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Review Article

Possible involvement of acetylcholine-mediated inflammation in airway diseases

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Abbreviations:
ACh, acetylcholine; ASM, airway smooth muscle; cAMP, cyclic adenosine monophosphate; ChAT, choline acetyltransferase; CHT1, high-affinity choline transporter 1; CSE, cigarette smoke extract; ERK, extracellular signal-regulated kinase; ICAM-1, intercellular adhesion molecule 1; IκBα, inhibitor of NF-κB-alpha; LAMA, long acting muscarinic antagonist; M_1, type 1 muscarinic receptor; M_2, type 2 muscarinic receptor; M_3, type 3 muscarinic receptor; M_4, type 4 muscarinic receptor; M_5, type 5 muscarinic receptor; MMPs, matrix metalloproteinases; NF-κB, nuclear factor-kappa B; RNA, ribonucleic acid; STAT-1, signal transducer and activator of transcription 1; TGF, transforming growth factor; VAChT, vesicular acetylcholine transporter

ABSTRACT

Inhaled bronchodilator treatment with a long acting muscarinic antagonist (LAMA) reduces symptoms and the risk of exacerbations in COPD and asthma. However, increasing evidence from cell culture and animal studies suggests that anti-muscarinic drugs could also possess anti-inflammatory effects. Recent studies have revealed that acetylcholine (ACh) can be synthesized and released from both neuronal and non-neuronal cells, and the released ACh can potentiate airway inflammation and remodeling in airway diseases. However, these anti-inflammatory effects of anti-muscarinic drugs have not yet been confirmed in COPD and asthma patients. This review will focus on recent findings about the possible involvement of ACh in airway inflammation and remodeling, and the anti-inflammatory effect of anti-muscarinic drugs in airway diseases. Clarifying the acetylcholine-mediated inflammation could provide insights into the mechanisms of airway diseases, which could lead to future therapeutic strategies for inhibiting the disease progression and exacerbations.

Introduction

Inhaled bronchodilator treatment with a long acting muscarinic antagonist (LAMA) has been demonstrated to reduce symptoms and the risk of exacerbations as well as improve the health status and exercise tolerance in COPD.[1,2] Recently, LAMA has been also shown to reduce symptoms and decrease the risk of exacerbations in asthma.[3,4] These effects are thought to be mainly mediated by a bronchodilatory effect and inhibitory effect on mucus secretion by the drug. However, increasing evidence from cell culture and animal studies suggests that anti-muscarinic drugs could possess anti-inflammatory effects.[5,6] Recent studies have revealed that acetylcholine (ACh) can be synthesized and released from both neuronal and non-neuronal cells, and the released ACh could potentiate airway inflammation and remodeling in airway diseases.[6] This

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review will focus on recent findings about the possible involvement of ACh in airway inflammation and remodeling via muscarinic receptors, and the anti-inflammatory effect of anti-muscarinic drugs in airway diseases.

Cholinergic regulation in airways

ACh is recognized as a neurotransmitter in the nervous system that regulates various activities including neural transmission, smooth muscle contraction and mucus secretion. In airways, cholinergic innervation is the predominant neural bronchoconstrictor pathway.[7] Chronic irritants such as cigarette smoke and air pollution, or mediators released from inflammatory cells stimulate airway sensory nerve C-fibers, which release ACh from efferent nerve endings via the vagal reflex pathway[7,8] (Fig. 1). Recently, the cholinergic regulation of airways has actually been demonstrated in COPD patients by bronchoscopic ablation of parasympathetic pulmonary nerves surrounding the main bronchi.[9]

Until now, five muscarinic receptor ($M_{1\text{-}5}$) genes have been cloned, but, $M_{1\text{-}3}$ receptors are functionally recognized in the lungs.[5,10] Smooth muscle contraction is mainly mediated by M_3.[5,11] M_2 may also participate in the contraction via Gi protein which leads to a decrease in cAMP.[12,13] On the other hand, M_2 is located on postganglionic nerves and acts as feedback inhibitory receptors to inhibit ACh release from nerves. M_2 dysfunction is thought to be involved in airway hyperresponsiveness in asthma.[7,12] M_1 is detected on airway parasympathetic ganglion cells and shown to mediate facilitatory neurotransmission and also identified in airway submucosal glands.[14,15]

Nicotinic receptors are also stimulated by ACh and multiple isotypes of nicotinic receptors including muscle and neuronal types have been identified.[16] Nicotinic receptors are ligand-gated ion channels and are localized to parasympathetic ganglia, where they facilitate neurotransmission[5,16] (Fig. 1). Nicotinic receptors are also present in various cells including airway epithelial cells, macrophages, lymphocytes and type 2 innate lymphoid cells,[16–21] and the stimulation of nicotinic receptors mainly causes putative anti-inflammatory effects, but also causes mucus formation in airway epithelial cells and a proliferative effect on tumors.[16,22]

Currently available LAMAs show similar affinity to M_1, M_2, and M_3. However, LAMAs show greater kinetical selectivity for M_3 and M_1 than M_2 because they have a longer half-life of dissociation from M_3 and M_1 than that from M_2.[6,23] The bronchodilatory effect of LAMA is mainly attributed to M_3 inhibition. M_3 receptors are also involved in mucus secretion and, therefore, LAMAs are known to inhibit mucus secretion.[15] One of the LAMAs, tiotropium or

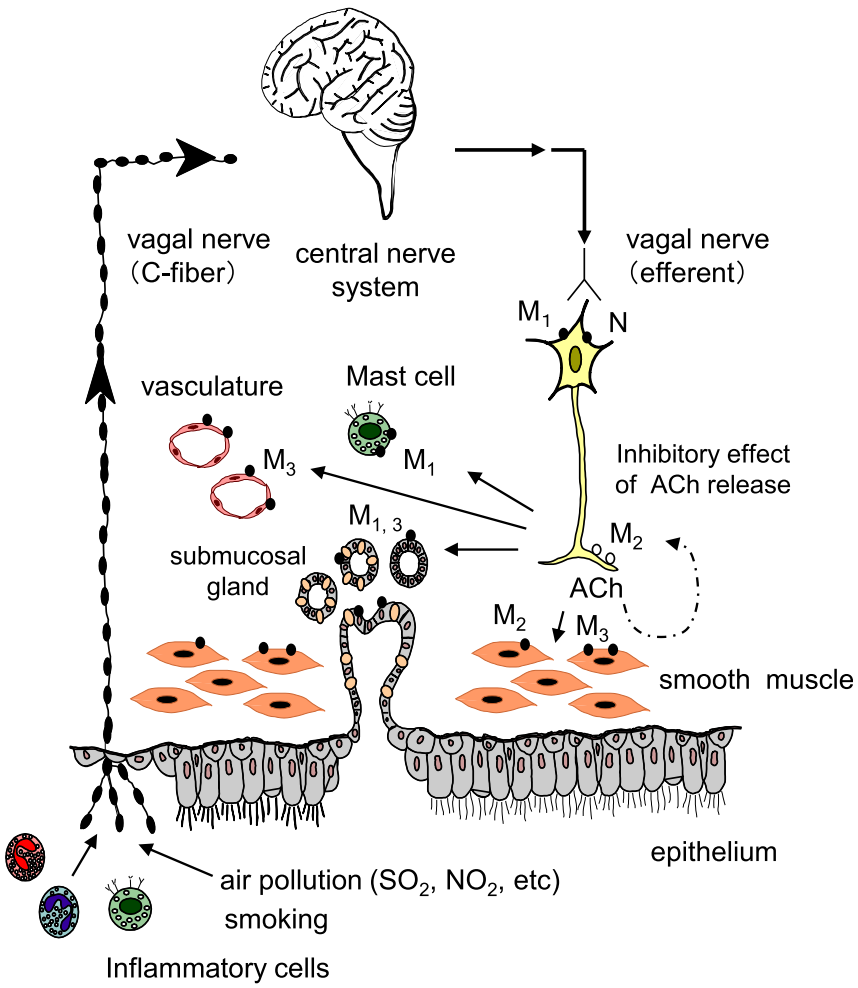

Fig. 1. Cholinergic regulation in airways. Chronic irritants such as cigarette smoke and air pollution, or inflammatory cells stimulate airway sensory nerve C-fibers, which release acetylcholine (ACh) from efferent nerve endings via the vagal reflex pathway. Released ACh induces smooth muscle contraction mainly via type 3 muscarinic receptors (M_3). M_2 may also participate in the contraction. On the other hand, M_2, which is located on postganglionic nerves, acts as feedback inhibitory receptor to inhibit ACh release from the nerve. M_1 and nicotinic receptors (N) are detected on airway parasympathetic ganglion cells to mediate facilitatory neurotransmission. ACh also induces mucus secretion via M_1 and M_3 and vasodilatation mediated by M_3. Modified from the Ref.[8] and extended.

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