Opioids are powerful analgesics that produce their effects at both spinal and supraspinal levels. These effects are largely mediated by actions at μ-type opioid receptors (MORs). Using whole cell recordings from neurons in the basolateral amygdala (BLA) in acute brain slices, Finnegan et al. (2006) in this issue of the Journal of Neurophysiology (p. 2032–2041) show that activation of μ-opioid receptors reduces GABAergic inhibition to these cells. This inhibition arises from local circuit interneurons that act as feedforward and -back neurons. With a combination of pharmacological manipulations and immunohistochemistry, the authors go on to show that these actions of μ-opioid receptors are due to modulation of Kv1.1 and Kv1.2 voltage-dependent potassium channels. Reduction of inhibition to these projection neurons leads to an increase in their activity thus potentiating excitatory inputs to the central amygdala. Finnegan and colleagues suggest that this modulation of GABAergic inhibition in the BLA may underlie the amygdala-dependent antinociceptive action of opioids.

Activation of nociceptive receptors in the periphery by stimuli that are potentially damaging leads to the perception of pain, a behavioral response that is critical to survival. However, a variety of emotional and motivational states can modulate this perception, often leading to heroic deeds of performance (Price 1999). Investigation of the descending control of pain has a long history since the early studies of the gate mechanism that mediates this effect is well known (Millan 2002), the key elements being two regions in the brain stem: the rostral ventromedial medulla (RVM) and the periaqueductal gray (PAG). The central components of this circuitry include limbic regions such as the prefrontal cortex and hypothalamus, and the amygdala. Micro-injection of MOR agonists into any of these sites reduces behavioral responses to noxious stimuli, whereas injection of opioid antagonists blocks antinociceptive responses, showing that the descending control of pain requires activation of opioid receptors at all levels of this circuitry.

Our understanding of the mechanism of action of opioids in nociception comes from studies in the RVM and PAG. The PAG innervates neurons in the RVM the projections of which to the dorsal horn inhibit ascending nociceptive neurons. These antinociceptive effects are largely mediated by release of opioids acting at μ-receptors (Fields 2004). The cellular actions of μ-opioids at these brain stem structures are either presynaptic inhibition of GABA release or postsynaptic activation of G-protein-coupled inward rectifier channels, thus hyperpolarizing and reducing the activity of the postsynaptic cell (Williams et al. 2001). These two effects produce opposing effects on neuronal activity and have been suggested to underlie the differences in state-dependent actions of opioids (Fields 2004).

The amygdala is a forebrain structure that has been associated with the evaluation of emotional and motivational states (Sah et al. 2003) and has a well-established role in conditioned and unconditioned fear and anxiety (LeDoux 2003; Sah et al. 2003). These learned behaviors are also associated with antinociceptive effects (Harris 1996) that have been shown to result from activation of MORs in the BLA (Shin and Helsemstetter 2005). Neurons in the BLA do not project to nociceptive areas such as the PAG but have extensive connections to the central nucleus of the amygdala (CeA) that in turn has dense reciprocal connections with the PAG (Hopkins and Holstege 1978; Rizvi et al. 1991). Activation of MORs in the BLA has potent nociceptive actions (Shin and Helsemstetter 2005). However, although much is understood about the action of opioids in brain stem and spinal cord, the cellular mechanisms of its central action are less well understood. To test the action of opioids on neurons in the BLA that are likely to be part of the nociceptive circuitry, Finnegan et al. injected a retrograde tracer into the central amygdala and made targeted recordings from neurons in the BLA that project to the CeA. They then show that μ-opioids reduce GABAergic inhibition by a mechanism that involves modulation of Kv1.2 and Kv1.2 channels. This action is shown to be presynaptic as it reduces transmitter release by the presence of Kv1.1 and Kv1.2 channels at presynaptic terminals and antagonism of opioid actions by antagonists of these potassium channels.

Opioids also reduce GABA release in the CeA (Finnegan et al. 2005), RVM (Finnegan et al., 2004), and PAG (Vaughan et al. 1997). In the PAG, these actions are also due to effects on Kv1.2 channels. A recent study has also described a reduction of cell spiking in response to μ-opioid activation in the lateral amygdala (Faber and Sah 2004). In contrast, reduction of inhibition would be expected to increase cell excitability. This differential modulation of neuronal excitability in the BLA is similar to the different actions of μ-opioids in the RVM (Heinricher et al. 1994), suggesting the presence of organizational principles in nociceptive circuits at both spinal and supraspinal levels.

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