A New Pathway to Airway Relaxation - Targeting the “Other” Cyclase in Asthma

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Significant concerns have recently been raised about sole therapy with inhaled short-acting $\beta_2$-adrenoceptor agonists (SABA) in poorly controlled asthma in the absence of prophylactic anti-inflammatory corticosteroids (ICS) (1, 2). Many individuals still have frequent exacerbations and persistent dyspnea despite escalation of combined ICS and long-acting $\beta_2$-adrenoceptor agonists (LABA). In both scenarios, higher doses of SABA as a rescue medication can lead to potential receptor desensitization and loss of dilator efficacy. Overuse of SABAs has been associated with higher risk of future exacerbations and hospital admissions (3, 4) and identified as one of several preventable factors that leads to higher asthma mortality with increasing disease severity (1, 5).

Given this background, it is important to identify alternative or adjunct bronchodilator therapies that are both safe and effective when responsiveness to $\beta_2$-adrenoceptor agonists has decreased. In a study reported here, Koziol-White and colleagues provide evidence supporting soluble guanylate cyclase (sGC) as a novel therapeutic target (6). Using human precision cut lung slices (PCLS), the authors confirmed the previously reported in vitro dilator responses to the sGC agonists BAY 41-2272 (BAY 41) and BAY 60-2270 (BAY 60) (7). These drugs increased cGMP to similar levels, and had comparable bronchodilator efficacy and potency to the LABA formoterol, which mediates relaxation via activation of the adenylate cyclase (AC) / cAMP / PKA pathway. Notably, responsiveness to both BAY 41 and BAY 60 was maintained under experimental conditions that induced $\beta_2$-adrenoceptor desensitization, when formoterol-mediated relaxation of the airways in human precision cut lung slices was almost completely abolished (6).

Relaxation of vascular smooth muscle via the nitric oxide (NO) / sGC / cGMP / PKG pathway underpins the established use of sublingual NO donors, inhaled NO and
oral phosphodiesterase inhibitors in the treatment of angina and pulmonary hypertension. sGC activators have also shown benefit in numerous preclinical models of pulmonary hypertension. Riociguat, which is structurally similar to BAY 41, was the first in class to move beyond controlled clinical studies to approval (reviewed by 8). However, the cGMP-dependent signaling cascade used by these drugs was previously thought to play only a relatively minor role in the regulation of airway smooth muscle tone, as exemplified by a study where inhaled NO had no effect on airway conductance in either healthy subjects or those with COPD and only elicited limited relaxation in subjects with asthma (9). Koziol-White speculated that the marked dilator responses to BAY 41 and BAY 60 they observed in human lung slices may be driven by their more effective agonism of sGC compared to NO itself (6). Future comparisons of cGMP synthesis by these sGC agonists relative to NO-dependent dilators are required to clarify this possibility since only BAY 41 causes direct NO-independent stimulation of sGC. Nevertheless, their results showed a distinct lack of crosstalk between cGMP and cAMP generation by sGC agonists versus formoterol (6), establishing a feasible mechanism whereby in vitro dilator efficacy of BAY 41 and BAY 60 could be maintained when LABA responsiveness was impaired.

Two major mechanisms have been shown to contribute to the contraction of small intrapulmonary airways in precision cut lung slices. The initiation of airway contraction, observed as agonist-induced Ca^{2+} oscillations localised to the sarcoplasmic reticulum, is termed Ca^{2+} signalling. Sustained contraction mediated via increased activity of protein kinase C and Rho-activated kinase is termed Ca^{2+} sensitivity, and is evident even when Ca^{2+} oscillations are abolished by prior treatment of the lung slices with caffeine and ryanodine (10). β_{2}-adrenoceptor agonists and sGC activators, as a consequence of their distinct second messenger
signalling pathways, could differentially oppose these regulatory mechanisms. In human PCLS, formoterol was previously shown to effectively inhibit histamine-induced Ca\(^{2+}\) sensitivity, but only reduced Ca\(^{2+}\) oscillations when tested at higher concentrations (11). In contrast, both the NO donor NOC-5 and a stable cGMP analogue inhibited serotonin-induced increases in the frequency of Ca\(^{2+}\) oscillations but not contraction due to increased Ca\(^{2+}\) sensitivity in mouse PCLS (12). Since both Ca\(^{2+}\) signalling and sensitivity may be dysregulated in asthma (reviewed by 13, 14), it will be important that the capacities of different dilators to oppose each pathway are separately defined. These results may then inform the potential benefits of sGC agonists relative to SABA and LABA, both separately and in combination, in asthma.

The novel findings of efficacy and resistance to desensitization of sGC agonists require validation in a disease context to support clinical translation. Given the limited availability of isolated airways from asthmatic subjects, human PCLS could be treated in vitro with asthma-relevant inflammatory cytokines such as IL-1, TNF\(\alpha\) and IL-13, an approach that has previously been shown to increase contractile responses and reduce responsiveness to \(\beta_2\)-adrenoceptor agonists (reviewed by 14). This would also complement the current study where overnight treatment with a high concentration of formoterol was used to cause \(\beta_2\)-adrenoceptor desensitization (6). In considering the therapeutic potential of sGC agonists as novel bronchodilators, it should be remembered that their efficacy has already been established in vivo in mouse models of allergic airways disease (7). Intra-tracheal administration of BAY 41 or BAY 60 prior to methacholine challenge in mice previously subjected to short-term exposure to ovalbumin or house dust mite extract afforded significant bronchoprotection. These findings are particularly pertinent for the potential application of sGC agonists as adjunct preventer therapy, but could be extended to...
longer term models when airway hyperresponsiveness is driven by airway remodelling as well as inflammation.

Further intriguing possibilities of therapeutic benefit in response to sGC agonists arise as a consequence of their other reported actions (8). The combined bronchodilator and vasodilator effects of sGC activators could potentially counteract hypoxic vasoconstriction in the treatment of hypoxia-induced pulmonary hypertension, as improved ventilation has the potential to add benefit to the direct vasodilator effect of these drugs. sGC activation has also shown promise in limiting fibrosis, with inhibitory effects both on myofibroblast differentiation in vitro and on the development of bleomycin-induced pulmonary fibrosis (8). If similar findings could be demonstrated in fibroblasts from subjects with asthma and with prophylaxis and treatment of mouse asthma models, this would clearly delineate the activity profile of these drugs from β2-adrenoceptor agonists, which relieve symptoms but not progressive airway fibrosis. sGC activation could have a dual effect in patients with asthma, reducing fibrosis as well as promoting airway relaxation (8).

Clearly, the combined findings obtained by Koziol-White (6) and Ghosh (7) support further investigation of sGC agonists as novel treatments for asthma. As sole SABA therapy loses favor in the face of accumulating evidence of greater benefit with combined LABA / ICS over ICS alone at all stages of asthma (1,2), the limitations of bronchodilator therapy with β2-adrenoceptor agonists still need to be addressed. While a plethora of potential candidates, ranging from calcilytics and bitter taste agonists to relaxin, have received significant support (14, 15), evidence is now accumulating that targeting sGC also effectively opposes airway contraction (6, 7). Showing that sGC agonists are superior bronchodilators to β2-adrenoceptor agonists
in a disease context is the next step to establishing a new pathway, traveling via sGC rather than the more familiar adenylate cyclase route.
References


