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MINIREVIEW—SPATIAL ORGANIZATION OF SIGNAL TRANSDUCTION

Dynamic Opioid Receptor Regulation in the Periphery

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ABSTRACT

Opioids serve a vital role in the current analgesic array of treatment options. They are useful in acute instances involving severe pain associated with trauma, surgery, and terminal diseases such as cancer. In the past three decades, multiple receptor isoforms and conformations have been reported throughout literature. Most of these studies conducted systemic analyses of opioid receptor function, often generalizing findings from receptor systems in central nervous tissue or exogenously expressing immortalized cell lines as common mechanisms throughout physiology. However, a culmination of innovative experimental data indicates that opioid receptor systems are differentially modulated depending on their anatomic expression profile. Importantly, opioid receptors expressed in the peripheral nervous system undergo regulation uncommon to similar receptors expressed in central nervous system tissues. This distinctive characteristic begs one to question whether peripheral opioid receptors maintain anatomically unique roles, and whether they may serve an analgesic advantage in providing pain relief without promoting addiction.

Introduction

Opioid receptor systems belong to one of three isoform families: μ, δ, or κ (Lord et al., 1977). Each isoform is composed of a seven-transmembrane–spanning G protein–coupled receptor (GPCR) that signals through Gαi/o subunits to inhibit adenylyl cyclase activity, reducing the production of cAMP and subsequent protein kinase A (PKA) activity. Activation of the accompanying G$\beta\gamma$ subunits results in activation of inward rectifying K^+ channels (Christie et al., 1987) and inhibition of voltage-gated Ca^{+2} channels (Gross and Macdonald, 1987), thereby hyperpolarizing neurons in which opioid receptors are activated. In several cell models, opioid receptor activation stimulates Gβ displacement from Gαi/o subunits and subsequent extracellular signal-regulated kinase/mitogen-activated protein kinase phosphorylation (Belcheva et al., 2003). However, it is well accepted that all three isoforms produce similar effects across physiology, resulting in outcome measurements appropriately reproducible between research groups and models.

Opioid receptors were originally and widely considered susceptible to canonical desensitization mechanisms, in which agonist activation of the GPCR stimulates β-arrestin–dependent internalization (Bohn et al., 1999, 2000; Gainetdinov et al., 2004). Within this model, opioid receptor activation triggers G protein receptor kinase 2/3 (GRK 2/3) to phosphorylate residues on the intracellular face of opioid receptors to uncouple the receptor from G proteins and attract β-arrestin association with the receptor (Zhang et al., 1998). Clathrin-mediated internalization then occurs, directing vesicles to degradation or recycling to the plasma membrane. This cycle represents a common desensitization mechanism for many GPCRs, including μ, δ, and κ. However, recent work has discovered anatomic differences in opioid receptor desensitization, as well as responsiveness.

Central Opioid Receptor Regulation

Opioid receptor function in vivo was initially characterized utilizing central nervous system (CNS) tissue, including brain and spinal cord. These studies, including work from the laboratories of Macdonald Christie, John Traynor, Mark Von Zastrow, and Chris Evans, among many others, found receptor behavior similar to studies in immortalized cell lines. All three isoforms of opioid receptors are constitutively sensitive to agonist activation, and undergo canonical, clathrin-mediated GPCR desensitization. Opioid receptor regulation in central nervous tissue involves dynamic protein kinase A phosphorylation events that dictate receptor function (Bernstein and Welch, 1998; Chakrabarti et al., 1998), G protein receptor

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ABBREVIATIONS: AA, arachidonic acid; AKAP, A-kinase anchoring protein; BK, bradykinin; CNS, central nervous system; COX, cyclooxygenase; DRG, dorsal root ganglia; GPCR, G protein–coupled receptor; GRK, G protein receptor kinase; LOX, lipoxygenase; PKA, protein kinase A; PKC, protein kinase C.

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kinase events that mediate receptor desensitization (Hasbi et al., 1998; Chakrabarti et al., 2001), β-arrestin association that can dictate downstream signaling function (Appleyard et al., 1999; Bohn et al., 1999, 2000; Zhang et al., 1999), and modulation by regulators of G protein signaling (Huang et al., 2015; Dripps et al., 2017). Importantly, these regulatory processes occur similarly throughout the CNS as well as in exogenously overexpressing immortalized cell lines. However, new and innovative studies have discovered unique differences in the regulation of opioid receptors in peripheral nervous tissue that could bear pharmacological utility.

Peripheral Opioid Receptor Priming

In 2011, members of the Tesmer group found that GRK2/3 inhibition in locus coeruleus neurons only partially blocks agonist-induced μ desensitization, indicating that other desensitization mechanisms may participate, or that GRK2/3 may play another role (Thal et al., 2011). Although this was one of the first reports identifying anatomic distinctions in opioid receptor desensitization, it was almost a decade earlier in which Stein and Schafer discovered anatomic differentiation in opioid receptor agonist responsiveness. Zollner et al. (2003) identified μ responsiveness in peripheral sensory neurons isolated from the dorsal root ganglia (DRG) as significantly greater following painful inflammation of the innervated tissue. These results were later confirmed by Clarke and colleagues across all three isoforms in both in vivo and in vitro models (Patwardhan et al., 2005; Berg et al., 2007, 2011). In these studies, the application of an inflammatory mediator, bradykinin (BK), stimulated increased responsiveness of opioid receptor signaling in peripheral nervous tissues. Importantly, basal opioid receptor responsiveness was considerably low, relative to other studies conducted with central nervous tissues (Whistler and von Zastrow, 1998; Arttamangkul et al., 2008; Dang et al., 2009). This disparity intimated that a type of braking mechanism was unique to peripheral nervous tissues expressing opioid receptors and naively repressing receptor responsiveness. However, the molecular players of this mechanism remained undiscovered, prompting additional studies to highlight potential targets to increase peripheral opioid efficacy.

The unique physiology and phenotype of peripheral nervous system tissues, including dorsal root and trigeminal ganglia neurons, serve as an important starting point for examining potential players in the mechanism that supports naive desensitization of opioid receptors. Peripheral sensory neurons have a bipolar phenotype, with afferent innervations that can extend over a meter in length from the cell body. Due to this length, many effects seen on opioid receptors in the periphery are likely due to temporally discriminative changes in protein–protein interactions and receptor coupling, in contrast to more time-extensive modifications in receptor translation and insertion (Jung et al., 2012). Therefore, investigations centered around post-translational mechanisms that would either stimulate or inhibit protein associations within short time frames appropriately represent previously published in vivo findings. In 2015, work by the Clarke group identified that δ functional competence in peripheral trigeminal sensory neurons was positively regulated by arachidonic acid (AA) and BK pretreatment (Sullivan et al., 2015). Additional work revealed various sensitivities to cyclooxygenase (COX) or lipoxygenase (LOX) inhibition, suggesting that COX and LOX metabolites of AA also stimulate opioid receptor functional competence. Importantly, BK and AA both activate protein kinase C (PKC) (O'Flaherty and Nishihira, 1987; Burgess et al., 1989), as do COX and LOX metabolites (Shearman et al., 1989; Liu et al., 1991; Abayasekara et al., 1993; Castrillo et al., 2003), suggesting that PKC may play an important role in reversing naive opioid receptor desensitization in peripheral afferent sensory neurons (Fig. 1).

PKC is an important kinase and signaling molecule in neurons, including peripheral sensory neurons. As a post-translational modifier, it reacts to changes in lipid composition, intracellular Ca^{+2}, and numerous upstream regulators to target ion channels, GPCRs, and other proteins to significantly change activities and downstream functions. Indeed, Brackley et al. (2016) discovered that PKC activation by BK was necessary to reverse functional incompetence of δ in peripheral DRG neurons. Results from this work demonstrated that application of the inflammatory mediator BK stimulated PKC to phosphorylate Raf kinase inhibitory protein. Phosphorylation of this scaffolding protein stimulates dimerization and sequestration of GRK2, which was found to be naively associated with δ in sensory neurons (Fig. 1). Importantly, expression of the kinase-dead mutant GRK2-K220R (Freedman et al., 1995) in sensory neurons failed to increase δ competence, suggesting that kinase activity of GRK2 was not the limiting factor for δ functional incompetence, but rather steric blockade of signaling molecules that would associate with the receptor. In this model, GRK2 occupation of G protein binding sites would prevent functional activation of pathways downstream from δ, thereby rendering the receptor system incompetent. Additional work corroborates the importance of basal participation by GPCR desensitization machinery as β-arrestin plays a role similar to GRK2 in μ and δ functional incompetence in trigeminal sensory neurons (Sullivan et al., 2016). Importantly, recent findings agree in that opioid receptors expressed in peripheral sensory neurons exist in a functionally desensitized state, unlike in neurons from central nervous tissues. Furthermore, inflammatory activation of PKC primes the opioid receptors for full responsiveness to agonist stimulation, providing a mechanism for this unique level of anatomically distinct receptor regulation.

GRK Biochemistry

Transient GRK isoform association with the opioid receptor has been detailed previously in multiple cell models. Homologous desensitization of opioid receptors is most often initiated by kinase phosphorylation of amino acids along the C terminus of the receptor. For μ, GRK2/3 phosphorylation predominantly occurs following high-efficacy opioid agonist administration, whereas GRK5 serves to phosphorylate the receptor following morphine (low-desensitizing agonist) (Schulz et al., 2004; Doll et al., 2012). Importantly, PKC has also demonstrated a role in receptor phosphorylation, although this typically occurs following activation of a coexpressing Gαq-coupled GPCR (Bailey et al., 2004; Doll et al., 2011; Feng et al., 2011). GRK2 is also responsible for postagonist phosphorylation and internalization of δ (Guo et al., 2000; Kouhen et al., 2000) and κ (Appleyard et al., 1997;

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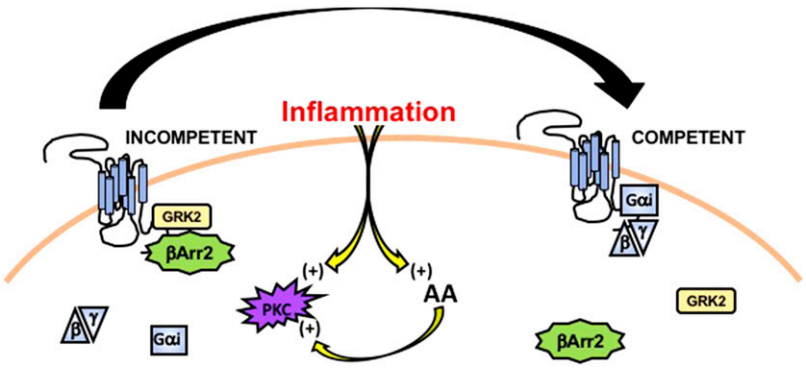


Fig. 1. Illustration of inflammation stimulating a conversion of the opioid receptor system from a state of incompetence to that of competence for activation on a peripheral nerve ending. βArr2, β-arrestin 2.

McLaughlin et al., 2003) in both immortalized and CNS cell models. Brackley et al. (2017) found that PKA phosphorylation of GRK2 drives plasma membrane targeting and constitutive association with δ in peripheral DRG neurons. GRK2 phosphorylation in this neuronal model was mediated by A-kinase anchoring protein (AKAP) 79/150, thereby utilizing a scaffolding protein necessary for post-translational upregulation of several pain-sensing transient receptor potential channels, including transient receptor potential family V1 (Jeske et al., 2008, 2009; Schnizler et al., 2008; Zhang et al., 2008) and transient receptor potential family A1 (Brackley et al., 2017). Importantly, the expression of an AKAP mutant with a deleted PKA binding domain resulted in a functionally competent δ in sensory neurons, indicating an important scaffolding role for AKAP in the naive and inhibitory association of GRK2 with δ in peripheral nervous tissue.

Previous studies in peripheral sensory neurons primarily examined initial opioid receptor responsiveness, and not desensitized responses, so little is known concerning the potential for anatomic distinction in receptor desensitization. Given that GRK2 constitutively associates with δ, is it possible that receptor desensitization follows a non-GRK2 mechanism? Phosphorylation at T394 of μ has been reported to be critical to acute D-Ala^2, N-MePhe^4, Gly-ol-enkephalin desensitization and not morphine but has no effect on chronic desensitization to either (Li et al., 2013). This is also the case for Chinese hamster ovary cells (Pak et al., 1997) and animals (Wang et al., 2016), suggesting similar desensitization mechanisms for μ in peripheral and central nervous tissues. Furthermore, phosphorylation of T394 μ appears to be GRK2-dependent (Zhang et al., 1998), suggesting that the kinase potentially governs both preagonist and postagonist functional competence of peripheral opioid receptors. Less information is available for δ and κ in peripheral sensory neurons; however, given their similarities in mechanisms of agonist-dependent desensitization, it can be presumed that all three isoforms follow similar patterns of desensitization, with similar dependencies on GRKs. Importantly, can the anatomic distinctions of opioid receptors between peripheral and central nervous tissues be targeted pharmacologically to increase receptor responsiveness in the periphery and reduce systemic side effects?

On the intracellular side, blocking constitutive GRK2 association with an opioid receptor would induce functional receptor competence and the possibility for analgesia. Tesmer et al. (2010), Thal et al. (2012), Homan and Tesmer (2015), and Bouley et al. (2017) have conducted a number of studies on the efficacies of various GRK inhibitors on GPCR function and physiology. However, as Brackley et al. (2016) found, GRK2 kinase activity was not a rate-limiting step in maintaining δ in a desensitized state. Rather, GRK2 provides steric hindrance to G protein activation by δ. Given the large number of proteins and enzymes that constitute the GRK interactome, it becomes difficult to speculate whether other intracellular pathways would be affected, thereby modifying tissue physiology beyond an opioid receptor. However, current and unpublished studies stretch the treatment possibilities for GRK inhibitors to unconsidered realms, providing hope for multiple diseases.

Opioid Receptor Translocation

Opioid receptor function is dependent on subcellular localization (Stoeber et al., 2018). Similar to many CNS models, δ function in DRG neurons is dependent upon plasma membrane expression (Scherrer et al., 2006). However, several studies have discovered mechanisms unique to primary afferent neurons that regulate opioid receptor function based on receptor translocation. For example, subcellular localization of δ to the plasma membrane was increased in DRG neurons following ipsilateral exposure to complete Freund's adjuvant (Gendron et al., 2006). BK, an inflammatory mediator increased in vivo following complete Freund's adjuvant administration, was reported to increase the number of DRG neurons positively expressing δ on its cell surface (Pettinger et al., 2013). Additionally, nerve growth factor activation of tropomysin receptor kinase A in DRG increases μ agonist efficacy by increasing receptor translocation to peripheral nerve terminals (Mousa et al., 2007). Pradhan et al. (2013) reported in 2013 that inflammation increases N-type Ca^{+2} channel contribution to δ-mediated analgesia in DRG neurons in a β-arrestin two-dependent manner. This intimates that β-arrestin 2 affects subcellular localization of the δ receptor isoform and its functional conjugation to Gβγ-mediated inhibition of voltage-gated calcium channel, a primary mechanism that supports hyperpolarization of primary afferent neurons. Interestingly, research from the same group found that δ receptor responses were increased in DRG neurons with β-arrestin 1 knocked out (Mittal et al., 2013). However, this mechanism was tied to Rho-associated protein kinase and LIM kinase-dependent translocation mechanisms to the plasma membrane, such that exposure to δ-specific agonists resulted in increased δ receptor expression on the plasma membrane.

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Multiple sources indicate varying amounts of δ/μ coexpression in primary afferent neurons, including values as low as 5% total (Scherrer et al., 2009) to approximately 30% (Bardoni et al., 2014). Despite their functional similarities/differences, coexpression of the two isoforms appears to regulate function in the periphery. Reduced δ expression concomitantly reduces cell surface expression and function of μ in DRG neurons (Walwyn et al., 2009). Unique to this pairing, others have demonstrated functional heterodimerization of μ and δ isoforms in peripheral afferents (Wang et al., 2010), even demonstrating dynamic changes in δ, μ, and κ isoform expression in DRG afferents following inflammation (Ji et al., 1995). Together, these reports indicate a unique interplay of cross-functionalization between opioid receptor isoforms that maintain unique characteristics in the peripheral nervous system.

Peripheral Opioid Targets

Spahn et al. (2017) designed a μ-specific agonist uniquely selective for receptor association in inflamed tissues only. Utilizing computer modeling of μ at low pH values, thereby attempting to recreate inflammatory conditions for agonist association, they designed a new agonist that only binds to μ when the pH is low and in a state of inflammatory flux. Importantly, this compound was capable of stimulating Gαi signaling when applied following inflammatory injury without affecting central autonomic centers, thereby avoiding depressed respiration, sedation, or addiction. This aspect was used by Jamshidi et al. (2015) while reporting on the functional selectivity of the peripherally restrictive κ opioid agonist U50488, which avoids CNS modulation of mood, and is especially important in reference to recent work on κ as a peripheral pain target (Snyder et al., 2018). Taken together, recent findings are important for understanding the anatomic complexity and differential possibilities of peripheral opioid receptors when designing safer and newer opioids for the treatment of pain.

Conclusions and Future Directions

A considerable amount of peripheral opioid receptor research has focused on the δ and μ receptor isoforms. However, previous work on the κ receptor system identifies that specific κ agonists may hold analgesic property isoforms in peripheral nervous tissue (Su et al., 1998; Labuz et al., 2006; Berg et al., 2011; Cunha et al., 2012), despite little biochemical evidence supporting whether κ opioid receptors are regulated similarly to δ and μ. Given recent breakthroughs associated with receptor dimerizm and allosteric agonists, multiple research groups are consistently identifying new mechanisms unique to peripheral opioid receptor systems that can be manipulated to provide accurate analgesia without central side effects. This remains an important goal in patient care in the generational combat against the worldwide opioid crisis.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Jeske.

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