

Opioid Modulatory Effects of the Spinal Neuropeptide Y System

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Abstract

The μ -opioid receptor (MOR) is the principal target of opioid analgesia, but its effects in the spinal dorsal horn (SDH) depend on the neuronal population in which it is engaged. MOR activation in primary afferent terminals or excitatory interneurons suppresses nociceptive transmission, whereas MOR activation in inhibitory interneurons can weaken endogenous sensory gating via circuit disinhibition. Neuropeptide Y (NPY) and the neuropeptide Y receptor Y1 (NPY1R) form a spinal inhibitory system that constrains excitatory pain- and itch-related circuits. Recent studies have further positioned MOR signaling within this NPY–NPY1R gate: MOR activation in NPY1R⁺ excitatory neurons contributes to morphine analgesia, whereas MOR activation in NPY⁺ inhibitory interneurons weakens inhibitory control, thereby limiting analgesic efficacy. In parallel, MOR-mediated suppression of NPY⁺ interneurons disinhibits gastrin-releasing peptide (GRP)–gastrin-releasing peptide receptor (GRPR)-related itch pathways, thereby promoting opioid-induced itch. In this review, we integrate recent studies on spinal MOR, NPY–NPY1R, and GRP–GRPR signaling and propose a circuit framework in which the therapeutic and sensory effects of spinal opioids are shaped by the balance between direct inhibition of excitatory neurons and disinhibition resulting from suppression of inhibitory interneurons.

Keywords: neuropeptide Y; neuropeptide Y receptor Y1; μ -opioid receptor; morphine; spinal dorsal horn; opioid-induced itch; pain; disinhibition

Introduction

Although opioids remain highly effective analgesics for moderate to severe pain, their clinical utility is limited by tolerance, opioid-induced hyperalgesia (OIH), respiratory depression, constipation, and itch^[1,2]. Morphine

and related opioids produce analgesia primarily through μ -opioid receptor (MOR)-dependent signaling^[2–4]. At the cellular level, MOR activation generally reduces neuronal excitability and suppresses neurotransmitter release through inhibitory guanine nucleotide-binding regulatory protein (Gi/o)-coupled mechanisms^[2]. However,

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the behavioral consequence of MOR activation is determined not only by its intracellular signaling, but also by the neuronal identity and the circuit position of the MOR-expressing neuron^[5]. Recent genetic studies have demonstrated that MOR expressed in distinct neuronal populations makes non-equivalent contributions to both opioid analgesia and opioid-induced adverse effects, highlighting the importance of neuronal identity in determining opioid actions^[6,7]. Likewise, disruption of central serotonergic circuits selectively impairs opioid analgesia without affecting morphine tolerance or reward, further supporting the concept that opioid efficacy depends on the organization of pain-modulating neural circuits rather than receptor activation alone^[8]. In the spinal dorsal horn (SDH), MOR is distributed across multiple neuronal compartments, including primary afferent terminals, excitatory interneurons, and inhibitory interneurons^[9,10]. Within primary sensory neurons, opioid receptor subtypes are organized in a cell-type-specific manner. MOR is predominantly expressed in peptidergic nociceptors, whereas delta opioid receptor (DOR) is enriched in myelinated and non-peptidergic afferents. This anatomical segregation is accompanied by distinct functional roles: MOR preferentially regulates heat pain, and DOR predominantly contributes to mechanical pain^[11]. These findings demonstrate that receptor localization across distinct sensory neuron populations is directly linked to modality-specific opioid control of nociception. Consequently, MOR activation in primary afferent terminals or excitatory interneurons suppresses nociceptive transmission and promotes analgesia^[5], whereas activation of MOR on inhibitory interneurons weakens endogenous inhibition and produces circuit disinhibition^[12,13].

This distinction is particularly important in persistent pain, where injury and inflammation reshape dorsal horn excitability and alter the functional contribution of receptor-defined neuronal populations. Beyond acute analgesia, recent studies further indicate that both endogenous opioid antinociception and chronic opioid adaptations, including OIH and analgesic tolerance, are mediated through defined MOR-dependent neural circuits, emphasizing the circuit-specific nature of opioid actions^[14,15]. In addition to circuit organization, MOR signaling is also shaped by interactions with endogenous modulatory systems. For example, programmed

cell death protein 1 (PD-1) signaling has been shown to facilitate opioid antinociception by cooperating with MOR, suggesting that opioid efficacy can be shaped by receptor crosstalk beyond canonical opioid pathways^[16]. Similar observations from neuropeptide FF (NPFF) signaling further support the view that opioid efficacy can be shaped by interactions with parallel neuromodulatory pathways^[17,18]. These findings suggest that opioid efficacy is determined not only by MOR activation itself but also by the molecular and circuit context in which MOR signaling is engaged.

Consistent with this view, peripheral nerve injury can sensitize MOR-expressing dorsal horn interneurons, indicating that the contribution of spinal MOR⁺ neurons is state dependent^[19]. Against this background, the spinal neuropeptide Y–neuropeptide Y Y1 receptor (NPY–NPY1R) inhibitory gate provides a mechanistically defined circuit through which the diverse actions of MOR can be interpreted. This review focuses on how MOR engagement of the spinal NPY–NPY1R gate contributes to opioid analgesia and how disruption of this inhibitory gate may participate in opioid tolerance, OIH, and opioid-induced itch under specific cellular or pathological conditions (Fig. 1)^[20,21].

The spinal NPY–NPY1R inhibitory gate in pain and itch circuits

In the SDH, NPY signaling functions as an inhibitory peptidergic system that dampens excitatory sensory processing. NPY receptors are generally Gi/o-coupled and can reduce neuronal excitability or transmitter release by inhibiting cyclic adenosine monophosphate (cAMP) production and calcium entry and promoting membrane hyperpolarization^[22,23]. Among these receptors, NPY1R has particular circuit significance because it is expressed by dorsal horn interneurons involved in excitatory sensory transmission^[24]. By contrast, Y2 receptors are more closely associated with primary sensory neurons and their central terminals, suggesting a more afferent or presynaptic mode of modulation^[22,25].

At the cellular level, this gate is organized by inhibitory NPY⁺ interneurons and NPY1R⁺ excitatory interneurons. NPY⁺ neurons are distributed across laminae I–IV of the dorsal horn, and those located in the superficial dorsal

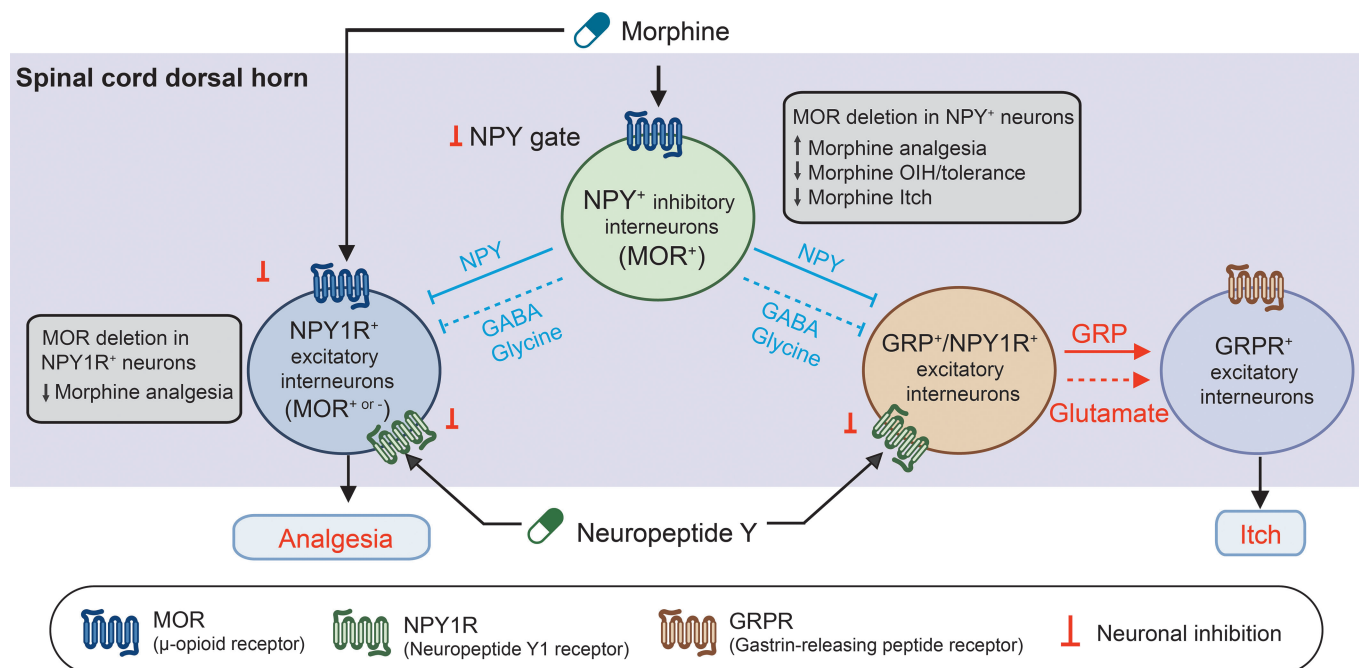


Figure 1: Spinal neuropeptide Y–neuropeptide Y1 receptor (NPY–NPY1R) circuitry in opioid analgesia and side effects.

Morphine exerts opposing actions within the spinal NPY–NPY1R circuit. MOR activation in NPY1R⁺ excitatory interneurons directly suppresses their activity and contributes to analgesia, whereas MOR activation in NPY⁺ inhibitory interneurons weakens inhibitory control over downstream excitatory circuits. In the pain pathway, the net analgesic effect of spinal morphine reflects the balance between direct inhibition of NPY1R⁺ excitatory neurons and disinhibition resulting from suppression of NPY⁺ inhibitory interneurons. Consistent with this model, deletion of MOR from NPY⁺ neurons enhances morphine analgesia, attenuates OIH, and delays morphine tolerance, whereas deletion of MOR from NPY1R⁺ neurons reduces morphine analgesia. In the itch pathway, morphine-induced inhibition of NPY⁺ interneurons is proposed to disinhibit GRP-related excitatory neurons, a subset of which may express NPY1R, thereby facilitating GRP–GRPR signaling and opioid-induced itch. In contrast, NPY suppresses downstream excitatory interneurons through NPY1R activation, thereby reducing nociceptive and itch-related transmission.

Abbreviations: NPY, neuropeptide Y; MOR, μ-opioid receptor; NPY1R, neuropeptide Y receptor Y1; GABA, γ-aminobutyric acid; OIH, opioid-induced hyperalgesia; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor.

horn (laminae I–III) are predominantly γ-aminobutyric acid (GABA)-expressing inhibitory interneurons^[26,27]. These interneurons receive both low-threshold mechanoreceptive and nociceptive inputs, and have been implicated in the modulation of inflammatory and neuropathic pain^[28,29]. Consistent with their inhibitory role, NPY-containing boutons innervate nociceptive projection neurons as well as several classes of excitatory interneurons within the dorsal horn, including protein kinase Cγ-positive (PKCγ⁺), neurokinin-1 receptor-positive (NK1R⁺), and other excitatory populations implicated in pain and itch processing^[30,31]. In parallel, NPY1R⁺ neurons are concentrated in the superficial dorsal horn and are enriched among excitatory interneuron populations in laminae I–II^[32,33]. Molecular profiling studies have shown that NPY1R⁺ neurons comprise multiple excitatory subpopulations, including somatostatin⁺ and gastrin-releasing peptide (GRP)⁺ interneurons^[34,35].

Functional studies in pathological pain models support this circuit organization. Loss of NPY1R signaling enhances pain sensitivity and prevents NPY-induced analgesia^[36], whereas pharmacological activation of spinal NPY1R reduces hypersensitivity in inflammatory, neuropathic, and postsurgical pain models^[29,37,38]. In neuropathic pain, NPY1R⁺ neurons become more excitable and can drive mechanical and cold hypersensitivity; their activation promotes pain-like behavior, whereas their inhibition reduces hypersensitivity^[37]. Furthermore, GRP/NPY1R-positive neurons define a pain-relevant excitatory subpopulation required for NPY-mediated relief of neuropathic hypersensitivity^[24]. Taken together, these studies support the view that NPY attenuates nociceptive transmission by constraining excitatory NPY1R⁺ interneurons^[34].

A similar inhibitory architecture also contributes to

spinal itch regulation. NPY⁺ inhibitory interneurons suppress mechanical itch, whereas NPY1R⁺ excitatory neurons contribute to light touch-evoked itch transmission^[28,39]. Chemogenetic activation of NPY⁺ inhibitory interneurons reduces behavioral responses associated with acute pain, inflammatory pain, neuropathic pain, and pruritogen-evoked itch, whereas silencing these neurons exaggerates itch responses in a gastrin-releasing peptide receptor (GRPR)-dependent manner^[38]. Although the strongest evidence links the NPY–NPY1R system to mechanical itch, NPY1R activation can also reduce histaminergic itch^[40], and activation of NPY⁺ interneurons suppresses chloroquine-evoked non-histaminergic itch^[38]. Importantly, NPY⁺ neuron-mediated inhibition extends beyond NPY–NPY1R peptidergic signaling. NPY⁺ dorsal horn interneurons engage both fast inhibitory neurotransmission and NPY-mediated peptidergic signaling; thus, cell type-specific manipulation of these neurons reflects their integrated inhibitory output, whereas exogenous NPY administration and pharmacological or genetic manipulation of NPY1R more selectively interrogate the peptidergic component of this inhibitory system.

At the postsynaptic level, NPY1R⁺ excitatory interneurons are themselves heterogeneous, comprising multiple molecularly distinct populations, including gastrin-releasing peptide gene (*Grp*⁺)/neuropeptide Y receptor Y1 gene (*Npy1r*⁺), neuropeptide FF gene (*Npff*⁺)/*Npy1r*⁺, and cholecystokinin gene (*Cck*⁺)/*Npy1r*⁺ neurons^[24]. Consistent with the functional heterogeneity of NPY1R⁺ interneurons, NPY1R signaling has been implicated in neuropathic pain, mechanical hypersensitivity, and itch-related sensory processing^[34,39,41]. Among these populations, *Grp*⁺/*Npy1r*⁺ neurons have attracted particular attention because they are required for NPY-mediated relief of neuropathic hypersensitivity and are conserved across mice, nonhuman primates, and humans^[24]. Given the established role of GRP–GRPR signaling in dorsal horn sensory transmission^[42–44], the overlap between NPY1R and GRP-related populations further supports the integration of NPY signaling into excitatory sensory-processing circuits. These observations highlight the functional diversity of NPY1R-expressing excitatory circuits and suggest that different NPY1R⁺ subpopulations may contribute to distinct aspects of sensory processing^[34]. Taken together, these findings establish

the NPY–NPY1R system as a major inhibitory gate that constrains excitatory dorsal horn circuits. This circuit organization provides the framework for understanding how MOR signaling interacts with the NPY–NPY1R gate.

MOR–NPY1R interactions in spinal opioid analgesia

Previous pharmacological studies have shown that NPY signaling can facilitate opioid analgesia, with NPY administration enhancing morphine antinociception, and NPY1R blockade attenuating opioid analgesic responses^[21,45,46]. Although the magnitude of this interaction varies across anatomical sites and experimental conditions, these findings provide evidence for functional coupling between NPY and MOR-dependent analgesic pathways.

Recent studies defining the spinal NPY–NPY1R microcircuit have provided a cellular framework for understanding how NPY signaling modulates opioid analgesia. Within the dorsal horn, *Oprm1*, the gene encoding MOR, is expressed in both NPY⁺ inhibitory interneurons and NPY1R⁺ excitatory neurons^[12,21,38]. Cell-type-specific genetic studies have provided direct evidence that MOR signaling exerts distinct functions in the NPY–NPY1R microcircuit. Conditional deletion of MOR from NPY⁺ neurons enhances morphine antinociception in inflammatory and formalin pain models, whereas deletion of MOR from spinal NPY1R⁺ neurons diminishes morphine analgesia^[21]. These opposing behavioral phenotypes indicate that MOR activation in NPY1R⁺ excitatory neurons contributes directly to opioid analgesia, whereas MOR signaling in NPY⁺ inhibitory interneurons may weaken their inhibitory output, which encompasses both fast GABA/glycine-mediated transmission and NPY-dependent peptidergic signaling. Importantly, blockade of NPY1R attenuates the enhanced morphine analgesia observed after MOR deletion from NPY⁺ neurons, supporting a contribution of endogenous NPY–NPY1R signaling to this effect^[21]. Consistent with these findings, co-administration of NPY and morphine produces synergistic analgesia in inflammatory and formalin pain models, and this interaction depends on intact NPY1R signaling^[21]. Taken together, these pharmacological and genetic findings support a functional contribution of endogenous NPY–NPY1R signaling to the regulation of morphine analgesia within the dorsal horn^[21].

Additional mechanistic evidence is provided by electrophysiological and latent sensitization studies. Electrophysiological recordings revealed that both NPY⁺ and NPY1R⁺ neurons exhibit increased excitability following complete Freund's adjuvant (CFA)-induced inflammation^[21]. These findings indicate that both components of the NPY–NPY1R circuit undergo activity-dependent plasticity during inflammatory pain. Morphine suppresses both NPY⁺ and NPY1R⁺ neurons through MOR-dependent mechanisms^[21]. In addition, inhibition of MOR-expressing NPY⁺ inhibitory interneurons reduces inhibitory synaptic input onto downstream NPY1R⁺ neurons^[21]. These findings indicate that opioid signaling can influence NPY1R⁺ neuronal activity through both direct inhibition and indirect modulation of inhibitory synaptic input^[21]. Complementing these findings, studies of latent sensitization following surgical incision have revealed a potent endogenous synergy between MOR and NPY1R signaling within dorsal horn interneurons^[47]. After recovery from injury, ongoing MOR–NPY1R cooperation suppresses latent postoperative hypersensitivity and ongoing pain, suggesting that endogenous opioid and NPY signaling jointly contribute to the sustained suppression of latent sensitization^[47]. Taken together, these observations support a model in which MOR and NPY1R signaling interact within the SDH to regulate both acute opioid analgesia and longer-lasting suppression of pain sensitization.

Despite this convergent evidence, NPY–opioid interactions are not uniform across the nervous system. Intracerebroventricular NPY does not necessarily modify morphine discrimination or acute thermal antinociception^[45], whereas NPY signaling in descending pain-modulatory regions can interact with opioid-sensitive mechanisms under neuropathic conditions^[48]. Supraspinal interactions have also been reported for morphine-induced thermal analgesia^[46]. These findings suggest that NPY–opioid interactions vary across the nervous system and therefore should not be generalized from one assay or anatomical site to another. Within the superficial dorsal horn, where NPY1R-expressing excitatory neurons constitute an important component of pathological pain circuits^[22,24,37,49–51], NPY–opioid cooperation appears to be most prominent when injury, inflammation, or recovery states recruit endogenous NPY signaling^[46,47,51,52]. In contrast, studies conducted in

other anatomical regions or behavioral paradigms have reported weaker or variable effects of NPY signaling on opioid responses, highlighting the circuit-dependent nature of NPY–opioid interactions^[24,45,53–59].

Extension of the NPY–MOR gate to opioid tolerance and hyperalgesia

Beyond its role in opioid analgesia, NPY signaling has also been implicated in opioid tolerance and OIH. These phenomena represent maladaptive consequences of repeated or intense opioid exposure and are associated with enhanced excitability within pain-processing circuits. Given the inhibitory role of NPY signaling in spinal and supraspinal pain pathways, several studies have examined whether alterations in NPY-dependent inhibition contribute to the development of opioid tolerance and OIH.

Multiple lines of spinal evidence support a role for NPY signaling in the regulation of OIH and opioid tolerance. Exogenous NPY attenuates [D-Ala², N-MePhe⁴, Gly-ol]-enkephalin (DAMGO)-induced mechanical hyperalgesia, and activation of NPY⁺ neurons or inhibition of NPY1R⁺ neurons similarly reduces OIH^[21]. Conversely, selective deletion of MOR from NPY⁺ neurons prevents DAMGO-induced OIH and delays morphine tolerance, indicating that MOR signaling in this inhibitory population contributes to the development of OIH and opioid tolerance^[21]. In chronic intrathecal morphine paradigms, NPY co-administration also delays the onset of tolerance and mechanical hypersensitivity^[21]. Consistent with these observations, recent studies demonstrated that deletion of peripheral MORs or MOR-expressing sensory neurons attenuates thermal tolerance but does not prevent mechanical OIH or anti-allodynic tolerance, indicating that these maladaptive responses are predominantly mediated by central rather than peripheral opioid circuits^[60].

Supraspinal studies provide complementary evidence that NPY signaling modulates chronic opioid responses. In neuropathic rats, intracerebroventricular NPY or NPY1R/neuropeptide Y receptor Y5 (NPY5R) agonist prevented the development of morphine tolerance and withdrawal-associated hyperalgesia, whereas NPY1R antagonism promoted hyperalgesia and weakened

morphine antinociception^[46]. Taken together, these findings indicate that NPY signaling influences chronic opioid responses at both spinal and supraspinal levels.

Previous studies have shown increased NPY expression and enhanced functional engagement of NPY signaling in several pathological pain states^[51,52,61,62]. The finding that MOR deletion from NPY⁺ neurons prevents OIH and delays opioid tolerance raises the possibility that MOR-mediated inhibition of these interneurons weakens their inhibitory output, thereby facilitating sensitization of downstream dorsal horn circuits^[21]. Given that enhancement of NPY signaling attenuates OIH and delays opioid tolerance in both spinal and supraspinal paradigms^[21,46], NPY–NPY1R signaling may represent one component of this protective inhibitory mechanism. Collectively, current evidence identifies the NPY–NPY1R system as an important regulator of opioid tolerance and OIH.

NPY-dependent gating of GRP–GRPR circuits in opioid-induced itch

In addition to shaping opioid analgesia, tolerance, and hyperalgesia, NPY-dependent inhibitory gating may also influence opioid-induced itch, a distinct sensory complication that can be rapidly triggered by spinal opioid administration. Clinically, pruritus is particularly prominent after neuraxial opioid administration^[63,64]. Mechanistically, opioid-induced itch appears to follow a disinhibitory principle: MOR activation suppresses inhibitory interneurons that normally restrain excitatory itch-transmission circuits.

The GRP–GRPR pathway provides a central excitatory axis for spinal itch transmission and has also been implicated in opioid-induced itch^[42–44]. GRPR⁺ dorsal horn neurons are required for opioid-induced itch^[12,65], and more recent evidence indicates that GRP⁺ excitatory interneurons and GRP itself are also necessary components of morphine-induced scratching^[20]. Taken together, these findings position GRP⁺ neurons and downstream GRPR⁺ neurons as a key excitatory pathway through which spinal opioids evoke itch.

However, GRPR⁺ neurons may not be the primary cellular site at which morphine initiates itch. RNAscope®

and single-cell analysis indicate limited co-localization between *Oprm1* and *Grpr* in the SDH^[12,35], suggesting that MOR activation engages the GRP–GRPR pathway indirectly through upstream opioid-sensitive interneurons. Consistent with this view, inhibitory interneuron populations have emerged as important substrates for opioid-induced itch^[12]. MOR signaling in dynorphin⁺ neurons can promote itch by disinhibiting downstream *Oprkl*⁺ (κ -opioid receptor-expressing) neurons, a population that overlaps with GRPR⁺ neurons in the spinal cord^[66,67]. MOR is also expressed in NPY⁺ dorsal horn neurons, and intrathecal NPY strongly suppresses morphine-induced itch^[12]. These observations suggest that opioid-induced itch arises from MOR-mediated disruption of inhibitory gates that converge on excitatory itch-transmission pathways.

A key issue is how opioid-sensitive inhibitory interneurons are linked to GRP–GRPR-dependent itch transmission. Although dynorphin/*Oprkl*-related disinhibition provides one route for opioid-evoked itch, the requirement for GRP⁺ neurons, GRP, and GRPR signaling suggests that upstream inhibitory circuits regulating GRP-related excitatory neurons are also likely to be involved^[20,68]. NPY⁺ inhibitory interneurons provide one such link. NPY1R⁺ interneurons receive synaptic input from NPY⁺ interneurons^[39], and the co-expression of NPY1R with GRP in the superficial dorsal horn suggests that a subset of GRP-related excitatory neurons may be subject to NPY1R-mediated inhibition^[20,24]. Functional evidence further indicates that NPY can reduce the excitability of GRP⁺ neurons, whereas morphine decreases inhibitory synaptic input onto these cells^[20]. These observations support a model in which MOR-mediated suppression of NPY⁺ interneurons releases GRP⁺ itch-transmission neurons from inhibitory control.

Exogenous NPY suppresses opioid-induced itch through NPY1R-dependent mechanisms, potentially by restoring inhibitory control over GRP-related excitatory populations, a subset of which may express NPY1R. In this framework, morphine-induced itch is not simply a direct excitation of the GRP–GRPR pathway; rather, it may involve opioid-mediated weakening of an upstream NPY⁺ neuron-mediated inhibitory gate that normally restrains GRP-related excitatory output.

Future directions and therapeutic implications

Studies on the modulation of opioid signaling by the spinal NPY system have provided a new conceptual perspective for understanding opioid analgesia, tolerance, hyperalgesia, and itch at the spinal level. These seemingly distinct sensory and pharmacological effects may, at least in part, be regulated by a shared mechanism of cell type-specific inhibitory gating. However, it is still unclear whether NPY1R⁺ neurons overlap with GRPR⁺ neurons, whether GRP/NPY1R double-positive neurons are commonly engaged by mechanical itch, chemical itch, opioid-induced itch, and neuropathic hypersensitivity, or whether these sensory states recruit partially distinct excitatory subpopulations.

Beyond anatomical and functional connectivity, the mode by which NPY⁺ neurons inhibit their downstream targets also requires further investigation. Although NPY⁺ neurons are generally classified as inhibitory neurons, their output may include both fast GABA/glycine-mediated synaptic inhibition and slower peptidergic inhibition mediated by NPY–NPY1R signaling. Distinguishing between these two forms of inhibition is particularly important for understanding opioid-induced sensory modulation, because MOR activation may suppress not only classical neurotransmitter release but also neuropeptide release. However, neuronal firing does not necessarily translate into peptide release in a simple linear manner. Future studies therefore need to directly determine how endogenous NPY release is regulated during pain states and opioid exposure, including whether it depends on sustained or high-frequency neuronal activity, whether it is altered under inflammatory or neuropathic conditions, and whether MOR activation suppresses NPY release in parallel with GABA/glycine release. Resolving this question will require experimentally separating classical transmitter release from peptide release in NPY⁺ interneurons. Future studies could combine cell type-specific manipulation of NPY⁺ neurons with direct measurements of NPY release and electrophysiological assessment of fast inhibitory synaptic transmission onto identified downstream neurons. Selective pharmacological or genetic disruption of NPY–NPY1R signaling while preserving GABA/glycine transmission, and conversely manipulation of fast

inhibitory transmission while monitoring NPY-dependent effects, may help determine the relative contribution of each output mode to opioid analgesia, OIH, tolerance, and itch. Such approaches will be particularly important for determining whether MOR suppresses these two inhibitory outputs in parallel or under distinct activity-dependent conditions.

The functional significance of this inhibitory gate is also likely to be state-dependent. The NPY–NPY1R system may not operate in the same way across different pain states, prolonged opioid exposure, and opioid-related sensory adverse effects. Under pathological pain conditions, enhanced NPY signaling may represent a compensatory inhibitory response that limits sensory amplification. In contrast, prolonged opioid exposure may weaken this gate by suppressing NPY⁺ inhibitory interneurons, thereby promoting disinhibition of downstream excitatory circuits. At the same time, the molecular heterogeneity of NPY1R⁺ neurons suggests that this population may contain distinct excitatory subgroups with different contributions to pain and itch, further increasing the complexity of this system across pathological states.

These mechanistic questions have therapeutic implications, but translation requires caution. Enhancing spinal NPY1R signaling could reinforce an endogenous inhibitory gating mechanism. However, NPY receptors are broadly involved in feeding, cardiovascular regulation, anxiety-related behavior, and autonomic control, making systemic NPY1R activation unlikely to be straightforward. Future strategies would need spinal, receptor-subtype, and cell-type selectivity before the NPY–MOR gate can be considered a practical therapeutic target.

Author contributions

Y. W. and Z. W. drafted the original and revised manuscript; D. P. and W. X. edited and revised the manuscript. All authors reviewed, edited, and approved the final version of the manuscript and agreed to its publication.

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Ethics statement

All figures are either original to this work or properly attributed. No original images have been previously published, and all images comply with research integrity standards without inappropriate manipulation or misrepresentation.

Data availability statement

No datasets were generated or analyzed for this work.

AI statement

The authors used DeepSeek, online version, as a language-editing tool to improve grammar, clarity, and readability. The AI tool was not used for data analysis, data generation, image processing, or scientific content creation. All outputs were carefully reviewed and verified by the authors, who take full responsibility for the final content.

Conflicts of interest

The authors declare no conflicts of interest.

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