International Journal of
Molecular Sciences

MDPI

Review

Update on the Role of β2AR and TRPV1 in Respiratory Diseases

Sara Manti [1,†], Antonella Gambadauro [1,*,†], Francesca Galletta [1], Paolo Ruggeri [2,*] and Giovanni Piedimonte [3]

[1] Pediatric Unit, Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina, Via Consolare Valeria 1, 98124 Messina, Italy; smanti@unime.it (S.M.); francygall.92@gmail.com (F.G.)
[2] Pulmonology Unit, Department of Biomedical and Dental Sciences, University of Messina, Via Consolare Valeria 1, 98124 Messina, Italy
[3] Office for Research and Departments of Pediatrics, Biochemistry, and Molecular Biology, Tulane University, New Orleans, LA 70112, USA; gpiedimonte@tulane.edu
* Correspondence: gambadauroa92@gmail.com (A.G.); paolo.ruggeri@unime.it (P.R.)
† These authors contributed equally to the manuscript.

Abstract: Respiratory diseases (RDs) constitute a common public health problem both in industrialized and developing countries. The comprehension of the pathophysiological mechanisms underlying these conditions and the development of new therapeutic strategies are critical for improving the quality of life of affected patients. β2-adrenergic receptor (β2AR) and transient receptor potential vanilloid 1 (TRPV1) are both involved in physiological responses in the airways. β2AR is implicated in bronchodilation, mucociliary clearance, and anti-inflammatory effects, while TRPV1 is involved in the mediation of pain and cough reflexes. In RDs, such as respiratory infections, asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, the concentration and expression of these receptors can be altered, leading to significant consequences. In this review, we provided an update on the literature about the role of β2AR and TRPV1 in these conditions. We reported how the diminished or defective expression of β2AR during viral infections or prolonged therapy with β2-agonists can increase the severity of these pathologies and impact the prognosis. Conversely, the role of TRPV1 was pivotal in neuroinflammation, and its modulation could lead to innovative treatment strategies in specific patients. We indicate future perspectives and potential personalized treatments in RDs through a comprehensive analysis of the roles of these receptors in the physiological and pathological mechanisms of these pathologies.

Keywords: asthma; bronchiolitis; β2AR; cystic fibrosis; COPD; respiratory diseases; RSV; TRPV1

check for updates

Citation: Manti, S.; Gambadauro, A.; Galletta, F.; Ruggeri, P.; Piedimonte, G. Update on the Role of β2AR and TRPV1 in Respiratory Diseases. *Int. J. Mol. Sci.* **2024**, *25*, 10234. https://doi.org/10.3390/ijms251910234

Academic Editors: Mohammad Shahidullah and Paul James Donaldson

Received: 24 August 2024
Revised: 16 September 2024
Accepted: 23 September 2024
Published: 24 September 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Respiratory diseases (RDs) are conditions affecting the lungs and the airways. RDs constitute a challenge to the public health systems in industrialized and developing countries due to their frequency and economic burden. In 2019, chronic RDs affected 454.6 million people and represented the third main cause of mortality globally [1]. Asthma and chronic obstructive pulmonary disease (COPD) are the principal culprits of chronic RDs, and numerous risk factors (e.g., smoking, air pollution, and high body mass index) are linked to these conditions [1].

RDs involve several cellular structures, from airway epithelial cells to immune cells. Their therapeutic management differs according to the specific pathophysiology of each disease. Membrane proteins and ion channels have a key role in their respiratory physiology and pathophysiology [2]. β2-adrenergic receptor (β2AR) is extensively expressed in the upper and lower respiratory tract, where it is responsible for several functions, such as bronchodilation, vasodilatation, mucociliary clearance, and anti-inflammatory actions [3]. Transient receptor potential vanilloid 1 (TRPV1) is prominently expressed in sensory nerves

and non-neurological sites, such as the airway epithelium, where it is involved in pain sensation and inflammatory responses.

The purpose of this review was to explore the current understanding of the contributions of β2AR and TRPV1 in lung pathophysiology. We further discuss potential areas for future research to better assess the impact of these transmembrane proteins in RDs. By combining the key terms "TRPV1" OR "Transient receptor potential vanilloid 1" OR "β2AR" OR "β2-adrenergic receptor" AND "respiratory diseases" OR "asthma" OR "wheezing" OR "respiratory infections" OR "COPD" OR "cystic fibrosis" in a computerized search of PubMed, we provide a complete overview of the current literature, based on a critical evaluation without standardized methodologies or statistical analyses.

2. β2AR and TRPV1: Structure and Function

2.1. β2AR

βARs are transmembrane glycoprotein structures belonging to the superfamily of G protein-coupled receptors (GPCRs) [4,5]. βARs are divided into three subtypes: β1ARs are mostly distributed on cardiomyocytes; β2ARs are mainly expressed on airway smooth muscles (ASMs), cardiomyocytes, uterine muscles, alveolar type I and II cells, mast cells, mucous glands, epithelial cells, vascular endothelium, eosinophils, lymphocytes, and skeletal muscles; β3ARs are principally involved in lipid metabolism in the adipose tissue [6–9]. Concerning β2ARs, their distribution in human lungs is prevalent in distal airways, especially in the alveolar walls [10,11]. The gene encoding for β2AR (*ADRβ2*) (MIM#109690) is located on chromosome 5q32 and contains only one exon [12]. This receptor mediates several physiological airway functions, including bronchodilation, vasodilatation, mucociliary clearance, and numerous anti-inflammatory effects (e.g., mast cell stabilization and cytokine production) [3].

The structure of β2AR consists of a polypeptide chain with seven transmembrane α-helix regions and an eighth helix arranged parallel to the cytoplasmatic surface of the plasma membrane [13] (Figure 1). There are three extracellular loops, with an amino (N)-terminus, and three intracellular loops, with a carboxy (C)-terminus with serine and threonine phosphorylation sites [14]. Most of the functions of the transmembrane β2-receptors are mediated by stimulatory G (Gs)-protein, which consists of α, β, and γ subunits [15]. β2AR exists in two different states, activated and inactivated, which are in balance. This receptor is activated by binding catecholamines (e.g., epinephrine) or other agonists. The ligand binding induces the receptor coupling with inactive guanosine diphosphate (GDP)-bound G protein complex and a subsequent guanosine triphosphate (GTP) exchange activates the G proteins-receptor complex [16]. The activation is provided by the binding of the α-subunit of the Gs protein to a molecule of GTP; conversely, it is inactivated when GTP is replaced by GDP, inducing dissociation of the α-subunit of Gs. The α-subunit activates the enzyme adenylyl cyclase (AC), which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [7]. In the airways, cAMP induces ASM relaxation by both activating protein kinase A (PKA), which phosphorylates various regulatory proteins involved in the muscle tone and reducing intracellular calcium ion (Ca^{2+}) concentration, which leads to the relaxation of ASM [7]. The role of PKA in inducing ASM relaxation has never been straightforwardly demonstrated, but it is assumed to lead to either a reduction in intracellular Ca^{2+} concentration or lower Ca^{2+} cellular sensitivity, which both impair ASM contraction [17]. β2-agonists and other cAMP-raising agents modulate Ca^{2+} intracellular homeostasis in ASM, resulting in a dynamic process that alternates between Ca^{2+} influx and efflux. A key element of this homeostasis is the Ca^{2+} removal from the cytosol, which is mainly facilitated by the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) transporter. The uptake of intracellular Ca^{2+} through the SERCA transporters facilitates ASM relaxation. Thus, bronchodilation results from cAMP accumulation after the β2AR activation [17]. The stimulation of cholinergic muscarinic receptors, coupled with inhibitory G (Gi)- protein, decreases the cAMP levels, leading to ASM contraction and bronchoconstriction [18]. ASM relaxation can also be induced by cAMP-independent

mechanisms involving the direct interaction between Gs and potassium ion (K^+) channels [19]. Of these channels, the most critical seem to be the big-conductance Ca^{2+}-activated K^+ channels (BK_{Ca}), which are abundant in ASM and a substrate for PKA [20,21]. Beyond its role in ASMs, the β2AR-PKA-cAMP pathway can interfere with the airway epithelial cells by accelerating mucociliary clearance and the polymorphonuclear leukocytes (especially eosinophils and neutrophils) by increasing intracellular cAMP levels and attenuating oxidative burst, resulting in anti-inflammatory effects [22,23].

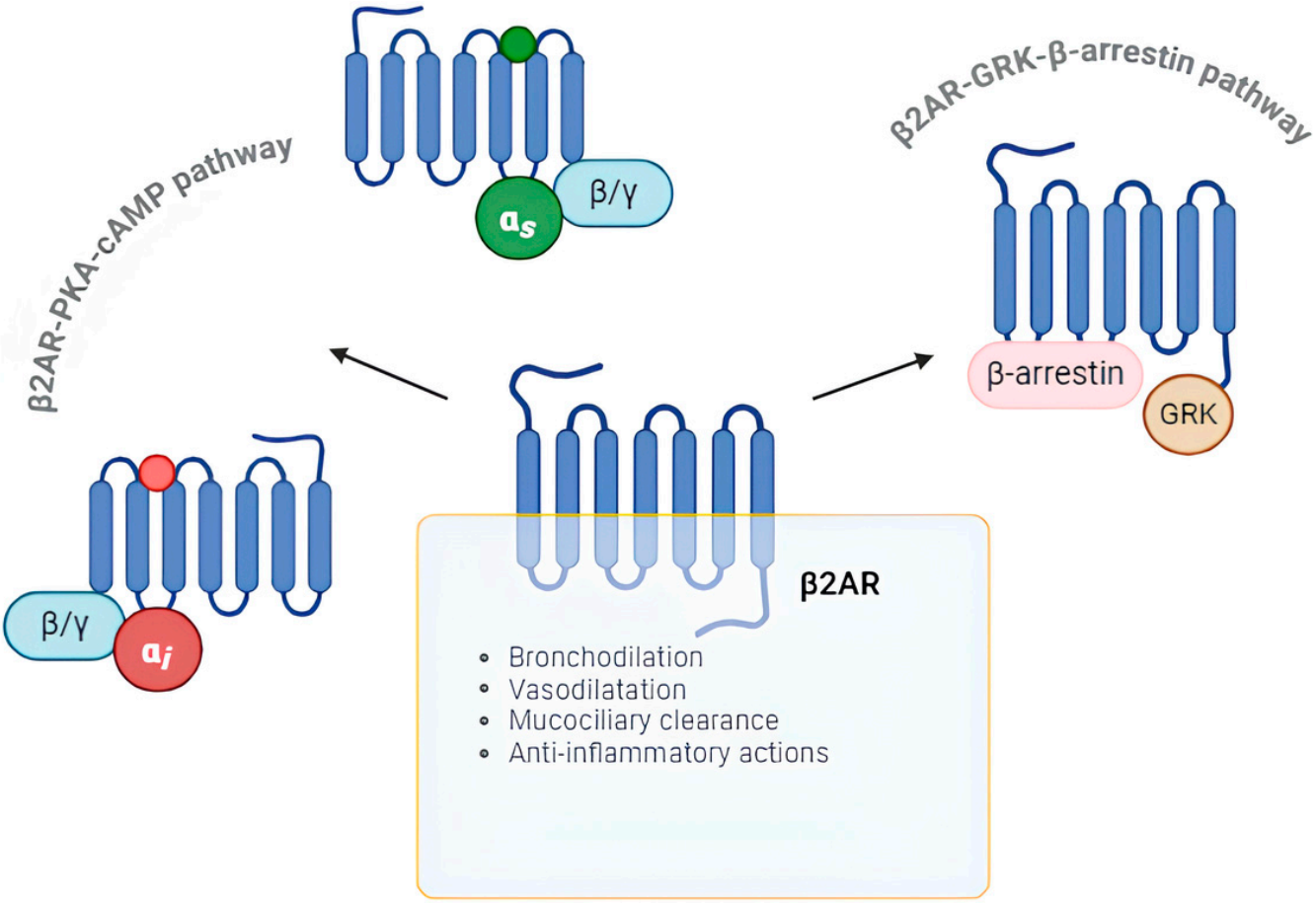

Figure 1. β2AR is a transmembrane glycoprotein belonging to the superfamily of G protein-coupled receptors (GPCRs) [4,13]. Most of the functions of this receptor are mediated by two pivotal pathways: the β2AR-PKA-cAMP pathway and the β2AR-GRK-β-arrestin pathway. The first one requires the participation of stimulatory or inhibitory G protein (α, β, and γ subunits) [15]. The stimulatory α-subunit activates the adenylyl cyclase (AC), which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [7]. In the second pathway, intracellular cAMP levels activate the G protein-coupled receptor kinase (GRK), which phosphorylates the receptor, leading to the recruitment and coupling of β-arrestin [24]. β-arrestin participates in the desensitization, internalization, and degradation of β2AR [25,26]. The main physiological airway activities of β2AR include bronchodilation, vasodilatation, mucociliary clearance, and anti-inflammatory actions (e.g., mast cell stabilization and cytokine production) [3,17,22,23].

The balance between activated and inactivated forms of β2ARs depends on intracellular cAMP levels. The cAMP accumulation stimulates the phosphorylation of the C-terminus of β2ARs by G protein-coupled receptor kinase (GRK), leading to the dissociation of the α-subunit of the Gs protein and the recruitment and coupling of β-arrestins [24]. β-arrestins are scaffold proteins that contribute to the desensitization, internalization, and degradation of β2ARs, mediating diverse signaling pathways, including extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-kB) [25,26]. By activating the ERK and p38 MAPK pathways, these proteins can induce the following: 1. the transcription and expression of the mucin-5AC (MUC5AC) gene, increasing the airway mucus secretion; 2. the mitosis of ASM cells; 3. the expression of chemokines in eosinophils [26,27]. Furthermore, β-arrestins can modulate the activation of the NF-kB pathway, which regulates the expression of chemokines and the polarization of macrophages [24,28]. Thus, the β2AR-GRK-β-arrestin pathway is implicated in inflammatory responses in the airways.

The two kinases, GRK and PKA, phosphorylate the activated form of β2AR, inducing its desensitization. The desensitized β2AR is then internalized into endosomes, dephosphorylated, and reprocessed to the plasma membrane as a resensitized form, a process that is facilitated by the activity of a specific protein phosphatase [29,30].

2.2. TRPV1

TRPV1 is a Ca^{2+}-permeable, non-selective cation channel included in the TRPV subfamily (TRPV1–6), which is part of the TRP ion channel family, widely distributed in the cellular membranes in humans and mammals [31]. TRPV1 is expressed in sensory nerves, and it is mainly located in non-myelinated C-fibers and a small subset of thin myelinated Aδ fibers. TRPV1-positive neural fibers innervate the respiratory system, from the upper (nose, larynx, and trachea) to lower airways (alveoli, ASM, and blood vessels) [32,33]. TRPV1 density is highest in the upper airway and gradually declines in the lower tracts [34]. Furthermore, this receptor is expressed in specific sites (e.g., vascular endothelium, respiratory system, skin, and muscle) and cellular groups (e.g., inflammatory and immune cells and adipocytes) [33]. The gene encoding for this receptor (*TRPV1*) (MIM#602076) is located on chromosome 17p13.2 and contains nineteen exons [35].

Structurally, TRPV1 is a multimeric protein with a four-fold symmetry axis forming a central ion channel enclosed by protein subunits. Every subunit has an N-terminus (with six ankyrin repeat domains), a transmembrane domain formed by six transmembrane helices (S1-S6), and a C-terminus (Figure 2). The S1-S6 transmembrane helices represent voltage-sensor-like domains, and at the N-terminus, there are ATP- and calmodulin-binding sites [36]. This channel can be stimulated by various endogenous and exogenous stimuli, including capsaicin, elevated temperature (>43 °C), protons, pro-inflammatory cytokines, and toxins (e.g., lipopolysaccharide) [37,38]. Once activated, a rearrangement takes place in the S5-S6 outside the pore-loop region of the central ion channel, while the external voltage-sensor-like domains S1-S6 remain unchanged [39,40]. Capsaicin causes burning pain by selectively activating sensory nerves. The capsaicin-binding site is intracellular on TRPV1 receptors, and the interaction induces the influx of Ca^{2+} and sodium ions (Na+), depolarizing the cell [40]. Moreover, TRPV1 is also a sensor of high temperature and acidic extracellular pH (i.e., protons). The reaching of the transition temperature (i.e., ~42 °C) induces the channel opening thanks to the thermosensitive property localized in the S1–S4 domains [41,42].

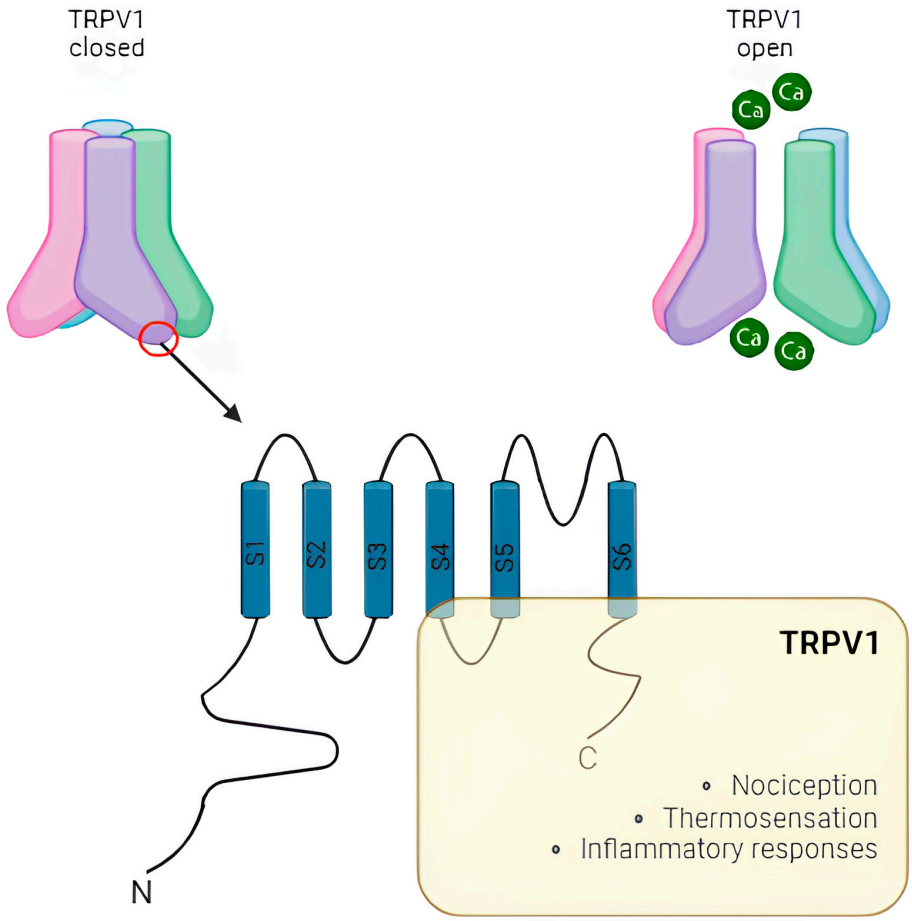

Figure 2. TRPV1 is a Ca^{2+}-permeable channel belonging to the TRP ion channel family [31]. It is a multimeric protein with a four-fold symmetric axis forming a central ion channel surrounded by protein subunits. Every subunit is constituted by an N-terminus, a transmembrane domain formed by six transmembrane helices (S1–S6), and a C-terminus [36]. This channel can be stimulated by various endogenous and exogenous stimuli, including capsaicin, elevated temperature (>43 °C), protons, pro-inflammatory cytokines, and toxins (e.g., lipopolysaccharide) [37,38]. It participates in nociception, thermosensation and inflammatory response [33,34,40].

The aminoacidic structure of TRPV1 contains many phosphorylation sites for protein kinase C (PKC), PKA, and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), implicating regulatory modulation by these kinases [43–45]. Direct phosphorylation of TRPV1 at specific intracellular sites by PKA and PKC increases the receptor sensitivity [46,47]. However, the specific phosphorylation by PKA of residues Ser116 and Thr370 in the N-terminus is associated with desensitization [45]. Thus, the balance between phosphorylation and dephosphorylation is pivotal for TRPV1 activity [48]. Phospholipase C (PLC) influences TRPV1 activity by hydrolyzing the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). When PIP2 is coupled to TRPV1, it promotes receptor inhibition, while its hydrolysis induces receptor activation. Both IP3 and DAG stimulate PKC, increasing TRPV1 phosphorylation and activation [46,49].

3. β2AR and TRPV1 in Respiratory Diseases

3.1. Respiratory Infections

Respiratory infections are a common public health problem, especially in infants and children [50,51]. They are typically caused by seasonal viruses, mainly affecting the upper respiratory tract (URT) [52]. However, in infants and children, the involvement of the lower respiratory tract (LRT) is not rare and is frequently caused by *Respiratory Syncytial Virus*

(RSV) and *Human Rhinovirus* (HRV) [53–55]. The impact of these two viruses on β2AR and TRPV1 has attracted attention, especially in patients with bronchiolitis.

β2-agonists, such as salbutamol, are not recommended in bronchiolitis management because they do not improve oxygen saturation, duration of symptoms or length of stay in the hospital [56,57]. The reason for their lack of efficacy was determined in previous studies. Moore et al. reported that RSV infection reduced β2AR density in infected cells by 32% compared with the controls (mock-infected cells). Moreover, RSV attenuated isoproterenol (ISO)-induced cAMP formation in a time- and concentration-dependent manner. These two modifications on β2AR density and ISO-induced cAMP formation were mainly expressed in individuals homozygous for the Arg16Gln27 haplotype, suggesting a potentially different pattern severity of RSV infection in patients with specific haplotypes [58]. RSV infection may induce β2AR desensitization either directly by the G protein-coupled receptor kinase 2 (GRK2) or protein kinase C zeta type (PKCζ) phosphorylation of the receptor or indirectly by the sequestration of the α-subunit of Gs [59]. In a mouse model, the ligation of CXCR2 (or interleukin 8 receptor β, IL8Rβ) by the chemokine named keratinocyte cytokine (KC), the murine homolog of human CXCL8 (or IL8) released in response to RSV infection, induced the activation of GRK2 or PKCζ, with the subsequent phosphorylation and desensitization of β2AR [60]. Thus, these findings emphasized how the RSV infection may decrease the response to β2-agonists by reducing the expression and the sensitization of β2AR, blocking this receptor in a phosphorylated and desensitized form. More recently, Harford et al. confirmed the prevalence of β2AR phosphorylated form due to RSV infection [61]. However, they demonstrated that RSV simultaneously caused more effects, such as a proteasome-mediated cleavage and degradation of β2AR (which explains the low density of the receptor on the plasma membranes) and a β2AR ligand-independent activation of AC. This non-canonical activation of AC results in impaired cAMP synthesis and increased levels of intracellular Ca^{2+}, generating a pro-contractile phenotype in RSV-infected ASM cells [61]. It could be supposed that RSV infection activates the cAMP-PKA axis in a non-canonical and ligand-independent way, leading to ASM contraction and bronchoconstriction. Furthermore, the non-responsivity to β2-agonists could be due to the β2AR's low density and high rate of their desensitized forms in the RSV-infected airways.

While β2AR density decreases in the airways during RSV infection, TRPV1 levels increase in the epithelial and neuronal cells [62,63]. Interestingly, the upregulation in TRPV1 expression seems independent of viral replication and related to virus-induced soluble factors, such as IL8 [62]. TRPV1 directly increases IL8 levels by activating the c-Jun N-terminal kinase 1 (JNK1)-dependent and JNK1-independent signaling pathways through the transforming growth factor-activated kinase 1 (TAK1) phosphorylation. The stimulation of these pathways generates NF-kB positive feedback control of JNK1/2 phosphorylation, which, in turn, increases the levels of IL8 [62]. This cytokine, along with other mediators, may facilitate the interaction of viral proteins with cell surface toll-like receptors (TLRs), enhancing the TRPV1 expression [62]. TRPV1 is implicated in regulating irritant-induced airway responses, particularly in cough [64]. During RSV infection, TRPV1 upregulation, together with the overexpression of nerve growth factor (NGF) and neurokinin 1 (NK1) receptor in the lungs, induces increased neuroinflammation, which may contribute to long-lasting airway inflammation and hyperreactivity [34,65,66]. In the acute phase, RSV stimulates the TRPV1-dependent Ca^{2+} influx in bronchial epithelial cells, which are responsible for augmented mucus production, disrupted barrier permeability, and enhanced bronchoconstriction, especially in asthmatic children [67].

In summary, during RSV infection, the functional impairment of β2AR and overexpression of TRPV1 facilitate bronchoconstriction and the persistence of inflammation in affected patients. Analyzing the cytokine profiles involved in regulating these receptors could be useful in identifying future target treatments. Interestingly, RSV enhances the expression of IL8, which is involved in β2AR desensitization and TRPV1 upregulation [60,62]. Authors showed the presence of specific haplotypes or genetic variants related to disease severity

phenotypes [58,68]. In the future, a personalized approach could improve the management of this condition.

HRV infects airway epithelial cells by binding to ICAM-1 [69]. In vitro studies showed that β2-agonists (such as salbutamol and terbutaline) reduce ICAM-1 expression, suggesting their use could decrease HRV entry and spread in the airways [70,71]. Despite these promising results, Bochkov et al. reported that the pre-treatment with a combination of budesonide and formoterol 24 h before HRV incubation did not affect viral replication in bronchial epithelial cells [72]. Interestingly, HRV induces β2AR desensitization in human ASM cells, probably thanks to autocrine prostaglandin (PG) production [73]. Recent studies have shown how respiratory viral infections can reduce the efficacy of β2-agonists (e.g., salmeterol and formoterol) during asthma and COPD exacerbations thanks to the activation of PGE2, an eicosanoid produced by cyclooxygenase (COX) against infection [74,75]. This reduction of the medication function is related to β2AR desensitization in ASM cells due to the PGE2 interaction with the prostanoid E 2 (EP2) receptor [75]. Moreover, PGE2 produced in response to inflammation seems to increase nerve fiber sensitivity, TRPV1 activity, and cough stimulation [76]. It has been demonstrated that administering an EP3 receptor antagonist inhibits PGE2-induced cough in a guinea pig model [76]. The use of selective EP2 or EP3 antagonists may offer a potential treatment option for respiratory infectious diseases in the future, especially in patients with asthma and COPD.

3.2. Asthma

Asthma is a complex and heterogeneous disease characterized by chronic inflammation of the airways [77]. The development of asthma is multifactorial, and although the causal mechanisms are not entirely understood, it is well-known that genetic factors, atopy, and early respiratory infections play a pivotal role in its pathogenesis [78,79].

Early-life or prenatal respiratory viral infections, specifically HRV and RSV, are associated with asthma onset [80,81]. Sigurs et al. demonstrated that 32% of infants hospitalized with severe RSV infection subsequently developed allergen sensitization by 3 years of age, compared with only 9% of age- and sex-matched controls [80]. A study on a three-dimensional human lung organoid (HLO) model showed how prenatal RSV infection may modify the architecture and cytological profile of the fetal lung by reducing the population of ciliated cells, increasing the proliferation of reactive club cells, and inducing the disruption of the actin cytoskeleton. Moreover, RSV also changes the expression of key receptors, inducing the presence of higher levels of phosphorylated β2AR and TRPV1 in the mesenchymal and epithelial compartments [63]. These modifications increase the predisposition to developing airway inflammation and hyperreactivity, both present in wheezing and asthma. Bronchial hyperreactivity may also be the consequence of the development of a pro-contractile phenotype related to increased cytosolic free Ca^{2+} in children with viral wheezing [61] and asthma [82]. The overexpression of TRPV1 channels and the intracellular Ca^{2+} levels in the bronchial epithelium are higher in asthmatic children compared with age-matched healthy controls and asthmatic adults [82]. Thus, viral infection affects TRPV1 expression regardless of the asthma status in children but not in adults [67,82].

The role of *TRPV1* and *ADRβ2* genetic variants was widely studied in past research, but contrasting results in different populations have been obtained. A meta-analysis of case-control studies, including 46 studies, analyzing the association of *ADRβ2* polymorphisms and the risk of asthma identified four single-nucleotide polymorphisms (SNPs): Arg16Gly (A46G, rs1042713), Gln27Glu (C79G, rs1042714), Thr164Ile (C491T, rs1800888), and Arg19Cys (T-47C, rs1042711) [83]. Significant correlation was found for Arg16Gly polymorphism in the South American population in an analysis stratified by ethnicity via dominant model comparison (OR = 1.754, 95% CI = 1.179–2.609, I2 = 16.9%, studies = 2, case = 314, control = 237). A protective association has been reported for the Gln27Glu polymorphism in children via recessive model comparison (OR = 0.566, 95% CI = 0.417–0.769, I2 = 0.0%) and homozygote genotype comparison (OR = 0.610, 95% CI = 0.434–0.856, I2 = 0.0%) and in adults via dominant model comparison (OR = 0.864, 95% CI = 0.768–0.971,

I2 = 46.9%) [83]. More recently, a specific genotype (AA) of the Arg16Gly variant was associated with increased rates of hospitalization in asthmatic children and adolescents compared with other genotypes (AG and GG) [84]. Cantero-Recasens et al. first described the involvement of TRPV1 in asthma pathophysiology and reported a protective effect of the TRPV1-Val-585 variant against the presence of wheezing or cough among asthmatics [85]. Further studies are needed to better define the implication of these SNPs on asthma severity and to identify the protective or non-protective effects of these variants. The results of future research could improve the personalization of treatment strategy.

β2-agonists and corticosteroids are the main treatments used in managing asthmatic patients from childhood to adulthood [77]. Despite the central role of β2-agonists in asthma treatment, data suggest that an increased prescription of this medication is related to higher asthma mortality [86–88]. Chronic use of β2-agonists induces tachyphylaxis and a rebound in airway hyperresponsiveness [89]. Approximately 70% of asthmatic patients with chronic use of β2-agonists lose the ability of this medication to induce bronchodilation [90,91]. The β2AR dysfunction in asthmatic human ASM cells is the result of the reduced resensitization of the receptor characterized by reduced dephosphorylation of β2AR due to diminished endosomal protein phosphatase 2A (PP2A) activity. The reduced PP2A activity, which normally resensitizes the receptor, permitting its recycling to the plasma membrane, induces the endosomal accumulation of phosphorylated β2AR, which is the desensitized form of the receptor. Furthermore, high levels of phosphodiesterase-4 (PDE4) in asthmatic patients accelerate the catalysis of cAMP and contribute to loss in β2AR response [92]. SNPs in *ADRβ2*, such as Arg16Gly (rs1042713), Gln27Glu (rs1042714), and Arg19Cys (rs1042711), may be associated with the downregulation of β2AR. In turn, the Thr164Ile (rs180088) polymorphism reduces the receptor binding affinity to β2-agonists [84,93,94]. Conversely, corticosteroids increase the number of β2ARs in human lungs in a time- and dose-dependent manner and prevent the β2-agonists-induced downregulation of β2ARs [95–97]. The synergism is bidirectional: β2AR action improves the anti-inflammatory activity of corticosteroids by enhancing the translocation of the glucocorticoid receptor (GR) from the cytoplasm to the cellular nucleus [98]. The effect of this synergism is the possibility of using low-dose drug combination therapy, minimizing the side effects of the drugs.

The expression of TRPV1 is increased in the airway epithelium of asthmatic patients and is more conspicuous in those with severe and uncontrolled disease [99]. The TRPV1 functions and the effects of TRPV1 antagonism on airway inflammation gained increasing interest and attention in the literature. Rehman et al. reported that the inhibition of TRPV1 reduced airway hyperactivity and remodeling, goblet cell metaplasia and subepithelial fibrosis in IL13-induced asthma model in BALB/c mice [100]. In another study in BALB/c mice, the sample group sensitized with ovalbumin (OVA) showed increased airway hyperactivity and the development of an asthmatic lung phenotype compared with controls. In this OVA challenge group, the expression of the TRPV1 receptor and the release of type 2 (T2) cytokines (IL3, IL5, IL5) were significantly elevated. The inhalation of TRPV1 antagomir, a small interfering mRNA (siRNA) directed toward TRPV1, efficiently controlled eosinophilic airway inflammation and remodeling. TRPV1 antagomir suppressed epithelial-derived cytokines, such as thymic stromal lymphopoietin (TSLP), IL33, and IL25, which are important regulators of T2 cytokines-associated inflammation [101]. Since TRPV1 expression seems to be related to asthma severity, its suppression could be helpful in decreasing chronic airway epithelial injury and asthma features, as observed in animal models. TRPV1 expressed in sensory neurons innervating the airways can be stimulated by inhaled irritants that increase Ca^{2+} influx and release of neuroinflammatory substances. Of these substances, pro-inflammatory neuropeptides, such as calcitonin gene-related peptide (CGRP) and NK1, are responsible for the development of neurogenic inflammation in the airways [102–104]. These neuropeptides lead to bronchoconstriction, mucus hypersecretion, airway irritation, and cough and influence the recruitment of neutrophils and eosinophils in the lungs, all elements associated with asthma [2,103]. Moreover, the activation of TRPV1 in bronchial epithelial cells promotes the release of pro-inflammatory mediators, such as

ILs, PGE2, NGF, and tumor necrosis factor α (TNFα), sustaining airway inflammation and airway hypersensitivity [105–107]. TRPV1-positive sensory neurons expressed the protease-activated receptor 2 (PAR2), which is implicated in neurogenic inflammation and hyperalgesia [108,109]. In the airways, PAR2 activation is associated with inflammatory responses, including exaggeration of allergic reactions, bronchoconstriction and plasma protein extravasation [110,111]. PAR2 stimulation upregulates the function of TRPV1 via a PKC-dependent mechanism, regulating the TRPV1 activity during neurogenic inflammation in the airway by the concomitant release of arachidonic acid and PGE2 [112,113]. Furthermore, in a study in primary human nasal epithelial cells and murine tracheal epithelial cells, both TRPV1 and PAR2 were implicated in innate responses against airborne allergens (i.e., house dust mite and *Alternaria alternata*) by an allergen-induced ATP release promoting IL33 secretion [114]. These data suggest that TRPV1 is strictly related to asthma pathogenesis and might be a promising therapeutic target, especially in patients with severe and uncontrolled asthma.

3.3. COPD

COPD is a heterogeneous lung disease characterized by chronic respiratory symptoms due to defects in the airways, which cause chronic, often progressive, airflow obstruction. This condition results from genetic and environmental factors (e.g., cigarette smoking) occurring during an individual's lifetime [115].

Several studies have supported that *ADRβ2* polymorphisms may influence the COPD severity and the sensitivity to the treatment. People homozygous for Arg16 have an increased risk of COPD and asthma, and the Arg16/Gln27 haplotype is associated with more severe respiratory symptoms in middle-aged and older adults with COPD [116]. The genotypes Gly16Arg (rs1042713) and Gln27Glu (rs1042714) increase the risk of severe exacerbation in COPD, potentially mainly by genetic influence of the 16Arg allele in rs1042713 [117]. In a randomized, double-blind study, COPD patients with the Arg16Arg genotype reported lower exacerbation risk compared with Arg16Gly and Gly16Gly genotypes in the salmeterol group, highlighting a different treatment response [118]. Identifying these polymorphisms could be used in future personalized treatment strategies to identify patients more at risk of severe disease.

Cigarette smoking is one of the main causative agents of COPD. Smoke exposure produces an early respiratory inflammation mediated by neuropeptides (such as NK1) that increases the recruitment of eosinophils and neutrophils and the production of reactive oxygen species (ROS) [119,120]. The principal ROS are hydrogen peroxide (H2O2) and hydroxyl radical (·OH) [121]. ROS directly activate TRPV1 receptors, stimulating the vagal lung afferent fibers and inducing excessive cough in smokers with COPD [122,123]. Furthermore, smoke exposure can modify the lung phenotype of TRPV1 receptors, increasing their expression and functionality. Thus, this phenotypic switch justifies the excessive cough responses to a range of inhaled irritants in smokers [123]. Apart from the smoking status, patients with COPD have a lower threshold to cough by different stimuli, including capsaicin [124,125]. In an in vivo study, an inhibitor (AMG9810) of TRPV1 diminished oxidative stress, prevented Ca+ influx, inhibited inflammatory response and improved antioxidant gene expression in bronchial and alveolar epithelial cells exposed to cigarette smoking [126]. Furthermore, the administration of a TRPV1 antagonist (SB-705498) significantly improved cough frequencies in patients with chronic cough [127]. However, researchers are still evaluating the role of TRPV1 inhibitors as a potential therapy for COPD, and it could represent a future therapeutic challenge in the management of these patients. Moreover, recent studies have analyzed the role of anti-oxidative treatments in modulating TRPV1 expression in COPD. A study in cigarette smoking-challenged mice exhibited how total flavonoids, the leading active components derived from loquat leaves, inhibited inflammation and oxidative stress response through down-regulating TRPV1 expression. This anti-oxidative treatment also reduced the synthesis of IL6, IL1β, TNFα, and nitric oxide (NO), modulating the

neurogenic inflammation and oxidative stress observed in chronic RDs [128]. The use of antioxidants with TRPV1 down-regulation properties could improve COPD management in future studies.

3.4. Cystic Fibrosis

Cystic fibrosis is a hereditary disease defined by an altered homeostasis of ion and water transports in secretory epithelial surfaces, including the airways. The disease is caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene coding for an epithelial chloride channel, which leads to impaired mucociliary clearance [129,130]. Although a wide range of literature research has analyzed the role of CFTR, few studies have defined the importance of other receptors in the interaction with CFTR and their possible application in disease management.

There are several causes of cough in cystic fibrosis, such as airway inflammation and impairment in mucociliary clearance. The increased cough frequency is one of the main signs of pulmonary exacerbations in patients with cystic fibrosis [131]. However, a comprehensive evaluation of the cough sensitivity in this condition is modest. In 1997, Chang et al. showed a pivotal difference between children affected by cystic fibrosis and asthma or recurrent non-asthmatic cough. Cough sensitivity to capsaicin was lower in children with cystic fibrosis compared to asthmatic children and healthy controls. Furthermore, children with cystic fibrosis had an increased threshold to cough compared to controls [132]. A study on cough in children with cystic fibrosis did not find any statistically significant difference in cough frequency before and after treatment for pulmonary exacerbations despite significant improvements in spirometry, suggesting a possible reduced sensitivity in this age group [133]. In adults with cystic fibrosis, cough sensitivity has not been studied, but the cough rate in patients treated for exacerbations seems to decrease at the end of treatment, in contrast with what was observed in children [134]. Since the capsaicin receptor is TRPV1, it could be supposed that a different pattern of activation of this receptor in the lung sensory neurons of patients with cystic fibrosis is present, with a low range of cough sensitivity in children and not in adults. However, further studies are needed to confirm this supposition. Interestingly, CFTR and TRPV1 have structural similarities in the cytoplasmatic domains, and both channels are regulated by ATP. It was demonstrated that capsaicin—by binding to the cytoplasmatic domain of CFTR—improves the activity of wild-type and mutant CFTR channels [135]. This result highlights the importance of future studies on TRPV1-CFTR interactions to develop future therapeutic strategies in patients with cystic fibrosis.

β2-agonists are commonly used in the management of patients with cystic fibrosis. CFTR can be activated by β2AR via raising cAMP intracellular levels and mediating PKA activation. In the airways, the β2AR-CFTR interaction is facilitated by scaffold proteins, such as Na+/H+ Exchanger Regulatory Factor (NHERF1), permitting its interaction with PKA and stabilizing it on the plasma membrane [136,137]. Studies in vitro human or in vivo animal models showed that single doses of β2-agonists increase mucociliary clearance and bronchodilation, explaining the frequent use of short-acting β2-agonists (such as albuterol) in clinical practice for daily airway clearance regimens in cystic fibrosis [138–140]. However, chronic exposure to β2-agonists (such as albuterol and formoterol) reduces cAMP generation following direct AC stimulation and PDE inhibition, which also leads to a defective CFTR activation. The reduction in CFTR function following long-term β2-agonists use seems to have little consequences in healthy individuals, and it appears to be more significant in cystic fibrosis, especially on modulatory therapy such as pharmacologic F508del correction [141]. Patients with cystic fibrosis may show different responses to β2-agonists. Some studies revealed individual differences related to specific *ADRβ2* polymorphisms, and the GG haplotype was associated with a greater response to albuterol compared with other haplotypes. However, there is no evidence of the impact of these polymorphisms on long-term outcomes in this population, and future studies could resolve this issue and improve the management of these patients [142].

4. Conclusions

As we showed in this review, β2AR and TRPV1 are widely involved in physiological mechanisms in the upper and lower airways, and their role in the pathogenesis of RDs is also crucial. To our knowledge, this is the first review summarizing the functions and dysfunctions of these two receptors in the main RDs. Previous studies only analyzed the individual receptor without reporting the peculiar interplay between β2AR and TRPV1 in the development and persistence of RDs. In Table 1, we reported the key points of our analysis. Respiratory viral infections, such as RSV and HRV infections, can alter receptor expression and function, leading to bronchoconstriction and persistent airway inflammation. Moreover, viral infections occurring during early childhood are related to asthma onset, and genetic variants in *ADRβ2* and *TRPV1* can influence disease severity and patient response to treatment. Chronic use of β2-agonists can induce tachyphylaxis and decrease treatment effectiveness due to β2AR desensitization. In COPD, *ADRβ2* polymorphisms can be related to disease severity and progression, and future personalized therapeutic approaches may improve the management of this condition. Moreover, patients with COPD have a lower threshold to cough, which is justified by an increased response to different stimuli, especially smoke, which is responsible for the high expression of TRPV1 in the airways. In cystic fibrosis, TRPV1 activation could improve CFTR function and cough effectiveness, while β2AR stimulation increases mucociliary clearance and favors bronchodilation.

Table 1. Key points of the roles of β2AR and TRPV1 in respiratory diseases.

Respiratory Disease	β2AR	TRPV1
Respiratory infections	RSV infection reduces β2AR density in infected cells and attenuates ISO-induced cAMP formation [58]. RSV induces β2AR desensitization either directly by the GRK2 or PKCζ phosphorylation of the receptor or indirectly by the sequestration of the α-subunit of Gs [59,61]. IL8, released in response to RSV infection, induces the activation of GRK2 or PKCζ, with the subsequent phosphorylation and desensitization of β2AR [60]. RSV induces a proteasome-mediated cleavage and degradation of β2AR (reducing its density) and leads to impaired cAMP synthesis and increased levels of intracellular Ca^{2+}, generating a pro-contractile phenotype in RSV-infected ASM cells [61]. HRV induces β2AR desensitization in human ASM cells, probably thanks to autocrine PG production [73]. Respiratory viral infections induce β2AR desensitization in ASM cells due to the PGE2 interaction with the EP2 receptor [75], reducing the efficacy of β2-agonists during asthma and COPD infectious exacerbations [74,75].	RSV increases TRPV1 expression in the epithelial and neuronal cells [62,63]. The upregulation in TRPV1 expression seems related to a NF-kB positive feedback control of JNK1/2 phosphorylation which increases IL8 levels, enhancing TRPV1 expression [62]. During RSV infection, TRPV1 upregulation, together with the overexpression of NGF and NK1 receptors in the lungs, induces increased neuroinflammation, which may contribute to long-lasting airway inflammation and hyperreactivity [34,65,66]. RSV stimulates the TRPV1-dependent Ca^{2+} influx in bronchial epithelial cells, which are responsible for increased mucus production, disrupted barrier permeability, and enhanced bronchoconstriction, especially in asthmatic children [67]. PGE2 produced during respiratory viral infections seems to increase TRPV1 activity and cough stimulation [76].

Table 1. *Cont.*

Respiratory Disease	β2AR	TRPV1
Asthma	Some *ADRβ2* polymorphisms are related to an increased risk of asthma, such as Arg16Gly polymorphism in the South American population. A protective association was reported for the Gln27Glu polymorphism [83]. The β2AR dysfunction in asthmatic human ASM cells is the result of the reduced resensitization of the receptor characterized by diminished dephosphorylation of β2AR due to decreased endosomal PP2A activity. Furthermore, high levels of PDE4 in asthmatic patients accelerate the catalysis of cAMP and contribute to loss in β2AR response [92]. Corticosteroids increase the number of β2ARs in human lungs in a time- and dose-dependent manner and prevent the β2-agonists-induced downregulation of β2ARs [95–97].	TRPV1-Val-585 variant seems to have a protective effect against the presence of wheezing or cough among asthmatics [85]. The expression of TRPV1 is increased in the airway epithelium of asthmatic patients and is more prominent in those with severe and uncontrolled disease [99]. In animal models, the inhibition of TRPV1 reduced airway hyperactivity and remodeling, goblet cell metaplasia and subepithelial fibrosis [100]. The activation of TRPV1 in bronchial epithelial cells promotes the release of pro-inflammatory mediators, such as ILs, PGE2, NGF, and TNFα, sustaining airway inflammation and airway hypersensitivity [105–107]. TRPV1-positive sensory neurons expressed the PAR2, which is implicated in neurogenic inflammation and hyperalgesia [108,109]. In the airways, PAR2 activation is associated with inflammatory responses, including exaggeration of allergic reactions, bronchoconstriction and plasma protein extravasation [110,111]. Both TRPV1 and PAR2 seems to be implicated in innate responses against airborne allergens [114].
COPD	Some ADRβ2 polymorphisms are associated with COPD severity. People homozygous for Arg16 have an increased risk of COPD, and the Arg16/Gln27 haplotype is associated with more severe respiratory symptoms in middle-aged and older adults with COPD [116]. The genotypes Gly16Arg (rs1042713) and Gln27Glu (rs1042714) increase the risk of severe exacerbation in COPD [117].	Smoke exposure can modify the lung phenotype of TRPV1 receptors, increasing their expression and functionality. This phenotypic switch justifies the excessive cough responses to a range of inhaled irritants in smokers [123]. Patients with COPD have a lower threshold to cough by different stimuli, including capsaicin [124,125].

Table 1. *Cont.*

Respiratory Disease	β2AR	TRPV1
Cystic fibrosis	CFTR can be activated by β2AR via raising cAMP intracellular levels and mediating PKA activation [136,137]. Single doses of β2-agonists increase mucociliary clearance and bronchodilation, explaining the frequent use of short-acting β2-agonists in clinical practice for daily airway clearance regimens in cystic fibrosis [138–140]. Chronic exposure to β2-agonists reduces cAMP generation following direct AC stimulation and PDE inhibition, which also leads to a defective CFTR activation. The reduction in CFTR function following long-term β2-agonists use seems to have little consequences in healthy individuals, and it appears to be more significant in cystic fibrosis, especially on modulatory therapy such as pharmacologic F508del correction [141].	Cough sensitivity to capsaicin (a well-known agonist of TRPV1) is lower in children with cystic fibrosis compared to asthmatic children and healthy controls. Furthermore, children with cystic fibrosis had an increased threshold to cough compared to controls [132].

β2AR = β2-adrenergic receptor; TRPV1 = transient receptor potential vanilloid 1; RSV = respiratory syncytial virus; ISO = isoproterenol; cAMP = cyclic adenosine monophosphate; GRK2 = G protein-coupled receptor kinase 2; PKCζ = Protein kinase C zeta type; IL8 = interleukin 8; Ca^{2+} = calcium ion; ASM = airway smooth muscle; HRV = human rhinovirus; PG = prostaglandin; EP2 = prostanoid E2; COPD = chronic obstructive pulmonary disease; NF-kB = nuclear factor-kappa B; JNK1/2 = c-Jun N-terminal kinase 1/2; NGF = nerve growth factor; NK1 = neurokinin 1; PP2A = protein phosphatase 2A; PDE4 = phosphodiesterase-4; TNFα = tumor necrosis factor α; PAR2 = protease-activated receptor 2; CFTR = cystic fibrosis transmembrane conductance regulator; PKA = protein kinase A.

The understanding of the regulation of β2AR and TRPV1 and their interaction can be crucial for developing more effective and personalized treatments in RDs. In this review, we discussed the implication of receptor dysfunction in each pathology and reported the most relevant novelties of therapeutic strategies. Future research on receptor modulation and targeted signaling pathways could be helpful in developing new management strategies and improving the outcomes of these conditions.

Author Contributions: Conceptualization, S.M. and G.P.; methodology and software, F.G. and P.R.; validation, S.M. and G.P.; writing—original draft preparation, A.G.; writing—review and editing, S.M., A.G. and G.P.; visualization, S.M., A.G., F.G., P.R. and G.P.; supervision, S.M. and G.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Momtazmanesh, S.; Moghaddam, S.S.; Ghamari, S.-H.; Rad, E.M.; Rezaei, N.; Shobeiri, P.; Aali, A.; Abbasi-Kangevari, M.; Abbasi-Kangevari, Z.; Abdelmasseh, M.; et al. Global Burden of Chronic Respiratory Diseases and Risk Factors, 1990–2019: An Update from the Global Burden of Disease Study 2019. *EClinicalMedicine* **2023**, *59*, 101936. [CrossRef] [PubMed]
2. Figueiredo, I.A.D.; Ferreira, S.R.D.; Fernandes, J.M.; da Silva, B.A.; Vasconcelos, L.H.C.; Cavalcante, F.d.A. A Review of the Pathophysiology and the Role of Ion Channels on Bronchial Asthma. *Front. Pharmacol.* **2023**, *14*, 1236550. [CrossRef] [PubMed]
3. Bai, T.R. Beta2 Adrenergic Receptors in Asthma: A Current Perspective. *Lung* **1992**, *170*, 125–141. [CrossRef] [PubMed]
4. Palczewskl, K.; Benovic, J.L. G-Protein-Coupled Receptor Kinases. *Trends Biochem. Sci.* **1991**, *16*, 387–391. [CrossRef] [PubMed]
5. Rockman, H.A.; Koch, W.J.; Lefkowitz, R.J. Seven-Transmembrane-Spanning Receptors and Heart Function. *Nature* **2002**, *415*, 206–212. [CrossRef] [PubMed]
6. Strosberg, A.D. Structure and Function of the β_3-Adrenergic Receptor. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 421–450. [CrossRef]
7. JOHNSON, M. The β-Adrenoceptor. *Am. J. Respir. Crit. Care Med.* **1998**, *158* (Suppl. 2), S146–S153. [CrossRef]
8. Steinberg, S.F. The Molecular Basis for Distinct β-Adrenergic Receptor Subtype Actions in Cardiomyocytes. *Circ. Res.* **1999**, *85*, 1101–1111. [CrossRef]

9. Abosamak, N.R.; Shahin, M.H. Beta2 Receptor Agonists and Antagonists. In *StatPearls [Internet]*; StatPearls Publishing: St. Petersburg, FL, USA, 2023.
10. Spina, D.; Rigby, P.J.; Paterson, J.W.; Goldie, R.G. Autoradiographic Localization of Beta-Adrenoceptors in Asthmatic Human Lung. *Am. Rev. Respir. Dis.* **1989**, *140*, 1410–1415. [CrossRef]
11. Carstairs, J.R.; Nimmo, A.J.; Barnes, P.J. Autoradiographic Visualization of Beta-Adrenoceptor Subtypes in Human Lung. *Am. Rev. Respir. Dis.* **1985**, *132*, 541–547. [CrossRef]
12. Kobilka, B.K.; Frielle, T.; Dohlman, H.G.; Bolanowski, M.A.; Dixon, R.A.; Keller, P.; Caron, M.G.; Lefkowitz, R.J. Delineation of the Intronless Nature of the Genes for the Human and Hamster Beta 2-Adrenergic Receptor and Their Putative Promoter Regions. *J. Biol. Chem.* **1987**, *262*, 7321–7327. [CrossRef] [PubMed]
13. Rasmussen, S.G.F.; Choi, H.-J.; Rosenbaum, D.M.; Kobilka, T.S.; Thian, F.S.; Edwards, P.C.; Burghammer, M.; Ratnala, V.R.P.; Sanishvili, R.; Fischetti, R.F.; et al. Crystal Structure of the Human β_2 Adrenergic G-Protein-Coupled Receptor. *Nature* **2007**, *450*, 383–387. [CrossRef] [PubMed]
14. Liggett, S.B. Update on Current Concepts of the Molecular Basis of β_2-Adrenergic Receptor Signaling. *J. Allergy Clin. Immunol.* **2002**, *110*, S223–S228. [CrossRef] [PubMed]
15. Robison, G.A.; Butcher, R.W.; Sutherland, E.W. Adenyl Cyclase as an Adrenergic Receptor. *Ann. N. Y. Acad. Sci.* **1967**, *139*, 703–723. [CrossRef]
16. Mafi, A.; Kim, S.K.; Goddard, W.A., III. The dynamics of agonist-β_2-adrenergic receptor activation induced by binding of GDP-bound Gs protein. *Nat. Chem.* **2023**, *15*, 1127–1137. [CrossRef]
17. Billington, C.K.; Ojo, O.O.; Penn, R.B.; Ito, S. CAMP Regulation of Airway Smooth Muscle Function. *Pulm. Pharmacol. Ther.* **2013**, *26*, 112–120. [CrossRef] [PubMed]
18. Buels, K.S.; Fryer, A.D. Muscarinic receptor antagonists: Effects on pulmonary function. *Handb. Exp. Pharmacol.* **2012**, *208*, 317–341. [CrossRef]
19. Giembycz, M.A. Beyond the Dogma: Novel 2-Adrenoceptor Signalling in the Airways. *Eur. Respir. J.* **2006**, *27*, 1286–1306. [CrossRef]
20. Pelaia, G.; Gallelli, L.; Vatrella, A.; Grembiale, R.D.; Maselli, R.; De Sarro, G.B.; Marsico, S.A. Potential Role of Potassium Channel Openers in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease. *Life Sci.* **2002**, *70*, 977–990. [CrossRef]
21. Kume, H.; Takai, A.; Tokuno, H.; Tomita, T. Regulation of Ca^{2+}-Dependent K^+-Channel Activity in Tracheal Myocytes by Phosphorylation. *Nature* **1989**, *341*, 152–154. [CrossRef]
22. Yang, A.; Yu, G.; Wu, Y.; Wang, H. Role of β_2-Adrenergic Receptors in Chronic Obstructive Pulmonary Disease. *Life Sci.* **2021**, *265*, 118864. [CrossRef] [PubMed]
23. Barnes, P.J. Effect of β Agonists on Inflammatory Cells. *J. Allergy Clin. Immunol.* **1999**, *104*, S10–S17. [CrossRef]
24. Carman, C.V.; Benovic, J.L. G-Protein-Coupled Receptors: Turn-Ons and Turn-Offs. *Curr. Opin. Neurobiol.* **1998**, *8*, 335–344. [CrossRef]
25. Shenoy, S.K.; Lefkowitz, R.J. β-Arrestin-Mediated Receptor Trafficking and Signal Transduction. *Trends Pharmacol. Sci.* **2011**, *32*, 521–533. [CrossRef] [PubMed]
26. O'Hayre, M.; Eichel, K.; Avino, S.; Zhao, X.; Steffen, D.J.; Feng, X.; Kawakami, K.; Aoki, J.; Messer, K.; Sunahara, R.; et al. Genetic Evidence That β-Arrestins Are Dispensable for the Initiation of β_2-Adrenergic Receptor Signaling to ERK. *Sci. Signal* **2017**, *10*, eaal3395. [CrossRef]
27. Zhou, Y.; Zhang, Y.; Guo, Y.; Zhang, Y.; Xu, M.; He, B. β_2-Adrenoceptor Involved in Smoking-Induced Airway Mucus Hypersecretion through β-Arrestin-Dependent Signaling. *PLoS ONE* **2014**, *9*, e97788. [CrossRef] [PubMed]
28. Oehme, S.; Mittag, A.; Schrödl, W.; Tarnok, A.; Nieber, K.; Abraham, G. Agonist-Induced β_2-Adrenoceptor Desensitization and Downregulation Enhance pro-Inflammatory Cytokine Release in Human Bronchial Epithelial Cells. *Pulm. Pharmacol. Ther.* **2015**, *30*, 110–120. [CrossRef]
29. Vasudevan, N.T.; Mohan, M.L.; Goswami, S.K.; Prasad, S.V.N. Regulation of β-Adrenergic Receptor Function. *Cell Cycle* **2011**, *10*, 3684–3691. [CrossRef]
30. Seibold, A.; Williams, B.; Huang, Z.-F.; Friedman, J.; Moore, R.H.; Knoll, B.J.; Clark, R.B. Localization of the Sites Mediating Desensitization of the β_2-Adrenergic Receptor by the GRK Pathway. *Mol. Pharmacol.* **2000**, *58*, 1162–1173. [CrossRef]
31. Pedersen, S.F.; Owsianik, G.; Nilius, B. TRP Channels: An Overview. *Cell Calcium* **2005**, *38*, 233–252. [CrossRef]
32. Tominaga, M.; Caterina, M.J.; Malmberg, A.B.; Rosen, T.A.; Gilbert, H.; Skinner, K.; Raumann, B.E.; Basbaum, A.I.; Julius, D. The Cloned Capsaicin Receptor Integrates Multiple Pain-Producing Stimuli. *Neuron* **1998**, *21*, 531–543. [CrossRef] [PubMed]
33. Watanabe, N.; Horie, S.; Michael, G.J.; Keir, S.; Spina, D.; Page, C.P.; Priestley, J.V. Immunohistochemical Co-Localization of Transient Receptor Potential Vanilloid (TRPV)1 and Sensory Neuropeptides in the Guinea-Pig Respiratory System. *Neuroscience* **2006**, *141*, 1533–1543. [CrossRef] [PubMed]
34. Piedimonte, G.; Rodriguez, M.M.; King, K.A.; McLean, S.; Jiang, X. Respiratory Syncytial Virus Upregulates Expression of the Substance P Receptor in Rat Lungs. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **1999**, *277*, L831–L840. [CrossRef] [PubMed]
35. Birnbaumer, L.; Yidirim, E.; Abramowitz, J. A Comparison of the Genes Coding for Canonical TRP Channels and Their M, V and P Relatives. *Cell Calcium* **2003**, *33*, 419–432. [CrossRef]
36. Liao, M.; Cao, E.; Julius, D.; Cheng, Y. Structure of the TRPV1 Ion Channel Determined by Electron Cryo-Microscopy. *Nature* **2013**, *504*, 107–112. [CrossRef]

37. Boonen, B.; Alpizar, Y.A.; Sanchez, A.; López-Requena, A.; Voets, T.; Talavera, K. Differential Effects of Lipopolysaccharide on Mouse Sensory TRP Channels. *Cell Calcium* **2018**, *73*, 72–81. [CrossRef]
38. Aneiros, E.; Cao, L.; Papakosta, M.; Stevens, E.B.; Phillips, S.; Grimm, C. The Biophysical and Molecular Basis of TRPV1 Proton Gating. *EMBO J.* **2011**, *30*, 994–1002. [CrossRef]
39. Cao, E.; Liao, M.; Cheng, Y.; Julius, D. TRPV1 Structures in Distinct Conformations Reveal Activation Mechanisms. *Nature* **2013**, *504*, 113–118. [CrossRef]
40. Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A.; Levine, J.D.; Julius, D. The Capsaicin Receptor: A Heat-Activated Ion Channel in the Pain Pathway. *Nature* **1997**, *389*, 816–824. [CrossRef]
41. Kim, M.; Sisco, N.J.; Hilton, J.K.; Montano, C.M.; Castro, M.A.; Cherry, B.R.; Levitus, M.; Van Horn, W.D. Evidence That the TRPV1 S1-S4 Membrane Domain Contributes to Thermosensing. *Nat. Commun.* **2020**, *11*, 4169. [CrossRef]
42. Luu, D.D.; Owens, A.M.; Mebrat, M.D.; Van Horn, W.D. A Molecular Perspective on Identifying TRPV1 Thermosensitive Regions and Disentangling Polymodal Activation. *Temperature* **2023**, *10*, 67–101. [CrossRef]
43. Bhave, G.; Hu, H.-J.; Glauner, K.S.; Zhu, W.; Wang, H.; Brasier, D.J.; Oxford, G.S.; Gereau, R.W. Protein Kinase C Phosphorylation Sensitizes but Does Not Activate the Capsaicin Receptor Transient Receptor Potential Vanilloid 1 (TRPV1). *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12480–12485. [CrossRef]
44. Dai, Y.; Moriyama, T.; Higashi, T.; Togashi, K.; Kobayashi, K.; Yamanaka, H.; Tominaga, M.; Noguchi, K. Proteinase-Activated Receptor 2-Mediated Potentiation of Transient Receptor Potential Vanilloid Subfamily 1 Activity Reveals a Mechanism for Proteinase-Induced Inflammatory Pain. *J. Neurosci.* **2004**, *24*, 4293–4299. [CrossRef]
45. Bhave, G.; Zhu, W.; Wang, H.; Brasier, D.J.; Oxford, G.S.; Gereau, R.W. CAMP-Dependent Protein Kinase Regulates Desensitization of the Capsaicin Receptor (VR1) by Direct Phosphorylation. *Neuron* **2002**, *35*, 721–731. [CrossRef]
46. Premkumar, L.S.; Ahern, G.P. Induction of Vanilloid Receptor Channel Activity by Protein Kinase C. *Nature* **2000**, *408*, 985–990. [CrossRef]
47. De Petrocellis, L.; Harrison, S.; Bisogno, T.; Tognetto, M.; Brandi, I.; Smith, G.D.; Creminon, C.; Davis, J.B.; Geppetti, P.; Di Marzo, V. The Vanilloid Receptor (VR1)-mediated Effects of Anandamide Are Potently Enhanced by the CAMP-dependent Protein Kinase. *J. Neurochem.* **2001**, *77*, 1660–1663. [CrossRef]
48. Docherty, R.J.; Yeats, J.C.; Bevan, S.; Boddeke, H.W.G.M. Inhibition of Calcineurin Inhibits the Desensitization of Capsaicin-Evoked Currents in Cultured Dorsal Root Ganglion Neurones from Adult Rats. *Pflug. Arch.* **1996**, *431*, 828–837. [CrossRef]
49. Chuang, H.; Prescott, E.D.; Kong, H.; Shields, S.; Jordt, S.-E.; Basbaum, A.I.; Chao, M.V.; Julius, D. Bradykinin and Nerve Growth Factor Release the Capsaicin Receptor from PtdIns(4,5)P2-Mediated Inhibition. *Nature* **2001**, *411*, 957–962. [CrossRef]
50. Gambadauro, A.; Galletta, F.; Li Pomi, A.; Manti, S.; Piedimonte, G. Immune Response to Respiratory Viral Infections. *Int. J. Mol. Sci.* **2024**, *25*, 6178. [CrossRef]
51. Mizgerd, J.P. Lung Infection—A Public Health Priority. *PLoS Med.* **2006**, *3*, e76. [CrossRef]
52. Tregoning, J.S.; Schwarze, J. Respiratory Viral Infections in Infants: Causes, Clinical Symptoms, Virology, and Immunology. *Clin. Microbiol. Rev.* **2010**, *23*, 74–98. [CrossRef]
53. Everard, M.L. Paediatric Respiratory Infections. *Eur. Respir. Rev.* **2016**, *25*, 36–40. [CrossRef]
54. Alonso, W.J.; Laranjeira, B.J.; Pereira, S.A.R.; Florencio, C.M.G.D.; Moreno, E.C.; Miller, M.A.; Giglio, R.; Schuck-Paim, C.; Moura, F.E.A. Comparative Dynamics, Morbidity and Mortality Burden of Pediatric Viral Respiratory Infections in an Equatorial City. *Pediatr. Infect. Dis. J.* **2012**, *31*, e9–e14. [CrossRef]
55. Piedimonte, G.; Perez, M.K. Respiratory Syncytial Virus Infection and Bronchiolitis. *Pediatr. Rev.* **2014**, *35*, 519–530. [CrossRef]
56. Licari, A.; Manti, S.; Mastellone, F.; Miraglia Del Giudice, M.; Marseglia, G.L.; Tosca, M.A.; Andrenacci, B.; Capristo, C.; Cutrera, R.; Di Cicco, M.E.; et al. Critical Reappraisal of Short-Acting Bronchodilators for Pediatric Respiratory Diseases. *Ital. J. Pediatr.* **2024**, *50*, 104. [CrossRef]
57. Manti, S.; Staiano, A.; Orfeo, L.; Midulla, F.; Marseglia, G.L.; Ghizzi, C.; Zampogna, S.; Carnielli, V.P.; Favilli, S.; Ruggieri, M.; et al. UPDATE—2022 Italian Guidelines on the Management of Bronchiolitis in Infants. *Ital. J. Pediatr.* **2023**, *49*, 19. [CrossRef]
58. Moore, P.E.; Cunningham, G.; Calder, M.M.; DeMatteo, A.D.; Peeples, M.E.; Summar, M.L.; Peebles, R.S. Respiratory Syncytial Virus Infection Reduces β_2-Adrenergic Responses in Human Airway Smooth Muscle. *Am. J. Respir. Cell Mol. Biol.* **2006**, *35*, 559–564. [CrossRef]
59. Davis, I.C.; Xu, A.; Gao, Z.; Hickman-Davis, J.M.; Factor, P.; Sullender, W.M.; Matalon, S. Respiratory Syncytial Virus Induces Insensitivity to β-Adrenergic Agonists in Mouse Lung Epithelium in Vivo. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2007**, *293*, L281–L289. [CrossRef]
60. Traylor, Z.P.; Yu, E.N.Z.; Davis, I.C. Respiratory Syncytial Virus Induces Airway Insensitivity to β-Agonists in BALB/c Mice. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2010**, *298*, L437–L445. [CrossRef]
61. Harford, T.J.; Rezaee, F.; Gupta, M.K.; Bokun, V.; Naga Prasad, S.V.; Piedimonte, G. Respiratory Syncytial Virus Induces β_2-Adrenergic Receptor Dysfunction in Human Airway Smooth Muscle Cells. *Sci. Signal* **2021**, *14*, eabc1983. [CrossRef]
62. Omar, S.; Clarke, R.; Abdullah, H.; Brady, C.; Corry, J.; Winter, H.; Touzelet, O.; Power, U.F.; Lundy, F.; McGarvey, L.P.A.; et al. Respiratory Virus Infection Up-Regulates TRPV1, TRPA1 and ASICS3 Receptors on Airway Cells. *PLoS ONE* **2017**, *12*, e0171681. [CrossRef]
63. Harford, T.J.; Rezaee, F.; Dye, B.R.; Fan, J.; Spence, J.R.; Piedimonte, G. RSV-Induced Changes in a 3-Dimensional Organoid Model of Human Fetal Lungs. *PLoS ONE* **2022**, *17*, e0265094. [CrossRef]

64. Adcock, J.J. TRPV1 Receptors in Sensitisation of Cough and Pain Reflexes. *Pulm. Pharmacol. Ther.* **2009**, *22*, 65–70. [CrossRef]
65. Hu, C.; Wedde-Beer, K.; Auais, A.; Rodriguez, M.M.; Piedimonte, G. Nerve Growth Factor and Nerve Growth Factor Receptors in Respiratory Syncytial Virus-Infected Lungs. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2002**, *283*, L494–L502. [CrossRef]
66. Auais, A.; Adkins, B.; Napchan, G.; Piedimonte, G. Immunomodulatory Effects of Sensory Nerves during Respiratory Syncytial Virus Infection in Rats. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2003**, *285*, L105–L113. [CrossRef]
67. Harford, T.J.; Grove, L.; Rezaee, F.; Scheraga, R.; Olman, M.A.; Piedimonte, G. RSV Infection Potentiates TRPV $_1$-Mediated Calcium Transport in Bronchial Epithelium of Asthmatic Children. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2021**, *320*, L1074–L1084. [CrossRef]
68. Wu, P.; Larkin, E.K.; Reiss, S.S.; Carroll, K.N.; Summar, M.L.; Minton, P.A.; Woodward, K.B.; Liu, Z.; Islam, J.Y.; Hartert, T.V.; et al. β_2-Adrenergic Receptor Promoter Haplotype Influences the Severity of Acute Viral Respiratory Tract Infection during Infancy: A Prospective Cohort Study. *BMC Med. Genet.* **2015**, *16*, 82. [CrossRef]
69. Ağaç, D.; Gill, M.A.; Farrar, J.D. Adrenergic Signaling at the Interface of Allergic Asthma and Viral Infections. *Front. Immunol.* **2018**, *9*, 736. [CrossRef]
70. Tamura, R.; Takahashi, H.K.; Iwagaki, H.; Yagi, T.; Mori, S.; Yoshino, T.; Nishibori, M.; Tanaka, N. Effect of β2-Adrenergic Receptor Agonists on Intercellular Adhesion Molecule (ICAM)-1, B7, and CD40 Expression in Mixed Lymphocyte Reaction. *Transplantation* **2004**, *77*, 293–301. [CrossRef]
71. Kuroki, K.; Takahashi, H.; Iwagaki, H.; Murakami, T.; Kuinose, M.; Hamanaka, S.; Minami, K.; Nishibori, M.; Tanaka, N.; Tanemoto, K. β_2-Adrenergic Receptor Stimulation-Induced Immunosuppressive Effects Possibly through Down-Regulation of Co-Stimulatory Molecules, ICAM-1, CD40 and CD14 on Monocytes. *J. Int. Med. Res.* **2004**, *32*, 465–483. [CrossRef]
72. Bochkov, Y.A.; Busse, W.W.; Brockman-Schneider, R.A.; Evans, M.D.; Jarjour, N.N.; McCrae, C.; Miller-Larsson, A.; Gern, J.E. Budesonide and Formoterol Effects on Rhinovirus Replication and Epithelial Cell Cytokine Responses. *Respir. Res.* **2013**, *14*, 98. [CrossRef]
73. Van Ly, D.; Faiz, A.; Jenkins, C.; Crossett, B.; Black, J.L.; McParland, B.; Burgess, J.K.; Oliver, B.G.G. Characterising the Mechanism of Airway Smooth Muscle β_2 Adrenoceptor Desensitization by Rhinovirus Infected Bronchial Epithelial Cells. *PLoS ONE* **2013**, *8*, e56058. [CrossRef]
74. Sander, W.J.; O'Neill, H.G.; Pohl, C.H. Prostaglandin E2 As a Modulator of Viral Infections. *Front. Physiol.* **2017**, *8*, 89. [CrossRef]
75. Bradbury, P.; Rumzhum, N.N.; Ammit, A.J. EP $_2$ and EP $_4$ Receptor Antagonists: Impact on Cytokine Production and β_2-adrenergic Receptor Desensitization in Human Airway Smooth Muscle. *J. Cell Physiol.* **2019**, *234*, 11070–11077. [CrossRef]
76. Choudry, N.B.; Fuller, R.W.; Pride, N.B. Sensitivity of the Human Cough Reflex: Effect of Inflammatory Mediators Prostaglandin E_2, Bradykinin, and Histamine. *Am. Rev. Respir. Dis.* **1989**, *140*, 137–141. [CrossRef]
77. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2024. Available online: www.ginasthma.org (accessed on 22 September 2024).
78. Pijnenburg, M.W.; Frey, U.; De Jongste, J.C.; Saglani, S. Childhood Asthma: Pathogenesis and Phenotypes. *Eur. Respir. J.* **2022**, *59*, 2100731. [CrossRef]
79. Manti, S.; Piedimonte, G. An Overview on the RSV-Mediated Mechanisms in the Onset of Non-Allergic Asthma. *Front. Pediatr.* **2022**, *10*, 998296. [CrossRef]
80. Sigurs, N.; Bjarnason, R.; Sigurbergsson, F.; Kjellman, B.; Björkstén, B. Asthma and Immunoglobulin E Antibodies after Respiratory Syncytial Virus Bronchiolitis: A Prospective Cohort Study with Matched Controls. *Pediatrics* **1995**, *95*, 500–505. [CrossRef]
81. Edwards, M.R.; Strong, K.; Cameron, A.; Walton, R.P.; Jackson, D.J.; Johnston, S.L. Viral Infections in Allergy and Immunology: How Allergic Inflammation Influences Viral Infections and Illness. *J. Allergy Clin. Immunol.* **2017**, *140*, 909–920. [CrossRef]
82. Harford, T.J.; Rezaee, F.; Scheraga, R.G.; Olman, M.A.; Piedimonte, G. Asthma Predisposition and Respiratory Syncytial Virus Infection Modulate Transient Receptor Potential Vanilloid 1 Function in Children's Airways. *J. Allergy Clin. Immunol.* **2018**, *141*, 414–416.e4. [CrossRef]
83. Liang, S.-Q.; Chen, X.-L.; Deng, J.-M.; Wei, X.; Gong, C.; Chen, Z.-R.; Wang, Z.-B. Beta-2 Adrenergic Receptor (ADRB2) Gene Polymorphisms and the Risk of Asthma: A Meta-Analysis of Case-Control Studies. *PLoS ONE* **2014**, *9*, e104488. [CrossRef]
84. Muchão, F.P.; de Souza, A.V.; Souza, J.M.; da Silva, L.V.R.F. Association between Beta-2 Adrenergic Receptor Variants and Clinical Outcomes in Children and Adolescents with Acute Asthma. *Einstein* **2022**, *20*, eAO6412. [CrossRef]
85. Cantero-Recasens, G.; Gonzalez, J.R.; Fandos, C.; Duran-Tauleria, E.; Smit, L.A.M.; Kauffmann, F.; Antó, J.M.; Valverde, M.A. Loss of Function of Transient Receptor Potential Vanilloid 1 (TRPV1) Genetic Variant Is Associated with Lower Risk of Active Childhood Asthma. *J. Biol. Chem.* **2010**, *285*, 27532–27535. [CrossRef]
86. Spitzer, W.O.; Suissa, S.; Ernst, P.; Horwitz, R.I.; Habbick, B.; Cockcroft, D.; Boivin, J.-F.; McNutt, M.; Buist, A.S.; Rebuck, A.S. The Use of β-Agonists and the Risk of Death and near Death from Asthma. *N. Engl. J. Med.* **1992**, *326*, 501–506. [CrossRef]
87. Suissa, S.; Ernst, P.; Boivin, J.F.; Horwitz, R.I.; Habbick, B.; Cockroft, D.; Blais, L.; McNutt, M.; Buist, A.S.; Spitzer, W.O. A Cohort Analysis of Excess Mortality in Asthma and the Use of Inhaled Beta-Agonists. *Am. J. Respir. Crit. Care Med.* **1994**, *149*, 604–610. [CrossRef]
88. Sears, M.R.; Taylor, D.R.; Print, C.G.; Lake, D.C.; Li, Q.; Flannery, E.M.; Yates, D.M.; Lucas, M.K.; Herbison, G.P. Regular Inhaled Beta-Agonist Treatment in Bronchial Asthma. *Lancet* **1990**, *336*, 1391–1396. [CrossRef]
89. Penn, R.B.; Panettieri, R.A.; Benovic, J.L. Mechanisms of Acute Desensitization of the β_2 AR–Adenylyl Cyclase Pathway in Human Airway Smooth Muscle. *Am. J. Respir. Cell Mol. Biol.* **1998**, *19*, 338–348. [CrossRef]

90. Salpeter, S.R.; Buckley, N.S.; Ormiston, T.M.; Salpeter, E.E. Meta-Analysis: Effect of Long-Acting β-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths. *Ann. Intern. Med.* **2006**, *144*, 904. [CrossRef]
91. Salpeter, S.R.; Ormiston, T.M.; Salpeter, E.E. Meta-Analysis: Respiratory Tolerance to Regular β_2-Agonist Use in Patients with Asthma. *Ann. Intern. Med.* **2004**, *140*, 802. [CrossRef]
92. Gupta, M.K.; Asosingh, K.; Aronica, M.; Comhair, S.; Cao, G.; Erzurum, S.; Panettieri, R.A.; Naga Prasad, S.V. Defective Resensitization in Human Airway Smooth Muscle Cells Evokes β-Adrenergic Receptor Dysfunction in Severe Asthma. *PLoS ONE* **2015**, *10*, e0125803. [CrossRef]
93. McGraw, D.W.; Forbes, S.L.; Kramer, L.A.; Liggett, S.B. Polymorphisms of the 5′ Leader Cistron of the Human Beta2-Adrenergic Receptor Regulate Receptor Expression. *J. Clin. Investig.* **1998**, *102*, 1927–1932. [CrossRef] [PubMed]
94. Chung, L.P.; Waterer, G.; Thompson, P.J. Pharmacogenetics of β_2 Adrenergic Receptor Gene Polymorphisms, Long-Acting β-Agonists and Asthma. *Clin. Exp. Allergy* **2011**, *41*, 312–326. [CrossRef] [PubMed]
95. Adcock, I.; Stevens, D.; Barnes, P. Interactions of Glucocorticoids and Beta 2-Agonists. *Eur. Respir. J.* **1996**, *9*, 160–168. [CrossRef]
96. Mak, J.C.; Nishikawa, M.; Barnes, P.J. Glucocorticosteroids Increase Beta 2-Adrenergic Receptor Transcription in Human Lung. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **1995**, *268*, L41–L46. [CrossRef]
97. Mak, J.C.; Nishikawa, M.; Shirasaki, H.; Miyayasu, K.; Barnes, P.J. Protective Effects of a Glucocorticoid on Downregulation of Pulmonary Beta 2-Adrenergic Receptors in Vivo. *J. Clin. Investig.* **1995**, *96*, 99–106. [CrossRef]
98. Roth, M.; Johnson, P.R.; Rüdiger, J.J.; King, G.G.; Ge, Q.; Burgess, J.K.; Anderson, G.; Tamm, M.; Black, J.L. Interaction between Glucocorticoids and β 2 Agonists on Bronchial Airway Smooth Muscle Cells through Synchronised Cellular Signalling. *Lancet* **2002**, *360*, 1293–1299. [CrossRef] [PubMed]
99. McGarvey, L.P.; Butler, C.A.; Stokesberry, S.; Polley, L.; McQuaid, S.; Abdullah, H.; Ashraf, S.; McGahon, M.K.; Curtis, T.M.; Arron, J.; et al. Increased Expression of Bronchial Epithelial Transient Receptor Potential Vanilloid 1 Channels in Patients with Severe Asthma. *J. Allergy Clin. Immunol.* **2014**, *133*, 704–712.e4. [CrossRef]
100. Rehman, R.; Bhat, Y.A.; Panda, L.; Mabalirajan, U. TRPV1 Inhibition Attenuates IL-13 Mediated Asthma Features in Mice by Reducing Airway Epithelial Injury. *Int. Immunopharmacol.* **2013**, *15*, 597–605. [CrossRef]
101. Choi, J.Y.; Lee, H.Y.; Hur, J.; Kim, K.H.; Kang, J.Y.; Rhee, C.K.; Lee, S.Y. TRPV1 Blocking Alleviates Airway Inflammation and Remodeling in a Chronic Asthma Murine Model. *Allergy Asthma Immunol. Res.* **2018**, *10*, 216. [CrossRef]
102. Geppetti, P.; Holzer, P. *Neurogenic Inflammation*; CRC Press: Boca Raton, FL, USA, 1996.
103. Lee, L.-Y.; Gu, Q. Role of TRPV1 in Inflammation-Induced Airway Hypersensitivity. *Curr. Opin. Pharmacol.* **2009**, *9*, 243–249. [CrossRef]
104. Piedimonte, G.; Hoffman, J.I.; Husseini, W.K.; Snider, R.M.; Desai, M.C.; Nadel, J.A. NK1 Receptors Mediate Neurogenic Inflammatory Increase in Blood Flow in Rat Airways. *J. Appl. Physiol.* **1993**, *74*, 2462–2468. [CrossRef] [PubMed]
105. Zholos, A. TRP Channels in Respiratory Pathophysiology: The Role of Oxidative, Chemical Irritant and Temperature Stimuli. *Curr. Neuropharmacol.* **2015**, *13*, 279–291. [CrossRef]
106. Sadofsky, L.R.; Ramachandran, R.; Crow, C.; Cowen, M.; Compton, S.J.; Morice, A.H. Inflammatory Stimuli Up-Regulate Transient Receptor Potential Vanilloid-1 Expression in Human Bronchial Fibroblasts. *Exp. Lung Res.* **2012**, *38*, 75–81. [CrossRef] [PubMed]
107. Yu, H.; Li, Q.; Zhou, X.; Kolosov, V.P.; Perelman, J.M. Transient Receptor Potential Vanilloid 1 Receptors Mediate Acid-induced Mucin Secretion via Ca^{2+} Influx in Human Airway Epithelial Cells. *J. Biochem. Mol. Toxicol.* **2012**, *26*, 179–186. [CrossRef] [PubMed]
108. Steinhoff, M.; Vergnolle, N.; Young, S.H.; Tognetto, M.; Amadesi, S.; Ennes, H.S.; Trevisani, M.; Hollenberg, M.D.; Wallace, J.L.; Caughey, G.H.; et al. Agonists of Proteinase-Activated Receptor 2 Induce Inflammation by a Neurogenic Mechanism. *Nat. Med.* **2000**, *6*, 151–158. [CrossRef]
109. Vergnolle, N.; Bunnett, N.W.; Sharkey, K.A.; Brussee, V.; Compton, S.J.; Grady, E.F.; Cirino, G.; Gerard, N.; Basbaum, A.I.; Andrade-Gordon, P.; et al. Proteinase-Activated Receptor-2 and Hyperalgesia: A Novel Pain Pathway. *Nat. Med.* **2001**, *7*, 821–826. [CrossRef]
110. Schmidlin, F.; Amadesi, S.; Dabbagh, K.; Lewis, D.E.; Knott, P.; Bunnett, N.W.; Gater, P.R.; Geppetti, P.; Bertrand, C.; Stevens, M.E. Protease-Activated Receptor 2 Mediates Eosinophil Infiltration and Hyperreactivity in Allergic Inflammation of the Airway. *J. Immunol.* **2002**, *169*, 5315–5321. [CrossRef]
111. Su, X.; Camerer, E.; Hamilton, J.R.; Coughlin, S.R.; Matthay, M.A. Protease-Activated Receptor-2 Activation Induces Acute Lung Inflammation by Neuropeptide-Dependent Mechanisms. *J. Immunol.* **2005**, *175*, 2598–2605. [CrossRef]
112. Amadesi, S.; Cottrell, G.S.; Divino, L.; Chapman, K.; Grady, E.F.; Bautista, F.; Karanjia, R.; Barajas-Lopez, C.; Vanner, S.; Vergnolle, N.; et al. Protease-activated Receptor 2 Sensitizes TRPV1 by Protein Kinase Cε- and A-dependent Mechanisms in Rats and Mice. *J. Physiol.* **2006**, *575*, 555–571. [CrossRef]
113. Amadesi, S.; Nie, J.; Vergnolle, N.; Cottrell, G.S.; Grady, E.F.; Trevisani, M.; Manni, C.; Geppetti, P.; McRoberts, J.A.; Ennes, H.; et al. Protease-Activated Receptor 2 Sensitizes the Capsaicin Receptor Transient Receptor Potential Vanilloid Receptor 1 to Induce Hyperalgesia. *J. Neurosci.* **2004**, *24*, 4300–4312. [CrossRef]
114. Schiffers, C.; Hristova, M.; Habibovic, A.; Dustin, C.M.; Danyal, K.; Reynaert, N.L.; Wouters, E.F.M.; van der Vliet, A. The Transient Receptor Potential Channel Vanilloid 1 Is Critical in Innate Airway Epithelial Responses to Protease Allergens. *Am. J. Respir. Cell Mol. Biol.* **2020**, *63*, 198–208. [CrossRef]

115. Agustí, A.; Celli, B.R.; Criner, G.J.; Halpin, D.; Anzueto, A.; Barnes, P.; Bourbeau, J.; Han, M.K.; Martinez, F.J.; Montes de Oca, M.; et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am. J. Respir. Crit. Care Med.* **2023**, *207*, 819–837. [CrossRef] [PubMed]
116. Matheson, M.C.; Ellis, J.A.; Raven, J.; Johns, D.P.; Walters, E.H.; Abramson, M.J. β_2-Adrenergic Receptor Polymorphisms Are Associated with Asthma and COPD in Adults. *J. Hum. Genet.* **2006**, *51*, 943–951. [CrossRef] [PubMed]
117. Ingebrigtsen, T.S.; Vestbo, J.; Rode, L.; Marott, J.L.; Lange, P.; Nordestgaard, B.G. β_2-Adrenergic Genotypes and Risk of Severe Exacerbations in COPD: A Prospective Cohort Study. *Thorax* **2019**, *74*, 934–940. [CrossRef] [PubMed]
118. Rabe, K.F.; Fabbri, L.M.; Israel, E.; Kögler, H.; Riemann, K.; Schmidt, H.; Glaab, T.; Vogelmeier, C.F. Effect of ADRB2 Polymorphisms on the Efficacy of Salmeterol and Tiotropium in Preventing COPD Exacerbations: A Prespecified Substudy of the POET-COPD Trial. *Lancet Respir. Med.* **2014**, *2*, 44–53. [CrossRef] [PubMed]
119. Lundberg, J.M.; Saria, A. Capsaicin-Induced Desensitization of Airway Mucosa to Cigarette Smoke, Mechanical and Chemical Irritants. *Nature* **1983**, *302*, 251–253. [CrossRef]
120. Baluk, P.; Bertrand, C.; Geppetti, P.; McDonald, D.M.; Nadel, J.A. NK $_1$ Receptor Antagonist CP-99,994 Inhibits Cigarette Smoke-Induced Neutrophil and Eosinophil Adhesion in Rat Tracheal Venules. *Exp. Lung Res.* **1996**, *22*, 409–418. [CrossRef]
121. Comhair, S.A.A.; Erzurum, S.C. Antioxidant Responses to Oxidant-Mediated Lung Diseases. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* **2002**, *283*, L246–L255. [CrossRef]
122. Ruan, T.; Shuei Lin, Y.; Lin, K.; Ru Kou, Y. Sensory Transduction of Pulmonary Reactive Oxygen Species by Capsaicin-sensitive Vagal Lung Afferent Fibres in Rats. *J. Physiol.* **2005**, *565*, 563–578. [CrossRef]
123. Belvisi, M.G.; Birrell, M.A.; Khalid, S.; Wortley, M.A.; Dockry, R.; Coote, J.; Holt, K.; Dubuis, E.; Kelsall, A.; Maher, S.A.; et al. Neurophenotypes in Airway Diseases. Insights from Translational Cough Studies. *Am. J. Respir. Crit. Care Med.* **2016**, *193*, 1364–1372. [CrossRef]
124. Wong, C.H.; Morice, A.H. Cough Threshold in Patients with Chronic Obstructive Pulmonary Disease. *Thorax* **1999**, *54*, 62–64. [CrossRef] [PubMed]
125. Doherty, M.J. Capsaicin Responsiveness and Cough in Asthma and Chronic Obstructive Pulmonary Disease. *Thorax* **2000**, *55*, 643–649. [CrossRef] [PubMed]
126. Wang, M.; Zhang, Y.; Xu, M.; Zhang, H.; Chen, Y.; Chung, K.F.; Adcock, I.M.; Li, F. Roles of TRPA1 and TRPV1 in Cigarette Smoke—Induced Airway Epithelial Cell Injury Model. *Free Radic. Biol. Med.* **2019**, *134*, 229–238. [CrossRef]
127. Khalid, S.; Murdoch, R.; Newlands, A.; Smart, K.; Kelsall, A.; Holt, K.; Dockry, R.; Woodcock, A.; Smith, J.A. Transient Receptor Potential Vanilloid 1 (TRPV1) Antagonism in Patients with Refractory Chronic Cough: A Double-Blind Randomized Controlled Trial. *J. Allergy Clin. Immunol.* **2014**, *134*, 56–62.e4. [CrossRef] [PubMed]
128. Jian, T.; Chen, J.; Ding, X.; Lv, H.; Li, J.; Wu, Y.; Ren, B.; Tong, B.; Zuo, Y.; Su, K.; et al. Flavonoids Isolated from Loquat (*Eriobotrya Japonica*) Leaves Inhibit Oxidative Stress and Inflammation Induced by Cigarette Smoke in COPD Mice: The Role of TRPV1 Signaling Pathways. *Food Funct.* **2020**, *11*, 3516–3526. [CrossRef]
129. Moliteo, E.; Sciacca, M.; Palmeri, A.; Papale, M.; Manti, S.; Parisi, G.F.; Leonardi, S. Cystic Fibrosis and Oxidative Stress: The Role of CFTR. *Molecules* **2022**, *27*, 5324. [CrossRef] [PubMed]
130. Manti, S.; Parisi, G.F.; Papale, M.; Marseglia, G.L.; Licari, A.; Leonardi, S. Type 2 Inflammation in Cystic Fibrosis: New Insights. *Pediatr. Allergy Immunol.* **2022**, *33*, 15–17. [CrossRef]
131. Stanford, G.E.; Dave, K.; Simmonds, N.J. Pulmonary Exacerbations in Adults With Cystic Fibrosis. *Chest* **2021**, *159*, 93–102. [CrossRef]
132. Chang, A.B.; Phelan, P.D.; Sawyer, S.M.; Del Brocco, S.; Robertson, C.F. Cough Sensitivity in Children with Asthma, Recurrent Cough, and Cystic Fibrosis. *Arch. Dis. Child.* **1997**, *77*, 331–334. [CrossRef]
133. Hamutcu, R.; Francis, J.; Karakoc, F.; Bush, A. Objective Monitoring of Cough in Children with Cystic Fibrosis. *Pediatr. Pulmonol.* **2002**, *34*, 331–335. [CrossRef]
134. Smith, J.A. Objective Measurement of Cough during Pulmonary Exacerbations in Adults with Cystic Fibrosis. *Thorax* **2006**, *61*, 425–429. [CrossRef] [PubMed]
135. Ai, T.; Bompadre, S.G.; Wang, X.; Hu, S.; Li, M.; Hwang, T.-C. Capsaicin Potentiates Wild-Type and Mutant Cystic Fibrosis Transmembrane Conductance Regulator Chloride-Channel Currents. *Mol. Pharmacol.* **2004**, *65*, 1415–1426. [CrossRef] [PubMed]
136. Naren, A.P.; Cobb, B.; Li, C.; Roy, K.; Nelson, D.; Heda, G.D.; Liao, J.; Kirk, K.L.; Sorscher, E.J.; Hanrahan, J.; et al. A Macromolecular Complex of β_2 Adrenergic Receptor, CFTR, and Ezrin/Radixin/Moesin-Binding Phosphoprotein 50 Is Regulated by PKA. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 342–346. [CrossRef]
137. Trotta, T.; Guerra, L.; Piro, D.; d'Apolito, M.; Piccoli, C.; Porro, C.; Giardino, I.; Lepore, S.; Castellani, S.; Di Gioia, S.; et al. Stimulation of β_2-Adrenergic Receptor Increases CFTR Function and Decreases ATP Levels in Murine Hematopoietic Stem/Progenitor Cells. *J. Cyst. Fibros.* **2015**, *14*, 26–33. [CrossRef]
138. Sabater, J.R.; Lee, T.A.; Abraham, W.M. Comparative Effects of Salmeterol, Albuterol, and Ipratropium on Normal and Impaired Mucociliary Function in Sheep. *Chest* **2005**, *128*, 3743–3749. [CrossRef]
139. Eggleston, P.A.; Rosenstein, B.J.; Stackhouse, C.M.; Mellits, E.D.; Baumgardner, R.A. A Controlled Trial of Long-Term Bronchodilator Therapy in Cystic Fibrosis. *Chest* **1991**, *99*, 1088–1092. [CrossRef]
140. König, P.; Poehler, J.; Barbero, G.J. A Placebo-Controlled, Double-Blind Trial of the Long-Term Effects of Albuterol Administration in Patients with Cystic Fibrosis. *Pediatr. Pulmonol.* **1998**, *25*, 32–37. [CrossRef]

141. Brewington, J.J.; Backstrom, J.; Feldman, A.; Kramer, E.L.; Moncivaiz, J.D.; Ostmann, A.J.; Zhu, X.; Lu, L.J.; Clancy, J.P. Chronic β_2AR Stimulation Limits CFTR Activation in Human Airway Epithelia. *JCI Insight* **2018**, *3*, e93029. [CrossRef]
142. Steagall, W.K.; Barrow, B.J.; Glasgow, C.G.; Mendoza, J.W.; Ehrmantraut, M.; Lin, J.-P.; Insel, P.A.; Moss, J. Beta-2-Adrenergic Receptor Polymorphisms in Cystic Fibrosis. *Pharmacogenet Genom.* **2007**, *17*, 425–430. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.