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Animal models of asthma and chronic bronchitis

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Human asthma is characterized by three critical phenotypic traits: intermittent reversible airway obstruction, airway hyperresponsiveness and airway inflammation. In animal models of asthma, airway hyperresponsiveness is an important feature. This trait is characterized by an exaggerated bronchoconstrictor response that would have little physiological consequence in an otherwise unaffected or normal individual. In this article we explore two distinct facets of airway responsiveness. The first is the genetic basis for variations in airway responsiveness that occur in mice in the absence of any specific environmental manipulation. We demonstrate that standard genetic approaches can be successfully applied to the identification of regions of the mouse genome linked to the expression of airway hyperresponsiveness. The second topic addressed in this review is the change in airway responsiveness induced in rats by repeated exposure to sulphur dioxide gas. With daily exposure to high concentrations of sulphur dioxide gas, there is chronic injury and repair of epithelial cells. Over time, rats develop mucous hypersecretion, airway inflammation, increased airway resistance and airway hyperresponsiveness. This model has provided useful information on the mechanisms underlying the pathophysiological events that typify the chronic bronchitis in humans.

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Animal models of asthma and bronchitis have been used in the process of discovery of the primary events that underlie these human diseases; because of the extensive nature of this topic, we have elected to focus on two aspects of these models, namely (i) genetic variation of airway responsiveness in mice, as a model of certain aspects of human asthma, and (ii) the induction of a pathological and physiological picture reminiscent of human chronic bronchitis as created in rats. Each of these areas will be reviewed separately.

Mouse models of inherited variance in airway responsiveness

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Human asthma is characterized by three critical phenotypic traits: intermittent reversible airway obstruction, airway hyperresponsiveness, and airway inflammation. In animal models of asthma, airway hyperresponsiveness [1–4] is an important feature. This trait is characterized by an exaggerated bronchoconstrictor response that would have little physiological consequence in an otherwise unaffected or normal individual [5]. Although environmental factors, such as allergen sensitization and challenge or ozone exposure, can influence airway responsiveness, there is significant variability of airway responsiveness that occurs in the absence of any specific antigenic or known environmental exposure and that is thought to be under genetic control [6–14].

Airway responsiveness linkage studies in inbred mice*Categories of airway responsiveness phenotypes*

There are two categories of airway responsiveness phenotypes in mice. The first, airway responsiveness in the absence of any specific experimental manipulation, is what we have termed 'genetic variation in airway responsiveness'. This variation in airway responsiveness, which is known to be heritable (see below), is similar to the variation in airway responsiveness noted in human populations (as outlined above) in the absence of specific exposure to allergens or air pollutants. It is this variation in airway responsiveness that is the subject of this paper.

The second airway responsiveness phenotype, present in both mice and humans, is the change in airway responsiveness that is induced by stimuli, such as recurrent pulmonary antigen or ozone exposure. In particular, in the mouse, antigen sensitization followed by aerosol antigen exposure is associated with an increase in airway responsiveness [15–26]. Although there is reason to believe that the magnitude of the change in airway responsiveness may be a heritable trait, this has not yet been clearly established.

Strain variations in airway responsiveness in inbred mice.

It is well established that airway responsiveness, in the absence of any environmental or antigenic manipulation, is a heritable trait. A decade ago, Levitt and Mitzner first demonstrated that there were substantial differences in airway responsiveness among strains of inbred mice [3, 4], but at that time no genetic loci linked to this trait had been identified. In their studies, the peak inflation pressure during each ventilation cycle before and after infusion of a single dose of acetylcholine was recorded, and the area under the peak pressure–time curve, termed the airway pressure–time index (APTI), was used as an indicator of airway responsiveness. The C57BL/6 J and the C3H/HeJ strains exhibited a low APTI response to acetylcholine infusion, whereas A/J or DBA/2 J mice exhibited a significantly greater APTI response [3]. There was a greater variation in the APTI response to a fixed dose of acetylcholine among the various strains of mice than there was within a given strain; this observation was consistent with the heritability of airway responsiveness in the mouse. When the same experimental approach was used to determine if the APTI response to serotonin infusion was heritable [4], they found substantial variation among mouse strains in the APTI response to serotonin and also that the variation among mouse strains exceeded that within a given strain. Because the distribution of responses among the mouse strains was different for serotonin than it was for

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acetylcholine, the investigators hypothesized that airway responsiveness to these two mediators was the result of variations at distinct genetic loci [4].

Konno *et al.*, in an examination of bronchial responsiveness to methacholine in six inbred strains of mice, found that the C57BL/6 J strain was a low responder and that the A/J strain was a high responder [27]. Thus, their data confirmed the findings of Levitt and Mitzner [3] and provided additional evidence for the heritability of airway responsiveness in the mouse. Because of these data indicating a strong heritable component to airway responsiveness, it appeared reasonable to use molecular genetic approaches to identify the loci associated with airway responsiveness in the mouse.

Genetic linkage studies of airway hyperresponsiveness in mice In these studies [28–30] a standard approach to genetic linkage for quantitative traits (QTLs), i.e. a trait that exists in a graded fashion rather than being simply present or absent, has been used. In this approach, two progenitor strains that differ substantially in their airway responsiveness, e.g. A/J and C3H/HeJ mice, are identified. Segregating progeny, i.e. F_2 or backcross progeny, derived from the mating of these progenitor strains are phenotyped to ascertain their airway responsiveness and DNA is obtained for genotyping. The DNA from animals representing the phenotypic extremes was genotyped at DNA markers that covered the murine genome, and the association between the presence of markers from one progenitor strain and the expression of the airway responsiveness phenotype was determined with standard computer software, such as QTL Mapmaker [30, 31]. This approach identifies regions of the genome to which expression of airway responsiveness is linked. Methacholine responsiveness in an A/J-C57BL/6 J cross.

We examined a cross between two inbred murine strains, A/J mice, which are hyperresponsive, and C57BL/6 J mice, which are relatively hyporesponsive [32]. Airway responsiveness was measured by ascertaining the amount of methacholine that had to be infused in order to double pulmonary resistance (R_L), as measured by standard techniques [33]; this value was termed the effective dose to double pulmonary resistance, or $ED_{200} R_L$. $ED_{200} R_L$ values were obtained for 42 A/J, 40 C57BL/6 J, 40 F_1 (C57BL/6 J $\times$ A/J), 40 F_1 (A/J $\times$ C57BL/6 J), 40 (C57BL/6 J $\times$ A/J) F_2 intercross mice, and 321 [(C57BL/6 J $\times$ A/J) F_1 $\times$ C57BL/6 J] backcross mice [32].

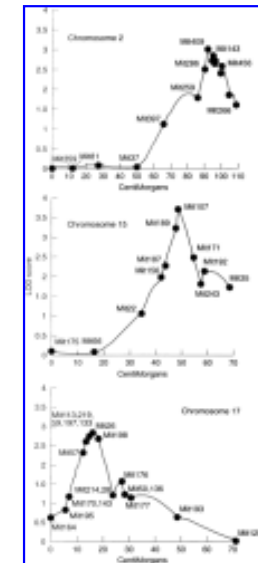
As expected [3, 4], A/J mice had an asthma-like phenotype with an $ED_{200} R_L$ threefold less than that in C57BL/6 J mice ($P < 0.0001$). However, different from the results reported by Levitt and Mitzner [3, 4], the $ED_{200} R_L$ for the F_1 mice, for both reciprocal crosses, demonstrated airway responsiveness similar to that observed in A/J mice, indicating that airway hyperresponsiveness was inherited as a dominant trait. Of particular importance was airway responsiveness measured in F_2 intercross mice. If airway responsiveness were inherited in a Mendelian fashion, the F_2 mice would be expected to segregate in a ratio of 1:3 or 3:1, depending on the recessive or dominant nature of this phenotype, respectively. Rather than a bimodal distribution, however, airway responsiveness in intercross mice was broadly and unimodally distributed between that observed in C57BL/6 J mice and that observed in A/J mice. These data suggested that airway responsiveness to methacholine amongst mice is not controlled by a single gene but by more than one gene, and that the genes controlling airway responsiveness act in a dominant fashion.

Because it seemed that airway responsiveness alleles functioned in a dominant fashion, the hyperresponsive F_1 mice were backcrossed to the hyporesponsive C57BL/6 J strain. This cross was chosen because the progeny have, at every locus, one obligate C57BL/6 J allele from the C57BL/6 J father, while approximately half of the maternal alleles from the (C57BL/6 J $\times$ A/J) F_1 mother are A/J in origin. Airway responsiveness was determined in 321 mice derived from the backcross described above. In these animals, airway responsiveness was approximately normally distributed with a mean responsiveness, as indicated by the $ED_{200} R_L$, between those of the two progenitor strains. Analysis of the variance of the log $ED_{200} R_L$ values in the backcross and F_1 mice indicated that 50% of the total variance in the backcross was genetic, with the remainder attributable to environmental variance. Because the animals were maintained in isolation, we attribute environmental variance to day-to-day changes in anaesthetic and surgical technique.

Selective genotyping of the phenotypically extreme backcross progeny ($n = 92$) was carried out with 157 simple sequence length polymorphic markers (SSLPs) spaced ≈ 9 centiMorgans (cM) apart. QTL analysis of this cohort of backcross mice revealed three regions of interest on murine chromosomes 2, 15, and 17. These regions were subsequently genotyped in all 321 backcross progeny with a denser map, an additional 31 SSLP markers at an average spacing of about 1 cM. Three loci influencing airway responsiveness were identified by QTL mapping using the computer

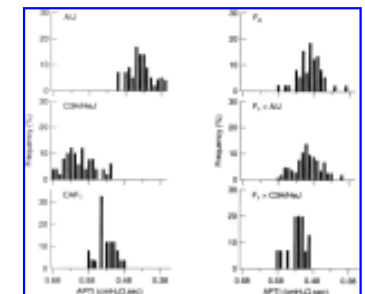
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Fig. 1 . Lod scores calculated by QTL Mapmaker from phenotypic and genotypic data from 321 SSLP markers...



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program QTL Mapmaker. These data suggested the existence of *Bhr1* on chromosome 2 with a lod score equal to 3.0; *Bhr2* on chromosome 15 with a lod score equal to 3.7; and *Bhr3* on chromosome 17 with a lod score equal to 2.83 (Fig. 1). Although the lod score for *Bhr3* was below the threshold value of 2.95 [34], we felt that it represented a viable locus because it demonstrated epistasis with both *Bhr1* and *Bhr2*. We tested for genetic interactions among the loci by using a standard analysis of variance approach, including cross terms for two-way and three-way interaction. There was no interaction between *Bhr1* and *Bhr2*, but there was a statistically significant interaction between *Bhr1* and *Bhr3* ($P = 0.01$) and between *Bhr2* and *Bhr3* ($P = 0.01$). The presence of such epistatic interactions would tend to decrease the lod score for *Bhr3* when considered alone.

Bhr1 maps close to an interesting candidate gene for asthma, interleukin-1 β . *Bhr2* is close to the murine genes encoding the receptors for interleukin-2 β , interleukin-3 β 1, and interleukin-3 β 2. In addition, the platelet-derived growth factor B chain is found in this region. *Bhr3* is closely linked to the mouse gene encoding tumour necrosis factor- α and mast cell proteases 6 and 7.

Acetylcholine responsiveness in a cross between A/J and C3H/HeJ mice.

Linkage has been established between genetic variations in airway responsiveness and a locus on murine chromosome 6 in a cross between A/J and C3H/HeJ mice [28]. In this study, two methods of phenotyping for airway responsiveness were used, namely the APTI and respiratory resistance (R_{RS}) response to intravenous infusion of a fixed dose of acetylcholine. A/J and C3H/HeJ, reciprocal F_1 , F_2 and backcrosses to both A/J and C3H/HeJ mice were performed (Fig. 2). Linkage analysis was performed in the mice representing each of the phenotypic extremes, i.e. high and low responders to acetylcholine infusion, using 94 DNA markers polymorphic between A/J and C3H/HeJ mice. Once tentative linkage was established in a region, additional closely spaced markers were evaluated in these regions. The investigators demonstrated linkage to a region of suppressed recombination on murine chromosome 6 with a maximum lod score of 3.11 in the region of markers D6Mit62 and D6Mit13. Similar lod scores were noted when either the APTI or the R_{RS} was used as the phenotypic indicator of airway responsiveness. In the backcross of F_1 mice to A/J mice, animals homozygous for A/J alleles in the region of marker D16Mit62 had $\approx$ threefold greater airway responsiveness than mice who were heterozygous for A/J and C3H/HeJ alleles.

Summary of murine genetic data

These data indicate that airway hyperresponsiveness in mice is a heritable trait, controlled by more than one gene, and that molecular genetic techniques can be used to identify QTLs for this phenotype. Even though no gene has been positionally cloned, a number of promising candidate genes with possible relevance to human asthma have been identified. These data provide cogent reasons to believe that the genes responsible for airway responsiveness can be identified in mice. As the search for human genes related to airway responsiveness continues, the murine data will be of value by providing a means for reducing the number of candidate genes of interest.

Animal models of chronic bronchitis

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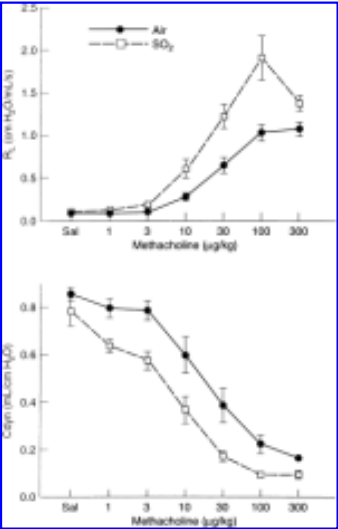
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Animal models have been developed that mimic many aspects of human chronic bronchitis. The two most frequently used methods used to generate animal models of chronic bronchitis are (i) chronic exposure to high concentrations of SO₂ gas, and (ii) chronic exposure to cigarette smoke. Though many different species have been used for these studies, in this review we will focus on data generated in rats exposed to SO₂. In most of these studies, rats are exposed to SO₂ at concentrations ranging from 200 to 500 p.p.m., 3–5 h/day, for periods of up to 6 weeks.

Epithelial changes in SO₂-induced bronchitis in animals

Ciliated epithelial cells are injured by SO₂ gas. With acute exposure, transmission electron microscopy shows evidence of loss of cilia and frank

Fig. 2 . Frequency distribution histograms showing the frequency (as a percentage of the population)...



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Fig. 3 . Changes in pulmonary resistance (R_L) and dynamic compliance (C_{dyn}) induced by intravenously...

exfoliation of ciliated cells in dogs [35, 36]. Airway lavage fluid of rats exposed to SO₂ for a single day contains about seven times as many sloughed ciliated epithelial cells as air-exposed controls [37]. Lamb and Reid [38] reported that after 2–4 days of exposure of rats to SO₂, cilia are lost throughout the trachea and mainstem bronchi, and the normal pseudostratified epithelium is replaced by one or two layers of small flat cells. In contrast, peripheral airways appear normal. After 6 weeks of exposure, the epithelial layer in the trachea and bronchi begins to regenerate, and becomes thicker than normal. Some of the cilia begin to reappear, although they are stunted in size. The investigators proposed that these changes in the epithelial lining made it more resistant to injury. They also speculated that the thickening of the mucus blanket over the course of the exposure period might protect the regenerating epithelial cells. Chronic exposure to SO₂ in ferrets also results in decreases in the number of cilia per cell, and the number of cilia per distance of apical membrane [39]. Additionally, widening of the intercellular spaces at the base of the epithelium is observed. The latter may be a histological correlate of the increased epithelial permeability that has been reported in SO₂-exposed animals [40].

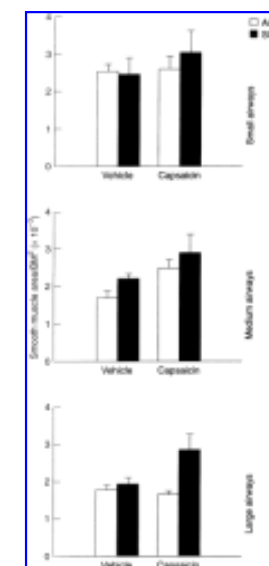
Mucous hypersecretion in SO₂-induced bronchitis

Reid [41] reported that after chronic SO₂ exposure in rats, mucus was sometimes present in sufficient quantities to be apparent on direct visualization. Shore *et al.* [42] reported that they sometimes observed a layer of mucus overlying the epithelium in the large airways of rats exposed to SO₂ gas for 4–5 weeks. More infrequently, mucous plugs were observed. They also measured increases in the amounts of acidic and neutral mucins extracted from lungs and tracheae removed from SO₂-exposed animals. Jany *et al.* [43] reported an elevation in mucous content in bronchoalveolar lavage fluid obtained from SO₂-exposed rats, while Knauss *et al.* [44] reported that the amount of mucus recovered increased with increasing duration of exposure. Taken together, these data indicate that chronic exposure of rats to SO₂ induces airway mucous hypersecretion. Although these changes are amplified by bacterial infection [43], SO₂ can cause mucous hypersecretion even in the absence of any infection [41].

Mucous hypersecretion likely results in part from increased mucus synthesis. There is an increase in the number of both PAS and Alcian Blue staining epithelial secretory cells in rats exposed chronically to high concentrations of SO₂ [38, 45, 46]. These cells also extend into more peripheral airways where they are not usually observed. As in human chronic bronchitis, there is substantial heterogeneity in this response: some bronchioli have normal numbers of goblet cells, whereas neighbouring ones had increased numbers [41]. The size of the tracheal mucous glands is also increased in SO₂-exposed rats and dogs [41, 47, 48]. Additionally, northern blot analysis of rat lung total RNA demonstrates increased levels of mRNA transcripts encoding for mucous glycoproteins following SO₂ gas exposure, indicative of *de novo* protein synthesis [43].

It is also likely that decreased clearance of mucus contributes to the increased amounts present in the airways of rats exposed chronically to SO₂. Lightowler and Williams [45] reported a reduction of ≈50% in tracheal mucous flow rates in rats after 4 weeks exposure to SO₂. They noted that the reduction in mucous flow rate correlated with increasing severity of the bronchopulmonary changes as represented by total histological scores. They suggested that the changes in mucous flow were likely due to a combination of changes in the nature of the mucus, along with decreases in the amount of cilia-bearing mucosa.

There are also changes in the nature of the mucous glycoproteins isolated from rats with SO₂-induced bronchitis [38, 42, 46, 47]. In normal rat lung extracts, the ratio of acidic (Alcian Blue staining) to neutral (PAS staining) mucins is ≈5:1 [42, 49]. Histological examination of rat lung sections also indicates substantially higher numbers of Alcian blue than PAS stained epithelial cells [38, 49]. Exposure to SO₂ gas caused an increase in both acidic and neutral mucous glycoproteins, in both the lungs and the trachea [42]; however, the percentage increase was much greater for the PAS staining mucins than for Alcian Blue staining mucins, both in the lungs and in the trachea. Similarly, Pon *et al.* [49] reported greater increases in PAS than Alcian Blue staining mucins in rats after chronic metabisulfite exposure, as well as greater increases in the numbers of PAS compared with Alcian Blue staining cells in the airways of these animals. Lightowler and Williams [45] also report greater numbers of PAS compared with Alcian Blue staining cells in bronchioles of chronic SO₂-exposed rats, after 4–6 weeks' SO₂ exposure. Changes in the nature of the mucus produced by SO₂-exposed rats are also evident from the observation that with increasing time of exposure, the mucus becomes increasingly resistant to sialidase [38]. Changes in the amount and composition of mucus are also observed with chronic SO₂ exposure in dogs [50, 51], and in these animals changes in



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Fig. 4 . Changes in airway smooth muscle area induced by SO₂ exposure in rats treated neonatally wit...

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composition correlate with changes in the rheological properties of the mucus [52].

The mechanistic basis for the mucous hypersecretion observed in these SO₂-exposed animals has not been established, but one possibility is that neutrophils recruited to the airways by chemotactic factors released from injured epithelial cells are involved, since neutrophil proteases are potent mucous secretagogues [53, 54].

Airway inflammation in SO₂-induced bronchitis in animals

Increases in both mononuclear and polymorphonuclear cells are observed in large but not small airways of rats with SO₂-induced bronchitis [42]. The number of PMNs in the airway tissue, as detected with an anti-RP-3 monoclonal antibody, is increased after even a single day of SO₂ exposure, and neutrophil influx can be completely inhibited with cortico-steroid treatment [55]. In addition, tracheae from chronic SO₂-exposed animals show increased expression of mRNA for KC and MIP-2, rat chemokines similar to human IL-8, a potent neutrophil chemotactic factor. Chemokine expression is observed after a single day of SO₂ exposure and is still observed after 4 weeks of exposure.

There are inflammatory cells in the airway lumen as well as the airway tissue of rats with SO₂-induced bronchitis. For example, inflammatory cells are observed in mucus isolated from these rats and increase in number with increasing duration of exposure [44]. We have also observed increased numbers of neutrophils in nasal, airway, and bronchoalveolar lavage fluid of SO₂-exposed rats [37]. After a single day of exposure, neutrophils are observed in nasal lavage, but not in airway or broncho-alveolar lavage, even though they are observed in airway tissue [37]. After 2 weeks of exposure neutrophils comprised almost 30% of the airway lavage fluid cells, but are not increased in the lung lavage. Indeed, only after 4 weeks is the number of neutrophils in lung lavage increased above control animals exposed to air, and even then the numbers are only about 2% of total cells. The finding that SO₂ had its greatest inflammatory effects in the nose and large airways is consistent with what we would expect from a highly soluble gas such as SO₂ [56], and with studies that have shown that SO₂ is removed from inhaled air primarily in the upper respiratory tract [57]. Hence the lower airways and alveoli are likely to have received a much smaller dose of SO₂. The progression of the inflammation down the respiratory tract with time may represent continuous airway injury and repair caused by the cumulative effect of these smaller doses, and is consistent with the histology of lungs of rats exposed to SO₂, which indicates the most pronounced effects in the trachea and large bronchi, while the alveoli appear normal [38, 42].

Whereas increased numbers of neutrophils are observed in lavage fluid of SO₂-exposed rats, lymphocytes and macrophages are not altered [37]. Similar results are obtained in SO₂-induced bronchitis in dogs [58]. Increased numbers of neutrophils but not mononuclear cells are also observed in lavage fluid of patients with chronic bronchitis [59, 60]. In contrast, increased numbers of mononuclear cells are observed in airway tissue of bronchitic rats [42], dogs [61], and humans [62–64]. We do not know why there are differences in the number of the inflammatory cells in the airway lumen vs the airway tissue, but one possibility is that there are important differences in the nature of the chemotactic factors and adhesion molecules expressed by epithelial vs subepithelial cells.

Airway mechanics and airway hyperresponsiveness in SO₂-induced bronchitis

Shore *et al.* [42] have reported that chronic exposure to SO₂ gas caused a small but significant increase in pulmonary resistance (R_L) in rats. Similar results have been reported by Levrier [65]. SO₂ exposure also caused a substantial increase in airway responsiveness, as indicated by an approximate half-log decrease in the doses of inhaled aerosolized methacholine required to double R_L or to decrease dynamic compliance by 50% [42]. To our knowledge, this is the only report of increased airway responsiveness in an animal model of induced chronic bronchitis. As noted above, patients with chronic bronchitis also show increased airway responsiveness relative to normal subjects in cross-sectional studies [66–68]. One possible explanation for this phenomenon is that patients with chronic bronchitis have pre-existing hyperresponsiveness, which predisposes them towards the development of bronchitis, i.e. that hyperresponsiveness is a cause and not a consequence of bronchitis. The fact that airway

hyperresponsiveness can develop with induction of a syndrome that strongly resembles many of the histopathologic features of bronchitis, argues against this explanation.

We favour the hypothesis that increased quantities of mucus (see above) present in the airways may account for both the increased resistance and the increased responsiveness observed in rats with SO₂-induced bronchitis. Levrier reported that during SO₂ induction of bronchitis in rats, administration of carbocisteine, a drug which reduces the amount of mucus in the airways, attenuated the increased R_L induced by SO₂ exposure [65]. Moreno *et al.* [69] have shown that changes in the diameter of the airway lumen due to the presence of mucus or to oedema of the airway wall, can substantially increase changes in pulmonary mechanics induced by subsequent smooth muscle constriction.

Another potential explanation for the increased airway responsiveness to inhaled aerosolized methacholine that is observed in rats with chronic bronchitis induced by SO₂ exposure, is that there is more rapid or increased uptake of inhaled methacholine across the epithelium leading to increased concentrations at the airway smooth muscle. Epithelial permeability is increased in SO₂-exposed rats [40], and rats with SO₂-induced bronchitis have enhanced and more heterogeneous deposition of particles (and presumably aerosol droplets) in central airways [70]. Such an explanation is unlikely, however, since we have shown that airway responsiveness to intravenously administered methacholine is also increased in rats chronically exposed to SO₂ compared with filtered air (Fig. 3).

It is also unlikely that the increased airway responsiveness observed in bronchitic rats is the result of alterations in the airway smooth muscle *per se*. Three separate studies examined tracheal smooth muscle isolated from rats chronically exposed to SO₂. Neither the sensitivity nor the maximal response to carbachol, eserine, acetylcholine, or serotonin was altered by SO₂ exposure [58, 71, 72]. There was also no change in the response of pulmonary parenchymal strips to contractile agonists [72], suggesting that neither central nor peripheral airways were altered. Increased airway smooth muscle mass resulting from chronic inflammation is also an unlikely explanation for the increase in responsiveness, as there was no difference in the amount of airway smooth muscle in any sized airway in rats exposed chronically to high concentrations of SO₂ compared with filtered air controls [72].

Role of C-fibres in SO₂-induced bronchitis in rats

C-fibres are a class of unmyelinated sensory neurons. In the airways, the terminal ramifications of these neurons are found underneath and between epithelial cells, near blood vessels, mucous glands, airway smooth muscle, and parasympathetic ganglia. C-fibres are stimulated by many inhaled irritants, including cigarette smoke and SO₂ gas, substances known to induce chronic bronchitis in humans and animals. In response to stimulation, action potentials are generated and result in central reflex changes in heart rate and breathing pattern. In addition, neuropeptides such as substance P and neurokinin A are released from the peripheral endings of these neurones. The actions of these neuropeptides include cough, mucous secretion, bronchoconstriction, and airway inflammation, events similar to those observed in chronic bronchitis (reviewed in [73]).

Based on these observations, we hypothesized that chronic stimulation of C-fibres by inhaled irritants may contribute to the pathophysiological changes observed during induction of bronchitis by these agents. In order to test this hypothesis, chronic bronchitis was induced by SO₂ exposure both in normal rats and in rats treated neonatally with a single high dose of capsaicin. This latter procedure has been demonstrated to deplete the lungs and airways of tachykinins and to cause permanent destruction of C-fibres [74]. We reasoned that if chronic stimulation of C-fibres by SO₂ exposure did contribute to the pathophysiological changes associated with chronic bronchitis, then we should observe reduced effects of SO₂ exposure in animals treated with capsaicin neonatally, compared with animals treated neonatally with the vehicle used to dissolve capsaicin. In fact, the opposite was observed. For example, pulmonary resistance increased to a greater extent after chronic SO₂ exposure in the capsaicin-treated rats than in the vehicle-treated rats. SO₂ also resulted in more pronounced airway hyperresponsiveness in the capsaicin rats [72]. This enhanced airway hyperresponsiveness may have been caused, at least in part, by changes in the airway smooth muscle *per se*. Maximal tension generated by tracheal rings in response to cholinergic agonists was significantly increased by SO₂ exposure in capsaicin-treated rats, whereas, as discussed above, it was

not altered in vehicle-treated rats [72]. The enhanced contractile responses of airways from the SO₂-exposed capsaicin-treated rats may result from increased airway smooth muscle mass. Morphometric analysis of histological sections of airways demonstrated that the average area of smooth muscle in the airway wall was ≈35% greater in SO₂ compared with air-exposed capsaicin-treated rats, but not in vehicle-treated controls [72]. As shown in Fig. 4, these changes in smooth muscle area were primarily observed in large airways, consistent with the greater inflammation and injury observed in these airways.

We do not know the mechanistic basis for the increase in airway smooth muscle that we observed in the neonatal capsaicin-treated rats exposed to SO₂. However, numerous cytokines and other inflammatory mediators are known to cause airway smooth muscle proliferation, and inflammation was greater and progressed more rapidly down the respiratory tract in capsaicin-treated rats than in vehicle-treated rats exposed to SO₂ [37]. In particular, we found that the number of neutrophils collected in nasal lavage fluid of capsaicin rats was consistently higher than in vehicle rats. In both the airway and the bronchoalveolar lavage, an increase in the number of neutrophils occurred with shorter periods of SO₂ exposure in the capsaicin than the vehicle rats. In the airway lavage fluid, a single day of SO₂ exposure was sufficient to increase neutrophils in capsaicin-treated rats, whereas 2 weeks' exposure was required in vehicle-treated rats. In bronchoalveolar lavage fluid, increased neutrophils were observed after 2 weeks of SO₂ exposure in capsaicin-treated rats and by 4 weeks accounted for about 8% of total cells. In contrast, in vehicle-treated rats, no change in the number of neutrophils was observed until 4 weeks of exposure and, even then, neutrophils accounted for only about 2% of total cells.

Taken together, these results support the hypothesis that rather than contributing to the pathophysiological manifestations of bronchitis, C-fibres limit the development of airway obstruction and airway hyperresponsiveness during induction of chronic bronchitis by SO₂ exposure. The sputum of patients with chronic bronchitis contains significantly higher substance P concentrations following challenge with hypertonic saline than the sputum of normal volunteers [75]. Similarly, the substance P content of the trachea is three-fold greater in rats with SO₂-induced bronchitis compared with filtered air controls [76]. Taken in light of the observations above, these changes would appear to represent an adaptive response to chronic irritation.

In summary, chronic exposure to high concentrations of SO₂ gas in rats results in a syndrome that mimics many aspects of human chronic bronchitis. With daily exposure, there is chronic injury and repair of epithelial cells. Over time, the animals develop mucous hypersecretion, airway inflammation, increased airway resistance, and airway hyperresponsiveness. The model may thus prove to be suitable for investigations of the mechanisms underlying the pathophysiological events that typify the condition in humans.

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