Brain Research 1658 (2017) 36–41

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Dissociation of morphine analgesic effects in the sensory and affective components of formalin-induced spontaneous pain in male and female rats

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ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form 27 December 2016
Accepted 9 January 2017
Available online 12 January 2017

Keywords:
Opioid
Pain
Conditioned place aversion
Affect
cFos
Sex difference

ABSTRACT

Sex differences in the analgesic effects of morphine have been previously reported in various models that represent the sensory component of pain. However, pain sensation is a complex process that consists of both sensory and affective components. It is presently unclear whether the analgesic effects of morphine between the sensory and affective components of pain are sexually dimorphic. Moreover, differences in morphine dose-response in the two components of pain have not been examined in male and female rats. Therefore, we examined the analgesic effects of morphine on the sensory and affective components of formalin-induced pain behaviors in male and female rats. To discern the sensory component, rats were pretreated with varying doses of morphine and then intraplantar formalin-induced paw flinches were measured. Morphine reduced the number of formalin-induced paw flinches at a treatment dose of 4.0 mg/kg. Morphine analgesia was similar across the sexes in the early (phase 1) and late phase (phase 2) of the formalin test. To examine the affective component, rats were pretreated with varying doses of morphine, and then intraplantar formalin-induced conditioned place aversion (CPA) was examined. Formalin produced CPA, which was blocked by morphine at doses of 1.0 mg/kg and higher in male and female rats. Lastly, formalin-induced cFos expression and the effects of systemic morphine were examined in the superficial dorsal horn of the spinal cord. Intraplantar formalin produced robust expression of cFos; however, morphine did not attenuate the cFos expression. These results demonstrate a notable dissociation of the analgesic effects of morphine by detecting a fourfold shift in the minimum effective dose between the sensory and affective components of formalin-induced spontaneous pain, that were similar between male and female rats. The findings further suggest disparate mechanisms involved in systemic morphine-induced analgesia in the two components of formalin-induced pain.

1. Introduction

Human and animal studies have provided evidence indicating that sex differences arise when opioids are exogenously administered (Dahan et al., 2008; Fillingim and Gear, 2004). Sex differences in the analgesic effects of morphine have been studied in various pain models, with majority of studies concluding that male rats exhibit a heightened sensitivity to morphine analgesia as compared to female rats (Cicero et al., 1996; Craft, 2008; Kest et al., 2000; Wang et al., 2006). To date, the findings of studies reporting sex differences have concentrated on the sensory (discriminative) component of pain. However, sensation of pain is a multifaceted process that can be divided into sensory and affective (emotional) components. These components play unique and important roles in the pain experience, which can be modulated by one another. The sensory component of pain is the initiator of the pain experience induced by a noxious stimulus, leading to negative affective experiences associated with the application of the stimulus or the related tissue or nerve injury. In chronic pain states, negative affect can diminish the quality of life of the person impacted, leading to the development of various psychiatric conditions, such as depression, anxiety, memory deficits, and emotional decision making (Apkarian et al., 2004; Fishbain et al., 1997; Leavitt and Katz, 2006; Romano and Turner, 1985; Walteros et al., 2011).

Activation of opioid receptors by morphine or other opioid analgesics attenuate sensory and affective components of pain. The analgesic effects of morphine have been thoroughly studied on the sensory component of pain using various rodent models. These studies have demonstrated that systemically administered mor-

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http://dx.doi.org/10.1016/j.brainres.2017.01.011
0006-8993/

phine effectively blocks spontaneous pain in the formalin model (Grégoire et al., 2012; Yaksh et al., 2001), as well as pain and hyperalgesia induced by inflammatory and neuropathic injuries (Cahill et al., 2013; Eidson and Murphy, 2013). Conversely, examination of the effects of opioids on the affective component is more recent. One method of measuring the effects of opioid analgesics on the affective component of pain is through the anti-aversive effects of opioids on noxious stimulus-induced conditioned place aversion (CPA) (Johansen et al., 2001). In such method, aversion would be evoked using a noxious stimulus capable of producing spontaneous pain with temporal proximity to the conditioning session of the CPA procedure. Opioids would then be applied to block the noxious-stimulus evoked aversion, and thus to prevent or attenuate the formation of a CPA. This approach has demonstrated that morphine and other opioid agonists block the aversive effects of carrageenan-induced pain in the CPA paradigm (Rutten et al., 2011; van der Kam et al., 2008), with morphine having a lower minimum effective dose in blocking the affective component, as compared to the sensory component. Similar to the findings in animals, lower doses of opioid analgesics appear to inhibit the affective component of pain, as compared to the sensory component in humans (Oertel et al., 2008; Price et al., 1985).

To our knowledge, there is a lack of evidence pertaining to the analgesic effects of systemically administered morphine on formalin-induced pain behaviors in female rats. Such analysis is further complicated by the presence of the two components of pain. The goal of the present study was to determine the presence of sex differences in the analgesic effects of systemically administered morphine in formalin-induced paw flinching behavior and CPA. Furthermore, we sought to determine the presence of sex differences in the minimum effective dose of morphine on formalin-induced pain behaviors. In addition, studies examining neuronal activation via the immediate early gene cFos have shown that opioids decrease nociception-evoked cFos activation in the spinal cord (Kondo et al., 2005; Nazarian et al., 2008; Sawamura et al., 1999; Trafton et al., 1999). However, it is unclear whether the effects of systemically administered morphine on suppression of cFos activation corresponds to doses that block the affective and/or sensory components of pain in male and female rats.

2. Results

Analgesic effects of morphine on formalin-induced paw flinches are shown in Fig. 1. Male and female rats treated with morphine (4.0 mg/kg) displayed a significant decrease in formalin-induced paw flinches compared to the saline treated groups [Drug main effect, $F(3, 56) = 19.344$, $p < 0.001$]. This significant difference was consistent across phase 1 and phase 2 of the formalin test. The lower doses of morphine did not decrease formalin-induced paw flinches in either phase. Overall, male and female rats did not differ in their response to formalin-induced paw flinches [Sex main effect $F(1, 56) = 0.389$, $p > 0.05$]. Moreover, male and female rats did not differ in their paw flinch behavior in response to morphine [Sex x Drug interaction $F(3, 56) = 0.807$, $p > 0.05$].

The effects of morphine on formalin-induced CPA are illustrated in Fig. 2A. The aversive effects of formalin were blocked by morphine (1.0, 2.0, and 4.0 mg/kg) as compared to saline [Drug main effect $F(4, 78) = 11.39$ $p < 0.001$]. Male and female rats did not differ in the formalin-induced CPA [Sex main effect $F(1, 78) = 0.378$, $p > 0.05$]. Likewise, male and female rats did not differ in response to the effects of morphine on formalin-induced CPA [Sex $\times$ Drug interaction $F(4, 78) = 0.497$, $p > 0.05$]. The effects of morphine on formalin CPA was not due to the direct rewarding effects of morphine, as a single pairing of morphine (0.5, 1.0, 2.0, and 4.0 mg/kg) did not produce a conditioned place preference (CPP) in rats that were not injected with formalin [Drug main effect $F(4, 136) = 1.647$, $p > 0.05$; Fig. 2B].

The effects of formalin-induced pain and morphine treatment on cFos expression in the dorsal horn of the spinal cord are demonstrated in Fig. 3. Formalin treatment produced a significant increase in cFos expression on the ipsilateral side of the dorsal horn of male and female rats, [Side main effect $F(1, 18) = 245.84$, $p < 0.001$]. Morphine (0.5, 1.0, and 4.0 mg/kg) did not decrease the formalin-induced cFos expression [Drug main effect $(3, 18) = 1.154$, $p > 0.05$]. Furthermore, formalin-induced cFos expression were similar between male and female rats [Sex main effect $F(1, 18) = 0.159$, $p > 0.05$]. These findings suggest that although systemic morphine decreases formalin-induced sensory and affective pain, there is no decrease in spinal cFos expression by the morphine doses tested.

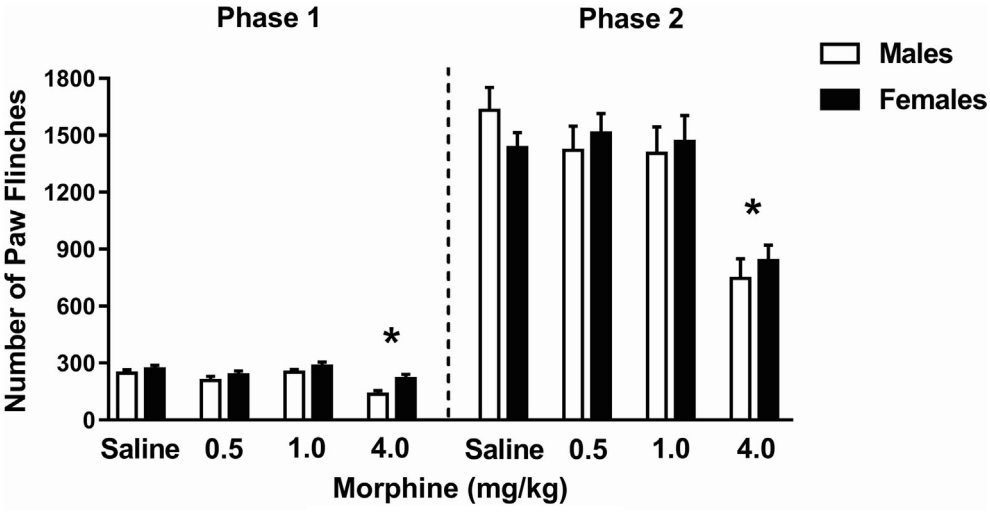

Fig. 1. Effects of morphine on formalin-induced paw flinches. Morphine at 4.0 mg/kg decreased the formalin-induced paw flinches during phase 1 and 2 in male and female rats. Data are expressed at mean (±S.E.M.). Asterisks represent differences from saline group ($p < 0.05$).