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Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Annu. Rev. Pharmacol. Toxicol.* 17:149-66, 1977.
(Physiological Institute, University of Freiburg, Federal Republic of Germany)

This paper reviewed the key role of calcium ions in the function of heart and vascular smooth muscle and the fundamental actions of drugs that antagonize or potentiate these calcium actions. [The *SCI*[®] indicates that this paper has been cited in over 1,380 publications, making it the most-cited paper from this journal.]

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Many years ago, between 1963 and 1970, we found that Ca-dependent myocardial contractile energy expenditure (and oxygen requirement), as well as Ca-dependent vascular smooth-muscle activity, can be damped directly with the use of a new family of drugs that in 1966 we designated "calcium antagonists." These agents inhibit transmembrane Ca supply to the contractile system so that the Ca-dependent transformation of phosphate-bond energy into mechanical work is restricted to any desired extent. Needless to say, these drugs also allow a neutralization of both hyperkinetic myocardial disorders and spastic smooth-muscle hyperactivity that mainly reflect an abnormal rise in transmembrane Ca inflow.

In our search for drugs that embody the new pharmacodynamic principle in a most specific manner, we discovered the prototypical Ca antagonists, verapamil, methoxyverapamil (D 600, gallopamil), nifedipine, and other 1,4-dihydropyridine derivatives. Later on we enriched this group of highly selective Ca antagonists by inclusion of a Ca antagonist that had originally been introduced in 1975 by Japanese researchers, i.e., diltiazem.¹

Nowadays, medicine is facing a worldwide Ca antagonist boom: thus, the three top Ca antagonists, verapamil, nifedipine, and diltiazem, are used for a host of indications having a damping effect on excessive transmembrane Ca uptake as the common therapeutic denominator. The three compounds cover more than 80 percent of the Ca antagonist market, amounting annually to an equivalent of almost two billion US dollars.

In fact, Ca antagonists turned out to be strong cardioprotective drugs against ischemic, anoxic, or catecholamine-induced myocardial fiber necroses. Hereditary cardiomyopathy of Syrian hamsters, hypertrophic cardiomyopathy in humans, and a variety of cardiac dysrhythmias can also be controlled with suitable Ca antagonists. Even more dramatic was the therapeutic success against all forms of arterial or arteriolar spasm in coronary, cerebral, mesenteric, or renal circulation as well as on systemic peripheral resistance vessels. With respect to the latter effect, the Ca antagonists have become the drugs of choice for the interruption of acute hypertensive crises, but they are also increasingly used for long-term treatment of essential or renal hypertension. Peripheral circulatory impairment in patients with Raynaud's disease is similarly responsive. Even spasms of visceral smooth muscle are not refractory to this medication.

The appearance in 1977 of my review of the fundamental actions of Ca antagonists coincided precisely—after 10 years of dispute—with the international breakthrough of these drugs in practical therapy. This fortunate constellation may have brought the interest in this topic to a climax, since other comprehensive reports^{2,4} that we published before or after 1977 did not attain comparably high citation frequencies. Since the mid-1980s, we have been in the calm, and academic distinctions are beginning to accumulate; for example, I have been awarded four honorary degrees in medicine, by the Universities of Munich, Heidelberg, Limburg/The Netherlands, and La Plata/Argentina. In addition, I received a series of 10 national and international prizes. The latest one was the ASPET-AWARD 1987 for Outstanding Basic Pharmacological Investigations of the American Society for Pharmacology and Experimental Therapeutics.

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2. Fleckenstein A, Kammermeier H, Döring H J, Freund H J, Grün G & Kienle A. Zum Wirkungsmechanismus neuerer Koronardilatatoren mit gleichzeitig Sauerstoff-einsparenden Myokard-Effekten, Prenylamin und Iproveratril (Action mechanisms of prenylamine and iproveratril, two new coronary vasodilators promoting efficient myocardial oxygen management). *Z. Kreislaufforsch.* 56:716-44; 839-58, 1967. (Cited 160 times.)
3. Fleckenstein A. Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention or production of myocardial lesions. (Harris P & Opie L, eds.) *Calcium and the heart. Proceedings of the meeting of the European Section of the International Study Group for Research in Cardiac Metabolism held at the Institute of Cardiology, London, on 6 September 1970.* London: Academic Press, 1971. p. 135-88.
4. ———. *Calcium antagonism in heart and smooth muscle. Experimental facts and therapeutic prospects.* New York: Wiley, 1983. 399 p. (Cited 175 times.)

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