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European Journal of Pharmacology 436 (2002) 127–134

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Mechanisms of wood smoke-induced increases in nasal airway resistance and reactivity in rats

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Received 8 October 2001; received in revised form 3 December 2001; accepted 14 December 2001

Abstract

We investigated the mechanisms of wood smoke-induced increases in nasal airway resistance (RNA) and airway reactivity in anesthetized rats. Delivery of wood smoke into a functionally isolated nasal airway produced an increase in RNA, which was attenuated by CP-96,345 [a tachykinin NK_1 receptor antagonist; (2*S*,3*S*)-*cis*-2-(diphenylmethyl)-*N*-((2-methoxyphenyl)-methyl)-1-azabicyclo(2.2.2.)-octan-3-amine] or atropine. Additionally, smoke pre-exposure animals displayed a greater amplitude and a longer duration of RNA responses to capsaicin or histamine provocation, as compared to air controls. This enhanced airway reactivity to capsaicin or histamine was largely alleviated by CP-96,345 or atropine. The nasal secretory responses to capsaicin or histamine in smoke pre-exposure animals were similar to those in air controls. We concluded that (1) reflex cholinergic and tachykininergic mechanisms play important roles in wood smoke-induced increases in nasal airway resistance and airway reactivity, and (2) this nasal airway hyperreactivity might not be due to an exaggerated secretory response, but is presumably due to augmented nasal swelling.

Keywords: Smoke; Hyperreactivity; Nasal irritation; Tachykinin; Cholinergic reflex

1. Introduction

Allergic rhinitis, characterized by increases in nasal airway resistance (RNA) and airway reactivity (Schoenwetter, 2000), is prevalent in areas with polluted air (Ishizaki et al., 1987). Wood smoke is a type of common indoor and outdoor pollutant to the human airway (Larson, 1994). Many clinical and animal studies have clearly demonstrated that wood smoke exposure is responsible for various adverse effects on the lower airway and lungs (Ellegard, 1996; Hsu et al., 1998a,b; Kou and Lai, 1994; Larson, 1994; Lin et al., 2001; Lin and Kou, 2000; Perez-Padilla et al., 1996). The nasal cavity is the first site in the upper airway susceptible to insult by wood smoke. However, nasal pathophysiological consequences resulting from wood smoke exposure have been largely overlooked and their underlying mechanisms are not known.

An increase in RNA is a common airway response to nasal irritants (Desrosiers et al., 1998; McLean et al., 1979; Morris et al., 1999; Schwartz et al., 1989; Shusterman et al., 1998; Willes et al., 1998). Nasal mucosa swelling due to dilation of vessels and tissue edema, and obstruction of the nasal airway due to increased glandular output and plasma exudation may contribute to the overall increase in RNA (Bernstein, 1991; Numata et al., 2000; Sanico et al., 1998). These nasal airway responses are thought to be induced by central reflexes via a cholinergic pathway and by local releases of chemical mediators (Bernstein, 1991; Van Gerth, 1991; Jankowski et al., 1993; Matran et al., 1990; Stjärne, 1991). Under pathological conditions, overreaction of these reflexes and local mechanisms to a certain nasal stimulus results in exaggerated airway responses, thus forming nasal airway hyperreactivity (Bernstein, 1991; Van Gerth, 1991; Stjärne, 1991). Among these mechanisms, cholinergic reflexes and endogenous tachykinins (e.g., substance P and neurokinin A) have been largely implicated in the development of increased RNA and nasal airway hyperreactivity (Bernstein, 1991; Van Gerth, 1991; Jankowski et al., 1993; Matran et al., 1990; Morris et al., 1999; Stjärne,

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0014-2999/02/$ - see front matter
PII: S0014-2999(01)01608-9

1991). Tachykinins are proinflammatory neuropeptides released locally from airway afferent C-fiber nerve endings in response to chemical irritants (Solway and Leff, 1991; Stjärne, 1991). Histological studies have demonstrated an abundant distribution of tachykinins containing C-fiber afferents in the nasal mucosa of various species (Lundblad et al., 1983; Stjärne, 1991; Uddman et al., 1983). Stimulation of these nasal afferents by chemical irritants may evoke central reflexes leading to dilation of blood vessels located in the nasal mucosa and to an increase in nasal secretion (Asakura et al., 1994; Kubo and Kumazawa, 1993), or may cause the local release of tachykinins resulting in nasal vasodilation, plasma exudation, and increased secretion via activation of tachykinin NK_1 receptors (Evangelista et al., 1997; Matran et al., 1990; Piedimonte et al., 1993; Stjärne, 1991). We recently reported (Ho and Kou, 2000) that chronic ablation of C fibers prevents the airway reflexes induced by nasal exposure to wood smoke in rats, suggesting that stimulation of nasal C-fiber sensory nerve endings is responsible for evoking these reflex responses. Additionally, our previous studies demonstrated that inhaled wood smoke stimulates C-fiber sensory nerve endings located in the lower airways (Kou et al., 1995; Lai and Kou, 1998), and that tachykinins play an important role in the pathogenesis of various airway responses to wood smoke inhalation (Hsu et al., 1998a,b; Lin and Kou, 2000; Lin et al., 2001). Taken together, these observations suggest that nasal exposure to wood smoke may increase RNA and nasal airway reactivity through reflex cholinergic and tachykininergic mechanisms. Nevertheless, experimental evidence to support this possibility remains to be established.

This study was undertaken in anesthetized rats to investigate (1) the increase in RNA and nasal airway reactivity induced by nasal exposure to wood smoke, (2) the possible involvement of reflex cholinergic and tachykininergic mechanisms in these two nasal responses, and (3) the role of nasal secretion in the enhanced nasal airway reactivity induced by wood smoke exposure.

2. Materials and methods

2.1. Animal preparation

Adult male Sprague–Dawley rats weighing 300 to 380 g were anesthetized with an intraperitoneal injection of chloralose (100 mg kg^{-1}; Sigma, St. Louis, MO, USA) and urethane (500 mg kg^{-1}). The femoral artery and jugular vein were cannulated for recording arterial blood pressure and for administration of pharmacological agents, respectively. During the experiment, the depth of anesthesia was regularly monitored at fixed intervals; supplemental doses of anesthetics were administered intravenously whenever necessary to maintain abolition of the pain reflex induced by pinching the animal's tail. The animal was tethered in a supine position, the neck opened in the midline, and the esophagus ligated as rostrally as possible. The superior and recurrent laryngeal nerves were sectioned to minimize possible mechanical irritation to the upper airway during the experiment. Body temperature was maintained at 36 °C throughout the experiment by means of a servo-heating blanket. All protocols were in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health, Bethesda, MD, USA, and were approved by the Committee of the National Science Council, Taipei, Taiwan.

2.2. Functionally isolated nasal cavity and measurement of RNA

Fig. 1 schematically illustrates the functionally isolated nasal airway preparation. As shown, a tracheal cannula (Clay Adams PE-260; Sparks, MD, USA) was inserted caudally just above the thoracic inlet, while an upper airway catheter (Clay Adams PE-206) was inserted cranially with its tip placed inside the nasopharynx. The outlet of the nostrils was covered by a plastic funnel that allowed the air or smoke to flow out. The oral cavity was stuffed with small cotton balls and sealed to prevent any air leak. The position of the catheter tip at the nasopharynx was confirmed by autopsy after animals had been sacrificed at the end of the experiment. For measurements of RNA, a constant flow (1.4 ml s^{-1}) of air or wood smoke, generated by a syringe pump (Sage model 367; Cambridge, MA, USA), was delivered into the upper airway catheter (Fig. 1) for a period of 8 or 11 s. During this flow delivery, the pressure

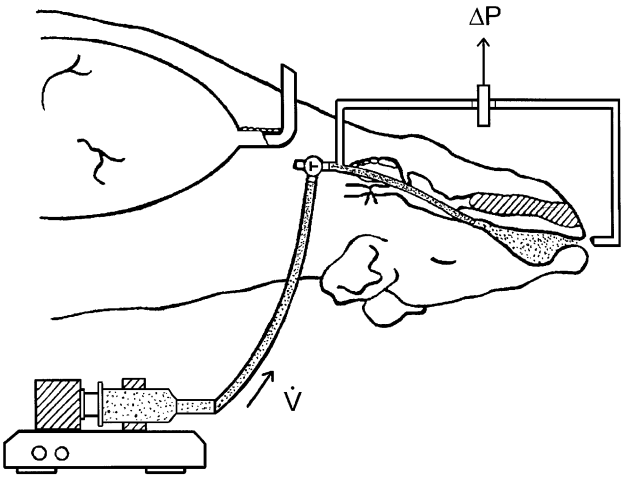

Fig. 1. Schematic drawing illustrating functionally isolated nasal airway preparation and measurement of nasal airway resistance. As shown, an upper airway catheter was inserted just below the larynx with its tip sitting inside the nasopharynx. A lower airway cannula was inserted into the trachea via a tracheostomy. A differential pressure transducer measured the pressure difference (ΔP) across the nasal airway. A constant flow ($\dot{V}$; 1.4 ml s^{-1}) of air or wood smoke was delivered into the nasal airway by a syringe pump. Nasal airway resistance (RNA) was calculated by dividing ΔP by $\dot{V}$.

difference (ΔP) across the nasal passage was measured by a differential pressure transducer (Validyne MP45; Northridge, CA, USA). These physiological signals were recorded on a chart recorder (Gould TA11; Cleveland, OH, USA) and a tape recorder (Neurocorder DR-890; New York, NY, USA) for later computer analysis. Data of ΔP were sampled at 1-s intervals, were averaged over the delivery period, and were divided by 1.4 ml s^{-1} to give values of total resistance. The resistance of the upper airway catheter (0.03 cmH_2O ml^{-1} s^{-1}) was then deducted from the total resistance to yield RNA.

2.3. Generation of wood smoke

The electric furnace and the methods for generating wood smoke are described in detail in our previous study (Kou and Lai, 1994). Briefly, 100 g of dry wood dust (lauan wood) was thermally decomposed by the furnace at a core temperature maintained at 500 ± 8 °C for 5 min, and the effluent smoke was collected in a 25-l plastic balloon attached to the furnace outlet. Wood smoke generated from this method contained approximately 2% O_2, 15% CO_2, 24% CO, and 25 mg l^{-1} particulates (Kou and Lai, 1994; Kou et al., 1995).

2.4. Nasal exposure to smoke or air

Immediately after thermal decomposition, fresh wood smoke was withdrawn into a 20-ml syringe and diluted to 33% by air. The smoke, at a temperature of 25 °C, was continuously delivered at a constant flow rate of 1.4 ml s^{-1} by a syringe pump (Sage 367) into a 6-ml section of Teflon tubing (8 mm ID) connected to the proximal end of the upper airway catheter. Communication between the Teflon tubing and the upper airway catheter was quickly blocked by a three-way stopcock at the end of smoke delivery. The total amount of smoke delivered in each instance of nasal smoke exposure was 15 ml. The smoke passed through the isolated nasal cavity and flowed out to the environment via the nostrils. In each instance of nasal air exposure, the same amount of air was delivered to serve as the control. To avoid contamination, the smoke that flowed out through the nostrils was drawn into a fume hood via a suction line, and the syringe and its connecting Teflon tubing were replaced after each smoke delivery.

2.5. Pharmacological pretreatment and nasal provocation

For systemic pharmacological pretreatment, CP-96,345 [a tachykinin NK_1 receptor antagonist; 1 mg kg^{-1}; Pfizer, Groton, CT, USA; (2*S*,3*S*)-*cis*-2-(diphenylmethyl)-*N*-((2-methoxyphenyl)-methyl)-1-azabicyclo(2.2.2.)-octan-3-amine] and atropine (an acetylcholine receptor antagonist; 1 mg kg^{-1}; Sigma) were separately dissolved in isotonic saline to a final concentration of 1 mg ml^{-1}. Pretreatment was made by injecting CP-96,345 or atropine as boluses into the vein 10 min before the air or smoke challenge. The doses of these two drugs have been shown previously to block wood smoke-induced airway responses (Hsu et al., 1998b; Lin and Kou, 2000). For nasal provocations, capsaicin (Sigma) was dissolved in isotonic saline with 10% ethanol and 10% Tween 80 (Sigma) to a concentration of 10 μg ml^{-1}, whereas histamine (Sigma) was dissolved in isotonic saline to a concentration of 1 μg ml^{-1}. Aerosolized capsaicin or histamine was generated by an ultrasonic nebulizer (Devilbiss Ultr-Neb 99; Somerset, PA, USA). Nasal provocations were achieved by delivering capsaicin or histamine aerosol into the nasal cavity via the upper airway catheter at a constant air flow (250 ml min^{-1}) for 8 s.

2.6. Experimental procedures

In Study 1, 64 rats were evenly divided into four groups: the Vehicle + Air, Vehicle + Smoke, CP-96,345 + Smoke, and Atropine + Smoke groups. These animals were pretreated with either saline vehicle, CP-96,345, or atropine 10 min before nasal exposure to air or smoke. Values of RNA were measured 5 min before and during air or smoke exposure to study the effect of smoke on RNA. Eighty minutes later when RNA returned to their baseline values, animals in each group were then evenly divided into two subgroups which were subjected to nasal provocation with capsaicin or histamine. Values of RNA were measured 5 min before and 3, 20, 40, and 60 min after nasal provocation with capsaicin or histamine to investigate the effect of smoke on nasal airway reactivity. In Study 2, another 32 rats were evenly divided into two groups. These animals were pretreated with saline vehicle 10 min before nasal exposure to air or smoke. Eighty minutes later, animals in each group were evenly divided into two subgroups that were subjected to nasal provocation with capsaicin or histamine. In these animals, measurements of nasal secretion were made 5 min before, and 3, 20, 40, and 60 min after nasal provocation to investigate the effect of smoke on the secretory response to nasal provocations. For each measurement, two small pieces of fresh, dry, and pre-weighed filter paper were inserted into the nasal cavity via the nostrils. One minute later, the filter paper was removed to measure the amount of secretion collected during this 1-min period. According to our pilot study, these filters could maximally carry 24.81 ± 1.22 mg of saline (mean ± S.E. of 10 trails).

2.7. Statistical analysis

Data of the smoke effect on RNA or nasal secretion were analyzed by a two-factor mixed factorial analysis of variance (ANOVA) followed by Duncan's test when appropriate. In this experimental design, the smoke effect was the within-group factor, whereas drug effect was the between-group factor. Data of smoke effect on nasal airway reactivity to capsaicin or histamine provocation were analyzed by one-way ANOVA followed by the same post-hoc test when

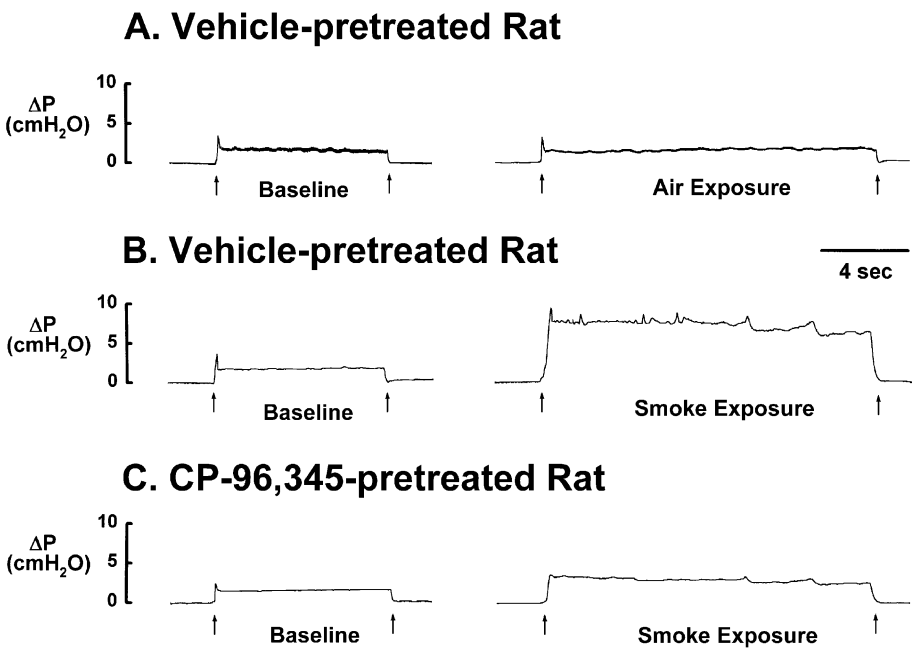

Fig. 2. Experimental tracings showing the pressure difference (ΔP) across functionally isolated nasal airway before and during nasal exposure to air or wood smoke in three anesthetized rats pretreated with saline vehicle (A and B) or CP-96,345 (C). In each panel, the period between the two arrows indicates the time of delivering air or smoke (33%) at a constant flow rate of 1.4 ml s^{-1} into the isolated nasal airway. Note that smoke exposure evoked a greater ΔP and thus a larger nasal airway resistance, which was attenuated by CP-96345.

appropriate. A P value of greater than 0.05 was considered significant. All data are presented as the mean ± S.E.

3. Results

3.1. Effects of wood smoke on RNA

In vehicle-treated rats, delivery of wood smoke into the nasal cavity at a constant flow rate instantly induced an increase in RNA, as evident by producing a ΔP across the nasal airway that was much greater than its baseline (Fig. 2A). In contrast, nasal exposure to air did not affect the baseline ΔP (Fig. 2B) or RNA (Fig 3). The mean baseline values of RNA measured in the Vehicle + Air, Vehicle + Smoke, CP-96,345 + Smoke, and Atropine + Smoke groups were 2.83 ± 0.44, 1.95 ± 0.37, 1.82 ± 0.21, and 1.62 ± 0.29 $cmH_2O\ ml^{-1}\ s^{-1}$ ($n = 16$ in each group), respectively, which did not vary significantly among the groups (Fig. 3). However, the mean value of RNA evoked during smoke exposure in the Vehicle + Smoke group was significantly greater than that during air exposure in the Vehicle + Air group (Fig. 3), and was also significantly greater than those during smoke exposure in the CP-96,345 + Smoke and Atropine + Smoke groups (Fig. 3). Additionally, the mean value of RNA evoked during smoke exposure in the Atropine + Smoke group was significantly smaller than that in the CP-96,345 + Smoke group (Fig. 3). These smoke-induced increases in RNA then gradually declined toward their baseline level. At 80 min post air or smoke exposure, the mean values of RNA in the Vehicle + Air, Vehicle + Smoke, CP-96,345 + Smoke, and Atropine + Smoke groups were 2.83 ± 0.79, 1.97 ± 0.42, 2.02 ± 0.31, and 1.90 ± 0.30 $cmH_2O\ ml^{-1}\ s^{-1}$ ($n = 16$ in each group), respectively, which did not significantly differ from their corresponding baseline values.

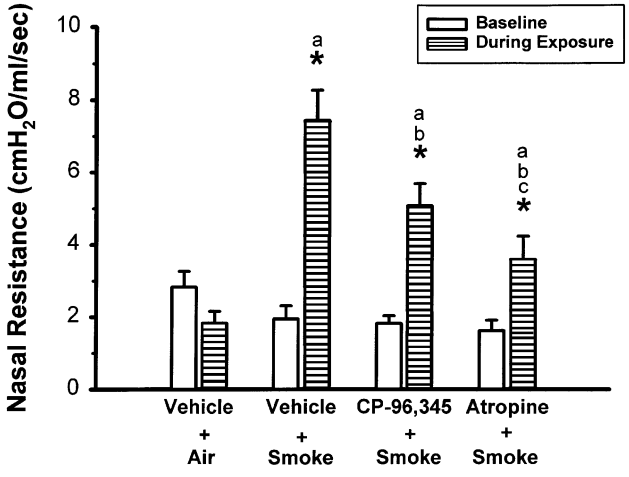

Fig. 3. Nasal airway resistance measured before and during nasal exposure to air or wood smoke in four groups of animals pretreated with either saline vehicle, CP-96,345, or atropine. * Significantly different from baseline data in the same group; [a]significantly different from data measured during exposure in the Vehicle + Air group; [b]significantly different from data measured during exposure in the Vehicle + Smoke group; [c]significantly different from data measured during exposure in the CP-96,345 + Smoke group. Data in each group are mean ± S.E. of eight animals.

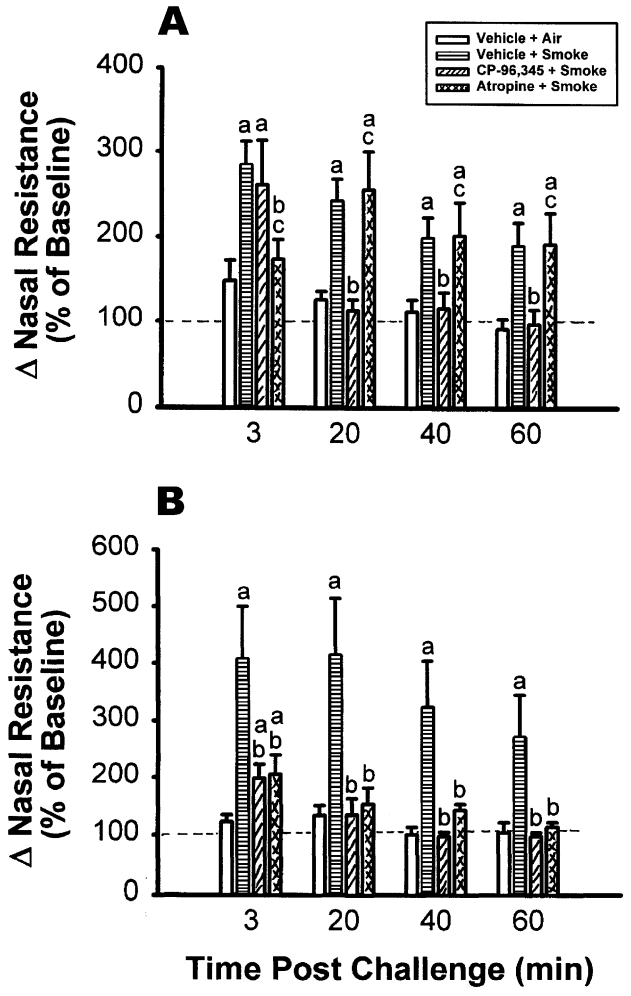

Fig. 4. Changes in nasal airway resistance measured at various time points post nasal provocation with capsaicin (A) or histamine (B) in animals pre-exposed to air or wood smoke. Animals were pretreated with either saline vehicle, CP-96,345, or atropine. [a]Significantly different from data in the Vehicle + Air group; [b]significantly different from data in the Vehicle + Smoke group; [c]significantly different from data measured during exposure in the CP-96,345 + Smoke group. Horizontal dashed lines indicate levels of 100% of baseline. Data in each group are mean ± S.E. of eight animals.

3.2. Effects of wood smoke on nasal airway reactivity to provocation

After their RNA values returned to baseline levels, these four groups of animals were divided into two subgroups which were subjected to two types of nasal provocations. In the Vehicle + Air group, nasal challenge with either capsaicin (Fig. 4A) or histamine aerosol (Fig. 4B) produced a slight increase in RNA measured at 3 and 20 min post provocation. The capsaicin- or histamine-induced increase in RNA declined to its baseline level within 40 min post provocation (Fig. 4). In the Vehicle + Smoke group, the nasal airway reactivity was enhanced by smoke exposure, and nasal challenge with either capsaicin (Fig. 4A) or histamine aerosol (Fig. 4B) at the same dose produced an exaggerated increase in RNA, which still persisted at 60 min post provocation. As a result, capsaicin- or histamine-induced increases in RNA measured at all time points in the Vehicle + Smoke group were significantly greater than those in the Vehicle + Air group (Fig. 4). This smoke-induced enhanced nasal airway reactivity was largely alleviated in the CP-96,345 + Smoke and Atropine + Smoke groups. However, the alleviative effects were quite dissimilar, depending on different provocations and pretreatments. In the CP-96,345 + Smoke group, nasal capsaicin induced a significantly greater increase in RNA only at 3 min, but not at 20, 40, or 60 min post provocation, when compared to the Vehicle + Air group (Fig. 4A). Conversely, in the Atropine + Smoke group, nasal capsaicin induced a significantly greater increase in RNA at 20, 40, and 60 min, but not at 3 min, post provocation, as compared to the Vehicle + Air group (Fig. 4A). When evoked, these exaggerated increases in RNA were similar to those in the Vehicle + Smoke group at the same time points post provocation (Fig. 4A). Addition-

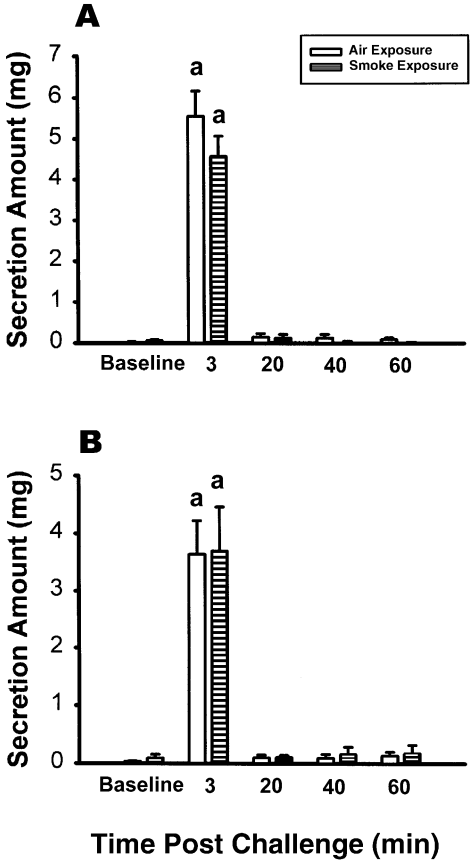

Fig. 5. Amount of nasal secretion measured during baseline conditions and at various time points post nasal provocation with capsaicin or histamine in animals pre-exposed to air or wood smoke. For each measurement, the amount of nasal secretion was collected for a period of 1 min. [a]Significantly different from corresponding baseline data. For each time point measured, no significant difference can be detected between the two animal groups. Data in each group are mean ± S.E. of eight animals.

ally, in the CP-96,345 + Smoke and Atropine + Smoke groups, nasal histamine induced a significantly greater increase in RNA only at 3 min, but not at 20, 40, or 60 min, post provocation, when compared to the Vehicle + Air group (Fig. 4B). Under this condition, these exaggerated increases in RNA were smaller than those in the Vehicle + Smoke group at 3 min post provocation (Fig. 4B).

3.3. Effects of wood smoke on nasal secretory responses to provocation

As compared to baseline levels, nasal challenge with either capsaicin (Fig. 5A) or histamine (Fig. 5B) produced a significant increase in nasal secretion measured at 3 min post provocation in animals pre-exposed to either air or wood smoke. The capsaicin- or histamine-induced increase in nasal secretion quickly vanished and was not seen at 20, 40, or 60 min post provocation in either animal group (Fig. 5). Statistical analysis revealed that the amounts of nasal secretion measured during baseline, and at 3, 20, 40, and 60 min post provocation by these two substances in animals pre-exposed to air did not significantly differ from those measured at corresponding time points in animals pre-exposed to wood smoke (Fig. 5).

4. Discussion

Results obtained in our first study series demonstrate that exposure to wood smoke in a functionally isolated nasal airway of rats immediately evokes an increase in RNA, which can be significantly reduced by pretreatment with either atropine or CP-96,345. These results suggest the important role of both cholinergic reflexes and endogenous tachykinins in producing this smoke-induced nasal response. Several clinical and animal studies have reported that increased RNA is one of the common airway responses to various types of inhaled irritants including cold air, acrolein, cigarette smoke and chlorine gas (Desrosiers et al., 1998; Jankowski et al., 1993; Morris et al., 1999; Schwartz et al., 1989; Shusterman et al., 1998; Willes et al., 1998), yet very few investigations have discussed the underlying mechanisms of this nasal response. In our previous studies, we have shown that nasal (Ho and Kou, 2000) or lower airway (Hsu et al., 1998a,b; Kou et al., 1995; Lin and Kou, 2000; Lin et al., 2001) exposure to wood smoke elicits various airway responses that are linked to stimulation of nasal and lower airway C-fiber afferents, and also to the resultant release of tachykinins. Furthermore, stimulation of nasal C-fiber afferents has been shown to produce dilation of vessels of the nasal mucosa, plasma exudation, an increase in nasal secretion, and a consequent increase in RNA through reflex control and local effects of endogenous tachykinins in several animal models (Asakura et al., 1994; Evangelista et al., 1997; Kubo and Kumazawa, 1993; Matran et al., 1990; Piedimonte et al., 1993; Stjärne, 1991). Additionally, nasal application of exogenous substance P has been demonstrated to increase nasal mucosal blood flow, nasal secretion, and RNA in humans (Chatelain et al., 1995; Konno et al., 1996). Collectively, these observations suggest that reflex cholinergic and tachykininergic mechanisms involving the smoke-induced RNA response observed in this study might originate from activation of nasal C-fiber afferents by wood smoke.

Results obtained in our second study series demonstrate that, as compared to air pre-exposure animals, animals pre-exposed to wood smoke display a greater amplitude and a much longer duration of RNA responses to nasal challenge with the same dose of either capsaicin or histamine aerosols. These results clearly illustrate the deleterious ability of wood smoke to enhance nasal airway reactivity to nasal provocation. The exact mechanisms by which capsaicin and histamine evoke an exaggerated RNA response after wood smoke exposure are still unclear. Conceptually, the exaggerated RNA responses observed in animals pre-exposed to wood smoke may be due to an augmentation of nasal responses such as dilation of vessels, increased glandular output, plasma exudation, and tissue edema. In this study, we measured the amount of fluid secreted into the nasal cavity following capsaicin or histamine provocation, which may arise from glandular output and/or from exudative fluid. Whatever the sources, the secretory responses are short-lived and totally vanished within 20 min, yet the exaggerated RNA lasted for >60 min. Additionally, the secretory responses to these provocations in animals pre-exposed to wood smoke did not significantly differ from those in animals pre-exposed to air. The dissociation of secretory and exaggerated RNA responses suggests that the former response might not contribute to the development of the latter response following wood smoke exposure. Thus, it would be assumed that amplification of the vasodilatory and/or edematous responses to nasal provocations is responsible for the exaggerated RNA observed in animals pre-exposed to wood smoke.

Since both capsaicin and histamine are stimulants of C-fiber afferents (Saria et al., 1988; Sekizawa and Tsubone, 1994) and because they have been shown to increase RNA through mechanisms associated with these afferents (Asakura et al., 1993, 1994), it is possible that the observed nasal airway hyperreactivity may result from an augmentation of both reflex cholinergic and tachykininergic mechanisms involving RNA responses to capsaicin or histamine. Indeed, as demonstrated in the present study, smoke-induced enhanced nasal airway reactivity was largely alleviated by pretreatment with either atropine or CP-96,345. How cholinergic and tachykininergic mechanisms are augmented by inhaled wood smoke remains largely unclear. Several hypotheses have been advanced with respect to the mechanisms underlying nasal airway hyperreactivity (Bernstein, 1991; Van Gerth, 1991; Stjärne, 1991), and some of them may be adopted to explain the present observations. For example, it has been shown that wood smoke exposure produces damage to the airway epithelial barrier (Barrow et

al., 1992), which would ease the accessibility of capsaicin or histamine to C-fiber sensory nerve endings. Additionally, wood smoke exposure may possibly cause hypersensitivity of C-fiber sensory nerve endings, which would result in a greater release of tachykinins and more powerful cholinergic reflexes. Furthermore, it has been demonstrated that wood smoke exposure inhibits airway neutral endopeptidase, the major enzyme for tachykinin degradation (Hsu et al., 1998b; Lin et al., 2001). Thus, reduced neutral endopeptidase activity after smoke exposure would lead to excess tachykinins, and thus exaggerated effects via tachykinin NK_1 receptors on the vessels and the parasympathetic ganglia (Evangelista et al., 1997; Piedimonte et al., 1993; Watson et al., 1993).

Our results also reveal that the capsaicin- or histamine-evoked exaggerated RNA responses observed in animals pre-exposed to wood smoke may consist of two phases whose time courses and underlying mechanisms differ. These two phases became apparent only when different mechanisms responsible for exaggerated RNA responses were blocked by atropine and CP-96,345. In response to capsaicin provocation, the early phase (within 3 min post provocation) of the exaggerated RNA response was completely abolished by atropine, but was unaffected by CP-96,345, whereas the late phase (20–60 min post provocation) was totally prevented by CP-96,345, yet was unaltered by atropine. These findings suggest that reflex cholinergic and tachykininergic mechanisms are separately and respectively responsible for evoking the early and late phases of the exaggerated RNA response to capsaicin in these animals. On the other hand, in response to histamine provocation, the early phase of the exaggerated RNA response was equally and partially reduced by either atropine or CP-96,345, whereas the late phase was totally eliminated by either atropine or CP-96,345. These observations indicate that both reflex cholinergic and tachykininergic mechanisms synergistically contribute to part of the early phase response, but participate in the full expression of the late phase response. It appears that there is an overlap of contributions by reflex cholinergic and tachykininergic mechanisms to the exaggerated RNA response to histamine occurring at both phases. One possibility to explain this overlap of contributions is that tachykinins may facilitate cholinergic ganglionic neurotransmission in airway tissues (Watson et al., 1993). The other possibility is that tachykinins may induce chemical mediators such as prostaglandins that can sensitize airway C-fiber sensory nerve endings (Ho et al., 2000). It is not known why this synergistic effect does not exist in the exaggerated RNA response to capsaicin. However, it is clear that different provocation tests may evoke exaggerated RNA responses with dissimilar mechanisms even in the same form of nasal airway hyperreactivity.

In summary, nasal exposure to wood smoke may increase RNA and nasal airway reactivity to capsaicin or histamine provocation in rats. Both reflex cholinergic and tachykininergic mechanisms play important roles in producing these two nasal responses. Smoke-induced nasal airway hyperreactivity is not due to augmentation of secretory responses to these provocations, but presumably results from exaggeration of nasal swelling involving vasodilation and/or tissue edema.

Acknowledgements

We thank Mr. D.P. Chamberlin for editorial assistance and Miss. Hui-Chen Lee (Veterans General Hospital-Taipei, Taiwan) for statistical consultation. We are grateful to Dr. J.A. Lowe, III (Pfizer) for providing CP-96,435. This study was supported by grants NSC-89-2314-B010-115 from the National Science Council, Taiwan and VGH341 from Veterans General Hospital-Taipei, Taiwan.

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