Strategy plan for Copenhagen Muscle Research Centre (CMRC), 2004-2006.

Background:

During the first 75 years of the twentieth century, by the individual efforts of several thoughtful and industrious Danish scientists a large number of fundamental observations within muscle- and exercise physiology were made. Gradually a strong international reputation was established, and so was a broader interest for the area in Denmark among biologically educated academics as well as within the general population. In this way the basis for a strong Danish scientific tradition for research within muscle biology was formed.

The persons, who contributed to this development were appointed at the Faculty of Science (e.g. Krogh, Hohwu-Christensen, Hansen, Asmussen, Marius Nielsen and Bodil Nielsen) or at the Medical Faculty (e.g. Lindhard, Lundsgård, Kruhøffer, Bøje, Bang, Buchtal, Errebo-Knudsen and Prætorius Clausen) of the University of Copenhagen. So, the interest for the field was present among leading teachers within biology, theory of sports and medicine as well as among clinicians. This has had the implication that theoretical and experimental achievements were easily implemented in a practical context, e.g. in athletes and exercising normal people as well as in the treatment of patients, e.g. patients with diabetes or a need for physical rehabilitation.

In 1994 the newly formed Danish National Research Foundation decided to establish the Copenhagen Muscle Research Centre as a “centre of excellence” based on the existing platforms at the two Faculties, which had been carried on by e.g. Saltin, Galbo, Secher and Richter. The Centre was organized as a research network, which also included various departments within the Copenhagen University Hospital, and very fruitful collaboration resulted. In consequence of the success of the Centre and also logical from a historical perspective, when at the end of 2003 the Danish National Research Foundation according to its rules could not further extend its support, the two Faculties and the University Hospital together granted the economical support necessary to secure another three years of continuation of the CMRC. Since then the area has been further strengthened by formation of a Muscle Cluster within the Faculty of Health Sciences (earlier: Medical Faculty) and a Ph.d. Academy within Muscle Biology, Exercise and Health Research (AMBEHR), both heavily depending upon the CMRC.

The superior vision for the continuing CMRC is to use and profit from the great potential, which has been created in the first 10 years of the Centre, in order to extend the Centre´s acquired frontline position within a number of key areas within the biology of muscle and its importance for the rest of the organism. Focus will still be on basal scientific questions and mechanisms. However, in parallel information highly relevant for sports and exercise as well as for prevention and treatment of diseases will be obtained.

Below the planned activities of the continuing CMRC are briefly the described. They are somewhat arbitrarily divided into areas for which the senior researchers indicated by big letters are responsible. The various areas will, as it will be apparent, dynamically interact. The exposition intends to bring overview and, accordingly, details and scientific documentation have mostly been avoided. Within all areas investigations will be carried out at all experimental levels from integrated healthy or diseased humans to experiments on rodents, including genetically modified animals, and to studies on isolated organs, cells and subcellular structures.

Research areas:

1. Regulation of carbohydrate and fat metabolism. Association with insulin sensitivity/resistance and type 2 diabetes (EAR,BK,JW,BSt,TP,FD,HG,JH,HP).

We will unravel the molecular signaling mechanisms by which insulin and muscle contraction, respectively, increase glucose uptake and glycogen deposition in muscle cells. The involved signaling molecules and enzymes will be defined and their points of attack in the muscle cells localized. Moreover, the regulation of the signaling mechanisms at the gene level will be elucidated. These studies bear immediate relevance for insulin resistance and type 2 diabetes and will also be accompanied by studies of animals and humans, who have or are predisposed for these diseases. The metabolism of fat in the muscle cells, too, seems of importance for development of insulin resistance. This relationship will be explored along with studies of poorly understood mechanisms of uptake of various kinds of lipid from blood into muscle cells and of mobilization of intramyocellular triglyceride as well as of the interplay between carbohydrate and fat metabolism. Release of free fatty acids from intraabdominal adipose tissue seems to play a key role in development of insulin resistance. Because physical training ameliorates insulin resistance we will study, whether training interferes with metabolism in intraabdominal adipose tissue in man. Fat cells probably influence muscle cells by other means than supply of free fatty acids, i.e. by release of hormones, and this phenomenon establishes a connection to Research area 3. In insulin resistance the endothelium dependent vasodilation is impaired. To unravel its mechanism and possible influence of physical activity , the endothelium dependent vasodilation will be determined in the studies of insulin resistance in humans. In this way, and because the circulation in general influences metabolism and insulin action in muscle, interplay with Research areas 4 and 6 is achieved. Moreover, Research areas 2 and 5, like Area 1, deal with regulation of metabolism. In the studies indicated above there is no sharp separation between basal scientific and practically applicable investigations and the same holds true for planned studies of effects of diet and gender. However, we will also carry out projects with predominantly applied aims, e.g. studies of a life style intervention program in morbidly obese people.

The vision within this line of research is to give a detailed description of metabolism in muscle and the influence of physical activity on this. A spin off will be a rational basis for counseling as regards performance of exercise, e.g. in prevention and treatment of diabetes. Moreover, the findings obtained will also have pharmacological perspectives as regards treatment of obesity and diabetes.

2. Ion transport in muscle cells and the implication for metabolism, blood flow and fatigue (JB, CJ, YH, HP).

The concentration of various ions in the interstitial fluid probably directly influences the local vascular tone and, in turn, muscle perfusion and probably also influences the activity in afferent nuscle nerves. In addition the interstitial ion milieu probably influences muscle metabolism. Accordingly, we want to examine the transport of potassium, sodium, hydrogen and lactate ions across the sarcolemma. We are able to reveal possible local differences in transport between different parts of a given muscle and are also able to associate transport with muscle fibre type composition, blood flow, nerve impulse traffic and metabolism. Adaptations in ion transport and the factors regulating the adaptations will be studied on both the protein and the gene level. All experimentel levels will be used, including studies on isolated mitochondria. The research area has wide interfaces with Research areas 1, 4, 5 and 6.
The vision within this line of research is to enhance the understanding of muscle performance capacity and fatigue and it has the practical aspect to improve counseling about exercise and rehabilitation of healthy and diseased subjects, respectively.

3. Hormone secretion from fat and muscle cells during exercise (BKP, BSt, TP, HG).

Within the last 10-15 years it has been accepted that fat cells secrete hormones which act on other cells including muscle cells. This field is rapidly developing and among the many unresolved questions are, whether –and if so, how- secretion of various fat cell hormones (adipokines) depends on acute and regularly repeated physical activity, and whether adipokines influence contracting muscle. Probably, abnormal secretion of adipokines has an essential role in development of insulin resistance in muscle and may also contribute to the pathogenesis of inflammatory diseases. This will be clarified in studies of various patient groups, including patients with rheumatoid arthritis and polymyalgia rheumatica. It will also be important to examine, whether training changes adipokine secretion in people, who has or are predisposed to type 2 diabetes. CMRC researchers have been the first to show that also contracting muscle cells secrete hormones (myokines). Some have been chemically characterized, but probably many more exist. These may explain the many fully or partly unexplained reactions taking place in response to exercise, ranging from local acute or chronic changes in circulation and connective tissue to stimulation of ventilation and hepatic glucose production and inhibition of insulin secretion and even to psychological phenomena like euphoria. A comprehensive unraveling of the hormone production in muscle and its regulation on the protein and gene level and the elucidation of the effects of the myokines will occupy CMRC researchers for a long period of time. This Research area has interfaces with all of the other Research areas. **Its vision is to continue to contribute substantially to the expansion of a very new field of knowledge with huge pharmacological perspectives.**

4. Central and peripheral circulation (NS, BS, YH).

The stimulation threshold of the arterial baroreceptors changes during exercise, and this is important for the increase in heart rate and the increase in sympathetic nerve activity, which accounts for the redistribution of cardiac output in favour of the working muscles. It will be studied, whether the change in baroreceptor threshold is induced by direct nervous control from motor centers in the central nervous system or by afferent nervous input from the working muscles. We will also elucidate which factors are responsible for the local dilatation of arterioles, which accounts for the fact that blood flow increases in working muscle in the face of an increased sympathetic nerve activity. Studies will be carried out in intact man as well as in in vitro isolated muscle and blood vessels and in isolated muscle and endothelium cells. The enzymes contributing to vasodilatation and impairment of sympathetic vasocontraction will be identified. Furthermore, new substances produced by muscle and influencing vascular tone or, like training, vessel proliferation will be searched for. Because regulation of peripheral circulation is altered in patients with arterial hypertension and type 2 diabetes, such patients will be studied to provide the explanation. The Research area has interfaces in particular with Research areas 2-6. However, because insulin increases muscle blood flow, and because the influence of insulin on muscle glucose uptake depends on supply to muscle of both insulin and glucose, the Research area is also connected with Research area 1.
The vision in this Research area is to provide new knowledge of importance for counseling e.g. patients with circulatory diseases about exercise performance. Furthermore, the Research area has a pharmacological potential e.g. by discovery of substances which may lower blood pressure or enhance vascular proliferation.

5. Studies of patients with monogenetic skeletal muscle diseases (JV).

These patients have a selective deficiency of a single protein. They may therefore, just as knockout animal models, serve in the elucidation of the role of that protein. Furthermore, the abnormal phenotypes, in general, offer unique possibilities of studying physiological problems, a fact CMRC researchers have been the first to benefit from in exercise studies. Some patients, e.g. have an impaired carbohydrate metabolism, and, accordingly, studies of these patients can reveal to which extent a normal carbohydrate metabolism is necessary for fat metabolism during exercise. Some patients show an exaggerated muscle blood flow during exercise, a fact which facilitates studies of the factors involved in regulation of muscle blood flow. In addition to dealing with such questions, which are intimately related to Research areas 1,2 and 4, we will also expand on our finding that the patients can improve their poor exercise performance by training. For instance, it will be investigated, whether the effect of training can be enhanced by protein supplementation. In this context, it should also be emphasized that patients with degenerative muscle diseases are obvious objects for studies of muscle satellite cell function.
The vision in this Research area is to use the huge potential, which this patient group has in respect to elucidation of physiological questions, and at the same time improve the treatment of the patients.

6. The interaction between muscle and connective tissue. Relationship with everyday activities (MK).

Muscle activity exerts an acute regulatory and chronical adaptive influence on collagen turnover and vascular capacity in the surrounding connective tissue. We will in healthy people and patients with e.g. arthrosis or subjected to rehabilitation study on protein and gene level, which growth factors, cytokines and enzymes are involved. Furthermore, we will examine, which training procedures result in optimum changes in structure and function of muscle and connective tissue. The Research area is in particular connected with Research areas 3 and 4, but in addition shares methods with all the other Research areas.
The vision in this Research area is to provide new knowledge about the interaction between muscle function and connective tissue and to apply this knowledge in optimizing training procedures in healthy and diseased humans.

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Vi have many national and international collaborators as well as advanced equipment and methodology allowing that we maintain our frontline position within all the above Research areas during the coming three years. The molecular biology (PS) and mass spectrometry (stabile isotope) (GvH) core facilities of the CMRC are involved in all the Research areas, and also the confocal microscope and the fibre typing units are expected to become essential for much of our work.

Other initiatives:

In order to promote the superior vision of CMRC (see Background) we will continue to arrange both internal, but open, seminars and international symposia and courses within our areas of interest. Our international network is being strengthened by formal collaboration, e.g. including exchange of students and scientists, with the Universities of Guelph (Canada), Melbourne and Maastricht. Furthermore, the international collaboration will be strengthened by invitation of foreign guest researchers and support to those of our young researchers, who want to visit laboratories abroad. We want to maintain and expand a marked role within the ph.d.-education, mainly by association of ph.d.-students to our laboratories, but also by educational courses. In order to enhance recruitment of young scientists we will introduce young academics to our laboratories by paying salaries for 3-6 months.

On behalf of the CMRC, Henrik Galbo, 20.11.2003.

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Abbreviations of names of senior scientists:
Employed by the University Hospital: BS (Bengt Saltin), NS (Niels Secher), BKP (Bente Klarlund Pedersen), JV (John Vissing), MK (Michael Kjær), HG (Henrik Galbo).
Employed by the Faculty of Science (August Krogh Institute, Institute of Sports Science): EAR (Erik Arne Richter), BK (Bente Kiens), JB (Jens Bangsbo), YH (Ylva Hellsten), CJ (Carsten Juel), HP (Henriette Pilegaard), JW (Jørgen Wojtaszewski).

Employed by the Faculty of Health Science (The Panum Institute): FD (Flemming Dela), TP (Thorkil Ploug), BSt (Bente Stallknecht), JH (Jørn Wulff Helge), PS (Peter Scherling), GvH (Gerrit van Hall).