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Capsaicin-like activity of some natural pungent substances on peripheral endings of visceral primary afferents

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Summary. 1. The effects of some naturally occurring pungent substances, piperine, mustard oil, eugenol and curcumin, were compared to those of capsaicin in the rat isolated urinary bladder. 2. All test compounds dose-dependently contracted the rat bladder and produced desensitization toward capsaicin (1 μmol/l). Development of cross-tachyphylaxis among the natural pungent substances on one hand and capsaicin on the other, suggested a common site of action on visceral primary afferents. 3. Contractile responses to piperine, mustard oil and eugenol were partially tetrodotoxin and ruthenium red-sensitive, suggesting that activation of sensory terminals by these agents takes place indirectly, as well as by a direct action on sensory receptors. 4. The presence of the secondary acylamide linkage (present in the backbone of capsaicin, but not in that of test compounds) does not appear to be essential to produce desensitization of sensory nerve terminals.

Key words: Capsaicin – Piperine – Mustard oil – Eugenol – Curcumin – Urinary bladder (rat)

Introduction

Capsaicin, the pungent ingredient of red peppers, is widely used as a tool for studying the function of primary sensory neurons (see Szolcsànyi 1984; Maggi and Meli 1988 and Holzer 1988, for reviews). There is evidence indicating that the capsaicin-sensitive primary afferents release transmitters from their central or peripheral nerve endings when activated by capsaicin, or other stimuli (Gamse et al. 1981; Saria et al. 1983; Maggi et al. 1988c). At the peripheral level, transmitters released from capsaicin-sensivite afferents (tachykinins, calcitonin gene-related peptide, CGRP) influence smooth muscle motility, blood flow and vascular permeability ("efferent" or "local effector function") (Szolcsànyi 1984; Holzer 1988; Maggi and Meli 1988). Just after the excitatory phase produced by a maximally effective dose of capsaicin, the sensory nerve terminals become inexcitable to natural stimuli (such as distension of the urinary bladder wall during urine collection) and capsaicin itself (Maggi and Meli 1988; Szolcsànyi 1984, 1989). This condition of inexcitability corresponds to the "sensory neuron blocking action" of capsaicin as defined by Szolcsànyi (1985, 1989)

We have shown that in the rat isolated urinary bladder, capsaicin produces a contraction that is tetrodotoxin-(TTX) resistant, abolished by chronic extrinsic denervation and reduced by a substance P (SP) antagonist (see Maggi and Meli 1986, 1988, for reviews). This contraction response, thought to be mediated by endogenous tachykinins, undergoes desensitization (Santicioli et al. 1986, 1987).

Some natural pungent substances and capsaicin derivatives have been compared by means of different bioassays to establish a rank order of potency with regard to their pungent and desensitizing properties, and structure-activity relationship (Szolcsànyi and Jancsò-Gàbor 1975, 1976; Lawless and Stevens 1984; Szolcsànyi 1983).

The present experiments were undertaken to compare the activity of capsaicin with that of some natural pungent principles, piperine, mustard oil, eugenol, and curcumin, on visceral primary afferents of the rat isolated urinary bladder (see Fig. 1 for chemical structures). Piperine and mustard oil are natural irritant agents, capable of stimulating capsaicin-sensitive afferents (Miyauchi et al. 1988, 1989; Szolcsànyi 1983; Heapy et al. 1987). Eugenol and curcumin possess local anesthetic and anti-inflammatory activities, respectively (Siemoniet et al. 1966; Mukhopadhyay et al. 1982) and to some extent also irritant properties (Sneddon and Glew 1973) of unknown origin.

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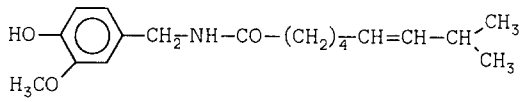
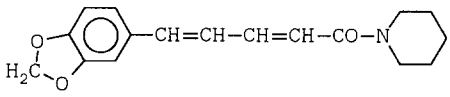
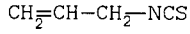
Capsaicin



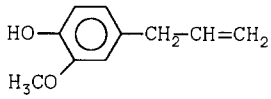
Piperine



Allyl isothiocyanate



Eugenol



Curcumin

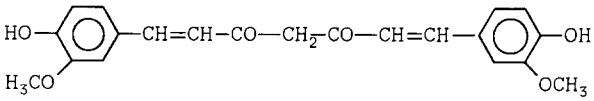


Fig. 1. Chemical structures of the natural pungent substances used in the present study

Methods

In vitro experiments. Male Albino rats of Wistar-Morini strain weighing 340–360 g were stunned and bled. The whole urinary bladder was rapidly removed. A strip of detrusor muscle (about 1 cm long) was dissected and placed in a 5 ml organ bath (at 37° C), containing oxygenated (96% O_2 plus 4% CO_2) normal Krebs solution of the following composition (mmol/l): NaCl 119; $NaHCO_3$ 25; KH_2PO_4 1.2; $MgSO_4$ 1.5; KCl 4.7; $CaCl_2$ 2.5 and glucose 11. A resting tension of 10 mN was applied and the preparations were allowed to equilibrate for 60 min before starting the experiments, as described previously (Santicioli et al. 1986, 1987; Patacchini et al. 1988). Tension was recorded by means of an isometric strain gauge connected to a Basile 7050 Unirecord. Electrical field stimulation (EFS) was made by means of two wire platinum electrodes placed at the top and the bottom of the organ bath. Square wave pulses (60 V, 0.5 ms) were delivered automatically at a frequency of 0.1 Hz by means of a Grass S11 stimulator. Contractions were expressed as a % of the response to electrical field stimulation, as described previously (Santicioli et al. 1986, 1987; Patacchini et al. 1988).

Only one concentration of each compound was tested in each preparation. In order to eliminate possible unspecific effects on the response under study, the following protocol was used: after the equilibration period, the response to electrical field stimulation was determined. At this stage electrical field stimulation was interrupted, the stated concentration of the test compound was added to the bath, and its effect recorded for 5 min. Thirty min later, after a previous thorough washing out, the response to electrical field stimulation was checked again, and 10 min later capsaicin (1 μmol/l) was administered, to check the ability of the previous exposure to test compounds to induce desensitization of capsaicin-sensitive afferents. In some experiments the response to the natural pungent substances was assessed on bladders made unresponsive to capsaicin by a previous exposure to a maximally effective concentration (10 μmol/l) of the drug.

In other experiments we assessed the ability of tetrodotoxin (TTX) or ruthenium red to interfere with the contractile response to capsaicin, piperine, mustard oil and eugenol. With this aim we used paired bladder strips from the same animal: one strip received TTX (1 μmol/l, 15 min before) or ruthenium red (10 μmol/l, 25 min before) and the other served as a control.

Statistical analysis. All data in the text and figures are means ± standard error of the means (S.E.M.). Statistical analysis was performed by means of Student's t-test for paired or unpaired data or by means of the analysis of variance when applicable. For evaluation of EC_{50s} a log dose-response curve was constructed for each test compound, where each point represented the geometric mean of 4–5 values obtained in different preparations. Regression analysis was performed by means of the least squares method. EC_{50} and 95% confidence limits (c.l.) were calculated accordingly.

Drugs. The durgs used were capsaicin (Sigma, St. Louis, MO, USA), piperine (Sigma, St. Louis, MO, USA), eugenol (Sigma, St. Louis, MO, USA), allyl isothiocyanate (mustard oil) (Aldrich, Milano, Italy), curcumin (Sigma, St. Louis, MO, USA), ruthenium red (Aldrich, Milano, Italy), tetrodotoxin (Sankyo, Tokyo, Japan). A stock solution of capsaicin (10 mmol/l) was made with absolute ethanol, and then diluted in water. All solutions of the natural pungent substances were made with DMSO. DMSO was ineffective per se at the volumes employed in this study. Final concentrations of curcumin higher than 300 μmol/l could not be tested because of precipitation.

Results

Contractile and desensitization effects of capsaicin and of the natural pungent substances

Capsaicin (10 nmol/l–10 μmol/l) produced a concentration-related contraction of the rat isolated bladder (Fig. 2, Table 1) and induced, with about the same potency, desensitization toward a second challenge with capsaicin (1 μmol/l, 40 min after the first application of capsaicin, see methods for details) (Fig. 2, Table 1).

Piperine (1–30 μmol/l) dose-dependently contracted the rat isolated bladder, and produced a marked de-

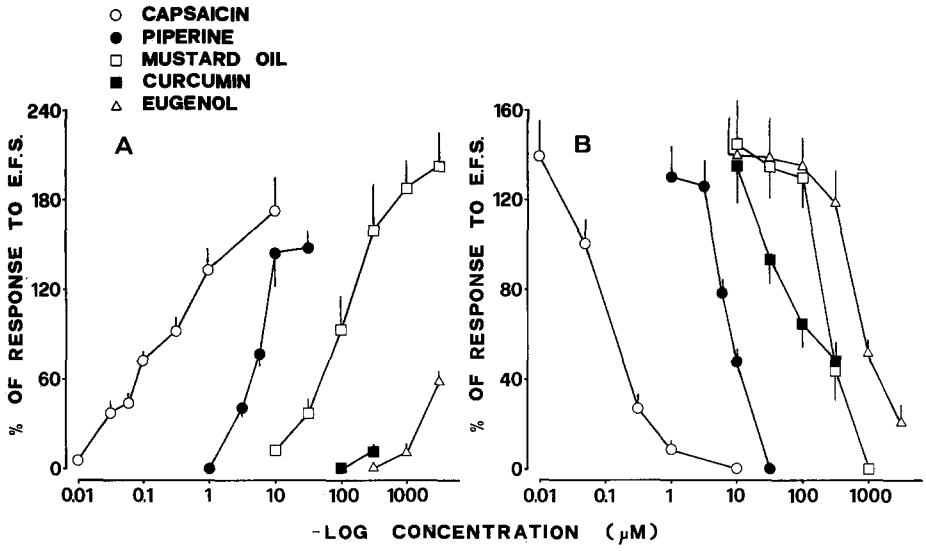


Fig. 2. (**A**): concentration-response curves for the contractile response to capsaicin, piperine, mustard oil, curcumin and eugenol on the rat isolated urinary bladder.
(**B**): concentration-response curves for the desensitizing effect of capsaicin, piperine, mustard oil, curcumin and eugenol toward the contractile response of the rat isolated urinary bladder to capsaicin (1 μmol/l). Contractions are expressed as a % of the response to electrical field stimulation (EFS) (single pulses, 60 V, 0.5 ms duration delivered at a frequency of 0.1 Hz)

Table 1. Comparison of the ability of capsaicin, piperine, mustard oil, curcumin and eugenol, to stimulate or induce desensitization of capsaicin-sensitive sensory fibers in the rat isolated urinary bladder

Compound	Contractile activity EC_{50} (μmol/l)	R.A.	Induction of desensitization EC_{50} (μmol/l)	R.A.
Capsaicin	0.2 (0.1–0.3)	1000	0.15 (0.03–0.5)	1000
Piperine	5.0 (2–15)	40	8.0 (5.8–12.2)	19
Mustard oil	110 (46–260)	1.8	271 (68–810)	0.6
Curcumin	> 300	< 0.6	112 (26–315)	1.3
Eugenol	> 3000	< 0.06	920 (232–2900)	0.16

Each EC_{50} value is obtained from 20–25 experiments. In brackets are 95% confidence limits EC_{50} = concentration of compound producing 50% of maximal response R.A. = relative affinity, expressed as a fraction of the affinity of capsaicin

sensitization. It was 1/25–1/53 as potent as capsaicin, (Table 1, Fig. 2).

Mustard oil (10 μmol–3 mmol/l) was weaker than capsaicin or piperine in eliciting contraction responses in the rat bladder (1/550 in comparison with capsaicin) (Fig. 2 and Table 1), but produced a maximal effect similar to that of capsaicin. Mustard oil also produced a concentration-dependent desensitization toward capsaicin, being about 1/1,800 as potent as capsaicin (Fig. 2, Table 1). After exposure to concentrations of mustard oil lower than 1 mmol/l, the bladder muscle recovered its basal tone, and the twitch response to electrical field stimulation returned to pre-drug values after repeated washings. At 1 mmol/l or higher concentrations, mustard oil increased the tone of the muscle, and the twitch response to electrical field stimulation was persistently depressed as compared to controls ($30 \pm 8\%$ reduction; $n = 4$) despite a thorough washing out. At this stage capsaicin 1 μmol/l had almost no motor effect. Preparations exposed to mustard oil 3 mmol/l remained strongly contracted despite washouts and became completely unresponsive to electrical field stimulation. Curcumin had no contractile effect up to 100 μmol/l. At 300 μmol/l (solubility limit) curcumin produced a slight contraction ($11 \pm 3\%$ of the response to electrical field stimulation) (Fig. 2, Table 1). By contrast, curcumin (10 μmol/l–300 μmol/l) was effective in desensitizing the rat bladder to a subsequent exposure to capsaicin, although its potency was about 1/750 of that of capsaicin (Fig. 2, Table 1). Despite repeated washouts, the tissues exposed to curcumin retained a yellow colour (whose intensity depended on the concentration), suggesting that a fraction of curcumin remained tightly bound to the tissue. Therefore we examined the possibility that the reduced responsiveness to a challenge with capsaicin, after previous exposure to curcumin, could have been due to a capsaicin 'antagonist' action of curcumin which bound to the tissue. To assess this point, we adminstered capsaicin 1 μmol/l in the presence of curcumin (10 μmol/l, 15 min before). Curcumin failed to antagonize the contractile response to capsaicin as compared to matched controls. In fact, the response to capsaicin averaged 150 ± 9 and $139 \pm 15\%$ of the response to electrical field stimulation in the absence and presence of curcumin, respectively ($n = 4$ each). Eugenol did not contract the bladder muscle up to 300 μmol/l. At 1 and 3 mmol/l, eugenol produced weak contractions (11 ± 5 and $58 \pm 1\%$ of the response to electrical field stimulation, respectively) (Fig. 2, Table 1), which faded rapidly (2–3 min) and were followed by a slow relaxation. We noticed

Table 2. Effect of tetrodotoxin (TTX) and ruthenium red (RR) on the contractile response of the rat isolated urinary bladder to capsaicin, piperine, mustard oil and eugenol

Compound	Control	TTX (1 μmol/l)	Control	RR (10 μmol/l)
Capsaicin (1 μmol/l)	140 ± 12	125 ± 9	136 ± 6	40 ± 13*
Piperine (10 μmol/l)	118 ± 4	60 ± 11**	133 ± 40	12 ± 7*
Mustard oil (1000 μmol/l)	195 ± 12	137 ± 14*	159 ± 14	71 ± 18*
Eugenol (3000 μmol/l)	48 ± 10	6 ± 4**	51 ± 8	2 ± 1**

Each value is mean ± SEM of 4–6 experiments. Experiments were carried out on paired bladder strips from the same animal: one received TTX 15 min before (or RR, 25 min before) administering the test compound, and the other served as a control

* Significantly different from control, $P < 0.05$
** Significantly different from control, $P < 0.01$
EFS = Electrical field stimulation (single pulses, 60 V, 0.5 ms duration delivered at a frequency of 0.1 Hz)

that in the presence of eugenol (100 μmol/l–3 mmol/l) contractile responses to both electrical field stimulation or exogenous SP (30 nmol/l) were dose-dependently inhibited and even abolished at the highest concentration of eugenol (90 ± 4 and 95 ± 3% inhibition of the response to electrical field stimulation or exogenous SP respectively, as compared to control responses, in the presence of eugenol 1 mmol/l, $n = 4$). In spite of this depressant effect, a complete recovery of contractility was achieved after a 30 min washout of eugenol. At this stage a dose-dependent desensitizing effect of eugenol was revealed by challenging the strips with capsaicin 1 μmol/l (Fig. 2). Eugenol was about 1/6,000 as potent as capsaicin in desensitizing sensory nerves of rat bladder (Table 1).

Effect of capsaicin pretreatment on the contractile responses to the natural pungent substances

The response to piperine (30 μmol/l), mustard oil (3 mmol/l), eugenol (3 mmol/l) and curcumin (300 μmol/l) was assessed on bladders exposed (40 min before) to a maximally effective concentration (10 μmol/l) of capsaicin for 5 min. Under these conditions, none of the drug tested produced contractile responses, thus indicating complete cross-desensitization ($n = 4$ for each substance).

Effect of TTX on the contractile responses to capsaicin, piperine, mustard oil and eugenol

Exposure to TTX (1 μmol/l for 15 min) did not significantly reduce the contractile response to capsaicin (1 μmol/l Table 2), as reported previously (Santicioli et al. 1986). On the other hand, the responses to piperine (10 μmol/l) and mustard oil (1 mmol/l) were significantly inhibited by TTX (Table 2), and that to eugenol (3 mmol/l) was almost abolished (Table 2).

Effect of ruthenium red on contractile responses to capsaicin, piperine, mustard oil and eugenol

We assessed the ability of the inorganic dye ruthenium red to prevent the contractile response to piperine (10 μmol/l), mustard oil (1 mmol/l) and eugenol (3 mmol/l). We observed previously that ruthenium red antagonizes the actions of capsaicin on peripheral terminals of primary afferents (Maggi et al. 1988a, b).

The responses to capsaicin, piperine, mustard oil and eugenol were significantly reduced in presence of ruthenium red 10 μmol/l (see methods for details) (Table 2).

Discussion

Piperine, the pungent agent of black peppers, has been reported to produce positive chronotropic and inotropic effects on isolated rat atria (Miyauchi et al. 1988, 1989) and contractile responses on guinea-pig trachea (Szolcsànyi 1983). Development of cross-tachyphylaxis between piperine and capsaicin has provided evidence for a common site of action for the two drugs.

Mustard oil (allyl isothiocyanate), the pungent agent of black mustard, has been reported to cause neurogenic inflammation and plasma extravasation when applied topically to the rat skin (Jancsò 1968), probably related to its stimulant action on both A-delta and C-primary afferents (Heapy et al. 1987; Harris and Ryall 1988). Furthermore, pretreatment with capsaicin, applied locally on rat peripheral nerves, has been shown to produce a long-lasting impairment in neurogenic plasma extravasation induced by mustard oil (Jancsò et al. 1980; Gamse et al. 1982). The ability of piperine and mustard oil to interact with peripheral endings of capsaicin-sensitive primary afferents was therefore confirmed in this study. Eugenol, the major constituent of clove oil, commonly used in dentistry for its mild analgesic and local anesthetic properties, is also endowed with some irritant activity (Sneddon and Glew 1973) of unknown origin. Curcumin is a yellow pigment from *Curcuma Longa L.*, which was reported to posses anti-inflammatory properties in acute as well as chronic models of inflammation (Srimal and Dhawan 1973) or both anti-inflammatory and irritant activity of unknown origin (Mukhopadhyay et al. 1982). Although both compounds share some chemical analogy with capsaicin, no information is available about their possible action on capsaicin-sensitive afferents.

The capsaicin-induced contraction of the rat isolated urinary bladder is due to release of transmitters

(tachykinins) from the peripheral endings of primary sensory neurons in the bladder wall, through a tetrodotoxin-resistant depolarization: e.g. the sensory receptor potential-coupled "efferent" response (see Maggi and Meli 1986, 1988 for reviews). No evidence for an axon reflex arrangement was found in this tissue using capsaicin (Maggi and Meli 1988). So far the molecular target of action of capsaicin is largely unknown: Szolcsànyi and Jancsò-Gàbor (1975) proposed a receptor model for capsaicin, responsible for both the excitatory and the desensitizing effect of the drug. This hypothesis seems to be confirmed by recent findings, showing the presence of a population of high affinity binding sites on primary sensory neurons, which recognize both capsaicin and resiniferatoxin (Szallasi and Blumberg 1989a), an ultrapotent capsaicin analog (Szallasi and Blumberg 1989b).

The present findings demonstrate that piperine, mustard oil, eugenol and curcumin all possess a capsaicin-like action on peripheral endings of primary afferents of the rat urinary bladder. Mustard oil and eugenol also exerted, at high concentration, motor effects (contraction and relaxation, respectively) which are either irreversible (mustard oil) or reproducible (eugenol), and probably represent unspecific direct actions on smooth muscle cells.

The contraction in response to piperine, mustard oil or eugenol was partially TTX-sensitive, suggesting that activation of an axon reflex arrangement, or axonal conduction through fast sodium channels, participates in the activation of sensory terminals by these agents. On the other hand the TTX-resistant component of the response to these compounds probably reflects direct activation of sensory receptors, e.g. the sensory receptor potential-coupled "efferent" response, as defined above. This latter possibility is also supported by the observation that the contractile responses to maximally effective concentrations of piperine, mustard oil and eugenol were almost abolished by ruthenium red, an inorganic dye capable of preventing the capsaicin-operated mode of activation of the 'efferent' function of sensory nerves (Maggi et al. 1989), by preventing the capsaicin-evoked cation influx in primary afferents (Amann et al. 1989). The potency ratio between piperine and capsaicin in the rat urinary bladder (1/25 for contraction, 1/53 for desensitization) is in good agreement with that (1/70) found by Szolcsànyi and Jancsò-Gàbor (1975) in producing, upon instillation, wiping of the rat eye. We did not observe any significant difference in potency between the stimulating and desensitizing activity of capsaicin or piperine. This is in contrast with that reported by Szolcsànyi and Jancsò-Gàbor (1976), who found the two drugs much weaker in producing desensitization, rather than in eliciting pain reaction, when dropped into the rat eye. The different experimental model probably accounts for this discrepancy.

The results of our investigation also allow some structure activity considerations. We noticed that the secondary acylamide linkage (present in the backbone of capsaicin, but not in that of piperine, mustard oil, curcumin and eugenol) is not a prerequisite for desensitization of sensory terminals. This finding is at variance with the, hypothesis of Szolcsànyi and Jancsò-Gàbor (1976), who proposed that this chemical group is essential for desensitization by capsaicin analogs. In accordance with our results, Szallasi and Blumberg (1989b) observed that resiniferatoxin, the recently discovered ultrapotent analog of capsaicin, possesses high desensitizing potency, although it lacks the acylamide linkage.

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