SLOW CALCIUM CHANNEL
AND THE HEART

Essay

Submitted for Partial Fulfilment of the
Master Degree of Cardiology

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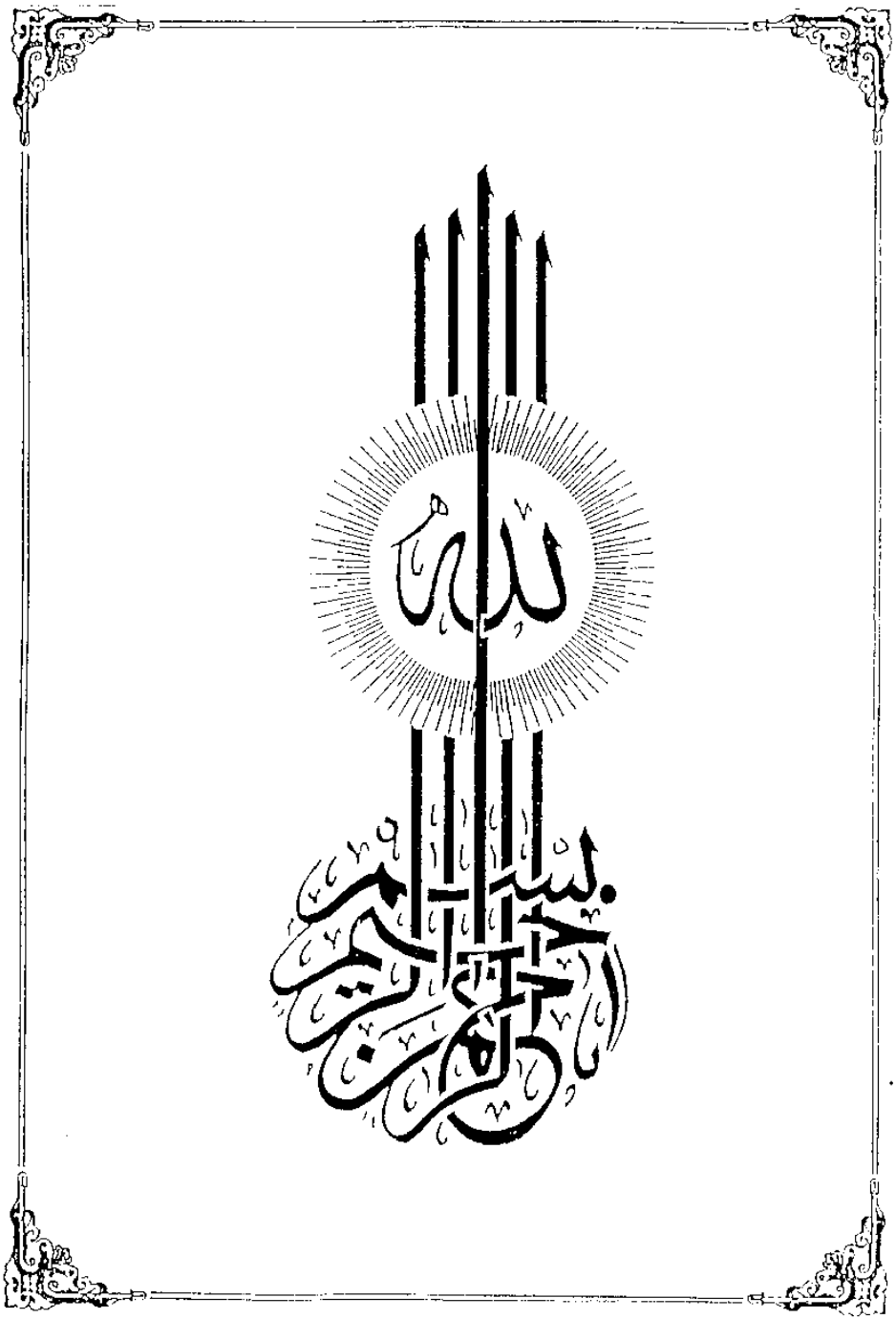
1987

ACKNOWLEDGEMENT

*I wish to express my sincere gratitude to Prof. Dr. **Mohammed Khairy Abd-Eldayem**, Prof. and head of department of Cardiology, Ain-Shams University, for his encouragement, continuous guidance and fruitful criticism. He generously gave me of his precious time and valuable advice.*

Joseph Fayez
1987



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Introduction

After the first recordings of transmembrane potentials in cardiac tissue (Woodbury L.A. et al, 1950), Noble constructed a mathematical model that reproduced the time course of Purkinje fiber action potentials (Noble D., 1962). He assumed that changes in transmembrane potential were due to voltage and time dependent alterations in specific membrane conductances to sodium (depolarization) and potassium (repolarization), much as Hodgkin and Huxley had shown previously for the action potential of the squid giant axon. However, other investigators demonstrated that action potential amplitude and duration in guinea pig ventricle were unchanged by lowering extracellular sodium ion concentration (Deleze J., 1959) and the upstroke and plateau phases of various cardiac action potentials could be dissociated in several ways (Reuter H., 1967). These reports suggest that the currents reponsible for the cardiac action potential differed qualitatively, as well as quantitatively, from those previously described in nerve.

Reuter strongly supported this suspicion by demonstrating directly the existence of an "inward calcium current" in Purkinje fibers using a voltage clamp technique.

The slow inward current contributes to the normal

electrical and contractile activity of several cardiac and vascular tissues and also may mediate the electrical abnormalities responsible for certain cardiac arrhythmias. The slow inward current differs from the fast inward sodium current in that it is carried primarily by calcium rather than sodium, requires a more positive level of membrane potential to be activated, has slow activation and inactivation kinetics, is responsible for normal depolarization in sinus and AV nodal cell. Recent data suggest that slow-channel openings occur in bursts, separated by silent periods, and that less negative membrane potentials and beta adrenergic stimulation will increase the probability that the channels will open. Inactivation of the channel is associated with a lower probability of channel opening (Gilmour R.F. and Zipes D.P., 1985).

The application of the voltage clamp technique has been instrumental in elucidating the ionic basis of depolarization in cardiac muscle (Hauswirth O. and Singh B.N., 1978). Cells in various parts of the myocardium differ significantly in their depolarization and repolarization characteristics in addition to the nature of their refractoriness to applied stimuli. In cardiac muscle, the inward current has two distinct components. The first is the "fast response" mediated by sodium. This current displays rapid activation

and inactivation kinetics, has a high conduction velocity, an activation threshold of -60 to -70 mV and is selectively inhibited by tetrodotoxin and local anaesthetic drugs. Inactivation of the fast response in such fibers reveals a slow inward current mediated predominantly by calcium with a minor contribution from sodium. The slow channel is activated at -35 to -45 mV and displays sluggish activation and inactivation kinetics relative to the fast response. In myocardial cells demonstrating fast response characteristics the slow current has two important functions. By mediating the intracellular transfer of calcium ions during depolarization it is responsible for excitation - contraction coupling. Second, because of its slow inactivation, it contributes to the maintenance of action potential plateau.

Although the fast and slow currents are felt to flow through separate channels, as yet there has been no identification of distinct anatomic structures (Antman et al, 1980). The slow channels have been postulated to be specific protein macromolecular structures which traverse the lipid bilayer (Ellrodt A.G. and Singh B.N., 1984).

In contrast to the role of the slow inward current in fibers displaying the fast response; in certain

normal myocardial cells, this current plays a dominant role. For example, these "slow response" fibers are particularly significant physiologically in the SA node and AV node (Cranefield P.F., 1977).

This slow response can also develop in partially depolarized fibers such as seen in myocardial ischaemia. Hence it may explain the occurrence of some types of arrhythmias occurring with ischaemic heart disease.

The slow inward current is often referred to as the slow inward calcium current, because the slow channel has been shown to be selectively (but no exclusively) permeable to calcium in various cardiac tissues (Akiyama T. and Fozzard H.A., 1979) and the calcium-dependance of slow channel current was originally used as one of the discriminating criteria to separate the fast and slow inward currents. Even though the slow channels may be 70 to 100 times more permeable to calcium than to sodium (Reuter H. et al, 1977), sodium may account for nearly one third of the slow inward current in certain instances, due to much higher extracellular concentration of sodium versus calcium.

Owing to the extreme importance of the slow channel and its relation to the important cation, calcium, both in physiology and pathophysiology of certain

cardiac and vascular disorders, the more profound understanding of the role of calcium channels will give a better chance for identifying and treating such conditions.

The calcium channel blockers form a new group of drugs which has wide acceptability among cardiologists. Intensive investigation in the experimental and clinical laboratories over the past decade have revealed that calcium channel blockers comprise a heterogenous group of drugs structurally, pharmacologically and electrophysiologically with corresponding differences in their net clinical effects and spectrum of therapeutic activity. A knowledge of the pharmacodynamic differences between the compounds allows the physician to select the appropriate agent for a given clinical situation. The development of such compounds offers further therapeutic possibilities in the control of cardiovascular disease.

Physiological Aspects of the Calcium Channel

Calcium channels are present in excitable cells, including those of coronary and arterial smooth muscle and the heart (Katz A.M., 1985). They are also present in the human red blood cells where they are an ideal model to study the action of calcium agonists and antagonists (Stimple M. et al, 1984).

The most important pathway for calcium entry across the sarcolemma is through calcium channels.

In this chapter, the ultrastructure of the myocardium including the sarcotubular system, role of calcium in the cardiovascular system, postulated structure of the calcium channel with its electrophysiologic effects and its control by the autonomic nervous system neurotransmitters will be discussed.

ULTRASTRUCTURE OF THE MYOCARDIUM

The functions of the heart may be classified into three types: electrical, mechanical and endocrine. Many myocardial cells are specialized for one of these functions. The myocardial cells concerned primarily with mechanical shortening are similar, although there are some differences between atrial and ventricular myocardium. Several different types of cells have electrical or endocrine activity as a major function,

and the structure of such cells is significantly different from that of contractile or "working" myocardial cells (James T.N. et al, 1974).

Some special cells of the heart are particularly developed for the generation and conduction of an electrical impulse to the working cells (Schlant R.C. and Silverman M.E., 1986). These are the P cells, transitional cells, ameboid cells and Purkinje cells. P cells are numerous in the sinus node, and are also found in the AV node and internodal pathways. Transitional cells are found predominantly in the sinus node, the AV node, and the internodal pathways, and for a considerable distance in the atrial tissue adjacent to both nodes. Ameboid cells are found predominantly in the eustachian ridge area. Purkinje cells are found primarily at the margins of the sinus node; in the internodal pathways, which also contain intermingled transitional cells and ordinary working myocardial cells; adjacent to the AV node; and in the His bundle and its branches. The His bundle consists primarily of Purkinje cells, while the bundle branches consist of Purkinje cells intermingled with ordinary working cells.

Contractile, or working, myocardial cells are characterized by hundreds of myofibrils in a special

arrangement. They are arranged longitudinally in series with multiple cells forming a fiber. Multiple fibers are generally arranged in parallel. Although cardiac muscle fibers have many lateral and end-to-side connections, the contractile cells are not a true anatomic syncitium.

Contractile cells contain an intricate sacrotubular system of tubules, vesicles and cisternae (Figure 1-1). One component of this system consists of the periodic invaginations of the sarcolemma by transversely oriented tubules knowns as the T-system. Focal dilatations of the T-system tubules are seen in the area of the Z-band, forming a cistern like structure, the intermediary vesicle. A second component of the sacrotubular system is the series of interconnecting longitudinal tubules that tend to be oriented parallel to the myofibrils, which they surround. Near the Z-band, these tubules have local dilatations - lateral sacs, or terminal cisternae - which, together with the intermediary vesicles, form a triad. A triad consists of an intermediary vesicle from the T-system and two lateral sacs from the longitudinal system. Although the three components of the triad are very close to each other, they probably are not in direct communication.

Transverse tubules are arranged perpendicularly