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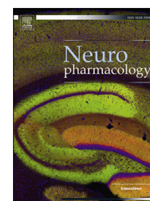

Expression and pharmacological modulation of visceral pain-induced conditioned place aversion in mice

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Pain encompasses both a sensory as well as an affective dimension and these are differentially processed in the brain and periphery. It is therefore important to develop animal models to reflect the non-reflexive assays in pain. In this study, we compared effects of the mu opioid receptor agonist morphine, the nonsteroidal anti-inflammatory drug ketoprofen and the kappa receptor opioid agonist U50,488H and antagonist JDTic on acetic acid-induced stretching and acetic acid-induced aversion in the condition place aversion (CPA) test in male ICR mice. Intraperitoneal administration of acetic acid (0.32–1%) was equipotent in stimulating stretching and CPA. Ketoprofen, morphine and U50,488H all inhibited the acid-induced stretching. Ketoprofen and morphine also blocked the acid-induced CPA but U50,488H failed to do so. The reversal ability of ketoprofen and morphine on acid-induced CPA is unique to pain-stimulated place aversion since these drugs failed to reduce non-noxious LiCl-induced CPA. Overall, this study characterized and validated a preclinical mouse model of pain-related aversive behavior that can be used to assess genetic and biological mechanisms of pain as well as improving the predictive validity of preclinical studies on candidate analgesics.

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1. Introduction

Pain has been described as a multi-dimensional state composed of sensory, affective, and cognitive components (Apkarian et al., 2004; Ji et al., 2010; Neugebauer et al., 2009). Furthermore, pain states that require clinical intervention are often accompanied by changes in affective behaviors (Hummel et al., 2008; Joshi and Honore, 2006; Mogil, 2009; Whiteside et al., 2013). Thus, animal models that measure pain-related changes in affective behaviors may serve as important tools in the development of more efficacious analgesic drugs. Recent behavioral studies suggest that these affective components of pain can be evaluated in rodents. For example, depression of positively reinforced operant responding maintained by delivery of food (Martin et al., 2004) or electrical brain stimulation (Do Carmo et al., 2009; Leitl et al., 2014) was reported after injury or treatment with experimental noxious stimuli. In addition, recent studies in rats showed that a aversion to a noxious stimuli can also be assessed with a conditioned place aversion (CPA) test after intraperitoneal (i.p.) injection of acetic acid (AA) (Deyama et al., 2010) or intraplantar injection of complete Freund's adjuvant (Johansen et al., 2001; Zhang et al., 2013). These studies revealed that several limbic brain areas, such as the anterior cingulate cortex (Deyama et al., 2007; Johansen and Fields, 2004; Johansen et al., 2001), central amygdala (Deyama et al., 2010), and bed nucleus of the stria terminalis (Deyama et al., 2008, 2007), mediate this CPA. There has been limited studies exploring the induction of CPA after noxious stimulus delivery in mice (Browne and Woolf, 2014; Daou et al., 2013), but such studies might be useful given the molecular and genetic applicability of mouse models to human disease phenotypes (Rosenthal and Brown, 2007).

Toward that end, the purpose of this study was to evaluate the expression and pharmacological modulation of CPA produced in

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mice by a commonly used acute visceral noxious stimulus (i.p. AA). We hypothesized that AA would induce place aversion, and that AA-induced CPA would be sensitive to blockade by pretreatment with two clinically effective analgesics, the nonsteroidal anti-inflammatory drug ketoprofen or the mu opioid receptor agonist morphine. Effects of the kappa opioid receptor agonist U50,488H and the kappa antagonist JDTic were also evaluated. Kappa agonists that readily cross the blood–brain barrier to produce centrally mediated effects after systemic administration constitute one class of drugs that produces antinociception in many conventional preclinical assays of pain (Broadbear et al., 1994; Horan et al., 1991); however, centrally acting kappa agonists have failed to meet safety and efficacy criteria for clinical use (Pande et al., 1996a, 1996b). Consequently, kappa agonists exemplify the potential for “false positive” outcomes in conventional preclinical assays of candidate analgesics (Mogil, 2009; Negus et al., 2006; Vierck et al., 2008; Whiteside et al., 2013), and U50,488H was tested here as a negative control. We hypothesized that U50,488H would fail to block AA-induced CPA. Conversely, it has been suggested that negative affective components of pain may involve activation of endogenous kappa opioid systems in limbic brain regions (Cahill et al., 2014). This hypothesis predicts that AA-induced CPA might be blocked by a kappa antagonist like JDTic.

The present study also included two other components. First, the expression and pharmacological modulation of AA-induced CPA were compared to the expression and pharmacological modulation of the AA-induced stretching response. The stretching (or “writhing”) response is a commonly used behavioral endpoint in studies of visceral pain elicited by i.p. injection of AA or other chemical irritants (Koster et al., 1959). However, we have categorized the stretching response as an example of a “pain-stimulated behavior,” which can be defined as a behavior that increases in rate, frequency or intensity after delivery of a noxious stimulus (Negus et al., 2010, 2006). Exclusive reliance on pain-stimulated behaviors in preclinical research can be problematic because they are sensitive not only to treatments that reduce sensory sensitivity to the noxious stimulus, but also to treatments that produce motor impairment. We hypothesized that AA-induced stretching would be blocked by ketoprofen, morphine and U50,488H but not by JDTic. Second, ketoprofen and morphine effects on AA-induced CPA were compared to their effects on CPA induced by lithium chloride (LiCl), a non-noxious aversive stimulus (Lett, 1985). Insofar as LiCl-induced aversion is not thought to involve nociception, we hypothesized that neither ketoprofen nor morphine would block LiCl-induced aversion.

2. Materials and methods

2.1. Animals

Male adult ICR mice (20–25 g) obtained from Harlan Laboratories (Indianapolis, IN) were used throughout the study. Animals were housed in an AAALAC approved facility in groups of four and had free access to food and water. Experiments were performed during the light cycle and were approved by the Institutional Animal Care and Use Committee of Virginia Commonwealth University.

2.2. Drugs

U50,488H [trans- (±) −3,4-Dichloro-N-methyl-N-[2- (1-pyrrolidinyl) cyclohexyl] benzeneacetamide methanesulfonate salt], AA and LiCl were purchased from Sigma–Aldrich (St. Louis, MO). Ketoprofen (100 mg/ml in distilled water with 0.25% Benzyl alcohol) was purchased from Fort Dodge (Fort Dodge, IA). Morphine sulfate [morphine hemi[sulfate pentahydrate]] was supplied by the National Institute on Drug Abuse (Washington, DC). JDTic [(3R)-7-hydroxy-N-((1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide], synthesized as previously described (Thomas et al., 2003), was a generous gift from the Research Triangle Institute (Research Triangle Park, NC). The AA was diluted with sterile water and ketoprofen working solutions were diluted with physiological saline (0.9% sodium chloride). All other drugs were dissolved in physiological saline and injected at a total volume of 1ml/100 g body weight unless noted otherwise. All doses are expressed as the free base of the drug. All test drugs were injected subcutaneously (s.c.), AA and LiCl were injected i.p. All experiments were performed blindly to the drugs. Test drugs were prepared by another researcher than the examiner.

2.3. Acetic acid-induced stretching

Each mouse was placed in a Plexiglas box (29 × 19 × 13 cm each) and allowed to acclimate for 20 min. Then, mice were treated as described below, and the number of stretches was counted in 10-min bins for 60 min. A stretch was operationally defined as a contraction of the abdomen followed by an extension of the hind limbs.

To evaluate AA potency, mice were treated i.p. with either sterile water as vehicle of AA or AA (0.32–1.0%) immediately prior to the 60 min observation period. To evaluate AA time course, mice were also treated i.p. with 1% AA 30 or 60 min prior to the 60 min observation period. To evaluate test drug effects, mice were pretreated with s.c. saline as vehicle of test drugs, the NSAID ketoprofen (1, 2, 4 mg/kg; 15 min pretreatment), the μ-opioid receptor agonist morphine (0.1, 0.32, 1.0, 3.2 mg/kg; 15 min pretreatment), or the κ-opioid receptor (KOR) agonist U−50488H (0.1, 0.32, 1.0, 3.2, 10 mg/kg; 10 min pretreatment) prior to i.p. injection of 1% AA, and observation began immediately after AA injection. Each mouse was used for only one experiment.

2.4. Acetic acid (AA) conditioned place aversion (CPA) studies

CPA was evaluated using an unbiased design as previously described (Papke et al., 2015). In brief, separate groups of mice were handled for three days prior to initiation of conditioning. The CPA apparatus (Med-Associates, St. Albans, VT, ENV3013) consisted of white and black chambers (20 × 20 × 20 cm each), which differed in floor texture (white mesh and black rod). The compartments were separated by a smaller grey chamber with a smooth PVC floor and partitions that allowed access to the black and white compartments. The black and white compartments also had different floor textures, and removable doors separated the center grey compartment from the two white and black side compartments. Experiments were conducted using a 3-day protocol. On day 1, mice were placed in the grey center compartment for a 5 min habituation period followed by a 15 min test period to determine baseline time spent in each compartment by removing the doors. A pre-preference score was recorded, and mice within each group were then randomly assigned such that an even number of mice received the experimental treatment on the black and white side. On day 2, the doors were in place to separate the compartments, and mice were exposed to two 40-min conditioning sessions no less than 4 h apart. Prior to one conditioning session, mice received one of the treatments described below and were placed into either the black or white compartment as dictated by their assignment on day 1. Prior to the other conditioning session, mice received vehicle injections and were placed into the other compartment. On day 3, the doors were again removed after habituation, and the day 1

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