Broad minded on narrow spikes

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It is natural to suppose that the longer and larger the action potential that arrives at a chemical synapse, the greater the rise in intracellular Ca^{2+} and the more neurotransmitter that it causes to be released. Just such a mechanism may contribute to the analgesic action of opioids in vertebrates¹ and to behavioural sensitization in *Aplysia*². But on page 636 of this issue³, A. N. Spencer, J. Przysiecki and J. Acosta-Urquidí report that at the neuromuscular junction of the jellyfish *Polyorchis penicillatus* precisely the reverse is true: short action potentials produce a larger postsynaptic event than longer ones. This is not a specialization of simple systems like jellyfish, for the explanation is a general one with implications for nervous systems as complex as those of the insects or mammals.

In 1967, Katz and Miledi⁴ used squid axon giant synapses treated with tetrodotoxin to show that transmitter release depends on the amplitude and duration of the depolarization at the presynaptic terminal. In depolarized squid axons, calcium activation develops so slowly that the rise in internal Ca^{2+} follows much the same course as the increase in potassium conductance⁵. Hence, when Llinás, Steinberg and Walton⁶ reconstructed the events during normal synaptic transmission, they showed that the calcium responsible for transmitter release enters the terminal during the repolarizing phase of the action potential. Accordingly, the slower the rate of repolarization, the greater the calcium influx at the presynaptic terminal and the larger the associated postsynaptic response. This has been confirmed experimentally in vertebrates by Lin and Faber⁷

using synapses on the Mauthner cell of the goldfish.

Prolonged action potentials are not always associated with a greater rise in intracellular Ca^{2+} , however. In molluscan neurons, successive impulses in a train of action potentials grow in duration as a result of the cumulative depression of voltage-dependent potassium currents⁸. Use of the calcium-sensitive dye arsenazo III injected into the giant neurons of *Aplysia* has shown that the action potentials may broaden by as much as 50 per cent with no apparent change in calcium influx⁹. This is because the pronounced shoulder on the falling phase of each of the prolonged action potentials is near 0 mV. Most calcium channels are closed at this voltage in these cells and so the prolongation has little effect on the change in intracellular Ca^{2+} measured by arsenazo.

Compared with *Aplysia*, the position of the calcium activation curve in squid¹⁰ and *Polyorchis*³ is shifted along the voltage axis so that there is a substantial inward current at 0 mV; this is illustrated for the *Polyorchis* motor neuron, (a in the figure) which shows a maximum inward current at about +10 mV. As a result, prolongation is most effective with relatively low amplitude action potentials. This is because the driving force on the calcium ion decreases as the membrane potential approaches the calcium equilibrium potential and, although the calcium channels are open, calcium entry becomes smaller not greater. With a large amplitude action potential it is not until the membrane begins to repolarize that the driving force becomes sufficient to promote calcium entry.

The *Polyorchis* preparation differs from

the squid synapse in that its action potential is sufficiently prolonged for calcium channel inactivation to become significant. In *Polyorchis*, the entire overshoot of the shorter action potential is associated with a near maximum inward calcium current (b in the figure) but the peak of the longer action potential is out of this range (c in the figure) and so there is relatively little calcium entry until the later stages of repolarization. Spencer *et al.* suggest that during the early stages of the action potential many calcium channels are inactivated and become unavailable. As a result, calcium enters the cytoplasm at a low rate and much of it is sequestered by cytoplasmic calcium buffers. With entry and sequestration rates nearly the same, there would be little change in Ca^{2+} and little release of transmitter, just as Spencer *et al.* observe.

Although it seems that the basic mechanism of synaptic transmission may be universal the performance of each synapse, whether from goldfish, squid or jellyfish, depends on the shape of the presynaptic action potential, the voltage dependence and kinetics of the presynaptic calcium channel, and the kinetics of cellular regulation. More preparations are needed to evaluate the influence of these different factors. The *Polyorchis* preparation developed by Spencer and colleagues has the advantage of good electrical access to the synaptic sites and so further dissection of the presynaptic currents may be possible. But it is just one such preparation identified in jellyfish. Others are the neuromuscular synapse of *Aglantha*¹¹, with its dual system of action potentials, and the bidirectional synapse of *Cyanea*¹². Researchers with patrons farsighted enough to support these ventures into the realms of the jellyfish have returned with great bounties. The advantages of using the simple nervous system of the jellyfish for experimentation are more than just travellers' tales. □

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a, Step changes in membrane potential at the presynaptic terminal produce a transient inward calcium current across the terminal membrane. In this representation of data from *Polyorchis* motor neurons³ the peak of the inward calcium current is shown on the horizontal axis with the membrane potential plotted vertically. The range of membrane potentials at which the calcium current is greater than 75 per cent of maximum lies between the dotted lines. In *Aplysia* neurons the relationship between inward calcium current and membrane potential is displaced to more positive voltages (upward in the figure); in squid axons the relationship is displaced downward. b, c Intracellularly recorded action potentials from *Polyorchis*³ showing that the calcium influx is near maximum for almost the entire time that the smaller shorter action potential (b) overshoots 0 mV, whereas the longer action potential (c) enters this range only after a considerable delay.

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