### Future Prospects of the Development of Calcium Antagonists

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In considering the mechanism of action of the calcium antagonists, it is important to realize that there are three distinct receptor types and that the new classification divides these three drugs as members of the dihydropyridine, phenylalkylamines and benzothiazepines, respectively. The World Health Organization as well as the International Union of Pharmacology and Cardiology have adopted this classification. Unlike every other class of drugs, such as the alpha and beta adrenergic blocking agents, diuretics, etc., the calcium antagonists need to be thought of as three distinct drug classes. The reason they share some, but not all of the pharmacological profile is that they all act at specific receptor domains present in one large protein of 165,000 daltons present in all excitable tissue. This protein along with several other subunits make up what is known as the voltage-dependent calcium channel (the so-called \( L \)-type: \( L \)-VDCC). The mechanism of action of the three drugs involve first a specific binding and then an inhibition of the movement of calcium into the cell. Some of these drugs, such as diltiazem, may have other interesting intracellular effects perhaps associated with protection of the mitochonadria during ischemic insults. The nature of the receptor is being explored by molecular genetic techniques, and we have recently cloned two of the major subunits: some of the data will be presented.

From the therapeutic point of view, it is important to recognize that the receptors for these drugs associated with the \( L \)-VDCC will probably differ in different areas of the body. Our preliminary evidence strongly supports the concept of isoforms of the channel. Thus the receptors in vascular smooth muscle and even in different vascular trees will be different, as well as the receptors in the heart and various portions of the heart, and specialized conducting tissue as well, and whatever channels are present in the hypothalamic region of the brain. The reason why these drugs have in general a low side effect profile and are highly specific is that the mechanism of action involves specifically the receptors alluded to above and these are relatively rare in contrast to other well-known receptors. The process of excitation-contraction coupling in heart as well as in other tissues involves a highly specific pool of calcium that is controlled by the calcium channel of interest. The spectrum of therapeutic action, therefore, is not surprising because calcium forms the major link between all processes of excitation in the final biological event. Thus all three calcium antagonists are useful as coronary vasodilators. It is of interest that only verapamil and nifedipine produce significant effects on afterload in the normotensive, while diltiazem is relatively inactive. However, diltiazem is highly effective in the hypertensive. This means that the receptors are different in the diseased state. In considering the possible protection of the ischemic myocardium, recent clinical experiments have substantiated the extensive animal studies that have shown diltiazem to be effective in protection of the heart and prevention of reinfarction.

The long-term future of the calcium antagonists is replete with considerable therapeutic opportunities.