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Exercise-induced bronchoconstriction: The role of inhaled therapy in identifying stimulus and mechanism

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Exercise-induced bronchoconstriction (EIB) and exercise-induced asthma (EIA) are terms used to describe the transient narrowing of the airways that follows vigorous exercise. The forced expiratory volume in one second (FEV_1) is used as a measure of airway narrowing. EIB is expressed as the fall in FEV_1 measured after exercise, as a percentage of the FEV_1 measured immediately before exercise. A fall of 10% or more in FEV_1 is regarded as diagnostic of EIB. While EIB most commonly occurs in people with clinically-recognized asthma, it is frequently documented in school children, defense force recruits and elite athletes without other symptoms of asthma. A fall in FEV_1 of 15% is more likely to be associated with active airway inflammation consistent with a diagnosis of asthma.

The factors determining the degree of bronchoconstriction provoked by exercise are the ventilation reached and sustained during exercise and the water content of the air inspired during exercise. The more intense the exercise and the drier the inspired air, the greater the decline in FEV_1 following exercise in a susceptible person.

While inspiring cold air during exercise can enhance EIB, severe EIB has also been documented when hot dry air (> 40°C) is inspired. EIB is inhibited or completely prevented when exercise is performed while inspiring fully-saturated air (100% relative humidity) at body temperature.[1]

Based on these observations, and the recognition that the volume of airway surface liquid (ASL) is very small (< 1 ml) in the 8 to12 generations of airways used to humidify the air, it was proposed that EIB was due to dehydration and a transient increase in osmolarity of the ASL.[2] This hyperosmolar environment provided a stimulus for release of mediators from surrounding mast cells and nerves. These mediators include histamine, prostaglandin D_2 and leukotriene E_4 and the neurokinins, with all having potential to act on specific receptors on airway smooth muscle to cause contraction and airway narrowing. The development of drugs to inhibit EIB helped to understand the mechanisms underlying EIB.

The 1960s: The first agent to treat EIB

Exercise is a common trigger for an attack of asthma and early studies of the effects of pharmacological agents on EIB in the 1960s included children. While the beta-sympathomimetic agent isoprenaline, given by inhalation, inhibited EIB, the duration of its protective effect was less than 1 hour and unwanted side effects, such as tachycardia and tremor, limited its use, particularly in children.

The first inhaled agent of significance for prophylactic treatment of EIB was disodium cromoglycate (DSCG) in 1968. Its potential benefit had initially been identified as inhibiting the IgE-mediated release of mast cell mediators in response to allergen inhalation. This drug was delivered as an encapsulated dry powder from a Spinhaler (Fisons, PLC) in a dose of 20 mg. The beneficial effect it provided after inhalation was immediate and DSCG prevented both the early- and late-phase response to inhaled allergens. The beneficial effect on exercise was variable, with excellent inhibition of EIB in about 37% of children, moderately good inhibition in about 30%, with the remaining subjects having no significant inhibition of their EIB.[3] DSCG provided no protection when given immediately at the end of exercise, indicating that the events that led to EIB occurred during exercise and before the FEV_1 began to fall. While the onset of action of DSCG was immediate, the duration of its protective effect against EIB was usually less than 2 hours.

The 1970s: Beta$_2$-agonists

By the mid 1970s, beta-agonists specifically targeting the beta$_2$-receptors in the lung, became widely available as aerosols. These drugs had fewer cardiac effects than isoprenaline and provided a longer duration of protection against EIB than did DSCG. A study comparing inhaled salbutamol (200 mcg) with oral salbutamol (4 mg) found that, while both formulations induced equivalent bronchodilation, only the aerosol prevented EIB.[4] It was proposed that the

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aerosol was more effective because it achieved sufficient concentration in the airways to prevent release of mediators from mast cells in addition to being a functional antagonist of their contractile effect on the smooth muscle.

In the early studies, designed to support this proposal, there were technical issues relating to identifying mast-cell-derived histamine in the blood and a rise in histamine levels after exercise was not a universal finding in asthmatics with severe EIB.[5] The direct evidence for prevention of the mediator, prostaglandin D_2, by a beta$_2$-agonist[6] has only recently become available and is consistent with findings from similar studies with DSCG.[7] Another recent study has reported higher numbers of mast cells in the epithelium of those with EIB than those without EIB.[8]

The 1980s: Inhaled corticosteroids and nedocromil sodium

Inhaled corticosteroids given daily over weeks were identified in 1983[9] as effective for inhibiting EIB, as were leuokotriene antagonists (administered as tablets) in the mid-1990's.[10] Nedocromil sodium aerosol (4 mg per actuation), with a profile similar to DSCG, replaced DSCG in the 1990s. All these agents confirmed the concept that inflammatory cells and their mediators were playing a central role in causation of EIB.

EIB stimulus and mechanism

The site of action for EIB being close to the airway surface was established by the inhibitory effects of breathing warm humid air during exercise. These studies provided evidence for dehydration of the airways being the stimulus to EIB. It was, however, the finding that inhaled drugs such as DSCG and the beta$_2$-agonists could inhibit EIB by preventing the release of mast cell mediators that finally indicated the mechanism for the transient airway narrowing in response to exercise.

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