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SPECIFIC PHARMACOLOGY OF CALCIUM IN MYOCARDIUM, CARDIAC PACEMAKERS, AND VASCULAR SMOOTH MUSCLE

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INTRODUCTION

The essential connection of the basic physiological processes of excitation and contraction with transmembrane movements of Na, K, and Ca ions probably originates from an early stage of cellular evolution. Despite innumerable modifications the fundamental processes that developed in the ocean have not undergone major changes during the course of development of higher forms of animal life. Thus in a wide variety of excitable cells the transmembrane exchange of the monovalent marine cations Na and K can be considered the substantial basis of bioelectric membrane activity, whereas Ca ions are required as mediators when, by this superficial process, intracellular reactions such as muscular contraction, glandular secretion, or liberation of transmitter substances are initiated (1, 2). Ca ions can exert this messenger function either in a primitive way, by penetrating into the intracellular space across the depolarized cell membrane or, at a more advanced stage of evolution, by being released from intracellularly located endoplasmic stores.

As to contractile tissues, the development of large endoplasmic Ca pools is most obvious in skeletal muscle, whereas myocardial fibers and, particularly, smooth muscle cells are less specialized in this respect. The natural consequences are as follows:

1. Excitation-contraction coupling of skeletal muscle is practically insensitive to changes in extracellular Ca concentration or transmembrane Ca conductivity since, here, intracellular stores provide sufficient quantities of Ca to guarantee full activation of the contractile system. Probably for this reason excitation-contrac-

tion coupling of skeletal muscle is also rather resistant to pharmacological interventions. Therefore, skeletal muscle is not discussed further in this article.

2. Myocardial and smooth muscle contractility, on the other hand, is much more susceptible to variations in environmental Ca or to pharmacological agents that affect transmembrane Ca supply, because the intracellular Ca stores of myocardial and smooth muscle cells are of rather limited capacity so that they have to be rapidly refilled from extracellular sources during mechanical activity.
3. The sudden inward movement of Ca ions across the excited myocardial or smooth muscle cell membranes is "electrogenic." This means that Ca ions, apart from Na and K, necessarily contribute to the changes in membrane potential during cardiac or smooth muscle activity. Under special conditions Ca ions may even substitute the Na ions as transmembrane charge carriers in the electrogenesis of action potential.

In general, however, there is a clear functional differentiation. For instance, in excited mammalian myocardial fibers the influxes of Na and Ca obviously use separate transmembrane carrier systems, a so-called *fast channel* for Na and a *slow channel* for Ca (3–5). In substantiating these observations it has been shown in our laboratory that, by a selective drug action on one of these two channels, either the particularly Na-dependent excitation phenomena or the strictly Ca-dependent contraction processes can be specifically modified. For instance, some local anesthetics (antiarrhythmic or antifibrillatory drugs such as procaine, procaine amide, lidocaine, or quinidine) predominantly inhibit the Na influx (6, 7). Substances of this type primarily reduce myocardial excitability. On the other hand, it turned out that the new group of organic Ca-antagonists [verapamil = Isoptin®, Iproveratril (8, 9), D 600 (10), nifedipine (11) etc.] first investigated in our laboratory selectively restricts myocardial contractility, because they block the slow channel (7). This article concentrates particularly on these agents. Opposite effects are exerted by sympathetic β-receptor stimulating agents [epinephrine (12), norepinephrine, isoproterenol]. These drugs selectively increase the transmembrane Ca inward current during cardiac excitation, thus augmenting contractile force without major changes in the action potentials (13, 14).

All the facts mentioned indicate that, related to the slow channel, there is indeed a special pharmacology of Ca in heart muscle. The same is true, according to our results, of practically all types of smooth muscle cells. Here the Ca-antagonistic inhibitors of excitation-contraction coupling act as powerful musculotropic relaxants. By this basic action they exert outstanding vasodilator effects in coronary and systemic circulation (15–16) as well as broncholytic and tocolytic activities (17–19). Although Ca-dependent excitation-secretion coupling is out of the scope of this article, it is noteworthy that, here too, the Ca-antagonistic inhibitors of excitation-contraction coupling proved to be surprisingly effective. Thus, in experiments on isolated tissues or perfused organs, suitably high concentrations of verapamil or D 600 specifically block the release of oxytocin and vasopressin from the depolarized neurohypophysis (20, 21) or of insulin from excited B-cells in the islets of Langerhans (22, 23). Extra calcium easily restores the secretory function even in the

presence of the inhibitors. Verapamil also interferes specifically with pituitary Ca uptake following in vitro depolarization, and thereby suppresses secretion of ACTH, GH, and TSH (24).

The present article can, of course, not cover more than a small section of this wide field. Therefore, it focuses on only a few important topics: the key-role of Ca ions in the function of heart and vascular smooth muscle, and on the special effects of drugs that antagonize or potentiate these Ca actions.

BASIC INTERACTIONS OF CA AND DRUGS IN CARDIAC ENERGY METABOLISM

The important role of Ca in sustaining myocardial contractility was first appreciated in 1882 by Sidney Ringer (25). He found on isolated frog hearts that Ca-free saline leads to cardiac arrest. As reported later by Mines in 1913, Ca withdrawal primarily impairs mechanical performance, whereas the bioelectric process of ventricular excitation may persist (26). Overwhelming evidence has accumulated in the last two decades that Ca ions are required during excitation to activate the biochemical processes that utilize ATP for contraction. Obviously the rapid rise in free intracellular Ca, resulting from the increased transmembrane Ca influx and a simultaneous liberation of Ca from endoplasmic stores, initiates the splitting of ATP by the Ca-dependent ATPase of the myofibrils so that phosphate-bond energy is transformed into mechanical work. Therefore, contractility is reversibly lost upon Ca withdrawal. As directly shown on isolated frog muscles (27) and beating rabbit auricles (28) the Ca-deficient myocardium exhibits a striking insufficiency in utilizing its high-energy phosphate compounds in the state of excitation. But after addition of Ca, high-energy phosphate consumption is normalized. If, on the other hand, the extracellular Ca concentration is increased above normal, more Ca is taken up by the beating heart so that both splitting of high-energy phosphates and contractility are potentiated. In fact, Ca ions not only trigger the contractile process but also control quantitatively the output of mechanical tension by regulating the amount of ATP that is metabolized during activity (8, 9, 27, 29, 30).

The splitting of ATP will, in turn, give rise to intensified glycolytic and oxidative recovery processes which have to refill, thereafter, the high-energy phosphate stores. This explains that the whole chain of metabolic reactions following contraction is "Ca-sensitive." Thus alterations in the extracellular Ca concentration generally lead to parallel changes in the following three parameters:

(*a*) the amount of ATP consumed by the contractile system,
(*b*) the magnitude of mechanical tension developed, and
(*c*) the extra-uptake of oxygen related to the contractile force generated.
In contrast, the basic respiration rate of the resting myocardium is rather irresponsive to Ca (8, 9, 27, 29).

The determinantal function of Ca in cardiac activity metabolism becomes particularly evident by virtue of the fact that many substances with a positive- or negative-

inotropic action on heart muscle exert their influence either by enhancing the Ca effect on utilization of high-energy phosphates, or by interfering with it. This applies, for instance, to β-adrenergic catecholamines (12, 13) and cardiac glycosides (31) which clearly increase, though by different mechanisms, the availability of Ca to the contractile system. In fact, upon administration of these drugs to isolated atria or papillary muscles there is a parallel rise in ATP consumption, contractile force, and oxygen uptake above resting level. Conversely, under the influence of Ca-antagonistic compounds the splitting of ATP, the contractile energy expenditure, and oxygen requirement of the beating heart are lowered (8, 9, 11, 13, 27–29, 32). However, even high doses do not change the basic respiration rate of the arrested myocardium. Hence, the oxygen-saving effects of Ca-antagonistic agents are only due to a restriction of cardiac activity metabolism in which Ca ions play the key role, whereas all other ATP-consuming reactions that are not connected with mechanical activity are insensitive to these drugs.

The restriction of extra-oxygen consumption during activity by the Ca-antagonistic agents listed in Figure 1 is linear to the decrease in isometric peak tension (13, 32, 33). As shown in experiments on isolated myocardial tissue, high concentrations of Ca-antagonistic drugs, just like complete Ca withdrawal, can totally suppress myocardial contractility (9, 13, 30, 33) and lower oxygen consumption even to resting level (13, 32, 33). However, with the relatively small doses applied in human therapy an only moderate reduction of cardiac work and oxygen demand is attainable. Furthermore, on the heart in situ, the cardiodepressant action of Ca-antagonistic compounds is to some extent self-controlled because, each time an unproportionate fall in arterial blood pressure occurs, a reflex release of endogenous sympathetic transmitters is elicited. This can partially neutralize the drug-induced cardiac inhibition because, unlike β-receptor blocking agents, the Ca-antagonistic substances do not abolish the responsiveness of the heart to β-adrenergic catecholamines (13, 29, 30, 34, 35). Thus the new Ca-antagonistic inhibitors of excitation-contraction coupling are safe drugs. They are widely used in Europe for the treatment of patients with a hyperkinetic heart function or coronary heart disease (36–43). Here a certain restriction of cardiac activity metabolism may be helpful to reestablish a suitable balance between the reduced coronary oxygen supply and the actual cardiac oxygen requirement. In this respect the Ca-antagonistic compounds have the same beneficial influence in patients with angina pectoris as the adrenergic β-receptor blocking agents do, even though the mode of action on the myocardial fiber membrane is different.

Ca-antagonistic substances interfere directly with the transmembrane Ca supply, whereas β-blocking agents reduce the transmembrane Ca influx indirectly by neutralizing the promoter effects of β-adrenergic catecholamines on transmembrane Ca uptake. Needless to say, eventually, both Ca-antagonists and β-receptor blocking agents lower Ca-dependent splitting of ATP, contractile tension, and oxygen requirement of heart muscle according to the same basic principle. But only the Ca-antagonistic compounds, by interfering with excitation-contraction coupling of vascular smooth muscle, offer the therapeutic advantage of a concomitant vasodilator action on coronary and systemic circulation comparable to that exerted by nitrites.

The ability of verapamil to reduce the size of experimental myocardial infarction (44, 45) is probably due to both an oxygen-saving effect and to circulatory improvement. Moreover it could be demonstrated in our laboratory that Ca-antagonistic compounds such as verapamil, D 600, or prenylamine are also capable of protecting the heart against noncoronarogenic myocardial necrotization. Since intracellular Ca overload proved to be the decisive factor in the pathogenesis of noncoronarogenic

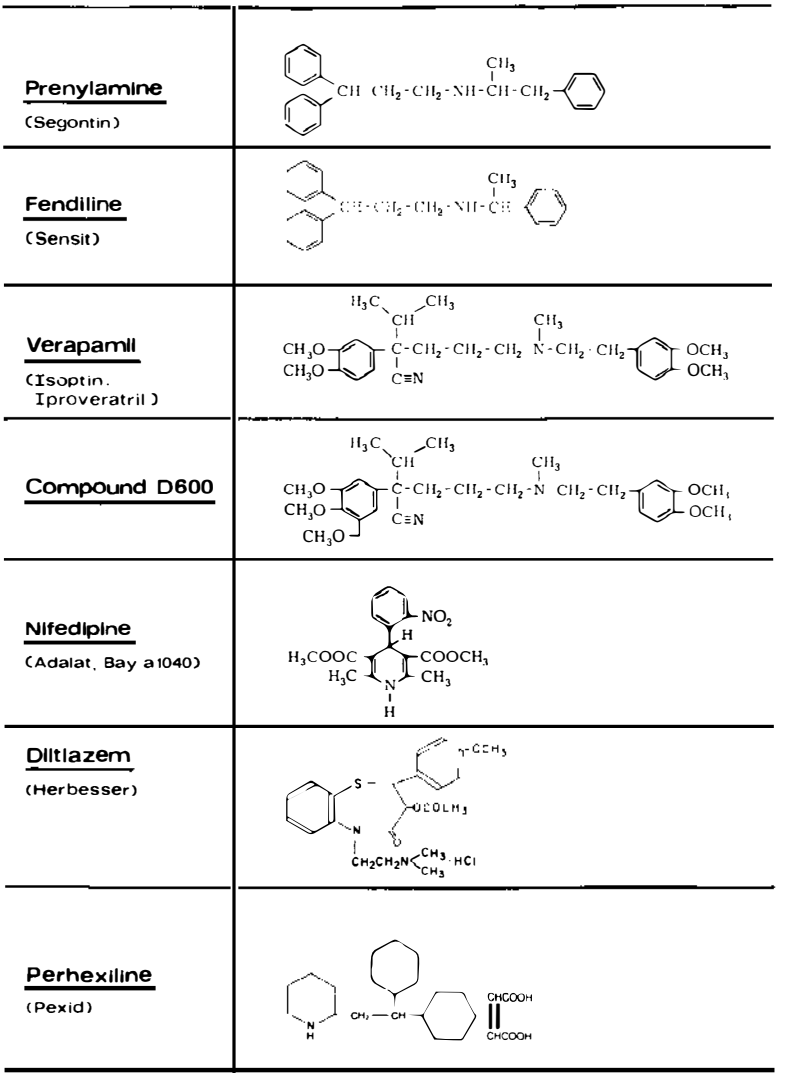

Figure 1 Ca-antagonistic inhibitors of excitation-contraction coupling in mammalian myocardium and vascular smooth muscle.

myocardial lesions, these Ca-antagonists, by inhibiting excessive Ca uptake, neutralize the cardiotoxic effects of large overdoses of β-adrenergic catecholamines, vitamin D, dihydrotachysterol etc [see (13, 33)]. Similarly, the development of spontaneous necrotization in cardiomyopathic hamster hearts could be prevented by long-term treatment with verapamil (46, 47).

BIOPHYSICAL MEMBRANE EFFECTS OF CA-ANTAGONISTIC AND CA-SYNERGISTIC DRUGS IN HEART MUSCLE

Evidence indicating that excitation-contraction coupling of the mammalian myocardium can be blocked in vitro and in vivo by pharmacological means was first presented in 1964 by Fleckenstein (8). He reported that two new compounds, namely Isoptin (= iproveratril, later given the generic name verapamil) and Segontin® (prenylamine) as well as high concentrations of certain adrenergic β-receptor blocking agents and barbituric acid derivatives mimic the cardiac effects of Ca withdrawal in that these substances

(*a*) diminish contractile force without a major change in action potential,
(*b*) reduce high-energy phosphate utilization of the contractile system,
(*c*) lower extra-oxygen consumption during activity,
(*d*) are easily neutralized by administration of additional Ca, β-adrenergic catecholamines, or cardiac glycosides.

In an extensive search for other Ca-antagonistic inhibitors of this type, a considerable number of substances that also meet these criteria were found in our laboratory. The Ca-antagonistic compounds can be classified as specific and nonspecific. In the group of nonspecific inhibitors, Ca-antagonism is merely a side effect which becomes apparent only if high doses are administered. For instance, the well-known cardiodepressant action of overdoses of barbiturates or, particularly, of certain β-receptor blocking agents such as dichloroisoproterenol, pronethalol, or propranolol is due to direct interference with Ca-dependent excitation-contraction coupling (9, 29, 30, 33).

Much more interesting, however, is the family of Ca-antagonistic drugs of the verapamil type which are capable, according to our observations, of blocking excitation-contraction coupling specifically (see Figure 1). Specificity means that the Ca-antagonistic action is so predominant that other pharmacodynamic properties, at least in a reasonable dosage range, are more or less negligible. Apart from verapamil, compound D 600 [a methoxy-derivative of verapamil (10, 13)], nifedipine [Bay at 1040, Adalat (11, 13)], and diltiazem (33, 48) proved to be the most specific and powerful Ca-antagonists. An exemplary experiment is shown in Figure 2. Here, contractility of an isolated guinea pig papillary muscle was completely abolished by a large dose of verapamil (30). But resting potential as well as the action potential parameters such as upstroke velocity and height of the overshoot, indicating the transmembrane Na influx across the fast channel, remained practically unchanged (13, 30, 33). Only the plateau of action potential appears to be slightly abbreviated by verapamil because Ca ions cannot continue to contribute to the maintenance of

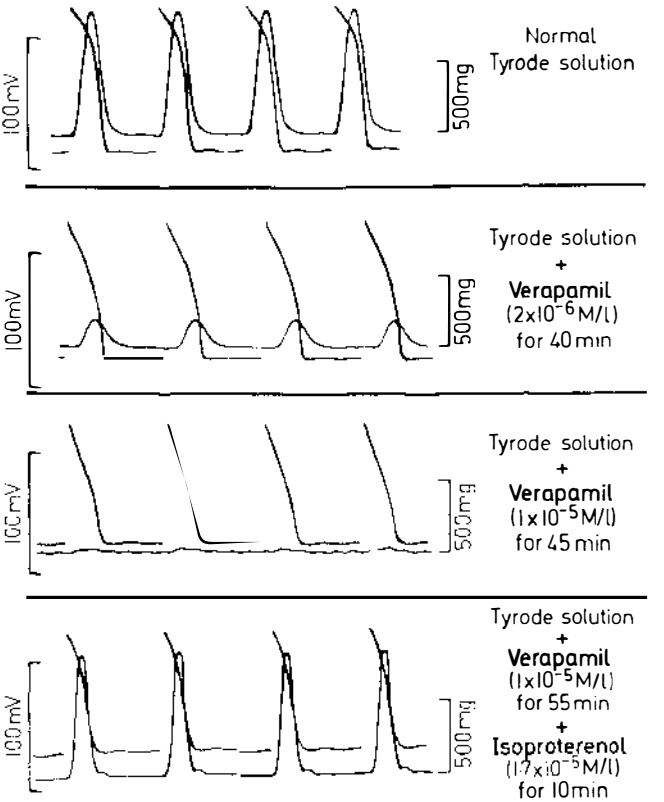

Figure 2 Selective loss of cardiac contractility under the influence of a high overdose of verapamil, and the reversal of this effect by isoproterenol. Experiments on an electrically driven (2 shocks/sec) isolated papillary muscle of a guinea pig [From A. Fleckenstein (30)].

depolarization during the late phase of the plateau when the transmembrane Ca conductivity has been blocked.

The selective inhibition of the slow channel following administration of verapamil and compound D 600 can be directly visualized by separate measurements of the transmembrane Na and Ca currents on ventricular trabeculae of cats with the use of a special voltage clamp technique (7). In fact, verapamil and D 600 produce a drastic reduction in transmembrane Ca conductivity just in the dosage range that suppresses contractile performance, whereas the fast Na current is not altered (7). The inhibitory effects of verapamil on Ca influx and contractile tension can be rapidly overcome by addition of excess Ca or isoproterenol, which is most effective among the β-adrenergic catecholamines tested (8, 9, 33). However, the possibility of controlling contractile force by acting on the Ca channel is lost in skinned myocardial fibers which we have prepared by glycerin water extraction or according

to Winegrad's technique (49). In such skinned fibers the Ca-antagonistic compounds produce no inhibition when contraction is directly induced by addition of ATP and Ca. This means that the Ca-antagonistic drugs lose their power if the Ca ions have free access to the myofibrils where ATP is split. Hence there is no direct effect of Ca-antagonistic compounds on myofibrillar ATPase.

Interestingly enough the divalent strontium (Sr) and barium (Ba) ions, which are capable of replacing Ca in excitation-contraction coupling, also use the slow channel when they penetrate into the myocardial fibers (50). This implies that a blockade of the slow channel produced by Ca-antagonistic agents also abolishes the influxes of Sr and Ba provided that the sarcolemma membrane is still intact. Nickel, cobalt, or manganese ions, on the other hand, block the slow channel by themselves because they probably compete with Ca, Sr, and Ba for certain active sites in this particular carrier system (51). Accordingly, nickel and cobalt ions selectively suppress excitation-contraction coupling of mammalian myocardium as found by us in 1965 (52). But again Ni, Co, and Mn have no direct inhibitory effect on the contractile system itself [for more details concerning the basic myocardial effects of Ca-antagonists see (13, 33)].

There is no indication that the Ca-antagonistic inhibitors of excitation-contraction coupling, apart from their well-established action on the slow membrane channel, might also interfere with intracellular Ca movements. For instance, in isolated mitochondria, only an excessive concentration of verapamil, more than 1000 times greater than that required to produce contractile failure, suppresses Ca uptake (53). Similarly in isolated sarcoplasmic reticulum all direct attempts at showing an inhibitory effect of negative inotropic doses of verapamil on accumulation, binding, or exchange of Ca have failed (54–56).

More promising, however, were some recent investigations into the particular action of verapamil on isolated cardiac sarcolemma membranes (54, 57). Here the existence of a membrane-located Ca store was found by Nayler & Szeto (1972) which could be depleted by verapamil (54). The assumption is justified that the Ca ions that enter the cell through the slow channel are derived from this intermediate pool of superficially bound membrane Ca. Thus the principal action of verapamil consists of reducing the Ca-accumulating activity or the Ca-binding capacity of these membrane-located storage sites, so that the availability of Ca to the slow membrane channel is restricted. Conversely, as indicated by observations from our laboratory, the potentiation of transmembrane Ca influx produced by β-adrenergic catecholamines might result from a promoter effect of these agents on sarcolemma Ca binding. Epinephrine and isoproterenol probably increase the affinity of these superficial storage sites to Ca, so that Ca uptake from the environment is intensified. By this action β-adrenergic catecholamines

(*a*) neutralize the symptoms of Ca deficiency as long as traces of Ca are available (58, 59),
(*b*) guarantee a sufficient Ca supply to the slow channel even at rather high stimulation rates, and
(*c*) accelerate the recovery of the transmembrane Ca current considerably when Ca is readmitted to previously Ca-deprived myocardium.

Under all these circumstances verapamil and β-adrenergic catecholamines operate in an exactly opposite sense. Possibly β-adrenergic catecholamines, through formation of cyclic AMP, induce phosphorylation of sarcolemma membrane proteins (60) thus augmenting the number of Ca-accumulating binding sites.

PHARMACOLOGICAL INTERVENTIONS IN CA-DEPENDENT CARDIAC PACEMAKER ACTIVITY

Apart from inhibiting mechanical performance, Ca deficiency impairs cardiac pacemaker activity. Thus the progressive reduction of cardiac work in Ca-free Ringer solution is accompanied by a parallel decrease in heart rate (58). Accordingly, Ca-antagonistic agents such as verapamil, D 600, diltiazem, or nifedipine suppress sinoatrial (SA) or atrioventricular (AV) pacemaker activity of isolated nodal tissue from rabbits, rats, and guinea pigs in the same dosage range that restricts atrial or ventricular contractility (61–64). There is again a recovery of both original heart rate and tension development if appropriate doses of β-adrenergic catecholamines, particularly isoproterenol, are administered (8, 9, 13). Extra Ca is less suitable to restore automaticity. The influence of verapamil on spontaneous pacemaker action potentials obtained from the SA node and the central zone (N-zone) of the AV node was studied by several research groups (63–65) with almost identical results: Verapamil reduces the steepness of the slow diastolic depolarization so that the rate of spontaneous impulse discharge drastically decreases. In addition, the rate of rise and the overshoot of the pacemaker action potential are lowered. Hence, under the influence of verapamil the velocity of impulse propagation within the SA node and especially through the AV node must be considerably diminished. The Ca-antagonistic divalent Co, Ni, and Mn ions too act like verapamil in that they equally suppress cardiac contractility and pacemaker function (64, 66–68). Verapamil, D 600, nifedipine, and Mn ions also block impulse conduction in the perfused AV node of dog hearts in situ (66, 69). Again isoproterenol proved to be an effective antidote.

The conclusions to be drawn from these observations are as follows:

(*a*) Impulse production and propagation in cardiac pacemaker tissues require Ca.
(*b*) Cardiac automaticity is as susceptible to inhibitors (Ca-antagonists) and promoters (β-adrenergic catecholamines) of transmembrane Ca influx as cardiac contractility.
(*c*) An apparently similar or perhaps identical Ca transport system operates as slow channel in both myocardial fibers and nodal cells.

As to the biophysical characterization of the slow channel it is generally agreed that this carrier mechanism works at a relatively low ventricular membrane potential, whereas the fast Na channel undergoes inactivation if the myocardial fibers are partially depolarized (3–5). Application of tetrodotoxin (TTX) is another means known to abolish fast channel function selectively. Nevertheless, such myocardial fibers are still capable of conducting propagated action potentials. But in this case upstroke and overshoot depend on the slow inward current of Ca which then substitutes, as an auxiliary transmembrane charge carrier, the lacking influx of Na.

The consequence is that upstroke velocity and propagation of Ca-mediated ventricular action potentials are much slower than normal and in addition become highly sensitive to verapamil and other Ca-antagonists (59). Needless to say, in this respect the bioelectric features of Ca-dependent action potentials of partially depolarized myocardial fibers closely resemble those of cardiac pacemakers. Hence it may be argued that this correspondence possibly results from the fact that the nodal cells too operate at a rather low level of membrane potential (70). But whatever the final answer, a decisive involvement of the fast Na channel in normal supraventricular automaticity can be excluded because the SA and AV pacemaker action potentials do not respond to TTX (67, 68). This, however, does not imply that Na is totally inert in pacemaker activity.

There are, indeed, observations indicating that major changes in the extracellular Na concentration also affect upstroke velocity and overshoot of pacemaker action potentials (64). The discrimination between extracellular Ca and Na by the slow channel is probably not so perfect that the influence of large alterations of the transmembrane Na gradient is reduced to zero. A similar finding is that lidocaine, procaine, procaine amide, and quinidine, which according to our voltage clamp studies on cat trabeculae predominantly act as Na-antagonists (7), also restrict SA and AV node automaticity provided that the doses are rather high (61). Nevertheless, the sensitivity of the supraventricular pacemakers to concentration changes in extracellular Ca and to substances that specifically act as slow channel promoters or inhibitors is by far greater. This applies certainly to nomotopic automaticity. But with regard to the successful use of Ca-antagonistic compounds in the treatment of many types of ectopic automaticity it is to be assumed that also in these cases Ca is basically involved.

Verapamil, in particular, has attracted much interest in recent years both pharmacologically (71) and clinically (39, 72–75) because of its pronounced antiarrhythmic and antifibrillatory properties. This is, however, not a peculiarity of verapamil since other Ca-antagonistic drugs listed in Figure 1 share this antiarrhythmic action (43, 76, 77).

INHIBITORS AND PROMOTERS OF CA ACTION IN VASCULAR SMOOTH MUSCLE

Extensive research work on smooth musculature of different origin has revealed that here too Ca ions are required not only for excitation-contraction coupling but also, in analogy to cardiac pacemaker function, for the discharge of propagated action potentials (78–80). Hence smooth muscle relaxation produced by Ca-antagonistic agents may result either directly from inhibition of Ca-dependent contractility or indirectly from suppression of Ca-dependent membrane excitation. For instance, spontaneous impulse discharge in smooth muscle preparations from uterus (18), taenia coli (81), and portal vein (82) is arrested by verapamil, D 600 (and nifedipine) in a concentration range that is considerably lower than that required for the blockade of excitation-contraction coupling. Conversely the latter action is most prominent in vascular smooth muscle from coronary, pulmonal, or brain arteries.

Here, inhibition of excitation-contraction coupling can easily be demonstrated on K-depolarized spiral strips which promptly relax under the influence of Ca-antagonistic drugs, whereas depolarization persists (15, 16, 83, 84). Contractures produced by histamine, serotonin, or pitressin are equally suppressed. Excitation-contraction coupling of coronary smooth muscle is generally three to ten times more sensitive to the Ca-antagonistic agents than that of ordinary myocardial fibers. This explains the high efficacy of Ca-antagonists as coronary vasodilators, even in doses that are insufficient to decrease myocardial contractility (85–90).

Figure 3 represents dose-response curves that indicate the potency of these new Ca-antagonists in neutralizing the K-induced spasm of pig coronary strips. In this study nifedipine proved to be several thousand times stronger than papaverine. However, the vasodilator action of Ca-antagonistic drugs is not confined to coronary circulation because they also lower systemic flow resistance by relaxing basic vascular tone and neutralizing autoregulative vasoconstrictor responses (15, 16, 91). For this reason Ca-antagonists, particularly verapamil and nifedipine, are also used for the treatment of certain types of arterial hypertension (72, 92).

With respect to this dual action on coronary and systemic circulation, the vascular effects of Ca-antagonists resemble those of nitroglycerin and other nitrites. Moreover, as recently found in our laboratory, nitroglycerin and related compounds

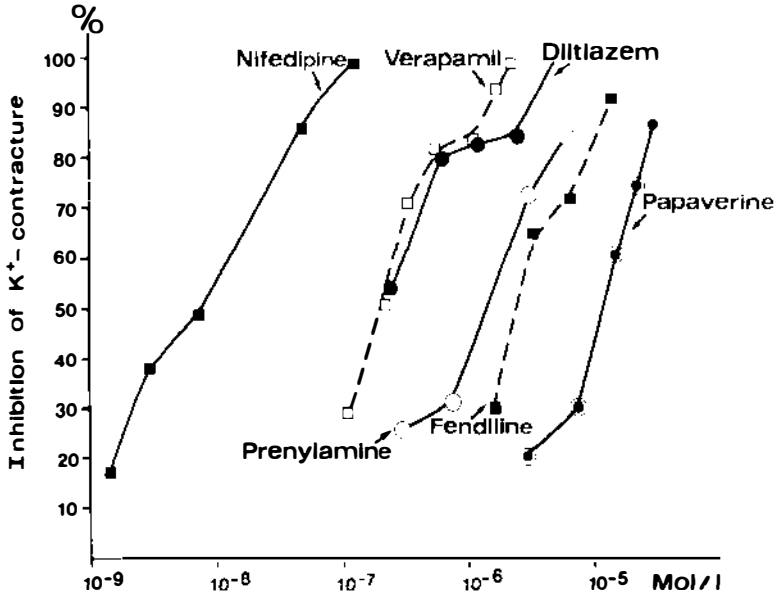

Figure 3 Suppression of K-induced contractures of pig coronary strips by Ca-antagonistic inhibitors of excitation-contraction coupling (From Fleckenstein, Nakayama, Fleckenstein-Grün & Byon. 1976. In *Ionic Actions on Vascular Smooth Muscle,* ed. E. Betz, 117–23. Berlin, Heidelberg & New York: Springer).

also interfere in some way with Ca-dependent excitation-contraction coupling of vascular smooth muscle, even though these drugs have no corresponding action on myocardial fibers (16, 93). However, the kinetics of nitrite-induced vascular relaxation, when thoroughly compared on K-depolarized coronary strips with the action of Ca-antagonists, proved to be rather different. The pecularities of the nitrites are as follows:

(*a*) The onset of nitrite-induced relaxation is much more rapid, particularly when nitroglycerin or amyl nitrite is applied.
(*b*) Nitrite-induced relaxation always remains incomplete. Even at high nitrite concentrations a residual contracture of 20–40% persists.
(*c*) Nitrite-induced relaxation is in most cases transient so that coronary tone tends to recover spontaneously in the presence of the drugs. Extra Ca instantaneously neutralizes the nitrite effects.

The experimental findings on isolated vascular smooth muscle correspond with the old clinical experience that nitroglycerin and amyl nitrite, because of their rapid coronary and systemic action, are most suitable for the interruption of an acute anginal attack. But for the basic long-term treatment of coronary heart disease the Ca-antagonists listed in Figure 1 are more promising. This applies particularly to the prevention of spastic coronary troubles classified as "variant angina" according to Prinzmetal's terminology.

Coronary spasms are facilitated by cardiac glycosides: Because of their interaction with Ca, originally discovered in 1917 by Loewi (94) on frog hearts, cardiac glycosides not only improve myocardial contractility but also increase tension development of coronary smooth muscle (95–98). Furthermore, under the influence of cardiac glycosides a massive sensitization to Ca takes place which again affects both cardiac muscle and coronary arteries (96, 98). Thus, in digitalized hearts, a sudden rise in extracellular Ca concentration not only endangers myocardial function but may also evoke, under certain conditions, coronary vasoconstriction. The same glycoside-induced potentiation of tension development occurs in coronary strips with electric (97, 98) and mechanical stimulation (quick stretch) or with administration of vasoconstrictor agents such as serotonin, histamine, or pitressin (99). However, with the help of Ca-antagonists, all these unpleasant vascular side effects of cardiac glycosides can easily be prevented. The doses of Ca-antagonists required for this purpose are so small that they practically do not impair the desired therapeutic glycoside effects on the myocardium (95).

SUMMARY

During the past decade evidence has been obtained of the existence of a dual membrane carrier system in atrial and ventricular myocardium: a *fast channel* for Na ions that initiate the cardiac fiber action potentials and a separate *slow channel* for Ca ions that activate the contractile machinery. Furthermore, it turned out that transmembrane Ca transport through the slow channel is also involved in nomotopic and ectopic pacemaker activity. Therefore, with the discovery of the new

family of highly potent organic Ca-antagonists which are capable of specifically blocking the slow channel, it became possible to limit both cardiac force and automatic impulse discharge to any desired extent. In this respect Ca-antagonists operate in an exactly opposite way than β-adrenergic catecholamines do, since the latter agents exert their positive inotropic and chronotropic effects by acting on the slow channel as promoters of transmembrane Ca influx. In vascular smooth muscle, contractility and tone as well as automaticity also depend on the availability of Ca. This explains the outstanding efficacy of Ca-antagonistic compounds as musculotropic vasodilators in coronary and systemic circulation.

The application of Ca-antagonists as antianginal, antiarrhythmic, antihypertensive, or cardioprotective drugs makes use of these different manifestations of the same basic membrane action. The beneficial influence of Ca-antagonists in coronary disease is probably complex because at least three therapeutically important factors seem to work together: (*a*) direct reduction of myocardial energy expenditure and, therefore, oxygen demand; (*b*) indirect decrease in cardiac oxygen requirement by facilitation of heart work at a reduced level of arterial blood pressure, and (*c*) improvement of myocardial oxygen supply due to vasodilator or spasmolytic effects particularly on extramural coronary vessels (stem arteries, collaterals, anastomoses).

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