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Recollection of lost memories

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Abstract

With age comes wisdom, or so they say. The reality is that, with age, the ability to store memories declines. One way of tackling this problem might be to raise neuronal levels of the signalling molecule EphB2.

Where did I put those keys? What did I have for dinner last night? Cognition — most notably, the ability to store memories — inevitably declines with age. What's more, for an increasing proportion of individuals, this decline progresses aggressively to the point that they cannot care for themselves. Alzheimer's disease is the leading cause of such dementia in the elderly, affecting almost 50% of people over the age of 85. But despite considerable progress in understanding the biology of this disease, an effective treatment remains elusive. On page 47 of this issue, Cissé *et al.*[1] provide compelling evidence that manipulation of a specific membrane protein — the receptor tyrosine kinase EphB2 — in a mouse model of Alzheimer's disease can reverse the characteristic memory deficits and so may make for a promising therapeutic strategy.

The leading hypothesis for the cause of Alzheimer's disease — based initially on human genetic findings, and supported by many cell-biological, animal-model and human studies — is chronically high brain levels of a peptide fragment termed Aβ. Indeed, mutations in the enzymes that generate Aβ or in the Aβ precursor protein, which lead to increased Aβ levels, are associated with early-onset Alzheimer's[2,3].

Mice genetically engineered to express these same mutations develop cognitive deficits as they age[2,3]. In normal mice, meanwhile, raising neuronal Aβ levels causes a loss of synaptic junctions between these cells that correlates well with the degree of dementia in humans. Furthermore, Aβ can now be imaged non-invasively in the human brain, and brain images of patients with Alzheimer's disease show Aβ accumulation, the extent of which correlates with memory decline[4]. Thus, there is great motivation to determine how Aβ accumulation leads to memory impairment.

Learning and memory are thought to require long-term potentiation (LTP) of transmission at synapses — a form of plasticity that occurs prominently in the hippocampus region of the brain. The hippocampus is not only required for memory formation, but is also affected early on during Alzheimer's disease[2,3,5]. It is perhaps not surprising, therefore, that hippocampal LTP is also impaired in mouse models of the disease and after Aβ application[2,3]. But the detailed molecular mechanisms that underlie the impairments in LTP and memory in models of Alzheimer's disease are unknown. More importantly, reversing these impairments has proved very difficult.

To make headway on these problems, Cissé *et al.*[1] examine the mechanisms behind the loss of a crucial synaptic protein complex, the NMDA receptor (NMDAR). This receptor is required for triggering LTP and for hippocampus-dependent memory formation[5], so it makes sense that its loss and malfunction would contribute to the symptoms of Alzheimer's disease. Indeed, previous studies have found that Aβ both reduces the synaptic function of NMDARs[6] and triggers their internalization from the cell surface[7].

Cissé and colleagues focus on EphB2. This protein interacts with NMDARs[8], and its deficiency reduces LTP[9,10]. The authors find that Aβ binds to EphB2, decreasing its levels. What's more, the effects of reducing EphB2 levels in the dentate gyrus — the input region of the hippocampus — in the normal mouse brain mimic the reduced synaptic NMDARs and LTP that occur in an Alzheimer's disease mouse model.

These findings lay the foundation for the key question: can virus-mediated expression of EphB2 in the dentate gyrus of an Alzheimer's mouse model overcome the associated synaptic and memory deficits? Remarkably, Cissé *et al.* report that this manipulation ‘cures’ the mice, with both NMDAR-mediated synaptic responses and LTP returning to normal levels. Of greatest clinical relevance, however, is the authors’ finding that EphB2 expression allows the Alzheimer's mice to learn and remember normally in three different behavioural tasks that test hippocampus-dependent memory.

Cissé and co-workers’ observations provide compelling evidence that EphB2 may be a valuable target for the treatment of Alz heimer's disease. The authors point out several ways by which treatment might be achieved, such as interfering with the binding of Aβ to EphB2, decreasing EphB2 degradation and increasing EphB2 expression. But before researchers in academia and the drug industry vigorously pursue this novel therapeutic mechanism, some cautionary notes are worth mentioning.

Given the complexity of this challenging subject, it is essential that these key findings be replicated. Moreover, which of the Alz heimer's disease models, if any, accurately reflects the human condition is debatable. As a result, whether EphB2 expression rectifies synaptic and memory deficits in other models of the disease should also be tested.

Alzheimer's disease affects several brain regions. So it is surprising that, in Cissé and colleagues’ mice, expression of EphB2 in the dentate gyrus alone could completely overcome the memory deficits. As the authors suggest, improving the function of a subset of neurons may be sufficient to improve the performance of the larger networks in which they function. Nonetheless, it must be determined whether EphB2 can remedy the Aβ-induced deficits in other brain areas.

Finally, a key challenge is determining the time point during the progression of Alzheimer's disease at which administering a certain treatment would still be effective. Cissé *et al.* expressed EphB2 before any of the classic neuropathological features of Alzheimer's disease occurred. It should be determined whether expression of this receptor at later time points is equally effective.

Despite these caveats, this work opens up a new avenue of investigation into the pathogenic mechanisms of Alzheimer's disease, and points to a previously unknown mechanism that can be targeted for therapeutic purposes. It also offers hope to a research field that has recently suffered several highly publicized failed clinical trials. These findings[1] should provide renewed energy and optimism that will hopefully lead to new drugs in time for many of us to take before we develop this devastating disorder.

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