Peripheral Opioid Regulation of Nociceptors. Focus on “Morphine Directly Inhibits Nociceptors in Inflamed Skin”

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In this issue of the Journal of Neurophysiology (p. 2083–2097), Wenk et al. describe a series of experiments demonstrating that opioids inhibit the majority of A-delta and C nociceptors innervating inflamed skin (Wenk et al. 2006). As elegantly demonstrated, the in vitro inflamed skin-nerve preparation used in their study exhibits two important properties. First, it contains isolated nociceptor terminals that continue to display sensitized responses to thermal and mechanical stimuli under these in vitro conditions. Second, this preparation permits focused investigations on opioid regulation of nociceptor function without the well recognized confound of central opioid effects. Their findings demonstrate that peripheral opioid inhibition of nociceptor responses is a highly specific effect: the response to local morphine application was only evident in inflamed skin-nerve preparations and not in control skin preparations, and the morphine effect was concentration-dependent, naloxone-reversible and reversible after washout. One important property for peripheral opioids on afferent encoding is the observation that peripheral morphine inhibited responses to both mechanical and thermal stimuli (Wenk et al. 2006), suggesting that peripheral opioids might modulate pain responses from several qualitatively distinct noxious stimuli. This is an important contribution and is consistent with the notion that peripheral opioids may represent a logical target for drug development. Collectively, the present findings contribute to the well-known actions of peripheral opioids and support a new approach for studying the development of “competence” of peripheral opioid receptors.

Interestingly, previous studies using behavioral methods have reported either a significant peripheral opioid inhibition of nociceptive response measures or sometimes no effect using both animal (Joris et al. 1987; Stein et al. 1989) and clinical assays (Dionne et al. 2001; Gupta et al. 2001). Several hypotheses have been proposed to explain the selective effects of peripheral opioids on inflamed tissue including migration of opioid-containing immune cells on the inflamed side, increased axonal trafficking of opioid receptors to the peripheral terminals, upregulation of opioid receptors and alteration of efficiency of G-protein-coupling, etc. (Stein et al. 2003). A recent study demonstrated that opioid receptors expressed on cultured sensory neurons are under heterologous regulation by other G-protein-coupled receptors (GPCR) expressed in these neurons (Patwardhan et al. 2005). In these studies, the bradykinin B2 GPCR was found to be co-expressed with the delta opioid GPCR. Under basal conditions, the delta opioid receptor did not activate inhibitory signaling pathways. However, the application of bradykinin to these neurons led to the rapid development of a competence for opioid receptor inhibition of prostaglandin-evoked signaling and bradykinin-evoked neuropeptide release by activation of the B2 bradykinin GPCR. Further, the studies demonstrate that B2 signaling via protein kinase C pathways mediates this rapid development of competence in sensory neuron opioid receptors. Thus the development of peripheral opioid receptor competence for inhibiting neuronal function appears to be due, at least in part, to heterologous regulation of opioid receptor signaling by other GPCRs (Patwardhan et al. 2005).

The present finding by Wenk et al. represents an important contribution to our understanding of peripheral opioid analgesia in inflamed tissue and demonstrates that the isolated skin-nerve preparation, intermediate between cell culture and behavioral methods, offers many advantages for parametric evaluation of the mechanisms mediating the rapid development of opioid receptor competence.

REFERENCES


