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Editorial overview: Respiratory: Pulmonary pharmacology – It is time for a breath of fresh air

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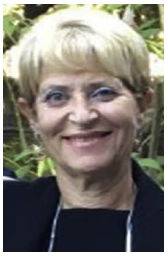

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Pulmonary pharmacology is probably one of the most neglected fields of pharmacology. Unfortunately, researchers who have dedicated or dedicate their interest in this field are very few in the world, probably because pulmonary pharmacology seems unattractive, with little chance of success and, consequently, with few professional opportunities. This explains the slow progress of our knowledge in the treatment of many respiratory diseases.

Basically, if we think as an example to chronic obstructive pulmonary disease (COPD), although it is one of the most prevalent diseases worldwide, for many years we are stuck with the use of bronchodilators, corticosteroids and antibiotics. It is difficult to determine whether this is due to the success that these classes of drugs still have because they can reduce symptoms and often the risk of exacerbations in many patients and also make it easier to choose the treatment with the typical 'one size fits all' attitude, still preferred by many physicians, or just to the fact that we are not yet able to identify new effective therapeutics.

Regrettably, not all patients respond to the 'one size fits all' approach also because the pathogenesis of pulmonary diseases is so complex that it is hard to find a panacea with just a single-target approach. Therefore, there is a strong need to go beyond it by moving towards precision medicine, which should ensure that patients get the right treatment at the right dose at the right time, with minimum harmful consequences and maximum efficacy [1]. This means that not only we must be able to broaden our knowledge on the currently available treatments in order to optimize their use, but also continue with patience and constancy to identify new pharmacological targets that will allow us to develop new therapies that we unquestionably need.

Nowadays, dual combination therapy is the cornerstone for the treatment of patients with COPD. In fact, combinations of LABAs and LAMAs may induce pharmacological and clinical synergistic interaction [2]. The exact nature of the interactions between the different pathways localized at the level of presynaptic parasympathetic fibres and airway smooth muscle cells is not completely understood [3], but there is cross-talk at many levels in airway smooth muscle cells that is also regulated by the activity of calcium-activated potassium channels and protein tyrosine kinases. It is now mandatory that dose-finding randomized controlled trials (RCTs) be conducted to establish the optimal dose ratio between LABAs and LAMAs that allows the identification of the minimal dose for each bronchodilator able to cause appreciable functional and clinical synergies.

Finding new classes of bronchodilators has proved to be very difficult, almost impossible. However, the best understanding of the pharmacological actions

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exerted by currently available bronchodilators can help us to improve the profile of the classes currently on the market [4]. Most bronchodilators are G protein-coupled receptors ligands, which exert their action by either promoting pro-relaxant or inhibiting pro-contractile signalling [5]. Agonists that show higher potency to specific signalling pathways over others are known as 'biased agonists' and have better therapeutic index [6]. Actually, emerging information is shedding new light on the mechanism(s) of biased signalling of the β_2-adrenoceptors and may lead to improved functionally selective molecules. Furthermore, it is likely that small molecule inhibitors of $G\alpha_q$ as well as pepducins targeting G_q-coupled receptors can broadly inhibit contractile agonist-induced airway smooth muscle function.

A possible explanation of the enormous delay in the development of new therapeutic possibilities lies in the complexity of the respiratory system, capable of performing multiple functions, all fundamental and closely related to the others. Actually, the various regulatory systems of which our body is equipped with are all, or nearly so, capable of influencing pulmonary activity sometimes in a positive way, but also in a negative way.

It is well known that airway tone is mainly controlled by the vagus nerve [5] but there is also evidence that the cholinergic anti-inflammatory pathway is one of the most important neuroimmune reflex mechanisms [7], although the role of the cholinergic anti-inflammatory pathway in chronic inflammatory respiratory diseases including COPD and bronchial asthma is not well understood. However, recent studies have shown that the α7 nicotinic acetylcholine receptor (α7nAChR) expressed on Type 2 innate lymphoid cells could be a potential therapeutic target for the treatment of airway diseases in which ILC2s are significantly involved [8].

This is real useful information because COPD is a multicomponent disorder with inflammation and the development of extensive tissue remodelling during the course of the disease process at its core. Therefore, suppression of the inflammatory response is a logical approach to the treatment of COPD [9]. However, hitherto, there is still no effective anti-inflammatory treatment also because inflammation in patients with COPD is at least partly glucocorticoid-resistant [10]. Furthermore, there are no clinically available therapies that prevent COPD disease progression. It is clear that there is a huge unmet medical need with regard to effective anti-inflammatory agents to treat COPD patients.

It has been suggested that inhaled unfractionated heparin may represent an effective add-on-therapy in chronic respiratory diseases with potential to modify disease progression because of its anti-inflammatory, antioxidant and mucolytic effects and also because it is safe and without adverse events associated with anti-coagulation [11]. In effect, there is evidence that inhaled unfractionated heparin provides additional clinical benefit for patients with moderate to very severe COPD through effects that are independent of its anticoagulant activity [12].

However, the recognition that oxidative stress is associated with inflammation suggests that also targeting oxidant-dependent mechanisms should be a promising therapeutic approach to the management of chronic respiratory diseases [13], although the therapeutic effects of antioxidants has been generally disappointing [14]. It is likely that the use of antioxidants in the treatment of asthma or COPD in the future will require the use of precision medicine to identify patients that are likely to benefit from these therapeutic interventions, and also their co-administration with anti-inflammatory therapies.