Phosphodiesterases as Drug Targets in Respiratory Diseases

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Recently, several new drugs have been introduced to treat obstructive lung diseases associated with inflammation. Inhibiting certain phosphodiesterase (PDE) isoenzymes (in particular PDE3 and PDE4) have become attractive drug targets because an increase in cAMP can relax smooth muscle and suppress inflammation. PDE inhibitors, both nonselective and selective, exert a broad spectrum of favorable effects potentially beneficial in acute lung damage as well as in impaired ciliary motility. Methylxanthines as representatives of nonselective PDE inhibitors may reduce cough, lead to bronchodilation as well as suppression of inflammation, potentially beneficial also in acute lung injury. Various (selective) PDE3, PDE4, and PDE5 inhibitors have also demonstrated stabilization of the pulmonary epithelial–endothelial barrier and reduction the sepsis- and inflammation-increased microvascular permeability, and suppression of the production of inflammatory mediators, which finally resulted in improved oxygenation and ventilatory parameters. The role of PDE inhibitors in airway cilia-driven transport may help in prevention of progressive loss of pulmonary function often observed despite current therapy. Furthermore, administration of selective PDE inhibitors by inhalation lowers the risk of their systemic effects. Selective (PDE1, PDE4) or dual PDE inhibitors (PDE3/4) also increase the intracellular level of cyclic nucleotides in airway epithelial cells and thus may be an important target in the development of new inhaled mucokinetic agents. Despite the fact that PDE inhibitors have been studied for decades, their full therapeutic potential in respiratory diseases after systemic and local (inhaled) administration is still unclear. However, the current lack of sufficient clinical evidence limits their recommendation for a broader use.

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