4 Neurotensin and related peptides

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4.1 Introduction

Originally thought to be a vasoactive peptide confined to the hypothalamus (Carraway and Leeman, 1973), neurotensin (NT) has come to be appreciated as a representative of a network of peptides present throughout the animal kingdom in multiple tissues and possessing an impressive pharmacological potential (Carraway and Reinecke, 1984). The various effects demonstrated for NT and its variants suggest roles in a number of basic physiological processes, e.g. blood flow, digestion, temperature regulation and nociception (Leeman and Carraway, 1982; St-Pierre et al., 1985). This may be a reason for the strong evolutionary conservation of the NT family. Here we present an overview of recent developments, focusing on the structural forms, distributions, receptors and potential functions of these peptides in various animals.

4.2 Structural forms

This family of naturally occurring biologically active peptides includes the structures shown in Table 4.1 which are strikingly similar in their C-terminal regions. These peptides share many of the pharmacological properties demonstrated for NT and in each case, structure–function studies indicate a strong dependence on the C-terminal five to six residues. Although less potent, for example, the NT-(9–13) pentapeptide exhibits full intrinsic biological activity in a number of test systems and is also able to displace NT fully from its receptors in tissues (Carraway and Leeman, 1975; Kitabgi et al., 1985).

Phylogenetic studies, performed using region-specific antisera, indicate that the C-terminal portion of NT is also highly conserved in evolution, while the N-terminal portion varies. Using C-terminal
antisera, NT immunoreactivity could be detected in representatives of all animal classes including Coelenterata, Porifera and even Protozoa (Carraway et al., 1982). As shown in Table 4.1, the structures of bovine, canine and human NT are identical, while guinea-pig NT has serine substituted for proline-7 (Hammer et al., 1980). Chicken NT has three substitutions, all located within its N-terminal half and having little effect on its biological abilities. Another peptide isolated from chicken intestine, LANT-6 ([Lys(8),Asn(9)]neurotensin-(8–13)) appears to be an intra-species variant of NT, the mammalian form of which might be neuro- medin N (NMN) originally isolated from porcine spinal cord (Minamino et al., 1984). While these various peptides have similar pharmacological properties, their effects are not always identical. For example, LANT-6 given peripherally promotes hypertension while NT is mainly hypotensive (Carraway and Ferris, 1983) and NMN given centrally is more effective than NT in altering motor activity and less effective in altering temperature (Kalivas, 1985).

Xenopsin (XP, Table 4.1) is another NT-related peptide isolated originally from toxin glands in the skin of the frog, Xenopus laevis (Araki et al., 1973). It exhibits an ability to contract the gastric fundus and inhibit gastric acid secretion, and recent studies indicate that the mammalian counterpart is present within the gastrin-producing G-cells of the dog and human stomach (Rix et al., 1986).

Some NT-related peptides (NRPs) exist primarily in precursor forms which can be processed artificially by the enzyme pepsin (Carraway et al., 1986). One of these peptides, plasma NRP (Table 4.1), is present within an albumin which circulates in mammalian blood at 1–5 µm concentrations (Carraway et al., 1987a) and another, skin NRP, has been isolated from extracts of turkey skin (Carraway et al., 1987b). Both substances share an ability to release histamine from isolated mast cells. A working hypothesis is that NRPs might be generated by the release of acid cathepsins from leucocytes during ischaemic or inflammatory states in order to modulate tissue perfusion.

Recent cDNA work has led to the identification of the canine mRNA sequence coding for NT and to the recognition that a region of the same message codes for NMN (Dobner et al., 1987). Both peptides are surrounded by double basic residues in the 170-amino acid precursor. Other studies indicate tissue-specific transcription of the rat gene giving rise to two distinct mRNAs of 1.0 and 1.5 kilobases (Kislauskis et al., 1988). Both mRNAs appear, however, to code for the same protein, the difference being attributable to the extent of their 3' untranslated regions.

Protein work has verified the existence of a 16–20 kDa precursor in cats (Carraway and Mitra, 1987) and humans (Carraway et al., 1988) which contains a 1:1 molar ratio of NT and NMN as well as a small protein containing only NMN. It is not yet clear whether the smaller protein is a