Fifty years of substance P

from T.M. Jessell

SUBSTANCE P, the doyen of the common peptides[1], is now 50 years old and on the verge of achieving respectability as a neurotransmitter. Yet by comparison with many other peptides of inferior pedigree, the physiological functions of substance P have remained obscure. Some of the reasons for the slow progress are easy to find. Although many of the peripheral actions and chemical properties were established by von Euler and Gaddum, it took 40 years before substance P was eventually isolated and its amino acid sequence determined. But even with the availability of synthetic material, advances in the chemistry of substance P have been disappointingly slow. Simple modifications in the native amino acid sequence did not immediately generate receptor antagonists or more potent agonists. More fundamental perhaps, the behaviour elicited by the central or peripheral application of substance P has been less easily interpretable than, for example, the elevation of pain threshold associated with administration of opioid peptides or the modification of feeding and drinking behaviour elicited by cholecystokinin and angiotensin.

At a recent CIBA Foundation symposium* there were encouraging signs that some of these obstacles have been, or are about to be, overcome. In particular, it is now apparent that modifications of the C-terminal sequence of substance P can generate receptor antagonists, stable agonists and analogues that are selective for substance P receptor subtypes within the central (CNS) and peripheral nervous systems (see Table 1). By substituting d-amino acids at residues 7 and 9, Rosell (Karolinska Institute) and colleagues have synthesized a peptide analogue that antagonizes the spasmogenic activity of substance P on intestinal smooth muscle and the vasodilatory actions on peripheral vessels. At present, effective blockade of substance P responses can be achieved only at relatively high antagonist concentrations (10^{-5} -10^{-4}M) and partial agonist activity has also been observed in some bioassay systems[2]. However, more potent and specific antagonists can now be anticipated and their availability will undoubtedly prove crucial for evaluating many of the postulated physiological functions of substance P.

Attaching a methyl group to the nitrogen atom in the peptide bonds at residues 8 and 9 and deleting the N-terminal tetrapeptide (Lee, Johns Hopkins Medical School) results in an analogue (termed Di Me C7) which is biologically active and completely resistant to degradation by a membrane-bound endopeptidase that inactivates substance P[3]. Whether the endopeptidase isolated by Lee, or any other enzyme for which substance P can act as a substrate, is actually involved in the inactivation of neuronally released substance P is still unclear. It is conceivable that diffusion alone could effectively terminate the actions of substance P. However, injection of Di Me C7 into the ventral tegmental area of rats (Iversen, University of Cambridge) produces a spectrum of behavioural responses that resembles, but greatly outlasts, the response elicited by substance P itself. The prolonged duration of action of Di Me C7 *in vivo* provides the first indication that substance P-inactivating enzymes may in fact function physiologically.

Comparison of the potency of substance P and its analogues on a battery of different bioassay systems is beginning to generate a pattern of activity which may reflect the existence of at least two subclasses of substance P receptors. The clearest demonstration of this derives from studies with the tachykinins, a family of naturally occurring peptides isolated from amphibian skin, which share a common C-terminal amino acid sequence with substance P[4]. For example, substance P is five times more potent than the tachykinin kassinin as a spasmogen in the guinea pig ileum, but is 100–1,000 times less active than kassinin in potentiating the electrically evoked contraction of the rat vas deferens. Iversen and Hanley (MRC Neurochemical Pharmacology Unit) have now extended this analysis to synthetic substance P analogues, including the methyl ester of substance P, which is 10,000 times less active than kassinin on the rat vas deferens but equipotent on the guinea pig ileum[5]. Iversen and Hanley have consequently introduced the terminology SP-P and SP-E receptors to represent these two extremes of biological activity. SP-P receptors predominate in the guinea pig ileum and exhibit greatest selectivity for the methyl ester of substance P and the tachykinin physalaemin. SP-E receptors are present in the rat vas deferens and are activated most potently by the tachykinins eledoisin and kassinin. Synthetic substance P analogues exhibiting specificity for CNS receptors may also exist. Iversen reported that extension of the C-terminal amide group produces an analogue that is ten times more potent than substance P itself in displacing ^{3}H-labelled substance P binding to rat brain membranes but has only one-thousandth its potency on peripheral bioassay systems (Table 1).

The existence of mammalian receptor subtypes that exhibit selectivity for peptides of amphibian or arthropod origin raises the possibility that similar tachykinins may also exist in mammalian species. In fact, Lazarus *et al.* have recently reported low amounts of physalaemin-like peptide in rat brain and intestine[6]. In addition, Keen (University of Bristol) has observed that rat dorsal root ganglia incubated with ^{35}S-methionine can synthesize authentic substance P and also a peptide that is immunoprecipitated by C-terminal- but not N-terminal-specific anti-substance P antisera[7]. Although the identity of this peptide is unknown, these findings suggest that there may be a second

*CIBA Foundation Symposium no.91 'Substance P in the Nervous System', organized by Dr Ruth Porter and chaired by Sir Arnold Burgen, was held at the CIBA Foundation 30 November — 3 December 1981 and followed by a one day meeting organized by the Centre for Neuroscience at University College London.

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100 years ago

NOTES ABOUT SNAKES

A serpent's first instinctive impulse of self-preservation, like that of every other animal, lies in escape; probably a more nervous creature does not exist. If surprised suddenly, or brought to bay at close quarters, it may be too terror-stricken to attempt flight; then it *bites*, following a curious general rule which seems to obtain throughout nearly the whole animal world, from a passionate child downward, no matter what the natural weapons of offence may be. Young *Felidœ* will keep their talons sheathed until they have exerted all possible force with their soft milk-teeth, and a lizard will seize the hand which restrains it with its insignificant little jaws, when its tail or claws might inflict far more injury. The *Boidœ* never use their constrictive powers in self-defence (unless they are gripped), and it seems probable that if a venomous snake's fangs lay in its tail, it would use its teeth *first* when attacked before bringing them into play.

I was walking in the Botanical Gardens of Rio de Janeiro some time ago, when I found myself literally upon an immense green tree-snake, at least nine or ten feet long. This serpent, of course, was harmless, so that there would have been no danger in grasping it; but it emitted a curious sound in its terror, such as I have never heard before or since. It *screamed*, and so loudly, that some people near, who saw nothing of what was going on, thought they heard a child cry. Serpants make all sorts of noises besides hissing, according to their different kinds; Crotali spring their rattles; the carpet-viper (*Echis carinata*) rubs the imbricated scales of its adjacent coils together; the fer-de-lance (*Trigonocephalus lanceolatus*) is said in St. Lucia to give out a series of little taps with its horny extremity; and many others — such as the rat-snake (*Spilotes variabilis*) of South America — certainly indicate their presence when angry by quivering their tails against the ground; but a crying snake would have been a decided novelty in one's collection.

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