Learning and Memory

Text is partly based on
Göttinger Tagung der Ges. f. Neurobiologie March 1998
R. Wandtner, FAZ Natur und Wissenschaft 1.4.98 und 18.10.00 and
R. Degen, Der Tagesspiegel 16.10.00.
Photo of E. Kandel from Der Spiegel 17/2000, p. 175

Concepts

Learning: acquiring knowledge about the world around us
Stimulus: painful signal, caused by mechanical contact or current pulse - *a biotechnical equivalent to a memorable event - see further*
Habituation: Repeated stimuli cause the reaction to weaken - the system gets used to it.
Sensibilization: Starting stimulus amplifies the reaction to identical stimuli, that may follow.
Memory: remembering previous stimuli
Short-term memory: stimulus is not remembered any more within an hour
Long-term memory: stays for longer than an hour
Extracellular space: the liquid medium outside the membranes / cellular walls
Neurotransmitter: messenger agent, which transmits signals via diffusion
extracellular ˜: agent, that are secreted by the cells into the extracellular space and by diffusing through it cause stimuli on foreign cell membranes.
intracellular ˜: agent, whose action is limited to the cell contents, for instance to the cell nucleus.
Serotonin: the central extracellular transmitter for pain stimuli. One can simulate stimuli by introducing Serotonin into the extracellular space.
cAMP and Mitogenes: important intracellular transmitters
Transcription: copying of the genetic information.
Transcription factors: Proteins that regulate the transcription process, i.e. start/stop/control it.
Synapse: Cell extrusions in neural cells, rich in Neurotransmitters which can be secreted to initiate a stimulus signal.
CREB-Proteins: cAMP-Responsive-Element-Binding-Proteins = Transcription factors for synapse generating genes

Aplysia

Aplysia (German: Seehase, English: sea snail) is from a genetical point of view a very archaic animal. It can reach up to 70 cm length and 15 kg in weight. Its main attraction for research is its nervous system, which consists of only about 20.000 nerve cells and fibers, which are on top of that very thick (about thousand times thicker mammalian). Their enormous thickness and low total number (bees carry 1 million, a lion about 10 billion and humans 100 billion neural cells) make Aplysia a preferred tested for bio models in neuro anatomy and molecular genetics of learning and memory processes. The connections between nerve knots (each consisting of about 10 cells) are already more or less completely charted out. Veritable snail farms are needed to supply hundreds of laboratories around the world, that specialized in the Aplysia research. Suffice to say that Aplysia occupies the second place (after the Drosophila melanogaster fruit fly) as the most favorite living research subject.
Despite its humble capacities Aplysia is eager to learn. Given a stimulus, which could be understood as dangerous, it retracts in a reflex its gills and siphon. Only 6 motoric neurons are needed to run this process. They obtain the necessary information partly directly and partly via interneurons in sensory cells of the siphon. After slightly touching the siphon 10 times, Aplysia does not react anymore. The habituation kills the reflex. If the training happened just one single time, the memory disappears in approximately a quarter of an hour. Training sequences on four consecutive days cause a habituation, that stays for 2 weeks. If its foot is electrically stimulated, sensitization instead of habituation happens. Additional effect is extreme sensibility to a mechanical contact in the siphon region.
E. Kandel and his colleagues used the enormous size of nerve cells and the simple connectivity of the gill retraction reflex to study transmitter processes. The short-time memory is, as expected, based on a reduction of the siphon sensory cell's secretion of transmitter at the synapse of the motor neuron to the gill muscle.

The sensitization of the snail foot on the other hand finds expression in a long-term memory that persists for days and weeks. The central question is: what are the cellular and molecular mechanisms of this memory types ?

Erich Kandel

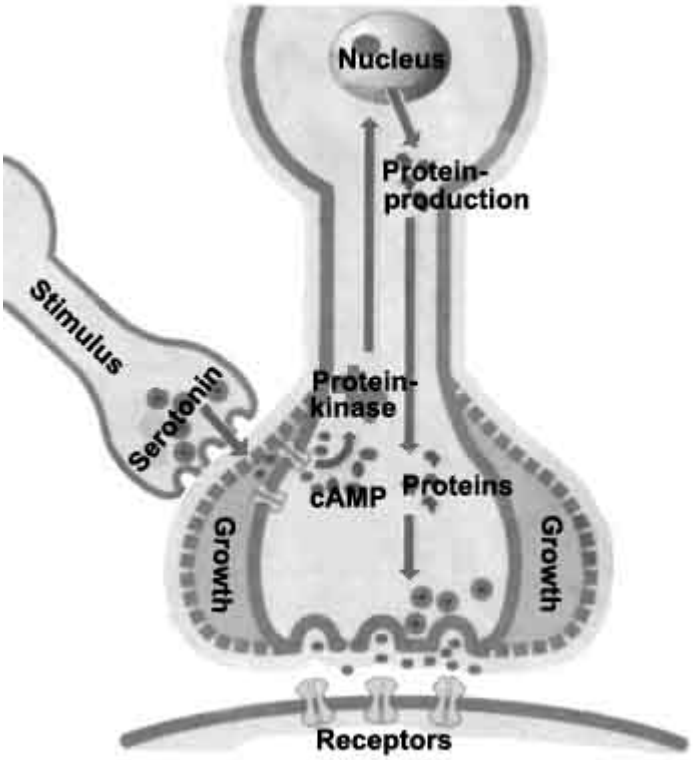
born 1929 in Wien, has been professor at the Center for Neurobiology and Behavior since 1974 and Senior Investigator at the Howard Hughes Medical Institute Columbia University NY since 1984. Kandel has been for the last 26 years doing research on the humble but ready-to-improve intelligence of Aplysia. He holds consulting positions with firms like Memory Pharmaceuticals, Biogene, Myriad Genetics and Hoffmann-LaRoche on the subject of ca.. 200 known substances, known under the collective name of "cognitive enhancers", which can be used to influence the learning and memory capabilities of these animals. He is sharing the Nobel prize for medicine in year 2000 with the neuroscientists Arvid Carlsson, Göteborg (role of Dopamin) and Paul Greengard, New York (role of the phosphorylation) "for their discoveries concerning signal transduction in the nervous system" (as announced by the Nobel prize committee). Kandel is a member of the Berlin-Brandenburgische Akademie der Wissenschaften www.bbaw.de.

The day after the laboratory's Nobel price party this depressed Aplysia had forgotten whatever she learned. Prof. Kandel suspects the influence of C_2H_5OH.

Learning through self-wiring

The narrow gaps between two neurons, where the polarization of cell walls can switched around by the transmitters (= synaptic gaps), are the place, where the so-called "LTP - Long Term Potentiation" process is taking place. If the two connected neurons fire at the same time, than the synaptic connection gets reinforced. The same stimulus later causes a stronger reaction:"sensibilization". Probably both cell walls are involved in this process. On the pre-synaptic delivery side, the synaptic bulb gets enlarged and on the receiving = post-synaptic side the sensitivity increases. Lately a rough picture of inner-cell processes has evolved: cAMP stimulates enzymes, the so-called protein kinases, which change forms and functions of substrate proteins by posphorylation. The effect is twofold. On one side the membrane proteins change in such a fashion that the whole membrane is more excitable (Ca+ ion permeability) and they increase the rate of emission of transmitters into the synaptic gap. The changes are not long-lasting, the effect is rather short-lived. In other words they seem to be the carriers of the short-term memory.

For a permanent change a much more complicated process is started: (1) increasing production of membrane proteins in the nucleus, (2) transport of these proteins toward the synapse, (3) mounting in the cell wall. After completion of these 3 tasks the short-term memory is fixed with the result of a permanently stronger and quicker synaptic reaction.



Long-term memory: repeated income pain signals enlarge the output-Synapse
After: Karolinska Institut, Stockholm

What did the group around E. Kandel discover?

The feedback mechanism of the short-term memory in a very much shortened version:
Extracellular serotonin stimulates the cell.
Intracellular secretion of cAMP transmitter results
cAMP activates protein kinases.
The protein kinases phosphorylate the existing proteins, without causing new synthesis.
The changed proteins increase the excitability of cell walls and thus make them more permeable for transmitters which gets released into extra cellular space.
Up to point 4 the long-term memory runs the same way.
Additionally the protein kinases travel into the cell's nucleus and activate the transcription factor Creb1 from the family of Creb proteins.
Creb1 tips a genetic switch, that starts off an autonomous process of protein generation, which eventually results in changes in the structure and walls of the cell, i.e. in a creation of new synapse candidates.
For the long-term memory there's additional transmitters, which act in parallel to cAMP, the so-called "Mitogenes".
They activate another Creb-Protein in the nucleus, the Creb2, which is already present in inactive state. It is interesting to note that Creb2 as antagonist of Creb1 depresses the transcription. Probably the repeated serotonin pulses change Creb2 in such a fashion, that his antagonistic behavior towards Creb1 is decreased. Without the presence of Creb2, a single shot of Serotonin would probably sensitize the nerve cell for a long period of time.
Jump to: Neurotransmitters and Gene Regulation

These pairs of activators and repressors have been found also in Drosophila and mouse, with the clear indication of the dominant role of Creb1. If the availability of Creb1 is increased through genetic manipulation or if the repressor function of Creb2 is lowered through Creb2 antigens, then the speed of learning these animals exhibit is increased in a spectacular fashion - by a factor of app. 5 (T. Tully und J.Yin Cold Spring Harbor Lab. Long Island NY).

Prospects

The brain structure, most important for the human learning process is the hippocampus at the bottom of the parietal lobe. In hippocampus / as opposed to Aplysia - glutamate is the predominant extracelullar transmitter and NMDA the receptor complex that has specialized in glutamate. There are three neuronal connection paths: the mossy fibres, the Schaffer-collaterals and the tractus perforans. For the mossy fibres and the Schaffer-collaterals the mechanism of senzibilisation (neurophysiologically: long term boost-up) is certain. It is, however, not prooved if it is based on the Creb1-Creb2 antagonism. There's indications that sensibilization is taking place in tractus perforans also. In any case there's not much reason to assume this mechanism is not available to humans as well. There's not much we know about genes, which get expressed because of Creb1 activity. From a functional point of view it would not make much sense if the gene's product would boost all ca. 1000 synapses of a given cell. There are two possibilities: either the membrane proteins get transported just to synapses involved. Or they do get to all synapses of the cell but just act at the involved synapses and at all other synapses they are present too but inactive. We do not know which of the two alternatives is correct. It seems nitrogen monoxide (NO) has some control functions, but it's not clear, how it differentiates the synapses involved in the process of learning from inactive synapses.

We can just predict that any memory-enhancing substance will probably turn out to be a double-edged sword: it opens the doors to random effects, because any random process will get imprinted just as much as repeatable cause-and-effect experiences. Such a drug will be safe only if we will be able to control the learning process to such a degree that randomness will not hamper it any more.
In any case we still have a lot to learn from Aplysia.

Humans for sure must have other learning mechanisms available as well. Without much effort we can memorize and recall ca. 3000 faces. A synapse-buildup based training process just does not apply in this case - the necessary times would be beyond what it takes us now.

Links

http://cpmcnet.columbia.edu/dept/gsas/biochem/faculty/kandel.html
http://web.sfn.org/content/Publications/BrainBriefings/creb.html
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?123810
http://www.cshl.org/gradschool/yin_.html
http://www.time.com/time/magazine/cover08.html