Nutrition and Stress

in

Diseases

like

AIDS and Cancer

Paracelsus:

Everything is dependent on the concentration

Paracelsus (11 November or 17 December 1493 in Einsiedeln, Switzerland – 24 September 1541) was an alchemist, physician, astrologer, and general occultist.

Paracelsus, sometimes called the father of toxicology, wrote:

German: *Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, dass ein Ding kein Gift ist.*

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."

Paracelsus is often cited as coining the phrase "the dose makes the poison". Although he did not say this precisely, it seems that Paracelsus was indeed well aware of the principle .

The Importance of Hormesis to Public Health

Ralph Cook[1] and Edward J. Calabrese[2]

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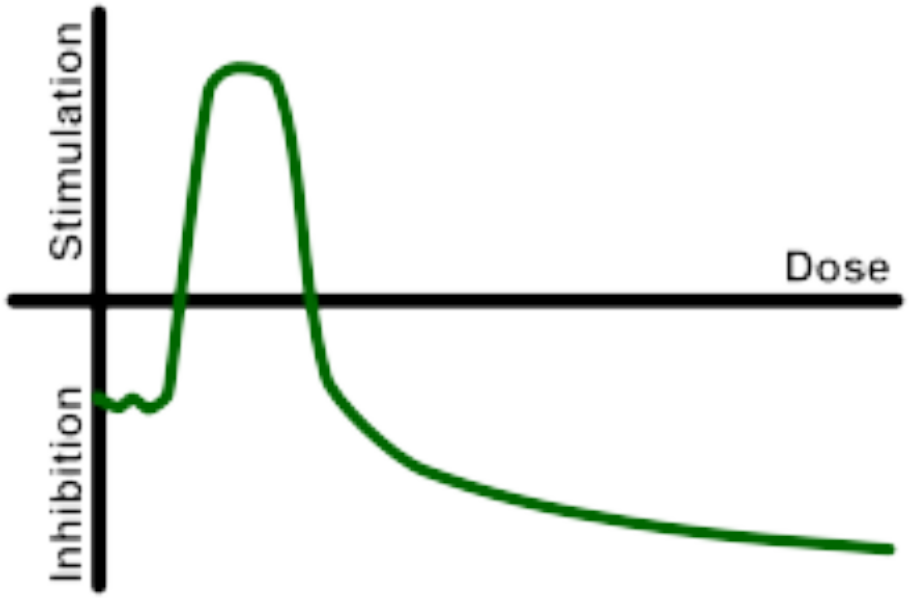
Abstract

Background: Hormesis is a specific type of nonmonotonic dose response whose occurrence has been documented across a broad range of biological models, diverse types of exposure, and a variety of outcomes. The effects that occur at various points along this curve can be interpreted as beneficial or detrimental, depending on the biological or ecologic context in which they occur.

Conclusions: We believe that ignoring hormesis is poor policy because it ignores knowledge that could be used to improve public health.

Schematic forms of the hormetic dose response:

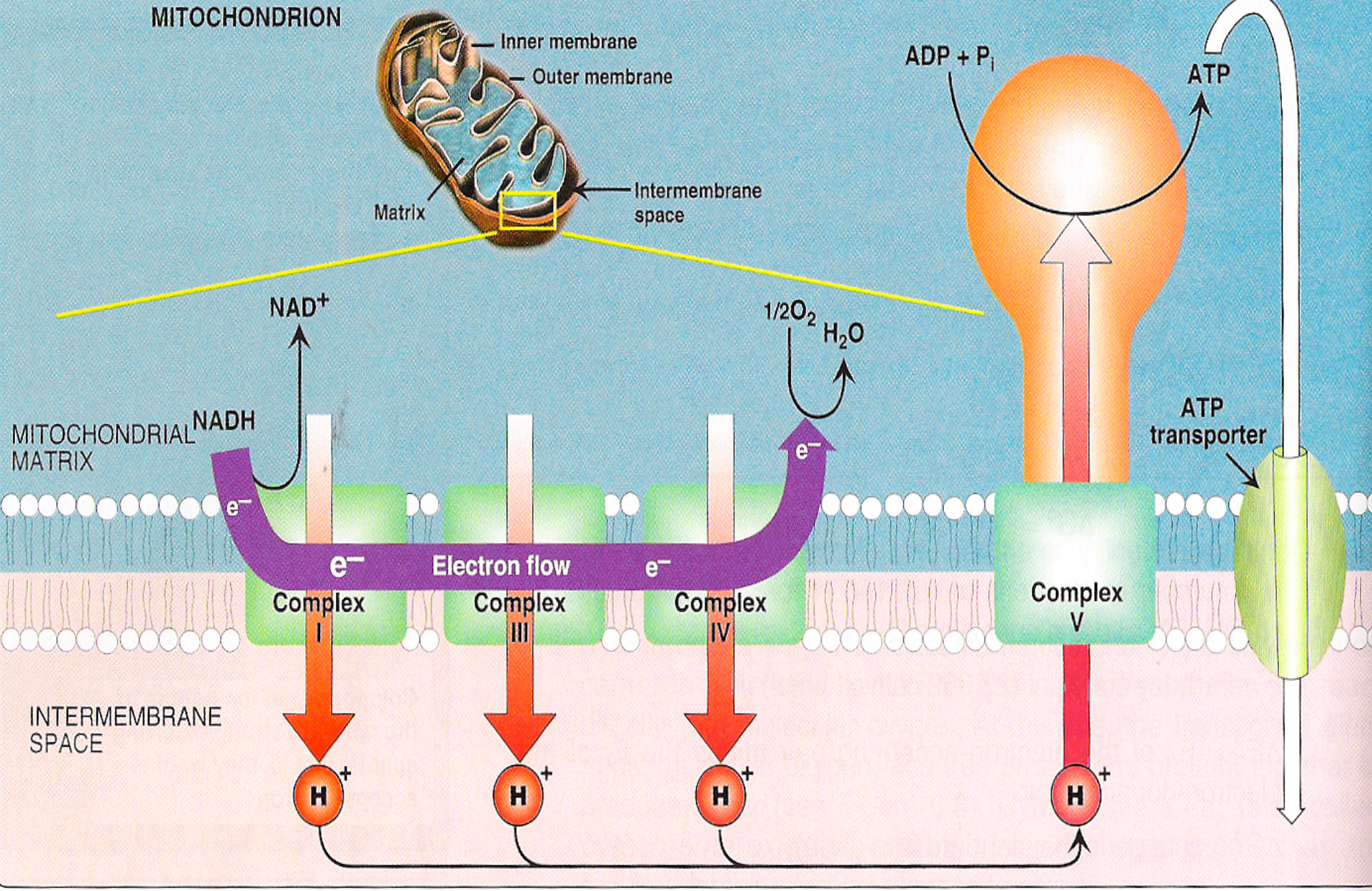
A.The most common form of the hormetic dose Ð-response curve showing low-dose stimulatory and high-dose inhibitory responses (β- or inverted U-shaped curve).



B.The hormetic dose Ð-response curve depicting low-dose reduction and high-dose enhancement of adverse effects would be a (J- or U-shaped curve).

A very low dose of a chemical agent may trigger from an organism the opposite response to a very high dose.

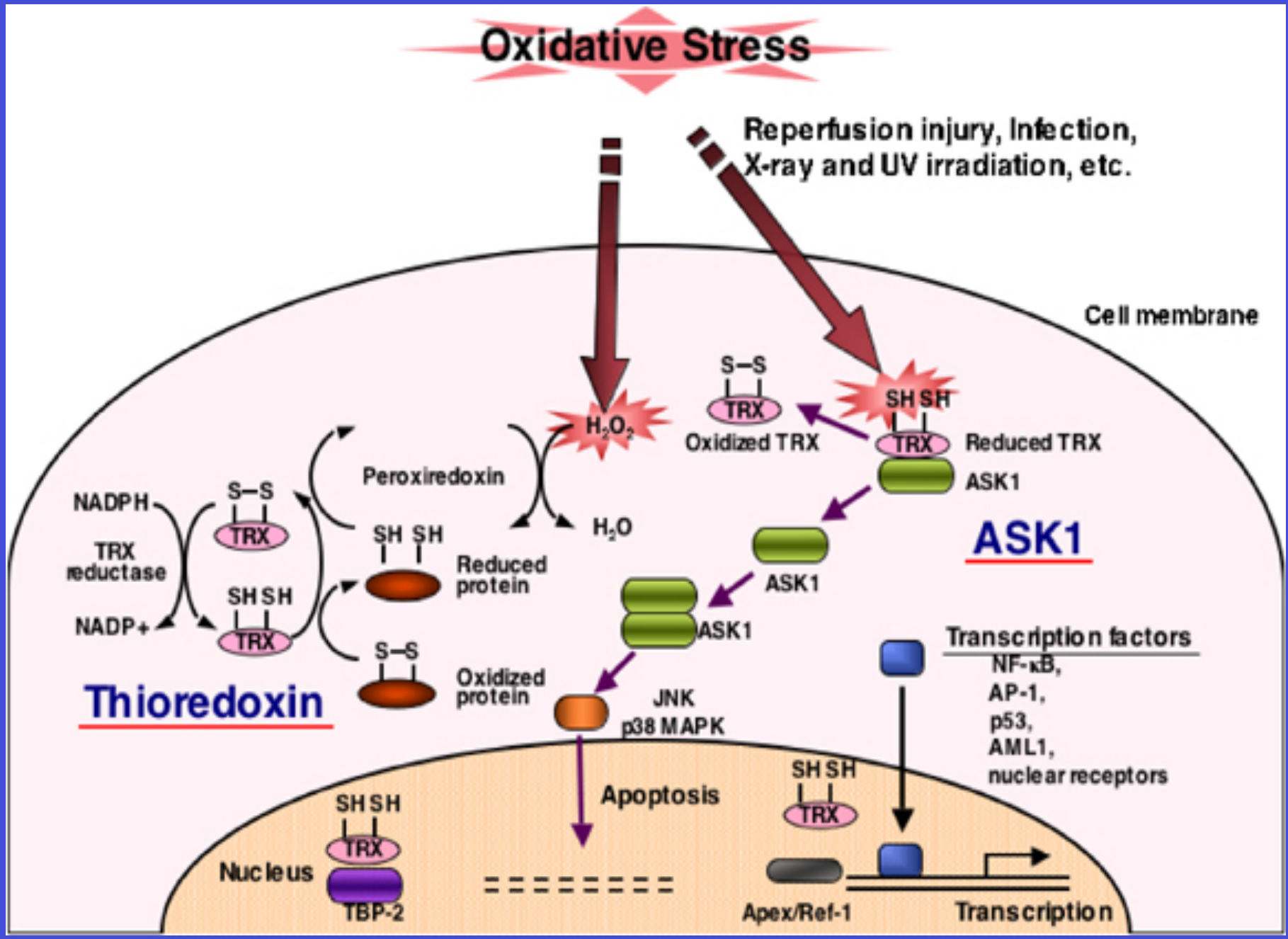
Oxygen metabolism, although essential for life, imposes a potential threat to cells because of the formation of partially reduced oxygen species. One electron reduction of oxygen produces *superoxide* whereas two electron reduction produces *hydrogen peroxide*. Therefore, electron flow through oxygen, utilizing processes such as the mitochondrial electron transport chain, flavoproteins, cytochrome P450 and oxidases, is tightly coupled to avoid partial reduction of oxygen.

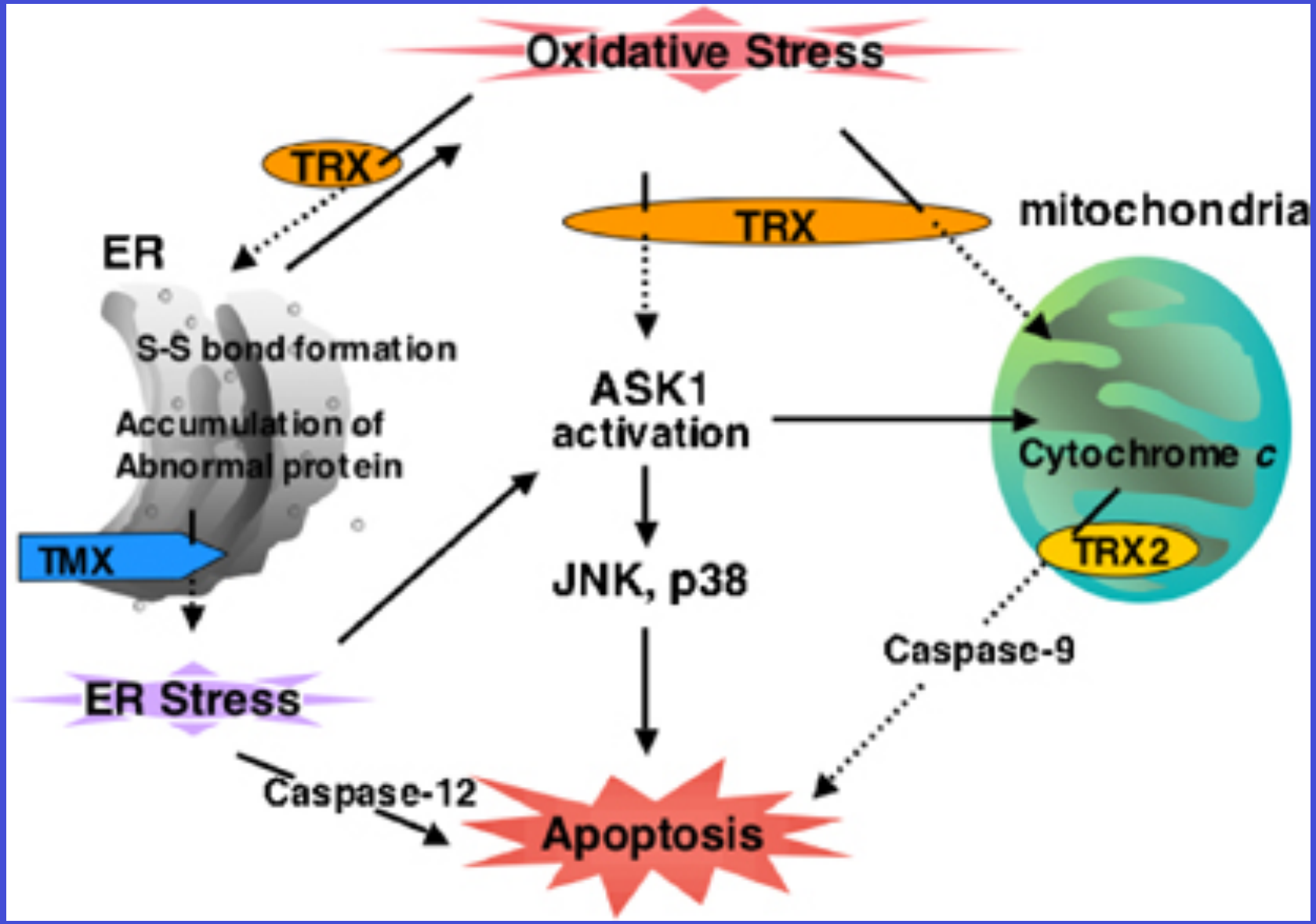


Electron transport chain shown coupled to the transport of protons. [Note: Complex II is not shown.]

Normal cellular *homeostasis* is a *delicate balance* between the rate and magnitude of *oxidant formation* and the *rate of oxidant elimination*.

Oxidative stress can, therefore, be defined as the pathogenic outcome of the overproduction of oxidants that overwhelms the cellular antioxidant capacity.


Oxidative Stress
Reperfusion injury, Infection,
X-ray and UV irradiation, etc.
Cell membrane
H_2O_2
S–S
TRX
Oxidized TRX
SH SH
TRX
Reduced TRX
ASK1
ASK1
ASK1
ASK1
Peroxiredoxin
H_2O
NADPH
TRX reductase
NADP+
S–S
TRX
SH SH
TRX
SH SH
Reduced protein
S–S
Oxidized protein
Thioredoxin
JNK
p38 MAPK
Transcription factors
NF-κB,
AP-1,
p53,
AML1,
nuclear receptors
Apoptosis
SH SH
TRX
Nucleus
TBP-2
SH SH
TRX
Apex/Ref-1
Transcription


Oxidative Stress
TRX
ER
S-S bond formation
Accumulation of
Abnormal protein
TMX
ER Stress
Caspase-12
TRX
mitochondria
ASK1
activation
JNK, p38
Cytochrome c
TRX2
Caspase-9
Apoptosis

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The signaling networks that mediate activation, proliferation, or programmed cell death of T lymphocytes are dependent on complex redox and metabolic pathways. T lymphocytes are primarily activated through the T-cell receptor and co-stimulatory molecules. Although activation results in lymphokine production, proliferation, and clonal expansion, it also increases susceptibility to apoptosis upon crosslinking of cell-surface death receptors or exposure to toxic metabolites. Activation signals are transmitted by receptor-associated protein tyrosine kinases and phosphatases through calcium mobilization to a secondary cascade of kinases, which in turn activate transcription factors initiating cell proliferation and cytokine production. Initiation and activity of cell death-mediating proteases are redox-sensitive and dependent on energy provided by ATP. Mitochondria play crucial roles in providing ATP for T-cell activation through the electron transport chain and oxidative phosphorylation. The mitochondrial transmembrane potential ($\Delta\Psi_m$) plays a decisive role not only by driving ATP synthesis, but also by controlling reactive oxygen species production and release of cell death-inducing factors. $\Delta\Psi_m$ and reactive oxygen species levels are regulated by the supply of reducing equivalents, glutathione and thioredoxin, as well as NADPH generated in the pentose phosphate pathway. This article identifies redox and metabolic checkpoints controlling activation and survival of T lymphocytes.

Mitochondria play crucial roles in providing ATP for T-cell activation through the electron transport chain and oxidative phosphorylation.

The mitochondrial transmembrane potential ($\Delta\Psi_m$) plays a decisive role not only by driving ATP synthesis, but also by controlling reactive oxygen species production and release of cell death-inducing factors. $\Delta\Psi_m$ and reactive oxygen species levels are regulated by the supply of reducing equivalents, glutathione and thioredoxin, as well as NADPH generated in the pentose phosphate pathway.

This article identifies redox and metabolic checkpoints controlling activation and survival of T lymphocytes.

Biochem J. 2003 August 1; 373(Pt 3): 845–853.
doi: 10.1042/BJ20030275.

Differential role of glutaredoxin and thioredoxin in metabolic oxidative stress-induced activation of apoptosis signal-regulating kinase 1.

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Abstract

Redox-sensing molecules such as thioredoxin (TRX) and glutaredoxin (GRX) bind to *apoptosis* signal-regulating kinase 1 (ASK1) and suppress its activation. **Glucose deprivation disrupted the interaction between TRX/GRX and ASK1 and subsequently activated the ASK1-stress-activated protein kinase/extracellular-signal-regulated kinase kinase-c-Jun N-terminal kinase 1 (JNK1) signal-transduction pathway.** L-Buthionine-(S, R)-sulphoximine, which decreases intracellular glutathione content, enhanced glucose deprivation-induced activation of JNK1 by promoting the dissociation of TRX, but not GRX, from ASK1. Treatment of cells with exogenous glutathione disulphide ester resulted in the dissociation of GRX, but not TRX, from ASK1 and the subsequent activation of JNK1. Nonetheless, overexpression of calatase, an H(2)O(2) scavenger, inhibited JNK1 activation and cytotoxicity as well as the dissociation of TRX and GRX from ASK1 during combined glucose deprivation and L-buthionine-(S, R)-sulphoximine treatment**. Taken together, glucose deprivation-induced metabolic oxidative stress may activate ASK1 through two different pathways: glutathione-dependent GRX-ASK1 and glutathione-independent TRX-ASK1 pathways.**

Taken together, glucose deprivation-induced metabolic oxidative stress may activate ASK1 through two different pathways: glutathione-dependent GRX-ASK1 and glutathione-independent TRX-ASK1 pathways.

Oxidative stress: role of mitochondria and protection by glutathione.

Biofactors 1998;8(1-2):7-11.

Increasing evidence has unraveled a dual functional role of mitochondria as suppliers of the energy required for cell viability, and critical players in the pathway leading to cell death. Glutathione (GSH) in mitochondria is the only defense available to metabolize hydrogen peroxide.

Glutathione deficiency is associated with impaired survival in HIV disease.

Glutathione is a selenoprotein and malnutrition leads to a lack of micronutrients like selenium. Thus the preventive effect of reduced glutathione against ROS is impaired in malnutrition.

Conclusion:

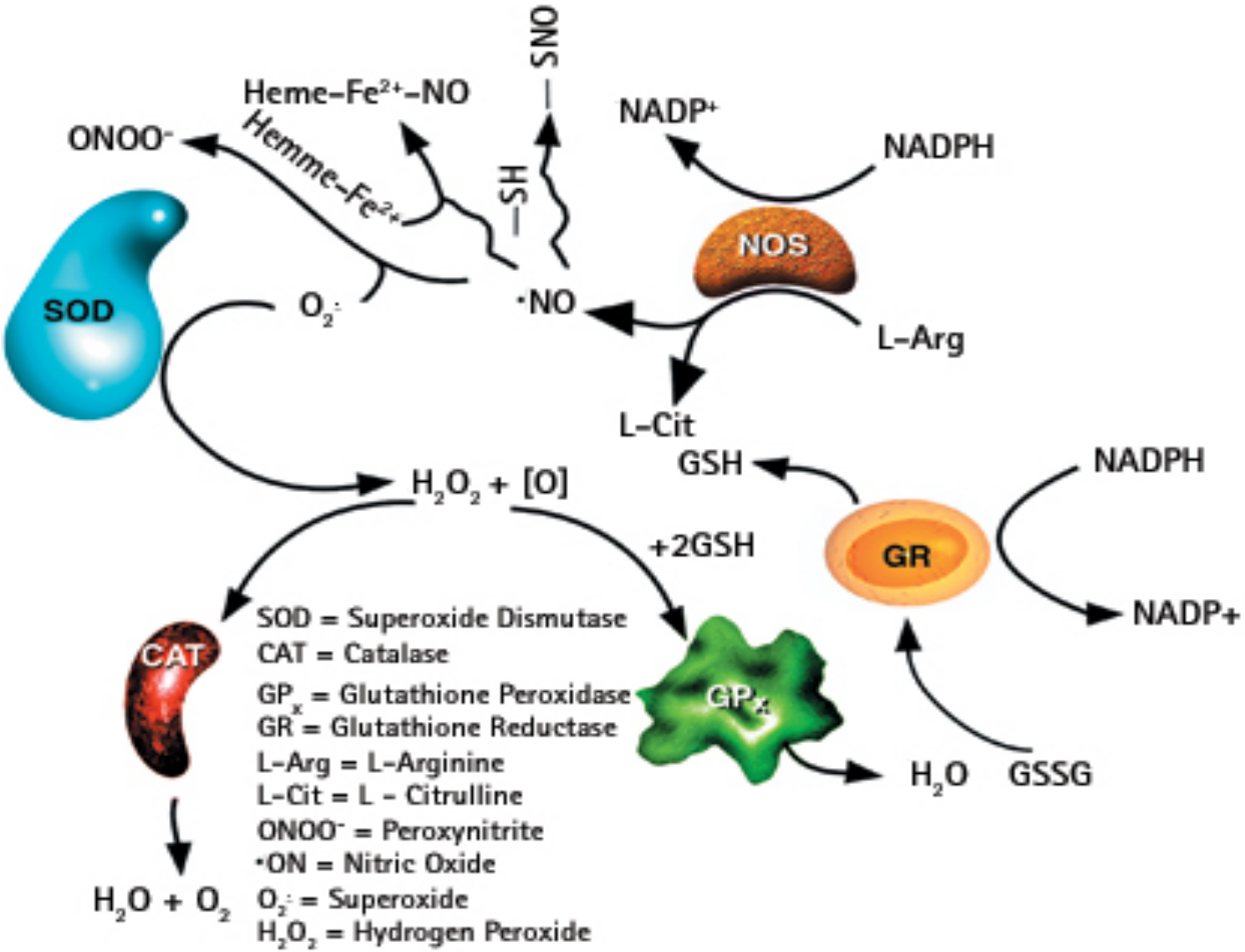
There is a relation between **starvation** and
induction of apoptotic cell pathways **(cell death).**

Thus T-cell decline in AIDS can depend on malnutrition.

A critical function of reactive species is immunological host response. Generation of reactive species and strong oxidants by inflammatory cells is essential for killing invading microorganisms.

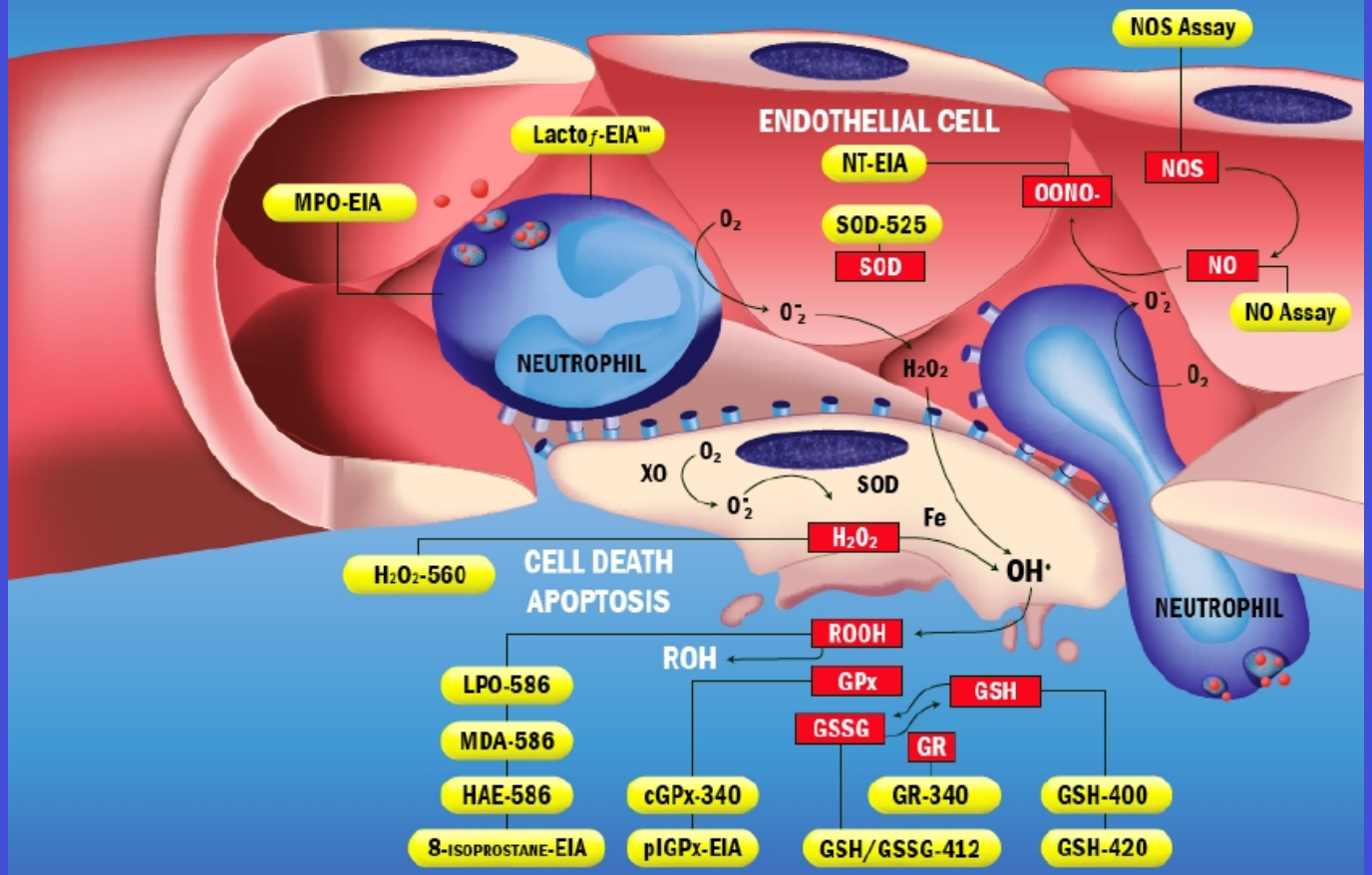
However, experimental evidence has implicated reactive species in the pathogenic mechanism of several diseases.

Oxidative Stress



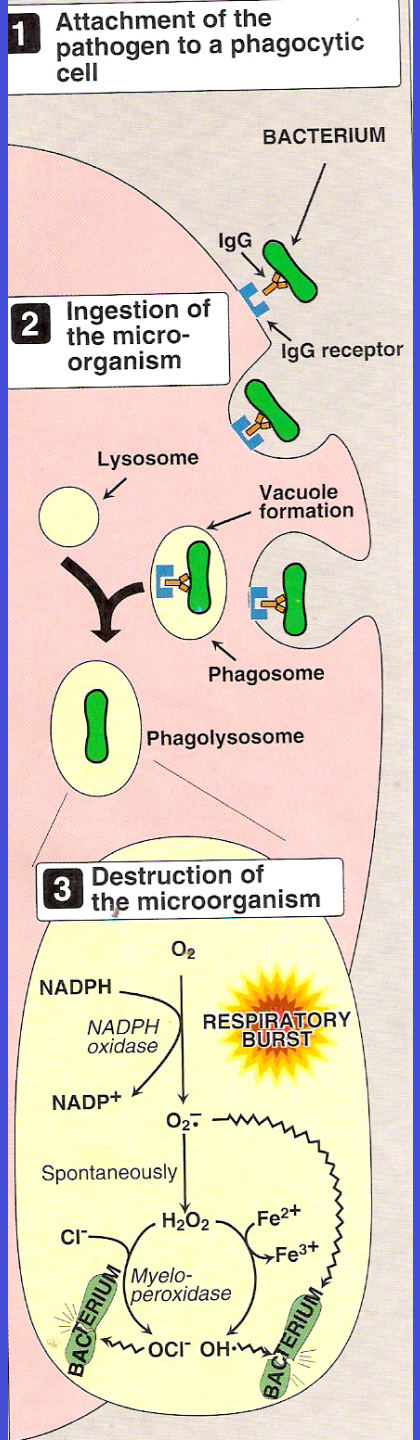
OXIS International, Inc.

Pathways of Oxidative Stress



Phagocytosis and the oxygen dependent pathway of microbial killing:

High respiratory burst with microbial infections (production of ROS for destruction of bacteria).



High concentrations of microbes, i.e. by ingesting nonpurified drinking water lead to high respiratory burst and ROS.

Antioxidant defenses fall into two categories:

1. enzymatic
2. nonenzymatic

superoxide dismutase
catalase
glutathion peroxidase

Non-enzymatic defenses include small molecules such as membrane associated α-tocopherol, ascorbate and glutathione.

ROS-formation and antioxidant enzymes

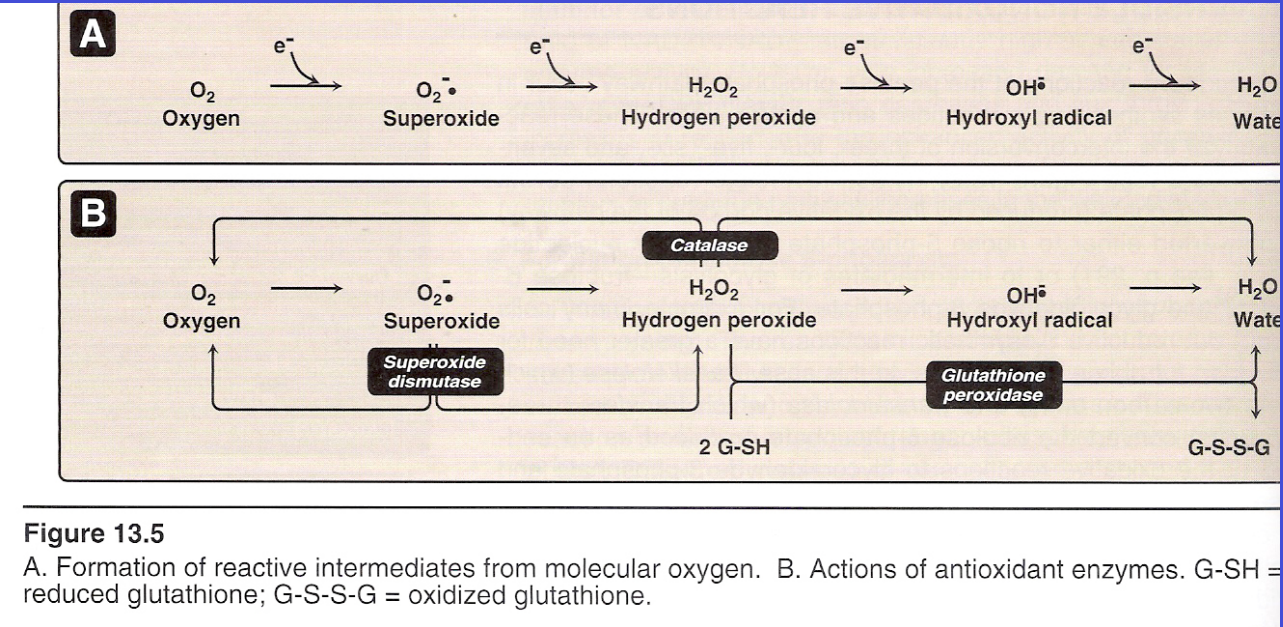
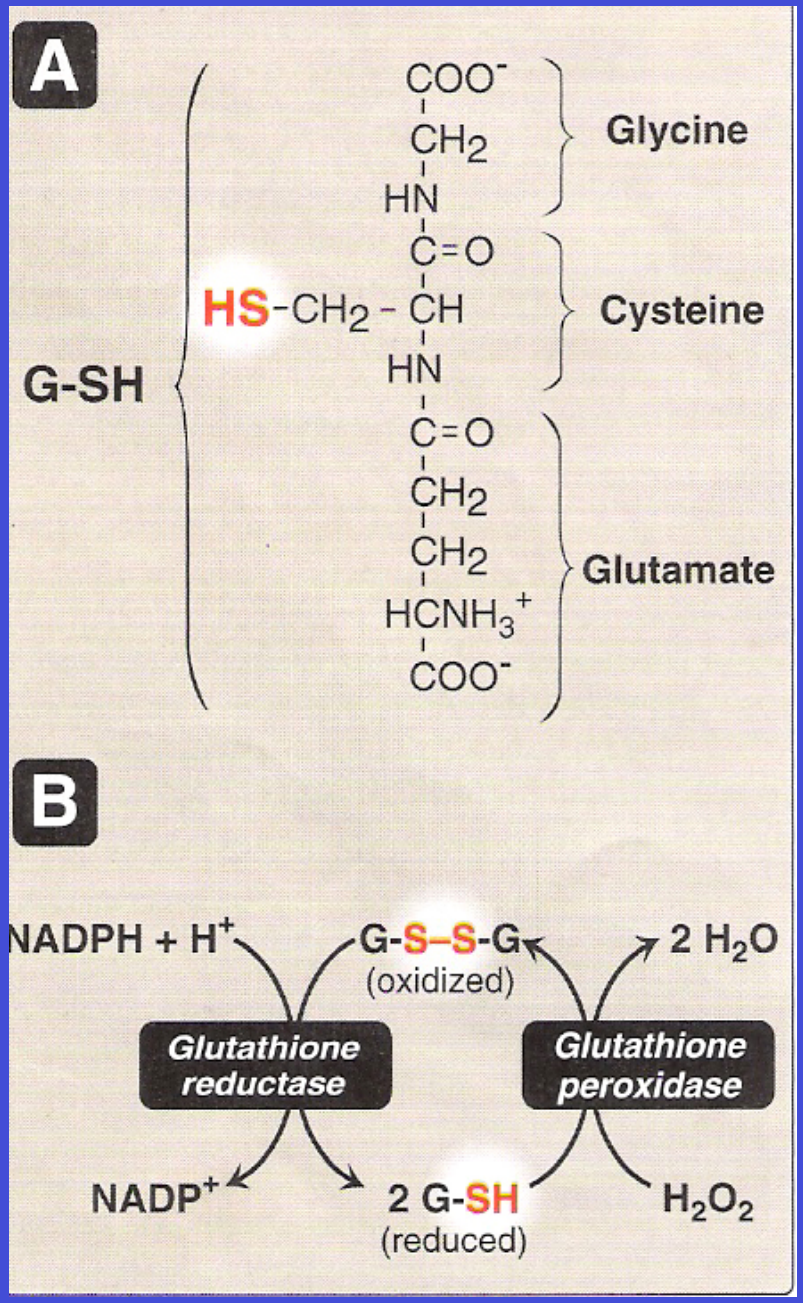


Figure 13.5

A. Formation of reactive intermediates from molecular oxygen. B. Actions of antioxidant enzymes. G-SH = reduced glutathione; G-S-S-G = oxidized glutathione.

A: Structure of glutathione

B: Glutathione-mediated reduction of hydrogen peroxide by NADPH.



Characterization of human thioredoxin-like-1 : Potential involvement in the cellular response against glucose deprivation

Auteur(s) / Author(s)

; GUSTAFSSON Jan-Ake ; MIRANDA-VIZUETE Antonio ; JIMENEZ Alberto ; PELTO-HUIKKO Markku

Résumé / Abstract

The thioredoxin system, composed of thioredoxin (Trx) and thioredoxin reductase (TrxR), emerges as one of the most important thiol-based systems involved in the maintenance of the cellular redox balance. Thioredoxin-like-1 (TXL-1) is a highly conserved protein comprising an N-terminal Trx domain and a C-terminal domain of unknown function. Here we show that TXL-1 is a substrate for the cytosolic selenoprotein TrxR-1. In situ hybridization experiments demonstrates high expression of Txl-1 mRNA in various areas of central nervous system and also in some reproductive organs. Glucose deprivation, but not hydrogen peroxide treatment, reduced the levels of endogenous TXL-1 protein in HEK-293 cell line. Conversely, overexpression of TXL-1 protects against glucose deprivation-induced cytotoxicity. **Taken together, the finding that Txl-1 mRNA is highly expressed in tissues which use glucose as a primary energy source and the modulation of TXL-1 levels upon glucose deprivation indicate that TXL-1 might be involved in the cellular response to sugar starvation stress.**

“… the modulation of TXL-1 levels upon glucose deprivation indicate that TXL-1might be involved in the cellular response to sugar starvation stress.”

WHO:

Ask the expert On-line Q&A
10 October 2007

About 20 million children under five worldwide are severely malnourished, which leaves them more vulnerable to illness and early death.

Relationship between stress and oxidative stress:

Psychological Stress-Induced Oxidative Stress as a Model of Sub-Healthy Condition and the Effect of TCM

Lei Wang[1,3], Gong Muxin[1,3], Hiroshi Nishida[1], Chieko Shirakawa[2], Shinji Sato[1] and Tetsuya Konishi[1]
[1]Niigata University of Pharmacy **and** Applied Life Sciences Niigata 950-2081,, [2]Niigata College of Medical Technology, Niigata 950-2076, Japan **and** [3]School of Traditional Chinese Medicine, Capital Medical University Beijing, China

Distress-mediated tissue **oxidative stress** was examined as a model of sub-healthy condition defined in traditional Chinese medicine theory. Mice were subjected to psychologically **stress**ful conditions by whiskers removal. Under this condition, spontaneous locomotive activity was significantly enhanced in the dark ($P < 0.05$ versus the control mice in three different movements), **and** granulocytes/lymphocytes balance shifted to granulocytes. At the same time, peroxynitrite level in blood plasma increased to

180% from that of the control mice at 6 h after removal of the whiskers ($P < 0.01$), **and** was maintained even after 12 h. Both protein carbonyl formation **and** lipid peroxidation were significantly increased under this condition in brain, heart, liver **and** spleen at 6 h after removal of whiskers ($P < 0.05$ or $P < 0.01$), **and** these levels were maximized after 12 h (increased to 120–160%, $P < 0.05$ or $P < 0.01$). The **oxidative** tissue injuries observed at 12 h after the removal of the whiskers were effectively prevented by two traditional Chinese medicine formula: Shengmai San (SMS) **and** Ling Gui Zhu Gan Tang (LGZGT), when administered for 5 days before the removal of the whiskers. Therefore, this **stress** model is considered useful in assessing the preventive potential of antioxidants **and** antioxidant-based herbal mixtures in treating the pathophysiology associated with psychological or emotional **distress**.

For reprints **and** all correspondence: Tetsuya Konishi, Niigata University of Pharmacy **and** Applied Life Sciences, Higashi-jima 265-1, Niigata, Niigata 956-8603, Japan. Tel: +81-250-25-5127; Fax: +81-250-25-5127; E-mail: konishi@niigata-pharm.ac.jp
Received January 20, 2006; accepted September 25, 2006

: Toxicology. 2002 Dec 27;181-182:219-22. Links

Oxy radicals, lipid peroxidation and DNA damage.

Marnett LJ.

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Oxygen radicals react with polyunsaturated fatty acid residues in phospholipids resulting in the production of a plethora of products, many of them reactive toward protein and DNA. One of the most abundant carbonyl products of lipid peroxidation is malondialdehyde (MDA), which also is generated as a side-product of prostaglandin biosynthesis. It reacts with DNA to form adducts to deoxyguanosine, deoxyadenosine, and deoxycytidine. The deoxyguanosine adduct (M(1)G) has been detected in liver, white blood cells, colon, pancreas, and breast from healthy human beings at levels ranging from 1 to 120 per 10(8) nucleotides. Random and site-specific mutagenesis experiments indicate that MDA-DNA adducts are mutagenic in bacteria and in mammalian cells. M(1)G is highly mutagenic when incorporated into viral genomes then replicated in E. coli. It is repaired by the nucleotide excision repair pathway. Lipid peroxidation appears to be a major source of endogenous DNA damage in humans that may contribute significantly to cancer and other genetic diseases linked to lifestyle and dietary factors.

PMID: 12505314 [PubMed - indexed for MEDLINE]

Lipid peroxidation appears to be a major source of endogenous DNA damage in humans that may contribute significantly to cancer and other genetic diseases *linked to lifestyle and dietary factors.*

As a consequence of aerobic metabolism, **polyunsaturated fatty acids** undergo reaction with oxygen to produce peroxyl radicals. **Peroxyl radicals** are the primary free radical intermediate of lipid peroxidation, a chain reaction which propagates through cellular membranes during conditions of oxidative stress.

Reporting last month in the journal Molecular and Cellular Biology, Kimmel Cancer Center director Richard G. Pestell, M.D., Ph.D., Professor and Chair of the Department of Cancer Biology at Jefferson Medical College, and colleagues showed for the first **time that cyclin D1 -- normally involved in promoting cell division -- inhibits the size and activity of the cell's energy-making mitochondria.**

Dr. Pestell notes that scientists have long suspected a link between mitochondrial malfunction and cancer, and since 1930 have known about such a *change in metabolism* when the cell turns cancerous.

Energy gain in aerobic glycolysis

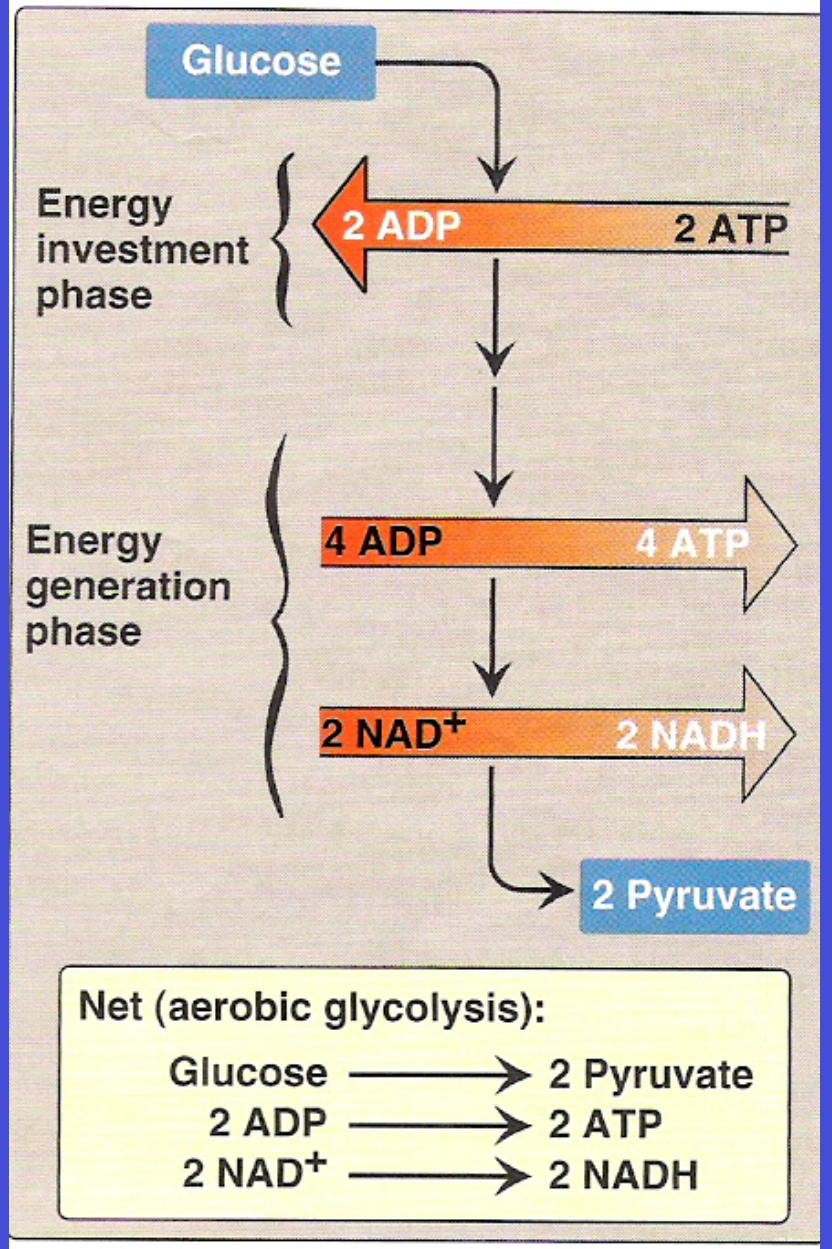
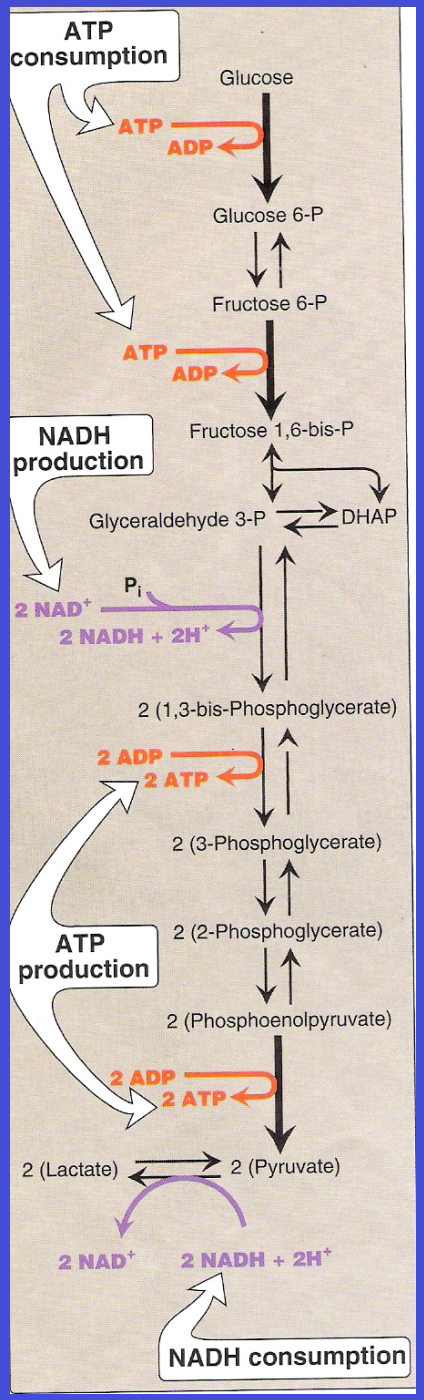
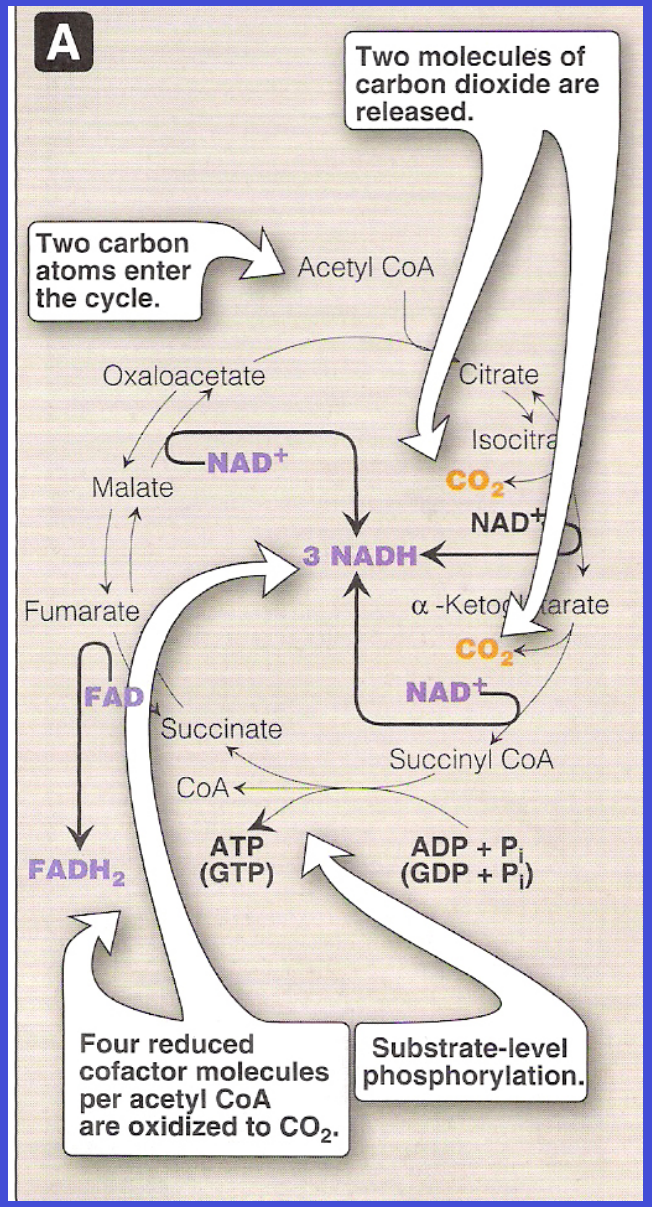


Figure 8.11
Two phases of aerobic glycolysis.

Anaerobic glycolysis:
2 molecules of ATP are generated for each molecule of glucose converted to 2 molecules of lactate.

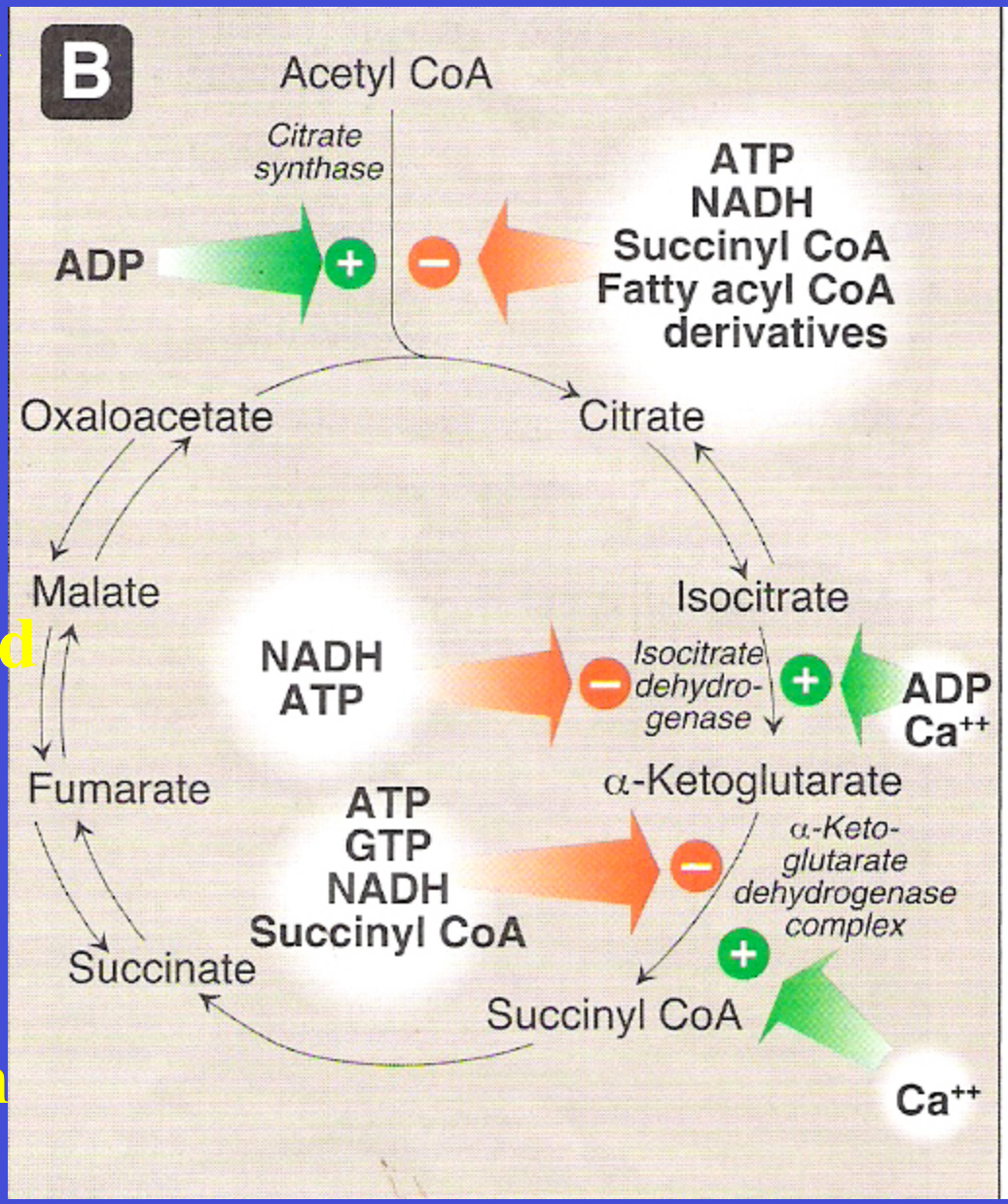


The citric acid cycle



Regulation of the citric acid cycle:

High concentration of *reductive equivalents*, ATP and CoA derivates (that means high energy compounds) block citric acid cycle and oxidative phoshorylation, leading to anaerobic metabolism and may be acidosis and cancer.A high concentration of these molecules is found in high caloric uptake.



A high concentration of *NADPH* promotes nucleic acid biosynthesis which is essential for cell division as in fast dividing cancer cells.

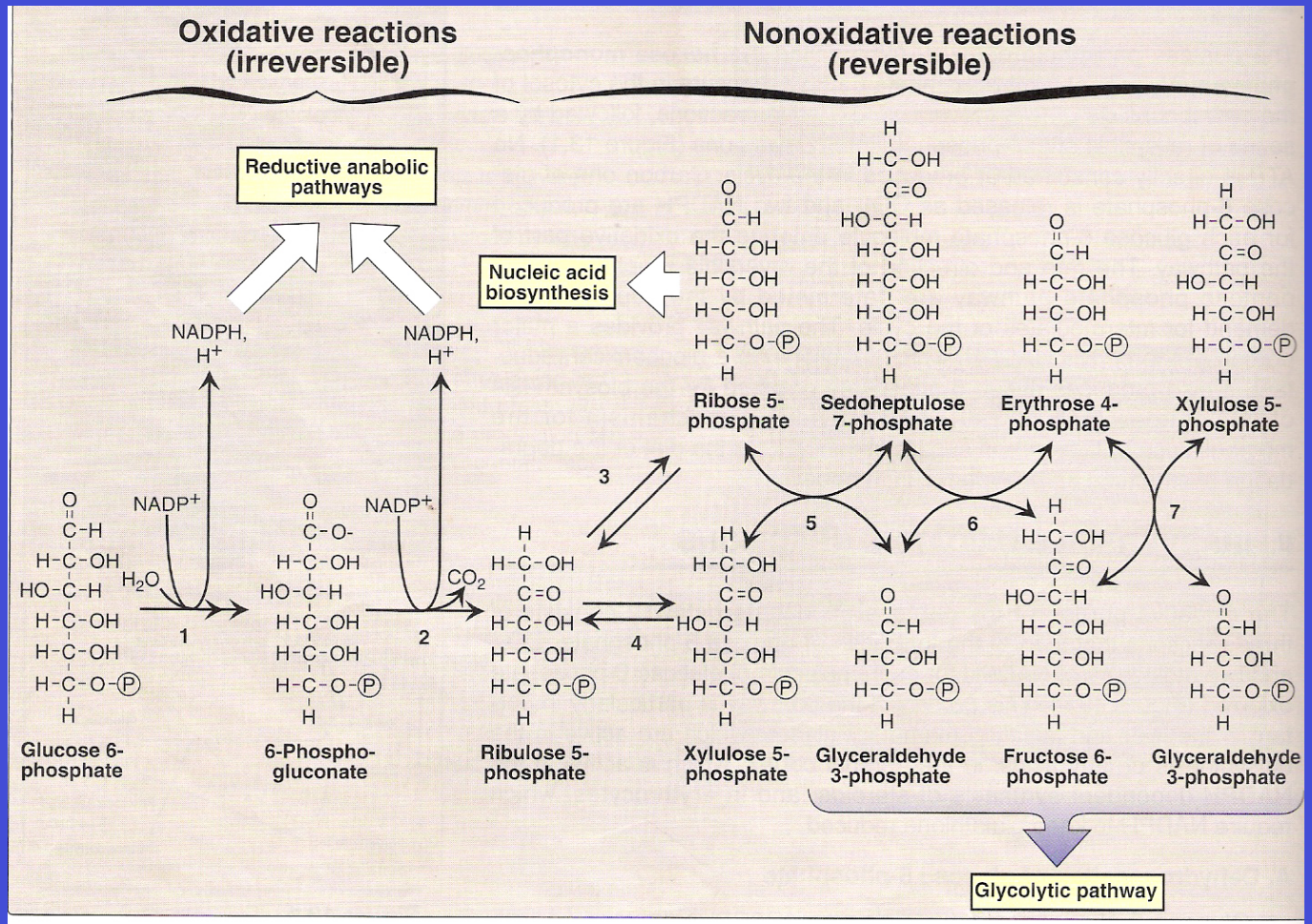


Figure 13.2
Reactions of the hexose monophosphate pathway. Enzymes numbered above are 1) *glucose 6-phosphate dehydrogenase* and *6-phosphogluconolactone hydrolase*, 2) *6-phosphogluconate dehydrogenase*, 3) *ribose 5-phosphate isomerase*, 4) *phosphopentose epimerase*, 5) and 7) *transketolase* (coenzyme: thiamine pyrophosphate), and 6) *transaldolase*.

Glucose Restriction Extends *Caenorhabditis elegans* Life Span by Inducing Mitochondrial Respiration and Increasing Oxidative Stress

Tim J. Schulz,[1,2] Kim Zarse,[1] Anja Voigt,[1,2] Nadine Urban,[1] Marc Birringer,[1] and Michael Ristow[1,2],
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Summary

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Increasing cellular glucose uptake is a fundamental concept in treatment of type 2 diabetes, whereas nutritive calorie restriction increases life expectancy. We show here that increased glucose availability decreases *Caenorhabditis elegans* life span, while impaired glucose metabolism extends life expectancy by inducing mitochondrial respiration. The histone deacetylase Sir2.1 is found here to be dispensable for this phenotype, whereas disruption of *aak-2*, a homolog of AMP-dependent kinase (AMPK), abolishes extension of life span due to impaired glycolysis. Reduced glucose availability promotes formation of reactive oxygen species (ROS), induces catalase activity, and increases oxidative stress resistance and survival rates, altogether providing direct evidence for a hitherto hypothetical concept named mitochondrial hormesis or “mitohormesis.” Accordingly, treatment of nematodes with different antioxidants and vitamins prevents extension of life span. In summary, these data indicate that glucose restriction promotes mitochondrial metabolism, causing increased ROS formation and cumulating in hormetic extension of life span, questioning current treatments of type 2 diabetes as well as the widespread use of antioxidant supplements.

Accordingly, treatment of nematodes with different antioxidants and vitamins prevents extension of life span. In summary, these data indicate that glucose restriction promotes mitochondrial metabolism, causing increased ROS formation and cumulating in hormetic extension of life span, questioning current treatments of type 2 diabetes as well as the widespread use of antioxidant supplements.

Advice:

Be careful in the uptake of high concentrations of vitamin pills. Try to have a balanced food uptake with 5 a day, which means 5 portions of fruit and vegetables including their fibers.

Low doses of reactive oxygen species protect endothelial cells from apoptosis by increasing thioredoxin-1 expression

Edited by Valdimir Skulachev

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Received 21 July 2004; Revised 4 October 2004; accepted 19 October 2004. Available online 27 October 2004.

Abstract

The redox regulator thioredoxin-1 (Trx-1) is required for the redox potential of the cell and exerts important functions in cell growth and apoptosis. Severe oxidative stress has been implicated in the oxidation of proteins and cell death. However, the role of low doses of reactive oxygen species (ROS) is poorly understood. Here, we show that 10 and 50 μM H_2O_2 and short-term exposure to shear stress significantly increased Trx-1 mRNA and protein levels in endothelial cells. Since it is known that Trx-1 exerts anti-apoptotic functions, we next investigated whether low doses of ROS can inhibit basal and serum-depletion induced endothelial cell apoptosis. Indeed, treatment of endothelial cells with 10 and 50 μM H_2O_2 significantly reduced apoptosis induction. Reduction of Trx-1 expression using an antisense oligonucleotide approach resulted in the induction of apoptosis and abolished the inhibitory effect of low doses of H_2O_2. **Taken together, our results demonstrate that low doses of ROS act as signaling molecules and exert anti-apoptotic functions in endothelial cells via upregulation of the redox-regulator Trx-1.**

doi:10.1016/j.febslet.2004.10.041

Conclusion:

Uptake of too high concentrations of antioxidants (vitamins) leads to abolition of free radicals in total and thus to downregulation of thioredoxin TRX-1. Without sufficient thioredoxin-concentration apoptosis is depressed, leading to continued lifespan of cells, including degenerated and mutated cells. This might promote cancer, because of accumulating mutations such as p53.

Taken together, our results demonstrate that low doses of ROS act as signaling molecules and exert anti-apoptotic functions in endothelial cells via upregulation of the redox-regulator Trx-1.

AIDS	versus	Cancer
Low energy (ATP,NADPH)		High energy (ATP,NADPH)
Low conc.glutathione reduced		High conc. glutath. reduced
Low glucose +		high lipid, (glucose)
High ROS > inflammation		high ROS > mutation of
TRX 1 activation		(p53?) or mitoch. DNA,
altered gene expression:		altered metabolism:
RNA, proteins,		glycolysis, acidosis,
transposition, mutation ,		(no citric acid-cycle-
apoptosis, T-cell decline		no CO_2-production)
Normal vitamin concentr.		high vitamin concentr.:
+ glucose: less ROS >		*no* ROS, lack of TRX 1 >
Downregulation of provirus		downregulation of
gene expression > healthier		apoptosis > cancer?

Promotion of Health:

- Low ROS (protection of mitochondria)
- Balanced nutrition (as recommended in the dietary pyramide)
- Natural vitamin and micronutrients uptake

What does this mean?

Avoidance of malnutrition
Promotion of sanitary conditions and pure water for prevention of infections.

Reduce stress! (in stress situations glucose and fatty acids are released into the circulation).
Promote muscle built-up instead of fat deposits.

Live a balanced life including the mental and spiritual dimension.

What is "STRESS"?

- "...a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation" -Merriam-Webster, 1998
- "Any factor that threatens the health of the body or has an adverse effect on it's functioning... The existence of one form of stress tends to diminish resistance to other forms. Constant stress brings about changes in the balance of hormones in the body." -Bantam Medical Dictionary, 1981

Good and bad stress

Distress versus Eustress

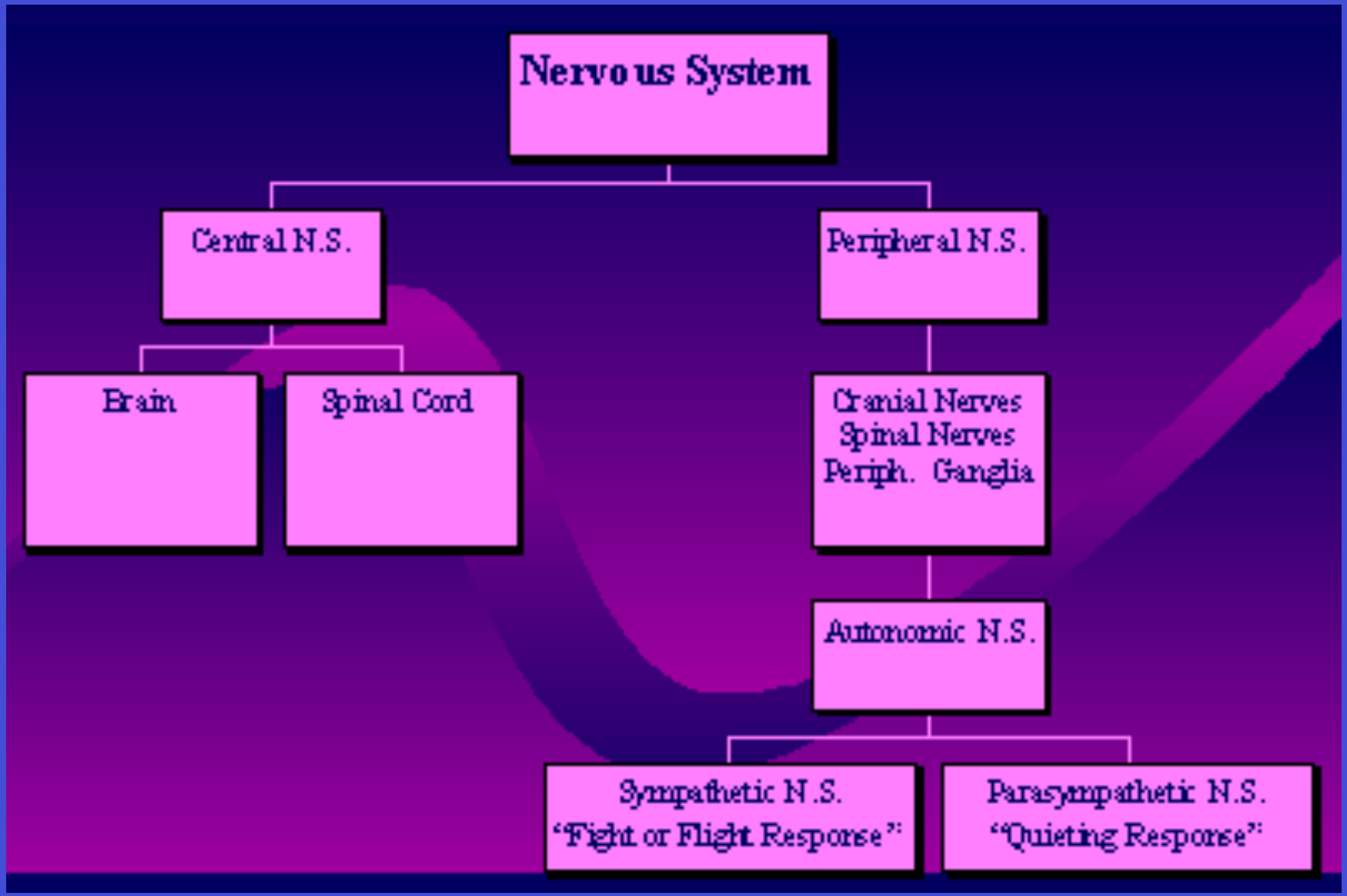
- The "dis" and the "eu" refer to the *stressor*, not the *impact* of the stressor.
- Both can be *equally* taxing on the body.
- Stress is *cumulative* in nature.

The scientist, Hans Selye, is best known for describing these polar responses. He defined stress as the ”nonspecific response of the body to any demands made on it.” He spoke of eustress as a normal response and distress as the abnormal response.

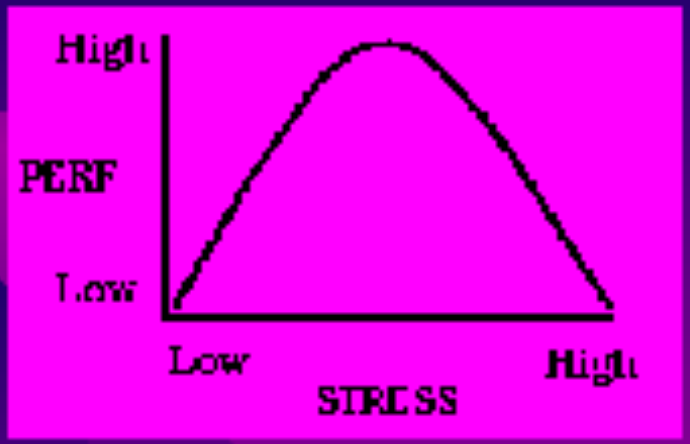
Why do we experience stress?

How the Autonomic Nervous System works...

- Sympathetic Nervous System:
  - "Fight or Flight" response
- Parasympathetic Nervous System:
  - Normalizing or "Quieting" response


Nervous System
Central N.S.
Peripheral N.S.
Brain
Spinal Cord
Cranial Nerves
Spinal Nerves
Periph. Ganglia
Autonomic N.S.
Sympathetic N.S.
"Fight or Flight Response"
Parasympathetic N.S.
"Quieting Response"

When is stress *good* for me?



- Moderate degrees of stress actually *improve* performance.
- Too much stress impairs performance.
- Too little stress decreases motivation.

Relaxation Training

- Diaphragmatic breathing
- Progressive muscle relaxation
- Guided imagery and visualization
- Hypnosis, Autogenics, Biofeedback

The Faculty and Staff Assistance Program (FASAP) is the employee assistance program of JHU, JHM, and MSC. FASAP provides confidential services to employees, dependents, and significant others. We provide consultation and training to supervisors and work organizations through confidential, timely problem identification and assessment to improve employee job performance and productivity. FASAP is a personnel benefit of the institutions, providing compassionate care and respecting the diversity that reflects our community.

Don`t Forget:

Everything is dependent on the concentration!