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Research Report

CC12, a P450/epoxygenase inhibitor, acts in the rat rostral, ventromedial medulla to attenuate morphine antinociception

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ABSTRACT

Brain cytochrome P450 epoxygenases were recently shown to play an essential role in mediating the pain-relieving properties of morphine. To identify the CNS sites containing the morphine-relevant P450s, the effects of intracerebral (ic) microinjections of the P450 inhibitor CC12 were determined on morphine antinociception in rats. CC12 inhibited morphine antinociception when both drugs were injected into the rostral ventromedial medulla (RVM), but not following co-injections into the periaqueductal gray (PAG) or into the spinal subarachnoid space. In addition, intra-RVM CC12 pretreatment nearly completely blocked the effects of morphine following intracerebroventricular (icv) administration. Although morphine is thought to act in both the PAG and RVM by pre-synaptic inhibition of inhibitory GABAergic transmission, the present findings show that 1) the mechanism of morphine action differs between these two brainstem areas, and 2) P450 activity within the RVM is important for supraspinal morphine antinociception. Characterization of morphine-P450 interactions within RVM circuits will further enhance the understanding of the biochemistry of pain relief.

1. Introduction

Morphine, the prototypical μ opioid analgesic, remains one of the most commonly used treatments for pain. However, the clinical utility of this drug is limited by the side effects, which include respiratory depression, constipation, and tolerance. In addition, the rewarding effects of opioids can lead to addiction (Gutstein and Akil, 2006). It is well established that μ opioid agonists like morphine act at μ opioid receptors in the midbrain periaqueductal gray (PAG), the rostral ventromedial medulla (RVM; consisting of the nucleus raphe magnus and adjacent reticular formation), and the dorsal horn of the spinal cord to produce antinociception (Yaksh and Rudy, 1978;Yaksh et al., 1976). These three CNS sites comprise an interconnected pathway responsible for the descending modulation of pain processing (Heinricher and Ingram, 2008). Activation of this circuit, by electrical stimulation, stress, or analgesic drugs, results in the depression of incoming nociceptive signals at the level of the spinal cord (Heinricher and Ingram, 2008).

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Previous work in our lab reported that CC12, a compound related to cimetidine, inhibits the antinociceptive activity of several types of pain-relieving drugs (Hough et al., 2007). Intracerebroventricular (icv) administration of CC12 blocked the antinociceptive effects of the μ opioid agonist morphine, the cannabinoid agonist WIN55–212, and the non-opioid analgesic improgan (Hough et al., 2007). It was shown that CC12 lacks affinity at a number of targets known to be involved in analgesic signaling (Hough et al., 2007). At the time, it was proposed that these three classes of analgesic drugs share a common, downstream, CC12-sensitive target, but the identity of this target was unknown. Subsequent studies found CC12 to be a potent inhibitor of a number of cytochrome P450 monooxygenase (P450) enzymes (Stadel et al., 2008), leading to the possibility that CC12 might block all three types of pain-relieving drugs via inhibition of P450 activity (Hough et al., 2007; Stadel et al., 2008). Several enzymes (including MAPK, phospholipase C, and phospholipase A_2) are known to participate in the supraspinal actions of μ opioid agonists, resulting in the release of a number of signaling molecules including inositol-1,4,5-triphosphate and arachidonic acid (Christie et al., 1999; Aoki et al., 2003; Law et al., 2000; Narita et al., 2003), but no evidence for P450-mediated opioid signal transduction existed.

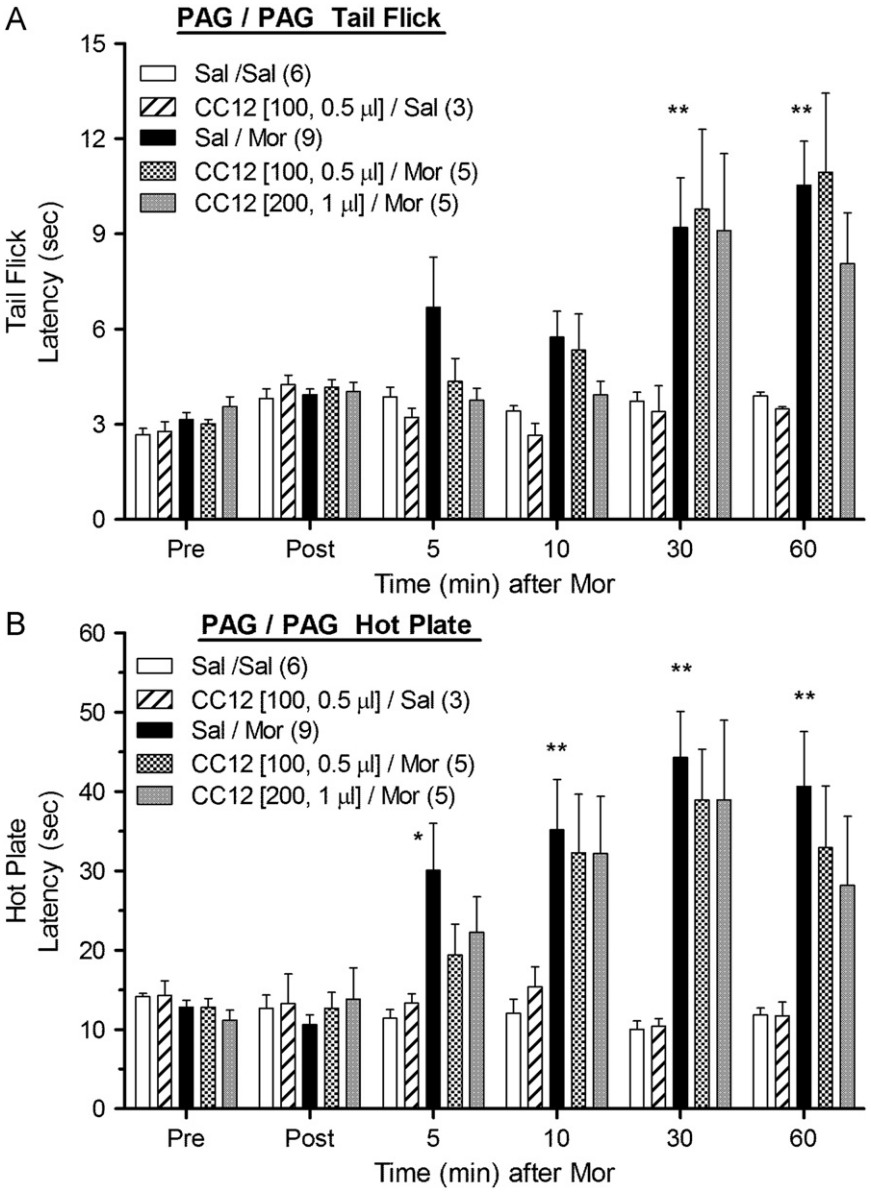

Fig. 1 – Effect of CC12 on morphine antinociception in the PAG. Surgically cannulated subjects were baseline (Pre) tested, received an ic injection of saline (Sal) or CC12 (dose in nmol and volumes specified in brackets), were re-tested 15 min later (Post), and immediately received a second injection into the same brain site of either saline (Sal) or morphine sulfate (Mor, 5 µg, 0.5 µl). The volume of the first injection (Sal) in the Sal/Sal and Sal/Mor groups was either 0.5 or 1.0 µl; within each group, there were no volume effects and data were pooled. Tail flick (A) and hot plate (B) latencies (ordinate, sec, mean ± SEM, number of subjects in parentheses) were recorded at the time points indicated after the second injection (abscissa, min). *,$P < 0.05$, 0.01, respectively, versus Sal/Sal at the same time. Cannula placements are shown in Fig. 4.**