news and views

Suppression of foreign synapses

from Jeremy Brockes

WHEN a foreign nerve is implanted into a normally innervated skeletal muscle, it grows out over the surface of the muscle fibres but does not synapse with them. If, at this juncture, the normal innervation is removed by cutting or crushing the nerve, then the foreign nerve will now form functional synapses on the denervated fibres. The original nerve eventually regenerates and synapses again with the muscle. This results in muscle fibres which have been 'tricked' into accepting innervation from two sources. The subsequent fate of these dually innervated fibres is currently of great interest to neurobiologists, since one can ask the basic question of whether the foreign innervation is recognised, and somehow suppressed or removed in favour of the original. Such a mechanism could be of considerable importance in trying to account for the great specificity and plasticity of connections that is exhibited by the nervous system.

The principal proponents of such a mechanism have been Mark and his colleagues who have provided evidence that in both goldfish eye muscle (Marotte and Mark, *Brain Res.*, **19**, 41, 53; 1970) and adult salamander muscle (Cass *et al.*, *Nature*, **243**, 201; 1973), the foreign innervation can be functionally suppressed. Furthermore, they have claimed that the suppressed synapses are not retracted, but remain on the muscle fibre and appear normal when examined in the electron microscope (Marrotte and Mark, *Brain Res.*, **19**, 53; 1970). The assay for function in the goldfish eye muscle was indirect, involving behavioural testing of the eye movements, and their interpretation of the results is currently controversial since a repetition and extension of these experiments has led to the conclusion that the foreign innervation is not suppressed (Scott, *Science*, **189**, 644; 1975). Meanwhile, in several other situations, including one where the different synapses were formed on a neurone, the dual innervation has proved perfectly stable with no evidence of suppression, even after several months (Frank *et al.*, *Nature*, **247**, 375; 1974 and Purves, *Nature*, **256**, 589; 1975). But in a timely contribution (this issue of *Nature*, page 350), Yip and Dennis have provided clear electrophysiological evidence that suppression does take place in dually innervated fibres of the adult newt. By intracellular recording from individual muscle fibres, they have been able to show that transmitter release from the foreign nerve terminals is reduced as a consequence of re-innervation by the original nerve. Specifically, the amplitude of the synaptic potential decreases during the first two months following re-innervation. The synaptic potential is derived from a number of packets, or quanta, of transmitter that are recruited synchronously by stimulating the nerve. By analysing a number of fibres at different times during the period of suppression, Yip and Dennis have shown that the number of packets recruited (the 'quantal content') declines while the amount of transmitter in a single packet does not change significantly. This is a most important insight into the suppression process, since it characterises it as a presynaptic effect on transmitter release rather than a postsynaptic effect on, for example, the chemosensitivity of the muscle membrane.

An important question, which has yet to be answered, concerns the eventual fate of the suppressed synapses. Are foreign synapses withdrawn from the muscle when the original nerve returns, or do they remain structurally intact but functionally suppressed, as suggested by Mark and his colleagues? When, after six months, the original nerve was interrupted for a second time, Yip and Dennis found that the re-establishment of functional transmission through the foreign nerve appeared to occur more rapidly than after the initial operation. This suggests that the foreign nerve axons remain in relatively intimate contact with the muscle, but does not necessarily mean that foreign synapses are present. In an analogous situation during normal development, it is known that mammalian skeletal muscle fibres are multiply innervated before birth (Redfern, *J. Physiol., Lond.*, **209**, 701; 1970; Bennett and Pettigrew, *J. Physiol., Lond.*, **241**, 515; 9174); when this multiple innervation is eliminated during development, the extra synapses are completed retracted. Although this process is not identical to that observed by Yip and Dennis, it does illustrate that competitive interactions between synapses can lead to the removal of extra innervation.

Meanwhile, one wonders what rules govern the operation of suppression, and why it did not take place in several other situations. Is it, as Yip and Dennis suggest, a question of retaining in the adult newt a faculty which is normally confined to development, or is it perhaps related to the way that foreign and original synapses are distributed along the length of the muscle fibres? It would be interesting to determine whether the foreign nerve in Yip and Dennis's study can become the correct one when the reciprocal experiment is performed in its own muscle. The most helpful insights, however, will probably come from an analysis of the mechanism. One would like to know if the interaction has to occur between synapses that are relatively close (of the order of microns) or whether it can occur over distances of the order of millimetres. If the latter is so, one might suspect that the muscle fibre plays a direct role in the process. An informative experiment could be to take a muscle that is only partially re-innervated by the orginal nerve, and determine if the suppressive influence can act on foreign synapses present on adjacent fibres that were not re-innervated. A second major question, which I have considered above, concerns the effect of the interaction on the anatomy of the suppressed synapses. If we knew the answers to these two questions, then the number of plausible mechanisms would be reduced.

I do not think that we can distinguish these possibilities with the available evidence, but some should be clearly excluded by an anatomical study. Other questions, such as the role of activity in the two nerves, and in the muscle fibre, also seem approachable. This whole problem illustrates the advantage of working on the neuromuscular junction—a preparation with which one can ask a basic question about synaptic function, and hope to answer it at several levels. Furthermore, there is every reason to believe that these answers will prove relevant to the experimentally less accessible situation of synapses in the central nervous system.