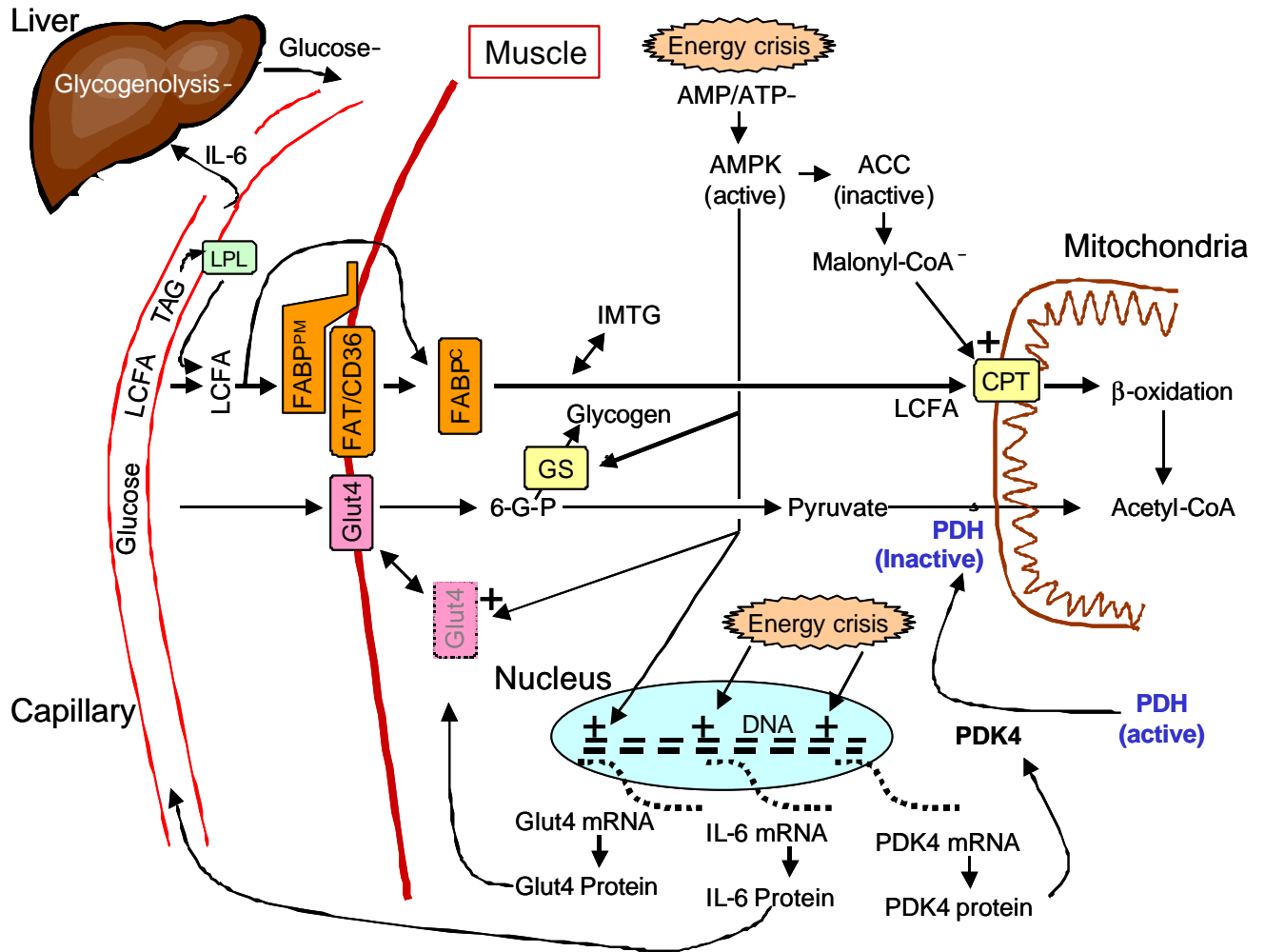


Annual Report 2001



The Copenhagen Muscle Research Centre
Rigshospitalet - University of Copenhagen

Founded by the Danish National Research Foundation

Legend to figure on front page

The figure is an updated version of the graph on the front page of the CMRC report for 2000 in which the advances made in 2001 have been incorporated.

A schematic illustration of cellular events in the energy metabolism of human skeletal muscles. Long chain fatty acids (LCFA) are taken up from the blood stream to be transported into the cell (by diffusion or by a transporter protein FAT/CDC36 and fatty acid binding proteins, FABP; membrane = m / cytosolic = c) and into the mitochondria (carnitine palmitoyl transferase, CPT). LCFA is either re-esterified and stored as intra-muscular triacylglycerol (IMTG) or provided as Acetyl-CoA. The LCFA come either from those bound to albumin in the blood stream or from hydrolysis of triacylglycerol (TAG) catalysed by lipoprotein lipase (LPL). A critical regulation is the AMP activation of protein kinase (AMPK), which brings about a reduction in malonyl-CoA via a phosphorylation of Acetyl-CoA carboxylase (ACC) opening for FA to be bound to CPT, which is a prerequisite for LCFA to be transported into the mitochondria. AMPK activation also changes glucose metabolism from an anabolic to a catabolic mode by activation of glucose transport via recruitment of glucose transporters (Glut4) to the plasma membrane and deactivation of glycogen synthase (GS), all in the course of restoring energy balance. Illustrated is also how the pyruvate dehydrogenase kinase (PDK) gene is activated by muscle contraction which in turn may contribute to the deactivation of pyruvate dehydrogenase (PDH) inhibiting decarboxylation of pyruvate and the formation of Acetyl-CoA. This process is enhanced when muscle glycogen stores are low (energy crisis). The IL-6 gene is also activated by muscle contractions and the protein is produced in prolonged exercise and released to the blood stream for possible action in the liver, enhancing liver glucose production. As for the PDK gene this activation is faster and more pronounced when muscle glycogen stores are low.

Summarized in:

Pedersen BK, Steensberg A, Schjerling P. Muscle – derived interleukin-6 – possible biological effects. Topical review. *J Physiol* 536, 329-337, 2001.

Pilegaard H, Saltin B, Neufer PD. The effect of short-term fasting and refeeding on transcriptional regulation of metabolic genes in human skeletal muscle. *Physiology Society Meeting, University of York, December 2001, 144P, 2001.*

Richter EA, Derave W, Wojtaszewski J. Glucose, exercise and insulin: emerging concepts. Topical review. *J Physiol* 535, 313-322, 2001.

CMRC Research

General

The number and quality of CMRC's publications reached a new "high" in 2001 with eighty original publications. Very satisfactory was also that outstanding contributions could be recorded within all major fields in which the CMRC works. Moreover, some breakthroughs were made and on other topics critical developments were achieved that can be used as building bricks in the years to come. Some reflections on possible reasons why the centre's research flourishes could be as follows:

- Our young researchers who finished their Ph.D. work within the first five-year funding period have now returned from their post doctoral work in various parts of the world and have brought back new knowledge, methods, and experience as well as a contact network with outstanding international scientists in their respective fields.
- Several of the scientists who were "junior" when the CMRC started have developed into independent senior researchers who still use the CMRC as base for their research or as a partner.
- A continuous exchange of foreign researchers at the senior and junior levels.
- Major investments in equipment, which have in part been the consequence of the needs of our homecoming post docs and younger scientists.

All in all these factors have formed the basis for the dynamics within the CMRC, thereby enhancing not only the number, but also the impact of the publications.

CMRC Research Highlights 2001

Exercise and cytokines.

Since the start of the CMRC the cytokine response to exercise has been an active area, but two years ago it took a turn and culminated in 2001. Earlier a focus was on cytokine production during exercise as part of the immune response. The new finding is that contracting muscle cells produce interleukin-6 (IL-6). An IL-6 gene, silent at rest, is quickly activated by exercise and the protein is made in and released from the muscle during ongoing exercise. One target tissue appears to be the fat pad, enhancing lipolysis and thereby contributing to fatty acid availability for the active muscles. This is the first time that human skeletal muscle has been proven to produce a substance with a hormone-like effect.

The activation of the IL-6 gene may occur via Ca^{2+} mediated activation of the calcineurin signal transduction pathway, and IL-6 itself may also be an inducer of gene activation within the muscle cell.

Central control of cardiovascular functions.

It was early postulated that when motor cortex became activated and elicited muscle contractions it also affected the cardiovascular system, e.g. by elevating the heart rate at onset of exercise and causing vasoconstriction in inactive muscles and various organs. The principal mechanisms by which this occurs has since long been worked out. Unanswered has, however, been the question of whether the motor cortex also exerts an influence during continuous activity. Good evidence is now at hand for this being the case, but whether this influence also involves the baroreceptors is a matter of discussion. During exercise blood pressure rises which via the baroreceptors should cause a slowing down of the heart rate. This does not happen. One school has flatly stated that the baroreceptors are uncoupled in exercise. Another school has argued that they operate, but are reset and continue to control blood pressure at a higher level. Our recent work has confirmed that this is the case, but the new and very important finding is that this resetting is a function not only of exercise intensity, but

also of muscle mass involvement in the exercise. This resetting is then in proportion with the motor cortex area activation and opens for the understanding of how cardiovascular regulation occurs in exercise engaging a large fraction of the muscle mass in the exercise, i.e. in the situation when the peripheral demands for a blood flow is larger than the blood flow that the heart can provide.

Chronic hypoxia.

In 1998 we made a field expedition to Bolivia in order to try to unravel the mechanisms by which heart rate during exercise is gradually lowered while at altitude, and why blood lactate followed the same pattern, the so-called "lactate paradox". The final data on these two issues were published in 2001.

For the cardiovascular regulation our hypothesis was that in chronic hypoxia the relative roles of the parasympathetic and sympathetic nervous systems changed, with the former operating over a wider range of exercise-induced heart rates. At sea level the former only plays a role in raising the heart rate some 20-30 beats per minute at onset of exercise. The hypothesis was convincingly proven as it could be shown that the parasympathetic influence was present up to exhaustive exercise. A phenomenon first observed in 1937 could now finally be explained.

The lactate paradox was not explained by our studies; on the contrary, a phenomenon also first observed in the early 1930's and later reconfirmed in several studies was proven not to exist. The main reasons why so many studies in the past have reported low blood lactate during exercise in chronic hypoxia were inappropriate study design and misinterpretation of findings.

Metabolic regulations.

The key molecule is the AMP activated protein kinase (AMPK), which in recent years has been named as main controller of many metabolic events when muscles contract. By the work in the CMRC it has clearly been demonstrated that the α_2 subunit is activated by exercise. The question is what it regulates. Possible targets are: a) GLUT4 translocation, thereby enhancing glucose transport into the cell; b) regulation of glycogen synthase deactivation, c) via a phosphorylation of Acetyl-CoA carboxylase (ACC) reducing the malonyl CoA concentration in the cytosol making it possible for fatty acids to link to CPT, enter the mitochondria and go through β -oxidation, forming acetyl CoA; and most importantly d) the AMP activated protein kinase may be an inducer of certain metabolic genes. One of these could be the PDK4 gene, which like the IL-6 gene becomes activated by exercise. The PDK4 is an alternative regulator of pyruvate or fatty acids contribution of acetyl CoA to the TCA cycle. PDK4 inhibits PDH_a with the result of less pyruvate being decarboxylated, which opens for fatty acids to supply more of the three-carbon skeleton for the TCA cycle.

Within the metabolic realm there has also been a successful method development that can contribute in further experimentation. The pH in the interstitium of a muscle is most critical as it directly affects or modulates several regulatory proteins. Furthermore, pH is proposed to activate sensory nerves nearby microcirculatory vessels. With the microdialysis technique pH can now be measured accurately in the dialysate with a reasonable time resolution.

Collaboration with senior researchers outside CMRC, resulting in publications in 2001.

In Denmark

- Fin Biering-Sørensen, Neurocenteret, Rigshospitalet
- Jens Bülow, Klinisk Fysiologisk Afd, Bispebjerg Hospital
- Bo Falck Hansen, Novo Nordisk
- Ole Schmitz, Aarhus Kommunehospital
- Hans Rasmussen, August Krogh Institutet, Københavns Universitet
- Ulla Rasmussen, August Krogh Institutet, Københavns Universitet

Internationally

- Robert C. Boushel, Dept. of Exercise Science, Concordia University, Montreal, Canada
- José A.L. Calbet, Dept. of Physiology, University of Las Palmas, Gran Canaria, Spain
- Terry E. Graham, Dept. of Human Biology and Nutrition, University of Guelph, Canada
- Paul Greenhaff, Dept. of Physiology, University of Nottingham, England
- Ronald D. Haller, University of Texas Southwestern Medical Center, Dallas, USA
- Peter Hespel, Katholic University, Leuven, Belgium
- Amira Klip, the Hospital for Sick Children, Toronto, Canada
- Jozef Langfort, Dep. Appl. Physiology, The Polish Academy of Science, Poland
- Johannes van Lieshout, Dept. of Internal Med., Academisch Medisch Centrum, Amsterdam, the Netherlands
- Jere H. Mitchell, University of Texas Southwestern Medical Center, Dallas, USA.
- P. Darrell Neuffer, John B. Pierce Lab. Foundation and Yale Univ., New Haven, USA
- Evelyn Ralston, National Institutes of Health, Bethesda, USA
- Peter D. Raven, University of North Texas Health Science Center, Fort Worth, USA
- Russ S. Richardson, Dept. of Medicine, University of California at San Diego, USA
- Ola Rønsen, Norwegian National Sports Centre, Oslo, Norway
- Anthony J. Sargeant, Neuromuscular Biology Group, Manchester Metropolitan University, Alsager, UK
- Naoko Shono, Saga Medical Research Center, Fukuoka, Japan
- Leonard H. Storlien, Astra Zeneca, Gothenburg, Sweden
- Timo Takala, Dept. of Health Sciences, University of Jyväskylä, Finland.
- Peter D. Wagner, Dept. of Medicine, University of California at San Diego, USA
- David H. Wasserman, Dept. Mol. Physiol. & Biol., Vanderbilt University School of Medicine, Nashville, USA

Exchange of researchers

For ***visiting researchers***, please see enclosure 1, list of CMRC personnel 2001.

CMRC Researchers abroad (> one month)

- Nikolai Nordsborg, Ph.D.-student, Dept. of Applied Physiology, University of Ulm, Germany, November 2000 – August 2001.
- Adam Steensberg, medical student, research associate, Dept. of Physiology, University of Melbourne, Australia, March 2001.
- Kristian Vissing, Ph.D.-student, Dept. of Molecular Cardiology, University of Texas Southwestern Medical Center, May-December 2001.

Conferences, etc.

Arranged by CMRC

4th Bispebjerg Symposium on Sports Medicine: "The Aging Muscle". December 2001. Arranged by Michael Kjær.

Attended by CMRC researchers as invited speakers

Jesper L. Andersen

- III Internationale Congress on Medicine and Sports. Universitario de Tafira, Las Palmas de Gran Canaria, Canary Islands, Spain, November 2001, "Influence of sprint training on muscle structure and function".
- 4th International Bispebjerg Symposium on Sports Medicine, The aging muscle: strength and function, Copenhagen, Denmark, December 2001. "Muscle fibre type adaptation in elderly".

Flemming Dela

- University of Kuopio, Finland, June 2001. "Physical training in the treatment of type 2 diabetes".

Henrik Galbo

- American College of Sports Medicine, Annual Meeting, Baltimore, Maryland, June 2001, "Hormonal regulation of metabolism in exercise, from bench to bedside".

José Gonzáles-Alonso

- International Symposium on Exercise, Muscle and Metabolism. Melbourne, Australia, August 2001. "Effects of hyperthermia and dehydration on circulatory and metabolic function".
- International Symposium on Thermal Physiology. Wollongong, Australia, September, 2001. "Limits to Physical Performance under both hot and cold thermal extremes".
- II Congress of the European Federation of Sports Medicine. Oviedo, Spain, November 2001. "Temperature and Fatigue".

Jørn W. Helge

- American College of Sports Medicine, Baltimore, USA, May 2001. "Effects of long-term adaptation to a high-fat diet on metabolism, training capacity, and performance".

Ylva Hellsten

- Oxidative stress in physical exercise and training., Rennes, France, December 2001. "Urate metabolism in human skeletal muscle".

Carsten Juel

- Scandinavian Physiological Society: Pumps and Channels, October 2001. "Measurement of interstitial K⁺ in exercising human skeletal muscle using the microdialysis technique".

Bente Kiens

- First International Scientific Congress on Nutrition and Athletic Performance, Edmonton, Canada, August, 2001. "Creatine Supplementation, Muscle Hypertrophy and Rehabilitation".

Bente K. Pedersen

- Two symposia at Karolinska Institutet organised by Institute of Allergy, March 2001 Stockholm, Sweden. "Exercise and the immune system – neuroendocrinological role" and "The cytokine response to exercise".
- International Society of Exercise and Immunology Symposium, May 2001 Baltimore, USA. "Muscle-derived IL-6".
- American College of Sports Medicine, May 2001, Baltimore, USA. "Exercise Stress, Hypoxia and Immunology".
- European College of Sport Science, July 2001, Cologne, Germany. "The cytokine response to exercise".
- Symposium on Muscle and Metabolism, August 2001 Melbourne, Australia. "Muscle-derived IL-6 – biological effects".

Erik A. Richter

- First International Scientific Congress on Nutrition and Athletic Performance, Edmonton, Canada, August, 2001. "Creatine Supplementation, Muscle Hypertrophy and Rehabilitation"
- BRUCOSPORT, Gent, Belgium, October, 2001. "Muscle metabolism in recovery from exercise".
- Joint Meeting of the Biochemical and Physiological Society, York, UK, December, 2001. "Interactions between Exercise and Muscle Glucose Utilization and Storage".
- Division of Molecular physiology and School of life Sciences, Dundee, UK, December, 2001. "Regulatory roles of Glycogen and AMP-activated protein kinase in muscle glucose transport.

Göran Rådegran

- Japan Women's College of Physical Education and Tokyo Medical College, one week, December 2001. Tutorial lecture series on the use of Doppler ultrasound for measurement of peripheral blood flow.

Bengt Saltin

- Svenska Läkarsällskapet; Stockholm, January 2001. The Thureus Lecture: "Skeletal muscle, training, and health".
- Norwegian Physiological Society Annual Meeting, Oslo, February 2001. "Muscle metabolism in exercise".
- SCIF Prize lecture, Stockholm, February 2001: "Why are Kenyan runners so fast".
- European Cultural City Lecture Series on "Body and Mind", Porto, Portugal, April 2001. "Physical activity, skeletal muscle, and health".
- IUPS Satellite Symposium on Exercise, Muscle, and Metabolism, Melbourne, Australia, August 2001. Opening lecture: "Metabolic links to the regulation of skeletal muscle blood flow".
- IUPS Congress, Christchurch, New Zealand, August 2001. August Krogh Lecture: "Skeletal muscle metabolism; from genes to function".

- CSEP Annual Meeting, Montreal, Canada, November 2001. "Regulation of skeletal muscle blood flow and oxygen uptake".
- University College Fall Lecture Series, London, December 2001. "Regulation of skeletal muscle metabolic response; role of acutely induced gene activation".

Mikael Sander

- Danish Society of Hypertension. Ordinary meeting. Copenhagen, January 2001. "Nitric oxide deficient hypertension".
- Nordic Clinical Physiological Society Annual Meeting, Aarhus, April 2001. "Chronic hypoxia and sympathetic nervous activation".
- International Union of Physiological Sciences: Symposium on autonomic nervous control, Christchurch, New Zealand, August 2001. "Sympathetic mechanisms in hypertension".

Peter Schjerling

- Genes in Sport Conference, London, England. November 2001. "Gene doping"
- Doping Symposium, Oslo, Norge. December 2001. "Præstationsforbedring med gen-teknologi"
- Geniale Inspanningen, Utrecht, Holland. December 2001. "Gene doping"

Niels H. Secher

- Japanese Women's College of Physical Education: "Blood pressure and regulation of muscle flow during exercise".

Jørgen Wojtaszewski

- ADA, 61st scientific meeting, USA, June 2001. "Effects of exercise in muscle with disrupted insulin signalling".
- IUPS satellite meeting, Melbourne Australian, August 2001. "Regulation of muscle metabolism during exercise".
- IUPS 2001, New Zealand, August 2001. "Exercise and Insulin signalling in skeletal muscle".
- Danish Biochemical Society, November 2001. "Regulation of glucose transport in skeletal muscle".

Examiner/opponent at doctoral dissertations

Jens Bangsbo

- Doctoral thesis examiner, University of Trondheim. Student: Jan Hoff.

Henrik Galbo

- Doctoral thesis examiner, University of Copenhagen, February 2001. Student: Nari-man Mohd Sharif Abdulla al Mulla.

Jørn W. Helge

- Phd thesis examiner, University of Otago, New Zealand, September 2001. Student: David S. Rowlands.
- Phd thesis examiner, Royal Melbourne Institute of Technology, Melbourne, Australia, October 2001. Student: Jong Sam Lee.

Bente Kiens

- Phd thesis examiner at the Department of Physiology, University of Melbourne, Australia, June 2001. Student: Shannon Cambell.

- Phd thesis examiner at Division of Biochemistry, University of Tasmania, Australia. September 2001. Student: Lucy H. Clerk.

Michael Kjær

- Phd thesis examiner at The University of Copenhagen. Student: Rasmus Damsgaard
- Phd thesis examiner at the University of Turku, Finland. Student: Kari Kalliokoski
- Phd thesis examiner at the University of Oslo, Norway. Student: Troels Raastad
- Phd thesis examiner at the University of Copenhagen. Student: Jonas Winkel Holm
- Phd thesis examiner at the University of Aarhus. Student: Mogens Strange Hansen

Bente K. Pedersen

- Doctoral thesis examiner, University of Oslo, Norway. Student: Ine Wigernæs
- Phd thesis examiner, University of Melbourne, Australia. Student: Rebecca Starkie

Erik A. Richter

- Phd thesis examiner at Deakin University, Melbourne, Australia, July 2001. Student: Georgious Kraniou

Jørgen Wojtaszewski

- Phd thesis examiner, RMIT University, Melbourne, Australia, October 2001. Student: N.K. Stepto.

Committee work, etc.

Jens Bangsbo

- Member of TEAM DANMARK's Research Council

Flemming Dela

- Member of the organising committee of the 18th Annual Meeting of the Anglo-Danish Dutch Diabetes Group, May 2001.
- Board member of the Danish Society of Endocrinology.
- Board member of the Danish Society of Physical Activity and Health.

Henrik Galbo

- Member of evaluation committee in regard to professorship in internal medicine at the University of Copenhagen.
- Member of evaluation committee in regard to adjunct professorship in molecular diabetology at Aarhus University.

Bente Kiens

- Several committees at the Science Faculty related to development of curricula and assessment of student performance.

Michael Kjær

- President Elect, the European College of Sport Science

Bente K. Pedersen

- Board member of the Research Council at Medical Faculty, University of Copenhagen
- Member of "Strategiudvalget" at the Medical Faculty, University of Copenhagen
- Board member of the Danish Society of Physical Activity and Health.

Erik A. Richter

- Board member of the Danish Society of Physical Activity and Health.

Bengt Saltin

- Director, Baltic Summer School
- Chairman, Anti Doping Danmark, appointed by the Minister of Culture
- Chairman of the Board of the Danish Society of Physical Activity and Health
- Member of selection committee for a professorship in rheumatology at the University of Copenhagen.
- Research Council Member; the Novo Nordisk Foundation

Niels H. Secher

- Editor, The European Journal of Applied Physiology
- Editor, Experimental Physiology

Research education**Bengt Saltin**

- Karolinska Institutet, Stockholm, Sweden, March 2001. Lecturer at post graduate course on methods in cardiovascular physiology.

The Baltic Summer School 2001.

Theme: "Cardiovascular systems in health and disease", Lund, Sweden, May 2001. Arranged jointly by the universities in Copenhagen (CMRC), Lund, and Kiel. 60 students from a large number of countries in the world participated in the theoretical course in Lund. Of the 20 students who continued with lab courses, four worked in Denmark at the CMRC where Ylva Hellsten, Jens Bangsbo and Niels Henry Secher arranged lab courses.

Lecturers from CMRC:**Carsten Juel**

- Title of presentation: "Water movements in skeletal muscle".

Bengt Saltin

- Title of presentation: "Integration of cardiovascular regulation during exercise in humans".

Mikael Sander

- Secretary, member of the local scientific committee and presenter. Title of presentation: "Sympathetic vascular control the baroreceptor function".

Collaboration with Industry

Several CMRC researchers have contacts with Industry, primarily with Novo Nordisk, but also with other companies such as Arla Foods and its daughter companies. With the former, the research is on fundamental issues or clinical evaluation of new products. At the moment, there are no intentions within CMRC to seek for intellectual property rights or patents. The goal of the work with the dairy company is to produce products (protein hydrolysates) which if patented include CMRC rights.

CMRC “external” funding
 (defined as funding given to CMRC key-research projects and primarily meant to be used in 2001; all figures in DKK)

Research councils, etc.

European Commission:

- Salary: 1.196.178 + Running expenses: 422.758, totalling: 1.618.936

Kulturministeriets Udvalg for idrætsforskning:

- Salary: 200.000 + Running expenses: 115.000 + Equipment: 50.000, totalling: 365.000

Nordisk Forskningskomité:

- Running expenses: 75.000

Major private foundations

The Diabetes Association:

- Salary: 125.000 + Running expenses 75.000, totalling: 200.000

Novo Nordisk Foundation:

- Running expenses: 504.000 + Equipment: 88.110, totalling: 592.110

Other private foundations/Institutions

Arla Foods:

- Salary: 300.000

The Gatorade Sport Science Institute:

- Running expenses: 240.000

Lægeforeningens Fond:

- Salary: 7.500

Frk. P.A. Brandts Legat:

- Running expenses: 40.000

The Swedish Olympic Committee:

- Running expenses: 130.000

Team Danmark:

- Running expenses: 465.000

Anonymous Foundation v/Dir. E. K. Hansen:

- Salary: 360.000 + Running expenses: 100.000, totalling: 460.000

Aage Louis Hansens Fond:

- Running expenses: 38.000

External funding for CMRC projects in total: 4.531.546

“Ved nedenstående underskrift bekræftes det, at nærværende beretning og det for år 2001 tidligere indsendte regnskab med tilhørende noter og oversigter indeholder alle oplysninger, som vedrører årets aktiviteter i Center for Muskelforskning under Danmarks Grundforskningsfond”

København, den 15. april 2002

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