Cardiac Metabolism

Edited by

Angela J. Drake-Holland

and

Mark I. M. Noble

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Angela J. Drake-Holland

Department of Medicine 1,
St George's Hospital Medical School,
London, UK

and

Mark I. M. Noble

Midhurst Medical Research Institute,
Midhurst, West Sussex, UK

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Contributors

H. Van Belle *Department of Biochemistry, Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium*

L. Blayney *Department of Cardiology, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK*

R. G. Butcher *Midhurst Medical Research Institute, Midhurst, West Sussex GU29 0BL, UK*

J. B. Chapman *Department of Physiology, Monash University, Clayton, Victoria 3168, Australia*

R. A. Chapman *Department of Physiology, University of Berne, Bühlplatz 5, 3012 Berne, Switzerland*

A. Coray *Department of Physiology, University of Berne, Bühlplatz 5, 3012 Berne, Switzerland*

M. J. Dawson *Department of Physiology, University College London, Gower Street, London WC1E 6BT, UK*

A. J. Drake-Holland *Department of Medicine 1, Jenner Wing, St George's Hospital Medical School, London SW17, UK*

G. Elzinga *Department of Physiology, Free University, Amsterdam, The Netherlands*

P. J. England *Department of Biochemistry, University of Bristol Medical School, Bristol BS8 1TD, UK*

M. Fillenz *University Laboratory of Physiology, Oxford OX1 3PT, UK*

S. S. Galhotra *Division of Biological Science and Pritzker School of Medicine, 950 East 59th Street, Chicago, Illinois 60637, USA*

H. E. D. J. ter Keurs *Department of Experimental Cardiology, Academisch Ziekenhuis, Leiden, The Netherlands*

J. D. Laird *Department of Physiology and Physiological Physics, University of Leiden, The Netherlands*

B. Lewartowski *Medical Centre of Postgraduate Education, Marymonka 99, 01-813 Warsaw, Poland*

H. Lüllmann *Department of Pharmacology, University of Kiel, 2300 Kiel, West Germany*

J. A. S. McGuigan *Department of Physiology, University of Berne, Bühlplatz 5, 3012 Berne, Switzerland*

J. Nauman *Medical Centre for Postgraduate Education, Marymonka 99, 01-813 Warsaw, Poland*

M. I. M. Noble *Midhurst Medical Research Institute, Midhurst, West Sussex GU29 0BL, UK*

R. A. Olsson *Suncoast Cardiovascular Research Laboratory, Department of Internal Medicine, University of South Florida College of Medicine, Tampa, Florida 33612, USA*

L. H. Opie *Department of Medicine, University of Cape Town, Observatory 7925, Cape Town, South Africa*

T. Peters *Department of Pharmacology, University of Kiel, 2300 Kiel, West Germany*

J. Preuner *Department of Pharmacology, University of Kiel, 2300 Kiel, West Germany*

R. S. Reneman *Department of Physiology, Biomedical Centre, University of Limburg, Maastricht, The Netherlands*

G. J. van der Vusse *Department of Physiology, Biomedical Centre, University of Limburg, Maastricht, The Netherlands*

A. Williams *Cardiothoracic Institute, 2 Beaumont Street, London W1N 2DX, UK*

R. Zak *Division of Biological Science and Pritzker School of Medicine, 950 East 59th Street, Chicago, Illinois 60637, USA*

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Preface

The idea of a book on Cardiac Metabolism which represented current ideas and theories based on recent experimental evidence was an appealing, if somewhat daunting, task. The concept of Cardiac Metabolism covers a vast area, every aspect of which is important in its own right. There has been such an advance in techniques and thinking over the last few years that it is not possible for any one person (or laboratory) to be able to cope with research into all the aspects of cardiac metabolism. We have, therefore, produced a multi-author book. This has the advantage of bringing a spectrum of approaches and opinions together. Where overlap of subject matter has occurred, we have retained the material where different chapter authors have different opinions. We have tried to introduce some newer personalities in the field whose views deserve consideration. Many of the ideas presented are unconventional, and are intended to stimulate thought and argument.

It has been necessary to make many omissions of important subjects in cardiac metabolism. We have concentrated on various aspects of calcium metabolism and energy utilization, but also included some relatively neglected subjects and interesting methodological approaches (NMR and histochemistry). We failed to persuade anyone to write about membrane protein phosphorylation. This would have made a real gap in view of the inclusion of other chapters on cyclic AMP, contractile protein phosphorylation and catecholamines. We have therefore written such a chapter based on our literature reading and thank Drs. Tsien and England for their help with this.

The presentation of the book is to offer to the reader many aspects of cardiac metabolism, beginning with the handling of calcium ions, through biochemical reactions, to the metabolic factors concerning blood flow and performance. The heart is not an isolated organ: it is surrounded by a changing environment. Each chapter may be read on its own as a source of information relevant to the particular subject of interest, though the reader will find himself gently directed to other chapters that we feel should be considered as well. It is hoped that each reader, be they teacher or research worker of any discipline, will find interesting and provoking reading, in or related to their own subject.

One or both of us have been privileged at one time or another to visit, or to have visit us, many of the authors in this book. To visit other laboratories is stimulating and extremely worthwhile; it benefits both the visitor and host. Our thanks go particularly to Professors Lewartowski, Lüllman, Elzinga, Laird, and Drs. ter Keurs, van der Vusse, Reneman and Nauman for their generosity and hospitality during our 'invasion' of their laboratories. Of the remaining authors we thank those who have visited us and/or for stimulating discussions.

Our interest in cardiac metabolism stems from two main sources. Firstly one of us was basically trained in Biochemistry (when privileged to work with Professor Opie) and though having now 'changed courses' to Physiology, retains a fondness for the subject. The other has been persuaded (over the years) that though the mechanics are interesting, metabolism is more fundamentally important.

The invitation to compile this book arose from conversations between representatives of John Wiley from nearby Chichester and Professor G. Cumming, Director of the Midhurst Medical Research Institute.

We are indebted to our colleagues who put up with the trials of trying to meet deadlines, and our laboratory colleagues who put up with us during the writing and editing of this book. We are also grateful to the many typists who helped with the manuscripts.

ANGELA J. DRAKE-HOLLAND
MARK I. M. NOBLE

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CHAPTER 1

Role of the Plasmalemma for Calcium Homeostasis and for Excitation–Contraction Coupling in Cardiac Muscle

Heinz Lüllmann, Thies Peters, and Jürgen Preuner

Department of Pharmacology, University of Kiel, 2300 Kiel, West Germany

INTRODUCTION

Abundant efforts have been made in the past to elucidate the mechanisms involved in the calcium homeostasis and in the excitation–contraction (EC) coupling process of mammalian heart muscle cells. For a pharmacologist it is of more than academic interest to resolve these problems: these mechanisms are fundamental to the molecular basis of drug action.

In skeletal muscle, depolarization of the plasmalemma is conducted to the transverse tubules from where it spreads to the terminal cisternae of the sarcoplasmic reticulum (SR), whence it is thought to release Ca ions (Ca^{++}). These Ca^{++} diffuse to the nearby Z-lines of the sarcomeric units and activate contraction. Contraction is terminated by an active, ATP-driven calcium sequestration into the longitudinal tubules of the sarcoplasmic reticulum from whence it is translocated back to the terminal cisternae. This hypothesis is far from being proven.

In cardiac muscle, it is necessary to postulate essential modifications as far as the mechanism of Ca^{++} release is concerned. By means of voltage clamp experiments it could be demonstrated that some calcium enters the cell during depolarization: slow, inward directed calcium current. Initially, it was suggested that the amount of calcium invading the cell during depolarization would suffice to activate contraction. Yet the amount turned out to be too small (of the order of up to 1×10^{-6} mol per kilogram of cell per beat). As a consequence, a calcium-triggered calcium-release mechanism from the SR was postulated (also called regenerative calcium release). At the time of writing, a mechanism of this kind has not been proven under physiological conditions. Recently, by using isolated cells, which are deprived of their glycocalyx, Isenberg and Klöckner, (1980) demonstrated a much more pronounced influx of Ca^{++} into the cardiac cell which would be able to activate contraction *per se*. The physiological relevance of this finding remains unclear, since the permeability of these cells

does not appear to agree completely with that observed in intact cells (see below as regards the rate of radio-calcium entry and exchange). Moreover, it has been difficult to visualize the ability of cardiac sarcoplasmic reticulum to terminate contraction or induce relaxation by actively pumping back calcium from the cytosol. Both the paucity of cardiac SR and its affinity constant for calcium with respect to the Ca^{++} concentration present in the cytosol during and after contraction do not seem to allow a significant contribution to relaxation (Mullins, 1981). From experiments conducted on mechanically skinned cardiac fibres of different sections of the heart muscle it was claimed that the SR does contribute to contraction and relaxation (for a review see Fabiato and Fabiato, 1979). However, the property of a preparation of this kind to display spontaneous contraction and relaxation does not necessarily reflect what happens in intact tissue; especially as these skinned fibres require loading at rather high calcium concentrations.

We propose a mechanism of excitation–contraction coupling in heart muscle of a completely different type. Before this hypothesis is outlined below, we discuss several essential aspects of the movements and distribution of calcium in heart muscle; these are prerequisites for further consideration of the problem.

Ca MOVEMENTS UNDER VARIOUS CONDITIONS

Resting Heart Muscle

When cardiac tissues are not beating for a while, all intracellular Ca compartments are in equilibrium with an extremely low cytosolic Ca^{++} concentration ($<10^{-7}$ M); only the outer layer of the plasmalemma is in equilibrium with the extracellular Ca^{++} concentration ($\sim 10^{-3}$ M Ca^{++}, see Figure 1.1). Net movements of Ca do not occur under this condition. The Ca leaking along the high gradient into the cell is counterbalanced by the plasmalemmal Ca pump. Studying Ca movements under this condition by means of radio-Ca reveals that ^{45}Ca is initially rapidly taken up; but the rate declines with time, attaining its final equilibrium not before 30–60 min of exposure. Thus the ^{45}Ca uptake process does not obey an exponential function, but rather reflects the exchange of ^{45}Ca with Ca bound at differing dissociation rate constants or reflects different accessibilities (deep compartments). The reverse experiment, namely the efflux of ^{45}Ca from a heart muscle previously equilibrated with radio-Ca, yields mirror-like curves: again initially a rapid loss of ^{45}Ca followed by a declining process of exchange. From this type of experiment it can be concluded that even in resting heart muscle a high turnover of Ca proceeds within (and through) the plasmalemma as indicated by the initial rate, which soon slows down since the amount of rapidly exchangeable binding sites is limited It should be kept in mind that the freely exchangeable Ca^{++} present in the cytosol amount only to about 6×10^{-8} mol. kg^{-1} w.w. and is thus quantitatively negligible with respect to exchange processes at a tissue Ca

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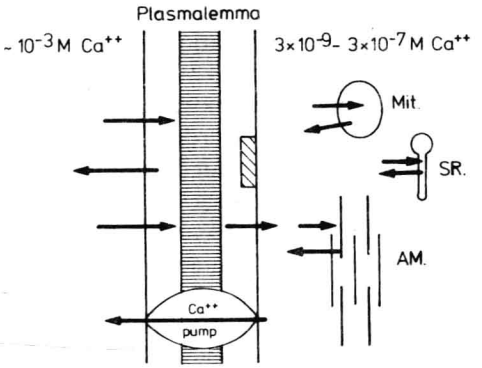

Figure 1.1 Schematic presentation of Ca movement in resting heart muscle. Under this condition only Ca exchange processes will occur (black arrows). The extracullular Ca^{++} concentration ($\sim10^{-3}$ M) is in equilibrium with the Ca bound to the outer leaflet of the plasmalemma. The barrier between the high extracellular and low intracellular Ca^{++} concentrations is posed by the highly hydrophobic middle layer of the unit membrane (horizontally hatched area). The Ca bound to or stored by intracellular organelles is in equilibrium with the low cytosolic Ca^{++} concentration. Mit = mitochondria, SR = sarcoplasmic reticulum, AM = actomyosin, → = exchange. The plasmalemmal Ca pump compensates for the leak of Ca along the extemely steep gradient. The high affinity potential-dependent binding sites are marked by a hatched box at the inner membrane surface

content of about 1.2×10^{-3} mol. kg^{-1} w.w. (at an extracellular Ca^{++} concentration of about 1.0 mM).

The initial ^{45}Ca uptake rate can be considered – though with reservation – to reflect the turnover rate of Ca in the plasmalemma. Since a heart muscle preparation is always a multicellular system with complex geometry, the rate of disposition of ^{45}Ca might, however, become rate-limiting. This applies particularly to resting muscles whereas strongly beating preparations might accelerate the diffusion and therewith the disposition of ^{45}Ca. If this consideration holds true for the present case the initial uptake (and release) rate of ^{45}Ca provides an underestimate of the initial exchange rate, which therefore should be even faster than experimentally determined. (For further studies, see Lewartowski, Chapter 5 in this volume). In conclusion, in resting heart muscles net Ca movements do not occur but a vigorous Ca exchange proceeds at rates varying over a wide range, according to the dissociation of Ca from different binding sites.

Net Movements after Raising the Extracellular Ca Concentration

A sudden rise of the Ca^{++} concentration is followed by a rapid increase o contractile force of beating preparations. Its time course depends on the rate o

disposition of Ca^{++}, in perfused preparations (Langendorff hearts) at about $t_{1/2} = 10$ s and in superfused preparations at about $t_{1/2} = 20$–30 s. This observation suggests that alterations of the extracellular Ca^{++} concentration are almost immediately transferred to the cardiac cells and are available for EC coupling. Which net Ca movements occur in resting preparations, a simpler situation than that of contracting muscles?

The increased Ca^{++} concentration has to approach the cell surface by diffusion. As shown in experiments with guinea-pig and cat atrial and ventricular muscles, a sudden increase of the Ca^{++} concentration in the bath up to about 8 mM does not alter the resting tension. This indicates that the cytosolic Ca^{++} concentration remains below the threshold concentration as regards the activation of actomyosin ($\sim 3 \times 10^{-7}$ M), but a pronounced net uptake of Ca results, which depends upon the degree of increase of the extracellular Ca. The muscles require 15–20 min to attain the new equilibrium (Körnich and Lüllman, 1970). From recent experiments on guinea-pig atria, the initial rate of net uptake could be calculated because of a proper time resolution within the first minutes, after raising the Ca^{++} concentration from 0.9 to 3.6 mM. The initial net uptake rate amounted to 5×10^{-7} mol kg^{-1} s^{-1} (H. Lüllmann and A. Ziegler, unpublished). This figure lies in the same range as the electrogenic Ca flux determined for the plateau phase of the action potential ($\sim 6 \times 10^{-7}$ mol kg^{-1}), which is considered to carry part of the inward current necessary to keep the membrane depolarized. In contrast, no depolarization whatsoever occurs when a heart muscle is suddenly exposed to higher Ca^{++} concentrations, a condition under which a correspondingly high net uptake proceeds. This indicates strongly that Ca taken up does not cross the plasmalemma as an ion but becomes primarily bound to the outer leaflet of the plasmalemma, i.e. the net uptake appears to be non-electrogenic.

From the outer leaflet Ca will, according to the higher gradient, increasingly leak into the cytosol, slightly raise the free Ca^{++} concentration (but still less than 3×10^{-7} M), and supply all intracellular compartments which slowly adapt to the new level within 10–15 min. The cell's outward directed Ca pump supposedly participates in keeping the cytosolic Ca^{++} concentration low. In contrast to ventricular muscles of guinea-pigs and cats, rat ventricular muscles possess a Ca pump of only minor potency (Olbrich and Preuner, 1982). In this species a stepwise increase of extracellular Ca results in an increase in resting tension.

What has been outlined for the resting heart muscle is also applicable for contracting muscles after raising the Ca^{++} concentration: the diastolic tension remains unaltered over a wide range of stepwise increases (guinea-pig, cat) and the net uptake of Ca is also non-electrogenic.

In conclusion, a rise in extracellular Ca^{++} concentration results in a corresponding net uptake of Ca which is non-electrogenic, i.e. the Ca becomes primarily bound to the plasmalemma and is slowly distributed to intracellular binding sites via a cytosolic Ca^{++} concentration still below threshold with respect to the actomyosin.

Excitation-dependent Ca Movements

During depolarization two events take place: (a) a Ca^{++} influx through a specialized pore (slow inward current); (b) a release of Ca^{++} from high affinity, potential-dependent binding sites. From their location at the inner surface of the plasmalemma, Ca^{++} ions diffuse into the cytosol and activate the contractile apparatus in a concentration-dependent way.

As outlined above the slow inward current is not sufficient to supply the amount of Ca^{++} required to activate the contractile system. Nevertheless it provides a net cellular uptake of Ca which eventually has to be counterbalanced by the Ca pump. Comparing the initial ^{45}Ca exchange rates of resting and beating atrial tissue, an extra Ca exchange of 0.5 $\mu M\ kg^{-1}$ per beat can be calculated which is in good agreement with the estimates of Ca^{++} flux during the plateau.

The depolarization-dependent release of Ca^{++} from high affinity binding sites located at the inner surface of the plasmalemma is a cellular event and does not primarily involve extracellular Ca. These binding sites are thought to possess the following properties: a high affinity for Ca if the plasmalemma is polarized, a low affinity during depolarization of the membrane, and a capacity sufficient to supply Ca^{++} in excess for activation of the contractile system.

The requirements are met by an array of phosphatidylserine (PS) molecules which are part of the Na, K-ATPase and are integrated into the inner leaflet of the plasmalemma.

At low proton concentrations present in the polarized membrane due to the strong electric field across the plasmalemma, PS complexes Ca with high affinity. When the membrane depolarizes the proton activity drastically increases within the membrane, approaching the bulk pH because the transmembrane field has collapsed. This results in protonation of the PS amino groups and a loss of affinity for Ca (Lüllmann and Peters, 1977; 1979). PS is an essential constituent of cardiac plasmalemma, it can be calculated to amount to about 2% of membrane wet weight and is clustered around the protein moiety of the Na,K-ATPase (Figure 1.2) (Zwaal *et al.*, 1973). The total capacity of PS to bind Ca is of the order of $2 \times 10^{-4}\ M\ kg^{-1}$ cell. At a 2:1 ratio, the maximum Ca binding capacity of plasmalemmal PS would amount to about $10^{-4}\ M\ kg^{-1}$, a store thus large enough to activate the contractile system even upon partial release.

During the plateau phase the intracellular structures such as the actomyosin system, the mitochondria, and the sarcoplasmic reticulum will face an increasing Ca^{++} concentration. The actomyosin displaying a K_{DCa} of about $1 \times 10^{-6}\ M$ will react correspondingly, whereas the mitochondria having a K_{DCa} of about $1 \times 10^{-4}\ M$ will hardly participate in sequestering Ca.

Ca Movement During and after Repolarization

Beginning in phase 4 of the action potential, the electric field across the plasmalemma is built up again with increasing polarization and therewith the

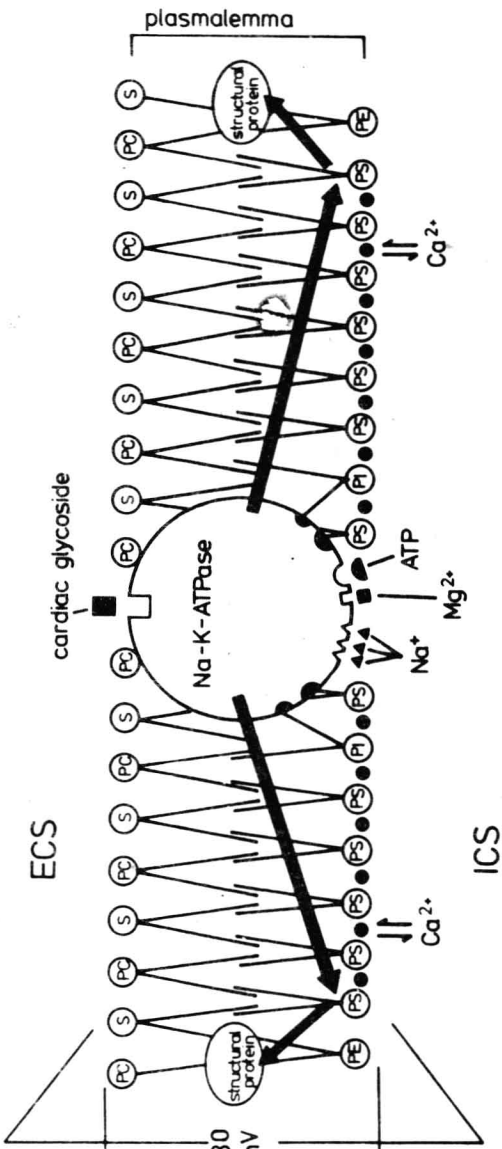

Figure 1.2 Schematic drawing of the plasmalemma including one Na,K-ATPase molecule and the associated Ca binding phospholipids, the acidic lipids representing an essential part of the Na,K pump. The actual array of the phospholipids and structural proteins is controlled by the functional state of the ATPase protein (indicated by black arrows). The voltage of ~80 mV across the unit membrane (~8 nm) creates an electric field in the order of 10 kV mm^{-1}. The affinity of Ca to the acidic phospholipids depends on the existence of the electric field (for details see text). PC = phosphatidylcholine; S = sphingomyelin; PE = phosphatidylethanolamine; PS = phosphatidylserine; PI = phosphatidylinositol

high affinity binding sites for Ca reoccur. Ca^{++} from the adjacent cytosolic space will become bound and the diffusion gradient within the cytosol will be reversed. Due to the high affinity of the potential-dependent binding sites the actual Ca^{++} concentration will decrease below the threshold concentration with respect to actomyosin, which accordingly relaxes with a time course determined by the diffusion of Ca^{++} directed towards the plasmalemma. After relaxation has been established, the high affinity Ca store will be refilled corresponding to the prevailing conditions (extracellular Ca^{++} concentration, end-diastolic cytosolic Ca^{++} concentration, beat frequency). Although the Ca^{++} released from the high affinity, potential-dependent binding sites will be rebound at the end of the diastole, the cardiac cell has gained some Ca by the slow inward current. It is this Ca load which has to be pumped out by the Ca,Mg-ATPase such that the Ca homeostasis is maintained. Thus, simultaneously with the refilling of the high affinity binding sites, the Ca pump will bind cytosolic Ca^{++} and translocate them against the high gradient to the outside (compensatory net transport). The plasmalemmal Ca pump possessing a K_{DCa} of 7×10^{-7} M will essentially participate in reducing the cytosolic Ca^{++} concentration below 3×10^{-7} M (for details see below).

PLASMALEMMAL Ca PUMP

The presence of an active Ca outward transport in heart muscle, similar to that described for erythrocytes by Schatzmann and Vincenzi (1969), has been postulated for a long time (Lahrtz *et al.*, 1967; Sulakhe and Dhalla, 1971; Sulakhe and St Louis, 1976) as a necessity to counterbalance the net uptake of Ca occurring both under conditions of rest and of activity. Recently, a highly active Ca,Mg-ATPase located in the plasmamembrane has been ascertained (Cielejewski *et al.*, 1980; Kliem and Preuner, 1980; Kliem 1981). One of the reasons for the difficulty to detect the plasmalemmal Ca pump in heart muscle is based on the fact that the methodical procedures which have proven successful in preparing Ca-pumping vesicles (microsomes) of sarcoplasmic reticulum of skeletal muscles have been transferred to cardiac muscle without modification. But there are two experimental pitfalls: (a) in contrast to vesicles obtained from sarcoplasmic reticulum, the vesicles derived from the plasmalemma of ventricular muscle cells with the abundant T-tubular system consist mainly of inside-out vesicles (hiding the plasmalemmal marker enzyme Na.K-ATPase!) (Lüllmann and Peters, 1976); (b) the Ca pump activity of the cardiac plasmalemma is completely lost if Ca complexing agents have been used during the preparation procedure of the vesicles, this is in contrast to vesicles obtained from sarcoplasmic reticulum. In contrast to earlier reports on the activity of the plasmalemmal calcium pump, ranging between 2 and 30 nmol Ca per milligram of protein per minute (Stam *et al.*, 1973; Lüllmann and Peters, 1976; Caroni and Carafoli, 1981a,b; Spitzer *et al.*, 1981), the activity yielded by preparing

sarcolemmal microsomes in the absence of Ca chelating agents, like EDTA or EGTA, results in a pump activity between 90 and 130 nmol Ca per milligram of protein per minute at 22 °C but otherwise comparable conditions. At 37 °C the pump activity was even found to be increased up to 350–400 nmol Ca per milligram of protein per minute. This value has to be compared with the maximum pump activity reported so far by Caroni and Carafoli (1981a), who obtained a value of 31 nmol Ca per milligram of protein per minute at this temperature.

According to these considerations the existence of Ca pump activity in a microsomal fraction can no longer be accepted as a general and characteristic marker of the sarcoplasmic reticulum, as has been claimed previously (Dhalla *et al.*, 1976; Bers, 1979; Van Alstyne *et al.*, 1979). This assumption can only be made, if – by the use of special procedures of preparation and the use of Ca chelating agents – the activity of the plasmalemmal Ca pump is minimized, while the sarcoplasmic reticular Ca pump, which is rather insensitive to this treatment, is selectively preserved (Cielejewski *et al.*, 1980; Kliem and Preuner 1980; Kliem, 1981).

When plasmalemmal inside-out vesicles obtained from guinea-pig heart muscles are exposed to increasing Ca^{++} concentrations in the presence of 2.5 mM oxalate they accumulate Ca in a dose-dependent way as shown in Figures 1.3 and 1.4. At 22 °C, the half maximum saturation, K_D, was calculated to be about 7×10^{-7} M (actual calcium ion concentration). The maximum uptake rate amounted to 90–130 nmol per milligram of protein per minute and to 350–400 nmol per milligram of protein per minute at 37 °C, yielding a Q_{10} of 3.5 (22–32 °C). Recalculating the maximum accumulation rate on the basis of membrane protein yield per unit of wet weight, a transport capacity of 0.45 mmol per kilogram wet weight per minute was estimated. The efficacy of the Ca pump, therefore, easily matches the Ca load imposed on cardiac cells under physiological conditions (Preuner, 1981). The data are compiled in Table 1.1.

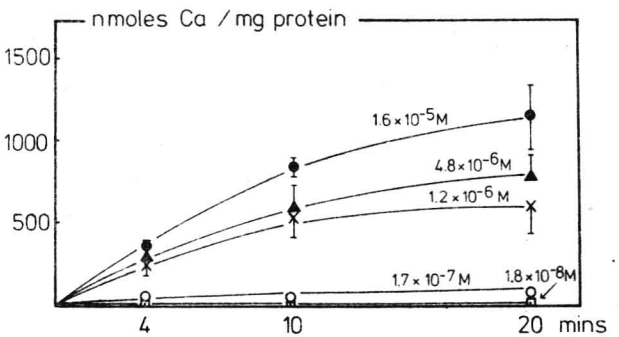

Figure 1.3 Time course of Ca accumulation by plasmalemmal microsomes (guinea-pig heart muscle) at different Ca^{++} concentrations (22 °C). Abscissa, time in minutes; ordinate, nanomoles of Ca per milligram of protein

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