pendent, this system would be expected to work quite well, since the new recruit bees tend to take the same route as the experienced scout bee. What do the ants do when they cover similarly several kilometres on foot to look for food? Preliminary evidence indicates that they don't use an odometer but instead might count steps!

Suggested Reading

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Learning from a Sea Snail: Eric Kandel

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In the year 2000, Eric Kandel shared the Nobel Prize in Physiology and Medicine[1] with two other neurobiologists: Arvid Carlsson and Paul Greengard. Whereas Carlsson and Greengard were awarded for their work on dopamine, an important neurotransmitter in the brain, changes in the level of which result in Parkinson's disease, Eric Kandel was honoured for his extensive and invaluable contribution to our understanding of the cellular and molecular mechanisms of learning and memory.

If learning may be defined as the acquisition of information during the lifetime of an individual, which may be used to direct and modify future behaviour, then memory is the form in which this information is stored. Together, they represent one of the most valuable and powerful adaptations ever to have evolved in nervous systems, for they allow the future to access the past, conferring flexibility to behaviour and improving the chances of survival in unpredictable, rapidly changing environments.

The scientific study of learning began only at the end of the nineteenth century. Before that, learning and behaviour in general, were attributed to vital forces rather than to materialistic processes. The latter half of the nineteenth century saw an increasing interest in animal psychology, due in large part to Darwin's views: "The difference in mind between man and the higher animals, great as it is, certainly is one of degree and not of kind" (Charles Darwin, 1871).

Resonance readers can look forward to another article on the same subject in a forthcoming issue.

The objective study of observable behaviour was greatly extended by two psychologists, Edward Thorndike (1898) and Ivan Pavlov (1906) who developed two of the most widely studied learning paradigms: instrumental conditioning (or learning by reinforcement) and classical conditioning. Thorndike placed a hungry cat in a wooden cage, from which it could escape if it pulled a latch. By rewarding the cat with food every time it performed the correct behaviour, he found that the cat soon learned how to pull the latch. The time taken to learn this behaviour was shorter when a reward (reinforcement) was provided than when it was not, hence the term learning by reinforcement. The cat thus learned to perform the specific *behaviour* that was associated with a reward. Pavlov, on the other hand, showed that salivation in dogs, which is usually a reflex or unconditioned behaviour that occurs at the smell of food (the unconditioned stimulus), could be induced by a normally ineffective stimulus (the conditioned stimulus) such as the sound of a bell, if the latter was repeatedly presented just before the food. In other words, the animal learned to associate the ringing of a bell with the imminent appearance of food. Both instrumental and classical conditioning are associative, that is, the animal either associates a particular *behaviour* that it carries out with a reward, or it learns to associate two *stimuli* that occur in quick succession, using the first, usually biologically irrelevant one as a predictor of occurrence of the second, biologically relevant stimulus.

In addition to these associative forms of learning, there are several non-associative forms, two of the most ubiquitous being habituation and sensitization. Habituation is simply the decline in response to a stimulus that is repeatedly presented. Sensitization is the enhancement of the response to a stimulus as a result of presentation of another, often strong or noxious stimulus: this increase in response does not depend on pairing of the two stimuli in time and is therefore non-associative in nature.

Psychologists had defined a number of different kinds of learning based on rigorous behavioural experiments on laboratory animals. Although it was generally accepted that the basis for the changes in behaviour that characterised the different learning paradigms must lie within the nervous system, the exact physiological or structural changes were not understood. The idea that changes in the strength of connections (synapses) between neurons (nerve cells) were responsible for the changes in behaviour was conceived as early as the 1890s but was further developed by two psychologists, Jerry Konorski and Donald Hebb, in the 1940s. Hebb proposed that coincident activity in two neurons, which were connected to each other would result in the strengthening of the connection (synapse) between them. He also emphasised the distinction between two forms of memory: short term memory, lasting minutes or hours, and long term memory, lasting for days. Over the last forty years, thanks in large part to the work of Eric

Kandel*, we now understand much more about the cellular and molecular basis of the different forms of learning and memory.

Born in Vienna on November 7th, 1929 Kandel emigrated to the United States, where he graduated from Harvard College, majoring in history and literature. He then obtained a medical degree at the New York University School of Medicine. After a short stint as a Resident in Psychiatry at the Harvard Medical School (1960-1965) he moved to Columbia University, New York, where he has worked ever since. Casting around for a model organism in which to study the neuronal basis of learning, Kandel eschewed the typical rats, mice and pigeons that psychologists had used for decades to develop their theories of learning and settled instead on an unfamiliar, unloved and unlovely organism: the humble sea snail *Aplysia californica*. This decision was to have far-reaching consequences, leading ultimately to the Nobel Prize.

At first sight, *Aplysia* hardly appears to be the kind of organism one would choose for any behavioural study, leave alone learning. But, in common with a number of other molluscs to whom we owe much of our current understanding of neurobiology, *Aplysia* has one great asset: a relatively modest number of large, individually identifiable neurons. It is therefore possible to consistently perform recordings of the activity of single, identified neurons in a number of different individuals and to work out the details of every neuronal circuit to the last cell. It was this advantage that attracted Kandel to *Aplysia*. During the early years of his work, he used two approaches to develop Aplysia into a model system for the study of the cellular basis of learning. The first approach was behavioural: Kandel established that *Aplysia* was in fact capable of at least three of the four most widely studied types of learning: habituation, sensitization and classical conditioning. And also the gill-withdrawal reflex behaviour (withdrawing the gill in response to touch), could be habituated, sensitized or classically conditioned. He thus showed that a single behaviour could be modified in different ways. He then went on to painstakingly elucidate the entire neuronal circuitry underlying the gill withdrawal reflex. By developing a semi-intact preparation in which it was possible to simultaneously monitor both the behavioural response of gill withdrawal and the electrical activity of neurons in a behaving animal, he was able to closely examine the physiological changes in individual neurons of this circuit. He was able to pinpoint *which* of the neurons in the circuit were modified as a result of learning and in *what manner* they were modified.

*For the sake of clarity of the text, I have avoided giving references to the hundreds of original papers on which this article is based. When I refer to Kandel, it goes without saying that the edifice of his work rests on the generations of students, technicians and postdocs that have passed through his laboratory in almost four decades.

Using this approach, he showed that habituation of the gill-withdrawal reflex was accompanied by a decrease in the strength of the synaptic input from sensory neurons (which receive the tactile stimulus) to succeeding (postsynaptic) interneurons: there was a decrease in the amount of neurotransmitter released. This immediately suggested a molecular mechanism for habituation: since the reserves of readily available (mobilized) neurotransmitter at the synapse are limited, repeated stimulation would result in depletion of this transmitter pool, decreasing the amount released on successive stimulation. This would result in a decreased excitation of the following neurons and hence the behaviour would no longer be elicited.

Kandel also went on to show that the physiological and molecular basis of both sensitization and classical conditioning were essentially the same: presynaptic facilitation, or an increase in neurotransmitter release at synapses, which were thus strengthened. The central player in this process of presynaptic facilitation was a well-known molecule: cAMP (cyclic adenosine mono phosphate), a cyclic nucleotide involved in a variety of cellular processes. The sensitizing or conditioning stimulus typically causes an increase in the level of cAMP which binds to the regulatory subunit of an enzyme called protein kinase A (PKA), releasing its 'active'or catalytic subunit. This catalytic subunit of PKA, via a biochemical cascade of events, causes an enhancement in the amount of calcium entering the neuronal cell terminals, which is in turn responsible for the enhanced amount of neurotransmitter released (increase in strength of the synapse). Thus, Kandel showed that, in *Aplysia*, two different forms of learning, one associative and the other non-associative, shared a common molecular mechanism!

Further, since most forms of learning are reversible (much of what is learned is forgotten!), it follows that memories have finite duration. On the basis of retention time, there are two major forms of memory which were again first described by psychologists: short term memory (STM) lasting minutes or at most, hours, and long term memory (LTM) lasting days, weeks or years. Whereas STM is induced by just one or a few trials, repeated or prolonged presentation of stimuli is necessary for LTM to be induced. Very interestingly, studies in animals as diverse as *Aplysia*, birds and humans have shown that memory retention is much longer if the training is distributed rather than massed: that is, presenting stimuli a large number of times within a short duration ('cramming') is essentially ineffective in inducing LTM! This is surely one of the strongest arguments against memory-based, examination-oriented systems of education.

All forms of learning involve both short and long term memory, suggesting that STM may be the first stage of memory acquisition, which is then followed by consolidation in the form of LTM. It is well known that STM does not require the synthesis of new proteins or nucleic acids, whereas LTM does.

Kandel showed that the physical basis (or the 'trace') of short term memory was in fact simply the elevated cAMP level and all its contingent modifications of protein structure and function. It follows that the duration of short-term memory is determined by the turnover time of this cAMP. Having explored the cellular and biochemical basis of STM, Kandel then turned his attention to the molecular basis of LTM in *Aplysia*. He showed that the crucial step in the transition from STM to LTM is that, with multiple stimulation, some of the 'active' PKA catalytic subunit induced by STM moves into the nucleus of the cell, where it interacts with a number of transcription factors (proteins that regulate gene expression). The most important of these are CREB1 and CREB2 (cAMP responsive element binding proteins): CREB2 is a repressor of LTM, whereas CREB1 induces it. The central role of PKA, then, is probably to derepress CREB2 and activate CREB1: there is now also evidence for such dual control of memory induction from studies in Drosophila. The final steps of LTM are the strengthening of the connections by the formation of new synapses, thus consolidating the memory.

In recent years, Kandel has moved on from *Aplysia* to studies of the mammalian hippocampus, the region of the brain on which many of the studies of LTM in mammals have been focused. The hippocampus is known to mediate spatial learning, which is somewhat more complex than the simple paradigms studied in *Aplysia*. Kandel found that many of the molecular mechanisms elucidated in *Aplysia* also underlie learning in the mammalian hippocampus, although there are some additional mechanisms, such as Hebbian learning, where the activity of the postsynaptic cell is important for the strengthening of the synapse. Nonetheless, Kandel established that cAMP has a central role in the induction of LTM in the mammalian hippocampus as well.

Kandel's work showed that very different forms of learning may share common physiological and molecular mechanisms; further, the fundamental molecular processes involved in short and long-term memory appear to be conserved across a variety of diverse phyla. Evolutionarily conserved molecular mechanisms of learning and memory will surely stand as one of the most profound discoveries of the twentieth century, vindicating Darwin's views on the essential unity of all life forms.

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