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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 inhibited 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 M_2 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 aminoguanidine abolished bronchial relaxant effects [4].

Altogether, these data strongly support that BNP induces relaxation of human bronchi through the downstream activation of M_2 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 [7,8], 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

[1] Hulks G, Jardine AG, Connell JM, Thomson NC. Effect of atrial natriuretic factor on bronchomotor tone in the normal human airway. Clin Sci (Lond) 1990;79:51–5.
[2] Inoue Y, Kawayama T, Iwanaga T, Aizawa H. High plasma brain natriuretic peptide levels in stable COPD without pulmonary hypertension or cor pulmonale. Intern Med 2009;48:503–12.
[3] Matera MG, Calzetta L, Parascandolo V, Curradi G, Rogliani P, Cazzola M. Relaxant effect of brain natriuretic peptide in nonsensitized and passively sensitized isolated human bronchi. Pulm Pharmacol Ther 2009;22:478–82.
[4] Matera MG, Calzetta L, Passeri D, Facciolo F, Rendina EA, Page C, et al. Epithelium integrity is crucial for the relaxant activity of brain natriuretic peptide in human isolated bronchi. Br J Pharmacol 2011;163:1740–54.
[5] Wessler I, Kilbinger H, Bittinger F, Unger R, Kirkpatrick CJ. The non-neuronal cholinergic system in humans: expression, function and pathophysiology. Life Sci 2003;72:2055–61.
[6] Wessler I, Kirkpatrick CJ. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. Br J Pharmacol 2008;154:1558–71.
[7] Suurmeijer AJ, Clement S, Francesconi A, Bocchi L, Angelini A, Van Veldhuisen DJ, et al. Alpha-actin isoform distribution in normal and failing human heart: a morphological, morphometric, and biochemical study. J Pathol 2003;199:387–97.
[8] Rydell-Tormanen K, Risse PA, Kanabar V, Bagchi R, Czubryt MP, Johnson JR. Smooth muscle in tissue remodeling and hyper-reactivity: airways and arteries. Pulm Pharmacol Ther 2012.
[9] Wright DB, Trian T, Siddiqui S, Pascoe CD, Johnson JR, Dekkers BG, et al. Phenotype modulation of airway smooth muscle in asthma. Pulm Pharmacol Ther 2012.
[10] Johnson JR, Wiley RE, Fattouh R, Swirski FK, Gajewska BU, Coyle AJ, et al. Continuous exposure to house dust mite elicits chronic airway inflammation and structural remodeling. Am J Respir Crit Care Med 2004;169:378–85.
[11] Rogliani P, Mura M, Mattia P, Ferlosio A, Farinelli G, Mariotta S, et al. HRCT and histopathological evaluation of fibrosis and tissue destruction in IPF associated with pulmonary emphysema. Respir Med 2008;102:1753–61.
[12] Orlandi A, Bennett M. Progenitor cell-derived smooth muscle cells in vascular disease. Biochem Pharmacol 2010;79:1706–13.
[13] Ferlosio A, Arcuri G, Doldo E, Scioli MG, De Falco S, Spagnoli LG, et al. Age-related increase of stem marker expression influences vascular smooth muscle cell properties. Atherosclerosis 2012;224:51–7.
[14] Tarallo V, Vesci L, Capasso O, Esposito MT, Riccioni T, Pastore L, et al. A placental growth factor variant unable to recognize vascular endothelial growth factor (VEGF) receptor-1 inhibits VEGF-dependent tumor angiogenesis via heterodimerization. Cancer Res 2010;70:1804–13.

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[15] Manenti G, Bolacchi F, Perretta T, Cossu E, Pistolese CA, Buonomo OC, et al. Small breast cancers: in vivo percutaneous US-guided radiofrequency ablation with dedicated cool-tip radiofrequency system. Radiology 2009;251:339–46.
[16] Salvati E, Scarsella M, Porru M, Rizzo A, Iachettini S, Tentori L, et al. PARP1 is activated at telomeres upon G4 stabilization: possible target for telomere-based therapy. Oncogene 2010;29:6280–93.
[17] Cassinelli G, Zuco V, Petrangolini G, De Cesare M, Tortoreto M, Lanzi C, et al. The curative efficacy of namitecan (ST1968) in preclinical models of pediatric sarcoma is associated with antiangiogenic effects. Biochem Pharmacol 2012; 84:163–71.
[18] Spitalieri P, Quitadamo MC, Orlandi A, Guerra L, Giardina E, Casavola V, et al. Rescue of murine silica-induced lung injury and fibrosis by human embryonic stem cells. Eur Respir J 2012;39:446–57.
[19] Cervelli V, Scioli MG, Gentile P, Doldo E, Bonanno E, Spagnoli LG, et al. Platelet-rich plasma greatly potentiates insulin-induced adipogenic differentiation of human adipose-derived stem cells through a serine/threonine kinase Akt-dependent mechanism and promotes clinical fat graft maintenance. Stem Cells Trans Med 2012;1:206–20.
[20] Matera MG, Calzetta L, Segreti A, Cazzola M. Emerging drugs for chronic obstructive pulmonary disease. Expert Opin Emerg Drugs 2012;17:61–82.

Maria G. Matera
Unit of Pharmacology, Department of Experimental Medicine, Second University of Naples, Naples, Italy

Luigino Calzetta
Laboratory of Systems Approaches and Non Communicable Diseases, IRCSS San Raffale Pisana, Rome, Italy

Daniela Passeri
Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy

Paola Rogliani
Department of System Medicine, University of Rome "Tor Vergata", Rome, Italy

Augusto Orlandi*
Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy

* Corresponding author. Tel.: +39 06 20903960; fax: +39 06 20902209.
E-mail address: orlandia@uniroma2.it

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