NEWS & VIEWS

BEHAVIOURAL NEUROSCIENCE

Down memory lane

J. David Sweatt

In mice, two treatments — environmental enrichment and a chemical that regulates gene expression — boost new memory formation and restore the recall of old memories that seemed to have been lost.

If a pill were available that could boost your memory, would you take it? Odds are, most of us would say yes. What if that pill could improve the memory recall of someone suffering from a neurodegenerative disorder — would you get it for them? Almost certainly, yes again. Fascinating work by Fischer *et al.*[1], described on page 178, indicates potential new enzyme targets — histone deacetylases — for developing such a pill*. The authors provide a convincing proof-of-principle demonstrating that the inhibition of histone deacetylases can improve memory capabilities in a genetically engineered mouse model of neurodegeneration in the central nervous system (CNS).

Histone deacetylases (HDACs) are enzymes that remove acetyl groups from lysine amino acids in proteins, including proteins in the nucleus called histones. Histones interact with DNA to form a complex known as chromatin and control the accessibility of DNA for gene transcription. Generally, acetylated histones form active chromatin complexes with DNA, which makes the DNA accessible to RNA polymerases, thereby regulating gene transcription[2]. Inhibitors of HDACs block the ability of these enzymes to deacetylate histones, promoting histone acetylation in the nucleus and thus altering gene expression. Because altered transcription is known to be necessary for the formation of long-term memories, HDAC inhibitors have the potential to boost memory formation. This has been demonstrated in normal rats and mice; and the effectiveness of HDAC inhibitors in restoring memory function in mouse models of a human learning disability called Rubinstein–Taybi syndrome has also been documented[3–6].

Fischer and colleagues[1] extend these findings through their studies of a genetically manipulated mouse model that they have generated. Such animals show age-dependent neurodegeneration in the hippocampus, a brain region that is essential for long-term spatial-memory formation in rodents. Indeed, using a variety of behavioural assays, the authors previously showed[7] that these mice have pronounced deficits in recalling long-term spatial memories.

*This article and the paper concerned[1] were published online on 29 April 2007.

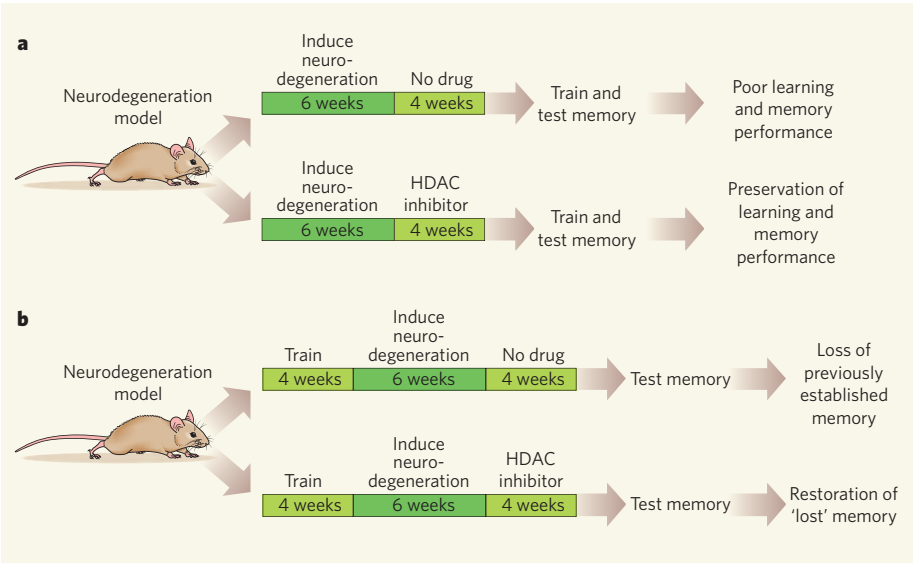

Figure 1 | Histone deacetylase (HDAC) inhibitors and memory restoration. a, Mouse models of age-dependent neurodegeneration exhibit poor learning and memory performance in spatially based learning tasks. However, when Fischer *et al.*[1] administered HDAC inhibitors for 4 weeks before training, the performance of the mice was restored to essentially normal levels. **b**, After receiving HDAC inhibitors, the mice could even recall memories that had been formed and then apparently lost through neurodegeneration.

In their present work[1], Fischer *et al.* demonstrate that HDAC inhibitors restore the capacity for spatial memory (Fig. 1a). They also show that another known memory-boosting manipulation — environmental enrichment through exposing the animals to a variety of experiences over their lifetime — improves the memory of the genetically engineered mice by increasing the levels of histone acetylation in their hippocampi. Together, these findings provide compelling evidence that increased histone acetylation can overcome the diminution of memory function seen in this mouse model of age-dependent neurodegeneration.

The results implicate HDAC inhibitors as potential treatments for disorders such as Alzheimer's disease, Parkinson's disease, fronto-temporal dementia and other human cognitive disorders that arise from neurodegeneration. The principal caveat in interpreting the work of Fischer *et al.*, and indeed all other studies using HDAC inhibitors, is that 'histone deacetylase' is actually a misnomer. Histone deacetylase enzymes are more accurately described as lysine deacetylases. Lysine amino acids are acetylated in a wide variety of other cellular proteins, in addition to histones. The list of known lysine-acetylated proteins is quite long, and includes transcription factors, cytoskeletal proteins and many metabolic enzymes. HDACs modify all of these proteins, not just their prototype substrate, histones. Therefore, as Fischer and colleagues point out[1], any behavioural effect of HDAC inhibitors could be due to alterations in the acetylation of a wide variety of intracellular targets, and it is essential to determine the consequences of the off-target effects of HDAC inhibitors on non-histone proteins.

To return to my initial question, what if the hypothetical magic pill did more than just improve the ability to make new memories? What if it could allow someone with a neurodegenerative disorder to recover memories that had apparently been lost? This would seem almost beyond the realms of possibility, but it

is exactly what Fischer *et al.* observed to be the effect of HDAC inhibition in their mouse model. They trained a group of these animals using fear conditioning — a learning method by which organisms learn to associate a neutral stimulus with another, unpleasant stimulus. They then allowed the animals' memory for that training event to decay over time (directly or indirectly through neurodegeneration), and confirmed that the animals had lost the capacity to recall that memory (Fig. 1b). Remarkably, administration of an HDAC inhibitor then restored the ability of the animals to recall that memory, which had apparently been lost.

The cellular and neuronal changes responsible for this remarkable finding remain elusive. It seems that the HDAC inhibitor has somehow restored sufficient robustness in the remaining neurons of the memory circuit to unmask a latent memory trace. Studies on the mechanism underlying this effect should provide fundamental insights into the molecular and cellular basis of memory recall.

It is interesting to consider the results of Fischer *et al.*[1] in the context of other studies into how, by modifying chromatin structure[8], long-term functional changes in the nervous system can be regulated[3–6]. Taken together, these findings implicate the regulation of chromatin structure in long-term brain plasticity involving a range of CNS-based phenomena. These include drug addiction, the development of epilepsy, long-term memory formation and the regulation of visual-system development[8,9].

The work of Fischer *et al.* adds to this list by including the effects of chromatin-structure modifications, as well as environmental enrichment, on memory dysfunction associated with neurodegeneration. It is intriguing to consider that, as it is a broadly acting and potentially genome-wide regulator of gene transcription, altering the structure of chromatin through histone acetylation might serve as a generic mechanism for regulating long-term functional changes in neurons. So it remains to be seen just how long the list of the CNS processes affected by the regulation of chromatin structure will grow. ■

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ORGANIC CHEMISTRY

Radical catalysis

Santanu Mukherjee and Benjamin List

The domination of metals in catalysis is under threat as organic catalysts gain ground. The latest example may expand chemical reactivity beyond the achievements of traditional metal complexes.

Chemists are currently excited about a different take on organic synthesis, in which purely organic molecules are used as catalysts, rather than metals or enzymes. This previously neglected strategy holds great promise in areas such as drug discovery and materials science, and has already been used in several valuable reactions. But so far, these processes have involved only charged intermediates. Reporting in *Science*, MacMillan and colleagues[1] now describe a general strategy for organocatalysis using radical intermediates — molecules that contain reactive single electrons. The principle behind this could lead to a new family of useful reactions.

Most naturally occurring compounds are chiral: they are not superimposable on their mirror images. Using enzymes as catalysts, nature is the uncontested master at producing chiral compounds as just one mirror-image version — in enantiomerically pure form, to use the technical jargon. Chemists, however, have to rely on different approaches to render their reactions enantioselective, although their inspiration may still come from nature. Early efforts emulated metal-containing enzymes, and many metal catalysts have been developed that induce one particular chirality in a wide range of chemical transformations[2]. But half of all known enzymes are metal-free, and it is these that organic chemists seek to mimic. Organocatalysis has now emerged as a promising strategy that avoids using protein catalysts or potentially toxic and expensive metals[3,4]. Not only does it complement established methods, but it sometimes also overcomes their limitations, so that many unprecedented transformations can be realized.

MacMillan and co-workers' radical reactions[1] are catalysed by chiral amines — organic compounds that contain a basic nitrogen atom. Such organocatalysis is related to that seen in certain enzymes that are crucial for sugar metabolism, and has ancient synthetic roots[5]. But although amines and amino acids were used in a narrow context as chiral catalysts in the 1970s, a clear understanding of their catalytic behaviour was lacking. It was another 30 years before the mechanistic principle was realized; this was termed 'enamine catalysis', after the intermediate that forms during the process[6]. The true potential of this approach then became apparent with the discovery of several valuable and predictable transformations. A related method, known as iminium catalysis, was developed in parallel[7]. These two concepts are collectively known as aminocatalysis[8].

To understand how aminocatalysis works, one has to know a little about molecular orbitals. Two need to be considered — the most energetic orbital that contains electrons (known as the HOMO) and the least energetic orbital that doesn't contain electrons (the LUMO). Enamine formation increases the HOMO energy of the starting materials

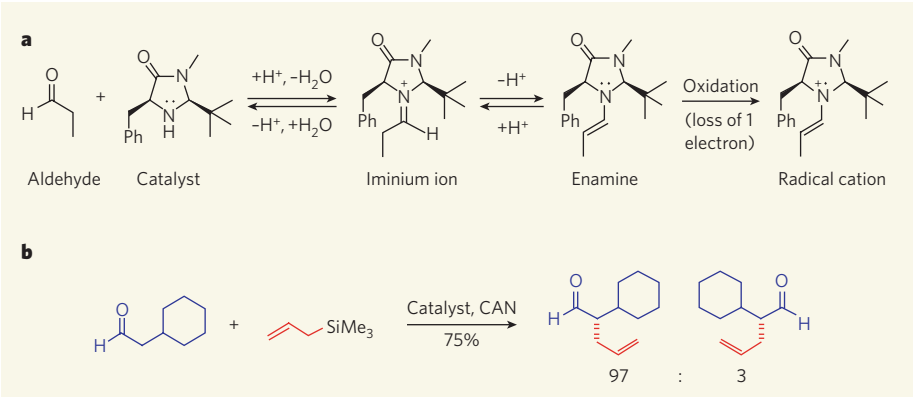

Figure 1 | A radical mode of organocatalysis. a, In organocatalysis, an aldehyde reacts with an amine catalyst to generate an iminium ion intermediate, which can be in equilibrium with an enamine. MacMillan and colleagues[1] use an oxidizing agent to remove a single electron from the enamine, so producing an enamine radical cation that is more prone to subsequent reaction than the original aldehyde. Ph represents a phenyl group; dots represent reactive electrons. **b,** The radical organocatalytic system is used in this reaction to add an allyl group (red) to an aldehyde, where ceric ammonium nitrate (CAN) is the oxidizing agent. One of the two possible mirror-image products (enantiomers) is formed preferentially.