Greenwich Observatory) and R. Cohen (University of California, San Diego). However, A. Wilson (University of Maryland) argued that there exists a distinct difference in radio properties between Type I and Type II Seyferts. Some Type II Seyferts are really Type I Seyferts obscured by gas and dust; others may be 'switched off' Type I Seyferts — when the central radiation source switches off, the compact high density, high velocity cloud region will soon also disappear, but the very large low density regions may remain glowing for from hundreds to a few thousand years. Evidence for AGN changing their type on a timescale of decades was shown by Lawrence, Cohen and N. Bochkarev (University of California, Berkeley).

At least some of the classical Type II Seyferts may be quite different. J. Miller (Lick Observatory) reported that the Seyfert Type II NGC1068 has a highly polarised non-stellar continuum which extends through to the UV and soft X rays. The emission lines are less polarised and those preferentially emitted from low density gas (the so-called 'forbidden lines') are polarised at a different angle from the permitted lines. This suggests that the central high density gas is present after all but for some reason is not moving at the great velocities characteristic of Type I Seyferts. G. Ferland (University of Kentucky) presented UV data for several Type II Seyferts which further showed that they do have a non-stellar continuum but that it is very weak.

Sitting through the workshop, one had the feeling of assembling a giant jigsaw puzzle. We have at least the majority of the pieces and have completed the edges. Now we must take a deep breath before attempting to make sense of the picture in the middle. □

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Neurobiology

Memory and molecular turnover

from Francis Crick

RECENT spectacular advances in molecular biology will, before long, begin to make a massive impact on certain key problems in neurobiology. A synapse is a complex piece of molecular apparatus, but there is now no technical reason why all its components — not merely the major ones — should not be isolated, sequenced and characterized. We can expect to have a detailed knowledge of the many ion channels, receptors and so forth, almost at will, for any type of neuron in any species. All this, together with techniques such as patch-clamping, should put the behaviour of synapses on a solid foundation and in the process tell us something about the molecular basis of memory. However, in spite of recent advances in understanding memory, in both *Aplysia* and long-term potentiation in the hippocampus, one aspect is often overlooked.

The time span of human memory (without obvious rehearsal) is often a matter of years, sometimes even tens of years. Yet it is believed that almost all the molecules in our bodies, with the exception of DNA, turn over in a matter of days, weeks or at the most a few months. How then is memory stored in the brain so that its trace is relatively immune to molecular turnover?

Several possible solutions of the problem suggest themselves. For example, memory might be coded in alterations to particular stretches of chromosomal DNA. Much current thinking assumes that memory is stored, at least in part, in the 'strength' of (many) individual synapses, so this would imply that in any neuron there is a special piece of DNA for each of its synapses, generated perhaps by similar means to those used in cells of the immune system. This seems unlikely. A related alternative is that there is a special *local* piece of DNA (or perhaps RNA) for each relevant synapse. For example, it is conceivable that each spine apparatus has its own piece of nucleic acid which is modified when the system needs to alter the strength of that synapse. This idea also does not seem very likely but might be worth bearing in mind, since each mitochondrion has its own piece of DNA.

Another alternative is that each synapse has at least one macromolecule which is relatively immune from molecular turnover. Again this does not seem very probable but such a molecule could be looked for by appropriate pulse-chase experiments during development.

Since none of these alternatives seems especially attractive, one is more inclined to suggest models that are cooperative in nature. That is, the molecules in the synapse interact in such a way that they can be replaced with new material, one at a time, without altering the overall state of the structure. It is easily possible to conceive many such hypothetical models. It occurred to me to think of the simplest.

Consider, for example, a protein molecule that is an essential part of a synapse and can exist in two states: active and inactive. Suppose the molecule forms a dimer, probably with a two-fold rotation axis, that can be modified chemically by, for example, the attachment of a phosphate group. Let us assume that when both monomers are modified the protein is in the active state, symbolized by (+,+) and that when both are unmodified the dimer is inactive, symbolized as (−,−). In addition, let us assume the existence of an enzyme that will add a phosphate group (or whatever the modifer is) to one monomer if the other monomer of the dimer is already modified but not otherwise. That is, it will turn a (+,−) into a (+,+) but will not touch a (−,−).

Assume, furthermore, that the mechanism for altering the synaptic strength can phosphorylate the dimer when more parts of the synapse are to be made active and can dephosphorylate it when activity is to be reduced. That is, the mechanism can turn a (+,+) into a (−,−), or vice versa.

Finally I assume that individual monomers of a single dimer can be replaced one at a time by the mechanisms responsible for molecular turnover and that these new monomers are initially unmodified.

This system will have the property that whether the dimer is in the active (+,+) state or in the inactive (−,−) state, the substitution of a single new unmodified monomer for either of its two components will leave it in the same state. That is, molecular turnover will turn a (+,+) into a (−,+) but the hypothetical enzyme will convert this back to (+,+). The (−,−) state will of course remain (−,−) during metabolic turnover. This mechanism is obviously modelled on known mechanisms for the maintenance methylation of DNA, as reviewed by Razin, A. and Friedman, J. in *Progress in Nucleic Acid Research and Molecular Biology*, Vol. 25 (ed. Cohn, W.E.) 33 (Academic Press, 1981).

It is possible to imagine more complicated models of this general type. The macromolecule could be a trimer or a tetramer; there might be more than one modifiable site per monomer; rather than phosphorylation, the modification might be dephosphorylation, or methylation, glycosylation and so forth.

There are a number of subsidiary conditions. The macromolecule should be anchored to a particular synapse and not be free, in its mature form, to migrate from one synapse to another. This might suggest it would probably be a membrane protein and perhaps form part of a larger aggregate of some form. The supply of newly synthesized monomers should be immune to the modification (or demodification) process. The old monomers, due to be discarded by molecular turnover, should not interfere with the above processes.

Since the proposed mechanism is not implausible it would be sensible to look carefully for modifications to synaptic proteins and for the enzymes which modify and demodify them, in case one of these enzymes should have the peculiar characteristics described above. If such an enzyme were found it might prove to be a pointer to the seat of long-term memory. □

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