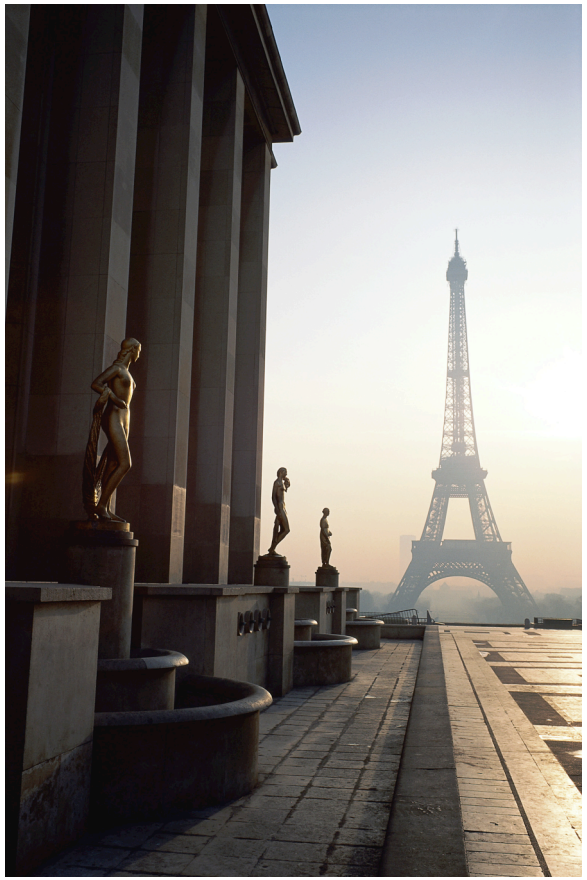
Institut National de la
Recherche Agronomique
Direction Scientifique
Nutrition Humaine &
Sécurité des aliments
(NHSA)

Institut national
de la santé et de la recherche médicale

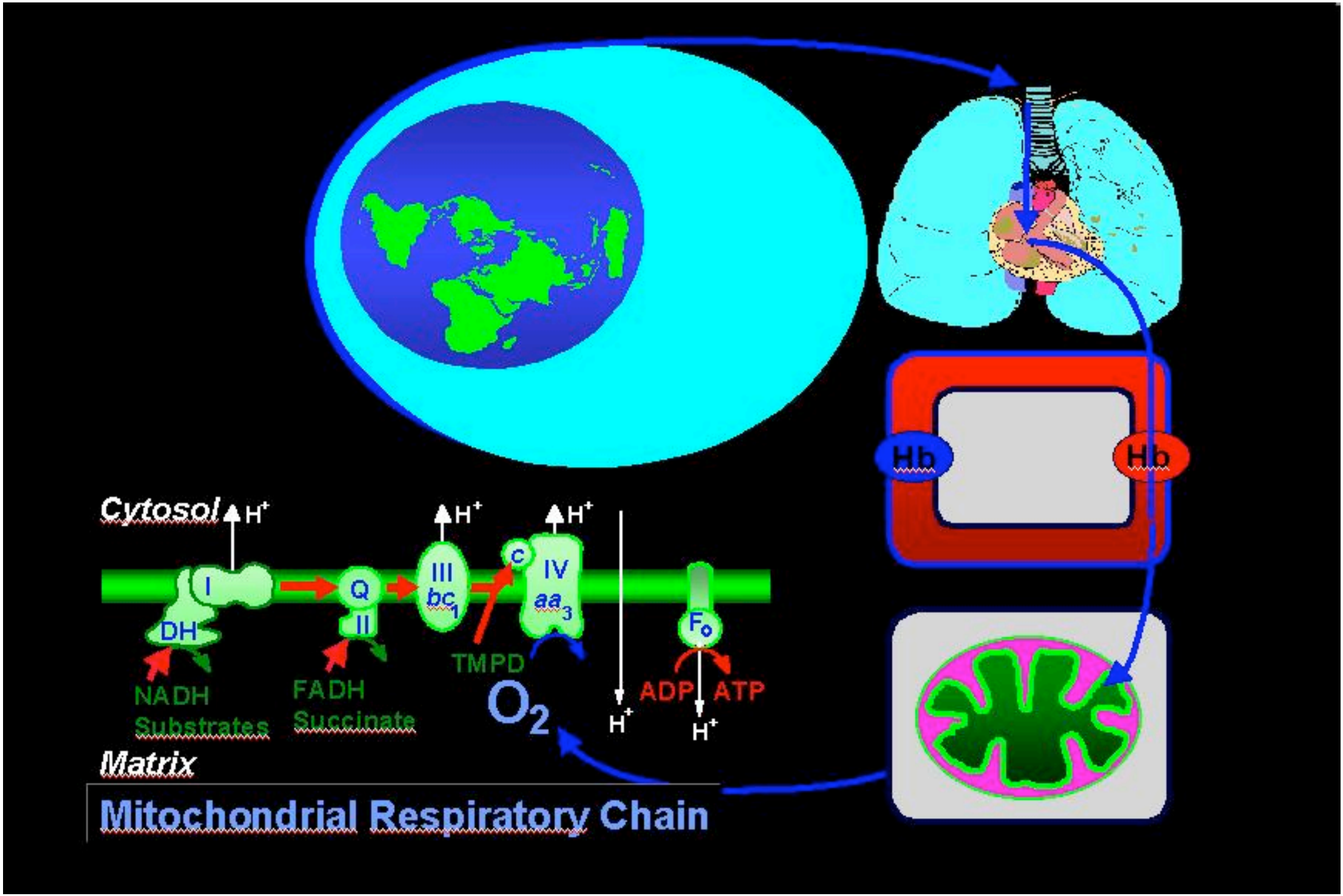
UNIVERSITE JOSEPH FOURIER
SCIENCES. TECHNOLOGIE. MEDECINE
GRENOBLE 1

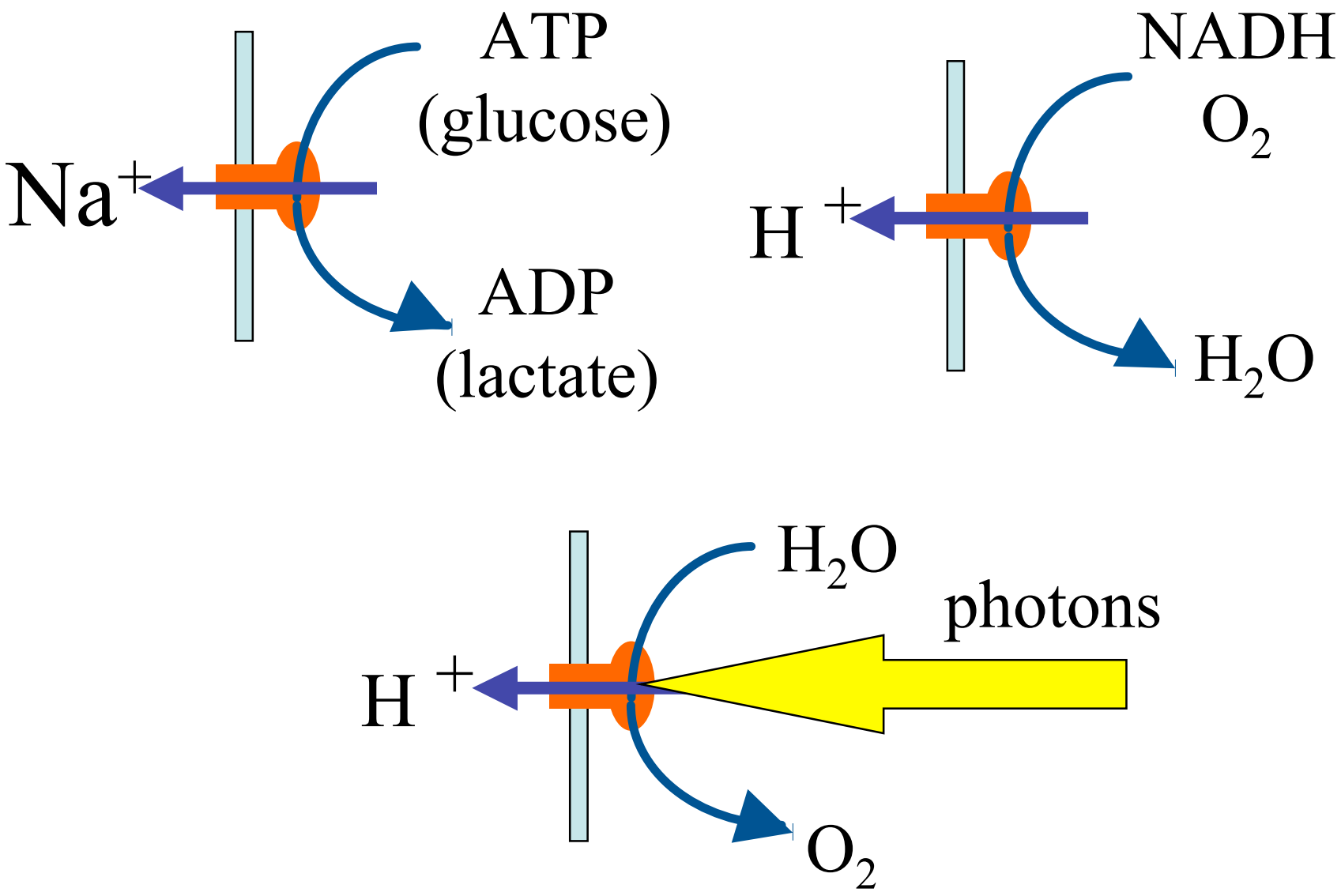


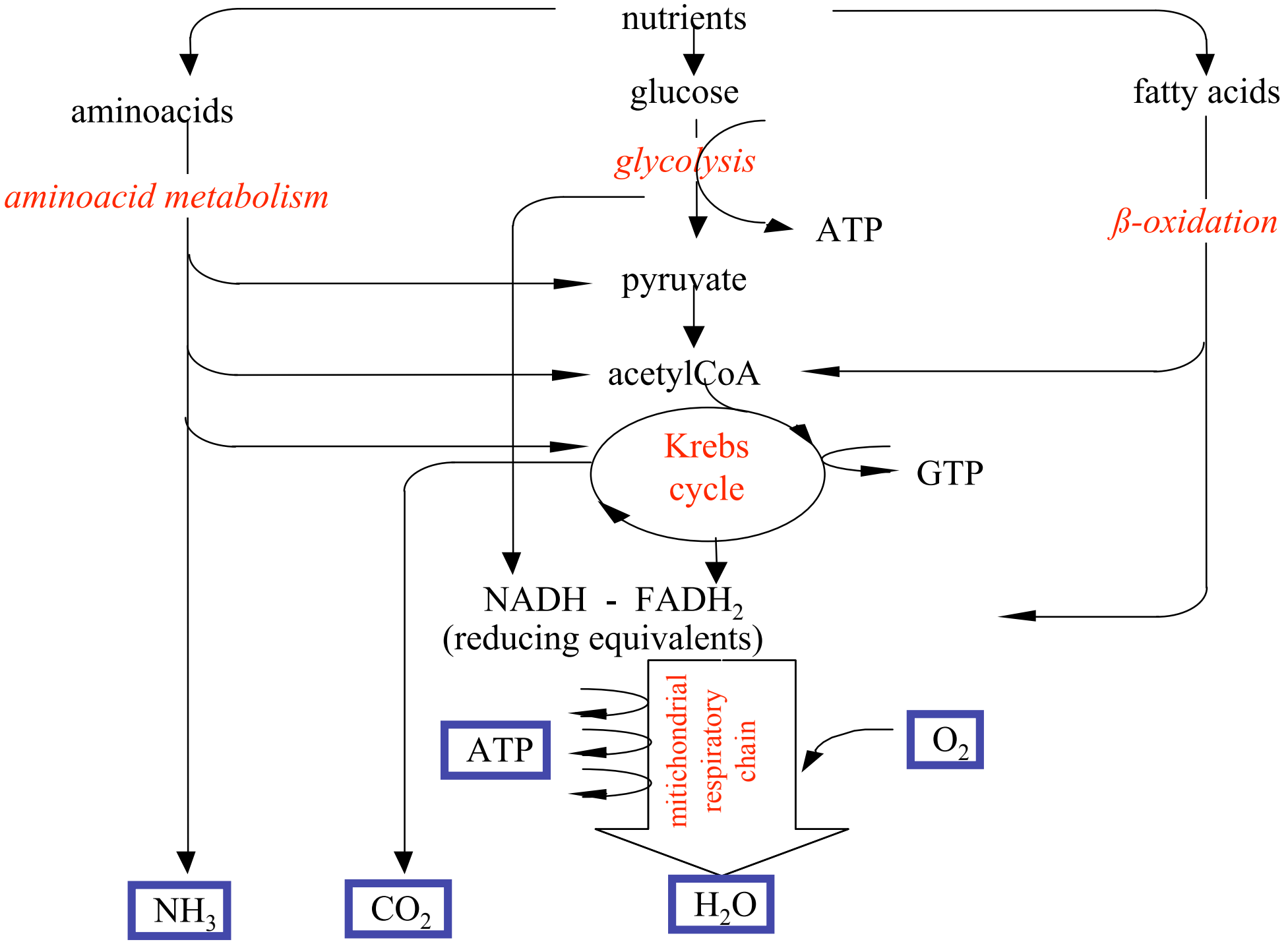
Xavier Leverve

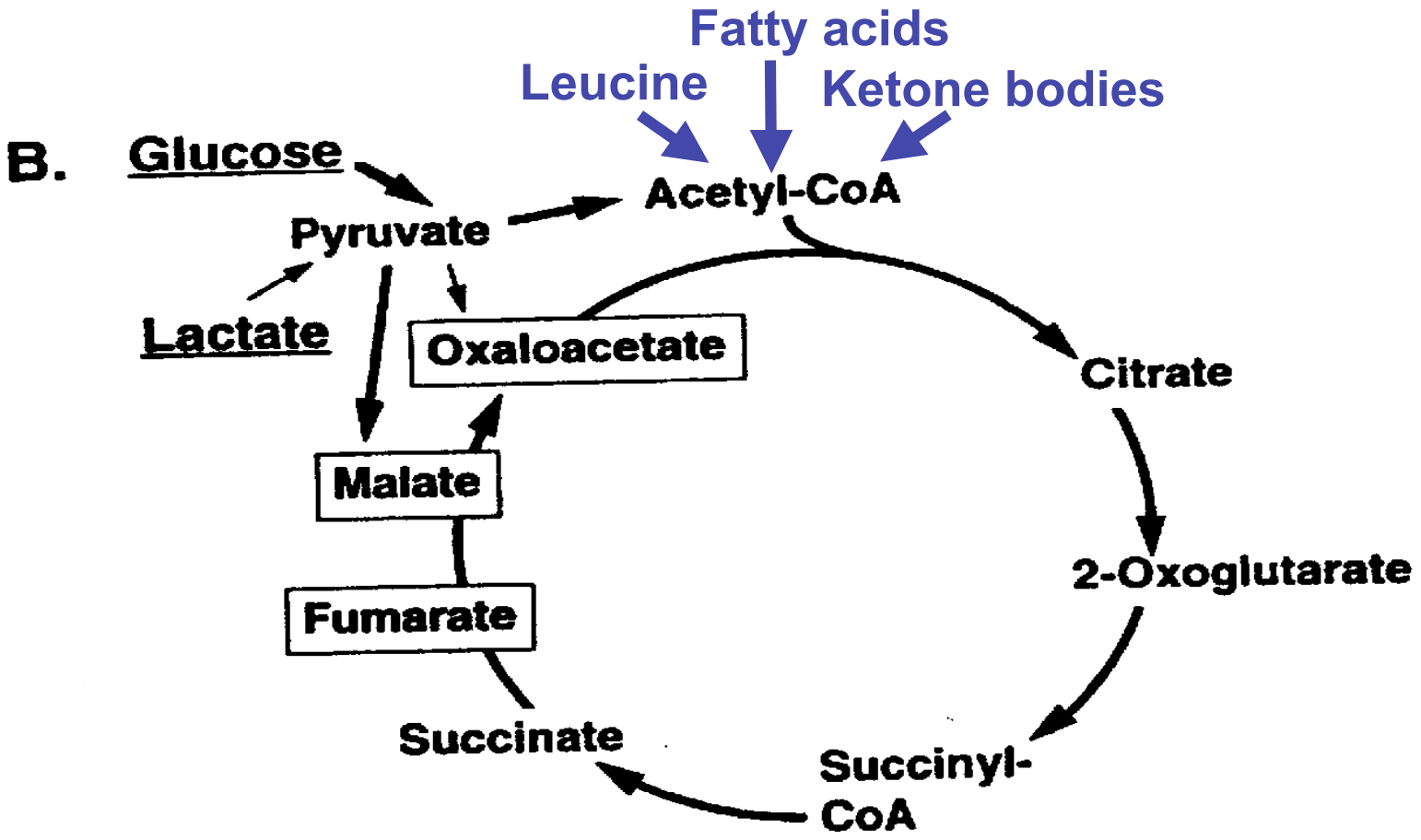
Cellular Bioenergetic Pathways

Vth World Congress of Pediatric Critical Care (WCPCC)
Geneva, Switzerland, June 24th – 28th, 2007


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


ATP
(glucose)
Na+
ADP
(lactate)
NADH
O2
H +
H2O
H2O
photons
H +
O2

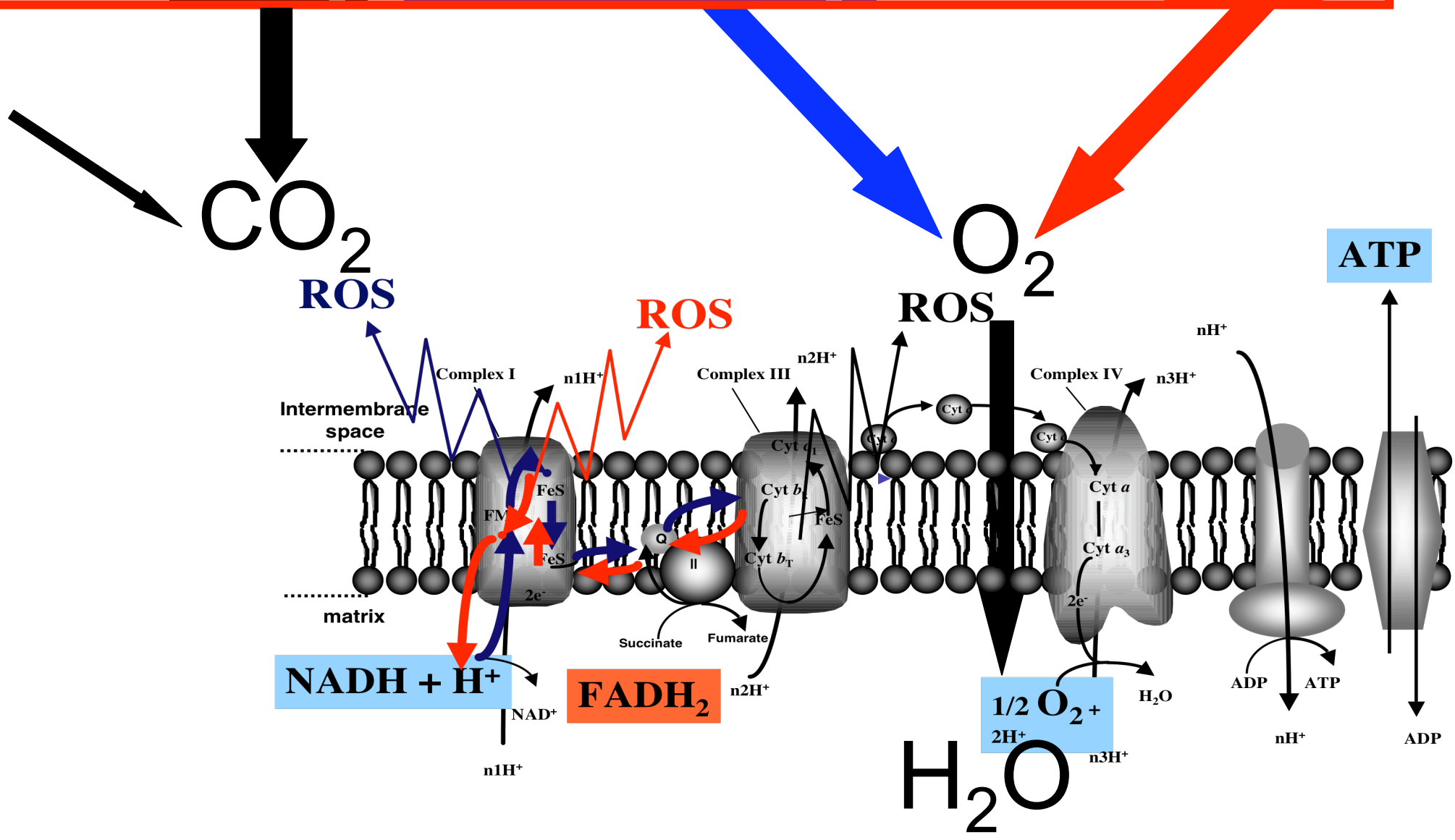

nutrients
glucose
aminoacids
fatty acids
glycolysis
aminoacid metabolism
ATP
ß-oxidation
pyruvate
acetylCoA
Krebs cycle
GTP
NADH - FADH2
(reducing equivalents)
ATP
mitichondrial respiratory chain
O2
NH3
CO2
H2O



Essential and non-essential fuels for energy production: glucose, lactate and pyruvate provide both substrates for the citrate synthase reaction : acetyl-CoA and oxaloacetate.

$CH_3COSCoA + 3NAD^+ + FAD + GDP^{3-} + Pi^{2-} + 2H_2O$

$\Rightarrow CoASH + 2CO_2 + 3NADH + FADH_2 + GTP^{4-} + 2H^+$



CO_2

- Is an endproduct that we (mammals) cannot use

(only plants can incorporate CO_2 into biological molecules)

- It must be first hydrated into bicarbonate
- This spontaneous reaction is rather slow
- However it is considerably activated by carbonic anhydrase

=> Hypercapnia will affect processes and tissues according to carbonic anhydrase activity and distribution

Permissive Hypercapnia

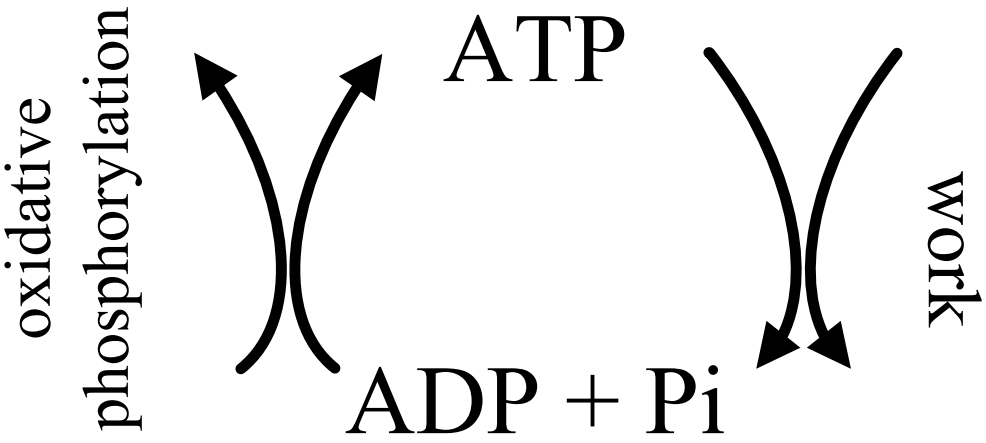
$$CO_2 + H_2O \overset{CA}{\Leftrightarrow} H_2CO_3 \overset{\text{Spontaneous}}{\Leftrightarrow} HCO_3^- + H^+$$

- The resulting effect is pH modulation
- However in a highly compartmentalized and channeled way:
  tissues and pathways are differently affected according to CA activity

⇒ hypercapnia is a way to induce acidosis toward specific targets

⇒ acidosis induces a slowdown of energy metabolism (*i.e.* ATP turnover and oxygen consumption)

⇒ hypercapnia leads to tissue specific (CA) decrease energy-dependent processes: it is a way of inducing tissue hibernation.

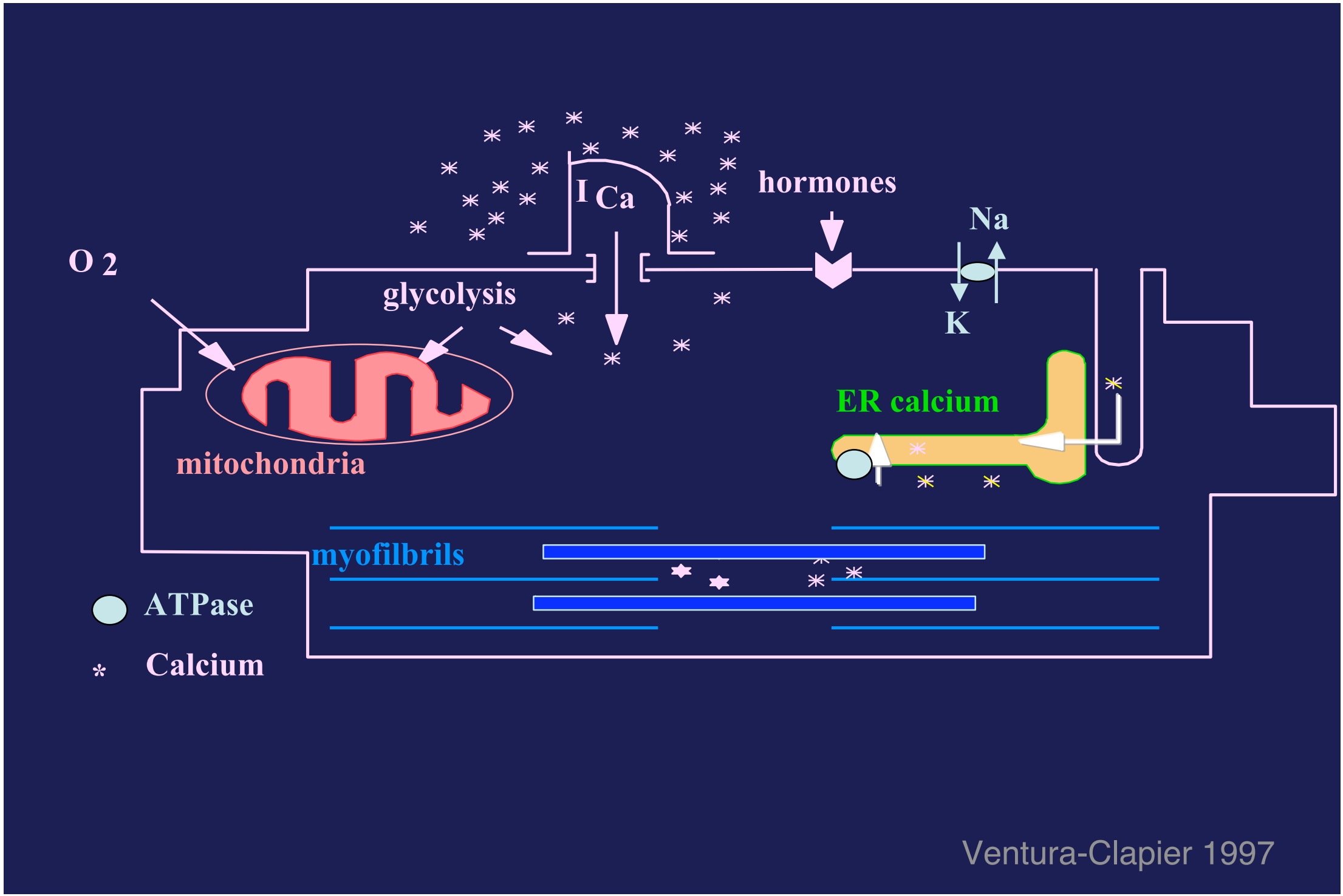


$$\frac{ATP}{ADP \times Pi}$$

ATP turnover = 70 kg / day

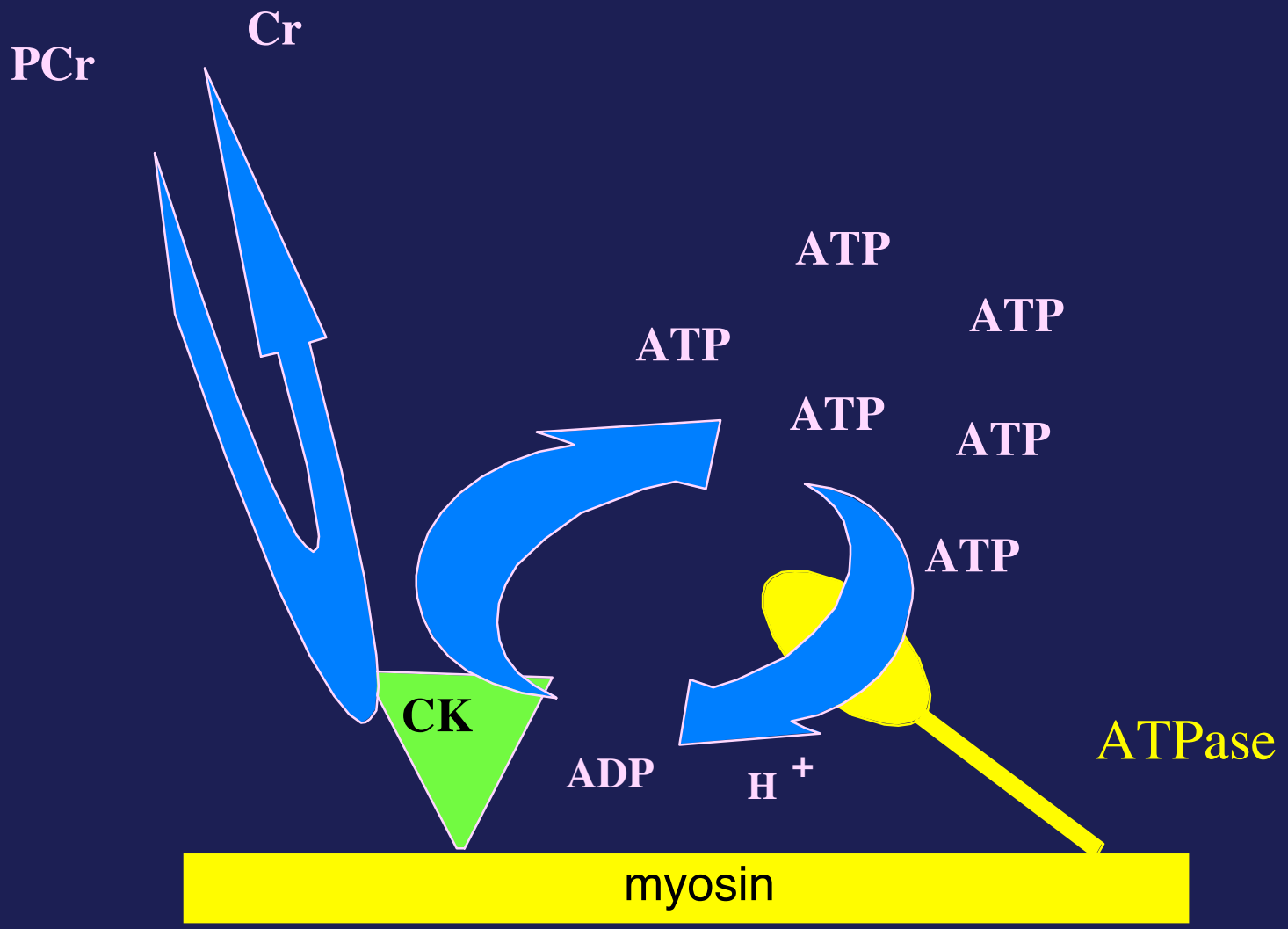
Total adenine nucleotides = 100g

Autonomy = 2 - 3 min



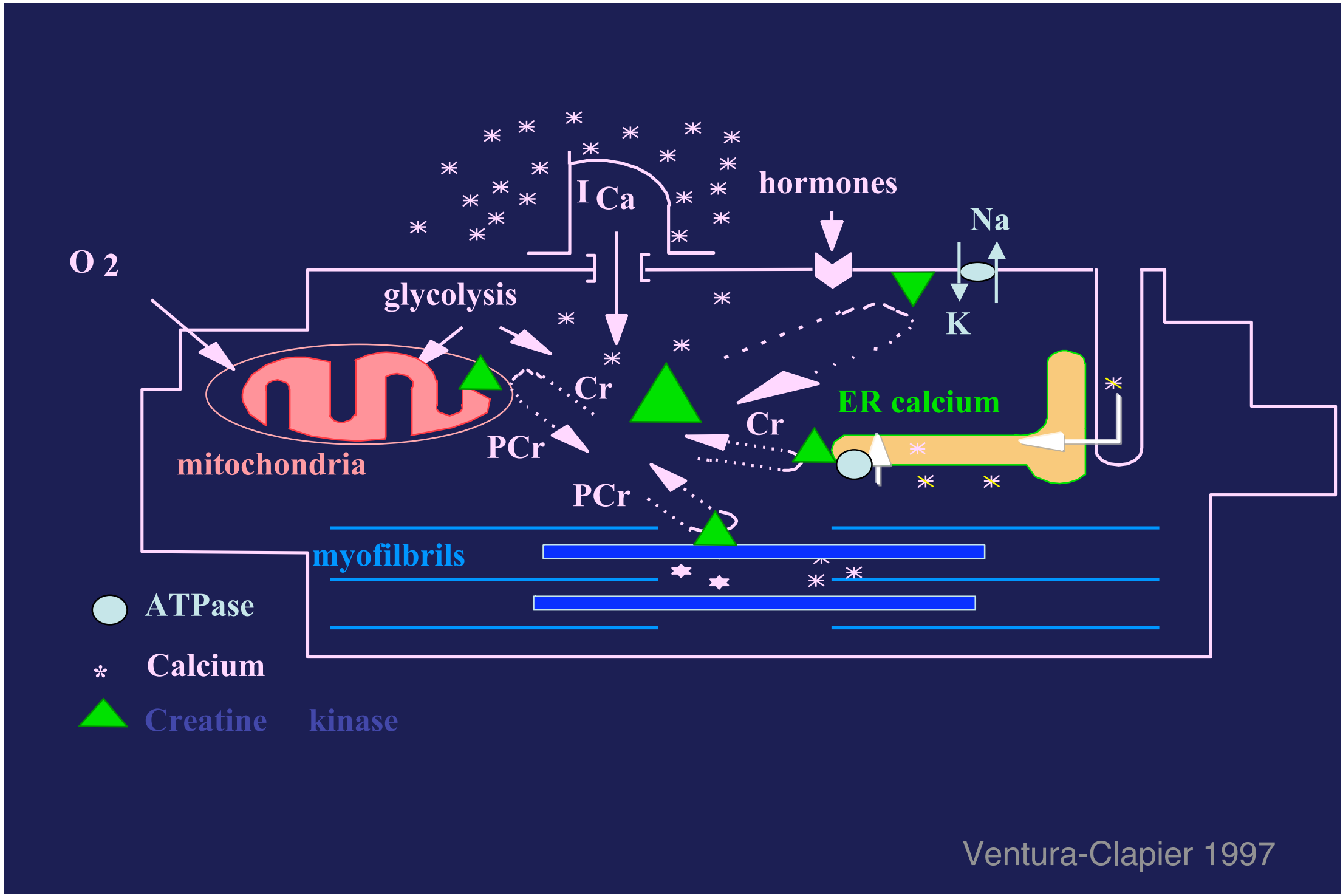
Ventura-Clapier 1997

Myofibrillar CK compartmentation

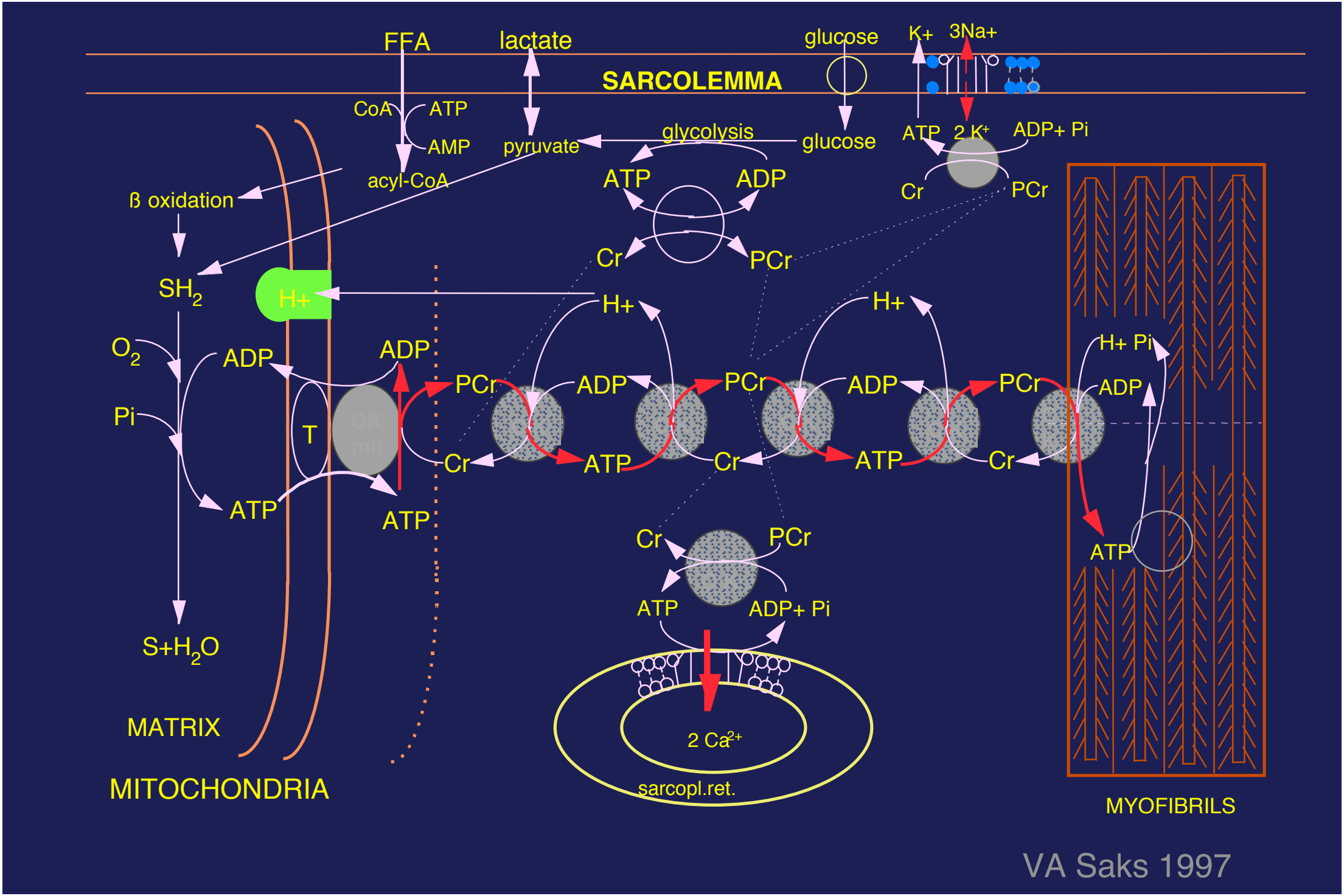


myofilaments

Veksler et al, Cardiovasc Res 1997



Ventura-Clapier 1997


FFA
lactate
glucose
K+
3Na+
SARCOLEMMA
CoA
ATP
AMP
acyl-CoA
pyruvate
glycolysis
glucose
ATP
2 K+
ADP+ Pi
ß oxidation
ATP
ADP
Cr
PCr
SH2
H+
O2
ADP
ADP
PCr
ADP
PCr
ADP
H+ Pi
Pi
T
CK mit
Cr
ATP
Cr
ATP
Cr
ATP
ADP
ATP
Cr
PCr
S+H2O
ATP
ADP+ Pi
2 Ca2+
MATRIX
sarcopl.ret.
MITOCHONDRIA
MYOFIBRILS
VA Saks 1997

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 9493–9498, September 1996
Biochemistry

Unifying theory of hypoxia tolerance: Molecular/metabolic defense and rescue mechanisms for surviving oxygen lack

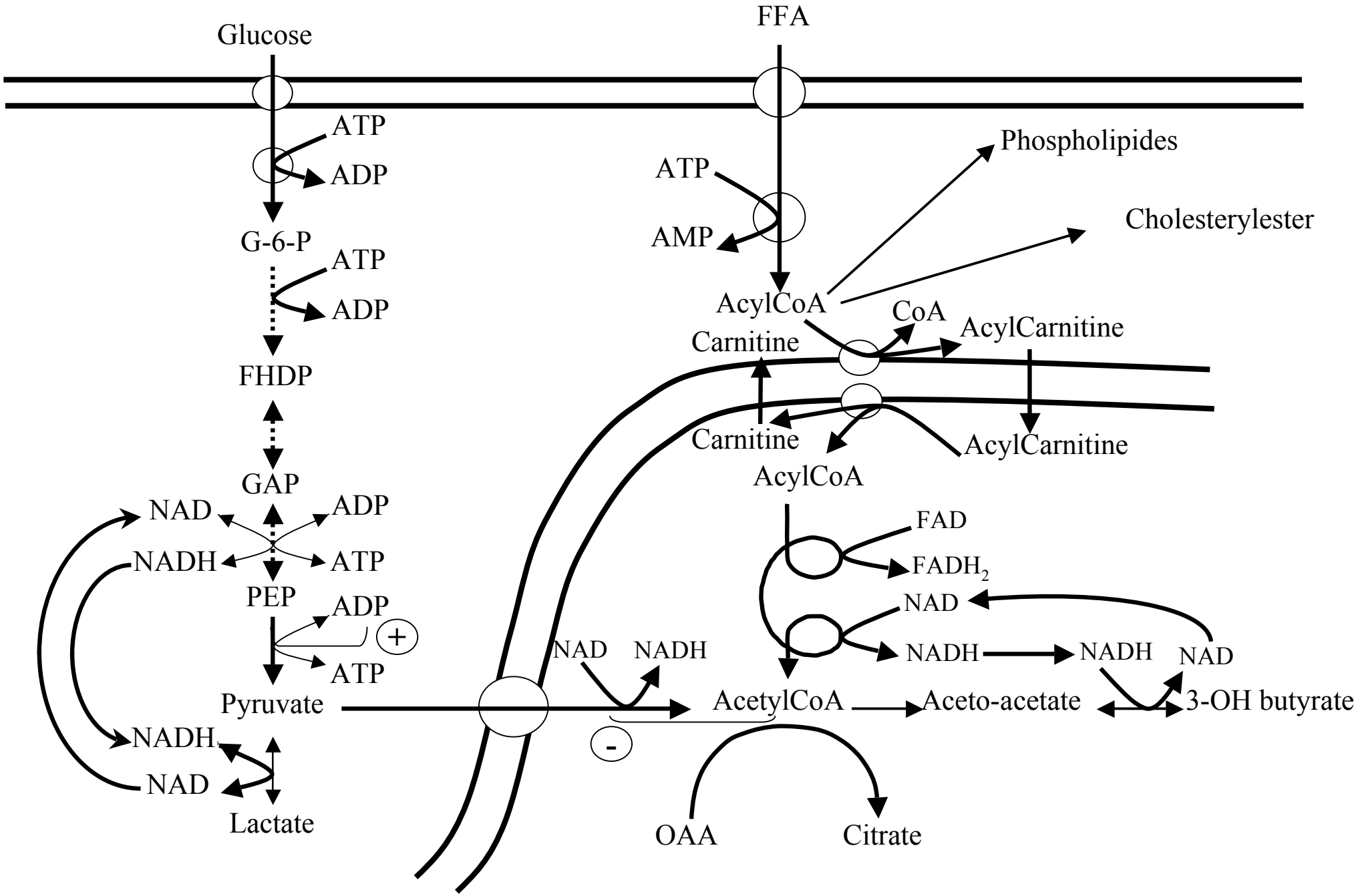
(oxygen sensing/hypoxia defense/turtle hepatocytes/turtle brain)

P. W. HOCHACHKA, L. T. BUCK*, C. J. DOLL†, AND S. C. LAND‡

Table 1. The main ATP-demand pathways during normoxia and anoxia in turtle hepatocytes

Pathway	ATP demand, μmol ATP $\times$ g^{-1} $\times$ h^{-1}		
	Normoxia	Anoxia	% suppression
Total	67.0	6.3	94
Na^+ pump	19.1	4.8	75
Protein synthesis	24.4	1.6	93
Protein breakdown	11.1	0.7	94
Urea synthesis	2.0	0.6	70
Gluconeogenesis	11.4	0.0	100

Modified from Buck and Hochachka (20) and Land and Hochachka (22, 23).

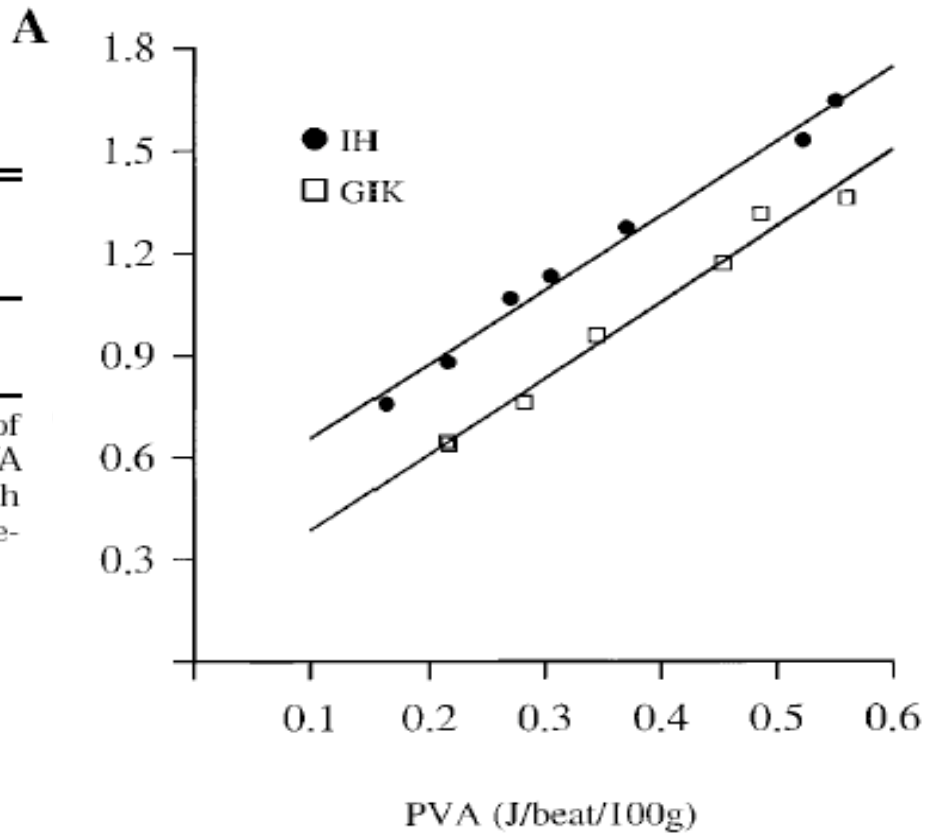

Glucose
FFA
ATP
ADP
ATP
AMP
Phospholipides
Cholesterylester
G-6-P
ATP
ADP
AcylCoA
CoA
AcylCarnitine
Carnitine
FHDP
Carnitine
AcylCarnitine
AcylCoA
GAP
NAD
ADP
FAD
NADH
ATP
FADH2
PEP
NAD
ADP
+
NAD
NADH
NADH
NADH
NAD
ATP
Pyruvate
AcetylCoA
Aceto-acetate
3-OH butyrate
NADH
NAD
-
Lactate
OAA
Citrate

		glucose	palmitic acid	standard protein
molar mass (g)		180	256	2257.4
O_2 consumed (l /g)		0.747	2.013	1.045
CO_2 produced (l /g)		0.747	1.4	0.864
H_2O produced (g/g)		0.6	1.125	0.427
RQ		1.00	0.70	0.83
energy potential (kcal/g)		3.87	9.69	4.704
energy equivalent	O_2 (kcal/l)	5.19	4.81	4.50
	CO_2 (kcal/l)	5.19	6.92	5.44
synthesized ATP				
	mol/mol	38	129	450
	kcal/mol	456	1548	5400
	yield	0.65	0.62	0.51

Table 3. *Substrate influence on left ventricular energetics*

	$M\dot{V}O_2$-PVA Relationship		
	y-Intercept	Slope	*r*
GIK	0.29 ± 0.18	2.3 ± 0.7	0.99 ± 0.01
IH	0.48 ± 0.17*	2.2 ± 0.3	0.98 ± 0.02

Values are means ± SD, $n = 8$. $M\dot{V}O_2$-PVA relations are means of linear regression coefficients, derived from the sets of $M\dot{V}O_2$ and PVA values obtained by stepwise steady-state preload reduction in each experiment. *y*-Intercept (unloaded $M\dot{V}O_2$), $J \cdot beat^{-1} \cdot 100\ g^{-1}$. *r*, correlation coefficient. $^*P < 0.01$.



Korvald, Am J Physiol, 2000

Additive effect of training and High Fat diet on energy metabolism during exercise

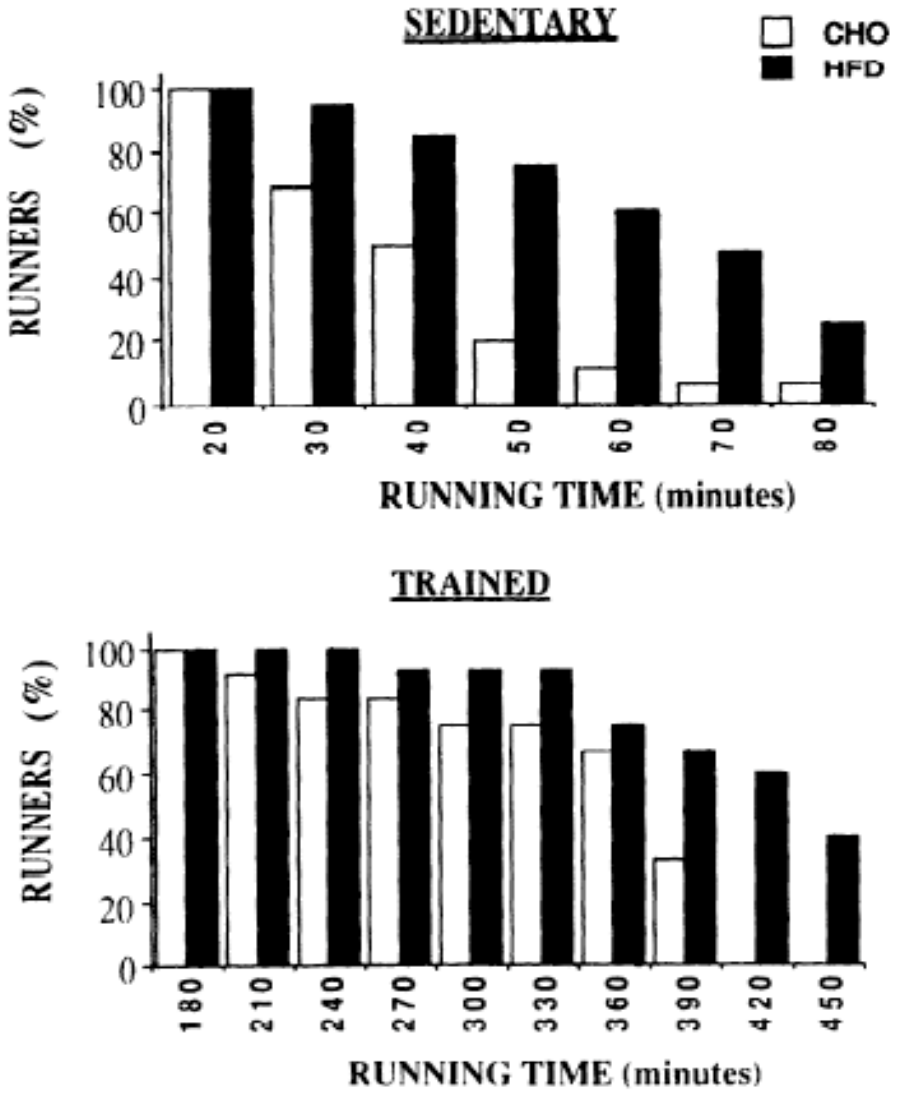


FIG. 1. Submaximal running endurance. Values are means ± SE for 12–15 values per group: Treadmill test was set at 30 m/min with 10% slope. Proportion of 100% runners for a group corresponds to totality of starting animals running on treadmill. After 5 h (300 min) trained rats have 1-min sprint at 50 m/min every 10 min.

TABLE 1. *Composition of the diets*

	CHO diet, g/100 g dry wt	HFD, g/100 g dry wt
Cornstarch	62	0
Casein	22.7	30
Vegetable oils	4.5	5
Lard	0	48
Minerals-vitamins	6.25	7.0
Cellulose	4.5	10.0
Energy value, kcal/100 g	379	597

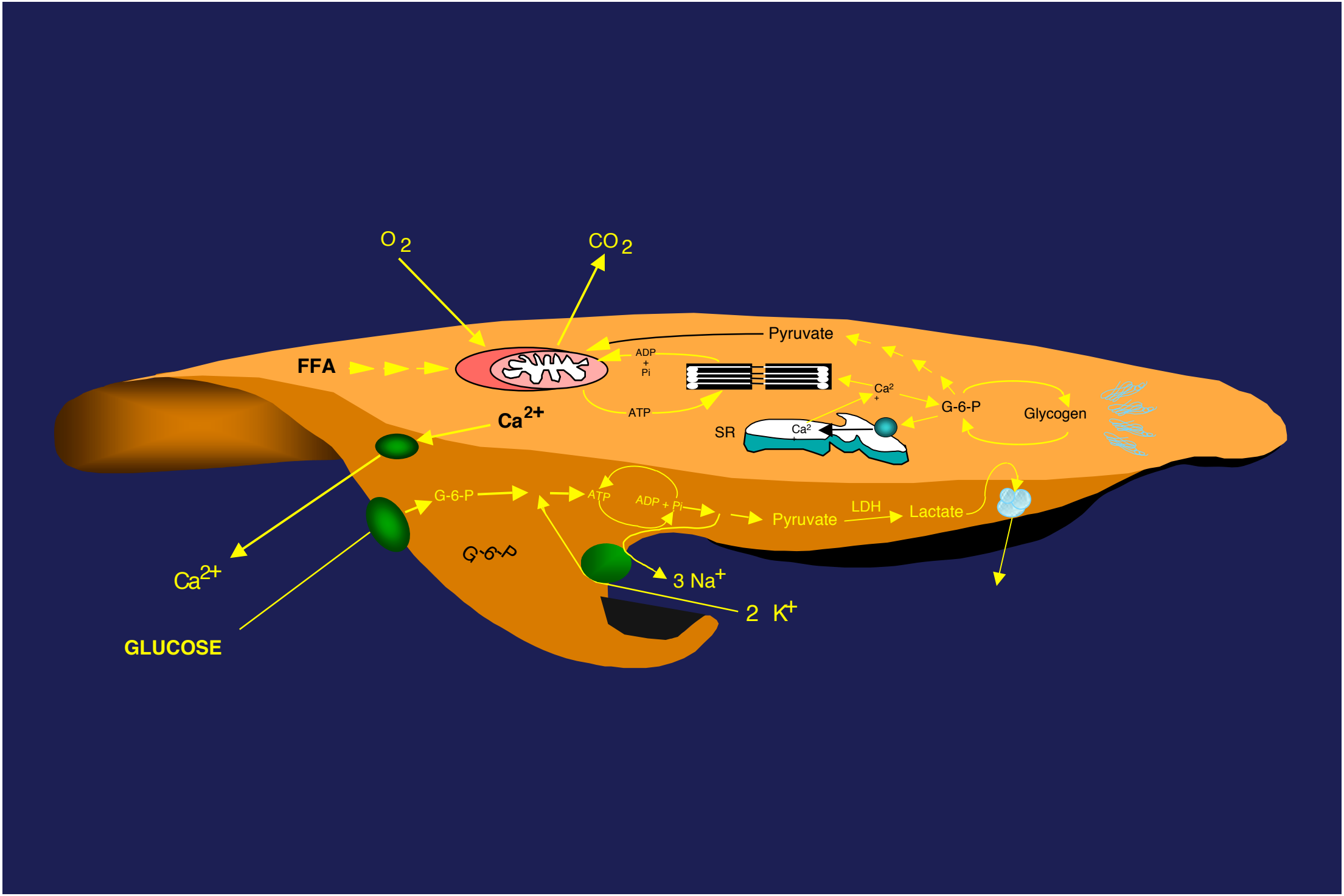
CHO, carbohydrate; HFD, high-fat diet.

TABLE 2. *Body mass and $\dot{V}O_{2\,max}$*

	CHO		HFD	
	Sedentary	Trained	Sedentary	Trained
Body mass, g	375±9	371±9	373±8	359±7
$\dot{V}O_{2\,max}$, ml · min^{-1} · kg^{-1}	90.3±3.3	109.0±2.1*	101.7±2.1†	122.7±2.7*†

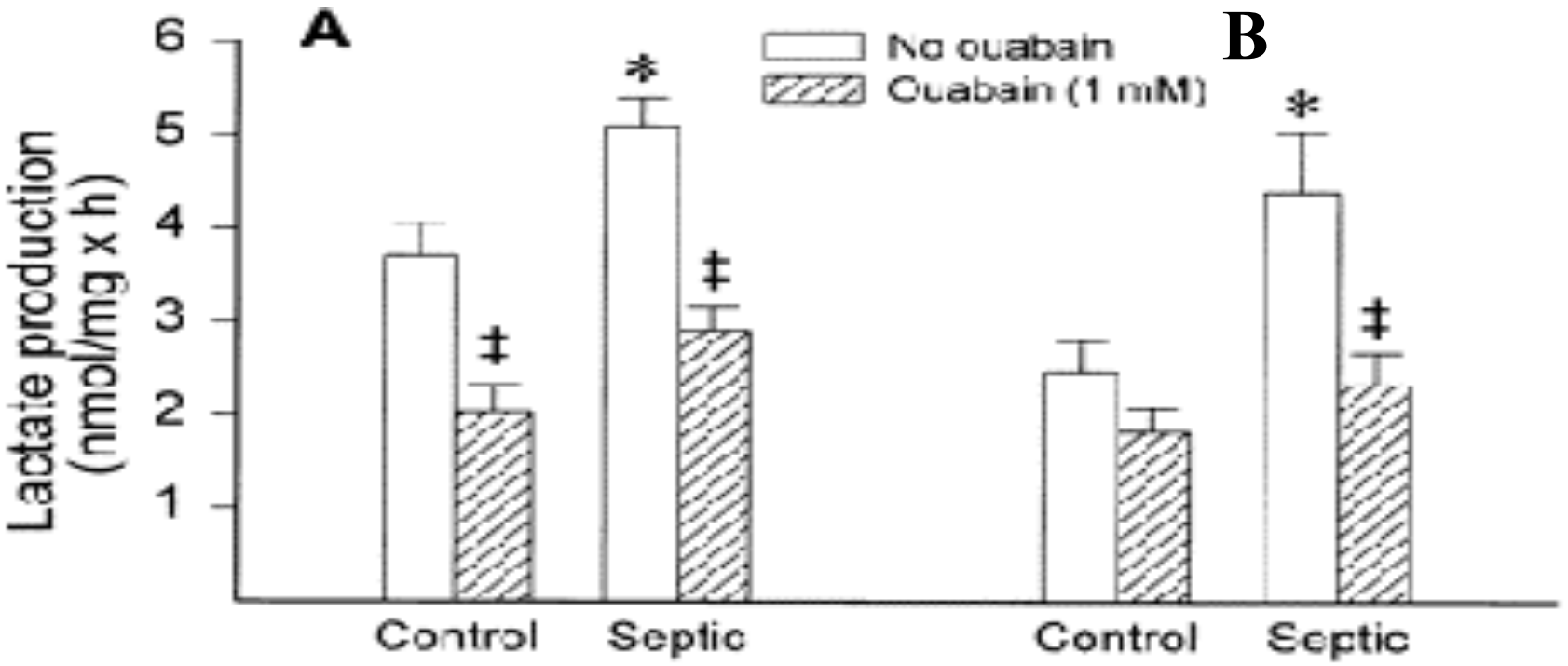
Values are means ± SE for 14–19 values per group. $\dot{V}O_{2\,max}$, maximal uptake. * Significantly different ($P < 0.05$) from sedentary on the same diet. † Significantly different ($P < 0.05$) from corresponding CHO group.

Favier, et al, J Appl Physiol, 1991


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

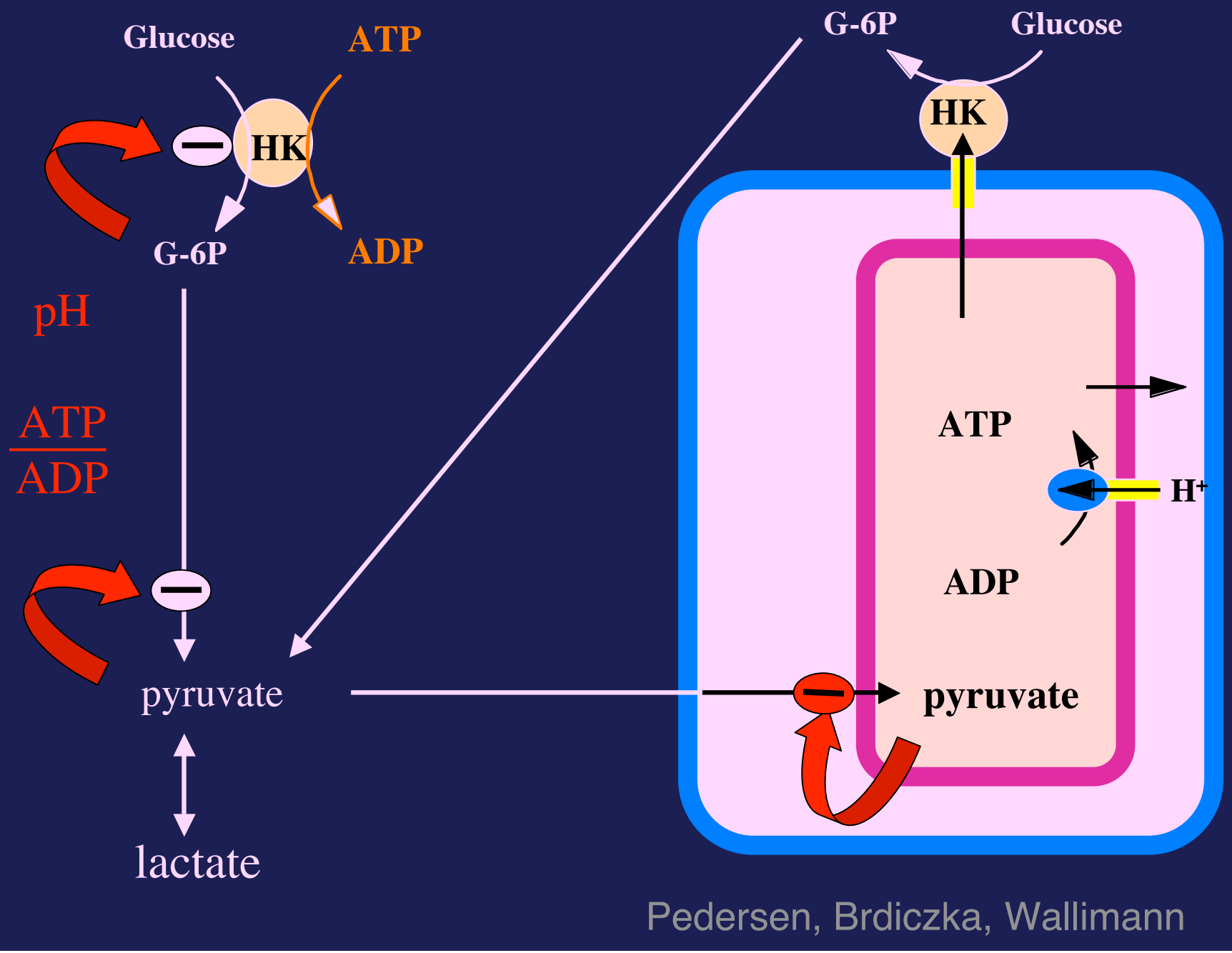
LACTATE sepsis and Na/K ATPase

James *et al*, J Clin Invest 1996; 10: 2388-97

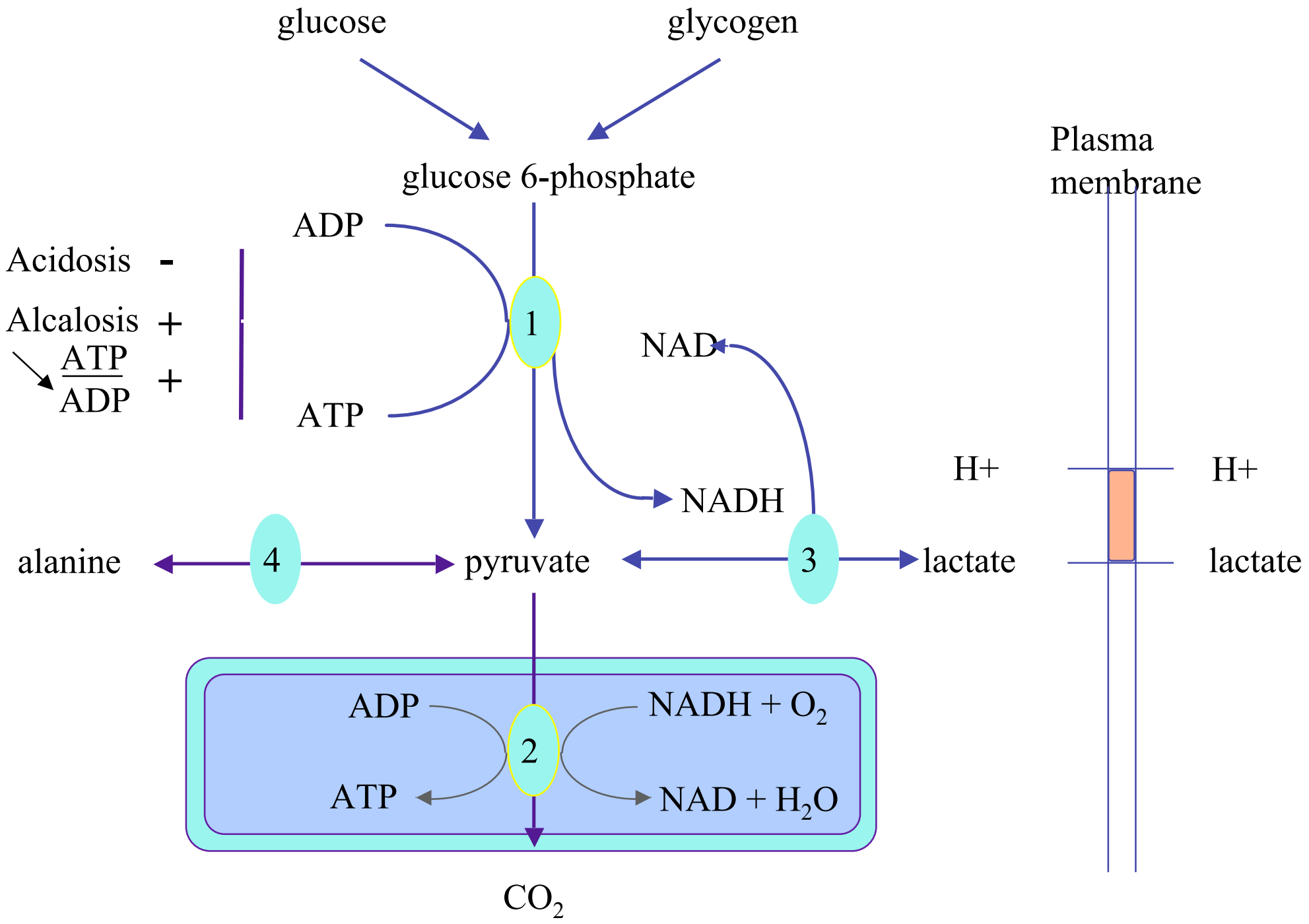


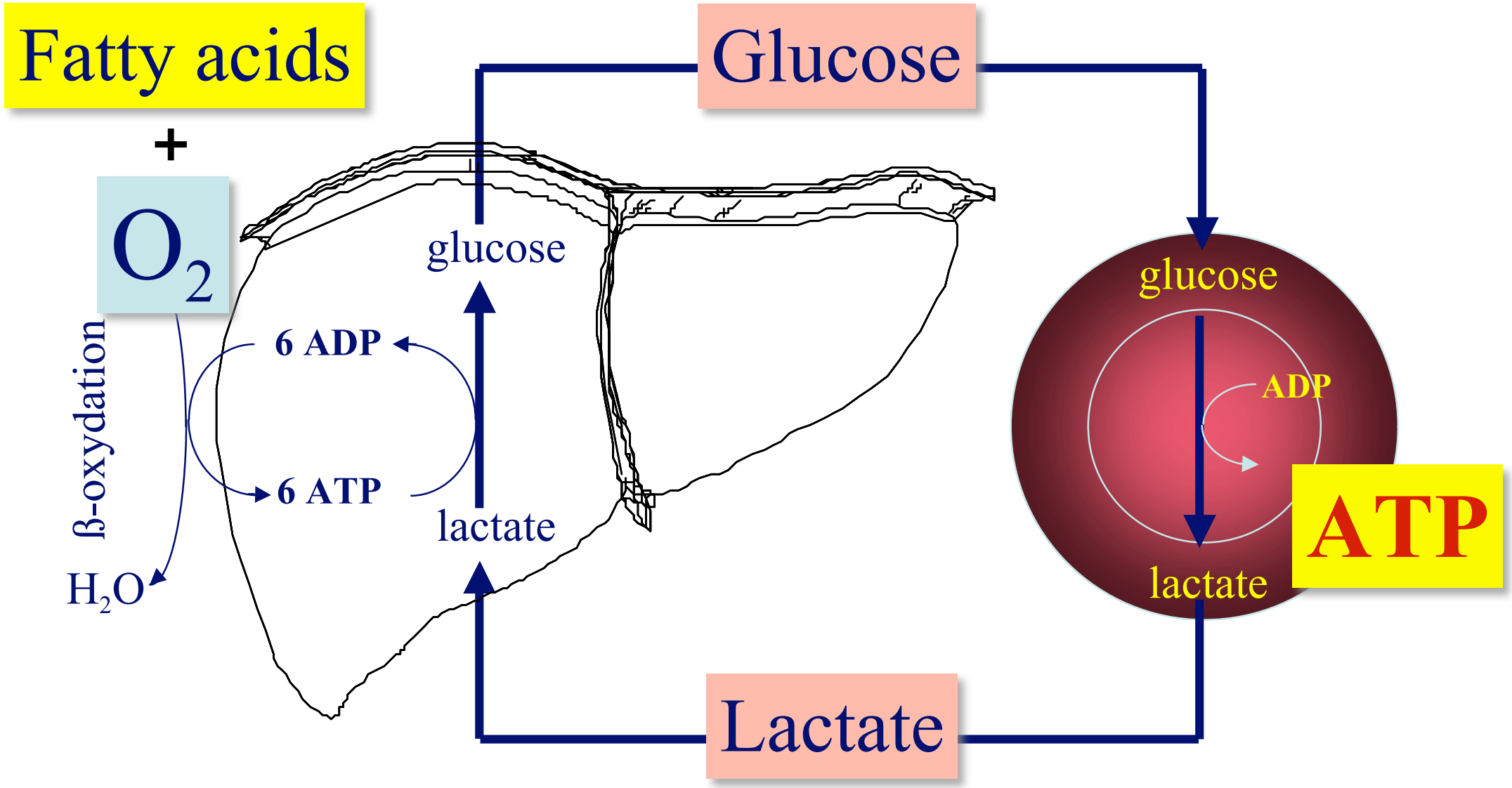
A : caecal ligation
B : ip LPS injection

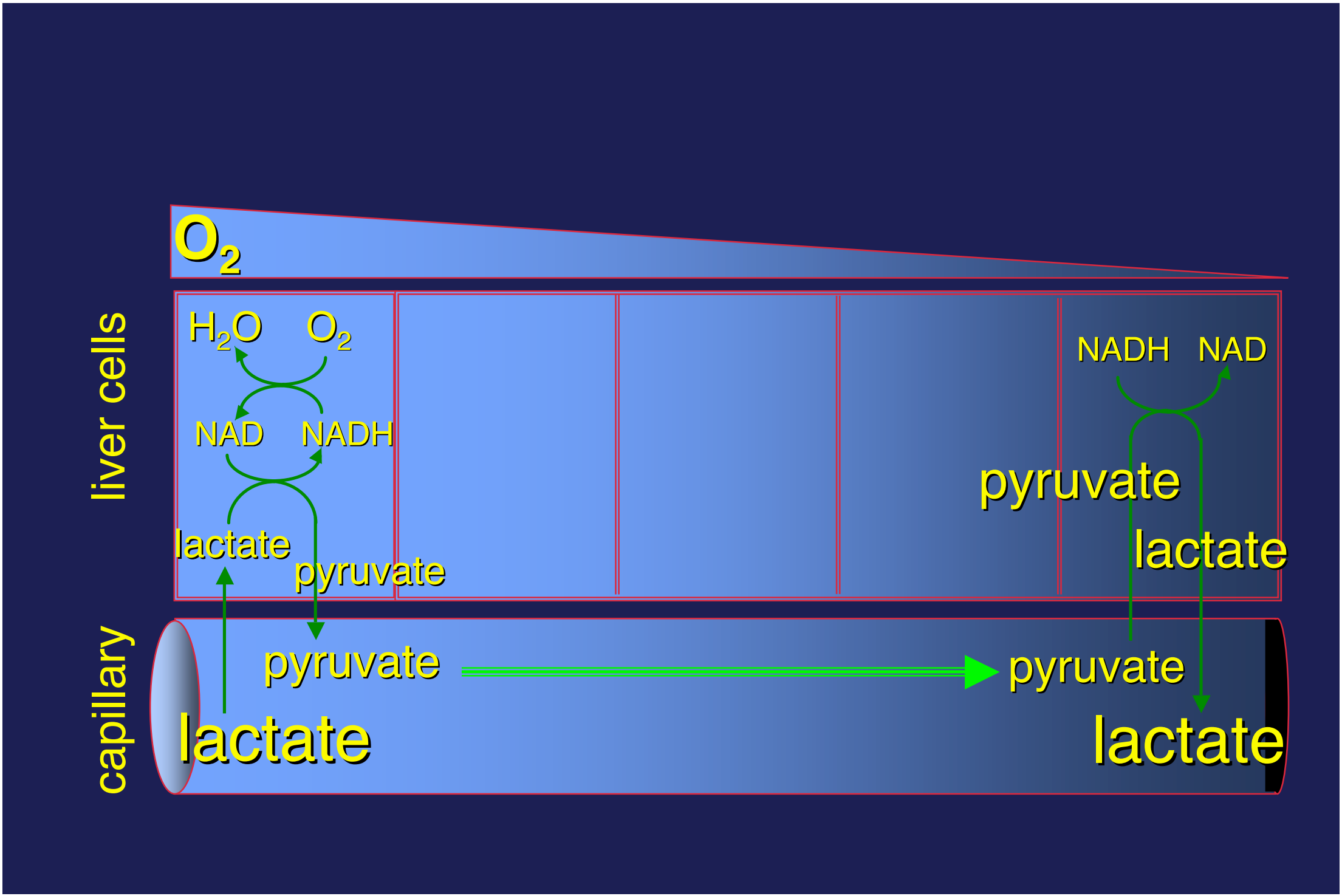
Regulation of glycolysis



Pedersen, Brdiczka, Wallimann

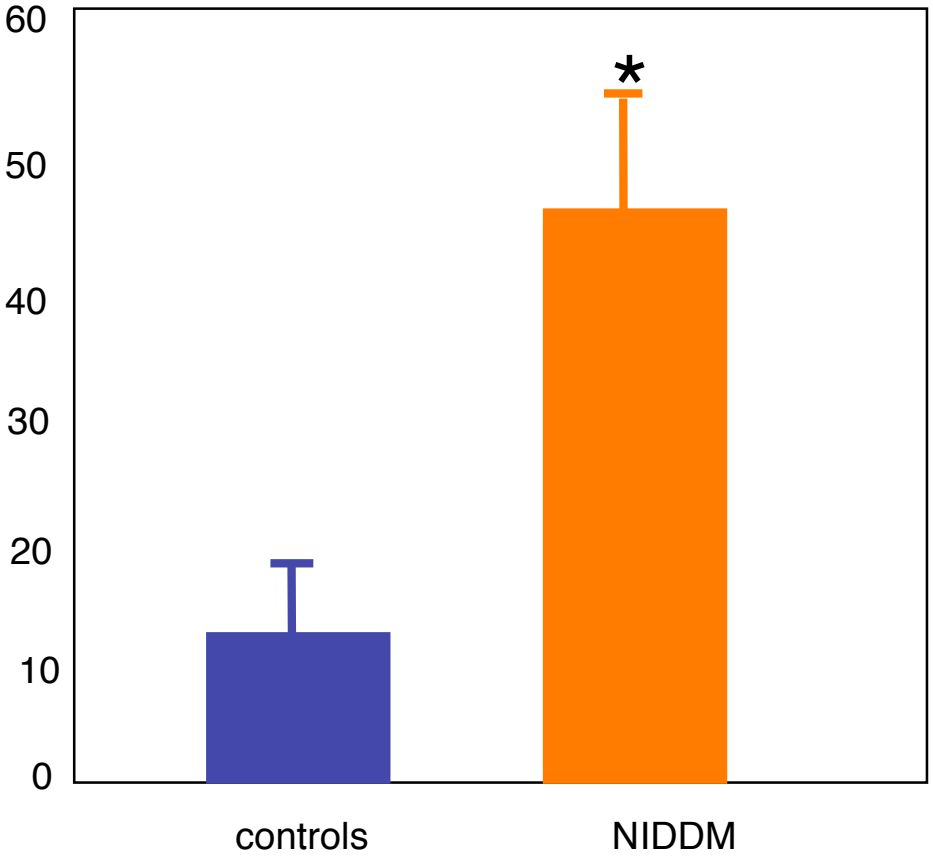

glucose
glycogen
glucose 6-phosphate
ADP
ATP
1
Acidosis -
Alcalosis +
ATP/ADP +
NAD
NADH
H+
H+
alanine
4
pyruvate
3
lactate
lactate
Plasma membrane
ADP
ATP
2
NADH + O2
NAD + H2O
CO2


Fatty acids
+
O_2
Glucose
glucose
6 ADP
6 ATP
lactate
ß-oxydation
H_2O
glucose
ADP
lactate
ATP
Lactate


O_2
liver cells
H_2O
O_2
NAD
NADH
lactate
pyruvate
NADH
NAD
pyruvate
lactate
capillary
pyruvate
lactate
pyruvate
lactate

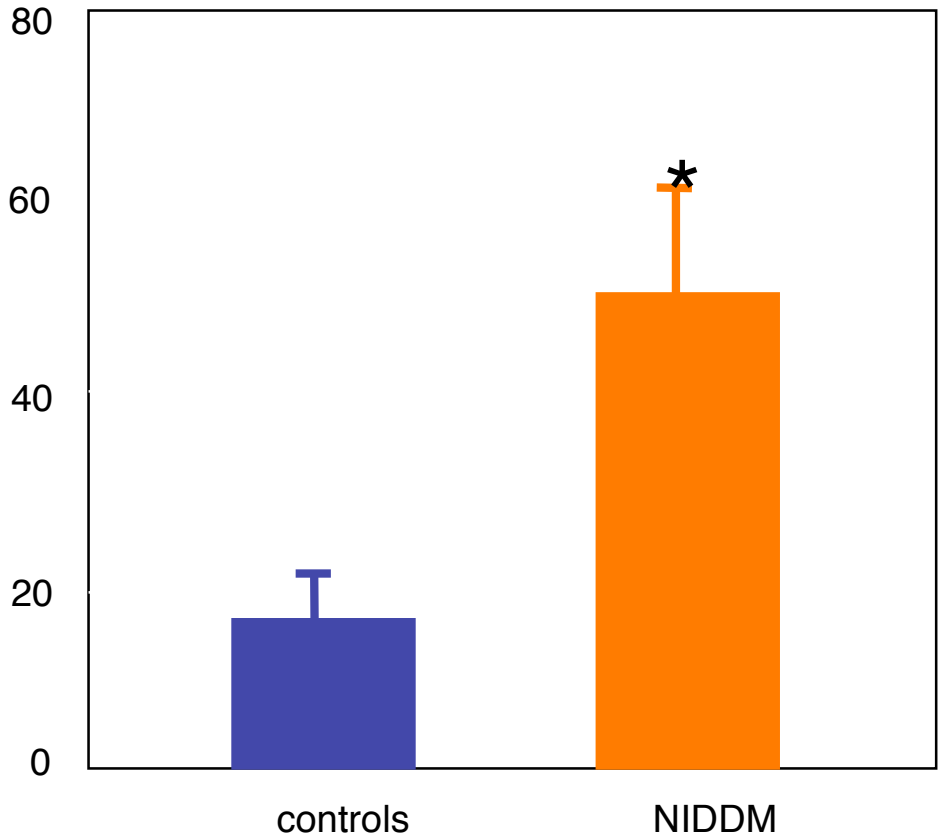
Lactate into pyruvate conversion rate

(μmol/L x min)



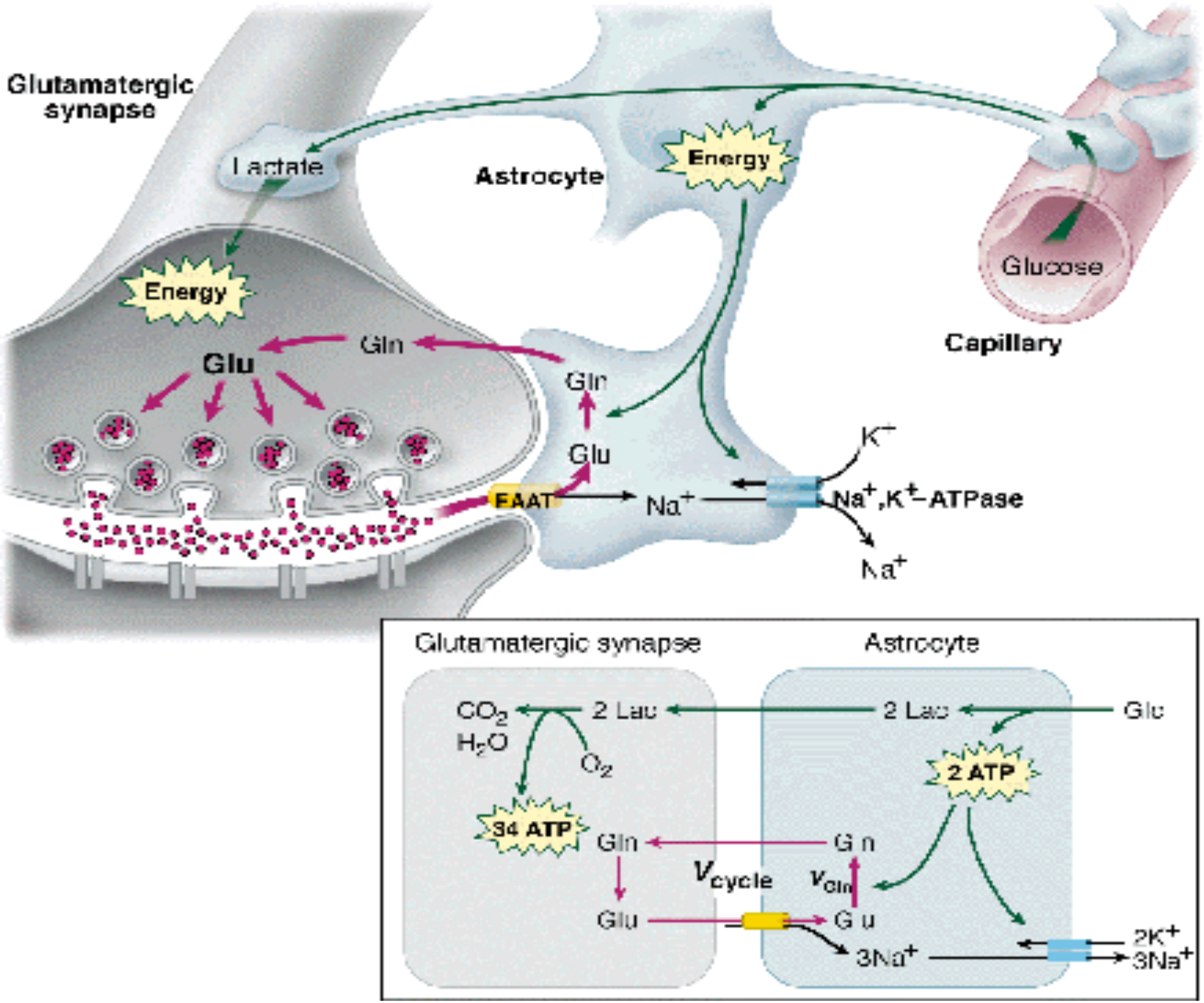
Pyruvate into lactate conversion rate

(μmol/L x min)



Interconversion rates of lactate to pyruvate and pyruvate to lactate occuring in the forearm muscle tissue of Control individuals and NIDDM patients after a 10 - 12 h overnight fasting

Avogaro A., J Clin Invest, 1996


Glutamatergic synapse
Lactate
Astrocyte
Energy
Glucose
Capillary
Energy
Gln
Glu
Gln
Glu
K+
EAAT
Na+
Na+,K+-ATPase
Na+
Glutamatergic synapse
Astrocyte
CO2
H2O
2 Lac
2 Lac
Glc
O2
2 ATP
34 ATP
Gln
Gln
Vcycle
Vgln
Glu
Glu
2K+
3Na+
3Na+

Protection by Lactate of Cerebral Functions during Hypoglycemia

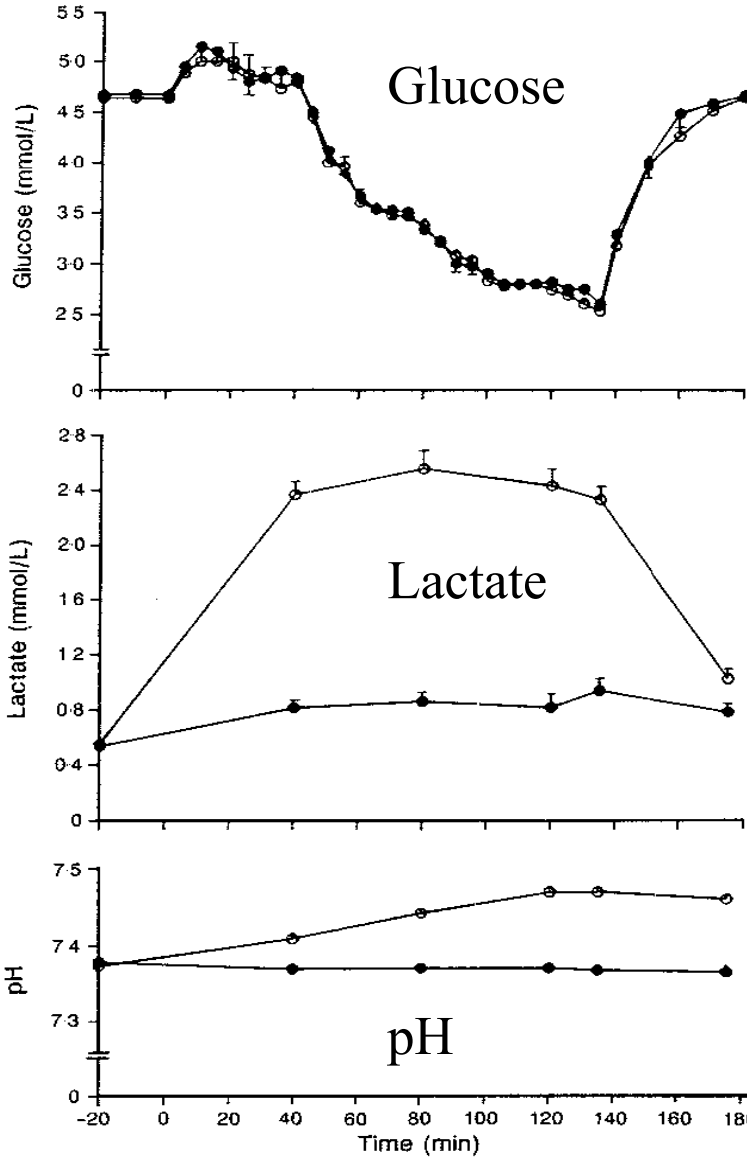


Figure 1: **Blood glucose, lactate, and pH profiles during clamp studies**

Studies during saline (●) and lactate (○) infusion (mean and SE)

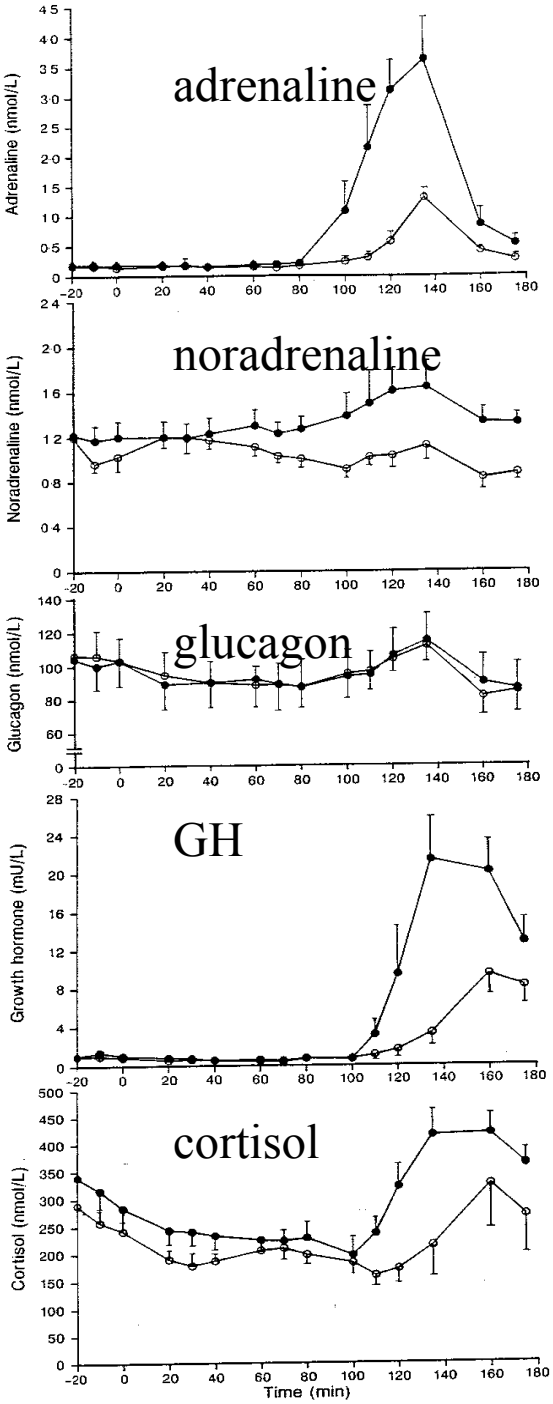


Figure 2: **Hormonal responses to hypoglycaemia**

● = absence and ○ = presence of lactate.

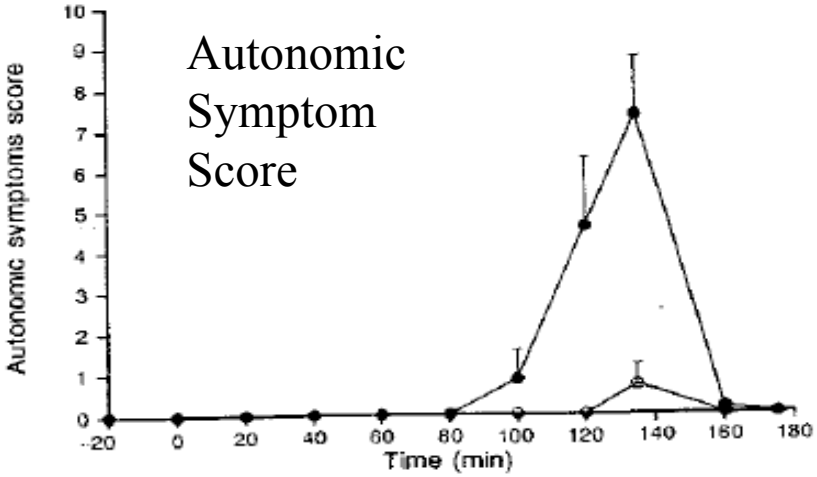
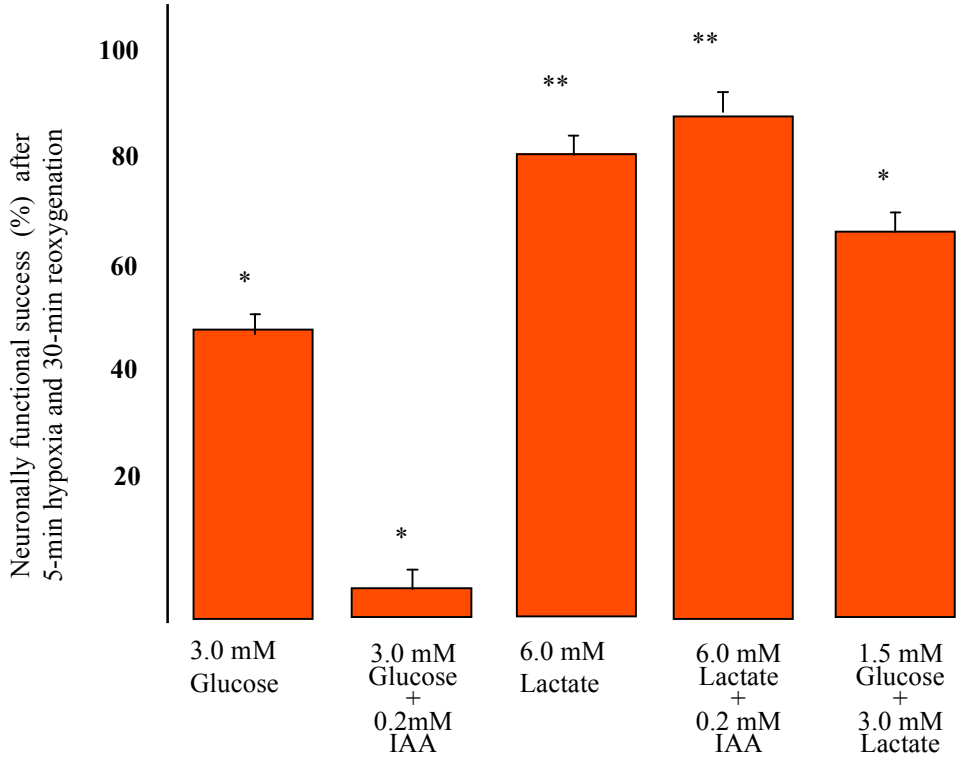


Figure 3: **Autonomic symptom scores**

● = absence and ○ = presence of lactate.

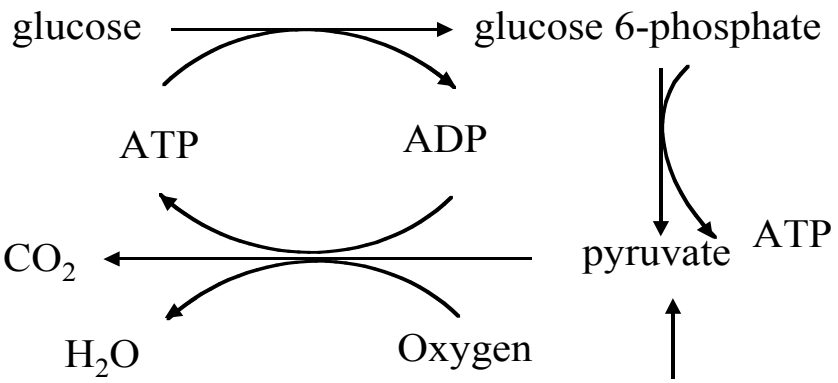
Maran et al, Lancet, 1994 343: 17-20

Lactate and brain recovery from ischemia-reperfusion injury



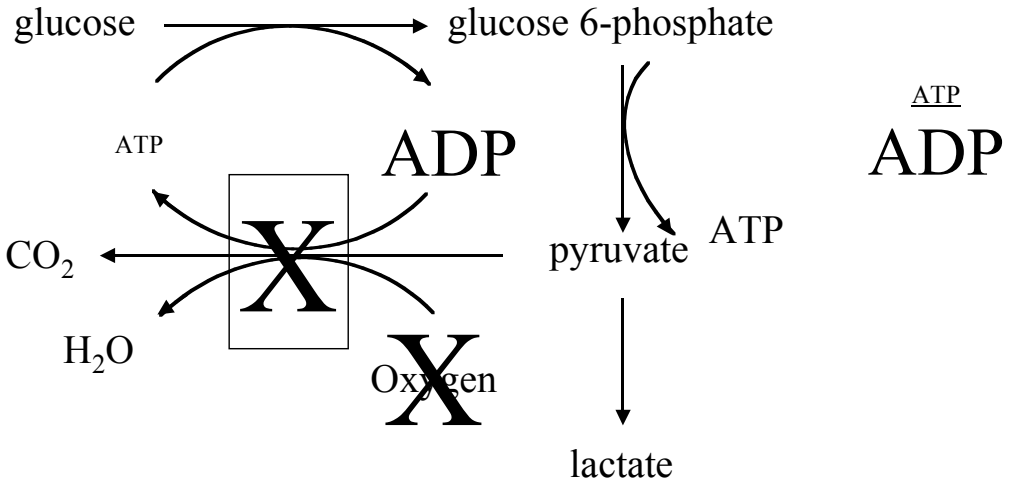
- Slices with lactate showed a significantly higher degree of recovery
- Slices with anaerobic lactate production by pre-hypoxia glucose exhibited functional recovery
- 80% recovery even glucose utilization was blocked during the later part of the hypoxic period and reoxygenation
- Slices in which anaerobic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

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



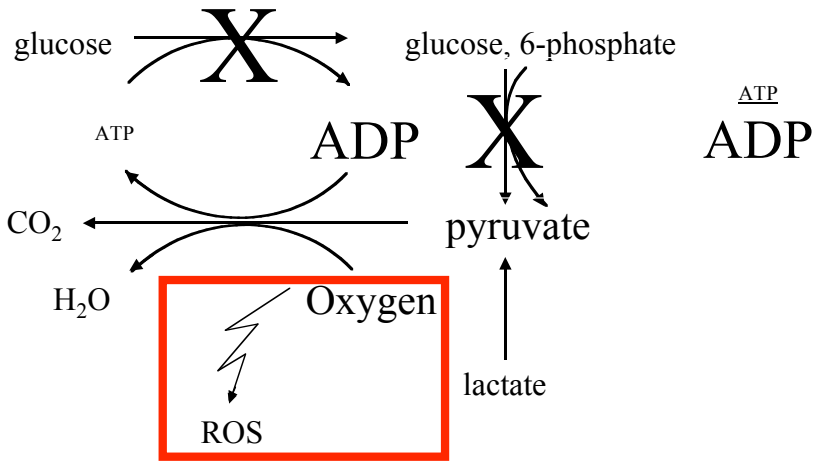
ATP / ADP

Normal condition



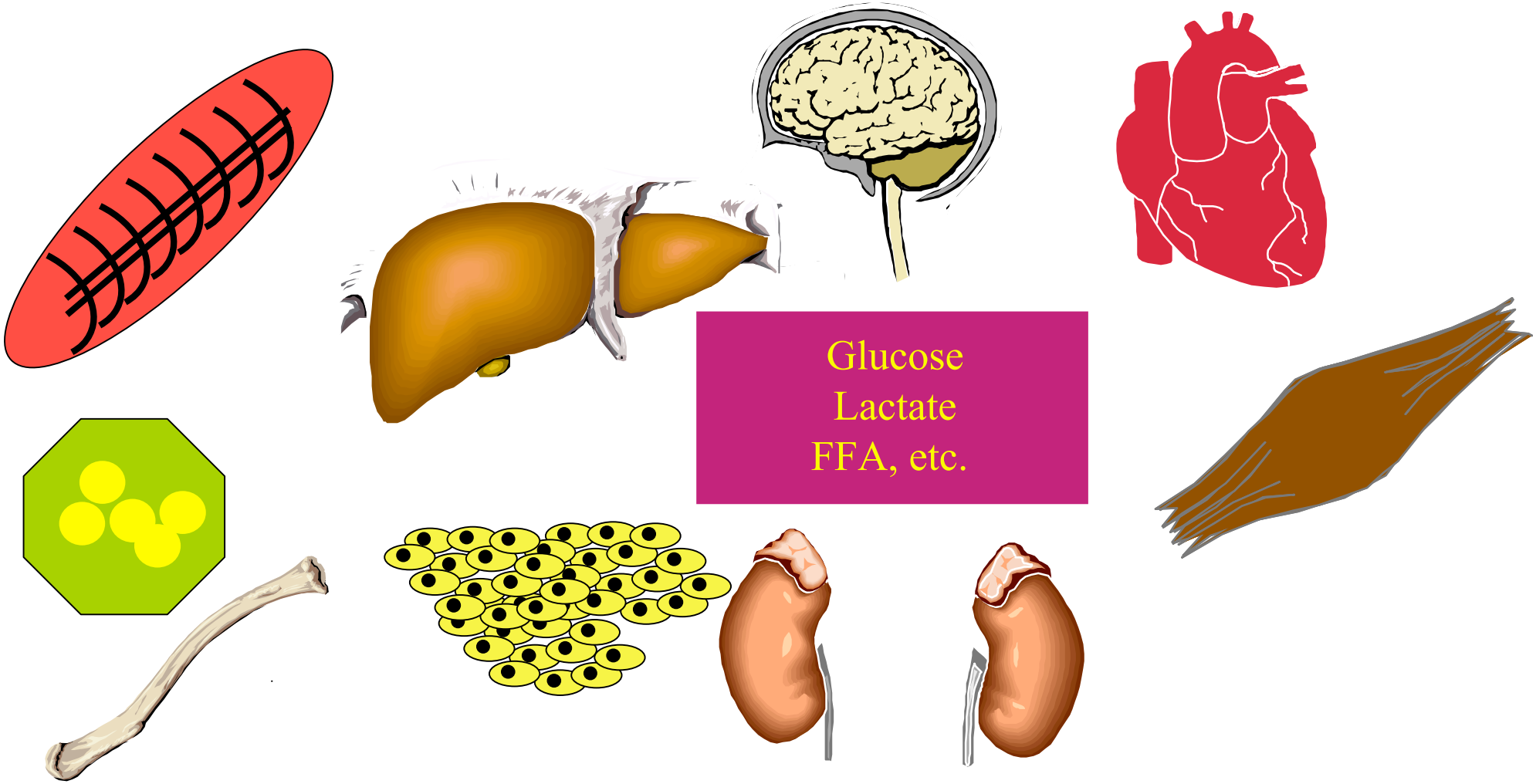
ATP / ADP

Reaction during hypoxia



Reaction after oxygen restoration post hypoxia

The steady state of the "*milieu interieur*" results from the metabolism of each and every cell



A compromise between cell and organ priorities?