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Title: Involvement of the BK channels/G proteins processes in the synergistic effects between anticholinergic agents and beta₂-adrenoceptor agonists in airway smooth muscle

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Body: Rationale: Long-acting muscarinic antagonists (LAMAs) and long-acting beta₂-adrenoceptor agonists (LABAs) are widely used therapy for COPD. This study was designed to determine whether synergistic effects are observed between LAMAs and LABAs in airway smooth muscle. Moreover, signal transduction pathways were examined in this phenomenon. Methods: For record of isometric tension, the strips of tracheal smooth muscle of guinea pigs were placed in the organ bath and were perfused with the physiological solution at constant flow rate of 3 ml/min. Results: 1 nM indacaterol, a LABA, and 10 nM glycopyrronium bromide (GB), a LAMA, caused 8.9% (n=21) and 24.9% (n=12) inhibition of 1 μM methacholine-induced contraction, respectively. However, when 10 nM GB was applied in the presence of 1 nM indacaterol, the inhibitory effects of GB/indacaterol combination were markedly augmented to 49.1% inhibition (n=10, P<0.01). In contrast, in the presence of 100 nM charybdotoxin, an inhibitor of large conductance Ca²⁺-activated K⁺ (BK) channels, this greater effect in indacaterol/GB combination was markedly attenuated. When the tissues were treated with 1 μg/ml pertussis toxin, which inhibits G_i, or 2 μg/ml cholera toxin, which activates G_s, for 6h, the effects of GB was significantly enhanced. Conclusions: The combination of indacaterol with GB causes synergistic action against muscarinic contraction in airway smooth muscle. This phenomenon is mediated by attenuation in the G_i/BK channel inhibitory linkage and augmentation in the G_s/BK channel stimulatory linkage. Therefore, LAMA/LABA combination may be a useful therapy for COPD.