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Review

Spinal mechanisms of NPY analgesia

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ABSTRACT

We review previously published data, and present some new data, indicating that spinal application of neuropeptide Y (NPY) reduces behavioral and neurophysiological signs of acute and chronic pain. In models of acute pain, early behavioral studies showed that spinal (intrathecal) administration of NPY and Y2 receptor agonists decrease thermal nociception. Subsequent neurophysiological studies indicated that Y2-mediated inhibition of excitatory neurotransmitter release from primary afferent terminals in the *substantia gelatinosa* may contribute to the antinociceptive actions of NPY. As with acute pain, NPY reduced behavioral signs of inflammatory pain such as mechanical allodynia and thermal hyperalgesia; however, receptor antagonist studies indicate an important contribution of spinal Y1 rather than Y2 receptors. Interestingly, Y1 agonists suppress inhibitory synaptic events in dorsal horn neurons (indeed, well known μ-opioid analgesic drugs produce similar cellular actions). To resolve the behavioral and neurophysiological data, we propose that NPY/Y1 inhibits the spinal release of inhibitory neurotransmitters (GABA and glycine) onto inhibitory neurons, e.g. disinhibition of pain inhibition, resulting in hyporeflexia. The above mechanisms of Y1- and Y2-mediated analgesia may also operate in the setting of peripheral nerve injury, and new data indicate that NPY dose-dependently inhibits behavioral signs of neuropathic pain. Indeed, neurophysiological studies indicate that Y2-mediated inhibition of Ca^{2+} channel currents in dorsal root ganglion neurons is actually increased after axotomy. We conclude that spinal delivery of Y1 agonists may be of use in the treatment of chronic inflammatory pain, and that the use of Y1 and Y2 agonists in neuropathic pain warrants further consideration.

Contents

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1. Introduction

Normally, a noxious stimulus elicits a constellation of coordinated responses to prevent or minimize tissue damage. The signaling system for acute pain includes behavioral withdrawal from the threatening stimulus, as well as hormonal and autonomic activation [42,56]. Aspirin, acetaminophen, anti-inflammatory drugs, such as ibuprofen, and opioids such as morphine are quite effective in reducing these responses. Much more difficult, however, is the treatment of pathological (chronic) pain, a major complication associated with tissue or neuronal injury. Clinical examples include migraine, severe back pain, chronic widespread pain, fibromyalgia, and neuropathic pain, all of which reduce the patient's ability to work, walk, or sleep [27,67]. Over the past two decades, the development of animal models of arthritic and neuropathic pain, and changes in gene expression associated with these models, has led to an explosion of research on the pathophysiological neural changes underlying chronic pain [12]. Changes in the gene expression of peptidergic neurotransmitters and receptors at the level of the primary afferent neuron, spinal cord dorsal horn, and brain are thought to take an injured individual from a state of acute pain to one of chronic pain [27]. Key candidates include neuropeptide Y and the NPY Y1 receptor [24,57,73,74]. Both are highly expressed at key sites of pain transmission, including lamina II of the spinal cord dorsal horn [5,18,31,39,40], and tissue or nerve injury dramatically alters their expression profiles. These anatomical findings underline the importance of the NPY system in the development of pathological pain. This review describes behavioral actions of NPY agonists in animal models of acute and chronic pain, and seeks to explain the effects of NPY administration *in vivo* in terms of recent *in vitro* neurophysiological studies [3,43,44].

2. NPY in animal models of acute pain

As described in detail below, behavioral studies show that intrathecal administration of NPY Y2 receptor agonists inhibits acute nociception [26]. This may be explained in terms of the electrophysiological observation that Y2-agonists reduce the release of excitatory transmitters from primary afferent fibers in lamina II of the dorsal horn in a manner similar to μ-opioids [44].

2.1. *Behavioral pharmacology of acute thermal pain*

The majority of studies in awake rodents indicate that intrathecal administration of NPY Y2 receptor agonists reduces behavioral responsiveness to noxious heat [26,55]. As illustrated in Fig. 1A and B, we found that intrathecal NPY dose-dependently increased hotplate latency, similar to conventional analgesic drugs, such as morphine. These effects of NPY are not likely secondary to nonspecific behavioral effects, since even the maximal antinociceptive dose of NPY (30 μg) does not disrupt motor coordination [55]. Furthermore, intrathecal NPY profoundly decreases the nociceptive flexor reflex in anesthetized rats (although lower doses of NPY increase the flexor reflex [71], such pronociceptive effects have not been reported in awake animals). Using several NPY fragments with varying affinities for NPY receptor subtypes, Hua et al. suggested that agonists at Y2 receptors, rather than Y1 receptors, inhibit the spinal processing of noxious heat stimuli [26].

2.2. *Neurophysiological mechanisms of spinal Y2 analgesia*

As illustrated in Fig. 2A, we propose that the neurophysiological mechanism of Y2 antinociception involves inhibition of pronociceptive, excitatory neurotransmitter release from primary afferent neurons. This conclusion is based on a comparison of the spinal actions of morphine, NPY and Y1 and Y2 agonists.

Fig. 1C illustrates "classical" μ-opioid attenuation of a primary afferent, glutamatergic EPSC evoked in a *substantia gelatinosa* (lamina II) neuron by stimulation of the dorsal root entry zone. Fig 1D illustrates that NPY attenuates these EPSCs in a very similar fashion to DAMGO. This effect of NPY was seen in 17/24 cells tested. Fig. 1E illustrates the use of a paired-pulse protocol to test whether the effects of NPY are exerted pre- or postsynaptically. When two EPSCs are evoked in rapid succession, a variety of presynaptic processes conspire to affect the ratio of the second to the first response. These include depletion of readily-available transmitter stores and accumulation of submembrane Ca^{2+} [79]. If the actions of NPY are purely postsynaptic, the ratio of the amplitude $EPSC_2$:$EPSC_1$ should not change; both should be suppressed to the same extent. However, Fig. 1E shows a reduction in the $EPSC_2$:$EPSC_1$ ratio in the presence of NPY suggesting that it