SESSION I: CURRENT CONCEPTS IN SMOOTH MUSCLE PHARMACOLOGY

Chair: A.W. Jones

Use of Airway Smooth Muscle to Evaluate Anti-Inflammatory and Anti-Asthmatic Agents

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Introduction

Arachidonic acid (AA) is a normal constituent of many mammalian cell membranes. Appropriate stimulation releases AA from the phospholipid pools and the AA is subsequently oxidized to biologically active products, including prostaglandins, thromboxanes and leukotrienes. A number of these products have been implicated in various respiratory and inflammatory disorders. Selective antagonists or inhibitors of these substances may lead to the control or prevention of asthma and other inflammatory disorders in the lung.

It appears that the major sources of these products in the airways are mast cells and macrophages. The products and the proportions produced depend on the species, the area of the lung tested, the pathophysiological state of the tissue, and the type and strength of the stimulus. In addition, the role of each of the mediators is not fully defined. Although extracellular fluid concentrations can be easily measured and biological functions defined by administering exogenous mediators to the tissues, the precise actions are still not clear because local tissue or membrane concentrations and interactions between mediators are not known. It now appears that AA metabolites, such as leukotrienes, can influence the biological activity of other mediators, such as histamine (1).

Because non-sterodial anti-inflammatory agents (NSAID) have not been effective anti-asthmatic drugs, it has been implied that lipoxygenase products, particularly the peptidoleukotrienes, are involved in bronchoconstriction and inflammation (2). Indeed, NSAIDs exacerbate asthma in susceptible individuals. However, recent evidence for prostaglandin and thromboxane involvement, either secondary to leukotrienes (i.e. TXA2: ref.4) or as primary mediators (PGD2: ref.5), does not negate a role for cyclooxygenase products. Thus, development of selective lipoxygenase inhibitors and/or dual inhibitors of the cyclooxygenase and lipoxygenase pathways will provide useful tools for determining the selective roles of lipoxygenase and cyclooxygenase products in asthma and airways inflammation. In addition, these compounds will be of therapeutic interest in airways diseases.

Methods

English short-hair guinea pigs (200-250g) of either sex (Connaught Laboratories, Toronto, Ontario or Charles River Laboratories, Montreal, Quebec) are utilized. The guinea pigs are euthanized by administering a blow to the head and the lungs and trachea rapidly removed. The trachea is spirally cut (6) divided into four segments, and each suspended under 1 g tension in 10 ml organs baths containing Krebs-

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Henseleit solution maintained at 37°C and aerated with 95% 02-5% C02. Parenchymal strips are carefully cut from the distal edges of lung lobes (7) and suspended under 500 mg tension in 10 ml organ baths as described above.

Contraction of the tracheal spirals and parenchymal strips is measured isotonically using rotary motion transducers (Type 386 heart/smooth muscle transducers, Ealing Scientific, St. Laurent, Quebec). Tissues should be incubated for 1 hr prior to use. Constant maximal contractions to histamine (10-4M) are obtained before indomethacin is administered. Indomethacin (8.4 X 10-6M) is administered to trachea 45 min prior to administration of AA. Parenchymal strips are not treated with indomethacin for the intial screening procedures. Test drugs at varying concentrations are added to the organ baths 30 min before AA. One parenchymal strip and one tracheal spiral should not be treated with drugs other than indomethacin to act as controls. AA (6.6 X 10-5M) is then added to all the tissues and contraction measured for 60 min.

Analysis And Statistical Evaluation Of Results

Responses to AA are measured as a percentage of the maximum response obtained with histamine on each tissue in the absence of any modulatory agent. These responses are calculated for a period of 60 min beginning at the point of challenge. The response over this period of time constitutes the contraction curve. The areas under the contraction curves over the 60 min can be integrated on a computer programme to give a numerical value for the total contractile response. Data for areas under the curves can then be analyzed for significance using Student's t-test for paired data. A p value of <0.05 would be considered significant. A minimum of four animals should be used for each experiment. For each animal, the areas under the contractile curves in the presence of test agents can be expressed as a percentage of the area in the absence of drug. The IC50 concentration of the drug can be interpolated from this data and then be converted to a pD2 value for determining the mean $\pm$SE concentration to compare the potency of different agents.

Drugs

In the experiments presently described, histamine dihydrochloride and arachidonic acid (99% pure) were purchased from Sigma (St. Louis, MO). Indomethacin was obtained as a gift from Merck-Frosst Laboratories (Pointe Claire-Dorval, Quebec). Indomethacin (1 mg/ml) and arachidonic acid (2 mg/ml) are dissolved in 1M Tris-HCl buffer (pH 8.4) and kept in the dark at -5°C until used. Histamine is dissolved in Krebs-Henseleit solution.

All test drugs are dissolved in either dimethyl sulphoxide (DMSO) or distilled water depending on their solubility. The vehicles (Tris-HCl or DMSO; maximum concentration 1%) did not affect tissue responses.

Results and Discussion

Tracheal spirals and lung parenchymal strips were chosen as the

initial screening test for lipoxygenase and cyclooxygenase inhibitors, respectively, because of the spectrum of AA metabolites produced by each tissue. The primary AA metabolites produced in the trachea are PGE2 and LTC4 and D4 (8,9). Indomethacin, a cyclooxygenase inhibitor, enhances AA-induced contractions of trachea by 400-500% (10), apparently due to a reduction in PGE2 which normally is bronchodilator and also inhibits mediator release. Thus AA-induced contractions of trachea in the presence of indomethacin appear to be primarily the consequence of leukotriene action on smooth muscle and inhibition of this concentration should reflect either lipoxygenase inhibition or leukotreine receptor site antagonism.

In order to demonstrate that the tracheal spiral and parenchymal strip were good testing tissues to screen potential cyclooxygenase and lipoxygenase inhibitors, known inhibitors were tested on the model. Indomethacin is a potent cyclooxygenase inhibitor without an appreciable effect of the lipoxygenase pathway. In contrast, nordihydroguaiaretic acid (NDGA) is a selective lipoxygenase inhibitor. The present experiments demonstrated that indomethacin has no significant effect on tracheal contractions induced by AA but did reduce parenchymal contractions dose-dependently (Figure 1). The pD2 value for indomethacin on the parenchyma was 5.26 $\pm$ 0.37 (Table 1) which is comparable to its cyclooxygenase inhibiting activity in other systems (11). The experiment of using indomethacin on trachea already pretreated with indomethacin was done purely for consistency.

In contrast to the trachea, the lung parenchymal strip produces large amounts of TXA2 and PGF2 and smaller amounts of LTs (12). Indeed, indomethacin (8.4 x 10-6M) reduces AA-induced contractions of parenchyma by 60-80% (ref. 10; Figure 1). Indeed, some of the contraction induced by LTs in the parenchymal strip may be due to synthesis of TXA2 (4). Thus, although there is a residual lipoxygenase component, the presence of a strong contraction by cyclooxygenase products allows this tissue to be quite satisfactory to be used to examine whether products tested have any inhibitory activity on the cyclooxygenase pathway.

NDGA also was selective, inhibiting AA-induced contractions of trachea dose-dependently, but without effect on parenchyma (Figure 2). The pD2 value for NDGA on trachea was 5.31 $\pm$ 0.18 (Table 1). Again this value was comparable to that obtained by others (13).

Several other drugs were tested as well as those listed in Table 1. Sodium meclofenamate is interesting in that it appears to be capable of blocking both the cyclooxygenase and lipoxygenase pathways. It appears to be greater than 10 times as potent in inhibiting AA-induced contractions of parenchymal strips than in inhibiting PG synthesis by seminal vesicle enzyme preparations (11). This may reflect a higher degree of sensitivity of the airways preparation to sodium meclofenamate. The inhibition of the lipoxygenase-dependent contractions of trachea was unexpected since sodium meclofenamate enhances leukotriene release (measured as SRS-A) in bovine and guinea pig lung (15,16), while inhibiting PG synthesis. The difference may

Table 1. Inhibitory effects of drugs on AA-induced contractions.

Drug	pD2 Values	
	Trachea	Parenchyma
Indomethacin	no effect	5.26 ± 0.37
NDGA	5.31 ± 0.18	no effect
Sodium Meclofenamate	5.80 ± 0.19	6.28 ± 0.53
Piriprost	4.68*	not done
Nafazatrom	4.15*	"
BW755C	no effect*	"
FPL55712	5.40*	"

* values derived from results in ref. 14.

be due to the preparation since differences in mediator release have been noted between chopped lung, trachea spiral, and parenchymal strip preparation (10). However, some authors have provided circumstantial evidence that meclofenamate inhibits lipoxygenase, particularly in inflammatory situations (17).

Secondly, the screening technique described in this paper does not differentiate between enzyme inhibition and receptor antagonism. Sodium meclofenamate has been reported to non-selectively block PGs and SRS-A on bovine airways both in vitro and in vivo (18,19). The lack of selectivity of sodium meclofenamate (i.e. ability to inhibit the cyclooxygenase enzyme, block receptors, and possibly inhibit the lipoxygenase enzyme) may actually increase the efficacy of this drug. This may be reflected in the particular ability of sodium meclofenamate to inhibit anaphylactic and endotoxin shock in cattle, guinea pigs and cats (18,20,21).

As noted above, there is a possibility that an agent which inhibits AA-induced contractions of trachea could be either inhibitors of the lipoxygenase pathway or LT receptor antagonists, or both. FP55712 and piriprost, both LT receptor antagonists, also inhibit LT synthesis (14,22). Thus, once inhibition of AA-induced contractions is determined, further pharmacological characterization should be carried out.

First, it should be determined whether the agent is acting at an LT receptor. This can be done with concentration-response analysis using exogenous LTs C4 and D4 in the presence and absence of the agent on the tracheal spiral and LTB4 on the parenchymal strip. Other agents such as histamine, acetylcholine, and potassium should be used to check selectively. If potassium concentration-response curves were shifted it would indicate that the agent had possible calcium channel blocking properties.

Secondly, inhibition of LT and TX synthesis and release, if revealed in the tracheal and parenchymal preparations, respectively, should be confirmed using radioimmunoassays, which are now readily available commercially. Further pharmacological tests can be carried

out as necessary.

In summary, the indomethacin-treated tracheal spiral and the lung parenchymal strip preparations appear to be effective models to screen and pharmacologically evaluate lipoxygenase and cyclooxygenase inhibitors respectively. They offer the distinct advantage of examining drugs that would be used in airways disease directly in the airways. A prime example of where this would be an advantage is in the situation of BW755C which is a dual cyclooxygenase/lipoxygenase inhibitor in polymorphonuclear leukocytes (23), but is only a cyclooxygenase inhibitor in the lung (14). In addition, these tissues are very sensitive to the effects of cyclooxygenase and lipoxygenase inhibitors. We are currently using this model to screen a number of putative lipoxygenase inhibitors and have found some compounds which are 50-100 times more potent than piriprost and nafazatrom, two lipoxygenase inhibitors which are currently in clinical trials. Further testing is currently underway to pharmacologically characterized them and evaluate whether they should be further developed for clinical usage.

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Actions of Leukotriene Agonists and Antagonists on Smooth Muscle

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The sulfidopeptide leukotrienes, LTC4, LTD4, and LTE4, components of slow reacting substance of anaphylaxis (SRS-A), are derived from arachidonic acids. They differ from each other by their amino acid substituents on the 6 position of the C20 fatty acid backbone. Leukotrienes are potent airway and intestinal smooth muscle stimulants and can increase vascular permeability. They have been proposed to play a role in various human disorders including asthma and shock. The pharmacologic receptor for LTC4 differs from those for LTD4 and LTE4. The evidence to support this hypothesis comes from experiments showing that, under controlled in vitro conditions, currently available antagonists block LTD4- and LTE4-induced contractions but not those caused by LTC4. Some information is available suggesting that receptors for LTD4 and LTE4 might differ. However, to date, antagonists have not been able to distinguish between the 2 receptor sites. LY171883 and LY163443, tetrazole substituted acetophenones, have been developed at The Lilly Research Laboratories as LTD4 and LTE4 antagonists. They antagonized LTD4- and LTE4-induced contractions of guinea pig ileum, trachea, and lung parenchyma. LY163443 is the most potent of the 2 compounds with pKB values between 7.5 and 8.0. This compound is presently undergoing preclinical evaluation. LY171883 is the most widely studied of our leukotrine antagonists. The high degree of selectivity of this agent is evidenced by its lack of antagonist activity against LTB4, PGF2 , serotonin, histamine, bradykinin, or carbamylcholine in isolated smooth muscles. Given orally to guinea pigs, LY171883 antagonized the bronchospasm caused by i.v. administered LTD4 and it also blocked the increase in vascular leakage caused by intradermal administration of LTD4. Furthermore, similarly dosed LY171883 decreased the bronchoconstriction caused by antigen challenge in sensitized guinea pigs pretreated with pyrilamine, propranolol, and indomethacin. Clinical studies revealed that oral doses of 10 to 700 mg LY171883 were well tolerated in healthy volunteers and showed a plasma half life of 10 to 12 hours. Current studies in humans have been designed to determine the compound's efficacy in patients with well documented asthma. Thus, this new class of drugs should have an immediate impact in the research laboratory providing new tools to help understand the action of leukotrienes in physiologic and pathologic processes and in addition hopefully will provide the health practitioner with novel approaches for treating disease.

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Impairment of Homeostasis in Airway Smooth Muscle by Pulmonary Infection

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In humans, it is known that upper respiratory tract infections frequently exacerbate, or precipitate, asthma, and that they also increase airway reactivity to bronchospastic agents. Szentivanyi proposed that an autonomic nervous system imbalance characterized by a diminished beta adrenergic response of bronchial smooth muscle was important in the pathogenesis of asthma (1). It has been shown previously that mice vaccinated with Bordetella pertussis were hyperreactive to histamine and other mediators (2), and that this hyperreactivity resembled that seen in asthmatics. Szentivanyi also showed that B. pertussis-vaccinated mice have decreased metabolic responses to catecholamines (3). Findings of decreased biochemical and physiological responses to beta adrenergic drugs in human asthmatics support Szentivanyi's proposal (4,5,6,7).

Empey et al. showed that viral respiratory infections which produce airway epithelial damage cause a temporary increase in airway reactivity to inhaled histamine (8). They hypothesized that, since the effect was blocked by atropine, a vagally-mediated reflex involving 'sensitized' airway receptors with a lower excitation threshold was involved.

In humans, asthma is a disease characterized by excessive airway irritability. Inhalation of histamine (9), acetylcholine (10), prostaglandin F_2alpha (11), and non-specific irritants have been shown to increase bronchial sensitivity. Respiratory infections disrupt lung function in both normal and asthmatic subjects. Bush et al. infected volunteers with rhinovirus and found decreased beta adrenergic and H_2 histaminergic receptor responses in peripheral granulocytes, as well as increased airway reactivity (12). Upper respiratory viral infections in people have often been associated with limited clinical manifestations, but may induce persistent physiological abnormalities for 3 to 12 weeks (even after symptoms have disappeared) (13).

In a microbiological study of people prone to apparently 'infectious asthma', Minor et al. found a wide variety of respiratory pathogens, including rhinoviruses, parainfluenze type 3 virus, adenovirus type 1 and two other unidentified viruses (14). In a group of asthmatic children experiencing asthma attacks, they had previously found that 42 of 61 episodes of wheezing were associated with the presence of symptomatic respiratory infections, the majority of which had a viral etiology (15).

Buckner et al. found that infection of guinea pigs with the human respiratory pathogen, parainfluenza 3 virus, impaired the ability of a beta adrenoceptor agonist to inhibit antigen-induced contraction of airway smooth muscle (16). They suggested that the guinea pig may be a

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useful model in physiological studies of viral-induced asthma.

The study of human granulocytes has provided a model for the examination of virus incubation in vitro on agonist response. Busse described an impaired inhibitory action of isoproterenol on the release in vitro of lysosomal enzymes from the granulocytes of asthmatics (17). During respiratory infections that provoked asthmatic attacks, the granulocyte response to isoproterenol was further reduced. He postulated that the apparent disruption of beta adrenoceptor function may have been duplicated in the airways, thus explaining the onset of asthmatic symptoms during colds. After exposure to influenza virus (18), or rhinovirus (19), in vitro, human granulocytes exhibit impaired enzyme-release modulating mechanisms which normally downregulate to isoproterenol, histamine and prostaglandin E_1. These receptor types have been shown to inhibit lysosomal enzyme release through stimulation of adenyl cyclase with a subsequent increase in cAMP (20).

The human respiratory pathogen Haemophilus influenzae (sometimes found in the deeper airways of asthmatics) has been studied in laboratory animals. Schreurs et al. found that there was thromboxane A2 from the lungs of Haemophilus-vaccinated guinea pigs (21). Similar vaccination of rats impaired the beta adrenergic eosinophilic response to adrenaline (22) and, in guinea pig tracheal muscle, produced impaired B1 and B2 adrenoceptor responsiveness and increased contraction to carbachol (23).

A theory of H2 histaminergic receptor deficiency in bronchial asthma has been proposed (24). These receptors, like beta adrenoceptors, also operate through the cAMP system and have been shown to be important in inhibition of neutrophil enzyme release and in hypersensitivity reactions (20,25,26). H2 receptor stimulation in some species relaxes airway smooth muscle and may be disrupted by the effects of respiratory infection (27).

Norris and Eyre found that rats vaccinated with Bordetella pertussis had impaired tracheal relaxation to isoprenaline and histamine, but that this impairment was prevented by pretreatment of the animals with hydrocortisone (28). These authors also reported that guinea pigs or rats, vaccinated with the bovine respiratory pathogen Haemophilus somnus, have impaired beta adrenoceptor and H_2 histaminergic responses in tracheal smooth muscle. Much of the research todate supports the possibiliy that there is alteration of a common mechanism, since both beta adrenergic and H2 histaminergic and certain prostaglandin receptor types operate through stimulation of adenylate cyclase.

Work in our laboratory with the common bovine respiratory pathogen Infectious Bovine Rhinotracheitis Virus (IBRV) has shown that calves, infected with the virus 6 days earlier, exhibit decreased in vitro tracheal and bronchial relaxation to the non-selective beta agonist isoproterenol (29). When other animals were re-exposed to the virus one month later, only tracheal responses were impaired. This may reflect the ability of an immune response to remove the virus from the lower airways before receptor alterations could occur.

The homeostasis-blocking effects produced by respiratory pathogens are not well understood. Scheurs and Nijkamp found that guinea pigs vaccinated with Haemophilus influenzae had fewer pulmonary beta adrenoceptors than control animals (30). Treatment of the animals with a dopa-decarboxylase inhibitor increased the number of beta receptors and mimicked the bacterial effects. They suggested that compensatory regulation adapts the number of respiratory beta adrenoceptors to changes in sympathetic input, and that a similar mechanism might underlie H. influenzae-induced loss of beta receptors.

In another study (31), the authors reported that vaccination of guinea pigs with H. influenzae induced a significant increase in norepinephrine levels in lung and plasma (31). They concluded that endogenous catecholamines may regulate beta adrenoceptor numbers in the lung and that exogenous stimuli may affect this mechanism.

These authors also examined the correlation between isoproterenol-induced relaxation of tracheal smooth muscle and pulmonary norepinephrine levels in normal and H. influenzae-vaccinated guinea pigs (32). In those animals vaccinated with the bacteria, there was a significant impairment of the isoproterenol-induced relaxation of tracheal spirals by approximately 50%. Treatment of control animals with desipramine mimicked the effect. One day after vaccination, levels of norepinephrine in lung tissue and plasma were significantly elevated. The authors suggested that catecholamine metabolism is changed in the lungs of H. influenzae-vaccinated animals and that catecholamines play a role in the desensitization of beta adrenoceptors by this pathogen.

Taki et al. examined the role of phospholipase in reduced beta-adrenergic responsiveness in a guinea pig asthma model (33). They found that the phospholipase activity of lung membranes in the experimental group was significantly increased, and that the numbers of beta receptors were significantly decreased. Their conclusion was that enhanced activation of phospholipase in asthmatic subjects could degrade phospholipids necessary in the maintenance of normal beta receptor function.

Inoue et al. studied a model of airway hyperreactivity in dogs infected with Type C influenza virus (34). They reported that airway reactivity to acetylcholine was significantly increased in the 3 weeks following infection with the virus. They proposed: 1) that airway epithelial damage could alter the permeability of the bronchial mucosa and increase the accessability of irritant receptors to stimulants; 2) that viral infection could decrease beta receptor responsiveness; or 3) that immune complexes may be involved in producing lung injury.

Therefore, the exact ways in which respiratory pathogens distrupt airway homeostasis remain unknown. It is probable that no single process is involved, but that the physiological disruptions seen during respiratory infection represent the cumulative result of several mechanisms.

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