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# Will Calcium Antagonists Find a New Role in Respiratory Therapy?

The introduction of calcium channel blocking drugs has had a major impact on the management of coronary artery disease. Will respiratory disease be next?

Many pathophysiologic events that underlie bronchial asthma and hyperreactive airway disease are indeed calcium-dependent phenomena. In a recent report (*Chest* 86:475-482, 1984), Eric W. Russi, MD, and Tahir Ahmed, MD, of the Division of Pulmonary Disease at Mount Sinai Medical Center in Miami Beach, cite numerous examples of these calcium-linked processes. For instance, the release of mediators from mast cells (stimulus-secretion coupling), contraction of airway smooth muscle (excitation-contraction coupling), and nerve impulse conduction all depend on the availability of free calcium and on the flux of calcium ions.

## Bronchial Asthma and Cystic Fibrosis

In bronchial asthma, Drs. Russi and Ahmed note, the principal pathogenic features are initiated by the release of chemical mediators from sensitized mast cells in an IgE-mediated reaction. This release leads to constriction of airway smooth muscle and mucous hypersecretion produced through cholinergic reflex mechanisms. Therefore, it's easy to speculate that a primary disturbance of cellular calcium metabolism may be an important factor in the pathogenesis of bronchial asthma. [See Figure.]

Research suggests that calcium metabolism also may be important in cystic fibrosis. The sweat of patients with cystic fibrosis is high in salt, implying a defect in calcium ion transport.

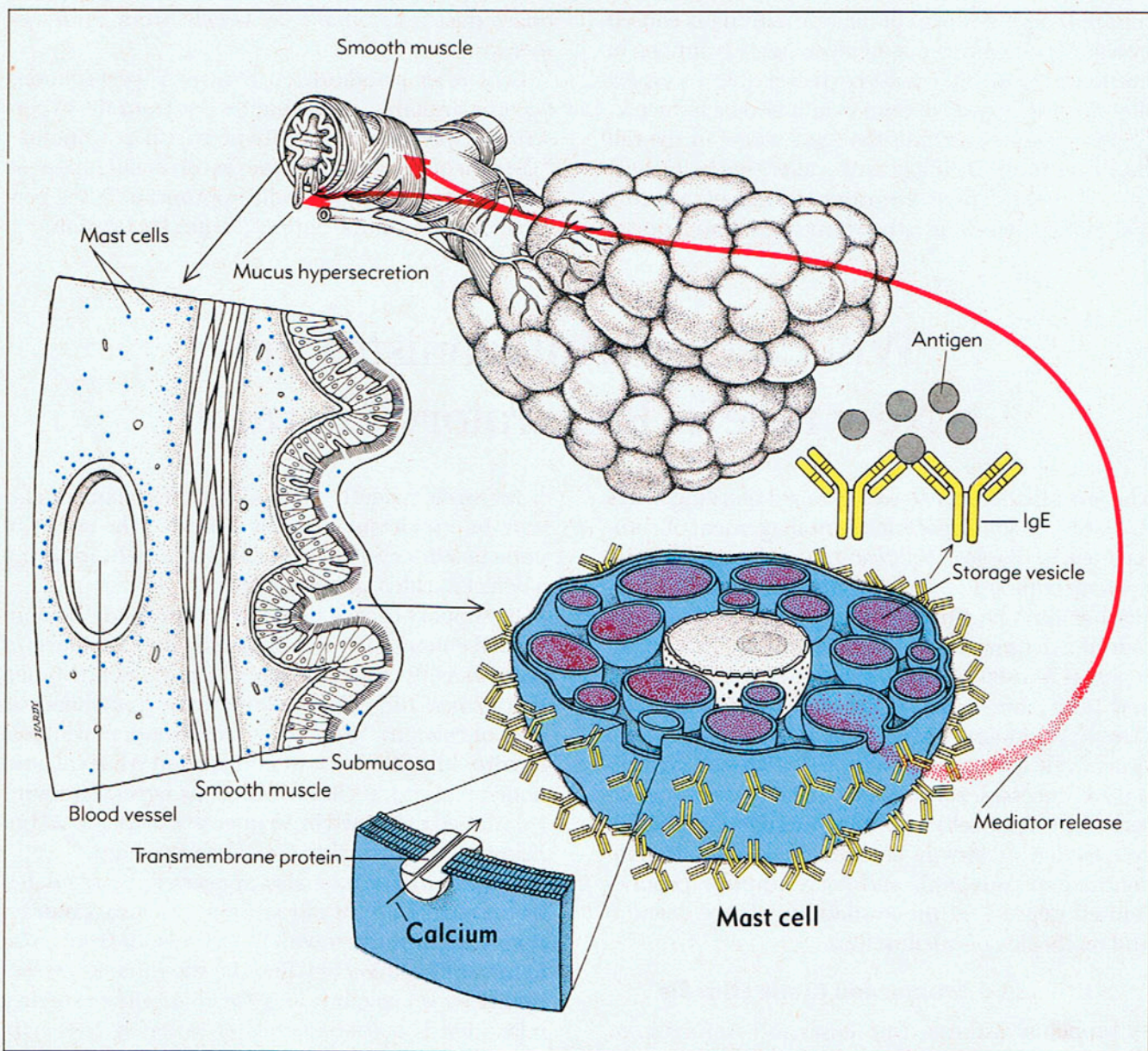
In support of this hypothesis, one study demonstrated enhanced  $^{45}\text{Ca}^{++}$  uptake by the fibroblasts of patients with cystic fibrosis. The authors attributed this to possible enlargement of the mitochondrial pool of calcium. "There is no information available in vitro, in animals, or in humans, on what calcium antagonists do in cases of mucous hypersecretion," Dr. Ahmed explained in an interview with *RMT*, "but it seems likely that they could be important."

Bronchomotor tone also appears to be regulated by the availability of intracellular calcium. Contraction of respiratory smooth muscle results from a rise in intracellular calcium and the subsequent interaction between calcium and the contractile proteins; relaxation is a consequence of lowering free cytoplasmic  $\text{Ca}^{++}$  by sequestering this ion away from the contractile apparatus.

## In Vivo Studies in Exercise-Induced Asthma

The role of calcium in respiratory physiology is well known, but respiratory effects of calcium antagonists are just beginning to be investigated. In one in vivo study, sublingual nifedipine protected against

## Calcium Antagonists



**Figure — Calcium's Role in Bronchial Asthma.** Asthma is triggered by a chemical reaction within mast cells, which are located (left) near mucosal surfaces, in the submucosa, and around blood vessels of bronchial tissue. Y-shaped IgE molecules attach themselves to mast cells (right), and in susceptible individuals they attach themselves so densely that they can be bridged by antigens. When this happens, the mast cell membrane becomes more permeable to extracellular calcium, which penetrates the

mast cell via transmembrane proteins. This extracellular calcium, as well as calcium already inside the mast cell, plays a still-undefined part both in the synthesis of some chemical mediators, such as leukotrienes, and in their expulsion from the mast cell. The released mediators—leukotrienes, prostaglandins, and histamine—set off the reactions familiar to all long-suffering asthmatics (top): contraction of airway smooth muscle and hypersecretion of mucus.

exercise-induced bronchospasm and also blunted the bronchial obstruction induced by eucapnic hyperventilation with dry, subfreezing air. In another *in vivo* study of patients with asthma, nifedipine reduced plasma histamine concentrations and prevented the usual exercise-induced rise in plasma histamine. According to Drs. Russi and Ahmed, this may reflect mediator release from circulating basophils rather than from pulmonary mast cells. Other studies have shown that calcium channel blockers protect against methacholine- and antigen-induced bronchospasm.

### Clinical Implications

As these examples illustrate, calcium antagonists have demonstrated protective effects against exercise-induced, hyperventilation-induced, and histamine-induced bronchoconstriction, among other findings. So far, however, reported benefits have been disappointingly small.

What does this say about the future use of calcium channel blockers in airway disease? "There isn't going to be a major revolution in therapy right away," predicts Dr. Ahmed. "Maybe five or ten years from now, but not at the moment, and that's because of the dosage problem with currently available calcium antagonists."

The problem is that airway smooth muscle uses both internal and external sources of calcium, so it's less sensitive to calcium channel blockers than vascular smooth muscle. "To produce effective airway tissue levels, you need high oral doses," Ahmed explains. "But if you give high doses, you're risking systemic side effects."

### Inhalation Forms

One way to reduce side effects is to change the route of drug delivery. Ahmed and his colleagues have, in fact, done some preliminary work with inhaled verapamil. As Dr. Ahmed explained in a telephone interview, "Oral verapamil doesn't work that well, but inhaled verapamil works fantastically. Once we have a handle on inhalation forms, they may replace or at least substitute for beta-agonists in patients

with coronary artery disease." However, hand-held calcium nebulizers are still years away.

Higher-potency calcium antagonists are another possibility. Studies have already shown that in some subjects verapamil protects better against antigen-induced bronchospasm than does nifedipine. In vascular smooth muscle, nifedipine is approximately a hundredfold more active than either diltiazem or verapamil in inhibiting calcium entry via voltage-dependent channels. According to Drs. Russi and Ahmed, derivatives of existing calcium blockers—nisoldipine, nitrendipine, and nimodipine, for example—may be more potent and have more selective actions on smooth muscle or mast cells.

### Calcium Antagonist Combinations

Inconsistency of results with calcium antagonists both within and between patients, which is another frequent problem, may reflect different sensitivity of various tissues to these drugs. Mast cells in particular appear to have varying sensitivity to calcium blockers. Drs. Russi and Ahmed believe administration of a combination of calcium antagonists may help to solve this problem.

At present, calcium antagonists are not recommended as a primary therapy for exercise-induced asthma, allergic bronchial asthma, or any other airway problem. "Other drugs are better and much safer," says Dr. Ahmed. But calcium blockers do have one undisputed role in respiratory medicine: "The most important application of calcium antagonists is for patients who have coronary artery disease with coexisting obstructive airway disease—asthma, COPD, and so forth. For them," says Dr. Ahmed, "calcium antagonists are the therapy of choice."

### REVIEW OUR REVIEW

Turn to page 33 for a six-question quiz on some of the fine points drawn in these four "Research Reviews." Then call us toll-free for recorded explanations of the right answers.