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News and Reviews

The role of nociceptin and dynorphin in chronic pain: Implications of neuro–glial interaction

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ABSTRACT

Nociceptin-opioid peptide (NOP) receptor, also known as opioid receptor like-1 (ORL1), was identified following the cloning of the kappa-opioid peptide (KOP) receptor, and the characterization of these receptors revealed high homology. The endogenous ligand of NOP, nociceptin (NOC), which shares high homology to dynorphin (DYN), was discovered shortly thereafter, and since then, it has been the subject of several investigations. Despite the many advances in our understanding of the involvement of NOC and DYN systems in pain, tolerance and withdrawal, the precise function of these systems has not been fully characterized. Here, we review the recent literature concerning the distribution of the NOC and DYN systems in the central nervous system and the involvement of these systems in nociceptive transmission, especially under chronic pain conditions. We discuss the use of endogenous and exogenous ligands of NOP and KOP receptors in pain perception, as well as the potential utility of NOP ligands in clinical practice for pain management. We also discuss the modulation of opioid effects by NOC and DYN. We emphasize the important role of neuro–glial interactions in the effects of NOC and DYN, focusing on their presence in neuronal and non-neuronal cells and the changes associated with chronic pain conditions. We also present the dynamics of immune and glial regulation of neuronal functions and the importance of this regulation in the roles of NOC and DYN under conditions of neuropathic pain and in the use of drugs that alter these systems for better control of neuropathic pain.

Contents

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1. Introduction

Despite the many advances in our understanding of the involvement of different neuropeptide systems in pain, the precise function of these systems has not yet been fully characterized. In this review, we provide an examination of the roles of the nociceptin (NOC) and dynorphin (DYN) systems in neuropathic pain. The NOC and DYN systems share many similarities in structure and in their distributions within the CNS and PNS despite belonging to distinct neuropeptide groups. DYN belongs to the classical opioid system, whereas NOC acts similarly to traditional opioids, as it produces membrane hyperpolarization through the opening of potassium channels (Connor et al., 1996; Vaughan and Christie, 1996); however, in contrast to opioids (e.g., DYN), NOC does not act on any classical opioid receptors because of its lack of an N-terminal tyrosine (Meunier et al., 2000; Nothacker et al., 1996; Reinscheid et al., 1995). NOC (Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln), which was previously known as orphanin FQ (OFQ; Reinscheid et al., 1998), is produced from the precursor pronociceptin (PNOC; Boom et al., 1999; Houtani et al., 1996; Lapalu et al., 1997; Meunier et al., 1995) and is an endogenous ligand of the nociceptin-opioid peptide (NOP) receptor, which was previously known as opioid receptor like-1 (ORL1). The prodynorphin (PDYN)-derived peptide, DYN (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln), is the endogenous ligand for the kappa-opioid peptide (KOP) receptor (Bunzow et al., 1994; Danielson and Dores, 1999; Danielson et al., 2001; Dooley et al., 1997; Fukuda et al., 1994; Mollereau et al., 1994, 1999; Nishi et al., 1994; Laughlin et al., 1997; Stevens and Yaksh, 1986; Vanderah et al., 1996).

As has been demonstrated in many studies, the NOC and DYN peptides (in contrast to enkephalins or endomorphins) have dual effects on nociception processes that appear to be highly dependent on the effective peptide concentration. The exogenous application of NOC into the CNS of rodents can induce either pronociceptive or antinociceptive effects depending on the drug dose, route of administration, type of pain stimulus and animal species (Grisel and Mogil, 2000; Mogil and Pasternak, 2001; Yamamoto et al., 1999; more details in Table 1). DYN, which exhibits antinociceptive properties when injected at relatively low doses because of its binding of the KOP receptor, can alternatively produce non-opioid receptor-mediated neurotoxicity, severe, long-lasting motor dysfunction and hyperalgesia after a single intrathecal (i.t.) administration at a higher dose (Laughlin et al., 1997; Stevens and Yaksh, 1986; Vanderah et al., 1996; more details in Table 1). Both peptides may play a physiological role leading to antinociception and/or may induce pathological effects by pronociceptive actions (Chavkin et al., 1982; Inoue et al., 1999; Laughlin et al., 1997; Meunier et al., 1995; Mika et al., 2004; Mogil and Pasternak, 2001; Obara et al., 2005; Reinscheid et al., 1995; Tan-No et al., 2002; Wang et al., 1998; Yamamoto et al., 1999). The biosynthesis and activity of the NOC and DYN systems increase with chronic pain, which indicates their involvement in the development and maintenance of neuropathic pain symptoms. It has been clearly documented that the induction of chronic pain states, especially neuropathy, is associated with upregulation of NOC and DYN biosynthesis (Dubner and Ruda, 1992; Kajander et al., 1990; Malan et al., 2000; Mika et al., 2010; Fig. 1). The enhanced levels of DYN diminish morphine effectiveness in neuropathic pain, which can be restored by intrathecal injection of antiserum against DYN_{1-17}. Whereas the elevation of PDYN mRNA levels in neuropathic pain is responsible for allodynia and hyperalgesia, the involvement of the PNOC system in pain associated with nerve injury is less clear. Many studies have supported the finding that the analgesic effectiveness of the NOC and NOP receptor ligands is increased with neuropathic conditions (Abdulla and Smith, 1998; Bertorelli et al., 1999) and that this effect is associated with the upregulation of NOP receptor mRNA in the spinal cord and dorsal root ganglia DRG (Briscini et al., 2002). The potentiation of morphine effectiveness by NOP antagonists in neuropathic pain has also been reported in many papers (Mika et al., 2004; Obara et al., 2003; Wu et al., 2005). Thus, because of the dichotomy present in NOC

Table 1
A comparison of the effects induced by application of nociceptin and dynorphin on acute pain sensitivity and motor function/activity (ND - no data).

Rout of injection	Nociceptin		Dynorphin	
	pmol/fmol	nmol	pmol/fmol/nmol	<nmol
Subcutaneous	• ND	• No changes in pain sensitivity (Obara et al., 2005)	• Analgesia (Ko et al., 2000)	• No changes in pain sensitivity (Ko et al. 2000)
Intraplantar	• Hyperalgesia (Inoue et al., 1998) • Itch (Andoh et al. 2004)	• No changes in pain sensitivity (Obara et al., 2005)	• Analgesia (Beyer et al., 1997)	• ND
Intrathecal	• Hyperalgesia • Allodynia • Decreased locomotor activity (Hara et al., 1997; Reinscheid et al., 1995; Zhang et al., 1997; Zhu et al., 1998; Bertorelli et al., 1999)	• No changes in pain sensitivity (Courteix et al., 2004; Vanderah et al., 1998; Obara et al., 2005) • Analgesia (Jhamandas et al., 1998; Tian et al., 1997a; Wang et al., 1999a; Xu et al., 1996, 2000)	• Analgesia (Jhamandas et al., 1986; Przewlocki et al., 1983a,b)	• Hyperalgesia • Allodynia • Nociceptive behavior • Motor dysfunction (Tan-No et al. 2002; Laughlin et al. 1997; Vanderah et al. 1996; Stevens and Yaksh 1986)
Intracerebroventricular	• Hyperalgesia • Decreased locomotor activity (Meunier, 1997; Suaudeau et al., 1998; Reinscheid et al., 1995)	• No changes in pain sensitivity (Zhu et al., 1998; Vanderah et al., 1998; Darland et al., 1998; Grisel et al., 1996) • Hyperalgesia (Citterio et al., 2000)	• Analgesia (Kuzmin et al., 2006)	• Motor dysfunction • (Nakazawa et al. 1985)
Into periaqueductal grey	• Hyperalgesia (Wang et al., 1998)	• ND	• No changes in pain sensitivity (Han and Xie, 1984)	• No changes in pain sensitivity (Han and Xie, 1984)
Receptor involvement	• NOP receptor (Inoue et al., 1998, 1999)	• NOP receptor (Inoue et al., 1998, 1999)	• KOP receptor (Chavkin et al., 1982)	• NMDA receptor (Laughlin et al., 1997; Vanderah et al., 1996) • Bradykinin receptor (Lai et al., 2008)