Epithelial-smooth muscle cooperation is needed for brain natriuretic peptide-dependent bronchorelaxant activity

Brain natriuretic peptide (BNP), a member of the natriuretic peptide family, plays an important role in several activities in the lung, such as bronchodilatation, pulmonary permeability and surfactant production [1]. Plasma levels of BNP are elevated in subjects with stable chronic obstructive pulmonary disease (COPD) even in patients without pulmonary hypertension or cor pulmonale [2]. The BNP-related relaxation of human isolated bronchi, particularly in passively sensitized tissues, suggests that many local factors might regulate the biological activity of BNP [3]. In effect, epithelial integrity is needed for BNP-related post-transductional mechanisms regulating human bronchial contractility in response to both cholinergic and histaminergic stimulation [4]. In humans, acetylcholine has been found in epithelial cells and several studies confirm the pathobiological role of the non-neuronal cholinergic system [5,6]. Effectively, recently it has been demonstrated that, in human isolated bronchi, the BNP-dependent bronchial relaxant effect is induced by quinine, an inhibitor of organic cation transporters that reduces acetylcholine release [4]. This finding suggests that BNP may interact with the muscarinic receptor signalling, mainly with the M2 receptor subtype, regulating the airway smooth muscle function [6]. BNP-dependent relaxant activity is also coupled to the increase of iNOS transcript levels in the isolated bronchi but not in bronchial epithelial cells, and the inhibition NO synthesis by aminoxyguanidine abolished bronchial relaxant effects [4].

Altogether, these data strongly support that BNP induces relaxation of human bronchi through the downstream activation of M2 smooth muscle receptors and that the NO-mediated pathway is a critical downstream regulatory mechanism. Possible mechanisms of muscarinic receptor-mediated regulation of airway smooth muscle tone in asthma and COPD are the increased expression and/or function of signalling molecules essential for muscarinic receptor-mediated contraction, and the exaggerated release of neuronal acetylcholine due to inflammation. Pharmacologically, airway and vascular smooth muscle cells are similar in terms of adrenaline and noradrenaline-mediated signalling, yet they demonstrate opposite effects after exposure to acetylcholine and other inflammatory mediators [7]. Similarly to their vascular and cardiac counterparts [8,9], phenotypic differences of smooth muscle cells have been evoked to explain the different response and suggested to play a role in the pathogenesis of COPD. Phenotypic changes are ultimately determined by multiple stimuli and occur as the consequence of alterations in the intricate balance or reversible state that controls airway smooth muscle cell phenotypic state [9]. Remodelling leading to airway smooth muscle thickening has been reported in experimental models of repeated exposure to allergens [10] and reported to characterize arterial vessels during extensive fibrotic and emphysematous lung remodelling [11]. Additional research is needed to clarify the mechanisms of inflammatory-induced airway smooth muscle hyperplasia in asthma and COPD and the possible contribution of circulating and resident stem cells [12], similarly to vascular smooth muscle cells with aging and cancer [13–17], and to verify the efficacy of new stem cell-mediated therapies [18,19]. The prevalence of synthetic and proliferative features may better explain the airway smooth muscle remodelling and the increased expression and/or function of signalling molecules essential for muscarinic receptor-mediated contraction and the different response to pharmacological stimulation [20].

Conflicts of interest

We declare that we have no conflicts of interest.

References

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