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Using guinea pigs in studies relevant to asthma and COPD

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Abstract

The guinea pig has been the most commonly used small animal species in preclinical studies related to asthma and COPD. The primary advantages of the guinea pig are the similar potencies and efficacies of agonists and antagonists in human and guinea pig airways and the many similarities in physiological processes, especially airway autonomic control and the response to allergen. The primary disadvantages to using guinea pigs are the lack of transgenic methods, limited numbers of guinea pig strains for comparative studies and a prominent axon reflex that is unlikely to be present in human airways. These attributes and various models developed in guinea pigs are discussed.

Keywords

Leukotrienes; Autonomic; Influenza; IL-5

1. Introduction

Guinea pigs have been the most commonly used small animal species in preclinical studies related to asthma and COPD [1]. Many fundamental processes, mediators and regulators of airways disease pathogenesis were discovered or demonstrated first in guinea pigs, including the Schultz–Dale (immediate type hypersensitivity) reaction, the actions of histamine, the cysteinyl-leukotrienes and their two receptors, beta adrenoceptor subtypes, thromboxane, vascular endothelial growth factor (VEGF), eotaxin, alveolar macrophage derived neutrophil chemotactic factor(s) (leukotriene B₄ and/or IL-8) and the roles of cAMP and inositol triphosphate in signal transduction [2–19]. Receptor pharmacology in guinea pigs more closely matches that of human receptor pharmacology than most other commonly used species [1, 20,21] (Table 1, Figs. 1 and 2). Several breakthroughs in measuring lung mechanics were developed first in studies using this species, while models of the late phase response following an allergen challenge have been perfected in guinea pigs [22–27]. The emergence of transgenic mouse studies has and will continue to result in the diminished use of guinea pigs for modeling airways disease. This is unfortunate, as for many endpoints guinea pigs are superior to mice for studies of processes related to asthma and COPD [1,27–29]. These advantages as well as the disadvantages of using guinea pigs to study basic processes related to asthma and COPD pathogenesis are briefly reviewed.

2. Anatomy and physiology

The anatomy and physiology of the guinea pig lung resembles that of humans [20,21,30–35]. A pseudo-stratified epithelium lines the trachea, mainstem bronchi and large intrapulmonary bronchi of both species [31,36]. Vagal afferent nerves, including C-fibers and

mechanoreceptors, innervate the epithelium and subepithelial spaces [35,37]. Goblet cells and mucus glands are found in the large airways and their function is regulated both neuronally and by locally released autacoids [32,34,38]. A subepithelial vasculature is found between the epithelium and smooth muscle layer [30,39,40]. These features are similar in guinea pig and human airways but very different from that of the mouse, which largely lacks a subepithelial vasculature, and has few if any glands (but many goblet cells) and a sparsely innervated epithelium [28,41-43]. Neuroendocrine cells and neuroepithelial bodies are also localized to the epithelium of guinea pigs and humans [44-47].

Airway smooth muscle in guinea pigs is both anatomically and functionally similar to that of human airway smooth muscle. Contractile and relaxant agonists of human airway smooth muscle have nearly identical potency and efficacy in guinea pig airway smooth muscle (Table 1; Fig. 1). Due to the size of the airways and thus the limited number of cells recoverable from guinea pigs, few studies of muscle proliferation and/or muscle synthesizing activity have been completed in guinea pigs. But smooth muscle hyperplasia has been observed in models of allergic inflammation [27,48]. Airway smooth muscle (and the epithelium) is also a major source of eotaxin in human and guinea pig airways [49,50]. In both species, isolated airway smooth muscle preparations display a spontaneous tone that has been attributed to locally produced autacoids. In human airways, this basal tone has been attributed to histamine and cysteinyl-leukotrienes released from resident mast cells [51]. In guinea pigs, basal tone is mediated by prostaglandin E₂, formed tonically by cyclooxygenase-2 activity [52-55]. Human airways also have a tonic cyclooxygenase activity but may lack the EP₁ receptors on the smooth muscle that mediate basal tone as seen in the guinea pig [55-57]. Similarly, there is evidence for a tonic cysLT₁ receptor mediated regulation of airways in guinea pigs [58,59]. In both species, this basal tone mediated by autacoids appears to be manifest both in vivo and in vitro [58,60-62].

The autonomic innervation of airway smooth muscle in guinea pigs closely resembles that of humans [35]. Parasympathetic cholinergic nerves mediate contractions of human and guinea pig airway smooth muscle through the actions of acetylcholine acting on post-junctional muscarinic M₃ receptors [63-67]. In both species, a basal level of cholinergic tone is measurable in vivo as evidenced by the bronchodilating effects of M₃ receptor antagonists [35,68-70]. Also present in both species are prejunctional M₂-like receptors that autoregulate (inhibit) acetylcholine release [64,71-73]. Other mediators regulating cholinergic tone prejunctionally, either inhibiting or facilitating acetylcholine release, act similarly in humans and in guinea pigs. These include PGE₂, serotonin, tachykinins, beta adrenoceptor agonists, μ -opioid receptor agonists, and vasoactive intestinal peptide (VIP) and related peptide neurotransmitters [74]. In both species, nicotinic-cholinergic receptors mediate synaptic transmission in airway parasympathetic ganglia [35]. Sympathetic-adrenergic relaxant innervation is sparse and/or nonexistent in the intrapulmonary airways of both species (the guinea pig trachea is densely innervated by sympathetic adrenergic nerves). The primary functional relaxant innervation in both species is parasympathetic and noncholinergic in nature. VIP (and related peptides) and the gaseous transmitter nitric oxide (NO, synthesized from arginine by the neuronal isoform of NO synthase) have been implicated in nonadrenergic-noncholinergic nerve-mediated relaxations of human and guinea pig airway smooth muscle [35,75-78]. VIP and NO synthase have both been identified in the airway parasympathetic nerves of human and guinea pig airways. Stimuli initiating reflex bronchospasm in human subjects evoke similar reflexes in the guinea pig [35]. Stimuli evoking cough in humans also evoke cough in guinea pigs [37]. It is debatable as to whether rats or mice possess a cough reflex. It has also been shown that rats and mice and dogs lack entirely a direct, functional nonadrenergic relaxant innervation of their airway smooth muscle [35,79,80].

Signal transduction in airway smooth muscle cells and in inflammatory cells is also very similar in human and guinea pig airways [81-95]. Smooth muscle contractions are associated with a rise in intracellular Ca^{++} (following influx from extracellular spaces and release from intracellular stores) secondary to inositol phosphate turnover [67,96-98]. Contractile agonists likely work through receptors coupled to the G-protein G_q , which has been localized to or demonstrated functionally in airway smooth muscle in both species [81]. Some agonists are also coupled to G_i , which when activated can inhibit adenylate cyclase activity [99-102]. Relaxant agonists work in both species through the cyclic nucleotides cAMP (formed from ATP by adenylate cyclase) and cGMP (formed from GTP by soluble guanylate cyclase) as well as through Ca^{++} activated K^{+} channels [94,103-106]. Cyclic nucleotides are subsequently inactivated by several isozymes of phosphodiesterase (PDE). PDE III, PDE IV and PDE V have all been identified in airway smooth muscle and in inflammatory cells in both guinea pigs and humans [92,94,107-113]. PDE VII, which has been implicated in regulating human immune responses, has not been studied in guinea pigs.

The immediate hypersensitivity response of human and guinea pig airways to allergen (smooth muscle contraction, mucus secretion, vasodilatation and plasma exudation) is attributable in large part to the actions of histamine and leukotrienes acting on histamine H_1 receptors and leukotriene $cysLT_1$ receptors [20,21,38,82,⁸⁵-87,91,114-124]. Resident mast cells in the airways likely mediate this acute response to allergen challenge. In both species, airway mast cells are activated by the purine adenosine but are insensitive to substance P and contain little, if any, serotonin [121,125-128]. This contrasts with mice and rats. Histamine, LTC_4 and LTD_4 are largely inert in rat and mouse airways and mouse and rat mast cells store and release abundant serotonin [125,129-132]. Also unlike guinea pig and human lung mast cells, rat mast cells are degranulated by substance P [127,133,134]. Dissimilar to human lung mast cells, cross-linking of either IgE or IgG1 receptors activates guinea pig mast cells, whereas only IgE receptors appear to be functional in humans [135-137]. Murine mast cell activation is also largely IgE independent [138-140]. Some but not all studies also indicate that that unlike human mast cells, guinea pig (and mouse) mast cell activation is directly inhibited by corticosteroids [86,141-145].

The primary cell type found in bronchoalveolar lavage of both humans and guinea pigs is the alveolar macrophage. The guinea pig is thought to be more "eosinophilic" at baseline, as evidenced by the higher percentage of eosinophils recovered by lavage of unchallenged guinea pigs relative to that seen in humans and the presence of eosinophils in cross-sections through airways of seemingly healthy, unchallenged guinea pigs [25-27,95,146-148]. This may be due to a constitutive expression of the chemokines eotaxin and CCL5 (RANTES) in the airways of guinea pigs [49,149]. Upon challenge, lymphocytes, monocytes, eosinophils and neutrophils are recruited to the airways of guinea pigs with varying kinetics and numbers depending on the stimulus. Unlike that in human and mouse airways, the precise phenotypes of the monocytes and lymphocytes in the airways of guinea pigs have been poorly characterized [25,26,141,150].

3. Response to experimental challenges

3.1. Agonist mimicry studies

Mediators implicated in the pathogenesis of asthma and COPD produce inflammation and physiological responses in guinea pigs predictive of their role in these human respiratory diseases. Autacoids and neurotransmitters that evoke bronchospasm in human subjects, including the cysteinyl-leukotrienes, histamine, neurokinin A, platelet activating factor (PAF), substance P, bradykinin, endothelin, thromboxane, acetylcholine and other muscarinic receptor agonists all evoke bronchospasm in guinea pigs (Table 1; Fig. 1). In both species, a component of the response to these constricting agonists is reflex in nature [35]. Inflammatory autacoids,

chemokines and cytokines including LTD₄, LTB₄, TNF α , IL-5, IL-8, IL-13, PAF and eotaxin induce inflammation and cellular infiltration into the airway wall and the airspaces of guinea pigs as they are likely to do or have been shown to produce in human subjects [11-13,87, 147,151-175]. Mucus secretion and mucus production can be induced in both species by muscarinic receptor agonists, the cysteinyl-leukotrienes, elastase, TNF α , IL-13 and PAF [34, 38,155,172,175-183].

3.2. Allergen challenge

The acute response to allergen challenge in guinea pigs is nearly identical to that evoked in atopic human subjects. A combination of H₁ and cysLT₁ receptor antagonists essentially abolishes the effects of allergen on lung mechanics [20,21,114-117,120,124]. Other mediators associated with the acute allergic response in humans including bradykinin, PGD₂ and PAF have been recovered or demonstrated (through antagonism or inhibition) acutely following allergen challenge in guinea pigs [114,117,142-144,163,184-190]. Autacoids, chemokines and cytokines shown to be or likely to be formed secondary to the effects of histamine and leukotrienes, including PGE₂, thromboxane, HETEs, IL-5, IL-13, eotaxin, nerve growth factor and bradykinin have also been recovered from the airways or found active based on functional studies in both species [12,13,49,114, 143, 146, 147, 149, 158, 161, 185-187,189-208]. The late phase physiologic response in human subjects is largely inhibited by a combination of histamine and leukotriene receptor antagonists and is associated with an influx of eosinophils into the airway wall and air spaces [124,135,143,155,158]. Comparable results have been reported in studies of the late response in guinea pigs [25-27,86,120, 121, 141, 145, 155, 162, 192, 195-197,201,204]. Therapeutics including steroids and anti-IL-5 prevent the late phase eosinophilia evoked by allergen challenge in both species [141,143,145,154, 158, 162, 192,194-197,204]. An effect on airway nerves following allergen challenge has been documented in both human subjects and in guinea pigs [35,199].

Guinea pigs share with mice the shortcoming of utilizing IgG1 as well as IgE in regulating the immediate hypersensitivity response to allergen [137-140]. Otherwise, guinea pigs are superior to mice and rats for modeling both the acute and late phase physiologic response to allergen. As mentioned above, the mediators of the acute response in humans and guinea pigs are histamine and the cysteinylleukotrienes. Histamine, LTC₄ and LTD₄ have no direct effects on murine or rat airway smooth muscle [129-131]. Murine and rat mast cells store and release 5-HT as their primary biogenic amine and 5-HT is the primary mediator of the acute response to allergen in these rodents [125,132]. Human and guinea pig mast cells store little, if any, 5-HT, and 5-HT is without effect on human airway smooth muscle [21,125,126]. The potent neural activator and vasoconstrictor serotonin, with both ionotropic and metabotropic receptors, likely has very different actions than the vasodilator histamine, which acts only on metabotropic receptors.

3.3. Cigarette smoke

As the lifespan of a guinea pig (2–3 years) is shorter in duration than the number of smoking pack years of the vast majority of patients with COPD, it is difficult to equate typical cigarette smoke exposure protocols in guinea pigs with the human condition of COPD. But the pathology of cigarette smoke exposure is similar in guinea pigs and humans. Features of the cigarette smoke-exposed lung of guinea pigs similar to that seen in COPD include an acute neutrophilia, a slowly developing but sustained recruitment of monocytes, alveolar destruction, mucus secretion, increased epithelial permeability, altered reflexes and pulmonary hypertension [209-219].

3.4. Viral infections

Guinea pigs are susceptible to infections by respiratory syncytial virus, influenza virus, parainfluenza virus and adenovirus, each of which having been associated with or used to model exacerbations of asthma and COPD [72,220-230]. In both humans and in guinea pigs, these infections are characterized by inflammatory cell recruitment (neutrophils, lymphocytes and eosinophils), bronchiolitis, enhanced cytokine gene expression, enhanced responsiveness to experimental challenge (cigarette smoke exposure, allergic inflammation) and airways hyperresponsiveness. These viral infections are particularly effective at altering nerve function in the airways of guinea pigs [72,231]. This may also be relevant to the pathogenesis of viral infections in human subjects [225,232].

3.5. Ozone

Ozone challenge has been used in human subjects and in animals to evoke an inflammatory response in the airways. Ozone produces an acute inflammatory response in the airways of guinea pigs along with a short-lived hyperresponsiveness to bronchoconstricting stimuli [233-235]. The acute inflammatory response to ozone is similar in human subjects and in guinea pigs, with an immediate influx of neutrophils and a coincident vascular leak as measured by serum constituents (urea, albumin) in bronchoalveolar lavage fluid [234,236-238]. More recent studies have documented an eosinophilia in the airways of guinea pigs and asthmatic subjects following ozone exposure [148,238-240]. Prostanoids may mediate some of the acute physiologic effects of ozone exposure, as they have been recovered in lavage and serum of ozone exposed guinea pigs and human subjects [241-243]. Ozone also acts in part on airway nerves to initiate airways hyperresponsiveness in human subjects and in guinea pigs [148, 234,244]. Comparable inflammatory and physiologic effects in humans and in guinea pigs have been reported in studies with the occupational toxin toluene diisocyanate [245-249].

4. Pharmacology and therapeutic interventions

4.1. Receptor pharmacology

With few exceptions, the pharmacology of metabotropic and ionotropic receptors relevant to asthma and COPD is nearly identical in human and guinea pig airway preparations. Even more complex regulators of cell function related to neuronal and mast cell activation, second messenger formation and metabolism, and cytokine gene expression are nearly identical in these two species [20,21,35,37,73-77,83,86,94-97,101-103,108,109,143,145,-194]. The rank order of potency for airway smooth muscle contractile and relaxant agonists is nearly identical in guinea pigs and humans. Similarly, the rank order of potency of antagonists for these various receptors in guinea pigs predicts with nearly perfect fidelity the rank order of potency of these antagonists in the human airway (Table 1, Fig. 1).

Exceptions to the predictive value of guinea pig airway receptor pharmacology for that of humans include the expression of a cysLT₂-like leukotriene receptor on guinea pig airway smooth muscle but not on human airway smooth muscle, and the expression of neurokinin₁ receptors and contractile prostanoid EP₁ receptors on the airway smooth muscle in guinea pigs but not in human airway smooth muscle [19,55,57,250-253]. Serotonin also contracts guinea pig (and mouse and rat) airway smooth muscle but not that of humans [21]. In human pulmonary vessels, a cysLT₂-like receptor regulates several vascular endothelial functions [254]. This is not observed in guinea pig pulmonary vessels, where most effects are attributable to a homogeneous population of cysLT₁ receptors [255]. Despite these exceptions, the utility of guinea pig airway preparations for pharmacological analyses relevant to asthma and COPD pathogenesis and therapy far exceeds that of mice or rats. Many contractile agonists considered relevant to the pathogenesis of asthma have no effect on murine (or rat) airway smooth muscle or are bronchodilators in mice and rats [21,79,80,129-131,256-258]. As mentioned previously,

mouse and rat airway smooth muscle has no direct relaxant innervation [79,80]. Moreover, the beta adrenoceptors mediating airway smooth muscle relaxation in mice are the β_1 subtype, not the β_2 subtype as it is entirely in human and primarily in guinea pig airways [259]. Receptor agonist and antagonist potency and efficacy in rats and mice are also known to differ from that in humans, prompting some researchers to develop transgenic mice expressing human receptors [260-270]. This renders the mouse of limited utility in preclinical studies of many classes of therapeutic interventions designed for treating asthma and COPD.

4.2. Therapeutic interventions in experimental challenges

The guinea pig has had excellent predictive value for the effects of therapeutics used in the treatment of asthma and COPD. This includes therapeutics with established efficacy in human disease (β_2 adrenoceptor agonists, anticholinergics, PDE inhibitors, steroids, cysLT_1 receptor antagonists, 5-lipoxygenase/five lipoxygenase activating protein (FLAP) inhibitors) and therapeutics with modest or no beneficial effects in human disease, including anti-IL-5 antibodies, anti-TNF antibodies, and bradykinin, histamine, thromboxane and PAF receptor antagonists [9,10,20,21,35,48,60,65,82,85,87,91,94,95,103,115,119,120,124,141,143,146,147,154,156,158,162,166,191,192,194,197,204,271-278]. A notable exception to this has been the many reports in guinea pigs showing beneficial effects of neurokinin receptor antagonists (see below). Therapeutics contra-indicated in human subjects with asthma and/or COPD including propranolol, ACE inhibitors and cyclooxygenase inhibitors have been shown to similarly exacerbate airway responses in guinea pigs [62,185,186,202,278-285].

The results of the studies in guinea pigs with therapeutics that provided only modest benefit in clinical trials in asthma deserve further discussion, as these studies could be misinterpreted as evidence that the guinea pig and other animal models have had poor predictive value for human disease. This has rarely been the case. Rather, it has been the interpretation of the results that has probably been incorrect. Implicit in many studies carried out in animals for much of the past 20 years has been the assumption that therapeutics that can prevent airways eosinophilia and the modest shifts in airways reactivity produced following one or several (rarely more than three) allergen challenges would be beneficial in asthma. It is now abundantly clear that the presence of eosinophils in the airways is neither sufficient nor necessary for producing asthma. It is also clear that while most asthmatics are allergic, only a minority of allergic patients develop asthma. This makes the typical model of allergic asthma in animals of questionable relevance or similarity to the disease asthma. In this light, studies in guinea pigs were highly predictive of the effects of therapeutics such as anti-IL-5 and PAF receptor antagonists in human subjects. Both IL-5 and PAF are potent eosinophil chemoattractants, and blockers of both reduced airways eosinophilia evoked by allergen challenge.

5. Drawbacks

5.1. Axon reflex

The pioneering work of Lundberg and others showing that activation of the peripheral terminals of capsaicin sensitive nerves in the airways of rats and guinea pigs results in local tachykinin (substance P and neurokinin A) release that subsequently induce many of the characteristic features of asthma (bronchospasm, mucus secretion, vascular engorgement, plasma extravasation, inflammatory cell recruitment) lead to nearly two decades of intensive research into the role of the axon reflex in airways disease [35,286,287]. These studies revealed that tachykinin and capsaicin receptor pharmacology is very similar in human and guinea pig airways, and in both species tachykinins are metabolized in the lung by neutral endopeptidase [253,288-291]. Despite many important and fundamental discoveries relating to afferent nerve excitability, the axon reflex and tachykinin and capsaicin receptor pharmacology, it now seems likely that the axon reflex as it manifests in the lungs of guinea pigs and rats is not present in

the human lung. This perhaps more than any other feature of the airways and lungs of guinea pigs is the greatest drawback to using guinea pigs to model asthma and COPD. The axon reflex seems to be relevant to every response of the guinea pig lung to experimental insults and challenges [190,206,245,248,286,287,292-294]. Given its profound influence over the airways of guinea pigs and the likely limited role of the axon reflex on human airway function, it seems imperative that the actions of peripherally released tachykinins in the airways of guinea pigs be considered and if possible blocked pharmacologically to minimize their effects when modeling asthma and/or COPD.

5.2. Genetics

There are no published reports describing transgenic guinea pigs and given their gestation time (60–75 days) relative to that of mice (20–30 days), their smaller average litter size (4 vs. ≥ 7) and the maximum number of litters/ year (5 vs. 10), it seems unlikely that transgenic strains of guinea pigs will be available in the foreseeable future. Far less of the genome of guinea pigs is currently known relative to that of the mouse as well and this will limit discovery of the function of novel genes in the guinea pig and might limit the ability to monitor expression of known genes in response to experimental interventions. There are also very few strains of guinea pigs available for research. But many genes relevant to the pathogenesis of asthma and COPD have been cloned from guinea pigs (Tables 2 and 3). More recently, inflammation/ infection related microarrays have been developed and validated to some extent in guinea pigs. Immunohistochemical and flow cytometric analyses are also possible in guinea pigs and siRNA gene silencing and adenoviral gene transfection have been used in guinea pigs [295-303].

5.3. Cardiovascular system

Guinea pigs have been domesticated for centuries but were endemic to high altitude locations in South and Central America. Perhaps as an adaptation to this environment, guinea pigs have a remarkably low mean arterial blood pressure (30–50mmHg) relative to that of humans and other commonly used species (80–100mmHg) and are thus far more susceptible to cardiovascular collapse, as in anaphylaxis [2,141,292]. The guinea pig pulmonary circulation also responds only modestly to hypoxia, with a slight elevation in pulmonary arterial pressure relative to the response of humans, pigs or rats [304]. The extensive peptidergic afferent innervation of the bronchial vasculature and the axon reflex also makes the guinea pig particularly susceptible to a profound neurogenic inflammation, with coincident leukocyte recruitment, bronchospasm, vasodilatation, increased airway epithelial and endothelial permeability and mucus secretion. The axon reflex may be precipitated by changes in blood oxygen or carbon dioxide concentrations or pH [293,294,305].

5.4. Airways hyperresponsiveness

The key elements of the lung that regulate airways responsiveness—the airway smooth muscle, the innervation of the airways and lungs, the mast cells and the epithelium—function similarly in humans and in guinea pigs. As with all animals, however, models of human airways hyperresponsiveness in guinea pigs are woefully inadequate [1,306]. Key to quantifying airways hyperresponsiveness are the peculiarities of the forced expiratory maneuver [307]. There is no comparable respiratory maneuver in guinea pigs. Relative to other species, the guinea pig is considered “hyperresponsive” even at baseline, given their tendency to constrict excessively, leading to airway closure, gas trapping and ultimately collapse [308]. In vitro studies of guinea pig airway smooth muscle responsiveness do not support the notion that the guinea pig is uniquely responsive to contractile agonists. On the contrary, guinea pig airway smooth muscle closely resembles human airway smooth muscle (Fig. 1, Table 1). This latter observation is not surprising, given that smooth muscle from asthmatics studied in vitro show

few if any signs of “hyperresponsiveness” [1]. Rather, the hyperresponsiveness in asthma and apparently in guinea pigs is only manifest within the context of the intact lung.

6. Conclusions

Guinea pigs offer many advantages in preclinical studies relevant to asthma and COPD. Receptor pharmacology in guinea pigs closely resembles that of the human airway. The airway response to allergen challenge is very similar to that of the human airways and very different from that of the mouse. The autonomic innervation of guinea pig airways is also very similar to that in humans. The responses to experimental interventions in guinea pigs parallel the responses seen in human subjects. These advantages are more significant than the several disadvantages, which include a prominent axon reflex in the airways, limited prospects for transgenic animals and few sufficiently different strains for comparative studies. As with all animal models, guinea pig models of airways hyperresponsiveness are inadequate. But the key elements of the airway that determine airways reactivity function similarly in humans and in guinea pigs.

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Fig. 1.

Potency estimates (pD2) and potency correlations for airway smooth muscle contractile and relaxant agonists in humans, guinea pigs and mice and the relationship between estimated potencies of receptor antagonists in guinea pig airways to that reported in studies using human airways. The potencies of contractile (panel A) and relaxant (panel C) agonists in guinea pigs are highly predictive of their potencies and efficacies (not shown) in human airways. This contrasts with murine airways (panel B), in which many contractile agonists implicated in asthma and COPD (LTC₄, LTD₄, histamine, NKA, PGD₂) do not contract murine airway smooth muscle (for the purposes of graphic illustration, these agonists were given pD2 values of 4 in mice). Receptor antagonist potencies (pA2 and/or pKB values) in guinea pigs were also highly predictive of their potency in human airways. Data from studies of M₃ (■), cysLT₁, (▲), NK₂, (▼), TP (◇) and ET_B (○) receptor antagonists are depicted. See Table 1 for more details.

Fig. 2.

Methacholine-induced gas trapping in guinea pigs and hamsters and various strains of mice and rats. Data are the mean $\pm$ SEM of 4–6 experiments and expressed as a percentage of the excised lung gas volume (ELGV) in unchallenged (control) animals of similar weight, sex, species and strain. Relative to other small mammalian species, guinea pigs are far more susceptible to gas trapping during bronchospasm. Figure modified from [308].

Table 1Receptor antagonist pA₂/pK_b values at guinea pig and human receptors

Receptor subtype	Guinea pig	Human
<i>Muscarinic M3</i>		
Atropine	9.0, 9.5	9.1
Ipratropium	9.9, 9.6	9.3
Methoctramine	5.6, 5.6	5.3
Pirenzepine	6.7, 7.0	6.8
Tiotropium	9.97	9.99
<i>Leukotriene cysLT₁</i>		
ICI 198615	10.1	9.8
SKF 104353	8.9	8.4
MK-0476	9.3	9.1
MK 571	9.4, 8.0	8.5
ONO-1078	10.4	8.3
FPL55712	7.5, 6.4	6.0, 6.5
<i>Neurokinin₂</i>		
SR 48968	9.1, 9.2, 9.4	9.0, 9.5, 9.5
SCH 206272	7.7	8.2
MEN10376	6.5	6.2, 6.3
GR159897	8.2	8.6
MDL103392	7.0	7.2
<i>Prostanoid TP</i>		
BAY u3405	8.1	9.0, 9.4
AH 6809	5.3	5.5
ICI 192605	10.0	9.5
GR 32191	9.5	8.4
AA2414	7.7	7.6
<i>β₂ Adrenoceptor</i>		
Atenolol	5.7	5.3
ICI118551	8.2, 8.8, 9.2	9.1
Propranolol	8.6, 9.0	9.3, 9.4
<i>Endothelin ETB</i>		
BQ123	<5	<5
SB209670	6.1	6.1
Ro470203	5.6	5.4
PD145065	6.8	7.7

Data obtained from published reports in the literature [20,63,67,251,309-334]. When multiple studies reported pA₂ or pK_b values, all are presented. Similar potencies of PAF and NK1 receptors in humans and guinea pigs have also been reported [253,267,274,276]

Table 2

Cloned and characterized guinea pig genes: autacoid and nerve related genes relevant to asthma and COPD

	Guinea pig	Human homolog
<i>Autacoid-related Genes</i>		
Histamine H ₁ receptor	[335,336]	[337]
Histamine H ₃ receptor	[338]	[339]
Histamine H ₄ receptor	[340]	[341]
Cyclooxygenase-2	[342]	[343]
Prostanoid CRTH2 receptor	[344]	[345]
PAF receptor	[346]	[347]
PAF acetyl hydrolase	[348]	[349]
Leukotriene BLT receptor	[350,351]	[352]
Plasma prekallikrein	[353]	[354]
Bradykinin B ₂ receptor	[355]	[268]
Complement C3a receptor	[356]	[357]
Complement C3b receptor	[358]	[359]
Complement C5a receptor	[360]	[361]
Adenosine A ₁ receptor	[362]	[363]
Adenosine A ₂ receptor	[364]	[365]
5-HT ₃ receptor	[366]	[367,368]
5-HT transporter	[369]	[370]
Inducible NO synthase	[371]	[372]
<i>Nerve-related genes</i>		
Nerve growth factor	[373]	[374]
β_2 -Adrenoceptor	[375]	[376]
VPAC2 receptor	[377]	[378]
NK ₁ receptor	[379]	[380]
NK ₂ receptor	[324]	[381]
NK ₃ receptor	[382]	[383]
TRPV1	[290]	[291]
Preproenkephalin	[384]	[385]
μ -opioid receptor	[386]	[387]
Sigma ₁ receptor	[388]	[389]

The lists of cloned guinea pig genes relevant to asthma and COPD that are summarized in Tables 2 and 3 were generated from PubMed journal and nucleotide databases. Unpublished sequences of many more guinea pig genes relevant to asthma and COPD are reported on the nucleotide database, including the genes for all 5 muscarinic receptors, both cysteinyl-leukotriene receptors, 4 NPY/peptide YY/pancreatic polypeptide receptors, 3 preprotachykinin genes, and various ion pumps and exchangers and sodium, potassium and chloride channels

Table 3

Cloned and characterized guinea pig genes: immunity related and other miscellaneous genes relevant to asthma and COPD

	Guinea pig	Human homolog
<i>Cytokine and lymphocyte related genes</i>		
Interferon gamma	[390]	[391]
Interleukin-2	[392]	[393]
Interleukin-5	[394,395]	[396]
Interleukin-5 receptor	[397]	[398]
Interleukin-10	[392]	[399]
Interleukin-12	[400]	[401]
Tumor necrosis factor	[174]	[402]
CD1	[403]	[404]
T-cell receptor	[405]	[406]
CD8 α + β	[407]	[408,409]
FcGammaRI, RII, RIII	[410,411]	[412-414]
<i>Chemokine, neutrophil and eosinophil-related genes</i>		
Eotaxin	[12,13]	[415]
Interleukin-8	[416]	[417]
CCL5 (RANTES)	[418,419]	[420]
MCP-1	[421]	[422]
GRO	[423]	[424]
Interleukin-8 receptor(s)	[425,426]	[427]
CCR3 receptor	[169]	[428]
CCR4 receptor	[429]	[430]
Major basic protein	[431]	[432]
<i>Miscellaneous genes relevant to airways disease</i>		
VEGF	[5]	[14]
TGF- β	[392]	[433]
Surfactant protein-A	[434]	[435]
Alpha ₁ -antitrypsin	[436]	[437]
MUC2	[438]	[439]
MUC5AC	[438]	[440]
Glucocorticoid receptor	[441]	[442]
TIMP-2	[443]	[444]
PPAR gamma	[445]	[446]

Unpublished sequences of other immune-related genes relevant to asthma and COPD that are reported on the PubMed nucleotide database include various integrins and CD markers for immune cells as well as MCP-3