Modulation of Transmitter Release

ALTHOUGH it is clear that intercellular communication in the nervous system generally involves the release of chemical transmitter substances from nerve terminals, the mechanisms which may exist for modulating the process of chemical transmission are still obscure. In the past two years, however, several findings have been reported which suggest how the amount of transmitter release at nerve terminals in response to the arrival of nerve impulses may be regulated by the state of ongoing activity at such terminals. In particular, two mechanisms have been proposed to account for the fall-off in the release of noradrenaline from adrenergic nerve terminals during periods of repetitive stimulation.

The first of these mechanisms, proposed by Hedqvist (*Acta Physiol. Scand.* Suppl., 345; 1970), suggests that the release of noradrenaline is controlled by a negative feedback system which involves a local synthesis of prostaglandin E. Sympathetic nerve stimulation or the addition of exogenous noradrenaline has been shown to stimulate the production and release of prostaglandin E from various adrenergically innervated tissues. Furthermore, the exposure of these tissues to exogenous prostaglandin E severely depresses noradrenaline release from the adrenergic terminals, whereas the addition of drugs known to inhibit prostaglandin E synthesis enhances the neurally evoked release of noradrenaline.

A second feedback mechanism, supported by several recent findings (Enero *et al., Brit. J. Pharmacol.*, **44**, 672 ; 1972 ; N. S. Starke, *Archiv. Pharmacol.*, **274**, 18 ; 1972), suggests that noradrenaline may inhibit its own release by an action on α-adrenergic receptors, probably located on the surface of the presynaptic adrenergic terminals. This suggestion is supported by the finding that a variety of α-adrenergic receptor stimulating drugs depress the release of noradrenaline from adrenergic terminals in the heart and other tissues. Conversely, α-adrenergic receptor blocking drugs, such as phenoxybenzamine or phentolamine, enhance the release of noradrenaline from sympathetic terminals in response to nerve stimulation. Both proposed mechanisms thus suggest that the release of noradrenaline from adrenergic terminals is a self-limiting process, which is controlled by local negative feedback mechanisms. Whether those mechanisms are independent, or coupled parts of a single control system, however, has not been clear.

Two new reports throw new light on these problems. Stjärne (*Nature New Biology*, **241**, 190 ; 1973) puts forward evidence which suggests that both of the braking mechanisms described earlier may co-exist in the adrenergic terminals of guinea-pig vas deferens. He studied the stimulus-evoked release of radioactivity from the adrenergic terminals of the isolated vas deferens prelabelled by exposure to radioactive noradrenaline and found that the addition of an inhibitor of prostaglandin synthesis enhances noradrenaline release, whereas low concentrations of prostaglandin E inhibit release. Addition of the α-receptor blocking agent phentolamine, however, after inhibition of prostaglandin synthesis causes a further large increase in noradrenaline release; this suggests the removal of a second braking system capable of operating even when prostaglandin synthesis is inhibited. The α-receptor stimulating drug methoxamine can also inhibit noradrenaline release, after inhibition of prostaglandin synthesis. These results suggest that noradrenaline release, at least from the terminals in guinea-pig vas deferens, is controlled by two different braking systems. Furthermore, these systems do not seem to be interrelated, but to be mediated by different basic mechanisms.

The findings reported by Szerb and Somogyi (*Nature New Biology*, **241**, 121 ; 1973), furthermore, suggest that an "auto-inhibition" mechanism for modulating the amount of transmitter released from nerve terminals may also exist in cholinergic neurones. These authors monitored the release of acetylcholine from slices of rat cerebral cortex exposed to electrical field stimulation, by measuring the outflow of radioactivity from slices preloaded by incubation with tritium-labelled choline. With this recently developed technique acetylcholine release from cortical slices can be measured *in vitro* in the absence of a cholinesterase inhibitor, usually added to prevent the hydrolysis of released acetylcholine. Szerb and Somogyi found that the evoked release of acetylcholine from such slices is inhibited by the addition of an inhibitor of acetylcholinesterase, and a similar inhibi-

Beetles and Archaeology

BEETLES, it seems, can tell one more about ecological conditions in late glacial and post-glacial times than any other group of fossil land animals, and their Quaternary fossil record can be linked very closely with ecological and distributional knowledge of the species today. This was first clearly demonstrated in Britain through the pioneer researches of G. R. Coope, R. G. Pearson and others. Recent archaeological investigations of a site near Doncaster (see page 405 of this issue of *Nature*) indicate that Bronze Age men of about 1,100 BC made extensive clearances in a major oak forest, in which occurred a number of species of beetles no longer part of the British fauna.

These findings of Buckland and Kenward give some hint of the extent to which the original forest fauna of post-glacial Britain has been impoverished through human clearances and exploitation of lowland woods. Such fragments as still remain of deciduous woods, for example, in parts of the New Forest and of Sherwood Forest, are themselves gravely threatened with further faunal impoverishment—there is not one nature reserve in the Sherwood Forest area, and even Denny Wood in the New Forest, which is a nature reserve, has recently been subject to considerable felling in the service of interests other than those of nature conservation. Many more species of woodland beetles, which might provide valuable archaeological evidence, are in imminent danger of extinction in such places.

—From a Correspondent.