# news and views

## Neuropharmacology of peptides

SEVERAL amino acids, such as glutamate, aspartate, glycine and gamma-aminobutyrate, have powerful excitatory or inhibitory effects on neuronal firing in the mammalian central nervous system. Recent findings have shown that certain peptides also have highly specific neuropharmacological actions, and it seems possible that some neurones may release peptides which have a neurotransmitter or modulatory role in the nervous system.

It has been known for some time that neurones in certain regions of the hypothalamus contain and release peptides with important endocrine functions. Thus neurones in the hypothalamus synthesise the hormones vasopressin and oxytocin which are released into the blood stream from the terminals of these cells in the posterior pituitary gland. Nicoll and Barker (*Brain Res.*, **35**, 501; 1971) found that vasopressin exerted potent inhibitory effects on the firing of neurones in the supraoptic nucleus, and suggested that vasopressin might be released by recurrent collateral fibres mediating inhibition of the neurosecretory cells. Vasopressin in low concentrations was also found to cause long lasting changes in pacemaker potential activity in a specific neurosecretory neurone of the land snail *Otala lactea* (Barker and Gainer, *Science*, **184**, 1371; 1974). Other hypothalamic neurones secrete 'releasing factor' peptides into the portal circulation to the anterior pituitary and these peptides represent the final link whereby neural influences control the endocrine activity of this gland.

Recent findings suggest, however, that the neuropharmacological activity of certain hypothalamic releasing factor peptides may not be confined to the endocrine functions of the hypothalamic–pituitary system. The tripeptides TRH (thyrotropin releasing hormone) and MIF (melanocyte inhibitory hormone inhibitory factor) have a wide variety of behavioural effects in man and animals. In animals these peptides potentiate the psychomotor stimulant actions of L-dopa (Plotnikoff *et al.*, *Science*, **178**, 417; 1972) and enhance the behavioural excitation produced by a combination of tranylcypromine and L-tryptophan (Green and Grahame-Smith, *Nature*, **251**, 524; 1974), and accelerate the rate of turnover of noradrenaline and dopamine in the brain (Friedman *et al.*, *Science*, **182**, 831; 1973; Keller *et al.*, *Nature*, **248**, 528; 1974). Several groups have claimed that TRH has transient mood elevating effects in depressed patients and in normal subjects (Prange *et al.*, *Lancet*, **i**, 999; 1972; Tiwary *et al.*, *Lancet*, **ii**, 1086; 1972; Wilson *et al.*, *Lancet*, **ii**, 43; 1973; Wilson *et al.*, *Archs. gen. Psychiatr.*, **29**, 15; 1973). The suggestion that TRH may have a role in controlling neuronal excitability in the central nervous system, apart from its endocrine function, is also supported by the recent report that more than two thirds of the total TRH in rat brain is located in brain regions outside the hypothalamus, with particularly high concentrations in certain septal and preoptic areas (Winokur and Utiger, *Science*, **185**, 265; 1974; Brownstein *et al.*, *Science*, **185**, 267; 1974).

Another peptide with powerful neuropharmacological effects is the undecapeptide substance P, discovered by von Euler and Gaddum in 1931 in extracts of brain and small intestine (*J. Physiol., Lond.*, **72**, 74; 1931). The amino acid sequence of substance P purified from bovine hypothalamus was reported by Chang *et al.* (*Nature*, **232**, 85; 1971) and the synthetic material is now available. In this issue of *Nature* (page 734) Konishi and Otsuka show that substance P has a potent excitatory action on mammalian spinal cord motoneurones. They used an isolated spinal cord preparation from newborn rats, in which substances can be applied to the perfusion fluid in precisely controlled concentrations, and found that substance P was about 200 times more potent than the powerful excitant amino acid L-glutamate in causing a depolarisation of motoneurones. Substance P also facilitated monosynaptic spinal cord reflexes. In previous studies Konishi and Otsuka had shown (*Brain Res.*, **65**, 397; 1974) that substance P and the related peptides physalaemin and eledoisin were potent excitants of motoneurones in frog spinal cord, the latter compounds being 1,500–2,000 times more potent than L-glutamate. Takahashi *et al.* (*Brain Research*, **73**, 59; 1974) also confirmed earlier reports that substance P is present normally in bovine dorsal root nerves, and that its concentration in these sensory nerves was 10–30 times higher than in the ventral root spinal motor nerve. These findings thus strongly support the view that substance P may be selectively concentrated in sensory nerves and that it could function as the transmitter substance released from sensory nerve terminals in the spinal cord, as suggested earlier by Lembeck (for review see Lembeck and Zetler, *Int. Rev. Neurobiol.*, **4**, 159; 1962). Substance P is also present in various regions of the brain, and in brain homogenates the peptide is highly localised in nerve terminal particles, or synaptosomes (Whittaker, *Progr. Biopsys. molec. Biol.*, **15**, 39; 1965). When applied iontophoretically from microelectrodes on to single neurones, in the cerebral cortex or cuneate nucleus, substance P has been found to be a powerful excitant of neuronal firing (Phillis and Limacher, *Expl. Neurol.*, **43**, 414; 1974; Krnjevic and Morris, *Can. J. Physiol. Pharmac.*, **52**, 736; 1974). The latter authors, however, found the actions of substance P to be slow in onset and long-lasting, and suggest that the substance is unlikely to represent the quick acting transmitter released from sensory nerve terminals.

The possibility that 'peptidergic' neurones may exist, releasing peptide neurotransmitter substances, or that peptides may exert other long-term modulatory influences on neuronal function is one to delight the neuropharmacologist and the pharmaceutical industry. With modern techniques of peptide chemistry it should be possible to design and test a large number of structural analogues of the naturally occurring materials, and perhaps to develop peptides with highly selective neuropharmacological actions. For example, it may be possible to dissociate the behavioural and endocrine effects of substances such as TRH and MIF, or to obtain analogues of substance P that will penetrate more readily into the central nervous system from the circulation. If the initial promise is sustained, this seems likely to become an important new area for neuropharmacological research.

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