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TACHYKININ ANTAGONISTS

Editors
Rolf Håkanson
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Preface

The elucidation of the functional significance of neuropeptides would benefit greatly from access to specific antagonists. Such agents might also prove to have clinical and therapeutic value. So far, antagonists are available for only a few neuropeptides. It is not surprising that antagonists to substance P were amongst the first neuropeptide antagonists to be synthesized. Not only is substance P one of the first neuropeptides to be recognized as such, it is also widely distributed in both the central and peripheral nervous systems and thought to be involved in a number of important physiological processes.

The first antagonists to substance P were developed through the joint efforts of Karl Folkers and Sune Rosell. Their association was initiated in 1977 and culminated with reports of success in 1981. The antagonists rapidly became prominent tools in the study of the mechanisms behind pain, inflammation and gut peristalsis. Since then more than one hundred reports have appeared dealing with various aspects of the substance P antagonists.

Substance P is only one member of a whole family of chemically related peptides, the so-called tachykinins. Tachykinins other than substance P have previously been identified in lower species but recently several different tachykinins have also been demonstrated in mammalian tissues. It was soon realized that antagonists to substance P also antagonized other tachykinins. For these reasons the name tachykinin antagonists is perhaps more appropriate than the name substance P antagonists.

The rapid progress since 1981 seemed to justify a symposium, focussing on the topic of tachykinin antagonists. Originally it was our intention to bring together all scientists connected, however remotely, with this group of agents. This turned out to be impossible, since the number of such people was well over hundred. We therefore had to settle for a meeting on a more limited scale with participants who had made significant contributions to the development of the field. The meeting offered a good look at the current state of knowledge and provided a much desired opportunity to discuss where to go from here.

Tachykinin antagonists have already proved to be useful tools in

neurobiology. Their future use, experimentally and therapeutically, will depend on problem-solving in the following areas:

1) *Potency*. The antagonists so far described have a fairly low potency (pA_2 values in various *in vitro* systems are around 7 or below). In most cases the antagonists have been tested in one system only. Rank order potencies may not apply to other test systems.

2) *Specificity*. Available data suggest that the antagonists tested have a fairly high specificity. The effects of tachykinins and closely related peptides (such as bombesin) are antagonized, whereas responses to other agents are not. This has to be further substantiated.

3) *Selectivity*. Although the antagonists tested so far seem to antagonize the effects of all tachykinins there is preliminary evidence suggesting that antagonists differ in their antagonistic profile, being more effective on one type of tachykinin receptors than on others. This suggests a possibility to design antagonists which are selective for one receptor subtype.

4) *Histamine release*. Substance P and other tachykinins release histamine from mast cells. Many tachykinin antagonists are even more potent than substance P in this respect. From structure-activity studies of a whole range of tachykinin antagonists it appears that the histamine-releasing capacity is not related to the C-terminal tachykinin (or anti-tachykinin) sequence but to the N-terminal sequence, particularly to basic amino acid residues. The histamine-releasing effect limits the usefulness of tachykinin antagonists in experimental as well as therapeutic settings. The effectiveness by which the various SP antagonists release histamine does not parallel their effectiveness as SP antagonists. Conceivably, therefore, it should be possible to design antagonists without histamine-releasing effects or antagonists which are much more potent as antagonists than as histamine-releasing agents.

5) *Local anaesthesia (neurosuppressive action)*. Recent reports have suggested that tachykinin antagonists act as local anaesthetic agents, and that they might be general neurosuppressive agents. There is much experimental evidence indicating that this is not the case. Further studies, no doubt, will clarify the situation.

6) *Neurotoxicity*. The suspicion that tachykinin antagonists are neurotoxic arose from the observation that local application of (D-Pro^2-D-$Trp^{7,9}$)SP in the ventral tegmental area caused nerve cell degeneration. It was also found quite early that intrathecal application resulted not only in analgesia but also in irreversible motor paralysis of the hind limbs, and more recently, that the latter effect reflected necrosis of motor neurons in the ventral horn of the spinal cord. There is some evidence of a neurotoxic effect on neurons in the dorsal horn

as well. These neurotoxic effects are produced at high local concentrations of SP antagonists and there is no evidence that this phenomenon occurs after systemic or local peripheral administration. The mechanisms behind these effects are poorly understood. It still remains to be seen whether the neurotoxic action is related to the antagonistic effect or to some other property of the peptides tested.

Clearly, the tachykinin antagonists represent a new type of drug with interesting properties and with a potential clinical usefulness in relation to e.g. local inflammation and pain suppression.

Rolf Håkanson
Frank Sundler

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