CALCIUM CHANNEL BLOCKERS : EFFECTS AND CLINICAL APPLICATIONS

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PHYSIOLOGICAL CONSIDERATIONS

Calcium is an important cation and is involved in many physiological and biochemical processes. Consequently drugs affecting the function of calcium can have multiple and complicated effects.

One of the important functions of calcium is to act as an ionic messenger which triggers events such as muscle contraction. It can do this because of the existence of concentration gradients between intracellular and extracellular fluid as well as within the cell (figure 1). The extracellular calcium concentration is high relative to the intracellular concentration. Inside the cell calcium pools are present and subsequently the calcium distribution within the cells is not uniform. To simplify the physiology the cellular membrane and the cytosol will be considered separately.

1. The cell membrane

It is thought that the primitive sea in which the first life forms appeared had a low calcium concentration and that these cells had a similar intracellular calcium content. As the calcium content of the primitive sea increased, the organisms developed protective mechanisms to assure constancy of the internal environment in the face of a changing external milieu. (1)

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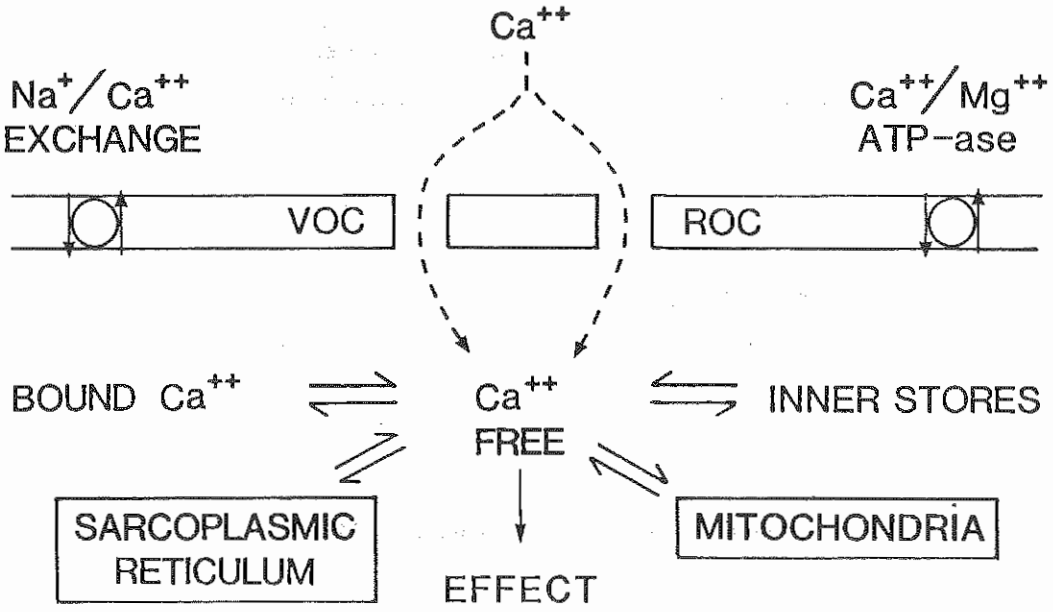

Figure 1 **Schematic representation of factors governing calcium movement**

The relatively low intracellular calcium content is maintained by a poor membrane permeability for calcium, energy-requiring pump and exchange mechanisms, as well as the presence of inactive calcium channels at rest.

Inward calcium movement through channels can be triggered by a change in voltage or by the effects of agonists on certain receptors. We thus differentiate between voltage operated channels (VOC's) and receptor operated channels (ROC's). It also seems that these channels are in some way linked and that activation of ROC's might result in the activation of VOC's.(2)

2. Intracellular calcium distribution

Intracellular calcium gradients exist because of calcium pools maintained by energy-requiring processes (figure 1). The sarcoplasmic reticulum is an important example of such a calcium pool. Entry of calcium via VOC's or ROC's trigger the release of intracellular calcium which then produces effects such as muscle contraction.(2)

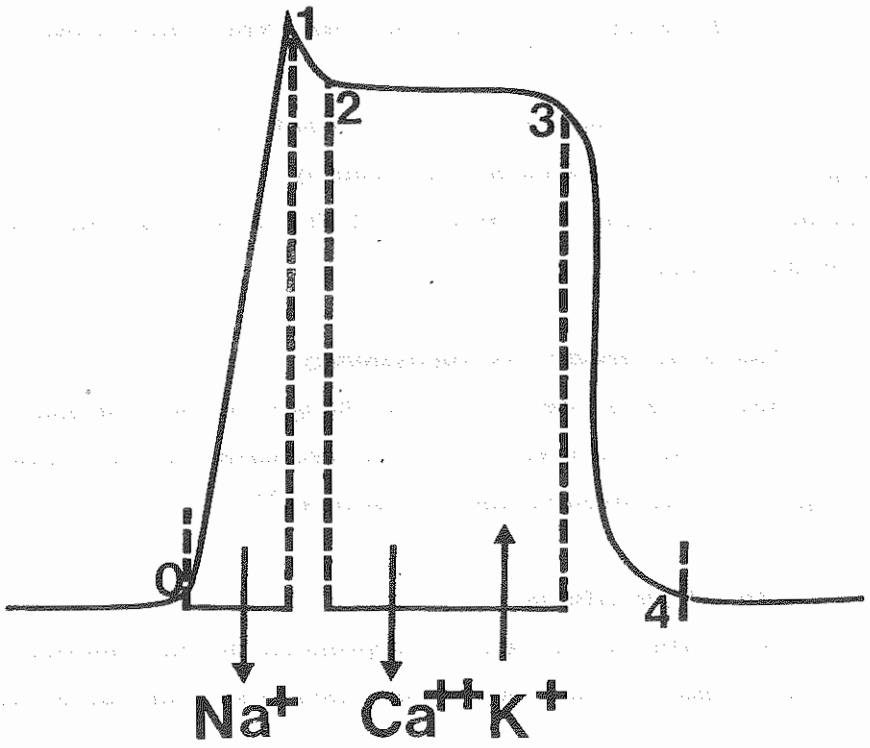

Figure 2 **Role of calcium in the cardiac action potential**

Apart from eliciting intracellular effects, calcium movement also plays an important role in the generation of the cardiac action potential (figure 2). Whereas phase O (the rapid upstroke) is due to the fast inward movement of sodium, the plateau phase (phase 2) is due to a balance between slow inward calcium movement and the outward movement of potassium. A change in calcium movement can therefore affect the configuration of the action potential, particularly its duration and consequently the duration of the refractory period. (3) A change in calcium movement can therefore induce changes in automaticity and conduction. As the role of calcium is much more important in supraventricular tissues, the effect of calcium blockers on supraventricular automaticity and conduction is pronounced, whereas the effect on ventricular action potentials is relatively small.

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EFFECTS OF CALCIUM CHANNEL BLOCKERS

The calcium channel blockers impair the movement of calcium through membrane channels, particularly the VOC's.[4] From the foregoing physiological considerations it should be clear that they produce two distinct effects :

1. **Effects on cardiac electrophysiology**

These effects are due to a change in the configuration of the action potential, manifesting as a decrease in automaticity and a prolongation of atrioventricular conduction.[5]

2. **Intracellular effects**

These effects are due to suppression of the function of calcium as an ionic messenger and usually manifests as smooth muscle relaxation.

There appears to be differences in the site of action of calcium channel blockers in terms of these two effects. One can in fact see the pharmacodynamic profile as two poles of a spectrum of effects (figure 3) with verapamil having a major effect on the one side (cardiac electrophysiology)[6] and nifedipine on the other side (intracellular response such as relaxation of vascular smooth muscle).[7] The effect on cardiac muscle (negative inotropism) seems to be shared by both drugs and this effect is therefore placed midway between the two poles (figure 3). Most of the newer calcium channel blockers can be classified as either verapamil-like or nifedipine-like and will fit into a position on this spectrum of effects.

ESTABLISHED CLINICAL USES

Based on figure 3, we can recognise three pharmacodynamic mechanisms underlying the clinical effects of these drugs :

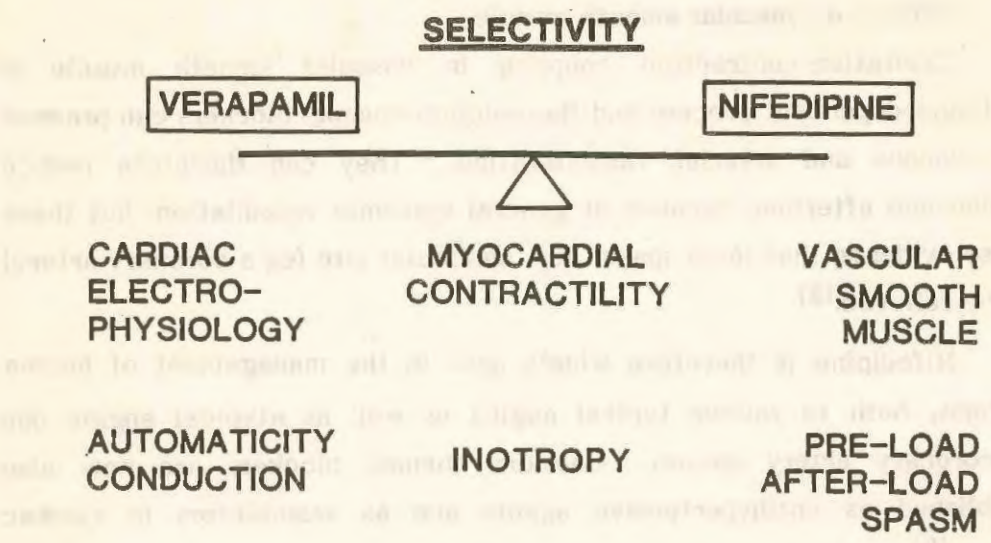

Figure 3 **Pharmacodynamic profile of the calcium antagonists**

1. **Effects on cardiac electrophysiology**

As a result of its depressant effect on supraventricular automaticity and atrioventricular conduction, verapamil is currently the drug of choice in supraventricular tachyarrhythmias.[8] It either terminates the arrhythmia by suppressing discharge from the ectopic focus or by delaying atrioventricular conduction and protecting the ventricles from excessive stimulation.

2. **Effects on myocardial contractility**

Calcium channel blockers have marked negative inotropic effects in vitro.[9] In vivo, however, these effects are more pronounced with a drug such as verapamil because of the concommitant depression of the sino-atrial node. In contrast to this, reflex sympathetic activation, particularly tachycardia, induced by drugs such as nifedipine tend to attenuate the negative inotropic effect. Negative inotropism might be potentially useful to decrease cardiac work load and to prevent ischaemic damage, but might on the other hand decrease cardiac output and cause untoward effects related to this, such as heart failure and cardiogenic shock.

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3. Effects on vascular smooth muscle

Excitation-contraction coupling in vascular smooth muscle is a calcium-dependent process and the calcium channel blockers can produce both venous and arterial vasodilatation. They can therefore reduce preload and afterload because of general systemic vasodilation, but there is also evidence that local spasm at a particular site (eg a coronary artery) can be relieved.(8)

Nifedipine is therefore widely used in the management of angina pectoris, both to relieve typical angina as well as atypical angina due to coronary artery spasm. Calcium channel blockers are now also established as antihypertensive agents and as vasodilators in cardiac failure.(9)

POTENTIAL CLINICAL USES

There appears to be evidence that there might be site selectivity with regard to the vascular effects of these drugs and that we might eventually have drugs that are selective for sites such as the coronary or cerebral blood vessels.(10)

It has been furthermore suggested that calcium channel blockers might prevent the accumulation of calcium in blood vessels that occurs with degeneration with age and which appears to be accelerated in the presence of conditions such as diabetes and hypertension.(11) There is some evidence from animal experiments for this notion, but this has not been confirmed in humans and would be a formidable task in terms of the time period that would be required. We have some doubts about the relationship between degenerative vascular disease and increased intracellular calcium in human blood vessels. This might simply be the result and not the cause of degeneration. Although black South Africans show the same calcium accumulation (12) with age as whites (11), the incidence of coronary artery disease is a fraction of that seen in white South Africans.

EFFECTS ON THE RESPIRATORY TRACT

The effect of calcium channel blockers on smooth muscle is not limited to blood vessels. This follows as calcium is also involved in the contraction of smooth muscle at other sites such as the gastrointestinal and respiratory tracts.

We have investigated the effects of these substances on respiratory smooth muscle as potential bronchodilators in the management of asthma. Furthermore, because beta-adrenergic blockers are contraindicated in patients with bronchospasm, it is important to ascertain whether for appropriate indications the calcium channel blockers would be safe alternatives to the beta-adrenergic blockers.

Both nifedipine and verapamil are physiological antagonists of spasm of guinea pig tracheal muscle induced via cholinergic receptors (metacholine) and the H_1-receptor (histamine).[13] Both drugs potentiate the relaxant effect of theophylline [14], but differ in terms of their interaction with isoprenaline. Whereas verapamil potentiates the relaxant effect of isoprenaline, this effect is antagonized by nifedipine. Biochemically nifedipine blocks the increase in cyclic AMP induced by isoprenaline [15], whereas it is not affected by verapamil. This effect of nifedipine is even more apparent when a dose-response curve is obtained from tracheal muscle in the presence of the spasmogen and isoprenaline. Under these circumstances increasing concentrations of nifedipine produce increasing spasm due to the progressive removal of isoprenaline-induced relaxation. Only at high concentrations of nifedipine does relaxation occur, resulting in a biphasic bell-shaped dose-response curve (figure 4).

Our work has shown that :

(i) Nifedipine (ED_{50} = 5 x 10^{-7}M) and verapamil (ED_{50} = 5 x 10^{-4}M) both antagonise histamine and metacholine induced spasm. Nifedipine appears to be more potent in this regard and the ED_{50} suggests that this effect might be seen with systemic therapeutic

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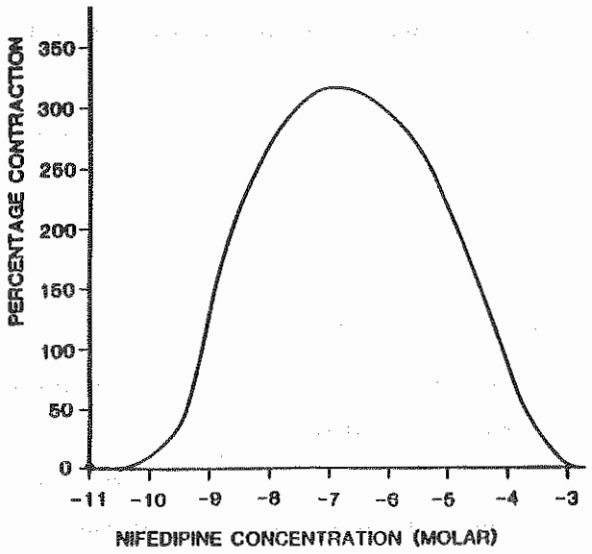

Figure 4 **Biphasic nifedipine dose response curve in the presence of methacholine and isoprenaline**

concentrations. The ED_{50} of verapamil suggests that this effect is unlikely to occur with systemic therapeutic concentrations.

(ii) Both drugs have a potentially beneficial interaction with theophylline.

(iii) Verapamil has a potentially beneficial and nifedipine a potentially harmful interaction with isoprenaline.

It therefore seems that in relation to the spectrum of effects already discussed (figure 3), differences between nifedipine and verapamil are also manifest in the respiratory tract. There is some evidence that calcium channel blockers can relieve exercise-induced bronchospasm [16,17], but it is not clear whether this is an effect on histamine release or whether it is a bronchodilatory effect. Our work suggests that neither verapamil, because of its low potency, nor nifedipine, because of its potentially harmful interaction with beta-stimulants, have potential as systemic bronchodilators. In the context of pre-existing asthma, verapamil appears to be the safer alternative, but clearly work in humans is mandatory before firm conclusions can be made.

CONCLUSIONS

The major problem with calcium channel blockers is that they affect so many different physiological processes at so many different sites. A better understanding of mechanisms of action would help us to understand why these drugs have differential effects and might lead to the development of greater site-specificity and ultimately more rational therapeutic use.

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