XXVIIIth INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES

SATELLITE SYMPOSIUM

initiated by the Commission on Muscle
Chairman W. MOMMAERTS

MECHANISM OF MUSCLE ADAPTATION TO FUNCTIONAL REQUIREMENTS

Szeged, Hungary
10 to 12 July 1980

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ADVANCES IN
PHYSIOLOGICAL SCIENCES

Satellite Symposium of the 28th International Congress of Physiological Sciences
Szeged, Hungary 1980

Volume 24

Mechanism of Muscle Adaptation to Functional Requirements

Editors

F. Guba
G. Maréchal
Ö. Takács
Budapest, Hungary

PERGAMON PRESS

AKADÉMIAI KIADÓ

Pergamon Press is the sole distributor for all countries, with the exception of the socialist countries.

HUNGARY	Akadémiai Kiadó, Budapest, Alkotmány u. 21. 1054 Hungary
U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon of Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, 6242 Kronberg-Taunus, Hammerweg 6, Federal Republic of Germany

British Library Cataloguing in Publication Data

International Congress of Physiological Sciences
Satellite Symposium (28th : 1980 : Szeged)
Advances in physiological sciences.
Vol. 24: Mechanisms of muscle adaptation to functional requirements
1. Physiology - Congresses
I. Title II. Guba, F. III. Maréchal, G.
IV. Takács, Ö.
591.1 QP1 80-42250

Pergamon Press ISBN 0 08 026407 7 (Series)
ISBN 0 08 027345 9 (Volume)
Akadémiai Kiadó ISBN 963 05 2691 3 (Series)
ISBN 963 05 2750 2 (Volume)

In order to make this volume available as economically and as rapidly as possible the authors' typescripts have been reproduced in their original forms. This method unfortunately has its typographical limitations but it is hoped that they in no way distract the reader.

Printed in Hungary

PREFACE

I very profoundly regret that my increasing age and the burden of local obligations prevents me from attending your conference. Though I am working now on quite different lines I am deeply attached to muscle which gave me such an exciting time. I am equally deeply attached to the town of Szeged where I spent so many delightful years with my pupils who also were my friends. It would have been a great honor for me to act as honorary chairman. My absence does not mean a loss since I have not touched muscle for years, on which I have spent twenty of my most active years. I still feel that muscle is the most wonderful material of study for anybody who wants to penetrate into the deeper secrets of life.

Please convey my best wishes and warm regards to the members of the conference and convey also the expression of my deeply felt gratitude for the honor of being your honorary chairman.

Yours very truly,

Albert Szent-Györgyi, M.D., Ph.D.

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CONCLUDING REMARKS ON MECHANISM OF MUSCLE ADAPTATION TO FUNCTIONAL REQUIREMENTS

F. Guba and Ö. Takács
Institue of Biochemistry, University of Medical Sciences, Szeged, Hungary

This symposium is the third event of a series of symposia organized on the authority of IUPS Muscle Commission /Chairman: Prof. W. F. H. M. Mommaerts, Los Angeles/. The first event of the series was the Functional Specifity of Muscle Fibres held in Szeged in 1977 and the second the Plasticity of Muscle held in Konstanz in 1979. The presidency of the International Physiological Congress of IUPS in Budapest invited Prof. G. Marechal /Brussels/ to organize this scientific program. The local organizing committee was formed by the members of the Institute of Biochemistry of the Szeged University of Medical Sciences preserving the traditions of the school of Nobel Prize winner Prof. A. Szent-Györgyi.

At this symposium the general biological aspects of the specifities of the muscle cell were discussed i.e. both the outer factors and the function variations modify -rapidly in time- the metabolism of the cells and their fundamental composition as well. This latter is especially marked in the case of the contractile apparatus.

The introductory lecture of Topic 1 summarized the latest results of the structural and functional specifity of muscle and pointed to the current problems. The present viewpoint is: The metabolic heterogenity of fibers makes a broad spectrum in which almost a continuous transition reveals. The most interesting question in fiber typing is whether the complex differences in fiber types observed through several methodological approaches can be detected in the quantitative parameters of the myofibrils.

Most lectures dealt with the effect of variation of functions on contractile apparatus and on metabolism. The restriction of activity or its complete lack results in the dedifferentiation of muscles with various functions which manifests itself in the converging change of the type of the metabolism i.e. the specific enzyme pattern, on one hand, and in the transformation of the structural proteins on the other hand. Transformation, however, can occur in the region of the denervated, stimulated and inactive electrode or in muscle wrapped in aluminium foil. The prolonged weightlessness leads to a decrease of muscle contraction strength upon their tetanic stimulation, loss of elasticity and decline of tolerance to fatigue. In the soleus a tendency toward shortening of time of tension development has been found. The experiments also show that the pattern of reactions of contractile system of various muscles to spaceflight effects is largely determined by the functional specialization of muscles. The adaptive transformation of the muscular system can be induced in physiological circumstances as well. It seems that the tension of muscle is an important factor in the increase of muscle fibers and number of sarcomers. It has been shown that even adult muscles are capable of responding to stretch. If a muscle is held in its lengthened position, it adds on sarcomers in series. If, on the other hand, a muscle is held in its shortened position, it loses sarcomers in series. When a muscle is recovering from immobilization, it adds on new sarcomers in series at the ends of the fibres. The increase of muscle in girth during post-natal growth and as a result of exercise occurs by longitudinal splitting of myofibrils. Exercise has been shown to facilitate this splitting process.

Muscle tension plays an important part in the regulation of protein turnover. But the contraction against little or no work-load may promote atrophy. Tension markedly increases cAMP levels suggesting a role of this nucleotide in mediating the tension effect. Protein synthesis is stimulated as well as inhibited by Ca^{++} although the overall effect of Ca^{++} on nitrogen balance is generally catabolic. The activation of the satellite cells seems to be a sign of increase in the protein synthesis in adult muscle. The trigger of activation is probably the overactivity of the fibres. Moreover, Neostigmine treatment increases the degree of activation. It was proposed that the trigger for activation of satellite cells should be searched among the mechanical and/or biochemical events associated with muscle overactivity.

Significant new results were reported on the differentiation of the various muscle types. The existence of the embryonic myosin light chain was demonstrated by applying a two-dimensional gel analysis. An embryonic form of myosin heavy chain has also been found in newly formed myotubes either in the animal or in cell culture. During post-natal development of future fast muscles, the embryonic heavy chain is replaced by neonatal form which differs from either the embryonic or adult forms. On the course of development, the transition of myosin light and heavy chains takes place gradually, though, the heavy chains change slower. The ratio of α-β tropomyosin subunits also changes. During the in vitro analysis of the hypertrophy of skeletal muscle, the following factors were demonstrated. Passive stretch stimulates the increase of cells in the cell cultures of skeletal muscle. This phenomenon is probably in causal connection with the activity of the Na pump that can be detected some minutes after the beginning of the stretch. Different types of hypertrophy of myocardium in model experiments: The preferential synthesis of a myosin isoenzyme V_3 exhibiting lower ATPase activity and specific biological and electrophoretic properties has been found. This suggests that in response to a mechanical overloading, a general mechanism of adaptation occurs which could account for the reduced shortening speeds of the hypertrophical myocardium.

The latest research work on the proteolytic enzymes aims at defining the significance of the lysosomal and extralysosomal proteolytic system of muscle and finding the reason of activation of proteases. The lectures of this symposium also dealt with these topics. The existence of lysosomal proteinases i.e. Cathepsin B, Cathepsin D, Cathepsin E, Cathepsin H and Cathepsin L in muscle is no more doubted. However, their physiological role is still questioned. According to some researchers they play an important role in the differentiation and dedifferentiation of muscle. This was demonstrated by experiments of tissue culture and their change during immobilization could not be detected. From among the proteases only the increase of lysosomal proteinase could be measured in the muscle of dystrophic chickens. According to other authors lysosomal proteinases take place only in the breakdown of the non-myofibrillar muscular proteins. The proteinase functioning in the alkaline range may have a role in the formation of muscular damage on the effect of hormone changes. Many authors measured an increased peptidase activity in damaged muscle that facilitated the further cleavage of protein breakdown products of higher concentration. On the effect of catabolic steroids both proteolytic systems are activated and this process may be affected by contractile activity of muscle. In the field of regeneration and transplantation of muscle tissue compared to the above topics are less examined. Though, at this symposium more lectures referred to it, the difficulties of basic research work were actually pointed to in Topic 5. The minced gastrocnemius muscles orthotopically autografted regenerate within

2 to 3 weeks. Histological studies suggest that regeneration largely recapitulates ontogeny. It is not clear yet whether theory of constant proportion of enzymes is valid to 100 % during regeneration. It was demonstrated that the five tested glycolytic enzymes decrease at rates that are constant during regeneration but that are different for each separate enzyme. Their absolute amount cannot therefore remain a constant proportion. According to the logical conclusion of the authors the growth of regenerating muscle does not occur by a simple addition of small physiological units of constant composition. The reported clinical experiments provide valuable results for practical application. Exact and reliable information about the steroid therapy of muscle dystrophy can be obtained by metabolic balance measuring and by computerized tomography. The determination of the satellite cell number is also applicable for the observation of the regeneration of dystrophic muscle. In the muscles of DMD /Duchene Muscular Dystrophy/ patients the satellite cell number is higher than in normal controls. Despite the fact that in DMD biopsy the cells are activated for protein synthesis, it was observed that regenerating fibres frequently appear abnormal in structure. According to the opinion of a group of participants, other characteristics of the organization and the biochemical processes should also be taken into consideration during the study of muscle damages and regeneration.

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