Endogenous CGRP plays an important role in the plastic neurogenic changes that occur in response to peripheral inflammatory events, including the development of nociceptive behaviors. While inflammatory pain is thought to involve a variety of transmitters released from the nerve terminals, including amino acids, substance P (SP), and calcitonin gene-related peptide (CGRP), pharmacologic treatments with peptide antagonists have not been shown to hinder readily the development of hyperalgesic nociceptive responses after induction of acute arthritis. Recent studies in our laboratory have compared nociceptive responses in mice deficient in the calcitonin/αCGRP gene (CGRP-/-) and their parent strain (wild type 129/c57). The mice deficient in the calcitonin/αCGRP gene (CGRP-/-) displayed normal responses to noxious heat stimuli. Peripheral inflammation was then induced in the rat kneep joint by injection of a mixture of kaolin/carrageenan (k/c) to produce a testable secondary hyperalgesia. Nociceptive response behaviors assessed included paw withdrawal latency (PWL) to radiant heat applied to the hindpaw, and the hot plate test. The CGRP-/- mice showed no signs of secondary hyperalgesia after development of knee joint inflammation, while a significant decrease in the PWL was observed in the CGRP+/+ mice as expected. The CGRP-/- mice also showed a prolonged rather than a shortened response latency in the hot plate test 4 h after knee joint injection of k/c. Immunohistological study showed that CGRP- like immunoreactivity (CGRP-LI) was absent in the spinal cord tissues taken from the CGRP-/- mice. These results more conclusively support the idea that CGRP plays a significant role in nociceptive events that occur in response to peripheral inflammation.