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Topical opioids in mice: analgesia and reversal of tolerance by a topical N-methyl-D-aspartate antagonist

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Abstract

In addition to its central actions, morphine has important peripheral effects. To examine peripheral analgesic mechanisms, we developed a topical opioid paradigm in which the tail was immersed in a dimethyl sulfoxide (DMSO) solution containing various drugs. Alone, DMSO was inactive in the tail-flick assay in mice. DMSO solutions containing morphine and peptides such as [D-Ala2,MePhe4, Gly(ol)5]enkephalin (DAMGO) produced a potent, dose-dependent analgesia with the radiant heat tail-flick assay. The actions of the drugs were local. Analgesia was observed only in regions of the tail exposed to the solution and not in more proximal unexposed portions of the tail. Immersion of the tail in a solution containing either 125I-labeled morphine or 125I-labeled DAMGO revealed no detectable uptake of radioactivity into the brain, spinal cord, or blood. In the tail, radioactivity was limited only to the regions actually immersed in the solutions. The topical drugs potentiated systemic agents, similar to the previously established synergy between peripheral and central sites of action. Local tolerance was rapidly produced by repeated daily exposure of the tail to morphine. Topical morphine tolerance was effectively blocked by the N-methyl-D-aspartate (NMDA) antagonist MK801 given either systemically or topically but not intrathecally. The ability of a topical NMDA antagonist to block local morphine tolerance suggests that peripheral NMDA receptors mediate topical morphine tolerance. Morphine was cross-tolerant to DAMGO, but not to morphine-6beta-glucuronide, implying different mechanisms of action. These observations are significant in the design and use of opioids clinically.