Over the last several decades it has become increasingly clear that neural networks within the brain act in a specific fashion to modulate pain. These modulatory networks are the target of centrally acting analgesic drugs and contribute to pathological pain states. Imaging studies increasingly confirm that these modulatory systems are functional in humans, and deficiencies in descending control are seen in a range of pain syndromes. The best-studied and most important pain-modulating network has links in the midbrain and medulla. My laboratory has concentrated on the physiological and pharmacological properties of neurons in the output of this system, the rostral ventromedial medulla (RVM), which provides an approachable model to investigate pain-modulation from a systems perspective. We have identified different physiological classes of RVM neurons that respectively inhibit or facilitate nociception, and have now begun to explore when and how these different cell classes are brought into play to produce analgesia or hyperalgesia. Our work has ranged from neuroimmune factors that recruit descending facilitation in models of “sickness,” to stress-induced analgesia and hyperalgesia, to anti-opioid peptide action. Our current areas of emphasis are understanding how nociceptive information gains access to modulatory systems as part of a recurrent circuit, and looking at how non-somatic sensory information, such as light, can activate pain-facilitating neurons.