Report from the lecture presented by Eric Kandel

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There are two major forms of memory – declarative (or explicit) and non-declarative (or implicit, procedural). When we speak about memory we usually mean declarative memory which involves conscious and subjective recall of events or facts. Non-declarative memory explains why we do not forget how to ride a bicycle once we have mastered it and probably why we like some types of foods more than others. Non-declarative memory can be studied in simple model organisms such as the marine mollusk *Aplysia* and in the fly *Drosophila.* Declarative memory can only be studies in an organism with at least the ability to pay close attention. Indeed, rodents that do not pay attention rapidly forget.

For both these types of memory there are two distinct temporal phases called short-term memory and long-term memory. A problem that Eric Kandel has pursued over several decades is how short term memory is translated into long-term memory. This problem translates to a problem in signal transduction: How can signalling events that are able to manifest themselves very rapidly (i.e. in a matter of seconds or a few minutes) be related to changes that are if not permanent at least very long lasting? The long-term changes require protein synthesis and altered gene transcription – the short-term changes clearly occur too fast for these processes to be involved. Nevertheless, the initial signalling events are remarkably similar, but the intensity and repetition of the stimulus at least partly explains if the memory will be short or lasting.

Many of the long-lasting changes in mammals manifest themselves by changes in the very morphology of the synaptic contacts – and largely on the receiving end of the signalling event. This immediately raises the question how a neuron is able to restructure just a minute fraction of all the synaptic contacts that it has established.

In neurons from the marine snail *Aplysia* enhancements can be presynaptic and yet only affect those terminals where a “memorable” enhancing stimulus has been applied. This allowed

Kandel and co-workers to set up a very elegant model system. They cultured neurons such that they could make synaptic contacts with at least two different neurons. If the chemical 5-hydroxytryptamine (5-HT; serotonin) was locally applied at the region of the synaptic contact the transmission of impulses was enhanced and this was remembered over the short (a single 5-HT application) or long (5 consecutive 5-HT applications) term. The long-term changes required transcription of genes regulated by the so-called CRE element. The transcribed gene products travelled into all parts of the neuron, but only in synapses activated by 5-HT were the appropriate reactions set up and persistent changes established. Thus, conversion of short-term to long-term memories require a combination of neuron-wide transcriptional events and extremely localized events at the very synapse(s) which initiated the process.

There may be many such local events and the attempts to identify such mechanisms have already yielded some surprising answers. Thus, in the *Aplysia* system local formation, via non-traditional signalling cascades, stabilizes a protein that can increase local protein synthesis. Moreover this activation appears to involve a conformational switch that is self-propagating. Such self-propagating changes in protein-conformation with functional consequences is found in the so called prions a class of proteins that mediate diseases including Creutzfeld-Jacob disease, Kuru, Scrapie, so called mad cow disease and possibly Alzheimer's disease. This provides yet another reminder that the border between health and disease can be much less precise than one would wish.