International Boehringer Mannheim Symposia

Myocardial Failure

Editors:
G. Riecker, A. Weder, J. Goodwin

Co - Editors :
H. - D. Bolte, B. Lüderitz, B. E. Strauer, E. Erdmann

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Introduction

More than 10 years have passed since the memorable symposium on "Myocardial Contractility," edited by R. D. Tanz, F. Kavaler and J. Roberts (New York and London, Academic Press, 1967). Pathogenesis of myocardial failure still involves many questions. The latest scientific findings on fundamentals of myocardial contraction encouraged us to organize this international symposium held in Rottach-Egern at Tegernsee (Germany), June 17 to 19, 1976 sponsored by the European Society of Cardiology. It seemed appropriate to assemble prominent workers in this field in an attempt to correlate their respective information on cardiac function.

In this connection it must be remembered that our present understanding of the cardiovascular system and today's therapeutic and preventive measures are the fruits of yesterday's research. Further progress in this field will be conditioned by various circumstances: to win highly motivated creative people for clinical research, to mediate time and contacts for their learning new methods, and to provide adequate facilities for scientific work in our hospitals.

Therefore, the aim of the conference was to discuss those aspects of myocardial failure, that are believed to require further studies in the future by integrated efforts of research workers in several disciplines, especially to promote the pertinent exchange of ideas between basic and clinical research.

This book contains all parts of the proceedings of this meeting. The papers have been grouped into different sections:

(1) Molecular Basis of Myocardial Function
(2) Sarcoplasmatic Reticulum
(3) Membrane-Bound Receptors
(4) New Diagnostic Procedures
(5) Problems of Etiology and Classification
(6) Clinical Pharmacology, and finally
(7) Drugs Influencing Myocardial Contractility.

The advice and cooperation of the presidents and chairmen for the planning and the performance of the symposium are gratefully acknowledged. I also express my sincere gratitude to the editorial staff for

their part in the conduct of this symposium and in preparing this book. Concerning the generous support of this conference we express our gratefulness to the organizer of the symposium, Boehringer-Mannheim, who brushed aside all economic obstacles to promote this meeting. It is obvious, that Macaenas, the patron, has not become extinct. I should like to thank all contributors, busy people who nevertheless promptly submitted their manuscript, answered many queries and kindly accepted suggested changes. We are particularly grateful to Springer-Verlag who so efficiently made all the necessary arrangements for this edition.

G. Riecker

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Table of Contents

Part 2. Drugs Influencing Myocardial Contractility
Chairman: H. Reuter

Session I

Molecular Basis of Myocardial Function

Part 1. Regulatory and Contractile Proteins

Chairmen: A. WEBER and S. V. PERRY

Introductory Remarks

A. WEBER

Molecular biologists have been assembled at this meeting together with clinical cardiologists because of our desire to gain a complete understanding of heart disease. As yet there is still a great gap in our knowledge of clinical manifestations and therapy and our information about changes in the molecular biology of the proteins involved in the contractile process.

During the first part of the conference we shall hear about the molecular biology of muscle in general and heart muscle fibers and proteins in particular.

Dr. H. E Huxley will remind us that muscle contracts without any length change in the filamentous substructure as a result of the sliding of the myosin and actin filaments past each other, a process driven by the energy of ATP hydrolysis. Although this much has now been known for some time, evidence concerning many of the details of the reactions has eluded us so far. For instance, we have assumed that myosin bridges move the actin filaments by attaching to them at right angles and then swinging towards the center of the sarcomer over a distance of about 70-100 Å before letting go again of the actin filament. While such "rowing" along of the actin filament seems plausible nobody ever had demonstrated that myosin can bind to actin at right angles. Dr. K. Holmes will discuss some recent data derived from electron microscopy and X-ray diffraction, using ATP analogues rather than ATP, which show just that: myosin attachment to actin at 90^{o}. Dr. Huxley will describe to us certain new technical developments which should allow us to learn more about the movements of the myosin bridges during contraction. For the first time X-ray diffraction is being used to follow rapid structural changes as fast as they occur during muscle contraction. This is possible now because X-ray photons are registered by position-sensitive counters rather than film, and the power of X-ray beams has been greatly increased. During contraction there occur changes in the X-ray diffraction pattern that have been assigned to a movement of the bridges towards the actin filament and away from the myosin filament. The first question that can be answered as a result of the new technical advances is: are these bridges that apparently move out in fact attached to the actin filament? Dr. Huxley expects an answer from a comparison of the time course of tension development and the change in the diffraction pattern.

Dr. Kendrick-Jones addresses himself to the control of contraction by calcium with special attention to mechanisms built into the myosin molecule. Myosin-linked control was first discovered by him and A.G. Szent-Györgyi in scallop muscles. Later it was found that many muscles possessed a double control mechanism: during rest, in the absence of calcium inactivation by troponin as well as inactivation of myosin by the regulating myosin light chains. Although there is no direct evidence yet for myosin-linked control in vertebrate skeletal and cardiac muscle the tantalizing fact exists that these muscles possess calcium-binding light chains that are similar to the invertebrate-regulating light chains, and that these vertebrate light chains can substitute for the invertebrate ones in excercising control over invertebrate myosin. Dr. Kendrick Jones has obtained a great deal of information about the invertebrate regulatory light chains, including their primary sequence and is viewing them in comparison with the vertebrate calcium binding myosin light chains and other regulatory calcium binding proteins.

With Dr. Herzig we move a more or less direct viewing of myosin bridges to that of more physiological parameters such as tension development, stiffness and ATP hydrolysis in cardiac fibers. By using fibers with permeable membranes rather than living fibers the physiological response to calcium and phosphate ions could be explored.

Lastly, Dr. Wikman-Coffelt presents data where she studied myosin ATPase activity, calcium binding and light chain content in myosin from left and right ventricles of dogs with surgically induced pulmonary and aortic stenosis. She observed a number of changes in the myosin molecule in response to stress, some of them quite remarkable, such as an increase in the number of calcium-binding light chains per myosin molecule.

The Structural Basis of Contraction in Muscle and Its Study by Rapid X-Ray Diffraction Methods

H. E. HUXLEY and J. C. HASELGROVE

By way of introduction to this part of the symposium, we think we should first describe very briefly the basic features of the contractile structure of muscle, as far as we know them at present. These features are virtually the same throughout all types of striated muscle including heart muscle. For convenience of experimentation, a considerable amount of the structural work has been carried out using certain skeletal muscles of the frog or rabbit, but there are of course very good reasons to believe that the conclusions about the mechanisms derived from such studies will be of general application.

The contractile myofibrils are built up from alternating and partially overlapping arrays of longitudinally oriented actin and myosin filaments, and it is now generally accepted that changes in muscle length, whether active or passive, take place by a process in which the filaments remain virtually constant in length, but change their extent of overlap. This basic model was originally proposed in 1954, independently, by A. F. Huxley and R. Niedergerke (4) and by H. E. Huxley and the late Jean Hanson (15). The sliding force between the actin and myosin filaments is believed to be generated by cross-bridges projecting outwards from the myosin filaments, attaching in a cyclical fashion to actin, as suggested by Hanson and Huxley in 1955, (23) splitting ATP as they do so and thereby releasing the energy for contraction. These cross-bridges represent the enzymatically active parts of the myosin molecule.

Myosin is a molecule having a very remarkable structure (17). Basically it contains two very large polypeptide chains of molecular weight about 200,000 daltons each (the "heavy chains") and four smaller polypeptide chains having molecular weights in the 20,000 daltons range. Along part of their length, the two heavy chains are coiled around each other to form a 2-chain α-helical coiled-coil structure about 1400 Å in length and 20 Å in diameter. About one-half of each heavy chain is involved in this structue. The rest of each heavy chain is folded up separately in a globular form, together with some or all of the light chains. The two heavy chains are of very similar aminoacid sequence, and are arranged in parallel to each other with the same polarity so that the two globular regions are located at the same end of the molecule. The α-helical portions of the myosin molecules are involved in forming the