Some New Thoughts on the Effects of Calcium Channel Blockers

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Calcium is a cation essential to life as we know it. It is unequally distributed in the body and a multitude of mechanisms are responsible for maintaining concentration gradients across various membranes. These mechanisms include voltage and receptor operated channels, Na+/Ca++ exchange and Ca++/Mg++ ATP-ase. These mechanisms ensure a very high extracellular calcium concentration relative to the intracellular concentration. The intracellular calcium is also unequally distributed and intracellular pools include the sarcoplasmic reticulum, mitochondria and binding sites on the inner side of the plasmalemma.

Interfering with calcium in a general way will consequently have such diverse effects that it has no potential benefit except in the presence of calcium overload. The calcium channel blockers represent a development which enables us tointerfere selectively with certain processes affecting calcium movement and consequently altering certain calcium dependent processes. The processes affected by these drugs are mainly those concerned with action potential generation and the conduction of impulses in the heart and those concerned with excitation-contraction coupling in vascular smooth muscle. Therapeutically the calcium channel blockers have been established as antiarrhythmic agents effective in the management of supraventricular tachyarrhythmias. Furthermore they are vasodilators and are widely used for the management of angina pectoris. The antianginal effect appears to be more than pre- and afterload reduction and evidence for antagonism of coronary artery spasm has emerged. The vasodilatory effects have also been applied in the management of hypertension and cardiac failure. There are also animal studies suggesting that calcium antagonists can prevent calcium accumulation characteristic of degenerative vascular disease.

Amongst the various calcium channel blockers there is a subdivision in terms of site of action. The best-known difference is that between nifedipine and verapamil. The latter has pronounced effects on the heart in terms of electrophysiology and contractility as well as on vascular smooth muscle. In contrast to this, the effect of nifedipine on these processes in the heart is negligible in relation to its effects on vascular smooth muscle. There are also indications that calcium channel blockers might differ with respect to their effects on blood vessels and it might become possible to selectively dilate blood vessels at specific sites such as the cerebral vasculature.

The effects of calcium channel blockers are however not limited to vascular smooth muscle, but effects are also seen in smooth muscle at other sites such as the respiratory tract. Investigating the effects of calcium-channel blockers on respiratory smooth muscle is important for two reasons. Firstly as potential bronchodilators in the management of asthma and secondly as they are used as alternatives to β-adrenergic blockers, we need to define their safety in the presence of a history of bronchospasm, as the latter is a contra-indication for the use of β-adrenergic blockers.

Nifedipine and verapamil are effective physiological antagonists of bronchospasm produced in vivo by methacholine and histamine, but differ in terms of their interaction with bronchodilators. Both tend to potentiate the bronchodilatory effect of theophylline. Although the bronchodilatory effect of β-adrenoceptor agonists such as isoprenaline is potentiated by verapamil, this effect is antagonised by nifedipine. This appears to be due to prevention of the increase in cyclic AMP induced by β-agonists.

It therefore seems that although the calcium channel blockers have potential as bronchodilators, there is also the possibility of adverse drug interactions between drugs such as nifedipine and certain bronchodilators.

The last word on calcium channel blockers has certainly not been spoken. These drugs are still inadequately understood and their full therapeutic potential has not yet been achieved.