

PP1: Tracking down the protein of Forgetfulness



Most students acknowledge the fact that "cramming" just before an exam is not the ideal way to retain information. Yet even when matter is learnt in a more effective way, much of our memory becomes blurred unless it is in frequent use. This, for many, is just common knowledge, but today we take it a little further and can assert that it is all a question of molecules and that a protein - PP1 - is at the root of it all.

Where is the seat of our memories?

The subject of memory is a vast one and also a very puzzling one. While we effortlessly remember altogether insignificant details, at other times we are incapable of recalling a telephone number at the right moment - when we need it, it seems to slip away into the meanders of our brain. Who's the culprit? It's just the complexity of our brain. Our memory is held within an immense network of cells - billions of neurons interconnected by further links known as "synapses". How on earth is it possible to find out where and how memories are stored in such an entanglement?

It was in the 1940's that Donald Hebb, a psychologist at McGill University, Montreal, suggested that the synapses were the key element to memory. Ten years later, they could be seen under the electronic microscope: a synapsis is the narrow gap - only 15nm¹ wide - between the axon (extension) of the neuron which sends out a signal and the membrane of the neuron which receives the signal (cf. diagram below).

One must bear in mind that in order to transmit information, our nervous system uses a curious combination of electrical and chemical signals. Indeed, most of the distance is covered via electrical propagation along the neurons. But in order to be transmitted across the gap, or synapsis, from one neuron to another, the electric impulse has first to go through a much slower chemical stage: the electrical signal brings on the release of synaptic vesicles into the synaptic gap. These vesicles resemble tiny pouches filled with chemical molecules, called neurotransmitters. The neurotransmitters are freed, span the gap and finally join up with receptors on the surface of the following cell. This causes channels to open in the receiving membrane and consequently the passage of "charged" atoms into the cell. This creates a further electric signal which proceeds towards the next synapsis, and so on.

Thus, a single neuron may receive several thousand signals from other neurons. In order to adapt the information it will transmit to the next cell, it must first sum up all the messages received. In the same way, it can receive signals from synapses that it shares with several other neurons and then combine them in more ways than one. This could explain the origin of "associative" memories such as the flood of memories which can

¹ 1 nanometer (nm) = 0,000000001 meter

be caused, for instance, by biting into something the taste of which brings back long-forgotten childhood memories.

Regarding the phenomenon of learning, it seems that - in the short and the long term - molecular changes which ease communication between the neurons are involved. Digital information is engraved on a CD, thus altering its surface. In the same way, memories seem to be registered by altering the synapses of the brain during the process of learning. It is still not clear how, but the neurons seem to decode these changes and then use them to reconstruct the information committed to memory.

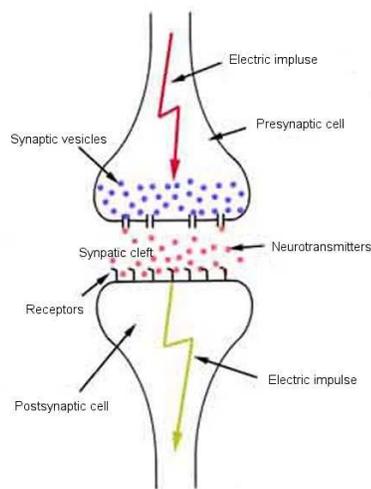


Fig.1 Synapsis

Researchers have concentrated on identifying the molecules associated with what is called "synaptic plasticity". Observation of a marine mollusk, the *Aplysia* - which has very large neurons arranged according to a particular pattern - has revealed that short-term memory (stocked for a few minutes to a few hours) and long-term memory (which can persist over a period of several weeks) are due to different molecular mechanisms. It has been known since the end of the 60's, that blocking the synthesis of proteins causes memory deficiencies after several hours of work. It is now clear that the transition from short to long-term memory - in the event of a conscious effort of memorization for instance - depends on the synthesis of specific proteins. It is in fact a change in the expression of genes which will enable new proteins to be produced. These novel proteins will affect the shape, size and sensitivity of certain synapses permanently.

To return to the comparison with a CD, but unlike it, the brain could well retain information in

a highly dynamic manner: studies in psychology suggest that the brain selects the usefulness rather than the precision of memories. Furthermore, most things we perceive and "process" are quickly set aside and what we do remember tends to fade and change with time. Why? Simply because a perfect memory would overcharge the brain with insignificant details, perhaps to the detriment of worthwhile information.

So, although the question of memorization is far from being solved, we now know that it is only half the problem: to make the best use of the remarkable capabilities of our brain, we must also learn to forget. Imagine for a moment remembering everything you see and hear ... Life would become unbearable! For example, people afflicted with the "Savant Syndrome" - which is always associated with some severe mental handicap such as autism - have an exceptional memory in a particular field. To the extent of actually memorizing an entire telephone directory! Naturally, this inability to forget details is extremely inconvenient.

Something new for students

Every student knows there are no miracles. There is nothing like repetition to determine whether what has been learned is remembered or forgotten, precise or vague. As early as 1885, Herman Ebbinghaus demonstrated that learning in several short sessions was more productive than learning in one long session. Today, the molecular bases of mechanisms as complex as cognitive processes can now be studied by new techniques which can modify, increase or remove the expression of a gene in an animal. And so, one century later, in conjunction with experiments on behavior, an EPFZ team of researchers has just revealed the molecular origin of one of the first discoveries made at the end of the 19th century in modern experimental psychology.

Earlier studies had already implied that the PP1 protein was involved in the mechanisms of learning. To find out more, these researchers bred genetically modified mice in which the protein can easily be controlled, much in the same way as with an "on/off" switch. To verify the importance of the activity of PP1, the mice were trained to recognize objects. Since they show more interest for unknown objects than those they have already encountered, the results of such training are easily assessed.

First observation: as with students, mice learn better when given five "working" sessions separated by 15 minute intervals rather than the same sessions with only 5 minute intervals, and

indeed a single session of 25 minutes with no interval at all. But if PP1 is "switched off", learning by cramming (i.e. a 25 minute session) becomes as effective as five sessions with 15 minute intervals! So "switching off" PP1 or allowing long intervals between working sessions both aid learning and memorizing. Moreover, the activity of PP1 in "normal" mice (those that are not genetically modified) is weaker when long periods of rest between working sessions are allowed. To conclude: it appears that working sessions spaced out by long intervals are more effective because the "constraint" that PP1 imposes can then be avoided.

But can this protein's activity influence the persistence of memory in time? To verify this, the Zürich researchers trained their mice to search and find a platform in a pool filled with cloudy water; they had to guide themselves by markers hung at various points in the room. Trial after trial, new markers had to be recognized and memorized in order to reach the platform. After nine days of this intensive training (3 a day over a period of 9 days), the performances of the "normal" mice and the genetically modified mice were identical. Then the researchers removed the platform. At first, the "normal" mice looked for the platform in the right place but their memory faded fast and they had forgotten everything after 6 weeks. The performance of those mice whose PP1 had been "switched off" diminished but remained better than that of the "normal" mice. Even if the PP1 was "switched off" only once the working sessions were over, they remembered the platform 6 weeks later! So, quite apart its function in learning, PP1 also helps us to forget: our memories do not fade at random, on the contrary, our brain actively erases memories that have not been used for some time thanks to the PP1 protein.

So could PP1 be also responsible for the decline of memory in old age? The researchers then undertook to study the performances of "old" mice. In spite of their "old age", both "normal" and genetically modified mice were able to learn the exact position of the platform after intensive training. But only one day after the training, the "normal" mice showed signs of forgetfulness, whereas the modified mice were still going strong 24 hours later and even 4 weeks after training. So, yes, PP1 is also responsible for the decline of memory in old age. But how?

The Yin and the Yang

As with many other biological processes, memory is regulated by what is known as "Yin-Yang" interactions between molecules with opposing functions. For instance, PP1 is a phosphatase, i.e.

it removes atoms of phosphorus from other proteins known as "targets". In this way, PP1 "deactivates" them. This is called dephosphorylation. Conversely, proteins called kinases add an atom of phosphore to a protein in order to "activate" it. And this is termed phosphorylation.

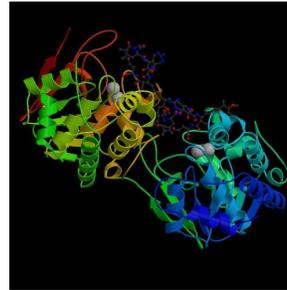


Fig.2 Three-dimensional structure of the PP1 protein

Proteins known to be involved in memory formation are of course amongst the targets of PP1. More specifically, the results of the Zürich team suggest that the dephosphorylation, and hence inactivation, of a protein called CREB limits memorization in the course of "cramming".

CREB is what is called a transcription factor. Combined with other transcription factors and in answer to different signals, CREB will decide whether or not a given gene is expressed, i.e. whether proteins should or should not be produced according to the information contained in the gene. As we have seen, this is a process that is necessary in the training of long-term memory. When PP1 is active, CREB's activity is greater after work sessions with long intervals in between. On the other hand, when PP1 is not active, CREB's activity remains strong whatever the length of the intervals. So, in reality, deactivating PP1 hinders the dephosphorylation (i.e. the inactivation) of CREB. In other words, if PP1 obstructs learning, it is because it deactivates CREB, thus preventing the expression of certain genes and therefore the production of new proteins. During intensive work sessions, PP1 may well be our safeguard against "overload". In short, a kind of natural fuse! By introducing periods of rest between work sessions, we enable the kinases to restock the reserves of "phosphorylated" (active) CREB.

In terms of the decline of short-term memory - which does not involve the synthesis of new proteins - this study suggests that PP1 has an effect on two other "target" proteins already thought to be involved in the first stages of the memorizing process.

Memory of the "future"

With the recent progresses achieved in genomics and proteomics, many proteins involved in the complex phenomenon of memory formation have been discovered. At the moment, they are but isolated pieces of a large puzzle waiting to be assembled. In this context, PP1 appears to be one of the keys to the mechanism of acquiring and retaining information. During an intensive work session, it does away with both short- and long-term memory, thereby preserving the synaptic circuits from saturation and guarding our brain from "blowing a number of fuses". But it also appears that PP1 helps our brain sort out our memories: like a "molecular eraser", it seems to blot out memories that are no longer needed.

Also, it seems likely that the real cause of the deterioration of our memory in old age is the deregulation of PP1 and not, as was believed until recently, the irreversible reduction of molecular components. If this is so, there is scope for new therapies for the elderly. At least, the results obtained through research suggest that memory loss could be avoided by administering drugs

directed against a small number of "target" molecules. This of course would have nothing to do with severe cases of memory loss, such as those associated with Alzheimer's disease or cerebral attacks, caused by the destruction of millions of neurons.

It would be tempting though to block the activity of PP1 in young people in order to try and improve their faculties of learning and thus obtain a "super" memory. Yet if our brain has provided such a safeguard, it has its reasons and to try and bypass this could bring on disagreeable consequences. Not to mention the fact that, if such drugs were discovered, there would be no more excuses for a failing memory - which are sometimes so useful to get us out of a sticky situation...

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For further information

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At UniProtKB/Swiss-Prot:

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- PP-1G, Homo sapiens (human): P36873

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