- Note that the opinions expressed within the abstracts and presentations are those of the authors/presenters alone and do not necessarily reflect the opinions of WADA.

The 2nd WADA Symposium on Gene Doping

December 2005

Karolinska Institutet Stockholm

Human training and

skeletal muscle gene activation

Carl Johan Sundberg

Dpt Of Physiology & Pharmacology

Karolinska Institutet, Stockholm

- ADAPTATION TO REGULAR ENDURANCE TRAINING

Effects on organ systems/tissues

- Heart
  - Bigger – greater stroke volume
  - Increased maximal cardiac output

- Blood vessels (in the heart & those skeletal muscles that have been trained):
  - More capillaries
  - Improved dilatory capacity

Effects on organ systems/tissues

- Blood
  - Increased total amount of red blood cells
  - Even larger expansion of plasma volume
    - → => reduced blood count in a blood sample
- Adipose tissue
  - Reduced amount
- Connective tissue/bone/cartilage
  - Increased amount/strengthened

Effects on organ systems/tissues

- Endocrine system
  - Insulin sensitivity
  - Catecholamine & Growth hormone responses to exercise
- Skin
- Immune system
- Lungs
- Nervous system/brain

Effects on skeletal muscle

- ↑ # & volume of mitochondria
- ↑ capillary amount

- ↑ glycogen storage
- ↑ insulin sensitivity/ glucose transport capacity
- ↓ proportion of type IIb/x-fibres

What factors regulate human muscle performance ?

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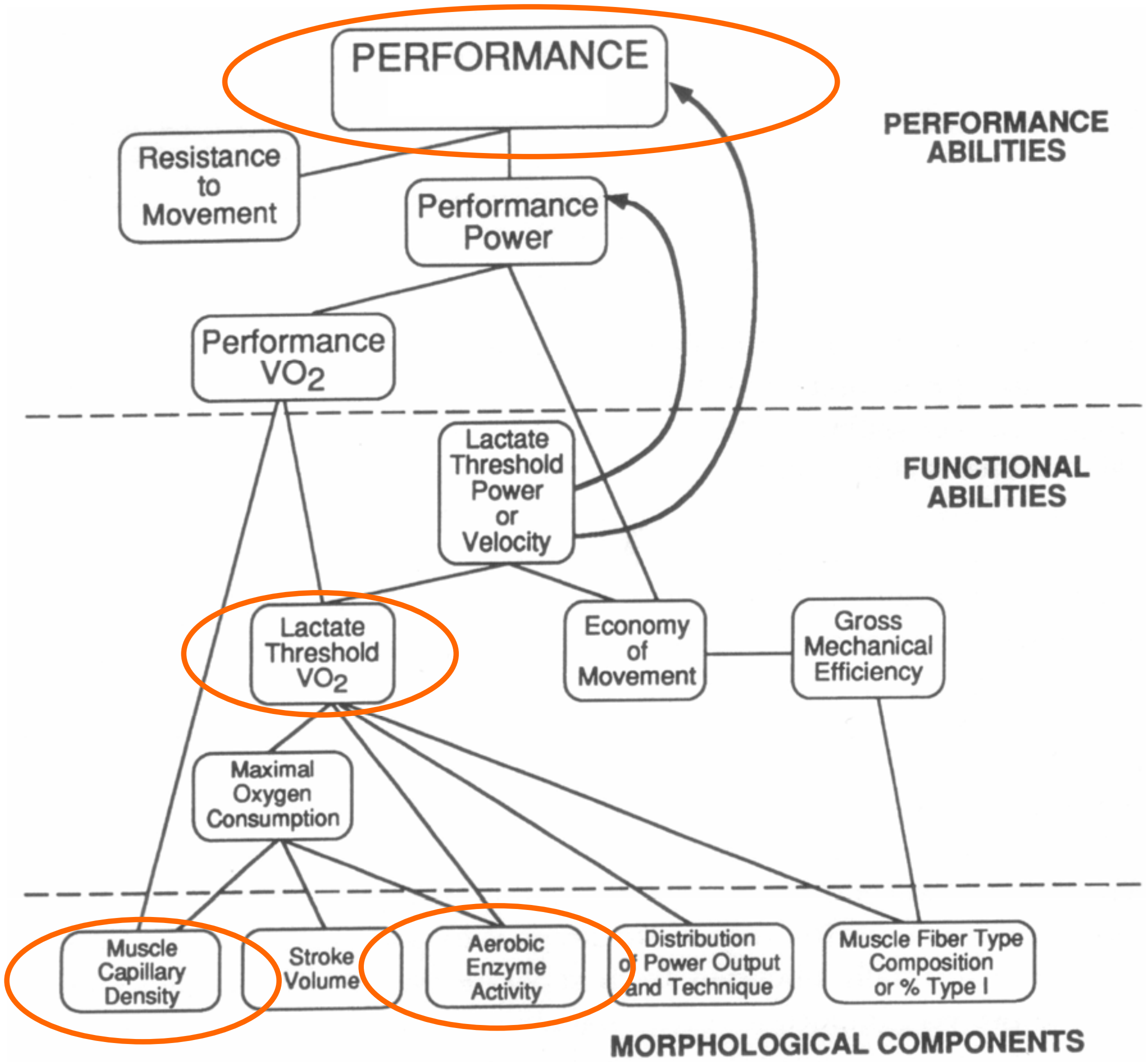
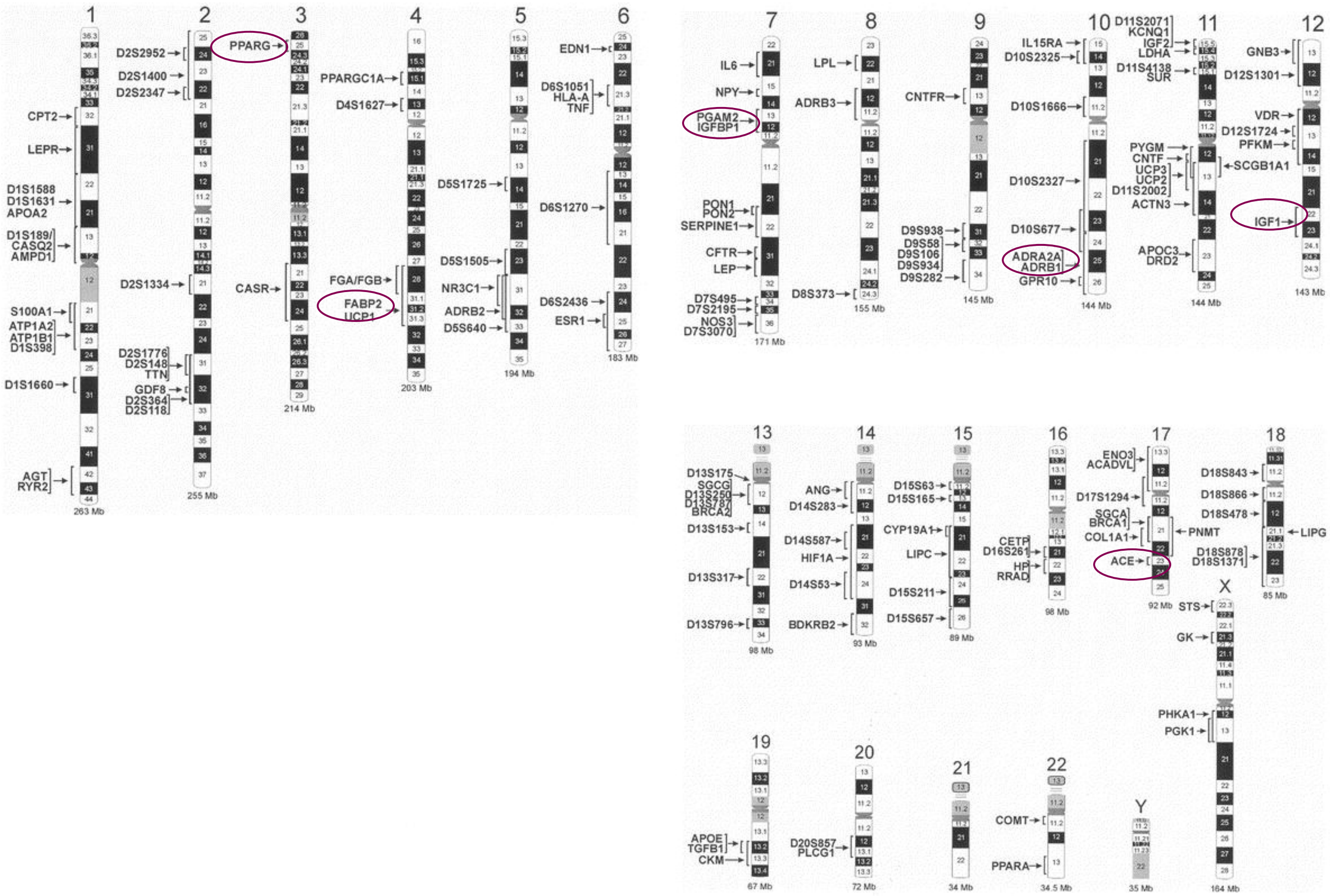


Coyle, E ESSR 1995

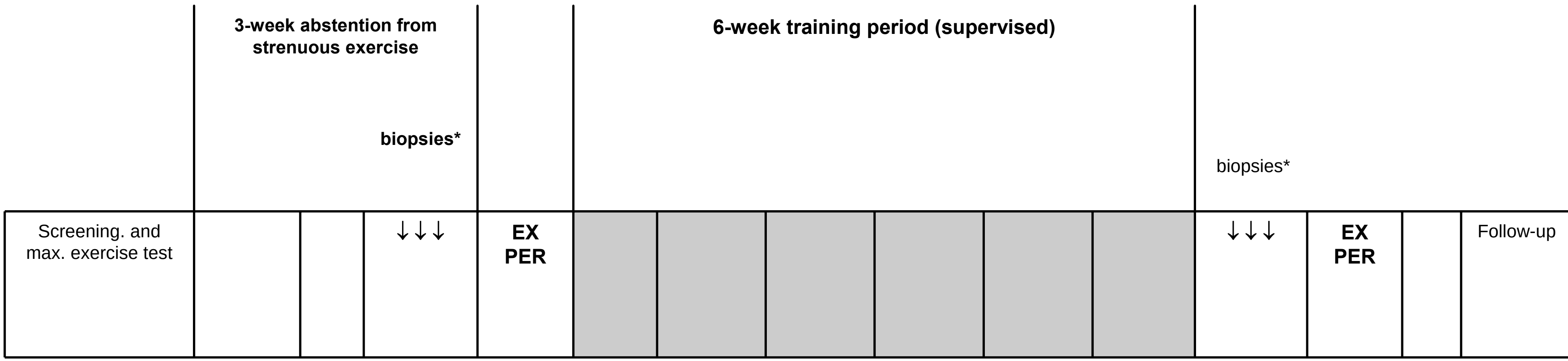
What factors regulate human muscle performance – genes ??



- No agreement yet on ‘key genes’ using population genetics
- Difficult to validate – separate population studies required

Bouchard, C et al 2005

Generating a human endurance ‘transcriptome’



- 24 sedentary subjects - 4 training days/week – 45min of cycling@ 75% of **<u>pre-training</u>** VO2max
- 240 muscle biopsies, 20 biochemical endpoints, Affymetrix U95 platform and >500 significant gene changes 24hr post exercise
- Physiological adaptation was quantified as:
  - A. % improvement in peak aerobic capacity
  - B. % reduction in Heart rate response
  - C. % improvement in work done during 15min cycle

- Top 8 subjects (A+B+C) used for Affymetrix analysis

Timmons *et al FASEB J* 2005

> 500 genes 'activated' by exercise in humans

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A2M	CaMKIINalpha	DDR2	GJA1	LAMP1	OAS1	S100A13	TRDN	60050_at
ACLY	CAP1	DHRS8	GLS	LAP1B	OLFML2A	S100A4	TREM4	62263_at
ACTA2	CAPN3	DKFZP434B044	GLUL	LASP1	OLFML2B	SCN4B	TRIB1	62480_at
ACTB	CAV1	DKFZp434B1231	GNA12	LDHB	OSRF	SCOTIN	TUBA3	62539_at
ACTC	CAV2	DKFZp434L142	GNAI2	LGALS1	OTUD1	SDPR	TUBB	62594_at
ACTG1	CCDC3	DKFZp564I1922	GNB1	LGALS3	PABPC1	SEMA3C	TXNDC5	63296_at
ACTN1	CCND1	DKFZP564O0823	GNG11	LHFP	PALM2	SERPING1	TYROBP	64084_at
ACTN2	CD164L1	DKFZP566K1924	GPAM	LILRB1	PC326	SERPINH1	UBE2G1	65114_at
ACTN3	CD34	DKFZp761C169	GPNMB	LIM	PCDH18	SESN1	UBE2S	65904_at
ACTN4	CD81	DLC1	GPR124	LNK	PCOLCE2	SESN3	UCP2	67792_r_at
ADAMTS5	CDH5	DMD	GPR34	LOC162073	PDGFRB	SFRP2	UCP3	71786_at
ADAR	CDW92	DNCL1	GPX3	LOC283241	PDK4	SH3BGRL	URB	72674_at
ADD3	CFL1	DPYSL2	GRP58	LOC339924	PDLIM3	SH3BGRL3	USP13	72728_at
AGTRL1	CGI-121	DSTN	GSN	LOC387763	PEA15	SIPA1L2	UTRN	73441_at
AMPD1	CHST1	ECM2	GUCY1A3	LOC388962	PECAM1	SLC20A2	VAT1	74566_at
ANGPTL2	CIDE-3	ECRG4	HBAP1	LOC51668	PFN2	SLC38A1	VDP	75430_r_at
ANKRD1	CKLFSF6	EDIL3	HBB	LOXL1	PHKG1	SLC41A1	VIM	75969_f_at
ANTXR1	CLDN5	EEF1A1	hIAN2	LOXL2	PHLDB2	SMOC2	VWF	76236_r_at
ANXA1	CLIC1	EFHD2	HIPK3	LPL	PLAC9	SNRPN	WSB1	77207_at
ANXA2	CLIC4	EHD2	HLA-B	LUM	PLN	SOX4	YWHAQ	78727_at
ANXA2P3	CLU	EIF4A1	HLA-C	MADH1	PLS3	SOX7	ZAK	79933_at
ANXA5	CMIP	ELOVL5	HLA-DPB1	MAFB	PLSCR4	SPARC	ZC3HAV1	83026_i_at
AOC3	CMYA5	ELTD1	HLA-DRA	MAGED2	PLTP	SPARCL1	ZFP36	85922_r_at
APOE	CNK2	EMCN	HLA-DRB1	MALAT-1	PLVAP	SPIN	ZFP36L2	90557_at
APP	CNN3	EMP3	HLA-F	MARCKS	PODN	SPON2	ZNF145	
ARHGAP1	CNNM3	ENG	HN1	MEOX2	PORIMIN	SPP1	1164_at	
ARHGAP8	COL15A1	ENPP2	HSPC121	MESDC1	PP1057	SPTBN1	1173_g_at	
ARHGDIB	COL1A2	EPS8	HSPC242	MGC1136	PP2135	SSPN	1664_at	
ARPC5	COL3A1	ERG	HSPG2	MGC15606	PPIA	SULT1A1	1882_g_at	
ARRDC3	COL4A1	ETS1	IER5	MGC4083	PPIB	TAGLN	296_at	
ART3	COL4A2	F11R	IFI27	MGC45780	PRCP	TARSH	311_s_at	
ATP2B2	COL5A2	FABP4	IFITM1	MGC45871	PRKAG2	TAZ	35474_s_at	
B2M	COL6A1	FABP5	IFITM3	MGC52010	PRND	TCF7L2	40657_r_at	
BASP1	COL6A2	FADS3	IGF1	MIDORI	PRSS11	TGFBI	41732_at	
BGN	COL6A3	FASN	IGF2	MLF1	PTMA	TGFBR2	44066_s_at	
BMPR2	CORO1C	FBN1	IGFBP2	MRC2	PTPLB	THBS4	44583_at	
BNIP3L	COTL1	FBXL7	IGFBP4	MSN	PTRF	THRSP	44868_s_at	
BOC	COX6A1	FBXO3	IGFBP5	MT1X	PTTG1IP	TIMP1	45660_at	
BRP44L	CPE	FCGR3A	IGFBP7	MYADM	QKI	TIMP2	46653_at	
BTEB1	CRIP1	FER1L3	IGLJ3	MYH11	RAB8B	TIP-1	46898_at	
BTG1	CRIP2	FKBP2	IL17D	MYH9	RAFTLIN	TM4SF1	47482_at	
C10orf104	CSPG2	FKBP5	IQGAP1	MYL6	RAI14	TM4SF3	48069_at	
C10orf58	CTBP2	FLJ10849	ITGB1	MYL9	RAP1B	TMEM16E	48074_at	
C14orf139	CTGF	FLJ14146	ITGB1BP3	MYLK	RBM3	TMSB10	48853_at	
C19orf10	CTNNA1	FLJ20618	ITGB5	MYLK2	RBMS3	TMSB4X	49967_at	
C1QA	CTSO	FLJ23153	ITM2A	MYO1B	RBP1	TNA	50007_at	
C1QG	CXCL12	FLNA	JAM2	NEB	RBP4	TNC	50411_at	
C1QR1	CXCL14	FN1	JPH1	NEXN	RCN1	TncRNA	51939_at	
C1S	CYBRD1	FNDC1	K-ALPHA-1	NGFRAP1	RHOC	TNFAIP3	54668_at	
C20orf3	CYGB	FOS	KCNJ8	NID	RNASE1	Tnfrsf6	54980_at	
C6orf198	D2S448	FOXO3A	KCTD10	NID2	ROD1	TOB2	55328_r_at	
C9orf19	DAB2	FOXP1	KCTD12	NOTCH3	RPL3	TP53INP1	55837_at	
C9orf58	DACH1	FSCN1	KIAA1109	NPC2	RRAD	TPM1	56323_at	
CACNA2D1	DACT1	FXYD6	LAMA4	NR2F2	RSN	TPM2	56543_i_at	
CALD1	DC2	FYN	LAMB1	NRAP	S100A10	TPM3	56600_at	
CALM2	DC-TM4F2	GANAB	LAMC1	NRP1	S100A11	TPM4	59809_f_at	

Timmons *et al* FASEB J 2005

Does gene expression reflect functional adaptation?

BMC Biology

BioMed Central

Research article

Open Access

Modulation of extracellular matrix genes reflects the magnitude of physiological adaptation to aerobic exercise training in humans

James A Timmons*[1,2], Eva Jansson[3], Helene Fischer[3], Thomas Gustafsson[3], Paul L Greenhaff[4], John Ridden[1,5], Jonathan Rachman[1,6] and Carl Johan Sundberg[1]

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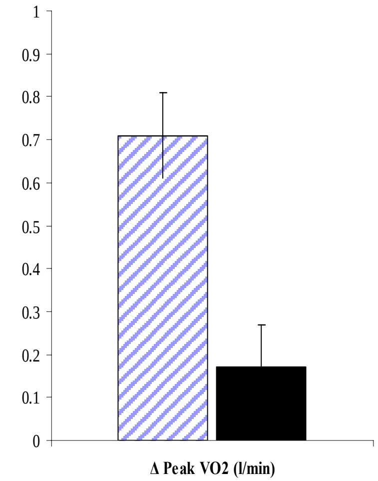
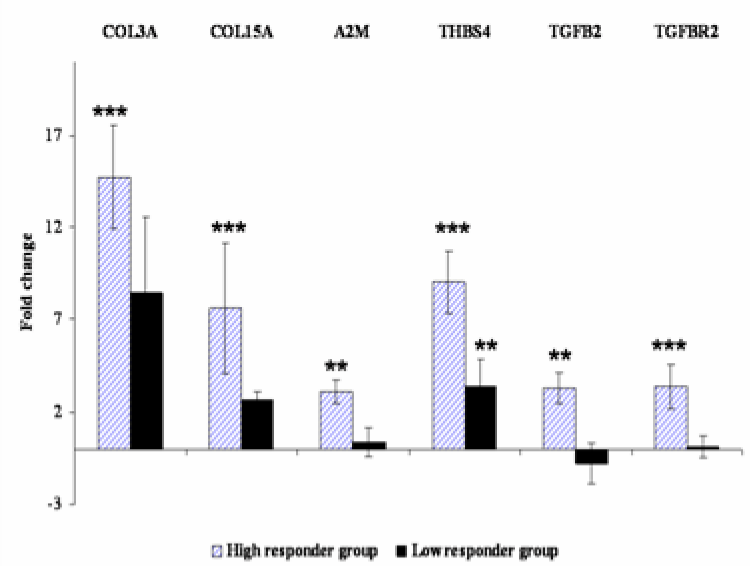
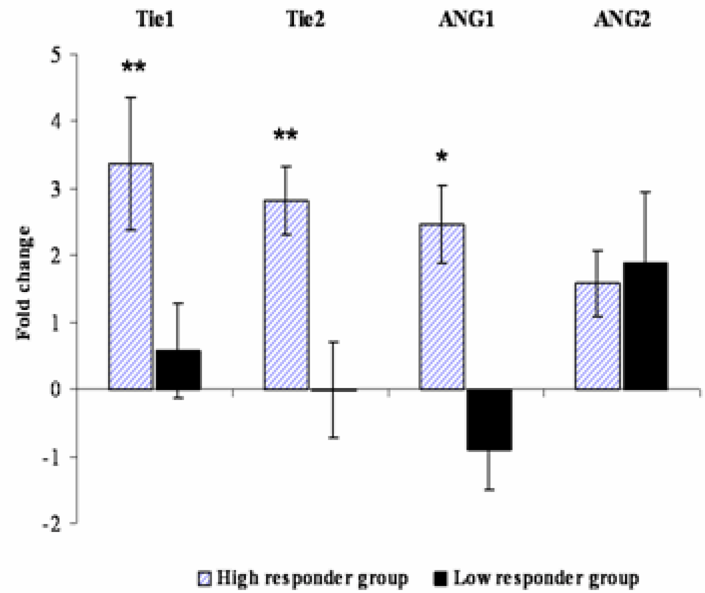




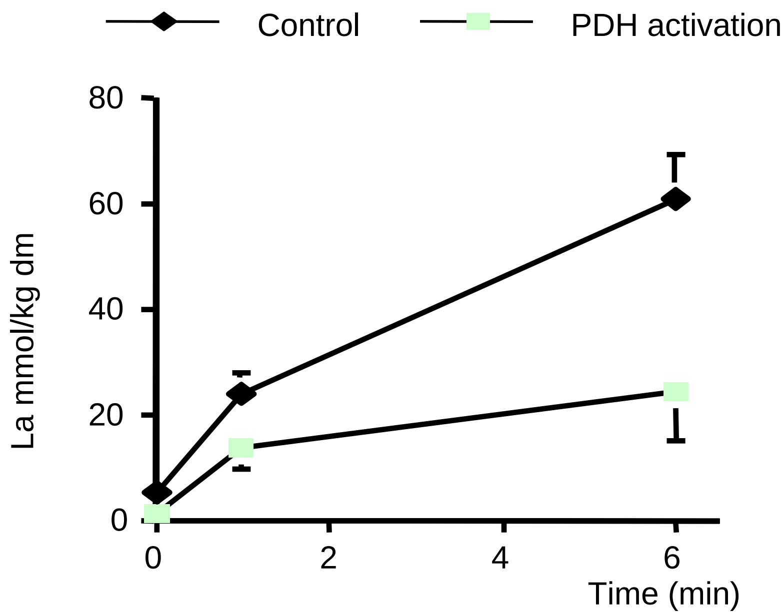


Also See: http://dsc.discovery.com/news/briefs/20051003/exercisegene.htm

What regulates this change in muscle metabolism post training?

- Altered metabolic gene expression to 'better' use the oxygen?
  - requires increased mitochondrial function !

What regulates muscle lactate accumulation during exercise?

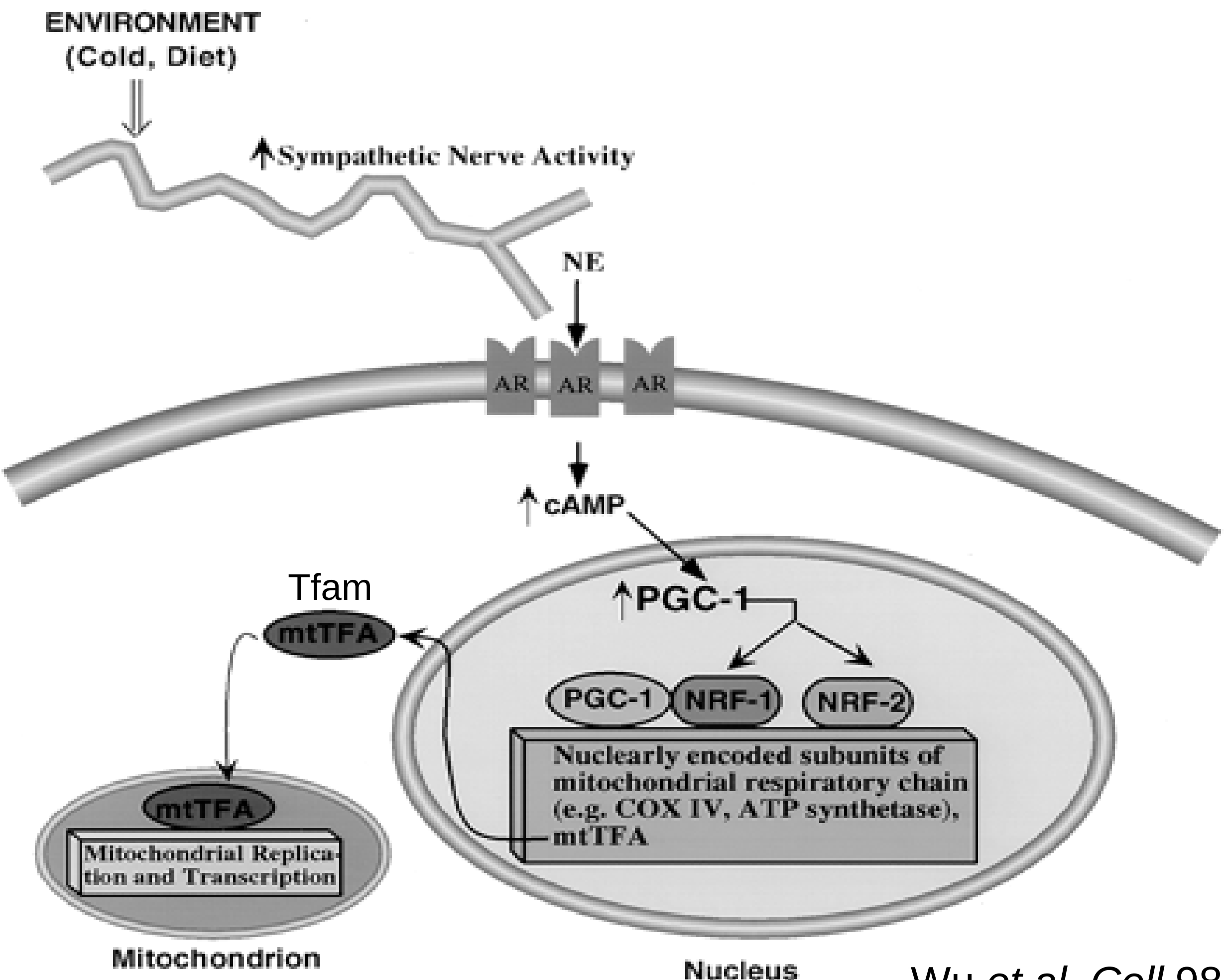


• **Muscle lactate accumulation can be <u>reduced</u> by increasing mitochondrial activity (PDH activation, a flux generating enzyme)**

• **How does exercise training regulate mitochondrial gene expression?**

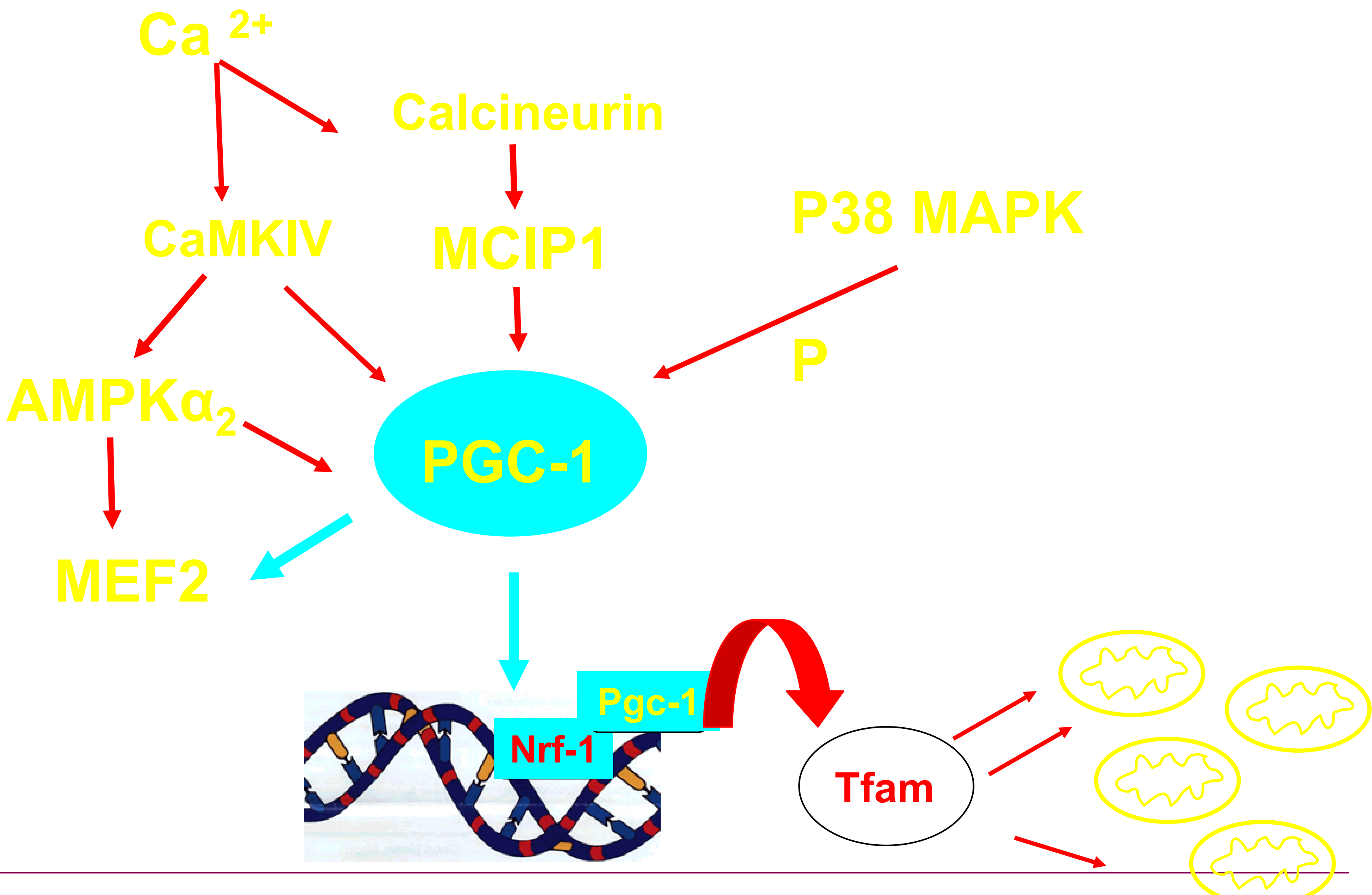
Timmons *et al* Am. J Physiol 1997 & J Clinical Investigation 1998

Regulation of Tfam by PGC-1 & NRF

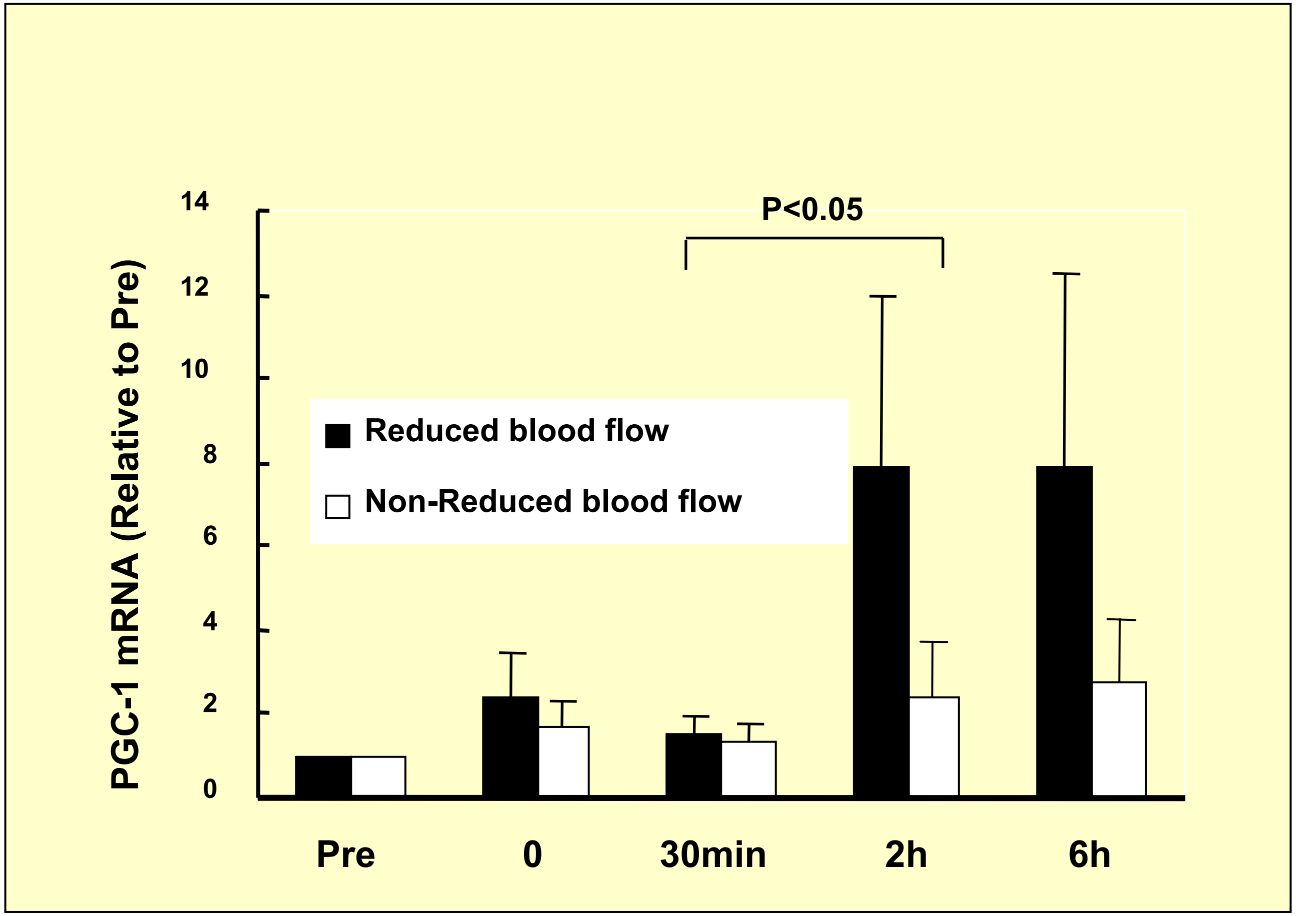


Wu *et al. Cell* 98: 115-124, 1999.

Contractile activity



PGC-1 mRNA



Norrbom *et al* 2003

Karolinska Institutet

Endurance training

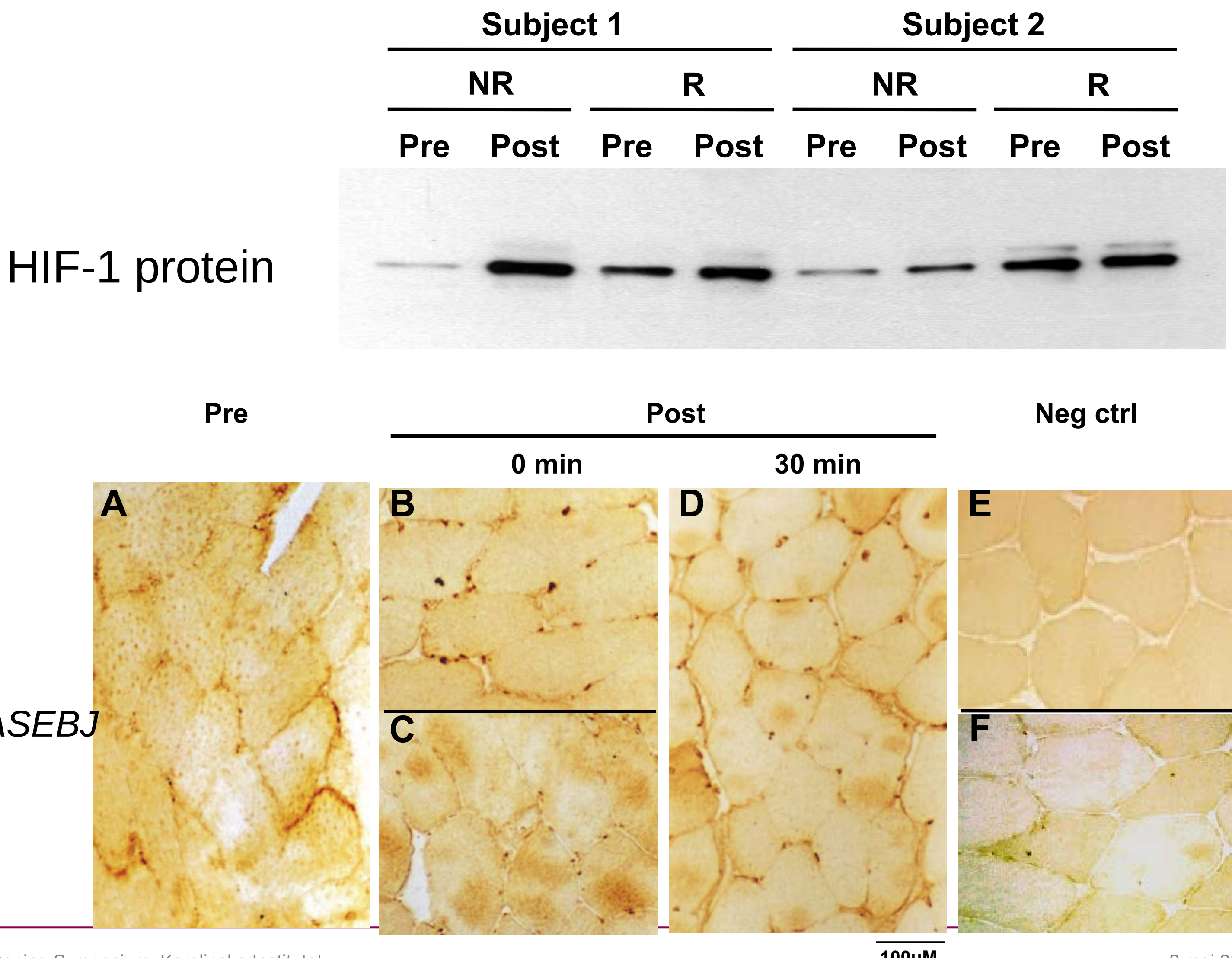
Skeletal muscle structural and metabolic adaptation

- Glycolytic enzymes
- Energy storages
- Fiber type changes
- Mitochondrial biogenesis
- **Angiogenesis**

Gustafsson 2005

HIF-1 in exercising human skeletal muscle

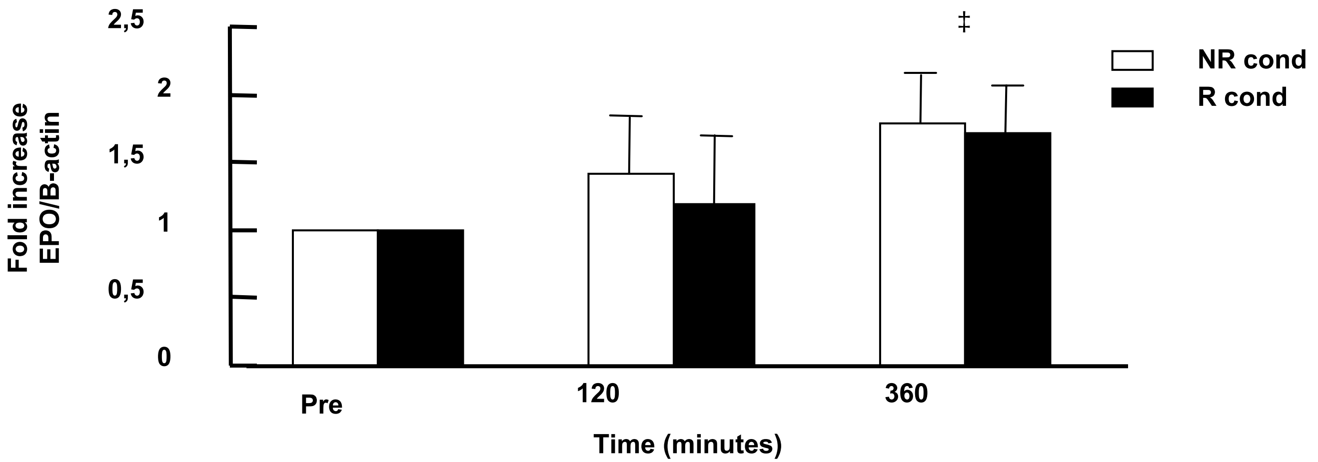
Karolinska Institutet



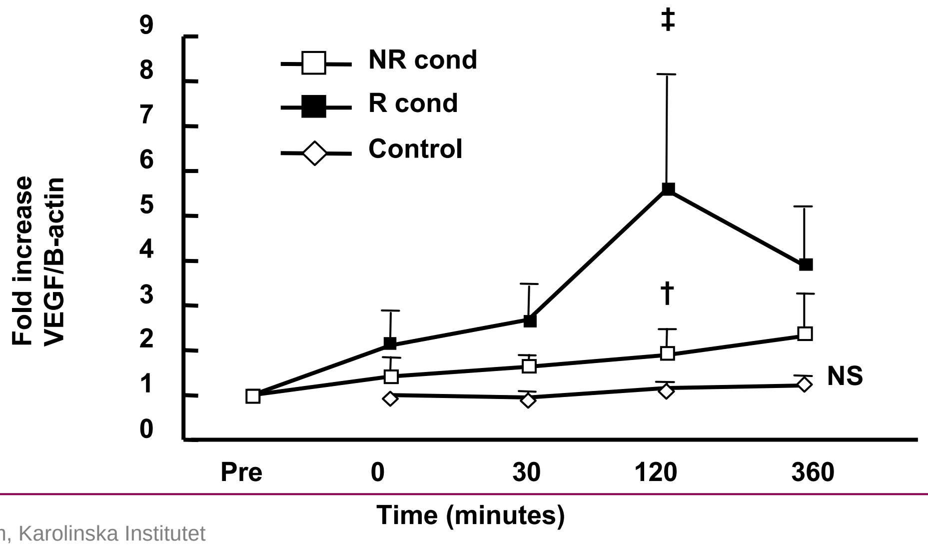
Ameln et al , *FASEBJ* 2005

HIF-1 in exercising human skeletal muscle

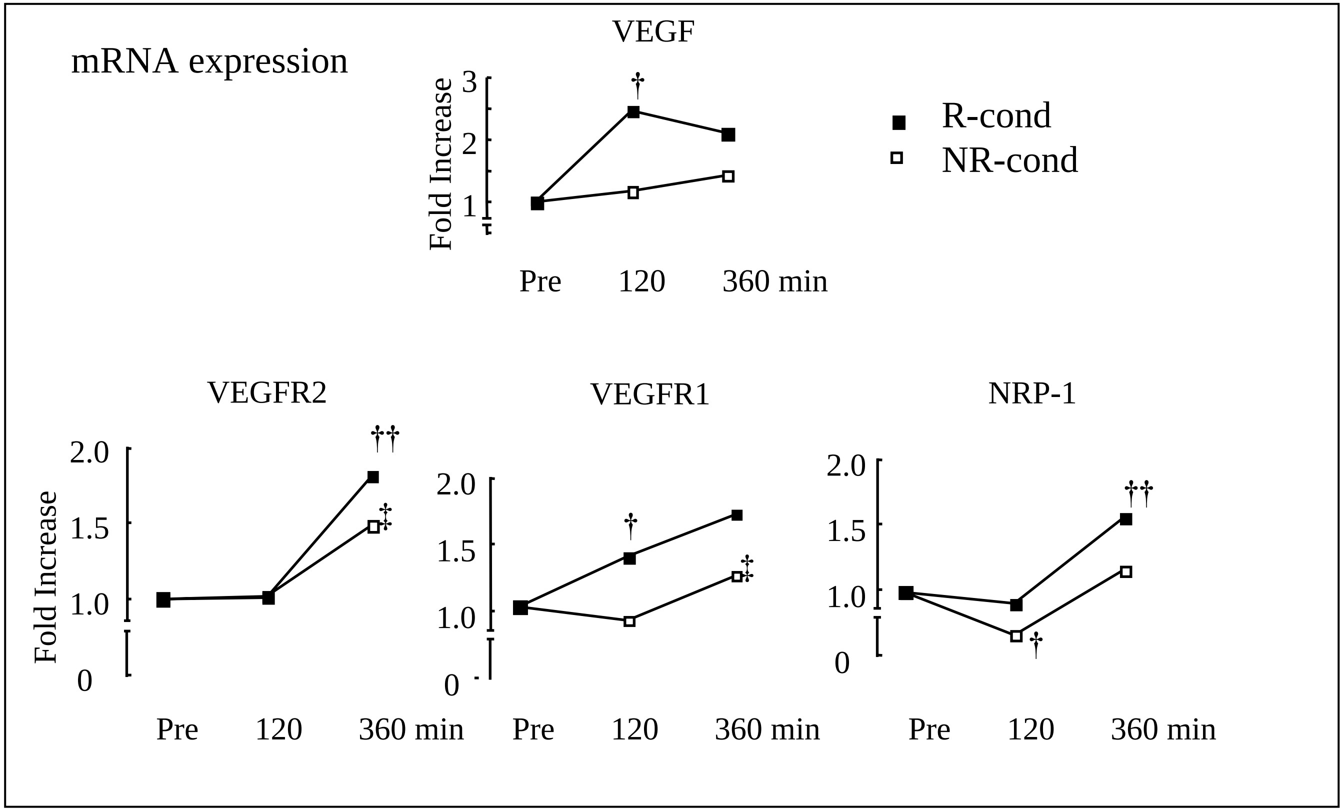
EPO



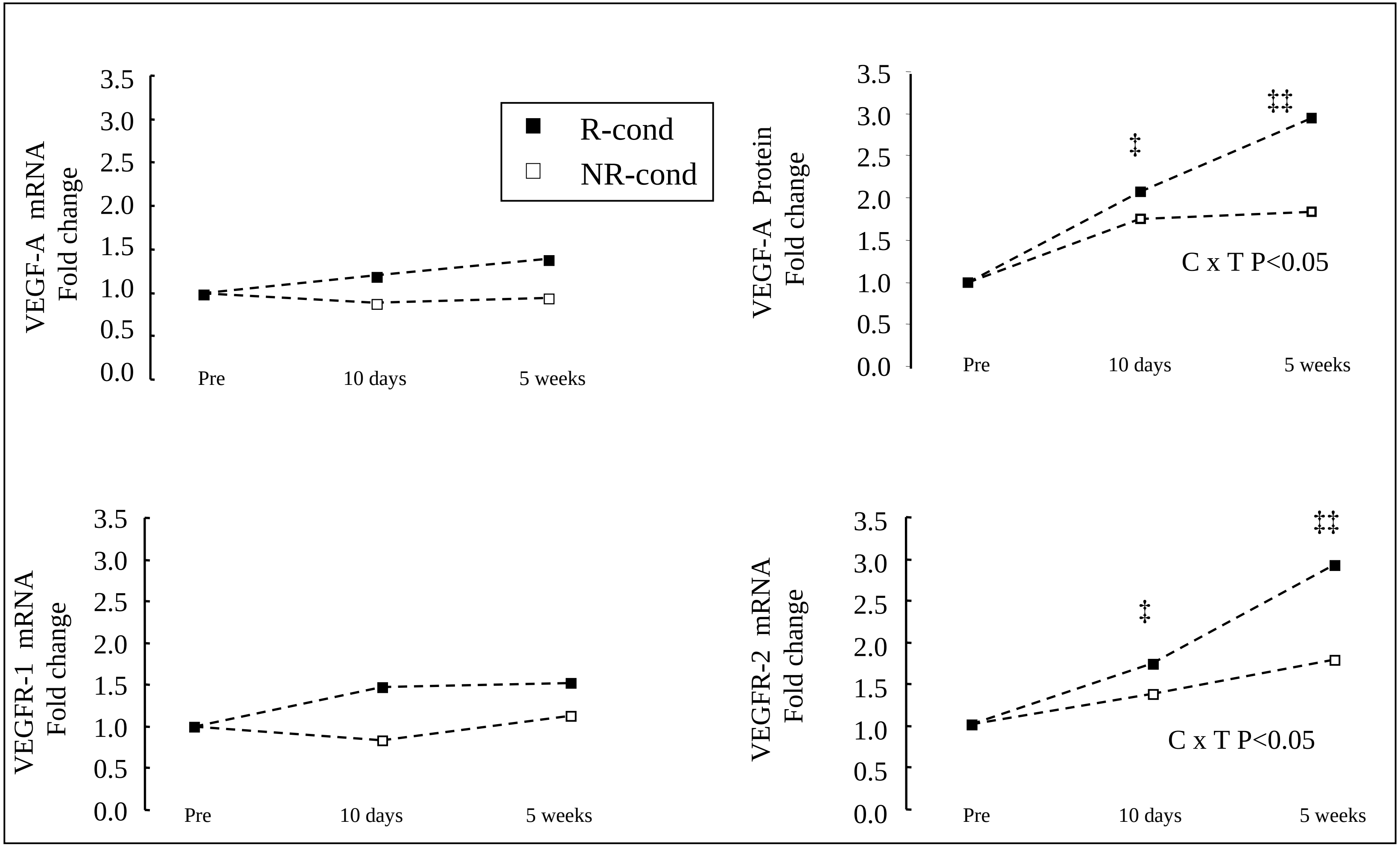
VEGF



Ameln et al , *FASEBJ* 2005



Gustafsson 2005



Gustafsson 2005