Thorax 1983;38:481–485

Editorial

Calcium-channel blockers and asthma

The concentration of free calcium ions (Ca^{++}) in the cytoplasm regulates many aspects of cell function, including muscle contraction and the secretion of mediators, neurotransmitters and hormones. Contraction of airway smooth muscle, secretion of mast cell mediators and mucus, and vagal neurotransmission, all of which may be increased in asthma, are dependent on movement of Ca^{++} into the cell. This raises the possibility that an increase in Ca^{++} flux may be a fundamental abnormality in asthma and might be an explanation for bronchial hyperreactivity.[1] The development of drugs that interfere with the entry of Ca^{++} into cells has now made it possible to study the role of Ca^{++} in disease, and these drugs are widely used in the treatment of cardiovascular disease. There has recently been increasing interest in the use of calcium-channel blockers in asthma, not because of their therapeutic potential but because of what they may reveal about underlying mechanisms.

CALCIUM IONS AND CELL FUNCTION

The concentration of free intracellular Ca^{++} in resting cells is approximately 0·1 μmol/l, whereas that in extracellular fluid is 1 mmol/l;[2,3] and recent studies using bioluminescent indicators of free intracellular Ca^{++} have found that the Ca^{++} concentration increases 100-fold after cell activation.[4,5] When intracellular Ca^{++} rises to a critical concentration (about 1 μmol/l) it binds to a specific binding protein called calmodulin, which then activates the specific kinase and enzyme system that brings about the response, such as contraction or secretion. This increase in cytoplasmic Ca^{++} is derived from extracellular Ca^{++} or intracellular stores (mainly sarcoplasmic reticulum), or both. Indeed, the entry of Ca^{++} into the cell may trigger the release of Ca^{++} from intracellular stores. The source of Ca^{++} required for the cellular response may differ from tissue to tissue. The cell membrane itself is impermeable to Ca^{++} and Ca^{++} moves into the cell through specific channels. These are macromolecular structures traversing the membrane which selectively permit Ca^{++} to enter the cell down its concentration gradient. There are at least two types of calcium channel, one opening in response to cellular depolarisation (voltage-dependent) and one in response to activation of a specific receptor, such as an α-adrenoceptor (receptor-operated).[6] It has been calculated that there are up to 10 000 voltage-dependent calcium channels in each cardiac cell.[3]

The interrelationships between Ca^{++} and cyclic nucleotides are complex. In smooth muscle cyclic AMP accelerates Ca^{++} removal from the cytoplasm and prevents the influx of Ca^{++}, thus reversing the effects of activation.[7] Ca^{++} also inhibits adenylate cyclase and stimulates guanylate cyclase.[8] Many of the drugs used in treating asthma may reduce intracellular Ca^{++}. Thus β-adrenoceptor agonists bring about relaxation by increasing cyclic AMP and cholinergic antagonists by directly reducing Ca^{++} influx by reducing Ca^{++} in the smooth muscle cell. Theophyllines and cromoglycate may also have their primary actions on Ca^{++} influx.

CALCIUM-CHANNEL BLOCKERS

Voltage-dependent calcium channels are specific to calcium, although cations of similar size such as barium may also enter. Larger cations, such as manganese and lanthanum, block the channel. Recently organic compounds that specifically block these channels have been developed; they include verapamil, nifedipine, and diltiazem, which have no apparent structural similarities.[8,9] Binding studies using labelled derivatives indicate that these drugs bind with high affinity to different sites on the calcium channel[9a,10] but there may be complex allosteric interactions between the different classes of calcium-channel blocker.[10a] Their precise mode of action at a molecular level is still debated.

Calcium-channel blockers are now extensively used in cardiac disease, and appear to be safe and without troublesome side effects.[8,9,11] These drugs appear to be relatively specific for voltage-dependent calcium channels, and have little action on receptor-operated channels. At higher doses they may have other effects, such as α-adrenoceptor

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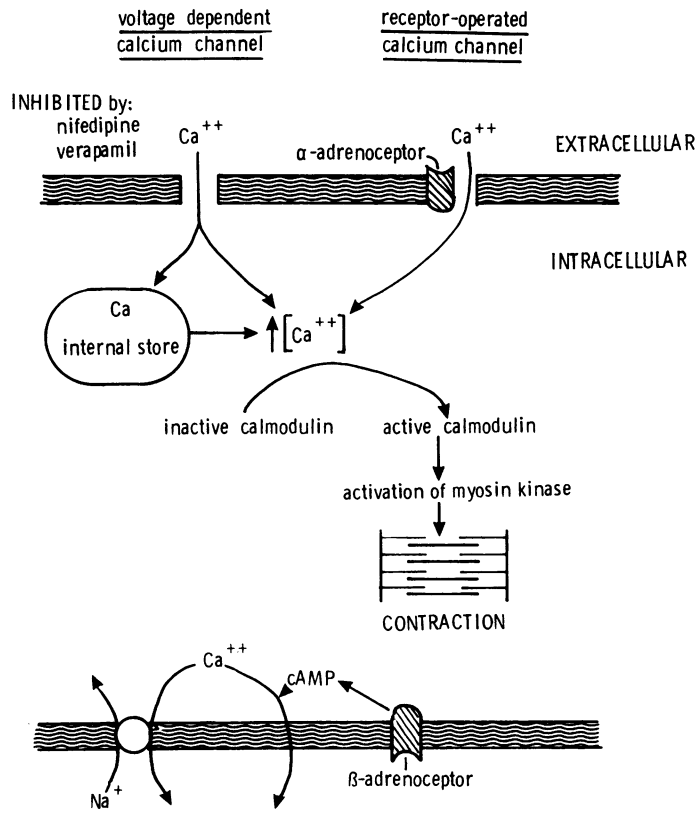
blockade, phosphodiesterase inhibition, and inhibition of Na-K ATPase, and may not be as selective as previously believed.[12]

AIRWAY SMOOTH MUSCLE

The source of calcium for muscle contraction differs between muscle types, and even between the same muscle type in different tissues. Skeletal muscle is dependent only on intracellular calcium stores and contraction is therefore unaffected by calcium-channel blockers, whereas vascular smooth muscle is dependent on extracellular Ca^{++} and is therefore susceptible to blockade. The dependency of smooth muscle on extracellular Ca^{++} may vary between different sites since smooth muscle in arterioles is much more sensitive to calcium-channel blockers than is that from veins.[12]

Airway smooth muscle has been less extensively studied and appears to be dependent on both external and internal sources of Ca^{++}, but this may vary with the contractile stimulus (fig). Serotonin-induced contraction of canine tracheal strips is strongly inhibited by lanthanum and by verapamil, whereas acetylcholine-induced contraction is relatively resistant to blockade.[13] In the same preparation it was found that verapamil inhibited contraction due to low concentrations of acetylcholine but not contraction due to high concentrations.[14] Similar results have been reported with guinea-pig trachea,[15] suggesting that the relative contribution of intracellular and extracellular Ca^{++} may depend not only on the stimulus but also on its magnitude. In vitro nifedipine inhibits contraction induced by histamine and by antigen in guinea-pig trachea[16 17] and human airway smooth muscle.[18 19] Since nifedipine is equally potent in guinea-pig lung strip preparations, this suggests that small airways may behave in the same way.[16] Animal studies in vivo have shown that nifedipine given intravenously or by inhalation has no effect on resting bronchomotor tone,[16 20 21] but gives appreciable protection against bronchoconstriction induced by histamine, prostaglandin $F_{2\alpha}$, and citric acid in dogs,[20 21] and against constriction induced by histamine and carbachol in guinea-pigs.[16]

Similar findings have been reported in patients with asthma. Neither nifedipine given sublingually nor verapamil given by inhalation had any significant effect on resting airway function.[22–25]



Calcium ion (Ca^{++}) fluxes in an airway smooth muscle cell. The rise in intracellular Ca^{++} causes contraction and may be due to entry of Ca^{++} from outside via voltage-dependent or receptor-operated calcium channels or from internal stores. Only the voltage-dependent calcium channel is effectively inhibited by calcium-channel blockers, such as nifedipine and verapamil. Ca^{++} is removed from the cell by an $Na^{+} - Ca^{++}$ exchange pump or by a cyclic-AMP-dependent mechanism.

There was, however, significant protection against bronchoconstriction induced by exercise,[22-24] hyperventilation,[26] histamine,[23 25 27] methacholine,[27] deep inspiration,[28] and antigen,[18] although in one study no protection against histamine-induced bronchoconstriction was found.[29] In only one study was protection completely effective,[22] the others showing partial protection with considerable inter-subject variability. Perhaps the dose of calcium-channel blocker used in these studies was too low, but the dose of sublingual nifedipine is limited by cardiovascular side effects and possibly administration by aerosol (as in some of the animal studies) would be more effective. It is also possible that induced bronchoconstriction in asthma is regulated by receptor-operated rather than voltage-dependent calcium channels, and it may be more dependent on internal calcium stores. Further studies on the calcium dependency of human airway smooth muscle are required before these questions can be answered.

An interesting aspect of these findings is that calcium-channel blockers appear to change the bronchoconstrictor response without causing bronchodilation. The long-term effects of calcium-channel blockers on bronchial reactivity are not yet known, although a small improvement in airway function has been reported in some patients with labile airways obstruction after two weeks of treatment.[30]

MAST CELLS

It has long been recognised that extracellular Ca^{++} is necessary for antigen-induced mediator release.[31] The calcium ionophore A-23187 (which carries calcium into the cell) and the direct intracellular injection of calcium stimulate histamine release from rat peritoneal mast cells, the amount released being proportional to the calcium influx.[32] It is proposed that bridging of IgE receptors increases phospholipid methylation in the cell membrane, which leads to Ca^{++} influx.[33] Lanthanum and methoxyverapamil inhibit IgE-mediated histamine release from rat peritoneal cells[34 35] and nifedipine passive cutaneous anaphylaxis in rat skin.[36]

Mediator secretion from human lung is also dependent on extracellular Ca^{++}[37] and recently both verapamil and nifedipine have been found to inhibit IgE-mediated secretion of slow-reacting substance of anaphylaxis (SRS-A) from passively sensitised human lung fragments,[38 39] although the concentrations of drug used were high and there was little or no effect on histamine secretion. Nifedipine has also been shown to inhibit secretion of SRS-A and platelet-activating factor by human polymorphs,[40] and the release of histamine from human basophils (SP Skov *et al*, paper presented to Eleventh International Congress of Allergology and Clinical Immunology, 1982). In vivo, nifedipine reduces plasma histamine concentrations and prevents the rise in plasma histamine with exercise in individuals with asthma,[23] although this is likely to reflect mediator release from circulating basophils rather than from pulmonary mast cells.

OTHER PULMONARY EFFECTS

Neurotransmission is similarly dependent on external Ca^{++} and it is possible that Ca^{++} channel blockers have an inhibitory effect on reflex vagal bronchoconstriction, although this has not been studied systematically. The secretory activity of airway submucosal glands and transport of ion and water across the airway epithelium are also dependent on external Ca^{++},[41] but the effects of calcium-channel blockers on airway gland secretion are not known. Nifedipine has an inhibitory action on acute hypoxic pulmonary vasoconstriction, which may be beneficial in pulmonary hypertension secondary to chronic lung disease;[42] but this effect is potentially disadvantageous in asthma since it might increase ventilation-perfusion mismatching, particularly during an acute exacerbation. In anaesthetised dogs calcium-channel blockers have been shown to have a more potent effect on tracheal blood flow than on airway smooth muscle,[43] raising the possibility that these agents cause an increase in airway blood flow in asthma, which might lead to increased vascular leakage and mucosal oedema. Chemotaxis of inflammatory cells is also a calcium-dependent process[44] and it is possible that calcium-channel blockers might have an effect on the inflammatory response in asthma. These possibilities have not yet been explored.

FUTURE DEVELOPMENTS

Experimental studies have shown that airway smooth muscle and pulmonary mast cells are dependent on external sources of Ca^{++} and that calcium-channel blockers protect against induced bronchoconstriction and possibly mediator release. But these effects are disappointingly small and the reasons for this require further elucidation. The limitation of the dose that can be given systematically is one possible explanation, although the doses used do have appreciable actions on peripheral blood vessels. The sensitivity of a tissue to calcium-channel blockers will depend on its requirement for extracellular Ca^{++}. Airway smooth muscle appears to use both internal and external sources, so that it is less sensitive to calcium-channel blockers than vascular smooth muscle.[43] Since the source of Ca^{++} for airway smooth muscle contraction depends on the

contractile stimulus and even its magnitude, the effects of calcium-channel blockers are likely to be variable. Furthermore, the role of receptor-operated calcium channels, which are not susceptible to conventional calcium-channel blockers, requires further study. There are also differences between species. For example, rat vessels are more sensitive to blockers than those of the cat or rabbit.[12] More work on human airways is needed.

There are also differences in potency and effects between the various calcium-channel blockers available. The demonstration that each class of calcium-channel blocker binds to a different site in the calcium channel raises the possibility that combinations of different blockers may be more effective. Furthermore, it is possible that derivatives of existing blockers, such as nisoldpine, nitrendipine, and nimodipine, or new classes of blocker might be more potent or have a more selective action on airway smooth muscle or mast cells. Other drugs which interfere with Ca^{++} availability may also prove to be of value. Drugs similar to methylene dioxyindenes which block intracellular calcium release might eventually prove to be beneficial, although drugs now available are likely to be too toxic for clinical use.[45] Several drugs are known to affect calmodulin binding, although they lack specificity.[46] Studies on calcium-channel blockers and the role of abnormal Ca^{++} flux in the pathogenesis of asthma are only just beginning and future developments are likely to be exciting as new drugs become available.

A practical message from the existing studies is that calcium-channel blockers are safe to use in asthma. Since they are effective treatment for angina and hypertension,[8 9 11] they may be the treatment of choice for these conditions in patients who also have asthma and chronic airway obstruction, when β-adrenoceptor antagonists are contraindicated.

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