Inserm
BIOENERGETIQUE FONDAMENTALE ET APPLIQUEE – E221

CHU
de
Grenoble

UNIVERSITE JOSEPH FOURIER
SCIENCES. TECHNOLOGIE. MEDECINE
GRENOBLE 1

Oxygen and stress or sepsis

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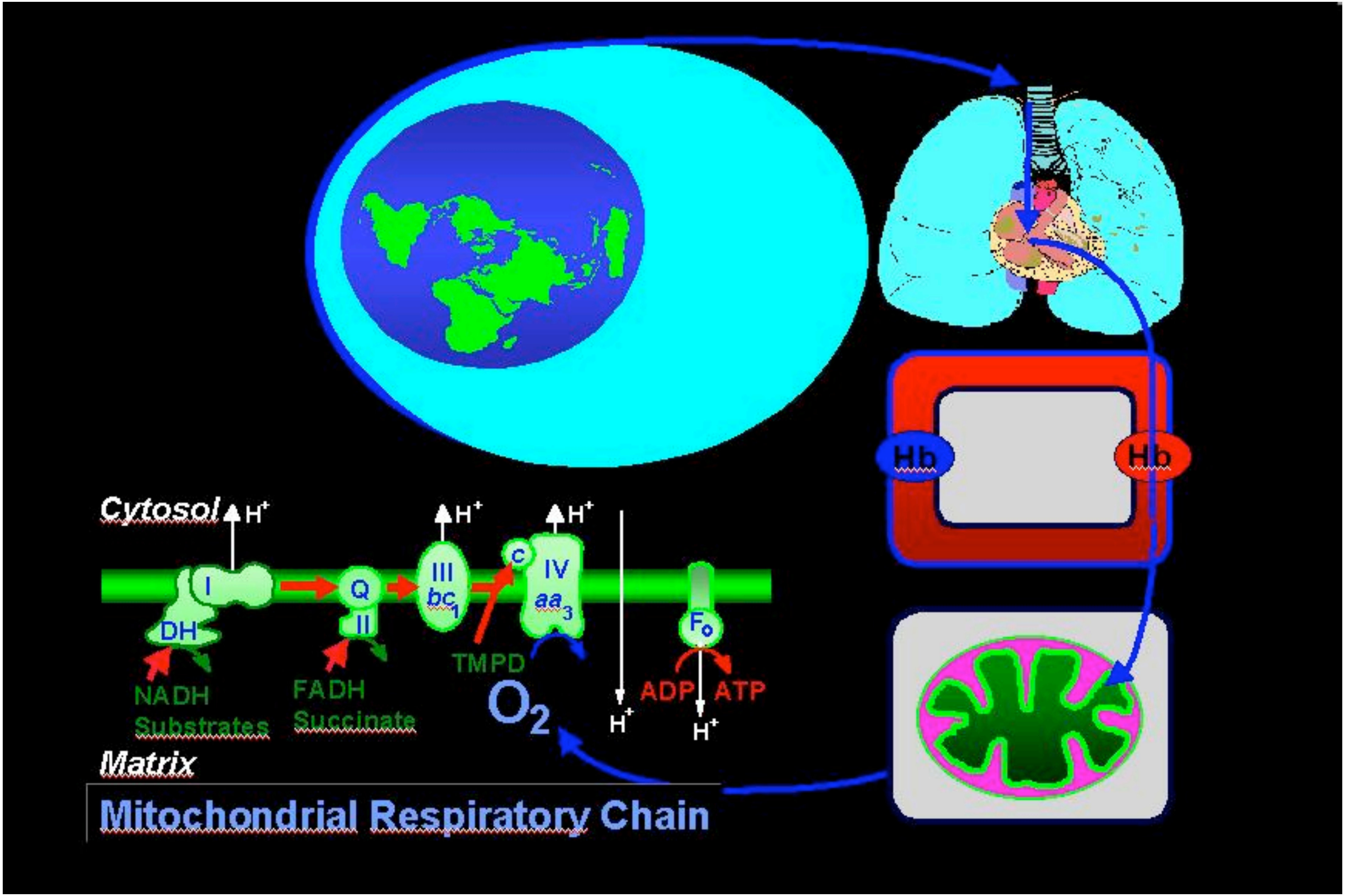
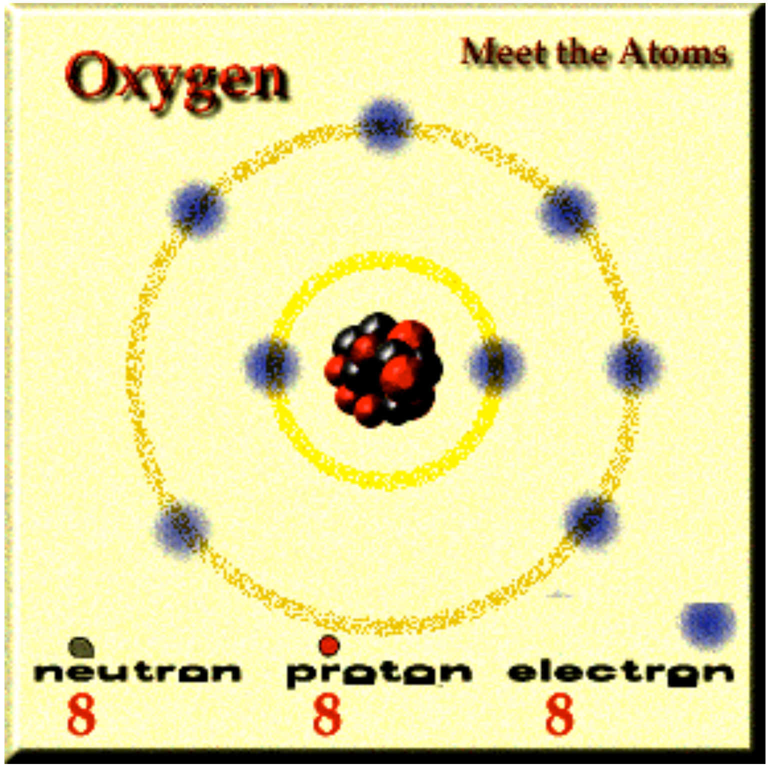
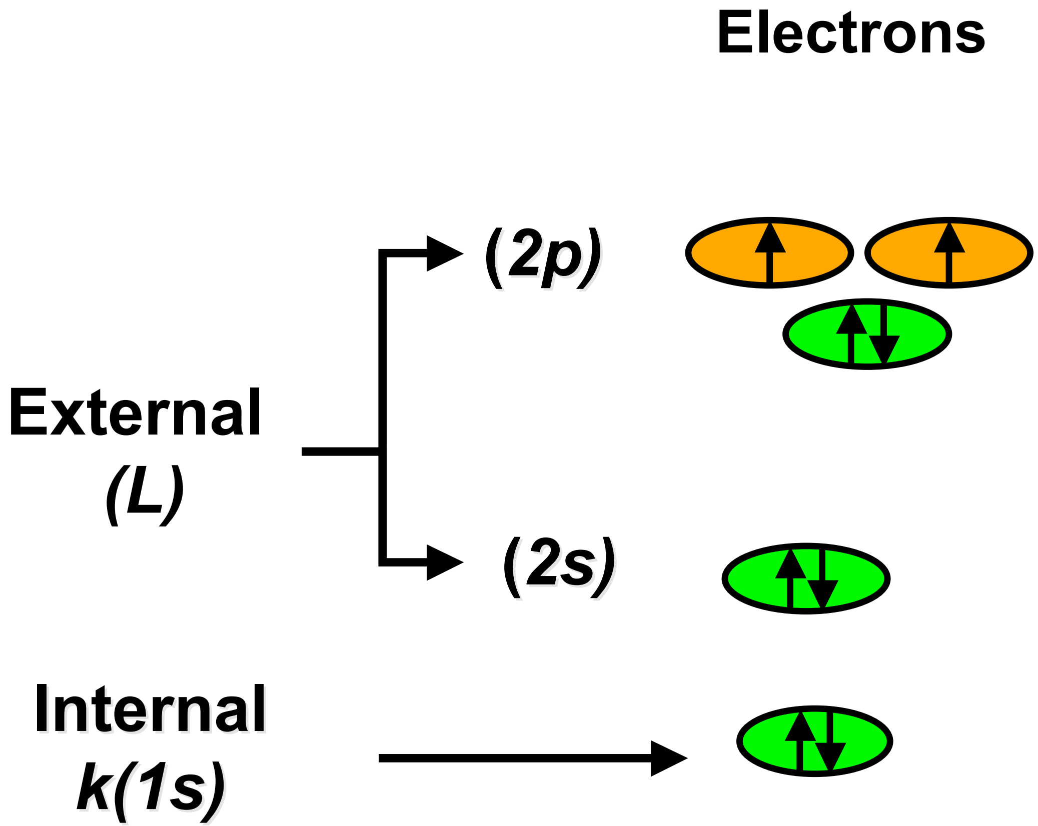
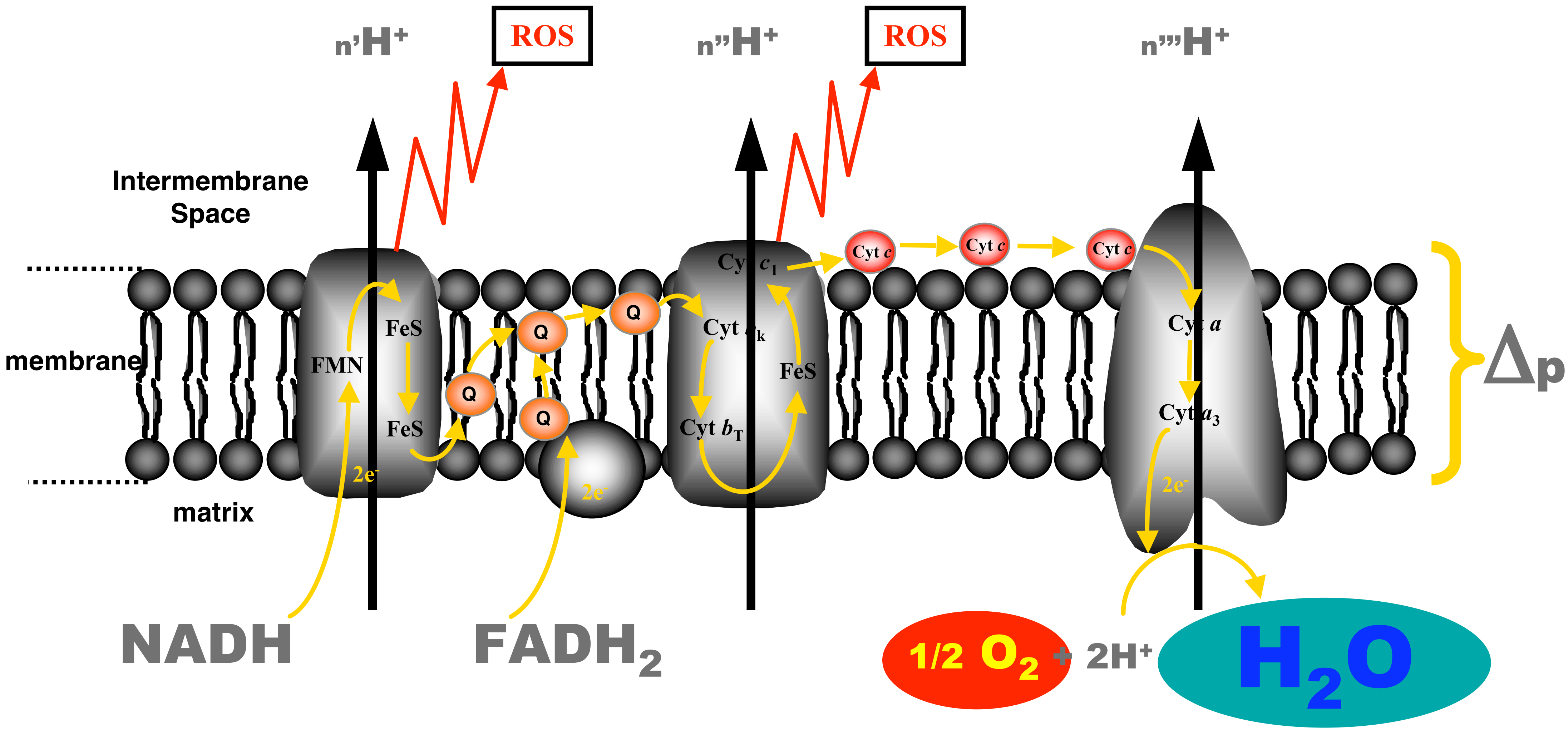
5th WCPCC- Geneva June 2007


Hb
Hb
Cytosol
H+
H+
H+
I
Q
III
bc1
c
IV
aa3
DH
II
Fo
TMPD
NADH
Substrates
FADH
Succinate
O2
H+
ADP
ATP
H+
Matrix
Mitochondrial Respiratory Chain

Oxygen atom

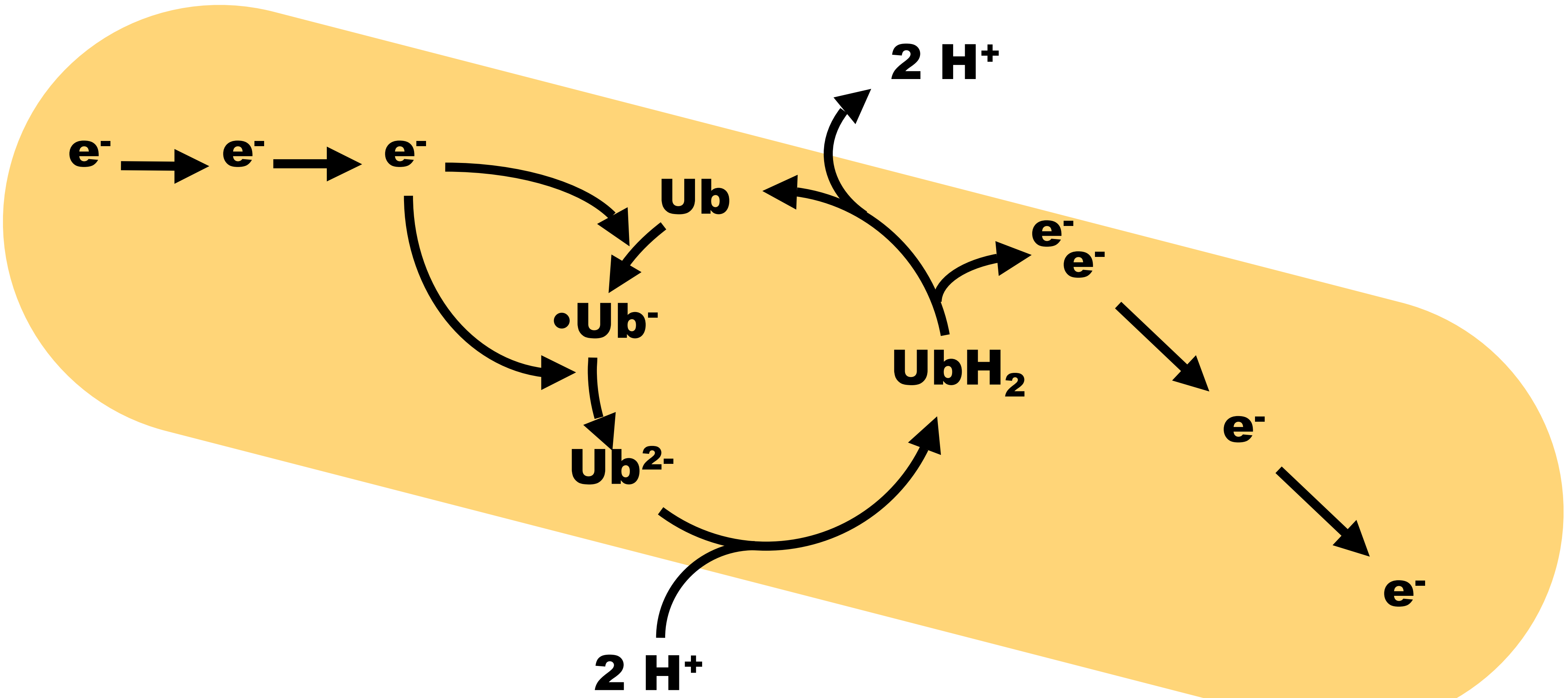

Oxygen
Meet the Atoms
neutron
8
proton
8
electron
8


Electrons
(2p)
External
(L)
(2s)
Internal
k(1s)

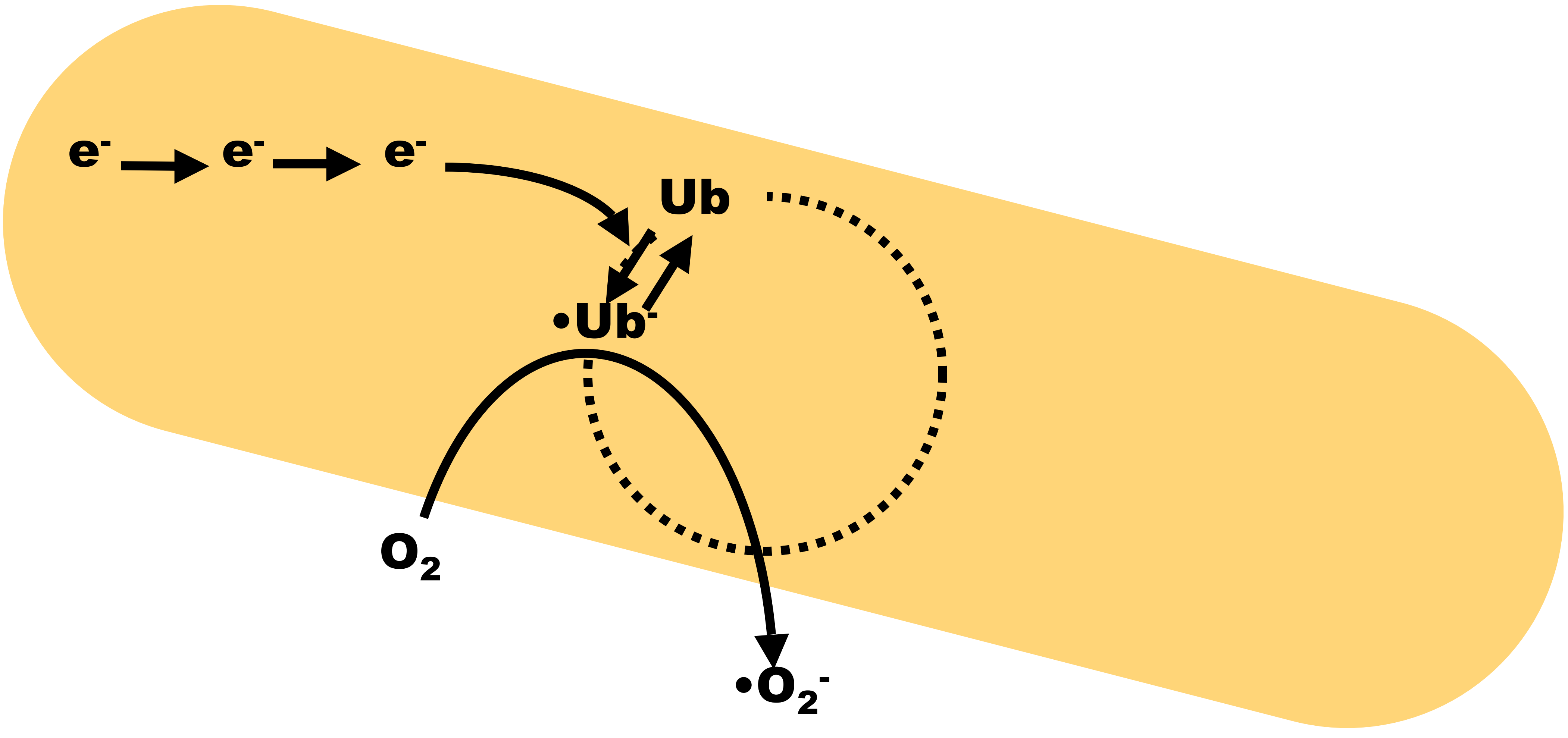


n'H+
ROS
n''H+
ROS
n'''H+
Intermembrane Space
membrane
matrix
FMN
FeS
FeS
2e-
Q
Q
Q
Q
2e-
Cyt c1
Cyt bk
FeS
Cyt bT
Cyt c
Cyt c
Cyt c
Cyt a
Cyt a3
2e-
Δp
NADH
FADH2
1/2 O2 + 2H+
H2O

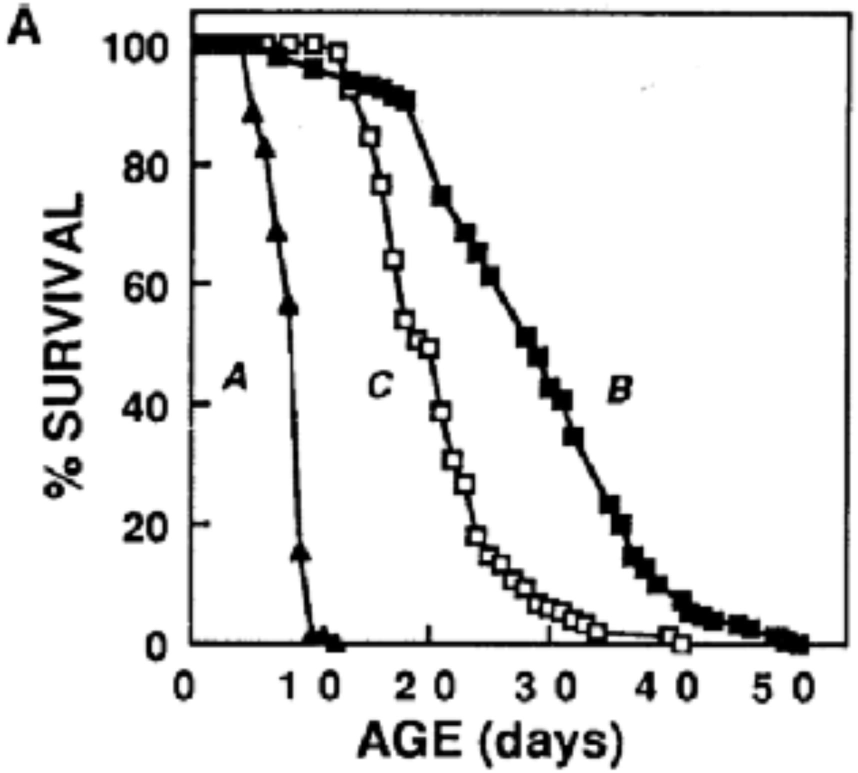
Mitochondries
Production du gradient de H^+



Mitochondries
Production $\bullet O_2^-$



Oxygen and life span

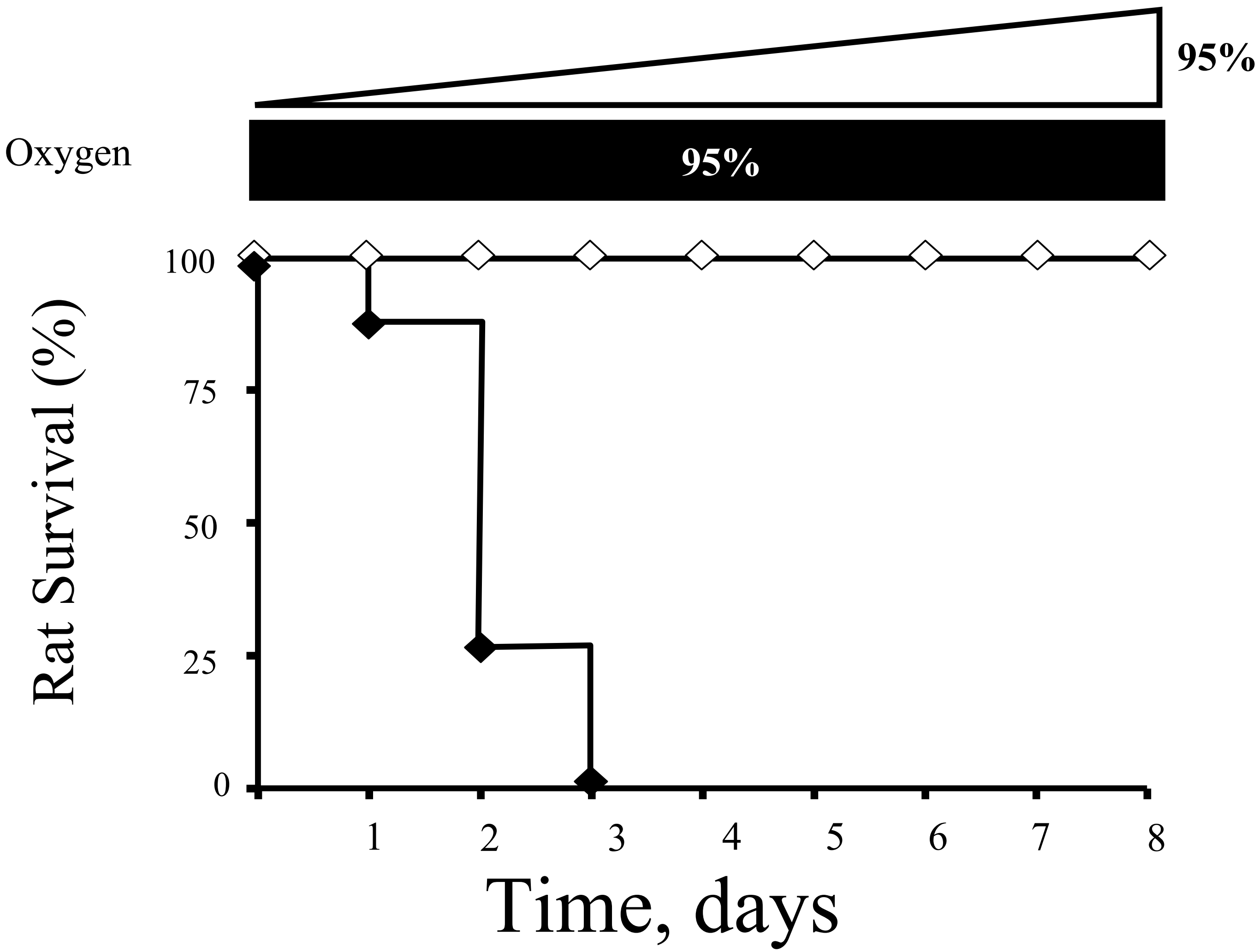


Flies

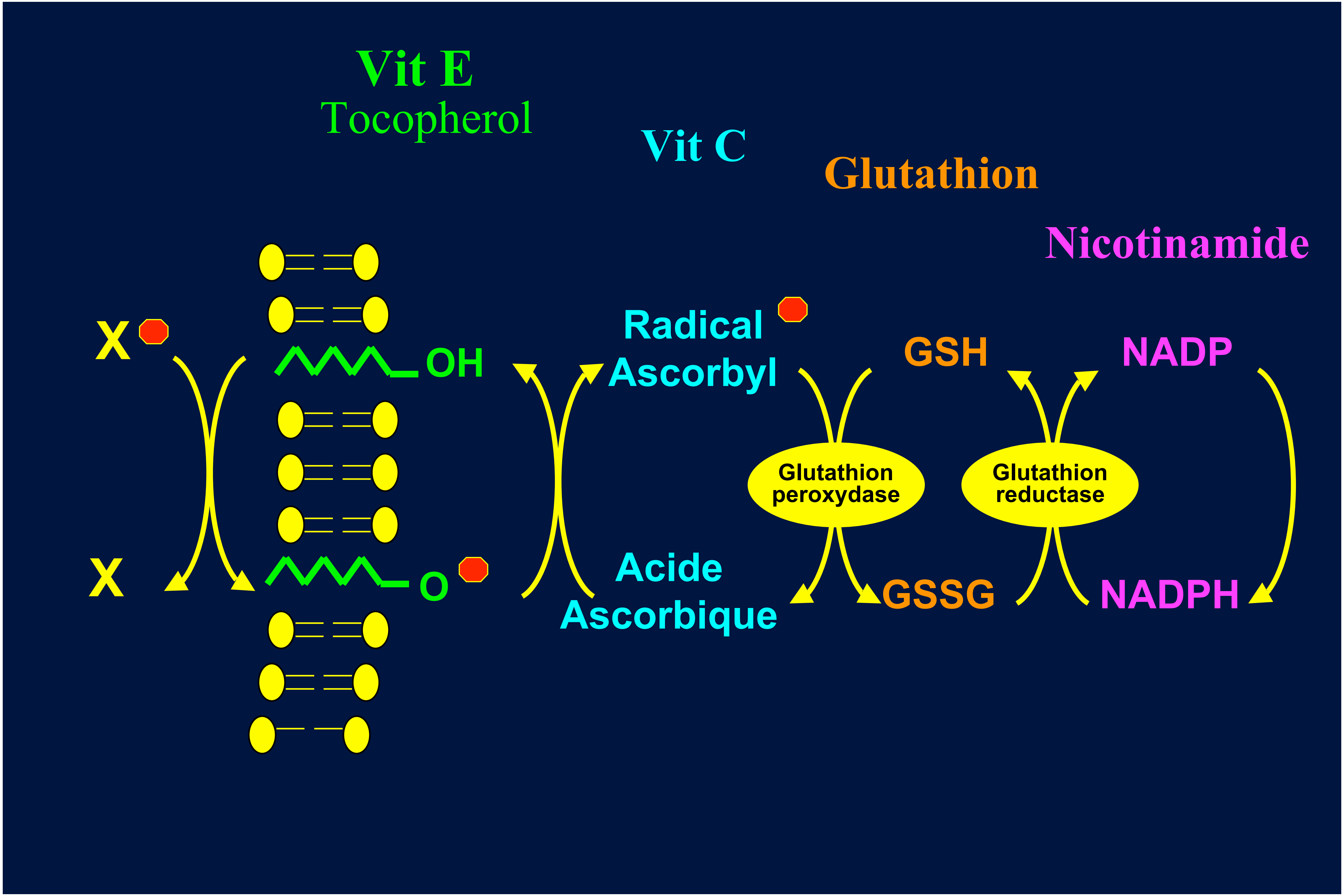
A = 100% Oxygene (continuous)
B = 100% Oxygène (3 days and air)
C = Air

Sohal & al. *Proc Natl Acad Sci USA*, 1993

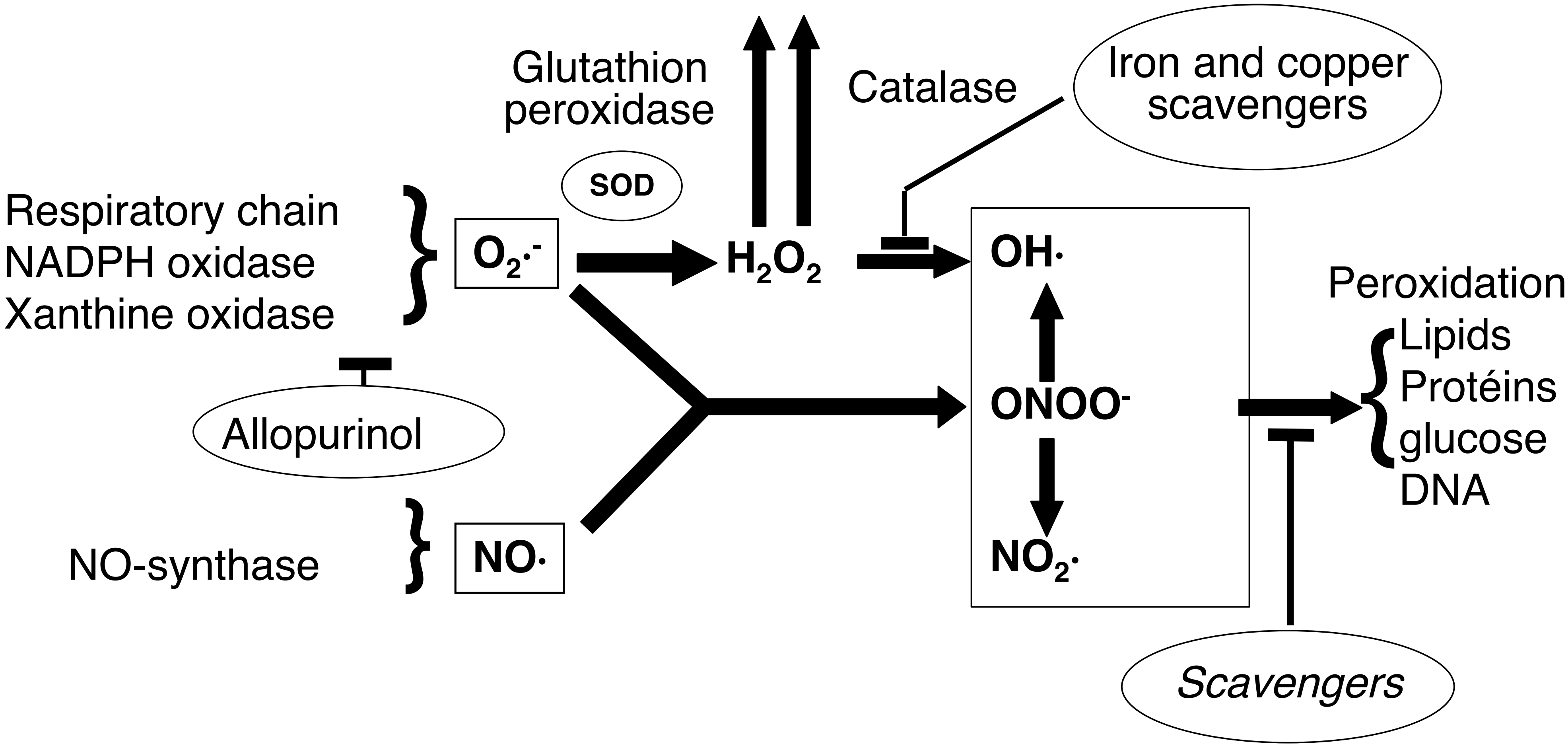
Oxygen toxicity



B. Coltey et al. Unpublished



Vit E
Tocopherol
Vit C
Glutathion
Nicotinamide
X
OH
X
O
Radical
Ascorbyl
Acide
Ascorbique
GSH
NADP
Glutathion peroxydase
Glutathion reductase
GSSG
NADPH



Glutathion peroxidase
Catalase
Iron and copper scavengers
SOD
Respiratory chain
NADPH oxidase
Xanthine oxidase
$O_2^{\cdot -}$
H_2O_2
OH·
Peroxidation
Lipids
Protéins
glucose
DNA
$ONOO^-$
Allopurinol
NO-synthase
NO·
$NO_2\cdot$
Scavengers

Wild type SOD

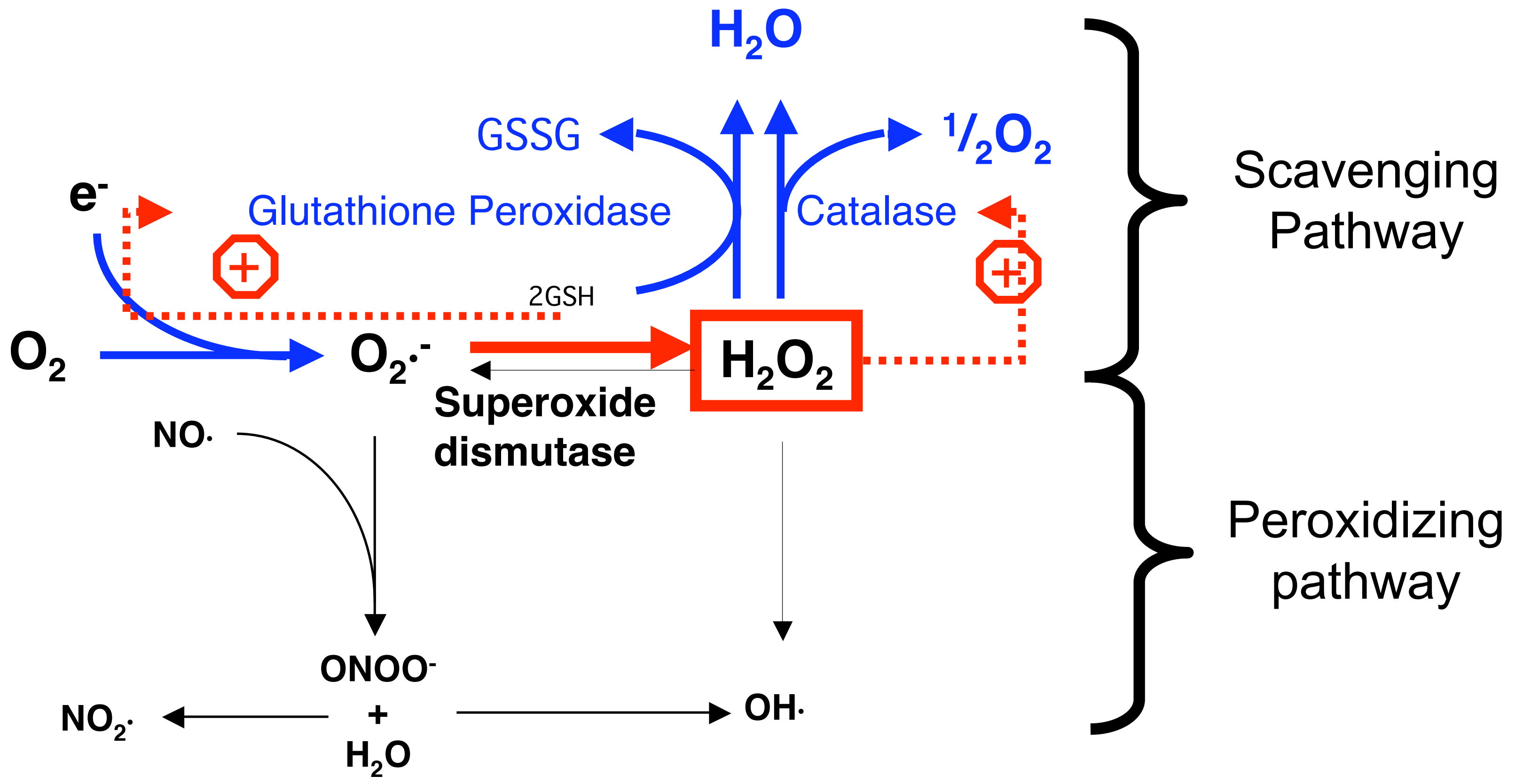
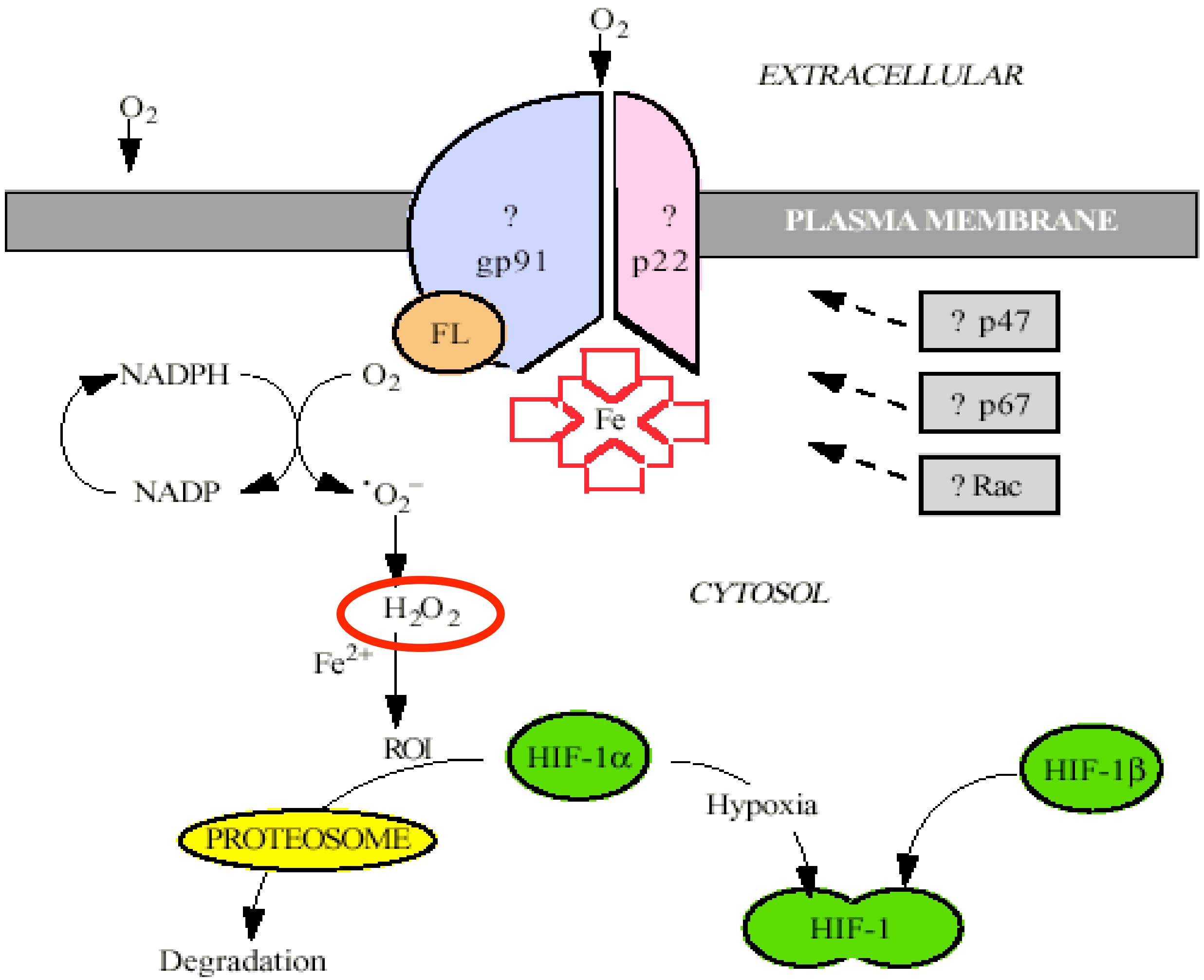
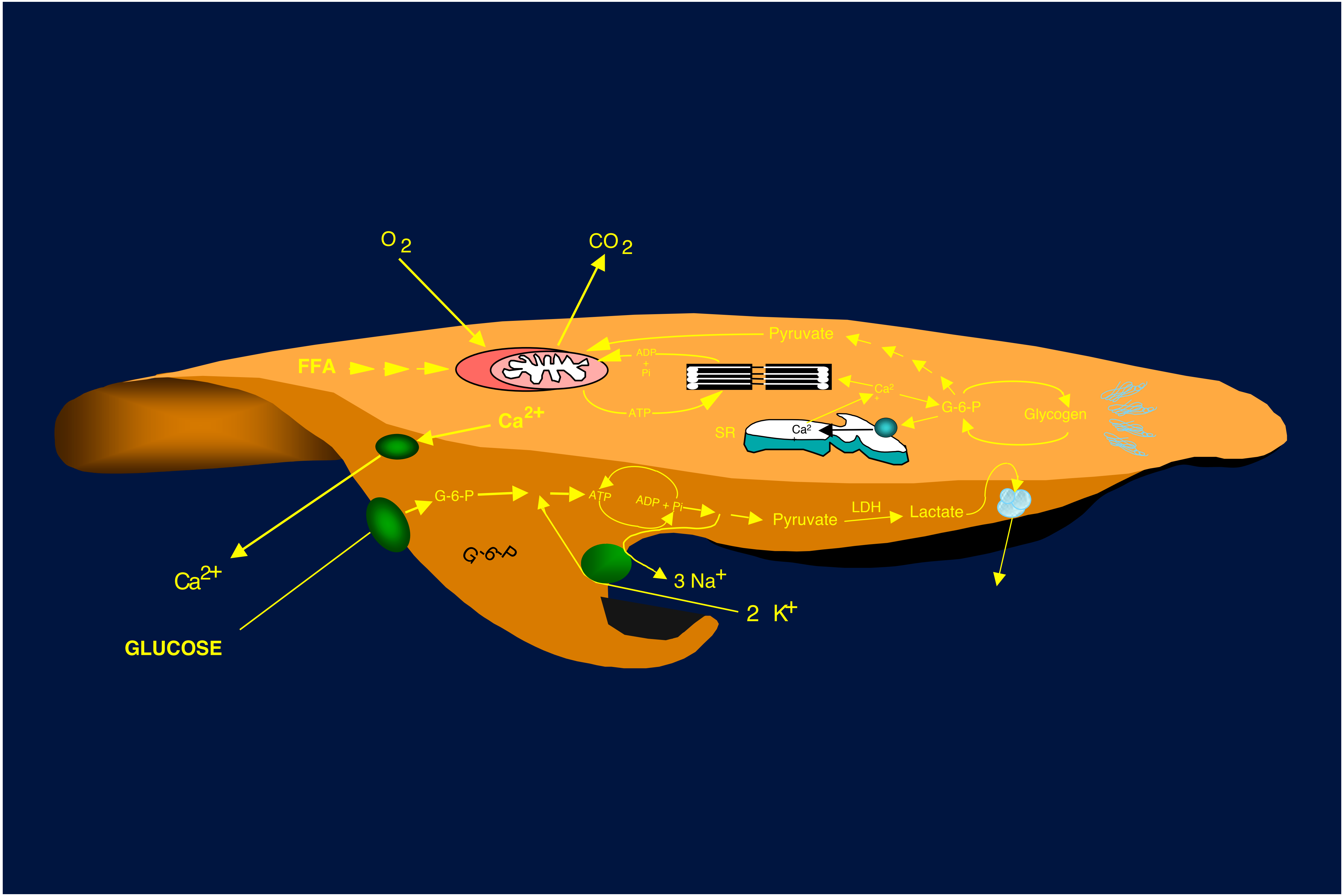


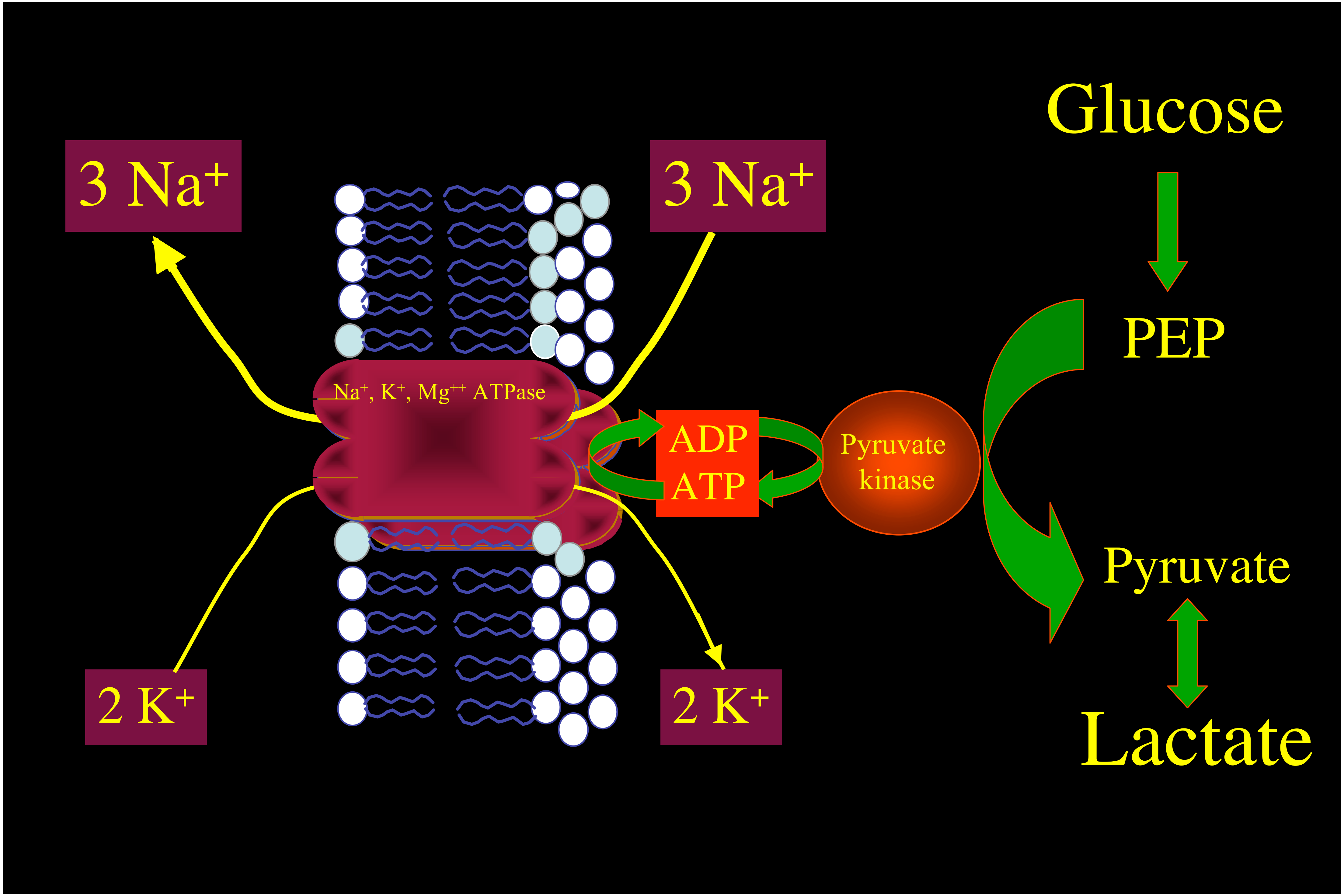
Fig. 1. Model of the hypoxia-sensing and signaling pathway based on the neutrophil macrophage NAD(P)H oxidase. It is likely that oxygen is sensed by a heme protein. Cobalt may simulate deoxy-heme by substituting for iron in the protoporphyrin of this heme protein. A flavin group (FL) is likely to participate in the transfer of electrons that enables oxygen to be reduced to superoxide ($^{\bullet}O_2^{-}$) *via* the oxidation of NADPH to NADP. In neutrophil/macrophage activation, cytosolic proteins p47, p67 and Rac participate in a macromolecular assembly. However, there is no evidence that these molecules or gp91 or p22 participate in the oxygen-sensing and signal transduction pathway. The formation of reactive oxygen intermediates (ROI) from peroxide is catalysed by iron in the iron-dependent Fenton reaction. It is likely that these oxidizing equivalents mediate the degradation of HIF-1α subunits in the proteosome, thereby preventing the formation of the activated HIF-1 heterodimer that is required for the induction of hypoxia-responsive gene expression.



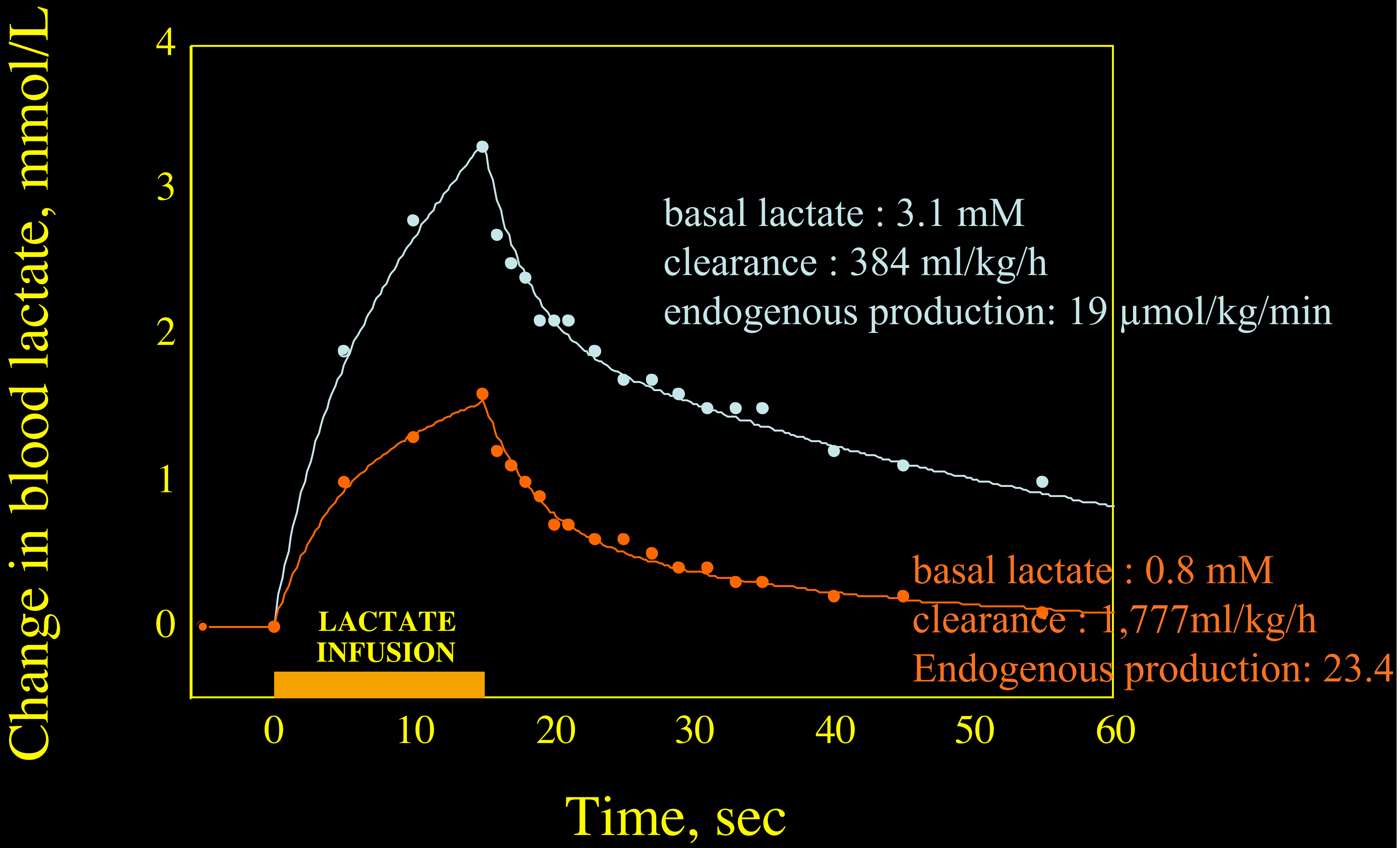
HF Bun et al J Exp Biol 1998,



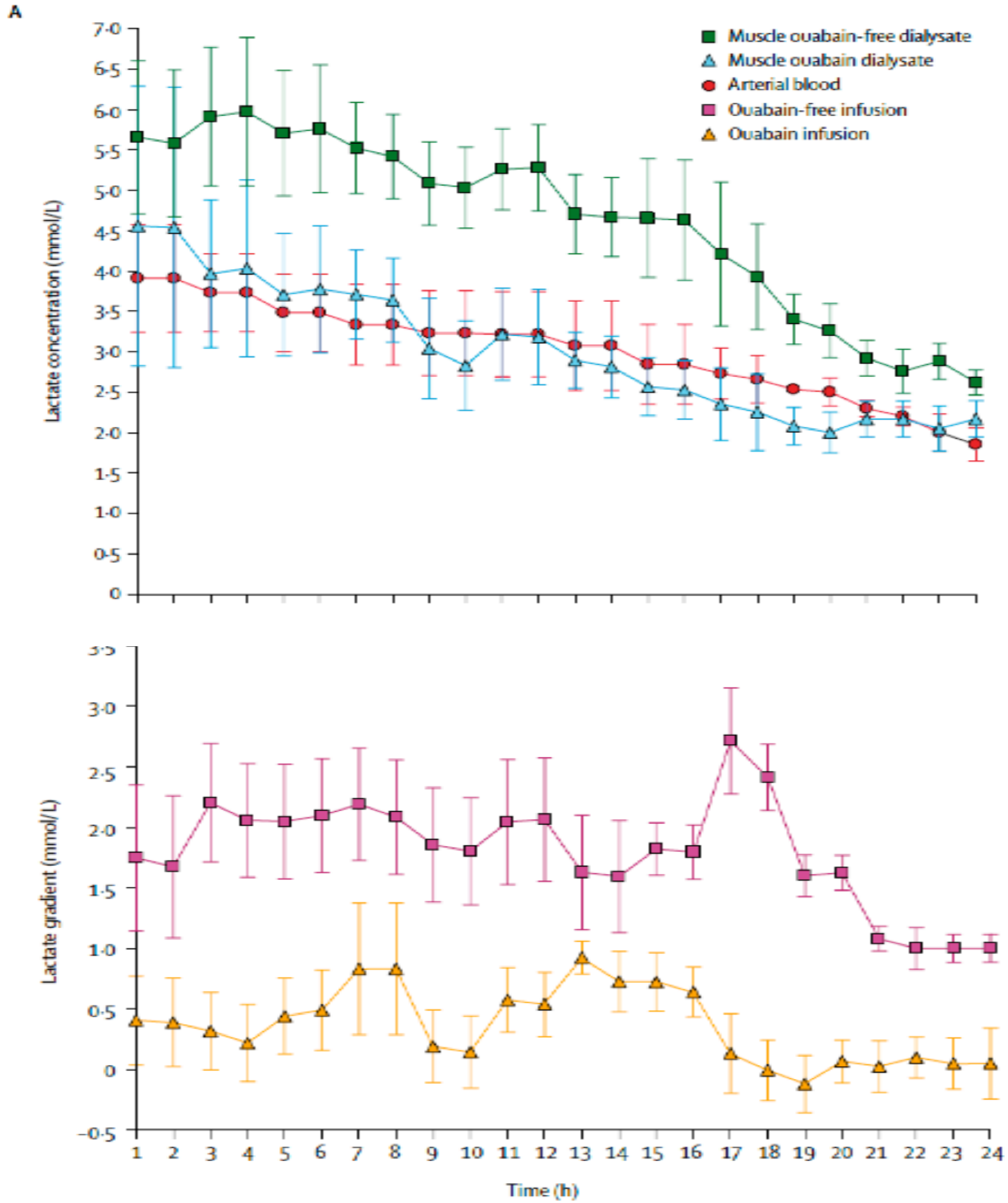
O 2
CO 2
Pyruvate
FFA
ADP
+
Pi
ATP
Ca2
+
G-6-P
Glycogen
Ca2+
SR
Ca2
+
G-6-P
ATP
ADP + Pi
Pyruvate
LDH
Lactate
G-6-P
Ca2+
3 Na+
2 K+
GLUCOSE



3 Na+
3 Na+
Glucose
PEP
Na+, K+, Mg++ ATPase
ADP
ATP
Pyruvate kinase
Pyruvate
Lactate
2 K+
2 K+

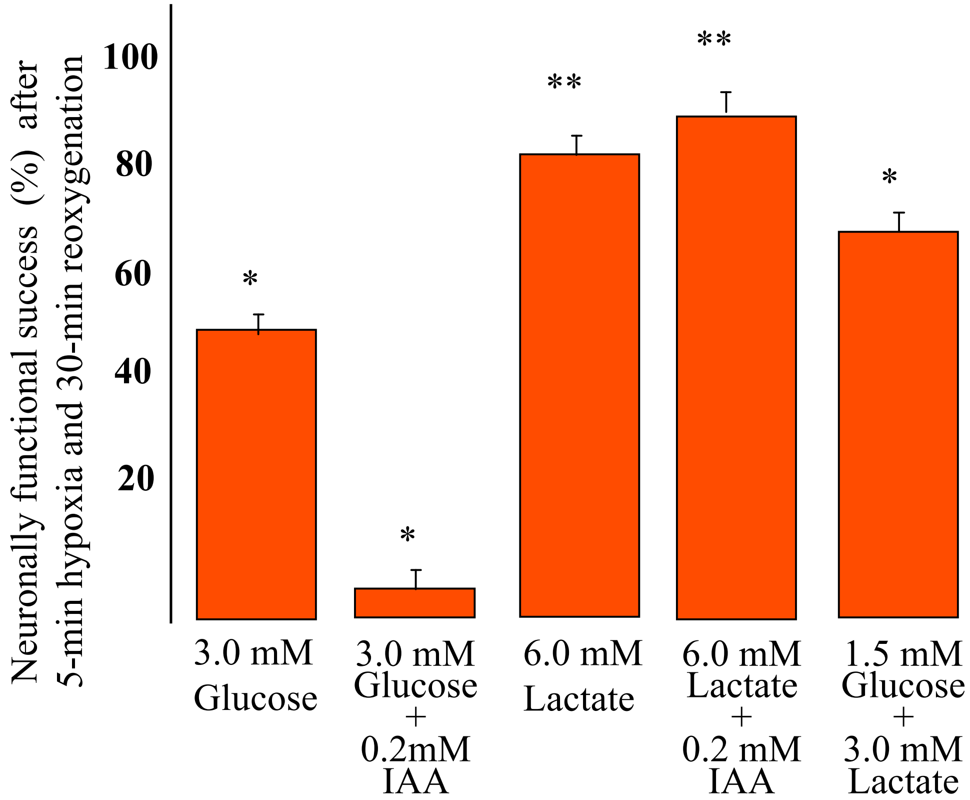


Levraut et al, AJRCCM, 1998



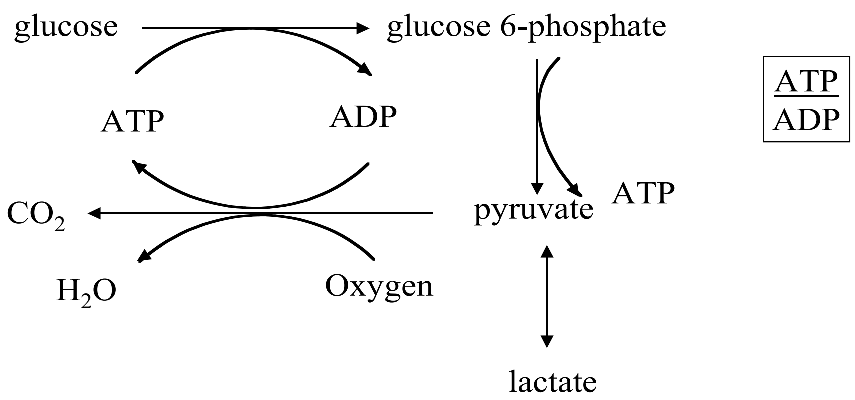
Levy et al Lancet, 2005

Lactate and brain recovery from ischemia-reperfusion injury

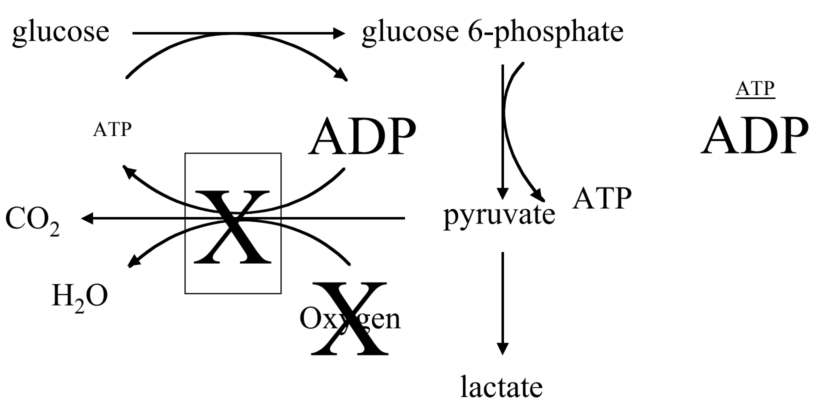


- Slices with lactate showed a significantly higher degree of recovery
- Slices with anaerobic lactate production by pre-hypoxia glucose exhibited functional recovery
- 80% recovery even glucose utilization was blocked during the later part of the hypoxic period and reoxygenation
- Slices in which anaerobic lactate production was blocked during the initial stage of hypoxic did not recover

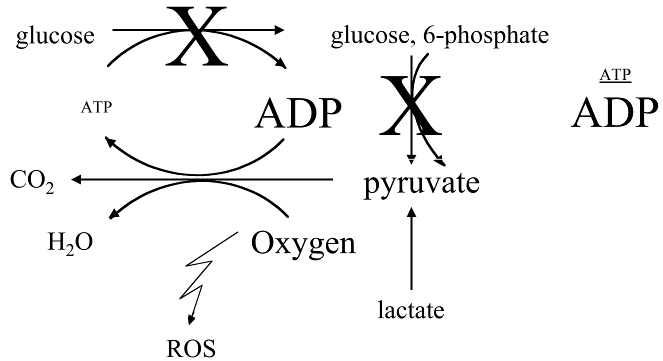
Schurr et al, Brain Res., 1997, 744, 105 -11



Normal condition

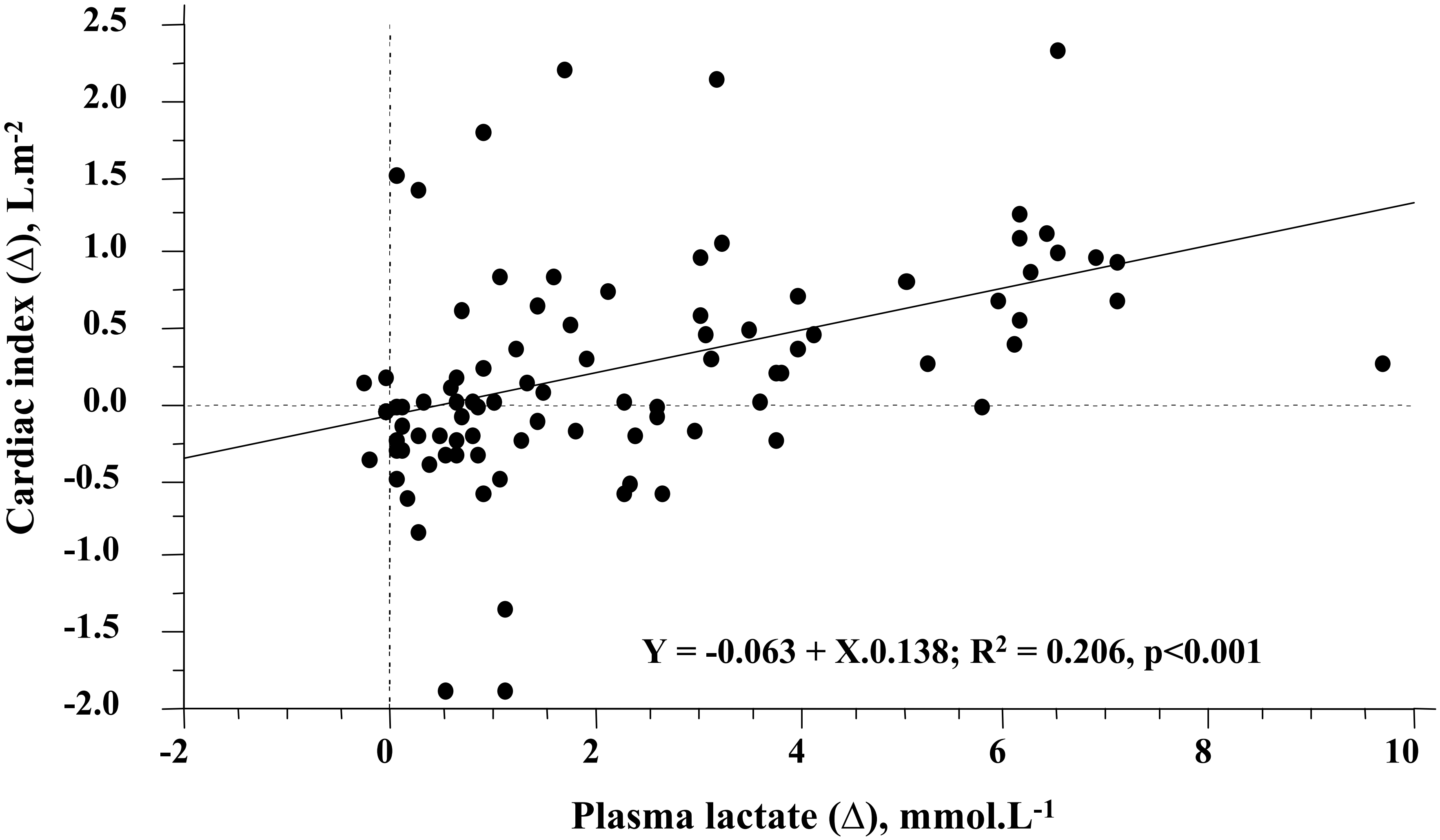


Reaction during hypoxia

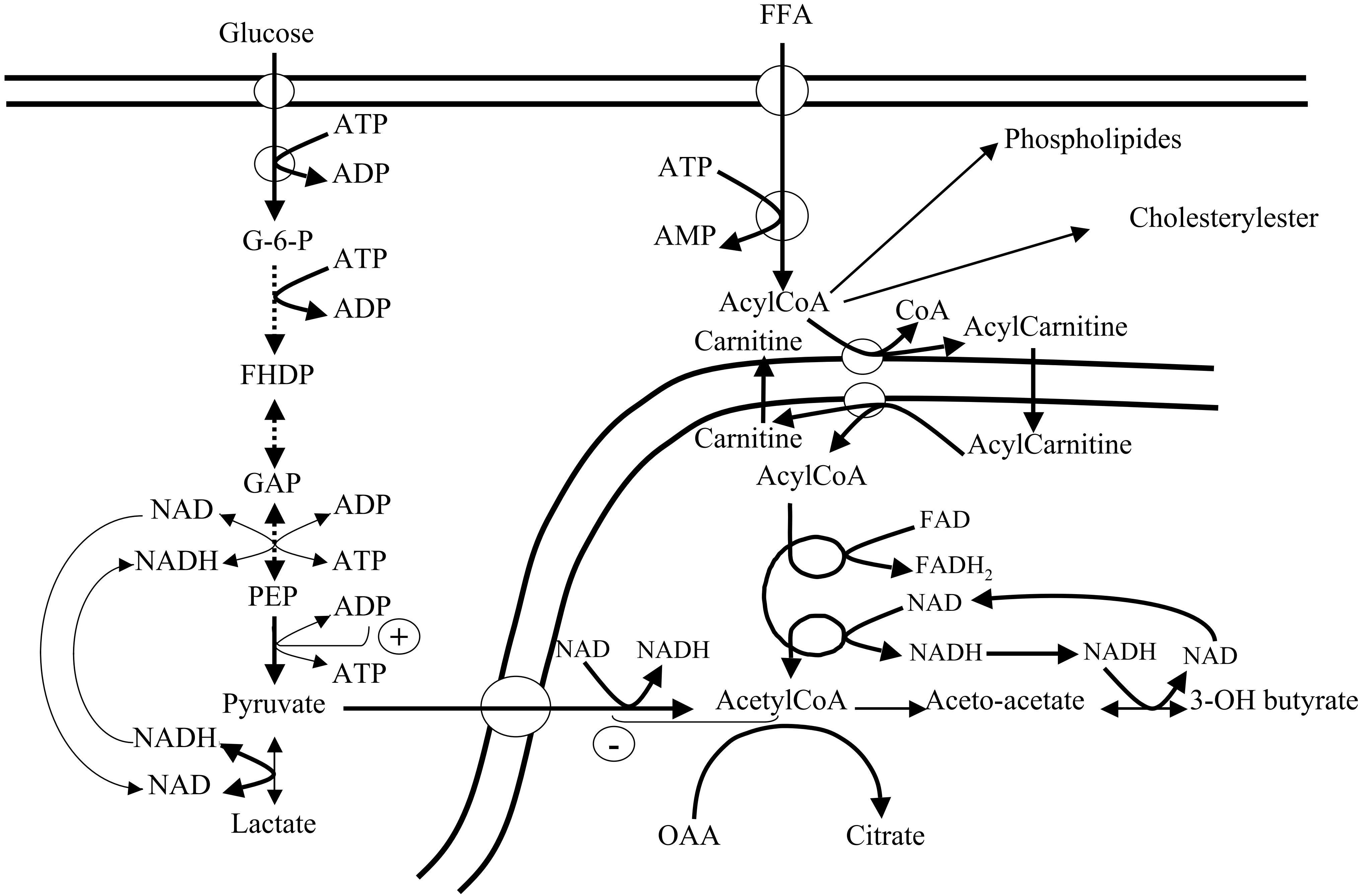


Reaction after oxygen restoration post hypoxia

Figure 5



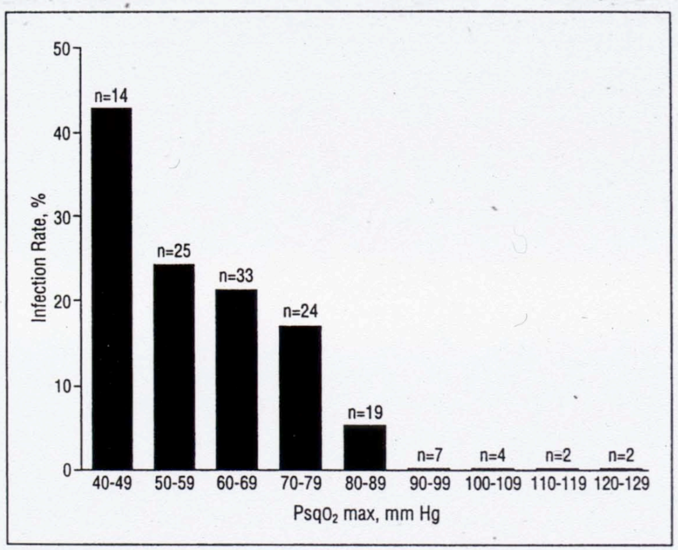
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Cardiac index (Δ), L.m-2
Y = -0.063 + X.0.138; R2 = 0.206, p<0.001
-2
0
2
4
6
8
10
Plasma lactate (Δ), mmol.L-1


Glucose
FFA
ATP
ADP
G-6-P
ATP
ADP
FHDP
GAP
NAD
NADH
ADP
ATP
PEP
ADP
+
ATP
Pyruvate
NADH
NAD
Lactate
ATP
AMP
Phospholipides
Cholesterylester
AcylCoA
CoA
AcylCarnitine
Carnitine
Carnitine
AcylCarnitine
AcylCoA
FAD
$FADH_2$
NAD
NADH
NADH
NAD
NAD
NADH
AcetylCoA
Aceto-acetate
3-OH butyrate
-
OAA
Citrate

Beneficial effect of oxygen ?

	Before HBO	After HBO
fMLP-induced Chemotaxis	12 ± 6	3 ± 4 #
Bacteria-induced Phagocytosis	325 ± 99	539 ± 57 #
Bacteria-induced Oxidative burst	229 ± 27	431 ± 92 #
NO_3^-	22 ± 6	17 ± 5

Labrouche et al, Thromb Res 1999;96:309



Hopf HW et al.; Arch Surg 1997; 132: 997