Strain dependence of the airway response to dry-gas hyperpnea challenge in the rat

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Yang, X. X., W. S. Powell, L. J. Xu, and J. G. Martin. Strain dependence of the airway response to dry-gas hyperpnea challenge in the rat. J. Appl. Physiol. 86(1): 152–158, 1999.—The aim of the study was to investigate strain dependence and mechanisms of airway responses to dry-gas hyperpnea challenge in the rat. We studied responses in a strain that is hyperresponsive to methacholine, Fischer 344 (F-344); in two normoresponsive strains, Lewis and ACI; and in an atopic but normoresponsive strain, Brown Norway (BN). We examined the effects of a neurokinin (NK) 1-receptor (CP-99994), an NK2-receptor antagonist (SR-48968), and a leukotriene D4 (LTD4) antagonist (pranlukast) on responses to hyperpnea challenge in BN rats. The animals were ventilated with a tidal volume of 8 ml/kg and a frequency of 150 breaths/min with either a dry or humidified mixture of 5% CO2–95% O2 for 5 min for hyperpnea challenge, whereas responses to challenge were measured during spontaneous breathing. Pulmonary resistance increased after dry-gas challenge in BN and ACI but not in F-344 and Lewis rats. CP-99994, SR-48968, and pranlukast significantly attenuated the increase in pulmonary resistance after dry-gas challenge. There were no significant differences in responsiveness to airway challenge with LTD4 among the BN, F-344 and ACI rats. We conclude that responses to dry-gas hyperpnea challenge are strain dependent in rats and are mediated by NKs and LTD4.

Exercise-induced asthma has been modeled in animals by using responses to dry-gas isocapnic hyperventilation as a surrogate for exercise challenge. Hyperventilation with dry air evokes a complex airway response associated with microvascular leak and bronchoconstriction in several mammalian species, including guinea pigs, dogs, rabbits, and monkeys (1, 4, 9, 11, 23, 24). The mechanisms responsible for the airway response have been extensively investigated in the guinea pig. In this animal, tachykinin release from C-fiber afferents has been demonstrated to play a crucial role in the development of hyperpnea-induced bronchoconstriction (11, 28). However, the mechanism of airway narrowing caused by the tachykinitins is not clear because cysteinyl leukotriene (LT) synthesis is also stimulated by dry-gas hyperpnea challenge, and a selective LTD4 antagonist abolishes hyperpnea-induced bronchoconstriction (34). These findings indicate a significant interaction between tachykinitins and LTD4 in the induction of hyperpnea-induced airway changes. The increase in LT synthesis after isocapnic hyperpnea challenge can be prevented by prior administration of specific neurokinin (NK) 1- and NK2-receptor antagonists, suggesting that tachykinitins act on LT-synthesizing cells in the airway wall (34). Other eicosanoids are also involved, as indicated by the fact that a cyclooxygenase inhibitor and a combined cyclooxygenase-lipoxygenase inhibitor also attenuate the airway response to challenge (10).

Human asthmatic subjects have variable responses to exercise challenge. The host factors accounting for this variability do not appear to have been elucidated. We wished to establish an animal model that would provide an opportunity to shed light on the characteristics that might modify responsiveness to dry-gas hyperpnea challenge. We selected the rat as a model for such studies because of the availability of highly inbred strains differing in certain potentially relevant characteristics. We chose to evaluate the importance of airway hyperresponsiveness to contractile agonists and the atopic predisposition of the animals as determinants of responsiveness to hyperpnea challenge. To do this, we examined the responses of a strain hyperresponsive to inhaled methacholine, Fischer 344 (29); two control normoresponsive strains, Lewis and ACI (15); and an atopic but normoresponsive rat, Brown Norway (BN) (26). We tested the four strains for airway responses to dry-gas hyperpnea challenge, whereas we examined the efficacy of NK- and LTD4-receptor antagonists on responses to challenge in the BN rat only. To test the hypothesis that interstrain differences in responsiveness to dry-gas hyperpnea challenge may relate to airway responsiveness to the specific mediators released by this form of challenge, we examined the responsiveness of three of the rat strains to LTD4. Although the interstrain differences in responsiveness to methacholine have been described (5, 6, 21), it is possible that differences in responsiveness to methacholine might not reflect similar differences in responsiveness to LTD4, a mediator that is potentially more relevant to responses to dry-gas-induced hyperpnea challenge (34).

Materials and Methods

Animal Preparation

We studied BN (n = 41), Fischer 344 (n = 18), Lewis (n = 18), and ACI (n = 18) rats, ranging in weight from 190 to 220 g, that were purchased from Harlan Sprague-Dawley (Walkerville, MD). All animals were anesthetized with xylazine (7 mg/kg) and pentobarbital sodium (30 mg/kg) intraperitoneally and placed on a heating pad (37°C). The animals were intubated with polyethylene tubing (PE-240; 0.165 cm ID, 6 cm long) and connected to a small-animal respirator (Harvard rodent ventilator model 360, South Natick, MA). The external jugular vein was cannulated with Silastic medical-grade tubing (Dow Corning Medical Products, Midland, MI) for fluid and drug administration. The inspiratory and expiratory tubes of the ventilator were attached to the tracheal cannula.
through a Y connector with a 3-cm common segment (total dead space 0.30 ml) to minimize conditioning of the inspired gas. The inspiratory port of the ventilator was connected to a warmed (35–37°C) humidifier through which room air was passed. All animals were mechanically ventilated for the purposes of hyperpnea challenge but breathed spontaneously for measurements of pulmonary responses to challenge. Supplemental amounts of pentobarbital sodium (30% of initial dose in 0.3 ml saline) were injected as required during the course of the experiments.

The bile duct was cannulated with polyethylene tubing (PE-20) through a small incision in the abdominal wall. After surgery the animals were allowed to stabilize for a period of 120 min before hyperpnea challenge.

Experimental Protocol

Dry-gas hyperpnea challenge (BN, n = 9; Fischer 344, n = 7; Lewis, n = 6; ACI, n = 7) was performed by introducing a dry mixture of 5% CO2-95% O2 from a balloon into the ton, CA) by using a wavelength of 620 nm.

The NK1 antagonist CP-99994 (1 mg/kg; n = 5) was administered similarly. Only BN rats were used for studies of receptor antagonists.

Outcome Measurements

RL. The transpulmonary pressure was measured as the difference between airway opening and distal esophageal pressures by using a water-filled polyethylene tube in the lower esophagus attached to a piezoresistive differential pressure transducer (model SCX01DN, SenSym, Sunnyvale, CA). Airflow was measured by placing the tip of the endotracheal tube of the spontaneously breathing rat into a small Plexiglas chamber that was connected to a Fleisch-type pneumotachograph (model no. 0). A commercial software package (RHT Infodat, Montreal, PQ, Canada) was used to fit the equation of motion of the lung by using multiple linear regression analysis as so to obtain RL.

Microvascular leak. All rats, comprising the 74 that underwent hyperpnea challenge and an additional 18 normal rats (BN, n = 4; Fischer 344, n = 4; Lewis, n = 6; ACI, n = 4) as negative control groups, were injected with 30 mg/kg of Evans blue dye in saline. Those rats undergoing hyperpnea challenge were injected 5 min before the challenge. Bronchoalveolar lavage (BAL) was performed 2 h after challenge. The concentration of Evans blue dye in BAL fluid was determined by spectrophotometry (DU-64, Beckman Instruments, Fullerton, CA) by using a wavelength of 620 nm.

Measurement of biliary N-acetyl LTE4. To determine the extent of pulmonary cysteinyl LT synthesis, we collected and analyzed the bile of BN rats undergoing both dry-gas and wet-gas challenge; bile is the principal route of excretion of cysteinyl LTs in the rat. For 1 h before and for 2 h after hyperpnea challenge, bile was collected under a stream of argon into Eppendorf tubes that were kept on ice and stored at −80°C before analysis by reverse-phase HPLC and radioimmunoassay. After precipitation of protein with methanol, the bile samples were subjected to pre-column extraction and reverse-phase HPLC. N-acetyl LTE4 (the major cysteinyl LT species in rat bile) was quantitated in the column fractions by radioimmunoassay as described previously (22).

Measurement of airway responsiveness to instilled LTD4 in ACI, BN, and Fischer 344 rats. To determine responsiveness to LTD4, animals underwent inhalational challenge with progressively increasing doses of LTD4 from 1 to 100 ng in 100 µl of saline in ACI (n = 7) and Fischer 344 rats (n = 9). In BN rats (n = 6), the starting dose was 0.5 ng. Challenge was performed by insufflation to avoid unnecessary losses of LTD4 associated with aerosolization and was performed through a small catheter placed inside the endotracheal tube. Measurements of RL were performed 30 s after insufflation. Measurements were repeated at intervals until a stable value was achieved before proceeding to the next dose of LTD4. Responsiveness to LTD4 was calculated as the dose required to increase the RL to 50% of the difference between the baseline and the maximal values (ED50) by using a commercial software package (GraphPad Software, San Diego, CA).

Statistical Analysis

All results are expressed as means ± SE. Comparison of two means was performed by using paired or unpaired t-tests as appropriate. For comparison of several means, an ANOVA followed by Fisher’s least significant difference test was used. Differences were considered to be statistically significant when P values were <0.05.

Chemicals and Drugs

N-acetyl LTE4, the monoclonal antibody to LTC4, the NK1 antagonist CP-99994, and the NK2-receptor antagonist SR-48968 were kindly provided by Dr. Ian Rodger (Merck-Frosst, Pointe Claire, PQ, Canada). The LTD2 antagonist pranlukast was provided by Dr. T. Leonard (SmithKline Beecham Pharmaceuticals, Collegeville, PA). Pentobarbital sodium was supplied by MTC Pharmaceuticals (Cambridge, ON). Evans blue dye was purchased from A&C American Chemicals (Montreal, PQ, Canada).

RESULTS

Airway Response to Hyperpnea Challenge in Various Rat Strains

There were no differences in baseline values of RL between dry-gas and wet-gas hyperpnea-challenged BN rats. After hyperpnea challenge, RL gradually increased from a baseline of 0.22 ± 0.007 cmH2O·ml−1·s−1 and reached significantly higher values at 60 min (0.33 ± 0.03 cmH2O·ml−1·s−1) and at 120 min (0.41 ± 0.08 cmH2O·ml−1·s−1) in the dry-gas group of BN rats [P < 0.01; ANOVA and Fisher’s least significant difference (LSD) test; Fig. 1]. The value of RL at these time points was also significantly higher than the corresponding values in animals exposed to wet gas (60 min, 0.22 ± 0.01 and 120 min, 0.19 ± 0.02 cmH2O·ml−1·s−1;
Dry-gas hyperpnea challenge (dry gas vs. wet gas, dye test) and 10 min (wet gas 0.21 vs. dry gas 0.29 \( P < 0.01 \)). There were no significant differences in RL between the wet-gas- and dry-gas-challenged groups at 3 min (dry gas 0.21 ± 0.01 vs. wet gas 0.29 ± 0.03 cmH_2O\cdot m^{-1}\cdot s^{-1}; P = 0.05; t-test) and 10 min (wet gas 0.21 ± 0.01 vs. dry gas 0.29 ± 0.02 cmH_2O\cdot m^{-1}\cdot s^{-1}; P < 0.05; t-test) after challenge.

Airway Microvascular Leak Caused by Hyperpnea Challenge in Various Rat Strains

The effects of dry-gas and wet-gas hyperpnea challenge on Evans blue dye extravasation in the airways of various rat strains are illustrated in Fig. 2. For all strains the concentration of Evans blue dye in BAL fluid after hyperpnea challenge with dry gas was significantly higher than that in unchallenged animals (\( P < 0.05 \); unweighted-means ANOVA, Fisher’s least significant difference test). ACI showed the greatest increase in Evans blue dye, whereas the BN showed the smallest change. The amount of Evans blue dye in BAL fluid after dry-gas challenge was significantly higher than that in the wet-gas-challenged controls for BN (17.5 ± 2.82 vs. 9.4 ± 2.1 \( \mu \)g/ml; \( P < 0.05 \)) and Lewis (27.61 ± 6.16 vs. 12.92 ± 3.88 \( \mu \)g/ml; \( P < 0.05 \)) animals. Dry-gas challenge also evoked an increase in Evans blue dye extravasation in Fischer 344 (28.55 ± 4.55 \( \mu \)g/ml) and ACI rats (34.63 ± 5.27 \( \mu \)g/ml), but these response were not significantly different from those observed with wet-gas challenge (Fischer 344, 16.92 ± 6.42 \( \mu \)g/ml; ACI, 33.35 ± 7.28 \( \mu \)g/ml).

Effects of Receptor Antagonists on the Airway Responses to Hyperpnea Challenge

The specific NK1 antagonist CP-99994, the NK2 antagonist SR-48968, and the LTD4 antagonist pranlukast effectively prevented the increase in RL in BN rats in response to dry-gas hyperpnea challenge; RL at the 60- and 120-min time points was higher for the dry-gas-challenged animals compared with pranlukast, CP-99994, and SR-48968 (\( P < 0.05 \); ANOVA and Fisher’s LSD test; Fig. 3). Evans blue dye extravasation was significantly decreased in BN rats treated with pranlukast (9.08 ± 1.7 \( \mu \)g/ml; \( P < 0.05 \)) and SR-48968 (9.7 ± 1.2 \( \mu \)g/ml; \( P < 0.05 \)) compared with controls (17.5 ± 2.8 \( \mu \)g/ml) but not in rats pretreated with CP-99994 (13.95 ± 1.4 \( \mu \)g/ml; Fig. 4).

Fig. 1. Time course of pulmonary resistance (RL) in response to hyperpnea challenge. Values are means ± SE. A: Brown Norway (BN) rats. B: Lewis rats. C: Fischer 344 rats. D: ACI rats. RL was significantly increased from baseline at 60 and 120 min in BN rats after dry-gas challenge (\( n = 9 \); arrow indicates start of hyperpnea challenge; *\( P < 0.01 \); unweighted-means ANOVA, Fisher’s least significant difference test). RL in animals challenged with dry gas was also significantly higher than values at the same time point in animals exposed to wet-gas hyperpnea challenge (\( n = 8 \); **\( P < 0.05 \); t-test). There were no significant differences in peak values of RL either in dry-gas hyperpnea-challenged (\( n = 6 \)) compared with wet-gas hyperpnea-challenged (\( n = 6 \)) Lewis rats or in dry-gas (\( n = 7 \)) compared with wet-gas hyperpnea-challenged (\( n = 7 \)) Fischer 344 rats. There were significant increases in RL in ACI rats at 3 min (dry gas (\( n = 7 \)) vs. wet gas (\( n = 7 \); \( P = 0.05 \); t-test) and 10 min after dry-gas hyperpnea challenge (dry gas vs. wet gas, \( P = 0.03 \); t-test).

Fig. 2. Concentration of Evans blue dye in bronchoalveolar lavage (BAL) fluid. Concentrations of Evans blue dye in BAL fluid in all 4 rat strains with dry-gas hyperpnea challenge (*\( P < 0.05 \); unweighted-means ANOVA, Fisher’s least significant difference test) were significantly higher than those without any challenge. Concentrations of Evans blue dye in BAL fluid in the dry-gas-challenged animals was significantly higher than that in wet-gas-challenged BN and Lewis rats (\( P < 0.05 \)). Although there appears to be an increase in Evans blue dye extravasation in Fischer 344 rats of the dry-gas group above the wet-gas group, it did not reach statistical significance (\( P > 0.05 \)). Evans blue dye concentrations in BAL fluid in both dry- and wet-gas (34.64 ± 5.27 and 33.35 ± 7.28 \( \mu \)g/ml, respectively) hyperpnea-challenged ACI rats were not significantly different.
Biliary N-Acetyl LTE4 and Hyperpnea Challenge

The baseline concentration of biliary N-acetyl LTE4 in the group of BN rats challenged with wet-gas hyperpnea was somewhat higher than in the group challenged with dry gas and fell after challenge (Fig. 5). The N-acetyl LTE4 level fell in six and rose in two of the control rats subjected to challenge with wet gas. In contrast, N-acetyl LTE4 rose in five of the rats challenged with dry gas and fell in only three of these rats. However, these differences were not statistically significant.

Airway Responsiveness of BN, ACI, and Fischer 344 Rats to Inhaled Exogenous LTD4

To compare the responses to LTD4, rats were challenged with increasing doses of this substance by intratracheal insufflation. The Fischer 344 and ACI rats had comparable percent increases in RL, which reached a plateau at ~50% above the baseline (Fig. 6), whereas the BN rats responded to LTD4 with a maximal response of ~250% above baseline observed at the highest doses of LTD4 tested. However, neither the response at the maximal dose of LTD4 nor the dose of LTD4 required to increase RL by 50% of the change from baseline to the maximal response achieved (ED50) were significantly different among strains (geometric mean ED50: F-344, 1.34; ACI, 1.26; and BN, 1.15 ng; P = not significant).

DISCUSSION

The results of the present study demonstrate that isocapnic hyperpnea challenge with dry gas evokes an airway response in the rat. However, there are significant strain-related differences in the patterns of response. All four of the rat strains studied demonstrated airway microvascular leak, but only two of them showed evidence of airway narrowing as determined by RL. The rank order of change in microvascular permeability and airway narrowing was not the same. BN rats showed the largest increases in RL after challenge but had the lowest values of Evans blue dye in the BAL fluid after challenge, whereas the ACI strain showed the greatest changes in microvascular leak in response...
to either wet- or dry-gas challenge and had only modest changes in $R_l$. Differences in airway responsiveness to LTD$_4$ do not appear likely to account for the strain-related differences in response to dry-gas challenge.

The water content of inspired gas has been shown to be an important determinant of airway responses to dry-gas isocapnic hyperpnea in both human subjects and other animals (9, 14, 31). Consistent with these results, dry-gas hyperpnea challenge evoked airway narrowing in two of the rat strains studied. In contrast, humidified-gas hyperpnea challenge had no effect on pulmonary resistance after dry-gas hyperpnea challenge in any of the strains investigated. Dry-gas hyperpnea challenge significantly increased microvascular leak in all four strains of rat. However, hyperpnea with humidified inspired gas also had this effect in Lewis and ACI rats. Only the BN and Lewis strains exhibited greater microvascular leak in response to dry gas compared with humidified gas. Presumably, the failure of wet gas to prevent the airway responses in Fischer 344 and ACI rats resulted from an incomplete conditioning of the inspired air. The design of the experimental apparatus was not such as to ensure that inspired gas was at $37^\circ$C when it reached the airway opening. An alternative possibility is that hyperventilation per se may have caused microvascular leak through mechanical stress. However, the increase in tidal volume during hyperpnea challenge was modest, and, presumably, end inspiration was at a volume well below the total lung capacity.

Tachykinins, which include NKA and substance P (SP), are located in the airway afferent C-fiber endings and have been demonstrated to play a very important role in the development of hyperpnea-induced bronchoconstriction in guinea pigs (28). Both capsaicin pretreatment to deplete tachykinins and the NK$_1$ (CP-99994) and NK$_2$ (SR-48968) antagonists blunt hyperpnea-induced bronchoconstriction in the guinea pig (28, 30, 34). An important difference between the guinea pig and the rat is that NK receptors are expressed on airway smooth muscle in the guinea pig but not in the rat (7, 13). Despite the lack of NK receptors on rat airway smooth muscle, exogenous tachykinin does cause bronchoconstriction in some rat strains, but the effect is mediated indirectly through effects on the mast cell (17). In the present study there is also clear evidence of tachykinin involvement in the hyperpnea-induced airway response; both NK$_1$ and NK$_2$ antagonists prevented the increase in $R_l$ after dry-gas challenge in the BN rats. An indirect effect of exogenous SP and NKA has been shown in the rat as an increase in $R_l$ that is abolished by the serotonin (5-HT) antagonist methysergide and is therefore mediated by airway mast cells (16, 17). We did not test the effect of 5-HT antagonists such as ketanserin or methysergide on the response to hyperpnea challenge in the rat. However, we think that it is unlikely that 5-HT from mast cells is contributing significantly to the airway responses because of the completeness of the blockade by NK and LTD$_4$ antagonists. Interestingly, an antihistamine does not alter the response to hyperpnea challenge in the guinea pig, nor does the concentration of histamine increase in the BAL fluid after challenge (33), arguing that the mast cell is not triggered. Perhaps the sites of action of endogenously released tachykinins are more limited than those of exogenously administered tachykinins.

Eicosanoids are important contributors to dry-gas hyperpnea-induced bronchoconstriction in guinea pigs (10), dogs (8, 25), and humans (20, 27). Dry-gas-induced bronchoconstriction is inhibited by pretreatment of the guinea pig with the cyclooxygenase inhibitor piroxicam, the 5-lipoxygenase inhibitor A-63162, the LTD$_4$ antagonist ICI-198615 (10), or the 5-lipoxygenase inhibitor MK-0591 in dogs (25). The mechanism of release of eicosanoids has not been established. However, a direct link between tachykinins and LTD$_4$ in hyperpnea-induced airway responses in guinea pigs has been established by the demonstration that NK antagonists inhibited the synthesis of cysteinyl LTs, which are evoked by dry-gas challenge. A similar relationship seems likely in the rat given the efficacy of the selective LTD$_4$ antagonist pranlukast in attenuating the effects of dry-gas challenge. However, we were unable to evaluate a possible effect of NK antagonists on LT synthesis in the present experiments because the changes in biliary N-acetyl LTE$_2$ after dry-gas challenge were not significantly different from those observed in the wet-gas control animals. The cells of origin of the LTD$_4$ responsible for the airway response require elucidation, but macrophages are a possible source (3). Interestingly, the NK$_1$ receptor has been reported to be expressed by rat macrophages (2).

We anticipated that there might be a relationship between the magnitude of airway responses to hyperpnea challenge and the responsiveness to methacholine, a measure of so-called nonspecific airway respon-
siveness. However, there was no correlation between the magnitude of the airway response to hyperpnea challenge and the reported airway responsiveness to inhaled methacholine in the four rat strains studied. Fischer 344 rats are much more responsive to methacholine than are the other three strains (6, 21), but they did not show significant bronchoconstriction after dry-gas challenge. However, the relative airway responses of three strains to LTD₄ administered by insufflation differed from those results reported for methacholine provocation testing. The BN rats were slightly more responsive to LTD₄ than were either ACI or Fischer 344 rats. However, these differences did not reach statistical significance and are therefore unlikely to account for the greater responses of this strain to hyperpnea challenge. Whether the atopic character of the BN rat has any relationship to its responsiveness to hyperpnea challenge remains uncertain, but it is not implausible that the dependence on cysteinyl LTs of both responses may be the link between the high prevalence of hyperpnea- and allergen-induced airway responses in this strain.

In contrast to the lack of change in RL in two of the four strains after hyperpnea challenge, there was significant microvascular leak in all four rat strains. This indicates that the development of airway edema is not sufficient to cause detectable changes in lung mechanical properties. A further difference between changes in RL and microvascular leak is the finding that both NK₁ and NK₂ antagonists inhibited the former, whereas only the NK₂ antagonist inhibited the latter. Hyperpnea with dry gas has also been reported to cause bronchovascular leakage in other animals (11, 18, 19). In dogs, leakage occurs immediately after the cessation of hyperpnea and continues for at least 24 h after the challenge (24). Microvascular leakage also has been demonstrated to occur in guinea pigs after dry-gas hyperpnea challenge (10), but, in contrast to our results, the inhibition of the phenomenon is only partially prevented by LTD₄ and tachykinin-receptor antagonists. Joo and Pauwels (17) have demonstrated that capsaicin causes plasma extravasation in airways of Fischer 344 rats, which was effectively inhibited by a specific NK₁ antagonist RP-67580. The difference in findings may reflect the choice of rat strain studied or the fact that capsaicin challenge may not be equivalent to hyperpnea challenge with dry gas. The mechanism of protection of NK antagonists against microvascular leak is also somewhat uncertain. Although NK₁ and NK₂ receptors have been shown to be present on the microvascular endothelium of both human and guinea pig lungs as well the bronchial smooth muscle and artery media in guinea pigs (32), NK₁ and NK₂ receptors have been reported to be absent in homogenates of rat lung and bronchi (7). This suggests that tachykinins released by hyperpnea challenge may cause microvascular leak by indirect mechanisms. We postulate that the action of the NK₂ antagonist may not be on vascular cells but rather on cells synthesizing LTD₄ in BN rats.

In conclusion, dry-gas hyperpnea challenge causes a complex airway reaction involving bronchoconstriction and airway microvascular leak in rats. The increase in RL in response to dry-gas hyperpnea challenge is strain related and is greatest in the atopic strain, the BN. Tachykinins and cysteinyl LTs released after dry-gas hyperpnea challenge cause an increase in RL in BN rats. The effect of the tachykinins is presumably mediated by an indirect mechanism. Airway microvascular leak occurred in response to dry-gas hyperpnea challenge in all four rat strains, suggesting that bronchoconstriction, but not the increase in airway microvascular permeability, plays a crucial role in elevation of pulmonary resistance in BN rats. This is also suggested by the fact that NK₂, but not NK₁, receptors are responsible for the dry-gas-induced airway microvascular leakage, whereas both receptor subtypes participate in the increase in RL that is observed.

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