Le tissu adipeux brun humain

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Hôpital Necker-Enfants Malades et Institut Cochin
CNRS et INSERM

Le tissu adipeux brun humain (le retour!)

- AHENG, Caroline
- ALVES-GUERRA, Clotilde
- **CASSARD-DOULCIER, A-Marie**
- EMRE, Yalin
- **GELLY, Chantal**
- **GONZALEZ-BARROSO, Mdel Mar**
- HAGUENAUER, Anne
- **LEVI-MEYRUEIS, Corinne**
- **MASSCHELEYN, Sandrine**
- **MIROUX, Bruno**
- MOZO, Julien
- NUEBEL Tobias
- PECQUEUR, Claire
- RABIER, daniel
- ROUSSET, Sophie
- ZOONENS, Manuela

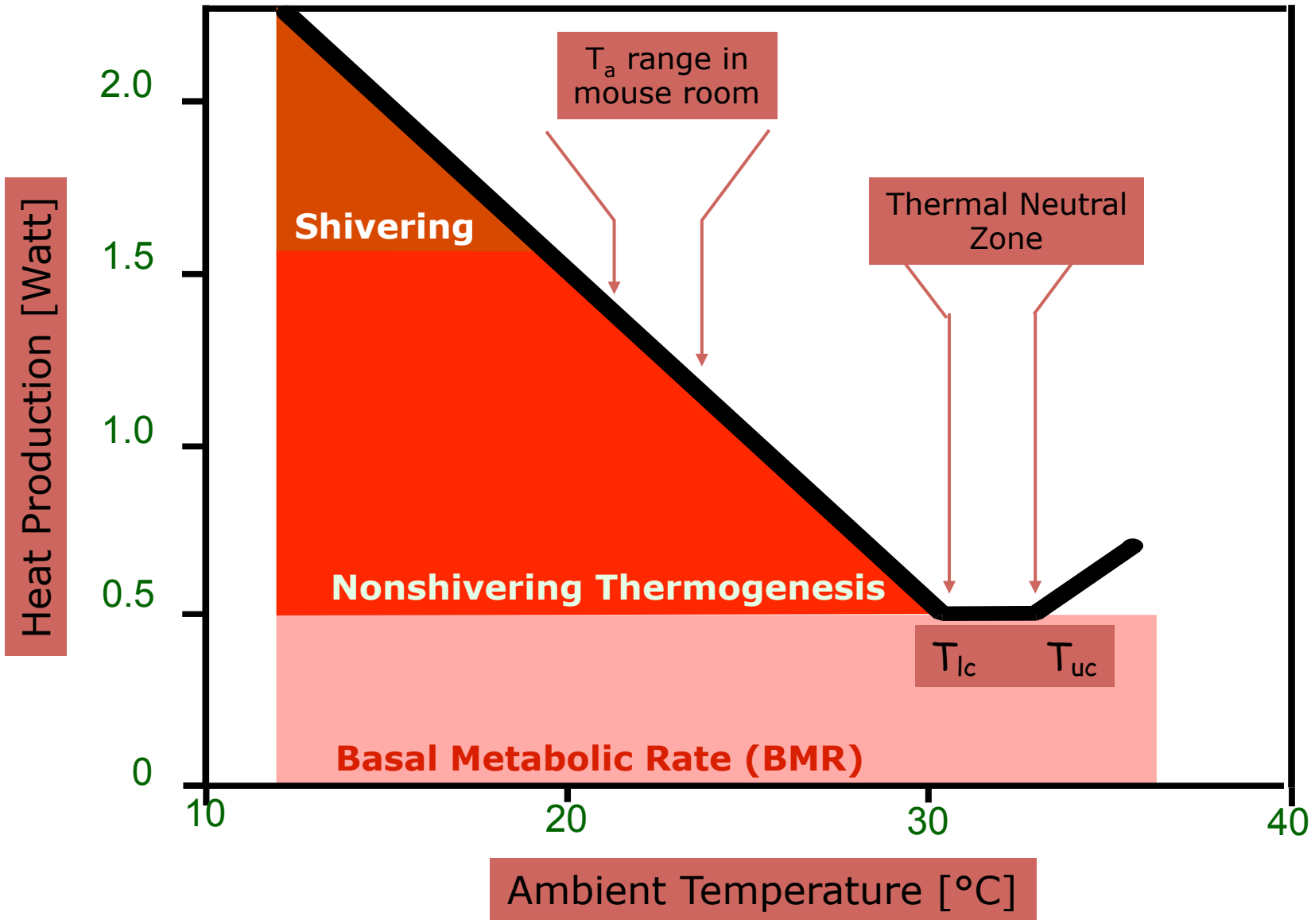
Collaborations

ARSENIJEVIC, Denis, Zurich
CINTI, Saverio, Ancona
COLLINS, Sheila and coll., Duke UMC
HORVATH, Tamas, Yale Univ
IBRAHIM, Saleh and coll, Rostock
LANGIN, Dominique and coll., Toulouse
de LONLAY, Pascale and coll, Necker
MALLAT, Ziad and TEDGUY, Alain, Paris
RIAL, Eduardo and coll., CSIC Madrid
RICHARD, Denis and coll., Laval U.
ZAVALA, Flora CNRS, Necker

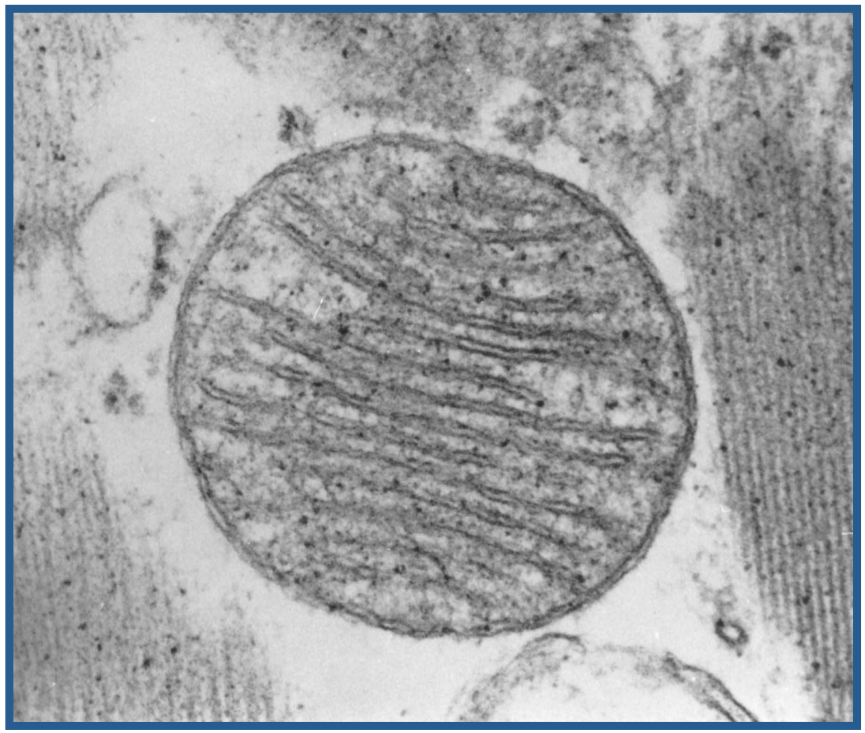
Le tissu adipeux brun humain

- **Qu'est-ce que c'est? Thermogenèse**

Basal Metabolic Rate and Thermoregulatory Heat Production

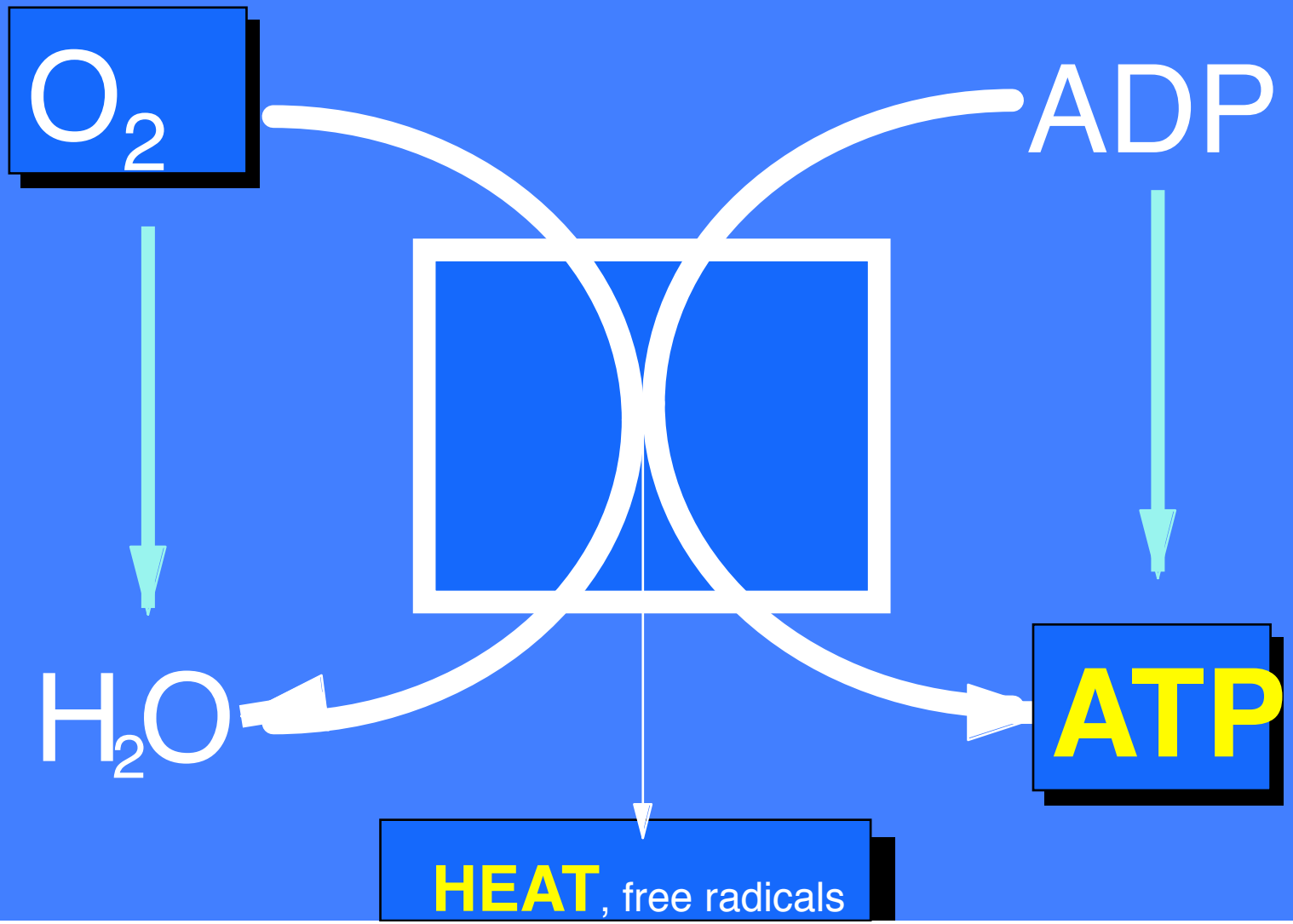


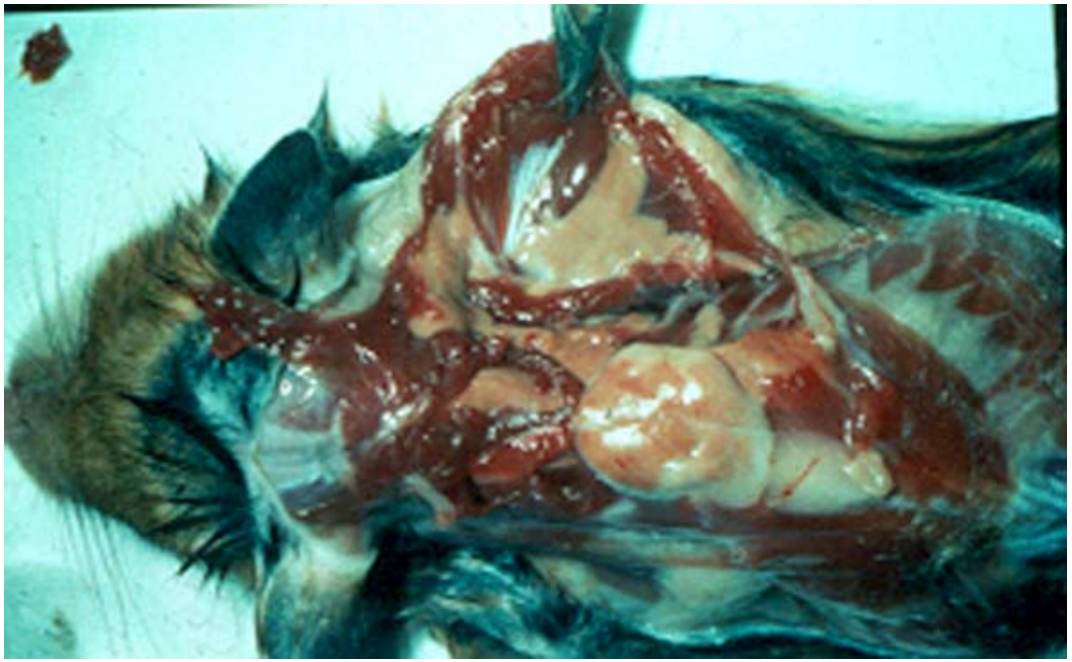
Mitochondria

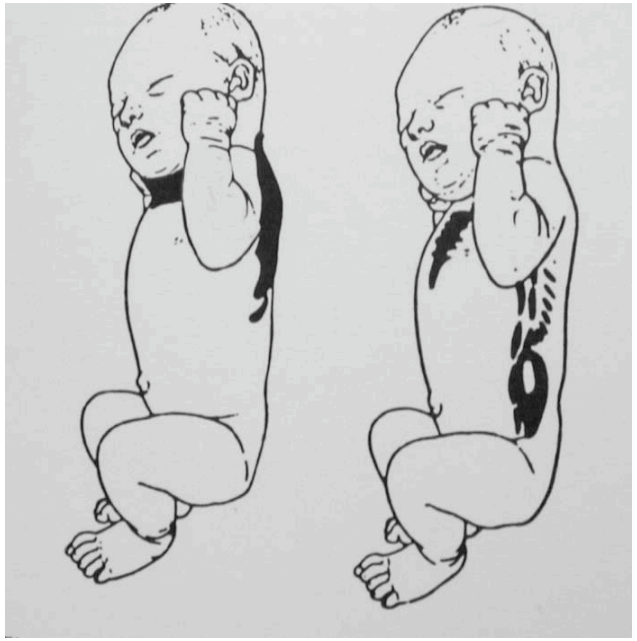


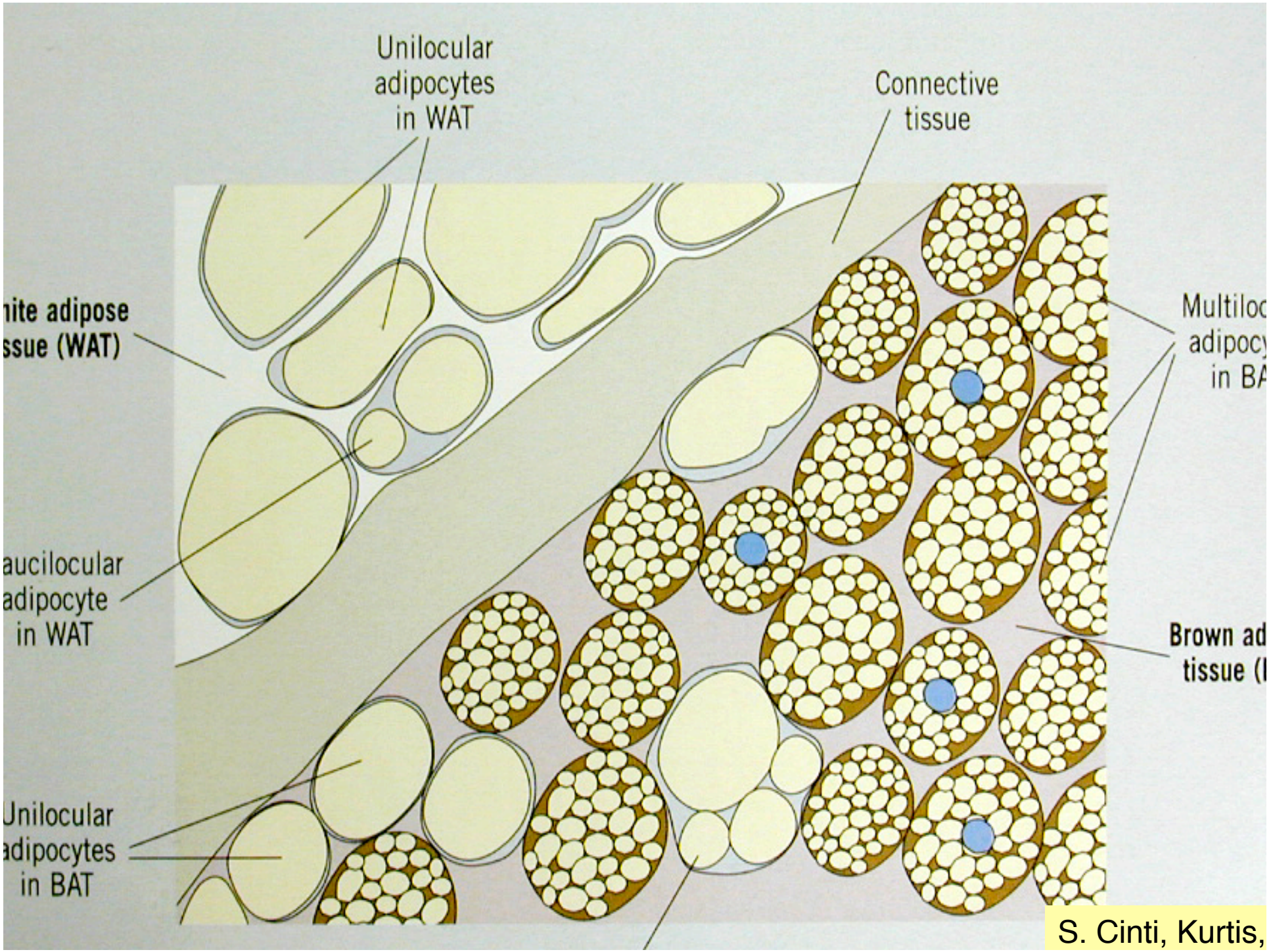
- 45 kg ATP per day !!
- Main cellular energy provider.
- > 90% ATP synthesized
- Respiratory chain, ATP-synthase and anion transporters

Oxidative phosphorylation is the mechanism coupling respiration to ADP phosphorylation

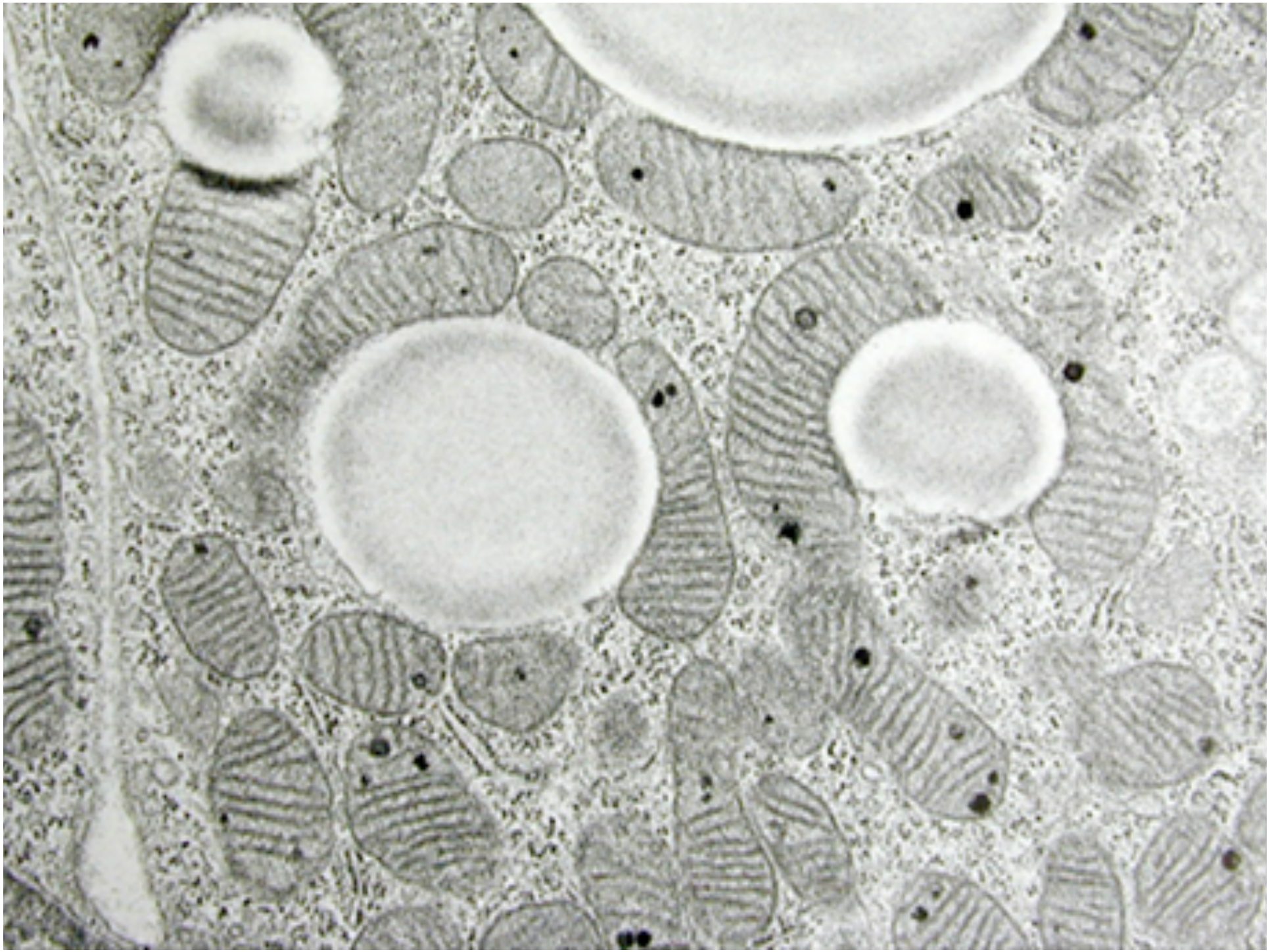


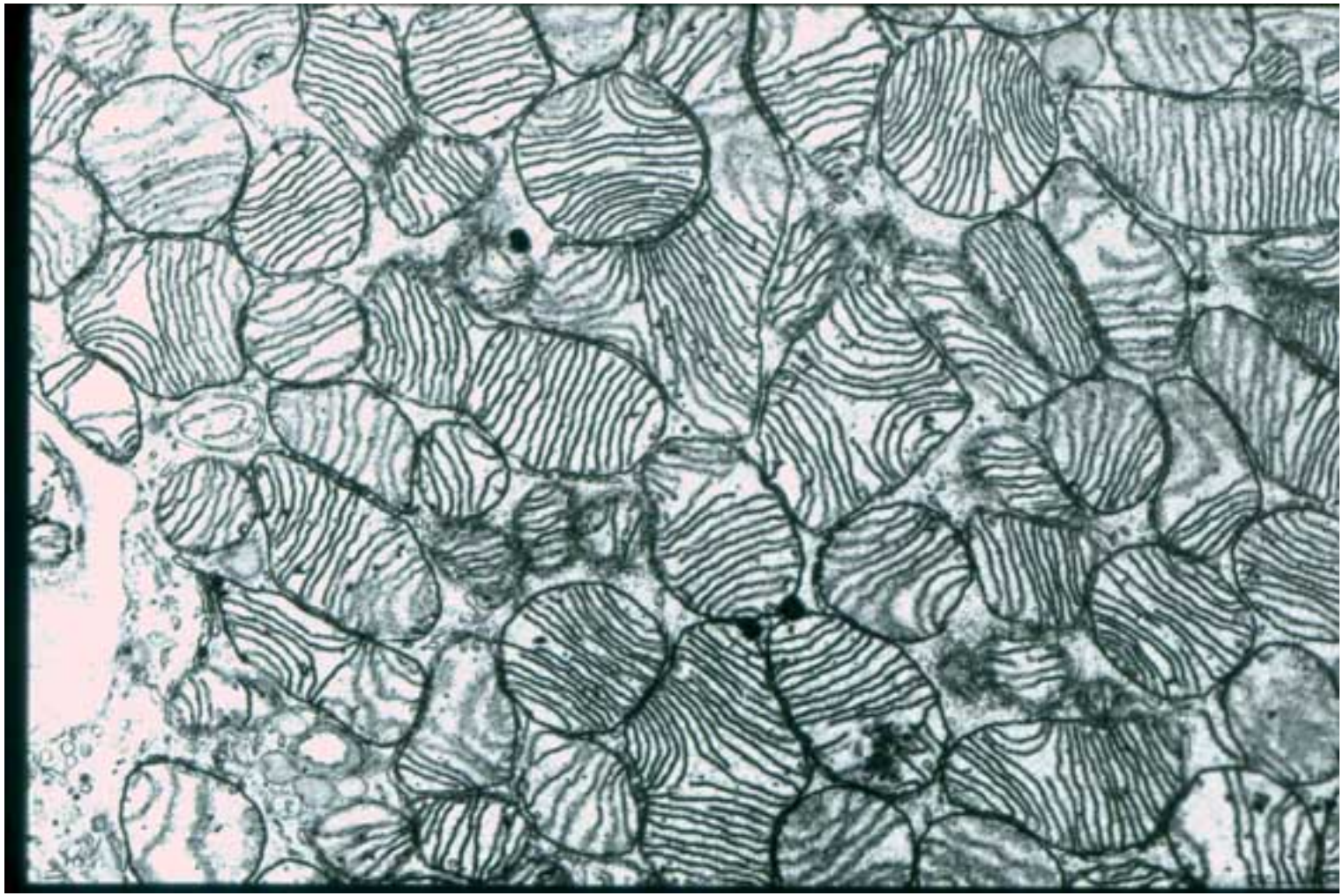




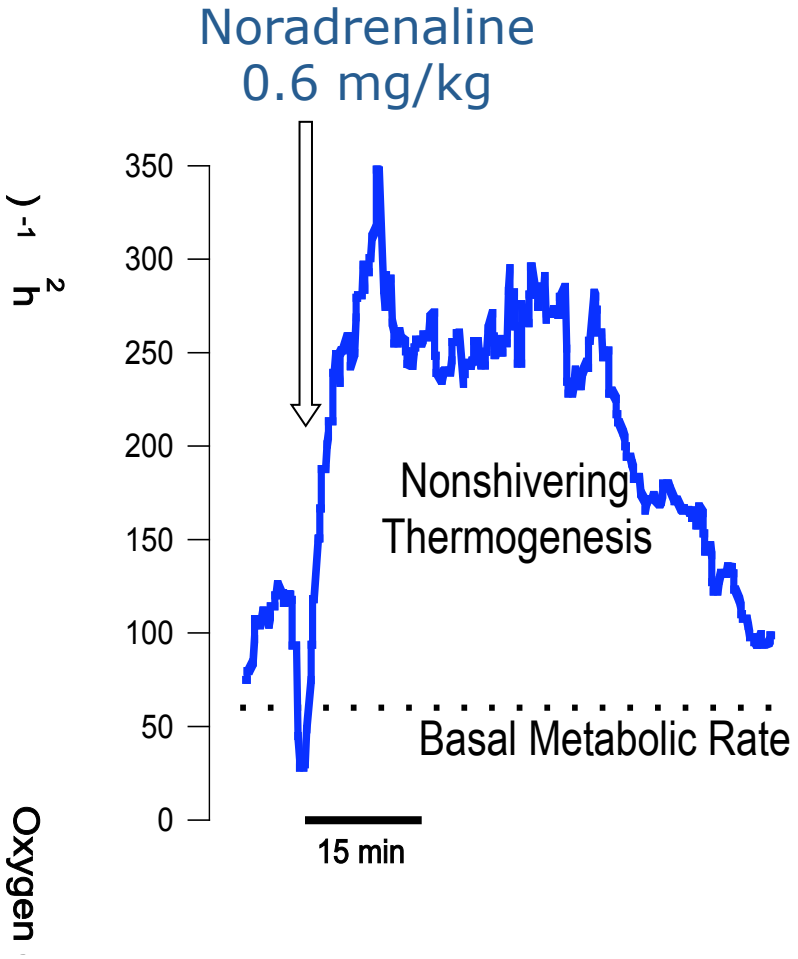


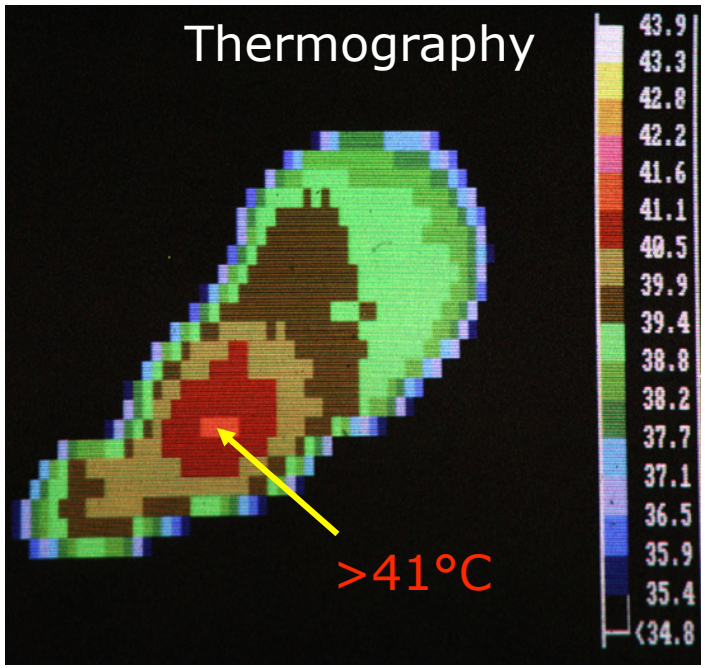
S. Cinti, Kurtis,





Noradrenaline Stimulates Nonshivering Thermogenesis in Brown Fat





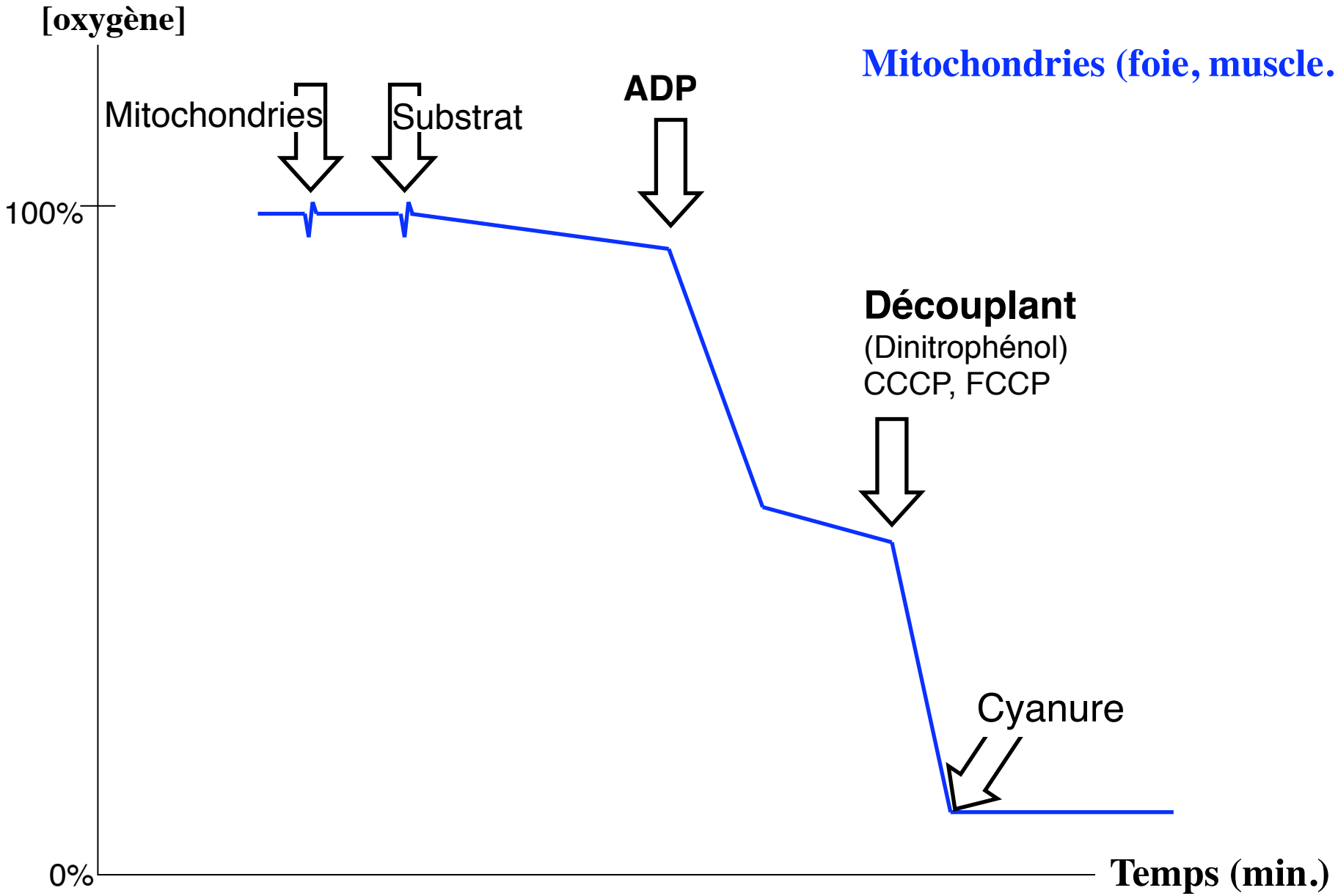
Jean Himms-Hagen 197?

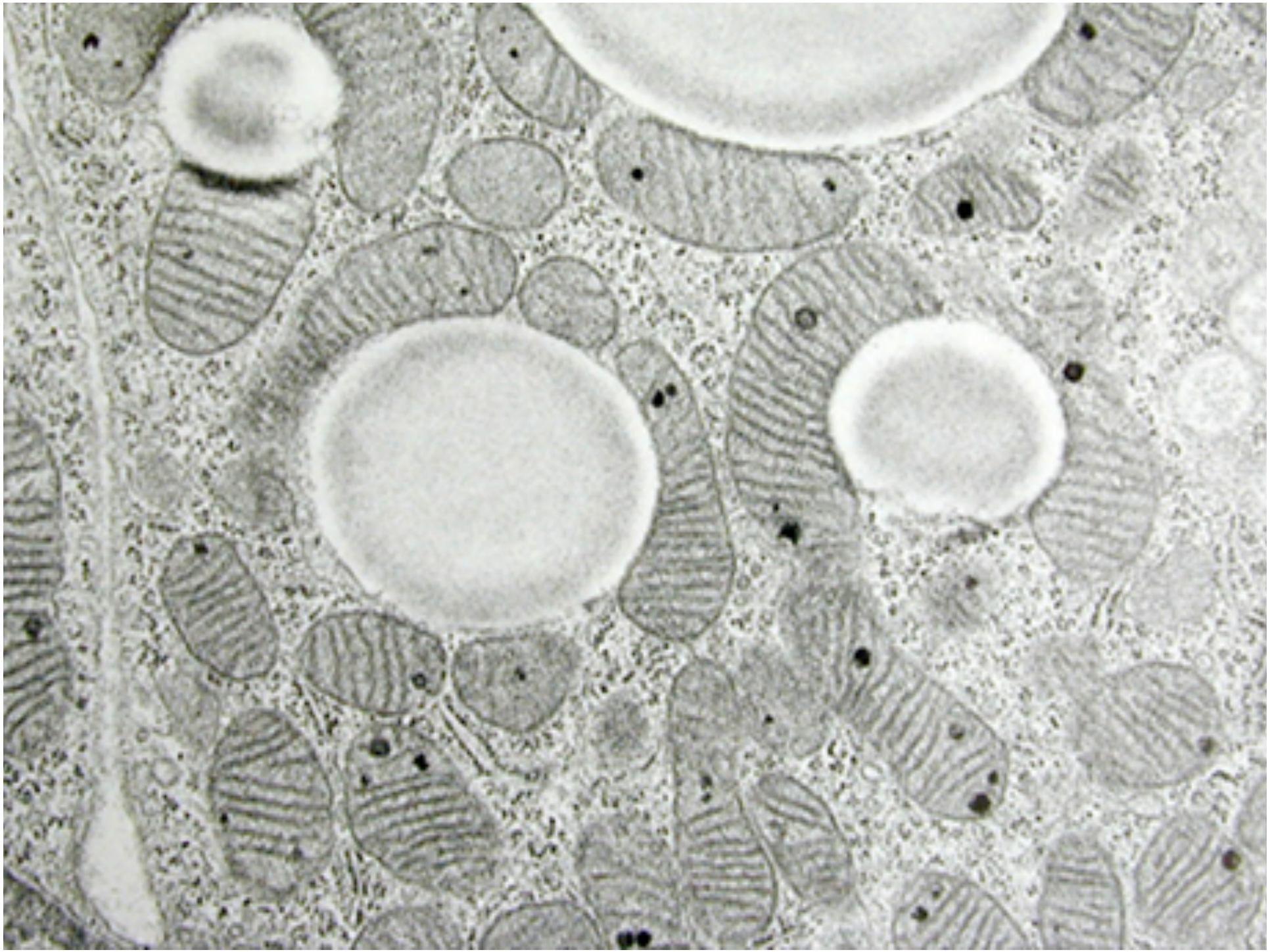
- Qu’est-ce que c’est? Thermogenèse
- Mécanisme? Mitochondries, découplage respiratoire, UCP1

A natural example of respiration uncoupling leading to fat oxidation and energy expenditure:

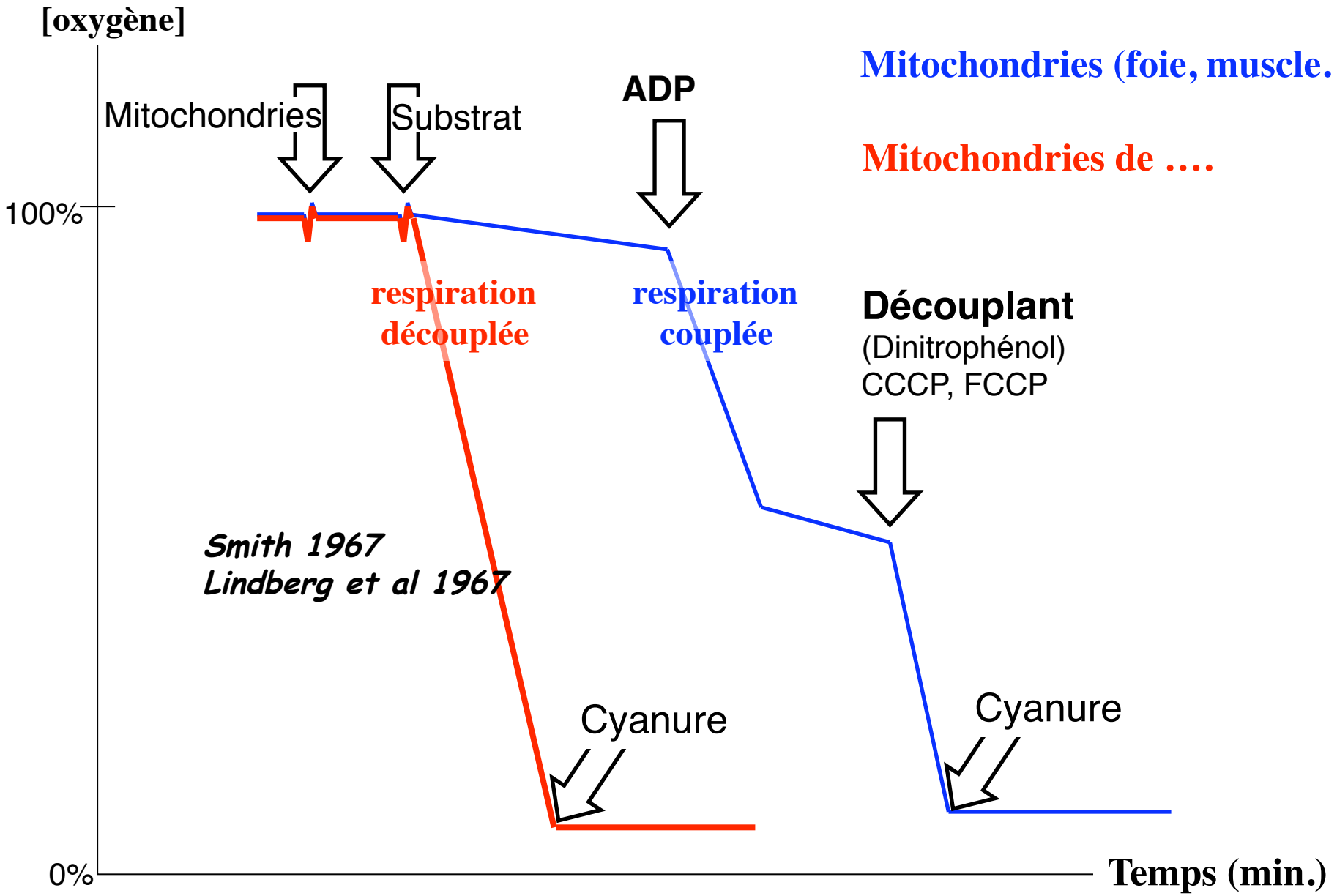
THE BROWN ADIPOCYTE and its Uncoupling Protein UCP (UCP1)

Oxygraphie


[oxygène]
Mitochondries (foie, muscle…)
Mitochondries
Substrat
ADP
100%
Découplant
(Dinitrophénol)
CCCP, FCCP
Cyanure
0%
Temps (min.)

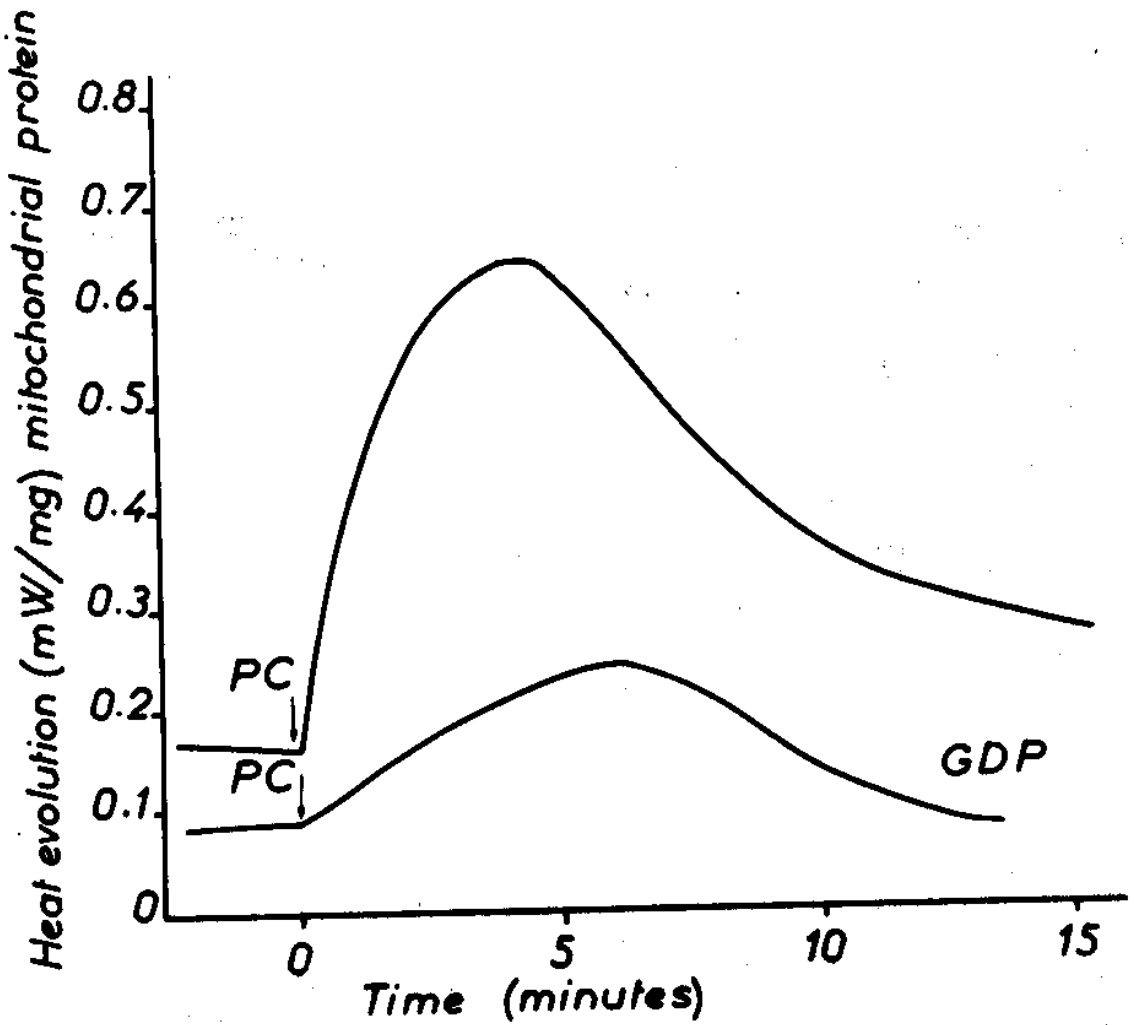


Oxygraphie



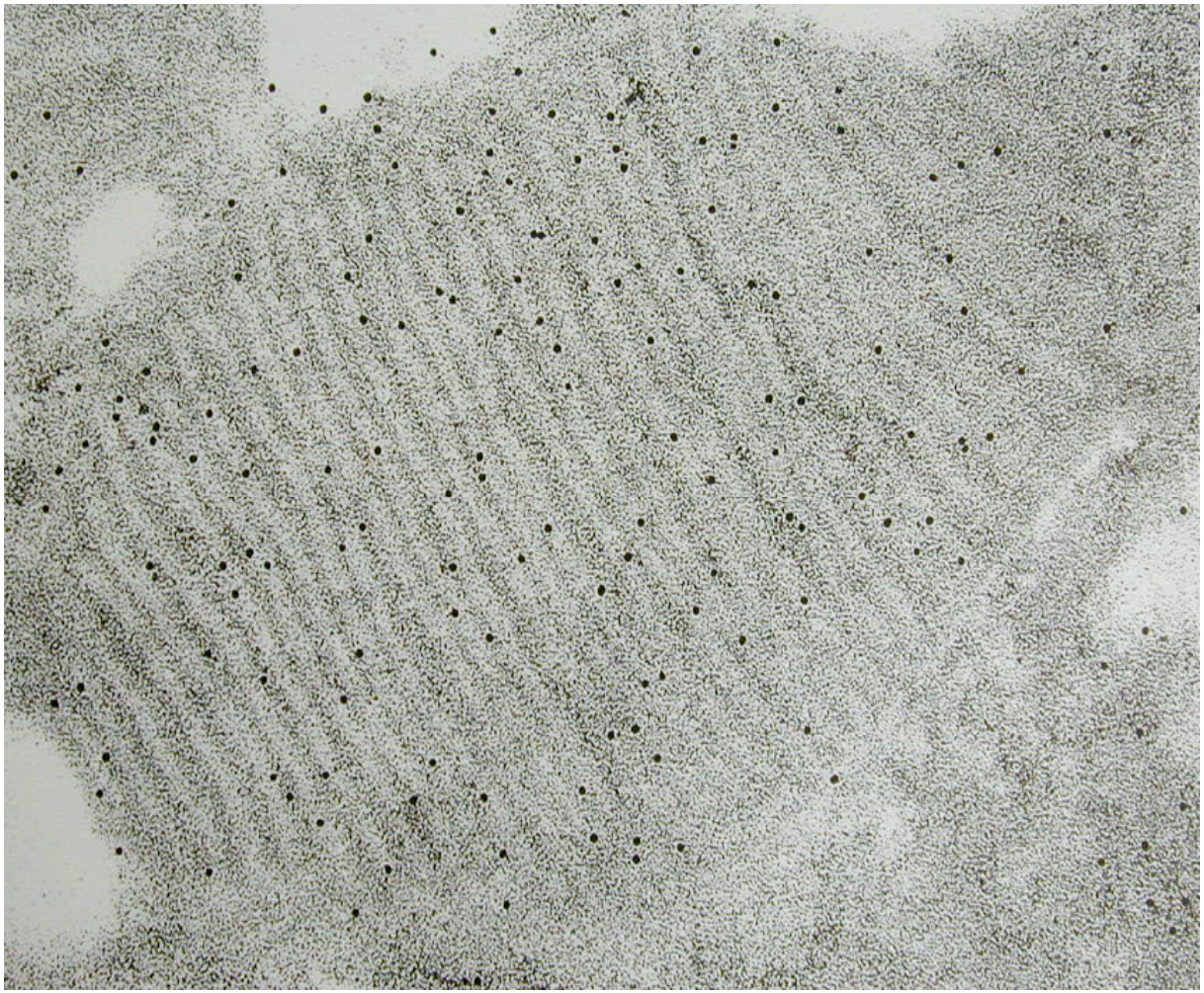
Mitochondries (foie, muscle…)

Mitochondries de ….

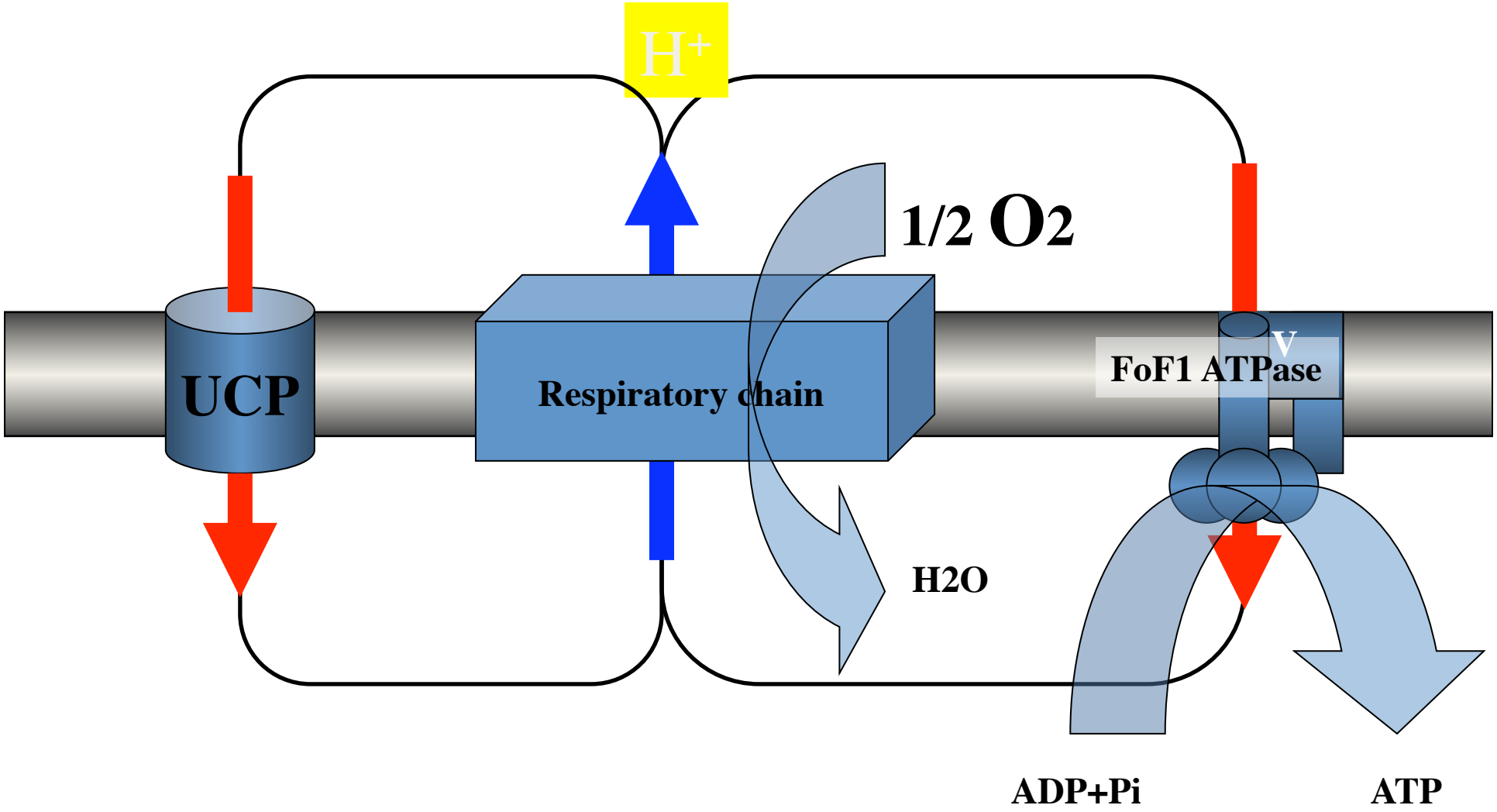


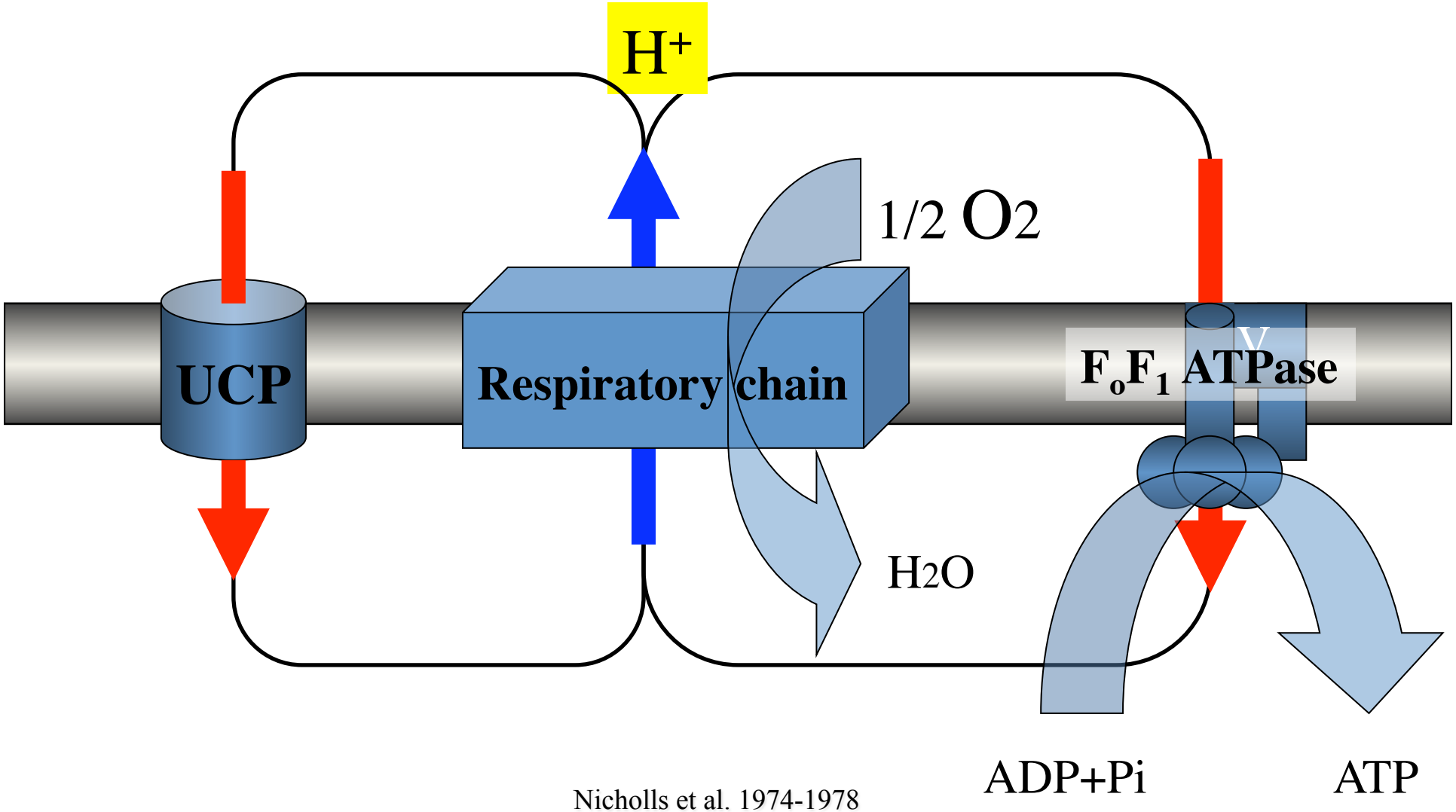
Ricquier et al. 1975

UCP1 detection



S. CINTI (Universitat di Ancona)

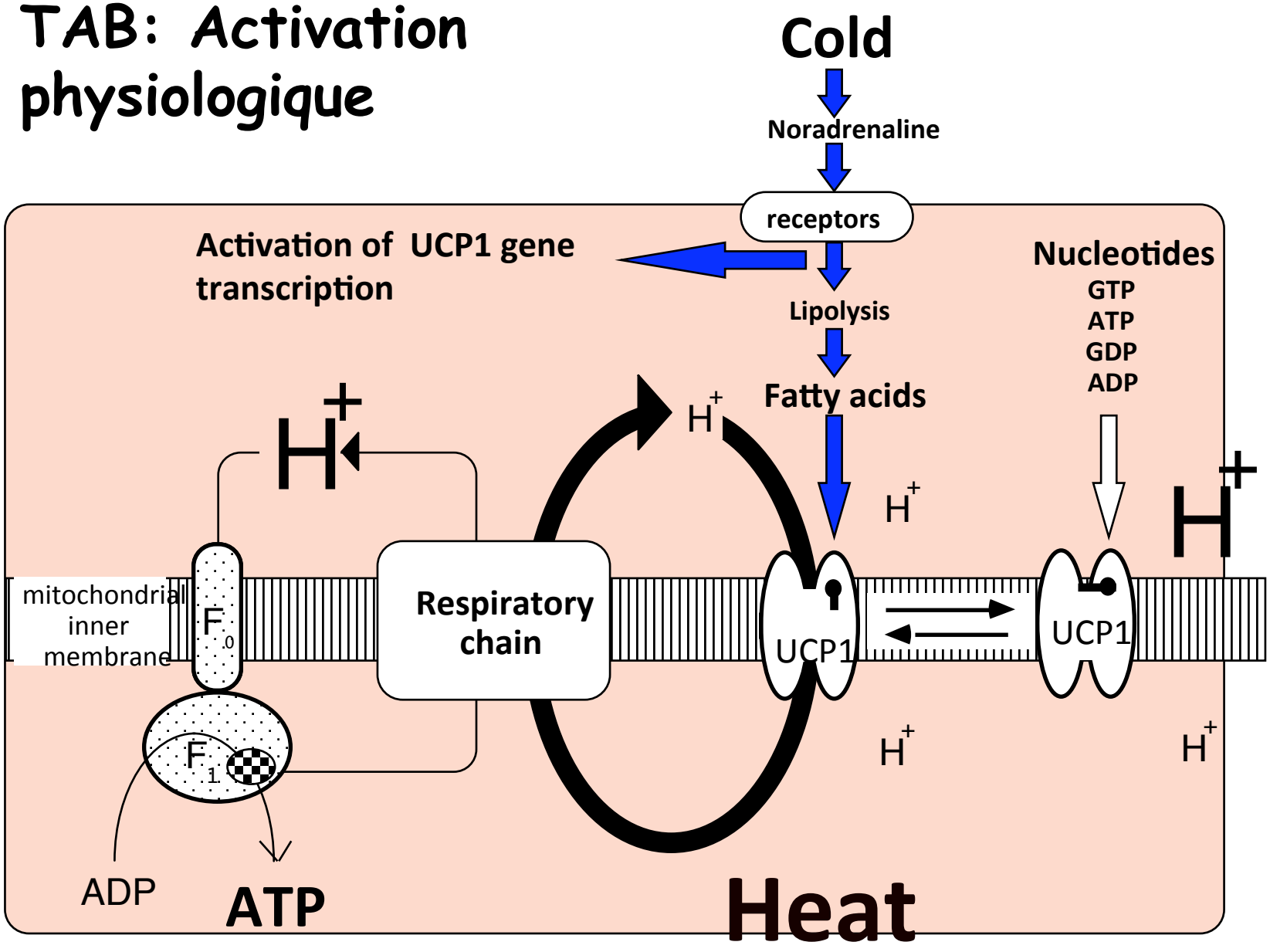

H+
1/2 O2
UCP
Respiratory chain
FoF1 ATPase
V
H2O
ADP+Pi
ATP



Nicholls et al. 1974-1978
Ricquier and Kader BBRC 1976
Heaton et al. EJB 1978
Bouillaud et al. PNAS 1985

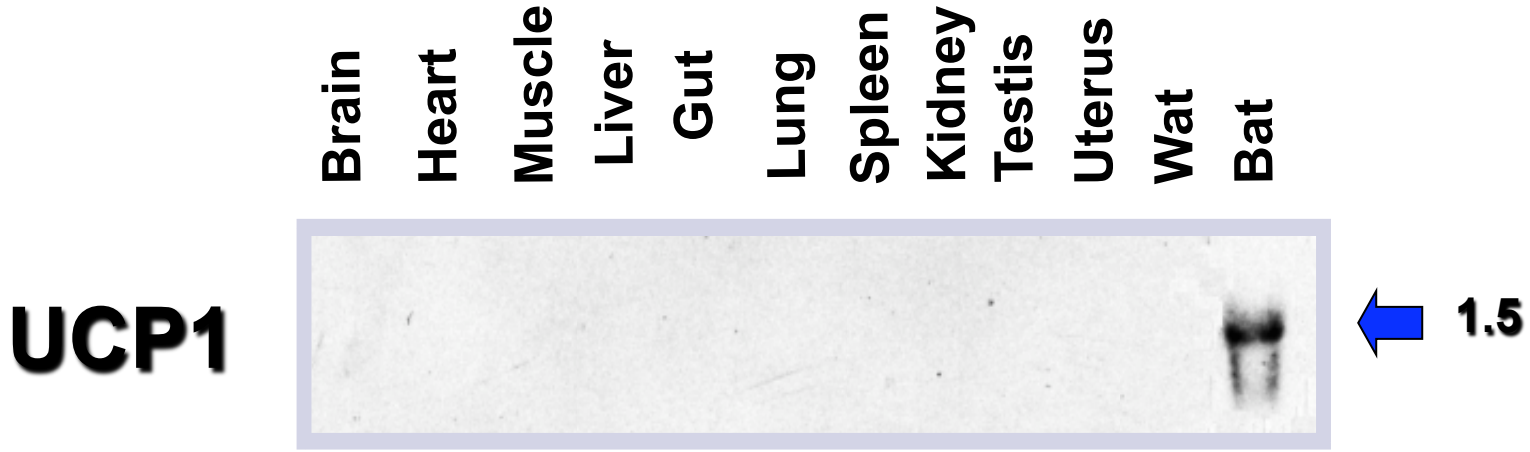
Ucp1-/- mice are sensitive to cold exposure Enerback et al. 1997

TAB: Activation physiologique



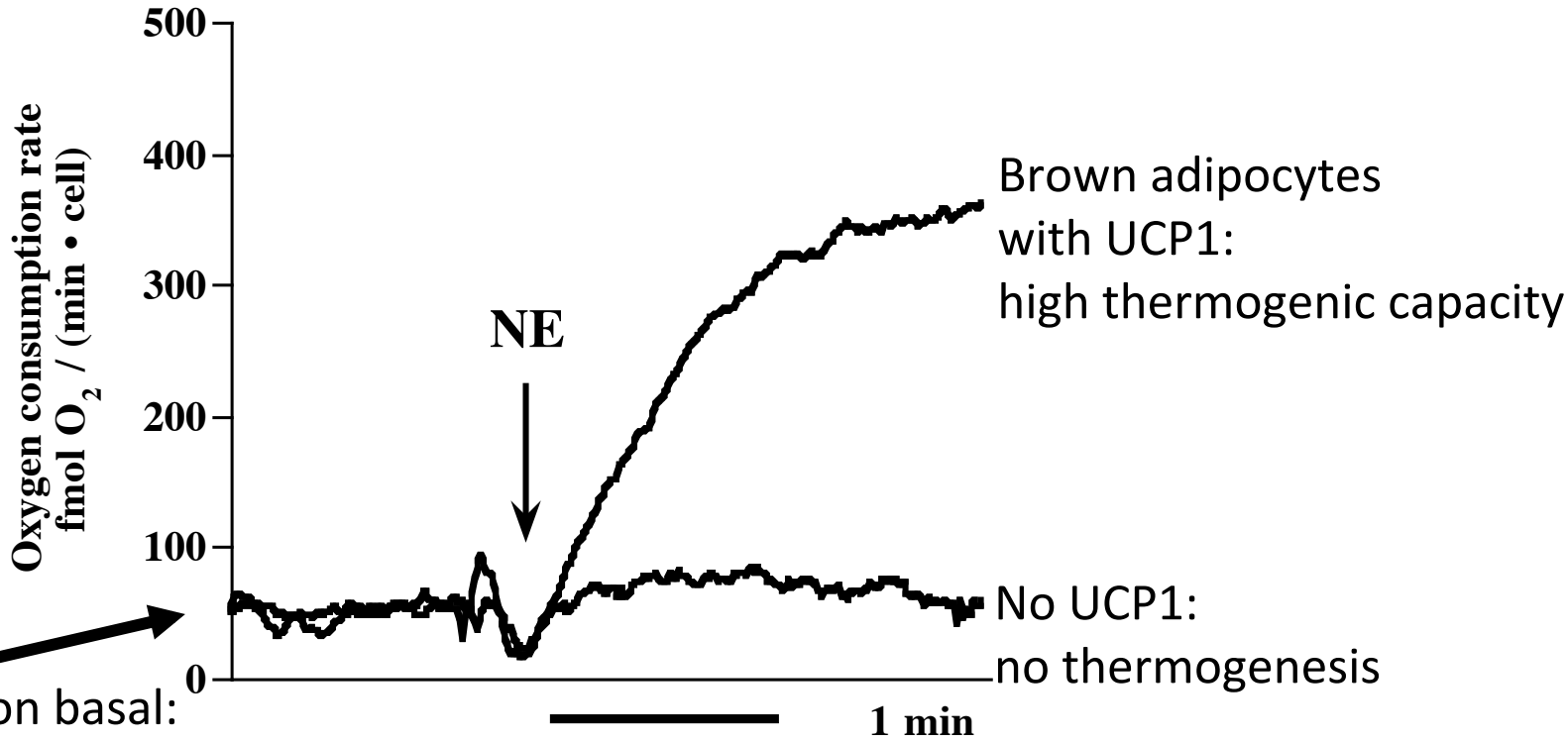
UCP1: a regulatable proton leak activating oxidation and heat output

Tissue distribution of UCP mRNA



- Qu’est-ce que c’est? Thermogenèse
- Mécanisme? Mitochondries, découplage respiratoire, UCP1
- Importance physiologique chez les rongeurs

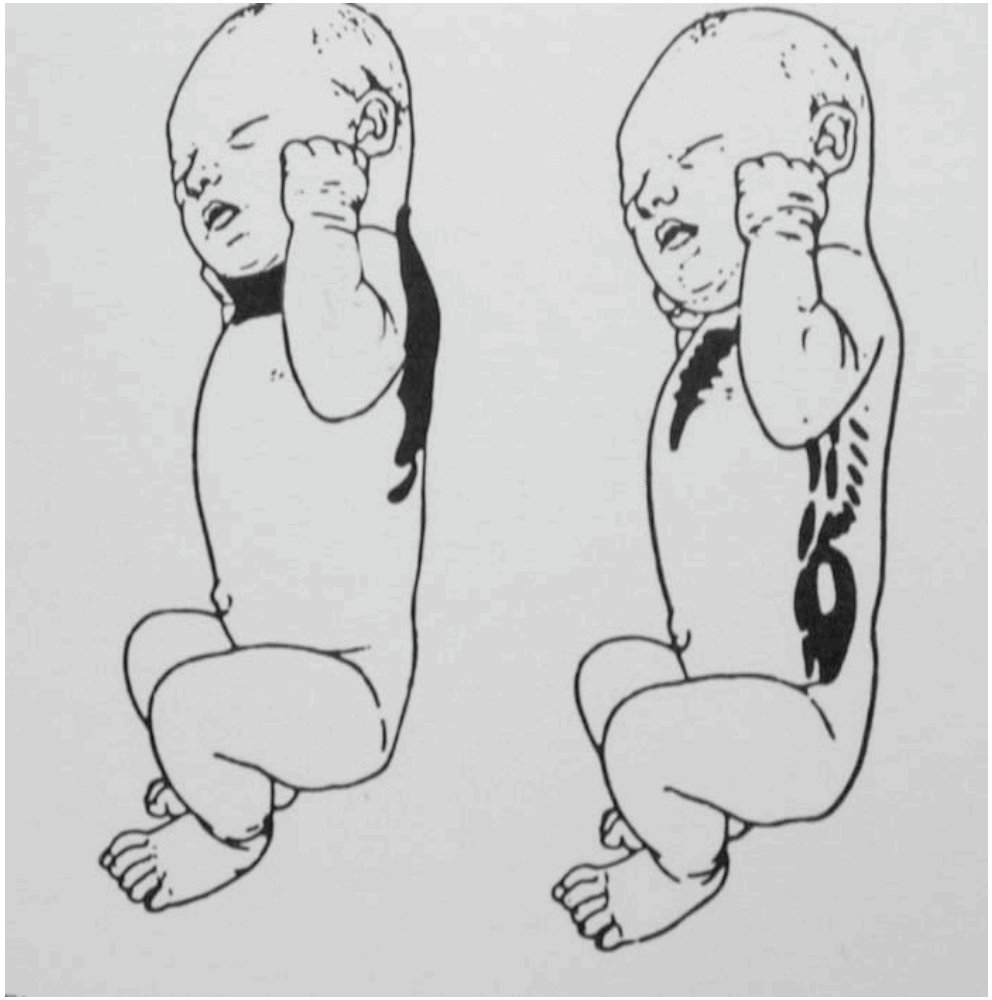
UCP1 is essential for norepinephrine-induced Thermogenesis in brown adipocytes



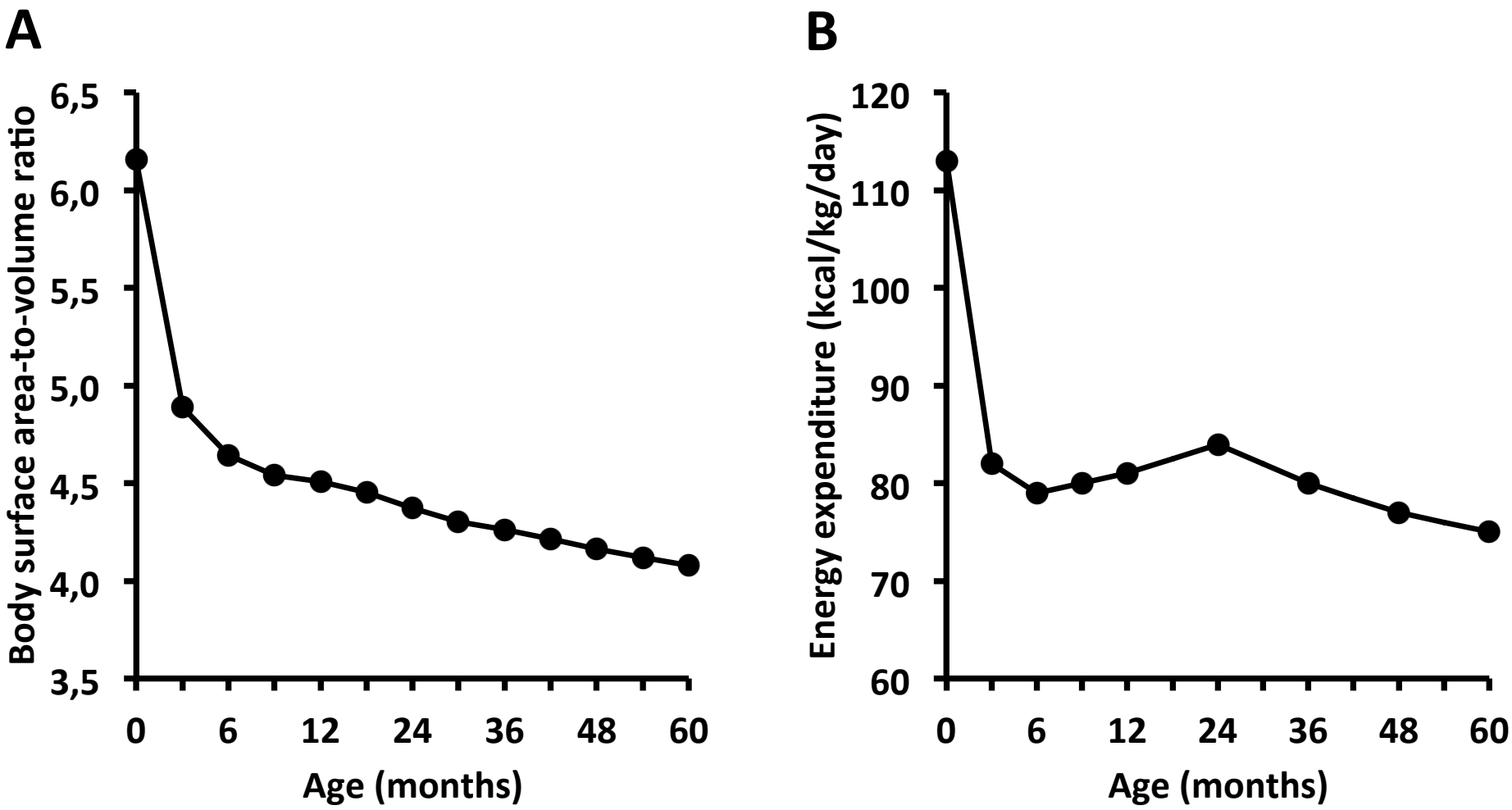
No effect on basal:
no inherent leakiness
of UCP1

B. Cannon & J. Nedergaard

- Qu’est-ce que c’est? Thermogenèse
- Comment ça marche? Mitochondries, découplage respiratoire, UCP1
- Importance physiologique chez les rongeurs
- Données anciennes chez l’homme

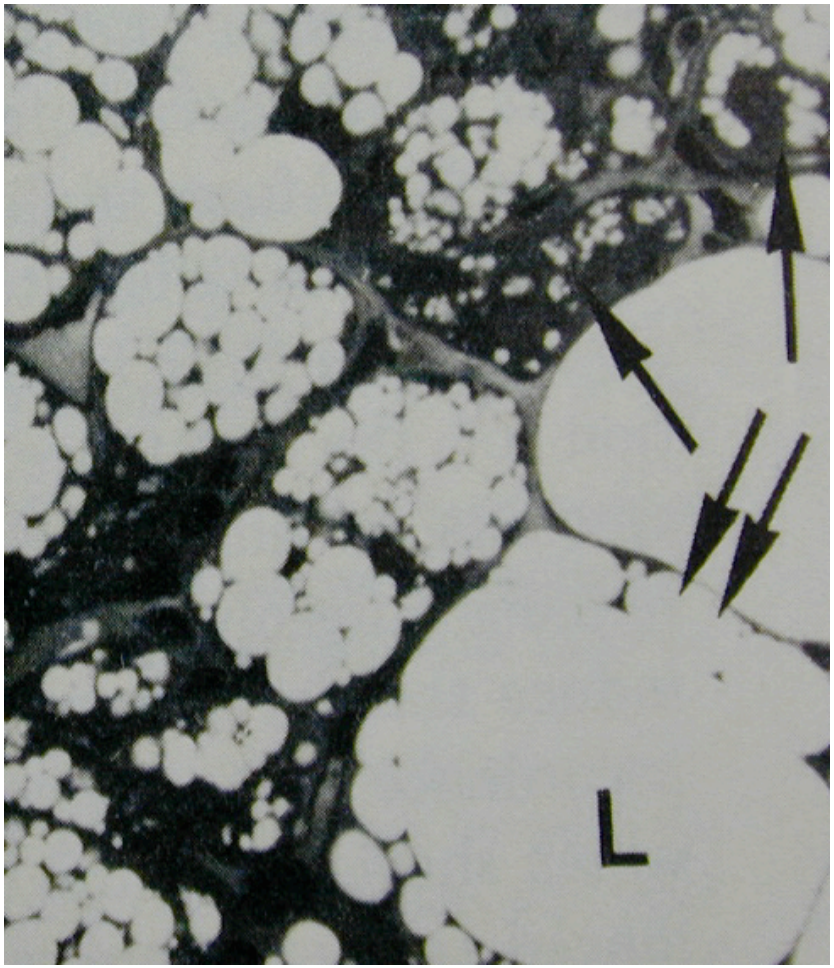


Dawkins et Hull, Scient. Am. 1965

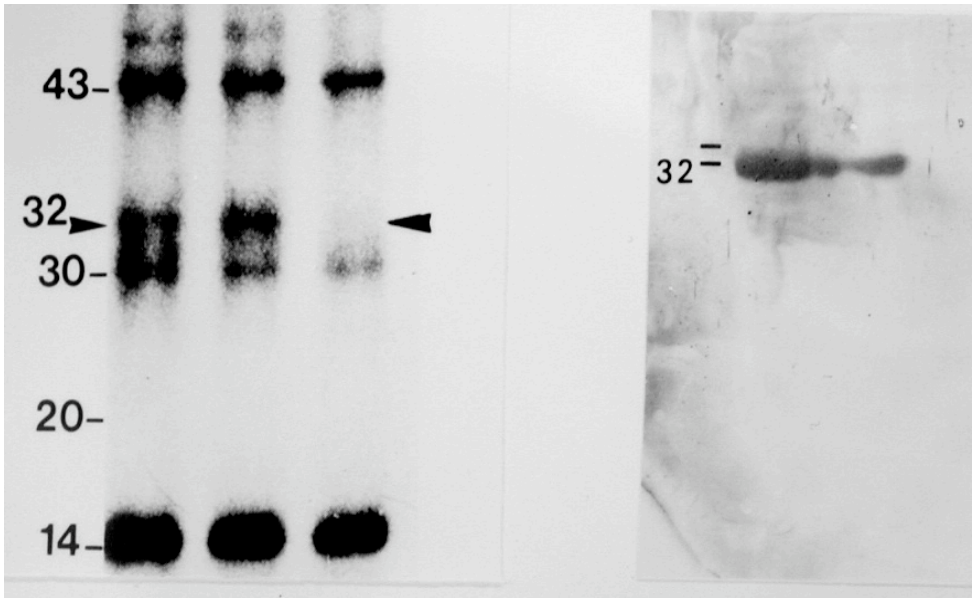


Eric Ravussin 2011

brown and white adipocytes in babies or pheochromocytoma patients



hUCP1 detection

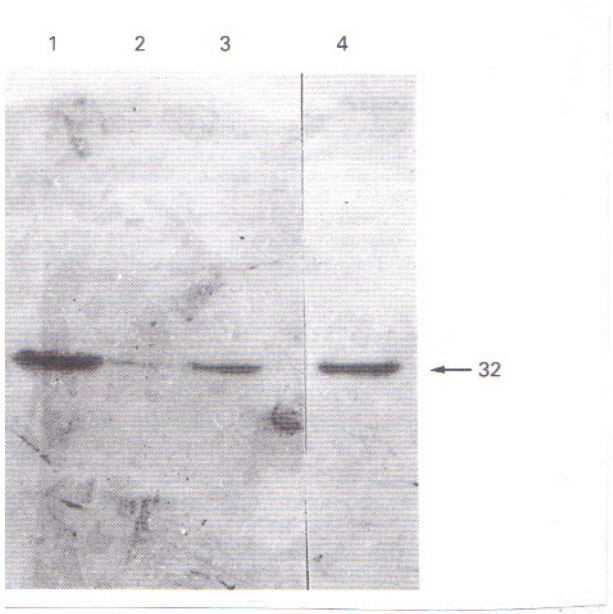


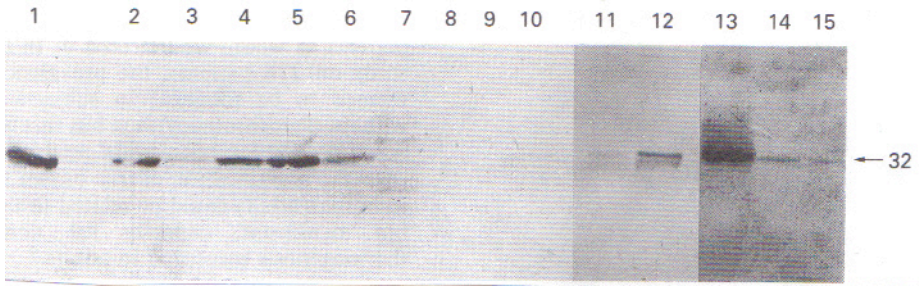
Azido ^{32}P-ATP

antibodies

Ricquier et al. 1982
Bouillaud et al. 1983
Garruti and Ricquier 1992

Immunodétection d'UCP1 chez l'homme



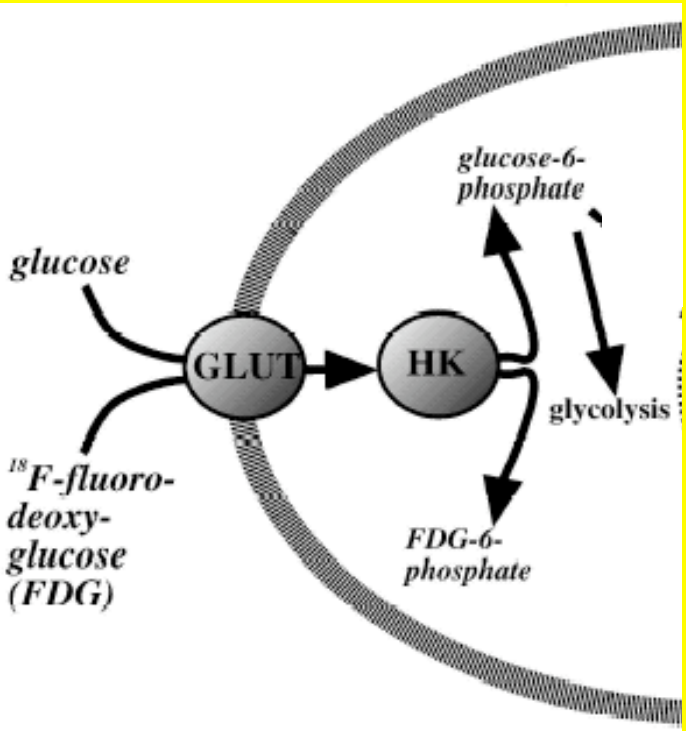


GARRUTI ET RICQUIER 1992
KORTAILANEN ET AL. 1993

- Qu’est-ce que c’est? Thermogenèse
- Mécanisme? Mitochondries, découplage respiratoire, UCP1
- Importance physiologique chez les rongeurs
- Données anciennes chez l’homme
- Données récentes chez l’homme

Nedergaard et al. 2007

FDG PET to identify tumours

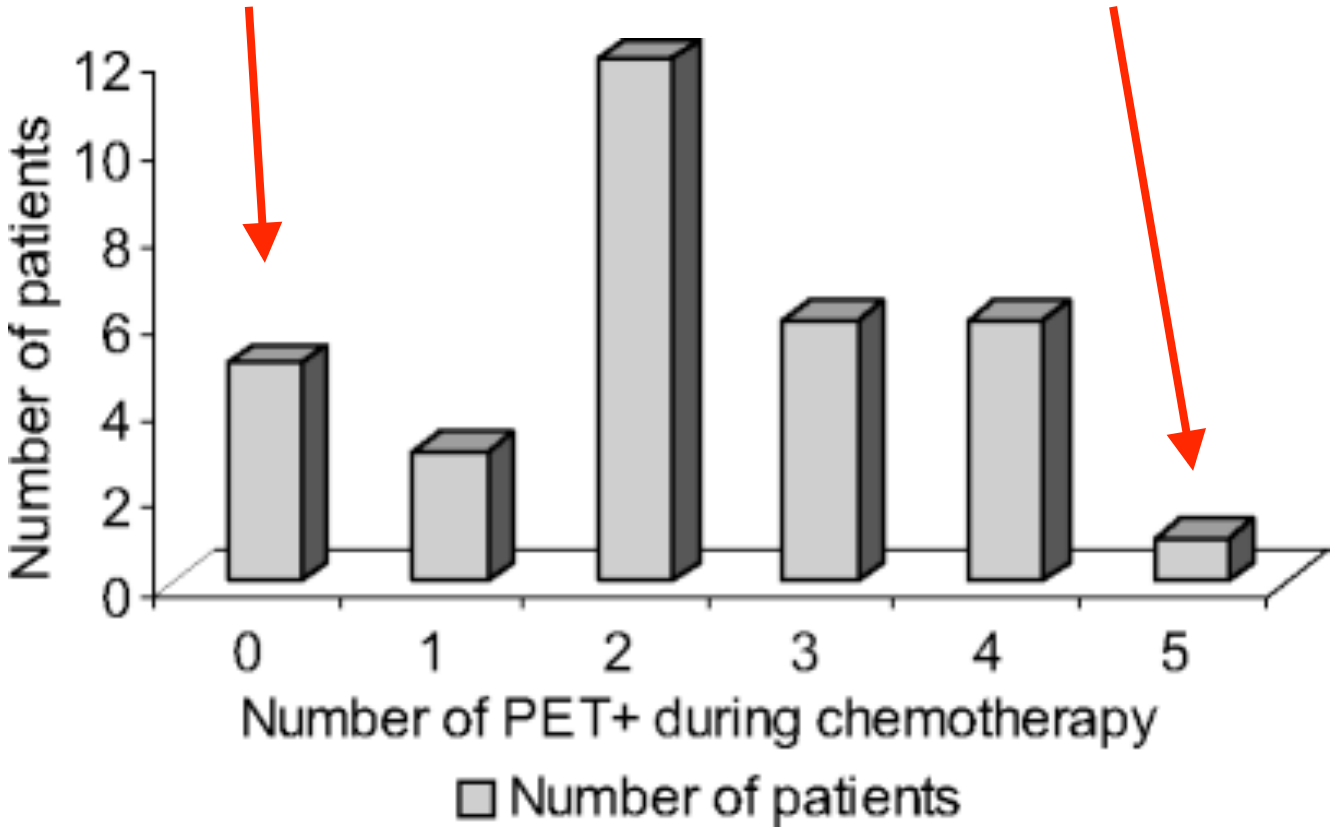


www.med.harvard.edu/

33 patients examined 5 times

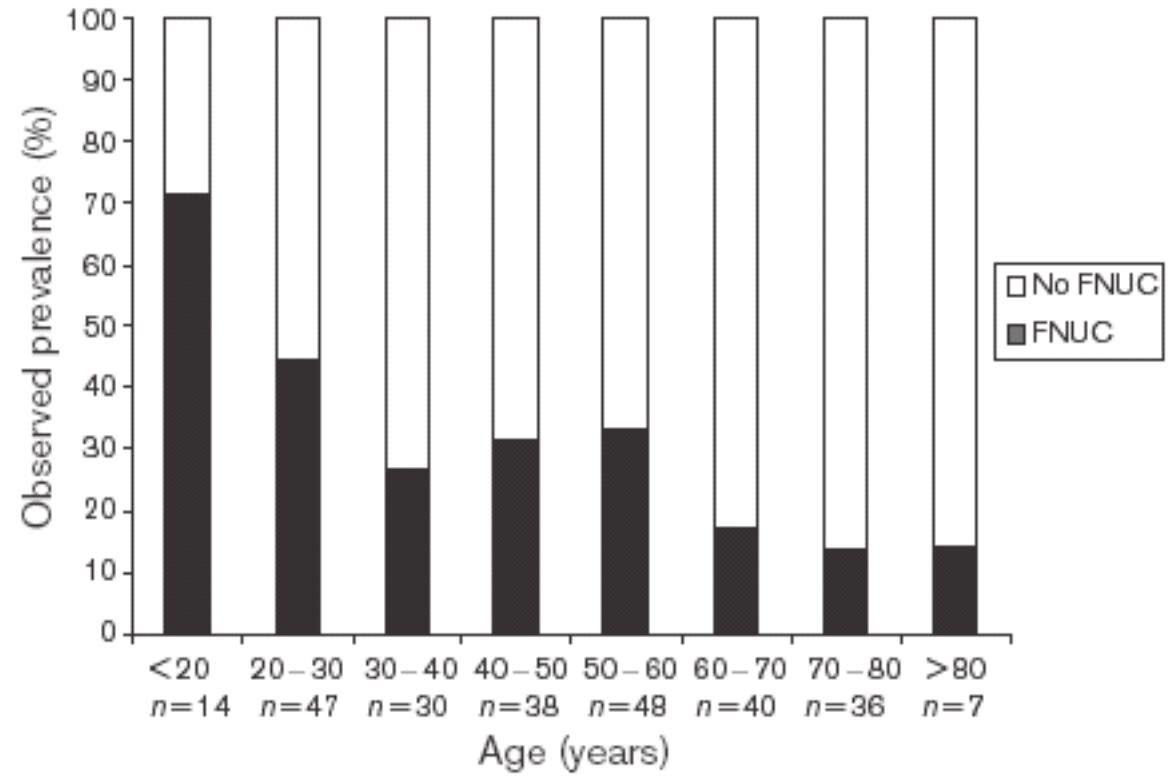
no brown fat
on any occasion

brown fat
on all occasions



Rousseau et al. 2006

80 % of the patients demonstrated brown fat glucose uptake at least at one occasion!



The observed prevlance of FDG in the neck and upper chest region in the different age categories.

Sturkenboom//Hoekstra 2004

- Qu’est-ce que c’est? Thermogenèse
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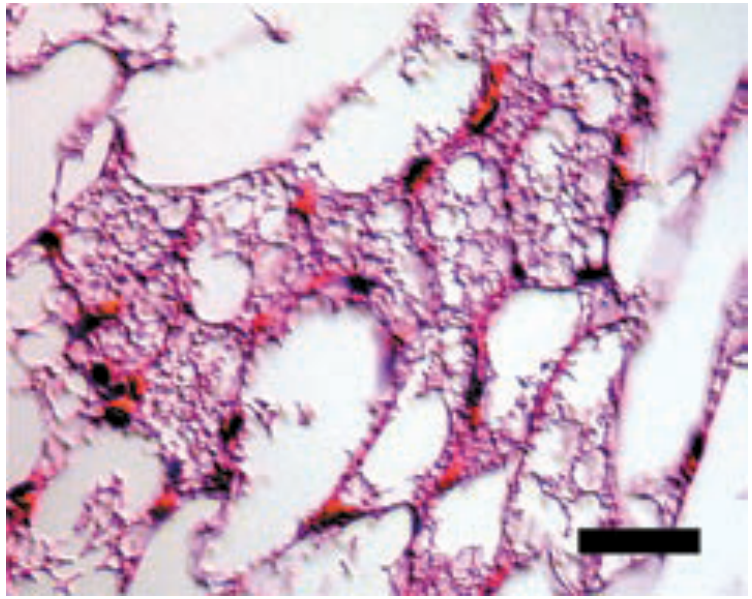
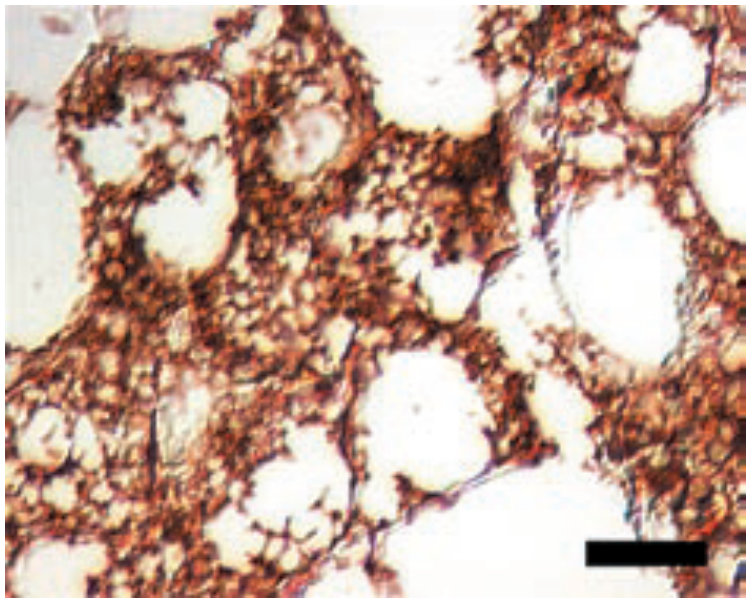
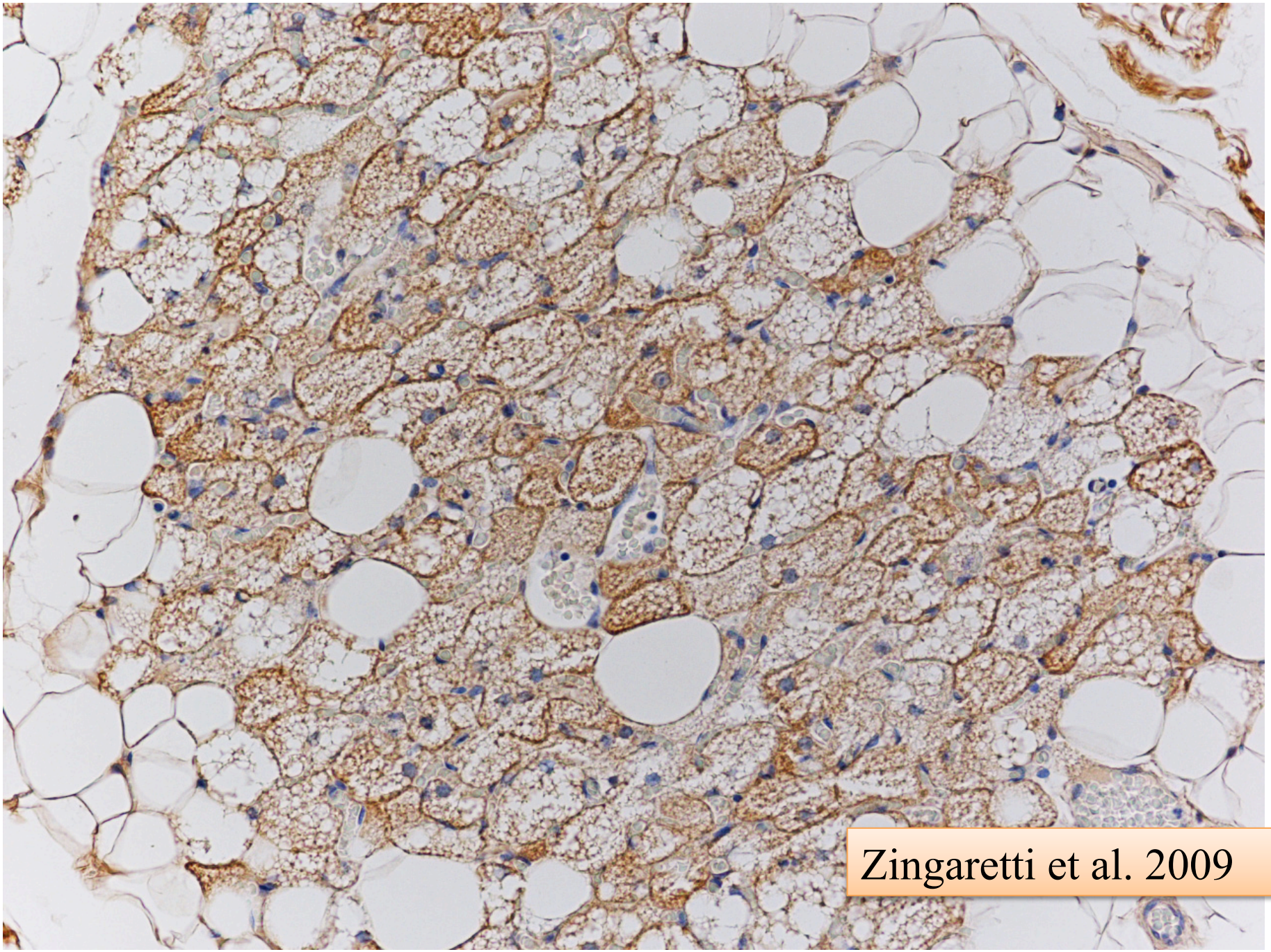
- **Est-ce du TABrun? est-il fonctionnel?**

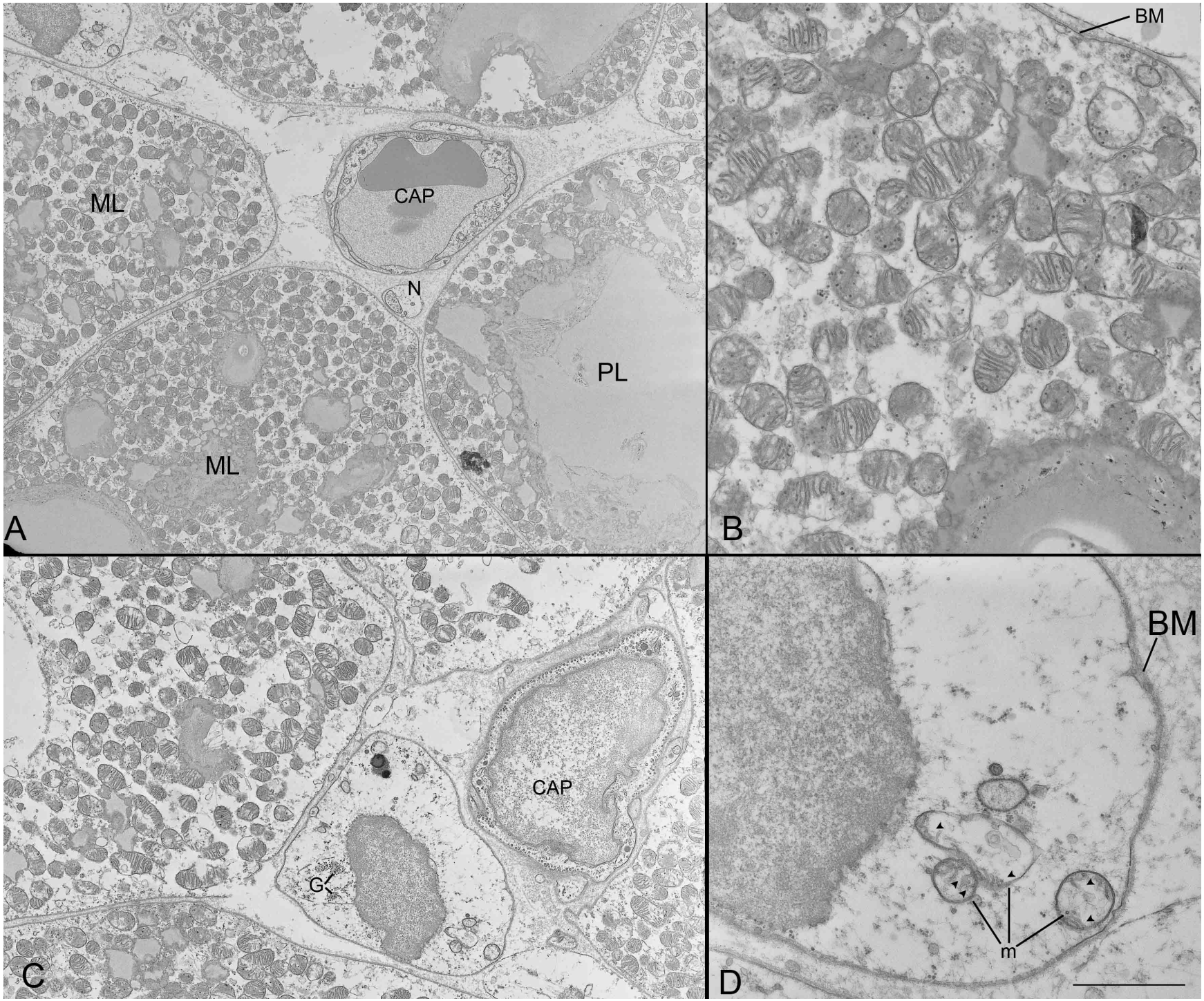
Virtanen et al. 2009

- **UCP1**

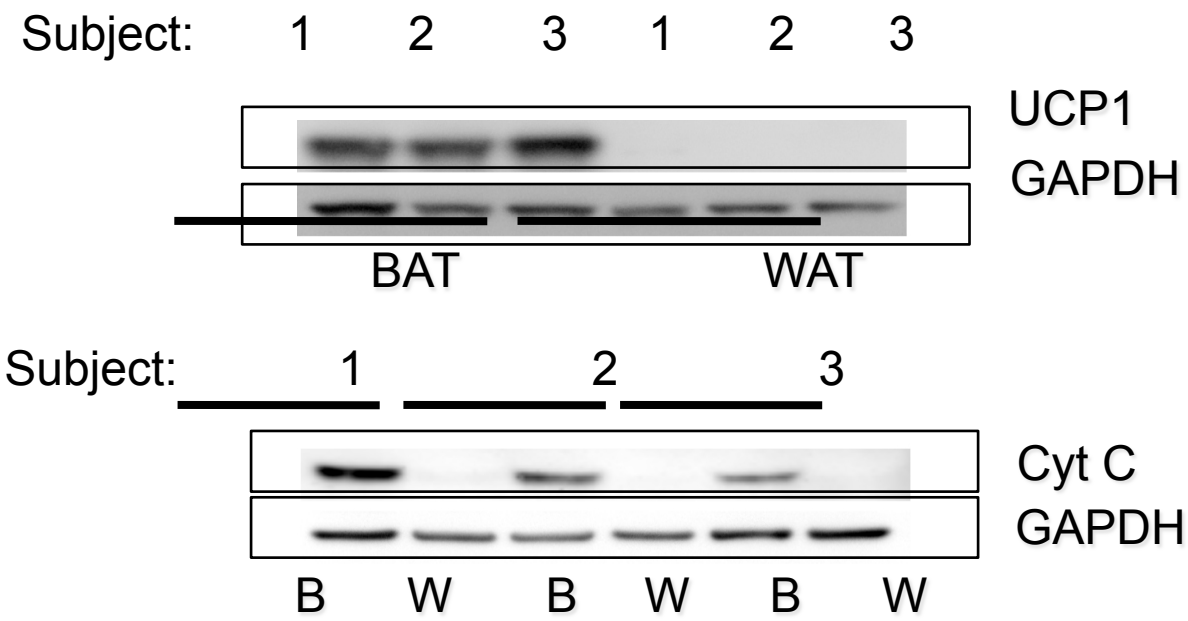




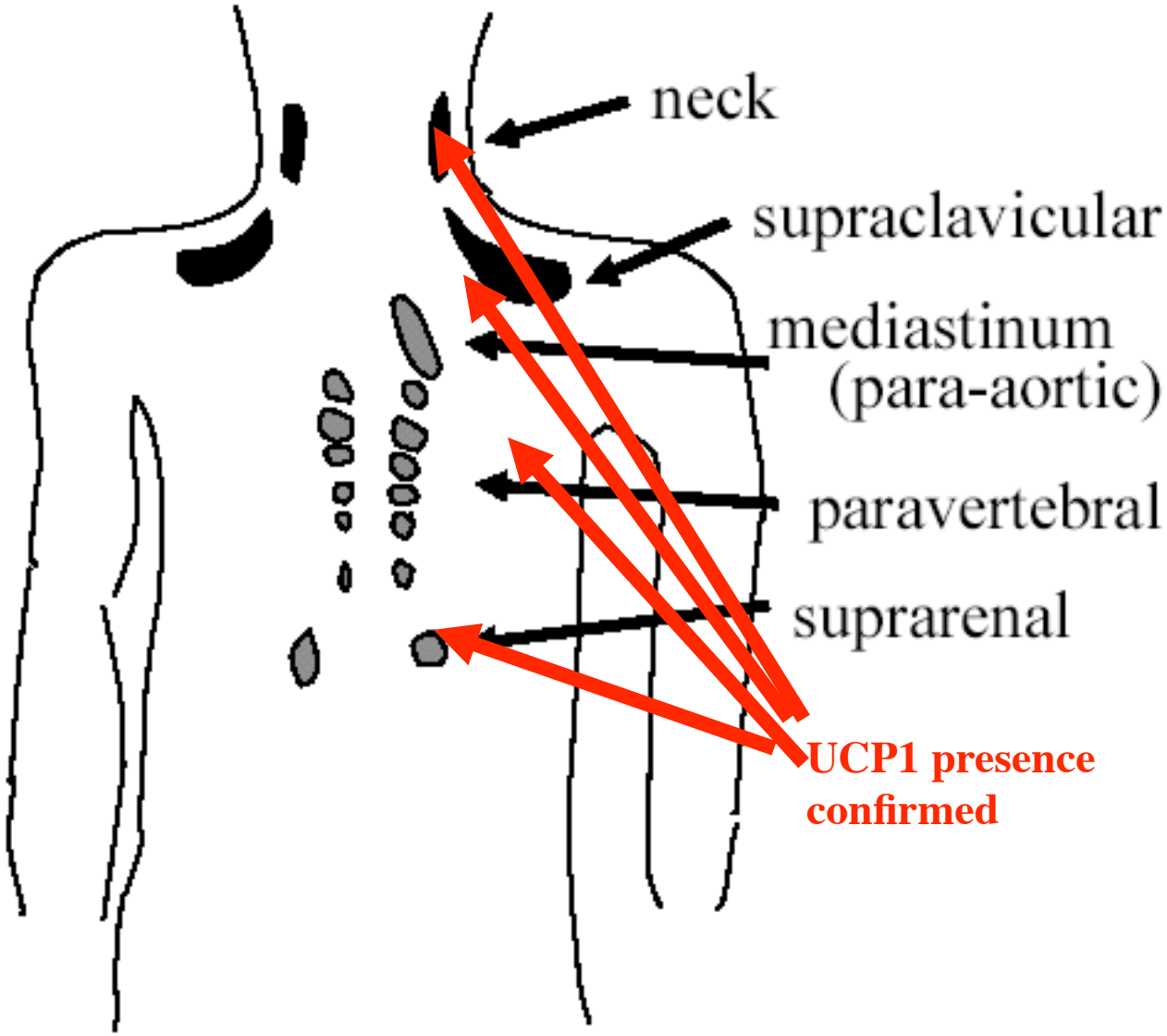

Zingaretti et al. 2009


ML
CAP
N
PL
ML
A
BM
B
CAP
G
C
BM
m
D

UCP1 and Cytochrome C protein levels in human BAT and WAT



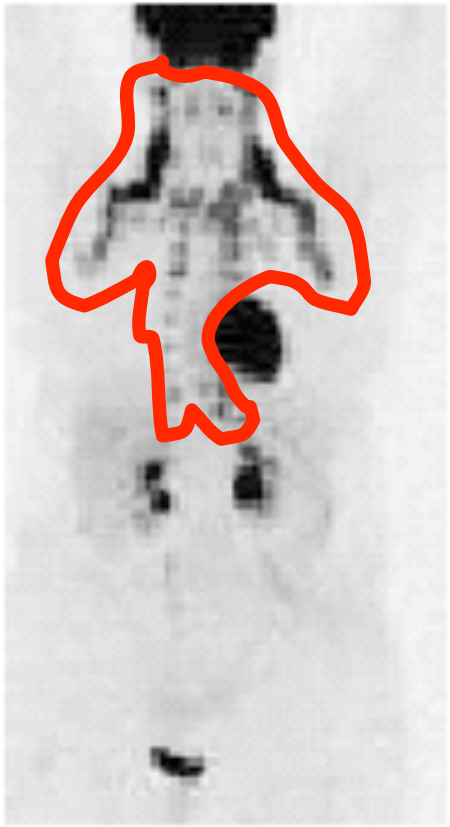
Enerbäck & Nuutila et al NEJM 360:1518-25, 2009


neck
supraclavicular
mediastinum
(para-aortic)
paravertebral
suprarenal
UCP1 presence
confirmed

A. Warm

A. Warm

B. Normal



Christensen et al. 2006

Femme pré-ménopausée, examen TEP avec 18fluoro-déoxy-glucose pour suivi de lymphome de Hodgkin

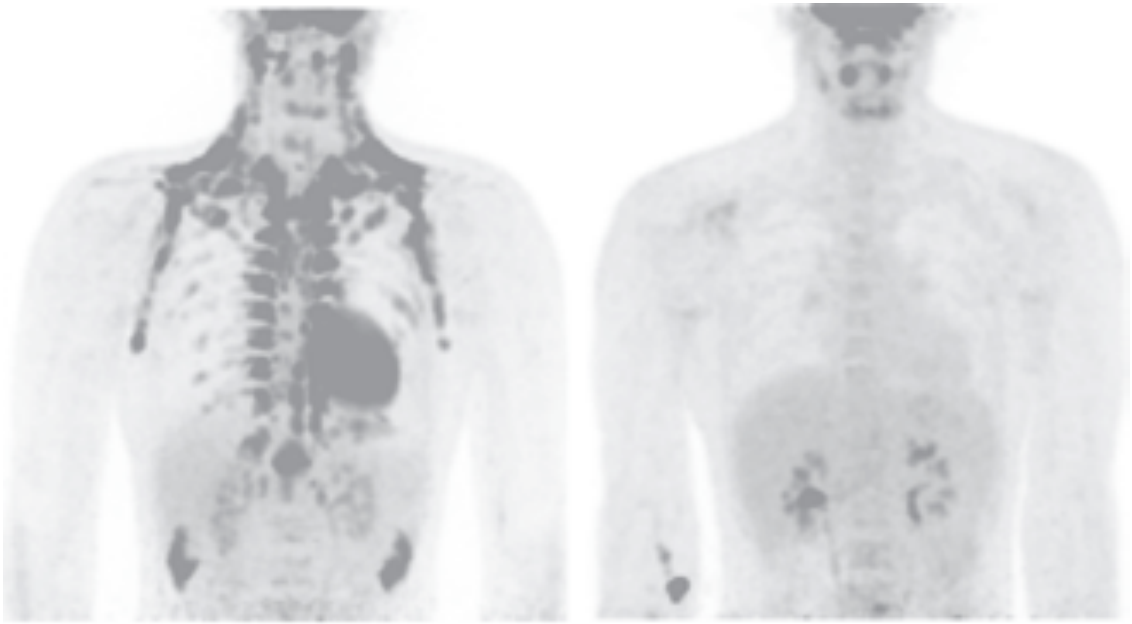
Centre d'imagerie moléculaire de Sherbrooke – gracieuseté du Dr Eric Turcotte

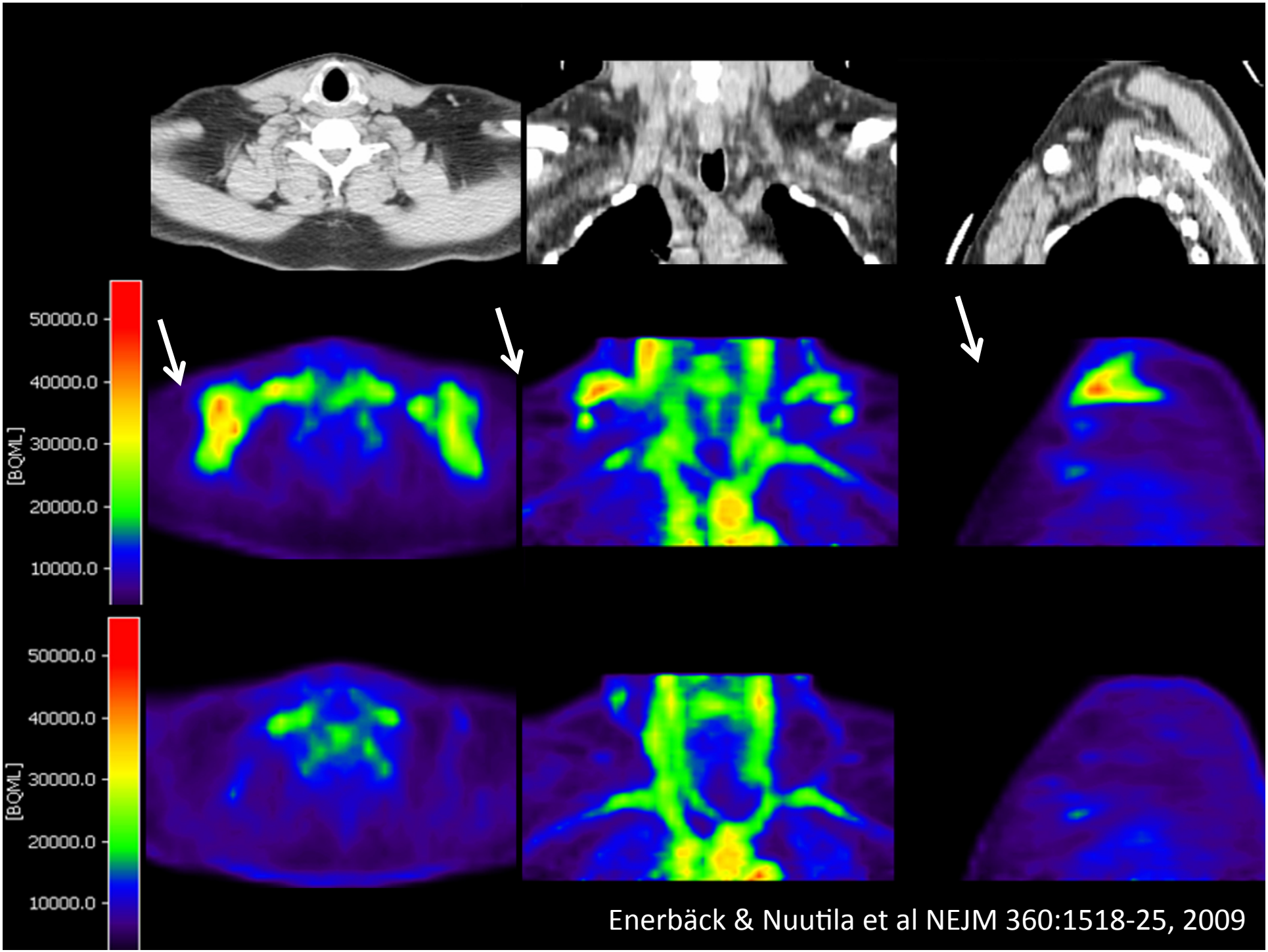
Après bain chaud x 6 jours + maintien de la chaleur corporelle avec vêtements chauds avant examen

Centre d'imagerie moléculaire de Sherbrooke – gracieuseté du Dr Eric Turcotte

PET-CT with ^{18}F-FDG Wouter et al. 2009

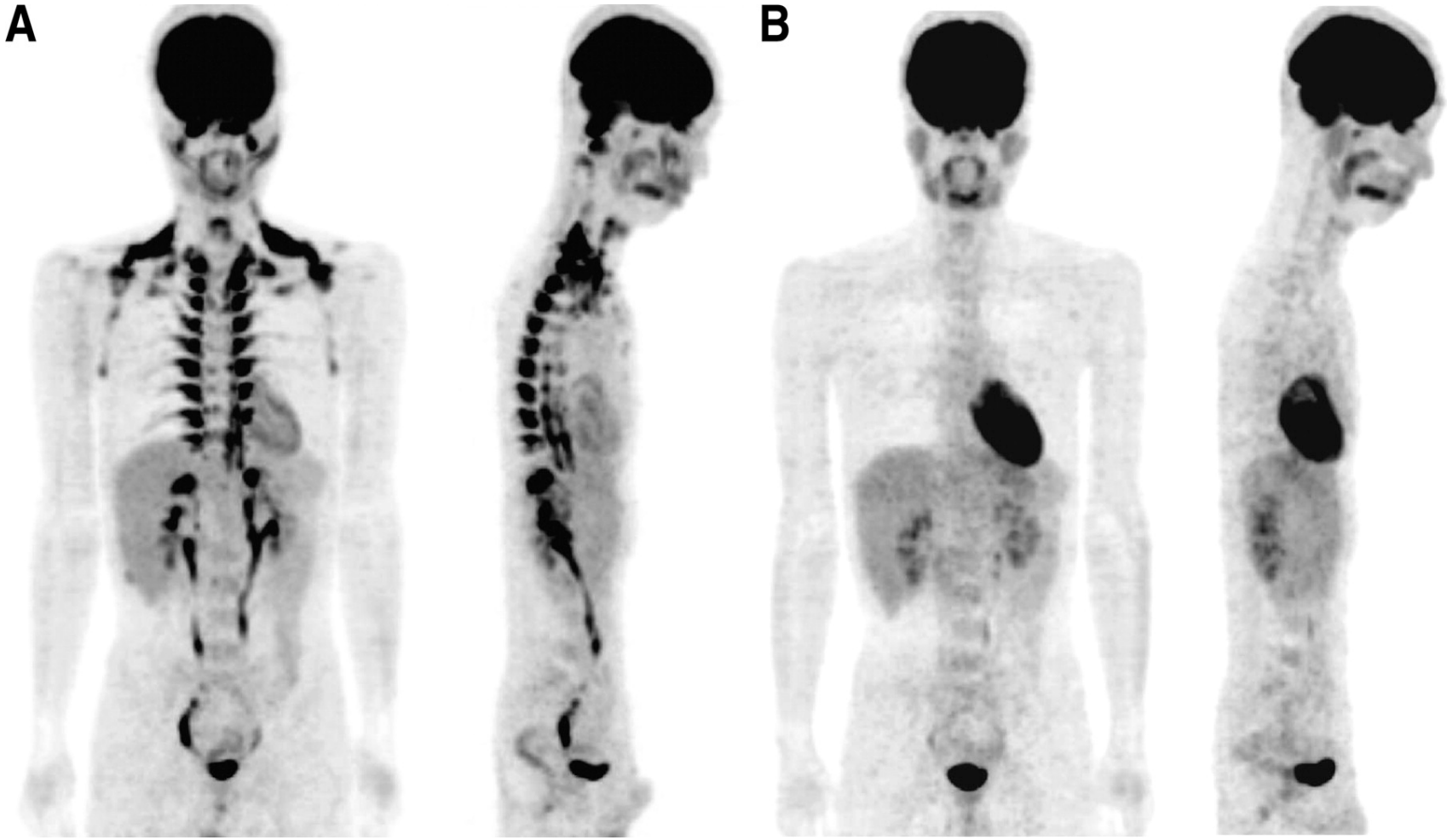
- Cold Warm





Enerbäck & Nuutila et al NEJM 360:1518-25, 2009

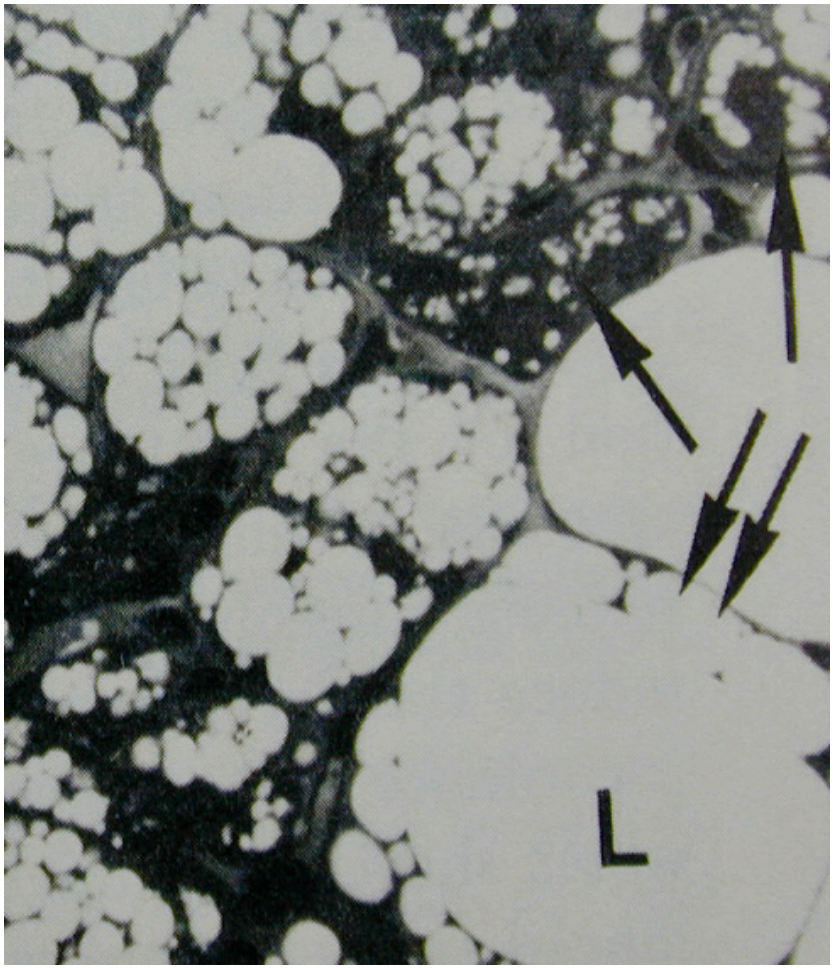
Exposition au froid



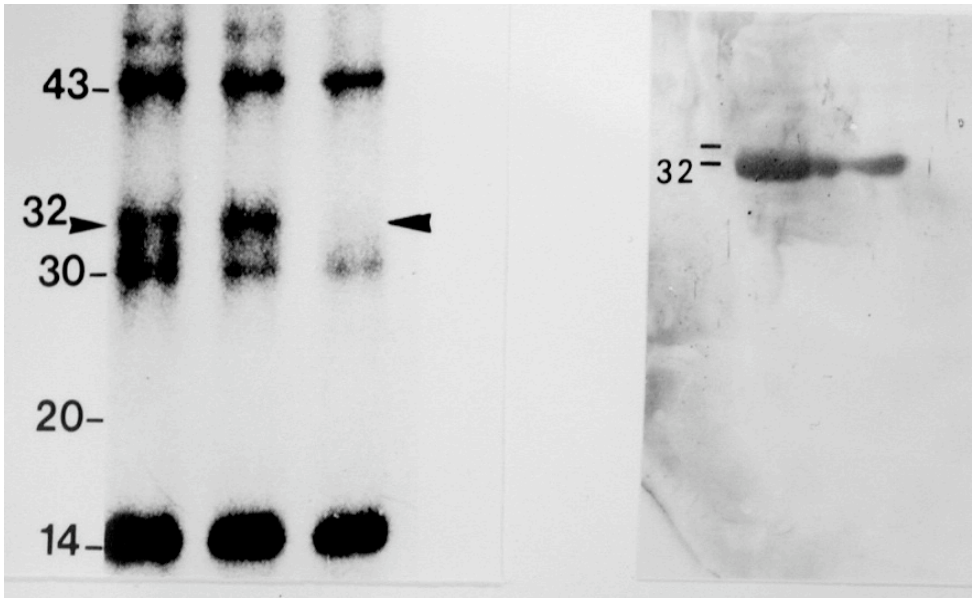
van Marken Lichtenbelt et al. N Engl J Med 360 (2009) 1500-1508.

Saito et al. Diabetes 58 (2009) 1526-31.

brown and white adipocytes in babies or pheochromocytoma patients

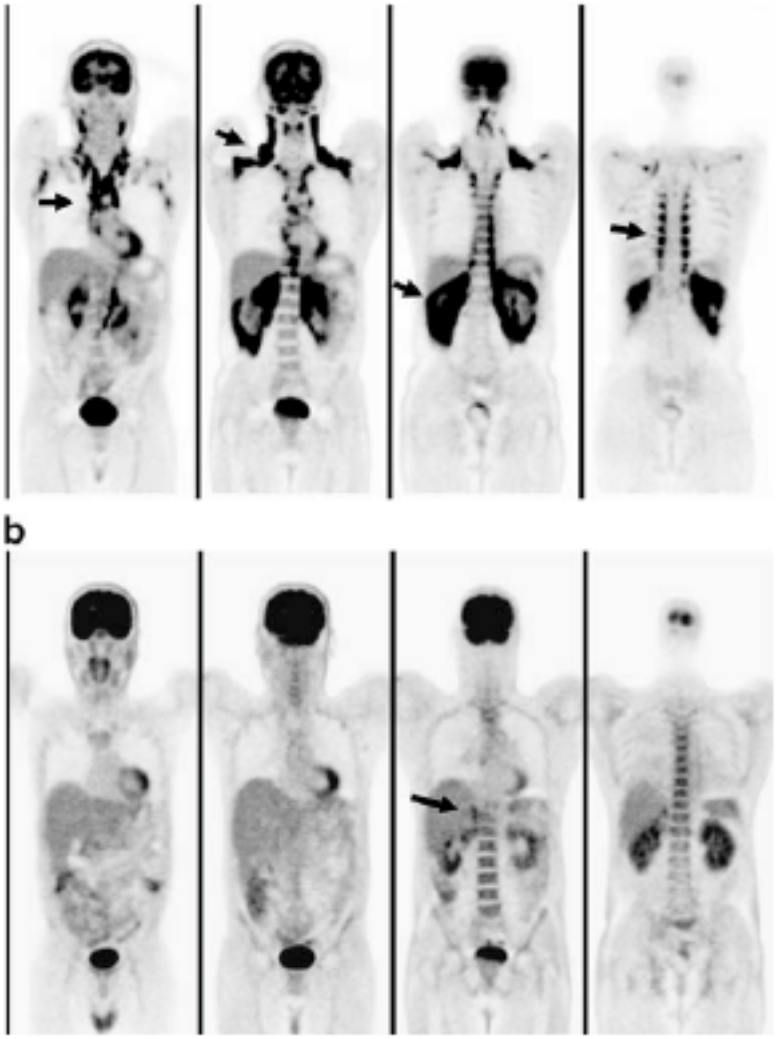


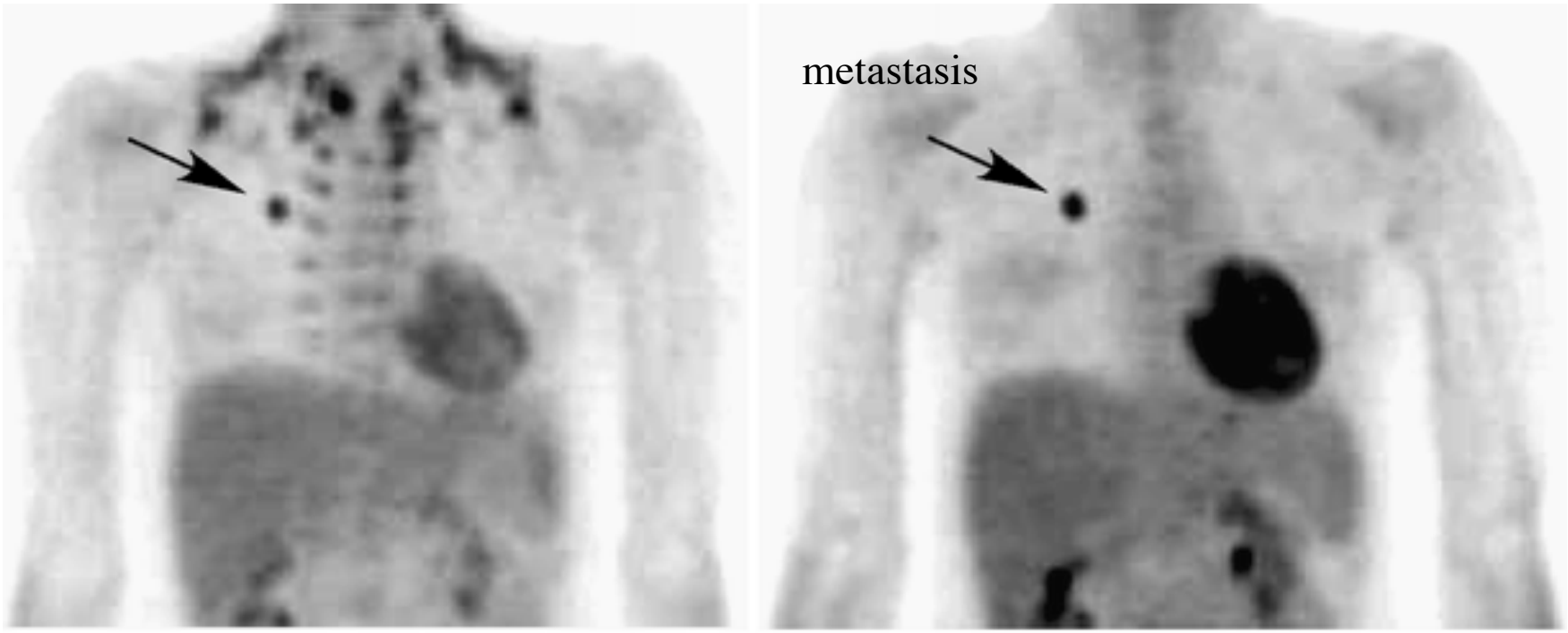
hUCP1 detection

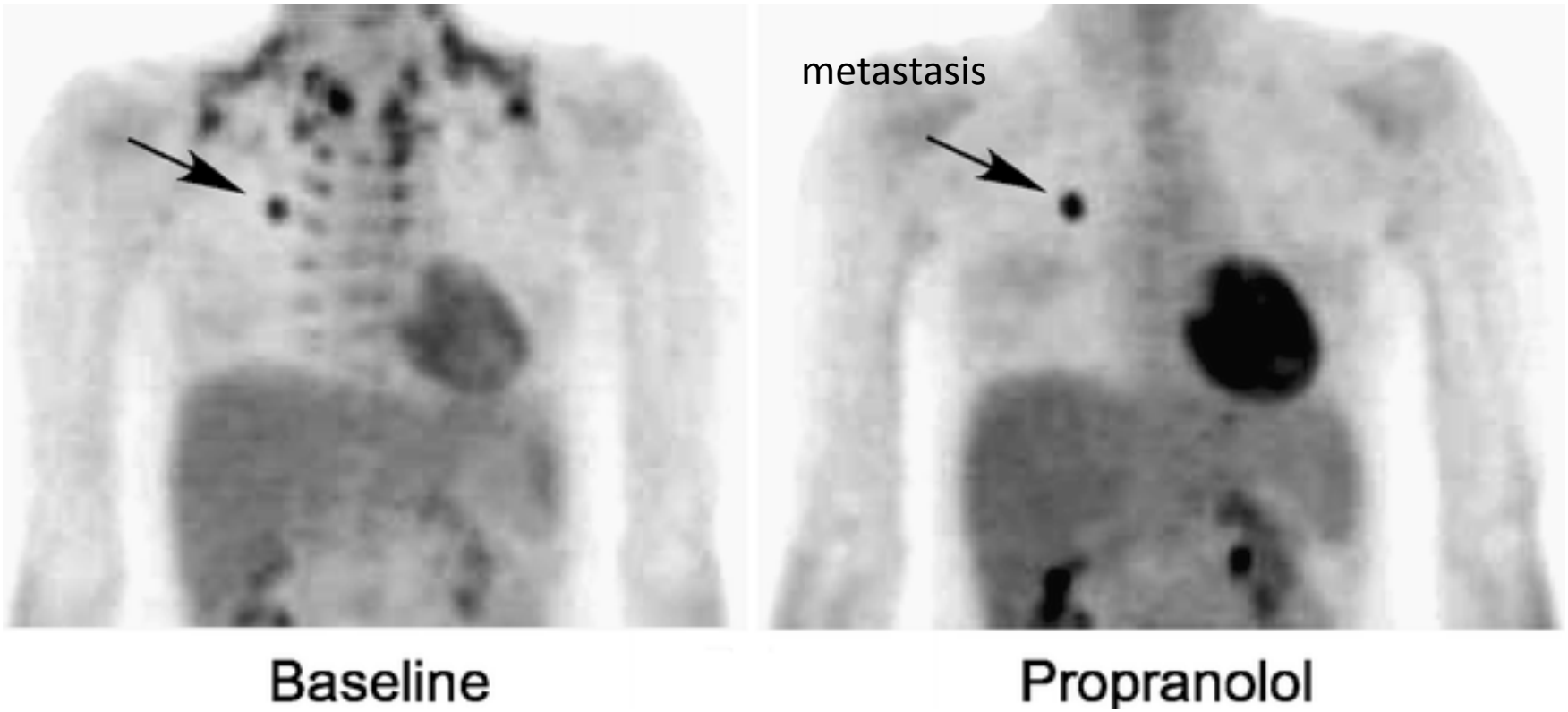


Azido ^{32}P-ATP antibodies

Ricquier et al. JCEM 1982
Bouillaud et al. 1983
Garrutti and Ricquier 200?

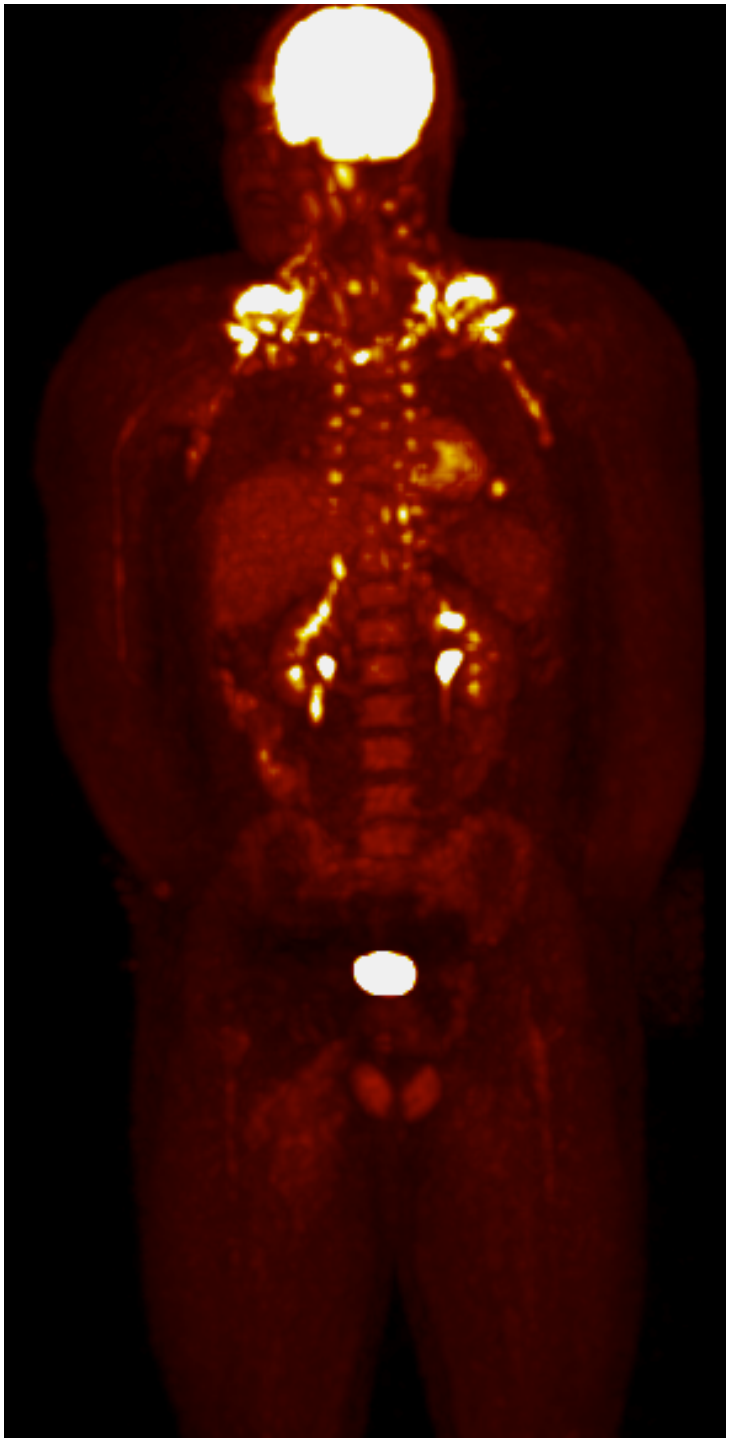

b


metastasis
Baseline
Propranolol



Söderlund et al. 2007

Thus, activity is fully sympathetically stimulated



Centre d’imagerie moléculaire de Sherbrooke

Gracieuseté du Dr Eric Turcotte

Cypess et al., Wouter et al. , Virtanen et al. 2009

- BAT: higher prevalence in females
- BAT: decrease with age
- BAT: decrease with BMI Increase

Cold-induced brown adipose tissue thermogenesis in humans

Ouellet et al. JCI in press

Using PET with 11C-acetate, 18FDG and 18F-fluoro-thiaheptadecanoic acid (18FTHA, a fatty acid tracer), BAT oxidative metabolism, glucose and nonesterified fatty acid (NEFA) turnover were quantified in six healthy men under controlled cold exposure condition designed to minimize shivering.

We showed significant NEFA uptake in addition to glucose upon cold exposure. We demonstrated significant cold-induced activation of oxidative metabolism in BAT, but not in adjoining skeletal muscles and subcutaneous adipose tissue.

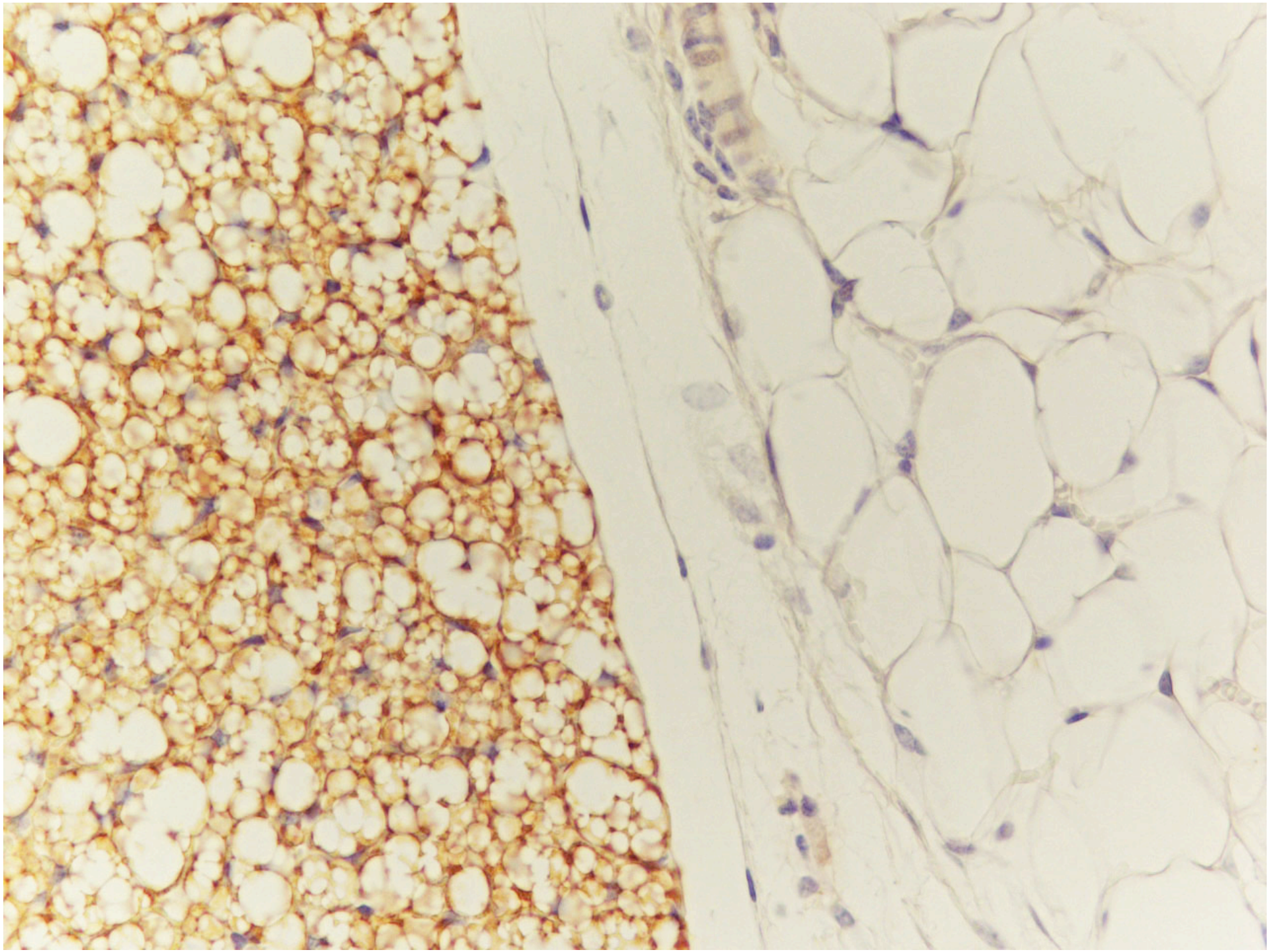
This was associated with a 1.8-fold increase in total energy expenditure. We found a significant increase in BAT radio-density, indicating reduced BAT triglyceride content.

The present study demonstrates that BAT represents a non-shivering thermogenesis effector in humans.

- Qu’est-ce que c’est? Thermogenèse
- Mécanisme? Mitochondries, découplage respiratoire, UCP1
- Importance physiologique chez les rongeurs
- Données anciennes chez l’homme
- **Est-ce du TABrun? est-il fonctionnel?**
- **Perspectives**

PERSPECTIVES

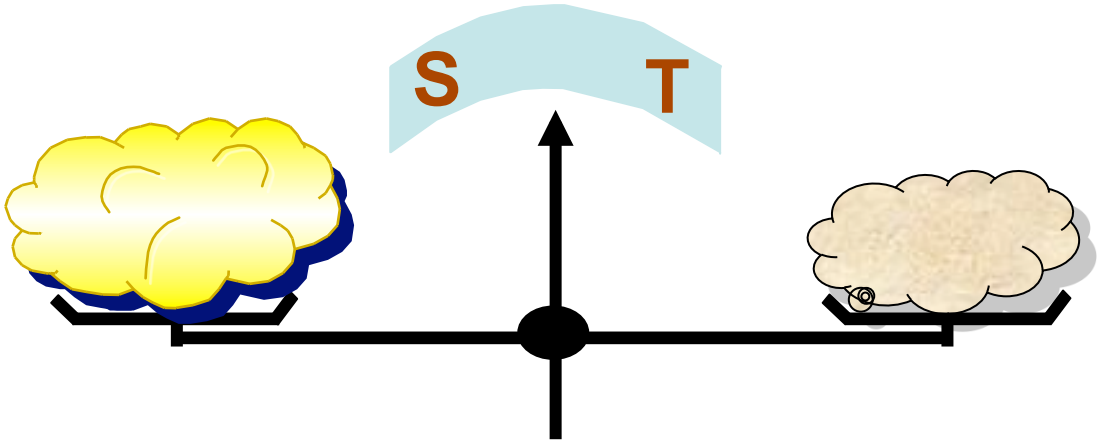
- Reconsidération du TABrun (sous-estimé?) pour comprendre et combattre certaines maladies métaboliques:
- activer ou induire UCP1 et les adipocyes bruns via le récepteur adrénergique ß3
- données récentes sur l'origine des précurseurs des adipocytes bruns



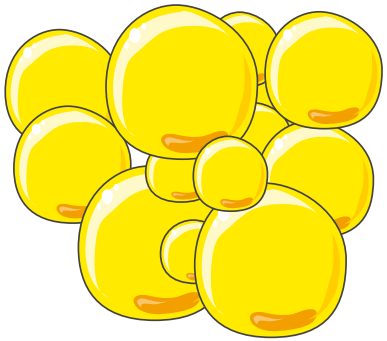
Deux types de tissus adipeux aux rôles opposés

Tissu adipeux blanc

Tissu adipeux brun



Stockage



Thermogenèse

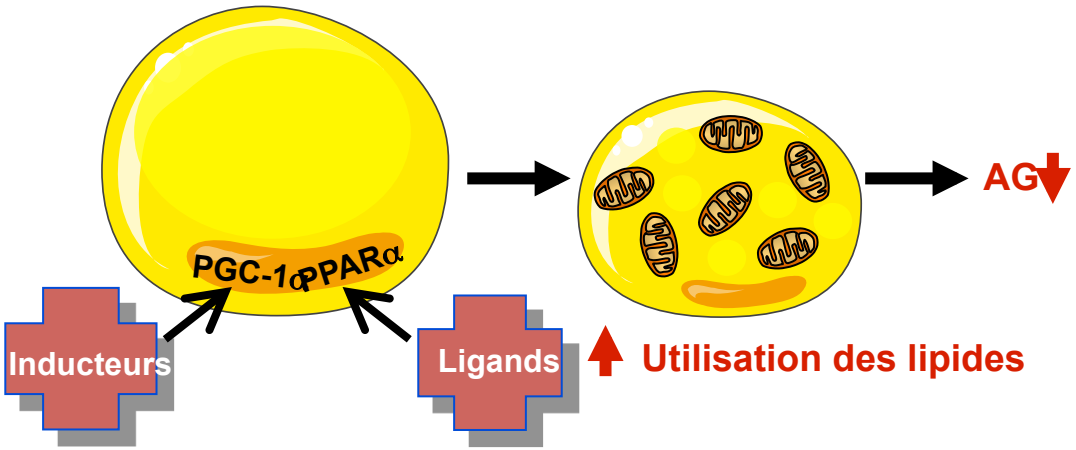
Quelles stratégies thérapeutiques ?

1. Activer le tissu adipeux brun : Le bain de Noël ou la chambre froide

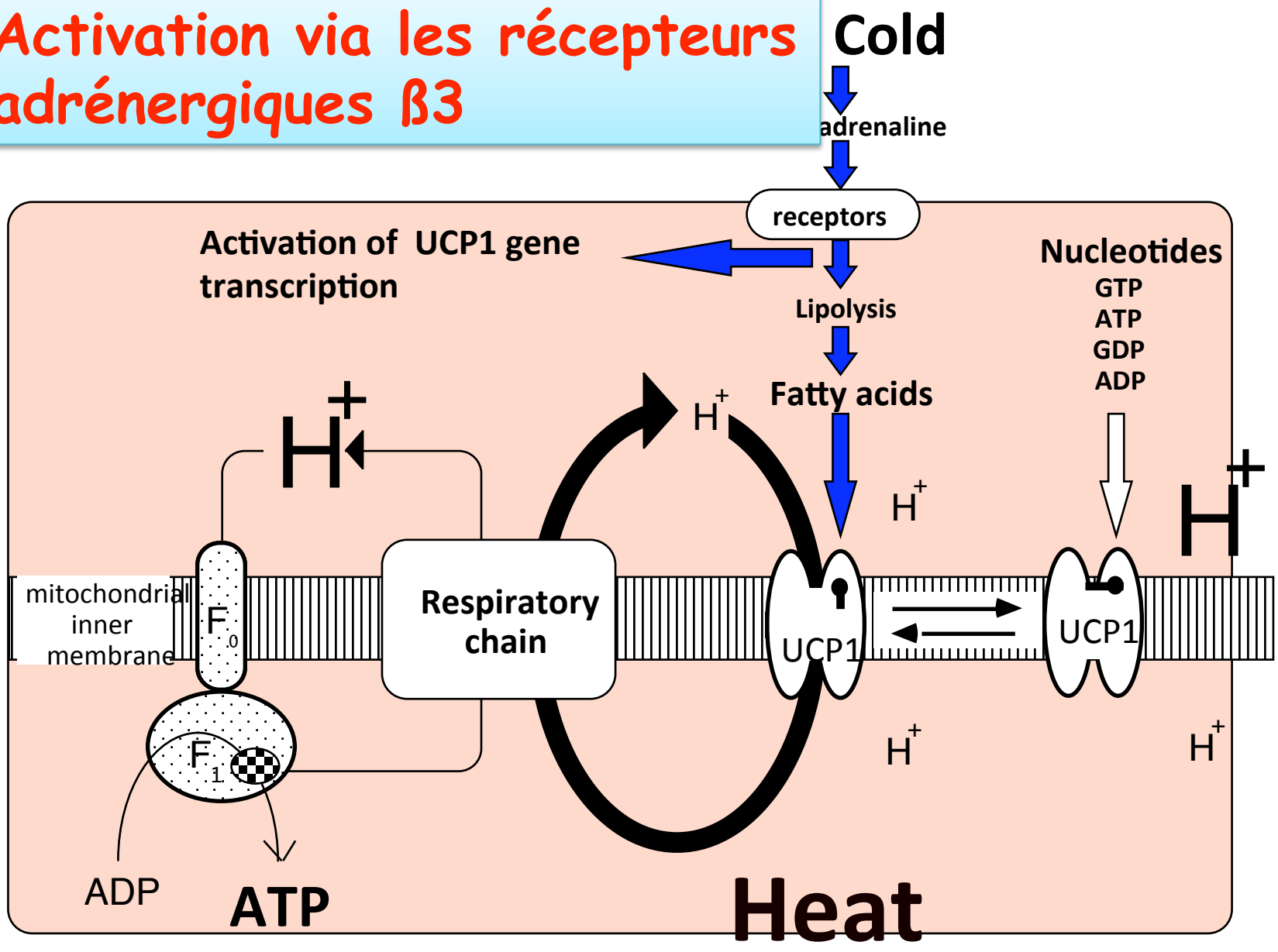
1bis. Mimer le froid : Agonistes β_3-adrénergiques, le retour ?

2. Recruter du tissu adipeux brun : inducteurs de PRDM16; implantation autologue de cellules progénitrices stimulées

3. Conversion des adipocytes blancs en adipocytes « bruns »



Activation via les récepteurs adrénergiques ß3



UCP1: a regulatable proton leak activating oxidation and heat output

Induction via les récepteurs adrénergiques ß3

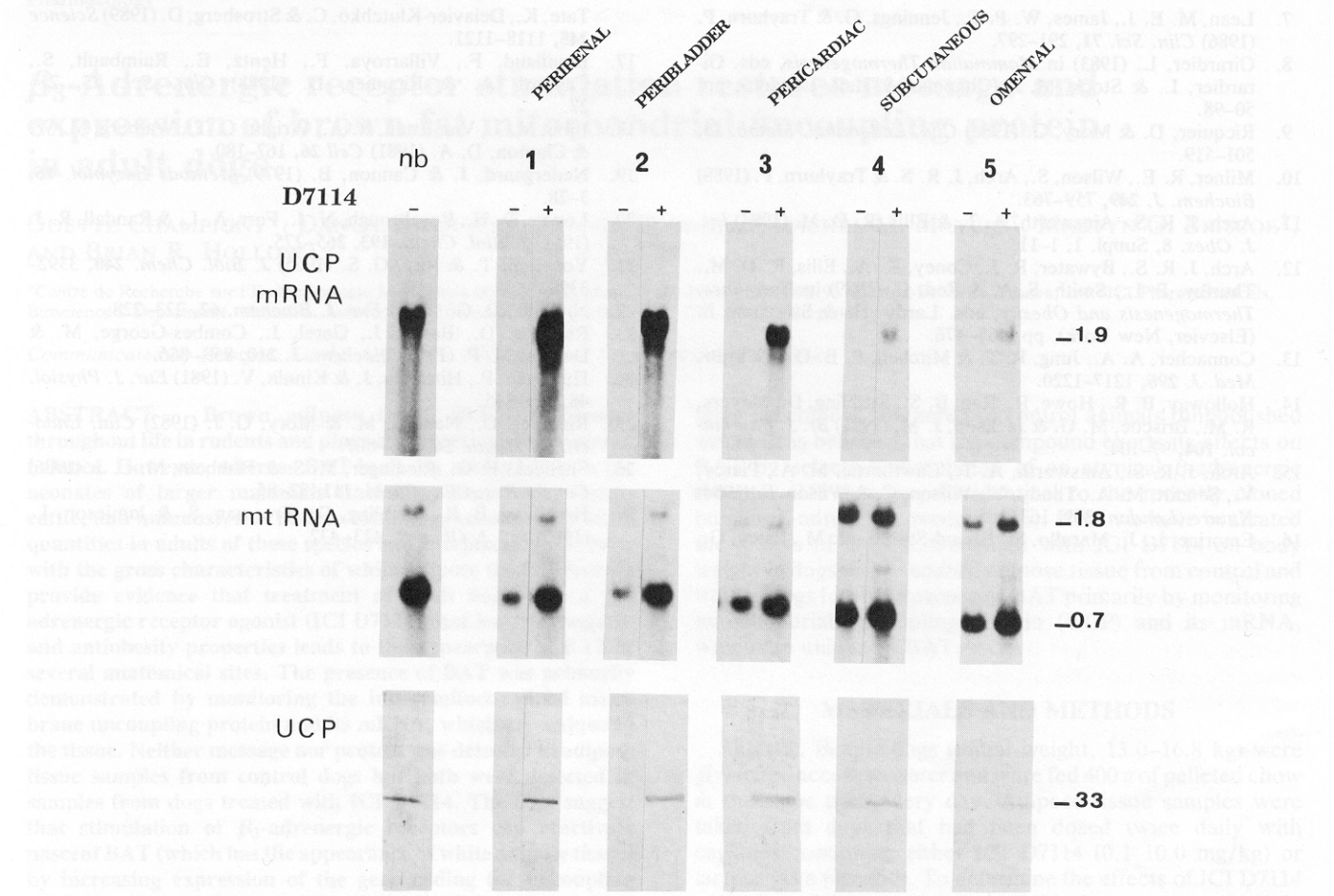
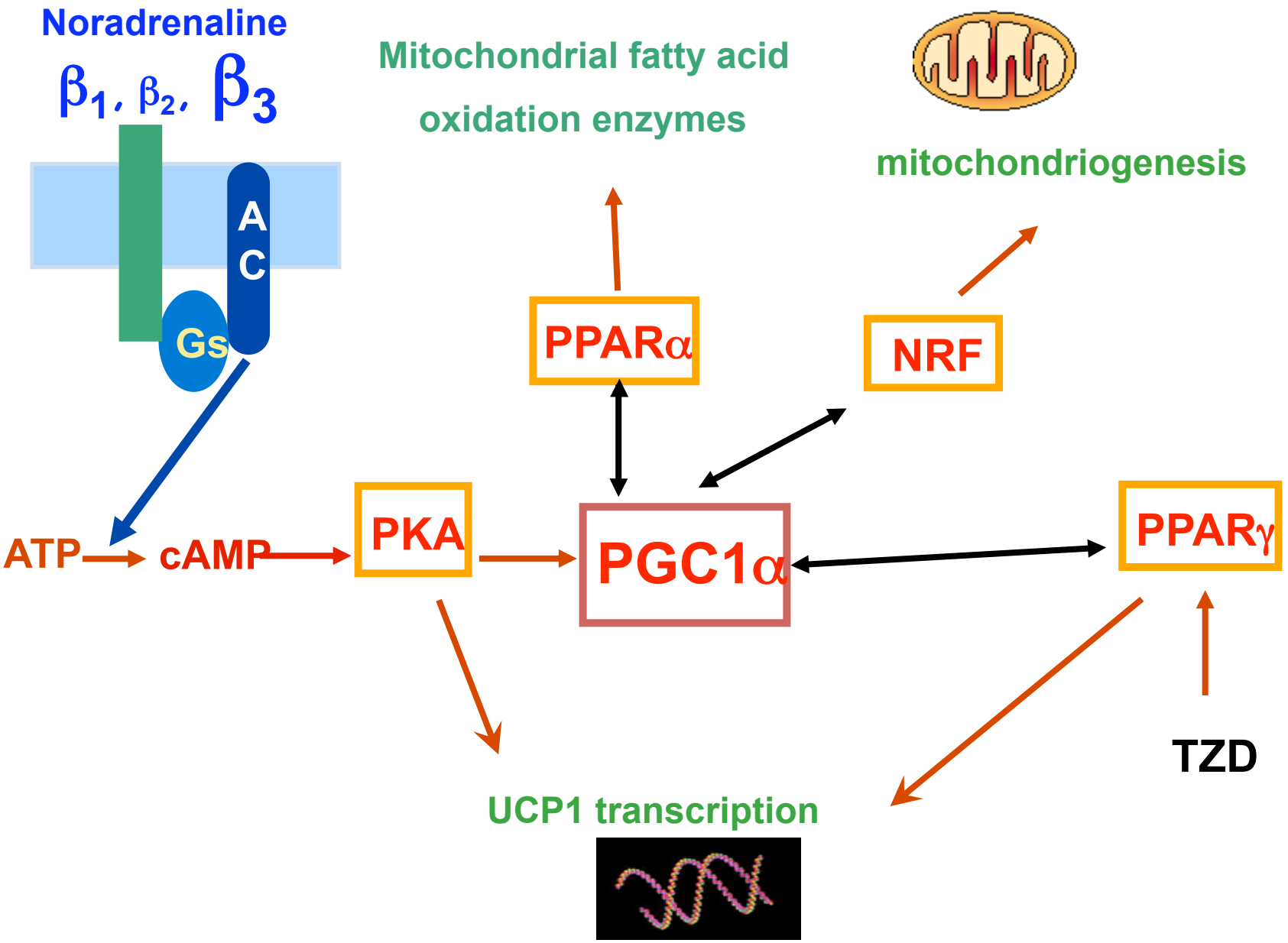


FIG. 2. Expression of UCP mRNA, mitochondrial RNA (mt RNA), and UCP in adipose tissue from several sites in placebo (−)- and ICI D7114 (+)-treated adult dogs. Dogs were dosed, twice daily *per os*, for 2 weeks with capsules containing ICI D7114 (10 mg/kg) or a placebo preparation. Samples of adipose tissue mitochondrial protein and RNA from a newborn (nb) dog were used as a positive control.

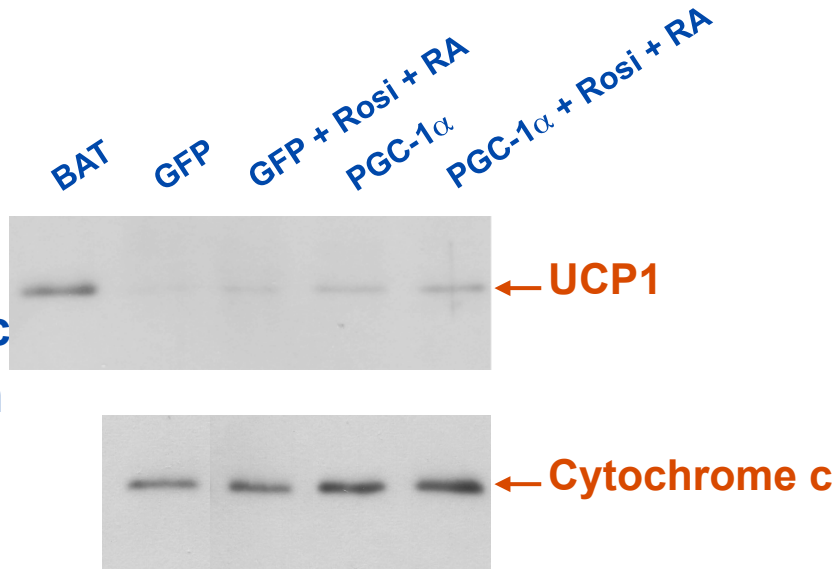
Indirect induction of UCP1 and fat oxidation in human white adipocytes

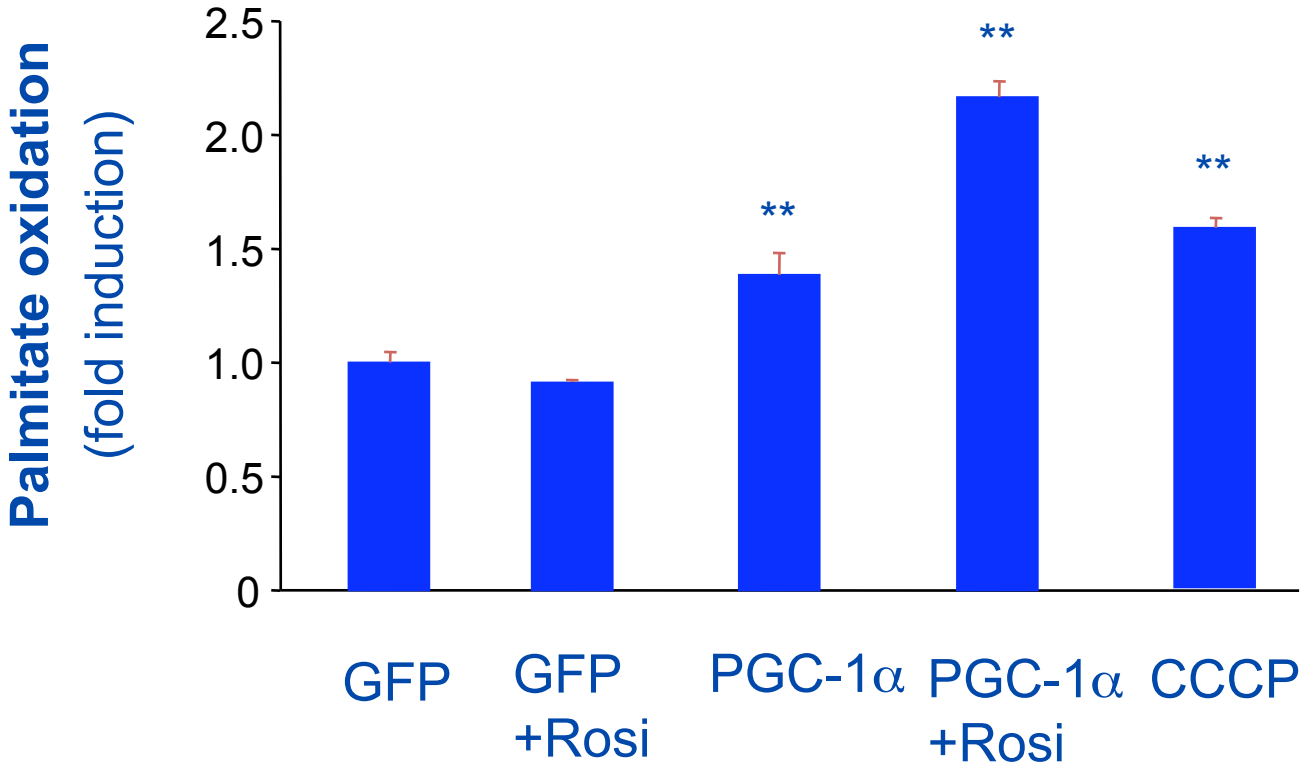
Tiraby et al. JBC 2003

Role of PGC1α in rodent brown adipose tissue

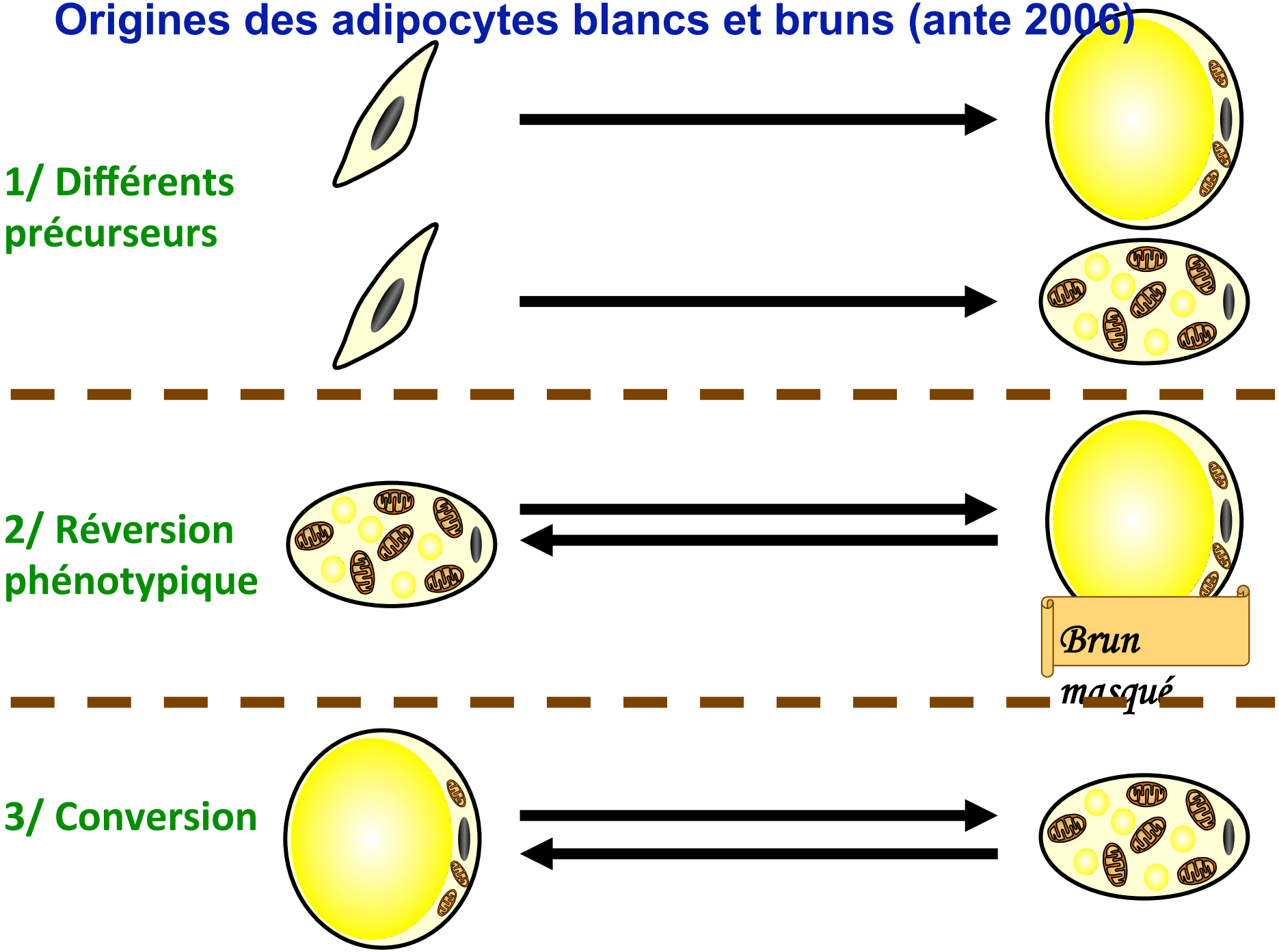


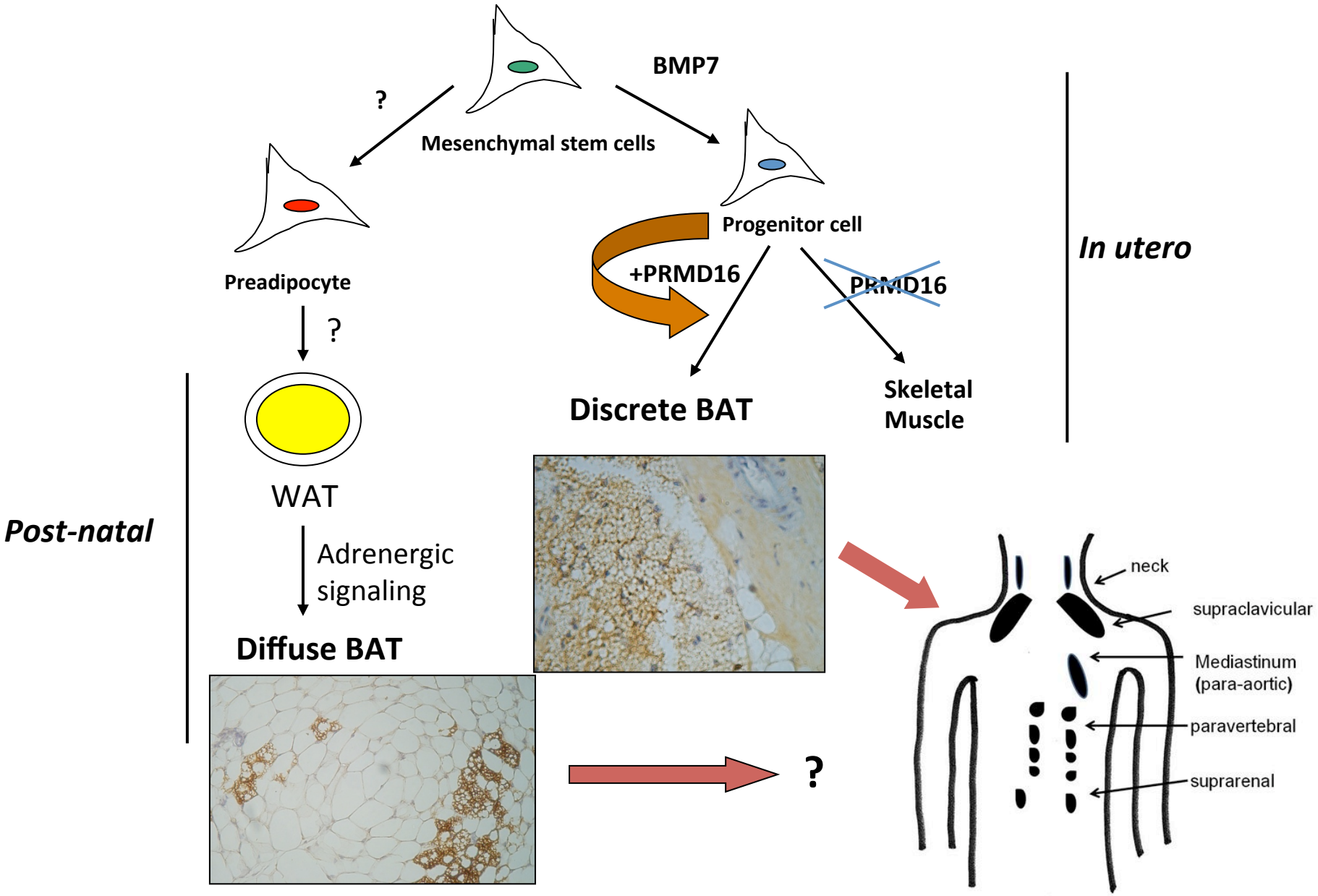
➢ **PGC-1α induces UCP1 and cytochrome c protein expression and palmitate oxidation**

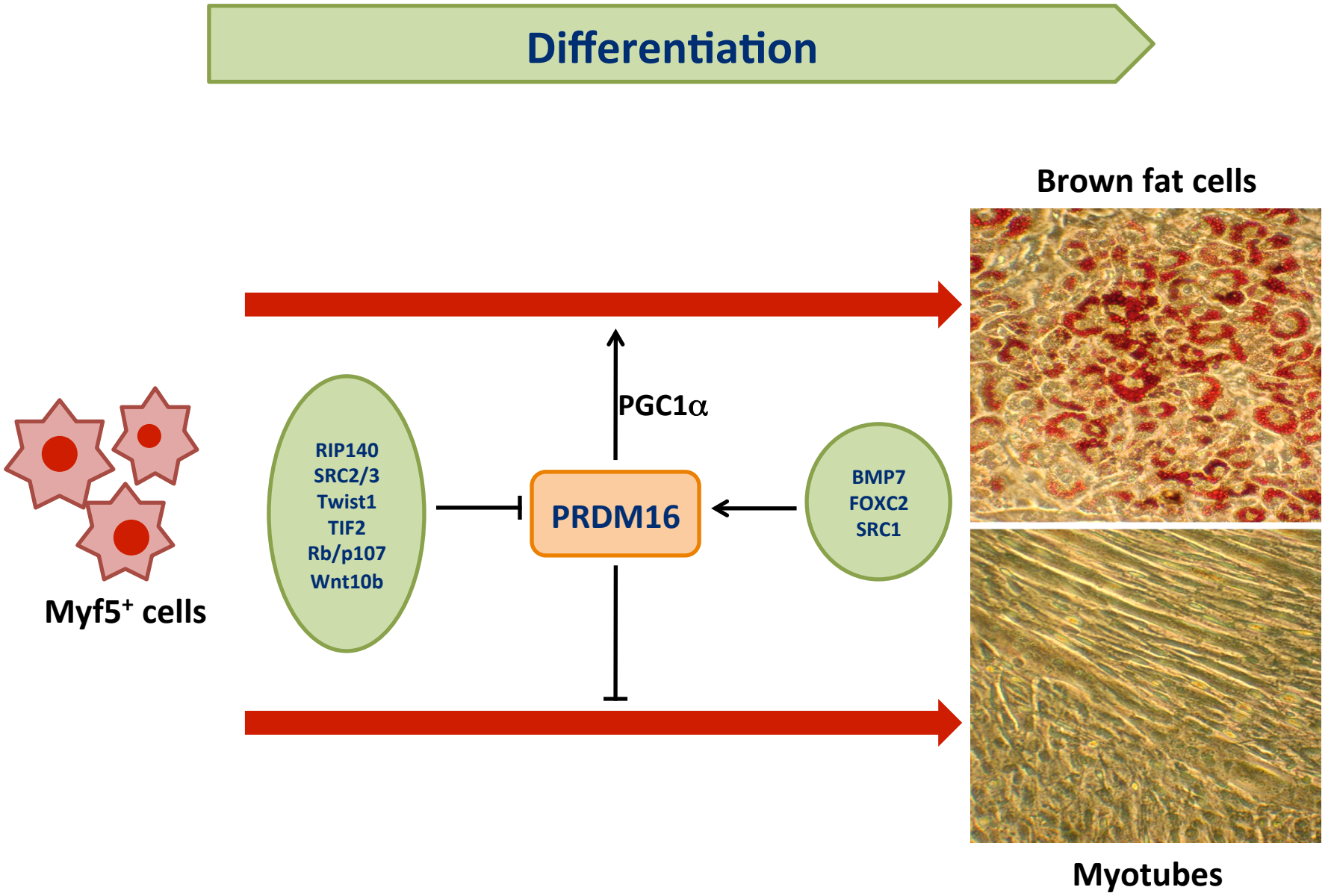




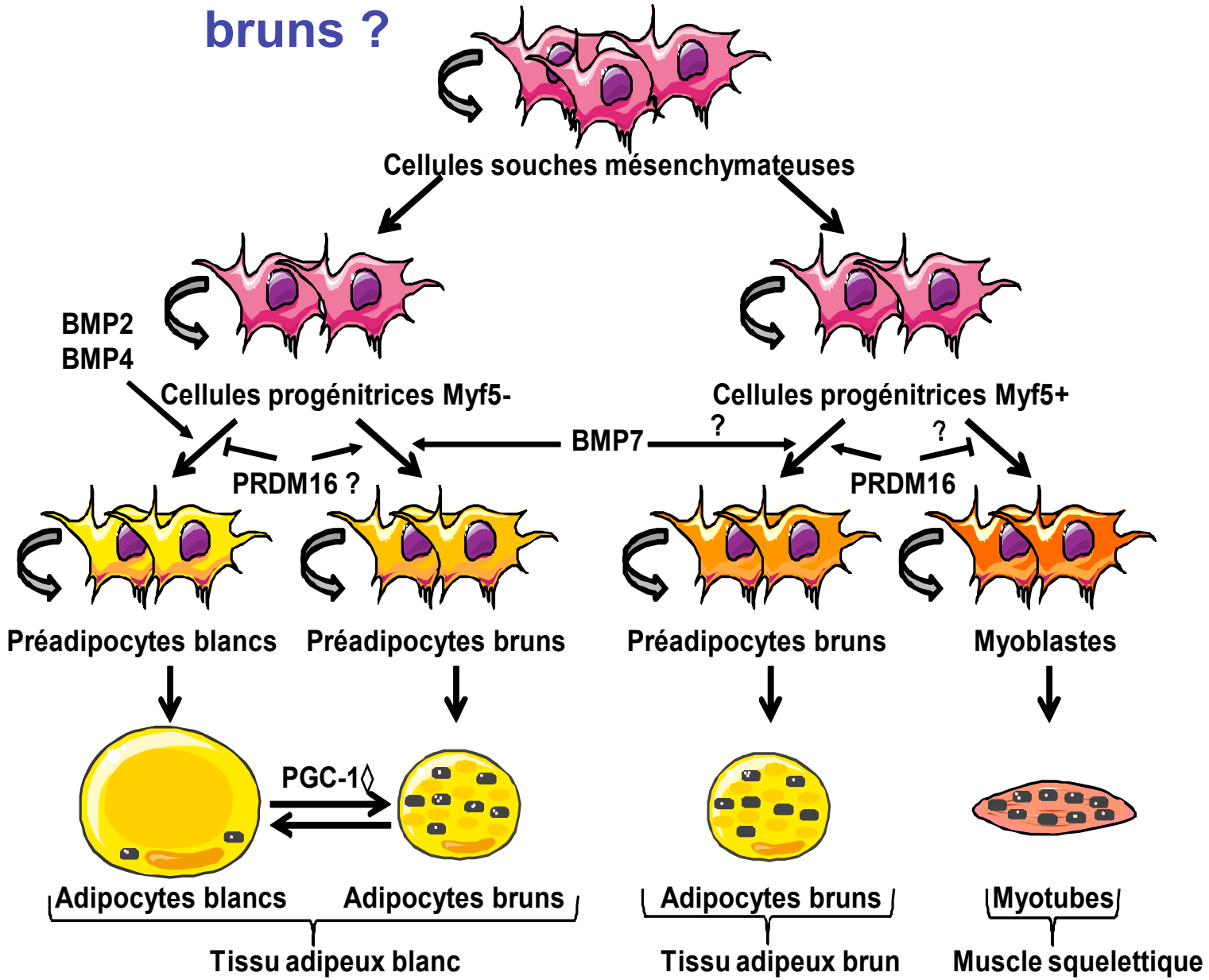
Origines des adipocytes blancs et bruns (ante 2006)




BMP7
?
Mesenchymal stem cells
Progenitor cell
Preadipocyte
+PRMD16
PRMD16
?
Skeletal
Muscle
In utero
Discrete BAT
WAT
Post-natal
Adrenergic
signaling
Diffuse BAT
?
neck
supraclavicular
Mediastinum
(para-aortic)
paravertebral
suprarenal


Differentiation
Brown fat cells
PGC1α
RIP140
SRC2/3
Twist1
TIF2
Rb/p107
Wnt10b
PRDM16
BMP7
FOXC2
SRC1
Myf5+ cells
Myotubes

Plusieurs types d'adipocytes bruns ?



Seale et al. Cell Metab 6 (2007) 38-54; Seale et al. Nature 454 (2008) 961-967
Tseng et al. Nature 454 (2008) 1000-1004

Crisan, Casteilla….Péault, Giacobino
Stem Cells 2008

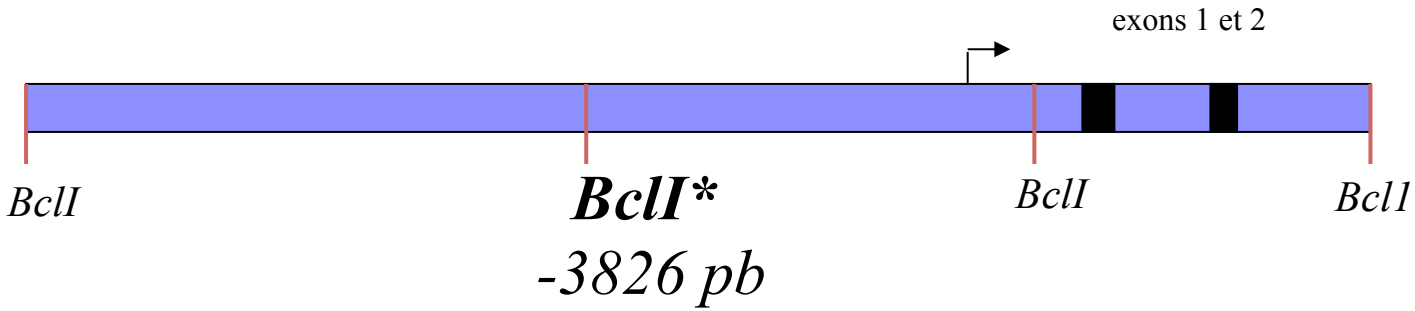
- **A reservoir of brown adipocyte progenitors in human skeletal muscle**

- A stationary population of skeletal muscle cells expressing the CD34 surface protein can differentiate in vitro into genuine brown adipocytes with a high level of UCP1 expression and uncoupled respiration

DNA polymorphism in the uncoupling protein (UCP) gene and human body fat *Intern. J. Obes. 1994*

Oppert JM, Vohl MC, Chagnon M, Dionne FT, Cassard-Doulcier AM, Ricquier D, Pérusse L, Bouchard

Susceptibilité à la prise de poids à long terme chez les individus Bcl1-/-



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dinitrophenol Rechercher

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Body's Cult - Une petite alerte

... adepte du culturisme, que des pilules dites « fat burner » commercialisées par Internet, contenaient des teneurs très élevées en 2,4-**dinitrophenol** (DNP). ...

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