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Morphine analgesic tolerance in 129P3/J and 129S6/SvEv mice

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Abstract

Morphine analgesic tolerance is heritable in both humans and rodents, with some individuals and strains exhibiting little and others exhibiting robust tolerance. 129S6/SvEv and 129P3/J mice reportedly do not demonstrate tolerance to morphine analgesia. Using our laboratory's standard morphine tolerance regimen and a between-subjects design, tolerance developed in the hot plate and tail withdrawal assays as indicated by a change in analgesic efficacy following a morphine challenge dose. Furthermore, the non-competitive NMDA receptor antagonist MK-801 (dizocilipine) blocked morphine tolerance in 129S6/SvEv and CD-1 mice in the hot plate assay. As previously reported, when a within-subjects design and cumulative dosing was employed, no tolerance was observed in the 129P3/J strain. However, using the same morphine regimen and a between-subjects design, comparable tolerance developed between 129P3/J and C57BL/6J strains following a single challenge dose of morphine. Spontaneous hyperalgesia was observed in the tail withdrawal assay following chronic morphine in C57BL/6J, but not 129P3/J mice. Additionally, morphine-tolerant C57BL/6J mice, but not 129P3/J mice, exhibited a large increase in the frequency of tail flicks during the first second following the baseline nociceptive response which may facilitate detection of the response during the tolerant state. We conclude that the method of tolerance assessment affects the ability to detect tolerance and thus may affect the degree and pattern of heritability of this trait and this could have implications for gene mapping studies.

Keywords: Opioid; Analgesia; Antinociception; Genetic; Intensity; Nociception; Pain; Tail flick; Inbred; Opiate

1. Introduction

Morphine analgesic tolerance can be observed in rodents and humans following chronic administration. Susceptibility to morphine tolerance is heritable, with some strains and individuals exhibiting robust tolerance, and others exhibiting very little tolerance (Foley, 1993; Hoffmann et al., 1998; Kest et al., 2002; Liang et al., 2006; Mas et al., 2000). The identification of genes that contribute to the heritability of morphine tolerance could aid in the identification of susceptible patients and the development of concurrent treatments that limit tolerance and subsequently drug dependence.

Using several inbred mouse strains and the tail withdrawal assay, it was demonstrated that morphine analgesic tolerance is heritable with some strains demonstrating robust tolerance (e.g., C57BL/6J), and others such as the 129P3/J strain showing no tolerance (Kest et al., 2002). A very recent report indicates a very different pattern of heritability of morphine tolerance in 7 of the same 11 mouse strains in which there is no correlation in tolerance liability rank between the two studies ($r=0.14$; $p>0.05$; (Liang et al., 2006). Thus, the pattern of heritability of morphine tolerance in inbred mouse strains is not consistent across studies.

Co-administration of NMDA receptor antagonists with morphine disrupts the development of tolerance. Although the signaling pathway(s) that mediate the contribution of NMDA receptors to morphine tolerance is not clear, one hypothesis is that upon activation of protein kinase C, opioid receptor activation leads to NMDA receptor activation, calcium influx,

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and activation of second messenger systems that mediate changes in gene expression and neuroplasticity responsible for morphine tolerance (Trujillo, 2002). Another possibility is that activation of NMDA receptors occurs indirectly in cells downstream of opioid receptors (Eitan et al., 2003) and adaptations in these cells contribute to morphine tolerance.