

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

“Why do some asthmatics have EIB and others not?”

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MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

The stimulus for EIB is

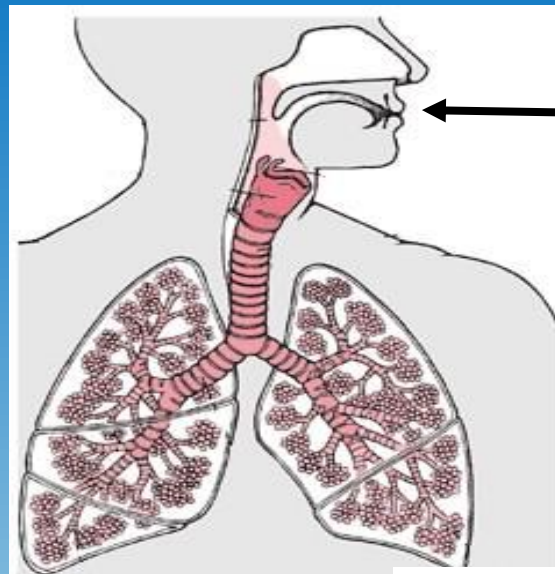
- * water loss from the airway surface liquid with high ventilator efforts, especially in dry air and,
- * heat loss from the airway

Much of the original research into the mechanisms of EIB focused on two different proposals:

The respiratory water loss mechanism: Dr. Sandra Anderson

The heat loss mechanism: Dr. Regis McFadden

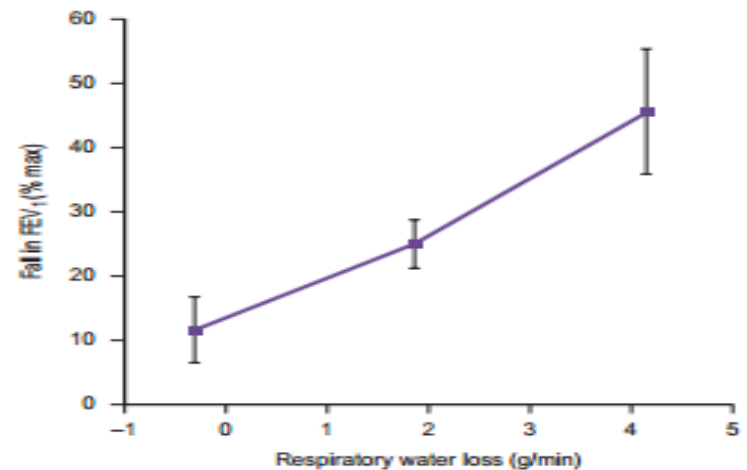
Water Loss During Exercise



Ambient Air
(60°F, 70% RH)

Transfer Heat
and Water

Lower Airways
(98°F, 100% RH)



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Figure 57-3 Relationship between respiratory water loss and bronchoconstriction during eucapnic voluntary hyperpnea. Asthmatic patients inhaled gases with identical heat-carrying but differing water-carrying capacities to demonstrate that severity of bronchoconstriction is strongly tied to amount of respiratory water loss, but not to amount of respiratory heat loss. During these experiments, esophageal temperature did not decline during exercise. FEV₁, Forced expiratory volume in 1 second. (Drawn from data in Argyros GJ, Phillips YY, Rayburn DB, Rosenthal RR, Jaeger JJ. Water loss without heat flux in exercise-induced bronchospasm. *Am Rev Respir Dis* 1993;147:1419-24.)

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

Water Loss During Exercise:

Water loss from epithelial cells causes release of ATP, which signals through specific G protein receptors, activating chloride channels.

This activates inflammatory cells such as mast cells, which then release inflammatory mediators.

Adenosine, a marker for ATP, increases in exhaled breath condensate after exercise

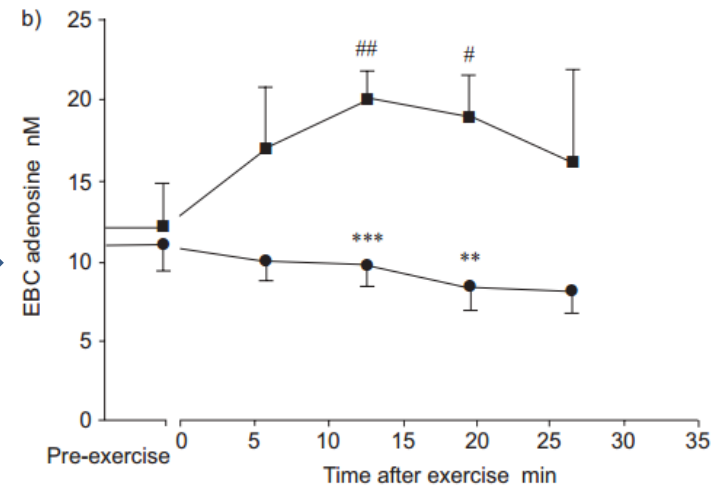


FIGURE 3. Time course of changes in post-exercise forced expiratory volume in one second (FEV₁; a) and in exhaled breath condensate (EBC) adenosine (b) in healthy control volunteers (●) and asthmatic patients (■). Data are presented as mean \pm sd for $n \geq 6$ subjects. Significances are expressed as the difference between controls and asthmatic patients (*) and the difference between baseline and post-exercise values (#). One symbol: $p < 0.05$; two symbols: $p < 0.01$; three symbols: $p < 0.001$.

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

RESPIRATORY HEAT LOSS:

Heat loss does occur and leads to constriction of the bronchial venules initially, but then after exercise there is rebound vasodilatation. This leads to bronchoconstriction.

Although the water loss stimulus appears to be primary, heat loss with rebound bronchoconstriction plays a significant role in cooler climates. Both mechanisms may apply in our EIB patients.

Kippelen P, Immunol Allergy Clin N Am 33 (2013) 299-312

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

The stimulus of airway drying and cooling is the same when asthma patients exercise, but:

- *Not all asthmatics have bronchoconstriction with exercise
- * EIB patients ONLY have asthma with exercise
- * Only some athletes have EIB, not all

Why do some asthmatics have EIB and others not?

Some reasons for this may be:

1. Genetic predisposition for EIB
2. Increased chemical mediators and cellular inflammation in EIB patients
3. Increased airway permeability
4. Ion channel changes/aquaporin dysregulation
5. Sensory nerves
5. Modulators/amplifiers

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

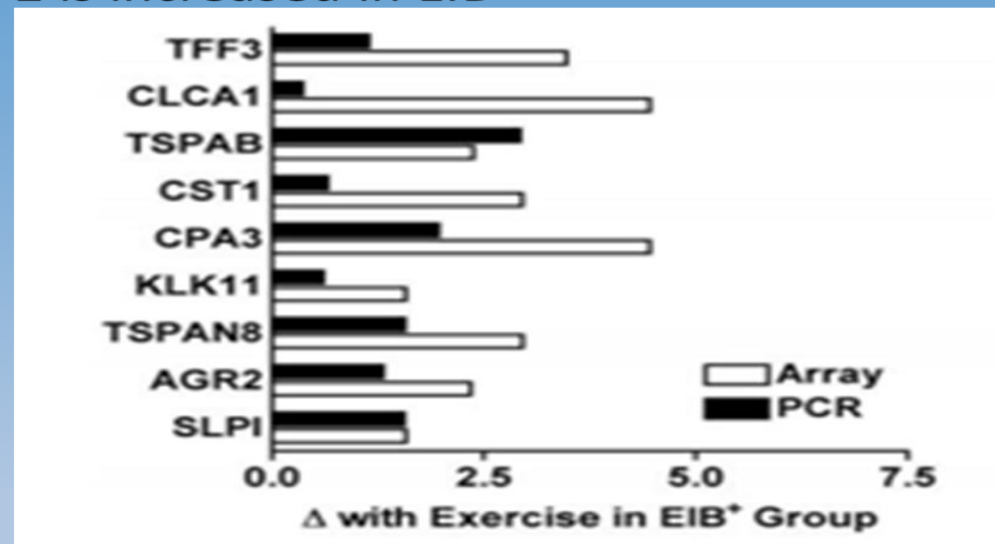
1. Genetic predisposition:

EIB patients may have different genetic makeup than non-EIB patients:
Transglutaminase-2, mucin, and aquaporin are implicated.

Mediators in EIB - Genes:

Genes which lead to inflammation are increased in the airways of subjects with EIB.

Specifically, transglutaminase-2 is increased in EIB and upregulates eicosanoid Formation.

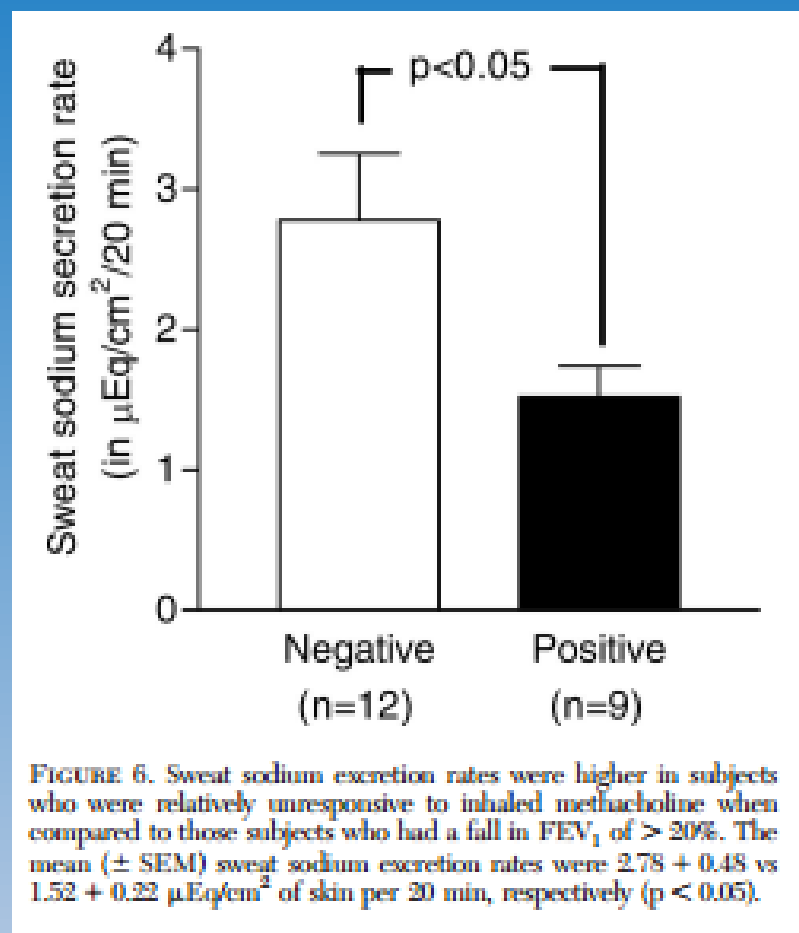


Genetics: Diminished Sweat Secretion in EIB

Subjects with positive methacholine testing showed reduced sweat secretion (by pilocarpine skin challenge).

This supports an abnormal muscarinic parasympathetic response in subjects with EIB due to less secretory capability.

Lack of aquaporin 5 (discussed in later slides) may be the reason for this (data from mice that have diminished sweat secretion).



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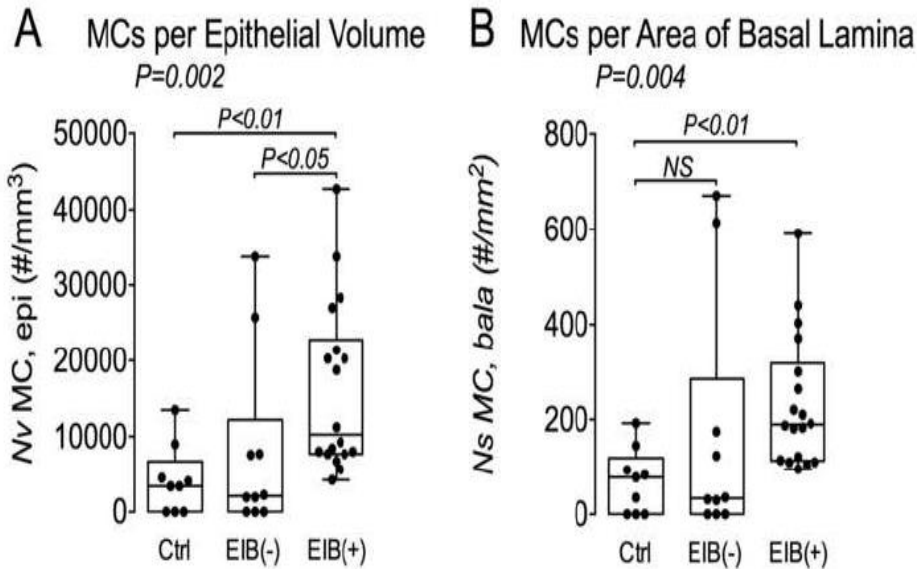
1. Genetic predisposition
2. Inflammatory Mediators in EIB

Susceptible EIB patients have increased cellular inflammation:

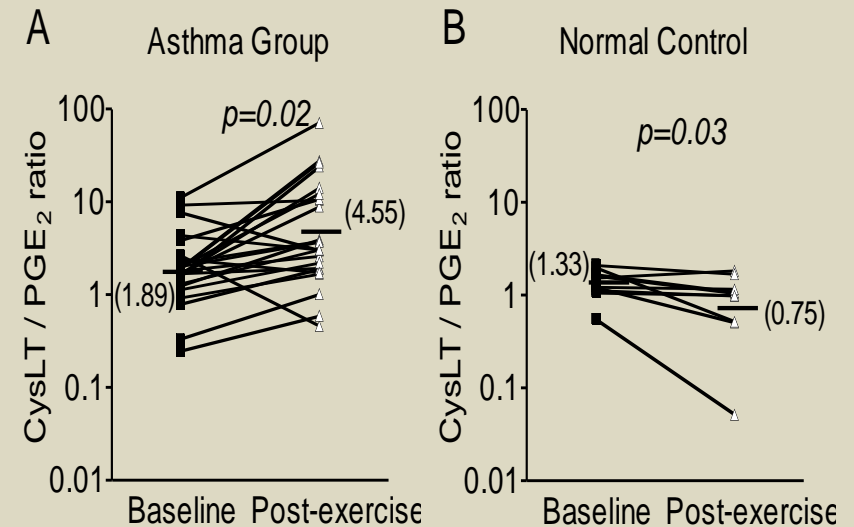
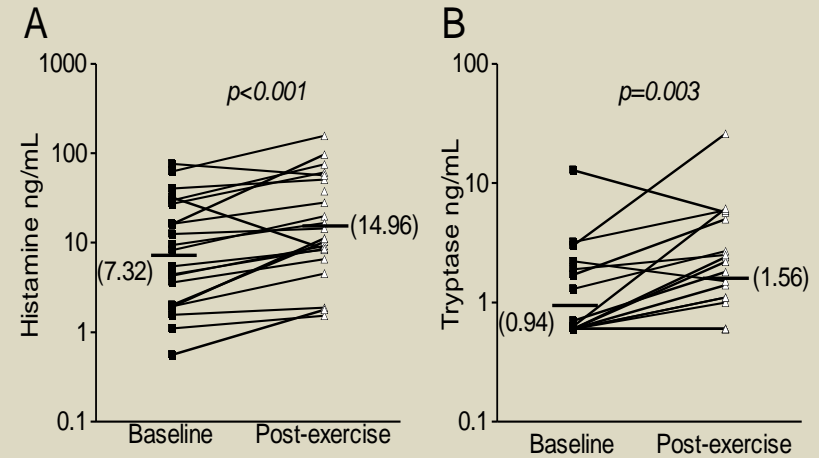
- *eosinophils, mast cells, leukotrienes, histamine
- *cytokines, PGD₂, MUC5A, eosinophil products, etc.

INCREASED MEDIATOR RELEASE IN EIB:

Mast cells are increased in patients with EIB



Histamine, Tryptase, Leukotrienes

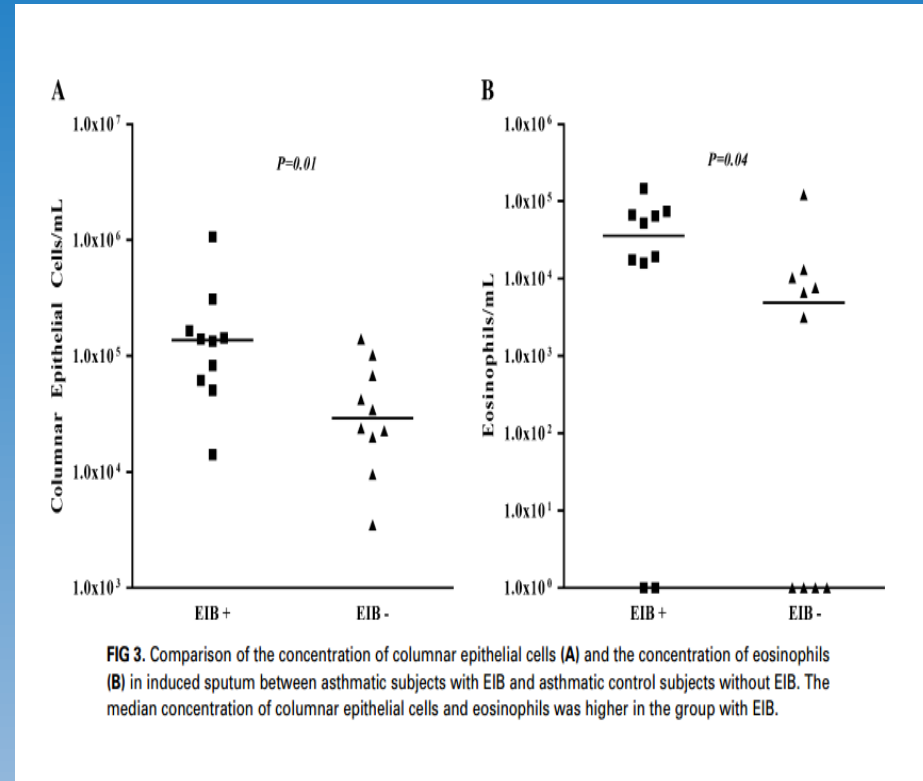


Mediators in EIB: eosinophils, epithelial cells

EIB+ patients have increased eosinophils and more columnar epithelial cell shedding.

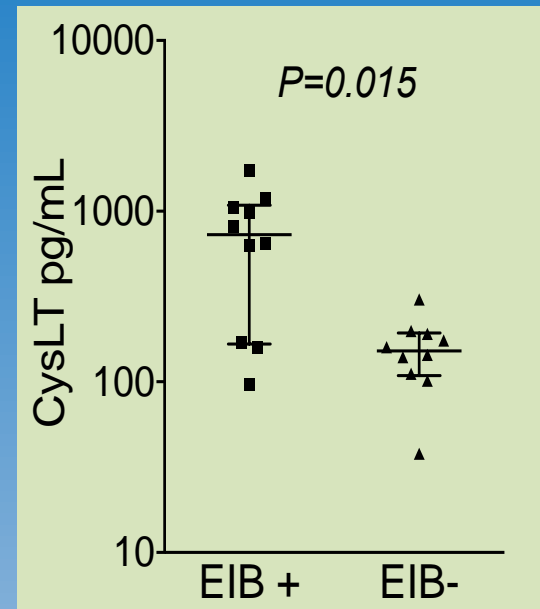
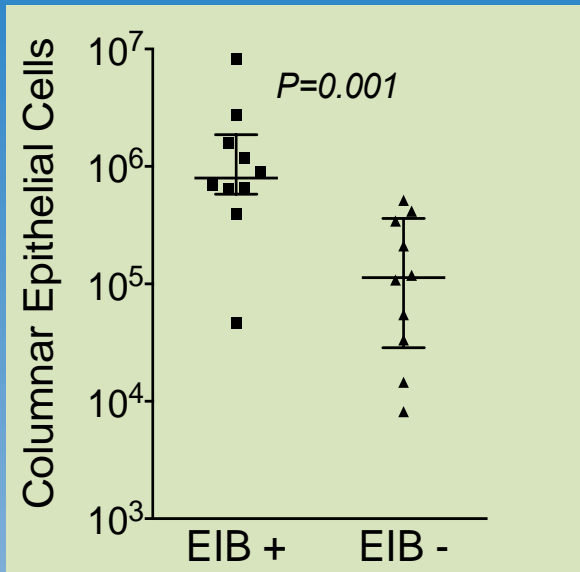
CC16 levels rise, indicating epithelial injury

Additionally, epithelial cells release phospholipase A2X, which activates eosinophils to release leukotrienes.



MEDIATORS: EPITHELIAL CELLS:

EIB+ patients have more epithelial cell disruption than non-EIB+ patients



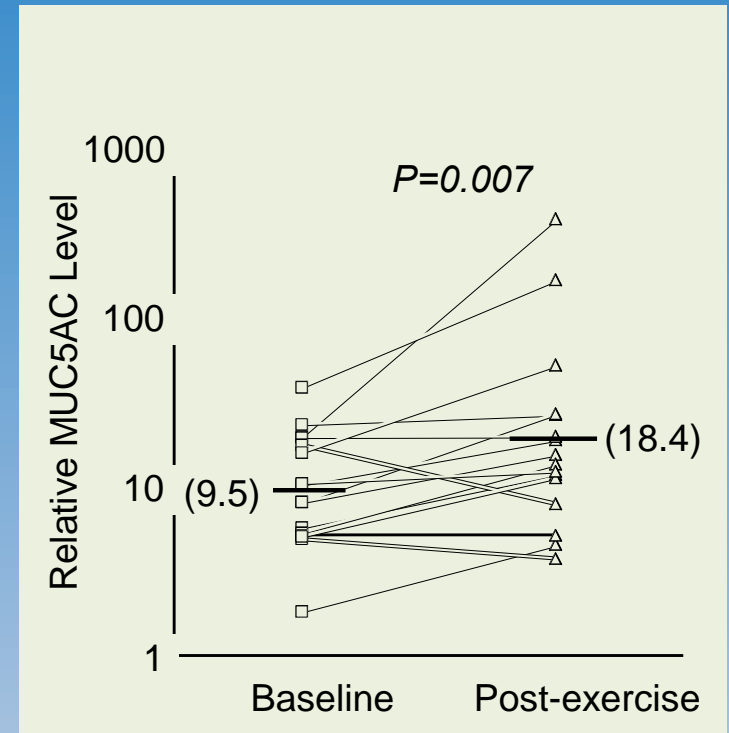
Epithelial shedding is also linked to increased IL-17 and IL-22.

There is a possible underproduction of PGDE2 and lipoxin (which inhibit EIB).

MEDIATORS: MUCIN

Patients with EIB have enhanced mucin release as compared to asthmatics without EIB.

MUC5AC is the predominant gel-forming mucin released in EIB. It is probably released thru leukotriene associated activation of sensory airway nerves.



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Why do some asthmatics have EIB and others not?

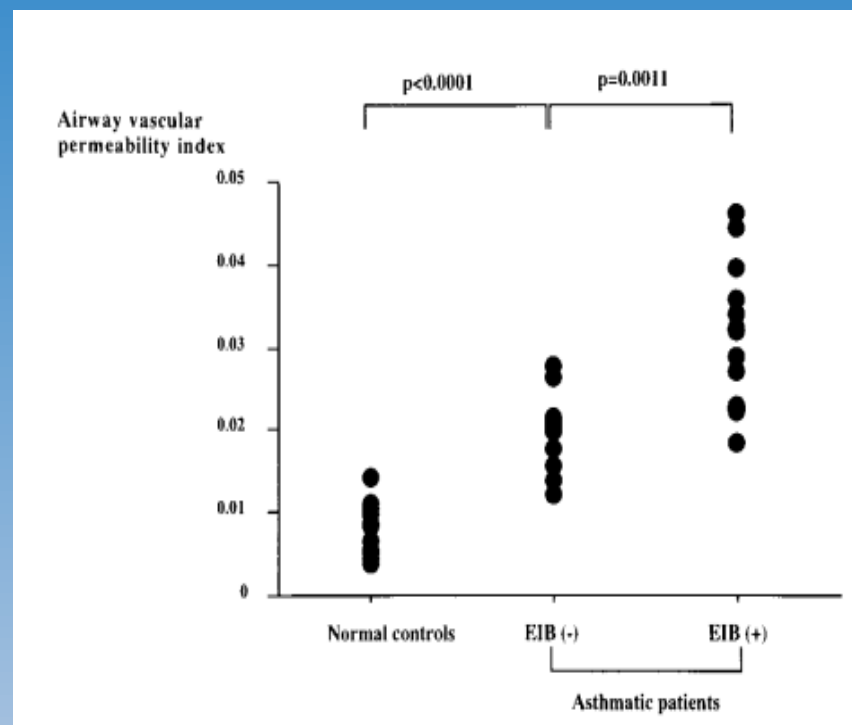
Some reasons for this may be:

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3. Increased airway permeability
4. Ion channel changes/aquaporin dysregulation
5. Sensory nerves
6. Modulators/amplifiers

Airway Vascular Permeability is Increased in EIB+ Patients

The airway vascular permeability index is the ratio of albumin in sputum versus serum.

EIB+ asthmatics have increased permeability, which leads to bronchoconstriction.



ION CHANNELS AND MEDIATORS IN EIB:

Water loss from epithelial cells activates chloride channels and leads to increased intracellular calcium (which may explain the protective effect of cromones).

Inflammatory mediators, chemical stimuli, pollutants and other inhaled substances may affect the TRP ion channels and cause sensory nerve stimulation and bronchoconstriction.



Aquaporins:

**the membrane water channels
of the biological world**

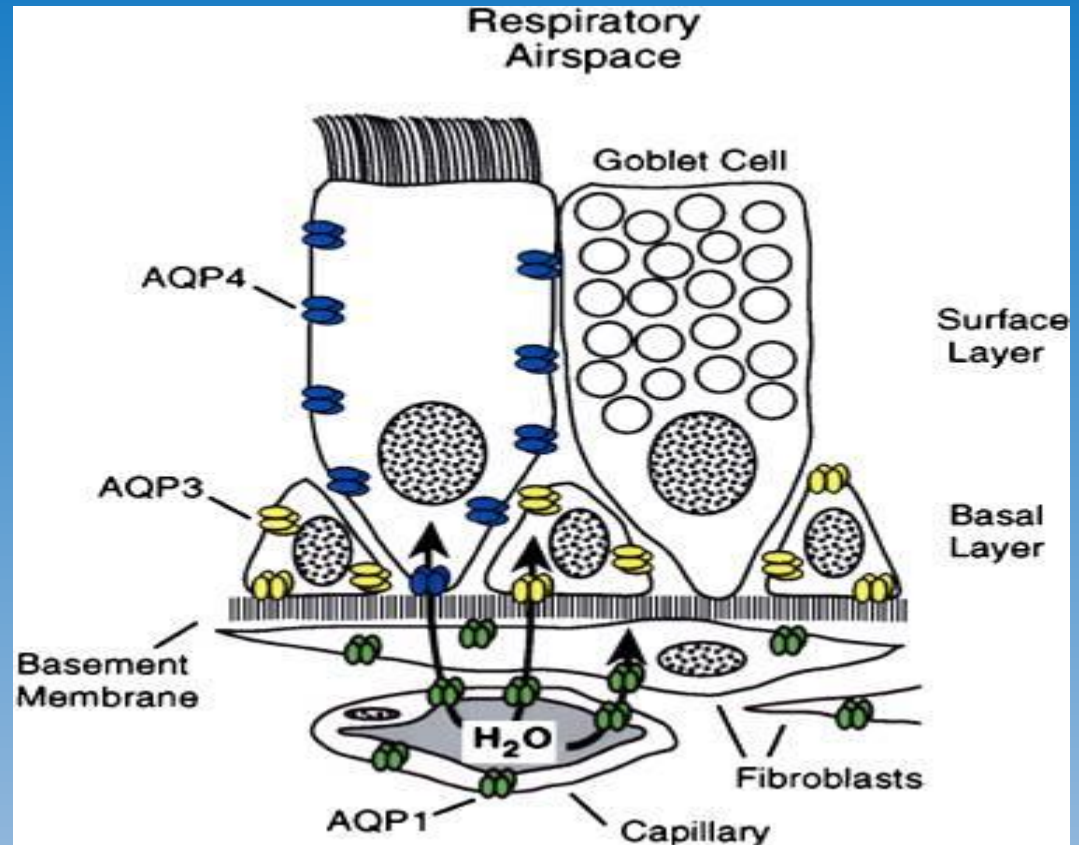
Aquaporins are membrane-spanning proteins present in many cells, including respiratory epithelium, blood vessels, fibroblasts, etc; they regulate water homeostasis in and out of cells.

Studies in animal models of asthma suggest that they may play a role in asthma and possibly EIB.

Peter Agre. The Aquaporin Water Channels

Proc Am Thorac Soc Vol 3. pp 5–13, 2006

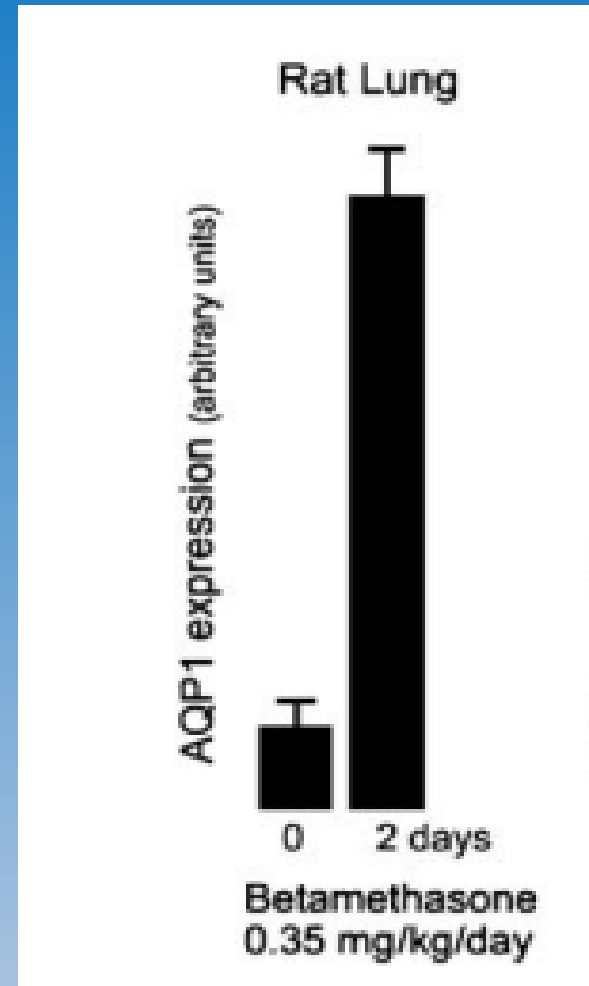
AQP4 is found in surface columnar cells;
AQP3 in basal cells; and
AQP1 in fibroblasts and capillaries



A dysregulation of aquaporins could explain why some patients have EIB and others do not.

Effects of Steroids on Aquaporins

Steroids Cause Marked Increases in Aquaporins (rat model).
This may explain one reason inhaled steroids work well in EIB.



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Role of Sensory Nerves in EIB: lessons from cough research:

TRPV receptors in the airway (red dots) interact with vagal afferent nerves; they can be activated by osmotic stimuli, irritants, gases, leukotrienes, etc.

Sensory nerves release neurokinins thru retrograde axonal transmission, which leads to bronchoconstriction and mucus release.

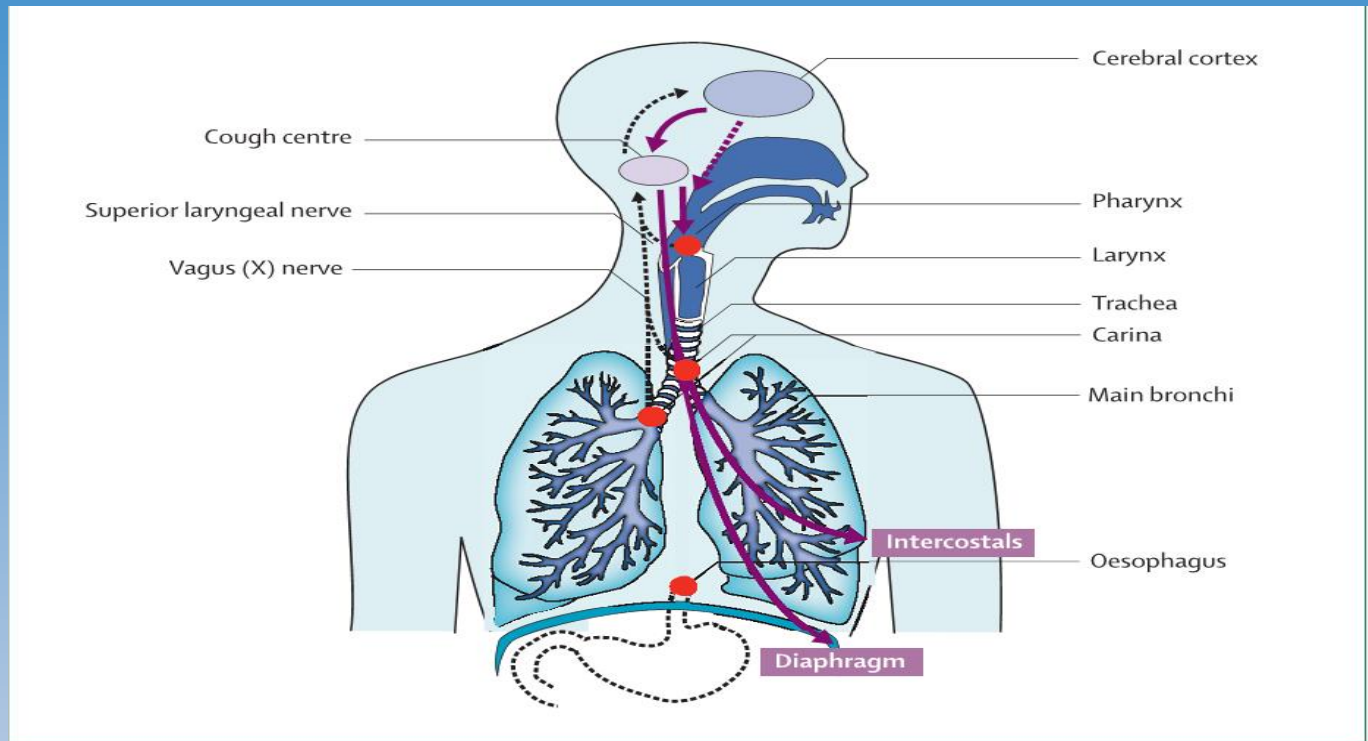


Figure 1: Anatomical representation of neural pathways for cough

Cough receptors (shown in red colour) at the airway bifurcations, in the larynx and at the distal oesophagus, link to cough afferents through the vagus and superior laryngeal nerves to the cough centre and cerebral cortex. Efferent pathways coordinate the muscle response that leads to a cough.

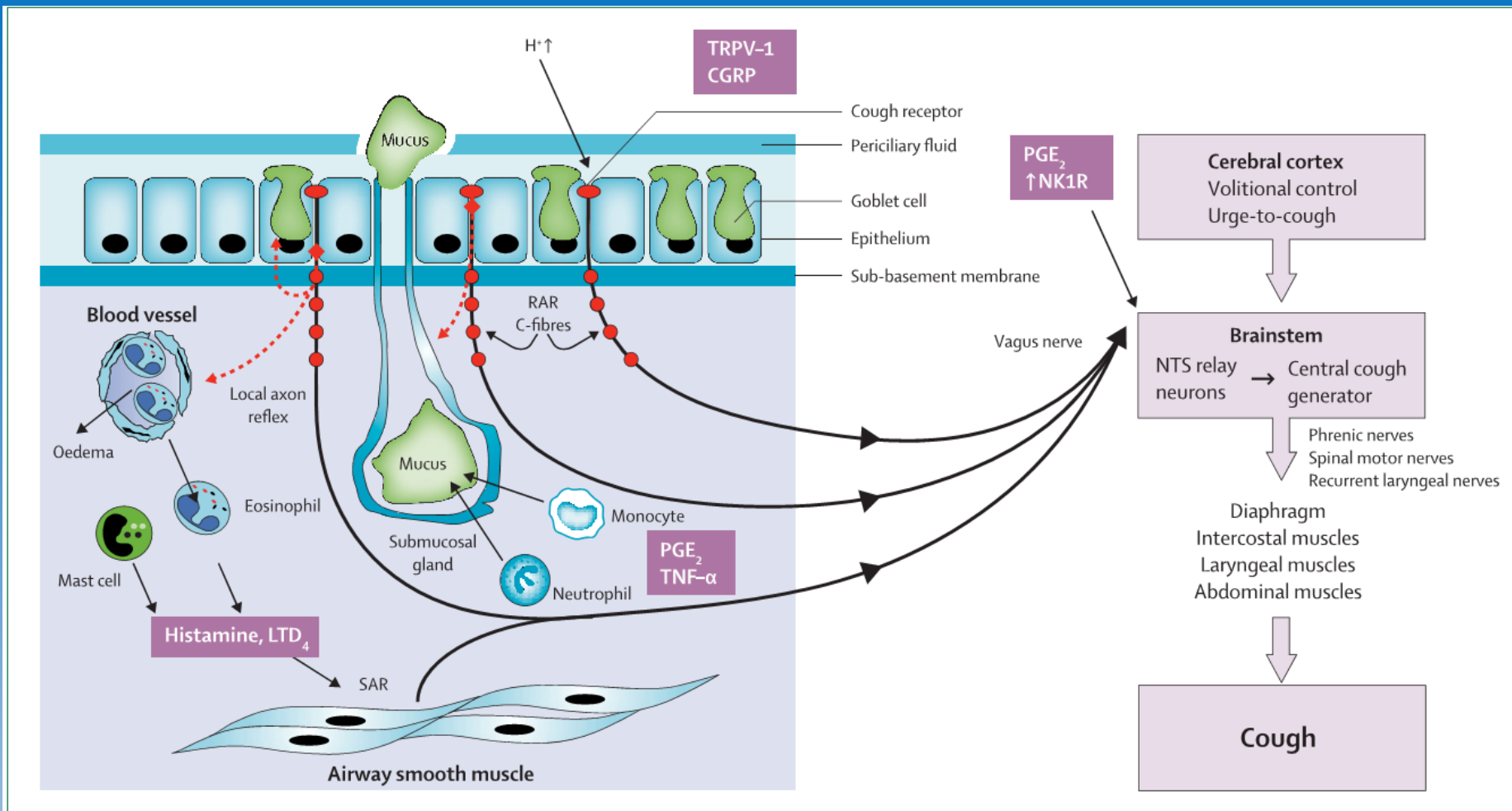


Figure 2: Representative scheme of afferent and efferent pathways that regulate cough, and of the pathophysiology of the enhanced cough reflex Laryngeal and pulmonary receptors, such as rapidly adapting receptors (RARs), C-fibres, and slowly adapting fibres (SAR), and cough receptors provide input to the brainstem medullary central cough generator through the intermediary relay neurons in the nucleus tractus solitarius (NTS). The central cough generator then establishes and coordinates the output to the muscles that cause cough. An output to airway smooth muscle and mucosal glands (not shown) is also present. The cerebral cortex can control the motor output of cough volitionally, or influence the urge-to-cough sensation. Factors that act in the upper airways or brainstem, to enhance the cough reflex, are illustrated. CGRP=calcitonin gene-related peptide. LTD₄=leukotriene D4. PGE₂=prostaglandin E. NK1=neulokinin-1. TRPV=transient receptor potential vanilloid. TNF=tumour necrosis factor.

TRPV receptors in the airways have 'plasticity'. Continued stimulation, such as frequent exercise, will cause the receptors to be hypersensitive and more reactive.

This hypersensitivity may be another reason that athletes exercising frequently will have EIB.

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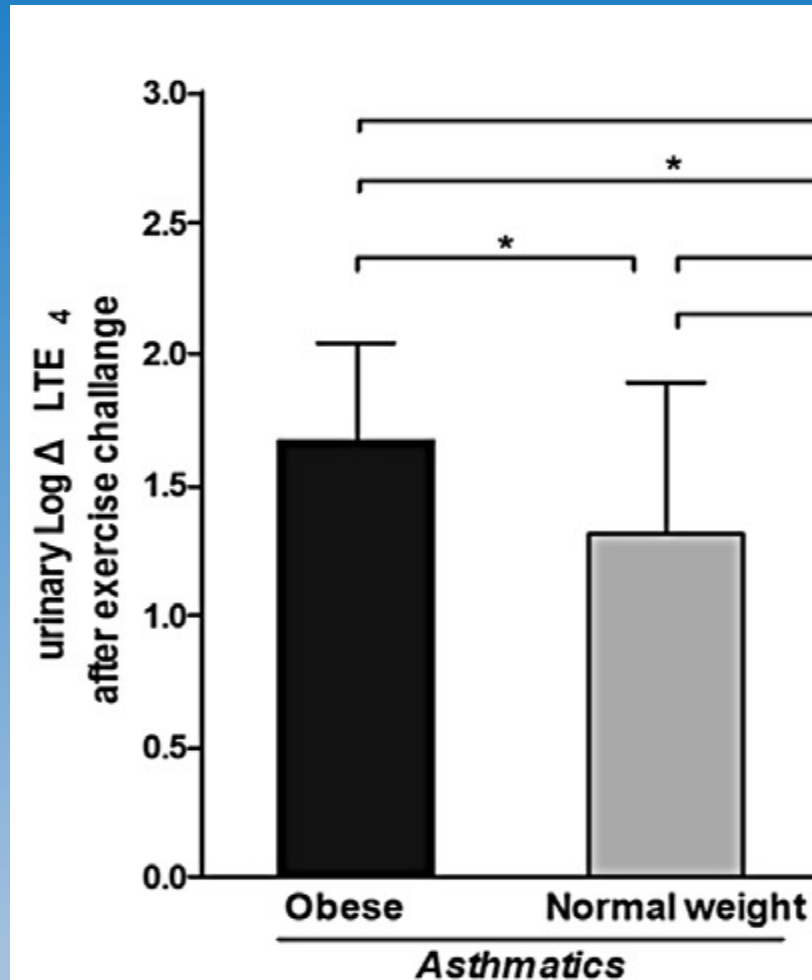
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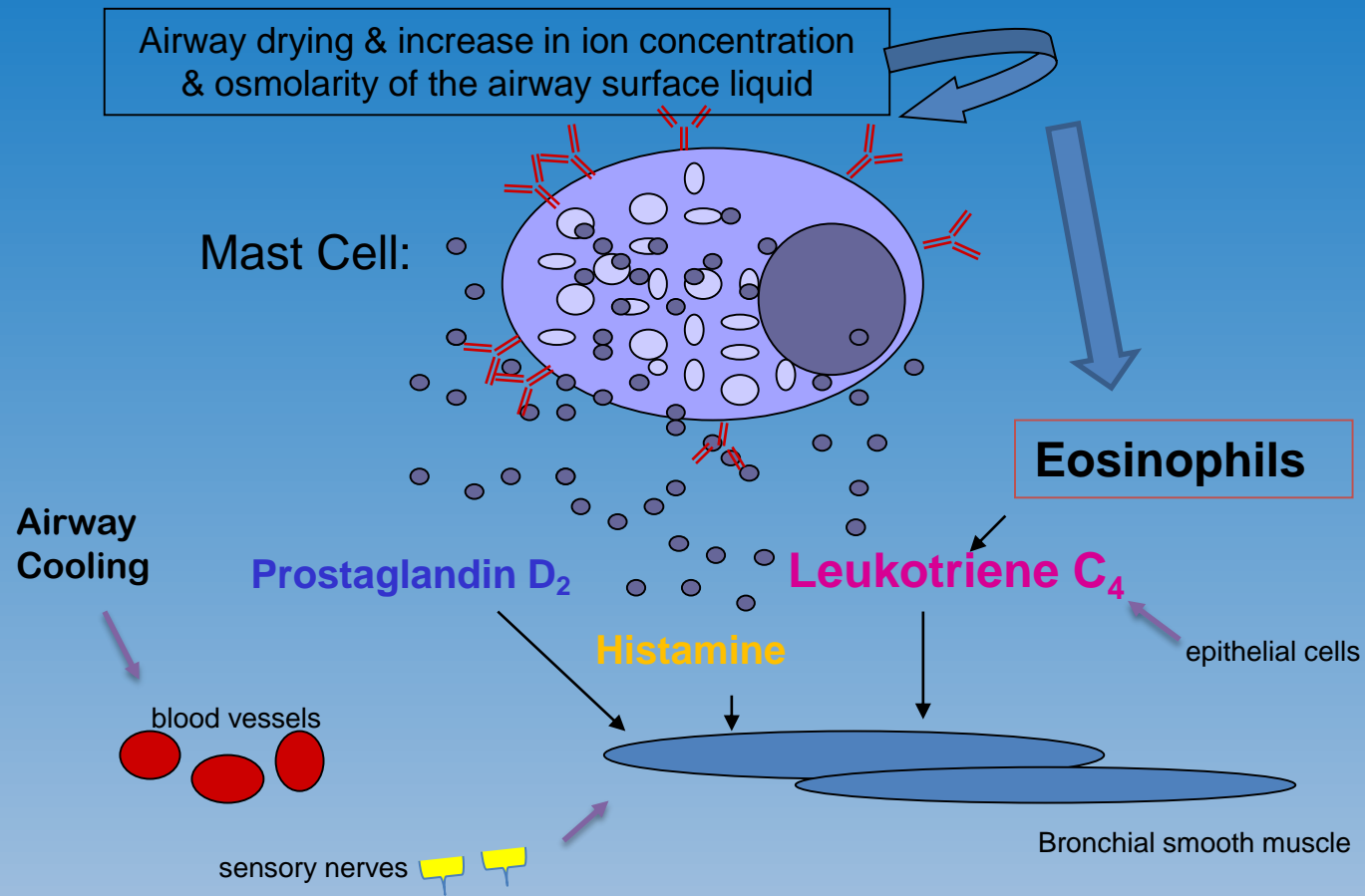
Modulators and amplifiers of EIB:

1. Inhaled pollutants and chemical irritants; exercising in polluted environments; nitrogen oxides in ice rinks; etc.
2. Obesity
3. Pollen exposure in atopic patients
4. Other conditions which aggravate asthma in general:
sinus disease (swimmers, boxers); cold air venues
5. GERD
6. ?? High salt diet

This may explain why athletes in some sport venues have EIB and athletes in other venues do not

Modulators and amplifiers of EIB: Obesity



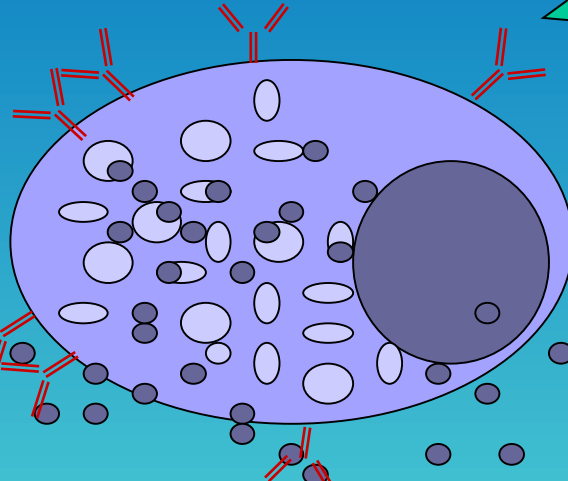


Adapted from S. Anderson

Genetic Susceptibility

Airway drying & increase in ion concentration & osmolarity of the airway surface liquid

Mast Cell:



Modulators:
Type of sport;
environment

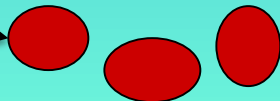
Eosinophils

Aquaporin dysregulation

Airway Permeability

blood vessels

Airway Cooling



TRPV receptors
sensory nerves



Prostaglandin D₂

Leukotriene C₄

Histamine

IL-17,22

epithelial cell shedding

Increased PGE₂ (protective)

Bronchial smooth muscle

MECHANISMS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

EIB+ vs. EIB- Asthmatics

1. Genetic predisposition to EIB
transglutaminase-2 genes, aquaporin
2. Increased inflammatory cell numbers: mast cells/eosinophils
3. Increased inflammatory mediator release
4. Epithelial cell shedding
5. Sensory nerve stimulation
6. Increased vascular permeability
7. Increased mucus release
8. Hypersensitive airway TRPV receptors (?)
9. Reduced aquaporin expression (?)
10. Abnormal parasympathetic responsiveness