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New scientific findings on the mucokinetic effect of ambroxol

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The use of ambroxol is recommended by the German Society for Pneumology and Respiratory Medicine [1] to reduce symptom intensity and accelerate the recovery from acute and subacute cough. As mucoactive, it stands out by its mucokinetic effects, increasing cilia beating in the airways to remove the mucus. A new study [2] has now shed light on further details of the signalling pathway responsible for the mucokinetic action of ambroxol.

Known mechanisms of action of ambroxol

Ambroxol stimulates the activity of goblet cells, thereby reducing the viscosity of bronchial mucus. It also stimulates the production of surfactant in type II pneumocytes, and in consequence, the mucus formed does adhere less to bronchial walls. Both mechanisms facilitate coughing up. Furthermore, in vitro studies suggest antibacterial and antiviral properties of ambroxol: it reduced both, the number of pathogens and the formation of inflammatory mediators in infections with rhinoviruses in primary human tracheal epithelial cells [3] and suppressed the multiplication of the influenza virus in a mouse model [4]. In addition, ambroxol has anti-inflammatory properties, by modulating various cytokines. Ambroxol also has a local anaesthetic effect via inhibition of sodium channels.

Importance of mucociliary clearance

Mucociliary clearance (MCC) is a defence mechanism of the lungs that comprises three components: the surface mucous layer (SML), the periciliary layer (PCL) and the beating cilia (tiny hair-like structures), which line the surface of the airways and perform coordinated beating movements within the PCL [2]. With regard to the latter, the ciliary beat frequency (CBF) and the ciliary bend angle (CBA) are of particular importance for the effectiveness of the ciliary beat, and therefore for the mucous movement. Inhaled particles (e.g. bacteria or viruses) are trapped by the SML and transported by the cilia beating in the PCL to the oropharynx, where they are swallowed or coughed up. Thus, drugs that directly activate cilia beating are of particular interest either for the prevention or improvement of many respiratory diseases related to enhanced mucus production. Despite the relevance of this specific effect of ambroxol, the underlying mechanism of action remains poorly understood.

Novel insights into ambroxol-induced and calcium-mediated signalling in murine ciliated lung airway epithelial cells

A prior investigation highlighted that ambroxol enhances the movement and bending amplitude of cilia in cells by raising the level of calcium within the cells [5]. This increase is achieved by facilitating the release of calcium from internal cell storage and, more importantly, through the entry of calcium into the cell via specific calcium channels ($Ca_V1.2$). The following research by Nakahari and colleagues [2] has further elucidated that the observed enhancements in ciliary activity are primarily governed by two cellular signalling mechanisms: one related to the cellular pH level, and the other one to the concentration of chloride ions within the cell. Initially, ambroxol triggers the specific calcium channels in ciliated lung epithelial cells, leading to a rise in cellular calcium. This surge in calcium activates a transporter mechanism that imports bicarbonate (HCO_3^-) into the cell, thereby elevating the cell's internal pH and, consequently, boosting ciliary beat frequency and amplitude. Additionally, the increase in calcium levels stimulates a protein (anoctamine 1 or ANO1) that speeds up the release of chloride ions from the cilia, reducing the internal concentration of chloride ions. Detailed analysis of these mechanisms showed that the pH-related pathway contributes to a significant increase in both ciliary beat frequency (by 30%) and amplitude (by 15–20%), whereas the chloride ion pathway also enhances amplitude (by 10–15%) but does not noticeably affect ciliary beat frequency.

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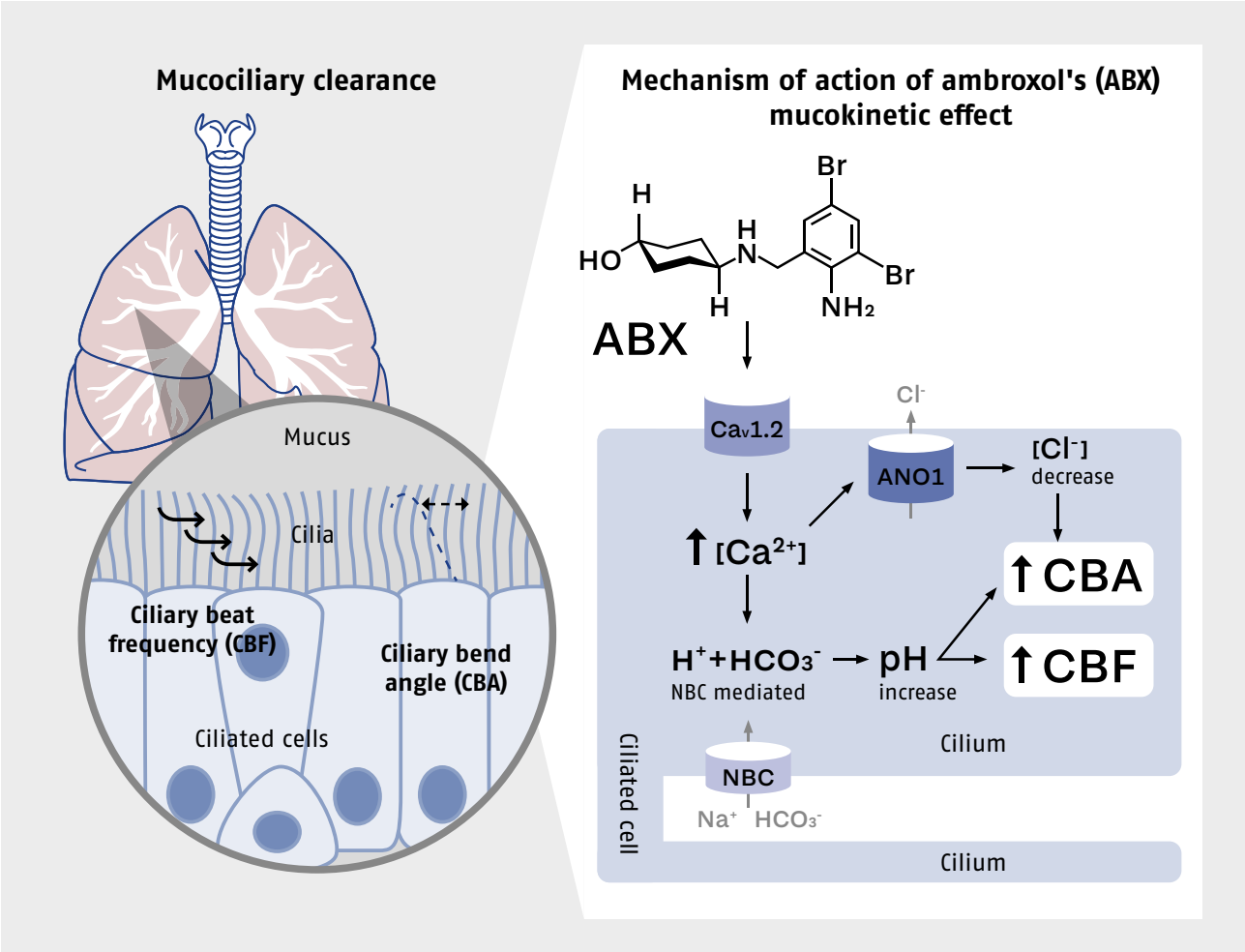

Fig. 1. Schematic diagram of the ambroxol-stimulated mucokinetic effect.
Ambroxol (ABX) stimulates the Ca^{2+} entry via $Ca_V1.2$ and increases internal calcium levels. In turn, calcium increase stimulates NBC to accelerate bicarbonate (HCO_3^-) entry. The HCO_3^- entering via NBC binds H^+ to increase internal pH. The Ca^{2+} entry directly stimulates ANO1 in cilia to activate Cl^- secretion, which decreases internal chloride levels. The internal pH increase enhances the CBF and CBA; while internal [Cl^-] decrease enhances the CBA [modified according to 2].

Clinical translation: Recommendation of ambroxol for acute cough

To our knowledge, ambroxol is the only mucoactive drug for which such a precise mucokinetic mechanism of action has been described. This underlines the striking evidence that its mucokinetic action, beside its secretolytic effect, takes an important role in the benefit of ambroxol treatment.

Literature

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