Tuning in to neurotransmitters

The slow-acting chemicals that modulate fast synaptic transmission in the nervous system may help to unify the disparate disciplines that make up neurobiology.

FOR too long it has been common to make the analogy between the central nervous system (CNS) and digital computers. Both are hard wired, and information is transmitted as digitally coded electrical signals. But in the nervous system communication at the synapses between the neurones is a graded release of chemical neurotransmitters, which have fast, brief effects on very limited targets. In the past ten years it has been realized that an enormous number of substances are involved in synaptic communication, subtly modulating the transmission process.

Unlike the fast transmitters, most of the neuromodulators are slow acting, long lasting and often work at long range in very complex ways. A new concept of the nervous system is emerging of hard-wired circuits constantly tuned by chemical signals. This modulation gives the nervous system its flexibility and adaptability to long-term changes, both internal and environmental.

The distinction between the fast transmitters and the neuromodulators was explored on 16-17 May at the symposium that inaugurated the Merck, Sharpe and Dohme Neurosciences Research Centre at Terlings Park, Harlow, United Kingdom. Fast transmitters generally open ion channels in the postsynaptic membrane, thus changing the membrane potential. Onset is rapid and duration brief. As well as acetylcholine at the neuromuscular junction, in the CNS the amino acids glutamate and aspartate seem also to be fast excitatory transmitters, whereas gamma-aminobutyric acid and glycine are inhibitory. Modulators, which include the catecholamines noradrenaline, dopamine and serotonin and numerous neuropeptides, act metabolically, like hormones, by activating a chemical second messenger in the postsynaptic cell.

But even this classification is breaking down: it is the postsynaptic receptor that determines the action of a transmitter, not the chemical. Most transmitters have more than one type of receptor; for example acetylcholine has a fast receptor associated with an ion channel and a slow receptor that works through a chemical second messenger. Both can be present on the same cell, so one transmitter can elicit both fast (milliseconds) and slow (seconds or minutes) changes in the membrane potential.

Nor do modulator chemicals all work through the same second messenger. Some alter the activity of adenylyl cyclase which

in turn changes the level of cyclic AMP; others stimulate the breakdown of phosphatidyl inositides (for review see Berridge, M.J. & Irvine, R.F. *Nature* **312**, 315; 1984). Again the pathway is determined by the receptors and several modulators have two types of receptor, one linked to each pathway.

Receptors for neuromodulators may be on any part of the neurone. Modulators interacting with receptors on presynaptic terminals, seem to modulate transmitter release, possibly by altering calcium flux. Other specific actions of neuromodulators include the suppression or enhancement of various postsynaptic ionic currents, which alter the excitability of the postsynaptic membrane (see *Nature News and Views*, 6 June, p. 454). Some of these effects seem to be mediated by cyclic AMP-dependent activation of protein kinases (S. Waalas, Rockefeller; Nestler, E. & Greengard, P. *Nature* **305**, 583; 1983). Protein phosphorylation could also be involved in the control of synaptic vesicle release; in short-term memory by altering synaptic efficacy; and in regulation of gene expression. The resulting changes in protein synthesis underlie long-term memory, by producing permanent changes at synapses, and in regulating receptor density, which might alter a neurone's sensitivity to transmitters.

Many modulators do not seem to be released at typical synapses but as a cloud that diffuses through the extracellular space to targets that may be over 100 μm away. Here again it seems to be the specific location of receptors that determines which cells respond to such 'parasynaptic' diffuse signals (F.O. Schmitt, Massachusetts Institute of Technology), creating order in place of potential chaos. Unless there is a predictable, structurally defined basis to the CNS, precise responses to such imprecise signals cannot be expected.

Modulators interact not only with fast transmitters but also with each other. Some neuropeptides, such as vasoactive intestinal polypeptide (VIP), work partly by increasing neuronal metabolism and possibly also by increasing local blood flow. Based on evidence for amplification of the action of noradrenaline by VIP, F. Bloom (Scripps, La Jolla) proposed that such interaction could produce very precise spatial control of cortical circuits. The mosaic of VIP-containing cells in the cortex may generate a localized, activity-dependent modulation of the global effects of noradrenaline, so regulating activity in single minicolumns of

neurones only 30 μm in diameter.

Although we are beginning to glimpse the complexity of neuromodulator effects at the cellular level, we know even less about the effect of neuromodulators on behaviour. The most dramatic analysis comes from E. Kravitz and his colleagues (Harvard; Kravitz, E. *et al.* in *Model Neural Networks and Behavior*, ed. Selverston, A. Plenum, New York; 1985) on the control of the reciprocal aggressive and submissive postures in the lobster. In the aggressive posture, all the flexors muscles are contracted; in the submissive, the extensors contract. Both postures can be elicited by injections of monoamine. Serotonin produces the aggressive posture, octopamine the submissive. These modulators act both in the periphery and in the CNS. At the neuromuscular junction both have similar actions producing long-lasting increases in transmitter release and enhancing muscle contractility. In the CNS, however, they have opposing effects on specific groups of motor neurones. The neuronal programmes that result in the two postures are hard wired but the readout of the appropriate programme seems to be facilitated by the particular modulator as it raises or lowers the thresholds of the relevant motor neurones (at least). The cellular mechanisms underlying the serotonin effects in the periphery are already being analysed and the central effects could be pursued to the cellular level. What causes the initial changes in modulator concentrations remains an open question.

It is a serious problem for neurobiological research that the subject is studied on a number of different levels, ranging from the molecular constituents of membranes to whole animal behaviour, and it is difficult to access one level from another. The lobster studies are a good example of the power of neuropharmacology to provide a bridge between these levels. In order to understand how neuronal circuits work, it is now necessary to appreciate the way a chemical messenger can cause short or long-term changes in receptors or channels, which in turn can influence a neurone's excitability, change its metabolism, modify transmitter release or affect the synthesis of new proteins, including receptors.

We are only just beginning to understand these processes, but it seems that the ever-increasing list of neuroactive substances and the complexity of their actions may be the unifying factor so far lacking in neurobiology.

Jennifer Altman