European Journal of Pharmacology 736 (2014) 16–25

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Neuropharmacology and analgesia

Citral: A monoterpene with prophylactic and therapeutic anti-nociceptive effects in experimental models of acute and chronic pain

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ARTICLE INFO

Article history:
Received 9 August 2013
Received in revised form
31 March 2014
Accepted 6 April 2014
Available online 30 April 2014

Keywords:
Citral
Neuropathic pain
Chronic pain
Postoperative pain
Chronic regional pain syndrome
Gastro-protective effect

ABSTRACT

Citral (3,7-dimethyl-2,6-octadienal) is an open-chain monoterpenoid present in the essential oils of several medicinal plants. The aim of this work was to evaluate the effects of orally administered citral in experimental models of acute and chronic nociception, inflammation, and gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs). Oral treatment with citral significantly inhibited the neurogenic and inflammatory pain responses induced by intra-plantar injection of formalin. Citral also had prophylactic and therapeutic anti-nociceptive effects against mechanical hyperalgesia in plantar incision surgery, chronic regional pain syndrome, and partial ligation of sciatic nerve models, without producing any significant motor dysfunction. In addition, citral markedly attenuated the pain response induced by intra-plantar injection of glutamate and phorbol 12-myristate 13-acetate (PMA, a protein kinase C activator), as well as by intrathecal (i.t.) injection of ionotropic and metabotropic glutamate receptor agonists (*N*-methyl-D-aspartic acid [NMDA] and 1-amino-1,3-dicarboxycyclopentane [trans-ACPD], respectively), substance P, and cytokine tumour necrosis factor-α. However, citral potentiated behaviours indicative of pain caused by i.t., but not intra-plantar, injection of a transient receptor potential vanilloid receptor type 1 (TRPV1) agonist. Finally, the anti-nociceptive action of citral was found to involve significant activation of the 5-HT_{2A} serotonin receptor. The effect of citral was accompanied by a gastro-protective effect against NSAID-induced ulcers. Together, these results show the potential of citral as a new drug for the treatment of pain.

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1. Introduction

Pain is a major public health problem that decreases quality of life, limits activity, and reduces functional capacity. Acute post-operative pain is followed by persistent pain in 10–50% of individuals who have undergone common surgeries. Because chronic pain can be severe in 2–10% of these patients, persistent post-operative pain represents a major, largely unrecognised clinical problem (Visser, 2006; Kehlet et al., 2006). The incidence of complex regional pain syndrome (CRPS) following orthopaedic surgery is estimated at between 74,000 and 191,000 new cases per year (Gottschalk and Raja, 2004; Hayes et al., 2002). CRPS is a chronic pain syndrome that occurs after injuries such as sprains, fractures, and crush injuries, and it is classified into 2 types: without (type I) or with (type II) major nerve injury (Feliu and Edwards, 2010).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs owing to their high efficacy in the treatment of pain, fever, inflammation, and rheumatic disorders. However, their continuous use is associated with adverse effects at the level of the digestive tract, such as gastrointestinal erosion and peptic ulcers, and can lead to more serious complications, such as overt bleeding or perforation, that greatly impair quality of life with prolonged use (Blandizzi et al., 2009; Fiorucci et al., 2001). The availability of different treatment options has fostered intensive preclinical and clinical research aimed at addressing a number of unresolved issues and establishing rational criteria for the

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http://dx.doi.org/10.1016/j.ejphar.2014.04.029
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appropriate use of analgesic and anti-inflammatory drugs in medical practice (Blandizzi et al., 2009). Research aimed at finding new therapeutic targets for the treatment of pain, including natural products from medicinal plants, has led to the discovery of numerous molecular regulators of ion channels in primary afferent nociceptive neurons.

Citral (3,7-dimethyl-2,6-octadienal), which is a mixture of 2 isomers (*cis*-isomer neral and *trans*-isomer geranial), is an open-chain monoterpenoid. It is present in volatile oils of several plants, such as *Cymbopogon citratus*, an herb commonly known as lemongrass. Lemongrass tea is popularly used in Brazil as a spasmolytic, analgesic, anti-inflammatory, antipyretic, diuretic, and tranquiliser (Ferreira, 1984). Furthermore, Stotz et al. (2008) reported that citral acts as a partial agonist of transient receptor potential (TRP) channels, and the prolonged inhibition of these receptors following activation was the most pharmacologically relevant effect of this monoterpene. Members of the TRP family of ion channels are activated or modulated by diverse exogenous noxious stimuli and selected molecules that are released during tissue damage and inflammatory processes (Morales-Lázaro et al., 2013). Thus, partial transient receptor potential vanilloid receptor type 1 (TRPV1) agonists might be useful as anti-inflammatory and analgesic compounds (Epstein and Marcoe, 1994). According to Stotz et al. (2008), citral has a broad spectrum of activity and its prolonged sensory inhibition effect may prove it to be more useful than capsaicin for allodynia and other types of pain. The aim of this work was to evaluate the effect of citral, administered via the oral route, in experimental models of chronic and acute nociception and on gastric ulcers in rodent models of pain that may be relevant to particular pain states.

2. Materials and methods

2.1. Animals

Experiments were conducted using adult male Swiss mice (weight, 25–35 g; approximately 6 weeks of age) obtained from Biotério Anilab (Paulínia, São Paulo, Brazil) or Universidade Federal de Santa Catarina (UFSC, Florianópolis, Santa Catarina, Brazil), and adult male Wistar rats (weight, 200–220 g) obtained from Biotério Central of Universidade Estadual Paulista 'Júlio de Mesquita Filho' (UNESP, Botucatu, São Paulo, Brazil). All animals were housed in collective cages at 22 ± 1 °C under a 12-h light/dark cycle (lights on at 0600 h) with free access to food and water. All animal care and experimental procedures were performed in accordance with the ethical statements established by the National Guidelines for the Use of Experimental Animals of Brazil and National Institutes of Health Animal Care Guidelines (NIH publication No. 80-23) and protocols approved by the Committee for the Ethical Use of Animals (CEEA/UNESP 366 and CEUA/UFSC PP00745). The animals were habituated to the laboratory conditions for at least 1 h before testing, and all experiments were performed during the light phase of the light/dark cycle. All efforts were made to demonstrate consistent effects of the drug treatments and to minimise both the number of animals used and their suffering (Zimmerman, 1983).

2.2. Drugs

The following substances were used: citral, L-glutamic acid hydrochloride, the cytokine tumour necrosis factor (TNF)-α, capsaicin, substance P, *N*ω-nitro-L-arginine, L-arginine hydrochloride, naloxone hydrochloride, WAY100635, ketanserin tartrate, ondansetron hydrochloride, phorbol myristate ester, indomethacin, carbenoxolone (Sigma, St. Louis, MO, USA), (6)-1-aminocyclopentane-trans-1,3-dicarboxylic acid (trans-ACPD), *N*-methyl-D-aspartic acid (NMDA) (Tocris Cookson Inc., Ellisville, MO), morphine (Cristália, São Paulo, Brazil), Tween 80 (Vetec, Rio de Janeiro, Brazil), and formaldehyde (Chemco Ind. e Com. Campinas, Brazil). The following agents were immediately dissolved in 0.9% NaCl solution before administration: citral (diluted in 1% Tween 80 solution), capsaicin (diluted in 1% ethanol solution), and glutamate (diluted in saline and neutralised with 3 M NaOH). The final concentration of Tween 80 did not cause any effect when it was administered alone.

2.3. Formalin-induced nociception

The experimental model used was essentially the same as that described previously (Hunskaar et al., 1985). Animals received an intra-plantar (i.pl.) injection of 20 μL of 2.7% formalin (1% formaldehyde) in saline in the ventral surface of the right hind paw, and were observed during the first 5 min (neurogenic phase) and between the 15 and 30 min (inflammatory phase) after injection. Mice were pretreated with citral (25, 100, or 300 mg/kg) or vehicle solution (10 mL/kg) via the oral route (by gavage) 1 h before formalin injection. After formalin injection, the animals were immediately placed into glass cylinders 20 cm in diameter, and the time spent licking the injected paw was recorded as an indicator of nociception by using a chronometer.

2.4. Plantar incision model of post-operative pain

Plantar incision surgery (PIS) was performed as previously described (Martins et al., 2012; Pogatzki and Raja, 2003). Briefly, mice were anaesthetised with 1–2% isoflurane delivered via a nose cone. After loss of the righting reflex and antiseptic preparation of the right hind paw with 10% povidone-iodine solution, a 5-mm longitudinal incision was made through the skin and fascia of the plantar surface by using a number 11 scalpel blade. The incision started 2 mm from the proximal edge of the heel and extended towards the toes. The underlying muscle was elevated using a curved forceps, leaving the muscle origin and insertion intact. The skin was opposed with a single mattress suture of 8-0 nylon monofilament, and the wound was covered with 10% povidone-iodine solution. The animals were allowed to recover in their cages, and the suture was removed at the end of post-operative day 2. Control mice underwent a sham procedure that consisted of anaesthesia, antiseptic preparation, and topical application of 10% povidone-iodine solution without plantar incision. The sham-operated mice received only vehicle (10 mL/kg, i.g.), and the operated mice were randomly divided into control and treatment groups, which received vehicle (10 mL/kg, i.g.) or citral (2.5, 25, 100, and 300 mg/kg, i.g.), respectively, 24 h after surgery. Mechanical hyperalgesia response was recorded before surgery (B), immediately before treatment (0 h), and after treatment (1, 2, 3, and 4 h) to verify the time-course effect of citral, as described below. To investigate the effects of repeated treatment with citral on the mechanical hyperalgesia response, citral (100 mg/kg, i.g.) was administered once daily for 6 consecutive days, and its antinociceptive effect was examined 2 h after treatment, which corresponds to the maximal effect observed during the time-course experiment.

2.5. Animal model of complex regional pain syndrome type-I

Chronic post-ischaemic pain (CPIP) is used as an animal model for CRPS-I in humans, and was established as previously described by Coderre et al. (2004). Briefly, mice were anaesthetised over a 3-h period with a bolus (7%, 0.6 mL/kg, i.p.) of chloral hydrate and 20% of the initial volume at the end of the first and second hour. After anaesthesia was induced, an elastic O-ring for braces (Elástico Ligadura 000-1237, Unident, Brazil) with 1.2-mm internal diameter was placed around the mouse's right hind limb just proximal to the

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