Mitochondrial Medicine

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Editor

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This Book is Dedicated To The Memory of My Late Husband

Professor Ján Gvozdják, MD, PhD, DSc, FESC Lecturer, WHO Consultant in Cardiomyopathy, Specialist in Cardiology, Internal Medicine, Biochemistry and Mitochondrial Bioenergetics and Expert in the Application of Experimental Research to Clinical Medicine.

Preface

The target groups of this textbook Mitochondrial Medicine are practitioners of medicine, specialists in individual medical branches, pharmacologists, and sports doctors. The updated scientific and clinical information and knowledge provide a broad spectrum for postgradual education of physicians, pharmacologists, and specialists in other life sciences. Students of relevant branches at universities may find in the book a valuable source of information, which might serve as direction indicator in their future professional career.

I am confident that the usefulness of this monograph is warranted also by the international participation of specialists as contributors. The textbook will hopefully provide relevant information for many scientific branches of clinical and experimental medicine and will assist doctors involved in establishing diagnosis and devising the management of mitochondrial diseases.

Professor Rolf Luft can be considered the father of Mitochondrial Medicine as he was the first to carry out a mitochondrial study in man. In the years 1959–1962, 1970 is the year of birth of Mitochondrial Medicine in Comenius University in Bratislava, Slovakia. The Pharmacobiochemical Laboratory of the Third Department of Medicine of the Medical Faculty was the birthplace of Mitochondrial Medicine. In cooperation with the Head of the Department, Professor Ján Gvozdzák, MD, PhD., DSc, we devoted 36 years of our married life to the problem area of mitochondria. From 1970 up to the present day, the focus of interest of several coworkers and institutions have been metabolic studies of mitochondria in different experimental models (smoke mitochondrial cardiomyopathy, alcoholic mitochondrial cardiomyopathy, ischemia-reperfusion of the isolated heart, diabetic mitochondrial cardiomyopathy, Huntington's disease, Alzheimer's disease, adjuvant arthritis, etc.) and therapeutic intervention in these conditions, particularly the effect of CoQ₁₀. The obtained results elucidated some metabolic processes involved in several diseases and have found their application in clinical medicine.

Mitochondria, small subcellular organelles, are present in all eukaryotic cells. They are considered the generators of energy production in the body and belong to the main sources of reactive oxygen species generation. Coenzyme Q₁₀, the mobile part of the mitochondrial respiratory chain, has a key position in energy production. Evidence on the biological clock of CoQ₁₀ and of oxidative phosphorylation of mitochondria has provided insight into the relationship of these processes with the

origin, development and course of many diseases, including cerebral episodes and acute myocardial infarction. CoQ₁₀ deficiency, impairment of mitochondrial function and oxidative stress belong to the underlying metabolic causes in the etiopathogenesis of many diseases.

This book presents joint aspects of clinical medicine with metabolic phenomena of mitochondrial function obtained in experimental medicine. Determination of mitochondrial respiration and oxidative phosphorylation does not belong to common diagnostic methods of mitochondrial diseases in patients since several milligrams or even grams of human tissue would be required for the isolation of mitochondria from individual organs or for the preparation of skinned fibers. For this reason we consider metabolic studies of mitochondria in experimental models of mitochondrial derangements to be useful in yielding valuable information also with respect to clinical medicine.

The textbook is focused on four problem areas: mitochondrial physiology, mitochondrial medicine, diagnostic methods in mitochondrial derangements and diseases, and therapeutic interventions aimed at regeneration of impaired mitochondria.

An important supplement of mitochondrial physiology is the information on the biological clock of coenzyme Q₁₀ and on the circadian cascade of oxidative phosphorylation, which is presented by Anna Gvozdjáková in Chapter 1. Zdenka Ďuračková presents an overview on oxidants, antioxidants, and oxidative stress in Chapter 2.

The general overview of chronobiology provided by Franz Halberg, considered worldwide the father of chronobiology, is combined in Chapter 3 with the specialized part on coenzyme Q₁₀ and mitochondrial medicine.

In the application of methods of chronobiometric analysis of mitochondrial functions, Miroslav Mikulecký, doctor of medicine and outstanding statistician, presents the mode of statistical evaluation of results with 95% statistical significance in Chapter 4. Chapter 5, presented by Anna Gvozdjáková provides basic information on mitochondrial medicine.

The author of Chapter 6 on mitochondrial cardiology is Ivan Pecháň, medical specialist and biochemist.

The original results of studies of the mitochondrial respiratory chain and coenzyme Q₁₀ in endomyocardial biopsies from the transplanted human heart and their relationship to the development of transplant rejection highlight the importance of well-functioning mitochondria with intact ATP production. Chapter 7, provided by Anna Gvozdjáková, is on the impairment, reduced function of the mitochondrial respiratory chain and CoQ₁₀ deficiency in direct correlation with the origin and development of human transplanted heart rejection.

In Chapter 8, Jozef Čársky gives an overview of metabolic processes in diabetes. Ram B. Singh and Franz Halberg shaped the idea of the involvement of biological rhythms in the possible relationship between ATP production as well as CoQ₁₀ concentration in mitochondria of the heart muscle and brain on the one hand and acute cerebral episodes and myocardial infarction on the other. At our institute, we were intrigued by the idea and on using Halberg's chronobiological method,

semicircadian and circadian rhythms of CoQ_{10} were established in mitochondria of the heart muscle and in the brain in healthy and diabetic rats, along with the mitochondrial circadian cascade of oxidative phosphorylation. The topic of diabetes was thus supplemented by findings on mitochondrial functions of the cardiac muscle in experimentally induced diabetes, the CoQ_{10} clock, and the circadian cascade of oxidative phosphorylation of diabetic mitochondria by Miroslav Mikulecký, Anna Gvozdjáková, Jarmila Kucharská, and Ram B. Singh.

Mitochondrial nephrology is the topic of Chapter 9, written by Katarína Gazdíková and František Gazdík. The survey presents both physiological and pathologically altered functions of the kidney.

The problem area of Chapter 10, by Janka Lipková is energy production in mitochondria of skeletal muscles, oxidative damage, antioxidants, and aspects of these issues relevant in sports.

Chapter 11 by Jozef Rovenský and Karel Pavelka gives a broad survey of rheumatoid arthritis, commenting on diagnostic and therapeutic issues of the disease. The chapter is supplemented by an experimental study of adjuvant arthritis and mitochondria by Katarína Bauerová and Jarmila Kucharská.

Updated knowledge on mitochondrial immunology is presented in Chapter 12 by František Gazdík and Katarína Gazdíková.

Chapter 13 presented by Anna Gvozdjáková is concerned with mitochondrial spermatopathy, providing current information on the role of spermatozoal mitochondria in male infertility.

Current diagnostic methods of mitochondrial defects, concerning particularly metabolic derangements, are presented in Chapter 14 by Anna Gvozdjáková, Jarmila Kucharská, and Anna Hlavatá.

A detailed theoretical survey of nuclear magnetic resonance and its application in metabolic studies can be found in Chapter 15 by Tibor Liptaj.

Chapter 16 falls within the therapeutic part of the monograph. The problem area of coenzyme Q_{10} is brilliantly treated of both from clinical and theoretical aspects. The author of the chapter is the President of the International Coenzyme Q_{10} Association, G. Paolo Littarru with his coworkers.

Supplementation with CoQ_{10} in children with metabolic derangements, in patients with nephropathy, asthma, and diabetes is presented in four individual studies, including original results, in Chapter 17. The first study is by Anna Hlavatá, Jarmila Kucharská, and Anna Gvozdjáková, the second by Anna Gvozdjáková and Jarmila Kucharská, the third by Anna Gvozdjáková, and the fourth by Anna Gvozdjáková, Patrik Palacka, Jarmila Kucharská, and Ján Murín.

Supplementation with CoQ_{10} in experimental models of Alzheimer's disease, Huntington's disease, and adjuvant arthritis is dealt with in three studies with original results, which are included in Chapter 18. The three studies are presented by Jaromír Horecký, Olga Vančová, Jarmila Kucharská, and Anna Gvozdjáková the first study, the second is by Anna Gvozdjáková, and the third by Katarína Bauerová, Jarmila Kucharská, Silvester Poništ, and Anna Gvozdjáková.

A theoretical overview of ω -3 and ω -6 PUFA and their supplementation in clinical and experimental medicine, including original results, are given in Chapter 19 by

Anna Gvozdjaková, Daniel Pella, Jarmila Kucharská, Kuniaki Otsuka, and Ram B. Singh.

The marked improvement recorded in male infertility on supplementation with hydrosoluble CARNI-Q-GEL (carnitine with CoQ₁₀, vitamin E and vitamin C) is considered a significant contribution. The results of carnitine and CoQ₁₀ supplementation in male infertility under clinical and experimental conditions are presented by Anna Gvozdjaková in the first study, the second by Anna Gvozdjaková, Jarmila Kucharská, and Pavol Lepieš, and the third presented by Anna Gvozdjaková and Jarmila Kucharská in Chapter 20.

In Chapter 21, Jarmila Kucharská presented an overview highlighting the beneficial effect of vitamin supplementation in mitochondrial derangements.

The survey of new prospective therapeutic methods includes the effect of polarized light on mitochondrial function (experimental studies). Ján Pálinkáš and Alfonz Smola prepared a comprehensive overview of the characteristics and effects of polarized light in Chapter 22. Photographic documentation of healing effects of polarized light on wounds of the diabetic foot and on pressure sores is attached to this chapter.

I am confident that this monograph will contribute to the understanding of the role that mitochondria and CoQ₁₀ exert in human mitochondrial medicine. The textbook was prepared with the aim to provide comprehensive information, including new data and aspects, relevant in the field of mitochondrial medicine which may be used to advantage in diagnosis and supplementary therapy (with CoQ₁₀, carnitine, polyunsaturated fatty acids, polarized light) in patients suffering from mitochondrial diseases.

Anna Gvozdjaková

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I would like to thank many of my coworkers, particularly PharmDr Jarmila Kucharská, PhD, for her cooperation of many years, and Maria Kaplánová, Anna Štetková, Valika Ješková and Emil Benko, MSc. for their excellent technical assistance.

I extend my greatest thanks to Dr R K Chopra, President of Tishcon Corp., USA. Under their auspices we performed several clinical and experimental studies. We acknowledge gratefully their donations of different forms of CoQ₁₀ (hydrosoluble Q-GEL[®], liposoluble, reduced, liposomal), ω -3, ω -6 PUFA, Q-GEL[®] with α -lipoic acid and CARNI-Q-GEL[®] with L-carnitine allowing us to carry out several experimental and clinical investigations. I wish to thank Dr Hemmi Bhagavan (Tishcon Corp., USA) for the valuable consultations in mitochondrial studies.

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Anna Gvozdjáková

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- Detection of abnormality during the night when medication is no longer effective, not seen during office visits in the afternoon (I)
- Detection of abnormal circadian pattern of blood pressure (CHAT, “overswinging”) associated with a risk of cerebral ischemia and nephropathy larger than other risks (including “hypertension”) assessed concomitantly (IIA and B)
- Finding that CHAT carries a very high risk even among MESOR-normotensives who do not need anti-hypertensive medication (IIC)
- Availability of statistical procedures such as a self-starting cumulative sum (CUSUM) applicable to the individual patient to determine whether an intervention such as autogenic training is effective and for how long the intervention remains effective (IIIA)
- N-of-1 designs for the optimization of treatment timing: the same dose of the same medication can further lower the same subject’s blood pressure MESOR and circadian amplitude when the timing of daily administration is changed (IIIB and C), as ascertained by as-one-goes (sequential) testing and parameter tests, procedures applicable to the given individual.

I: Stacked from 11 days of around-the-clock monitoring.
Office spot-checks cannot detect nocturnal pathology.

IIA: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of ischemic stroke most.

IIB: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of nephropathy most.

IIC: An excessive circadian blood pressure (BP) amplitude (A) is a risk factor for ischemic stroke independent from the 24-h mean (MESOR).

IIIA: Individualized assessment (by CUSUM) of a patient’s initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59 years).

IIIB: Individualized blood pressure chronotherapy. Lower circadian double amplitude (2A) and MESOR (M) after switching treatment time from 08:30 (*left*) to 04:30 (*right*).

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On the average, on top, peaks in temperature of the blinded group occur earlier and earlier, but there are uncertainties in such eyeballing. A transient antiphase at 22–23 days after blinding is readily seen. If, around that stage after blinding, 2-timepoint checks are carried out on the 2 groups, opposite results can be obtained on mice with and without eyes and later when they are again in phase, 2-timepoint checks show no difference, a puzzle readily resolved by an objective quantification of the rhythm characteristics. The need for this microscopy in time becomes obvious, notably if an inference is desired as soon as possible with an estimate of uncertainty. (Circadian desynchronization also characterizes congenitally blind ZRD mice.) (Copyright Halberg).

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- The effect of one entity (the actor) upon a second (the reactor), such as the pituitary acting upon the adrenal cortical corticosterone production may be influenced, predictably insofar as rhythmically, by a third entity such as melatonin (the modulator) at the level of the pituitary; the same melatonin also acts directly upon the adrenal. Reproducible sequences of attenuation, no-effect, and amplification, the time-qualified feedsideways, replace time-unqualified feedbacks and feedforwards (IIC-E). In sections II and III, feedsideways include the interaction of a modulator (such as ACTH) upon an actor (such as adrenocortical corticosterone production) acting upon DNA labeling in bone (the reactor). The roles played by endocrines can and do change in various feedsideways that replace time-unqualified feedbacks and feedforwards. Chronomolecular mapping of circadian acrophases has also begun (Fig. 3.21). (Copyright Halberg). 69
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