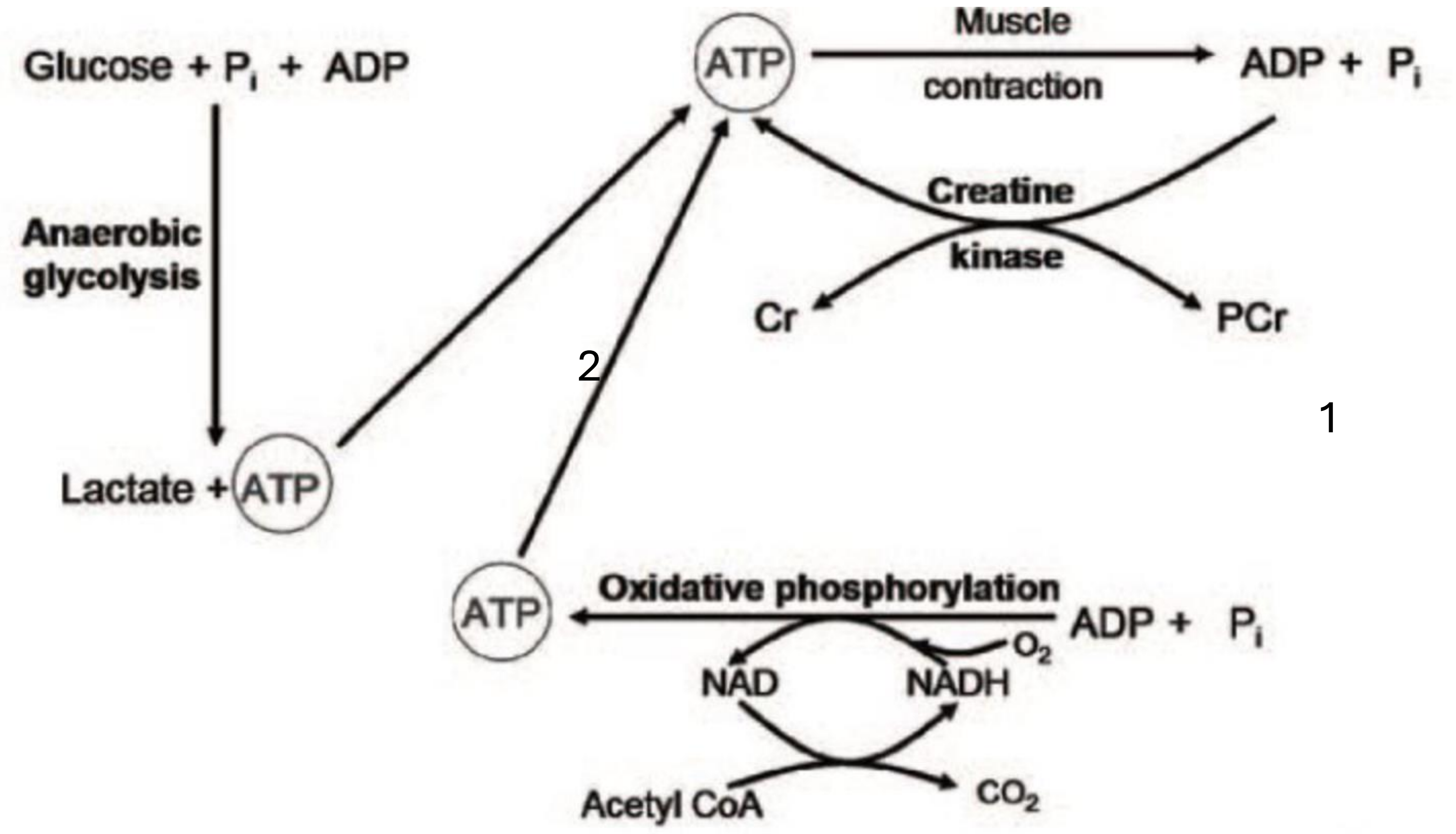
Hedersföreläsning
Eva Jansson

Human hjärt- och skelettmuskulaturs morfologi och metabolism

25 september 2024

Central questions now and then

ATP high turnover – limited storage

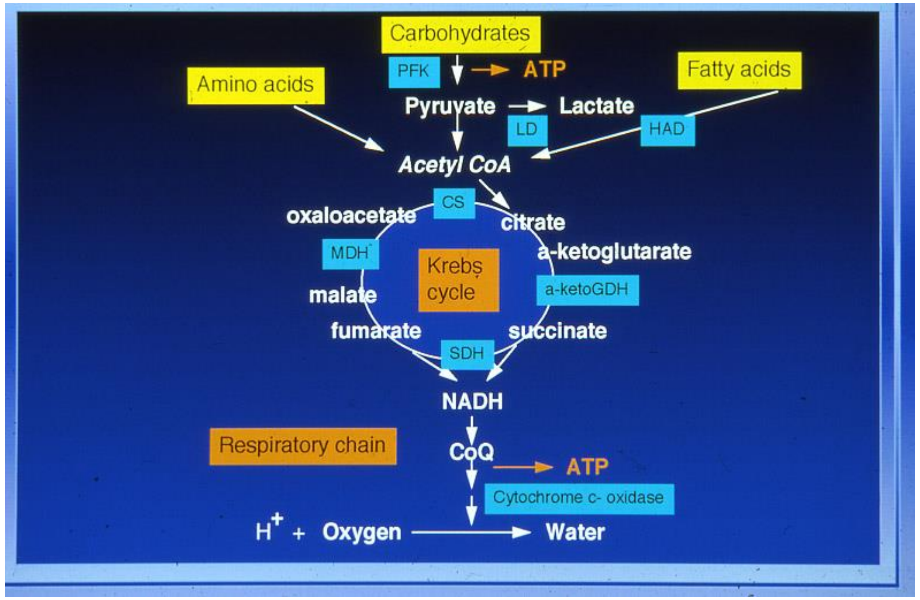


ATP – regeneration
Acute response
Capacity
Adaptation
Regulation
Limits

3

1. PCr
2. Anaerob glycolysis
3. Oxidative phosphorylation

Most conditions stable ATP
Exceptions:
- All-out sprint 30s



Lanza and Kent-Braun 2007

Krokiga väg mot ett klart mål – ATP i arbetande muskel

Matematik SU 1967

Först turen till GIH-stud 1968-70

Tillbaka till SU
biokemi, nutrition 1970-72

Andra turen till GIH – fysiologen – sommarjobb 72-73

Karolinska Solna – 73-91
Disputation 1980
Postdocprojekt1980-90
Läkarstudier 1978-91
Docent 1985
En dotter 1988

Karolinska Huddinge 91-
Lektor 91-97
En son 1992
Professor 1998
Gifter mig i Rom med barnens pappa – fredagen den 13 1998
Avdchef 2003 – 15 och biträdande prefekt
Programdirektor 2003-10

YFA – FYSS – 1998 – JH, CJS, EJ

En flygande start

Metabolic Adaptation to Prolonged Physical Exercise

Second International Symposium on Biochemistry of Exercise

Magglingen, Switzerland , 1973

Standing from left: David Costill, Albert W. Taylor, Bertil Sjödin, Jan Karlsson, Arne Lindholm, Bengt Saltin, Anders Lundin, Jan Henriksson, Alf Thorstensson, Philip Gollnick. Sitting from left: Eva Jansson, Birgitta Essén, Erik Hohwü Christensen, Karin Piehl, Bodil Hultén.

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Themes - models

Tissues and characterization
Skeletal muscle – fibre types
Heart – atria – ventricles
Adipose tissue

ATP – substrate turnover
Aerobic anaerobic
Acute response
Capacity – adaptation- training
Regulation
Limits

Stimulus
hypoxia – ischemia - nutrients

Mechanisms
Ischemia VEGF, PGC-A, HIF-A
Exercise ER
Nutrients mTOR, Vps34, SNAT 2

Life-time changes in physical performance and skeletal muscle
Cohort born in 1958 -- SPAF

Clinical models
Knee surgery - inactivity
COPD, PCV, IC
Hyperthyroidism
Diabetes
Heart surgery
Heart failure
Kidney failure
Reumatic diseases

Adipose tissue
Response to sprint exercise

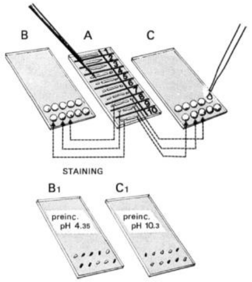
?

Factors of influence
Age
Sex
Chronic diseases
Genes- polymorphisms
Nutrients/diet
Substrate availability
Type of tissue
Skeletal muscle fibre types

Human experimental models and techniques

- One leg-models
- Pressure chamber for ischemia or hypoxia
- Leg and arm exercise model
- Sprint exercise model
- Clinical models for altered blood/O2 transport: COPD, HF, claudicatio, inactivity
- Ergospirometry
- Cohort for longitudinal research – 16 yrs old boys and girls – now 66 yrs - SPAF

- Catheterizations: artery, femoral vein, adipose tissue vein
- Isotopes for substrate metabolism – FFA, protein synthesis
- Tissue biopsies: skeletal muscle, heart, adipose tissue
- Explanted hearts – ”normal heart” – accidents
- Single muscle fibre dissection
- Tissue analyses – microscopic, substrates, enzymes proteins, molecular biological



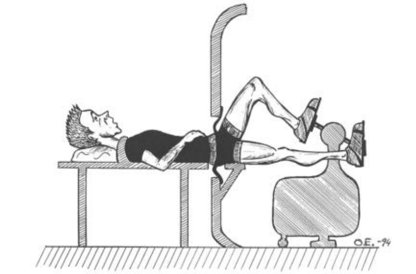
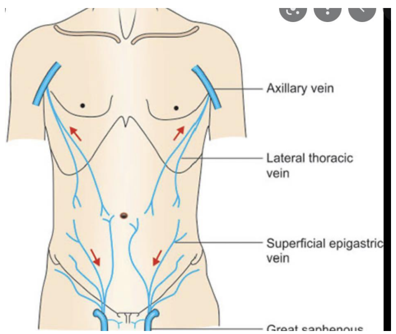
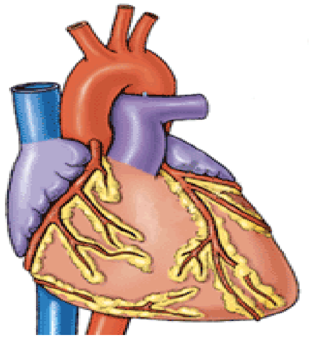


Figure 1. Use of pressure chamber for application of Leg Positive Pressure (LPP) during cycle exercise.





Coauthors - coworkers

Top coauthors – number of publications

- Mona Esbjörnsson 25
- Thomas Gustafsson 21
- Lennart Kaijser 43
- Barbara Norman 18
- Carl Johan Sundberg 27
- Christer Sylvén 53

- 250 coauthors in total
- 40 international coauthors

PhD – students – supervisor or coauthor

Knee- surgery
Tom Häggmark 1978
Inga Arvidsson 1986
Karl Eriksson 2001

Scoliosis
Per Bylund 1987

Extreme endurance exercise – 1500km
Peter Schantz 1986

ATP - breakdown
Barbara Norman 1993

Normal heart
Lin Lijun 1993

Stimulus - Mechanisms
Carl Johan Sundberg 1993
Thomas Gustafsson 2005
Anna Wiik 2008
Jessica Norrbom 2008
Anna Strömberg 2017

Children – dancers - controls
Monica Dahlström 1996

Heart failure
Allan Gordon 1996
Raija Tyni-Lenné 1998

Swedish Physical Fitness Cohort SPAF
Birgitta Glenmark 1997
Margareta Barnekow-Bergkvist 1997
Maria Westerståhl 2003

Sprint exercise
Mona Esbjörnsson 2000
Håkan Rundqvist 2017

Kidney failure
Helena Wallin 2023

GIH - First publication – Lidingöloppet 1973

Acta physiol. scand. 1973. 89. 374—383

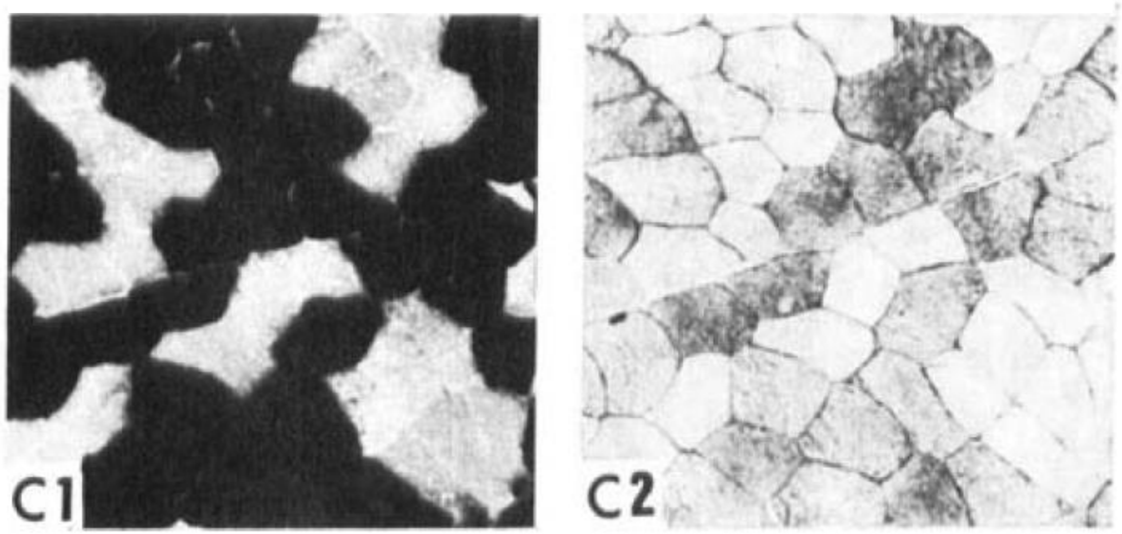
From the Department of Physiology, Gymnastik- och idrottshögskolan, Stockholm, Sweden

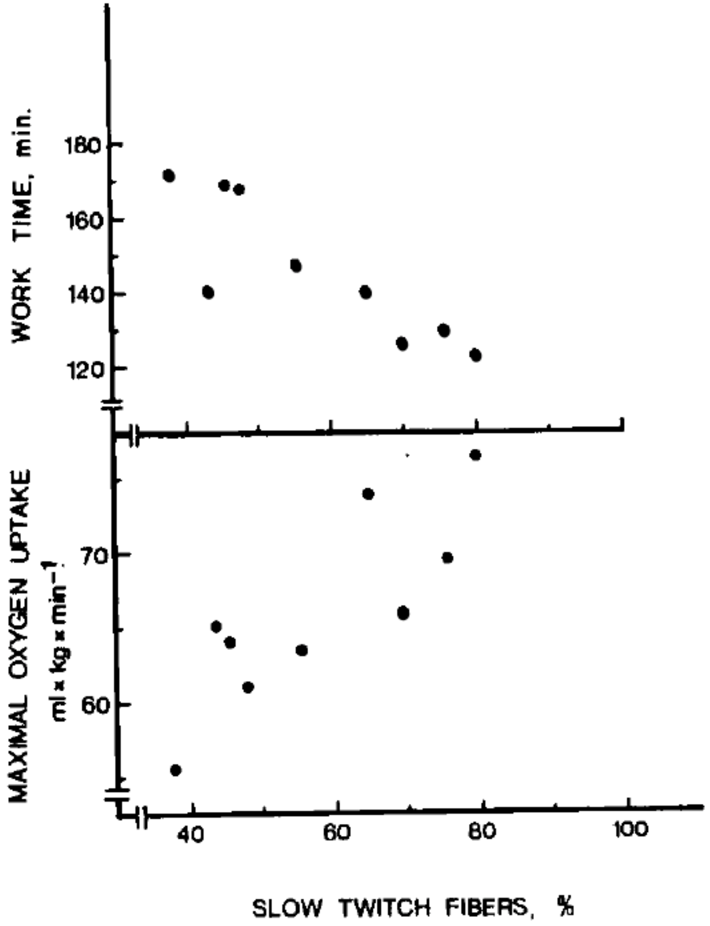
Glycogen Depletion Pattern in Human Muscle Fibres During Distance Running

By

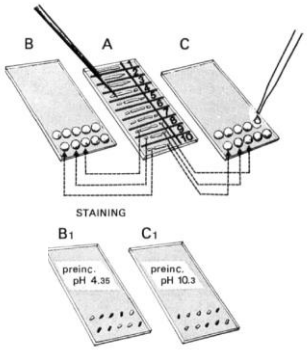
D. L. Costill, P. D. Gollnick, E. D. Jansson, B. Saltin and E. M. Stein

Received 19 January 1973





Karolinska 1973 – mötte 4 avhandlingsprojekt

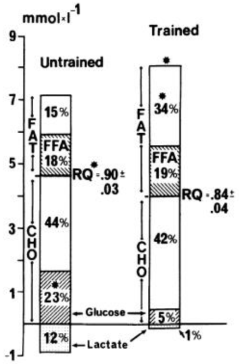


[Metabolic characteristics of fibre types in human skeletal muscle]
B Essen, E Jansson, J Henriksson, AW Taylor, B Saltin
Acta Physiologica Scandinavica 95 (2), 153-165, 1975

- **1. Single muscle fibre method**

  Theses: Birgitta Essén
  Jan Henriksson

- **2. Extreme endurance training**
  - **Muscle chacteristics**
  - **Substrate turnover**



[Muscle adaptation to extreme endurance training in man]
E Jansson, L Kaijser
Acta Physiologica Scandinavica 100, 315 – 324. 1977

[Substrate utilization and enzymes in skeletal muscle of extremely endurance-trained men]
E Jansson, L Kaijser
Journal of Applied Physiology 62 (3), 999-1005. 1987

- **3. Carbohydrate loading and depletion**
  - **Substrate regulation**

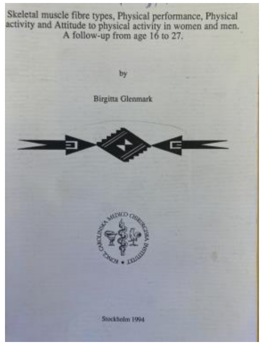
  My thesis

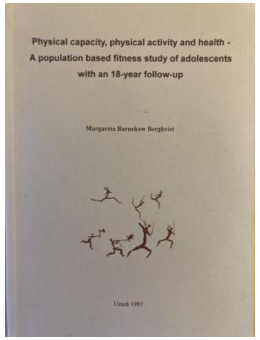


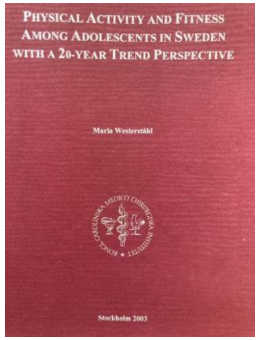
- **4. SPAF cohort - 16 y old boys and girls**
  - **Skeletal muscle biopsies and performance**

  20 publications

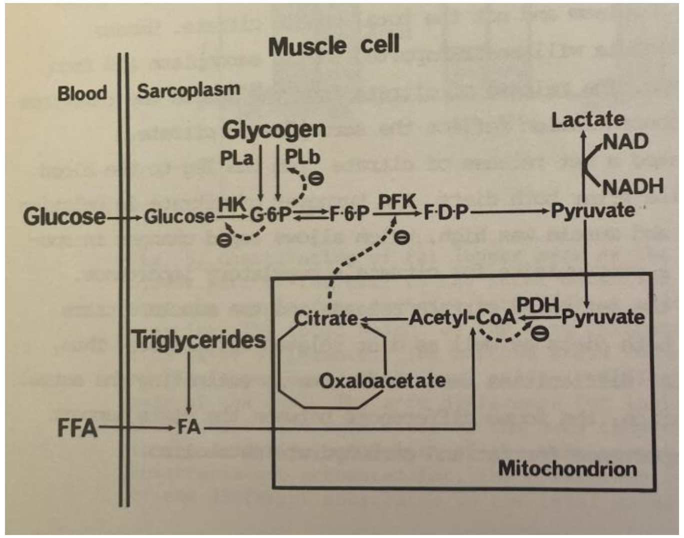
[Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners.]
B Saltin, J Henriksson, E Nygaard, P Andersen, E Jansson
Annals of the New York Academy of Sciences 301, 3-29, 1977







Main finding in my thesis: Citrate may inhibit glycolysis and PDH during exercise after high fat and low CH diet to spare glucose.



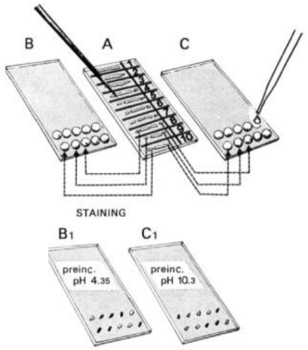
Based on measurements of citrate in

- Muscle biopsies
- Artery and femoral vein

Leg citrate metabolism at rest and during exercise in relation to diet and substrate utilization in man
Jansson E, Kaijser L. **Acta Physiol Scand. 1984 Oct;122(2):145-53.** .

Effect of diet on the utilization of blood-borne and intramuscular substrates during exercise in man.
Jansson E, Kaijser L.Acta Physiol Scand. 1982 May;115(1):19-30.

Karolinska 1973 – mötte 4 avhandlingsprojekt



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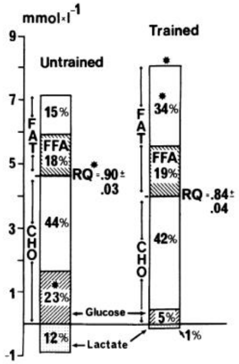

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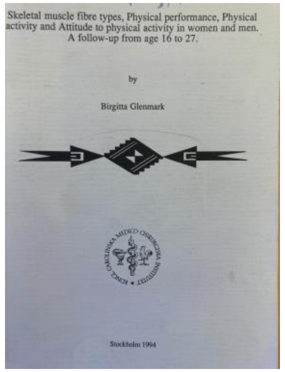
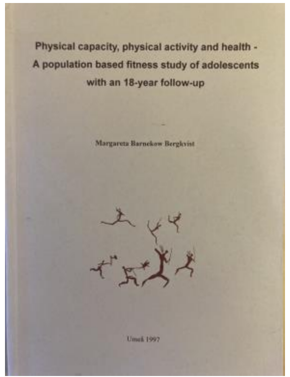
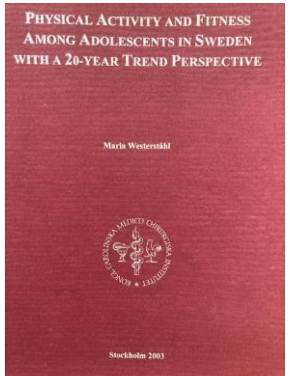
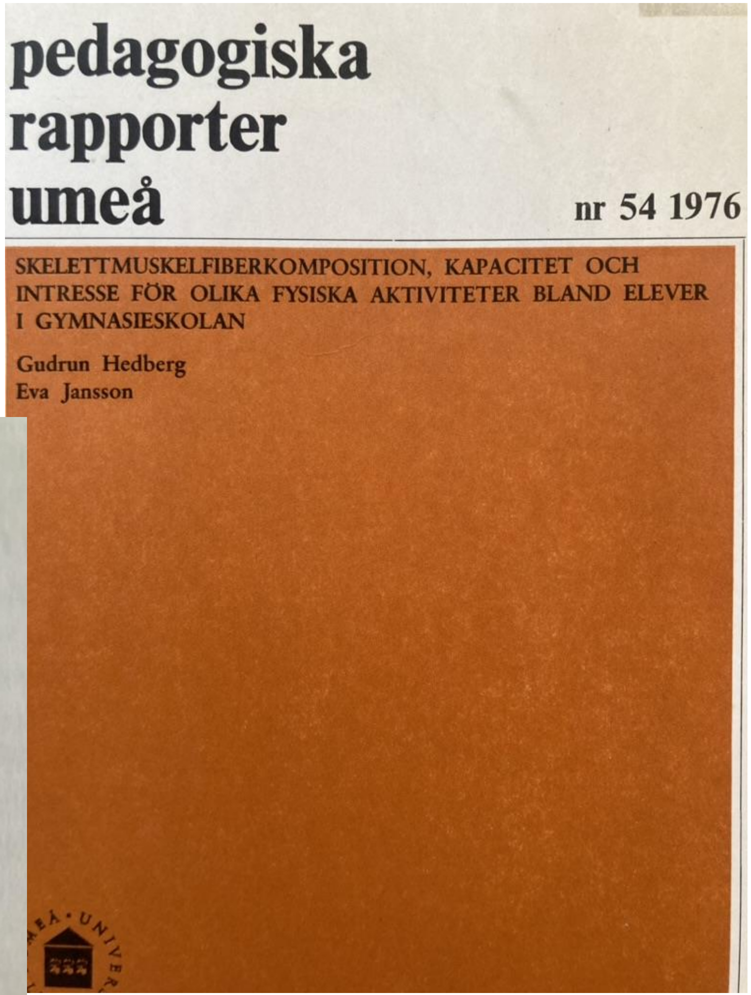




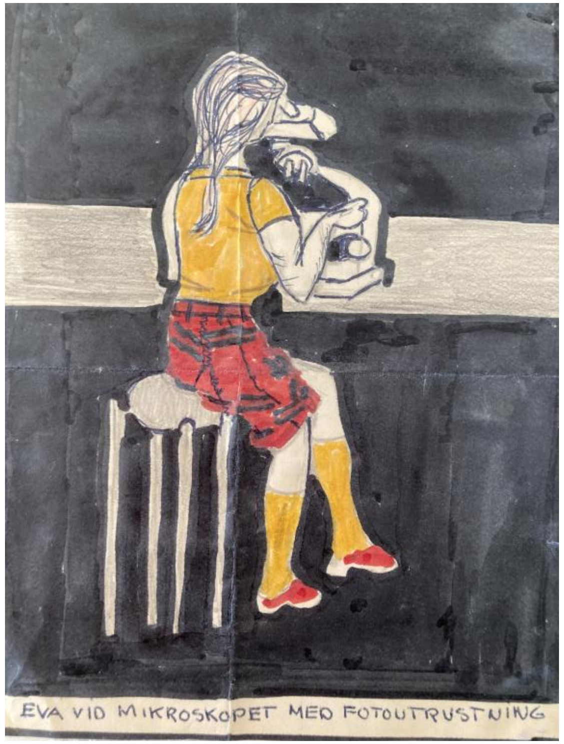


SPAF


pedagogiska
rapporter
umeå
nr 54 1976

SKELETTMUSKELFIBERKOMPOSITION, KAPACITET OCH INTRESSE FÖR OLIKA FYSISKA AKTIVITETER BLAND ELEVER I GYMNASIESKOLAN

Gudrun Hedberg
Eva Jansson

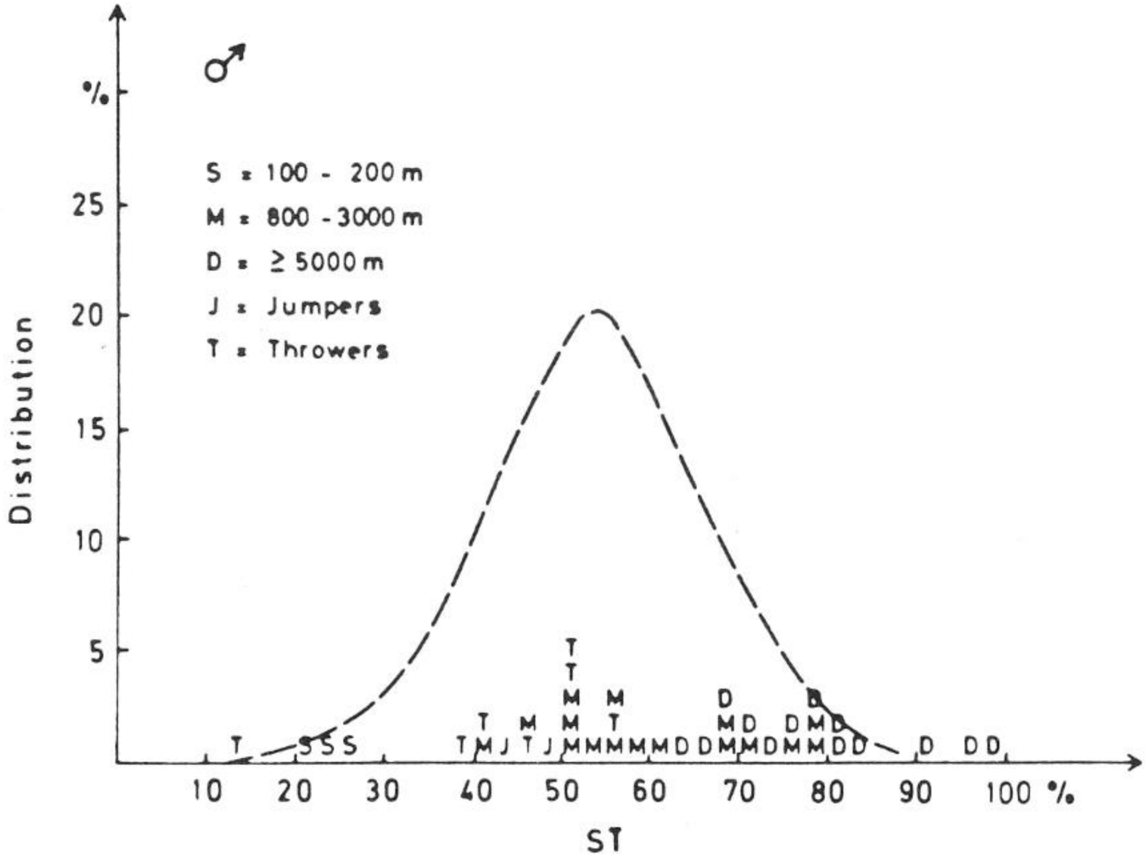


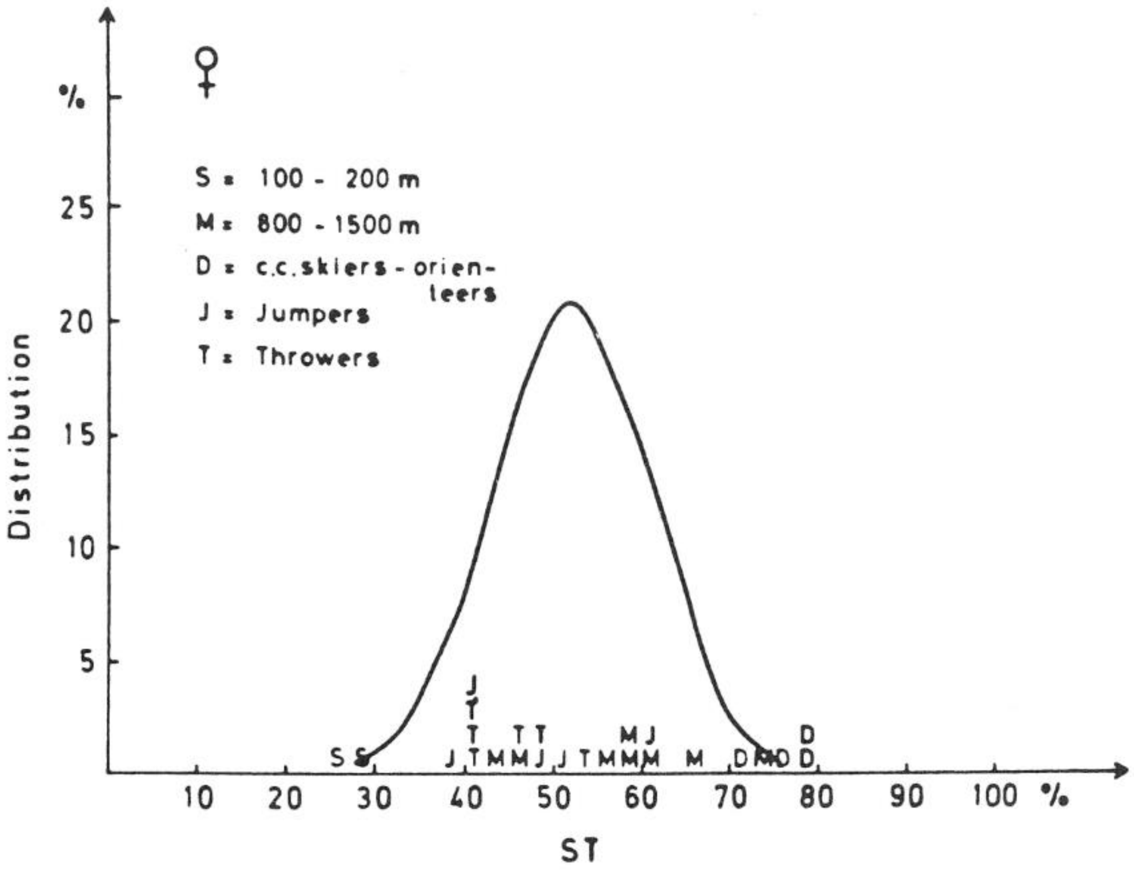
Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners.
B Saltin, J Henriksson, E Nygaard, P Andersen, E Jansson
Annals of the New York Academy of Sciences 301, 3-29, 1977

967 citeringar GS

Fiber type story:
Sprinters and long-distance runners within the population

Supports selection rather than adaptation ?





Hedberg, Jansson 1976, Saltin et al 1977, Jansson, Hedberg 1990

Large interindividual variations – factors of importance?

- Selection – hereditary factors - Yes
- Aerobic physical activity/inactivity – only small or no changes
- Extreme physical activity/inactivity – intermediate fibers Yes
  - Jansson Kaijser 1977
  - Jansson Sjödin Tesch 1978
  - Schantz, Billeter, Henriksson, Jansson 1983
- Hormones – testosterone, thyroid hormone, adrenergic stress - Yes
  - Celsing et al 1986 – Hyperthyroidism – decrease in typ 2 with treatment
  - Glenmark et al 1992 – Men -increase in typ 2 from 16 to 27 yrs
- Chronic disease – eg COPD - Yes
  - Hildebrand et al 1991 COPD – decrease in type 2 with treatment

Increase in intermediate fibers

- Elite orienteers

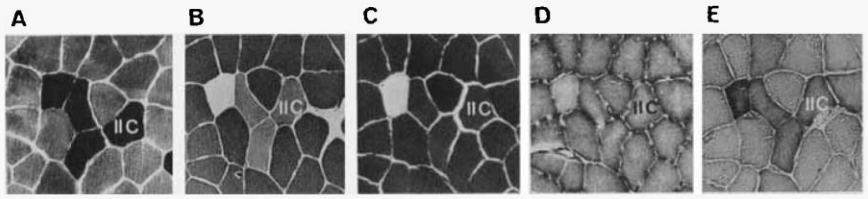


Fig. 2. Serial sections from vastus lateralis of an orienteer, stained for myofibrillar ATPase after preincubation at pH 10.3 (A), 4.3 (B) and 4.6 (C), NADH-dehydrogenase (D) and α-glycerophosphate dehydrogenase (E). Note the occurrence of IIC fibres.

- Elite runners – switch to anaerobic training

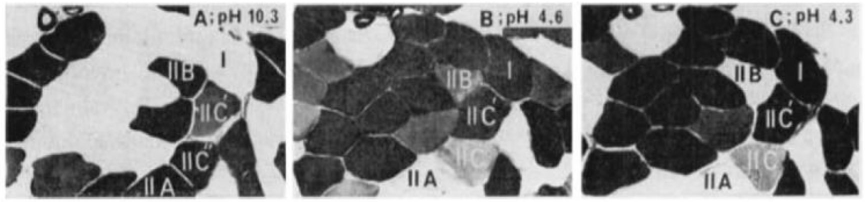


Fig. 2. Serial sections from vastus lateralis (subj. 1; anaerobic training) stained for myofibrillar ATPase after preincubation at pH 10.3 (A), pH 4.6 (B) and pH 4.3 (C). Type II C fibres with stain intensities similar to type I fibres (II C′) and to type II A fibres (II C″) are present.

- Skiing 1500 km in 8 weeks – triceps brachii

slow 1 – 1/2A (IIC) – 2A – 2A/2X - 2X fast

Intermediates

Jansson Kaijser 1977
Jansson Sjödin Tesch 1978
Schantz, Billeter, Henriksson, Jansson 1983

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Conclusions

- Fibre type transformations are possible in humans
- Aerobic training not the typical stimulus
- Still much unclear about stimulus and mechanisms

american physiological society
JOURNAL OF APPLIED PHYSIOLOGY
J Appl Physiol 136: 109–121, 2024.
First published November 23, 2023; doi:10.1152/japplphysiol.00337.2023

REVIEW

Fiber-type traps: revisiting common misconceptions about skeletal muscle fiber types with application to motor control, biomechanics, physiology, and biology

Silvia S. Blemker,[1]* Susan V. Brooks,[2]* Karyn A. Esser,[3]* and Katherine R. Saul[4]*

nature communications

Article
https://doi.org/10.1038/s41467-024-50632-2

Fibre-specific mitochondrial protein abundance is linked to resting and post-training mitochondrial content in the muscle of men

Received: 16 November 2023
Accepted: 16 July 2024
Published online: 03 September 2024

Elizabeth G. Reisman[1,2,13], Javier Botella[1,3,13], Cheng Huang[4], Ralf B. Schittenhelm[4], David A. Stroud[5,6,7], Cesare Granata[1,8,9,10], Owala S. Chandrasiri[1], Georg Ramm[11], Viola Oorschot[11,12], Nikeisha J. Caruana[1,5] & David J. Bishop[1]

sports 2021

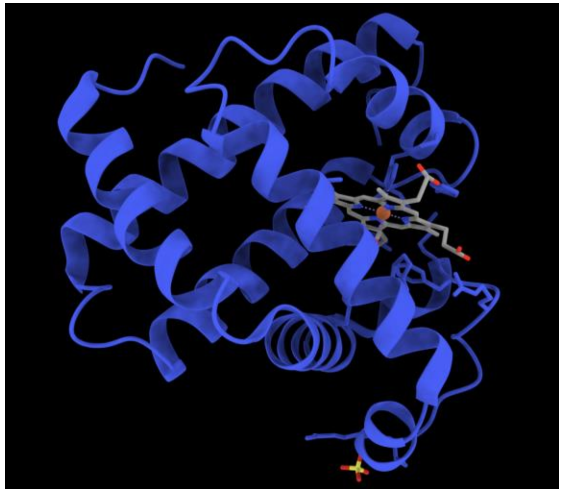
Review

Muscle Fiber Type Transitions with Exercise Training: Shifting Perspectives

Daniel L. Plotkin[1], Michael D. Roberts[2], Cody T. Haun[3,]* and Brad J. Schoenfeld[1]

Myoglobin story: – adaptations to exercise?

Role of Mb : temporary oxygen store, facilitate O2 - diffusion



What´s in the textbooks about training?

Discordant adaptation of myoglobin (Mb) and oxidative enzymes

- Skeletal muscle - Training

  oxidative enzymes increses

  Mb decreases ↓

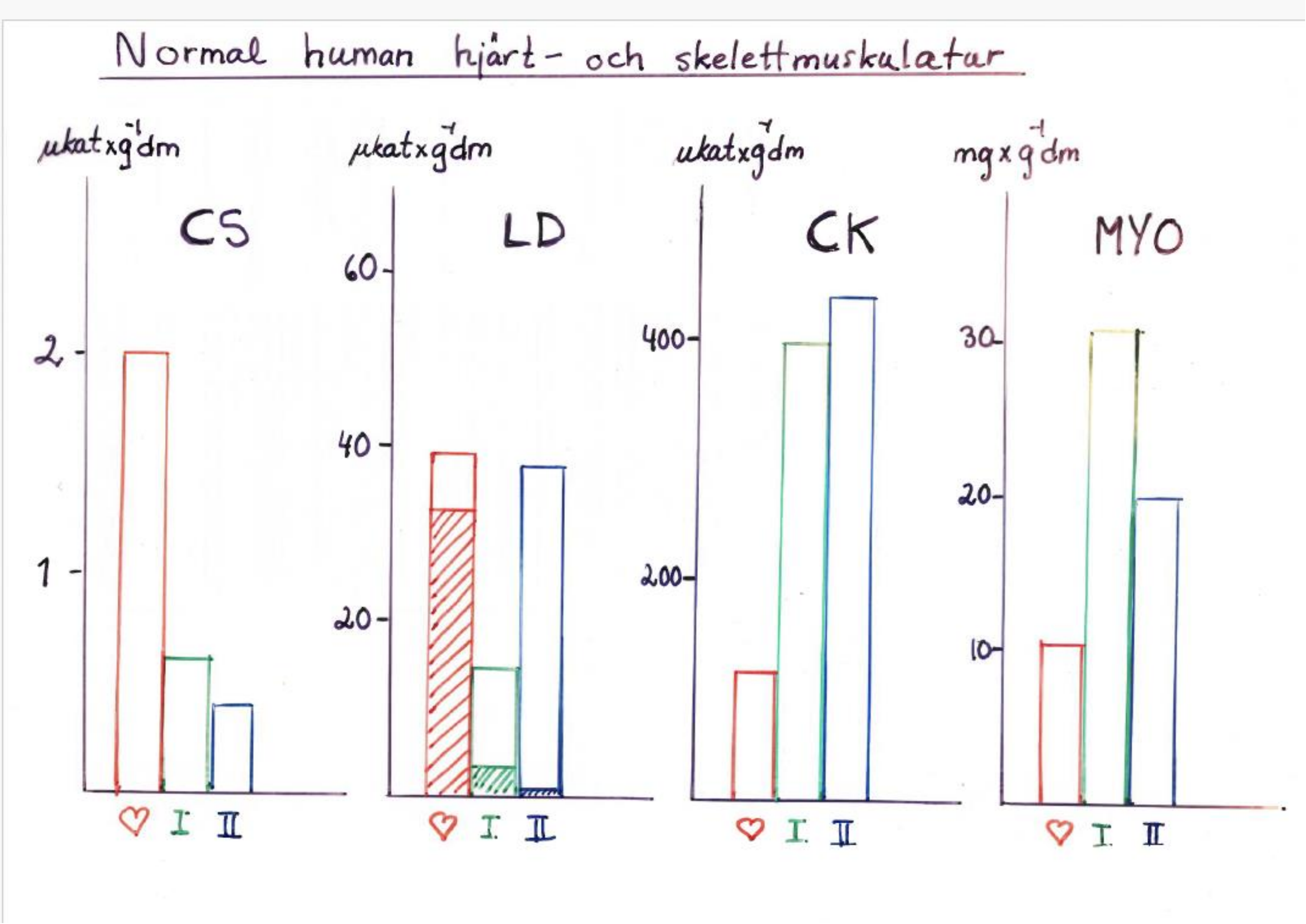
- Skeletal muscle - Immobilization

  oxidative enzymes decreases

  Mb increases ↑

Jansson et al 1982, 1988
Svedenhag et al 1983
Terrados et al 1986
Jacobs et al 1987

Myoglobin lower in heart than skeletal muscle



Jansson Sylvén 1983
Lin et at 1989
Lin et al 1990

Unclear role of myoglobin in skeletal muscle but our results have been confirmed

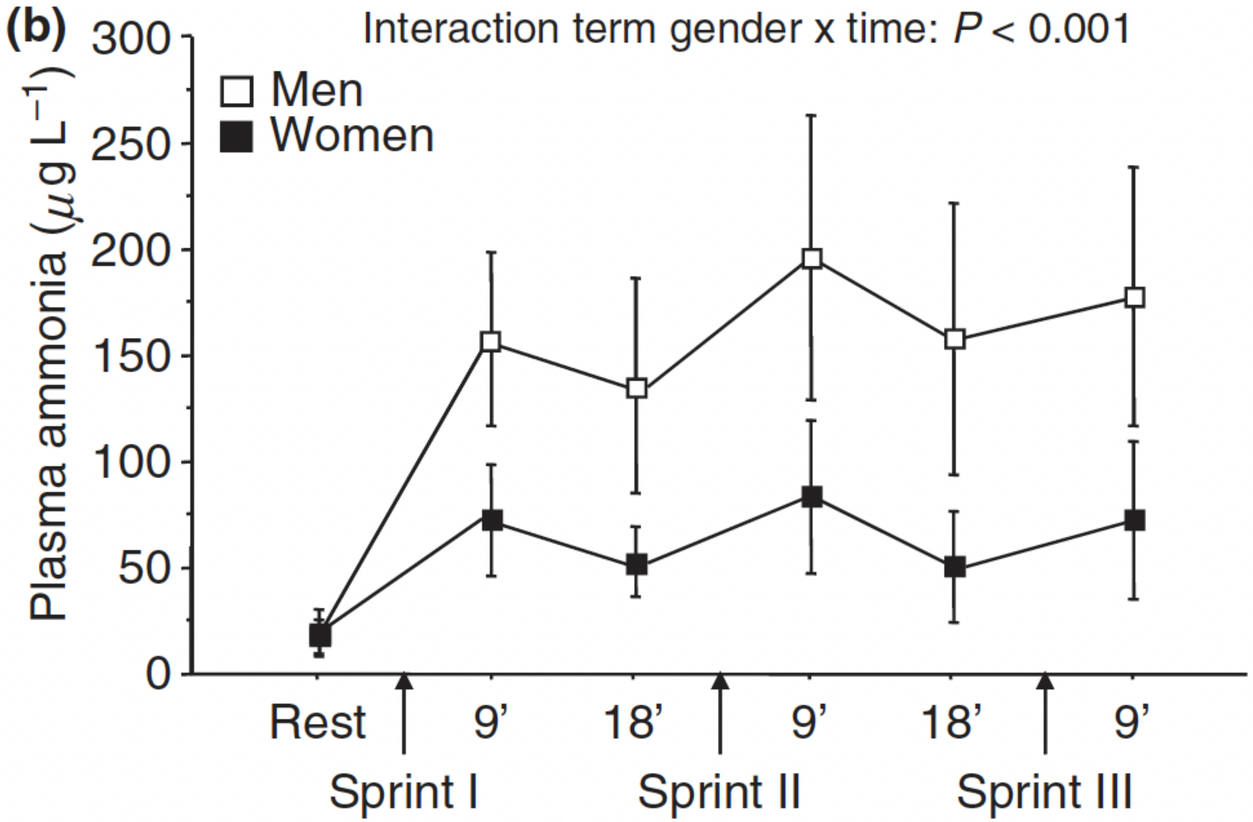
European Journal of Applied Physiology (2023) 123:1469–1478
https://doi.org/10.1007/s00421-023-05161-z

ORIGINAL ARTICLE

Low myoglobin concentration in skeletal muscle of elite cyclists is associated with low mRNA expression levels

Nina Jacobs[1,2] · Daniek Mos[1,2] · Frank W. Bloemers[3] · Willem J. van der Laarse[4] · Richard T. Jaspers[1,2] · Stephan van der Zwaard[1,2]

Ammonia story:
Why is plasma NH3 lower after sprint exercise in women?

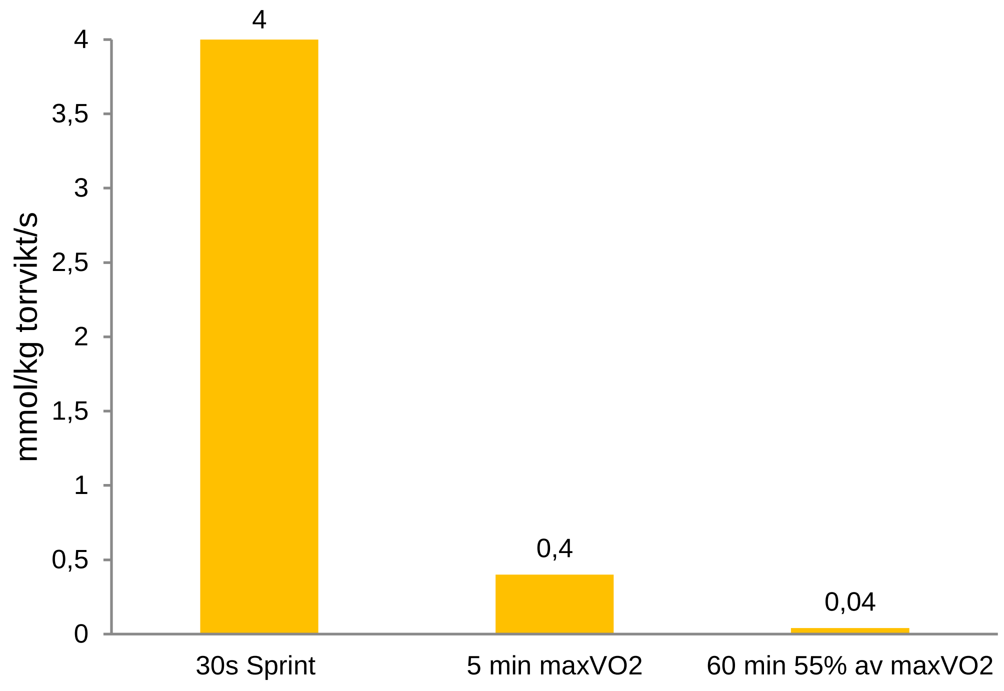


Production?

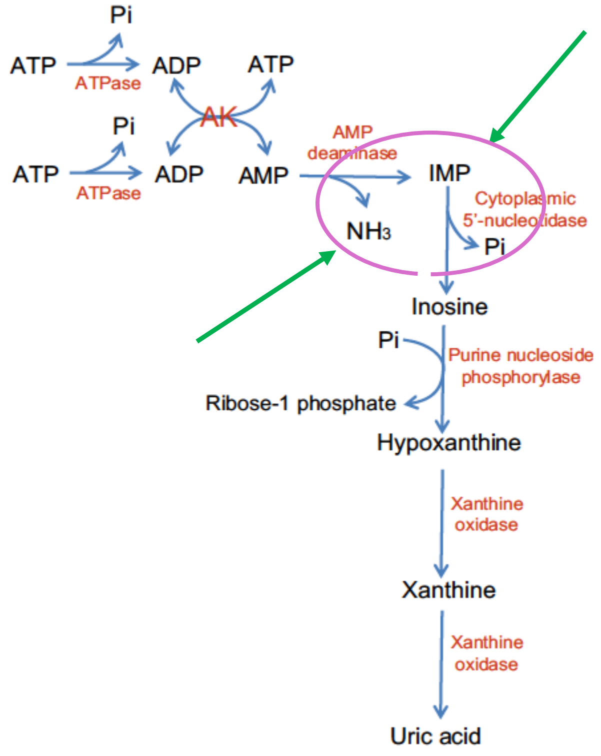
Elimination?

Esbjörnsson et al 2009

Sprint exercise – very high rate of glycogen depletion in type 2 fibres - energy chrisis? Starts to produce NH3 and IMP



Rate of glycogen depletion in typ 2 fibers



Large ATP depletion and IMP accumulation in type 2 fibers and similar in males and females

One 30-s sprint

Conclusion:
Females produced similar amounts of ammonia in type in 1 and in type 2 as males as based on accumulation of IMP

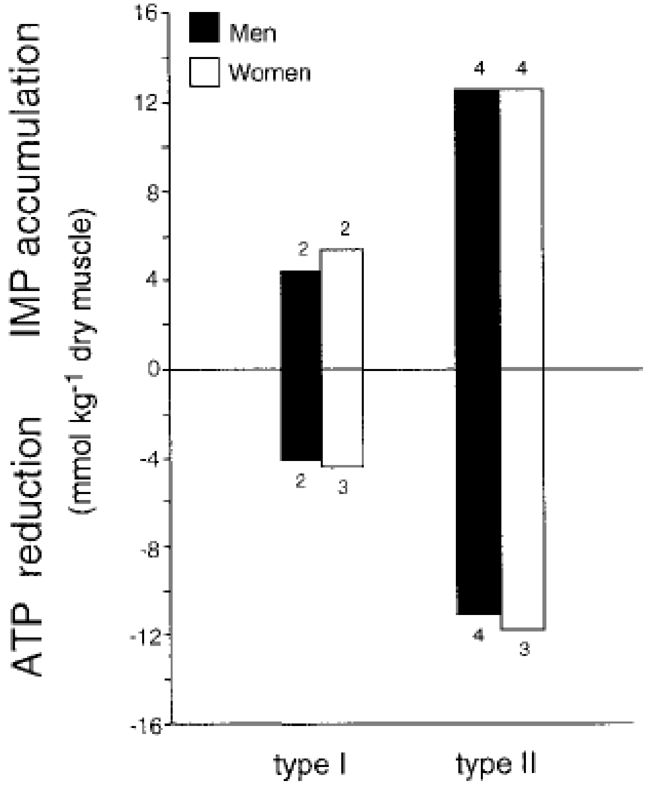


Fig. 2. Changes in muscle ATP and IMP content induced by 30-s sprint exercise in type I and type II fibers in 20 men and 18 women. Nos. within figure are SDs.

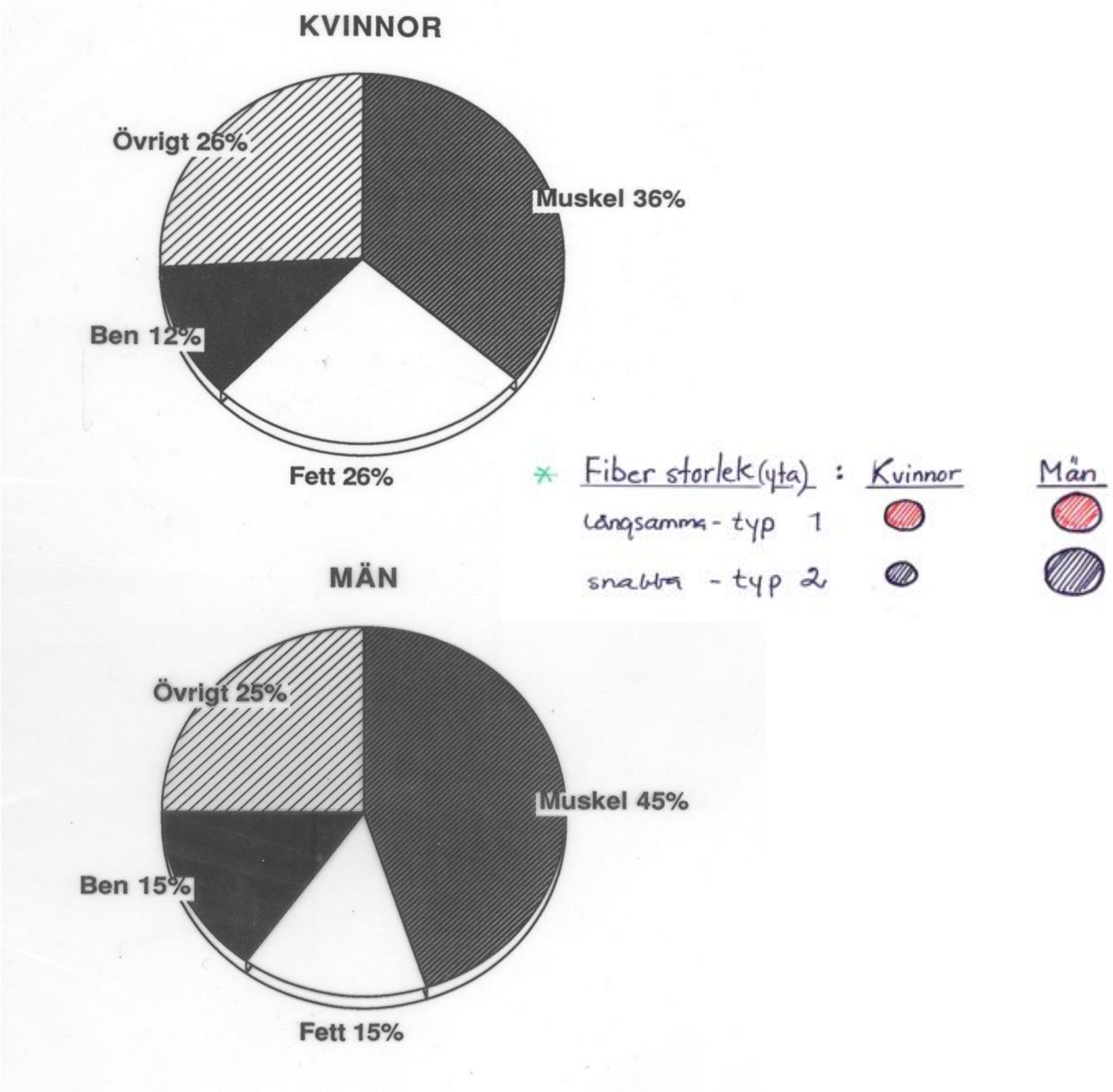
Esbjörnsson-Liljedahl et al 1999

Gender aspects -body composition

Females have:

1. smaller relative muscle mass
especially smaller relative type 2 area

2. larger relative fat mass
Fat might be a sink for e.g. ammonia



Hypothesis

- NH3 is temporarily buffered as glutamine in adipose tissue after SIT

$$\text{Glutamate} + \text{ATP} + NH_3 \rightarrow \text{Glutamine} + \text{ADP} + \text{phosphate}$$

RESULTS – the hypothesis was confirmed

Adipose tissue extracts plasma ammonia after sprint exercise in women and men

Mona Esbjörnsson, Jens Bülow, Barbara Norman, Lene Simonsen, Jacek Nowak, Olav Rooyackers, Lennart Kaijser and Eva Jansson

J Appl Physiol 101:1576-1580, 2006. First published 10 November 2005;
doi: 10.1152/japplphysiol.01119.2004

- AT biopsies
- Catheters: Subcut abdominal AT vein and artery

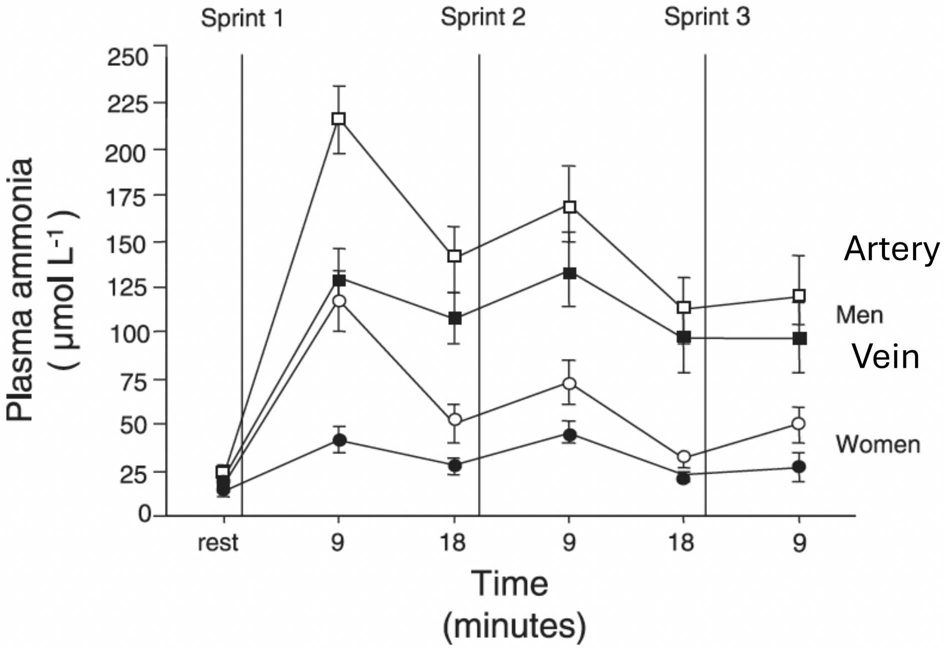
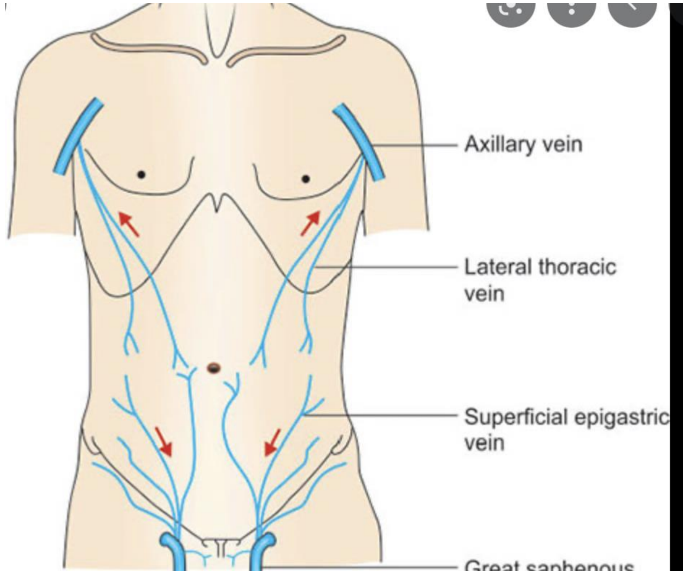


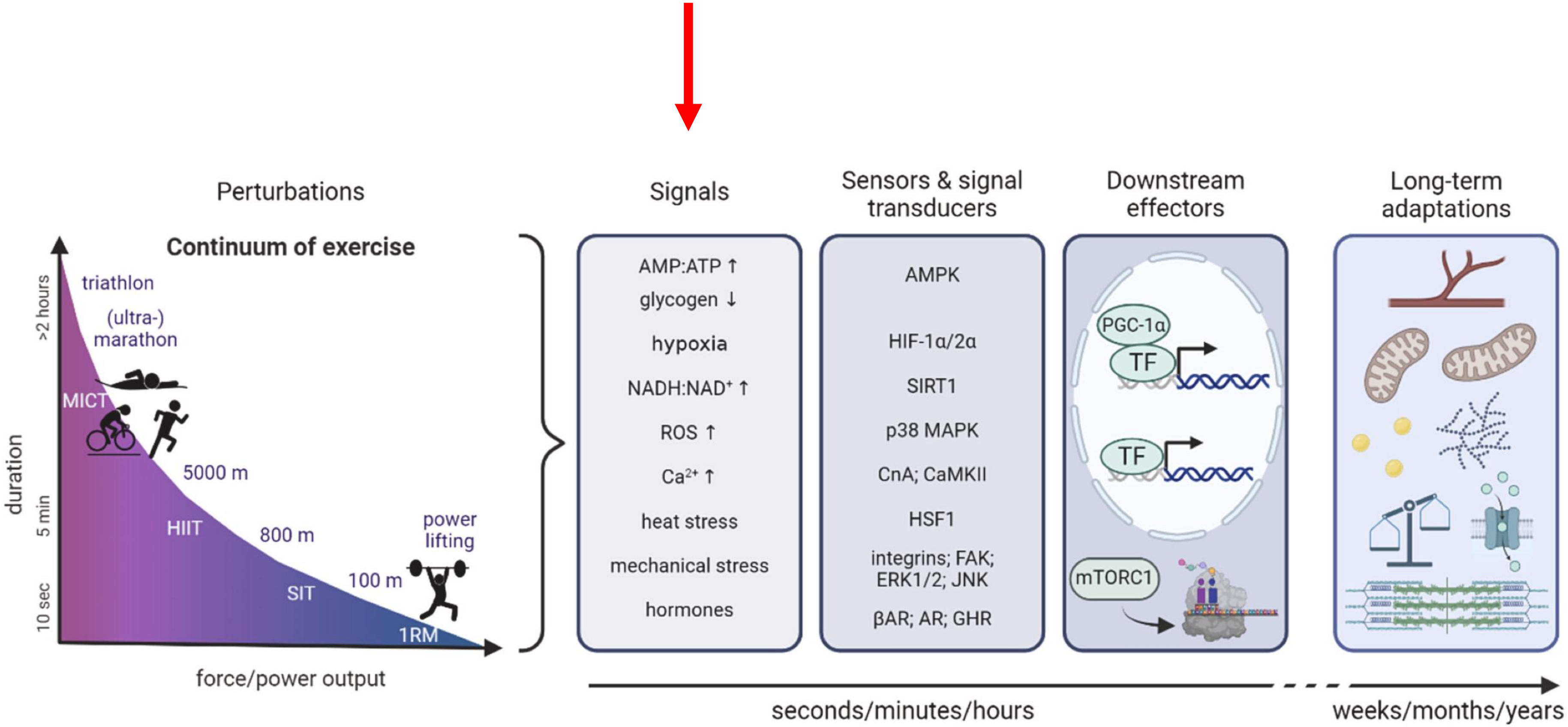
Fig. 3. Arterial and subcutaneous abdominal venous plasma NH_3 concentrations at rest and during recovery from sprint exercise in 6 men and 7 women. Open symbols, arterial concentrations; closed symbols, subcutaneous abdominal venous concentrations.



Why lower plasma NH_3 in women after sprint exercise ?

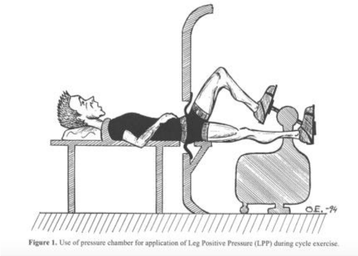
- Production similar between men and women in both fiber types
- Difference in body composition between men and women
- Adipose tissue a temporary buffer of NH_3 – women have more fat

Metabolic adaptation – stimulus

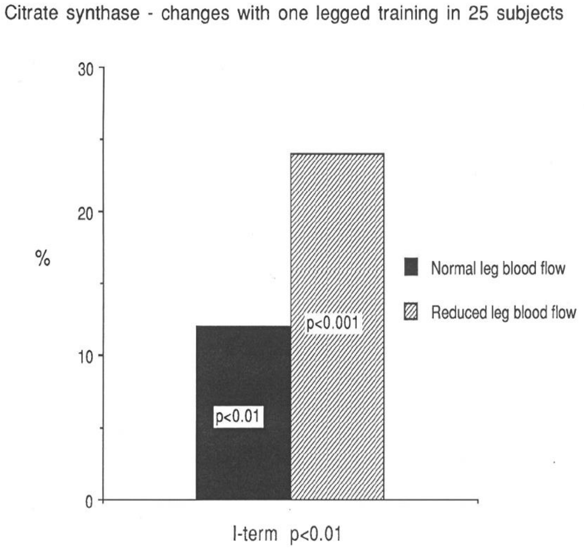


Furrer and Handshin et al 2024

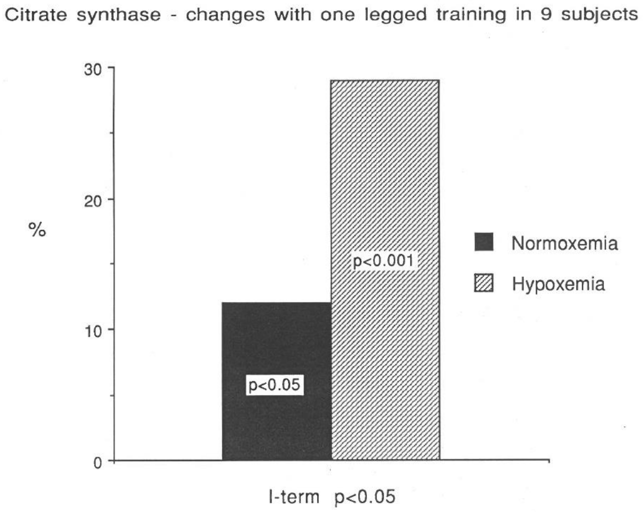
Stimulus - oxygen turnover or hypoxia/ischemia?
Skeletal muscle



Hyperbaric condition in a pressure chamber



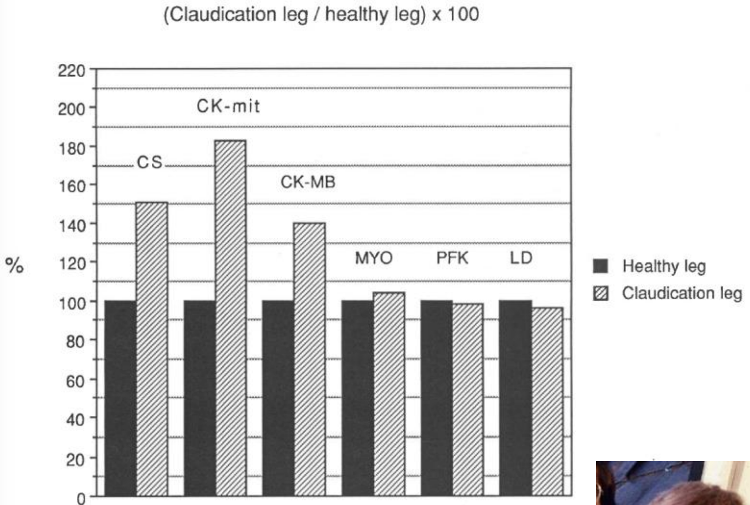
Kaijser et al 1990
Esbjörnsson et al 1993



Terrados et al, J Appl Physiol, 1990.68.2369-2372.

Hypobaric condition in a pressure chamber

Individuals with one-leg claudication



Jansson et al, Clin Physiol, 1988.8.17-29.

Stimulus - oxygen turnover or hypoxia/ischemia? Heart muscle

1300 *Cardiovascular Research* 1993;**27**:1300-1305

Increased expression of the lactate dehydrogenase M subunit in myocardial regions with decreased thallium uptake

Lijun Lin, Lennart Kaijser, Jan Liska, Christer Sylvén, Alf Holmgren, Katarina Lindström, and Eva Jansson

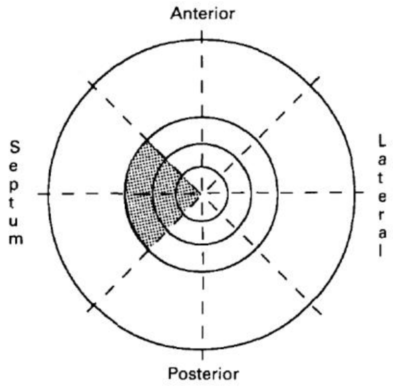


Figure 1 *Polar map of left ventricular myocardium. Hatched area indicates the region (20.8 pixels) within which the biopsy was taken during surgery.*

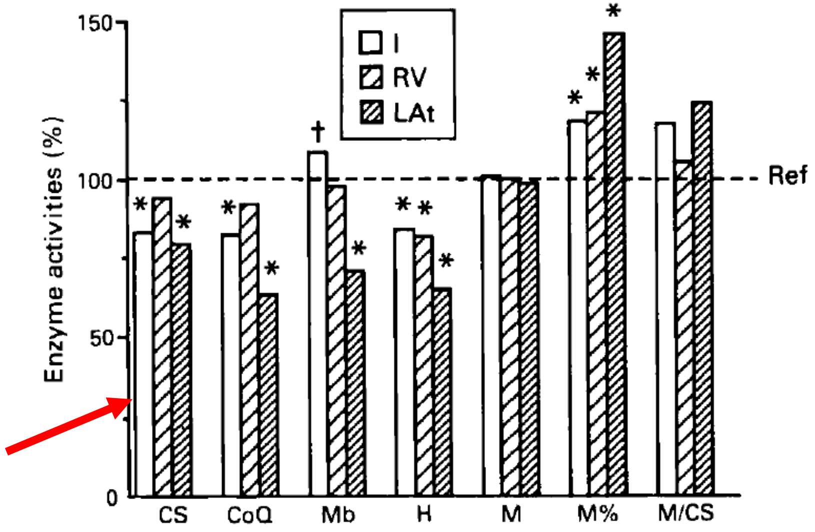
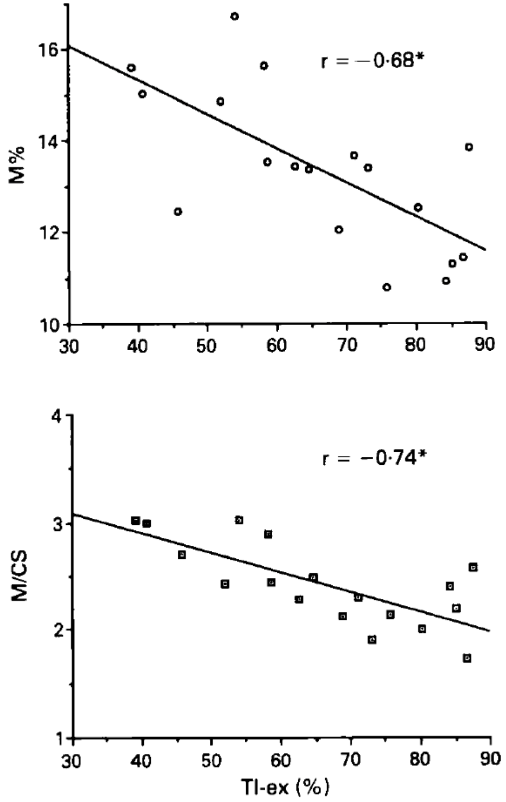


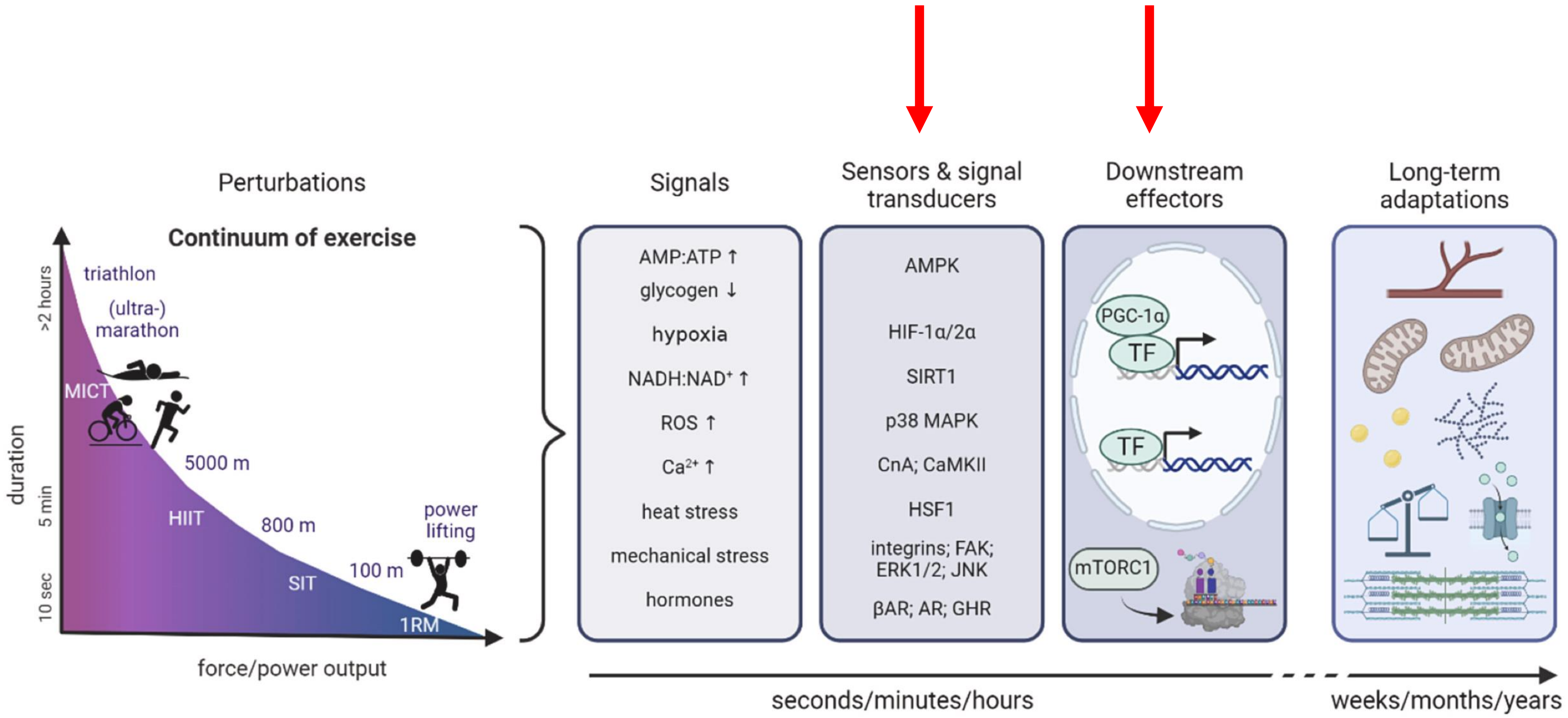
Figure 3 *Enzyme activities in the septal region (biopsy site) of the patients with low Tl-ex and redistribution >50% (ischaemic (I) group) and in the right ventricle (RV) and left atrium (LAt) of the reference (Ref) group expressed as % of the septal region of the Ref group (---).*
**p<0.05 v Ref group.*



Hypoxia and ischemia as stimulus for oxidative capacity

- Skeletal muscle: Yes
- Heart muscle: No

Metabolic adaptation - mechanisms

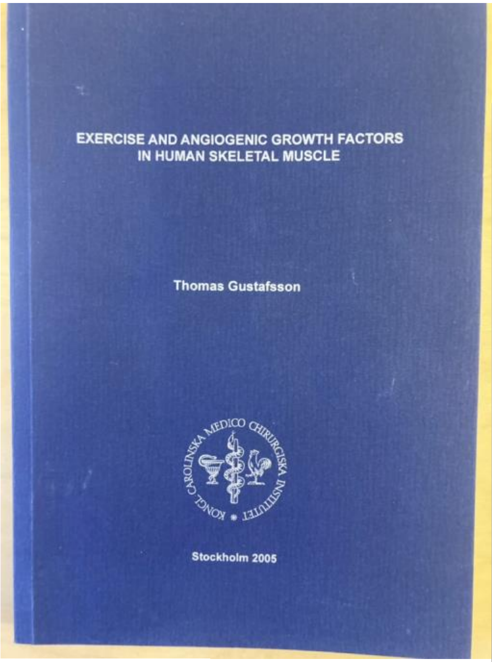


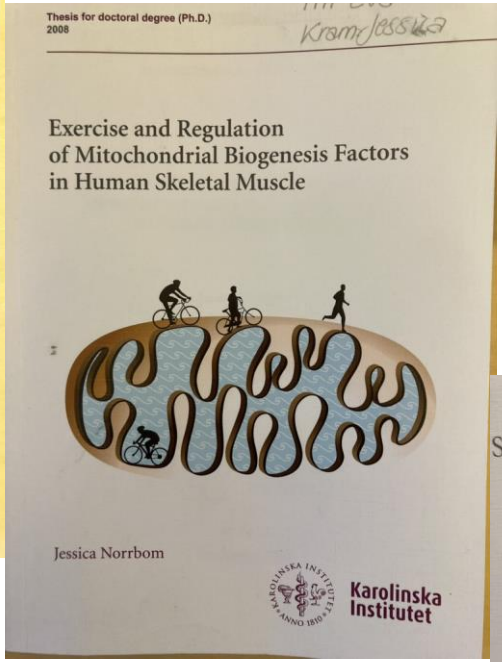
Furrer and Handshin et al 2024

Theses - mechanisms - adaptation

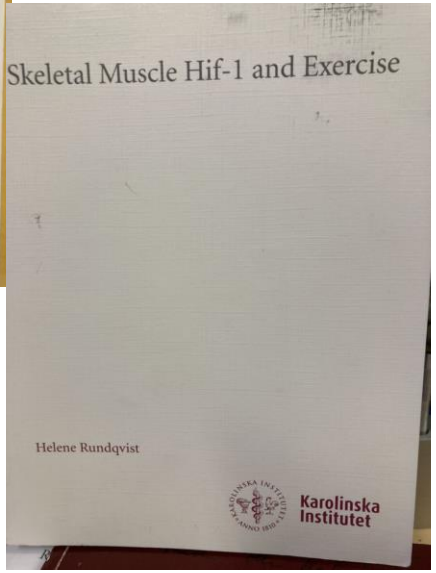
ER is increased in trained muscle

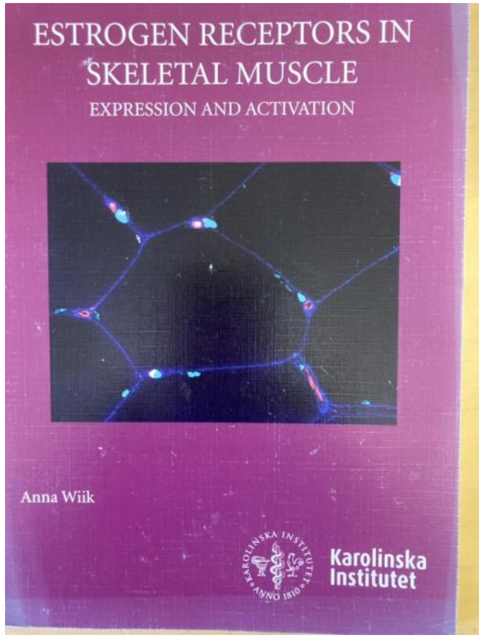
VEGF

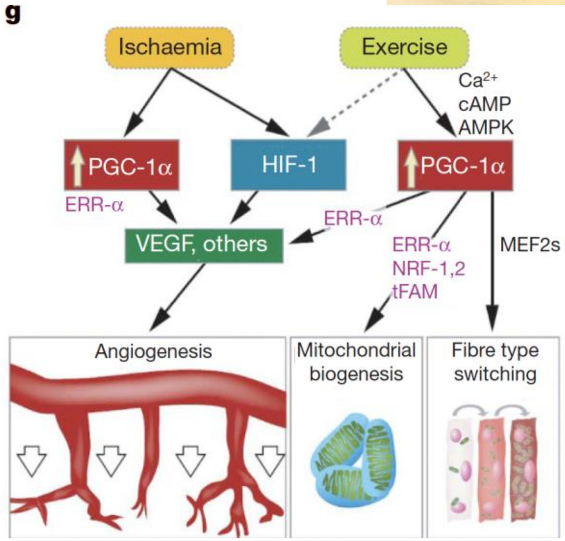




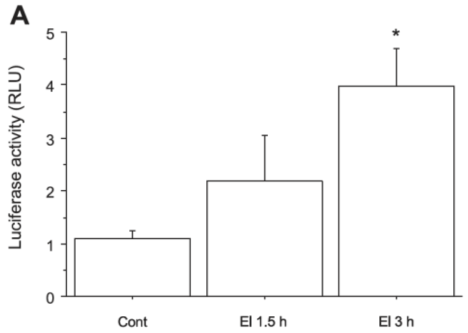
HIF-1







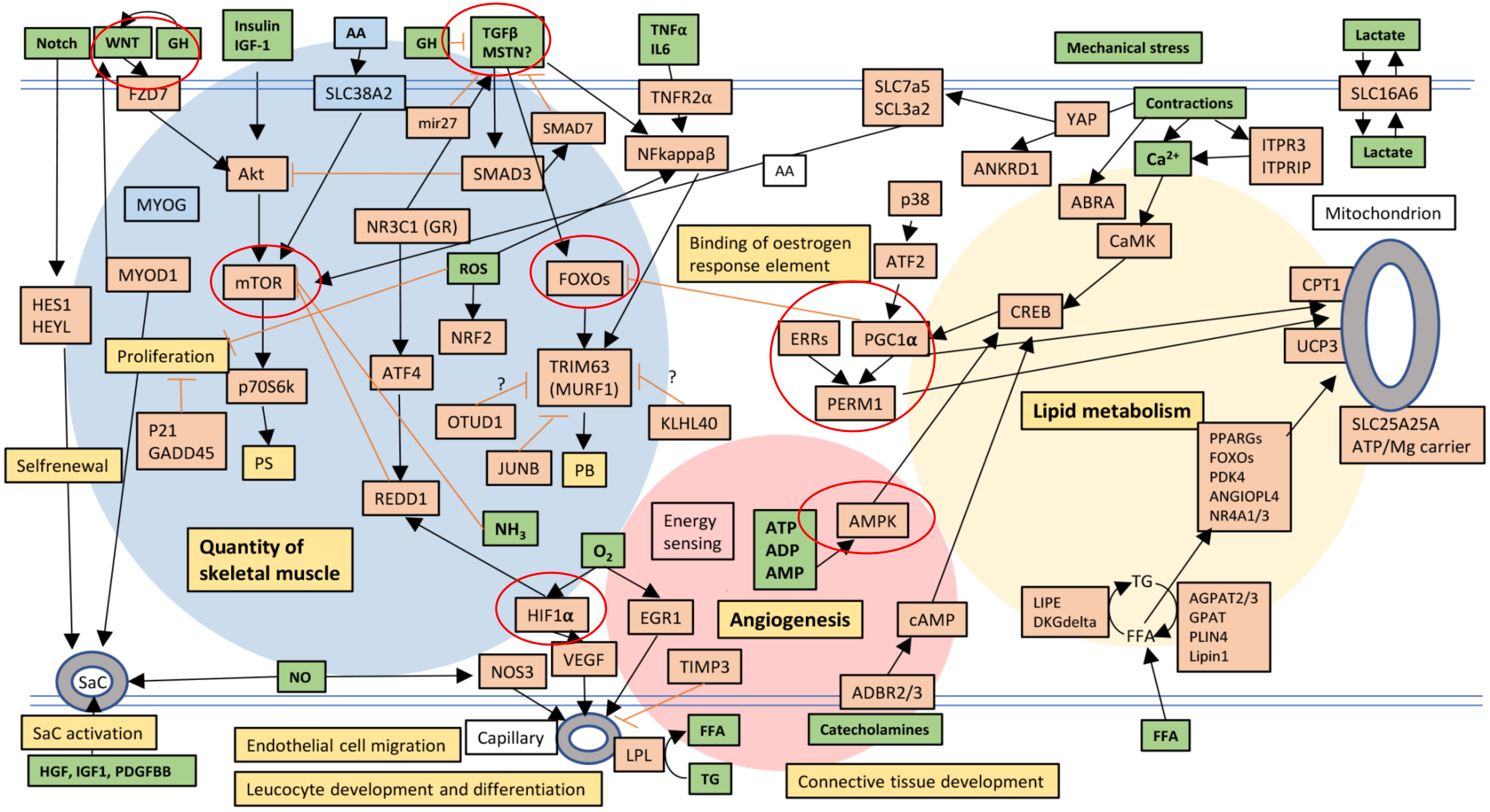
PGC-1



Nature letter Arany et al 2008 – ischemia and exercise

ERE is activated by both estrogen and by muscle contractions

Sprint exercise signalling – PGC-1,ERR, PERM1, HIF, VEGF



PERM1: PGC-1 and ERR induced regulator, muscle 1

Rundqvist et al 2019 PLOS ONE | https://doi.org/10.1371/journal.pone.0223024

New publication – supports the role of ERR

ERRs co-ordinate gene expression programes that regulate mitochondrial biogenesis and oxidative capacity

Mol Metab. 2023 Feb; 68: 101670.
Published online 2023 Jan 13. doi: 10.1016/j.molmet.2023.101670

PMCID: PMC9938320
PMID: 36642217

Loss of skeletal muscle estrogen-related receptors leads to severe exercise intolerance

Jean-Sébastien Wattez,[1,5,8] Elodie Eury,[1,2,6,8] Bethany C. Hazen,[2] Alexa Wade,[1] Sarah Chau,[1,7] Shu-Ching Ou,[1] Aaron P. Russell,[3] Yoshitake Cho,[2,4] and Anastasia Kralli[1,*]

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Ongoing activites

- Adipose tissue – response to sprint exercise – health effects VO2max, insulin sensitivity, body fat mass – e.g. Jens Bülow

- SPAF – follow-up at age 63 and 68 - Life time changes and ageing – sarcopenia related questions - Maria Westerståhl, Thomas Gustafsson, Brun Ulfhake and others

- Exercise training in clinical settings – reumatic systemic diseases such as SLE and systemic sclerois – Carina Boström and others

Increased lipolysis gives increased TG-FA cycling, i.e. increased thermogensis

K N Frayn • **Adipose tissue–muscle interaction**

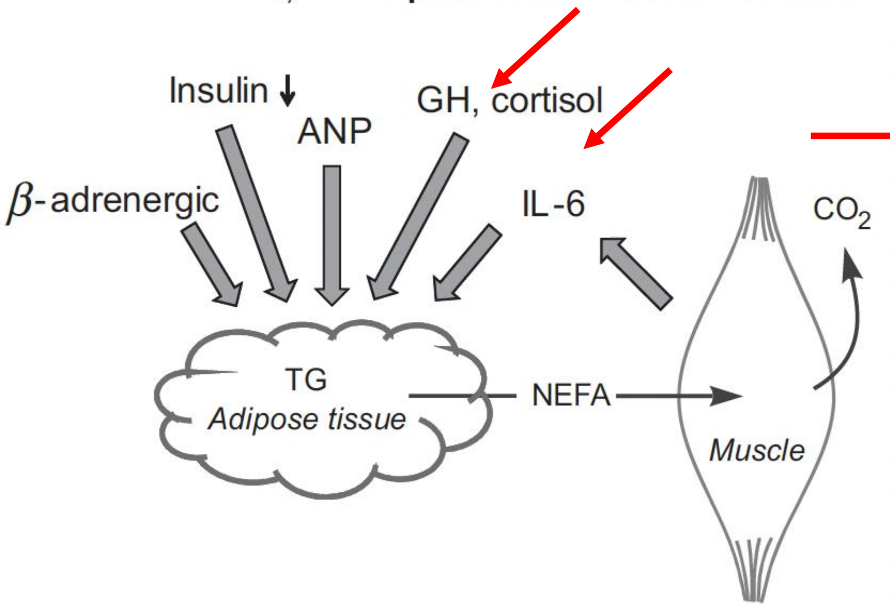


Figure 2 Potential stimuli to fat mobilization during exercise. The individual stimuli are discussed further in the text. ANP, atrial natriuretic peptide; GH, growth hormone; IL-6, interleukin-6; TG, triacylglycerol.

Frayn 2010

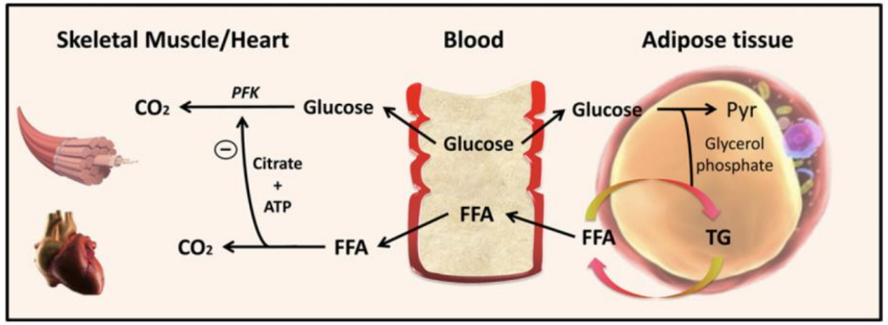


Figure 2 The glucose–fatty acid cycle (the Randle cycle) proposed by Randle, Garland, Hales and Newsholme first described in 1963

TG/FFA cycle – a thermogenic process 7-9 ATP per cycle

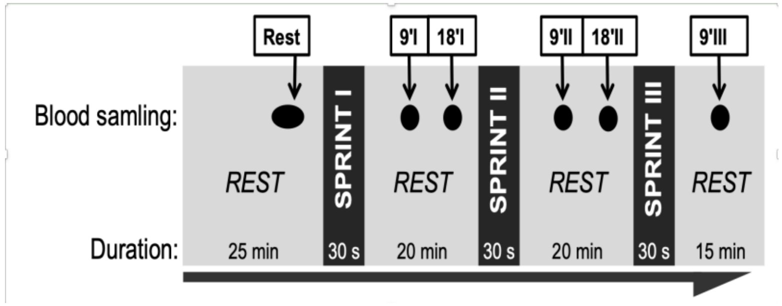
TABLE 2. *Energy cost of TG-FA cycle*

	kcal/h	% Energy Expenditure	% Increase Above Rest
Rest	0.8	1.2	
Exercise	1.7	0.4	0.5
Recovery	4.7	3.6	13.7

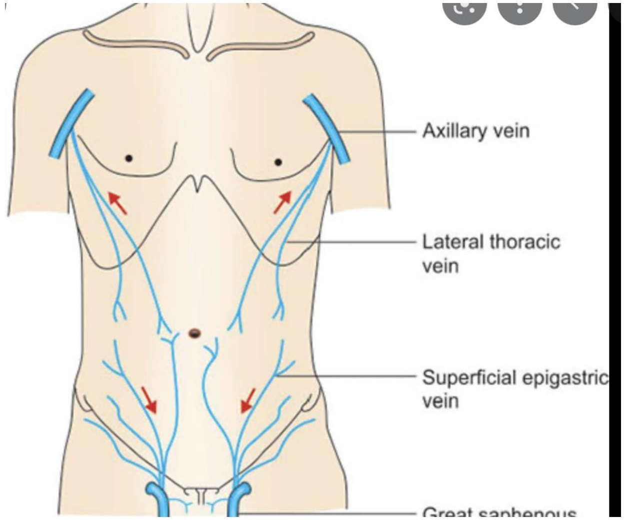
Wolfe et al 1990

Methods to study abdominal subcutaneous AT

- Biopsies
- Vein catheter – measure a-v diff
- Blood flow – xenon 133 clearence



First publication



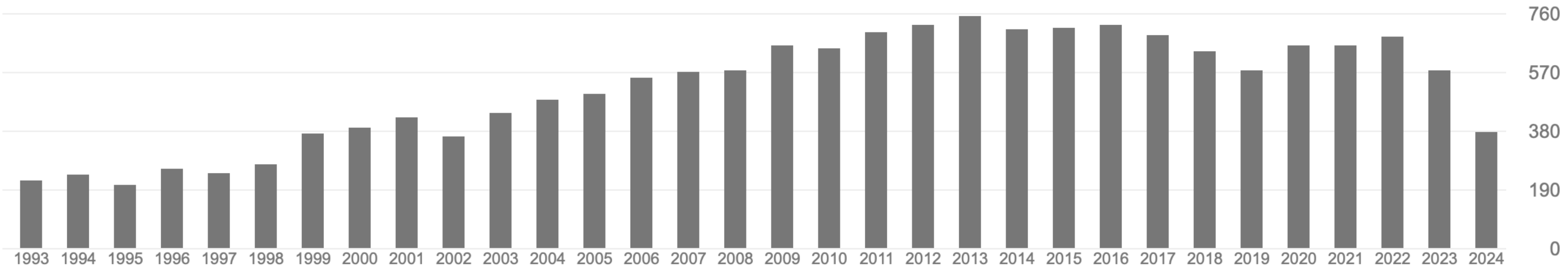
Sprint exercise

- Incresed release of glycerol
- Increased release of IL-6

Esbjörnsson et al 2023

Bibliometry

- 200 publications in peer reviewed journals
- 20 000 citations and 10 citations/w (Google Scholar)
- Last 5 years – 2 citations/day
- Highly cited
- Low cited



”Important” papers – and citations – high - low

- JOURNAL ARTICLE: ACTA PHYSIOLOGICA. 1975;95(2):153-165

METABOLIC CHARACTERISTICS OF FIBER TYPES IN HUMAN SKELETAL-MUSCLE

ESSEN B; JANSSON E; HENRIKSSON J; TAYLOR AW; SALTIN B – 829 citations

- JOURNAL ARTICLE: CARDIOVASCULAR RESEARCH. 1993;27(7):1300-1305

INCREASED EXPRESSION OF THE LACTATE DEHYDROGENASE-M SUBUNIT IN MYOCARDIAL REGIONS WITH DECREASED THALLIUM UPTAKE

LIN L; KAIJSER L; LISKA J; SYLVEN C; HOLMGREN A; LINDSTROM K; JANSSON E – 4 citations

- JOURNAL ARTICLE: JOURNAL OF APPLIED PHYSIOLOGY. 1990;69(3):899-901

MYOGLOBIN CONTENT AND CITRATE SYNTHASE ACTIVITY IN DIFFERENT PARTS OF THE NORMAL HUMAN HEART

LIN L; SYLVEN C; SOTONYI P; SOMOGYI E; KAIJSER L; JANSSON E - 29 citations

Slump – tillfälligheter som leder till nya upptäckter snarare än hypoteser som bekräftas - exempel

- Intermediära fibrer – grå fibrer – trodde att färgningen inte fungerade

- Låga glykogenvärden efter kolhydratuppladdning – en viss typ av glykogen hade läckt ut i syran som användes för att extrahera ATP och laktat - olika typer av glykogen med olika syralöslighet.

- AMP-deaminasbrist hos friska – vi trodde att HPLC inte fungerade

Något jag ångrar/ gjort annorlunda/nöjd med?

- Reviews – stannat upp mer reflektion
- Bredd och djup – balans?
- Jobba mer aktivt med att synliggöra forskningen
- FYSS – projektet – translationell aktivitet från forskning till allmänheten – spec hälso- och sjukvården och utbildning

YFA – 25 år

www.efyss.se

YFA = Yrkesföreningar för Fysisk Aktivitet

Tack

- Centrum för Idrottsforskning men många fler anslagsgivare
- GIH, Karolinska Institutet och Karolinska sjukhuset
- Avd för klinisk fysiologi
- Alla medarbetare
- Alla forskningspersoner
- Familjen