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A New Pharyngitis Model Using Capsaicin in Rats

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ABSTRACT. 1. Application of capsaicin solution onto the rat pharyngeal mucosa caused a well-reproducible increase in vascular permeability in the pharynx.
2. Capsaicin-induced pharyngeal inflammation was unaffected by a histamine H₁ blocker and non-steroidal anti-inflammatory agents, whereas dexamethasone was effective in its inhibition.
3. FK224, a dual antagonist of tachykinin NK₁ and NK₂ receptors, and FK888, a selective antagonist of NK₁ receptor, significantly inhibited capsaicin-induced plasma exudation in the pharynx.
4. In capsaicinized animals, the application of capsaicin solution in the pharyngeal mucosa did not induce pharyngitis.
5. These results suggest that the mechanism of the capsaicin-induced pharyngitis primarily involves tachykinins.

KEY WORDS. Pharyngitis, capsaicin, anti-inflammatory drugs, tachykinin receptor, rat

INTRODUCTION

The pharynx is always exposed to various external stimuli through nasal and oral cavities. Pharyngitis is a common inflammatory syndrome of the oropharynx which is attributed predominantly to infectious causes or, less commonly, to secondary involvement of systemic or noninfectious illness. The complaint of pharyngitis is frequently encountered and is responsible for an estimated 40 million outpatient visits in the United States (Vukmir, 1992). Irritation and sore throat accompanied by mild edema and erythema of the pharynx are present in about 80% of patients with the common cold syndrome due to viruses such as rhinoviruses, coronaviruses, influenza viruses, parainfluenza viruses and adenoviruses, and to bacteria including Streptococcus pyogenes (Lang and Singh, 1990; Peter, 1992). However, suitable animal models for studying pharyngitis and for development of effective drugs have not hitherto been reported.

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the pungent algesic ingredient in red peppers, activates a population of primary afferent sensory neurons and causes the release of neuropeptides such as substance P (SP) and neurokinin A (NKA) (Buck and Burks, 1986). Capsaicin-sensitive nerves are recognized to distribute to a variety of tissues including the lower respiratory tract (Buchan and Adcock, 1992) and nasal mucosa (Tani et al., 1986). Capsaicin has been used for inducing coughs in animals to assess antitussive drugs (Kamei et al., 1994) and for inducing bronchoconstriction to study cholinergic and axon reflexes in the respiratory tract (Buchan and Adcock, 1992).

In the present article, a new animal model for the study of pharyngitis was used. Capsaicin was applied onto rat pharyngeal mucosa, and the effects of several drugs on the capsaicin-induced plasma exudation in the pharynx were investigated.

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MATERIALS AND METHODS

Establishment of animal model of pharyngitis

Male Wistar rats, weighing 260–360 g (Tokyo Laboratory Animal Co., Japan), were used. Animals were anesthetized with urethane (2 g/kg SC), placed in the supine position and given spontaneous respiration through a tracheal cannula. Experimental pharyngitis was induced by application of capsaicin solution with a moistened cotton-tipped applicator on the surface of pharyngeal mucosa. When the capsaicin solution was applied, the tongue was slightly pulled out with a forceps and the pharynx area was opened deep in the oral cavity with a small rib spreader. Capsaicin-soaked cotton was swabbed each for about 3 sec gently three times at one time point (about 50 μl of the capsaicin solution left on the mucosa). Because capsaicin was dissolved in a mixture of 10% ethanol–10% Tween 80–80% distilled water, the rats in the control group were given vehicle alone. Capsaicin in concentrations of 0.1, 0.3 and 1.0 mM was used, and each concentration of the capsaicin solution was applied twice with a 30-min interval. In some experiments, capsaicin solution (0.3 mM) was applied only once, and a period of 30 or 60 min was allowed before evaluation of plasma exudation. For a quantitative evaluation of the capsaicin-induced plasma exudation in the rat pharyngeal mucosa, extravasation of Evans blue (EB) dye into the pharyngeal tissue was determined. Specifically, EB dye (30 mg/kg) was injected IV into the femoral vein 10 min prior to the first application of capsaicin. Thirty minutes (in some experiments, 60 min) after the last capsaicin application, exsanguination was done from the abdominal aorta. Each animal's head portion was perfused at a rate of 15 ml/min with 180 ml of citric acid buffer (5% of paraformaldehyde in 0.05 M sodium citrate solution adjusted to the pH 3.5 with 0.05 M citric acid solution) via the bilateral carotid arteries to remove blood. The bilateral carotid arteries were tied off with 3-0 silk, and the capsaicin-soaked cotton was swabbed each for about 3 sec gently three times at one time point (about 50 μl of the capsaicin solution left on the mucosa).
Effects of several drugs on pharyngeal plasma exudation induced by capsaicin

To study the involvement of chemical mediators in capsaicin-induced pharyngeal plasma exudation, rats were injected iv with several agents into the femoral vein 5 min (or 30 min in the cases of dexamethasone and glycyrrhizinic acid) prior to capsaicin treatment. As pretreatment drugs, chlorpheniramine (1 mg/kg, histamine H1 receptor antagonist), indomethacin (5 mg/kg), diclofenac (10 mg/kg), cyclooxygenase inhibitor), dexamethasone (0.3 mg/kg, steroidal anti-inflammatory drug), glycyrrhizinic acid (10 mg/kg), FK224 (1 and 3 mg/kg, tachykinin NK1, and NK2 receptor antagonist) and FK888 (1, 3 and 10 mg/kg, tachykinin NK1, receptor antagonist) were given. Control rats received vehicle or saline instead of drugs.

Systemic capsaicinization

In some experiments, rats were pretreated with systemic capsaicin to deplete sensory neuropeptides. Capsaicinization was done by using the method of Yonei et al. (1990) with a minor modification. Animals were administered subcutaneously with a total dose of 125 mg/kg capsaicin, in two increasing doses over 3 days, and used for the experiments 10 days after the last systemic capsaicin pretreatment. Each dose was made as follows: at day 1, 25 mg/kg; at days 2 and 3, 50 mg/kg. Capsaicin was dissolved in 10% ethanol-10% Tween 80-80% saline.

To counteract the respiratory impairment caused by systemic capsaicin, terbutaline (1 mg/kg SC, 60 min prior) and aminophylline (25 mg/kg IP, 30 min prior) were pretreated before each capsaicin treatment under anesthesia with ketamine (50 mg/kg IV) and thiopental sodium (40 mg/kg IP). The same dosage regimen was used in the control animals to deliver an equivalent volume of vehicle (10% ethanol and 10% Tween 80 in saline) without capsaicin. To check the effectiveness of the capsaicinization, a drop of 0.1-mg/ml solution of capsaicin in saline was instilled into one eye of the rat. This test was carried out 3 hr before the experiment. The untreated or vehicle-pretreated rats responded instantly with wiping of the eye, whereas the capsaicin-pretreated rats did not.

Drugs

The following drugs were used: capsaicin, citric acid, sodium citrate, sodium carbonate, Tween 80, dimethylsulfoxide and formamidine (Wako Pure Chemical Industries, Osaka, Japan); Evans blue (EB; Merck); chlorpheniramine maleate, indomethacin, diclofenac sodium and urethane (Sigma); dexamethasone (dexamethasone sodium phosphate for intravenous infusion, Banyu Pharmacy Co.); glycyrrhizinic acid (glycyrrhizinate dipotassium, Tokawa Plant Chemistry Research Co., Japan); and FK224 and FK888 (Fujisawa Pharmaceutical Co., Osaka). Indomethacin was dissolved in saline by adjusting to pH 7 with 1N sodium carbonate, and FK224 and FK888 were dissolved in dimethylsulfoxide (DMSO). The other drugs were dissolved and/or diluted in saline.

Statistical analyses

All data are expressed as mean and SEM. Statistical significance was determined by Student's t-test for unpaired data, Cochran–Cox test or one-way analysis of variance (ANOVA). ANOVA was carried out with Tukey's test for multiple comparisons.

RESULTS

Application timing and concentrations of capsaicin solution

Single or double applications of capsaicin at 0.3 mM on the surface of pharyngeal mucosa were attempted as shown in Figure 1. The increase in EB exudation was assessed 30 or 60 min after local application of capsaicin. EB exudation in the pharynx was significantly increased at 60 min after the single application (group B) or at 30 min after double application of capsaicin at a 30-min interval (group C) (P<0.01 vs. vehicle) (Fig. 1). The maximal percentage increase in EB exudation was observed in group C; the increase percentage versus vehicle control was 82.8%. As for the concentration of capsaicin, 0.1, 0.3 and 1.0 mM of the agent (about 50 μl) was applied on the surface of pharynx (Fig. 2). Capsaicin elicited a concentration-dependent increase in EB extravasation in the rat pharyngeal tissue, and the increase was significant at 0.3 and 1.0 mM (P<0.01 vs. vehicle). Based on these findings, induction of pharyngeal inflammation was performed by two applications with a 30-min interval with the capsaicin concentration of 0.3 mM in subsequent experiments.

Effects of several agents on capsaicin-induced pharyngeal plasma exudation

The influences of various agents on the enhanced pharyngeal plasma exudation by twice application of 0.3 mM capsaicin are summarized in Table 1. Chlorpheniramine (1 mg/kg IV), histamine H1 blocker, indomethacin (5 mg/kg IV), diclofenac (10 mg/kg IV), cyclooxygenase inhibitors and glycyrrhizic acid (10 mg/kg IV), triterpenoid sapogenin from Glycyrrhiza glabra L. possessing an anti-inflammatory effect (Finney and Somers, 1958) were without effect on the capsaicin-induced increase in EB exudation. In contrast, dexamethasone (0.3 mg/kg IV), steroidal anti-inflammatory drug, significantly inhibited the increase in vascular permeability induced by capsaicin (45.7%, P<0.05 vs. control). FK224 (1 and 3 mg/kg IV), a tachykinin NK1 and NK2 receptor antagonist, significantly inhibited the capsaicin-induced increase in EB exudation in a dose-dependent manner (63.9% and 82.4% inhibition, respectively; P<0.01 vs. vehicle) (Fig. 3). FK888 (1, 3 and 10 mg/kg IV), a tachykinin NK1 receptor antagonist, also significantly inhibited the increased plasma exudation at a dose of 10 mg/kg (66.4%, P<0.05 vs. vehicle) (Fig. 4).

Effect of sensory neuropeptides depletion on the capsaicin-induced pharyngeal plasma exudation

To deplete sensory neuropeptides such as SP and NKA, systemic capsaicinization (total capsaicin dose of 125 mg/kg SC) was performed, as described in Materials and Methods. The capsaicin-induced increase in EB exudation was significantly attenuated by systemic capsaicinization (P<0.01 vs. sham treatment group) (Fig. 5).

DISCUSSION

Pharyngitis is an inflammatory syndrome of the oropharynx derived predominantly from infectious causes or, less commonly, from secondary involvement of systemic or noninfectious illness. Cigarette smoking is also sometimes a cause of sore throat. The pathogenesis of infectious pharyngitis is infections from viruses such as rhinovirus, coronavirus and adenovirus, and of bacteria such as Streptococcus pyogenes, Chlamydia trachomatis, Mycoplasma pneumoniae, and...
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**FIGURE 1.** The effects of time schedule for capsaicin (cap) application onto the surface of rat pharyngeal mucosa on the amount of extravasated Evans blue dye (micrograms of EB/g wet weight tissue) in the pharynx. (A) EB exudation assessed 30 min after single application of 0.3 mM capsaicin; (B) assessed 60 min after single application of 0.3 mM capsaicin; and (C) assessed after twice applications of 0.3 mM capsaicin at a 30-min interval. White bars: Amount of EB exudation in vehicle control group; shaded bars: capsaicin-treated group. Each column represents the mean with SE from five or six animals. **P<0.01 vs. respective vehicle control. Hatched bars: EB exudation expressed as the increase percentage of that in respective vehicle control groups (calculated from the data of the left side of the figure).

*Haemophilus influenzae.* Virulence of *Streptococcus* infection is, for example, dependent on locally invasive cellular enzymes such as streptokinase and hyaluronidase (Vukmir, 1992). In our preliminary study, we attempted applications of capsaicin alone and hyaluronidase (400-1500 U/ml) plus capsaicin on the pharyngeal mucosa of the rat. As a result, no significant difference in inducing pharyngeal exudation was observed between groups. Therefore, we used capsaicin alone in the present study to induce experimental pharyngitis. Experimental pharyngitis in laboratory animals has not been reported as far as we know. The oropharynx consists of mucosal membrane layers with stratified squamous epithelium, which protects the mucosa from physical, chemical and thermal stimuli given by food, drink and inspired air. Such a robust oropharyngeal mucosa may be a reason why good models of pharyngitis have not been available so far.

Capsaicin is known to be the prototype of neurogenic irritants. The topical application of capsaicin to rat skin leads to excitation of afferent neurons (Kenins, 1982), increases in skin blood flow (Inoue et al., 1995), and vasodilation (Lynn et al., 1992). Neuropeptides such as SP and NKA, which are released by capsaicin from peripheral endings of afferent neurons, have been considered as chemical mediators of skin inflammation (Holzer, 1988, 1991; Maggi and Meli, 1988; Saria et al., 1988). SP, a tachykinin found in the C-fiber nerve endings of the airways of a variety of species including humans, influences several airway functions; it increases mucus secretion, epithelial chloride secretion, and vascular permeability and stimulates airway smooth muscle contraction (Mortling, 1987). In the present experiment, 0.3 or 1.0 mM capsaicin increased vascular permeability of the rat pharynx, reaching a significant effect at 60 min. It has been reported that ear edema developed rapidly and reached a maximum at 60 min after a topical capsaicin application on the surface of mouse ear (40 and 250 μg/ear of capsaicin) (Gabor and Raaga, 1992; Inoue et al., 1993). In our experiment, a concentration-dependent enhancement of plasma exudation was observed with increased concentrations of capsaicin (0.1-1.0 mM). The calculated amounts of capsaicin applied onto

**FIGURE 2.** The concentration-related effect of capsaicin (0.1, 0.3 and 1.0 mM) on Evans blue (EB) exudation in the rat pharynx. Capsaicin was applied twice with a 30-min interval on the rat pharyngeal mucosa. Each column represents the mean with SE from six or seven animals. **P<0.01 vs. vehicle control.
FIGURE 3. Effect of FK224, NK₁- and NK₂-receptor antagonist, on Evans blue (EB) exudation in the rat pharynx induced by local capsaicin treatment (two applications of 0.3 mM solution with a 30-min interval). FK224 was administered intravenously 5 min before the first capsaicin application. Each column represents the mean ± SE from six or seven animals.

**P < 0.01 vs. vehicle control.

The drugs tested were administered intravenously 5 min (chlorpheniramine, indomethacin and diclofenac) and 30 min (dexamethasone and glycyrrhizinic acid) prior to the first capsaicin application on the surface of the pharyngeal mucosa. Each value represents the mean ± SE from five to seven animals.

The pharyngeal mucosa were 4.6 and 15.1 µg/pharynx (50 µl of 0.3 and 1.0 mM capsaicin solution, respectively). Therefore, the effective dose needed to increase plasma exudation in the pharynx seems to be lower than that in the ear. The reason might be due to differences in capsaicin absorption from the application site between the mucosa and outer skin and/or to species difference.

An antihistamine, chlorpheniramine, had a negligible effect on the capsaicin-induced rat pharyngeal plasma exudation. The dose of chlorpheniramine (1 mg/kg IV) used presently is a dose sufficient to inhibit the bronchoconstriction induced by 0.2% histamine inhalation in dogs (Yamatake et al., 1977). It has been reported that the neuropeptides liberated by capsaicin through activation of sensory nerves are able to release histamine from mast cells (Gabor and Razga, 1992; Inoue et al., 1993; Wang et al., 1994). However, in the present study, that may not be the case. Our result might be consistent with the results of other studies in vivo experiments concerning the trachea, esophagus, conjunctiva, paw skin, urinary bladder and nasal mucosa (Saria et al., 1983) and lower respiratory tract of the rat (Lundberg and Saria, 1983). These groups reported that enough high local SP concentrations are necessary to activate mast cells and that SP in lower concentrations acts mainly via a mechanism whereby mast cells are not involved.

Cyclooxygenase inhibitors, indomethacin and diclofenac, had no effect on capsaicin-induced pharyngeal plasma exudation. The dose of indomethacin (5 mg/kg IV) completely blocked the decrease in arterial blood pressure produced by IV injection of 1 mg of arachidonic acid in the dog (Roberts et al., 1985), and has also been often used as a typical dose for complete blockade of cyclooxygenase in other in vivo experiments (Hong et al., 1995; Kuroiwa et al., 1996; Yoshihara et al., 1995, 1996). IV administration of diclofenac sodium (3 mg/kg) prevented EB leakage induced by electrical stimulation in the rat dental pulp (Kerezoudis et al., 1993). In addition, preadministration of diclofenac (9 mg/kg IV) inhibited the carrageenan-induced inflammation of the rat ankle and paw (Buritova et al., 1995). A diclofenac dose of 10 mg/kg IV seems sufficient for an anti-inflammatory effect, although presently it was without effect. From the present results with cyclooxygenase inhibitors, it is conceivable that the role of prostaglandins would be minimal, if any, in our pharyngeal model. This was in accordance with the results of Inoue et al. (1993) that indomethacin (10 mg/kg orally) and aspirin (200 mg/kg orally) did not suppress capsaicin-induced mouse ear edema. They suggested that prostaglandins did not primarily mediate the development of the capsaicin-induced ear edema. Furthermore, Wang et al. (1994) reported that pretreatment with indomethacin (10 mg/kg IP) had no effect on SP-induced ear edema in mice. Also, glycyrrhizinic acid (10 mg/kg IV) did not reduce the rat pharyngeal plasma exudation induced by capsaicin. The IV dose of glycyrrhizinic acid inhibited the passive anaphylaxis reaction in the rat conjunctiva (Iso et al., 1980). Glycyrrhizin is reported to have a similar action as steroidal anti-inflammatory drugs although the effect is much weaker than steroids (Finney and Somers, 1958). On the other hand, the steroidal anti-inflammatory agent, dexamethasone (3.3 mg/kg IV), was effective in suppressing the capsaicin-induced increase in plasma exudation in the present study. Inoue et al. (1993) applied capsaicin on the mouse ear to cause an edema on which dexamethasone (0.1 mg/kg, applied topically) was greatly effective (76% inhibition). Sheppard et al., (1992) reported that dexamethasone, in a dose of 0.25 mg/kg IV, significantly reduced edema by laser exposure in rat skin. The mechanism of the anti-inflammatory action of the steroid on the pharyngeal mucosa is now unexplainable, but could possibly be due to phospholipase A₂ inhibition leading to inhibition of generation of 5-lipoxygenase products, but not to inhibition of generation of cyclooxygenase products, because indomethacin and diclofenac were without effect in our model.

### TABLE 1. Effects of several agents on the increase in rat pharyngeal plasma exudation induced by capsaicin

| Drug               | Dose (mg/kg IV) | EB exudation (µg/g tissue) | Inhibition (%) |
|--------------------|----------------|---------------------------|----------------|
| Control            | —              | 37.5 ± 3.7                | —              |
| Chlorpheniramine   | 1              | 34.7 ± 1.7                | 15.8           |
| Indomethacin       | 5              | 34.0 ± 1.4                | 19.8           |
| Diclofenac         | 10             | 38.0 ± 2.5                | -2.8           |
| Control            | —              | 34.9 ± 3.0                | —              |
| Dexamethasone      | 0.3            | 27.4 ± 1.1†              | 45.7           |
| Glycyrrhizinic acid| 10             | 35.1 ± 3.3                | -1.2           |

The drugs tested were administered intravenously 5 min (chlorpheniramine, indomethacin and diclofenac) and 30 min (dexamethasone and glycyrrhizinic acid) prior to the first capsaicin application on the surface of the pharyngeal mucosa. Each value represents the mean ± SE from five to seven animals.

†p < 0.05 vs. control.
FK224 and FK888 effectively and dose-dependently suppressed the capsaicin-induced increase in pharyngeal plasma exudation. Because FK224 is a dual antagonist for both NK1 and NK2 receptors (Murai et al., 1992; Murai et al., 1992) and FK888 is a selective antagonist for NK1 receptor (Fujii et al., 1992), sensory neuropeptides such as SP and NKA are considered to be involved in our pharyngitis model. It is known that capsaicin stimulates sensory C-fibers, causing a release of SP and NKA from nerve endings (Ingenito et al., 1991; Sallasi et al., 1993), and that neurogenic plasma exudation induced by capsaicin is mediated via tachykinins released from capsaicin-sensitive sensory nerves (Lundberg and Saria, 1982; Murai et al., 1992). Edema resulting from increased microvascular permeability and vasodilation in the airway of the guinea pig is reportedly induced by SP more potently than by NKA (Murai et al., 1992; Rogers et al., 1988), suggesting that NK1 receptor is more important than NK2 receptor in airway edema induced by SP, NKA and capsaicin. In the present experiment, however, the inhibitory action of FK224 seemed to be stronger than that of FK888. Neurogenic plasma protein exudation in the rat paw induced by mustard oil, SP, and antidiromic stimulation of the saphenous nerve and vagal stimulation was inhibited by an NK1 receptor antagonist, CP-96345, although not completely (Lembeck et al., 1992). Capsaicin-induced plasma exudation in the guinea pig bronchi was also inhibited partly (not completely) by CP-96345 (Lei et al., 1992). Therefore, it is likely that capsaicin-induced pharyngeal plasma exudation in the present study involves both NK1 and NK2 receptors, because FK224 is an antagonist for both receptors with a similar potency (Murai et al., 1992). In addition, it is possible that the relatively weak effect of FK888 in the present study is due to the existence of species difference in potency of FK888. FK888 inhibited [3H]-SP binding to guinea pig lung membrane with an approximately 100-fold higher affinity than that to rat brain cortical membranes (Fujii, 1995), although another NK1 antagonist, RP67580, has been reported to be a potent inhibitor of [3H]-SP binding to rat brain membrane preparations (Kd=4.16 nM). Nevertheless, the effect of RP67580 on SP-induced guinea pig ileum contraction is relatively weak (pA2=7.16) (Garret et al., 1991). Therefore, the relatively weaker effect of FK888 on rat tissues might be derived from the characteristics of FK888 itself, and probably not from the characteristics of NK1 receptor in rat tissues. The participation of subtypes of neuropeptide receptors in rat pharyngitis induced by capsaicin is necessary to be clearly demonstrated in the future.

The present rat pharyngitis model is the first one capable of quantitative determination of induced pharyngeal inflammation, requires only a simple technique and provides well-reproducible results. However, throat inflammation in the common cold syndrome can be somewhat treated clinically by nonsteroidal anti-inflammatory drugs, which were without effect in this study, so the present model requires improvement.

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