Adaptations of "Free Radical Biology" to Acute and Chronic Exercise

Slide Contributed by:
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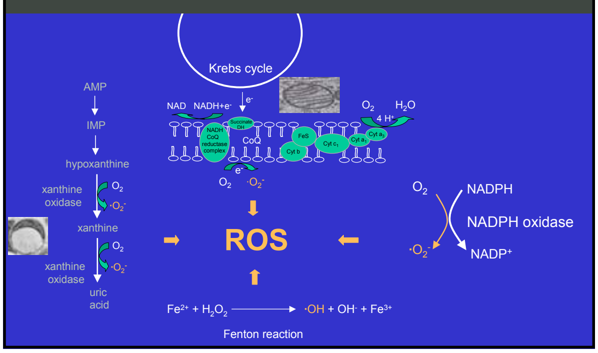
Outline

1. Mitochondrial production of oxidants during acute exercise
2. Production of oxidants by xanthine oxidase during exhaustive exercise
3. Exercise, Muscle Injury (Delayed Onset Soreness) Inflammation and Oxidative stress. Inflammation and production of oxidants by oxidases
4. Exercise Training and Longevity in Animals and Humans
5. Adaptations and Mechanisms with Exercise Training; Potential benefits as countermeasures to aging
6. Exercise and Physical Activity; Effects on Longevity in Humans
7. Reactive Oxygen Species and effects on muscle contractility (brief)
8. Exercise as a model to study cell signaling (brief)

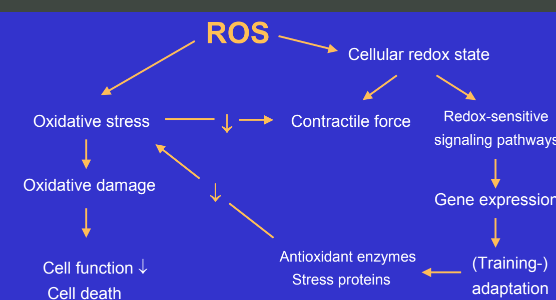
Exercise-induced ROS formation

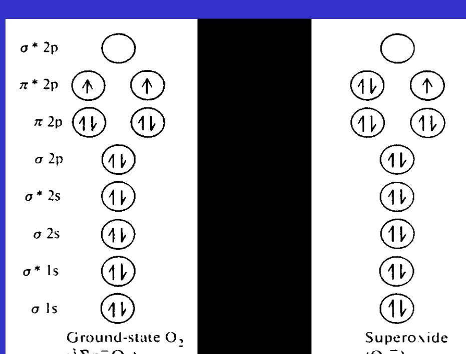
- Potential Sources -



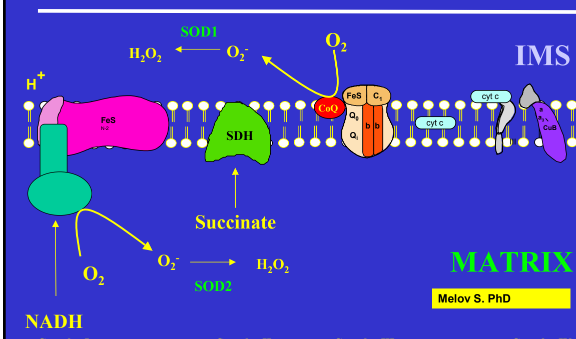
Overview

Reactive oxygen species (ROS) - good or bad guys ?





Reactive Oxygen species and the Respiratory Chain



Generation of Radicals: Main Source

- **Mitochondrial respiratory chain**
  ('Electron Transport Chain')

e.g. superoxide radical; H_2O_2 , hydroxyl radical;

More Oxygen More Radicals??

"Radical" Reactions

$O_2 + e \Leftrightarrow O_2^{\bullet -}$	Equation 1
$O_2 + 2e + 2H^+ \rightarrow H_2O_2$	Equation 2
$O_2^{\bullet -} + O_2^{\bullet -} + 2H^+ \rightarrow SOD \rightarrow H_2O_2 + O_2$	Equation 3
$H_2O_2 + 2GSH \rightarrow GPX \rightarrow H_2O + GSSG + ROH$	Equation 4
$2H_2O_2 + \rightarrow Catalase \rightarrow 2H_2O + O_2$	Equation 5
$Fe^{2+} + H_2O_2 \rightarrow HO^{\bullet} + HO^{-} + Fe^{3+}$	Equation 6
$O_2^{\bullet -} + NO^{\bullet} \rightarrow ONOO^{-}$	Equation 7
$O_2^{\bullet -} + M^{n+} \rightarrow O_2 + M^{(n-1)+}$	Equation 8

MITOCHONDRIAL OXYGEN RADICAL GENERATION & LEAK: SITES OF PRODUCTION IN STATES 4 & 3,

Gustavo Barja
Journal of Bioenergetics & Biomembranes.
31:4:1999

Background:

- What are mechanisms to reduce radical production during acute exercise?
- Comparing data from isolated mitochondria with the hypothetical *in vivo* ("physiological exercise") situation.
- Keep in mind!!!
  - Oxygen tension
  - State 3 vs. State 4
  - Tissue specificity!!! i.e.Heart vs. Muscle

Quantification of radical generation via:

1.**Substrate Type**
('fuel')

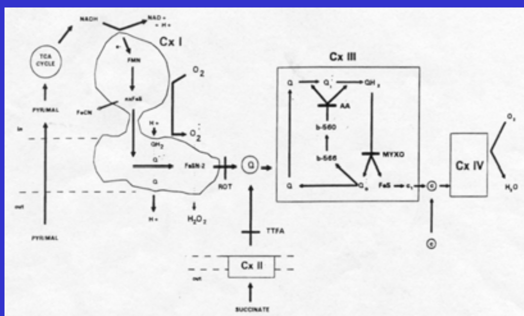
2.**"Stress" on mitochondria**
(rest vs active state)

Generation of Radicals

- Mitochondrial Stress:
  I.Resting (substrate only) ⇒ **STATE 4**

  II.Active (substrate + ADP) ⇒ **STATE 3**

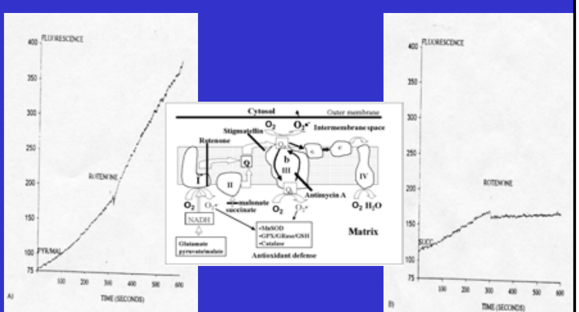
Mitochondrial Respiratory Chain



RESULTS: **STATE 4** (resting)

- COMPLEX I +/or III
  - contain O_2 radical generator(s)
- Pyr/Mal as substrate produce ↑ H_2O_2 than Succinate

INHIBITOR EFFECT



PYR/MAL SUCCINATE

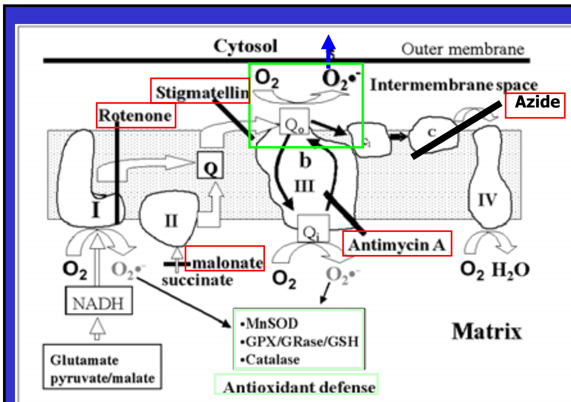


Figure 3: ETC showing production of ROS

RESULTS: STATE 3 (active)

- COMPLEX I produces O_2 radicals

* appears to be **ONLY** COMPLEX containing O_2 radical generator for this state*

NB. Mitochondria operate in 'flux' of states between 3 and 4; rarely at either end of the range for a prolonged period.

*SUMMARY: RADICAL GENERATION

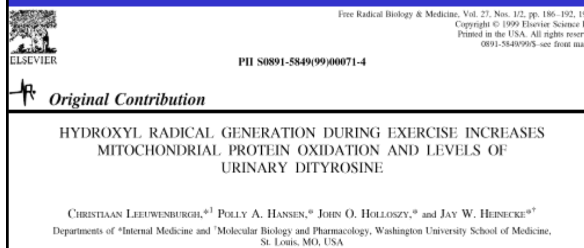
- COMPLEX I - always involved
  (regardless of substrate + state)
- COMPLEX II - partial involvement
- COMPLEX III - involved in STATE 4

*Data from heart mito; differences exist between tissue type.

Conclusions

- O_2 radicals mainly generated at COMPLEX I in STATE 4 + 3
- ↑ radical production NOT necessarily proportional to O_2 consumption
- ↑ radical formation with exercise and age inconclusive

(Comparative Studies ⇒ O_2 radical generation ↓ in long lived vs short lived animals)



Free Radical Biology & Medicine, Vol. 27, Nos. 1/2, pp. 186–192, 1999

0891-5849/99/$–see front matter
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PII S0891-5849(99)00071-4

Original Contribution

HYDROXYL RADICAL GENERATION DURING EXERCISE INCREASES MITOCHONDRIAL PROTEIN OXIDATION AND LEVELS OF URINARY DITYROSINE

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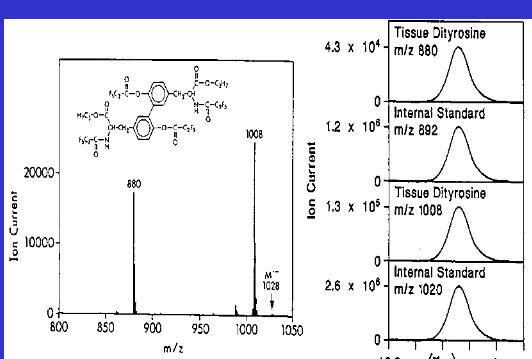
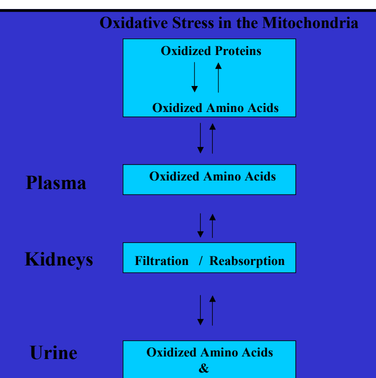
Background

- Studies with isolated mitochondria show that during normal respiration there is production of partially reduced oxygen species in the electron transport chain
- It is estimated that the release of reactive oxygen species accounts for about 1-5 % of the oxygen consumed during respiration

Hypothesis

- An increase in exercise-induced mitochondrial oxidative metabolism could result in an increase in oxidative stress
- Oxidative stress could therefore increase mitochondrial protein oxidation





Proposed formation and removal of oxidized amino acids in the mitochondria after acute exercise

Animals and Exercise Protocol

- Animals
- Male Wistar Rats
- Fasted Overnight

- Exercise
  1 bout of 30 min.
  weight of 1.5 % of body weight used
  3 bouts of 30 min (STRESS FULL and EXHAUSTIVE EXERCISE)

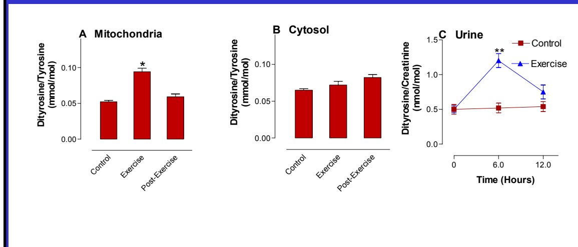
Design

1) Controls (Placed in Metabolic Cages for Urine Collection)

2) Acute Exercise (Immediately Sacrificed)

3)Acute Exercise (Placed in Metabolic Cages for Urine collection)

Hydroxyl radical generation during exercise increases mitochondrial protein oxidation and levels of urinary dityrosine.



Leeuwenburgh, C., Hansen, P. A., Holloszy, J. O., and Heinecke, J. W. (1999) *Free Radic Biol Med* 27, 186-192.

Leichtweis, S. B., Leeuwenburgh, C., Parmelee, D. J., Fiebig, R., and Ji, L. L. (1997) Rigorous swim training impairs mitochondrial function in post-ischaemic rat heart. *Acta Physiol Scand* 160, 139-148.

Conclusions

- **Exercise is a physiological relevant oxidative stress**
- **This study provides the first direct evidence of hydroxyl radical formation in the mitochondria of exercising animals**
- **Oxidized amino acids may be recognized by proteolytic enzymes degraded, released, and excreted into the urine**
- **Markers for oxidative stress in urine may be useful for non-invasive assessment of several disease states**

Production of oxidants during exhaustive exercise; Role of xanthine oxidase

- Sastre and Vina; Free Radicals in **Exhaustive** Physical Exercise: Mechanism of Production, and Protection by Antioxidants

Free-radical production in exercise

- At rest, about 2% of the Oxygen consumed by mitochondria is not converted into water but forms ROS.
- Thus it was assumed that during exercise there would be an increase in mitochondrial ROS production.
- This is not the case. During exercise, ROS formation by the mitochondria is negligible. **Mitochondria are very efficient in reducing the radical leak in State 3 (active state + ADP)**
- Possible explanation?
  - Alternate source of ROS production outside the mitochondria.
  - Xanthine Oxidase.
    - Past research has shown that Xanthine Oxidase levels correlate well with ROS levels and cellular damage.

Radical production in exercise: Past research

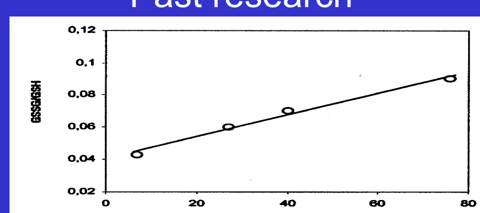


Figure 1. Linear relationship between oxidized (GSSG)-to-reduced glutathione (GSH) and lactate-to-pyruvate ratios in blood from humans subjected to physical exercise. Human blood was obtained from subjects before, immediately after, and 30 or 60 min after physical exercise to exhaustion on a treadmill using Bruce's protocol. Number of experiments = 10. (Reproduced with permission from reference (2).)

The role of Xanthine Oxidase in the production of ROS in exhaustive exercise: Protection by allopurinol

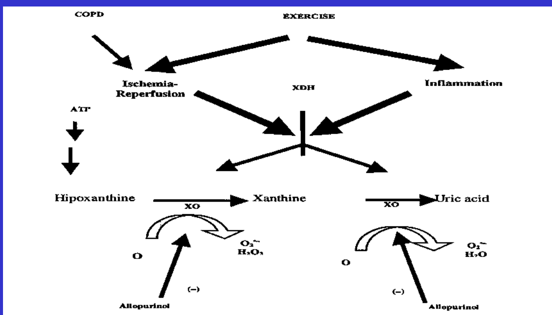


Figure 7. Role of xanthine oxidase in the production of free radicals in exhaustive exercise. Protection by allopurinol.

Mechanism of free-radical production in exercise

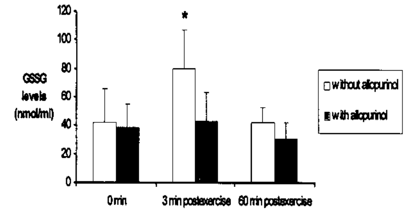


Figure 2. Effect of physical exercise on blood oxidized glutathione levels in chronic obstructive pulmonary disease (COPD) patients. Protection by allopurinol. Statistical differences between 0 minutes and 3 minutes postexercise groups is shown as #*($P < 0.05$). Number of experiments is 5. Patients performed light exercise (approximately 40 W for up to 6 minutes) in a cycloergometer. Allopurinol was administered orally at a dose of 300 mg/day for 3 days before the exercise. Drawn up with data from reference (14).

Protection of ROS generation by allopurinol

- Allopurinol inhibits xanthine oxidase, a likely source of ROS production during exhaustive exercise.
- The substrates for xanthine oxidase:
  - Xanthine
  - Hypoxanthine
- Hypoxanthine derives from the degradation of ATP via AMP.
- Therefore, the substrates needed for xanthine oxidase are available only after exhaustive exercise.

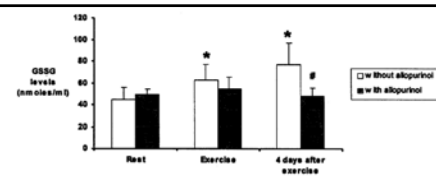


Figure 4. Effect of physical exercise on blood oxidized glutathione levels in humans. Protection by allopurinol. Difference between rest and exercise groups is shown: *$P < 0.05$ and between 4 days after exercise and 4 days after exercise treated with allopurinol: # $P < 0.05$. Number of experiments is 3. Drawn up with data from reference (14).

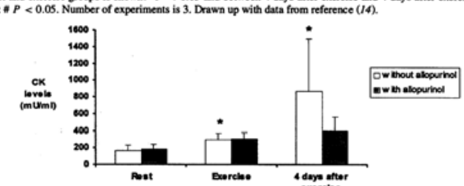


Figure 5. Effect of physical exercise on serum CK activity after exhaustive exercise in humans. Protection by allopurinol. Statistical difference between rest and exercise groups is shown as *#($P < 0.01$). Number of experiments is 4. Drawn up with data from reference (14).

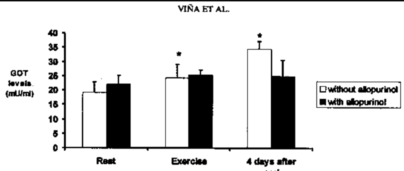


Figure 6. Effect of physical exercise on serum aspartate amino transferase (GOT) activity after exhaustive exercise in humans. Protection by allopurinol administration. Statistical difference between rest and exercise groups is shown as *#($P < 0.01$). Number of experiments is 4. Drawn with data from reference (14).

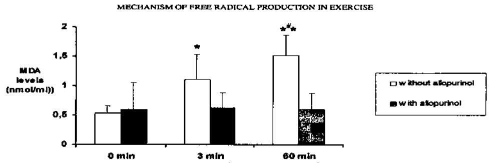
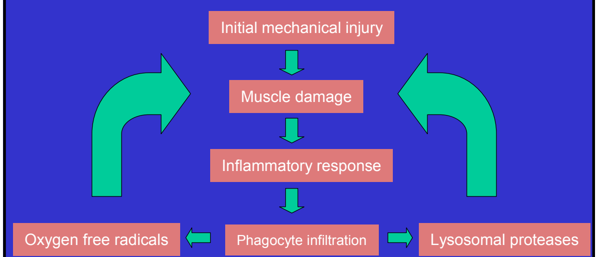


Figure 3. Effect of physical exercise on plasma malondialdehyde levels in COPD patients. Protection by allopurinol ad ministration. Statistical difference between 0 minutes and 3 or 60 minutes postexercise is shown as *#($P < 0.05$), an **($P < 0.01$). Statistical difference between 3 minutes postexercise and 60 minutes postexercise groups is shown as # ($P < 0.05$

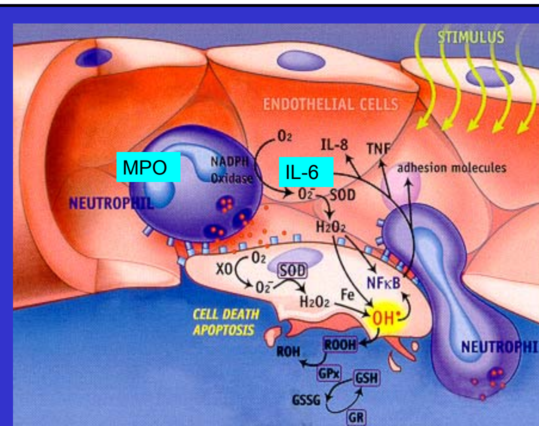
Radical production in exercise

- Exhaustive exercise increases blood xanthine oxidase levels, which leads to ROS production.
- Exhaustive exercise is also associated with an increase in glutathione oxidation (Quintanilha et al.).
  - There is a linear increase between exercise intensity (blood lactate, CK levels) and the oxidation of glutathione (Sastre et al.).
  - Glutathione oxidation (GSSG) is a 'marker' for oxidative damage.
- Inhibiting xanthane oxidase activity with allopurinol reduces glutathione oxidation, and therefore oxidative damage.
- Does Xanthine Oxidase play a role in the oxidation of glutathione?
- When Xanthine oxidase is inhibited by allopurinol, what happens to oxidized glutathione (GSSH) levels?

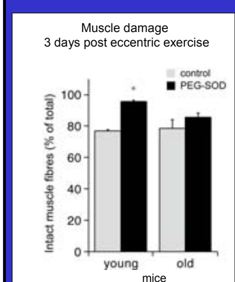
Exercise, Muscle Injury (Delayed Onset Soreness) Inflammation and Oxidative stress

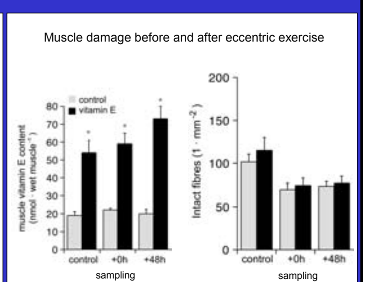


Adapted from Toumi & Best *Br J Sports Med* (2003) **37:** 284



Antioxidant intervention and muscle damage





Zerba et al. Am *J Physiol* (1990) **258:** 429-435

Warren et al. *J Appl Physiol* (1992) **72:** 2168

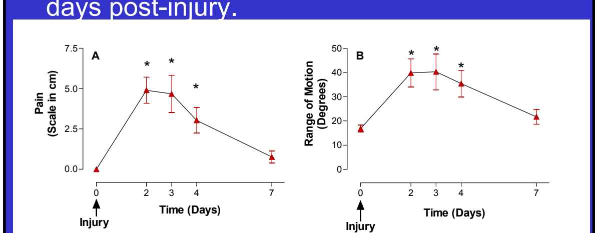
Human Oxidative Stress- Inflammatory Model

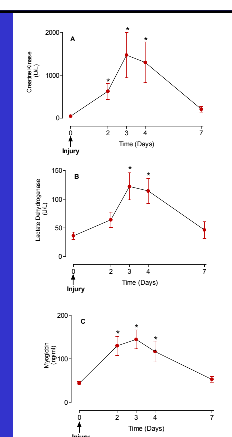
- Human model to rapidly and safely test the efficacy of a variety of anti-inflammatory and antioxidant compounds (pharmaceutical or non-pharmaceutical).
- Used the eccentric portion of a bicep curl to elicit muscle damage
- Subjects performed 3 sets of ten repetitions with 80% of their eccentric maximum
- Untrained Male Subjects

Eccentric Exercise Mode

Clinical Symptoms

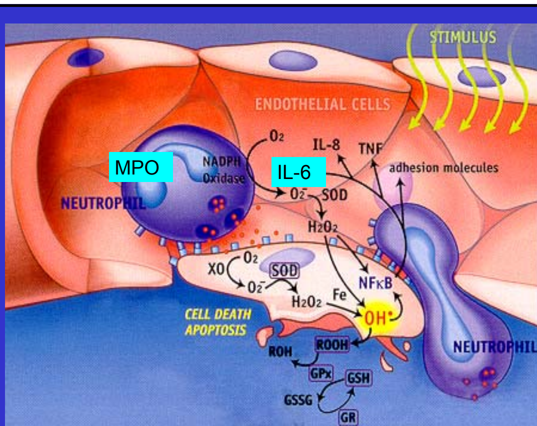
- Severe pain, decrease in range of motion of the injured arm, and edema characterize this type of exercise-induced injury for several days post-injury.



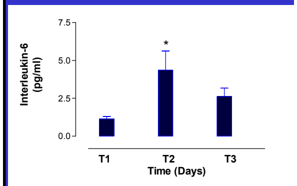


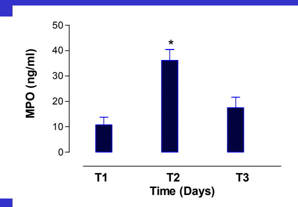
Blood Parameters

- **The increases in LDH and CK are comparable with plasma levels of patients who have suffered from a heart infarct.**



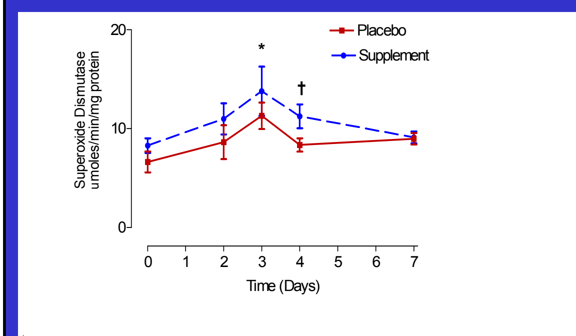
Interleukin-6 and Myeloperoxidase



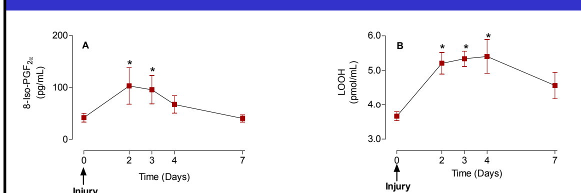


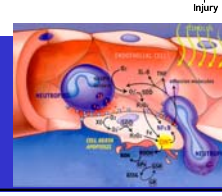
Superoxide Dismutase

$2O_2^{\bullet -} + 2H^+ \rightarrow SOD \rightarrow \mathbf{H_2O_2} + O_2$



Oxidative Stress





Publications
Exercise and Inflammation

- Childs, A., Jacobs, C., Kaminski, T., Halliwell, B., and Leeuwenburgh, C. (2001) Supplementation with vitamin C and N-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. *Free Radic Biol Med* 31, 745-753.
- Phillips, T., A. Childs, D. Dreon, S. Phinney, and C. Leeuwenburgh. Effects of a nutrient ingredient systems supplement on serum C-reactive protein following eccentric exercise-induced muscle injury. ***MSESS***.

Exercise and longevity in rodents and humans;
Can we retard aging and increase lifespan?

Common ways to exercise rodents

- Swimming
- Treadmill running
- Voluntary wheel running

Forced Treadmill Running

- Can control duration, intensity, and frequency of running
- ↑ in oxidative capacity of skeletal and cardiac muscle
- BUT…can elicit adaptations indicative of chronic stress (Moraska et al., 2000)
  - adrenal gland hypertrophy and thymic involution
  - ↓ serum CBG levels
  - ↓ lymphocyte proliferation and antigen-specific IgM production

Voluntary Wheel Running

- Increases mean lifespan (Holloszy et al., 1993, 1997, & 1998)
- Prevents stress-induced behavioral depression & immunosuppression (Moraska et al., 2001)
- ↓ body weights and enhanced survival (Narath et al., 2001)

Survival Data (Narath et al., 2001)

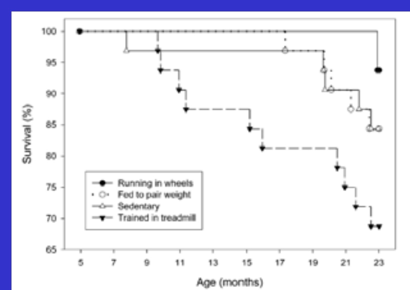
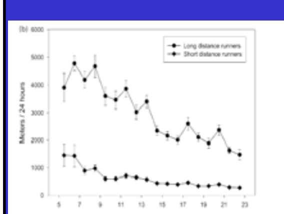
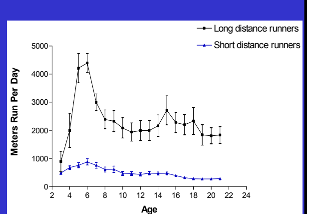


Fig. 2. Survival of animals in the experimental groups.

Variations in running activity



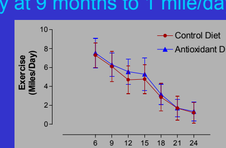


Narath et al., 2001

Our data

Effects of voluntary exercise on longevity of rats. Holloszy, Smith, Vining and Adams. J. Appl. Physiol. 59:826-831. 1985

- **What is the effect of v**oluntary wheel running on longevity?
- Mean running activity significantly declined with age, dropping from 4 miles/day at 9 months to 1 mile/day at 30 months of age.



- **Data from Holloszy, J.O. 1998. Longevity of exercising male rats: effect of an antioxidant supplemented diet. *Mech Ageing Dev* 100:211-219.**

216 J.O. Holloszy / Mechanisms of Ageing and Development 100 (1998) 211–219

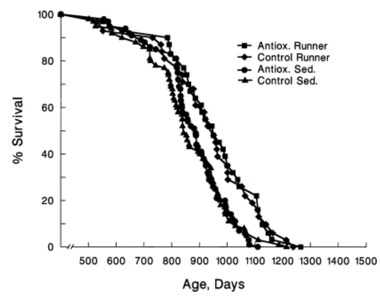


Fig. 3. Survival curves for the four groups. The survival curves for the runners are significantly different from those of the sedentary rats in both diet groups ($P < 0.02$).

-Antioxidants have no effect on longevity

-Exercise increase mean life-span

Mortality rate and longevity of food-restricted male rats: a reevaluation. Holloszy. J. Appl. Physiol. 399-403. 1997

- Voluntary wheel running has been shown to increase mean lifespan, but unlike caloric restriction, does not increase maximal lifespan.
- <u>Food restriction combined with voluntary wheel running</u> on survival when compared to sedentary pair-weight caloric restricted controls.

Group A Runners

Group B Sedentary

Group C Runners + **<u>R</u>**

Group D **<u>R</u>**estricted

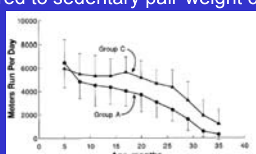


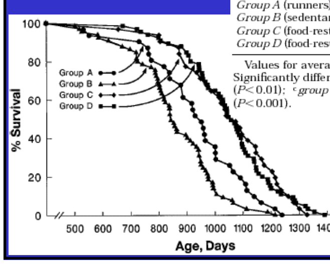
Fig. 1. Decrease with aging in average distance run per day by rats in groups A and C. Food intake of rats in group C was restricted to ~70% of ad libitum food consumption. After age 9 mo, group C rats ran significantly greater distance/24 h than group A rats ($P < 0.04$ to $P < 0.0001$).

Mortality rate and longevity of food-restricted male rats: a reevaluation. Holloszy. J. Appl. Physiol. 399-403. 1997

Table 3. *Longevity*

	n	Average Age at Death, days	Range, days
Group A (runners)	31	$937 \pm 171^{a,b,c}$	531–1,238
Group B (sedentary)	65	$858 \pm 152^{d,e}$	502–1,214
Group C (food-restricted runners)	31	$1,058 \pm 166$	656–1,328
Group D (food-restricted sedentary)	65	$1,051 \pm 157$	672–1,390

Values for average age at death are means ± SD; n = no. of rats. Significantly different compared with: [a] *group B* ($P < 0.02$); [b] *group C* ($P < 0.01$); [c] *group D* ($P < 0.01$); [d] *group C* ($P < 0.001$); [e] *group D* ($P < 0.001$).



Findings regarding Longevity

- Voluntary wheel running individuals **lived slightly but significantly longer than sedentary *<u>ad lib</u>* <u>controls</u> and <u>sedentary pair-fed controls</u>** (mean lifespan <u>1012</u>, <u>923</u>, <u>928</u> days respectively), but not compared to caloric restricted pair-weight sedentary controls (mean lifespan <u>1113 days</u>).
- Although, voluntary running improved survival it did not cause an extension in lifespan, unlike CR, and did not lead to a reduction in observed malignancies, unlike CR.

Conclusion

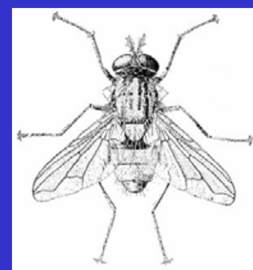
- The survival curves of the two groups were virtually identical, with no evidence of an increased early mortality in the exercise group (see Holloszy and Schechtman, 1991).
- The main finding of this study was that while exercise did not interfere with the extension of maximal lifespan due to caloric restriction, there was no additive or synergistic beneficial effect of voluntary exercise in tandem with caloric restriction on maximal lifespan in these rats.

Holloszy, J.O., and Smith, E.K. 1986. Longevity of cold-exposed rats: a reevaluation of the "rate-of-living theory". *J Appl Physiol* 61:1656-1660.

- The results of this study provide no support for the concept that increased energy expenditure decreases longevity

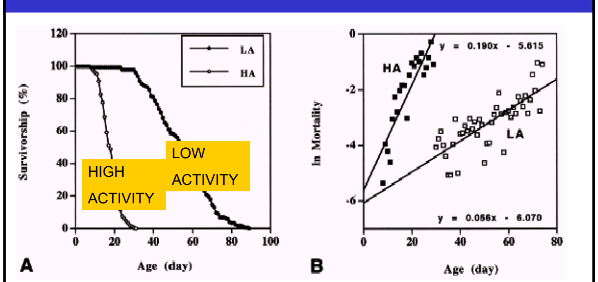
Can we exercise too much?
What will this do to your maximum life span potential?

Lessons from flies



- Liang-Jun Yan and Rajindar S. Sohal
  Prevention of Flight Activity Prolongs the Life Span of the Housefly, *Musca Domestica*, and Attenuates the Age-Associated Oxidative Damage to Specific Mitochondrial Proteins

Results



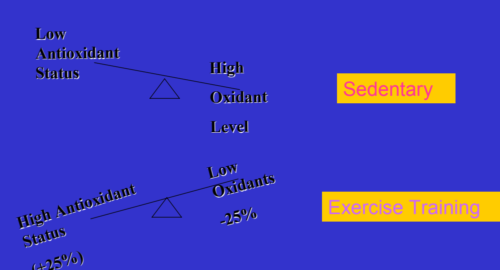
Other Interesting Facts about *Drosophila Melanogaster* or fruit Flies

- Crawlers vs. flyers
- Promiscuous Males vs. Females (males with multiple females)
- Promiscuous Females vs. Males????
  - off course not tested, but could give interesting results!! Theses or Dissertation?

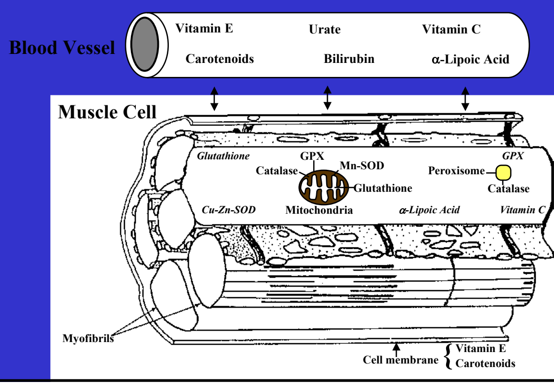
Free radical Biology; Adaptations to Exercise and Training

- Leeuwenburgh, C., and Heinecke, J. W. (2001) Oxidative stress and antioxidants in exercise. *Curr Med Chem* 8, 829-838.
- Powers, S. K., Ji, L. L., and Leeuwenburgh, C. (1999) Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. *Med Sci Sports Exerc* 31, 987-997.

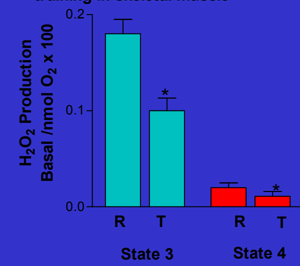
What happens to mitochondrial efficiency and deletions as well as oxidant and antioxidant balance?



Muscle-Antioxidant Defenses



Oxidant production is reduced following training in skeletal muscle



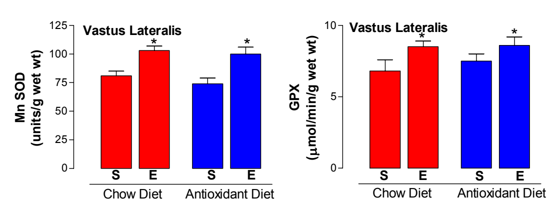
Venditti P, Masullo P, Di Meo S. Effect of training on H(2)O(2) release by mitochondria from rat skeletal muscle. Arch Biochem Biophys. 1999 Dec 15;372(2):315-20.

Key Points

- Oxygen consumption is the same in Trained and Untrained animals
- H_2O_2 production was lower in State 3 and State 4 (Succinate as substrate). Per Mitochondria!!
- Overall production H_2O_2 production was not different in State 3 or State 4 (Succinate)
- Overall production H_2O_2 production was slightly increased in State 3 or State 4 (Pyr-Mal)
- In this study <u>no changes</u> in antioxidant defenses, however this is swim exercise

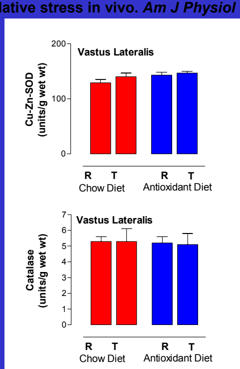
Leeuwenburgh, C., Hansen, P. A., Holloszy, J. O., and Heinecke, J. W. (1999) Oxidized amino acids in the urine of aging rats: potential markers for assessing oxidative stress in vivo. *Am J Physiol* 276, R128-135.

$O_2^{\bullet -} + O_2^{\bullet -} + 2H^+ \rightarrow SOD \rightarrow H_2O_2 + O_2$	Equation 1
$H_2O_2 + 2GSH \rightarrow GPX \rightarrow H_2O + GSSG + ROH$	Equation 2

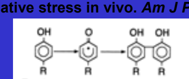


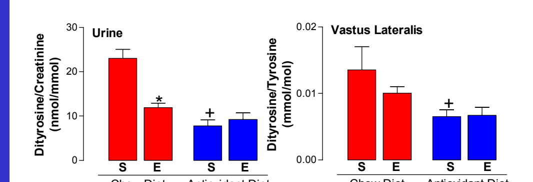
1) Mn SOD and GPX activity is increased with voluntary wheel running
2) Antioxidant diet does NOT effect two key endogenous enzymes.

Leeuwenburgh, C., Hansen, P. A., Holloszy, J. O., and Heinecke, J. W. (1999) Oxidized amino acids in the urine of aging rats: potential markers for assessing oxidative stress in vivo. *Am J Physiol* 276, R128-135.



Leeuwenburgh, C., Hansen, P. A., Holloszy, J. O., and Heinecke, J. W. (1999) Oxidized amino acids in the urine of aging rats: potential markers for assessing oxidative stress in vivo. *Am J Physiol* 276, R128-135.





Long-term wheel running

- ↓ lipid peroxidation & ↑ CAT activity in heart (Kim et al., 1996a)
- ↑ CAT, GPX, GSH & mito. membrane fluidity in liver (Kim et al., 1996b)
- ↓ urinary o,o'-dityrosine & ↑ skeletal muscle GPX & MnSOD (Leeuwenburgh et al., 1999)

Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems.

- Leeuwenburgh, C., Fiebig, R., Chandwaney, R., and Ji, L. L. (1994) *Am J Physiol* 267, R439-445.

Adaptations of glutathione antioxidant system to endurance training are tissue and muscle fiber specific.

- Leeuwenburgh, C., Hollander, J., Leichtweis, S., Griffiths, M., Gore, M., and Ji, L. L. (1997) *Am J Physiol* 272, R363-369.

GPX and SOD Adaptations following treadmill exercise training

- Treadmill training increases GPX and SOD activity in the Deep Vastus Lateralis, but not in the soleus muscle

Exercise as a Countermeasure to Aging; Mechanisms

- Delays onset of morbidity & mortality
- How???
  - ↓ oxidant production (Venditti et al., 1999)
  - ↑ antioxidant enzyme activity (Leeuwenburgh et al., 1994 & 1997; Powers et al., 1993 & 1994; Venditti et al., 1996)
  - ↓ oxidative damage, ↑ DNA repair & 20S proteasome activity (Radak et al., 1999, 2000, & 2002)

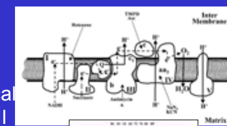
Evidence of training effects on the antioxidant network in skeletal muscle

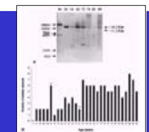
- Glutathione peroxidase activity ↑ (*Ji, 2002*)
- SOD protein and activity ↑ (*Suzuki et al. 2000, Ji, 2002*)
- Catalase → (*Powers & Sen, 2000*)
- Muscle glutathione (GSH) content ↑ (*Powers & Sen, 2000*)

Long-term wheel running

- Gene expression (heart) - 137 genes sig. affected by age (Bronikowski et al., 1999)
- Most were assoc. with inflammatory and stress response
- 32 mos. of wheel running attenuated age-related changes in 70 of the 137 genes

Potential benefits from life long exercise under investigation





- Increase in mitochondrion function
- Decrease oxidant production, specifically a decrease in free radical leak in Complex I and or complex III
- Decrease mitochondrial damage
- Decrease in mitochondrial deletions
- Removal of protein aggregates by proteosome activities
- Removal of damaged mitochondria by lysosomal autophagy (-imperfect autophagocytosis)

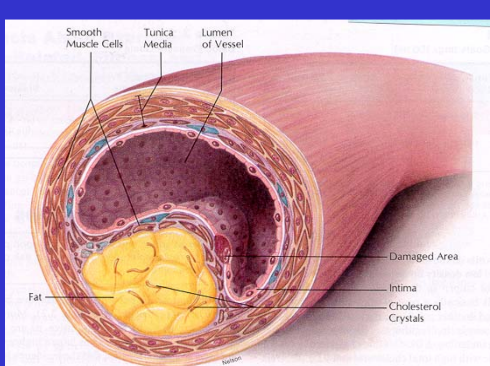
Protein aggregates

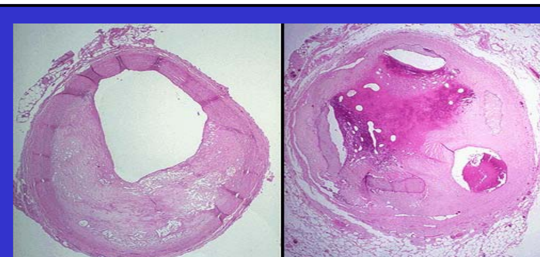
Exercise & Longevity Humans; The Human Story

Disease prevention

Historical Perspective

- Occupational = Leisure-time physical activity
- 1940's: Morris et al.
  - Bus drivers vs. conductors
  - Postal service workers vs. civil servants
- Initial findings
  - ↑ physical activity yields ↓ CHD





This is occlusive coronary atherosclerosis. The coronary at the left is narrowed by 60 to 70%. The coronary at the right is even worse with evidence of previous thrombosis with organization of the thrombus and recanalization such that there are three small lumens remaining.

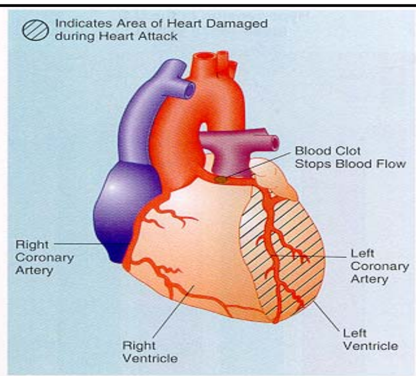


FIGURE 12.4 Example of a myocardial infarction (heart attack). Note that the shaded area of the heart is damaged due to a reduction in blood flow during the heart attack.

Historical details through 1978

- Physically inactive had
  - 50% higher incidence of CHD
  - 50% higher all-cause mortality
- Physical activity 'protected' independently of other risk factors:
  - Smoking, ↑ BP, ↑ BMI, Parental history of CHD, ↓ stature, hypercholesterolemia

Epidemiological studies

- College Alumni Health Study
- Harvard Alumni Health Study
- San Francisco Longshoremen

- I s exercise important to live longer?
- And How Much Exercise?

Harvard Alumni Health Study (Paffenbarger '86 '93 '95)

- Mortality lowest (↓ 54%) for those (men) expending 3000-3500 kcal/wk in physical activity
- Initial ↓ mortality risk (↓ 22%)
  at >500 kcal/wk
  (n=17,000)
- At >2000 kcal/wk (300 kcal/day):
  - 16% decline in mortality
  - Compare to avoiding: Smoking: 23% decline

<u>Caloric Expenditure</u>

- **<u>I. Caloric Expenditure</u>**
- 1-2 kcal/min (light work)
- < 5 kcal/min (housework, driving, etc)
- > 10 kcal/min (hard running)
- **<u>ACSM Advise to expend:</u>**
- 150-300 (kcal) per exercise session
- 800-900 (kcal) per week

Harvard Alumni Health Study

- >2000 vs <500 kcal/wk physical activity increases mean lifespan about 2 yrs (3%)

‘Fins’ in the 7 Countries Study (’87)

- Heavy physical activity (> 5km/d walking, farming profession etc.) improved mortality by 35% during 1st 10 years of study only.
- “premature mortality but not max life span can be improved by physical activity” (n=600)

Smoking negated physical activity benefit

Getting fit seems to be the key.. To reducing your risk

- previous physical activity does not reduce relative mortality risk (Harvard alumni)
- Contrasted by Aerobics center (’95):

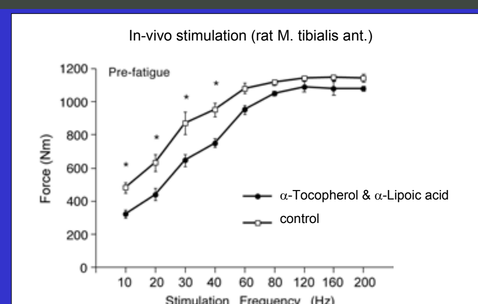
1st	vs	2nd Exam	relative risk
Unfit*		fit	↓ 45%
Fit		unfit	↓ 48%
Fit		fit	↓ 67%

*unfit = lowest 20% for TET (very unfit)

- Each 1 minute added to GXT = ↓ 10%

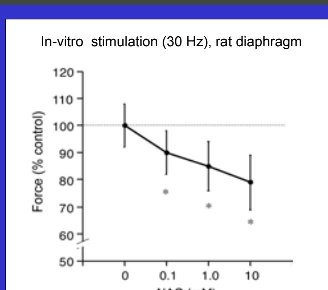
Reactive Oxygen Species and Potential effects on Muscle contractility (Brief)

ROS and contractile force in unfatigued skeletal muscle



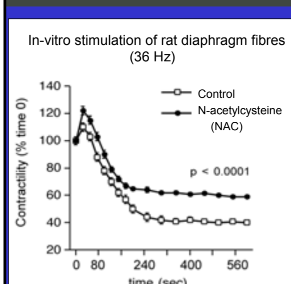
Coombes et al. (2001) *J Appl Physiol* **90**:1424

Antioxidants and contractile force in unfatigued muscle

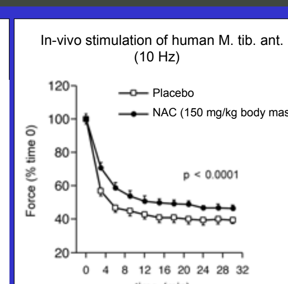


Khawli & Reid (1994) *J Appl Physiol* **77**: 317-324

Antioxidants and contractile force in muscle fatigue



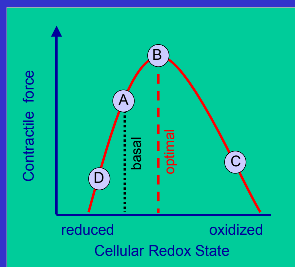
Khawli & Reid (1994) *J Appl Physiol* **77**: 317-324



Reid et al. (1994) *J Clin Invest* **94**: 2468-2474

Cellular redox state and contractile force

A: Basal conditions
B: + ROS (small amounts)
C: + ROS (large amounts)
D: + antioxidants



Reid, MB (2001) *J Appl Physiol* **90:** 724

Cell Signaling and Exercise Training

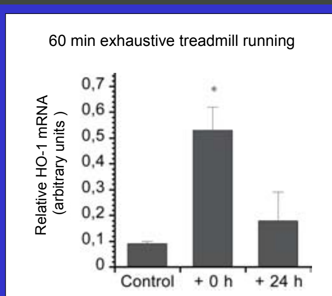
- Endogenous antioxidants
- Alimentary antioxidants
- Antioxidant enzymes

  Glutathione and thioredoxin system
  Superoxide dismutase (SOD), catalase

- Antioxidant stress proteins

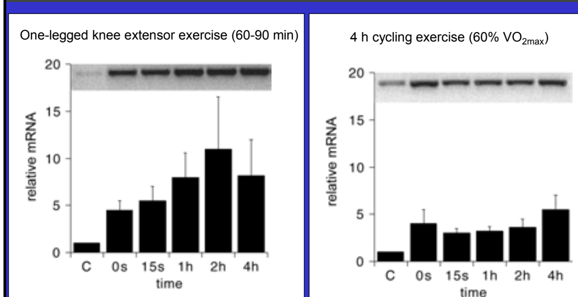
  Heat shock proteins: HSP25, HSP27, HSP70
  Heme oxygenase-1 (HO-1)

Exercise and HO-1 expression in rat muscle



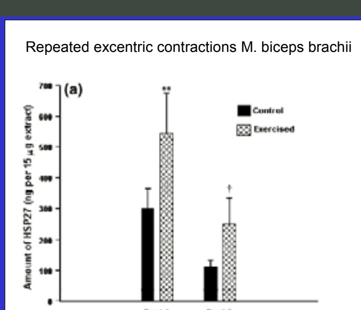
Essig et al. (1999) *Am J Physiol* **272:** C59-C67

Exercise and HO-1 expression in human skeletal muscle



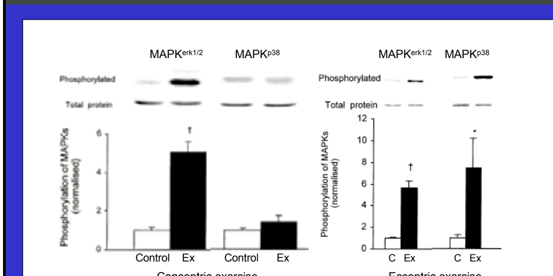
Pilegaard et al. (2000) *Am J Physiol* **279:** E806-E814

Exercise and HSP27 expression in human skeletal muscle



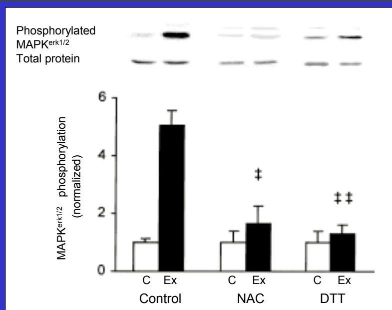
Thompson et al. (2001) Acta *Physiol Scand* **171:** 187-193

Exercise and phosphorylation of MAPKs in rat muscle



Wretman et al. (2001) *J Physiol* **535:** 155-164

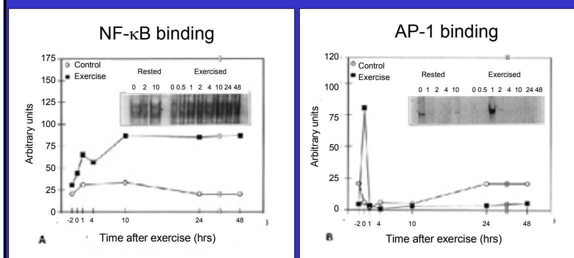
Antioxidants and exercise-induced MAPK$^{erk1/2}$ phosphorylation



NAC: N-acetylcysteine
DTT: Dithiothreitol

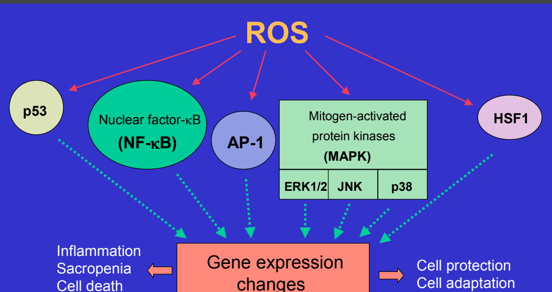
Wretman et al. (2001) *J Physiol* **535**: 155-164

Exercise and binding activity of NF-κB and AP-1 in rat skeletal muscle



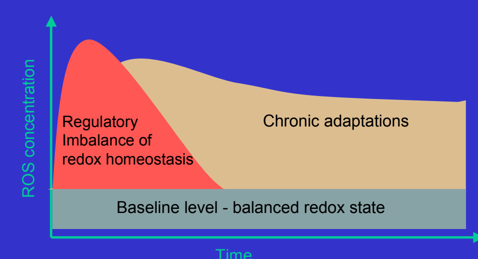
Hollander et al. (2001) *Pflügers Arch* **442:** 426

Exemplary signaling pathways sensitive to ROS



Martindale & Holbrook (2002) *J Physiol* **192:** 1-15

Conclusions



Dröge, W. (2001) *Physiol Rev* *82*: 47-95

Long-lived species

"CR" diet and life-long exercise habits will remain powerful interventions to reach maximum lifespan potential

Humans (~77-M ~80-F years) Maximum ~122y

Summary
Reactive oxygen species (ROS) - good or bad guys ?