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> ONE MONTH, ONE PROTEIN <

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Vita minima

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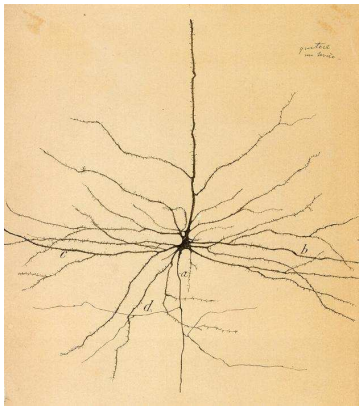
Trees are beginning to blossom, flowers are easing their way through the earth and frogs will soon begin their slow march out of hibernation. In short, Spring is on its way. And for the faultless unfolding of these awakenings, hosts of proteins will be summoned. Tau protein is one. Tau has become very popular since it was discovered that its presence seemed to coincide with the evolution of Alzheimer's disease. Though it may sound contradictory, tau protein could have a protective role towards neurons, as suggested by the process of hibernation in the European ground squirrel...

It all has to do with neuronal plasticity. The art of memory lies in the hippocampus and the way neurons are connected to one another. In disturbed conditions such as neurodegenerative diseases but also in natural and reversible conditions such as hibernation, starvation or hypothermia, neuronal networks are dismantled in part. The fact that – in the case of hibernation for instance – such networks can be re-established without loss of memory owes much not only to dendrite migration and synapse formation but also to tau. One of the first scientists to link Alzheimer's disease[1] and loss of memory to the hippocampus and neuron plasticity was the Spanish neuroscientist Santiago Ramón y Cajal (1852-1934). And the year 2006 celebrates the 100th year of his being awarded the Nobel Prize for Physiology or Medicine, jointly with the Italian neuroscientist Camillo Golgi (1843-1926) for their work on revealing the structure of the brain.

Tau proteins are found in the brain and under normal physiological conditions, they dock to microtubules. Microtubules go through what are termed continuous 'catastrophes' and 'rescues' where monomers assemble, to disassemble and then reassemble. One of tau's tasks could be to stabilise the microtubules possibly by binding lengthwise to two successive microtubule monomers. Conferring rigidity and invariability to microtubules has an effect both on a cell's cytoskeleton and intracellular organelle transport. Indeed, microtubules are not only an integral part of a neurons's architectural makeup but they also constitute the rails along which organelles are transported from one part of a neuron to another. Hence, tau would have a role in a brain cell's architecture as well as its intracellular transport.



Drawing of a neuron by Cajal (1899)

In the event of hibernation, the whole memory system – amongst other regulatory mechanisms – is disturbed. Dendrites degenerate, synapses are lost and, hence, memory too. What happens to tau proteins? They lose hold of the microtubules by way of hyperphosphorylation and self-aggregate – following both N-terminal

[1] Read 'Alzheimer's disease: when the mind goes astray', Protéines à la Une, Issue 16.

and C-terminal truncation – to form filaments. Though this causes the fading away of synapses, it is thought that the presence of hyperphosphorylated tau could in fact protect the neurons – hence the brain – in some unknown way. When animals emerge from hibernation, hyperphosphorylated tau disappears completely and the same synapses are reformed in a very short period. The fact that the same network is re-established, not only rapidly but also without losing pre-existing memories, must imply both neuronal plasticity and something which reminds the network where every route used to be. Such a reminder may reside in the very architecture of a neuron's cytoskeleton. Interestingly, there are many more synaptic connections made than there were prior to hibernation, and once the connections have been tapered down to their former number, memory is reconstituted. Exactly the same happens during neurogenesis in the newborn and the subsequent formation of memory in the mature brain.

One of the symptoms, which can be an indicator of Alzheimer's disease, is the presence of tau filaments. Many believe that tau is in fact the cause of the lesions observed in neurons. However, in the light of what is known regarding hibernation, phosphorylated tau and the filaments which form could be there as a means of protection, and the lesions may be the fruit of something else. Despite this knowledge, when animals emerge from their torpor, phosphorylated tau is completely eliminated from the hippocampus, strengthening the theory that such a conformation is in fact toxic to the brain one way or another, and that incomplete reversibility of tau phosphorylation could cause neurodegenerative diseases in animals.

Tau phosphorylation is directly involved in stunting and maintaining minimum memory functions in hibernating animals. The fact that such a phenomenon resembles that of Alzheimer's disease and that it is reversible, is thought-provoking for those involved in fighting against the progression of such a debilitating disease. There is no certainty today that tau will reveal any secret from which some kind of therapy for those suffering from Alzheimer's could blossom. So, in the meantime, let the buds do so.

Cross-references to Swiss-Prot

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