Acute and Chronic Treatment with Glucocorticosteroids, Modifying the $\beta_2$-Adrenergic Response of the Guinea Pig Trachea

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Abstract. The effect of $\beta_2$-adrenoceptor agonists on airway smooth muscle relaxation may be subject to desensitization. It could be modified by glucocorticosteroid treatment. An increase in the $\beta_2$ agonist response by glucocorticosteroids in vitro has been described. We studied the effects of acute and chronic treatment with dexamethasone on the relaxation response of tracheal smooth muscle to $\beta_2$ agonists, fenoterol and salbutamol. Fenoterol showed a greater force of relaxation than salbutamol, and both drugs induced desensitization. Acute treatment with dexamethasone reduced desensitization to both $\beta_2$ agonists. Chronic treatment (120 $\mu$g/kg of dexamethasone for 7 days) reduced the desensitization to fenoterol alone. Dexamethasone (200 $\mu$g/kg for 7 days) increased relaxation to salbutamol and reduced desensitization to both drugs. The interaction between $\beta_2$ agonists and glucocorticosteroids could be important in the clinical use of both drugs in the treatment of asthma.

Key words: $\beta_2$-adrenoceptor agonists—Glucocorticosteroids—Desensitization—Airways—Smooth muscle.

Introduction

Glucocorticosteroids are the main antiinflammatory treatment for bronchial asthma. They reduce the mediators released from different inflammatory cells [10, 16] but other actions could be involved in their antiasthmatic effects.
β2-adrenoceptor agonists are widely used in the symptomatic treatment of asthma. The chronic use of these drugs as bronchodilators may be subject to desensitization [14, 22, 23]. In vitro [1, 17] and in vivo [18] desensitization can be induced on airway smooth muscle after exposure to β agonists. However, the clinical importance of this process is not well established [2].

Some authors have indicated that glucocorticosteroids increase the bronchodilator effects of β2-adrenoceptor agonists and reduce desensitization [11–13, 21]. In vitro administration of glucocorticosteroids increases the response to β2 agonists [17, 21], but the effects of acute and chronic treatment with glucocorticosteroids in vivo on β2 agonist response are still not clear.

To study the effects of glucocorticosteroid treatment on β2-adrenergic response, we investigated the effect of treatment with a single dose and another daily dose of dexamethasone, given for a period of 7 days as “pure” glucocorticoid, on the airways smooth muscle-relaxing effects of two β2 agonists in vitro: salbutamol (partial agonist) and fenoterol (full agonist) [19]. In addition the effects of dexamethasone on the development of tachyphylaxis were examined.

Methods

Experimental Design

Male albino Dunkin-Hartley guinea pigs (400–500 g) were randomly allocated to one of the following experimental groups: (1) controls (untreated guinea pigs), (2) guinea-pigs subjected to acute treatment with one dose of dexamethasone (200 μg/kg i.p.), or (3) guinea-pigs subjected to chronic treatment with 120 or 200 μg/kg i.p. dexamethasone for 7 days. The treated animals were sacrificed 3 h after administration of the last dose of dexamethasone.

Guinea pig isolated trachea

Guinea pigs were killed by a blow to the back of the head, and the whole trachea was removed. After removing the adherent connective tissue, the trachea was cut into rings three cartilage bands in width, and each ring was suspended in a 6-ml organ bath containing Krebs solution of the following composition (mM): NaCl, 118; KCl, 4.75; CaCl2, 2.5; KH2PO4, 1.19; NaHCO3, 25; MgSO4, 1.2; and glucose 11. The preparation was maintained at 37°C and continually bubbled with 5% CO2 in O2. The tracheal ring was suspended vertically between two stainless steel wire hooks, one attached to a Letica TRI-110 isometric force transducer (Letica Scientific Instruments, Spain) and the other to a stationary support in the organ bath. Changes in isometric force were recorded on a four-channel Oscillographic Recorder L6-60-106 (Letica Scientific Instruments). The experiments were performed with the epithelium intact.

Protocols

At the beginning of each experiment a force of 1.0 g was applied to the tissues. A period of 90 min was allowed for equilibration of the tissue. The tone of the smooth muscle was then increased by the induction of a phasic contractile response with a submaximal dose of carbachol (3 × 10⁻⁶ M). When the contraction rate was stable, cumulative increasing doses of β2-adrenoceptor agonists