Cardiovascular effects of 1,8-cineole, a terpenoid oxide present in many plant essential oils, in normotensive rats

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Abstract: The cardiovascular effects of i.v. treatment with 1,8-cineole, a monoterpene oxide present in many plant essential oils, were investigated in normotensive rats. This study examined (i) whether the autonomic nervous system is involved in the mediation of 1,8-cineole-induced changes in mean aortic pressure (MAP) and heart rate (HR) and (ii) whether the hypotensive effects of 1,8-cineole could result from its vasodilatory effects directly upon vascular smooth muscle. In both pentobarbital-anesthetized and conscious, freely moving rats, bolus injections of 1,8-cineole (0.3–10 mg/kg, i.v.) elicited similar and dose-dependent decreases in MAP. Concomitantly, 1,8-cineole significantly decreased HR only at the highest dose (10 mg/kg). Pretreatment of anesthetized rats with bilateral vagotomy significantly reduced the bradycardic responses to 1,8-cineole (10 mg/kg) without affecting hypotension. In conscious rats, i.v. pretreatment with methylylprine (1 mg/kg), atenolol (1.5 mg/kg), or hexamethonium (30 mg/kg) had no significant effects on the 1,8-cineole-induced hypotension, while bradycardic responses to 1,8-cineole (10 mg/kg) were significantly reduced by methylylprine. In rat isolated thoracic aorta preparations, 1,8-cineole (0.006–2.6 mM) induced a concentration-dependent reduction of the contraction induced by potassium (60 mM). This is the first physiological evidence that i.v. treatment with 1,8-cineole in either anesthetized or conscious rats elicits hypotension; this effect seems related to an active vascular relaxation rather than withdrawal of sympathetic tone.

Key words: 1,8-cineole, essential oil, cardiovascular effects, autonomic nervous system, isolated thoracic aorta.

Résumé : On a examiné les effets d’un traitement par administration i.v. de 1,8-cinéole, un oxyde monoterpénique entrant dans le composition de nombreuses huiles essentielles, chez des rats normotendus. On a examiné (i) si le système nerveux autonome joue un rôle dans les variations induites par le 1,8-cinéole de la pression aortique moyenne (PAM) et de la fréquence cardiaque (FC) et (ii) si les effets hypotenseurs du 1,8-cinéole pourraient découler de ses effets vasodilatateurs directement sur le muscle lisse vasculaire. Des injections de bolus de 1,8-cinéole (0,3–10 mg/kg, i.v.) ont provoqué des diminutions similaires et dose dépendantes de la PAM chez les rats anesthésiés au pentobarbital et chez les rats conscients libres de circuler. Le 1,8-cinéole a aussi diminué significativement la FC mais à la dose la plus élevée uniquement (10 mg/kg). Chez les rats anesthésiés, un prétraitement au moyen d’une vagotomie bilatérale a réduit de manière significative les réponses bradycardiques au 1,8-cinéole (10 mg/kg) sans influer sur l’hypotension. Chez les rats conscients, un prétraitement i.v. de méthylprine (1 mg/kg), d’aténolol (1,5 mg/kg) ou d’hexaméthonium (30 mg/kg) n’a pas eu d’effet significatif sur l’hypotension induite par le 1,8-cinéole, alors que les réponses bradycardiques au 1,8-cinéole (10 mg/kg) ont été significativement réduites par la méthylprine. Dans des préparations d’aortes thoraciques isolées de rats, le 1,8-cinéole (0,006–2,6 mM) a provoqué une réduction concentration dépendante de la contraction induite par le potassium (60 mM). Cette étude est la première à présenter des résultats physiologiques montrant qu’un traitement par administration i.v. de 1,8-cinéole suscite de l’hypotension tant chez les rats anesthésiés que chez les rats conscients; cet effet serait davantage lié à une relaxation vasculaire active qu’à une suppression du tonus sympathique.

Mots clés : 1,8-cinéole, huile essentielle, effets cardiovasculaires, système nerveux autonome, aorte thoracique isolée.

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Introduction

1,8-Cineole, also known as eucalyptol, is a monoterpenic oxide present in many essential oils, such as eucalyptus, rosemary, psidium, croton, and sage (Kovar et al. 1987; Andrade-Neto et al. 1994; Göbel et al. 1995; Leal-Cardoso and Fonteles 1999, Farhat et al. 2001; De Vincentzi et al. 2002). This compound is used for pharmaceutical preparations as an external applicant, nasal spray, disinfectant, analgesic, or food-flavoring agent (Craveiro et al. 1981; Levison et al. 1994; De Vincentzi et al. 1996). 1,8-Cineole was also reported to be useful for the treatment of rheumatism, cough, bronchial asthma, and septic-shock-associated pathologies (McGilvery and Reed 1993; Laude et al. 1994; Juergens et al. 1998; Santos et al. 2001). Furthermore, it has been reported that 1,8-cineole induced hind-paw edema in rats through a mechanism involving mast cells (Santos and Rao 1997). The local edematogenic effect of 1,8-cineole was proposed as suitable animal model for screening anti-allergic and anti-inflammatory compounds (Santos and Rao 1998).

Recently, 1,8-cineole has been shown to possess gastroprotective activity in the rat, an effect that is related to both the antioxidant and the lipoxygenase inhibitory effects of this monoterpenic oxide (Santos and Rao 2001).

The aromatic plants Croton nepetaefolius Baill. (Euphorbiaceae) and Alpinia zerumbet (Pers.) B.L. Burtt & R.M. Sm. or Alpinia speciosa (J.C. Wend.) K. Schum (Zingiberaceae) are abundant in northeastern Brazil, where they are commonly known as “marmeleiro sabiá” and “colônia”, respectively. Infusions or decoctions of bark and leaves from C. nepetaefolius are commonly used for their antispasmodic properties and to relieve flatulence and increase appetite (Leal-Cardoso and Fonteles 1999), while infusions or decoctions of leaves from A. zerumbet are commonly used for their diuretic and anti-hypertensive properties (Mendonça et al. 1991; Matos 2001). Essential oil of C. nepetaefolius (EOCN) or A. zerumbet (EOAZ) is composed principally of mono- and sesqui-terpenes (Craveiro et al. 1980; Oliveira 1994). 1,8-Cineole is the main constituent of EOCN (25.4%) and the second most abundant constituent (15.02%) of EOAZ after terpinen-4-ol (28.09%). Previous studies from our laboratory showed that i.v. treatment with either EOCN or EOAZ induced dose-dependent decreases in mean arterial pressure (MAP) in either anesthetized or conscious normotensive rats (Lahlou et al. 1999, 2002). Both in vivo and in vitro data suggested that the hypotensive responses to EOCN (Lahlou et al. 2000) and EOAZ (Galindo et al. 2001; Lahlou et al. 2002) result from their vasodilatory action directly upon vascular smooth muscle rather than from withdrawal of sympathetic tone. However, no available reports in the international literature have systematically studied the cardiovascular effects of 1,8-cineole in rats. The present investigation was undertaken to address this issue, and it comprised two parts. The first part was performed in either conscious and freely moving or anesthetized rats to assess the cardiovascular effects of 1,8-cineole and the role of autonomic nervous system in the mediation of these effects. The second part was performed in vitro using rat isolated thoracic aortae to assess whether the hypotensive effects of bolus injections of 1,8-cineole could result, at least in part, from its vasodilatory effects directly upon vascular smooth muscle.

Materials and methods

Animals

Male Wistar rats (250–320 g) were kept at a constant temperature (22 ± 2°C) with a standard 12 h light : 12 h dark cycle and free access to food and water. All animals were cared for in accordance with the principles and guidelines of the Canadian Council on Animal Care.

In vivo experiments

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and catheters (PE-10 fused to PE-50) were implanted in the abdominal aorta (for the recording of arterial blood pressure) and in the inferior vena cava (for drug administration) through the left femoral artery and vein, respectively. These catheters, filled with heparin–saline solution (125 IU/mL), were exteriorized at the dorsal neck level. Postoperatively, the rats were housed individually in plastic cages and allowed to recover for 24 h before any circulatory experiments. At the time of experiment, the arterial catheter was connected to a blood pressure transducer (Statham P23 ID, Oxnard, Calif.) coupled to a polygraph recorder; HR was obtained from a cardiotachometer triggered by the pressure pulses. Blood pressure and HR signals were recorded on a Gilson model 5/6H polygraph (Medical Electronics Inc., Middletown, Wis.). Mean aortic pressure was calculated as diastolic + (systolic – diastolic)/3.

Before each experiment, blood pressure and HR were allowed to stabilize and were recorded during the 10–15 min (according to the duration of effects) after i.v. treatment with 1,8-cineole. When subsequent doses of 1,8-cineole were administered, MAP and HR were first allowed to return to the baseline levels obtained before the first injection of the compound. When the effects of an antagonist were tested, antagonist injection occurred 10 min before 1,8-cineole administration. Doses of agonists or antagonists were chosen according to those recommended in the literature (references cited in Series 1 and Series 2, below). Two series of experiments were performed as follows.

Series 1

This series of experiments was carried out in anesthetized rats to establish a dose–response relationship. Rats were again anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Rectal temperature was kept close to 37°C by placing the animals on a thermostatically controlled table. Each animal received a series of increasing bolus doses (100 µL of 0.3, 1, 3, 5, and 10 mg/kg) of 1,8-cineole via the i.v. catheter, and the time course of the changes in MAP and HR was recorded. These experiments were performed in both intact rats (n = 6), and in rats that had been subjected to a bilateral vagotomy performed at the cervical level 15 min earlier (n = 5).

Series 2

This series of experiments was performed in conscious rats to establish a dose–response relationship and to assess the role of the autonomic nervous system in the mediation of 1,8-cineole-induced cardiovascular changes. Therefore, the time course of the changes in MAP and HR elicited by injections of 1,8-cineole (0.3, 1, 3, 5, and 10 mg/kg, i.v.) was determined in conscious rats that had been pretreated i.v. with Lahlou et al., 2000; Gilson model 5/6H polygraph (Medical Electronics Inc., Middletown, Wis.).
with one of the following: vehicle (1 mL/kg, n = 6), hexamethonium (30 mg/kg, n = 6), atenolol (1.5 mg/kg, n = 7), or methylatropine (1 mg/kg, n = 7) (Vasquez and Krieger 1997). Each rat received increasing bolus doses as described above. It should be noted that the dose of hexamethonium chosen (30 mg/kg) was sufficient to achieve complete ganglionic blockade (Sapru et al. 1982). In another set of rats (n = 6), the time course of the decreases in MAP elicited by an injection of acetylcholine (5 µg/kg, i.v.) used as positive control (Degouville and Cavero 1991; Lahlou et al. 2000) was determined and compared with that of 1,8-cineole (10 mg/kg).

**In vitro experiments**

Rats were stunned and then exsanguinated. Thoracic aortae were removed and immersed in perfusion medium at room temperature. After removing adhering fat and connective tissue, the aorta was cut transversely into cylindrical ring-like segments (1 × 5 mm) and attached to triangular pieces of steel wire, which were suspended in 10-mL organ ring-like segments (1 × 5 mm) and attached to triangular tissue, the aorta was cut transversely into cylindrical strips were stretched with a passive tension of 0.5 g, and tension was recorded using an isotonic saline, and sonicated just before use, while verapamil was first dissolved in distilled water and brought to volume with Tyrode’s solution.

**Drugs and solutions**

For in vivo experiments, 1,8-cineole was dissolved in Tween 80 (2%), brought to the chosen volume with sterile isotonic saline, and sonicated just before use. Previous studies showed that this vehicle had no effects on either baseline MAP or HR during a period of 20 min (Lahlou et al. 1999, 2000). The perfusion medium used was fresh modified Tyrode’s solution of the following composition: 136 mM NaCl, 5 mM KCl, 0.98 mM MgCl₂, 2 mM CaCl₂, 0.36 mM NaH₂PO₄, 11.9 mM NaHCO₃, and 5.5 mM glucose. Sodium hexamethonium (30 mg/kg, i.v.) was prepared directly in Tyrode solution and sonicated just before use, while verapamil was first dissolved in distilled water and brought to volume with Tyrode’s solution.

**Statistical analysis**

All results are expressed as means ± SE. Maximal changes (expressed as a percentage of baseline values) in MAP after each dose of 1,8-cineole were used to construct a dose–response curve. The IC₅₀ value, defined as the 1,8-cineole concentration (nM) required to produce half of the maximum reduction of potassium-induced contraction, was used to evaluate vascular sensitivity to 1,8-cineole and was determined graphically in each individual experiment. The geometric mean IC₅₀ was calculated by averaging the IC₅₀ values of each concentration–response curve. The statistical significance (P < 0.05) of the results was assessed by paired and unpaired Student’s t tests, Mann–Whitney U tests, and one-way (groups, doses, or time) or two-way (treatment × dose or treatment × time) analysis of variance (ANOVA) followed by Tukey’s or Dunnett’s multiple-comparison test when appropriate.

**Results**

**In vivo experiments**

**Studies in pentobarbital-anesthetized rats**

In this series of experiments, baseline MAP and HR before the injection of each dose of 1,8-cineole did not vary in magnitude (P > 0.05, one-way ANOVA). Therefore, the mean values of baseline MAP and HR in this group of animals were 102 ± 2 mmHg (1 mmHg = 133.322 Pa) and 363 ± 7 beats/min, respectively (pooled data from 11 rats). Intravenous injections of 1,8-cineole (0.3–10 mg/kg) induced immediate and dose-dependent decreases in MAP (Fig. 1). This effect became significant at the dose of 1 mg/kg (Fig. 1) and was maximal within the first 20–30 s after 1,8-cineole treatment. After all doses were tested, predose values of MAP were fully recovered within the first 1 min following 1,8-cineole treatment, except that MAP remained significantly reduced 1 and 3 min after administration of the highest dose (10 mg/kg) (P < 0.05, Tukey’s test). After 0.3, 1, 3, or 5 mg/kg (i.v.) of 1,8-cineole, HR values remained statistically unchanged, while they were significantly (P < 0.05, Tukey’s test) reduced 30 s (–39 ± 7%) and 1 (–15.94 ± 6.70%), 3 (–21.40 ± 6.40%), 5 (–15.00 ± 2.88%), and 10 min (–20.50 ± 7.50%) after 10 mg/kg of 1,8-cineole. Bilateral vagotomy did not affect baseline MAP and HR before the injection of each dose of 1,8-cineole (104 ± 4 vs. 97 ± 4 mmHg in intact rats), but induced a significant (P < 0.05, paired Student’s t test) increase in baseline HR (420 ± 10 vs. 344 ± 17 beats/min in intact rats). Bilateral vagotomy did not alter the 1,8-cineole dose – hypotensive-response curve (Fig. 1), but it significantly reduced the 1,8-cineole-induced bradycardia at the highest dose (P < 0.05, Mann–Whitney U test).
Studies in conscious rats

As in experiments with anesthetized rats, baseline MAP and HR before the injection of each dose of 1,8-cineole in conscious rats remained essentially invariant ($P > 0.05$, one-way ANOVA). Mean values of MAP and HR in this group of animals before any pretreatment were 114 ± 2 mmHg and 384 ± 10 beats/min, respectively (pooled data from 32 rats). Only baseline MAP was significantly different from that measured in intact, pentobarbital-anesthetized rats ($P < 0.05$, unpaired Student’s t test). In rats pretreated with vehicle, injections of 1,8-cineole (0.3–10 mg/kg, i.v.) induced immediate and dose-dependent decreases in MAP (Fig. 2). The hypotension elicited by 1,8-cineole became significant at the dose of 1 mg/kg (Fig. 2) and was maximal within the first 20–30 s postinjection. After all doses of 1,8-cineole were tested, predose values of MAP were fully recovered within the first 1 min following 1,8-cineole treatment; however, MAP remained significantly ($P < 0.05$, Tukey’s test) reduced 30 s (–79.25 ± 3.73%) and 1 (–32.53 ± 5.24%), 3 (–31.40 ± 2.01%), 5 (–30.40 ± 2.63%), and 10 min (–23.11 ± 1.71%) after the highest dose (10 mg/kg) of 1,8-cineole.

Pretreatment with hexamethonium (30 mg/kg, i.v.) induced significant ($P < 0.01$, paired Student’s t test) decreases in baseline MAP (80 ± 5 vs. 111 ± 4 mmHg) without significantly affecting the baseline HR (341 ± 13 vs. 378 ± 22 beats/min). Pretreatment with either methylatropine (1 mg/kg, i.v.) or atenolol (1.5 mg/kg, i.v.) did not alter baseline MAP (116 ± 5 vs. 114 ± 5 and 116 ± 4 mmHg, respectively), while they significantly increased (490 ± 18 vs. 381 ± 26 beats/min) and decreased (334 ± 14 vs. 394 ± 26 beats/min) baseline HR ($P < 0.05$, paired Student’s t test), respectively. None of these pretreatments significantly affected the dose-dependent decreases in MAP elicited by 1,8-cineole (Fig. 2). However, maximal percent decreases in HR elicited by 10 mg/kg of 1,8-cineole (–79.25 ± 3.73%) were not significantly changed by i.v. hexamethonium (–54.18 ± 17.12%), while they were statistically reduced (–19.32 ± 4.93%) and enhanced (–96.93 ± 1.20%) by methylatropine and atenolol pretreatment, respectively ($P < 0.01$, Mann–Whitney U test).

The positive reference drug acetylcholine (5 µg/kg) also induced a significant decrease in MAP, the magnitude of which was maximal (–47.86 ± 1.68%) within the first 20 s...
after drug treatment (Fig. 3), as was observed with 1,8-cineole. However, unlike 1,8-cineole, preinjection values of MAP were fully recovered within the first 1 min following acetylcholine treatment (Fig. 3). A two-way analysis of variance revealed that the time course of acetylcholine-induced changes in MAP was significantly different from that obtained with acetylcholine ($P < 0.05$, two-way ANOVA); *, $P < 0.05$; **, $P < 0.001$ by Tukey’s tests with respect to preinjection values.

**In vitro experiments**

In isolated aorta preparations, 1,8-cineole (0.006–2.6 mM) inhibited the contraction induced by potassium (60 mM) in a concentration-dependent manner (Fig. 4; $P < 0.001$, one-way ANOVA). The first inhibitory effect of 1,8-cineole became significant at a concentration of 0.65 mM (Fig. 4). The IC$_{50}$ value for 1,8-cineole-induced reduction of potassium-induced contraction was 1.09 ± 0.12 mM. The positive reference drug verapamil (0.01–3 $\mu$M) also inhibited the contraction induced by potassium (60 mM) in a concentration-dependent manner (Fig. 5) ($P < 0.001$, one-way ANOVA). The inhibitory effect of verapamil became significant at a concentration of 0.03 $\mu$M (Fig. 5). The IC$_{50}$ value for verapamil-induced reduction of the contraction induced by potassium (60 mM) was 115.70 ± 36.60 nM.

**Discussion**

Baseline MAP and HR values of anesthetized or conscious, freely moving, normotensive rats were of the same order of magnitude as those previously reported using the same preparation (Lahlou et al. 1999, 2001). In both groups, i.v. treatment with 1,8-cineole induced immediate and dose-dependent decreases in MAP. To the best of our knowledge, this is the first time that such hypotensive effects of 1,8-cineole have been reported in rats. Different kinds of anesthesia have been reported to alter cardiovascular responses to neurotransmitters such as norepinephrine in rats (Brezenoff 1973). It is possible that norepinephrine may interfere with the cardiovascular responses to 1,8-cineole. However, in the current study, both the magnitude and time course of the depressor effect of i.v. 1,8-cineole did not differ greatly between pentobarbital-anesthetized and conscious rats. This suggests that the mechanism by which 1,8-cineole...
decreases blood pressure is not altered by general anaesthesia with sodium pentobarbital. It seems unlikely that 1,8-cineole-induced hypotension could be related to a putative toxic effect of this compound. Such a conclusion is supported by the results (Santos 1999) of an acute toxicity test showing that the 1,8-cineole could be classified in the group of slightly toxic substances on the basis for classification of chemical substances. In fact, the value of oral acute toxicity (LD₅₀) was 2.85 ± 0.33 g/kg.

In the present study, an attempt was made to determine the role of the autonomic nervous system in 1,8-cineole-induced cardiovascular effects in rats. Treatment of conscious rats with 1,8-cineole decreased MAP in rats, even when the central sympathetic nerve drive contributing to the maintenance of blood pressure was eliminated by ganglionic blockade using hexamethonium. Under these experimental conditions, 1,8-cineole-induced hypotension was of the same order of magnitude as that measured in vehicle-pretreated rats. This indicates that 1,8-cineole hypotension is not dependent upon the presence of an operational central autonomic drive to the vascular system, because this effect occurs irrespective of whether vessels are constricted by the sympathetic neural drive. This conclusion is supported by the observation that although the basal level of sympathetic nervous system activity is lower in pentobarbital-anesthetized rats (Baum et al. 1985), 1,8-cineole-induced hypotension was of the same order of magnitude as that observed in conscious rats. These findings with i.v. hexamethonium are in line with those previously reported in normotensive rats treated with EOAZ (Lahlou et al. 1999) and suggest that the hypotensive response to 1,8-cineole may be due to an active vascular relaxation rather than to a withdrawal of sympathetic tone. Such a hypothesis is corroborated by the present finding that in rat isolated aorta preparations, 1,8-cineole was able to inhibit the potassium-induced contraction in a concentration-dependent manner. Vascular muscarinic receptors that normally mediate hypotension are probably not involved, since i.v. pretreatment with methylyltrapine did not affect the 1,8-cineole-induced hypotension.

The effects of 1,8-cineole on isolated aorta are not peculiar to that tissue alone, since EOAZ and its constituents 1,8-cineole (25.4%), methyl eugenol (14.9%), and α-terpineol (4.96%), have been reported to induce concentration-dependent relaxation of the basal tone of guinea pig isolated ileum segments and to inhibit potassium-induced contracture using the same preparation (Magalhães et al. 1998). This myorelaxant activity explains the use of C. nepetefolius in folk medicine as an antispasmodic. However, 1,8-cineole was the component of least potency in inducing relaxation of basal tonus and inhibiting potassium-induced contracture in the isolated ileum (Magalhães et al. 1998). Such a pharmacological profile of 1,8-cineole has also been observed in rat isolated aorta preparations (Magalhães 2002). Previous studies from our laboratory showed that i.v. treatment with either EOAZ or EOAZ induced dose-dependent hypotension; this effect also peaked within the first 20–30 s and was due to an active vascular relaxation rather than withdrawal of sympathetic tone (Lahlou et al. 1999, 2000, 2002). In these studies, maximal percent decreases in MAP elicited by bolus doses (1, 5, and 10 mg/kg) of both EOAZ and EOAZ were signifi-

antly smaller than those evoked herein by the same doses of 1,8-cineole. These data, together with the present findings, did not preclude the possibility that 1,8-cineole, besides other constituents, contributes to the mediation of EOAZ- and EOAZ-induced hypotension.

Acetylcholine causes generalized vasodilatation that is an indirect effect mediated by nitric oxide released from vascular endothelial cells (Furchgott and Zawadzki 1980). In the present study, the time course of 1,8-cineole-induced changes in MAP was significantly different from that obtained with acetylcholine. In fact, only 1,8-cineole-induced hypotension remained significant during a period of 5 min postinjection. However, in view of the observation that the time to maximal hypotensive effect was similar for both 1,8-cineole and acetylcholine, it is possible that the hypotensive effect of 1,8-cineole is mediated, at least in part, by an endothelial t-arginine – nitric oxide pathway. Further studies using analogues of t-arginine (i.e., N⁵-monomethyl-L-arginine monoacetate or N⁵-nitro-L-arginine methyl ester) that inhibit nitric oxide formation are presently underway in our laboratory to test the latter possibility.

A previous study from our laboratory showed that bradycardic responses to EOAZ (1,8-cineole is its main constituent) were of vagal origin, as they were reduced by either cervical vagotomy or i.v. pretreatment with methylyltrapine (Lahlou et al. 1999). In the current study, the hypotension induced by the highest dose (10 mg/kg) of 1,8-cineole in both anesthetized and conscious rats was associated with significant bradycardia. The latter effect also appears to be from vagal origin, since it was significantly reduced by bilateral vagotomy or i.v. pretreatment with methylyltrapine. Such findings with methylyltrapine point to independent mechanisms for 1,8-cineole-induced hypotension and bradycardia and preclude any possibility that 1,8-cineole-induced hypotension may result from the concomitant bradycardia. In fact, if the hypotensive response to 1,8-cineole resulted from the bradycardia, any change in HR would be expected to induce a quantitatively and qualitatively similar change in blood pressure. The magnitude of the 1,8-cineole-induced bradycardia appears to be influenced by a baroreflex-mediated tendency to increase HR, resulting from the depressor response to 1,8-cineole. The possibility of such a baroreceptor reflex is suggested by the finding that blockade of the sympathetic nerve drive to the heart by i.v. atenolol enhanced the maximal percent decreases in HR evoked by 1,8-cineole.

The present study, using a combined in vivo and in vitro approach, shows for the first time that i.v. treatment of both anesthetized and conscious rats with 1,8-cineole lowers blood pressure, probably through an active vascular relaxation rather than withdrawal of sympathetic tone. Such findings may suggest that 1,8-cineole contributes to mediation of the hypotensive effects of essential oils of some aromatic plants popularly used for the treatment of hypertension. Further studies will be required to elucidate the underlying mechanisms of 1,8-cineole-induced vasorelaxant activity.

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References