cAMPS) or block HCN (ZD7288) or KCNQ (XE991) channels near the recorded neurons by iontophoresis. All of these agents restored firing rates to the levels found in younger monkeys. Conversely, etazolate — which increases cAMP signalling — further decreased the firing rate of aged neurons. Although no changes in test performance were recorded in this study, guanfacine and Rp-cAMPS have been shown to improve working memory performance in aged rats and monkeys. Indeed, guanfacine has already been approved by the US Food and Drug Administration for the treatment of attention deficit hyperactivity disorder (ADHD) and might also alleviate related conditions in which prefrontal cortical network connections are weakened. The possibility that age-related cognitive impairments could be reversible and restored by drug treatment offers hope for the rapidly growing ageing population.

Monica Hoyos Flight

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