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Endogenous and Exogenous Opioids in Pain

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Abstract

Opioids are the most commonly used and effective analgesic treatments for severe pain, but they have recently come under scrutiny owing to epidemic levels of abuse and overdose. These compounds act on the endogenous opioid system, which comprises four G protein-coupled receptors (mu, delta, kappa, and nociceptin) and four major peptide families (β-endorphin, enkephalins, dynorphins, and nociceptin/orphanin FQ). In this review, we first describe the functional organization and pharmacology of the endogenous opioid system. We then summarize current knowledge on the signaling mechanisms by which opioids regulate neuronal function and neurotransmission. Finally, we discuss the loci of opioid analgesic action along peripheral and

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central pain pathways, emphasizing the pain-relieving properties of opioids against the affective dimension of the pain experience.

Keywords

opioid; analgesia; pain; signaling; neuroanatomy; perception

INTRODUCTION

Throughout human history, opioids have been used medicinally as an analgesic and recreationally as a euphorigenic. In the 1970s and 1980s, the efficacy of opioids to treat illness was vastly improved by advancements in modern medicinal chemistry and neuroscience. Specifically, the identification of the endogenous opioid peptides and receptors, accompanied by the development of new hyperselective and potent opioid drugs such as fentanyl and heroin, contributed both beneficial and detrimental effects on society and medicine. Today, opioids remain the mainstay analgesic treatment for severe acute, perioperative, and chronic pain. Paralleling the outstanding magnitude of pain in the United States (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education 2011), the use of opioids for pain management has increased dramatically in the past two decades such that hydrocodone topped all prescriptions in 2011 (CDC 2013, Manchikanti et al. 2012). Unfortunately, opioids cause numerous detrimental effects, including analgesic tolerance, paradoxical hyperalgesia, nausea and vomiting, constipation, respiratory depression, and transition to addiction (Inturrisi 2002, Streicher & Bilsky 2017, Volkow & McLellan 2016). These side effects dramatically impact the quality of life of patients, and the number of deaths from opioid overdose now exceeds that of car accidents (CDC 2013). Elucidation of the neural mechanisms underlying opioid effects is urgently needed to develop innovative adjuvant therapies that dissociate opioid analgesia from side effects. In this review, we discuss the recent advancements made in understanding opioid mechanisms of function.

ENDOGENOUS OPIOID SYSTEM

Opioid Receptors

The endogenous opioid system comprises four seven-transmembrane G protein-coupled receptors (GPCRs): mu, delta, kappa, and nociceptin (MOPR, DOPR, KOPR, NOPR). Each receptor is encoded by a unique gene (*Oprm1, Oprd1, Oprk1, Oprl1*) but shares upward of 60% of its amino acid composition (Al-Hasani & Bruchas 2011, Kieffer & Evans 2009, Toll et al. 2016). Importantly, each receptor has a distinct expression pattern throughout the nervous system (Mansour et al. 1994, Neal et al. 1999). The recent crystal structures of all four receptors illustrate with unprecedented detail several similar molecular characteristics that may open new avenues for novel drug design (Granier et al. 2012, Manglik et al. 2012, Thompson et al. 2012, Wu et al. 2012). In particular, the crystal structures for the inactive state of each receptor have been identified (Figure 1a). These studies provided the first glimpse into atomic-level details of the receptors necessary for pinpointing the unique opioid binding pockets that maintain ligand preferences. For example, the active state of MOPR has

been crystalized with nanobodies to stabilize the structure; comparisons of the active and inactive states can identify potential sites of action for different molecules. A recent computational docking and drug design study, based on the active MOPR structure, was used to identify novel biased opioid analgesics (e.g., PZM21) that preferentially promote unique active-state conformations and signaling pathways (Manglik et al. 2016). In the case of NOPR, the least well understood of the opioid receptors, structural crystallization has indicated the lack of a salt bridge, which is common to the other receptors, resulting in an overall shift in the conformation of the fifth and sixth helices. This shift may be relevant for NOPR's lack of extracellular domain interactions with the other endogenous opioid ligands, which may be relevant for the development of receptor-specific drugs. Collectively, these results provide insight into how different agonists distinctly alter receptor conformations to direct downstream intracellular cascades, which may ultimately lead to more effective pharmacological treatments. Additionally, other mechanisms including alternative splicing and receptor interactions may contribute to the diversity of analgesic responses mediated by opioids (Fujita et al. 2015, Pasternak 2018, Samoshkin et al. 2015, Wieskopf et al. 2014).

Opioid Ligands

There are four major families of endogenous opioid ligands: β-endorphins, enkephalins, dynorphins, and nociceptin/orphanin FQ (Figure 1b). These opioid peptides along with their cognate receptors are widely expressed across the neuraxis and, in particular, pain pathways. In contrast to the amino acid or monoamine neurotransmitters, the opioid peptides are packaged into dense core vesicles in the soma and transported down to axon terminals. During this process, enzymatic splicing of the prepropeptides results in the formation of the diverse, receptor-specific peptide transmitters. The classic example of this process involves β-endorphin, the canonical mu-preferring ligand. β-Endorphin is cleaved from the parent molecule proopiomelanocortin (POMC), which is expressed in the arcuate nucleus and the nucleus of the solitary tract (Bloom et al. 1978, Lazarus et al. 1976). After packaging, POMC is cleaved into either proopiocorticotropin or adrenocorticotropin molecules, which are then again broken down into β-endorphin, α-melanocyte-stimulating hormone, and corticotropin-releasing hormone. These peptides act on MOPR, melanocortin, and corticotropin receptors, respectively. Additionally, 3-endorphin can be further cleaved into met-enkephalin, a nonselective agonist with affinity for both DOPR and MOPR.

Similar to β-endorphin, enkephalins and dynorphins arise from larger molecules that are broken down into more specific peptide transmitters. Preproenkephalin is cleaved into either met-or leuenkephalin (Bower et al. 1976). Prodynorphin can be cleaved into several KOPR-selective ligands, includingdynorphin-A[1–17], dynorphin-B[1–13], and α-neoendorphin. Further complicating the relationship between opioid receptors and their ligands, dynorphin can also be cleaved into less-opioid-selective leu-enkephalin or dynorphin-A[1–8], essentially making dynorphin a potential agonist for MOPRs, DOPRs, and KOPRs (Chavkin 2013, Goldstein et al. 1979). Last, nociceptin is derived from prepronociceptin and has a significantly higher affinity for NOPR than for the other opioid receptors (Meunier et al. 1995). This selectivity is likely due to the Phe amino acid in the first position of the nociceptin peptide sequence (James et al. 1982).

Contrasting with the tight, spatially controlled synaptic transmission of small-molecule transmitters such as glutamate or dopamine, opioids are thought to rely on volumetric release into synaptic and extrasynaptic spaces and diffuse toward their receptors (Banghart & Sabatini 2012, Duggan 2000). Indeed, electron microscopy illustrates that most MOPRs are extrasynaptic, being hundreds of microns away from release sites (Glass et al. 2009, Mansour et al. 1988, Svingos et al. 1996). That is, they are not found in the bed of symmetric or asymmetric synapses but rather shifted over, next to the synapse. Similarly, dynorphin release has been suggested to travel up to nearly 100 μm from the released terminal (Chavkin 2013, Drake et al. 1994), implying that opioid synapses may include a much broader area than typical fast transmitter synapses. The mechanisms that command the spatial and temporal dynamics of opioid release, and that direct peptides to these distant receptors, remain some of the biggest and exciting mysteries in the field.

SIGNALING

General Principles

Here, we briefly summarize the basic signaling properties of the four opioid receptors (Figure 2). Extensive reviews of opioid receptor signaling can be found elsewhere (Al-Hasani & Bruchas 2011, Lamberts & Traynor 2013, Toll et al. 2016, Williams et al. 2013). All four opioid receptors couple to the inhibitory G proteins ($G_{\alpha i}$ and $G_{\alpha o}$). Upon activation by agonists, either endogenous or exogenous, the G_{α} and $G_{\beta\gamma}$ subunits dissociate from one another and subsequently engage a variety of effectors and intracellular signaling cascades that typically depress neural functions. Note that MOPR, DOPR, and KOPR have been shown to signal through an agonist-independent mechanism called constitutive activity, including during persistent pain and stress (Corder et al. 2013, Polter et al. 2017, Yao et al. 2016). Although further in vivo studies are needed to understand the initiation mechanisms, constitutive activity of MOPR and DOPR is also observed after prolonged exogenous opioid stimulation (Liu & Prather 2001, Meye et al. 2012, Shoblock & Maidment 2006) and likely involves lowering the energy barrier to assume the active conformation, as predicted by the crystal structure (Manglik et al. 2012). Such activity might result from a variety of mechanisms, including changes in receptor density, changes in receptor phosphorylation, modulation of allosteric binding sites, or changes in interactions with accessory proteins such as β-arrestin and Src (Kenakin 2001, Walwyn et al. 2007).

Opioid receptor activity inhibits adenylate cyclase (AC), thereby reducing cyclic AMP production (Minneman & Iversen 1976), as evidence of pertussis toxin sensitivity was established in later experiments. Further studies revealed that guanine nucleotides such as GTP modulate agonist binding to opioid receptors in membrane preparations from brain tissue and that opioids stimulate GTPase activity (Barchfeld & Medzihradsky 1984, Childers & Snyder 1978). Beyond coupling to G_i and G_o proteins, all four opioid receptors engage other G proteins that modulate a multitude of effectors in addition to AC (Al-Hasani & Bruchas 2011, Toll et al. 2016, Williams et al. 2013).

Ion Channel Mechanisms

One of the most highly conserved pathways that opioid receptors use to alter neuronal function is the modulation of ion channels (Figure 2a). All four opioid receptors inhibit in N-, P/Q-, and L-type voltage-gated calcium channels (Rusin et al. 1997). This process, which occurs via the $G_{\beta\gamma}$ subunit inhibition of the channel, decreases the presynaptic calcium-dependent fusion of synaptic vesicles with the membrane terminal and subsequent neurotransmitter release. In dorsal root ganglion (DRG) neurons, N-type calcium channels along with opioid receptors can be co-internalized following prolonged agonist exposure, which may further reduce neurotransmitter release and the transmission of pain signals to the central nervous system (CNS) (Altier et al. 2006). Postsynaptically, opioids also cause a $G_{\beta\gamma}$-mediated activation of G protein gated inwardly rectifying potassium (GIRK) channels (Torrecilla et al. 2002). This process is particularly important in postsynaptic compartments where dendritic hyperpolarization filters synaptic input. Mutant mice lacking GIRK channels, or expressing dysfunctional channels, show reduced opioid antinociception, establishing the importance of G protein-mediated potassium conductance modulation for opioid analgesia (Lujan et al. 2014, Nagi & Pineyro 2014).

Although the acute action of opioids on calcium and potassium channels typically reduces neurotransmission within seconds to minutes, chronic (hours to days) or abruptly interrupted opioid signaling can also facilitate excitatory synaptic plasticity. For example, withdrawal of exogenous opioids can elicit long-term potentiation (LTP) of synaptic transmission between primary afferent DRG nociceptors and second-order spinal cord neurons (Drdla et al. 2009, Zhou et al. 2010). This form of spinal LTP is considered a major substrate for opioid-induced hyperalgesia (OIH), a paradoxical decrease in pain threshold following opioid administration, and might also contribute to analgesic tolerance. The detailed molecular mechanisms underlying OIH and analgesic tolerance are not fully resolved, but they require presynaptic MOPRs in nociceptors (Corder et al. 2017) and involve the activation of microglia and molecules, including pannexin1, P2X4, and Toll-like receptors, that differentially contribute to OIH and tolerance in these cells (Burma et al. 2017, Trang et al. 2015). Finally, spinal LTP is also induced by peripheral injuries and represents a major mechanism of pathological pain. In this setting, a high dose of MOPR agonist can depotentiate synaptic transmission and erase spinal pain memory (Drdla-Schutting et al. 2012, Ruscheweyh et al. 2011).

Desensitization and Trafficking

Following activation, opioid receptors are phosphorylated by GPCR kinases, leading to β-arrestin 2 or 3 recruitment (Figure 2b). Arrestin molecules are key proteins that bind to phosphorylated GPCRs to regulate their G protein signaling through desensitization and internalization. The interaction of an opioid receptor with arrestin is thought to depend on the cellular context, agonist type, and model system studied. Importantly, mice that lack β-arrestin 2 show enhanced morphine antinociception and increased conditioned place preference (Bohn et al. 1999, 2003). Additionally, studies examining the aversive qualities of KOPR stimulation have shown that GRK3 knockout mice show no conditioned place aversion to KOPR agonists, and that phosphorylation of the receptor is required for these effects, implicating arrestin signaling in behavioral function (Bruchas et al. 2007a, 2011).

Remarkably, and contrary to previous models, internalized GPCRs are not inactive but may still signal, including from endosomal compartments (Eichel et al. 2016, Irannejad et al. 2013). These observations suggest, on the basis of the intracellular fate and signaling of internalized receptors (Bahouth & Nooh 2017, Irannejad & von Zastrow 2014), an additional level of complexity through which distinct ligands acting on the same opioid receptor can produce different cellular effects.

Arrestin Signaling

Whereas arrestin and opioid-receptor interactions were originally defined by their ability to regulate receptors, more recent studies have shown that arrestin is in fact a key signal effector at these receptors, mediating an array of cellular and behavioral responses. Phosphorylated arrestin-bound GPCR complexes recruit alternate, critically important downstream signaling cascades, including the mitogen-activated protein kinase (MAPK) cascade (Figure 2b). These MAPKs, which consist ofthree major proteins [extracellular signal regulated kinase 1 and2 (ERK1/2), c-Jun N-terminal kinase 1–3 (JNK 1–3), and p38], notably modulate cell proliferation, differentiation, apoptosis, transcription factor regulation, ion channel regulation, neurotransporter regulation, and protein scaffolding (Raman et al. 2007). MAPKs can regulate these effects over either short or long temporal domains to affect intra-and extracellular functions. All the opioid receptor subtypes stimulate phosphorylation of ERK 1/2, as well as JNK and p38 (Al-Hasani & Bruchas 2011, Bruchas et al. 2006, Chen et al. 2008, Eisinger & Ammer 2008, Macey et al. 2006). However, recent studies have reported that JNK phosphorylation by MOPR and KOPR can additionally engage noncanonical, arrestin-independent signaling pathways that inhibit G protein signaling at these receptors for long periods (Bruchas et al. 2007b, Melief et al. 2010, Schattauer et al. 2017).

Recent efforts have aimed to take advantage of the G protein versus arrestin signaling pathways by creating biased opioid receptor ligands. G protein-biased ligands could have fewer adverse effects, including constipation, respiratory depression, and even abuse liability (Brust et al. 2016, Manglik et al. 2016, Raehal et al. 2011, Schmid et al. 2017, Spangler & Bruchas 2017). However, the utility of biased agonists toward mitigating complex side effects, such as analgesic tolerance and OIH, remains controversial as numerous alternate signaling pathways and compensatory mechanisms are likely to be involved (Chen et al. 2016, Roeckel et al. 2016). Finally, how these biased agonists work in vivo, within selected circuits, remains to be dissected.

NEUROANATOMICAL SUBSTRATES FOR OPIOID ANALGESIA

Somatosensory Neurons of the Dorsal Root Ganglia

A remarkable feature of opioid receptors is that they are present at virtually all neural loci contributing to the pain experience. Neurons of the DRG and trigeminal ganglia innervate peripheral organs and relay somatosensory information, including pain, to the spinal cord and medulla (Basbaum et al. 2009). All four opioid receptors are expressed by DRG somatosensory neurons (Arvidsson et al. 1995a,b; Zhu et al. 1998), and their activation by intradermal or intrathecal agonists produces antinociception (Chan et al. 2017, Gunther et al.

2017, Stein et al. 2009) (Figure 3a). Opioid receptor activation depresses glutamate and neuropeptide release from somatosensory afferents onto CNS neurons. Initial studies had suggested that the different types of opioid receptors, particularly MOPR and DOPR, were coexpressed by the same class of DRG neurons, namely unmyelinated peptidergic nociceptors. These neurons detect noxious stimuli in skin and internal organs and express the neuropeptides substance P and calcitonin gene-related protein (CGRP) and the heat-and capsaicin-sensitive transient receptor potential cation channel subfamily V member 1 (TRPV1) (Chen & Pan 2008, Ueda 2006, Vetter et al. 2006). MOPR expression in these cells is thought to contribute to the remarkable utility of mu agonists for perioperative pain management (Figure 2c). In recent years, this coexpression model has been reappraised following the emergence of novel techniques to investigate opioid receptor expression, particularly reporter mice expressing fluorescent opioid receptors and single-cell RNA sequencing (scRNA-seq) (Erbs et al. 2015, Scherrer et al. 2006, Usoskin et al. 2015). These studies suggest that each opioid receptor is differentially distributed among different DRG neuron classes, implying that receptor classes preferentially control distinct types of pain and somatosensory modalities. For example, delta opioid receptor-green fluorescent protein (DOR-GFP) knockin mouse line and scRNA-seq indicate that DOPR is enriched in myelinated mechanosensory neurons that project to the skin and that have been implicated in tactile hypersensitivity (allodynia) in the setting of chronic inflammatory or neuropathic pain (Bardoni et al. 2014, Scherrer et al. 2009, Usoskin et al. 2015). Note, however, that the expression pattern and function of DOPR in DRG remain debated and differ between species (Francois & Scherrer 2017, Gendron et al. 2015). MOPRs in DRG can be targeted by peripherally restricted agonists (i.e., limited blood-brain barrier permeability) to produce analgesia without CNS-derived side effects (DeHaven-Hudkins & Dolle 2004, Vadivelu et al. 2011). Recently, Spahn et al. (2017) refined this approach and developed an opioid analgesic with a low acid dissociation constant, such that this compound selectively activates MOPRs at acidic inflammation sites. Interestingly, however, studies using conditional knockout mice with a selective deletion of MOPRs in DRG nociceptors, but intact receptor expression in the CNS, showed that these MOPRs in DRG are not necessary for the antinociception resulting from systemic morphine (Corder et al. 2017, Weibel et al. 2013). Instead, MOPRs in DRG are important contributors to two of the adverse side effects associated with chronic MOPR agonist treatments, tolerance and OIH (Araldi et al. 2018, Corder et al. 2017; but see also Weibel et al. 2013). Other brain regions, including the periaqueductal gray and rostral ventromedial medulla, contribute to opioid analgesia, tolerance, and OIH (Connor et al. 2015, Eidson et al. 2013, Gaspari et al. 2018, Lane et al. 2005, Morgan et al. 2006, Vanderah et al. 2001, Wilson-Poe et al. 2017). However, activation of MOPR in peripheral nociceptor populations appears to be the key molecular event that initiates pathological plasticity within CNS pain circuits, thereby facilitating the onset of opioid antinociceptive tolerance, physical dependence, and the pronociceptive effects of opioids (Chu et al. 2008, Joseph et al. 2010, Kandasamy & Price 2015, Ossipov et al. 2005).

KOPR expression and function in DRG can now also be investigated with reporter mice (Cai et al. 2016, Liu-Chen 2017). Multiple preclinical studies provided evidence that KOPR in DRG may control visceral pain and suggested the use of peripherally restricted kappa

agonists for these types of pain (Kivell & Prisinzano 2010, Vanderah 2010). The function of NOPR in DRG is not well understood, but the recent generation of a NOPR-enhanced GFP (eGFP) receptor revealed a broad distribution of NOPR in DRG neurons, including in unmyelinated peptidergic nociceptors, and in several populations of myelinated neurons that may include cutaneous mechanoreceptors and proprioceptors (Ozawa et al. 2015).

Spinal Cord Dorsal Horn Circuits

Opioid receptors are expressed by second-order neurons of pain pathways (Figure 3b). MOPR has long been known to be expressed by nociceptive dorsal horn neurons, including excitatory interneurons and lamina I projection neurons of the anterolateral tract that relay nociceptive information to the lateral parabrachial nucleus, thalamus, and periaqueductal gray matter (Aicher et al. 2000, Spike et al. 2002). Immunohistochemical studies suggested that DOPR expression in the dorsal horn was restricted to primary afferent terminals (Dado et al. 1993), whereas DOR-GFP mice, as well as in situ hybridization and electrophysiological recordings in wild-type mice, support the idea that DOPR is expressed by multiple classes of spinal neurons (Wang et al. 2018). Specifically, DOPR expression in somatostatin-positive excitatory interneurons that gate mechanosensory inputs (Duan et al. 2014) contributes to the analgesic properties of DOR agonists. Additionally, DOPR and MOPR coexpression in projection neurons of the anterolateral tract (Wang et al. 2018) suggests that these two receptors may cooperate postsynaptically in cells receiving convergent inputs from segregated delta-positive and mu-positive afferents. The use of an antibody against the phosphorylated form of KOPR suggested expression of this receptor in inhibitory interneurons and spinal astrocytes (Xu et al. 2007), and electrophysiological recordings documented KOPR-selective, agonist U50488H-responsive neurons in the dorsal horn (Eckert & Light 2002). The development of reporter mice for KOPR, along with transcriptomic approaches, will enable the definitive identification of these neurons.

Dynorphin and enkephalin are expressed by distinct classes of dorsal horn interneurons (Boyle et al. 2017, Francois et al. 2017) and are upregulated in the spinal cord following peripheral injury to modulate chronic pain (Lai et al. 2008, Podvin et al. 2016, Xu et al. 2004). Additionally, recent evidence suggests that dynorphin, released by dorsal horn inhibitory interneurons, is an essential mediator of itch (Kardon et al. 2014). The NOPR-eGFP diffuse fluorescence signal throughout laminae I−III strongly suggests that NOPR may be expressed by dorsal horn neurons in addition to primary afferents (Ozawa et al. 2015), but the precise identity of these neurons, as well as the endogenous source of nociceptin peptide that acts on NOPR in laminae I−III, remains to be established. This identification of NOPR-expressing DRG and spinal neurons is likely to clarify the mechanisms by which NOPR agonists can facilitate or counteract mu-mediated antinociception (Toll et al. 2016).

Opioid Action in Brain Circuits for Pain Affect: Remodeling of Pain Percept

Painful experiences are both personal and complex; they are not linearly correlated to noxious input but rather are constructed from neural information relating sensory, emotional, interoceptive, inferential, and cognitive information, which coalesce into a unified perception of pain (Craig 2003, Wiech 2016).

A major site of action of mu opioid analgesics is the descending pain modulatory system, which includes the ventrolateral periaqueductal gray (vlPAG), rostral ventromedial medulla (RVM), and spinal cord (Basbaum & Fields 1984). Microinjection of mu opioids into the vlPAG, or the RVM, is sufficient to produce antinociception (al-Rodhan et al. 1992, Rossi et al. 1994). RVM neurons receive monosynaptic inputs from the vlPAG and have been categorized as on, off, or neutral cells on the basis of their action potential firing pattern, pronociceptive or antinociceptive properties, and response to opioids (Basbaum & Fields 1984, Cheng et al. 1986, Fang et al. 1989, Morgan et al. 1992). Mu opioids can inhibit on cells, and indirectly disinhibit off cells, to produce antinociception. Using endogenous opioids, genetic approaches have begun to molecularly identify RVM neuron subpopulations and clarify the synaptic mechanisms by which these neurons regulate pain thresholds at the spinal level. These studies showed that at least two populations of RVM GABAergic neurons project to the spinal cord and modulate pain (Figures2c and 3b). The first population coexpresses preproenkephalin (Penk) and projects directly onto nociceptor terminals in the dorsal horns to inhibit pain (Zhang et al. 2015); they functionally correspond to off cells. In contrast, the second population, which expresses MOPRs, projects onto Penk-positive dorsal horn interneurons that then presynaptically inhibit mechanosensory neurons to facilitate mechanical pain (Francois et al. 2017).

Furthermore, rostral, subcortical, and cortical sites appear to be especially important for affective processing of pain, as well as the affective and rewarding aspects of pain analgesia (Cahill et al. 2013, Fields & Margolis 2015, Hummel et al. 2008, Kupers et al. 1991, Price et al. 1985) (Figure 3c). Clinical studies suggest that opioids produce pain relief by altering affective and somatic responses. For example, patient self-reports of morphine analgesia reveal that the sensation of pain is still present but affective aversive qualities are reduced (Price et al. 1985). Interestingly, this experience appears to be a dose-dependent pharmacological phenomenon, whereby progressively increasing doses of opioids diminishes first pain affect, then pain sensation (Cobos et al. 2012, LaGraize et al. 2006, Navratilova et al. 2015). Consistent with this, human functional MRI (fMRI) studies showed that much higher doses of opioids are required to reduce blood-oxygen-level-dependent activity in sensory brain regions than in limbic regions (Oertel et al. 2008).

Human positron emission tomography (PET) binding and fMRI studies of the anterior cingulate cortex (ACC) reveal that endogenous opioid release occurs during sustained pain experiences and largely correlates with analgesia against pain affect (Borras et al. 2004, Zubieta et al. 2005). This finding is also true for placebo analgesia (Bingel et al. 2006, Wager et al. 2007, Zubieta et al. 2005). Rodent models have further pinpointed the role of MOPR signaling in the ACC toward the relief of pain-induced aversion (LaGraize et al. 2006, Navratilova et al. 2015). Injection of naloxone, an opioid antagonist, into the ACC reduces the positive affect associated with pain relief, including by nonopioid analgesics, suggesting that endogenous opioids not only reduce nociceptive processes but also facilitate the reinforcing features of exogenous analgesia (Remeniuk et al. 2015). This feature of the endogenous opioid system is further supported by the result thatMOPR blockade reduces dopamine release in the nucleus accumbens (NAc) that accompanies pain relief (Navratilova et al. 2012). Opioid analgesics thus act on multiple cortical and subcortical sites to influence dopaminergic neurotransmission between the ventral tegmental area (VTA) and NAc to

reduce pain aversion. Adding to this complexity, chronic pain is accompanied by changes in plasticity in the mesolimbic dopaminergic system. Inflammatory pain desensitizes MOPR in the VTA, promoting opioid consumption (Hipolito et al. 2015, Narita et al. 2005), and neuropathic pain is accompanied by decreased NAc dopamine release, an effect that involves microglial activation in the VTA (Taylor et al. 2015), as well as other negative regulators of dopamine transmission. Additionally, in the amygdala, a crucial node in affective brain circuits, MOPR is expressed by GABAergic neurons of the central nucleus and intercalated cell masses (Winters et al. 2017). Inhibition of these neurons by mu agonists may reduce aversive behavior and reduce amygdala inhibitory input onto descending brainstem pain pathway responses (Han et al. 2015, Namburi et al. 2015). Despite this progress, the precise aspects of the pain experience that are encoded in the NAc and amygdala (salience, valence, motivation, analgesia), and the identity ofMOPR-expressing neurons that modulate pain in the ACC, NAc, amygdala, and VTA, remain to be determined.

KOPRs, DOPRs, and NOPRs also modulate pain supraspinally (Miaskowski et al. 1991, Yamamoto et al. 2001). KOPR activation in the dorsal raphe nucleus mediates descending antinociception (Land et al. 2009, Zhao et al. 2007). Additionally, the KOPR system gates affective information relating to stress and anxiety from the basolateral amygdala to the bed nucleus of the stria terminalis, as well as from inputs from the locus coeruleus (Crowley et al. 2016, McCall et al. 2017, Nygard et al. 2016). Although it is not yet fully understood for pain perception, the KOPR system is well positioned within the NAc circuitry to modify the hedonic value of nociceptive events and shape motivational behaviors in response to painful experiences (Al-Hasani et al. 2015, Castro & Berridge 2014, Negrete et al. 2017, Park et al. 2015). The dynorphin-kappa system regulates stress, aversion, mood, and relapse to drug-seeking for all major classes of abused drugs (Bruchas et al. 2010; Land et al. 2008, 2009) and may also contribute to shaping pain-induced negative affect (Massaly et al. 2017) and to driving comorbid depression and addiction. Interestingly, a recent study supports the idea that KOPR antagonists could be used to prevent stress-induced migraine (Xie et al. 2017). DOPRs and NOPRs are broadly expressed in pain affect and descending control circuits and are particularly enriched in the amygdala and ACC (Goody et al. 2002, Mansour et al. 1994, Ozawa et al. 2015, Scherrer et al. 2006, Toll et al. 2016); however, how these different receptor populations alter the different dimensions of pain experience requires further clarification.

CONCLUSIONS: DISSOCIATING DELETERIOUS SIDE EFFECTS FROM ANALGESIA

There are currently two main research paths to battle the opioid epidemic: discovering nonopioid analgesic therapies that could replace opioids or improving current opioid analgesics. For both paths, the complete resolution of opioid analgesics' mechanism of action, at the circuit, neural ensemble, synaptic, and molecular levels, will be a decisive step. For instance, the identification of MOPR-expressing neuronal populations in affective circuits that mediate opioid-induced reductions in pain affect will enable transcriptional and proteomic studies to uncover novel nonopioid analgesic targets. These studies are facilitated by the development of genetically engineered mouse lines for visualizing and manipulating

opioid receptor-expressing neurons (Cai et al. 2016, Erbs et al. 2015, Scherrer et al. 2006). Similar tools can now be used in vivo to study the cells that endogenously release enkephalins, dynorphins, endorphins, and nociceptin (Al-Hasani et al. 2015, Cowley et al. 2001, Francois et al. 2017).

By contrast, improving current opioid treatments requires an understanding of the mechanisms that underlie their deleterious side effects. At the cellular level, the development of conditional knockout mice lacking opioid receptors in defined cell types will greatly facilitate an understanding of the CNS structures that mediate OIH, antinociceptive tolerance, respiratory depression, and transition to addiction (Convertino et al. 2015, Corder et al. 2017, Gaveriaux-Ruff et al. 2011, Nygard et al. 2016, Weibel et al. 2013). At the level of signaling, biased agonists will clarify which signaling pathways need to be engaged to facilitate analgesia and limit deleterious effects such as respiratory depression, addiction, and constipation (Bohn & Aube 2017, Manglik et al. 2016, Schmid et al. 2017, Siuda et al. 2017, Spangler & Bruchas 2017). Collectively, this suite of novel genetic and pharmacological tools, together with the development of new behavioral paradigms for evaluating the pain experience and opioid analgesia in animal models (see the sidebar titled Translational Hurdles in Pain and Opioid Research), will likely yield insights into previously unanswerable questions. These advances are likely to lead to the development of more effective and safer analgesic treatments.

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TRANSLATIONAL HURDLES IN PAIN AND OPIOID RESEARCH

Current preclinical models of pain have elucidated detailed mechanisms for sensory detection and spinal encoding of nociceptive information. Unfortunately, a disconnect exists between clinical and preclinical assessments of pain: Human studies primarily use patient self-reports, whereas animal models typically use withdrawal reflexes or other indirect measures of pain. This raises the concern that animal models do not capture the holistic (i.e., sensory and affective) experience of pain in patients. This limitation has likely hampered the discovery of novel analgesic strategies to dampen pain negative affect in the clinic. Looking forward, efforts need to be directed toward dissecting the brain circuits of pain and require the development of measures of pain in animal models that more accurately reflect the in-the-moment and perceptual qualities of what it is like to experience pain. Tight modulation of neural circuits in vivo (e.g., optogenetic holography), paired with high-resolution, mesoscale monitoring of brain activity, may hold tremendous promise for determining how neural networks encode various dimensions of pain. Indeed, the combination of human functional imaging, behavior, and machine learning has already led to important advances in linking dynamic brain states to pain, thus paving a new avenue for preclinical research to follow in kind.

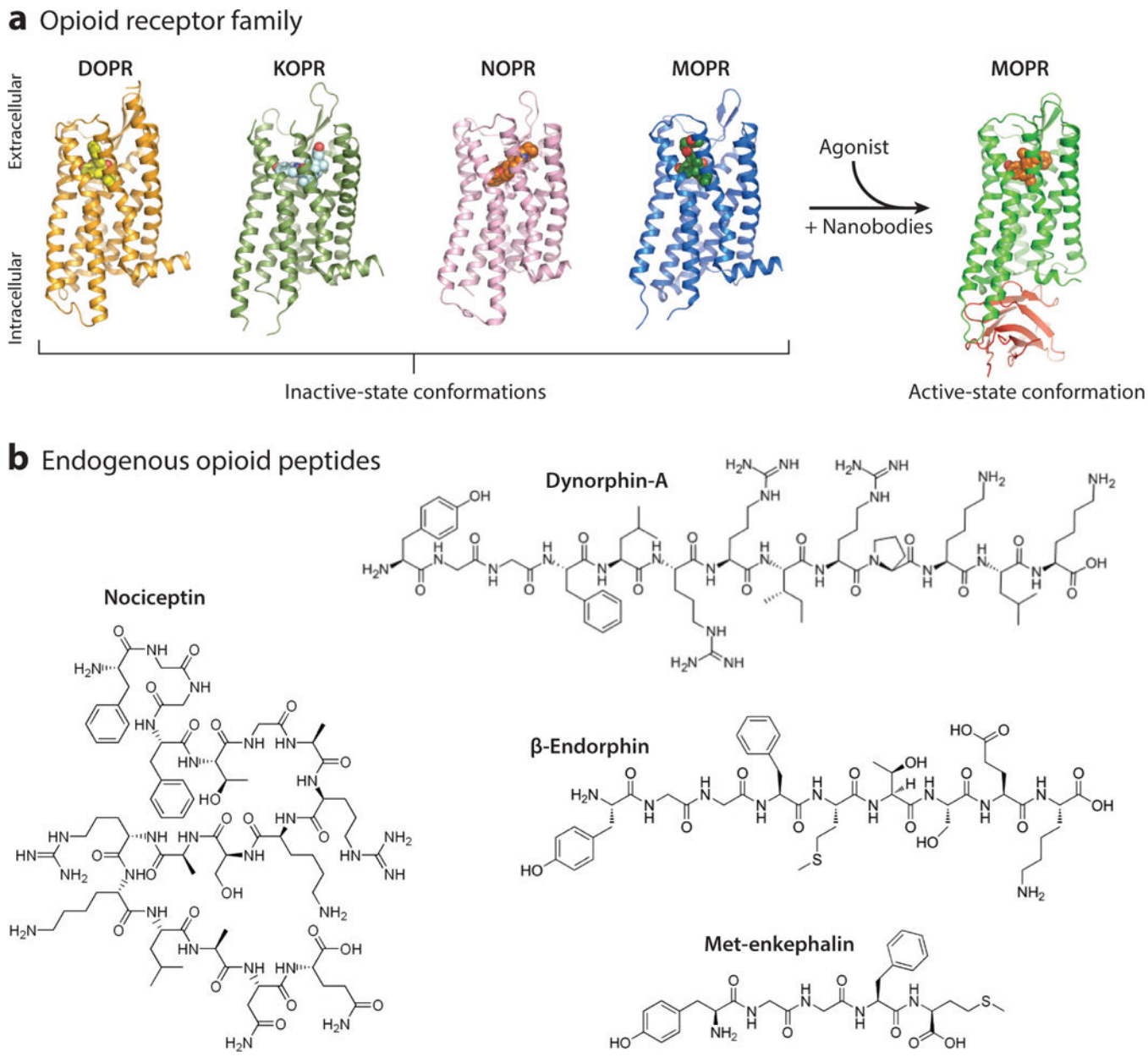

Figure 1.

The endogenous opioid system. (*a*) Crystal structures of the inactive state of all four opioid receptors (DOPR, KOPR, NOPR, and MOPR). When an opioid agonist enters the binding pocket of its cognate receptor, a conformational change in the transmembrane domains allows for intracellular effector molecules to bind and activate signaling cascades that modulate neural function. The addition of stabilizing nanobodies to the crystal preparation has elucidated the active state of MOPR. Images courtesy of Dr. Aashish Manglik (UCSF) and used with his permission. (*b*) Chemical structures of the four main classes of opioid peptides: met-enkephalin, dynorphin-A, nociceptin, and β -endorphin. Abbreviations: DOPR, delta opioid receptor; KOPR, kappa opioid receptor; MOPR, mu opioid receptor; NOPR, nociceptin opioid receptor.

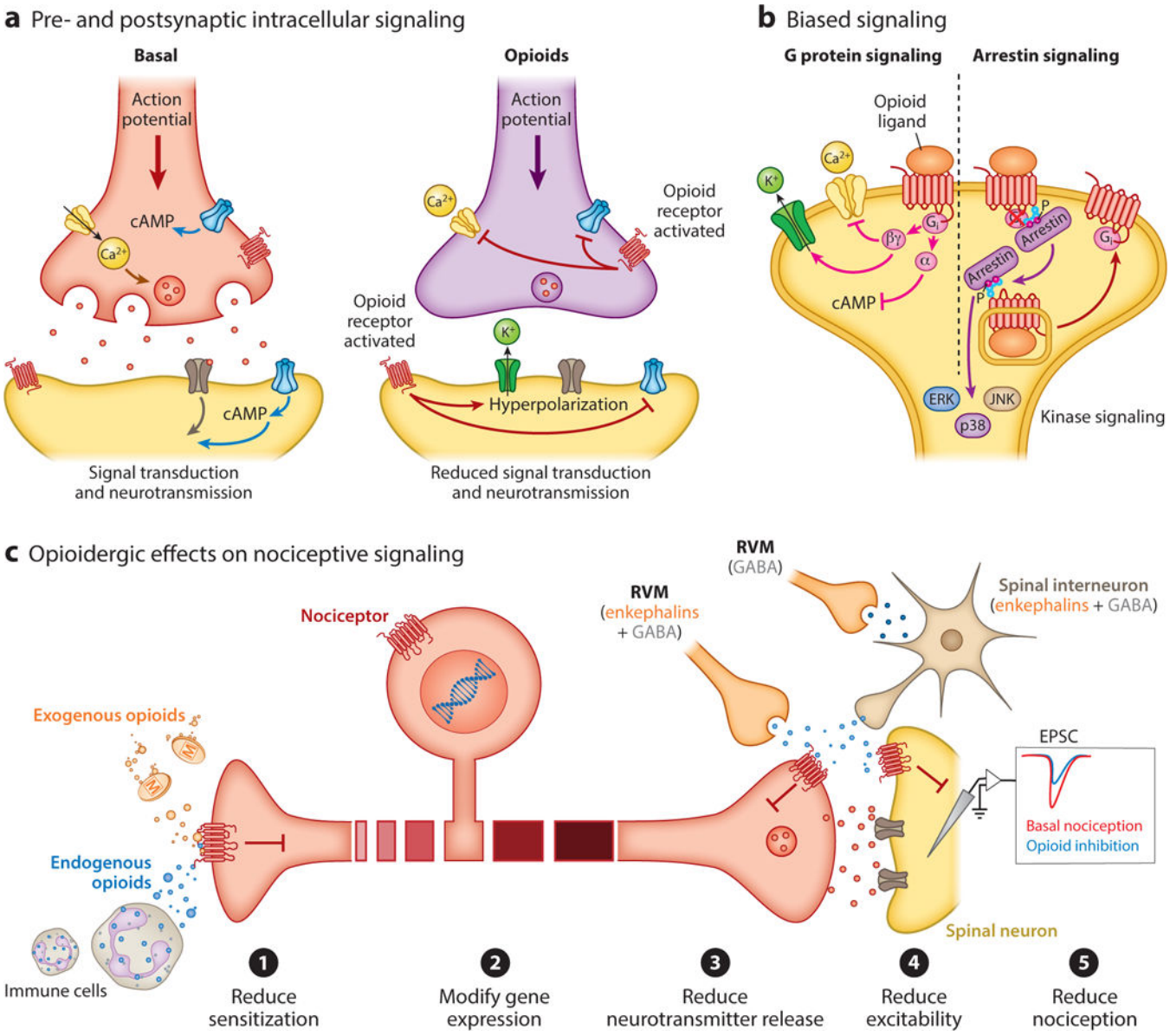

Figure 2.

Opioid modulation of signaling and synaptic transmission. (*a*) Presynaptic and postsynaptic effects of opioids on nociception. (*Left*) Noxious stimuli trigger action potential firing along DRG nociceptors. Upon reaching the synaptic terminal, VGCCs (*yellow*) open, facilitating neurotransmitter release. These neurotransmitters (e.g., glutamate) then open postsynaptic AMPA and NMDA receptors, which continue the nociceptive signals along pain circuits. (*Right*) Activation of opioid receptors promotes dissociation of inhibitory G_{α} and $G_{\beta\gamma}$ protein subunits. G_{α} subunits suppress adenylate cyclase, and $G_{\beta\gamma}$ subunits presynaptically inhibit VGCC opening and postsynaptically activate GIRK channels, resulting in reduced neurotransmitter release and membrane hyperpolarization, respectively. (*b*) Biased signaling pathways. Agonist binding to opioid receptors causes conformational changes that promote distinct recruitment of G protein and arrestin effector signaling cascades. While G proteins

mediate the inhibitory action of opioid signaling on neurotransmission, arrestin signaling is required both for internalization of opioid receptors and for kinase activities. The balance between G protein and arrestin signaling is thought, in part, to determine the analgesic versus detrimental effects of opioids. (*c*) Within pain circuits opioid receptors are activated by opioid analgesics such as enkephalin (endogenous) or morphine (exogenous). Endogenous opioids, such as enkephalins, can be released from infiltrating immune cells at the site of injuries and from neurons in the central nervous system. Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DRG, dorsal root ganglion; EPSC, excitatory postsynaptic current; ERK, extracellular signal regulated kinase; GIRK, G protein gated inwardly rectifying potassium; JNK, c-Jun N-terminal kinase; NMDA, *N*-methyl-D-aspartate; RVM, rostral ventromedial medulla; VGCC, voltage-gated calcium channel.

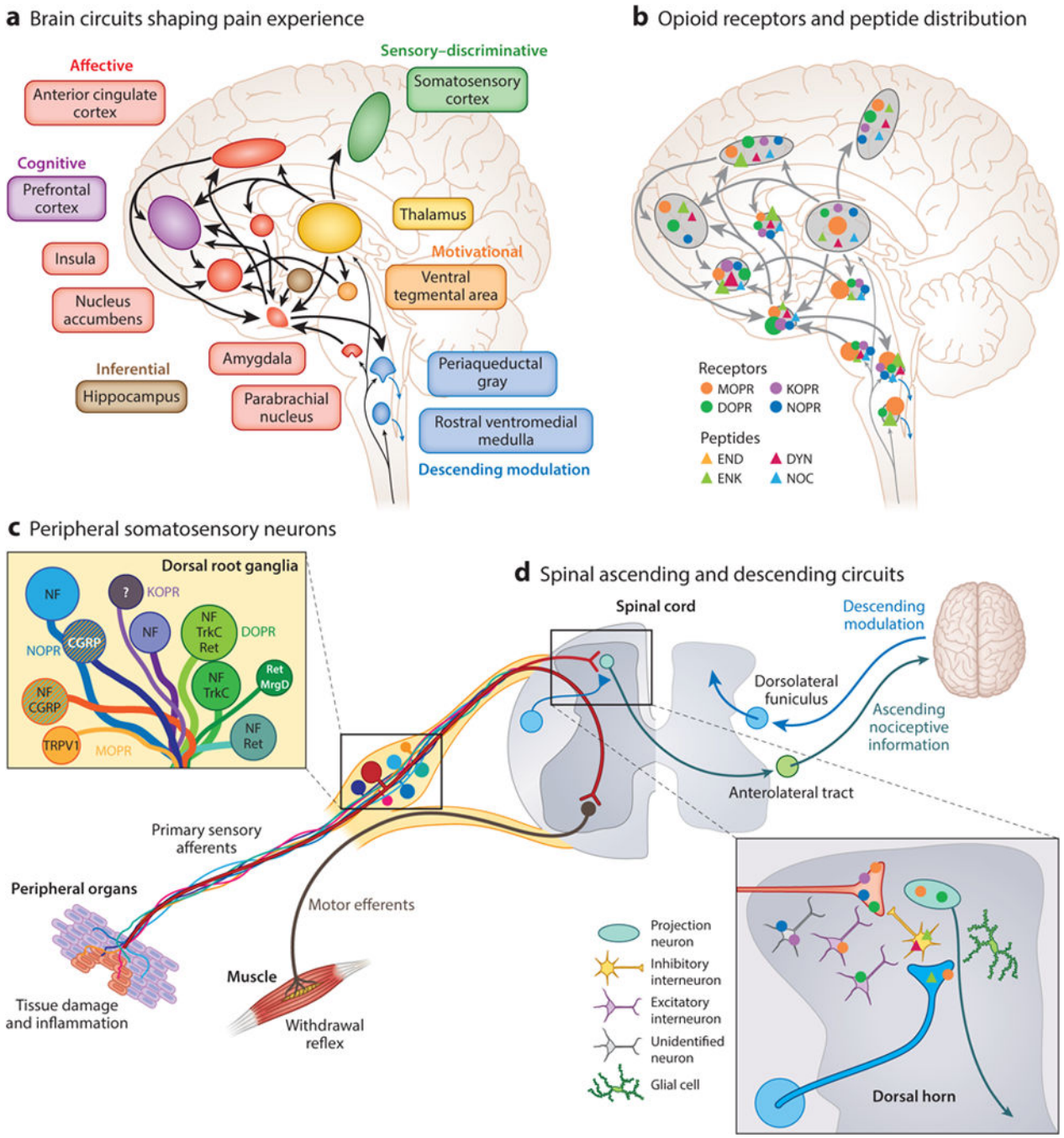

Figure 3.

Neuroanatomical substrates of pain perception and remodeling by opioids. (*a*) A large interconnected neural network of supraspinal brain circuits transforms nociceptive information ascending from the spinal cord into an aversive, painful experience. (*b*) The opioid system is well positioned within this brain network to modify the perception of pain. The different opioid receptors and peptides are distinctively, though broadly, expressed in different sites, the function of which is under intense investigation. Relative opioid receptor (*circles*) and peptide (*triangles*) expression levels are denoted by the size of the shapes. (*c*,*d*)

Opioid receptor types and peptides are also distributed in distinct subpopulations of (*c*) DRG neurons, identified with the indicated markers such as TRPV1, and (*d*) second-order spinal cord dorsal horn neurons. NF marks large-diameter DRG neurons with myelinated axons. Striped neurons coexpress different opioid receptor types. Abbreviations: CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; DOPR, delta opioid receptor; DYN, dynorphin; END, p-endorphin; ENK, enkephalin; KOPR, kappa opioid receptor; MOPR, mu opioid receptor; MrgD, Mas-related G protein-coupled receptor member D; NF, neurofilament; NOC, nociceptin/orphanin FQ; NOPR, nociceptin opioid receptor; Ret, Ret proto-oncogene; TrkC, tropomyosin receptor kinase C; TRPV1, transient receptor potential cation channel subfamily V member 1.