Abstract

The M_2 and M_3 subtypes of the muscarinic receptors are involved in smooth muscle contraction in the airways and lungs. Excessive activation of muscarinic receptors is associated with serious diseases such as asthma or chronic obstructive pulmonary disease. Blocking of muscarinic receptors is already utilized in the treatment of these diseases. Long-acting muscarinic antagonists are used as part of the therapy for these diseases simultaneously with anti-inflammatory corticosteroids and agonists of β_2-adrenergic receptors, which induce smooth muscle relaxation. The natural substances vasicine and vasicinone isolated from dull plant Malabar nut *(Justicia adhatoda)* have been historically used to treat lung diseases, where they stimulate smooth muscle relaxation. Based on modifications of their structures, a series of substances with a modified quinazoline skeleton of the original structure vasicinone was prepared. These substances exert bronchodialtional activity on isolated rodent trachea.

The aim of this diploma thesis was to confirm that the bronchodilatory effect of four quinazoline derivatives is mediated by the blocking of muscarinic receptors and also clarify in more detail the mechanism of action on muscarinic receptors. For this purpose, binding and functional pharmacological analysis of four quinazoline derivatives were performed. It has been confirmed that quinazoline derivatives bind to all muscarinic receptor subtypes M_1 to M_5. Quinazoline derivatives blocked the carbachol agonist-induced response of all subtypes of muscarinic receptors. Thus, the bronchodilatory effect of quinazolines from preliminary *ex vivo* experiments is at least in part due to the blockade of the muscarinic receptors M_2 and M_3. Binding and functional analysis further demonstrated the allosteric mode of interaction of quinazoline derivates with muscarinic receptors. Because of the structural similarity to the acetylcholinesterase inhibitor tacrine, the effect of the VN45b derivative on this enzyme was examined. It was found that at pharmacological relevant concentrations (corresponding to its affinity for muscarinic receptors M_2 and M_3) VN45b does not decrease acetylcholinesterase activity. [IN CZECH]

Keywords: muscarinic receptor, quinazolines, asthma, COPD, bronchodilatation, allosteric interactions, acetylcholinesterase [IN CZECH]