

Cross-tolerance to acute administration of mu and kappa opioid agonists at the spinal cord level in the rat

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Development of tolerance and cross-tolerance after acute administration of the μ agonist morphine and the K agonist U-50,488H was assessed in rats, through recording of a C-fiber-evoked spinal nociceptive reflex. Rats rendered tolerant to morphine (a single dose of 1 mg/kg i.p.) showed, after a 5-hour period, tolerance to morphine and cross-tolerance to the K-opioid receptor agonist U-50,488H, as revealed by depressed C-reflex responsiveness. In contrast, pretreatment with U-50,488H (a single dose of 1 mg/kg i.p.) rendered tolerant the rats to U-50,488H, but the animals did not develop cross-tolerance to morphine. Results indicate that acute administration of μ and K ligands leads to development of unidirectional cross-tolerance in rat spinal cord. This points to limitations in using alternated μ and K opioid agonists to bypass the problem of development of opioid tolerance in chronic pain complaints.