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Mini-review

Modulatory roles of the NPFF system in pain mechanisms at the spinal level

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ABSTRACT

The possible roles of the NPFF system in pain processing are summarized from the viewpoints of (1) biological activities of NPFF, (2) anatomical distribution of NPFF and its receptor(s) and (3) the regulation of NPFF and receptor(s) in animal models of pain. NPFF and NPFF analogues were found to have analgesic, pronociceptive and morphine modulating activities. Since the isolation of NPFF, several other RF-NH_2 peptides have been identified and some of them were found to have nociceptive or morphine modulating activity. Depending on the pharmacological doses and locations of administration, NPFF may exhibit the biological activities of other structurally related RF-NH_2 peptides thus complicating NPFF bioactivity studies and their interpretation. Acid sensing ion channels were found to respond to RF-NH_2 peptides including NPFF, raising the possibility that interaction of NPFF and acid sensing ion channels can modulate nociceptive activity. NPFF and NPFF receptor mRNAs are highly expressed and localized in the superficial layers of the dorsal cord, the two genes are also in dorsal root ganglia though at much lower level. The spinal NPFF system is up-regulated by peripheral inflammation in the rat. Furthermore, immunohistochemically, NPFF receptor 2-protein was demonstrated to be increased in the primary afferents in the spinal cord of rats with peripheral inflammation. Regulation and localization of spinal NPFF systems, taken together with the analgesic bioactivity of intrathecally administered NPFF, strongly suggest involvement of spinal NPFF system in pain processing.

1. Introduction

During early studies of the opioid peptide met-enkephalin-arg-phe (YGGFMRF), it was observed that, after intracerebroventricular (i.c.v.) injection, analgesic activity was found for YGGFMRF but not for YGGFMRF-NH_2. YGGFMRF-NH_2 can be viewed as a composite of the opioid peptides, YGGFMRF or YGGFM (met-enkephalin), and FMRF-NH_2, a cardioexcitatory peptide of molluscan origin [59]. In the perfused clam recta, YGGFMRF and FMRF-NH_2 exhibited opposite effects [24]. Using an antiserum against FMRF-NH_2 the presence of FMRF-NH_2-like peptide(s), distinct from FMRF-NH_2, was detected in mammalian CNS immunohistochemically [19]. In order to explore the biological role of FMRF-NH_2-like immunoreactive material, especially its possible modulatory role in pain processing and the opioid system, two FMRF-NH_2-like

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Fig. 1 – NPFF precursors in human, bovine, rat and mouse [67]. Arrows indicate the peptides NPFF, NPAF and NPSF and the two N-terminally extended NPFF peptides identified in rat and mouse, respectively (see Table 1).

peptides were isolated from extracts of bovine medulla oblongata, sequenced and biochemically characterized [73].

Since the isolation and characterization of NPFF (FLFQPQRF-NH_2) in 1985, the biological roles suggested for this peptide include pain modulation [23,54,55,62], water balance [33,49,64], food consumption [18,51,52], modulation of opiate mediated effects [52,62,73], cardiovascular actions [27,30,40] and body energy storage and utilization [42]. High affinity NPFF binding sites distinct from opioid receptors were demonstrated in rat spinal cord and brain [2]; furthermore, these receptors were demonstrated to couple to G-proteins [57].

The gene coding for the NPFF precursor protein was cloned by two separate groups in 1997 [58] and 1999 [67]. The NPFF precursor proteins of human, bovine, rat and mouse are shown in Fig. 1. The products generated from the NPFF precursor and actually biochemically identified in tissues of various species are listed in Table 1. The locations of these products in the precursors are indicated by arrows in Fig. 1. The N-terminally extended peptides, NPA-NPFF and SPA-NPFF, are the products generated from the cleavage of consensus processing sites [11] but processing of other peptides listed in Table 1 still remains unclear and to be determined. Interestingly, another novel gene coding for two N-terminal extended RF-NH_2 peptides, VPNLPQRF-NH_2 and SLNFEELKDWGPKNNVIKMSTPAVNKMPHSFANLPLRF-NH_2 was identified by genomic data base searches and cloned in mammals by two groups [26,44]. VPNLPQRF-NH_2, which is identical to NPFF in its C-terminal tetrapeptide sequence, was referred to as RFamide-related peptide 3 (RFRP-3) [26] or NPVF [44]. The peptide, SLNFEELKDWGPKNNVIKMSTPAVNKMPHSFANLPLRF-NH_2, was referred to as RFamide-related peptide 1 (RFRP-1) [26] or NPSF [44]. It should be noted that, in various studies, NPSF has been used to designate two separate peptides SLNFEELKDWGPKNNVIKMSTPAVNKMPHSFANLPLRF-NH_2 derived from the NPVF precursor and SLAAPQRF-NH_2 derived from NPFF precursor. In order to avoid confusion,

Table 1 – Peptides actually identified in tissue extracts of various species and contained in the NPFF precursor

Peptide	Sources
NPFF: FLFQPQRF-NH_2	Boviene spinal cord [48,73], rat spinal cord [5,10,35], mouse spinal cord [10], human CSF [63]
NPA-NPFF: NPAFLFQPQRF-NH_2	Rat spinal cord [10]
SPA-NPFF: SPAFLFQPQRF-NH_2	Mouse spinal cord [11]
NPAF: AGEGLSSPFWSLAAPQRF-NH_2	Bovine spinal cord [73]
NPAF: AGEGLNSQFWSLAAPQRF-NH_2	Human CSF [13]
NPSF: SLAAPQRF-NH_2	Rat spinal cord [10], mouse spinal cord [10], human CSF [13]

Locations of various peptides, listed in the table, in the NPFF precursor are indicated by arrows in Fig. 1.