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The formalin test in mice: dissociation between inflammatory and non-inflammatory pain.

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The formalin test in mice is a valid and reliable model of nociception and is sensitive for various classes of analgesic drugs. The noxious stimulus is an injection of dilute formalin (1% in saline) under the skin of the dorsal surface of the right hindpaw. The response is the amount of time the animals spend licking the injected paw. Two distinct periods of high licking activity can be identified, an early phase lasting the first 5 min and a late phase lasting from 20 to 30 min after the injection of formalin. In order to elucidate the involvement of inflammatory processes in the two phases, we tested different classes of drugs in the two phases independently. Morphine, codeine, nefopam, and orphenadrine, as examples of centrally acting analgesics, were antinociceptive in both phases. In contrast, the non-steroid anti-inflammatory drugs indomethacin and naproxen and the steroids dexamethasone and hydrocortisone inhibited only the late phase, while acetylsalicylic acid (ASA) and paracetamol were antinociceptive in both phases. The results demonstrate that the two phases in the formalin test may have different nociceptive mechanisms. It is suggested that the early phase is due to a direct effect on nociceptors and that prostaglandins do not play an important role during this phase. The late phase seems to be an inflammatory response with inflammatory pain that can be inhibited by anti-inflammatory drugs. ASA and paracetamol seem to have actions independent of their inhibition of prostaglandin synthesis and they also have effects on non-inflammatory pain.