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Pharmacologic Characterization of Latex Extracts by Isolated Guinea Pig Tracheal Tissue

Key Words
Latex extract
Airway smooth muscle
Respiratory symptoms

Abstract
Latex manufacturing workers are exposed to a heterogeneous aerosol of organic compounds. Previous studies of latex workers involved in glove production indicate that these individuals are at risk of developing respiratory symptoms and impaired lung function. The effect of latex extracts on isolated guinea pig tracheal smooth muscles was studied using latex water-soluble extracts obtained at different stages of the industrial process. Latex extracts were prepared as a 1:10 (w/v) solution. Dose-related contractions of nonsensitized guinea pig trachea were demonstrated using two latex extracts (latex 1 and latex 2). Latex 1 was prepared from the native latex and latex 2 from a processed form of latex which was relatively free of soluble proteins. Pharmacologic studies were performed by pretreating guinea pig tracheal tissue with drugs known to modulate smooth muscle contraction: atropine, indomethacin, pyrilamine, nordihydroguaiacetic acid, acivicin, trimethobenzoic acid and capsaicin. Constrictor effects of the dust extracts were inhibited by a wide variety of these agents. Atropine consistently and strikingly reduced the contractile effects of these extracts. This observation may suggest an interaction of the extracts with parasympathetic nerves or more directly with muscarinic receptors. Inhibition of contraction by blocking other mediators was less effective and varied with the dust extract. Pretreatment with capsaicin did not change the constrictor effects of latex 1 but enhanced the effects of latex 2. Depletion of neuropeptides, however, did not reduce the constrictor effect. We suggest that latex extracts cause dose-related airway smooth muscle constriction by nonimmunological mechanisms involving a variety of airway mediators and possibly cholinergic receptors. This effect is not dependent on the presensitization of guinea pigs.

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Introduction

Natural rubber (latex) is a milky substance which serves as the primary agent for the rubber industry. Latex is prepared in a water-based solution containing a complex colloidal suspension of rubber particles [1, 2].

It is produced by plants and trees of the sapodilla family. Most commercially used natural latex comes from hevea tree plantations of tropical Africa, Asia and South America (*Hevea brasiliensis* in particular). Rubber material extracted from these plants is preserved with ammonia, centrifuged, compounded, and after aging it is used to manufacture medical supplies and many everyday products. A number of chemical agents are used to transform the solution into a commercial product [3].

Worker exposure to pulverized latex may occur as a result of the inhalation as well as from the topical application of this product which is aerosolized in respiratory-sized particles during the manufacturing process. These particles are felt to be responsible for respiratory sensitization and irritative symptoms [4, 5]. Several authors report hypersensitivity reactions to latex in a large number of patients. These responses vary from urticaria to rhinitis, conjunctivitis, dyspnea and systemic reactions [5–8]. Brugnami et al. [9] reported that occupational asthma caused by latex may lead to permanent disability, even after removal from exposure. In the medical environment, the reaction is frequently associated with latex material which adheres to glove powder.

In our previously reported study of 17 workers in a latex-processing plant (from which our powder was obtained), 5.9% (1/17) of the workers had occupational asthma, but more than half had irritative lower and upper respiratory symptoms: chronic cough (cough present for at least 3 months in the previous year: 7/17), dyspnea (10/17), dryness of the nose and throat (12/17) and dry cough (cough without phlegm experienced during the work shift: 10/17) [10].

In a series of prior investigations [11–15] we have demonstrated that a number of organic dusts, e.g. coffee, soy, wool, brewery agents (hops, barley, yeast) and spices, cause nonspecific constriction of airway smooth muscle. The present study was performed to characterize possible mechanisms by which latex dust acts on the airways in workers occupationally employed in a rubber latex glove-manufacturing plant. The effect of latex extracts was tested on isolated guinea pig tracheal rings. In order to investigate whether these responses are mediated by the release of mediators from airway-associated cells (e.g. mast cells, sensory nerve fibers) or epithelial cells), we studied the effects of a number of agents which modify the effect of mediators.

Methods

Latex Extract Preparation and Protein Content Determination

Latex extracts were prepared from the natural latex material collected in a plant which manufactures rubber gloves and other rubber products (latex 1). In this plant the workers had been studied as part of an epidemiologic survey of respiratory health. The other latex extract was derived from latex which had been processed, thus the water-soluble proteins associated with the latex particles were at least partially removed (latex 2). This represents loosely bound protein which dissolved readily. Most of the protein associated with latex remained bound to the original product as demonstrated by the protein analysis. The biochemical properties of the proteins were not studied in this investigation. The latex extracts were prepared in a weight to volume ratio of 1:10 by the standard method of Sheldon et al. [16] at the Institute of Immunology in Zagreb.

The total protein content of the latex extracts was determined by the method of Lowry et al. [17].

Guinea Pig Trachea Preparation

We used the tracheas of young albino Hartley male guinea pigs (300–390 g) purchased from Charles River, Wilmington, Mass., USA. The animals were sacrified by CO_2 asphyxiation for 5 min and the tracheas were removed within 3 min of sacrifice. The animal tissues were manually trimmed to remove connective and other tissues. Four segments ('rings' each 4–6 mm wide) were cut from a single trachea, and each was suspended between two L-shaped stainless steel hooks mounted in a 20-ml organ chamber containing Krebs-Henseleit buffer of the following composition (μM): NaCl, 110.0; KCl, 4.80; $CaCl_2$, 2.35; $MgSO_4$, 1.20; $KHPO_4$, 1.20; $NaHCO_3$, 25.0, and dextrose, 110.0, in glass-distilled water. Organ chambers were maintained at 36.5 ± 0.5°C, and were continuously aerated with 95% O_2 and 5% CO_2 to maintain pH = 7.5 ± 0.1. The tissue segments were initially set to 2 g of tension, and were allowed to stabilize for approximately 1.5 h before the experiment began. During that period, the tissues were washed at 15-min intervals. After this stabilization period, the tension in each tissue ring was readjusted to 2 g for all subsequent assays. Isometric contractions were recorded using a Grass FTO3C force displacement transducer attached to a Grass polygraph recorder.

Steady-State Characterization of the Latex Extract Dose-Response Curve

After equilibration, each tissue segment was maximally contracted isometrically with carbachol ($10^{-4} M$). This response was measured in grams of tension and designated as the maximal carbachol response for that tissue (100%). All subsequent contractions of the segment were normalized to this maximal carbachol response and expressed as a percentage of maximal carbachol-induced contraction. Isometric contractions induced by latex extract were measured to the sequential cumulative dose increments administered in 1/2 log unit dose steps. Progressive aliquots of the standardized solution were added (10, 30, 100, 300, and 1,000 µl). Following the measurement of dose response the tissue was washed at 15-min intervals for a period of approximately 1 h until a stable baseline was reestab-

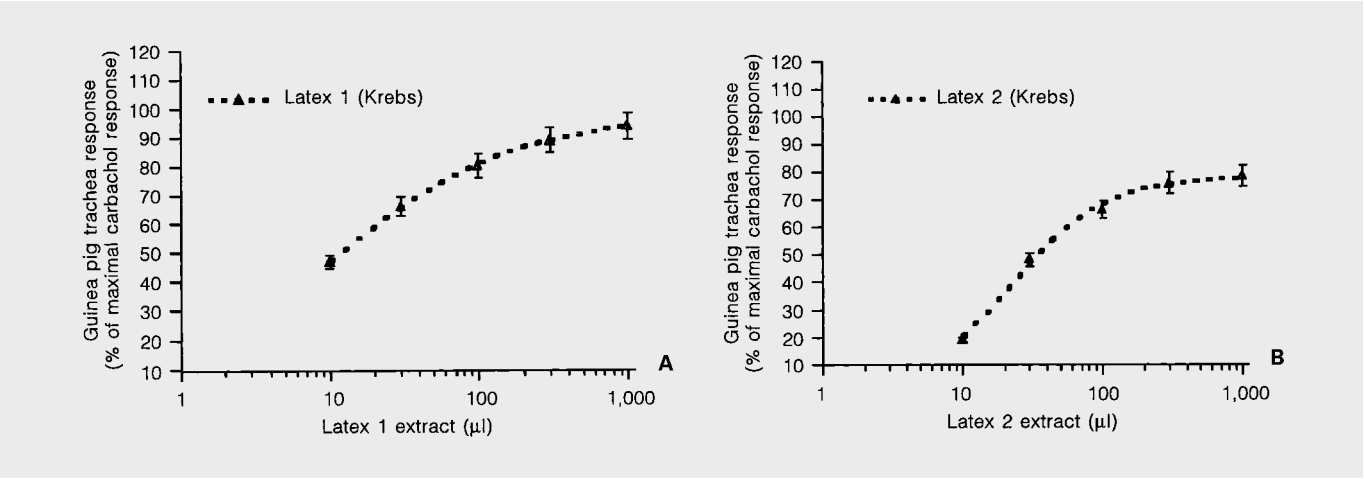

Fig. 1. Contractile activity of latex extracts. Latex 1 (**A**) and latex 2 (**B**) on isolated guinea pig tracheal smooth muscle as percentage of carbachol (10^{-4} *M*) conctraction (means ± SE). The designation (Krebs) in this figure indicates that prior to challenge with latex extract the tissue was challenged with Krebs solution equal in volume to the administered drugs.

lished. The tissue was then reset to 2 g tension, and was then ready for the subsequent drug protocols. Concentration-response curves were plotted using the Kaleidograph software (version 3.04, Cupertino, Calif., USA) for the Power Macintosh 8200. Data points were fit by iteration to the logistic function:

$$E = \frac{E_{max}}{1 + EC_{50}/[A]^n}$$

where E = observed muscle tension (grams above baseline), [A] = the concentration of the agonist, EC_{50} = the [A] eliciting one half of the maximal response and n = the slope of the curve.

Drug Treatment Protocol

In a typical drug experiment, the tissue was washed and baseline reestablished after an initial contraction with carbachol (10^{-4} *M*) demonstrated tissue viability and established maximal contractile tension. A specific blocking agent (or a control solution) was then added to the organ bath and incubated with the tissue for 20 min. A latex extract dose-response challenge was then performed. After the dose response the tissue was again washed and carbachol (10^{-4} *M*) was added to verify the viability of the tissue.

In the drug experiments, we studied the possible influence of a number of receptor as well as nonreceptor mechanisms. These agents studied included atropine (10^{-6} *M*; anticholinergic; n = 6), pyrilamine (10^{-6} *M*; antihistamine, H_1-blocking agent; n = 6), indomethacin (10^{-6} *M*; prostaglandin synthesis inhibitor; n = 6), 3,4,5-trimethoxybenzoic acid-8-(diethylamino)octyl ester]; TMB8; 10^{-5} *M*; inhibitor of intracellular calcium mobilization; n = 6) [18] nordihydroguaiaretic acid; NDGA; 10^{-5} *M*; arachidonic acid pathway inhibitor; n = 6) [19] and acivicin (10^{-5} *M*; leukotriene synthesis inhibitor; n = 6) [20]. In addition, in order to evaluate the possible role of preformed neurogenic peptides in the latex responses, we tested the tissue with capsaicin (5×10^{-6} *M*; 8-methyl-n-vanillyl-6-nonenamide) for 30 min (n = 6). Capsaicin was added as a single dose either before or after latex 1 or latex 2. In a separate experiment, capsaicin (5×10^{-6} *M*) was added twice in succession (separated by a 30-min interval), before the latex extract addition, to verify the depletion of neurogenic mediators.

All chemical agents were obtained from Sigma (St. Louis, Mo., USA).

Statistical Methods

Comparison of the dose-response characteristics (E_{max}, EC_{50}) of latex 1 and latex 2 was performed using the unpaired t test. For the drug studies, each trachea enabled the examination of three drugs and a control (4 rings). Mean values of the contractile response of the rings at a given dose of latex before and after drug addition were compared by the paired t test. In this way, we compared control and drug-treated tissue responses for the same trachea. Statview software (Brain Power, Calabasas, Calif., USA) for Macintosh was used to perform this analysis.

Results

Dose-response curves to latex extracts were measured in 36 guinea pig tracheas (each obtained from separate animals). The responses to latex were expressed as a percentage of the maximal carbachol (10^{-4} *M*) contraction. The dose response to latex 1 (n = 18) and 2 (n = 18) is shown in figures 1A and 1B. These extracts elicited different response characteristics (latex 1, E_{max} = 97.03%; EC_{50} = 10.80 µl, and latex 2, E_{max} = 78.30%; EC_{50} = 22.51 µl; $p < 0.01$).

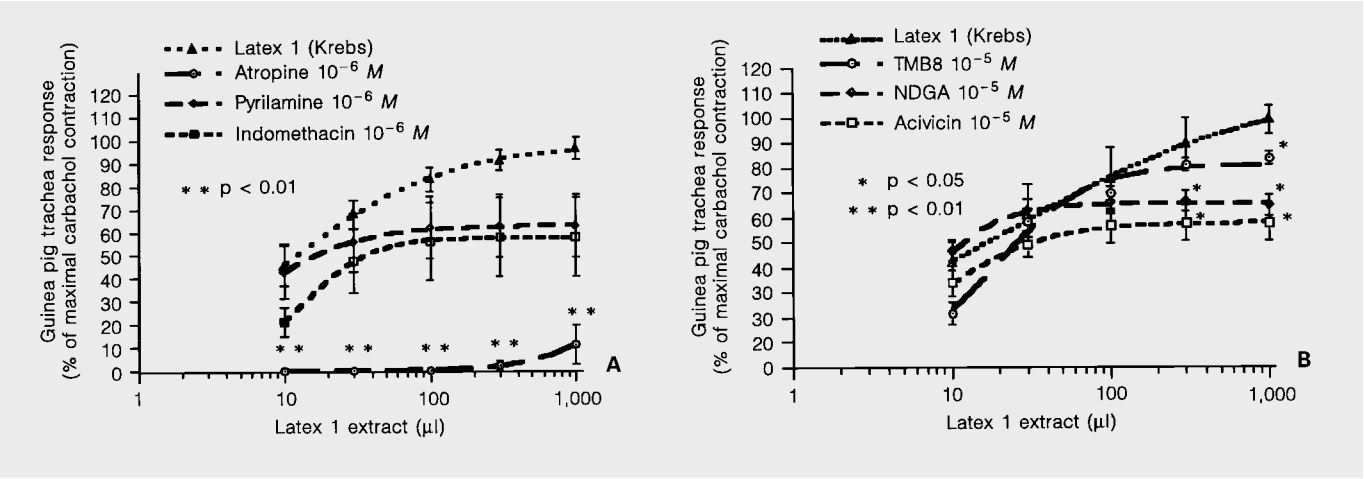

Fig. 2. The constrictor activity of latex extract (latex 1) on isolated guinea pig tracheal smooth muscle. Means ± SE. **A** Following pretreatment with Krebs, atropine (10^{-6} *M*), pyrilamine (10^{-6} *M*) and indomethacin (10^{-6} *M*). **B** Following pretreatment with TMB8 (10^{-5} *M*), NDGA (10^{-5} *M*) and acivicin (10^{-5} *M*).

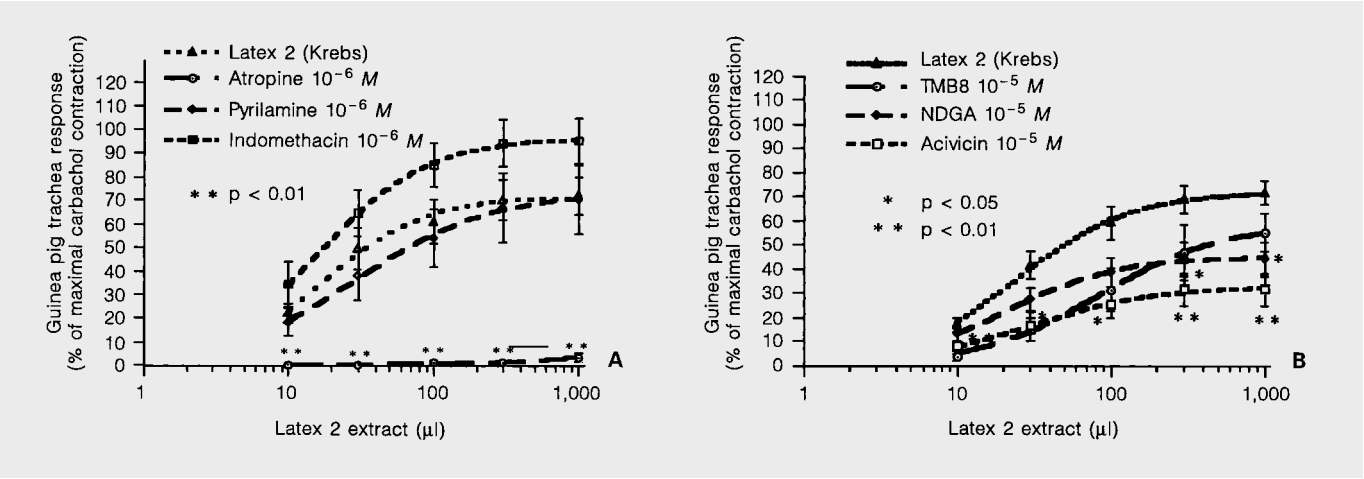

Fig. 3. The constrictor activity of latex extract (latex 2) on isolated guinea pig tracheal smooth muscle. Means ± SE. **A** Following pretreatment with Krebs, atropine (10^{-6} *M*), pyrilamine (10^{-6} *M*) and indomethacin (10^{-6} *M*). **B** Following pretreatment with TMB8 (10^{-5} *M*), NDGA (10^{-5} *M*) and acivicin (10^{-5} *M*).

The dose-response curves to latex 1 following pretreatment with atropine (10^{-6} *M*), indomethacin (10^{-5} *M*) and pyrilamine (10^{-5} *M*) are shown in figure 2A and following TMB8 ((10^{-5} *M*), NDGA (10^{-5} *M*) and acivicin (10^{-5} *M*) in figure 2B). Atropine virtually abolished the constrictor response to latex 1 for all the concentrations tested. The blocking effects of acivicin and NDGA were seen only at the higher doses (300 and 1,000 µl). Similarly, TMB8 had a significant blocking effect on latex 1 only at the highest dose (1,000 µl).

The effects of drug pretreatment on the latex 2 dose response with atropine (10^{-6} *M*), indomethacin (10^{-6} *M*), and pyrilamine (10^{-6} *M*) are shown in figure 3A. The effects of pretreatment with TMB8 (10^{-5} *M*), NDGA (10^{-5} *M*) and acivicin (10^{-5} *M*) are shown in figure 3B. Once again atropine completely blocked the latex 2 dose response. Acivicin blocked the constricting reaction to latex 2 at doses from 10 to 1,000 µl, while NDGA reduced the constrictor effect at doses of 300 and 1,000 µl.

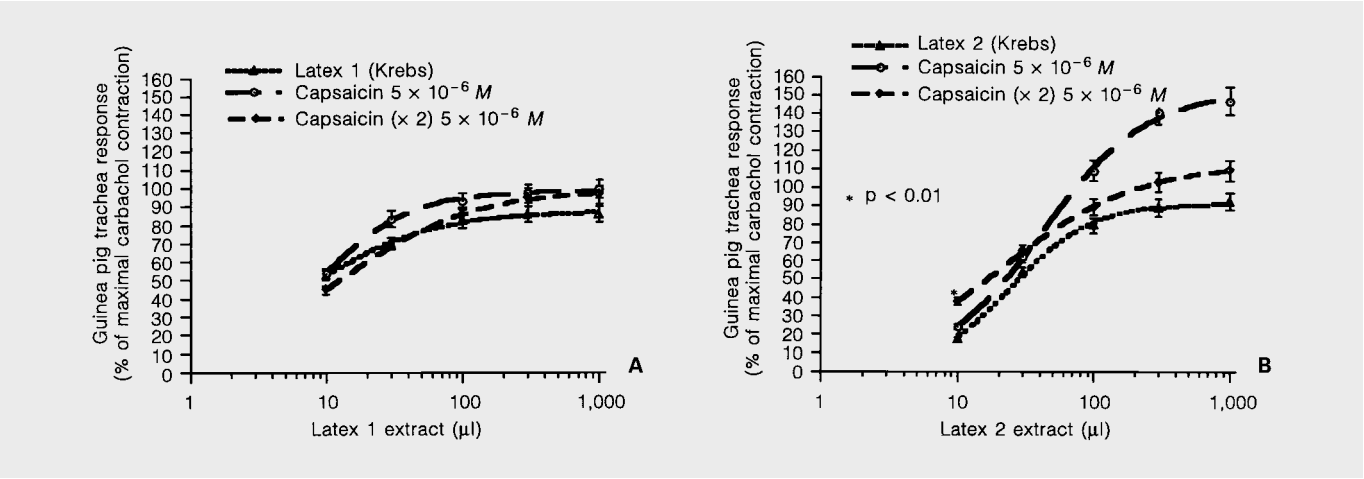

Fig. 4. The effect of capsaicin ($5 \times 10^{-6}\ M$) administered once or twice (at 30-min interval) on subsequent latex extract dose response on isolated guinea pig tracheal smooth muscle. Means ± SE. **A** Latex 1. **B** Latex 2.

The effect of capsaicin ($5 \times 10^{-6}\ M$) administered once (or twice) before latex 1 is shown in figure 4A and before latex 2 in figure 4B. Pretreatment with capsaicin did not block the latex 1 or the latex 2 effect; on the contrary it enhanced the constrictor effect of latex 2 (but not latex 1) for doses ranging from 10 to 1,000 µl when administered before the latex extract.

There were no significant differences in the effects of latex 1 and latex 2 on the ability of capsaicin to elicit constriction, so that data from these effects were pooled together. The maximal constrictor effect of capsaicin ($5 \times 10^{-6}\ M$) administered before and after latex extracts (latex 1 and latex 2 pooled data) dose response is shown in figure 5A. There was no significant difference in the constricting effect of capsaicin administered before or after latex extract, implying that latex does not act by depleting airway nerve fibers of their peptide mediators.

The constrictor effect of two doses of capsaicin ($5 \times 10^{-6}\ M$) administered consecutively (i.e. second treatment with capsaicin 30 min after the first treatment with capsaicin) is shown in figure 5B. As anticipated, the constrictor effect of capsaicin was significantly diminished following the second (30 min later) treatment with capsaicin ($p < 0.01$) indicating depletion of nerve fiber mediators.

Table 1 compares our previous experience with the effects of pharmacologic agents on the dose-response characteristics of two textile (cotton bracts and wool) extracts and our current two latex (latex 1 and latex 2) extracts. As can be appreciated while all the organic dusts listed are affected by mediator-blocking agents, there are differences in the patterns of these agents suggesting the possibility that different mechanisms (or variations in these mechanisms) are involved in these constrictor effects by organic dust extracts.

The total protein content of latex 1 was found to be 6.75 µg/ml and that for latex 2 was 6.00 µg/ml.

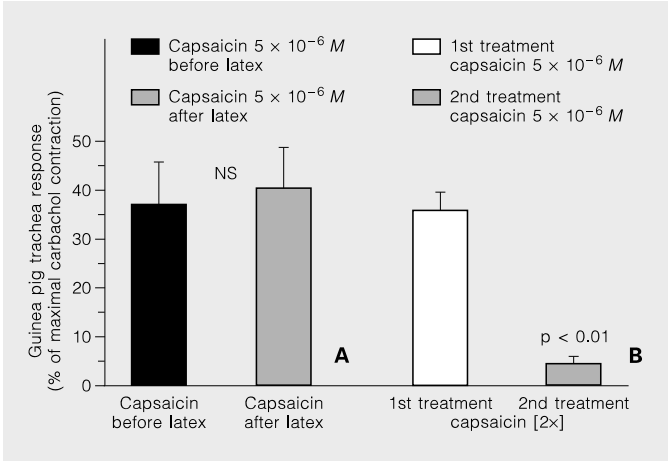

Fig. 5. A Contractile activity of capsaicin ($5 \times 10^{-6}\ M$) on isolated guinea pig smooth muscle administered before and after latex extract (latex 1 or 2). There was no significant difference between these two responses. **B** Contractile activity of capsaicin administered twice (with a 30-min interval between administrations). The difference in the reactivity between the first and second treatment with capsaicin was statistically significant ($p < 0.01$; means ± SE).

Table 1. Comparisons of pharmacologic agents of the dose-response characteristics of two textile (CBE and wool) [13, 21] and two latex (L1 and L2) extracts

	CBE	Wool	L1	L2
Pyrilamine	+	±	–	–
Atropine	+	–	+	+
Indomethacin	×	–	–	–
BW 755 C	×	×		
LY 171883	+	×		
Acivicin			+	+
NDGA			+	+
Verapamil		+		
TMB8		+	+	

CBE = Cotton bract extract; – = no effect; + = attenuation; × = attenuation at low concentrations of extract, enhancement at high concentrations.

Discussion

The data obtained in our study are similar to those of our previous investigations of airway smooth muscles in the isolated guinea pig trachea with different organic dust extracts, such as coffee, soy, spices, animal food, and brewery dust (hops, barley, yeast) [11, 12, 14, 22–24]. These pharmacologic studies of latex and other extracts of organic dusts on isolated guinea pig tracheal smooth muscle suggest a complex nonimmunologic (non-IgE) effect of these airway irritants. We propose that several mediators may be involved in promoting airway constriction in these situations. The greatest protective effect against latex airway constriction was noted following pretreatment with the muscarinic-blocking agent atropine, suggesting a possible role for the cholinergic nervous system in initiating these effects. This protective effect of atropine has been previously described with other organic dust extracts such as wool, brewery dust, and poultry confinement extracts [13, 14, 24]. Prior studies emphasize the allergic etiology of latex-induced asthma. Our findings need not be viewed as contradictory. It may be that nonspecific (non-IgE) inflammatory responses may be a prerequisite for tissue sensitization. Such an inflammatory response might promote the absorption and processing of antigen leading ultimately to classic hypersensitivity.

In the present study, the suppression of constrictor effects caused by latex extract using the intracellular calcium channel blocker TMB8 may simply reflect the reliance of this response on intracellular calcium mobilization. An increase in intracellular Ca^{2+} occurs in many smooth muscle preparations induced to constrict by receptor and nonreceptor mechanisms [25, 26]. Calcium mobilization for the contractile mechanism may originate from intra- or extracellular stores. Since elevation in cytosolic calcium is required in the cascade leading to smooth muscle constriction, intra- and extracellular calcium-blocking agents may play a role in the treatment of dust-related airway obstruction by acting as functional antagonists.

Regoli [27] reported that isolated guinea pig trachea may be activated to constrict by a number of different peptide receptors. There are many neuropeptides with potent effects on airways that are released by airway nerves. It has been shown that capsaicin acts largely through activation of nonselective cation channels [28–30] and it has been demonstrated that capsaicin is an agent which directly stimulates airway nerves initiating reflex effects. Capsaicin acts specifically by depleting stores of substance P from sensory neurons and blocking further synthesis of this neuropeptide [31]. In animals, capsaicin stimulates C-fibers causing the release of substance P [32, 33]. This response is subject to tachyphylaxis. The absence of a suppressor effect on latex extract contraction following capsaicin pretreatment suggests that sensory neuromediators are not primarily involved. Further confirming this statement is the observation that pretreatment of guinea pig trachea by latex extracts does not deplete neuromediators released by capsaicin since the latter remain active after latex extract challenge. By contrast, our study suggests that pretreatment with capsaicin may enhance the effect of latex 2. This suggests that preexisting airway irritation (such as that mediated by capsaicin) may amplify the effect of exposure to organic materials such as latex. By contrast, in our study exposure to capsaicin significantly decreased the constrictor reaction of guinea pig airway smooth muscle to a repeated capsaicin challenge indicating that a single challenge with this agent can deplete neuropeptide mediators. Similar results have been shown by O'Neil [28] who demonstrated that prolonged exposure to capsaicin produces a subsequent desensitization or neuroinhibition.

The present study presents further evidence that extracts of organic industrial products cause a nonspecific release of airway mediators. The source of these mediators does not appear to be sensory nerves. On the basis of these data, we can speculate that some of the nonspecific (nonallergic) clinical effects of latex exposure in workers employed in latex processing may in part be related to nonimmunologic (non-IgE) mechanisms since the ani-

mals tested in this study were not presensitized to these latex extracts. The role of individual mediators involved in occupational airway diseases appears to vary with different organic materials. The origin of these mediators is, as yet, not well defined.

Interest has recently focused on the allergic response of workers and other individuals to latex exposure. Marcos et al. [34] suggested that latex present in rubber gloves acts as inhalant allergen producing occupational asthma in exposed subjects probably by means of an IgE-mediated mechanism. Using a guinea pig model, Aamir et al. [35] indicated that this species is capable of making antibodies to latex protein components that mediate dermal and respiratory reactions paralleling clinical latex hypersensitivity in humans. Ishizaka et al. [36] injected latex particles intravenously or intra-arterially into guinea pigs and revealed massive accumulation of latex in the reticuloendothelial system suggesting that the phagocytic system may play a role in the development of lung injury in guinea pigs. Reijula et al. [37] reported studies which showed latex-induced dermal and pulmonary hypersensitivity in latex-sensitized rabbits. The authors demonstrated that subcutaneous injection of natural rubber latex may create a risk for subsequent systemic reaction. While allergic airway responses clearly occur in latex workers, the frequency of these reactions is uncertain [4–15] and the interaction between nonspecific and specific (IgE-mediated) reactions may be important. Our data, both in vitro and in vivo, suggest that in addition to allergic reactions there exists the potential for significant nonspecific airway reactions. The association between these forms of airway injury remains to be determined.

Our experimental data with latex extracts imply that the clinical effects of latex dust in workers may in part be related to a nonimmunologic (non-IgE) response of the airway. The effect of atropine suggests that cholinergic nerves and/or receptors may be involved. The role of other mediators appears to vary. Such findings may have clinical and therapeutic implications for acute and/or chronic respiratory symptoms and lung function changes that occur in latex workers and other individuals exposed to latex and its products.

Acknowledgments

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