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Effects of (−)-linalool in the acute hyperalgesia induced by carrageenan, L-glutamate and prostaglandin E_2

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Abstract

A series of studies performed in our laboratory have shown that (−)-linalool, the natural occurring enantiomer in essential oils, possesses anti-inflammatory and antinociceptive effects in different animal models. The antinociceptive effect of (−)-linalool has been ascribed to the stimulation of the cholinergic, opioidergic and dopaminergic systems, to its local anesthetic activity and to the blockade of *N*-Methyl-D-aspartate (NMDA) receptors. In this study, we investigated the effect of systemic administration of (−)-linalool in the paw withdrawal test in rats, a model of thermal hyperalgesia induced by monolateral subplantar injection of carrageenan, L-glutamate or prostaglandin E_2. Carrageenan and L-glutamate induced a hyperalgesic effect on the injection side. In contrast, prostaglandin E_2 induced hyperalgesia in both the injection side and the contralateral side. Pretreatment with (−)-linalool (50–150 mg/kg) inhibited the development of acute hyperalgesia induced by carrageenan in the injected paw, with no effect on the contralateral paw. Furthermore, (−)-linalool at the highest dose used (200 mg/kg), reduced and reverted the decrease in paw withdrawal latencies induced by L-glutamate on the ipsilateral side, showing antihyperalgesic and antinociceptive effects. An antinociceptive effect was apparent also in the contralateral paw. Finally, (−)-linalool (200 mg/kg) increased paw withdrawal latency on the side contralateral to prostaglandin E_2 injection, but not on the side of the injection. The efficacy of (−)-linalool in decreasing the hyperalgesia induced by carrageenan, L-glutamate and prostaglandin E_2 suggests that this compound might be useful in pain conditions sustained by the development of neuronal sensitization.

Keywords: (−)-Linalool; Hyperalgesia; Carrageenan; L-glutamate; Prostaglandin E_2

1. Introduction

(−)-Linalool is the natural occurring enantiomer of the monoterpene compound commonly found as a major volatile component of the essential oils in several aromatic plant series. (−)-Linalool administration in rats inhibits carrageenan-induced oedema (Peana et al., 2002) and antagonizes different pain responses elicited by the exposure to a chemical nociceptive stimulus such as acetic acid-induced writhing (Peana et al., 2003) or by a thermal nociceptive stimulus, applied in the hot plate, or by a tissue injury produced by formalin injection. (−)-Linalool antinociceptive effects were reduced by pretreatment with the unselective muscarinic receptor antagonist atropine or the opioid receptor antagonist naloxone or the dopamine D2 receptor antagonist sulpiride. Moreover, (−)-linalool effect was antagonized by the ATP-sensitive K^+ channel inhibitor glibenclamide, while the selective muscarinic M1 receptor antagonist pirenzepine and the dopamine D1 receptor antagonist SCH-23390 were ineffective (Peana et al., 2003, 2004). These observations suggest an involvement of muscarinic, opioid and dopamine transmission as well as an involvement of K^+ channels in the (−)-linalool antinociceptive effect.

It was also reported that linalool produces a negative modulation of glutamate transmission both in vitro and in vivo (Elisabetsky et al., 1999; Silva Brum et al., 2001a,b) and that this compound possesses local anesthetic activity (Ghelardini et al., 1999).

Tissue injury produces heightened sensitivity to subsequent noxious stimuli (hyperalgesia) consequent to periph-

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eral afferent sensitization. Hyperalgesia results in part from a complex cascade of events elicited by the activation of spinal neurokinin-1 and *N*-Methyl-D-aspartate (NMDA) receptors induced by the spinal release of substance P and glutamate. The activation of these receptors stimulates spinal phospholipase and cyclooxygenase activity leading to the synthesis and release of spinal prostanoids (Ebersberger et al., 1999; Yaksh et al., 2001).

Intraplantar injection of carrageenan induces a long-lasting inflammatory response with local oedema followed by a hyperalgesic condition. This inflammatory process is associated with the increase in prostanoids and glutamate production in the spinal cord (Jackson et al., 1995).

Glutamate plays an important role in both central and peripheral pain transmission (Beirith et al., 2002) and in the mechanism of hyperalgesia, particularly in sustained hyperalgesia associated with chronic pain (Follenfant and Nakamura-Craig, 1992; Jørum et al., 2003). In particular L-glutamate, following local intraplantar injection, evokes a stereospecific thermal hyperalgesia that is inhibited by the administration of NMDA antagonists (Jackson et al., 1995; Zhou et al., 1996).

Prostaglandin E_2 is a key mediator of inflammatory hyperalgesia: it induces a state of thermal hyperalgesia partially mediated by activation of substance P, NMDA, AMPA/Kainate and metabotropic glutamate receptors (Nakamura-Craig and Follenfant, 1995; Turnbach and Randich, 2002) as well as by the activation of adenylyl cyclase–cAMP–protein kinase A transduction system (Aley et al., 1998).

Thus, the aim of this study was to test the effect of systemic administration of (−)-linalool on the acute thermal hyperalgesic response induced by intraplantar injection of carrageenan or L-glutamate or prostaglandin E_2 into the rat paw.

2. Materials and methods

The present study was carried out in accordance with the Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance to the "Principles of the laboratory animal care" (NIH Publication No. 85-23, revised 1985). Effort was made to minimize the number of animals used and their suffering.

2.1. Subjects

The experiments were performed on male Wistar rats weighing 150–200 g (Harlan, Italy). They were maintained under controlled environmental conditions (temperature 22 ± 2 °C, humidity 60–65% and a regular light/dark cycle (lights on at 8:00_20:00 h)). All animals received standard laboratory diet and water ad libitum.

2.2. Drugs and treatments

(−)-Linalool (Sigma) was dissolved in Polyethylene glycol 200 (Sigma) and administered at doses of 50, 100, 150 and 200 mg/kg. Animals that did not receive (−)-linalool were administered the same volume of Polyethylene glycol 200. All treatments (vehicle and (−)-linalool) were performed by abdominal subcutaneous (s.c.) injection 30 min before intraplantar injection of the hyperalgesic substance or saline (control animals). All experiments were performed between 08:30 and 15:00 h.

2.3. Behavioral models of hyperalgesia

2.3.1. Paw withdrawal test

Thermal hyperalgesia was evaluated by the paw withdrawal test (Hargreaves et al., 1988) using a commercially available device (7370 Plantar Test, Basile, Italy). This device consisted of clear plastic chambers positioned on the glass floor of the testing apparatus, on which the rats were placed and allowed to acclimate to their surroundings for 5 min. Following acclimation, a radiant heat source was aimed at the plantar surface of each hind paw through the glass floor. A photoelectric cell automatically stops the heat source when the reflected light beam is interrupted (i.e. when the animal withdraws the paw) and records the paw withdrawal latency. A cut-off latency of 30 s was employed. Observers performing all the experiments were unaware of group allocation of the subjects.

2.3.2. Carrageenan-evoked thermal hyperalgesia

After baseline paw withdrawal latencies were recorded, the plantar surface of the left hind paw (ipsilateral) was injected subcutaneously with 1 mg of λ-carrageenan (1 mg in 100 μl of saline). Two hours later, three measurements of paw withdrawal latency at 5-min intervals were collected and averaged. Paw withdrawal latency was also recorded for the contralateral paw.

2.3.3. L-glutamate-evoked thermal hyperalgesia

Following baseline testing, L-glutamate (30 nmol/paw diluted in 50 μl of phosphate buffered saline) was injected into the ventral midplantar region of the left hind paw (ipsilateral). One hour later, three measurements of paw withdrawal latencies at 5-min intervals were collected and averaged. Paw withdrawal latency was also recorded for the contralateral paw.

2.3.4. Prostaglandin E_2-evoked thermal hyperalgesia

Following baseline testing, prostaglandin E_2 (200 ng/paw diluted in 50 μl of saline) was injected into the ventral midplantar region of the left hind paw (ipsilateral). Three hours later, three measurements of paw withdrawal latencies at 5-min intervals were collected and averaged. Paw withdrawal latency was also recorded for the contralateral paw.

2.4. Statistics

All data were expressed as the mean ± S.E.M. from each group and were analysed by one-way analysis of variance (ANOVA), followed by the post hoc Least Significant Difference (LSD) test.

3. Results

3.1. Effect of (−)-linalool on the carrageenan-evoked thermal hyperalgesia

ANOVA analysis relative to the effect of systemic administration of (−)-linalool on carrageenan-evoked thermal hyperalgesia in the ipsilateral hind paw revealed a significant main effect of treatment ($F(4,30)=5.61$, $P=0.0017$). LSD tests, performed to investigate the differences between the groups, showed that intraplantar carrageenan produced a significant decrease of thermal threshold compared to the control group ($P=0.0003$), whereas (−)-linalool pretreatment dose-dependently increased the paw withdrawal latency with respect to the carrageenan group (50 mg/kg ($P=0.017$), 100 mg/kg ($P=0.0062$) and 150 mg/kg ($P=0.0021$)) (Fig. 1).

ANOVA analysis demonstrated that, in the contralateral hind paw, carrageenan did not induce a significant thermal hyperalgesia; the same analysis revealed that (−)-linalool pretreatment did not show a significant effect ($F(4,30)=1.61$, $P=0.20$; Table 1).

Table 1
Effect of (−)-linalool on the contralateral paw of carrageenan-evoked thermal hyperalgesia

Treatment	Change in latency (s)
Control	− 1.12 ± 0.92
Carrageenan	− 1.68 ± 1.42
(−)-Linalool 50	− 2.82 ± 1.12
(−)-Linalool 100	0.80 ± 1.00
(−)-Linalool 150	0.60 ± 0.80

Change in latency with respect to the mean basal value (seconds) 2 h after intraplantar injection of carrageenan. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n=6–8$ per group.

3.2. Effect of (−)-linalool on L-glutamate-evoked thermal hyperalgesia

ANOVA analysis relative to the action of (−)-linalool on L-glutamate-induced hyperalgesia on the ipsilateral paw revealed a significant main effect of treatment ($F(4,31)=8.57$, $P=0.000089$). Post hoc analysis showed that intraplantar injection of L-glutamate produced a significant reduction in thermal paw withdrawal latency with respect to the control group ($P=0.05$). (−)-Linalool at the highest dose used (200 mg/kg) was effective in preventing the reduction in thermal paw withdrawal latency induced by L-glutamate ($P=0.000012$) and showed also a significant antinociceptive effect, since thermal paw withdrawal latency in this group was significantly higher than that in the control group ($P=0.0082$; Fig. 2).

ANOVA analysis relative to the effect of (−)-linalool on the side contralateral to L-glutamate-injection revealed a significant main effect of *treatment* ($F(4,32)=4.23$, $P=0.0073$). Post hoc analysis showed that L-glutamate did not induce thermal hyperalgesia in the contralateral paw. However, (−)-linalool pretreatment (200 mg/kg) had a significant antinociceptive effect since thermal paw withdrawal latency in this group was significantly higher than that measured in the control ($P=0.02$) and L-glutamate groups ($P=0.0015$), as illustrated in Fig. 3.

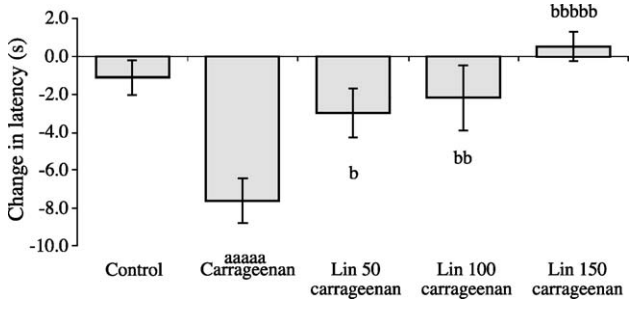

Fig. 1. Effect of (−)-linalool on the carrageenan-evoked thermal hyperalgesia. Change in latency with respect to the mean basal value (seconds) 2 h after intraplantar injection of carrageenan. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n=6–8$ per group. Significant differences from control group are indicated by ^{a} while from carrageenan group by ^{b} (^{a}, $^{b}P<0.05$; ^{aa}, $^{bb}P<0.01$; ^{aaa}, $^{bbb}P<0.005$; ^{aaaa}, $^{bbbb}P0.001$, ANOVA followed by LSD test).

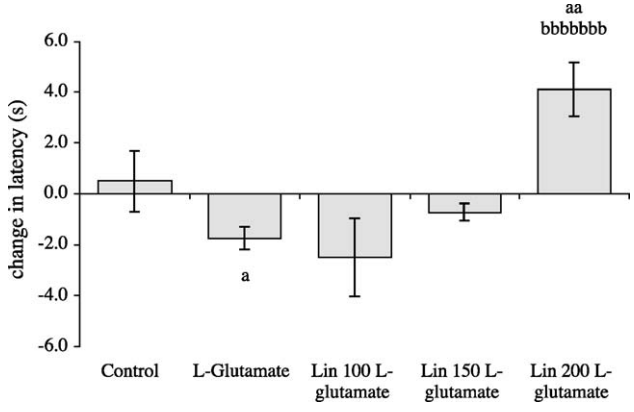

Fig. 2. Effect of (−)-linalool on the L-glutamate-evoked thermal hyperalgesia. Change in latency with respect to the mean basal value (seconds) 1 h after intraplantar injection of L-glutamate. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n=6–8$ per group. Significant differences from control group are indicated by ^{a} while from L-glutamate group by b ($^{a}P<0.05$; $^{a}P<0.01$; $^{bbbbb}P<0.0005$; ANOVA followed by LSD test).

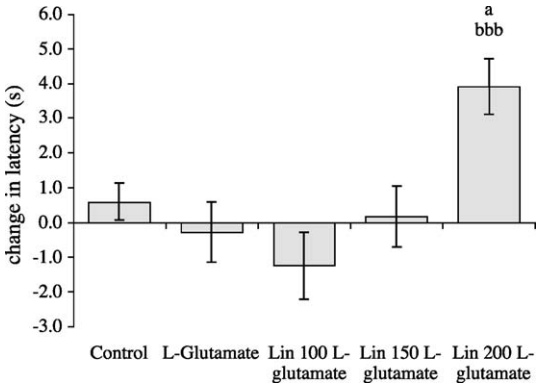

Fig. 3. Effect of (−)-linalool on the contralateral paw of L-glutamate-evoked thermal hyperalgesia. Change in latency with respect to the mean basal value (seconds) 1 h after intraplantar injection of L-glutamate. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n = 6–8$ per group. Significant differences from control group are indicated by [a] while from L-glutamate group by [b] ([a]$P < 0.05$; [bbb]$P < 0.005$; ANOVA followed by LSD test).

3.3. Effect of (−)-linalool on prostaglandin E_2-evoked thermal hyperalgesia

As illustrated in Fig. 4, local intraplantar injection of prostaglandin E_2 strongly reduced thermal threshold in the ipsilateral paw compared to thermal threshold in control group ($F(1,11) = 6.75$, $P = 0.0247$). ANOVA analysis relative to the effect of (−)-linalool pretreatment (100, 150 and 200 mg/kg) on prostaglandin E_2-evoked thermal hyperalgesia did not reveal a significant main effect of *treatment* ($F(4,30) = 2.04$, $P = 0.11$; Fig. 4).

ANOVA analysis relative to (−)-linalool effect on the paw contralateral to prostaglandin E_2 injection revealed a significant main effect of *treatment* ($F(4,30) = 3.097$, $P = 0.03$). As can be seen in Fig. 5, prostaglandin E_2 strongly reduced thermal threshold also in the contralateral paw ($P = 0.03$) and (−)-linalool pretreatment only at the highest dose used (200 mg/kg) significantly antagonized the reduction in thermal threshold induced by prostaglandin E_2 ($P = 0.032$).

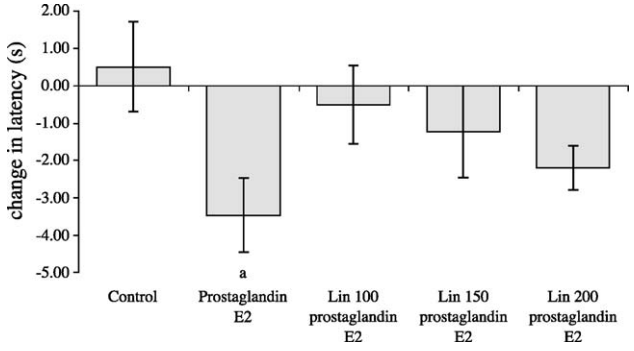

Fig. 4. Effect of (−)-linalool on the prostaglandin E_2-evoked thermal hyperalgesia. Change in latency with respect to the mean basal value (seconds) 3 h after intraplantar injection of prostaglandin E_2. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n = 6–8$ per group. Significant differences from control group are indicated by [a] ([a]$P < 0.05$; ANOVA followed by LSD test).

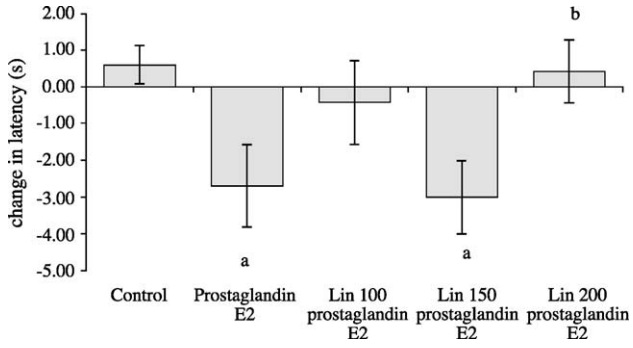

Fig. 5. Effect of (−)-linalool on the contralateral paw of prostaglandin E_2-evoked thermal hyperalgesia. Change in latency with respect to the mean basal value (seconds) 3 h after intraplantar injection of prostaglandin E_2. The doses are expressed as mg/kg. Data represent mean values ± S.E.M. $n = 6–8$ per group. Significant differences from control group are indicated by [a] while from PGE_2 group by [b] ([a], [b]$P < 0.05$; ANOVA followed by LSD test).

4. Discussion

The present study demonstrated that systemic administration of (−)-linalool dose-dependently attenuated the development of thermal hyperalgesia produced by carrageenan in the ipsilateral hind paw but did not modify withdrawal responses of the contralateral hind paw. The antihyperalgesic effect of (−)-linalool is in agreement with the observations of our previous study that showed that systemic administration of (−)-linalool attenuated the development of carrageenan-induced oedema in rat (Peana et al., 2002).

(−)-Linalool at the highest dose used (200 mg/kg) reduced and reverted the thermal hyperalgesia induced by L-glutamate in the ipsilateral paw, showing a significant antihyperalgesic and antinociceptive effect. The antinociceptive effect of (−)-linalool at the dose of 200 mg/kg was evident also in the hind paw contralateral to L-glutamate injection, which did not develop thermal hyperalgesia. The observation that the paw contralateral to the one that received L-glutamate did not show hyperalgesia could be due to the failure of L-glutamate, administered in periphery, to reach the central nervous system (CNS) and to evoke thermal hyperalgesia through mechanisms acting with the CNS.

Differently from L-glutamate, intraplantar injection of prostaglandin E_2 decreased thermal paw withdrawal response latencies on both the ipsilateral and the contralateral hind paw. The decrease in thermal paw withdrawal latency induced by prostaglandin E_2 was attenuated in the contralateral, but not in the ipsilateral side, by administration of (−)-linalool at the highest dose used. The hyperalgesia induced by prostaglandin E_2 (200 ng/paw) in the contralateral paw suggests that the effect obtained with this dose (Parada et al., 2003) involves central mechanisms. Thus the

efficacy of (−)-linalool in reducing hyperalgesia might be related to the effect of this compound on different transmission systems such as opioids, acetylcholine, dopamine, K^+ channels and glutamate possibly involved in the hyperalgesia induced by prostaglandin E_2. Local intraplantar injection of prostaglandin E_2 directly sensitizes nociceptors (Pitchford and Levine, 1991); since the induced hyperalgesia remained unaltered after (−)-linalool treatment, it is likely that this compound did not directly act on these nociceptors. These observations grant the study of the effect of (−)-linalool on thermal hyperalgesia induced by intrathecal prostaglandin E_2.

The present results are consistent with previous observations on the pharmacological properties of linalool, such as its ability to block NMDA receptors activity (Silva Brum et al., 2001a,b). It is generally accepted that NMDA transmission is involved in the nociceptive responses (Haley et al., 1990; Coderre and Van Empel, 1994; Chizh et al., 2001) and that the activation of peripheral NMDA receptors contributes to the development of thermal hyperalgesia (Eide et al., 1995; Jackson et al., 1995; Carlton and Coggeshall, 1999). Likewise, NMDA receptor antagonists have been reported to significantly increase thermal paw withdrawal latency following local intraplantar carrageenan and L-glutamate induced hyperalgesia in rats (Follenfant and Nakamura-Craig, 1992; Jackson et al., 1995; Zhou et al., 1996; Beirith et al., 2002), whereas thermal hyperalgesia evoked by intrathecal administration of prostaglandin E_2 was reported to be attenuated only by spinal application of NMDA receptor antagonists (Turnbach and Randich, 2002). In addition, it is well documented that systemic administration of local anesthetics induces antinociception that is dependent on a central cholinergic mechanism (Bartolini et al., 1987), since pretreatment with muscarinic receptor antagonists reduces this effect (Abelson and Höglund, 2002). Likewise, membrane-stabilizing agents such as local anesthetics or anticonvulsants are also used with some success in the treatment of neuropathic pain, a condition that is accompanied by a state of hyperalgesia (Fields, 1994; Jørum et al., 2003); thus the local anesthetic and anticonvulsant properties of linalool (Ghelardini et al., 1999; Elisabetsky et al., 1999) might also concur in determining its antihyperalgesic effect.

Beside the inhibition exerted by (−)-linalool on glutamatergic transmission in the mechanism of its antihyperalgesic effect, one might take into consideration the effect exerted by this compound on other neurotransmitter systems such as cholinergic M2, opioidergic and dopamine D2, as well as an effect on K^+ channels (Peana et al., 2004). The antihyperalgesic effect of (−)-linalool might result from the indirect stimulation of those three receptor families that are coupled to G_i/G_o proteins that are able to induce the opening of K^+ channels and consequent cellular hyperpolarization (Childers, 1991).

Collectively, these results indicate that (−)-linalool attenuated the development of inflammatory hyperalgesia produced by carrageenan and prevented the development of hyperalgesia induced by L-glutamate and prostaglandin E_2 probably through mechanisms mediated within the CNS. These antihyperalgesic effects of (−)-linalool occurred at doses that did not produced any visible modification of the animal's gross behavior.

The anti-inflammatory, antinociceptive and antihyperalgesic properties of (−)-linalool, shown in the present and in previous studies performed in our laboratory, suggest that this compound might be useful in pain conditions sustained by the development of neuronal sensitization.

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