Quercetin acutely relaxes airway smooth muscle and potentiates β-agonist-induced relaxation via dual phosphodiesterase inhibition of PLCβ and PDE4

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Townsend EA, Emala CW, Sr. Quercetin acutely relaxes airway smooth muscle and potentiates β-agonist-induced relaxation via dual phosphodiesterase inhibition of PLCβ and PDE4. Am J Physiol Lung Cell Mol Physiol 305: L396–L403, 2013. First published July 19, 2013; doi:10.1152/ajplung.00125.2013.—Asthma is a disease of the airways with symptoms including exaggerated airway narrowing and airway inflammation. Early asthma therapies used methylxanthines to relieve symptoms, in part, by inhibiting cyclic nucleotide phosphodiesterases (PDEs), the enzyme responsible for degrading cAMP. The classification of tissue-specific PDE subtypes and the clinical introduction of PDE-selective inhibitors for chronic obstructive pulmonary disease (i.e., roflumilast) have reopened the possibility of using PDE inhibition in the treatment of asthma. Quercetin is a naturally derived PDE4-selective inhibitor found in fruits, vegetables, and tea. We hypothesized that quercetin relaxes airway smooth muscle via cAMP-mediated pathways and augments β-agonist relaxation. Tracheal rings from male A/J mice were mounted in myographs and contracted with acetylcholine (ACh). Addition of quercetin (100 nM-1 mM) acutely and concentration-dependently relaxed airway rings precontracted with ACh. In separate studies, pretreatment with quercetin (100 μM) prevented force generation upon exposure to ACh. In additional studies, quercetin (50 μM) significantly potentiated isoproterenol-induced relaxations. In in vitro assays, quercetin directly attenuated phospholipase C activity, decreased inositol phosphate synthesis, and decreased intracellular calcium responses to Gq-coupled agonists (histamine or bradykinin). Finally, nebulization of quercetin (100 μM) in an in vivo model of airway responsiveness significantly attenuated methacholine-induced increases in airway resistance. These novel data show that the natural PDE4-selective inhibitor quercetin may provide therapeutic relief of asthma symptoms and decrease reliance on short-acting β-agonists.

IN SPITE OF AN IMPROVED UNDERSTANDING of the pathogenesis of asthma, there has been a global increase in the morbidity and mortality of asthma in recent decades (3). Asthma is characterized by increased airway reactivity, bronchoconstriction, and airway inflammation (10, 14, 27), and few novel therapeutics have been approved for targeting these symptoms in the last 40 years (1). In fact, asthma-related deaths have been attributed, in part, to β-agonist desensitization, a direct consequence of long-acting β-agonists, and a dependence on rescue inhalers for relief of symptoms (9). The efficacy and safety of long-acting β-agonists is currently under Food and Drug Administration-mandated review in five clinical studies (7). This highlights the need for therapies that acutely relax airways while limiting the reliance on β-adrenergic receptor activation.

Caffeine and theophylline, two methylxanthines derived from botanicals, have been used to treat asthma, although their exact mechanisms of action are still unknown (35, 37). The bronchodilating property of theophylline is attributed, in part, to inhibition of phosphodiesterase (PDE) activity, thereby increasing cAMP in airway smooth muscle (ASM) (2). PDE4 is the most important PDE enzyme in ASM, making it a relevant target in the treatment of asthma (6). The identification of airway-specific PDE4 subtypes and subsequent synthesis of PDE4-selective inhibitors have resurrected this therapeutic avenue for the development of novel bronchodilators. In preclinical studies, administration of selective PDE4 inhibitors prevented bronchial hyperresponsiveness (BHR) in allergic mice, an in vivo model for asthma (19, 24). Additionally, PDE4D knockout mice show blunted responses to the inhaled bronchoconstrictor methacholine (12). The prevention of BHR subsequent to the administration of PDE4 inhibitors is also seen in patients with allergic asthma (13, 26, 40) although no PDE4-selective inhibitor is currently approved for the treatment of asthma.

Quercetin, a naturally occurring selective PDE4 inhibitor found in tea, fruit, and vegetables, has many documented anti-inflammatory properties. While inflammation is undoubtedly a component of asthma, not all asthmatics have allergic or atopic symptoms. However, all asthmatics do suffer from bronchoconstriction during an exacerbation. As such, we investigated the acute effects of quercetin (within minutes) on airway relaxation both in mice that have a robust response to methacholine and in isolated ASM cells to determine if quercetin has effects on ASM that are not mediated by its well-characterized anti-inflammatory properties, thereby making it applicable to all asthmatics. We hypothesized that PDE4 inhibition by quercetin would promote relaxation by preventing the degradation of cAMP and increasing PKA signaling in ASM. We also hypothesized that, in the presence of quercetin, β-agonist stimulation would be more effective at relaxing ASM. This is the first study to detail signaling mechanisms in ASM responsible for observed bronchodilation due to quercetin.

METHODS

Myograph studies. All animal studies were approved by Columbia University’s Institutional Animal Care and Use Committee. Male A/J mice were killed with an overdose of pentobarbital sodium. Tracheas were rapidly removed and placed in modified Krebs-Henseleit buffer of the following composition in mM: 115 NaCl, 2.5 KCl, 1.91 CaCl2, 2.46 MgSO4·7H2O, 1.38 NaH2PO4, 25 NaHCO3, and 5.56 d-glucose; pH 7.4. Connective tissue was removed under a dissecting microscope, and tracheas were cut in half axially. One-half trachea was used in each myograph bath (DMT, Ann Arbor, MI). The tissue was held at a resting tension of 5 mN, and the buffer was exchanged every 15 min.
zyme). Enzyme was background corrected (substrate and buffer only, no en-
zyme). Assays were conducted as previously described (15). Briefly, confluent cells in 24-well plates were loaded with myo-[3H]inositol overnight. On the study day, after being washed two times in HBSS with 10 mM LiCl, cells were treated with vehicle (0.2% DMSO), rolipram (PDE4-selective inhibitor, 10 μM), or quercetin (100 μM) for 15 min before stimulation with 10 μM bradykinin or histamine in a final volume of 300 μl/well. Assays were stopped at 30 min by the addition of 330 μl cold methanol, and newly synthesized [3H]inositol phosphates were isolated by column chromatography as described (15).

**PDE4D assays.** The PDE4D Assay kit (no. 60345) was obtained from Life Technologies (P6466). The fluorescent indicator 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) was used as the enzyme substrate (Life Technologies D6567). The enzyme (0.25 U/ml) was incubated with increasing concentrations of quercetin (1 μM-100 mM, 3-isobutyryl-1-methylxanthine (IBMX; 250 μM), the PLC inhibitor U-73122 (50 μM), or vehicle (2% DMSO) for 30 min at room temperature in phosphate-free buffer containing 50 mM Tris-HCl, 0.1 mM CaCl2, pH 7.0. DiFMUP (100 μM) was added to the enzyme/inhibitor mix (50 μM final DiFMUP, 0.125 U/ml final PI-PLC), and the fluorescence was read every 2.5 min for 1 h on a FlexStation 3 microplate reader (Molecular Devices). Baseline fluorescence was measured, and either histamine or bradykinin (10 μM final concentration) was injected. Fluorescence was read every 4 s for 3 min. For studies in 0 mM external calcium, the cells were loaded as above. After being loaded, the cells were washed six times with 0 calcium HBSS (supplemented with 200 μM ethylene glycol tetra-acetic acid: EGTA). The remainder of the studies were carried out in calcium-free HBSS including the 15-min incubation with quercetin or vehicle.

**Calcium assays.** Primary human ASM cells were isolated and cultured as described above. They were plated in black-walled, clear-bottom 96-well plates and serum deprived 48 h before the study day. Human ASM cells were loaded with the calcium indicator fura 2-AM, cells were treated with either vehicle (0.1% DMSO) or quercetin (100 μM) for 15 min after which they were placed in a FlexStation 3 microplate reader (Molecular Devices). Baseline fluorescence was measured, and either histamine or bradykinin (10 μM final concentration) was injected. Fluorescence was read every 4 s for 3 min. For studies in 0 mM external calcium, the cells were loaded as above. After being loaded, the cells were washed six times with 0 calcium HBSS (supplemented with 200 μM ethylene glycol tetra-acetic acid: EGTA). The remainder of the studies were carried out in calcium-free HBSS including the 15-min incubation with quercetin or vehicle.

**In vivo airway resistance measurements.** Airway measurements were assessed using a Flexivent FX1 module with an in-line nebulizer (Scireq, Montreal, Canada), as previously described (38). Briefly, animals were anesthetized, paralyzed, and mechanically ventilated (150 breaths/min). Animals were given a 20-s nebulization of either vehicle (0.1% DMSO) or quercetin (100 μM) in PBS 15 min before methacholine challenge. EKG recordings were used to monitor the following this incubation, the binding agent was added for an additional hour at room temperature. The fluorescent polarization was read on a FlexStation 3 microplate reader (excitation 485 nm, emission 538, cutoff 530 nm; G-factor = 1.00), and measurements were corrected for plate blank and expressed as a percent of PDE4D inhibition over vehicle control.

**Isolation of primary human ASM cells.** Discarded human airway tissue was obtained incident to lung transplant at Columbia University, deidentified, and considered surgical waste (Institutional Review Board reviewed and considered exempt). Epithelium and connective tissue were removed, and cells were dissociated as previously described (39) using a papan/collagenase dissociation kit (Worthington Biochemical, Lakewood, NJ). Cells were grown in phenol red-free DMEM-F-12 supplemented with 10% fetal bovine serum and 1X antibiotic-antimycotic until 48 h before study when the serum was removed. In all studies, cells were used at 90–100% confluence and passage number 2–6.

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animals throughout the experiment. Data represent an average of the three highest resistance values at each dose of methacholine.

Statistical analyses. Data were analyzed using ANOVA with repeated measures. Bonferroni correction was applied for multiple comparisons. Statistical significance was established at $P < 0.05$ unless otherwise noted, and all values are expressed as means ± SE.

Materials. Unless otherwise stated, materials were obtained from Sigma-Aldrich. U-73122, rolipram, N$^\omega$-nitro-L-arginine methyl ester (L-NAME), and iberiotoxin were purchased from Tocris. PBS, fura 2-AM, DiFMUP, PLC$\gamma$, DMEM-F-12, FBS, and antibiotic-antimycotic were purchased from Invitrogen. myo-$[^{3}H]$inositol was purchased from Perkin Elmer. The PDE4 assay kit was purchased from BPS biosciences.

RESULTS

Quercetin concentration-dependently relaxes precontracted ASM. In myograph studies using ex vivo A/J mouse tracheas precontracted with an $\sim$EC$_{50}$ of ACh, increasing concentra-tions of quercetin yielded significant and acute relaxation. Relaxation began at 1 μM quercetin, with an EC$_{50}$ for quercetin of 57 μM. Complete relaxation was observed by the 1 mM dose ($n = 12$–16 rings, curve fit with a 4-parameter sigmoid $R^2 = 0.9845$; Fig. 1). In relaxation studies using 100 μM of quercetin, 60% relaxation was achieved within 15 min ($n = 9$ rings, $P < 0.01$ compared with vehicle; Fig. 2). In subsequent studies, 100 μM quercetin was used unless otherwise stated.

Quercetin-induced relaxation is not dependent on large-conductance Ca$^{2+}$-activated K$^+$ channels, or the synthesis of prostaglandins or nitric oxide. To determine the mechanisms responsible for quercetin-induced relaxation, subsequent myograph studies were conducted in the presence of iberiotoxin [100 nM to block large-conductance Ca$^{2+}$-activated K$^+$ channels], indomethacin (10 μM to inhibit endogenous prostaglandin synthesis), and L-NAME (100 μM to prevent nitric oxide production). None of these pretreatments (15 min) attenuated

Fig. 3. Quercetin prevents an ACh-induced contraction. In separate studies, mouse tracheas were precontracted to an $\sim$EC$_{50}$ of ACh. Once force stabilized, tissues were washed with buffer repeatedly and then exposed to vehicle (0.1% DMSO) or quercetin (100 μM) for 7 min at baseline tension. Tissues were exposed to the same EC$_{50}$ concentration of ACh. Following repeated buffer exchanges, tracheal rings were subjected to a third contraction with ACh. No diminution of force was observed in the vehicle-treated tissues; however, quercetin significantly abrogated an ACh contraction that was reversible. A: representative raw force tracings. B: summary of $n = 4$ experiments/group, *$P < 0.05$.

Fig. 4. Quercetin potentiates isoproterenol-induced relaxation in airway smooth muscle. A: in murine tracheal rings contracted with ACh, isoproterenol (ISO) elicited a concentration-dependent relaxation. Vehicle (0.05% DMSO; solid squares) or quercetin (50 μM; open squares) was added concurrently with the 300 pM concentration of ISO. Quercetin significantly potentiated isoproterenol-induced relaxations and caused a leftward shift in the relaxation curve. Curves were fit with a 4-parameter sigmoid to determine ISO EC$_{50}$ concentrations of vehicle (11.7 nM) vs. quercetin (207.9 pM) (**$P < 0.001$ and # $P < 0.05$ compared with vehicle, $n = 7$ rings/group). B: summary bar graph: tissues treated with 50 μM quercetin alone relaxed 35% while tissues receiving a combination of quercetin (50 μM) and isoproterenol relaxed significantly more than isoproterenol alone or quercetin alone (*$P < 0.05$, **$P < 0.001$, and ***$P < 0.001$ compared with vehicle + ISO; ##$P < 0.01$ and ###$P < 0.001$ compared with 50 μM quercetin only, $n = 7$–9 rings/group).
the relaxing capabilities of quercetin (100 μM) (n = 4–9 rings/group, P < 0.01 compared with vehicle; Fig. 2).

**Quercetin prevents an ACh-induced contraction.** Following the determination of an ACh ~EC50 in mouse tracheal rings, rings were then washed and returned to resting tension. Tissues were treated with either vehicle (0.1% DMSO) or quercetin (100 μM) for 7 min and then exposed to the ACh ~EC50 dose again. After 30 min, tissues were washed repeatedly and exposed to ACh ~EC50 for a final time. Pretreatment with quercetin significantly prevented an ACh contraction compared with vehicle-treated tissues. Interestingly, the effects of quercetin were reversible with washing, and there was no significant difference in the magnitude of force achieved in the final contraction between vehicle or quercetin-treated groups (P < 0.05, n = 4; Fig. 3).

**Quercetin potentiates isoproterenol-induced relaxations.** To investigate the effects of the PDE4 inhibitor on β-agonist-induce relaxation, mouse tracheas were contracted with ACh ~EC50 and exposed to increasing concentrations of isoproterenol (100 pM-10 μM; half-log concentrations) at 7-min intervals. Concurrent with the 300 pM isoproterenol concentration, tracheal rings were given a single dose of either vehicle (0.05% DMSO) or quercetin (50 μM). The quercetin-treated groups exhibited a leftward shift in the isoproterenol dose-response curve and a 1.75 log shift in isoproterenol EC50 (11.7 nM vehicle vs. 207.9 pM quercetin: n = 7, P < 0.01 and P < 0.05 compared with vehicle; Fig. 4A). In separate studies, 50 μM quercetin alone relaxed Ach-precontracted tissues by 35.4 ± 3.3%. Figure 4B shows significant potentiation of isoproterenol-induced relaxation in the presence of 50 μM quercetin compared with quercetin only or isoproterenol only treated tissues (n = 7–9, P < 0.05, P < 0.01, and P < 0.001 compared with vehicle + ISO; P < 0.01 and P < 0.001 compared with 50 μM quercetin only; Fig. 4B).

**Quercetin prevents in vivo methacholine-induced increases in airway resistance.** In male A/J mice, increasing doses of methacholine caused robust concentration-dependent increases in central airway resistance as measured using the Flexivent FX1 module. A 20-s nebulization of quercetin (100 μM in PBS) administered 15 min before methacholine challenge significantly attenuated increases in resistance at the 25 and 50 mg/ml doses of methacholine compared with animals nebulized with vehicle (0.1% DMSO in PBS) (n = 6–10, P < 0.01 and P < 0.001; Fig. 5). There was no difference in baseline resistance.
Quercetin inhibits PDE4D in a concentration-dependent manner. In assays using purified PDE4D, quercetin dose-dependently inhibited cAMP degradation when incubated with the enzyme (5 pg/µl) for 20 min. Quercetin (100 nM) showed no difference compared with vehicle (0.1% DMSO), whereas 1 mM showed inhibition of 91% (P < 0.01, n = 5; Fig. 6A). Increasing concentrations of the known PDE4-selective inhibitor rolipram showed significant inhibition of PDE4D (P < 0.05 and P < 0.01, n = 5; Fig. 6B). Quercetin (100 µM) and rolipram (10 µM) had similar inhibition of 80.2 and 74.6%, respectively. In separate studies, the relaxing effects of rolipram (10 µM) were tested in myograph experiments using A/J mouse tracheas as described above. Despite robust PDE4D inhibition in purified assays, rolipram treatment resulted in minimal relaxation of 16.8 ± 3.8% (P < 0.01 and P < 0.001, n = 5–9; Fig. 6C).

Quercetin inhibits phospholipase C activity. In assays using purified PLCβ, quercetin inhibited activity in a concentration-dependent manner. Significant inhibition was seen at 10, 25, 50, and 100 µM quercetin. Attenuation of activity was comparable to that of the known PLCβ inhibitor U-73122 (50 µM). The nonspecific cyclic nucleotide PDE inhibitor IBMX (250 µM) was used for comparison and exhibited no PLC inhibitory action compared with vehicle controls (2% DMSO) (P < 0.05 and P < 0.001, n = 5–9; Fig. 7).

Quercetin prevents inositol phosphate synthesis in human ASM cells. When PLCβ metabolizes phosphoinositol-4,5-bisphosphate, inositol trisphosphate (IP3) and diacylglycerol are produced. Inositol phosphate synthesis was measured in human ASM cells pretreated with either vehicle (0.2% DMSO) or quercetin (100 µM) for 15 min before stimulation with the Gq-coupled agonists bradykinin or histamine (10 µM). Quercetin significantly attenuated bradykinin-induced inositol phosphate synthesis by 53.4 ± 6.7%, likely as a result of PLCβ inhibition as seen above. Similarly, quercetin attenuated histamine-induced inositol phosphate synthesis by 33.3 ± 3.6%. For comparison, the selective PDE4 inhibitor rolipram (10 µM) did not attenuate bradykinin- nor histamine-induced inositol phosphate synthesis (P < 0.01, n = 3–6; Fig. 8A and B), thereby confirming additional signaling effects of the PDE4 inhibitor quercetin on an additional class of PDE enzymes (i.e., PLCβ) in human ASM cells.

Quercetin attenuates Gq agonist-induced increases in intracellular calcium. Following Gq-coupled agonist stimulation, newly synthesized IP3 binds to IP3 receptors on the sarcoplasmic reticulum, which results in increases in intracellular calcium. In primary human ASM cells loaded with the calcium indicator fura 2-AM, pretreatment with quercetin (100 µM; 15 min) attenuated increases in intracellular calcium caused by both bradykinin and histamine (10 µM each) compared with vehicle-treated (0.1% DMSO) controls (P < 0.01, n = 6; Fig. 9A). To determine the role of quercetin on calcium influx, these experiments were repeated in 0 mM external calcium supplemented with the calcium chelator EGTA (200 µM). In these studies, the calcium responses to either bradykinin or

![Fig. 7. Quercetin attenuates purified phosphatidylinositol-specific phospholipase C (PLCβ) activity. Using purified phosphatidylinositol-specific PLC, enzyme activity was measured using a substrate that fluoresces when cleaved. Quercetin inhibited enzyme activity in a concentration-dependent manner compared with vehicle (2% DMSO). The nonspecific cyclic nucleotide PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX, 250 µM) did not affect PLCβ activity, whereas the commercially available PLCβ inhibitor U-73122 (50 µM) significantly attenuated activity (**P < 0.05 and ***P < 0.001, n = 5–9). All measurements were taken at time (t) = 60 min and background corrected.](http://ajplung.physiology.org/)
histamine (10 μM) alone were reduced compared with the responses in 2 mM external calcium, indicating sufficient removal of external calcium. Furthermore, quercetin significantly reduced the calcium response to both of these Gq agonists in 0 mM external calcium (P < 0.01, n = 6; Fig. 9B).

**DISCUSSION**

We have shown for the first time that acute quercetin treatment prevents methacholine-induced increases in airway resistance in mice that respond robustly to inhaled methacholine without allergen sensitization. Additionally, we have shown that quercetin can dose-dependently relax a preconstricted airway as well as prevent a contraction when given before the bronchconstrictor agonist ACh. Furthermore, this PDE4-selective inhibitor potentiates β agonist-induced relaxation. These functional observations are attributed to several signaling mechanisms at the intracellular level, including decreases in intracellular calcium following Gq-coupled agonist stimulation, as well as inhibition of phospholipase C resulting in decreased IP3 synthesis.

Previous studies have examined the bronchorelaxant properties of quercetin, but most have used an allergic asthma model employing repeated ovalbumin sensitization (17, 18, 30, 31). Additionally, these studies have looked at chronic administration of quercetin in the diet, as well as intraperitoneal injections hours before airway measurements. Increasing dietary quercetin consumption is correlated with significant decreases in lung cancer and asthma in a large Finnish population, although no mechanistic data are provided (21). In animal studies, one group aerosolized quercetin, but used a concentration 1,000-fold higher than that used in the present study (30). The current study is the first to show that quercetin can prevent airway hyperresponsiveness in a murine model in the absence of inflammation, which allows for separating the anti-inflammatory components of quercetin from direct effects on the ASM. Additionally, this is the first study to show that quercetin maintains its bronchorelaxant effects when delivered acutely via aerosolization only 15 min before methacholine challenge. These data suggest that quercetin may have benefits during an acute asthma exacerbation regardless of whether there is concomitant airway inflammation.

Quercetin has previously been well-characterized as a cyclic nucleotide PDE inhibitor (6, 22), which has been confirmed in our own studies. PDE4 inhibition by quercetin approximates that of known PDE4 inhibitors rolipram and Ro-20-1724, with IC50 values of 9.9, 2.3, and 8.7 μM, respectively (11, 23, 34).
Studies in guinea pig and rat tracheal smooth muscle preparations show that quercetin and its derivative 3-O-methylquercetin relax ASM contracted with histamine, carbachol, and electrical field stimulation; however, the underlying mechanisms of action of quercetin were not clear (5, 23). In vascular smooth muscle, quercetin induces relaxation via a PKG-dependent mechanism (16). This is likely due to PDE inhibition in the vascular smooth muscle bed leading to increased cGMP, similar to results showing cyclic nucleotide PDE inhibition in the airway that is PDE4-selective. Previous studies in a PDE4D knockout mouse showed attenuated methacholine responsiveness compared with wild-type controls (12). Interestingly, we showed similar attenuations of methacholine responsiveness by acute nebulization of quercetin before bronchoconstrictor challenge, suggesting a functional role of PDE4D inhibition in airway mechanics. Additionally, we showed that quercetin potentiates β-agonist-induced relaxation in isolated airway tissues with a dramatic approximately twofold shift in the isoproterenol EC₅₀. Furthermore, at the concentrations used, synergistic effects were observed as the combination of quercetin (50 μM) and isoproterenol produced greater relaxation than either treatment alone. These data point to the potential therapeutic use of quercetin as a β-agonist-sparing agent.

Recently, an oral PDE4-selective inhibitor, roflumilast, has been approved for the treatment of chronic obstructive pulmonary disease. This is the first PDE inhibitor since nonselective theophylline to target obstructive airway disease; however, no PDE4-selective inhibitor is currently approved for asthma therapy. We have established efficacy of quercetin in preventing increases in airway resistance when delivered via inhalation, a method of delivery not currently available for PDE inhibitors yet the method of choice for many asthma therapies. Our data suggest that PDE4 inhibition is a viable mechanism to prevent airway constriction; however, by itself it does not lead to robust relaxation in our murine model as evidenced by the poor relaxation of airway tissues to rolipram. The combination of quercetin with known β-agonist isoproterenol did acutely relax precontracted airways, suggesting a potential combination therapy.

It was surprising that rolipram did not effectively relax precontracted murine airways in our studies and suggests that quercetin may have additional effects aside from PDE4D inhibition. We are the first to show that quercetin inhibits another PDE enzyme, namely PLCβ. While the importance of PLCβ in ASM is well characterized, it is rarely considered as a PDE in this tissue (4, 29). Additionally, no PLCβ inhibitor has been proposed to target bronchoconstriction in airway diseases; however, our in vivo data suggest that this may provide a complementary avenue for blunting responsiveness to contractile agonists that signal via PLCβ. Furthermore, this inhibition results in decreased inositol phosphate synthesis and intracellular calcium responses subsequent to Gq-coupled agonist stimulation in human ASM cells. Thus this single compound regulates two classical signaling pathways in ASM that pound regulates two classical signaling pathways in ASM that provide a complementary avenue for blunting responsiveness to contractile agonists that signal via PLCβ/H9252.

In addition to traditional asthma therapies, including β-agonists and inhaled corticosteroids, many asthmatics are turning to complementary and alternative medicine for symptom management. The use of alternative therapies is highest in moderate to severe asthmatics, a population that has historically had little relief with current therapies (36). Among alternative asthma therapies is the increasing use of herbal remedies and natural botanicals in the form of ointments, teas, and rubs for the relief of symptoms (20, 25, 28, 32); in fact, upwards of 40% of asthmatics report self-treating their symptoms with herbal therapies (8, 33). These herbal therapies are often used and their dosages modified through a trial and error system with little or no mechanistic evidence for beneficial or detrimental effects in the airway. This study elucidates various signaling mechanisms by which quercetin exerts beneficial effects on the airway in terms of bronchorelaxation and details how this phytotherapeutic may act beneficially with traditional β-agonists to alleviate asthma symptoms.

Taken together our data suggest that quercetin represents an entirely novel therapeutic option in the treatment of asthma due to its action as both an inhaled PDE4 and PLCβ inhibitor with acute bronchodilatory properties. It may have beneficial effects of relaxing ASM during an acute exacerbation when used alone or in combination with existing therapies such as short-acting β-agonists. Additionally, in combination with previous work detailing anti-inflammatory effects, quercetin may have potential as an asthma therapy when used daily to prevent exacerbations.

REFERENCES


