Brown Adipose Tissue a panacea against the metabolic syndrome?

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KUNGL. VETENSKAPS AKADEMIEN

THE ROYAL SWEDISH ACADEMY OF SCIENCES

Results in collaboration with
(among others)

The Cannon/Nedergaard lab:
Gustavo Abreu de Vieira
Helena Feldmann
Valeria Golozoubova
Anders Jacobsson
Elaina Maldonado
Natasa Petrovic
Tomas Waldén

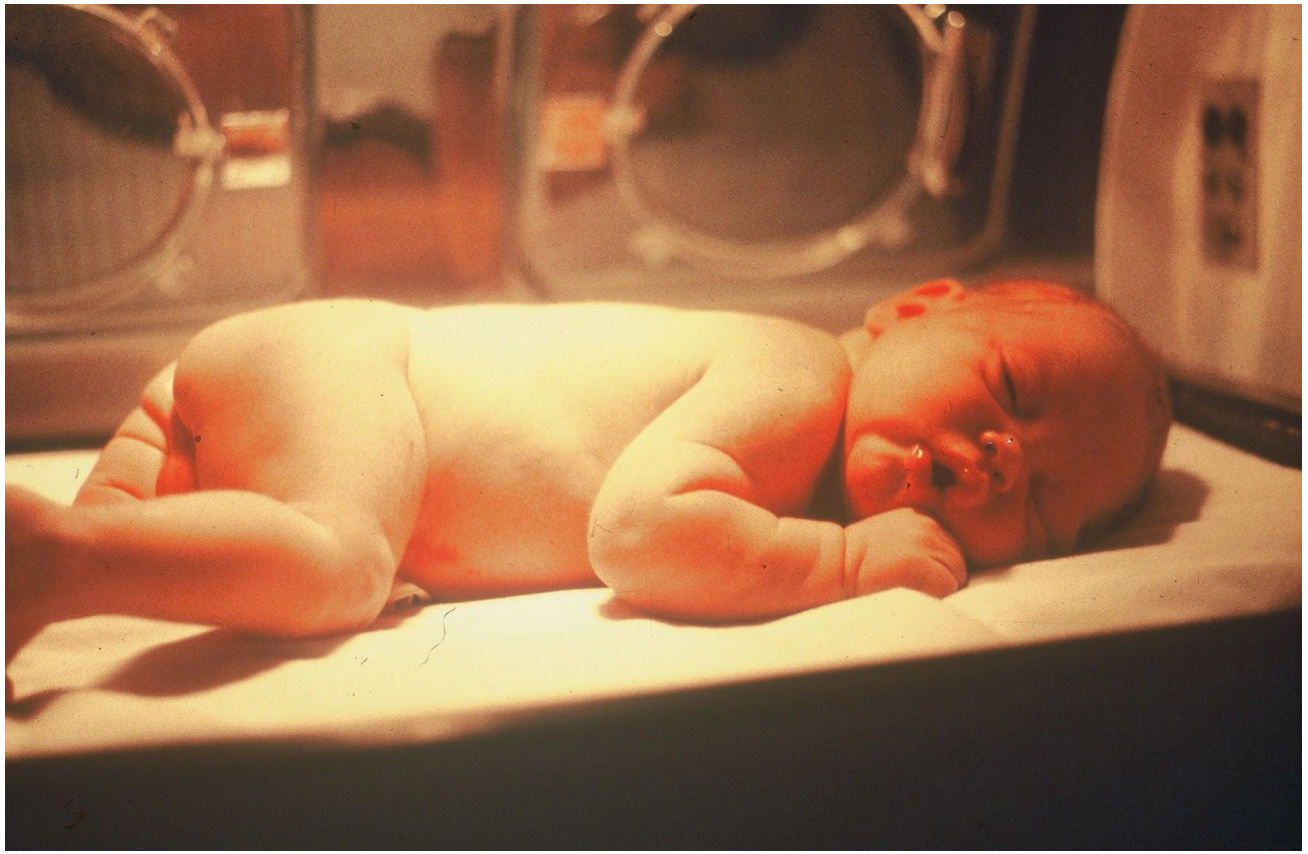
The Bengtsson lab:
Jessica Olsen
Maasaki Sato
Olof S. Dallner
Anna L. Sandström

A new organ in adult humans:

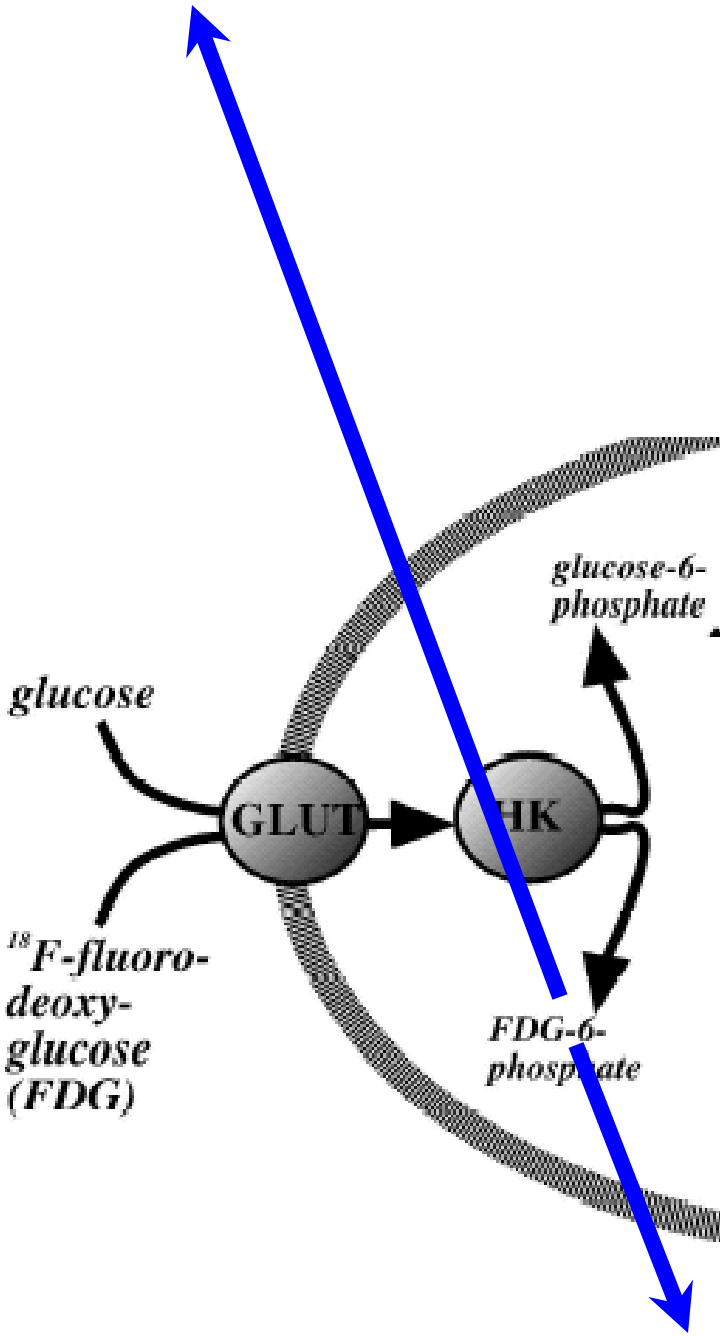
brown adipose tissue

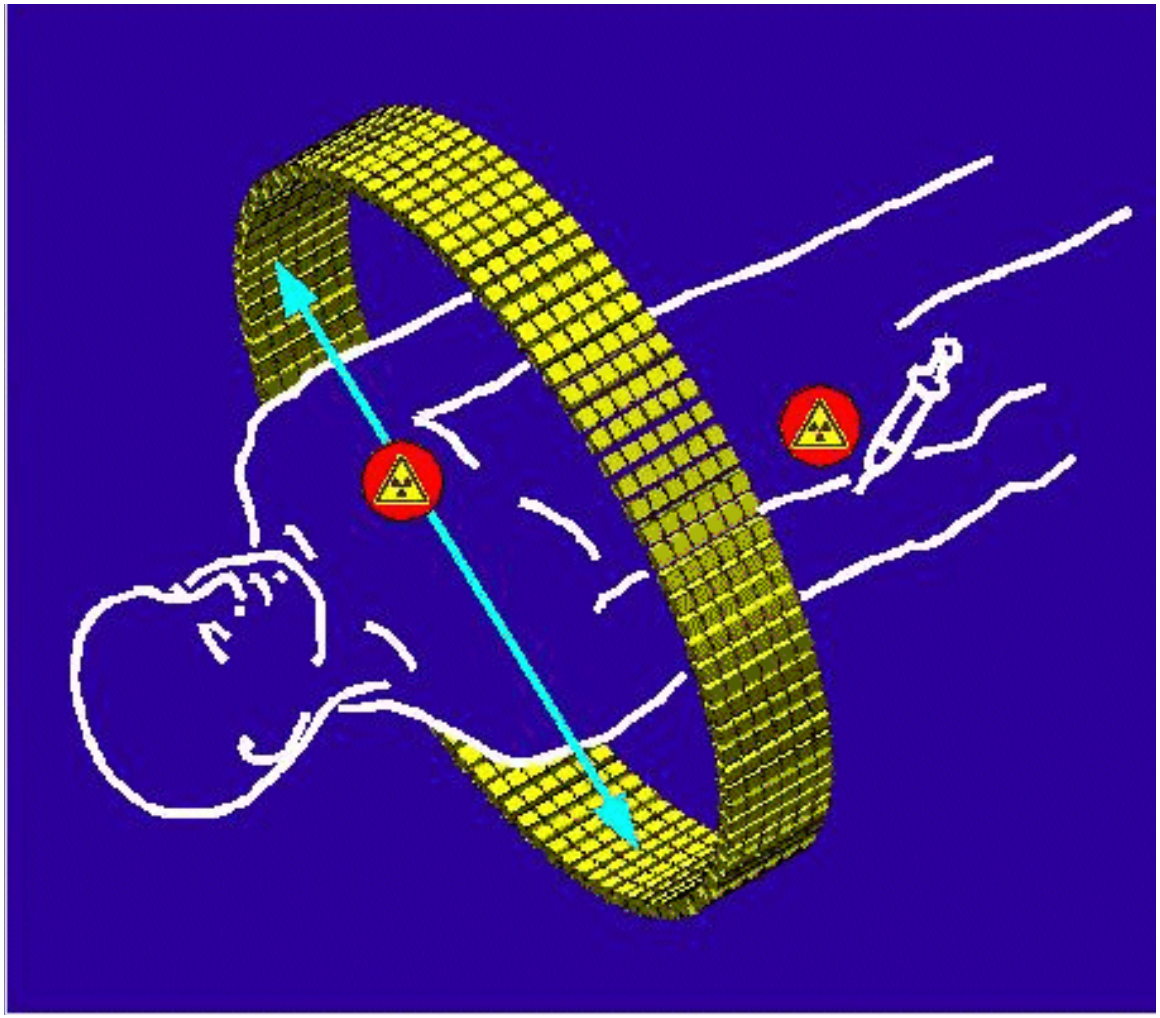
Before 2007:

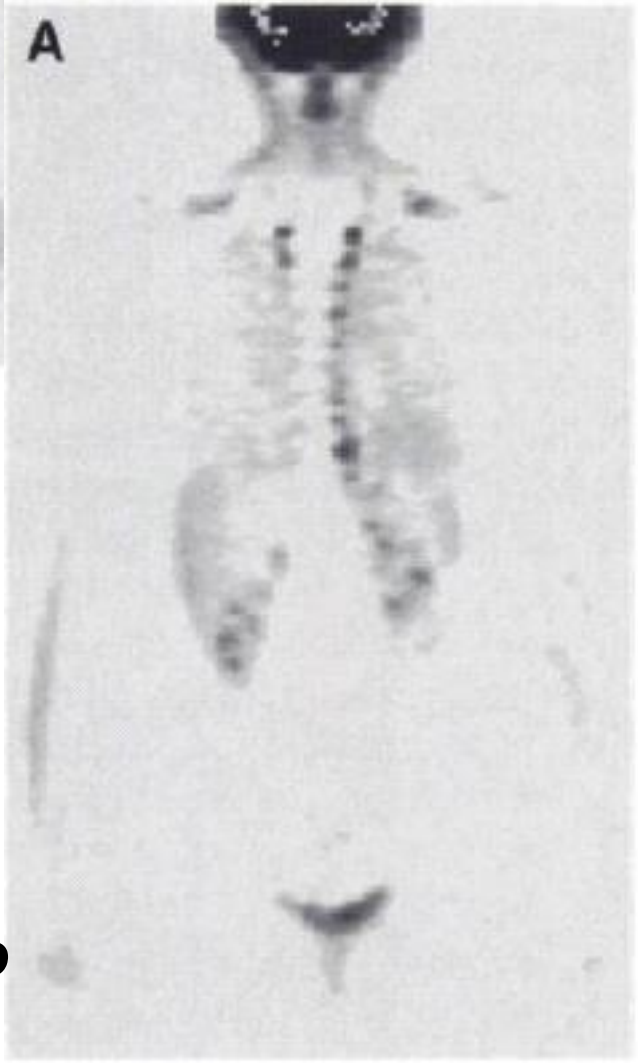
”in man, brown adipose tissue
is only found in newborns”



An unexpected development from radiology







Tense muscle?

Barrington & Maisey 1996

”In all patients, the soft tissue uptake
was clearly localised *within the fatty tissue*
of the shoulders
as demonstrated by PET/CT co-registration.”

Hany//von Schulthess 2002

Eur J Nucl Med Mol Imaging

2007:

Invited Review

Am J Physiol Endocrinol Metab 293: E444–E452, 2007.
First published May 1, 2007; doi:10.1152/ajpendo.00691.2006.

Unexpected evidence for active brown adipose tissue in adult humans

Jan Nedergaard, Tore Bengtsson, and Barbara Cannon

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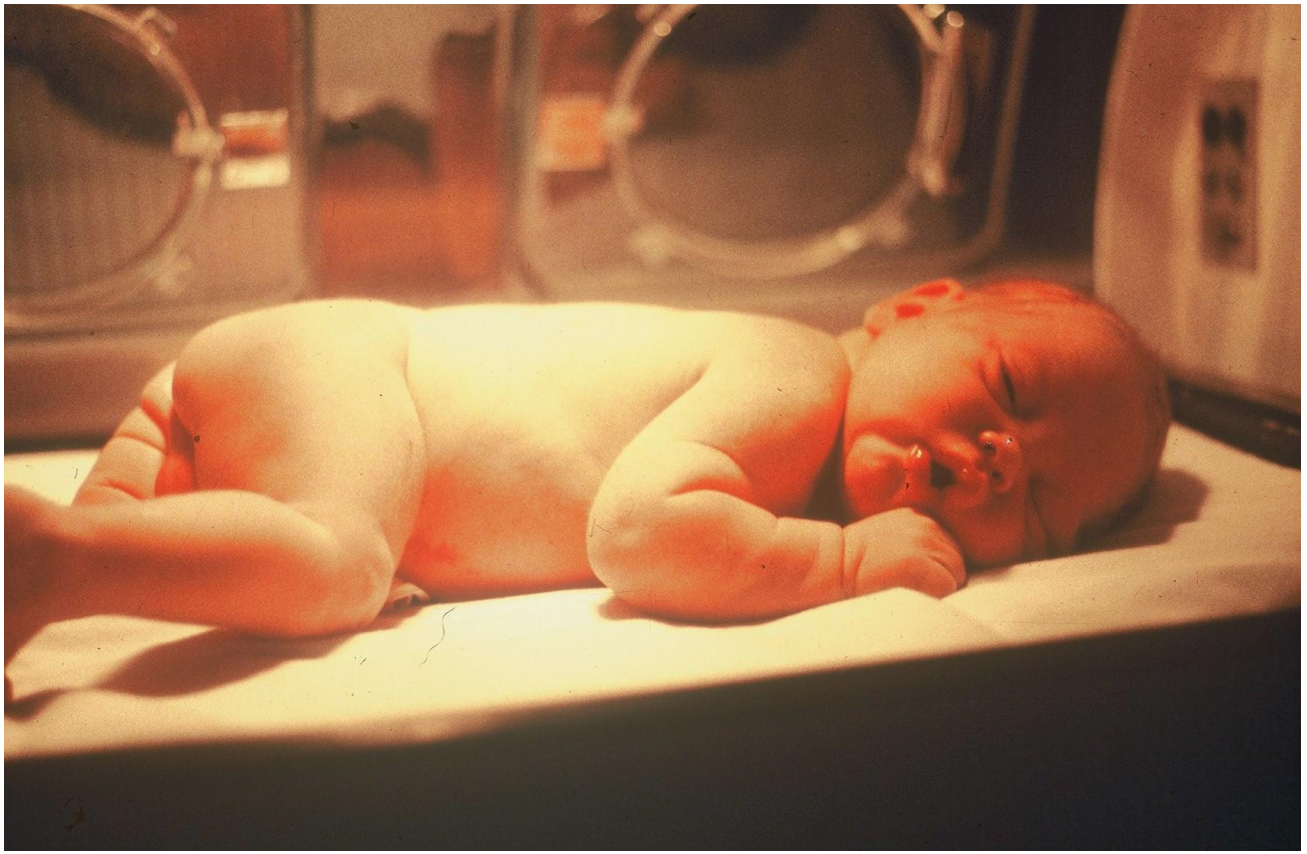
Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 293: E444–E452, 2007. First published May 1, 2007; doi:10.1152/ajpendo.00691.2006.—The contention that brown adipose tissue is absent in adult man has meant that processes attributed to active brown adipose tissue in experimental animals (mainly rodents), i.e., classical nonshivering thermogenesis, adaptive adrenergic thermogenesis, diet-induced thermogenesis, and antiobesity, should be either absent or attributed to alternative (unknown) mechanisms in man. However, serendipidously, as a consequence of the use means either that adult man does not possess classical nonshivering thermogenesis (i.e., the development with time of a heat-producing mechanism to replace shivering, as a consequence of chronic exposure to cold) or that man should possess an alternative method of nonshivering thermogenesis other than that found in experimental animals (rodents), where all classical nonshivering thermogenesis is dependent upon brown adipose tissue (34). Furthermore, this means that adaptive adrenergic thermogenesis [which in rodents originates from

After 2007:

” in man, brown adipose tissue
is found in newborns and in (certain?) adults”



1. Title: **Identification and Importance of Brown Adipose Tissue in Adult Humans.**
Author(s): Cypess, Aaron M.; Lehman, Sanaz; Williams, Gethin; et al.
Source: NEW ENGLAND JOURNAL OF MEDICINE Volume: **360** Issue: **15** Pages: **1509-1517** DOI: **10.1056/NEJMoa0810780** Published: **APR 9 2009**

2. Title: **Brief Report: Functional Brown Adipose Tissue in Healthy Adults.**
Author(s): Virtanen, Kirsi A.; Lidell, Martin E.; Orava, Janne; et al.
Source: NEW ENGLAND JOURNAL OF MEDICINE Volume: **360** Issue: **15** Pages: **1518-1525** DOI: **10.1056/NEJMoa0808949** Published: **APR 9 2009**

3. Title: **Unexpected evidence for active brown adipose tissue in adult humans**
Author(s): Nedergaard, Jan; Bengtsson, Tore; Cannon, Barbara
Source: AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM Volume: **293** Issue: **2** Pages: **E444-E452** DOI: **10.1152/ajpendo.00691.2006** **AUG 2007**

4. Title: **Cold-Activated Brown Adipose Tissue in Healthy Men.**
Author(s): Lichtenbelt, Wouter D. van Marken; Vanhommerig, Joost W.; Smulders, Nanda M.; et al.
Source: NEW ENGLAND JOURNAL OF MEDICINE Volume: **360** Issue: **15** Pages: **1500-1508** Published: **APR 9 2009**

5. Title: **High Incidence of Metabolically Active Brown Adipose Tissue in Healthy Adult Humans Effects of Cold Exposure and Adiposity**
Author(s): Saito, Masayuki; Okamatsu-Ogura, Yuko; Matsushita, Mami; et al.
Source: DIABETES Volume: **58** Issue: **7** Pages: **1526-1531** DOI: **10.2337/db09-0530** Published: **JUL 2009**

6. Title: **The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue**
Author(s): Zingaretti, Maria Cristina; Crosta, Francesca; Vitali, Alessandra; et al.
Source: FASEB JOURNAL Volume: **23** Issue: **9** Pages: **3113-3120** DOI: **10.1096/fj.09-133546** Published: **SEP 2009**

1. Title: **Identification and Importance of Brown Adipose Tissue in Adult Humans.**
Author(s): Cypess, Aaron M.; Lehman, Sanaz; Williams, Gethin; et al.
Source: NEW ENGLAND JOURNAL OF MEDICINE Volume: **360** Issue: **15** Pages: **1509-1517** DOI: **10.1056/NEJMoa0810780** Published: **APR 9 2009**

2. Title: **Brief Report: Functional Brown Adipose Tissue in Healthy Adults.**
Author(s): Virtan
Source: NEW E

3. Title: **Unexpect**
Author(s): Neder
Source: AMERIC
AUG 2007

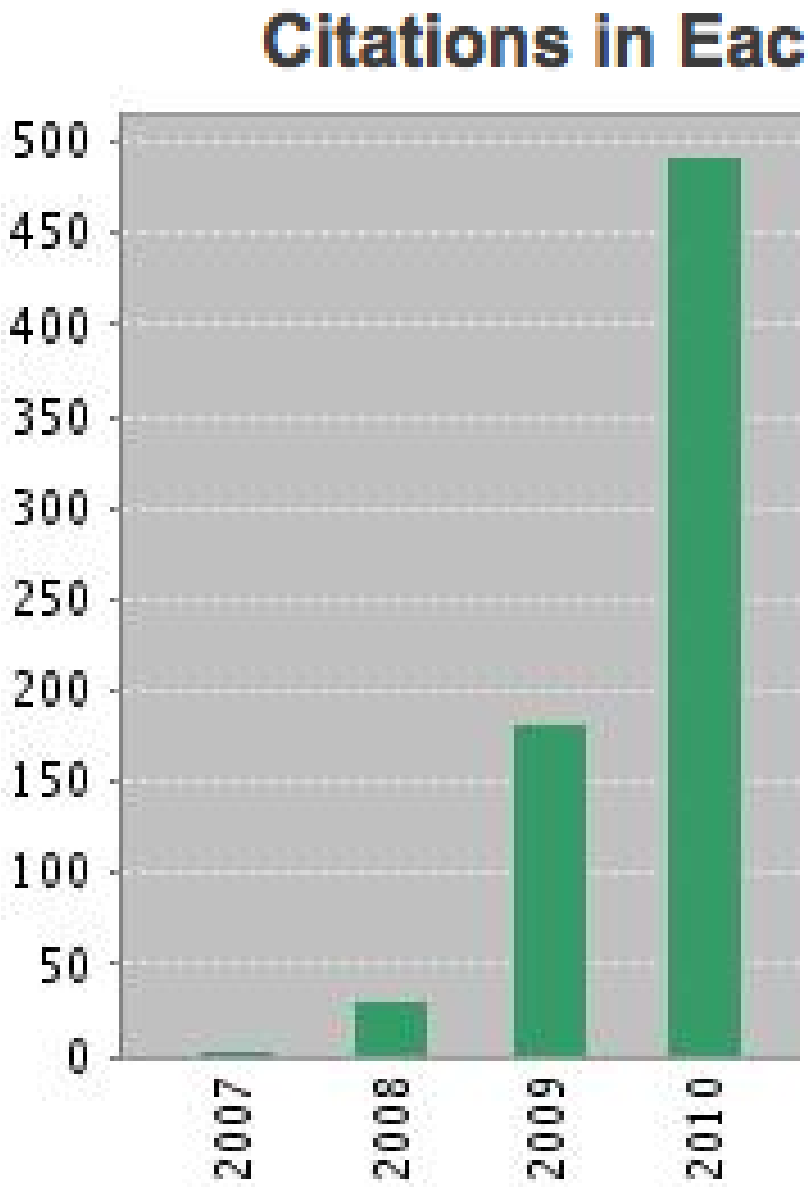
4. Title: **Cold-Acti**
Author(s): Lichte
Source: NEW E

5. Title: **High Inci**
Author(s): Saito,
Source: DIABET

6. Title: **The prese**
Author(s): Zinga
Source: FASEB

ndo.00691.2006

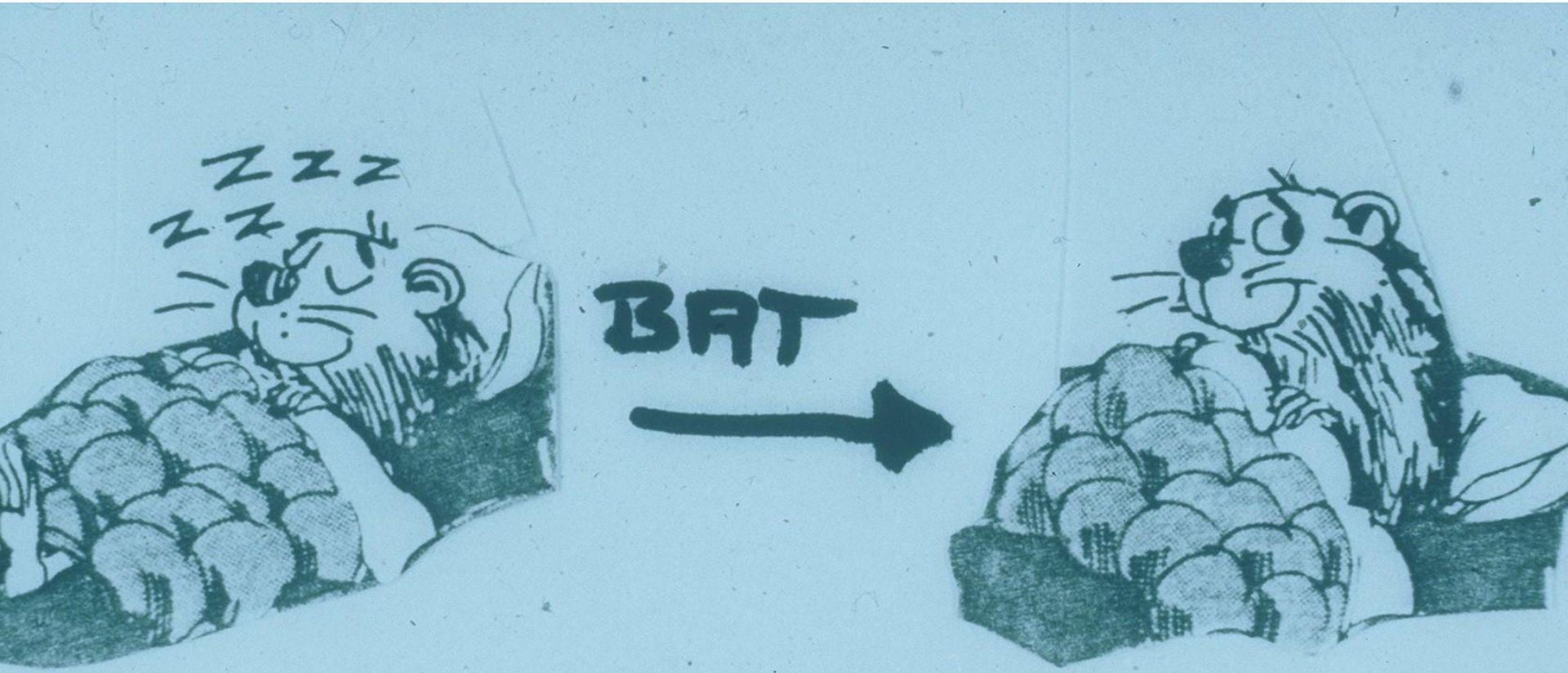
n adipose tissue



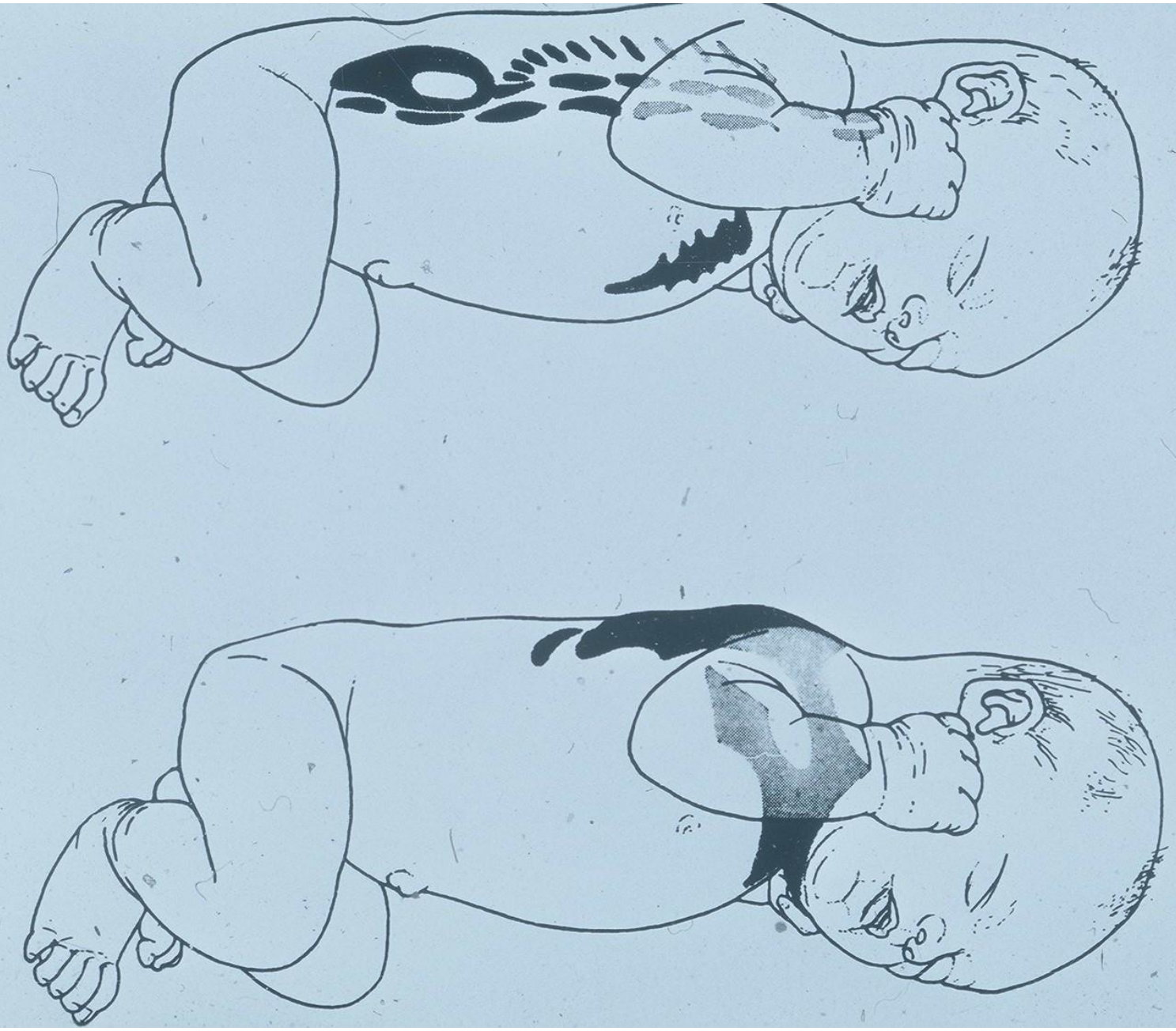
Brown adipose tissue: classical functions


Classically: keeping human newborns warm

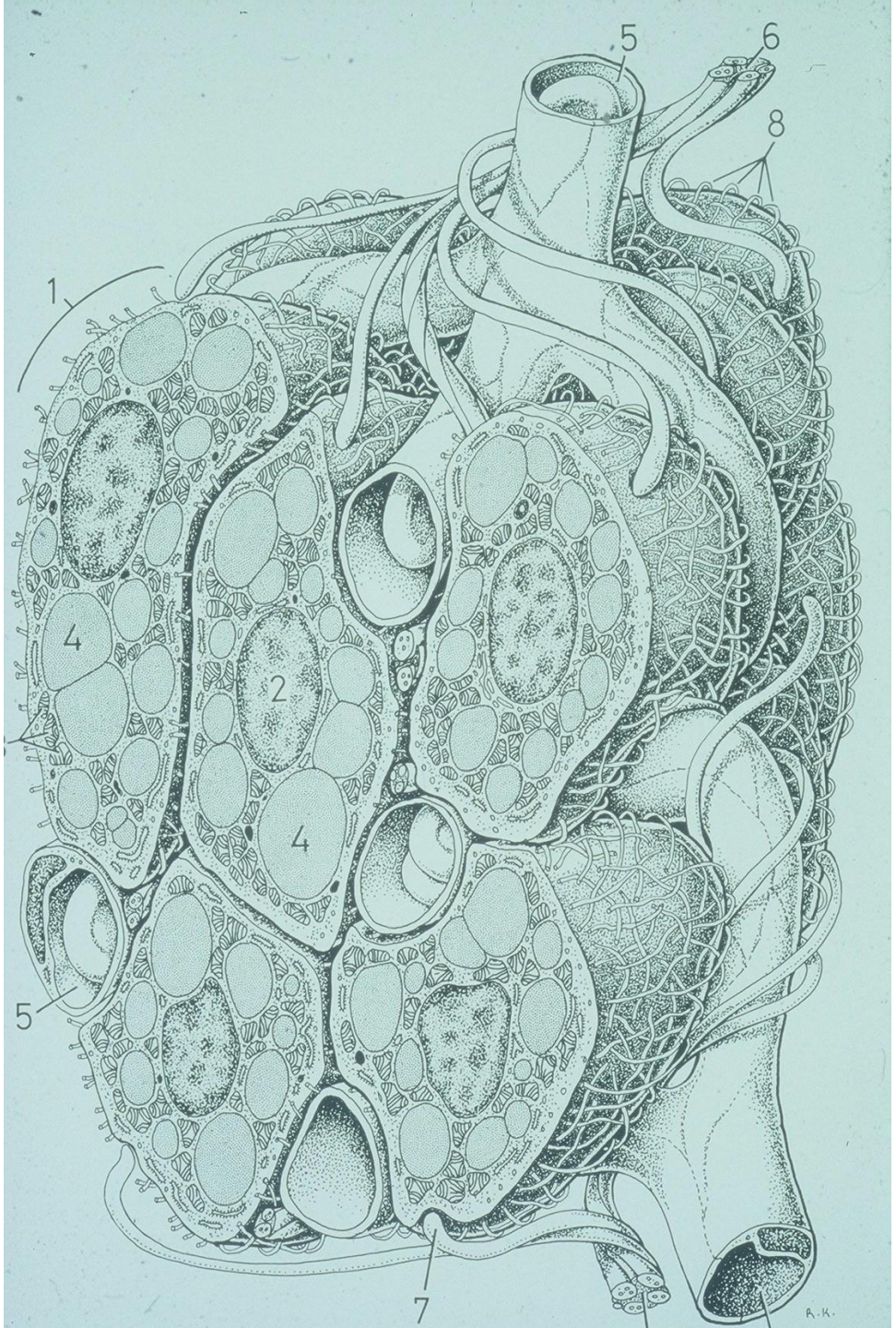
Classically: keeping small mammals warm

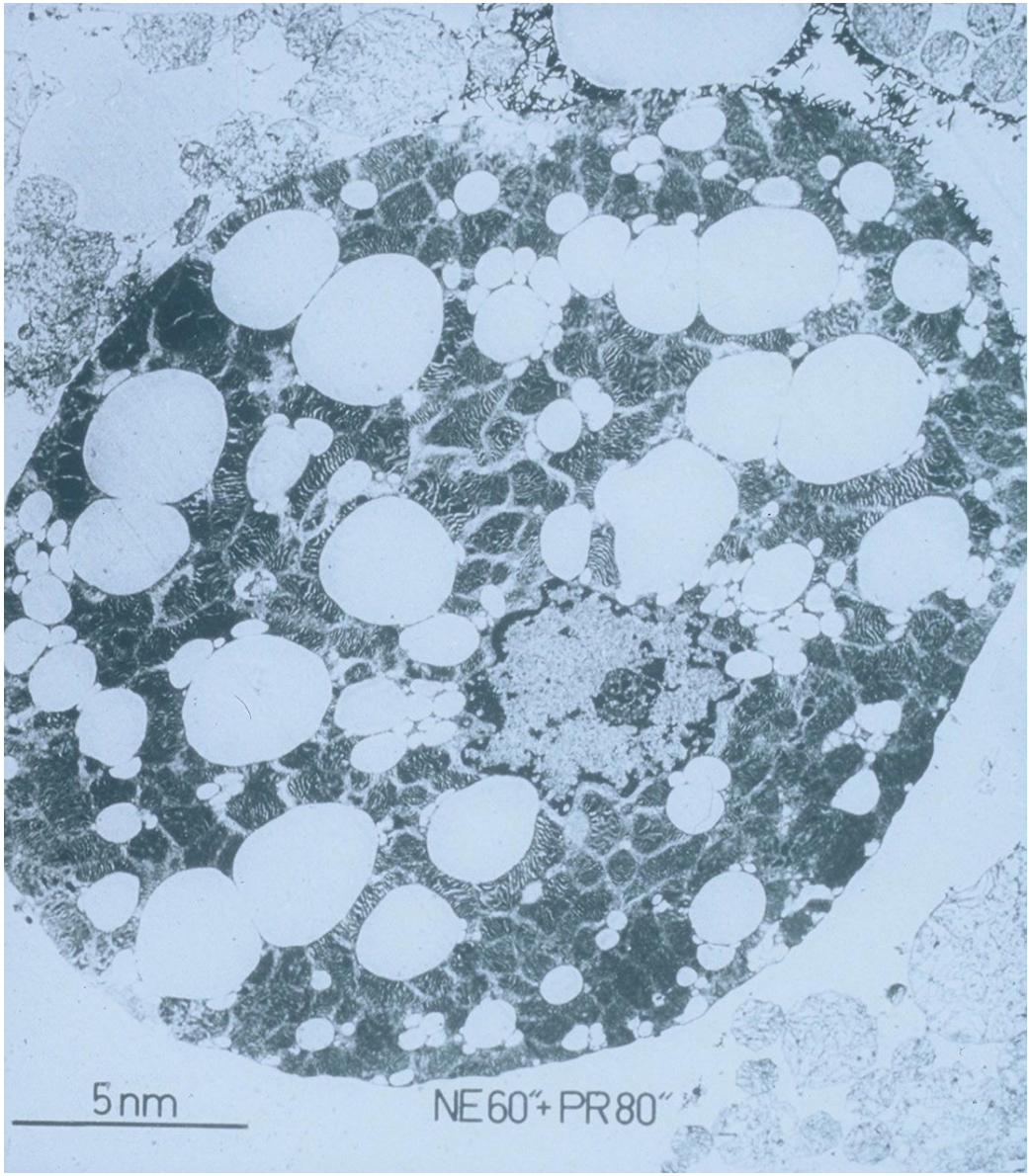


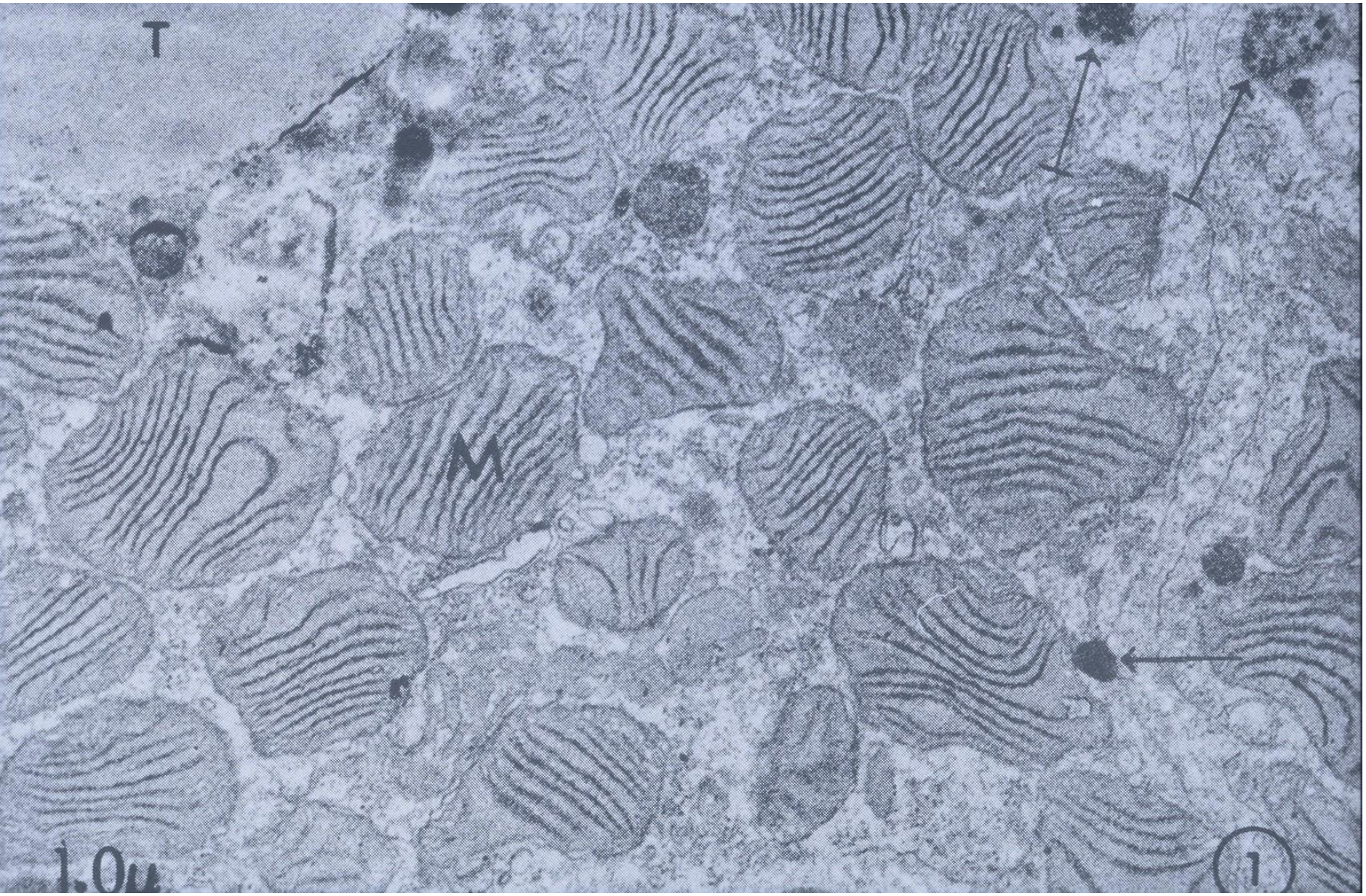
Classically: awakening from hibernation

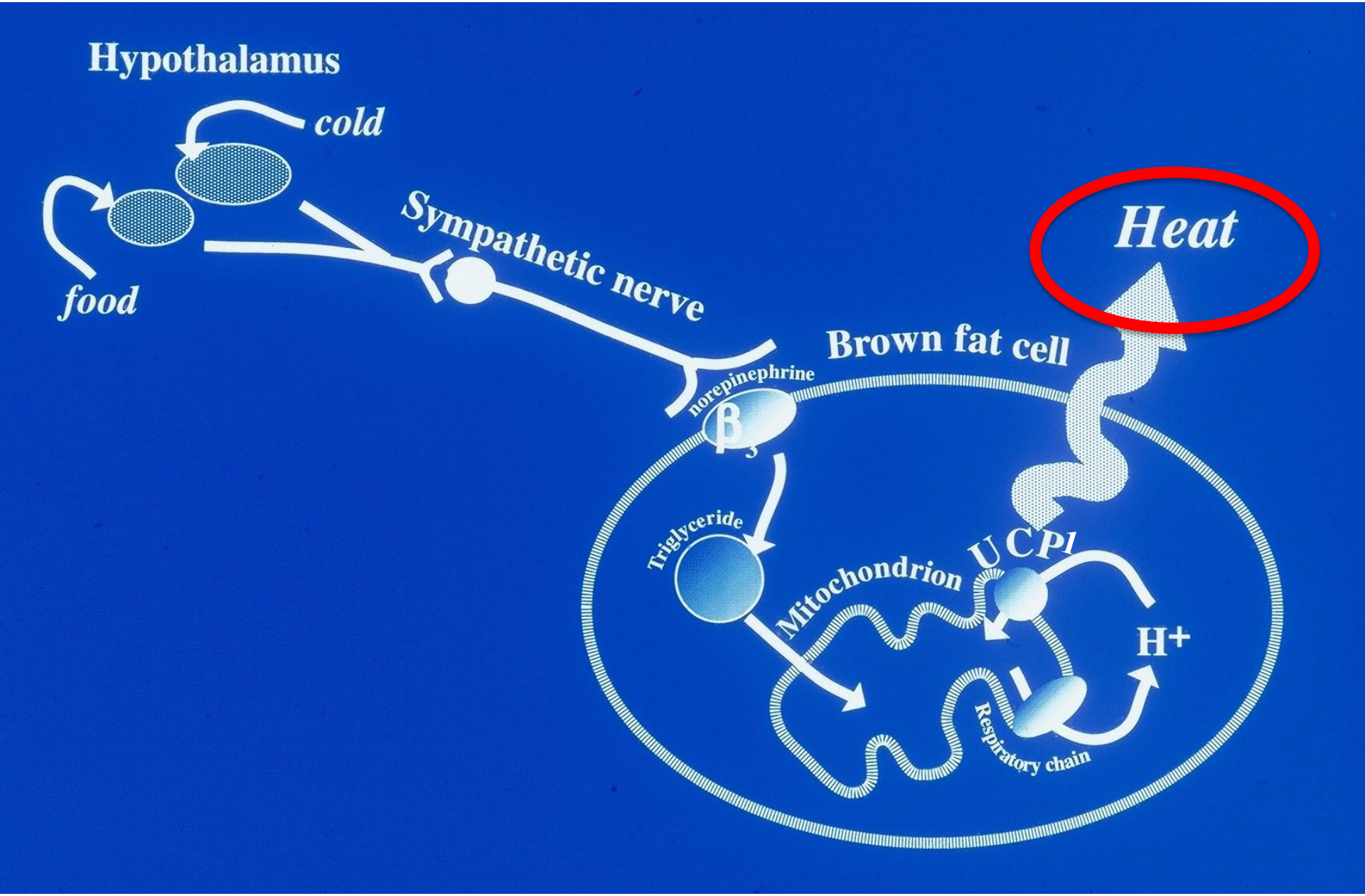


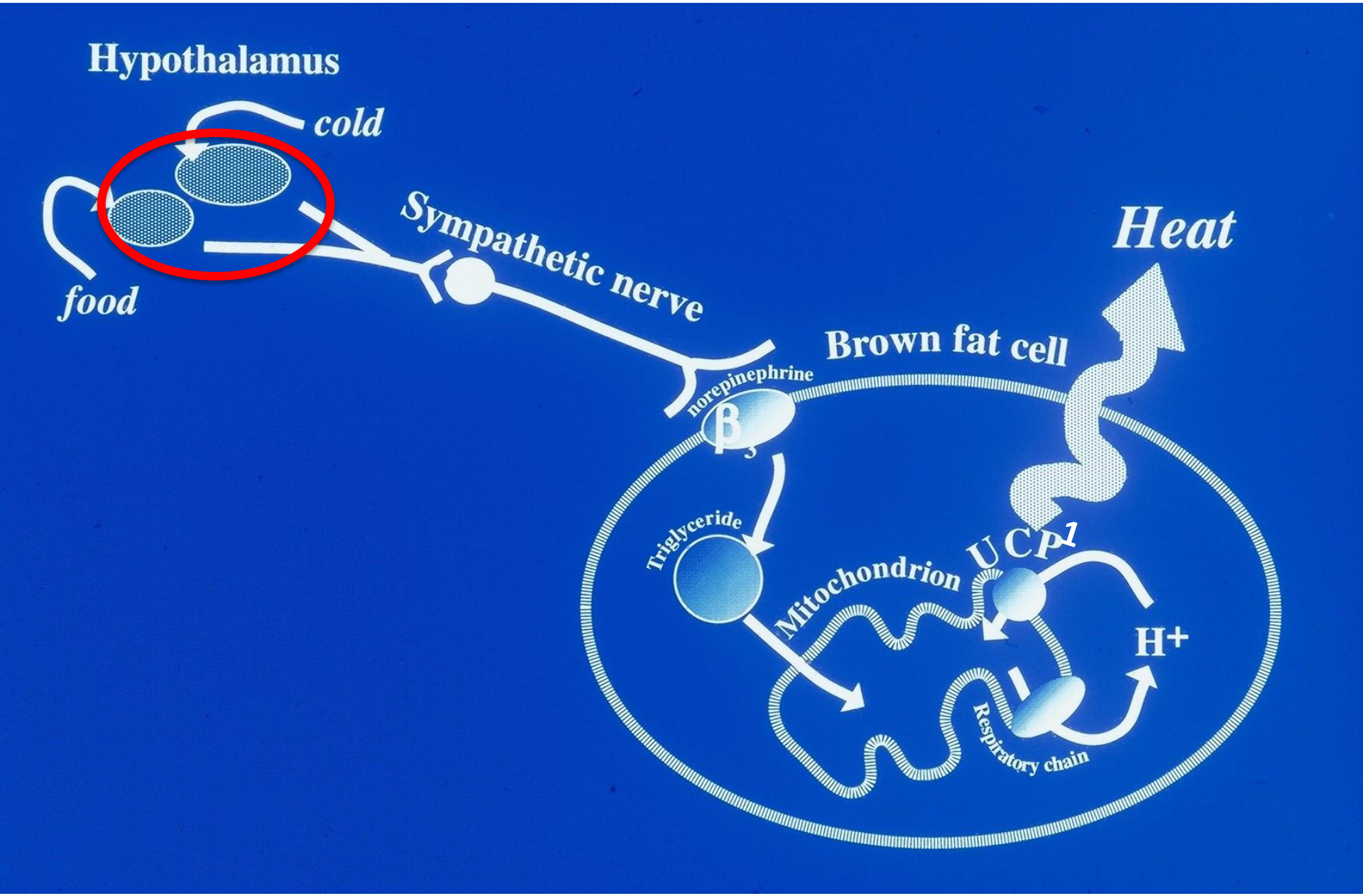
Brown adipose tissue

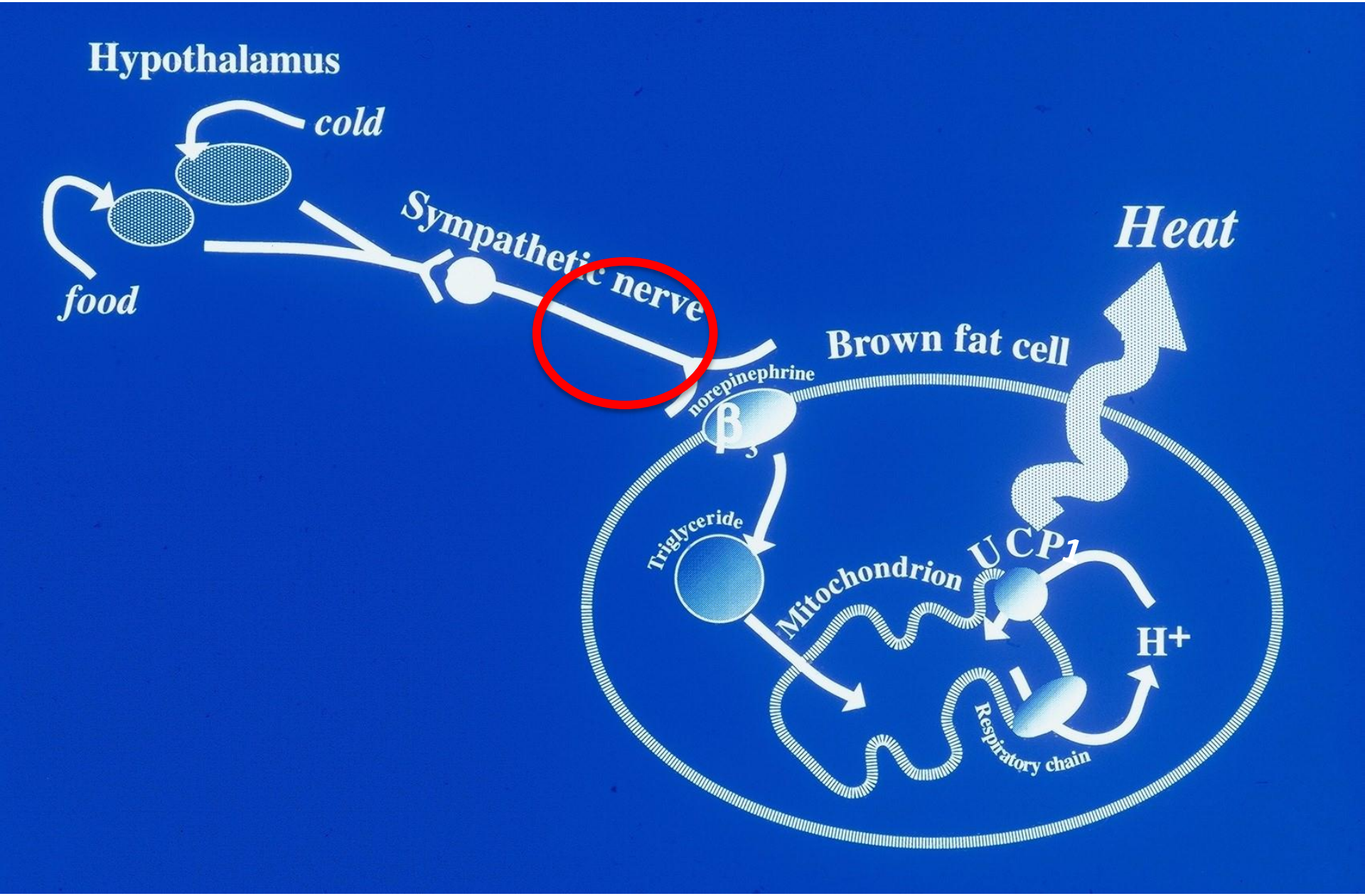


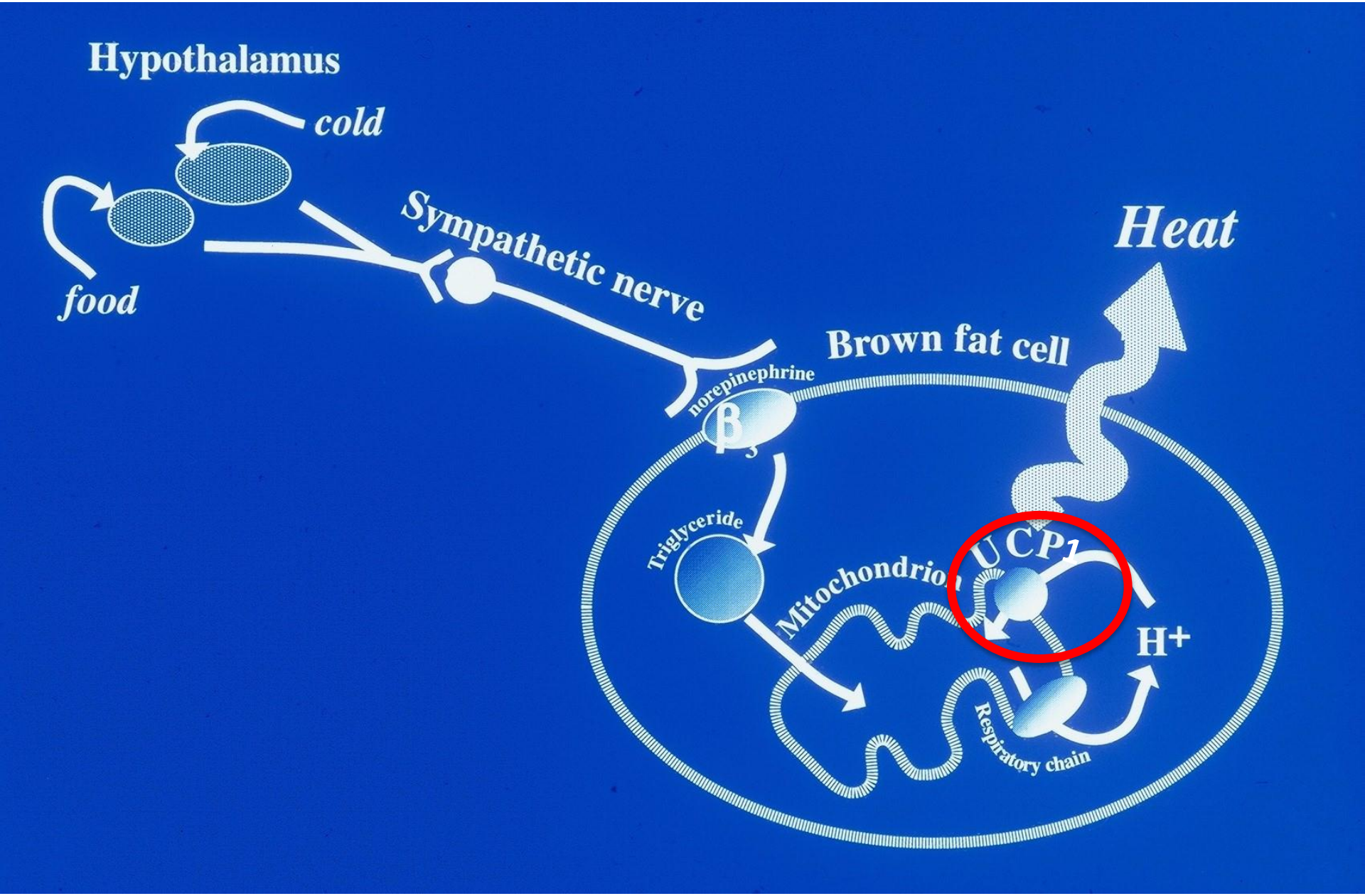

5nm
NE60″+PR80″

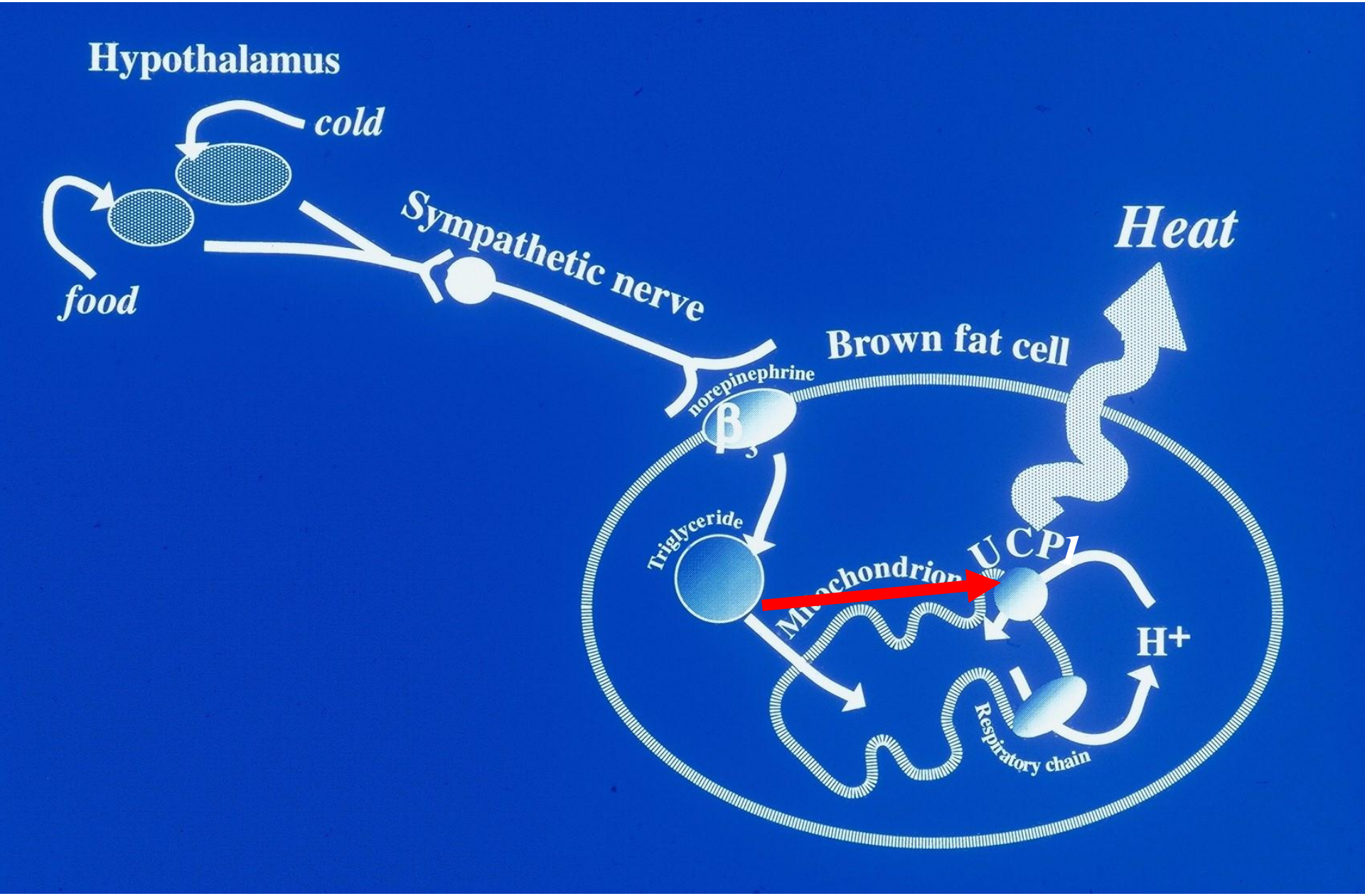

T
M
1.0μ
1


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
UCP1
H+
Respiratory chain

Worldwide increasing metabolic problems

Metabolic syndrome*:

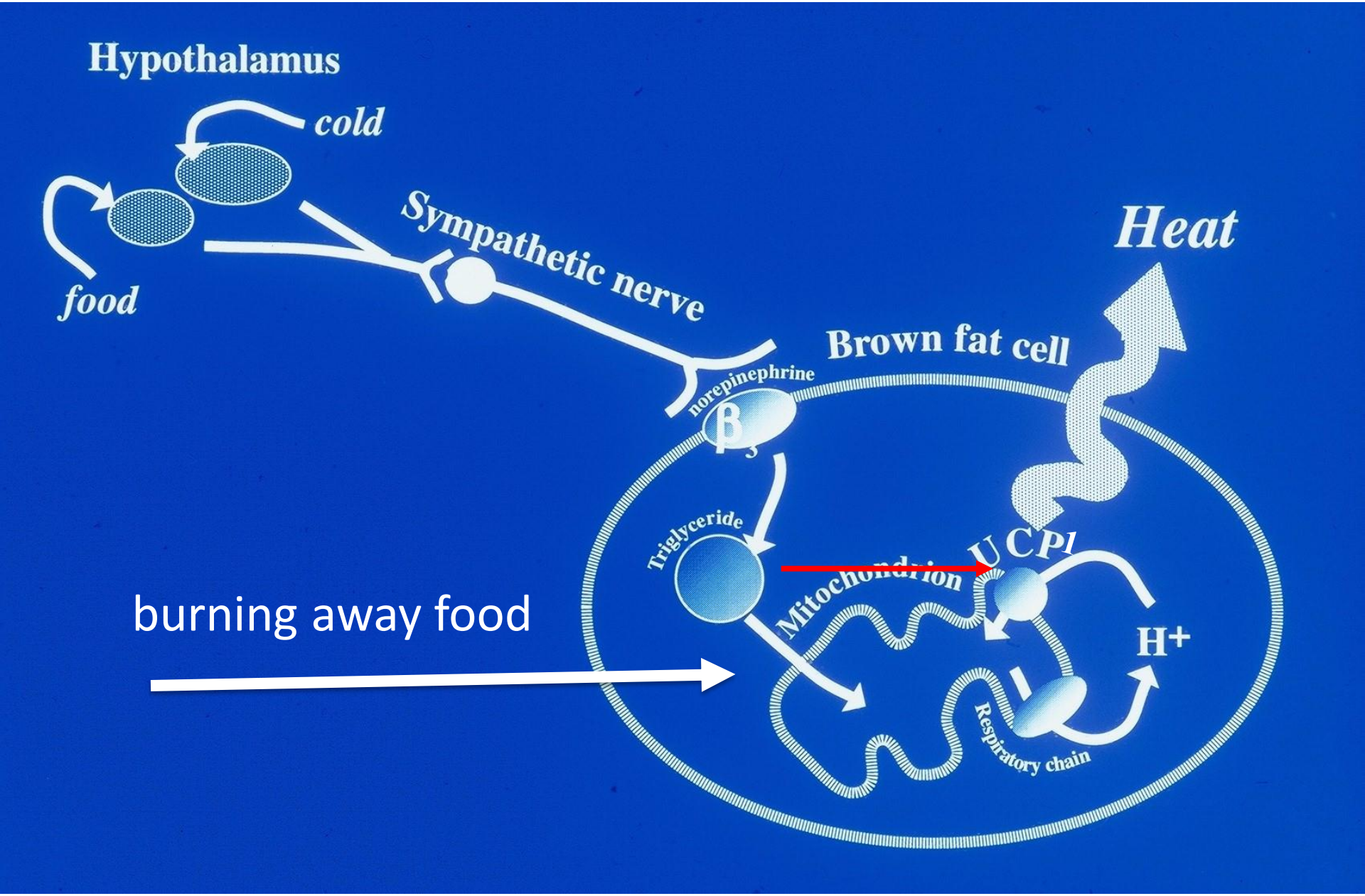
- **Central obesity**

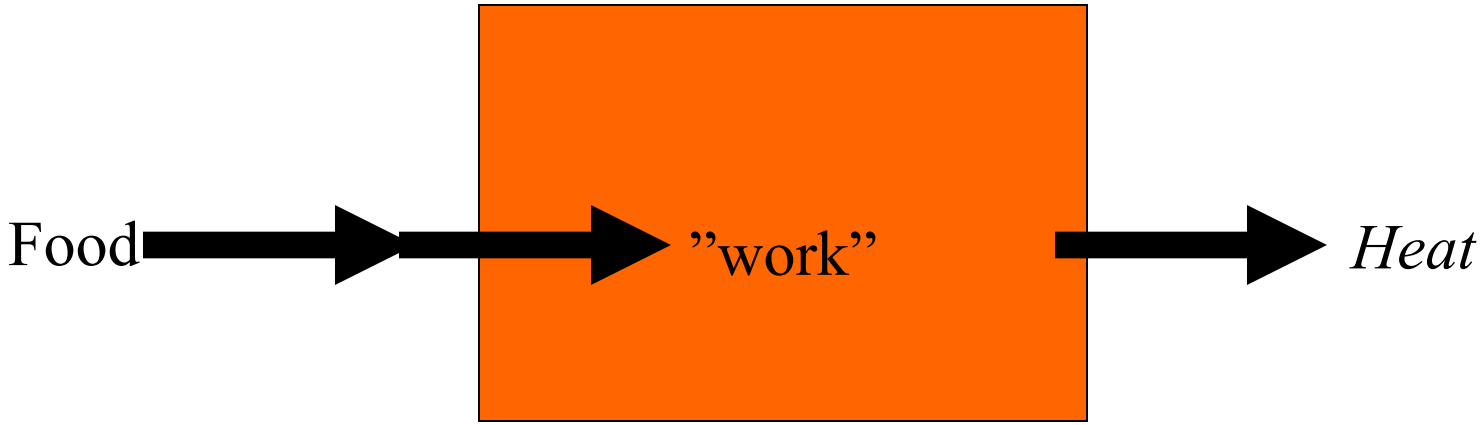
plus any two of the following four factors:

- **raised triglycerides level in blood**
- **reduced HDL cholesterol in blood**
- **raised blood pressure**
- **raised fasting plasma glucose or type 2 diabetes (insulin resistance)**

Active brown adipose tissue has the capacity to modulate most of above parameters

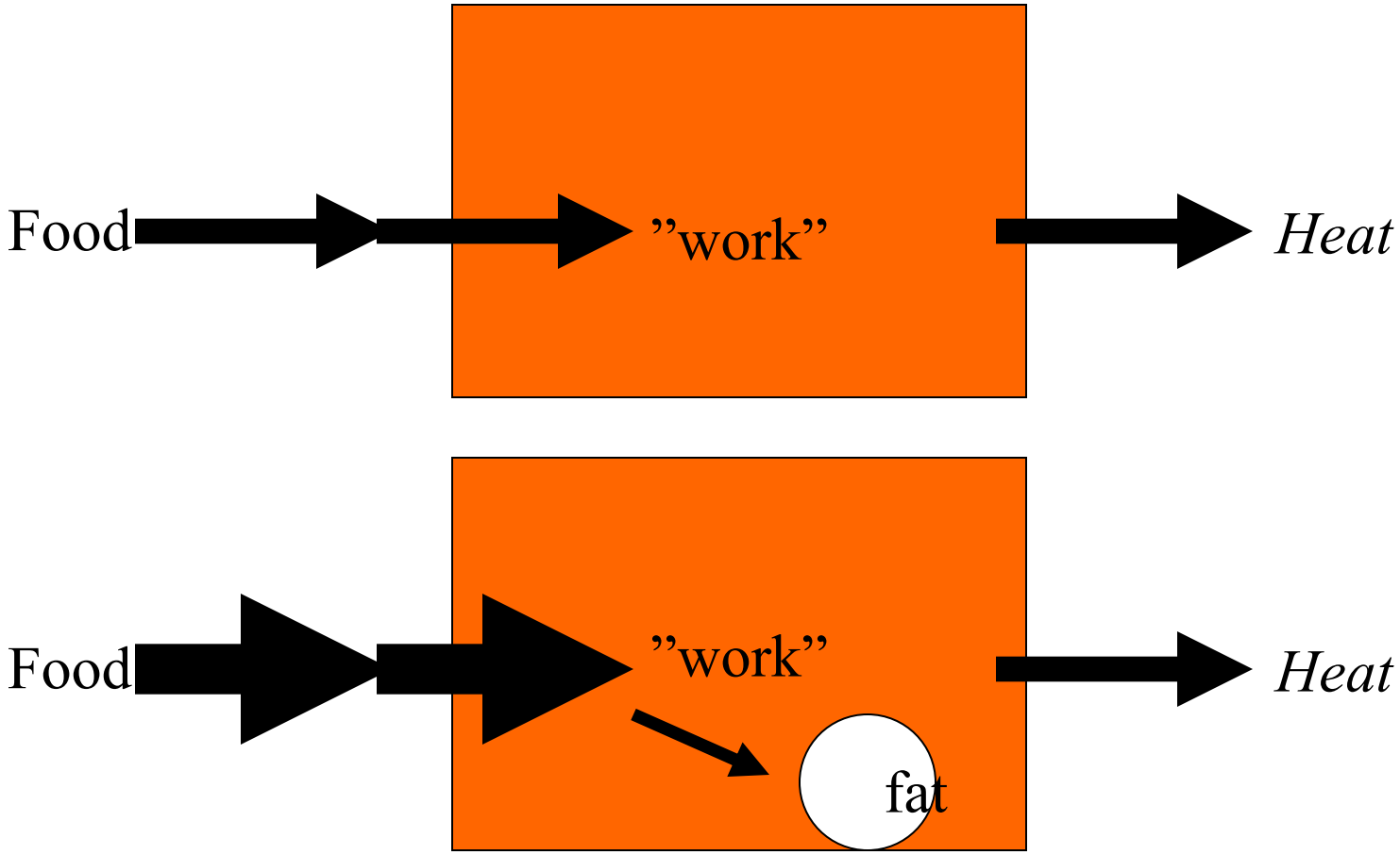
* newest IDF definition

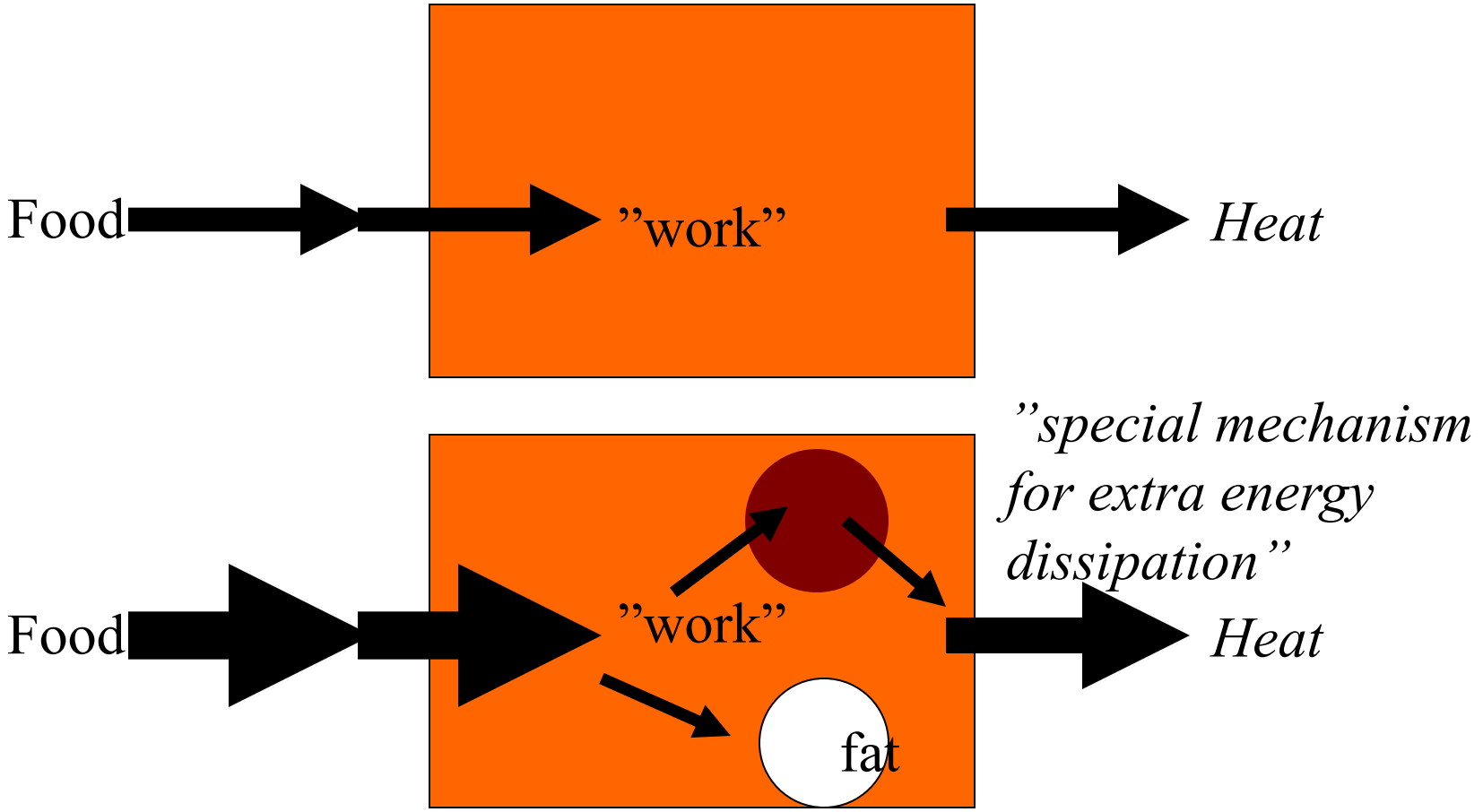

Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain
burning away food

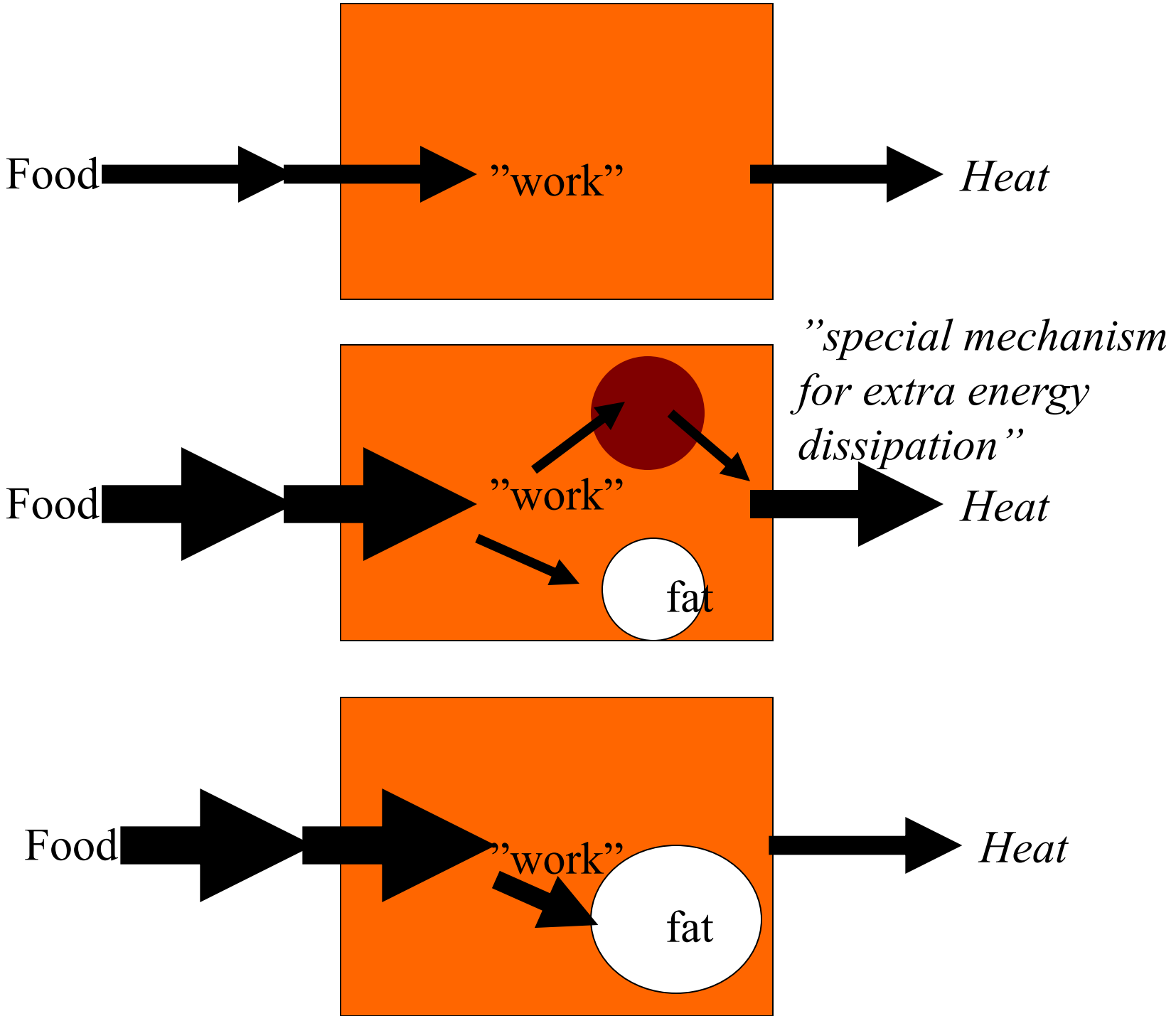

Food
”work”
Heat

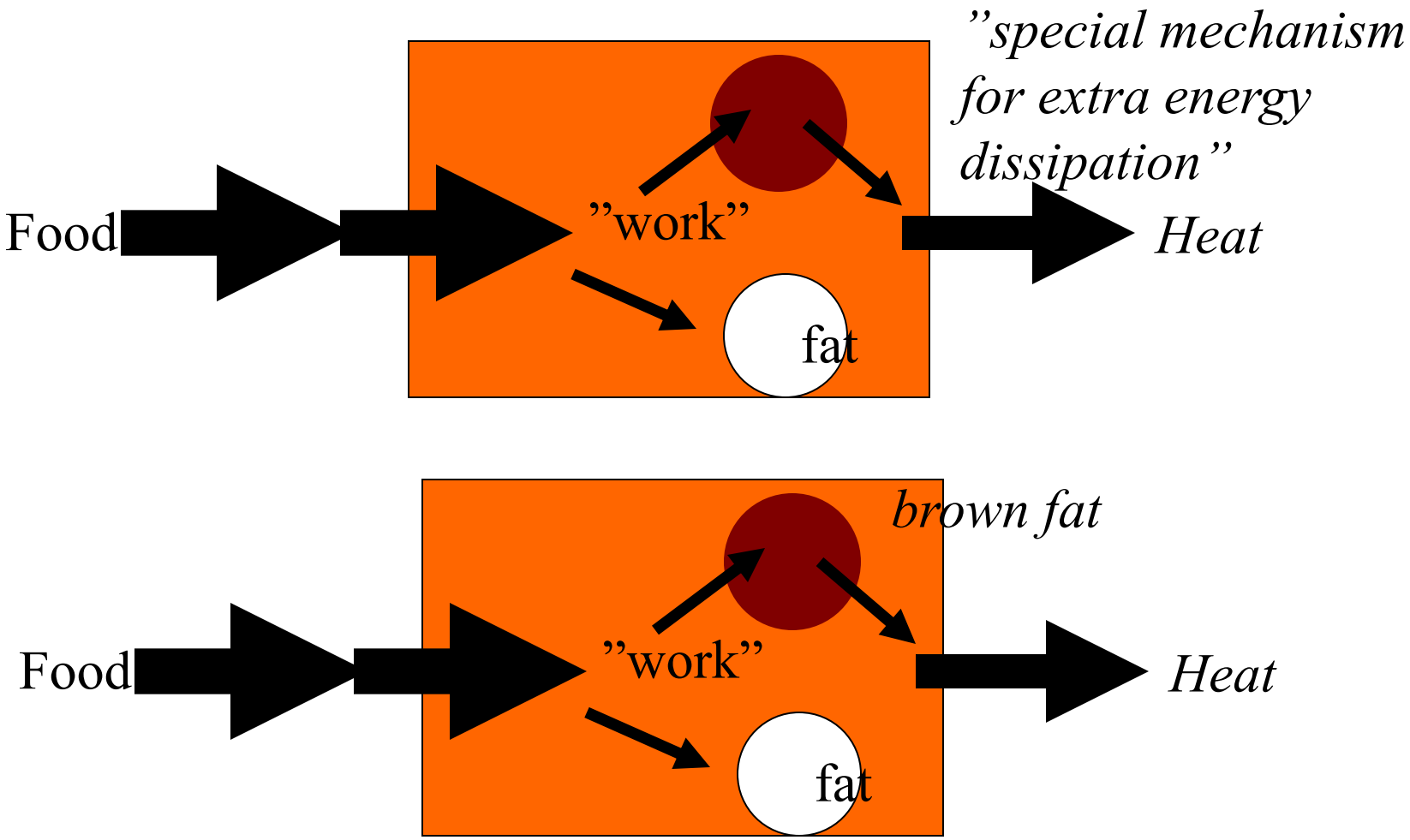
we can abstain - but what if we eat?

we can abstain - but what if we eat?


Food
”work”
Heat
Food
”work”
fat
Heat


Food
”work”
Heat
”special mechanism for extra energy dissipation”
Food
”work”
Heat
fat


Food
”work”
Heat
”special mechanism for extra energy dissipation”
Food
”work”
Heat
fat
Food
”work”
Heat
fat



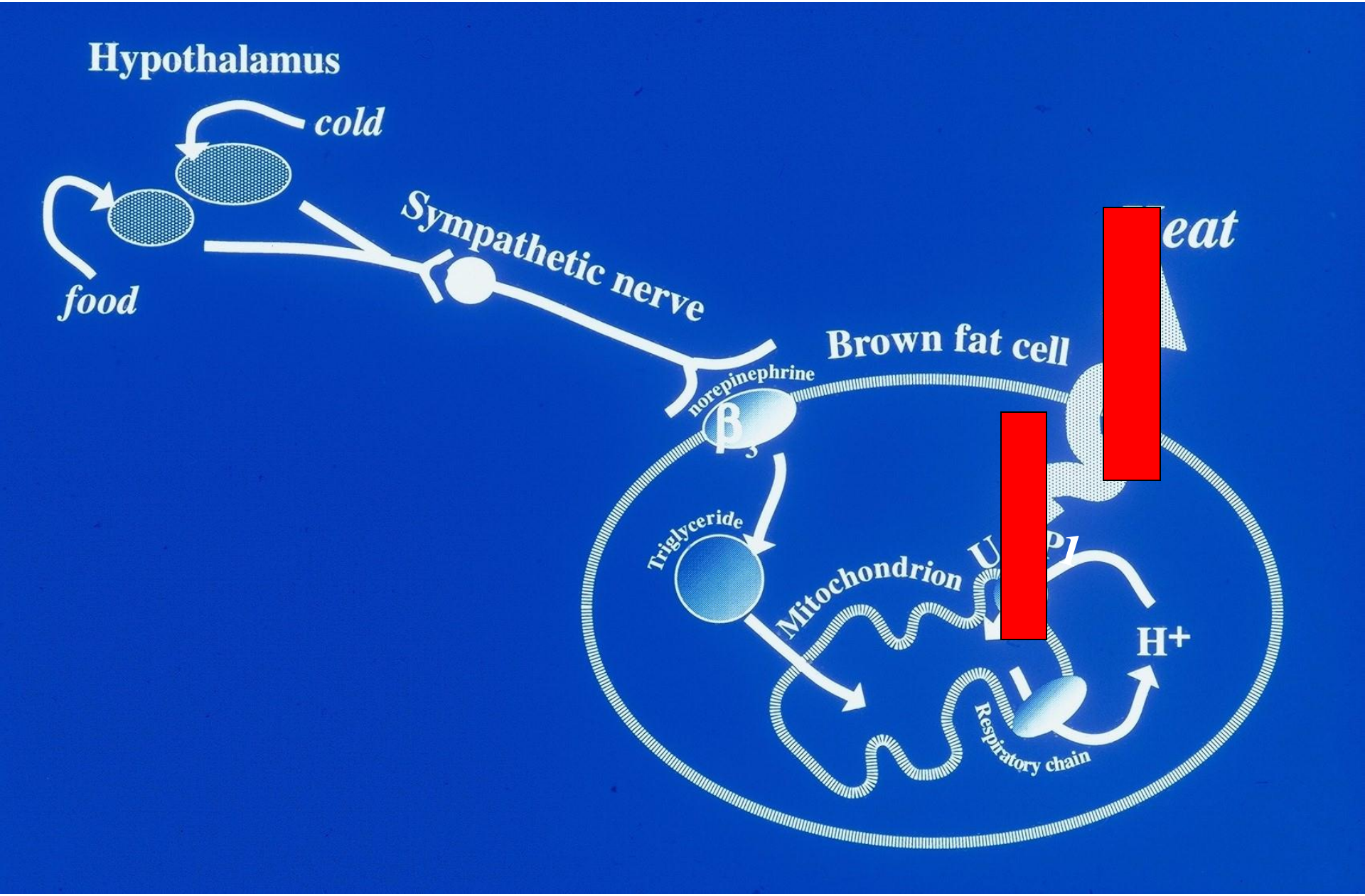
- such a special mechanism exists (diet-induced thermogenesis)

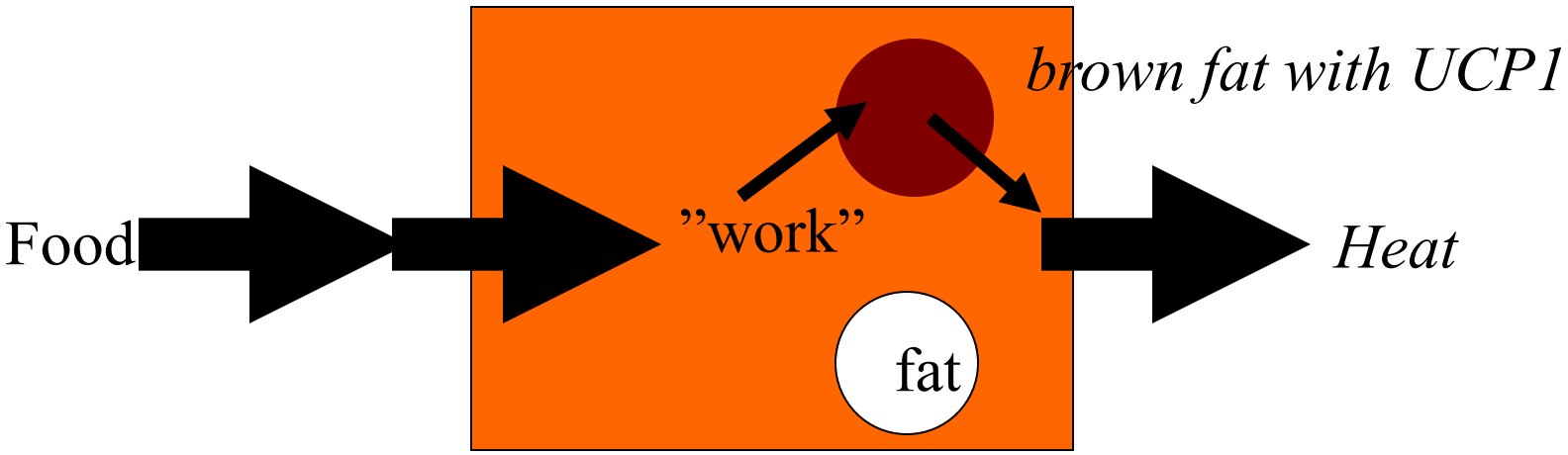
- and that it is entirely located to brown adipose tissue

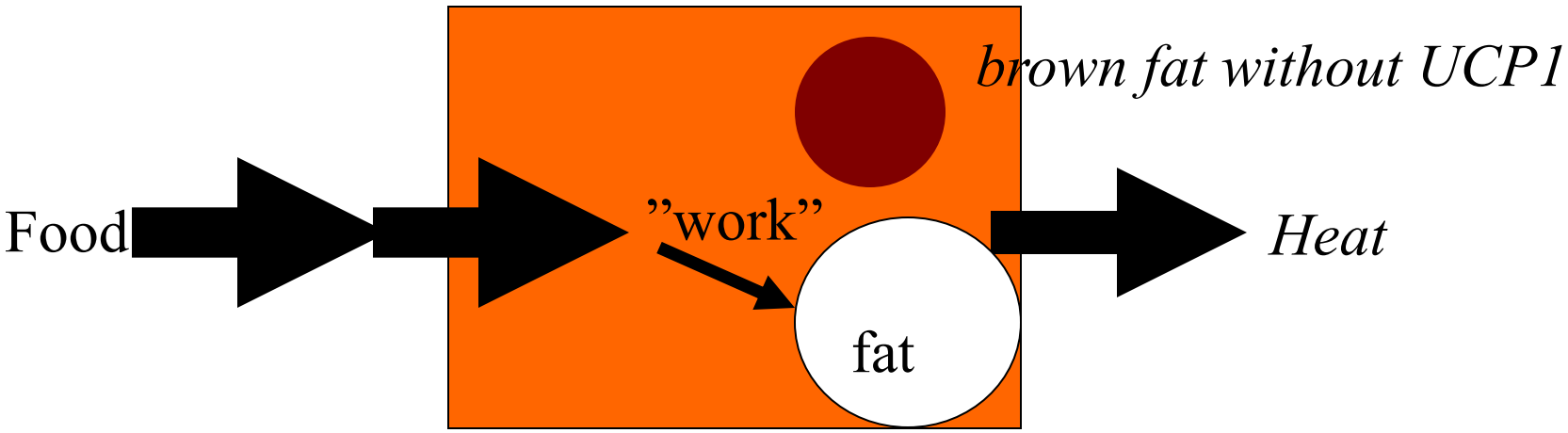
What are the consequences

of lack of

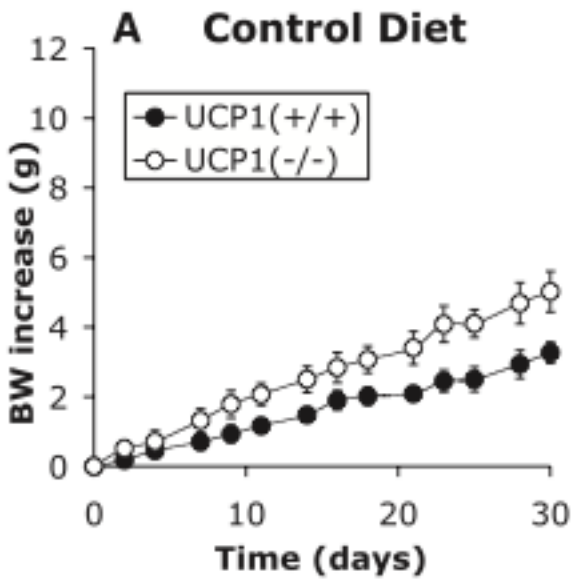
brown fat thermogenesis?

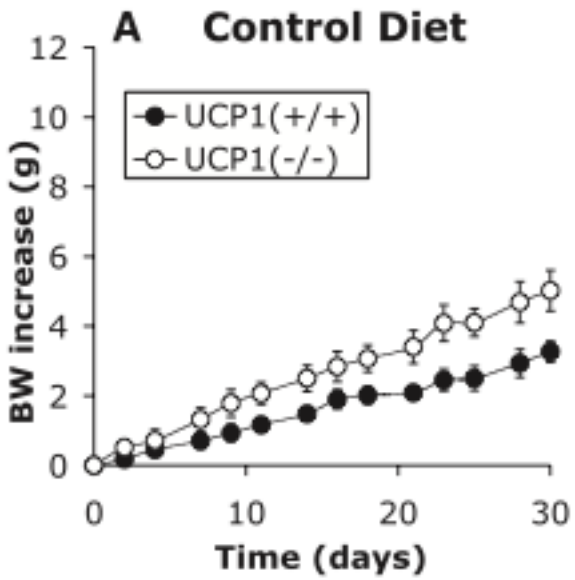

Hypothalamus
cold
food
Sympathetic nerve
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
H+
Respiratory chain

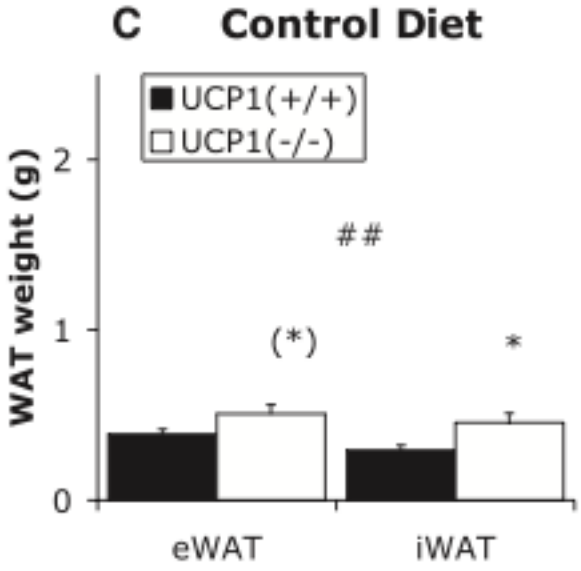

brown fat with UCP1
Food
”work”
Heat
fat



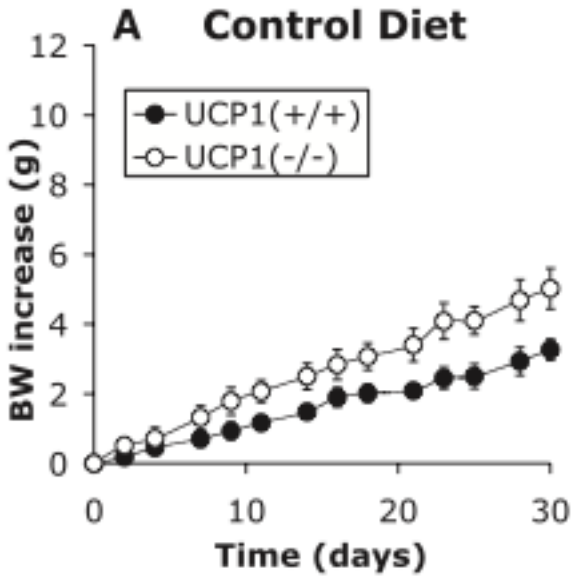
Thus, animals/humans without UCP1
should become obese

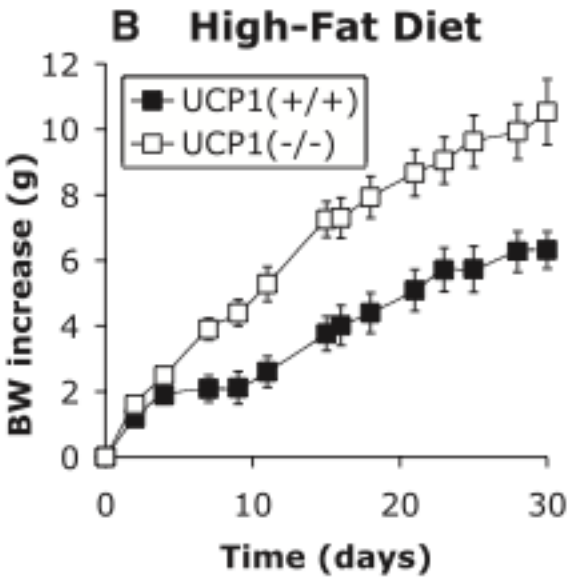

A Control Diet
UCP1(+/+)
UCP1(-/-)
BW increase (g)
Time (days)
0
2
4
6
8
10
12
0
10
20
30

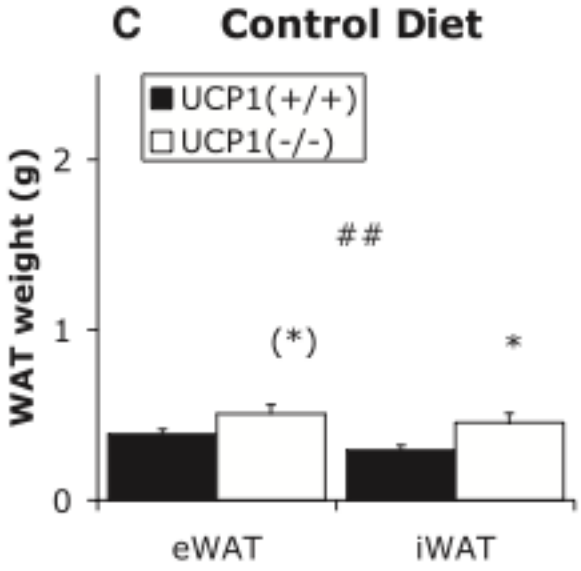

A Control Diet
BW increase (g)
Time (days)
UCP1(+/+)
UCP1(-/-)
0
2
4
6
8
10
12
0
10
20
30

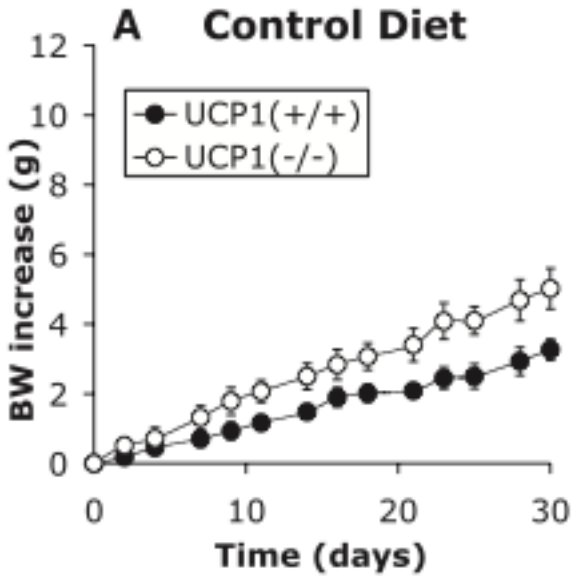

C Control Diet
WAT weight (g)
UCP1(+/+)
UCP1(-/-)
##
(*)
*
0
1
2
eWAT
iWAT

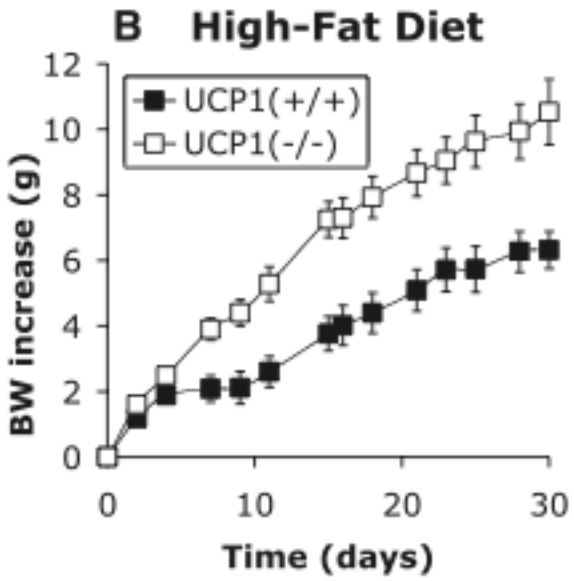
Effect of high fat diet


A Control Diet
UCP1(+/+)
UCP1(-/-)
BW increase (g)
Time (days)
0
2
4
6
8
10
12
0
10
20
30

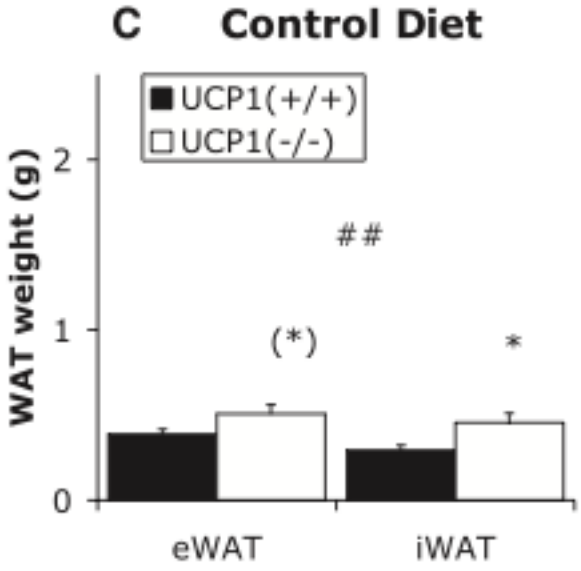

B High-Fat Diet
UCP1(+/+)
UCP1(-/-)
BW increase (g)
Time (days)
0
2
4
6
8
10
12
0
10
20
30

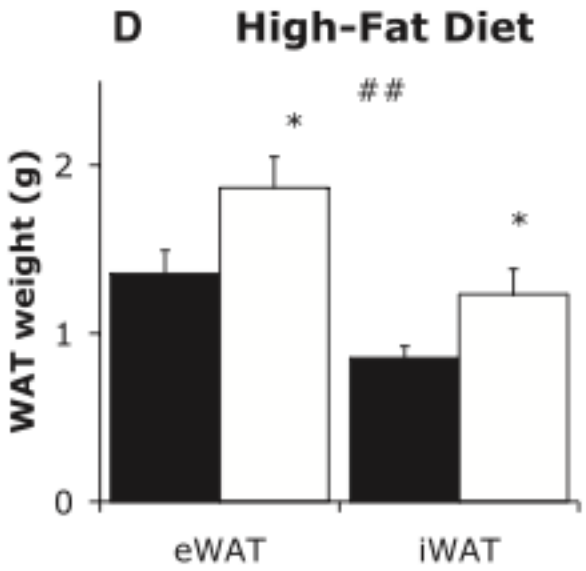

C Control Diet
UCP1(+/+)
UCP1(-/-)
WAT weight (g)
##
(*)
*
0
1
2
eWAT
iWAT

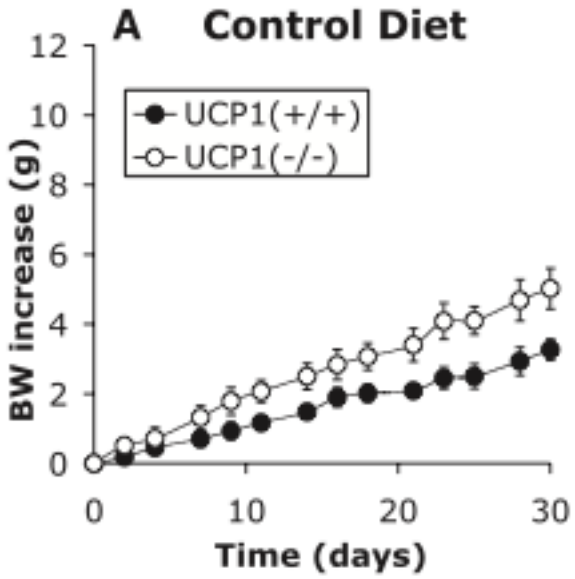


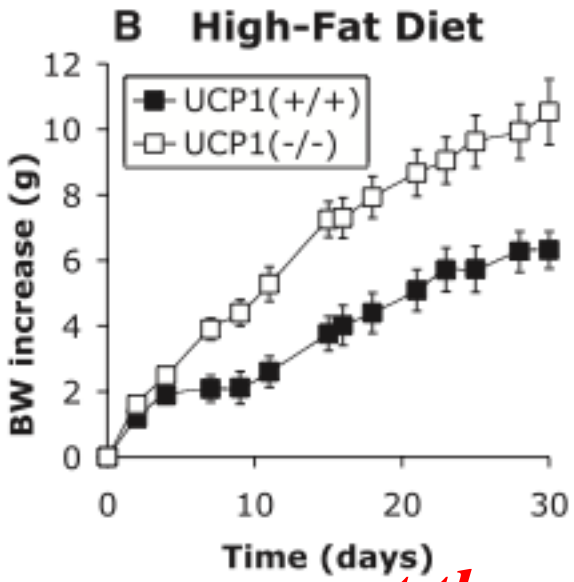


Without brown fat mice become fatter



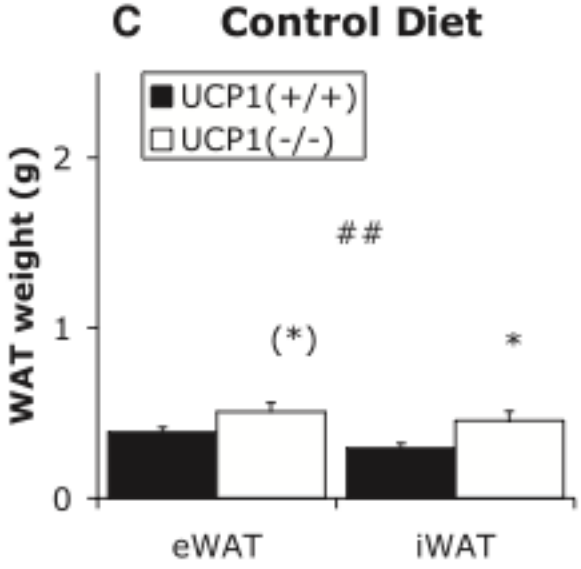


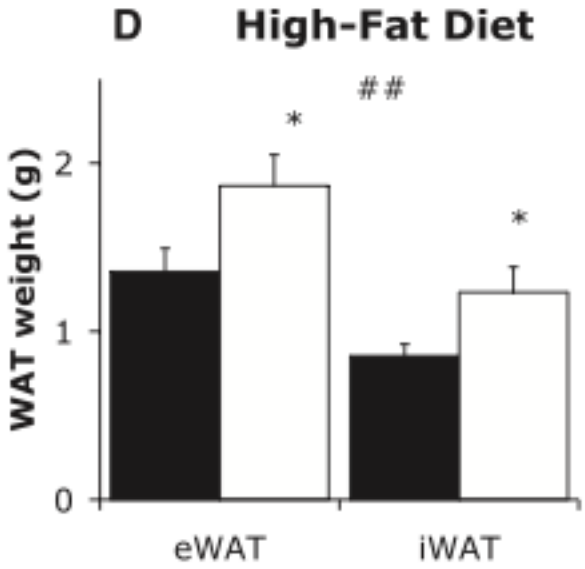




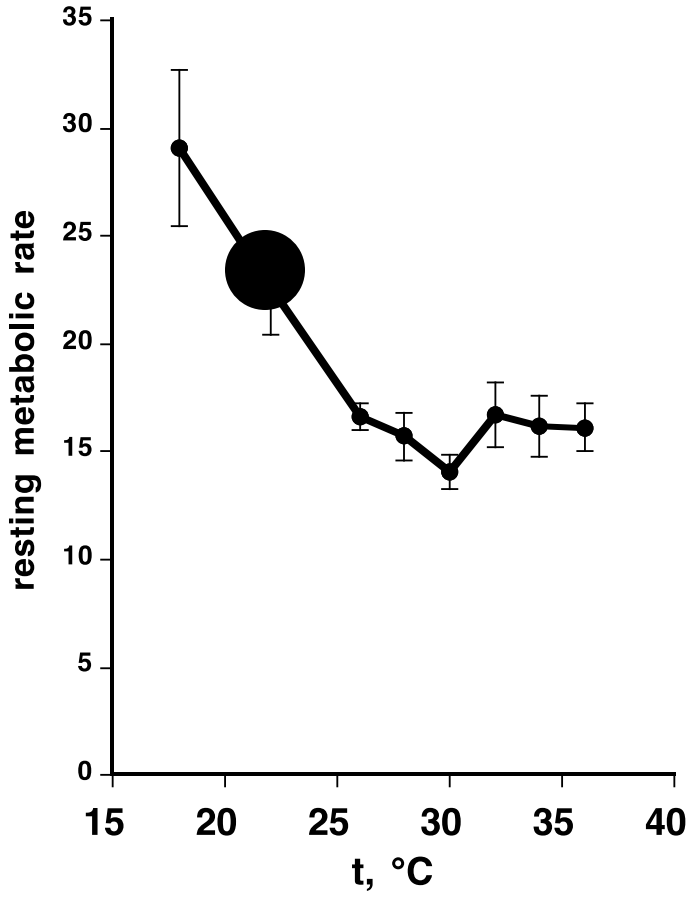
Without brown fat mice become fatter

at thermoneutrality!





”Normal” conditions impose a constant large metabolic stress on mice

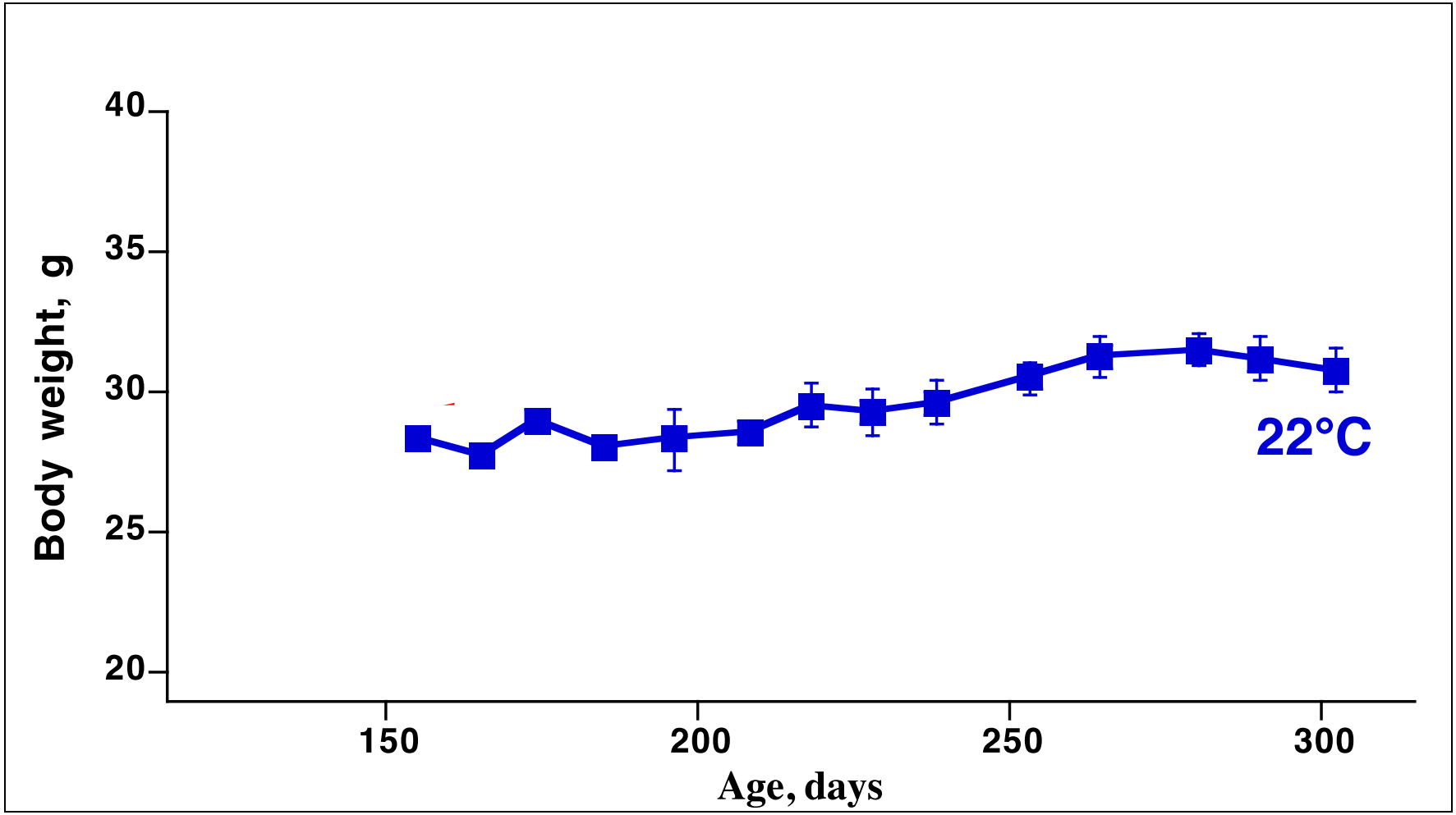


extra heat always needed under ”normal conditions”

basal metabolic rate

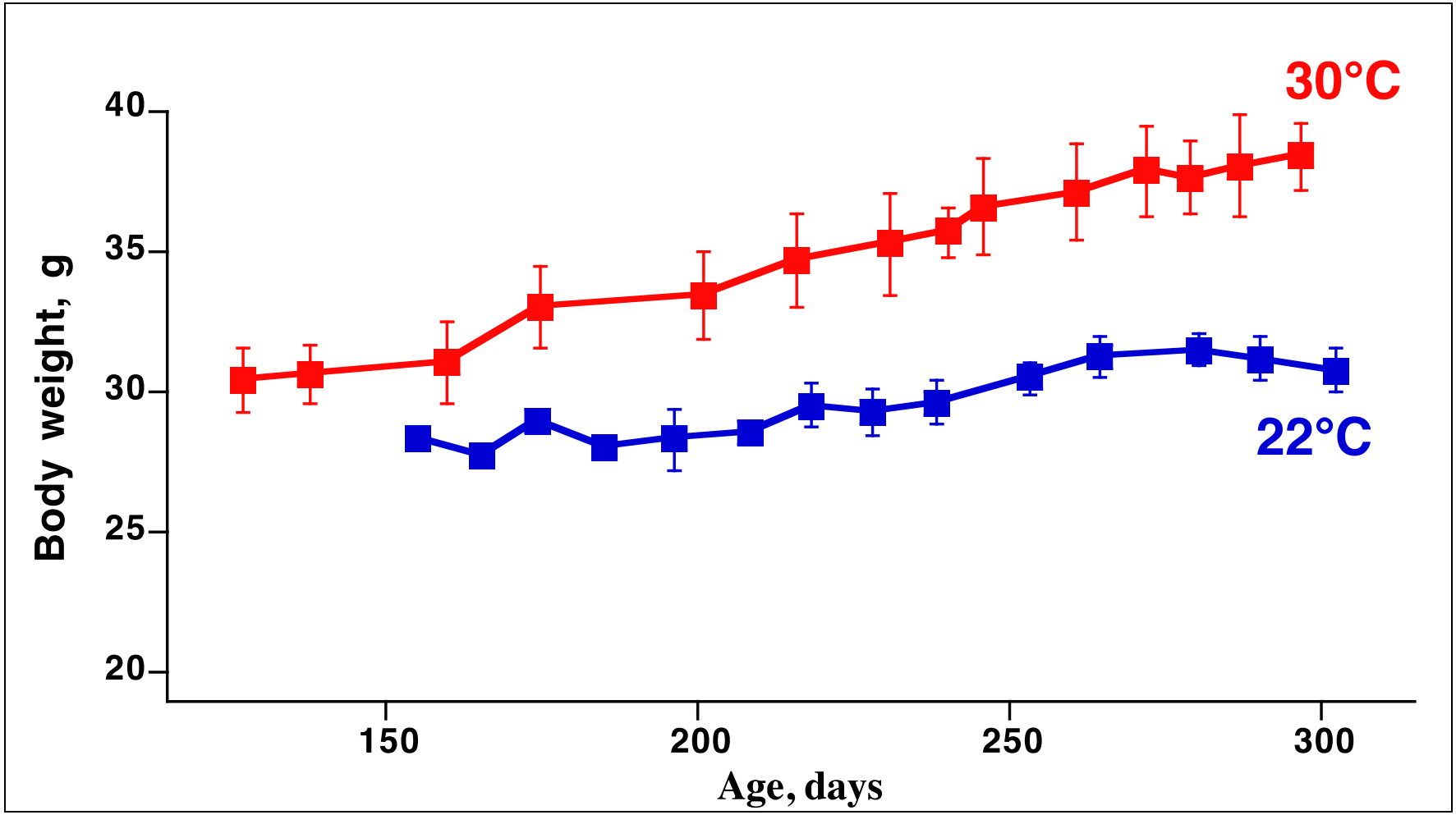
Body weight

wild-type mice



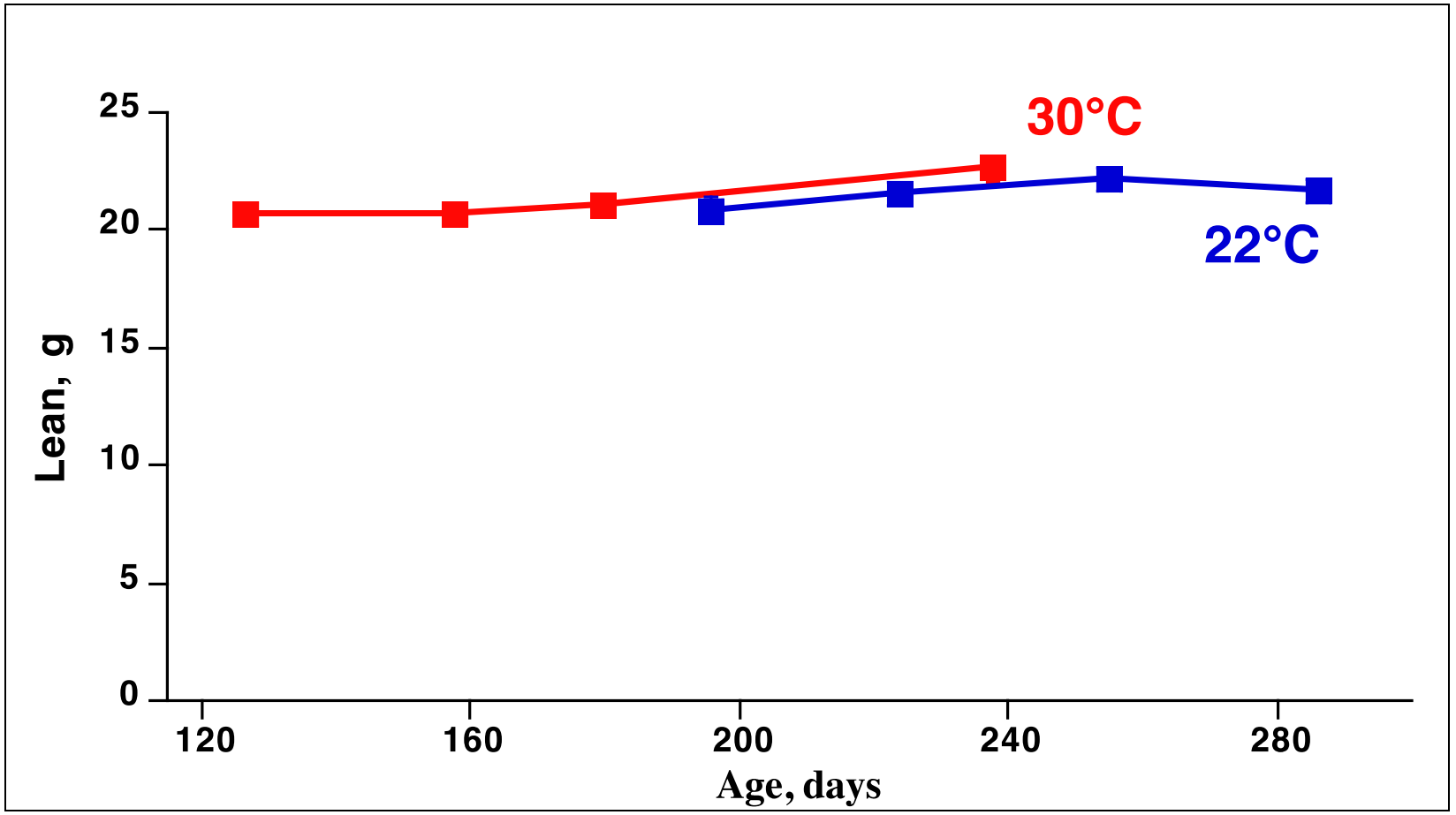
Body weight

wild-type mice



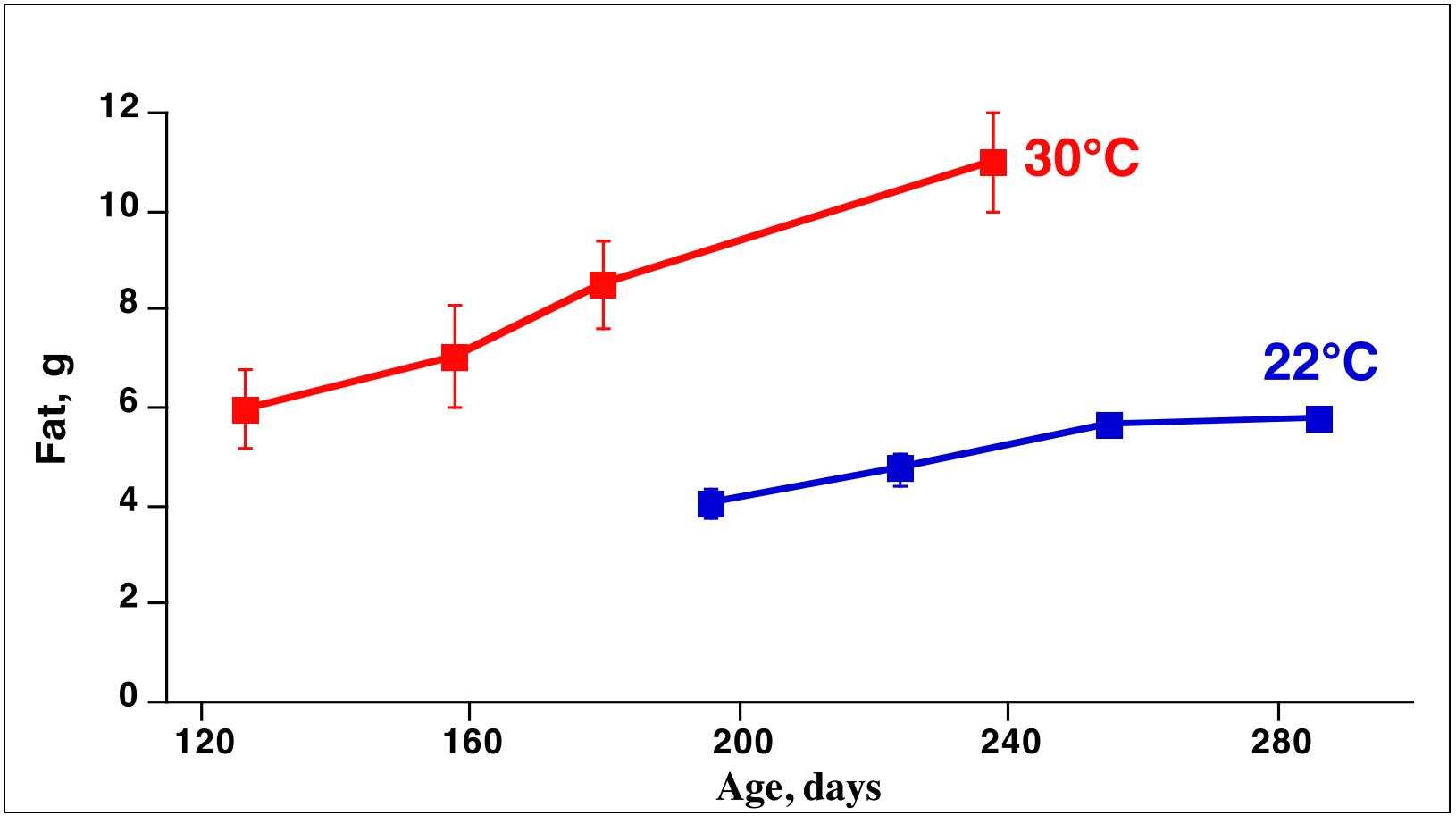
wild-type mice

No effect on lean mass:



wild-type mice

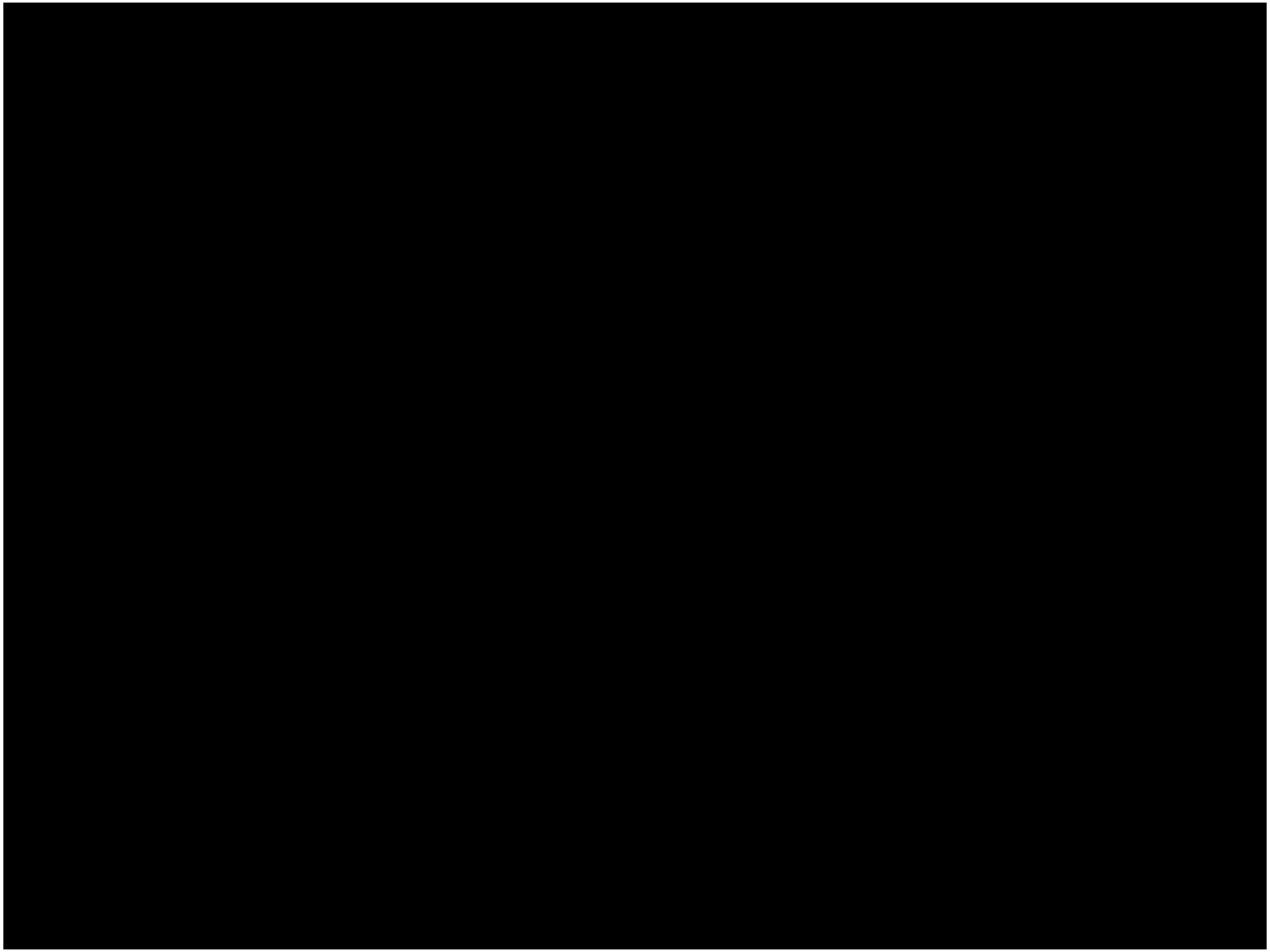
- so everything has to be fat accumulation:



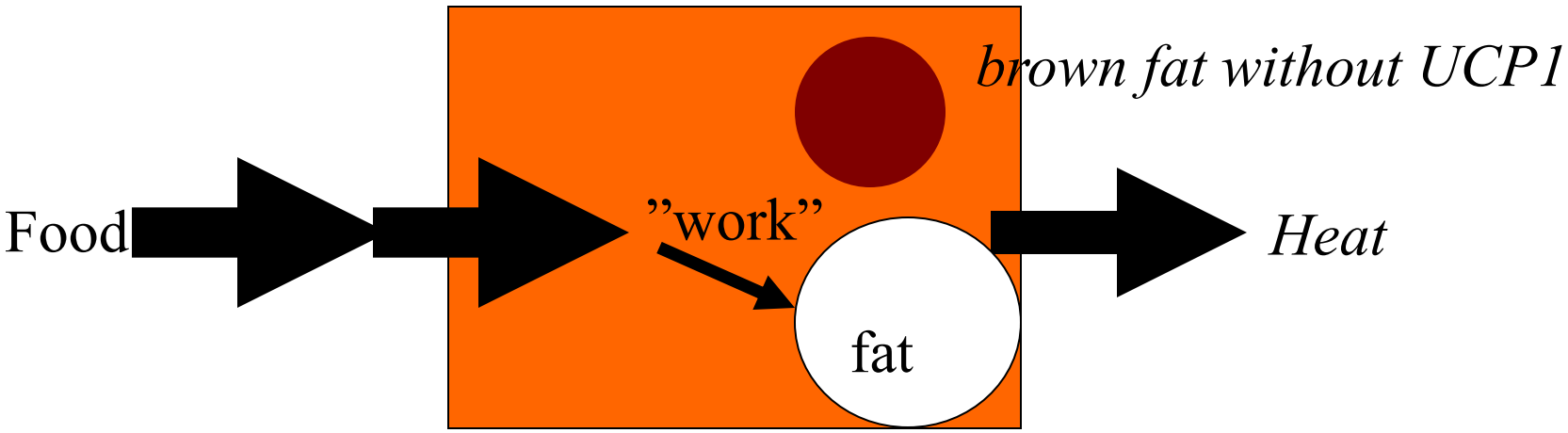
Thus, simply performing experiments
at a temperature without thermal stress
results in a large change in metabolic phenotype....

- the 30° C-phenotype of mice is probably
a better model of adult man....

("humanized" temperature conditions
have at least as large effects on metabolism
as many molecular manipulations)

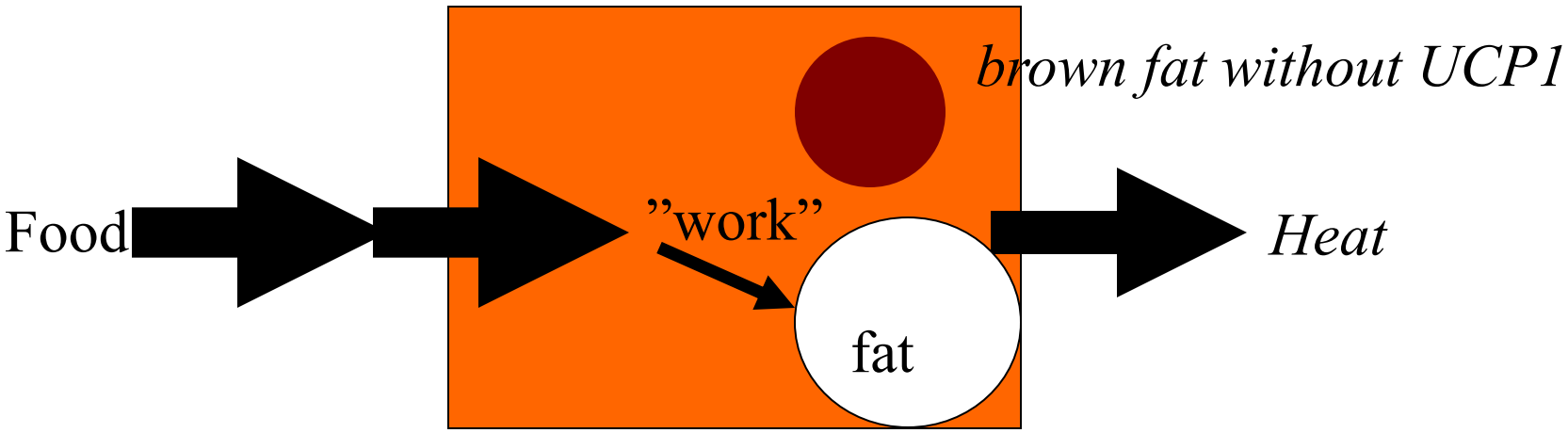


Bautista//Julius 2007



Thus, animals without UCP1
become obese!

i.e. brown fat protects against obesity



Thus, animals without UCP1
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Worldwide increasing metabolic problems

Metabolic syndrome*:

- **Central obesity**

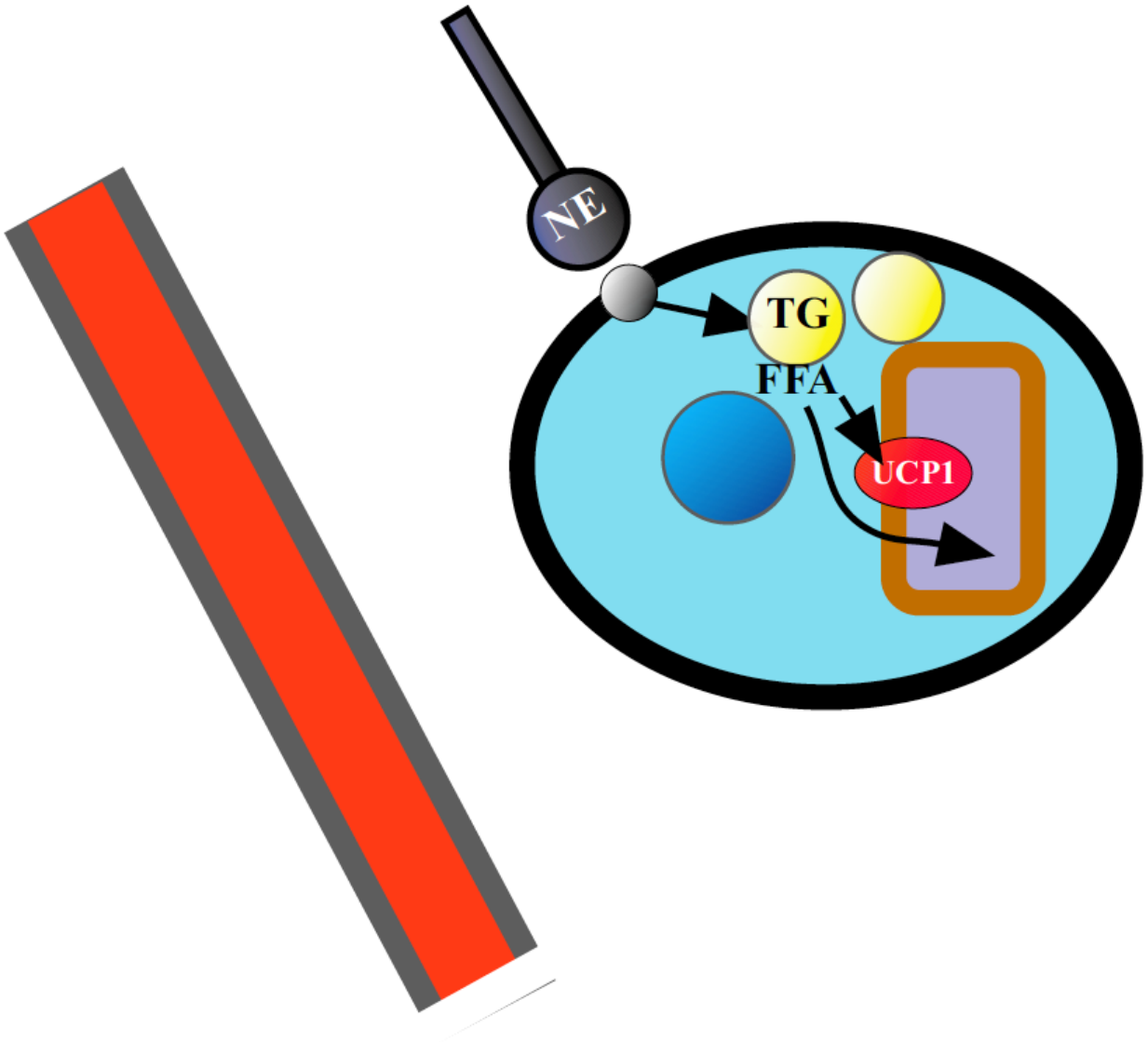
plus any two of the following four factors:

- **raised triglycerides level in blood**
- **reduced HDL cholesterol in blood**
- **raised blood pressure**
- **raised fasting plasma glucose or type 2 diabetes (insulin resistance)**

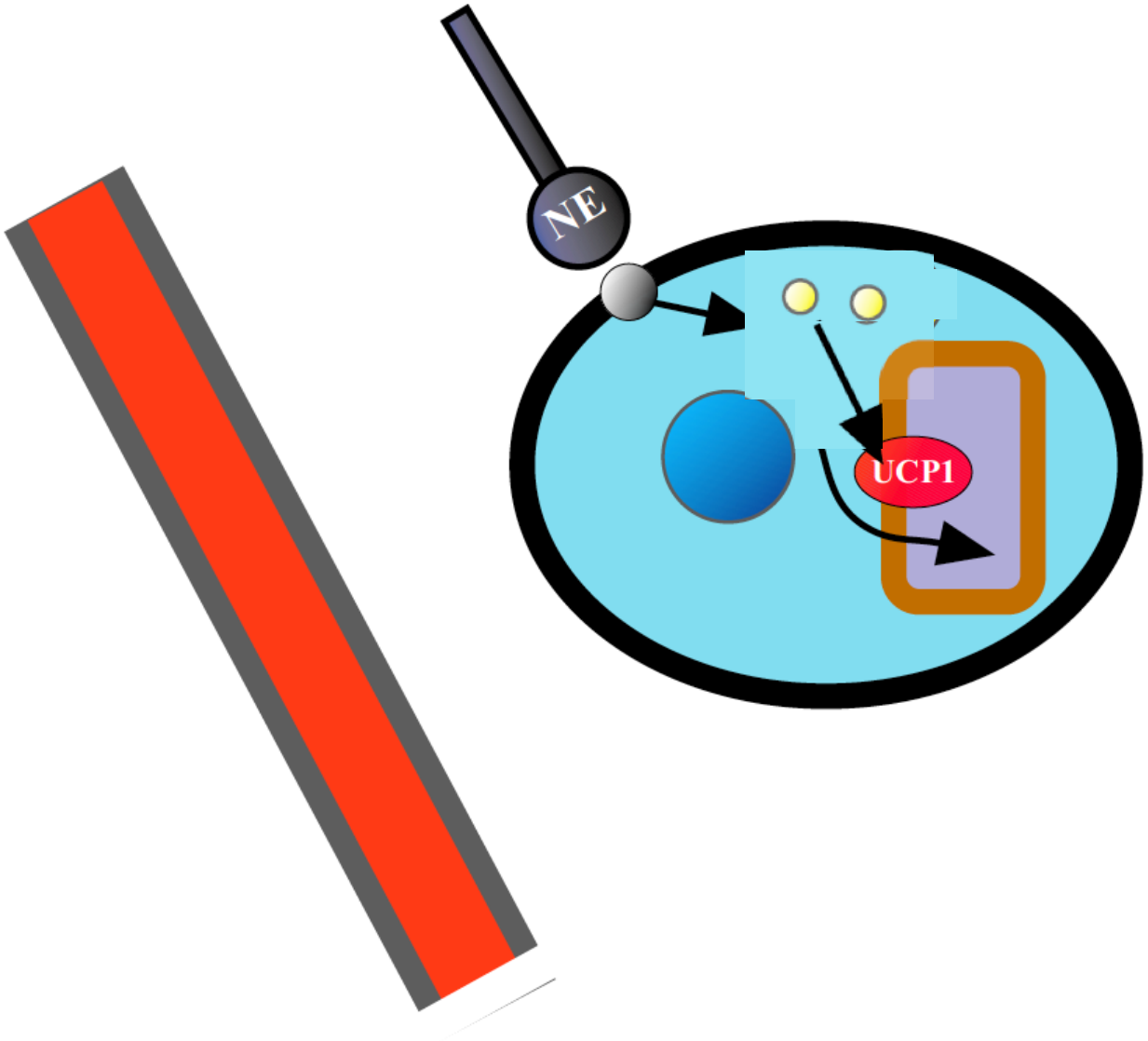
Active brown adipose tissue has the capacity to modulate most of above parameters

* newest IDF definition

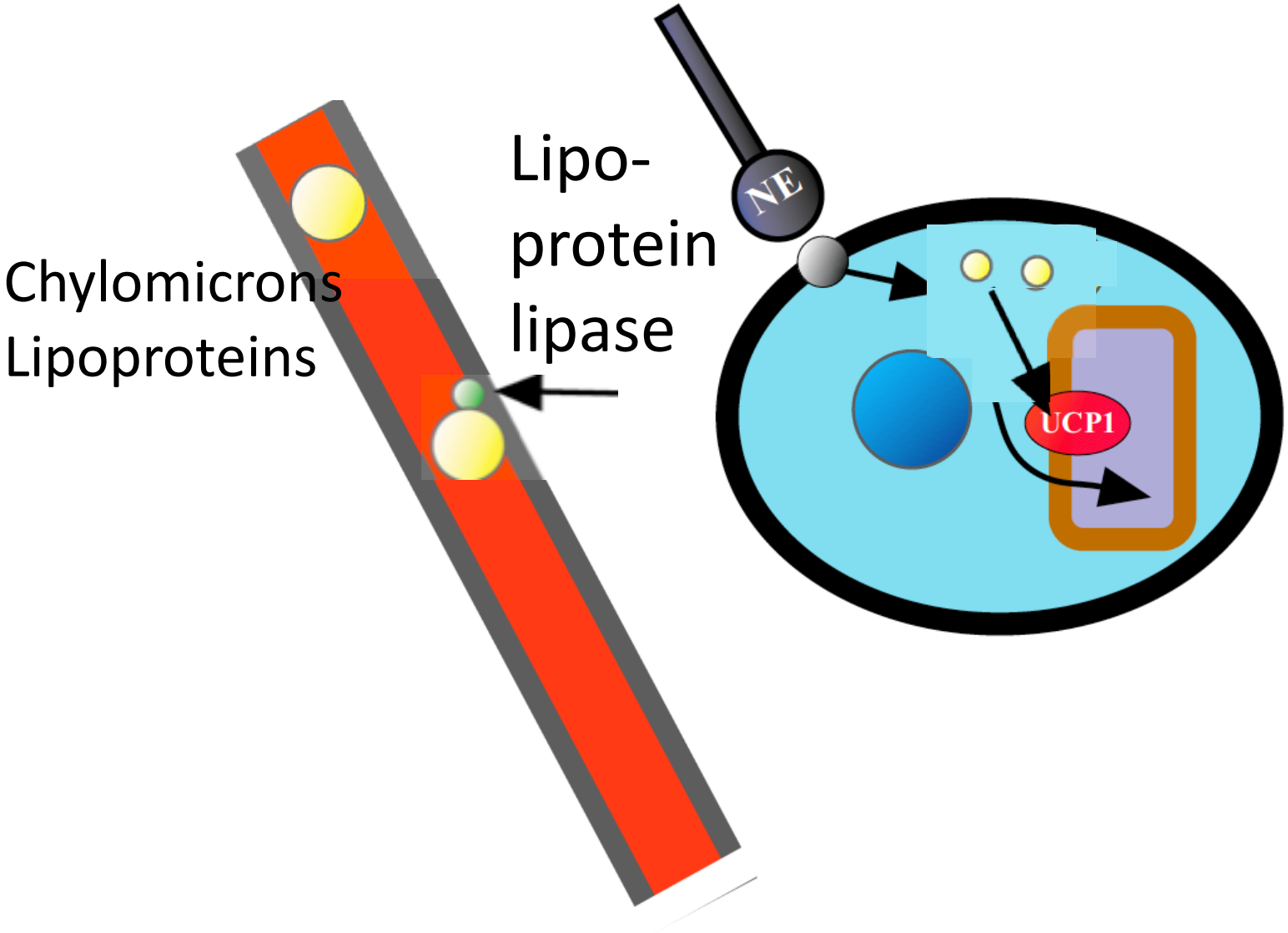
Initial activation



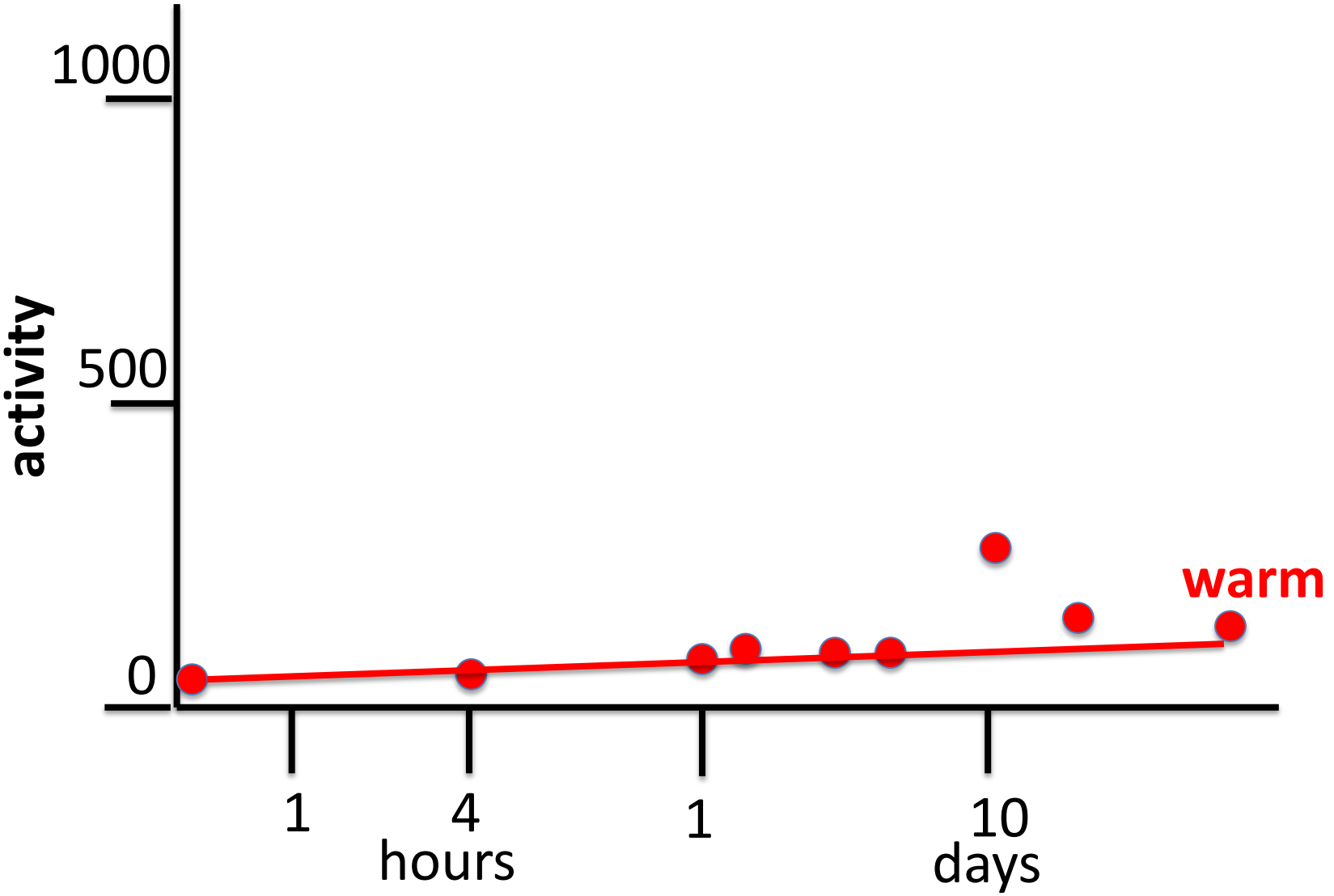
After some hours of activation



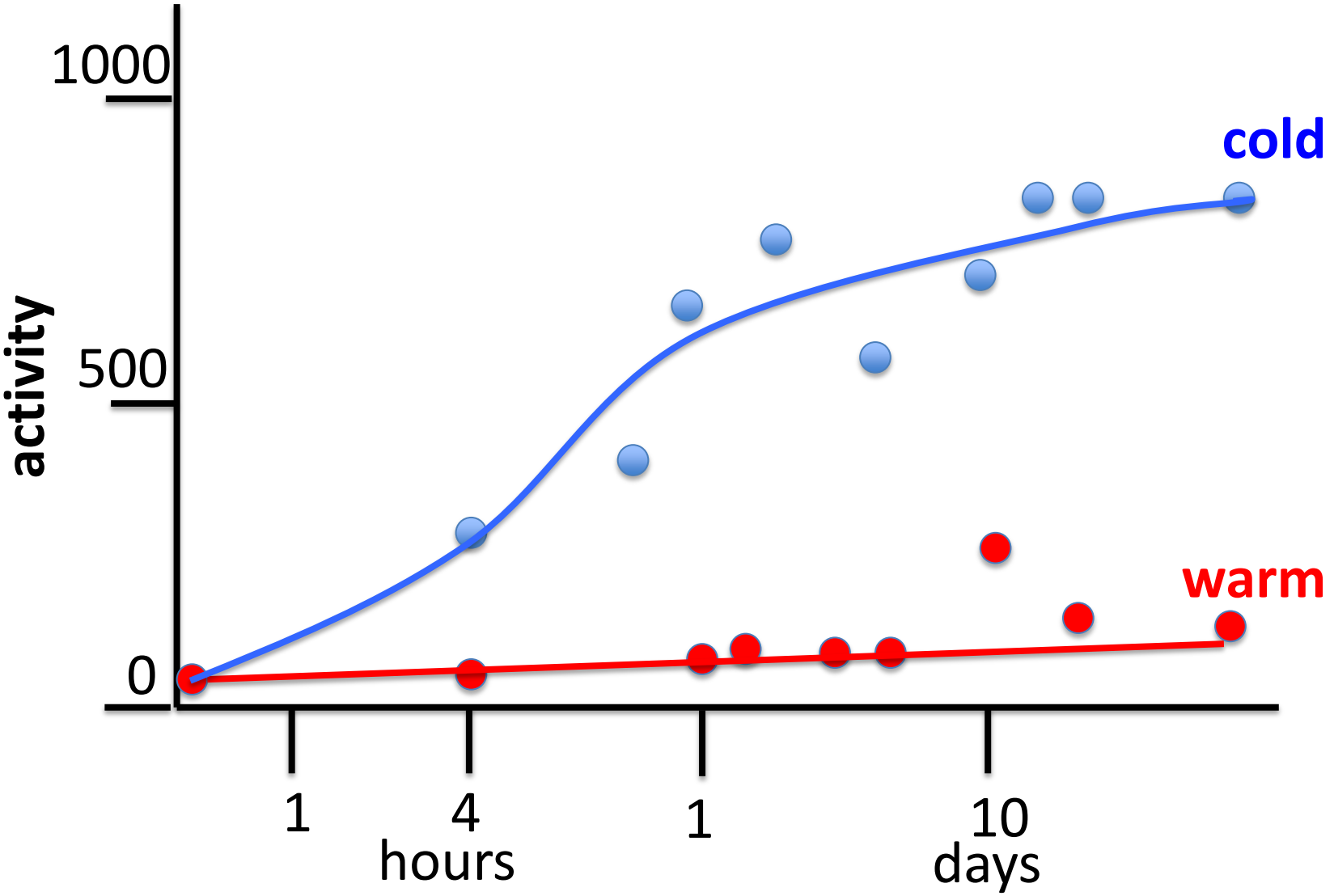
After some hours of activation



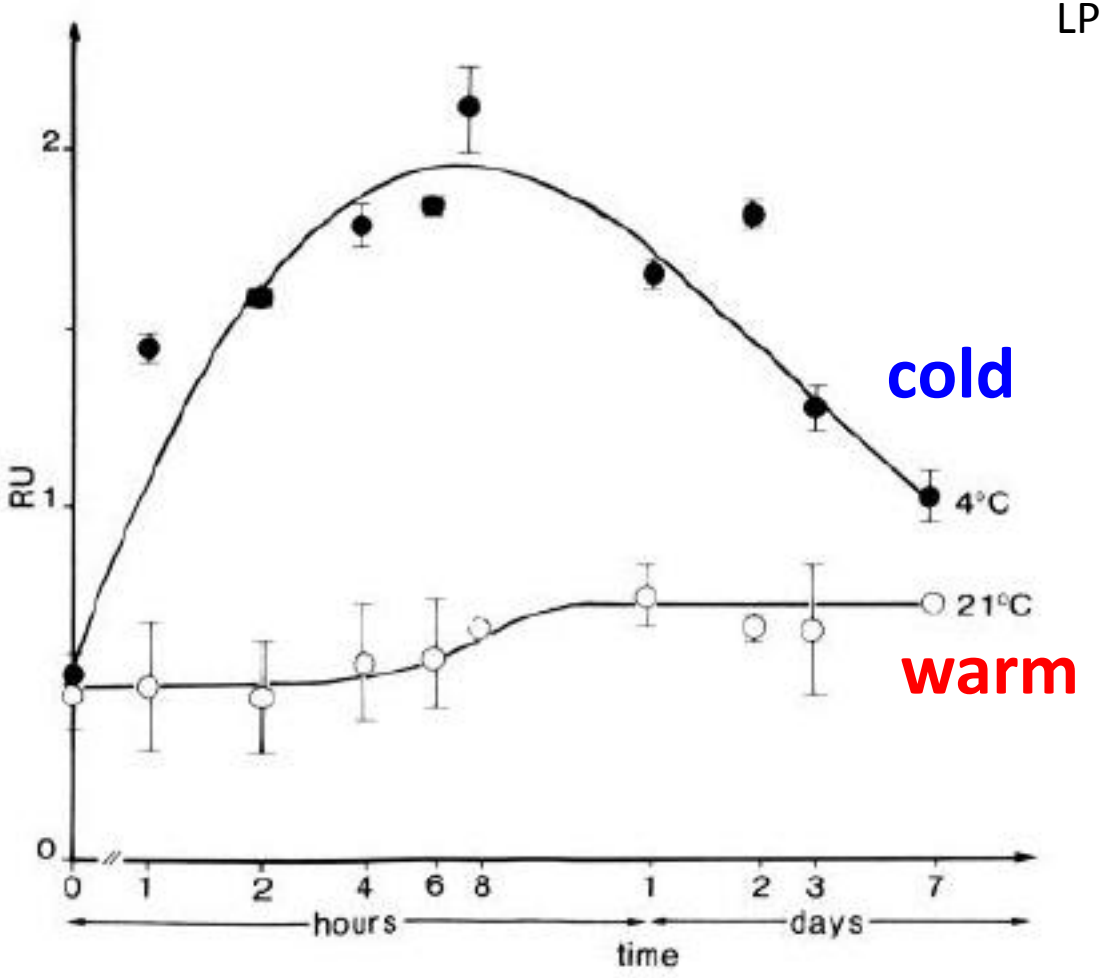
Lipoprotein lipase activity



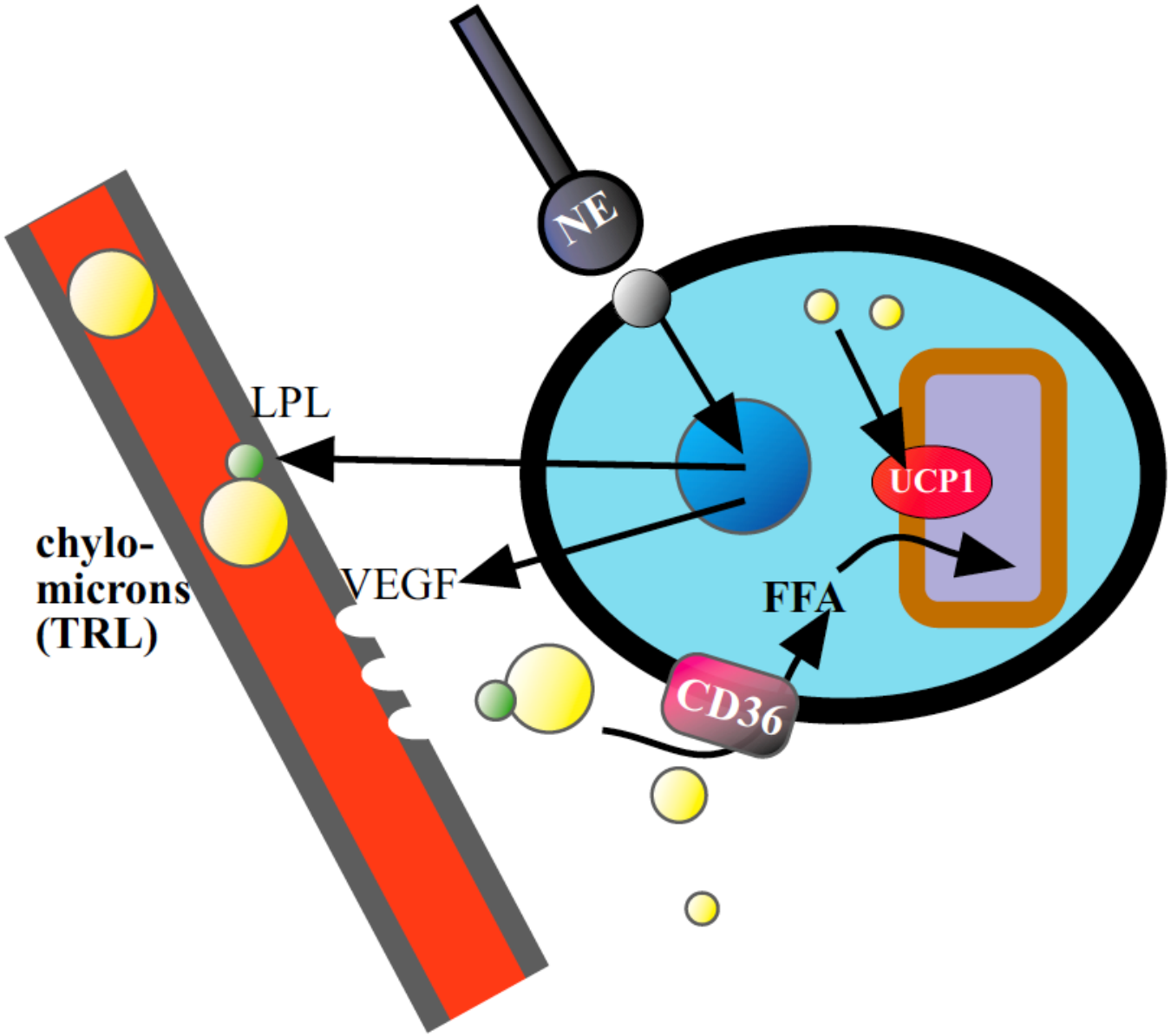
Lipoprotein lipase activity



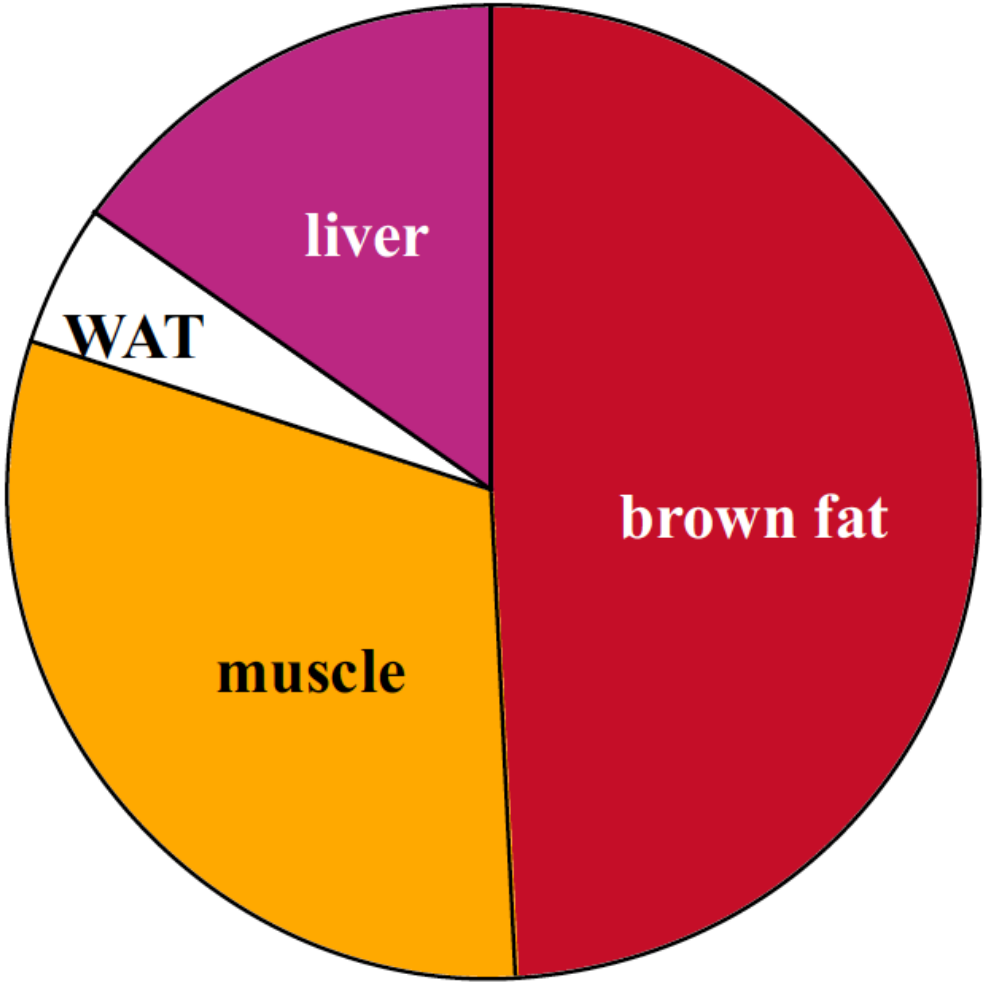
Lipoprotein lipase mRNA



Triglyceride pathway

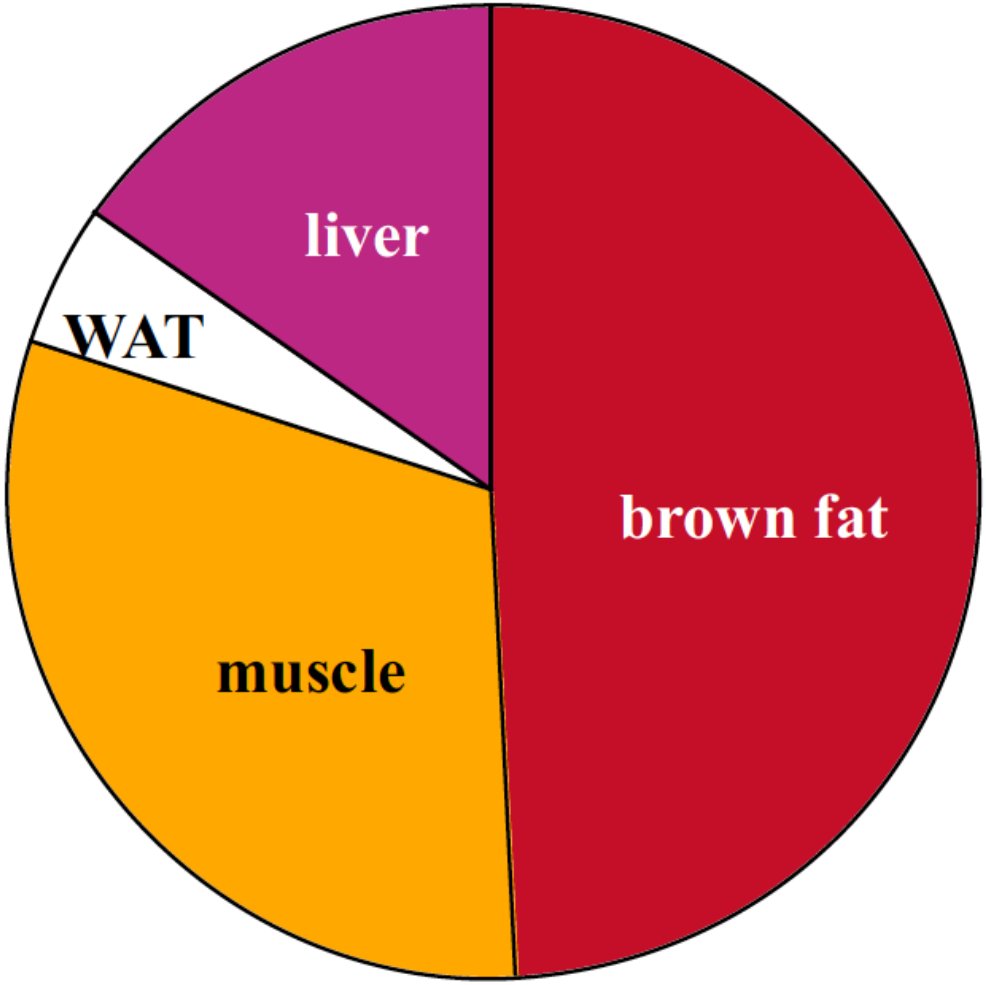


Triglyceride clearance



Bartelt//Heeren 2011

i.e. brown adipose tissue protects against hypertriglyceridemia



Bartelt//Heeren 2011

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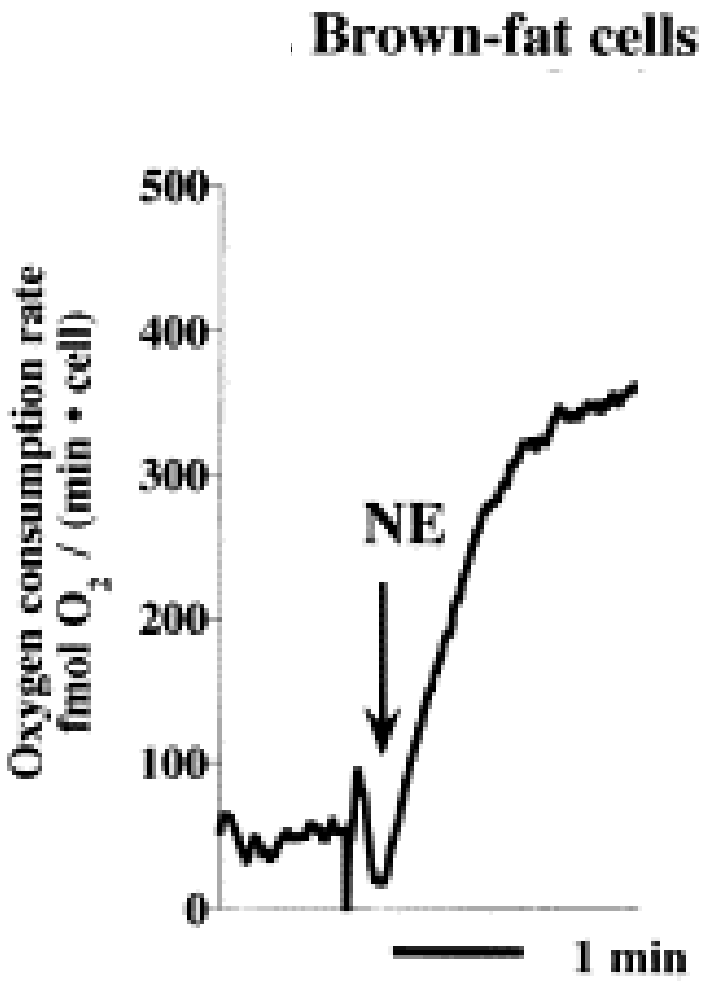
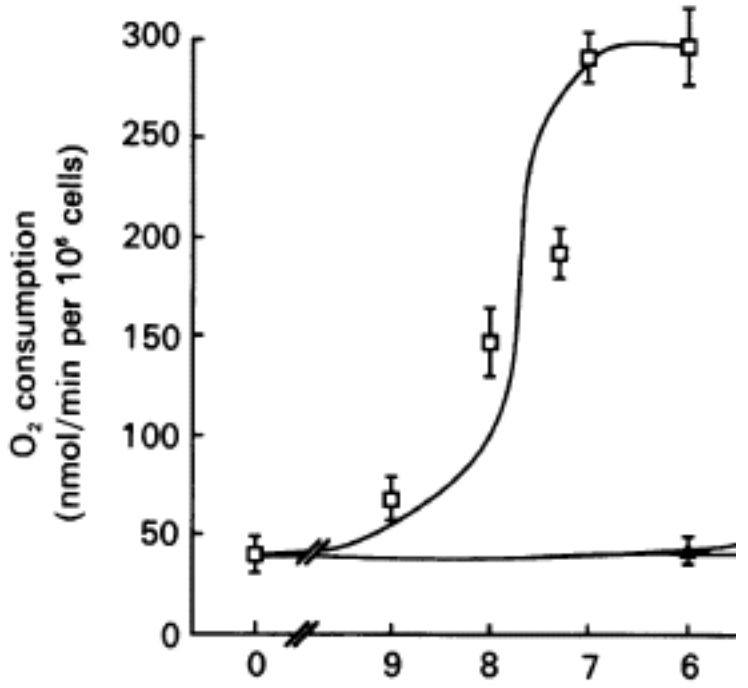
Brown adipose tissue and glucose disposal….

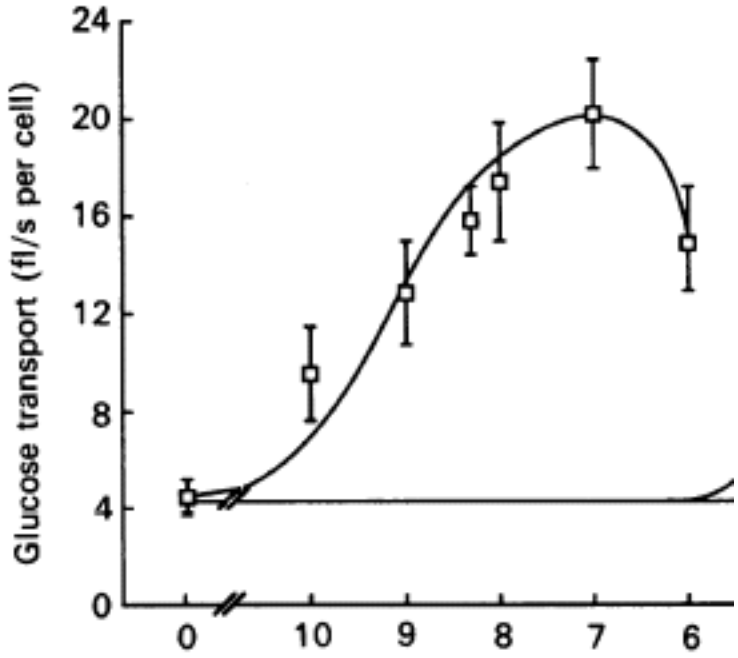

Brown-fat cells
Oxygen consumption rate
fmol O_2 / (min • cell)
500
400
300
200
100
0
NE
1 min

Brown-fat cells:



Thermogenesis

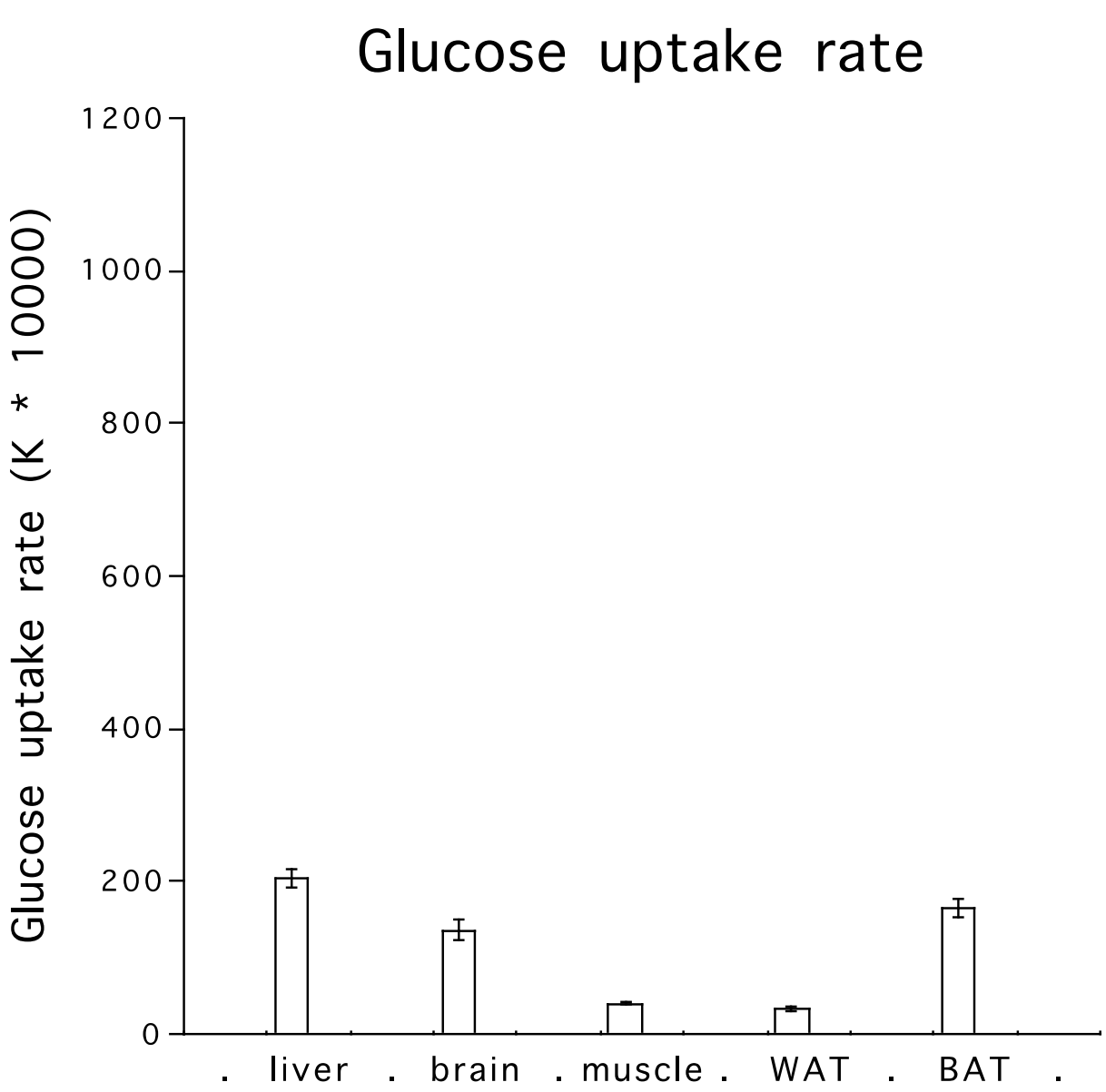
log[NE]



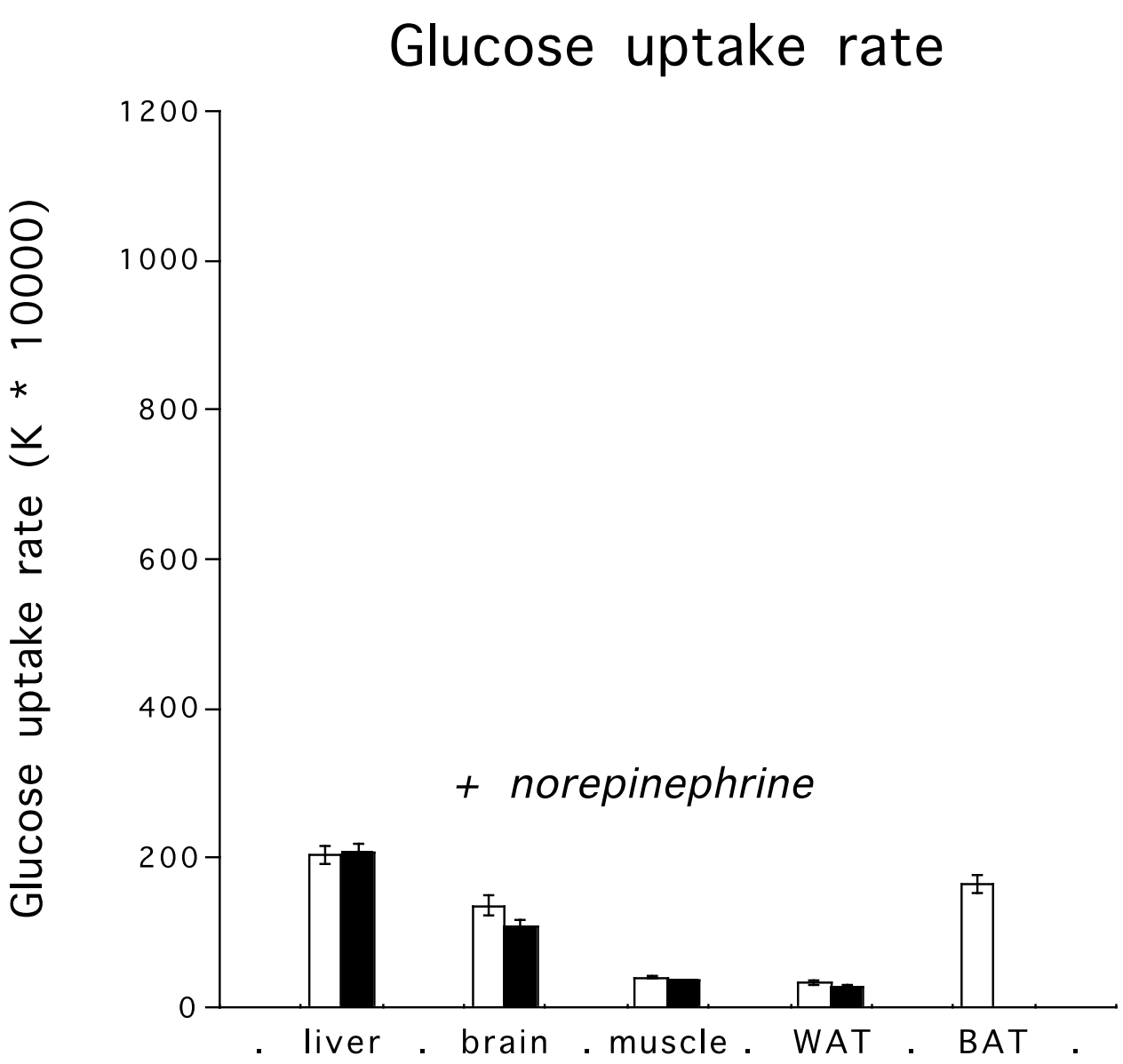
Glucose uptake

log[NE]

Marette & Bukowiecki 1991



Cooney et al. 1985



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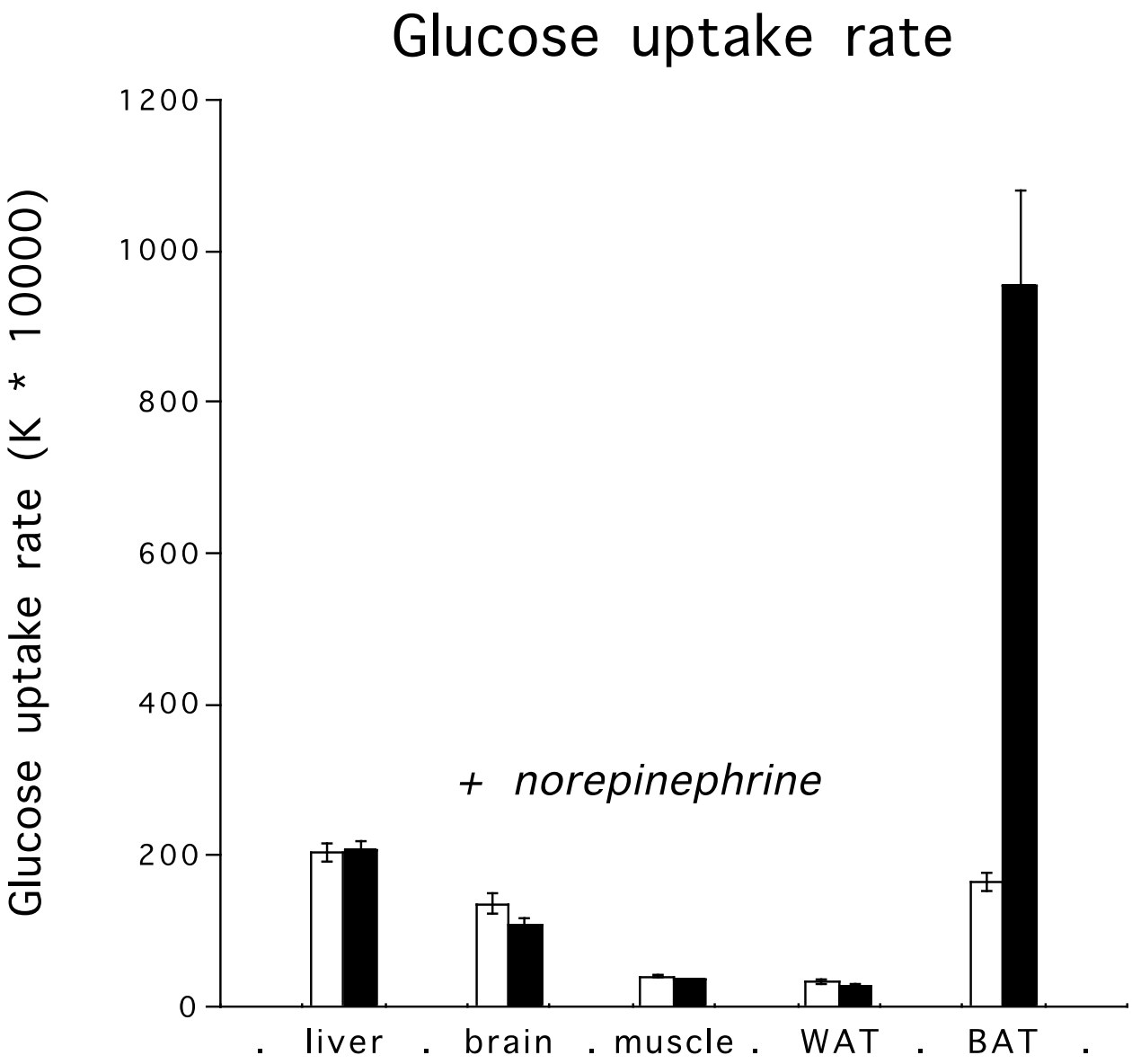
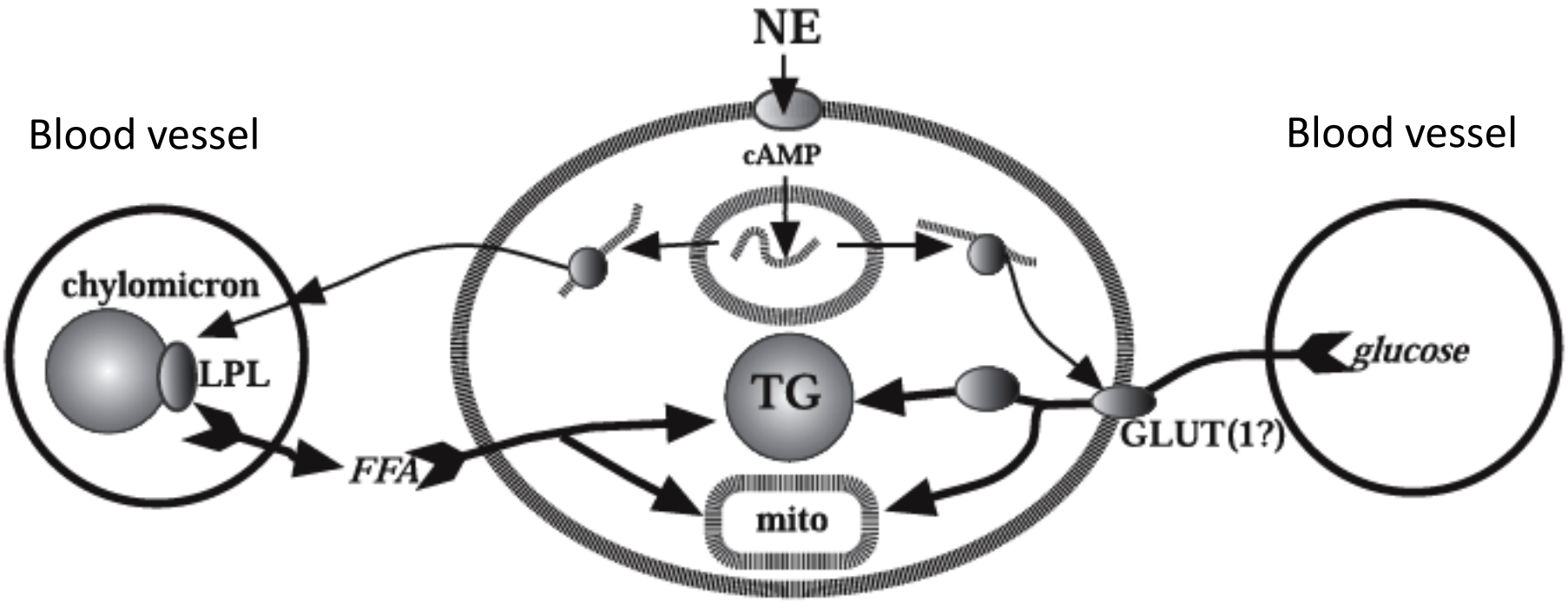
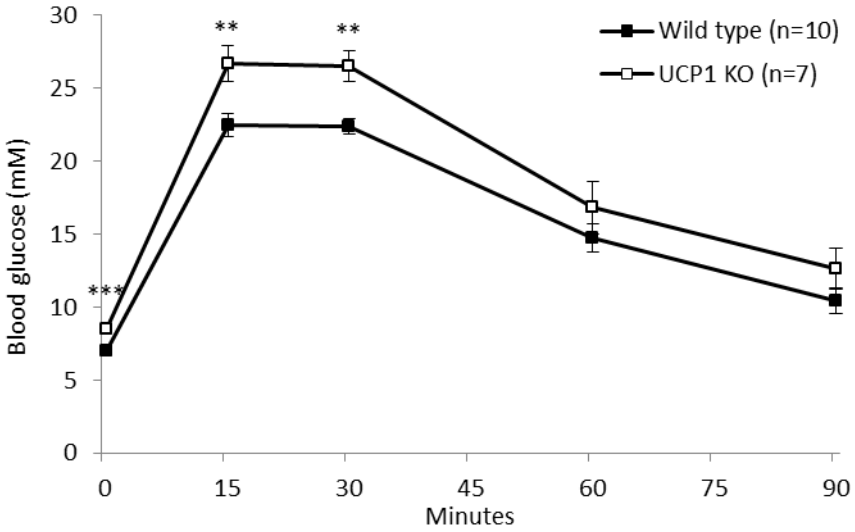


Cooney et al. 1985

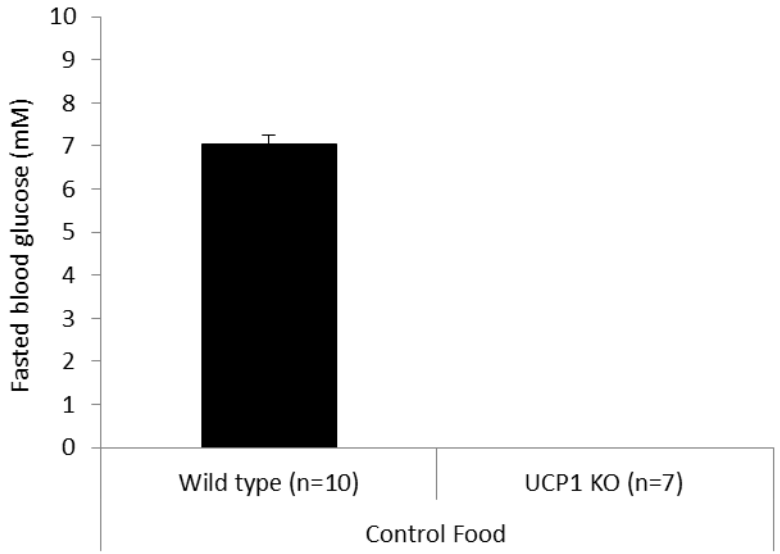
Brown adipocyte



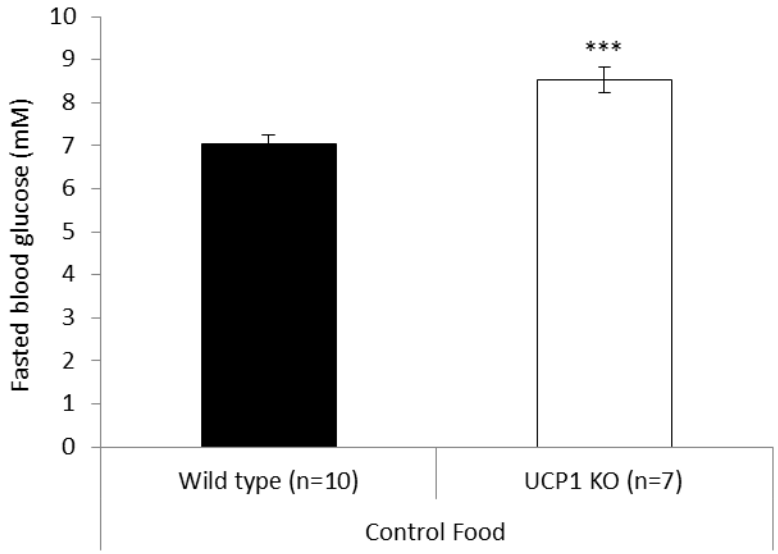
Glucose tolerance test



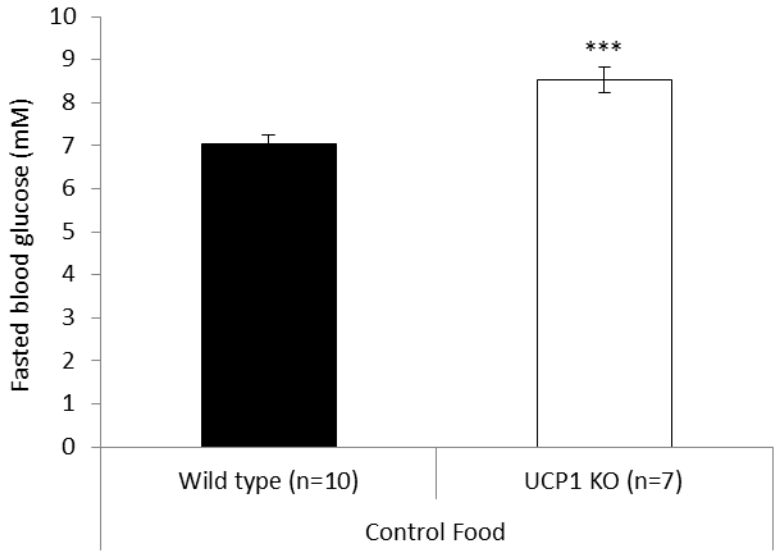
Fasting glucose



Fasting glucose



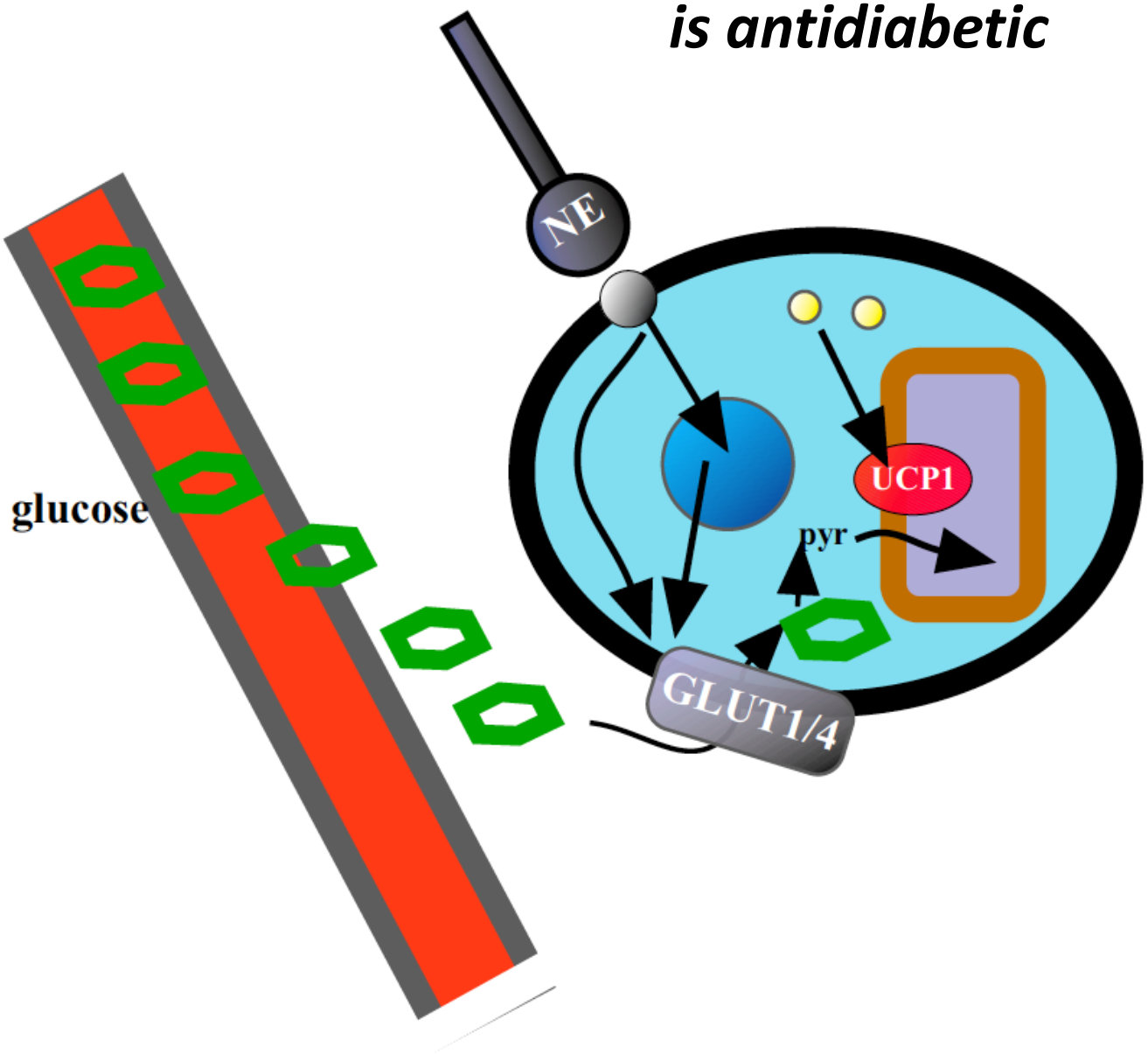
Fasting glucose



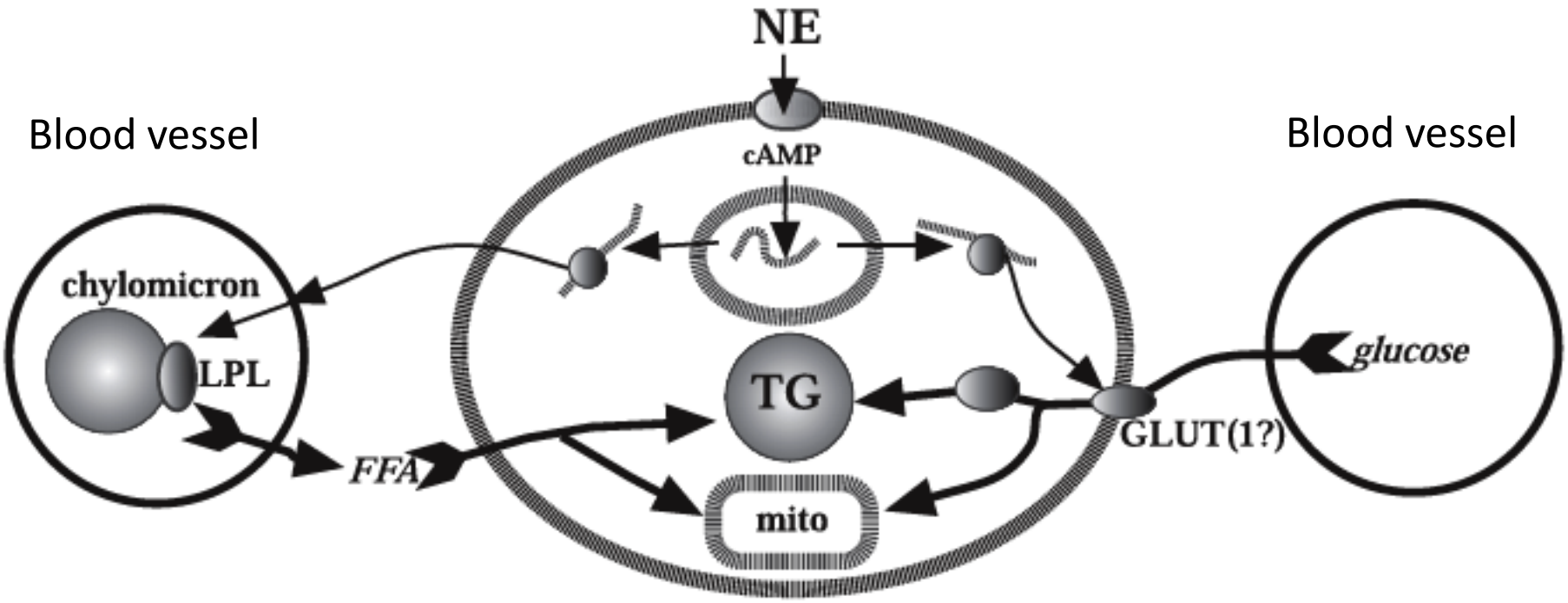
Brown fat is of significance for glucose control in mice

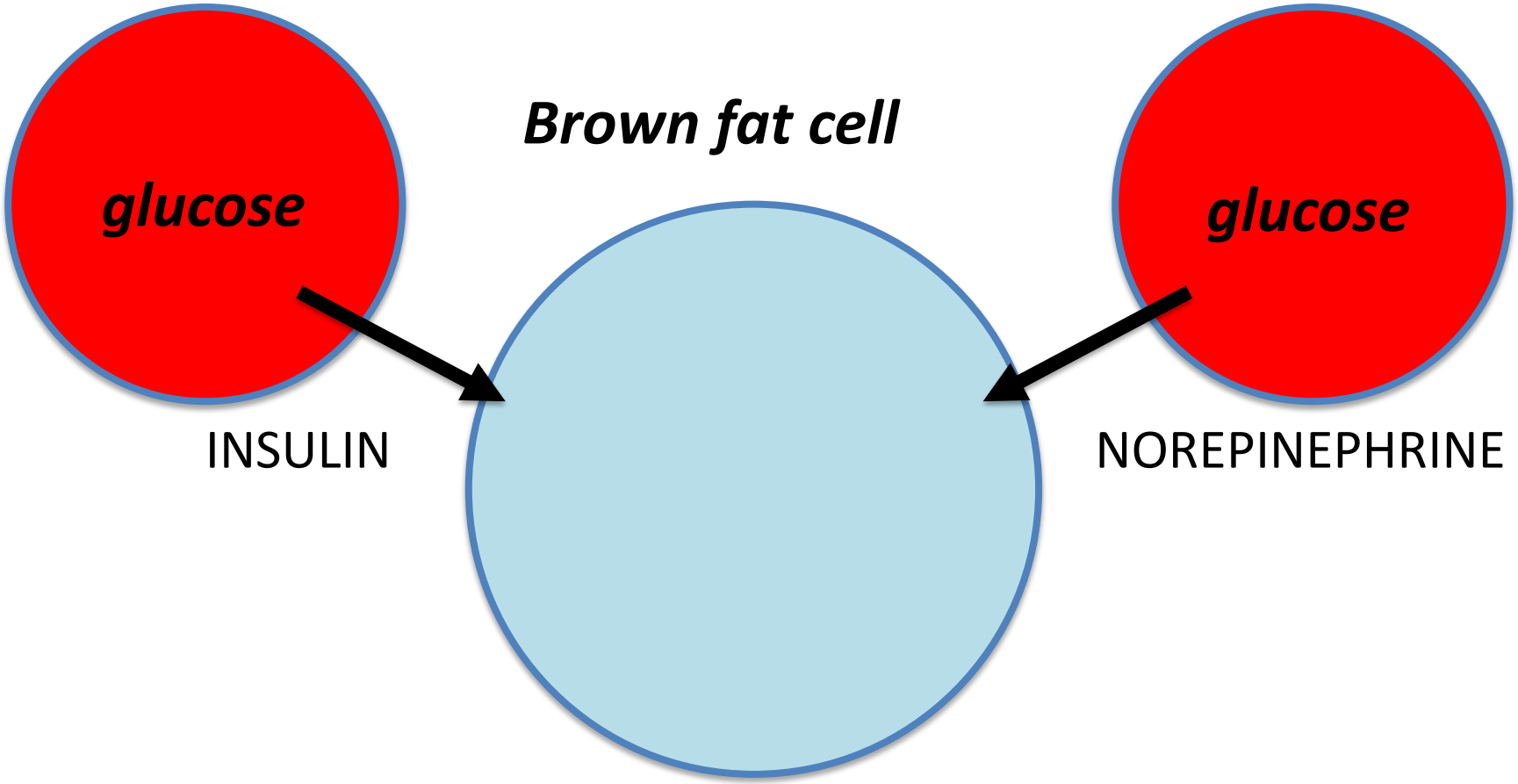
Glucose pathway

i.e. brown adipose tissue is antidiabetic

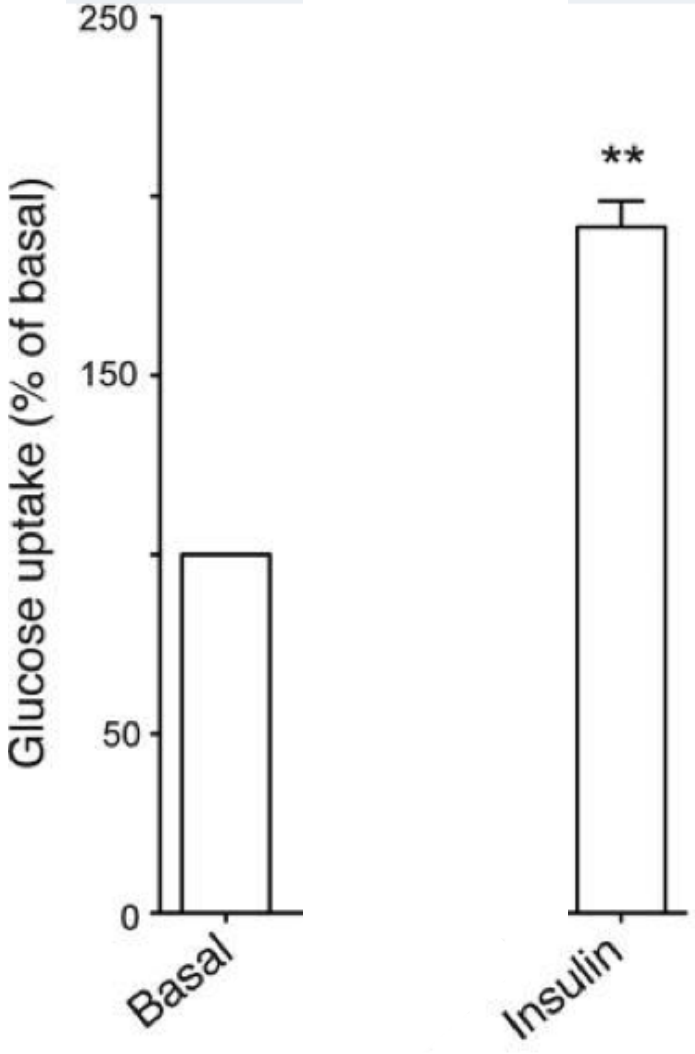


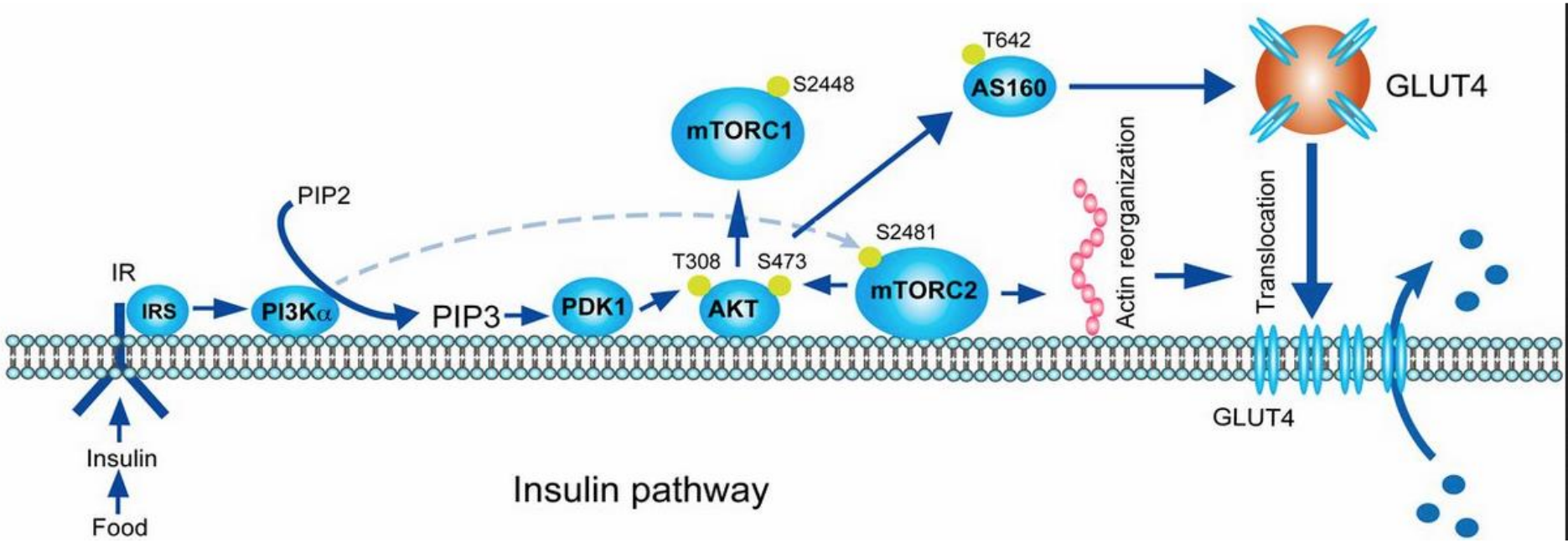
Brown adipocyte




Brown fat cell
glucose
glucose
INSULIN
NOREPINEPHRINE

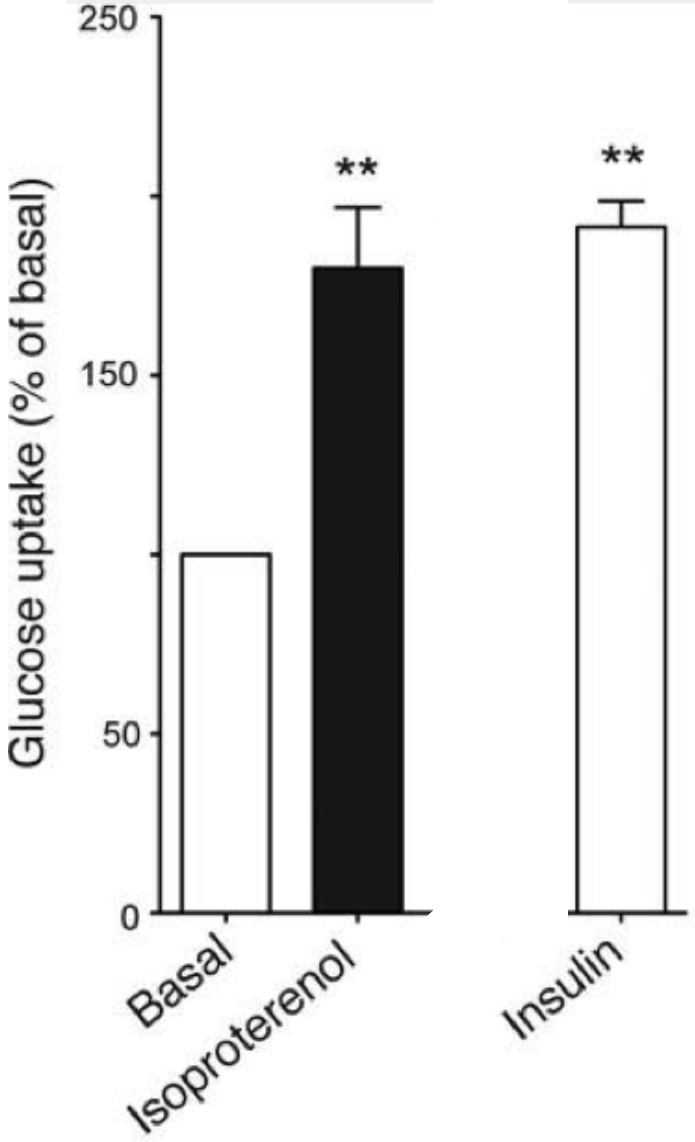
Brown-fat cell



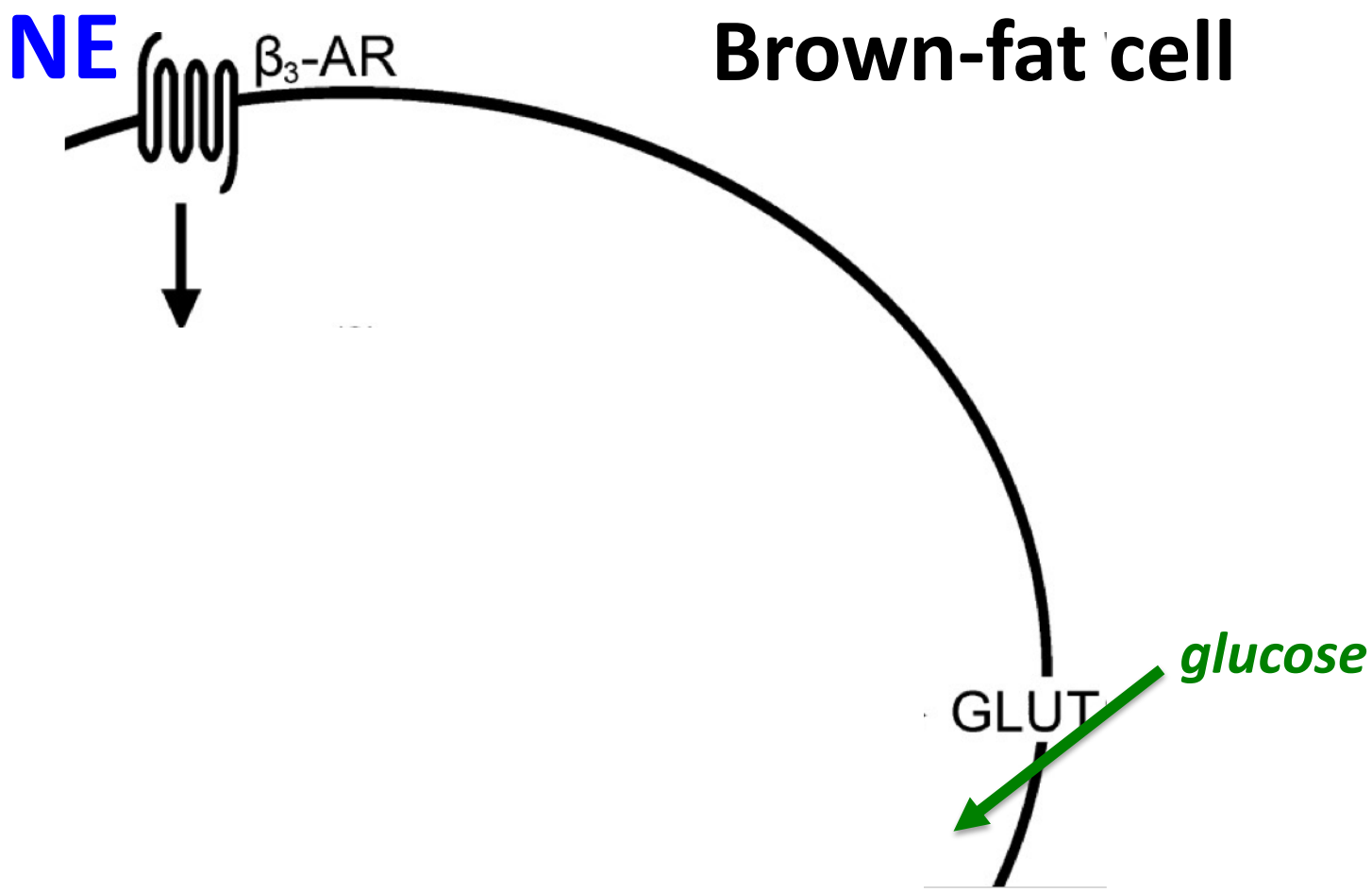


Insulin pathway

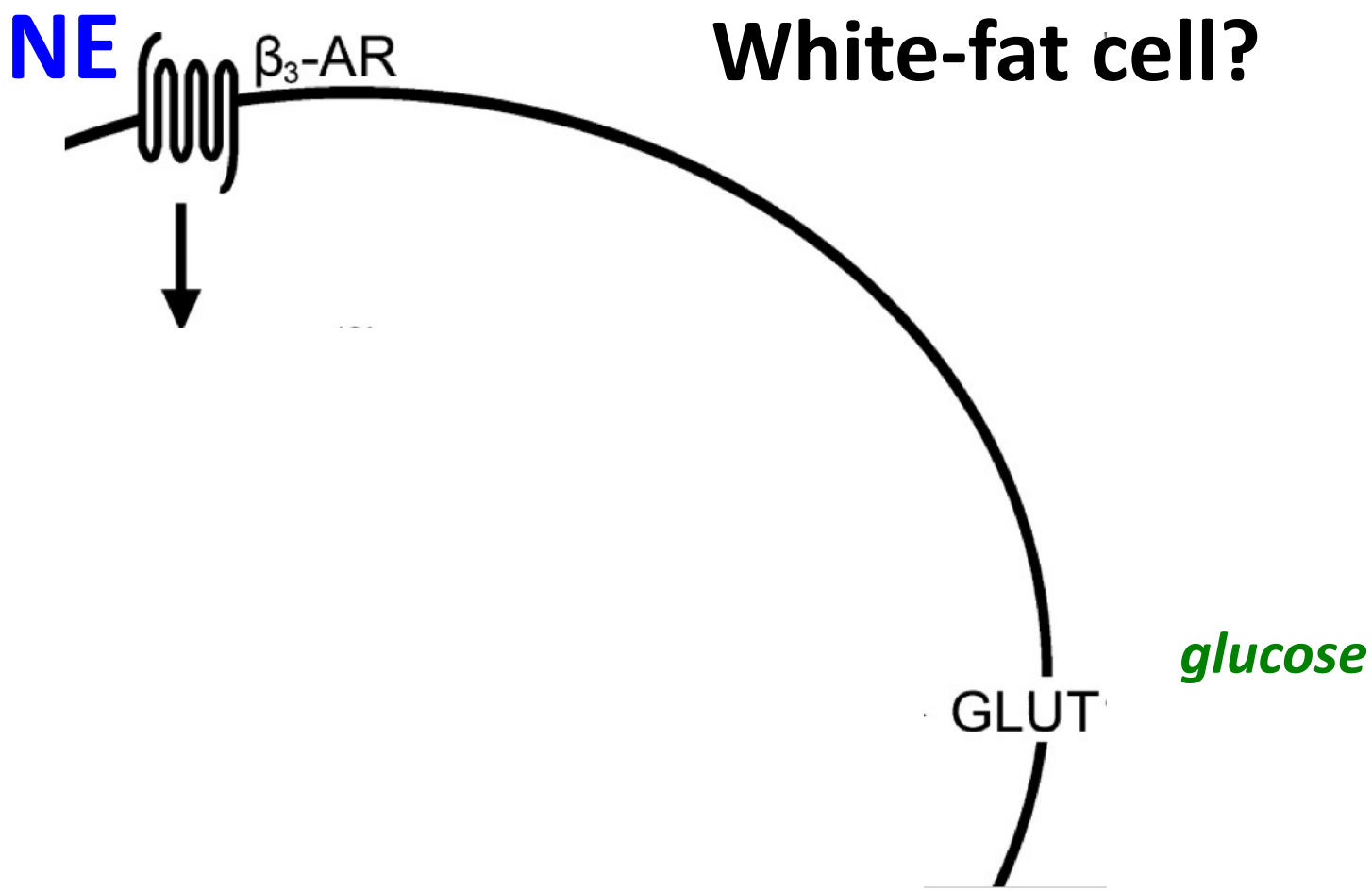
Brown-fat cell

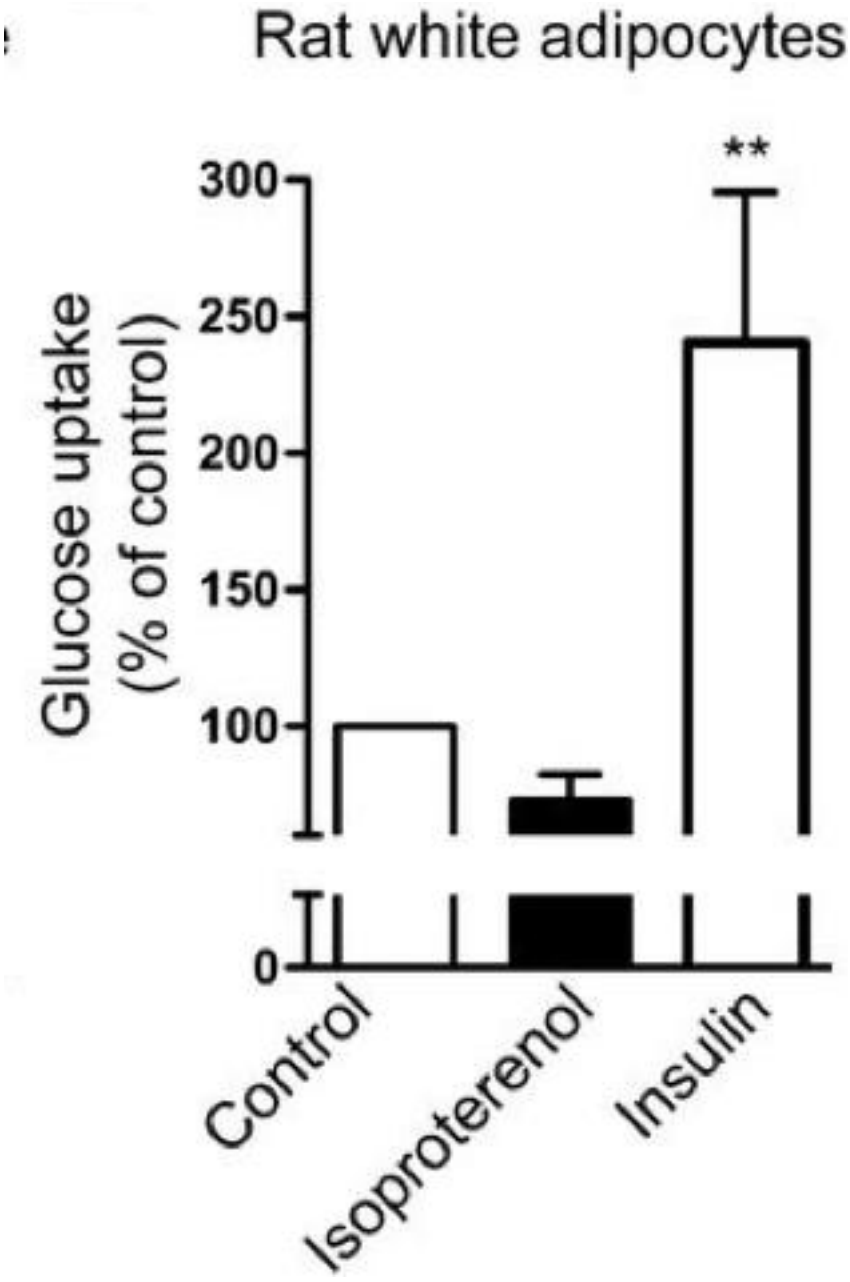


Brown-fat cell

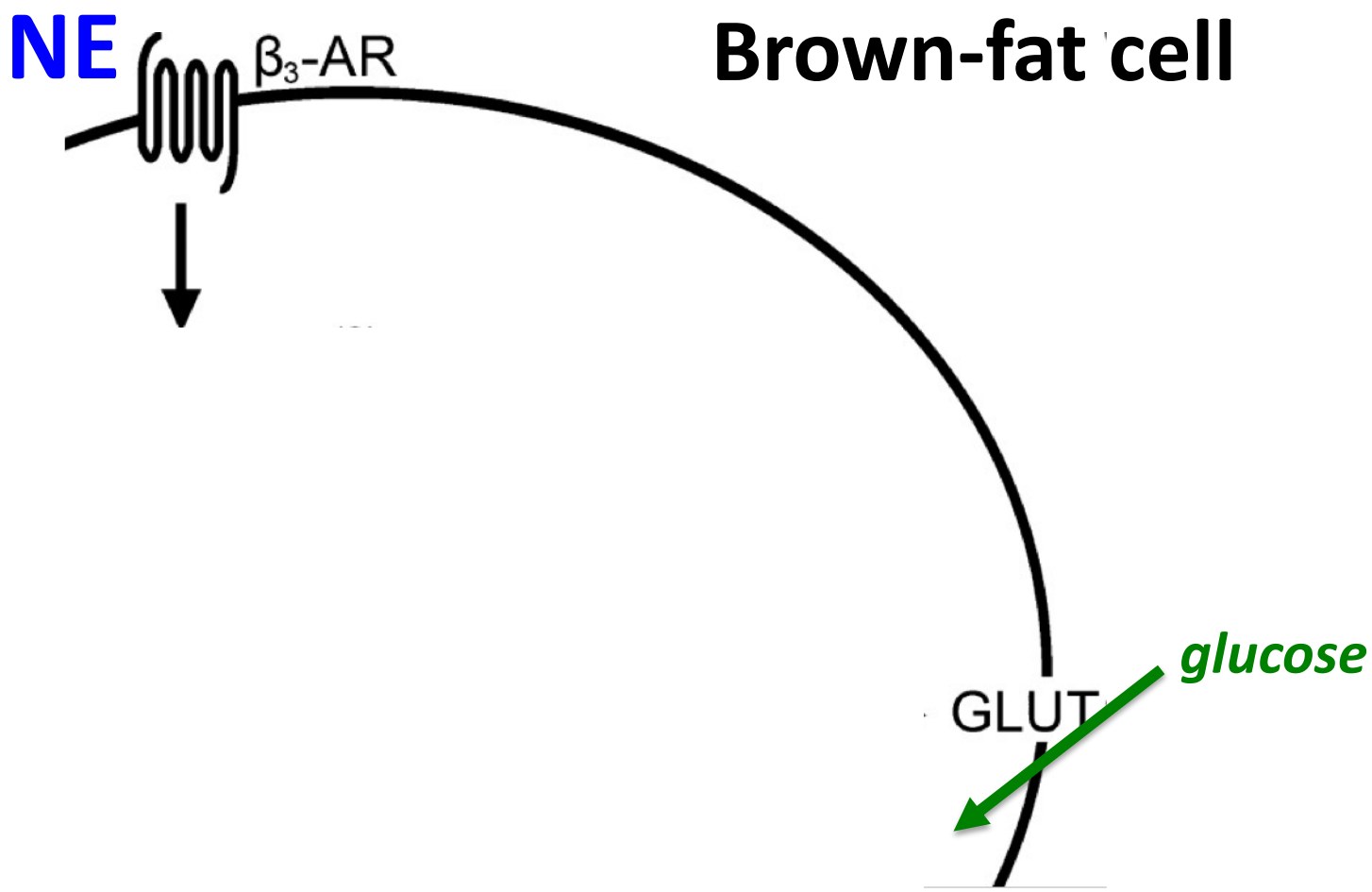


White-fat cell?

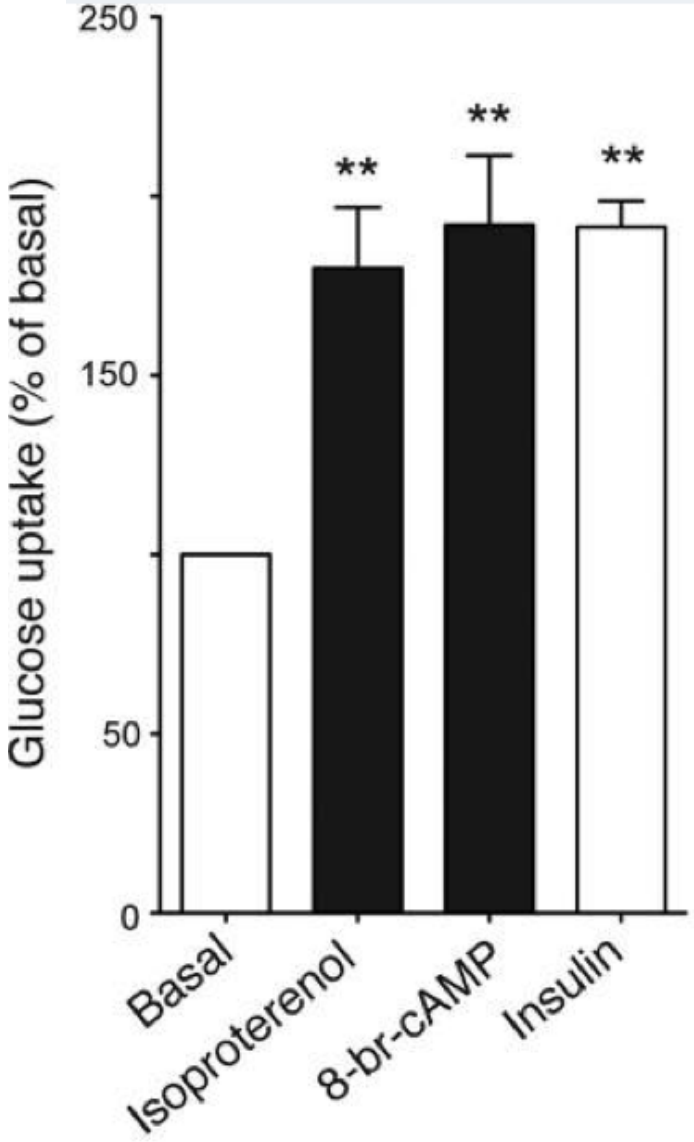



Rat white adipocytes
Glucose uptake
(% of control)
300
250
200
150
100
0
**
Control
Isoproterenol
Insulin

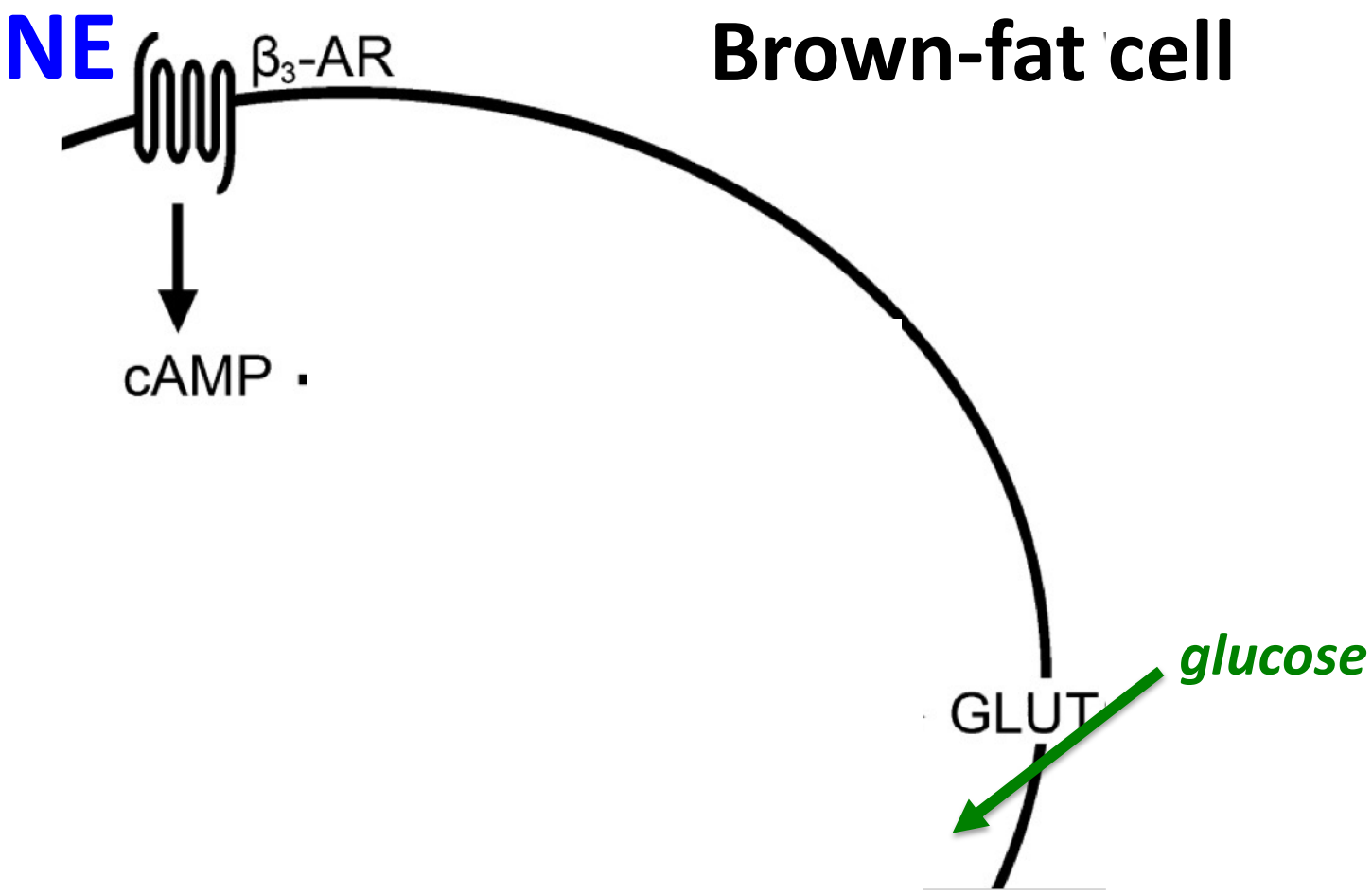
Brown-fat cell

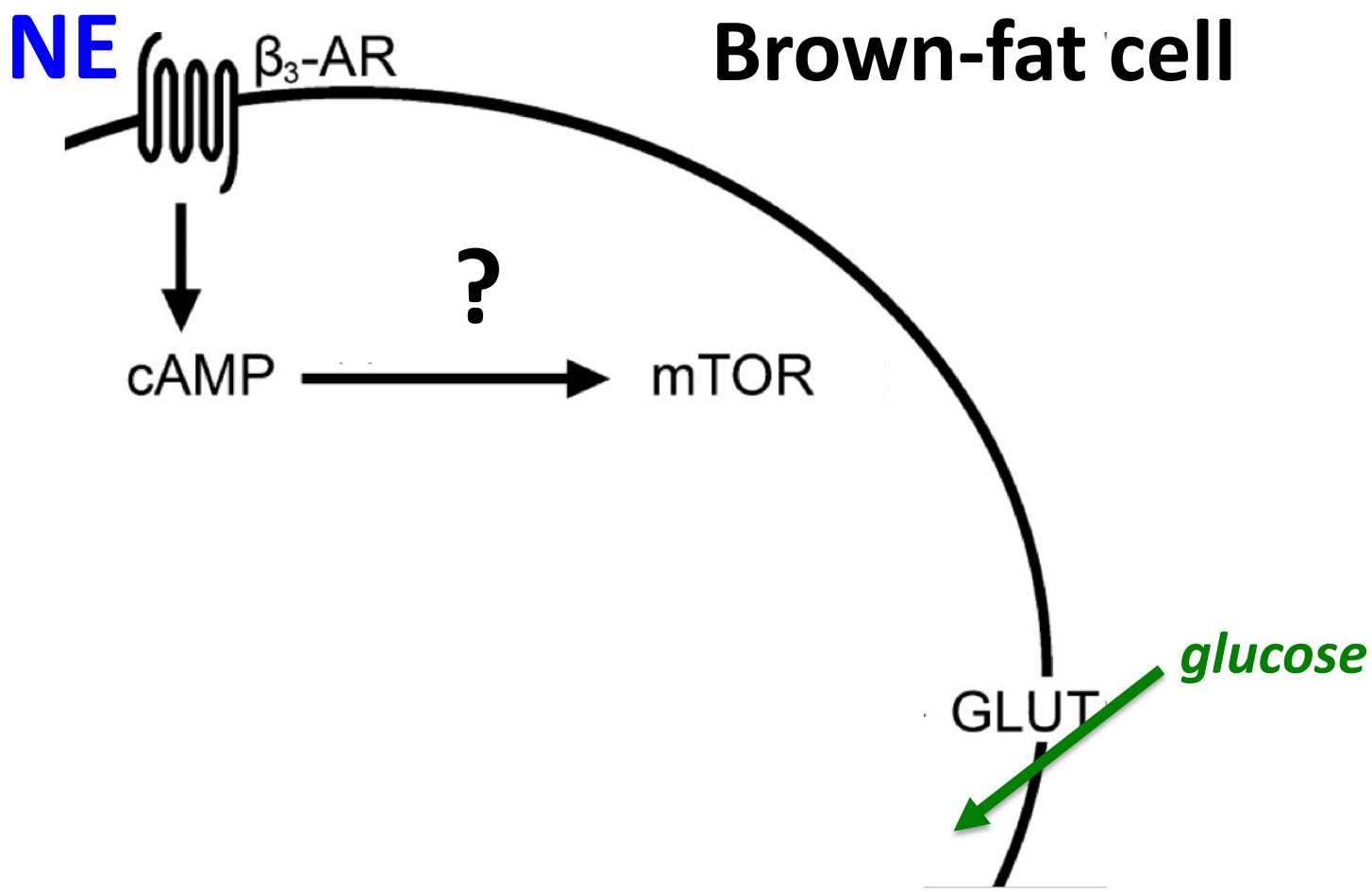


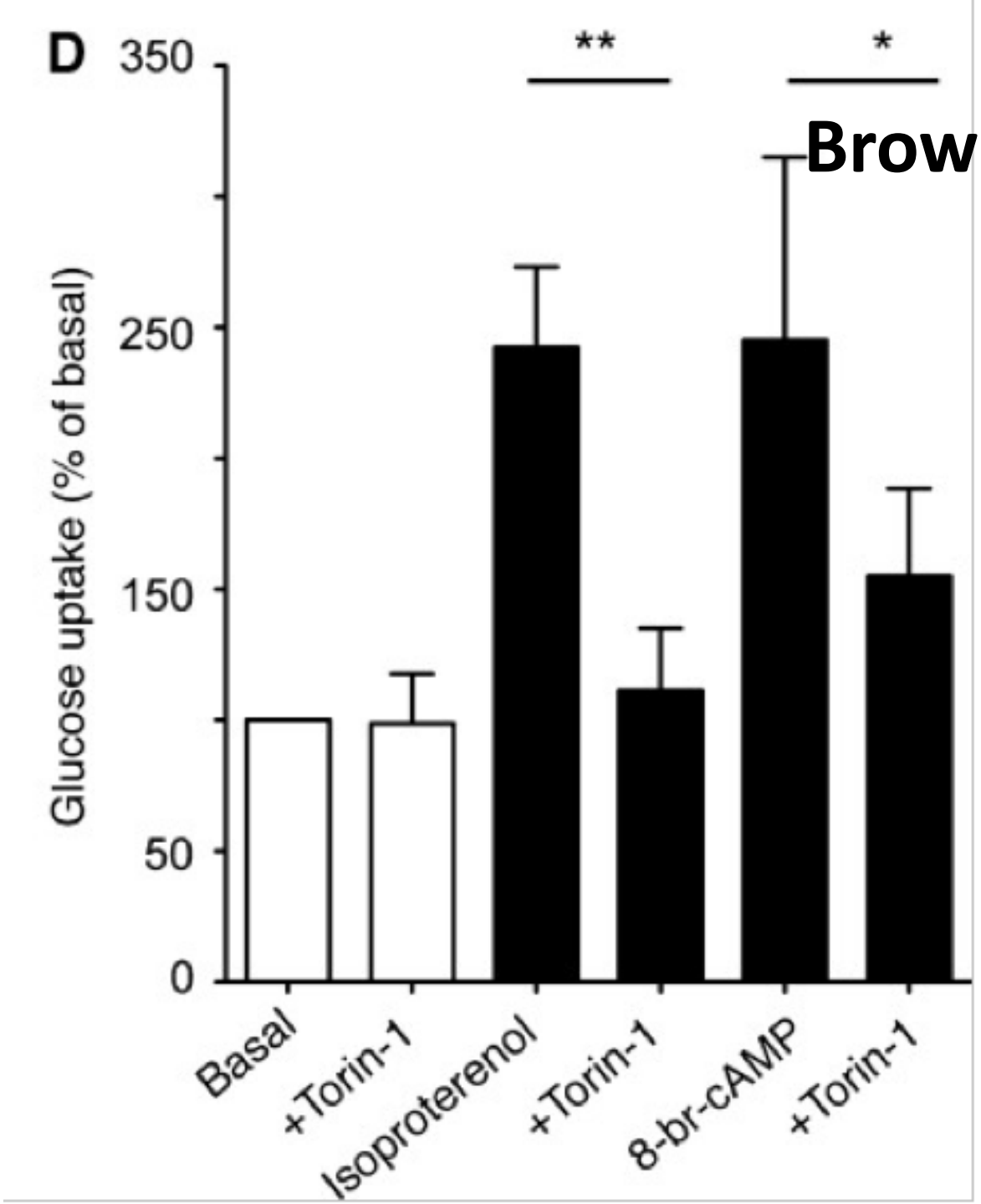
Brown-fat cell



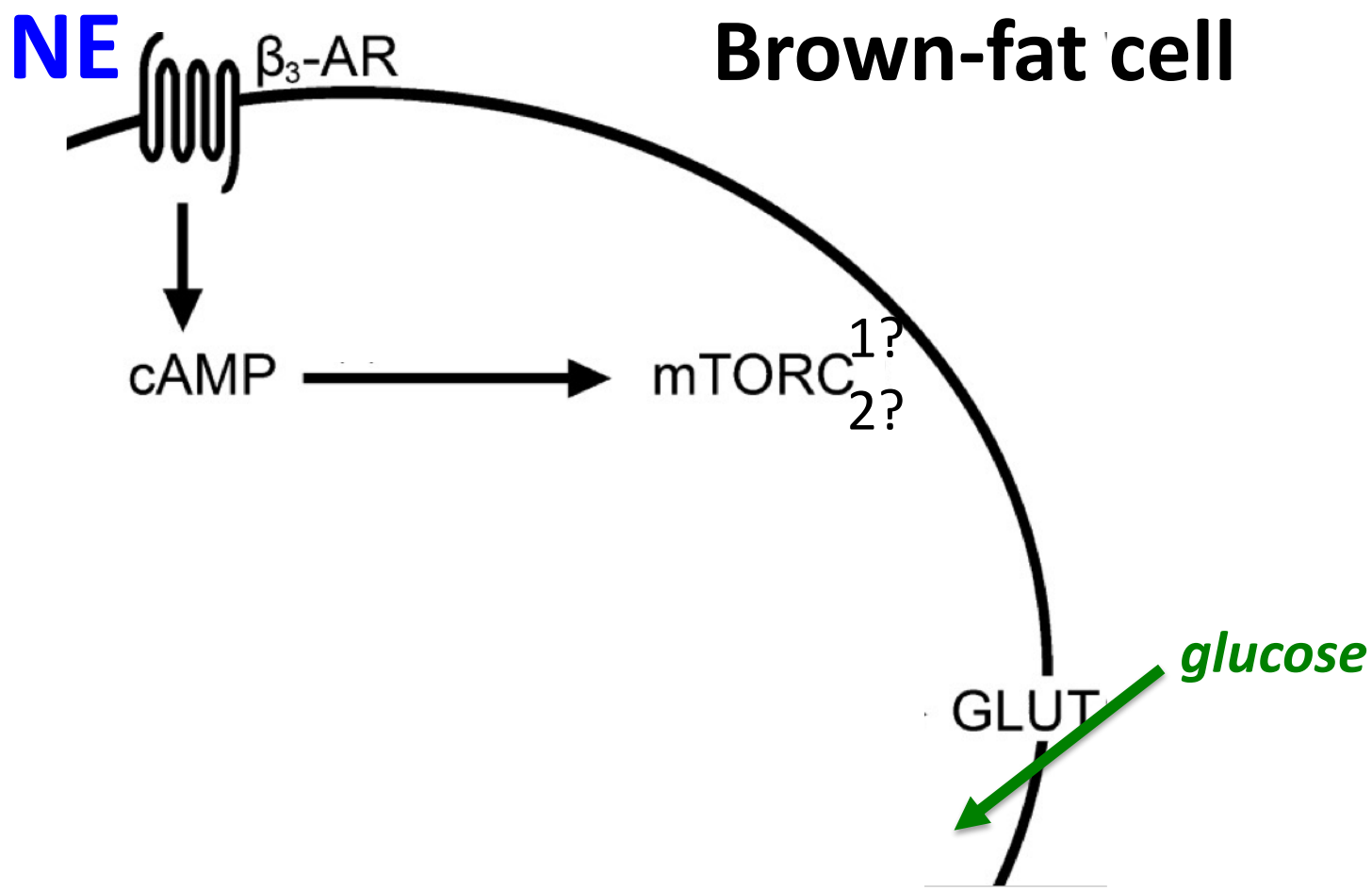
Brown-fat cell




NE
β3-AR
Brown-fat cell
?
cAMP
mTOR
GLUT
glucose

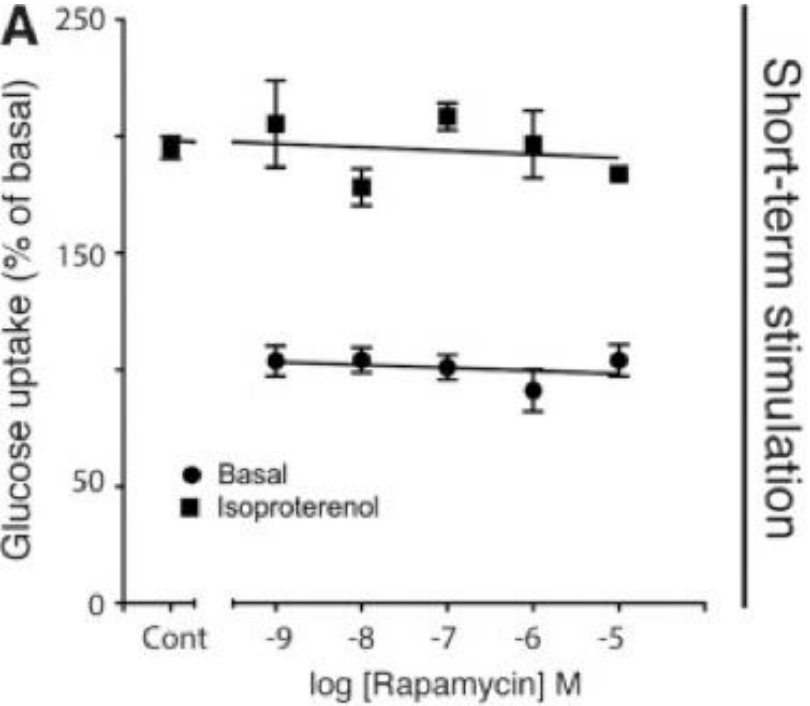


Brown-fat cell


NE
β3-AR
Brown-fat cell
cAMP
mTORC1?
2?
glucose
GLUT

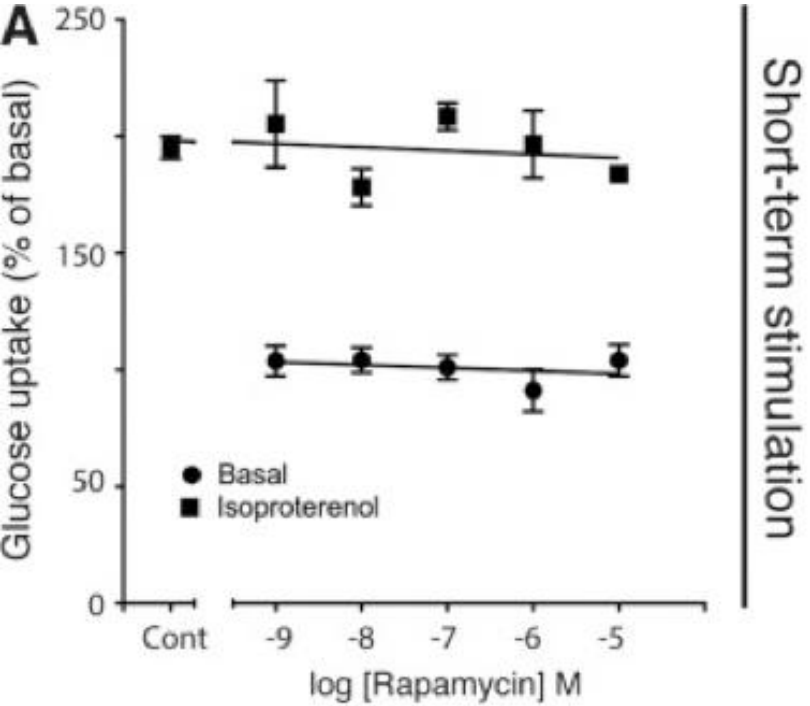
Brown-fat cell

mTORC1

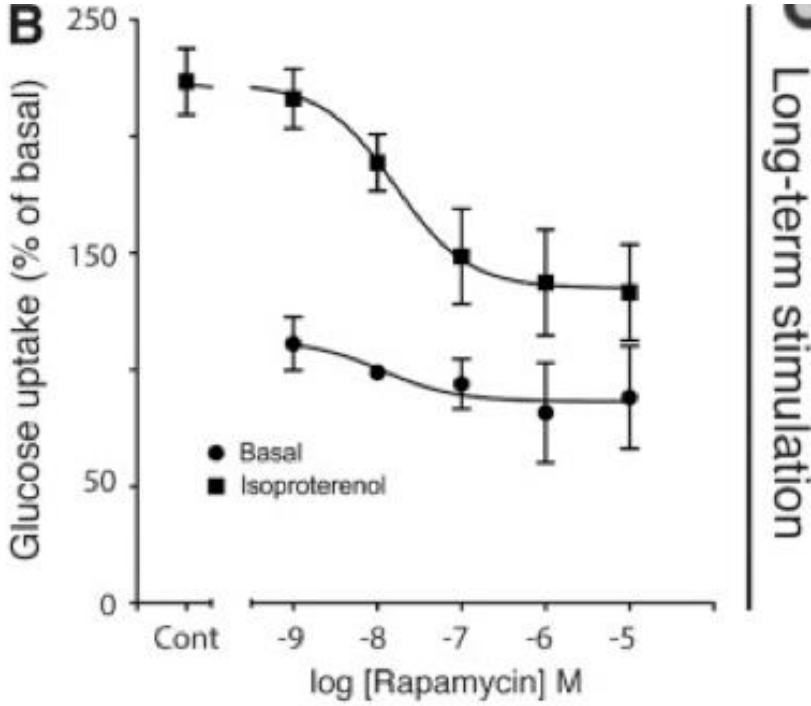


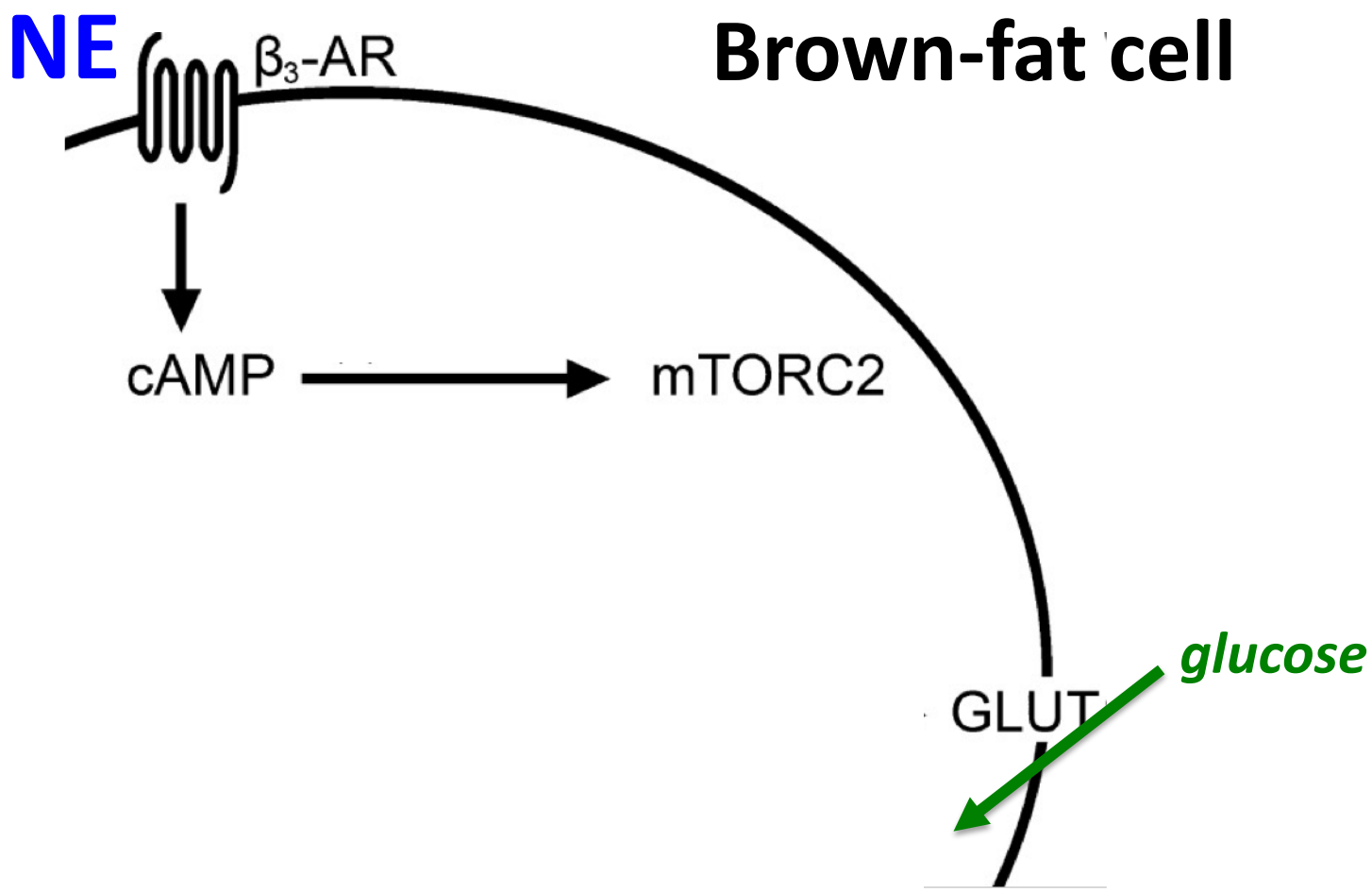
Brown-fat cell

mTORC1



mTORC2

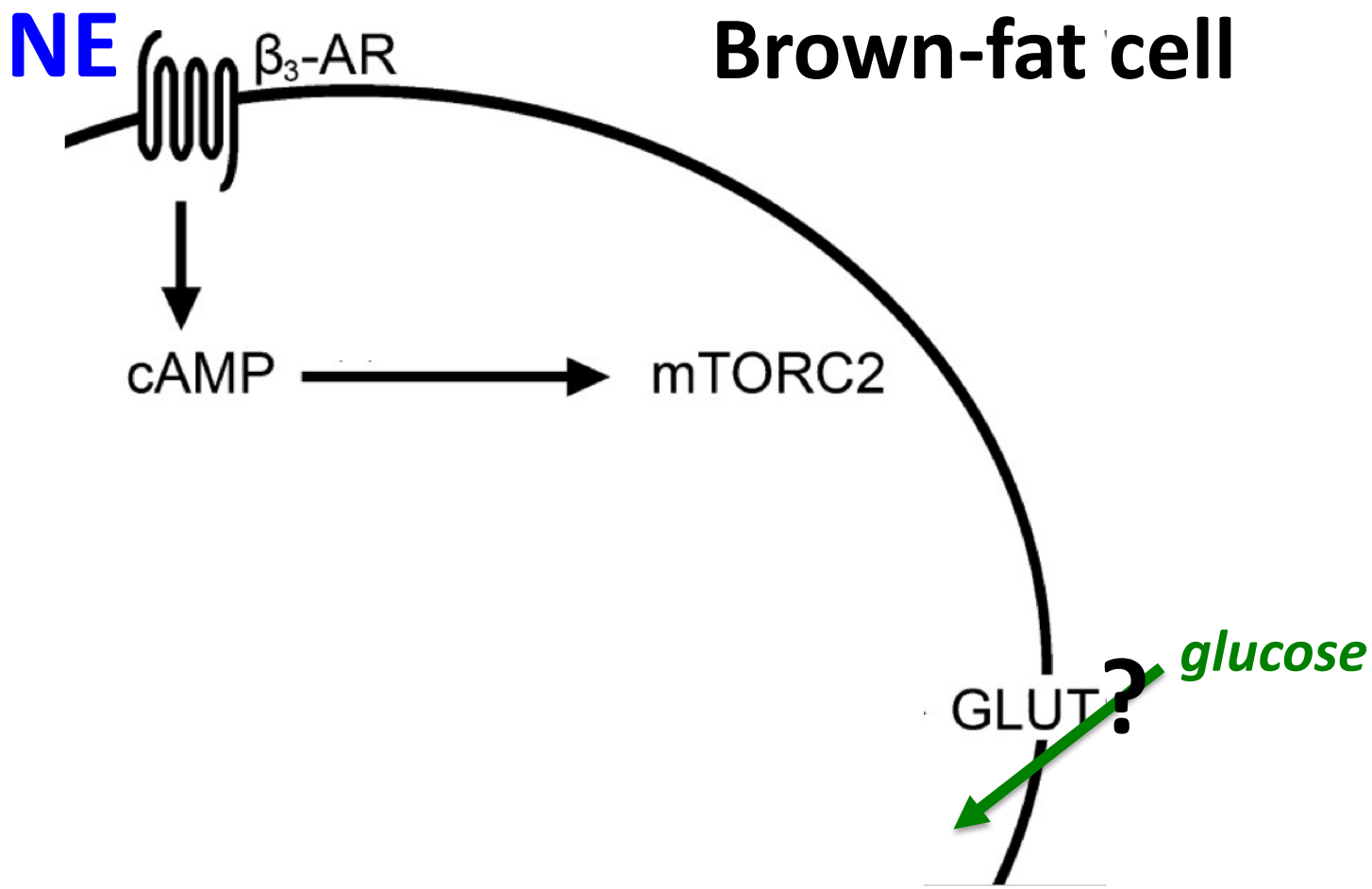


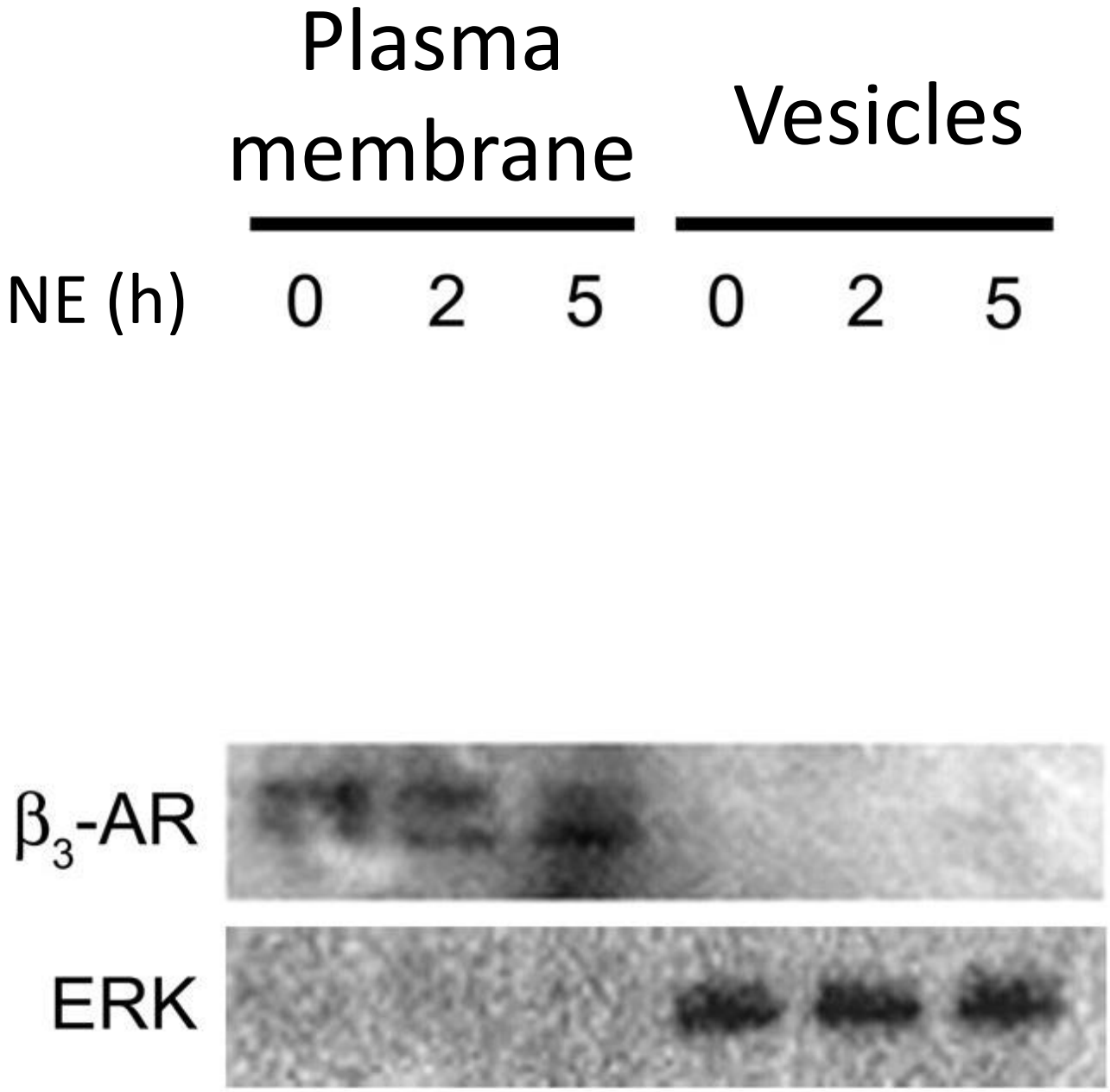

NE
β3-AR
Brown-fat cell
cAMP
mTORC2
GLUT
glucose

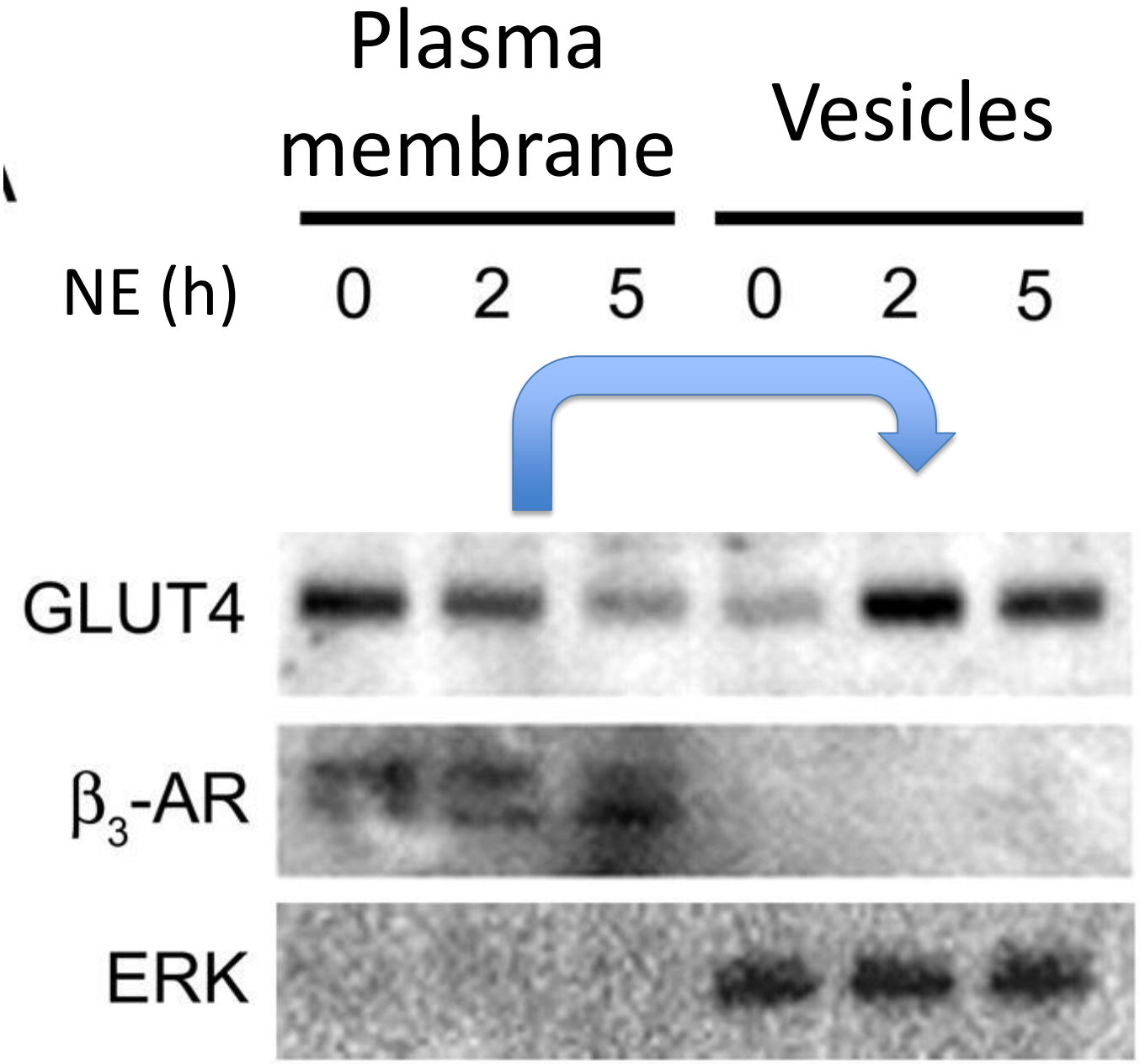
B

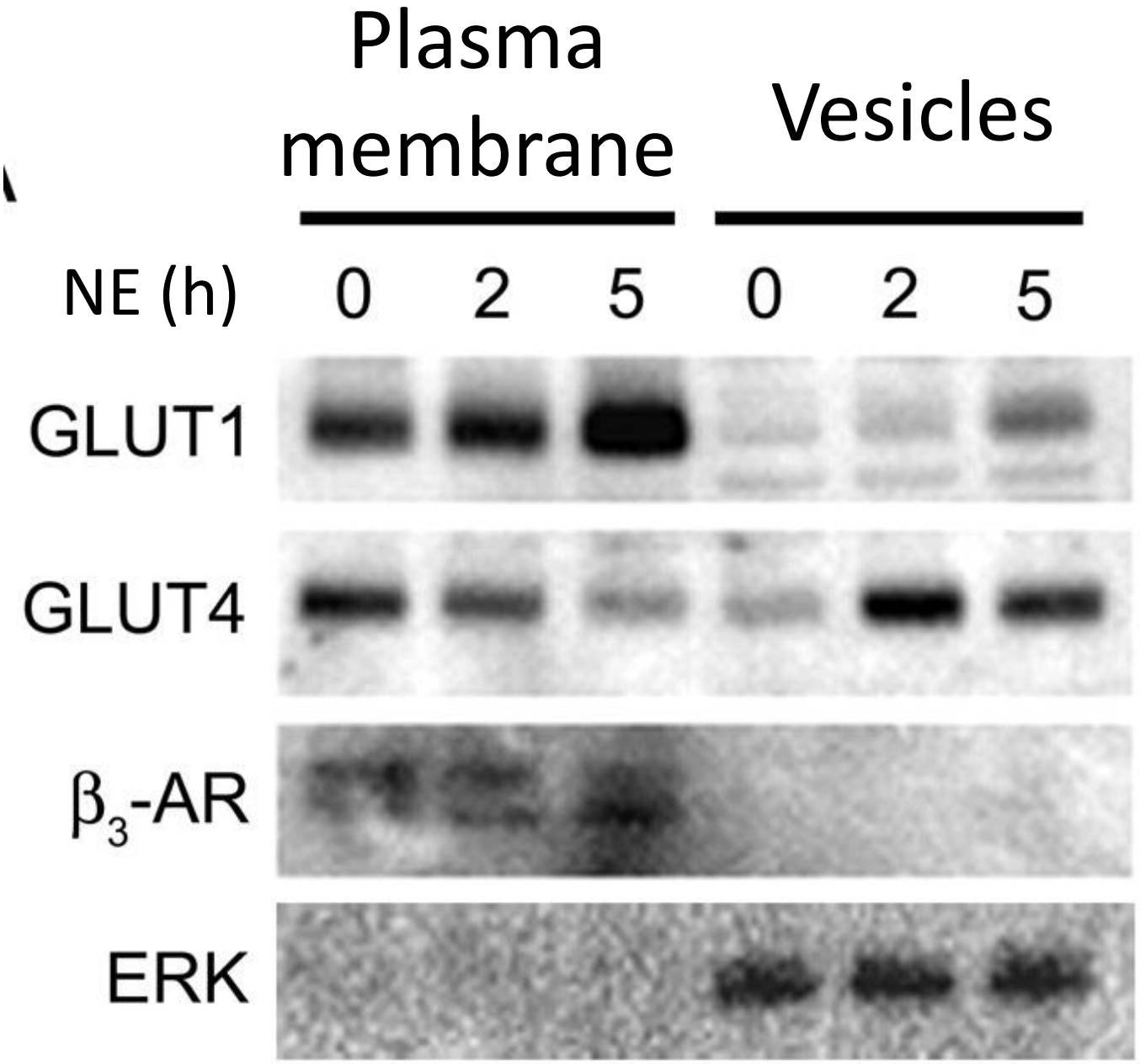
β1xβ2 KO and FVB Mice

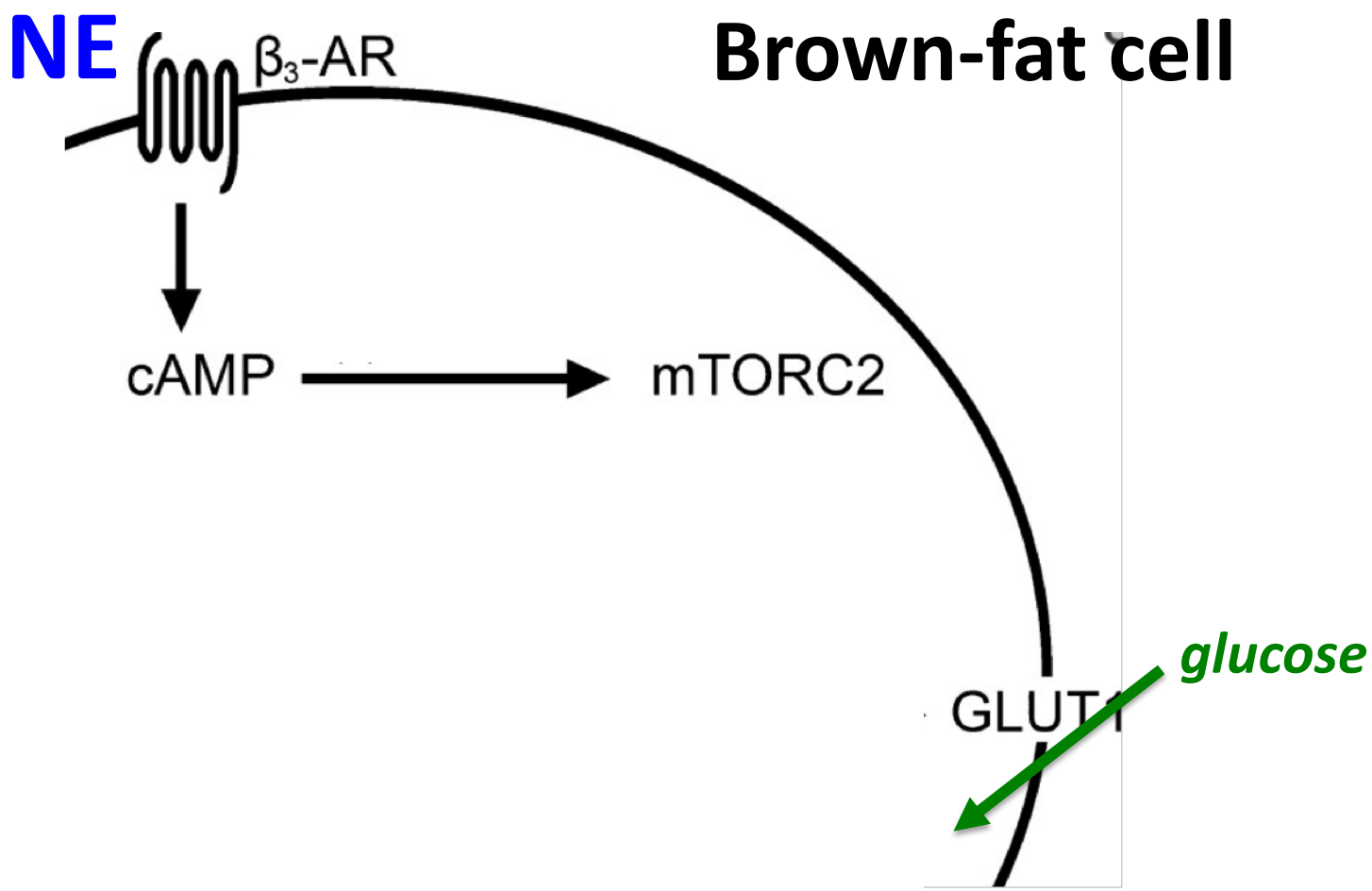
D
**
150
50
0
Glucose uptake (% of basal)
Basal
+KU0063794
Isoproterenol
+KU0063794
Human MADS cells


NE
β3-AR
Brown-fat cell
cAMP
mTORC2
GLUT?
glucose

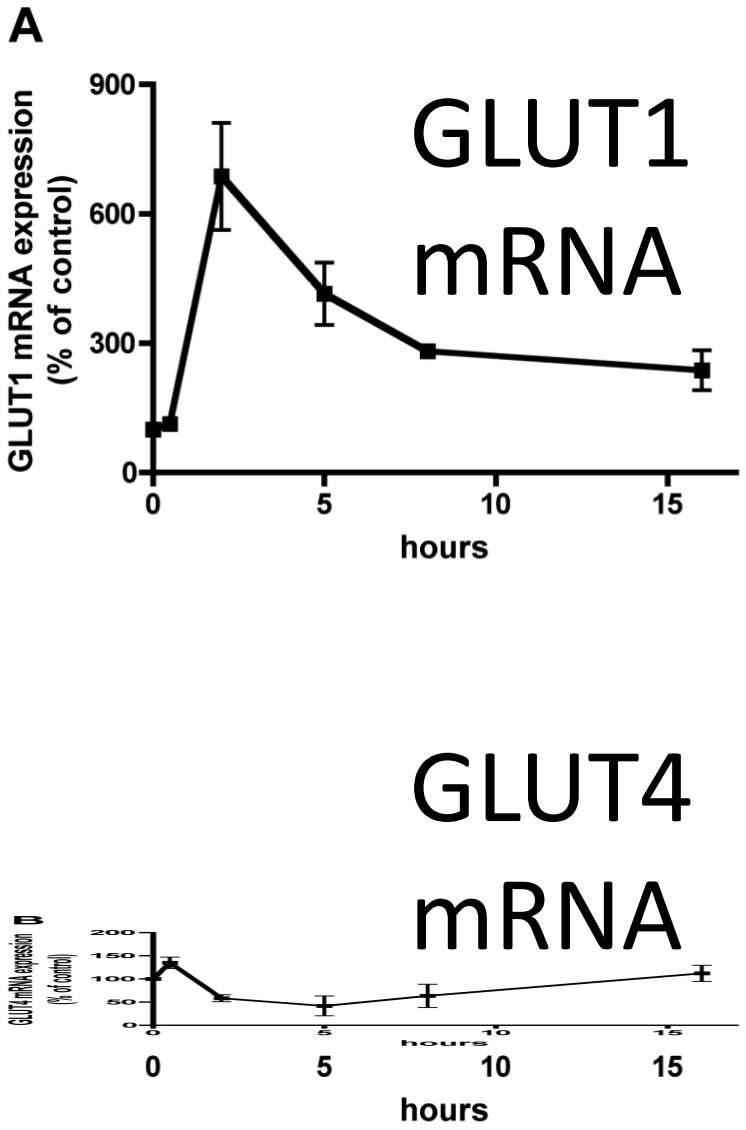

Plasma membrane
Vesicles
NE (h)
0
2
5
0
2
5
β3-AR
ERK


Plasma membrane
Vesicles
NE (h)
0
2
5
0
2
5
GLUT4
β3-AR
ERK

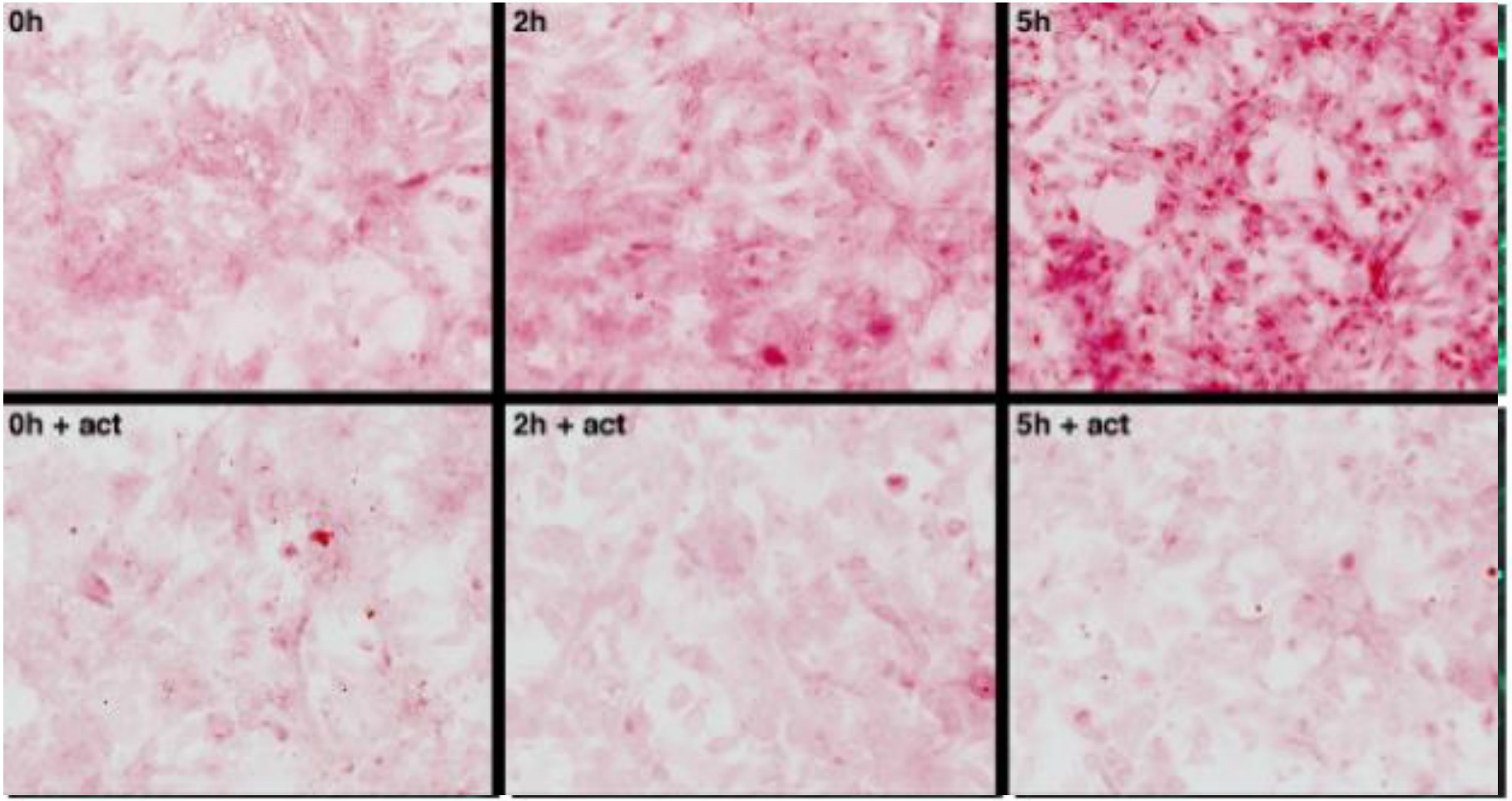

Plasma membrane
Vesicles
NE (h)
0
2
5
0
2
5
GLUT1
GLUT4
β3-AR
ERK


NE
β3-AR
Brown-fat cell
cAMP
mTORC2
glucose
GLUT1

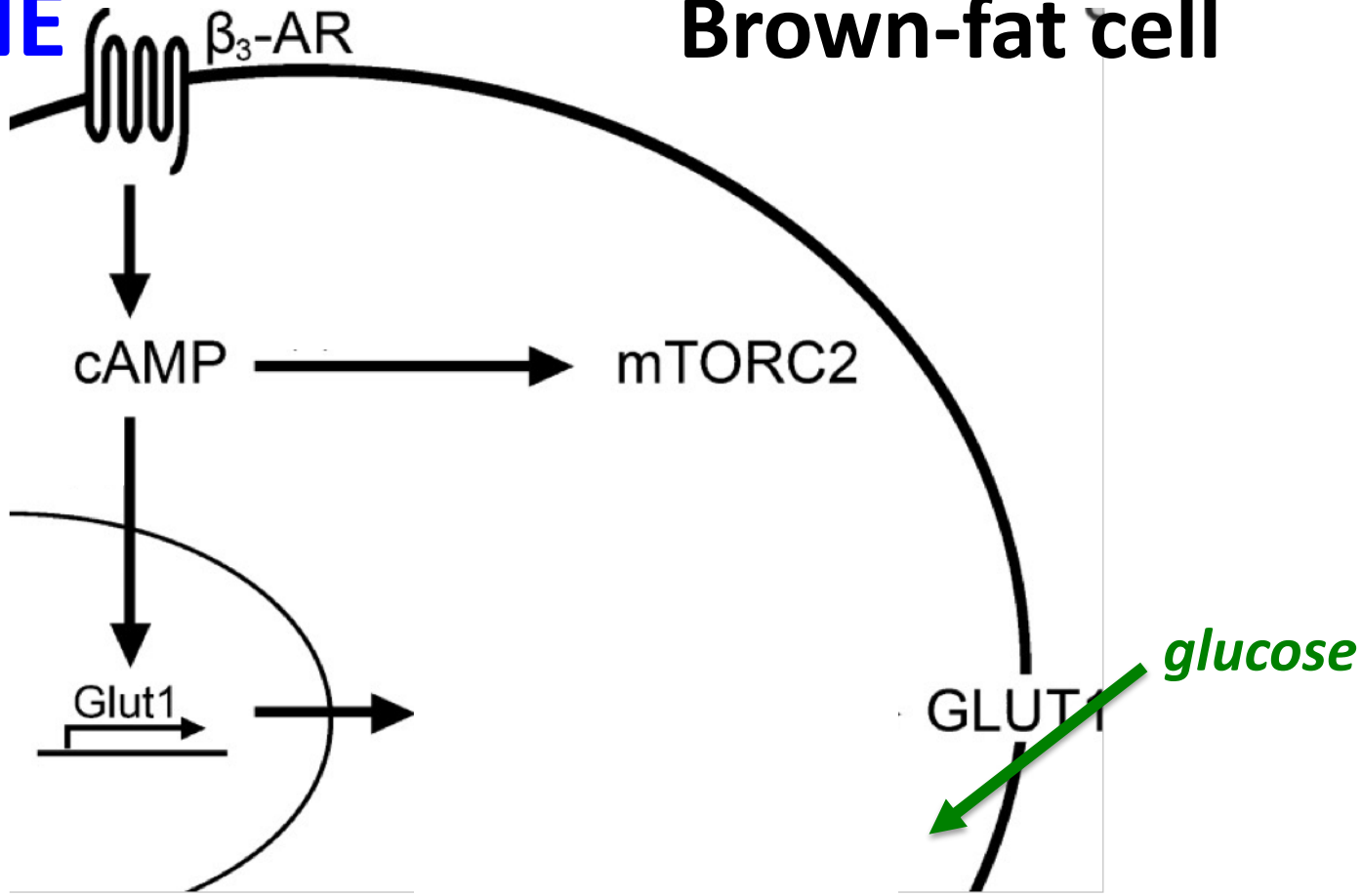
Acute effect of norepinephrine

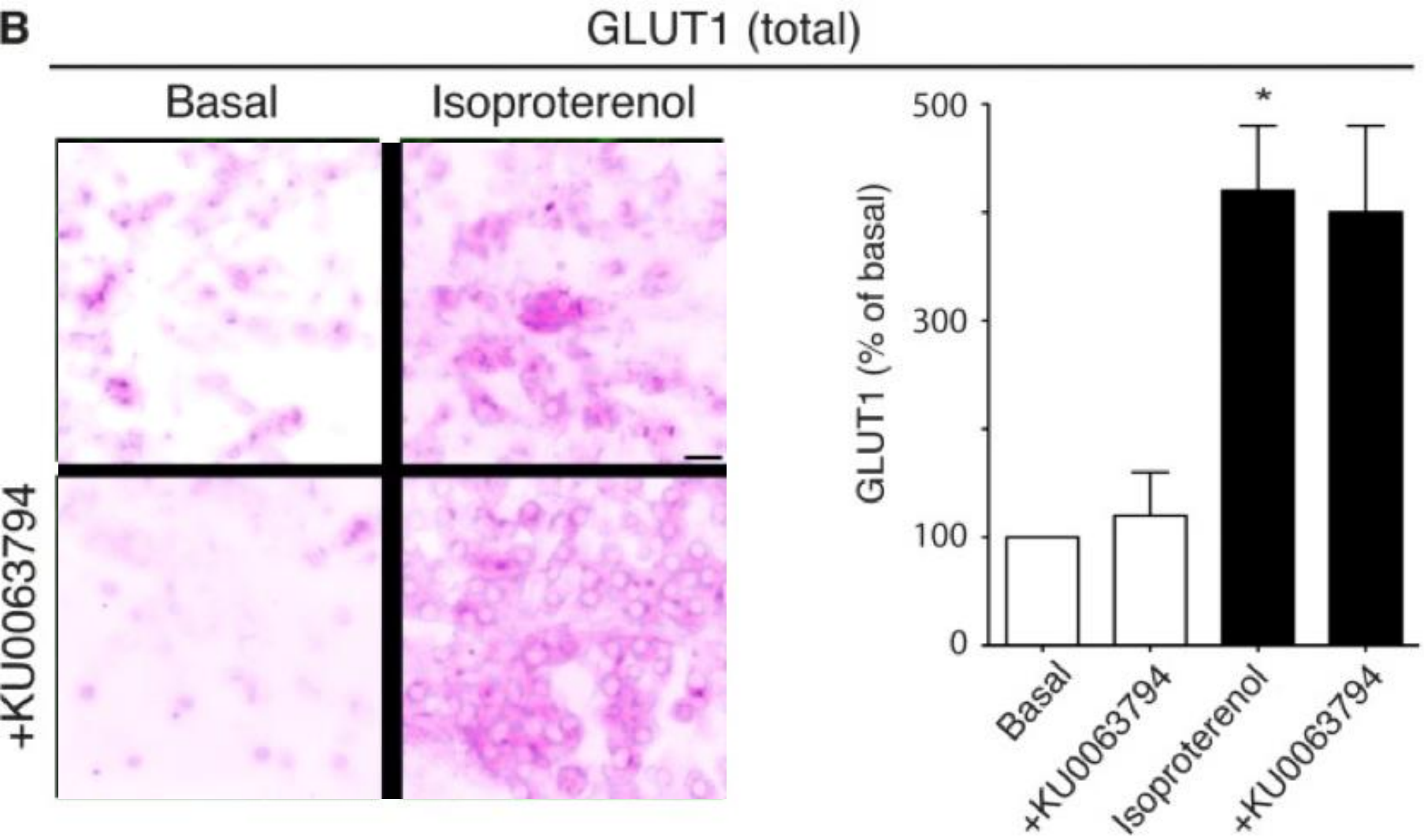


Adrenergically induced appearance of GLUT1 protein

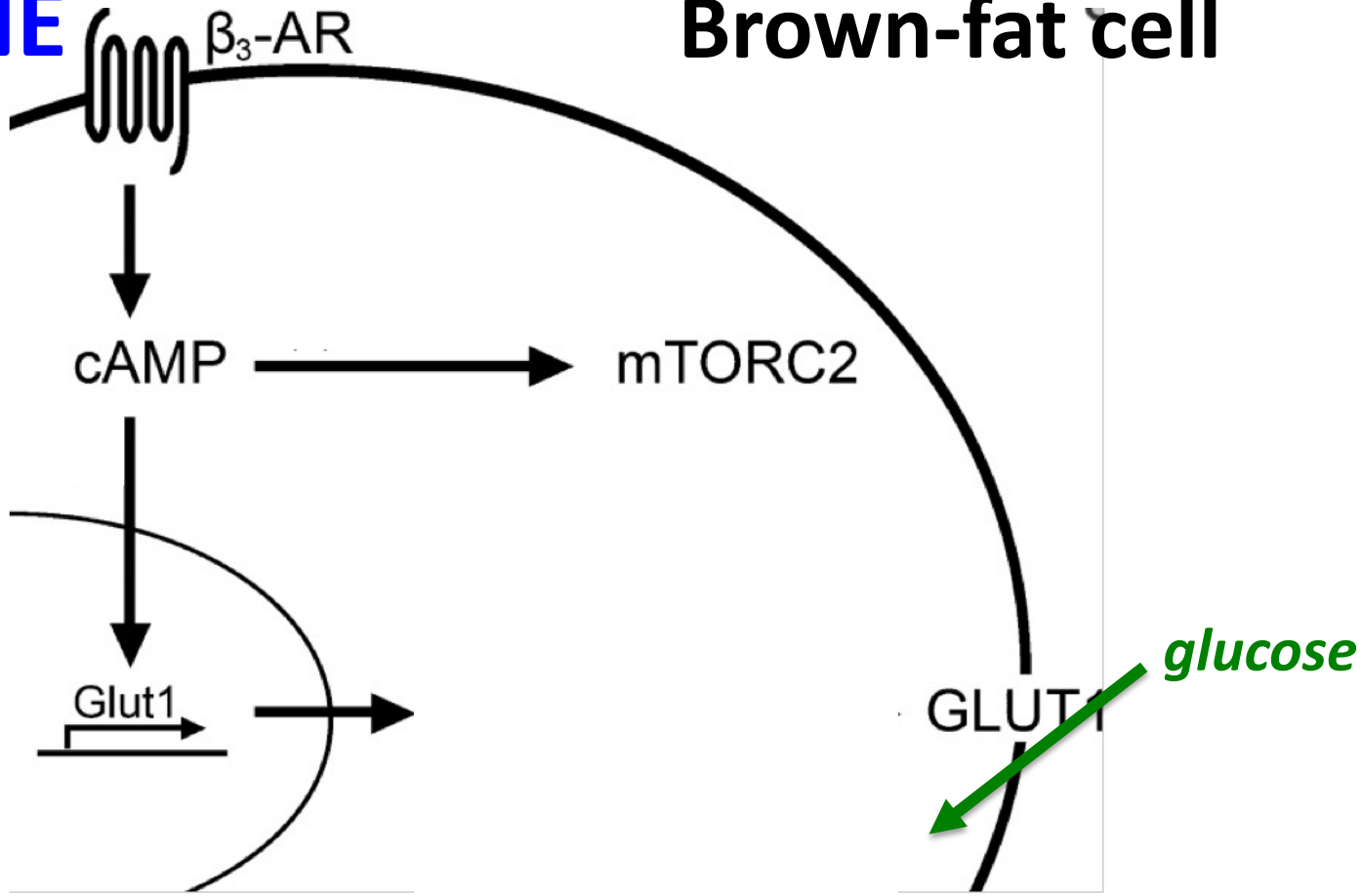


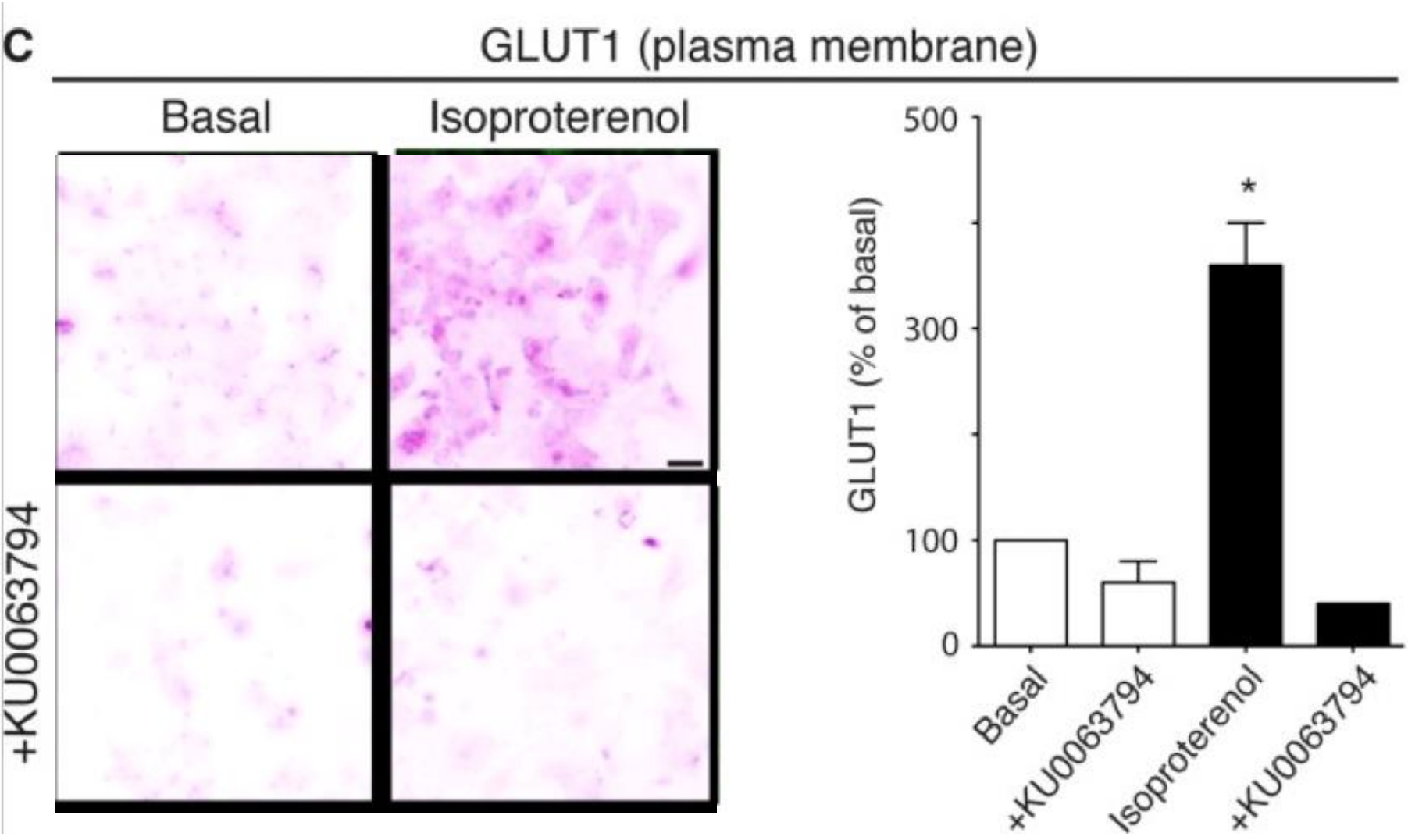
Brown-fat cell




B
GLUT1 (total)
Basal
Isoproterenol
+KU0063794
GLUT1 (% of basal)
500
300
100
0
*
Basal
+KU0063794
Isoproterenol
+KU0063794

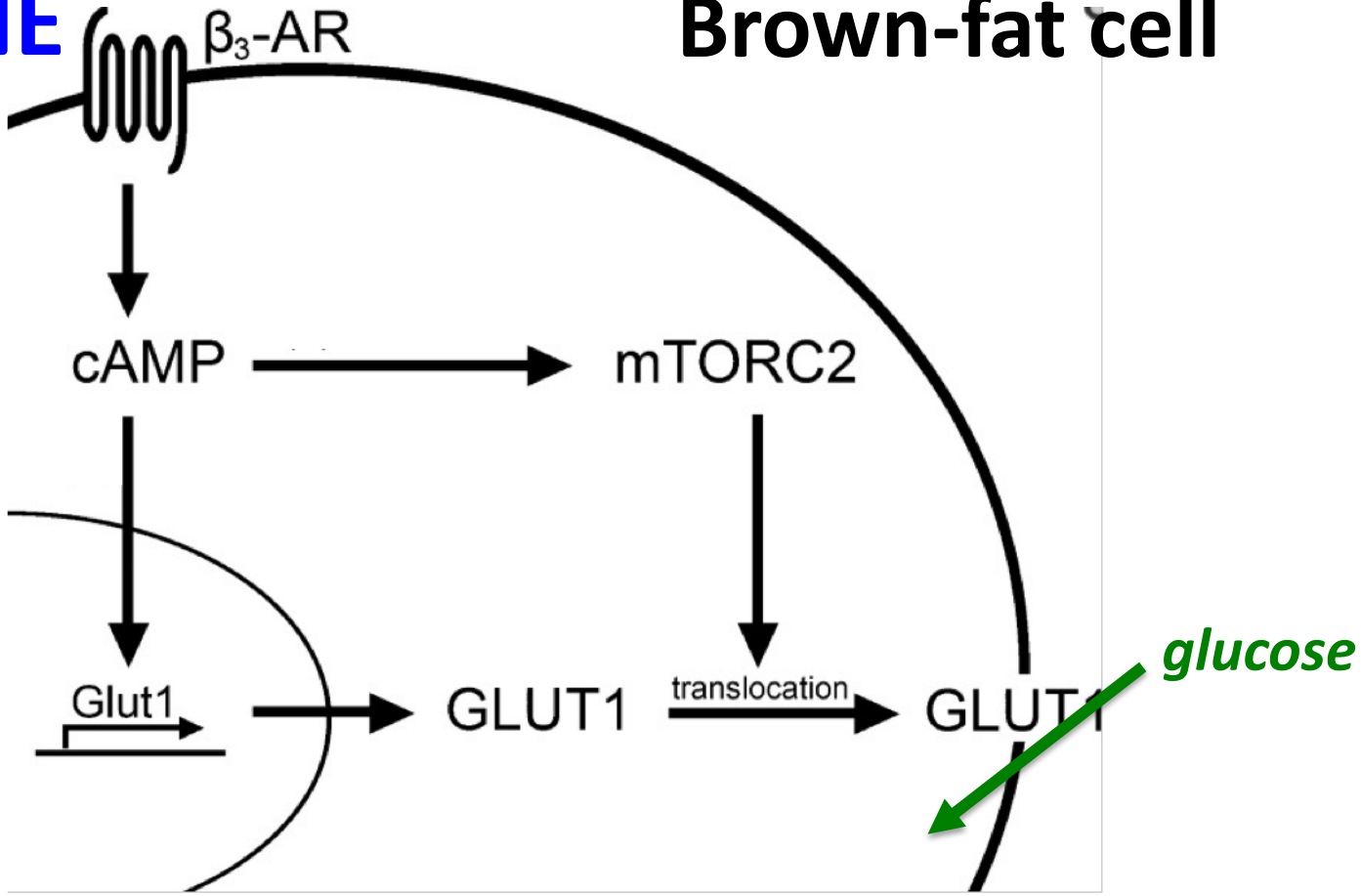
Brown-fat cell

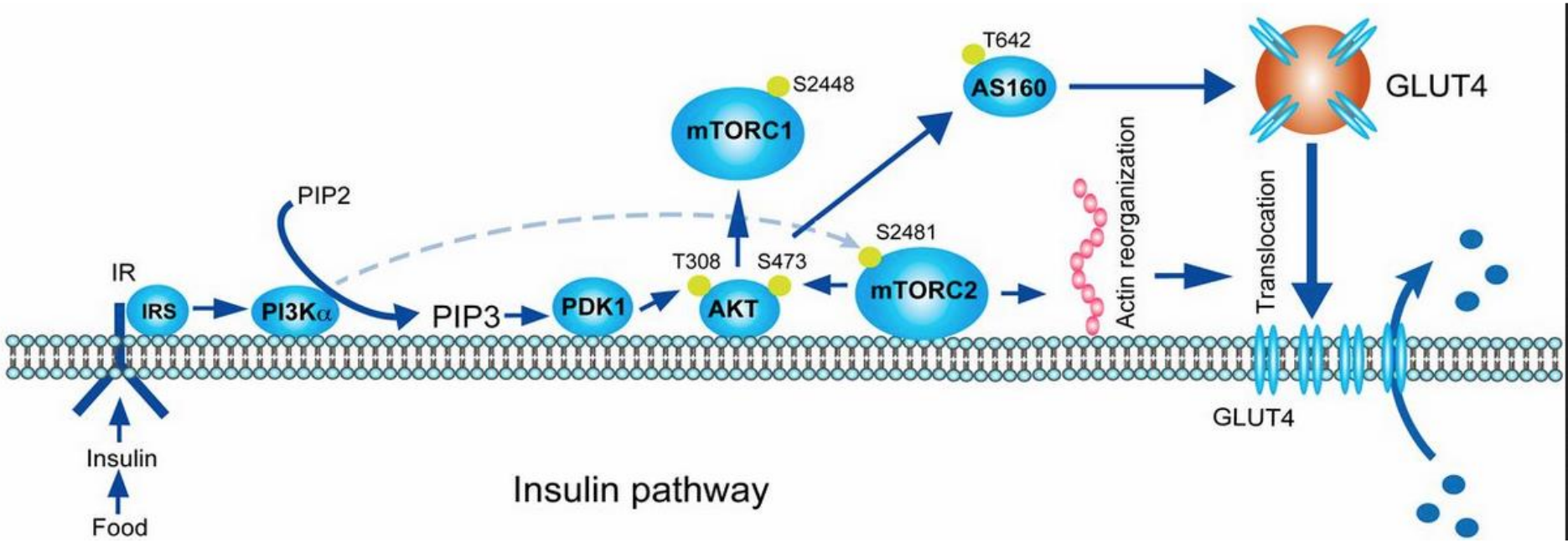



c
GLUT1 (plasma membrane)
Basal
Isoproterenol
+KU0063794
GLUT1 (% of basal)
500
300
100
0
*
Basal
+KU0063794
Isoproterenol
+KU0063794

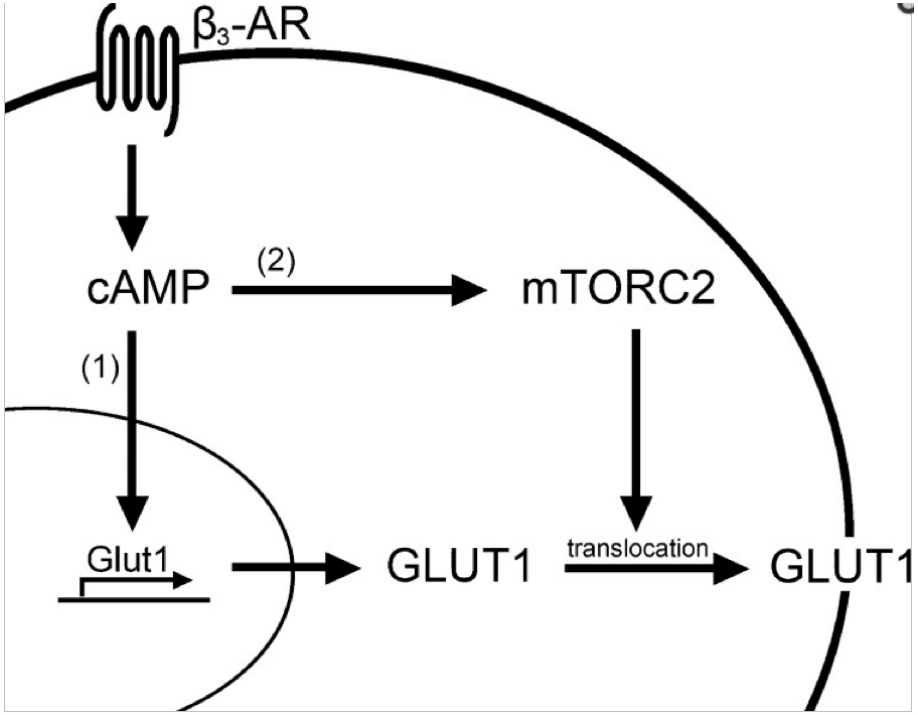
NE

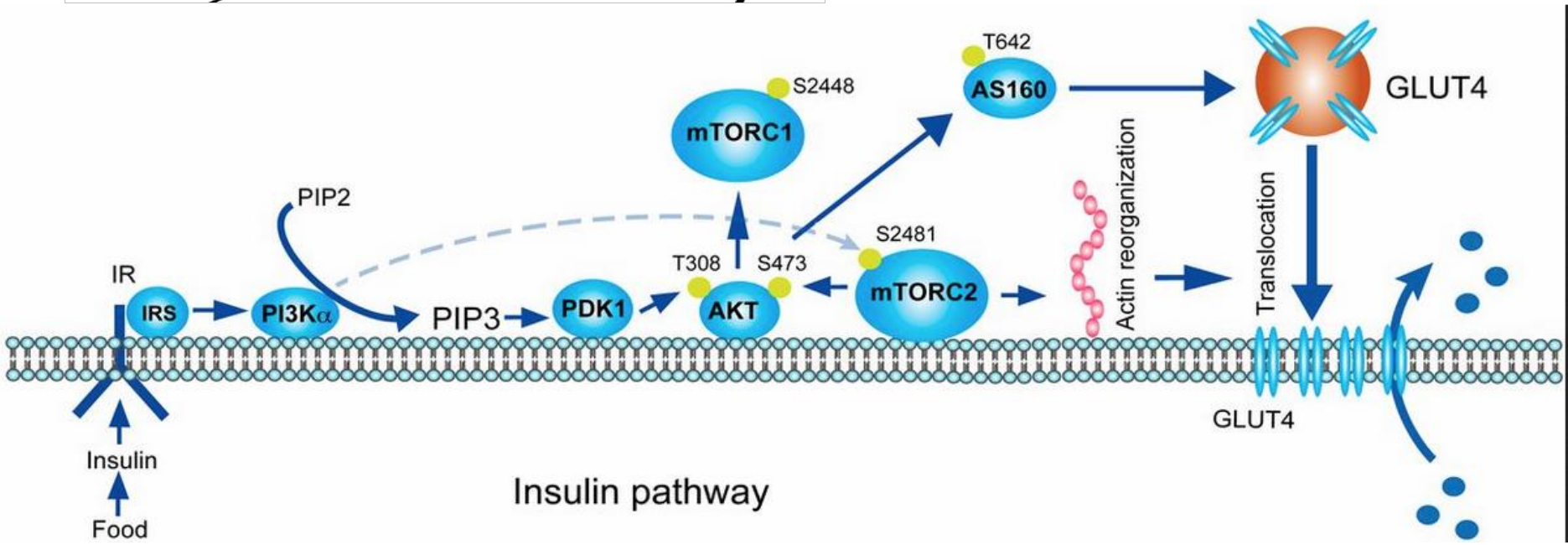
Brown-fat cell

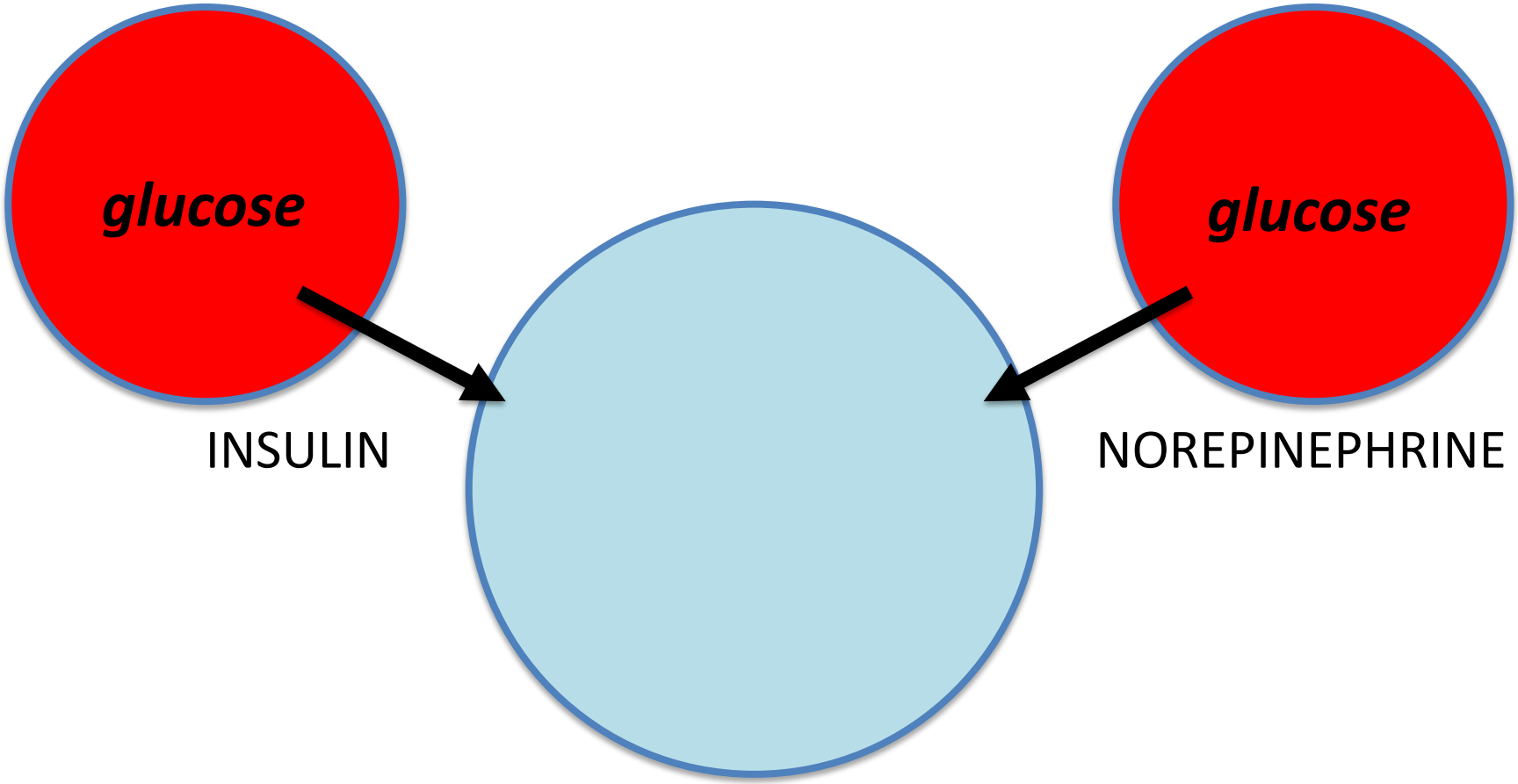




Insulin pathway


β3-AR
cAMP
(2)
mTORC2
(1)
Glut1
GLUT1
translocation
GLUT1


T642
AS160
GLUT4
S2448
mTORC1
PIP2
S2481
T308
S473
IR
IRS
PI3Kα
PIP3
PDK1
AKT
mTORC2
Actin reorganization
Translocation
GLUT4
Insulin
Food
Insulin pathway


glucose
glucose
INSULIN
NOREPINEPHRINE

Worldwide increasing metabolic problems

Metabolic syndrome*:

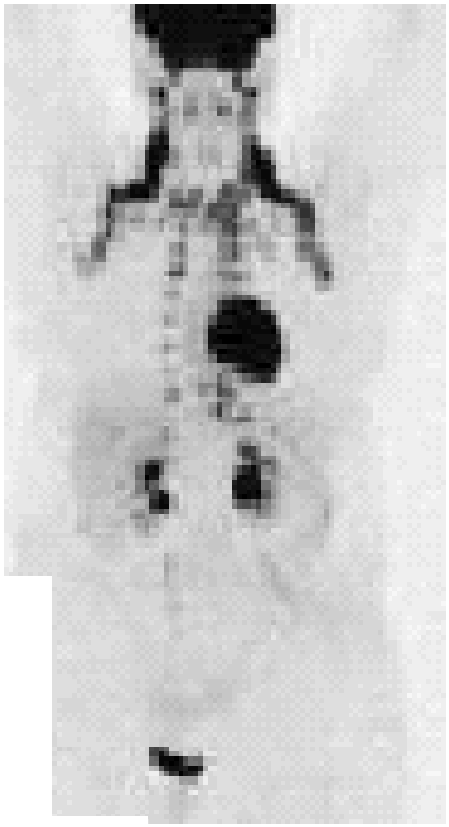
- **Central obesity**

plus any two of the following four factors:

- **raised triglycerides level in blood**
- **reduced HDL cholesterol in blood**
- **raised blood pressure**
- **raised fasting plasma glucose or type 2 diabetes (insulin resistance)**

Active brown adipose tissue has the capacity to modulate most of above parameters

* newest IDF definition



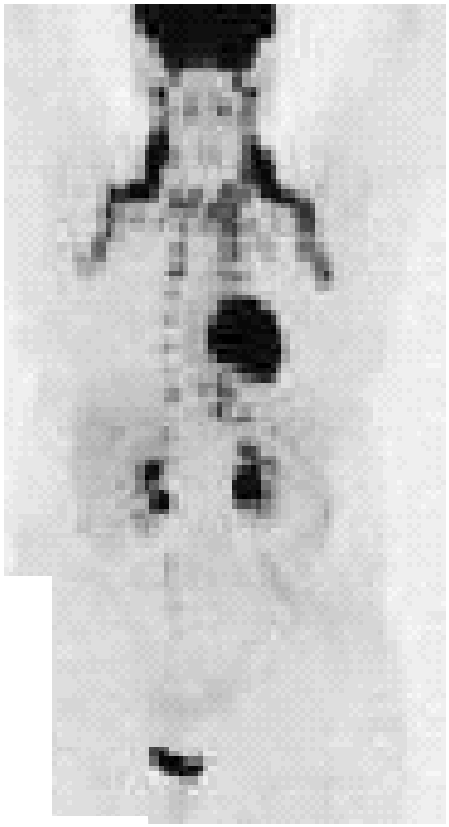
Brown fat only dominates

glucose uptake

when we are inactive

and not postprandial

- and slightly cold



Brown fat only dominates

glucose uptake

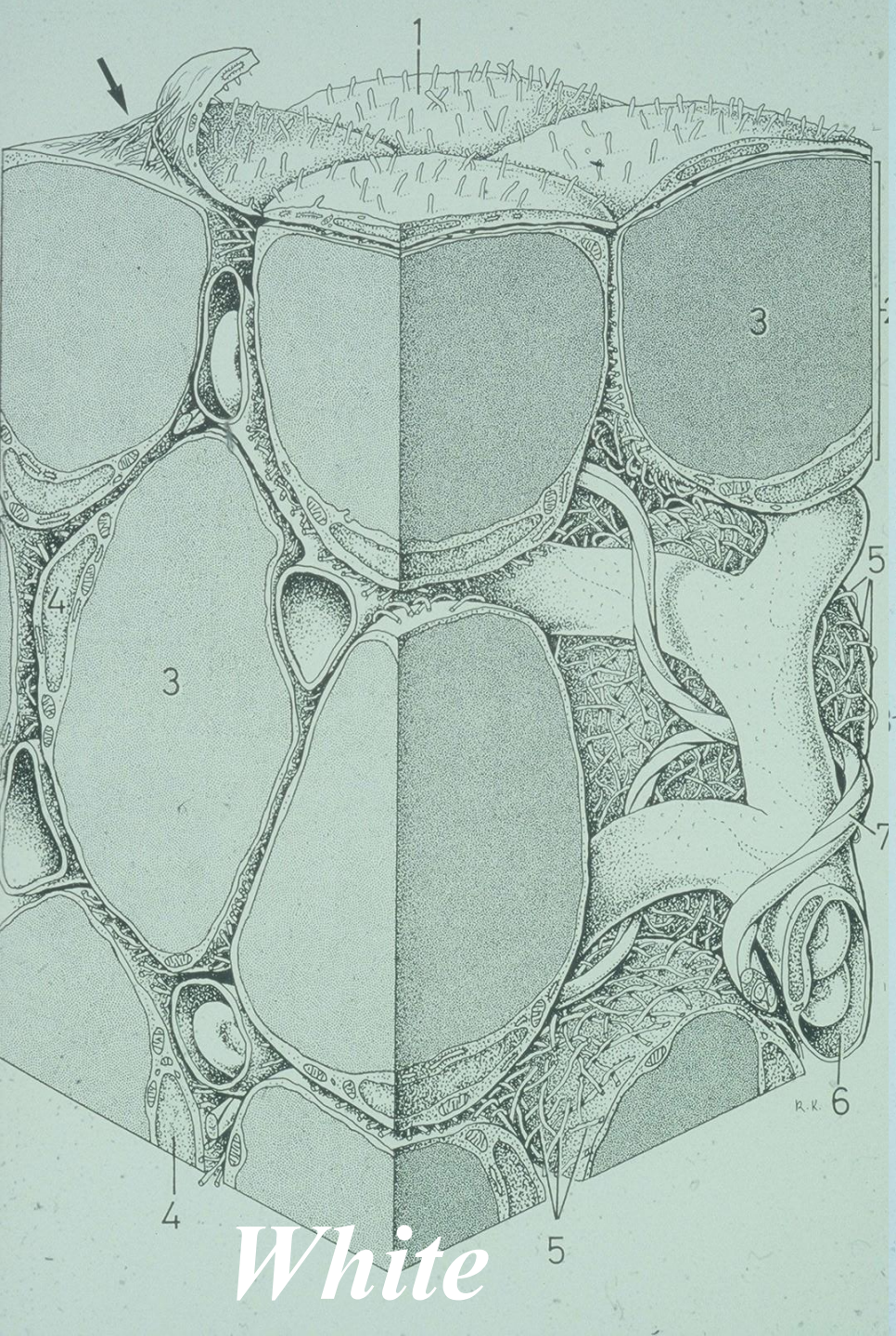
when we are inactive

and not postprandial

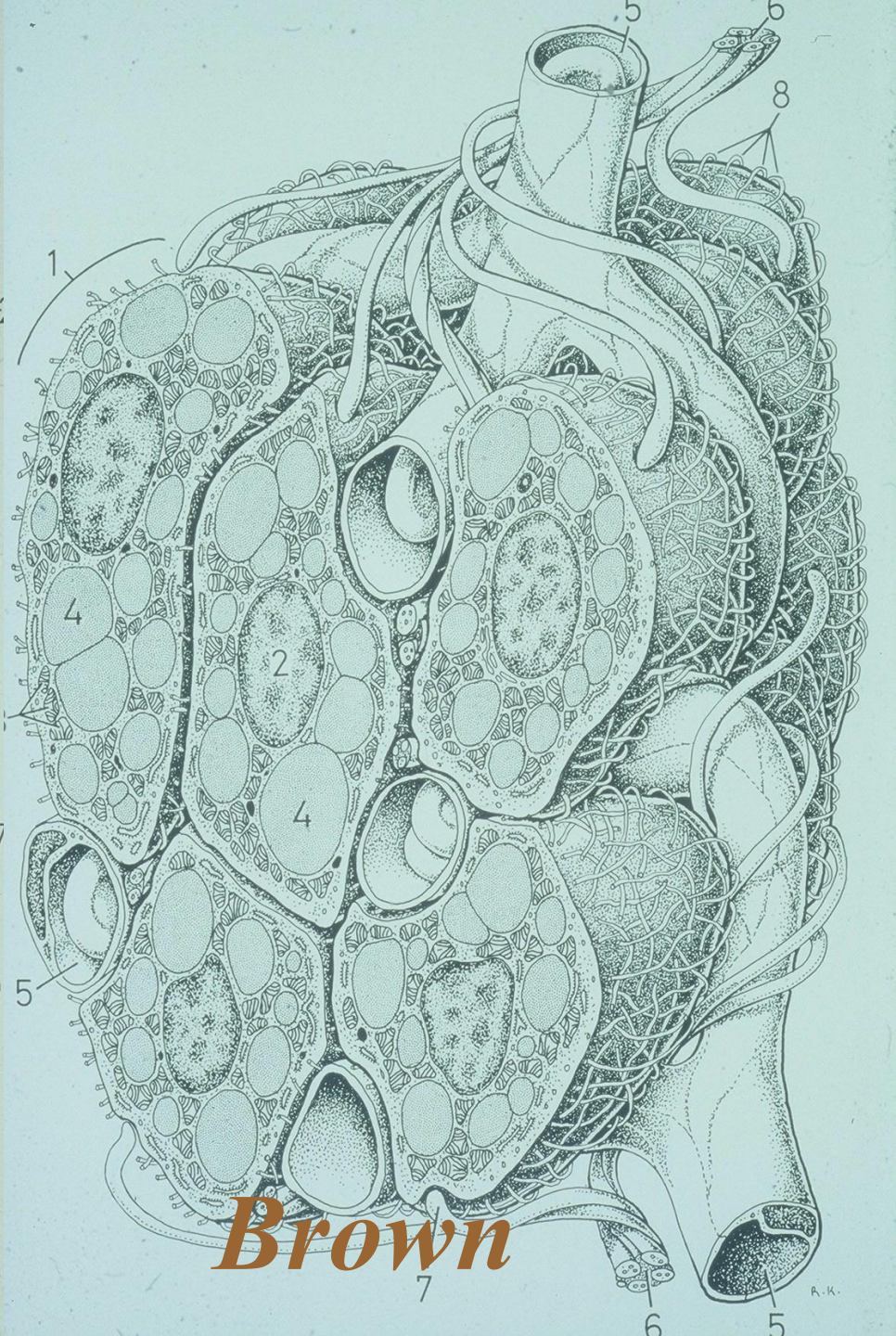
- and slightly cold

- that could be about

1/3 of our life……

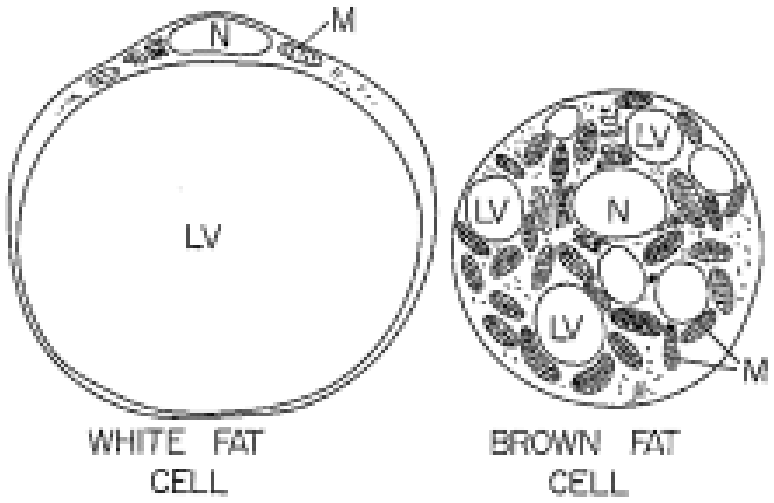


White



Brown

Brown and white fat cells: alike or different?



John Horowitz

Are the cells different due to external ”forces” - or are they inherently different?

Cell culture: brown *versus* white

precursors from

brown adipose tissue (interscapular)

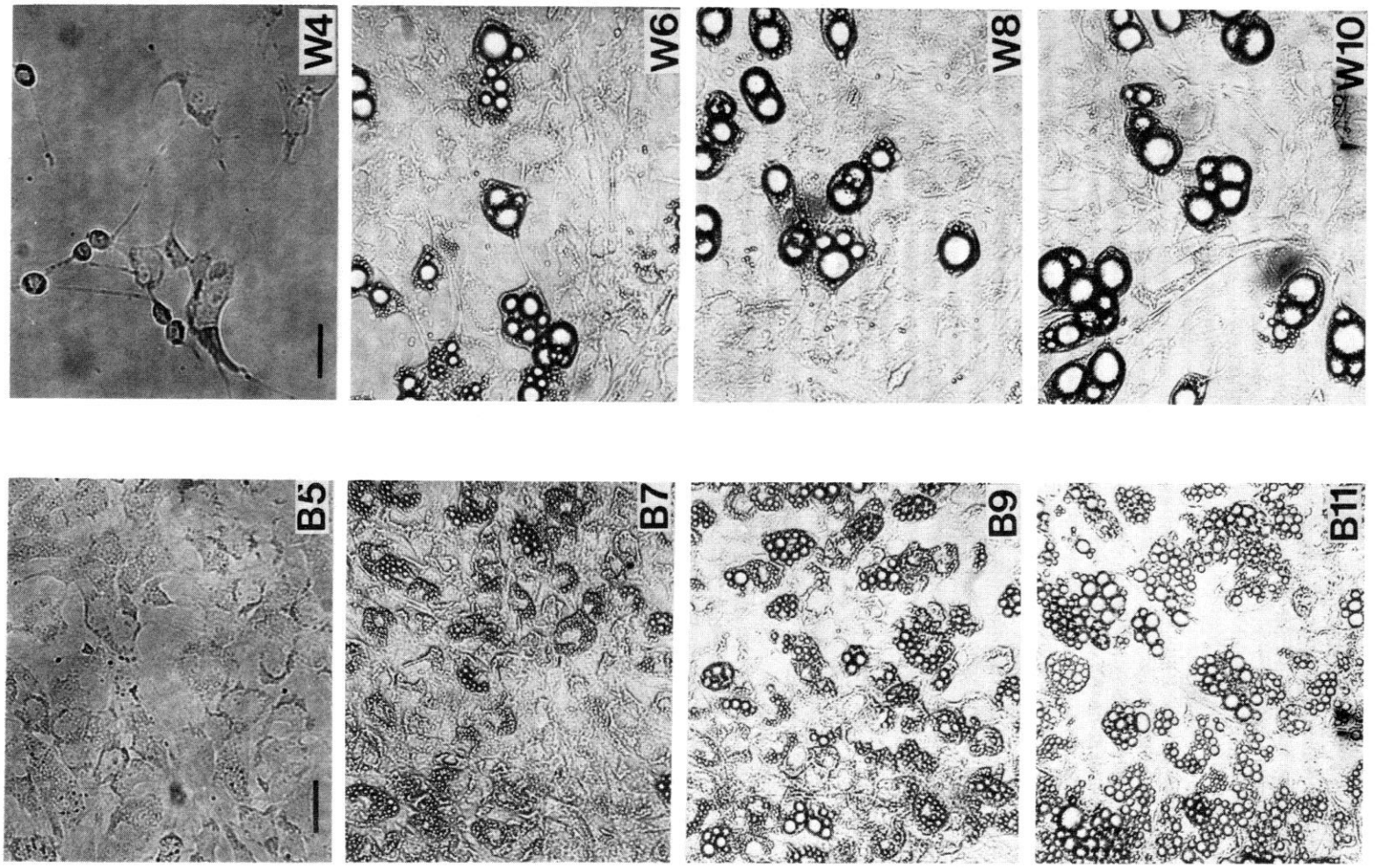
white adipose tissue (epidydimal)

identical culture conditions

differentiate in culture

White precursors

4 6 8 10 days in culture



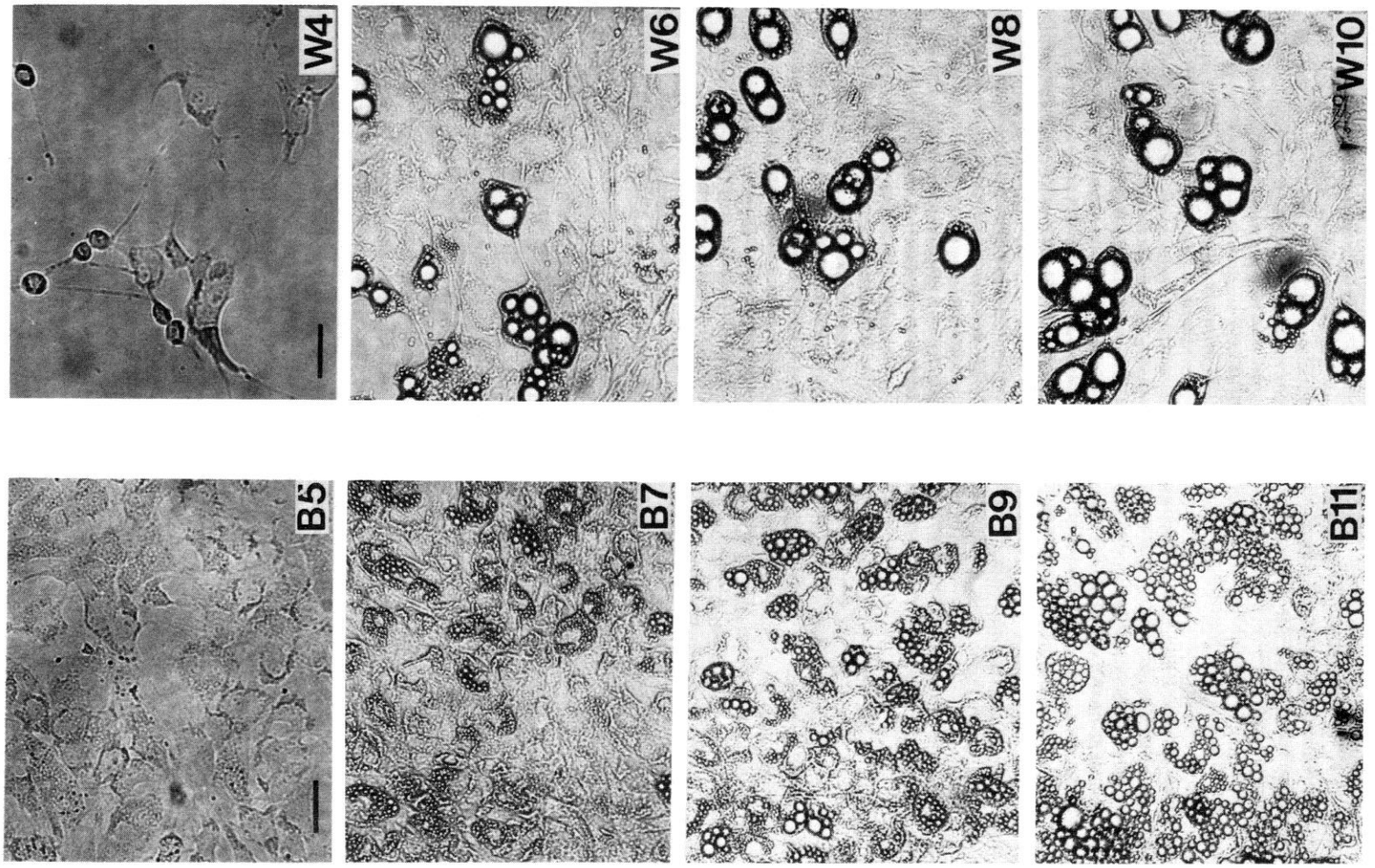
Brown precursors

Rat cells

White precursors

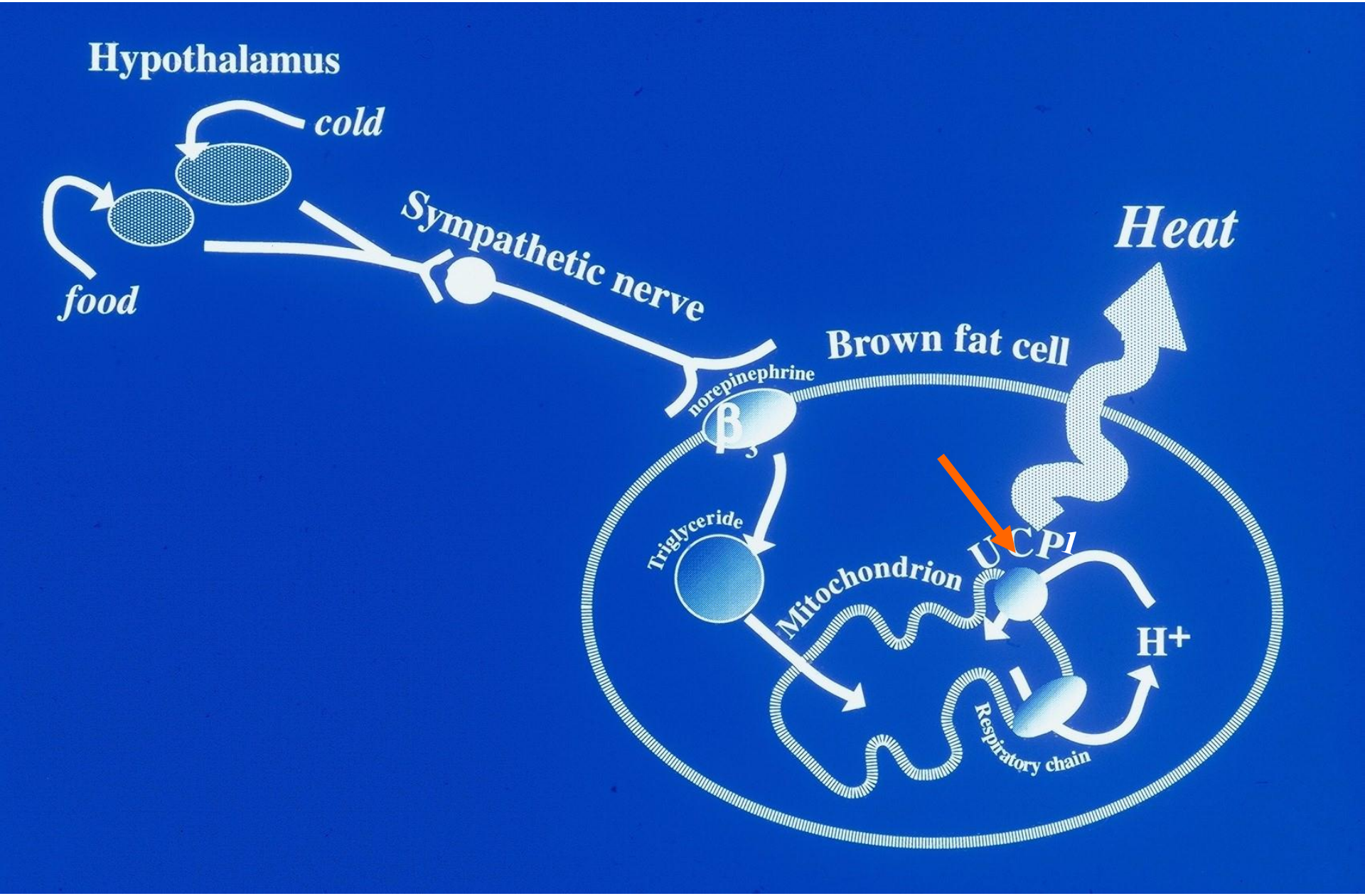
A cell-autonomous difference!

4 6 8 10 days in culture

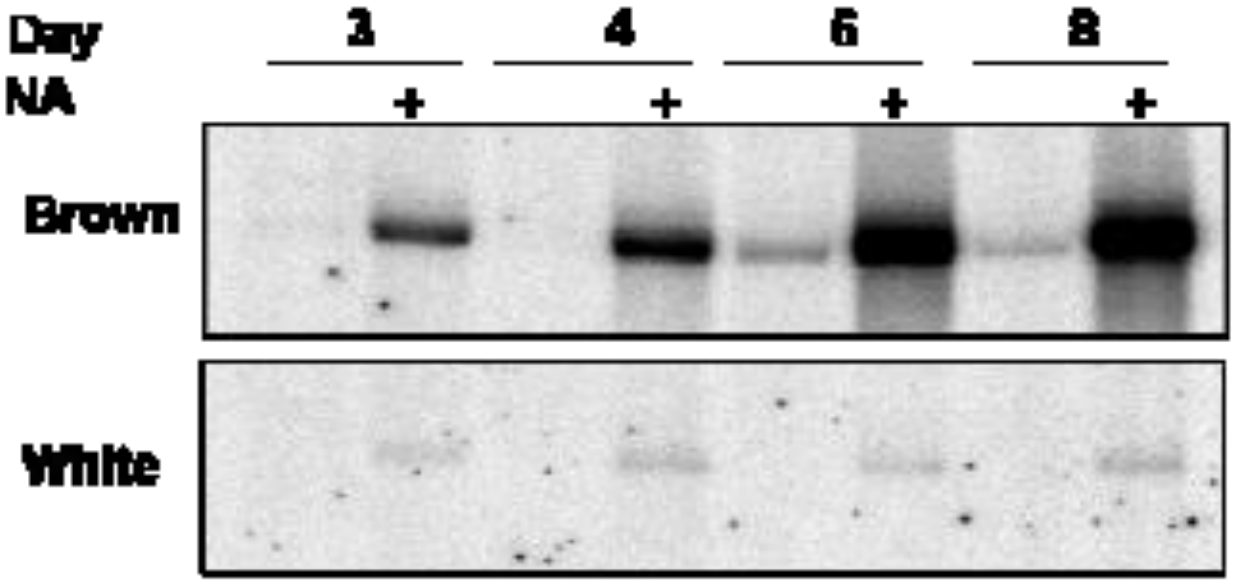


Brown precursors

Rat cells


Hypothalamus
cold
food
Sympathetic nerve
Heat
Brown fat cell
norepinephrine
β3
Triglyceride
Mitochondrion
UCP1
H+
Respiratory chain

brown and white remain different under identical conditions



UCP1

Cell culture:
brown *versus* white

precursors from

brown adipose tissue (interscapular)

white adipose tissue (epidydimal)

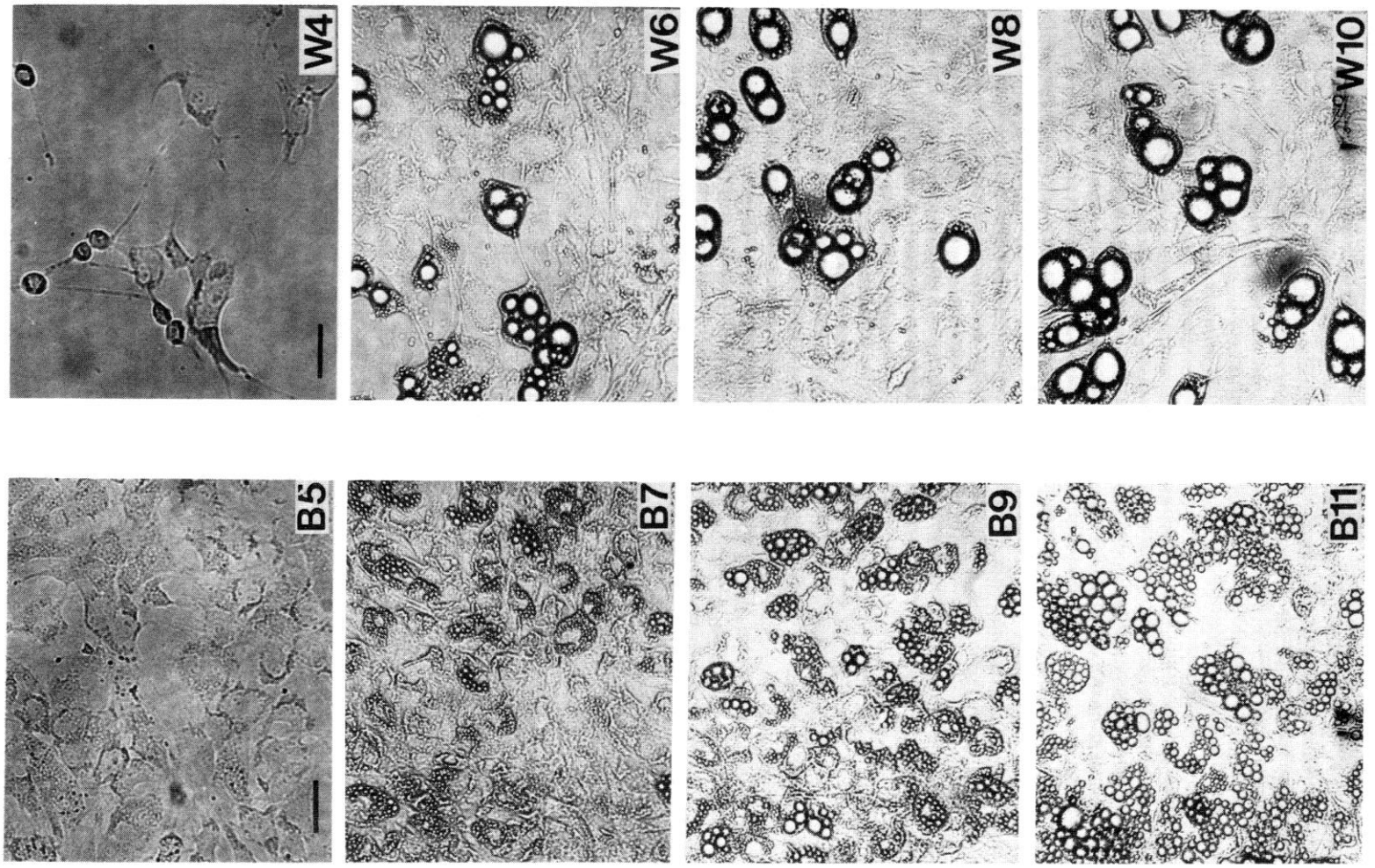
identical
culture
conditions

differentiate in culture

examine global gene expression

White precursors

4 6 8 10 days in culture



Brown precursors

Rat cells

Genes enriched >5 fold in brown versus white undifferentiated pre-adipocytes

Gene Symbol	Gene Title
Acta1	actin, alpha 1, skeletal muscle
Actc1	actin, alpha, cardiac
Cd83	CD83 antigen
Chrna1	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)
Cldn5	claudin 5
Icam2	intercellular adhesion molecule 2
Lhx8	LIM homeobox protein 8
Meox2	mesenchyme homeobox 2
Mme	membrane metallo endopeptidase
Myh3	myosin, heavy polypeptide 3, skeletal muscle, embryonic
Myl1	myosin, light polypeptide 1
Mylpf	myosin light chain, phosphorylatable, fast skeletal muscle
Myog	*myogenin*
Tbx15	T-box 15
Tnnc1	troponin C, cardiac/slow skeletal
Tnni1	troponin I, skeletal, slow 1
Tnnt3	troponin T3, skeletal, fast
Zic1	zinc finger protein of the cerebellum 1

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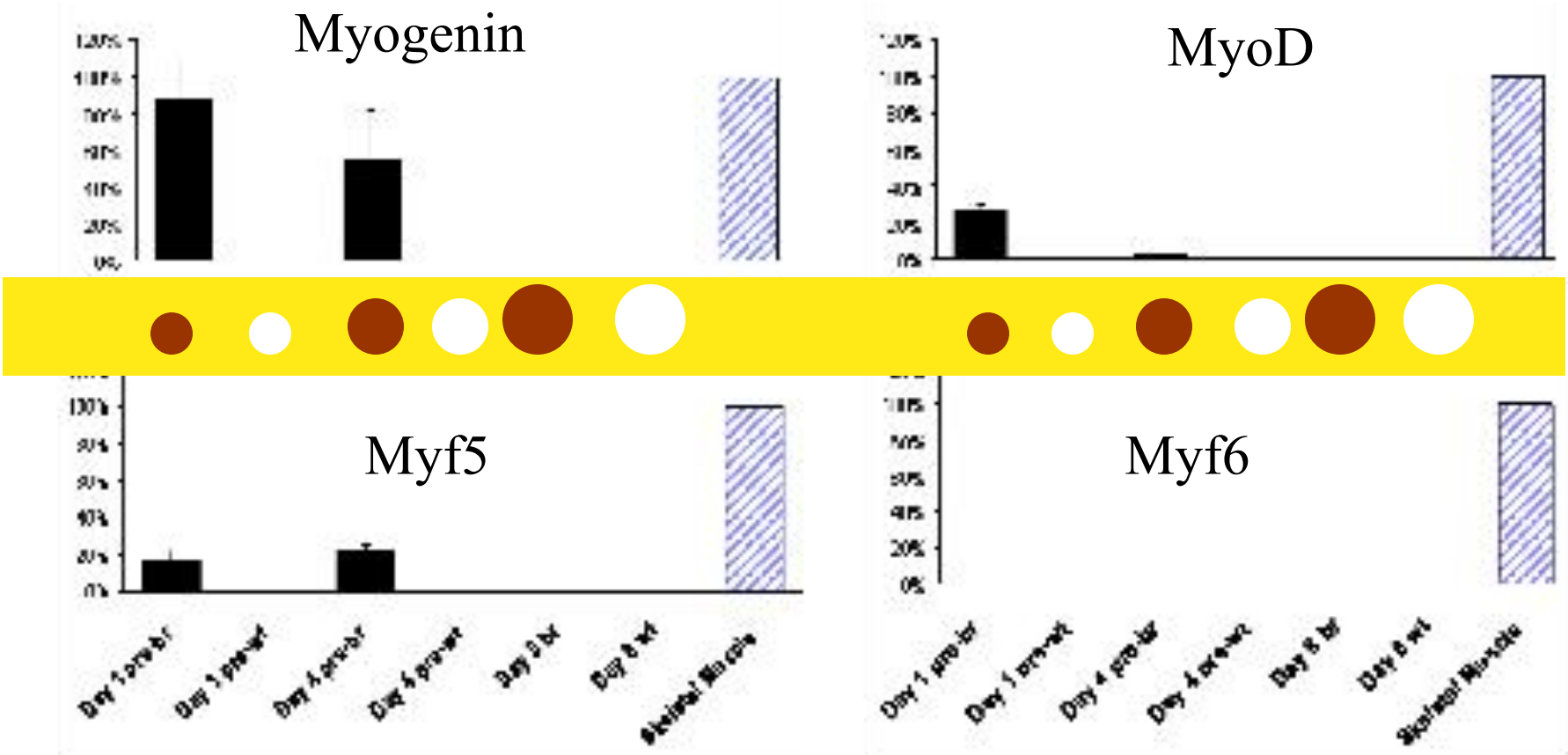
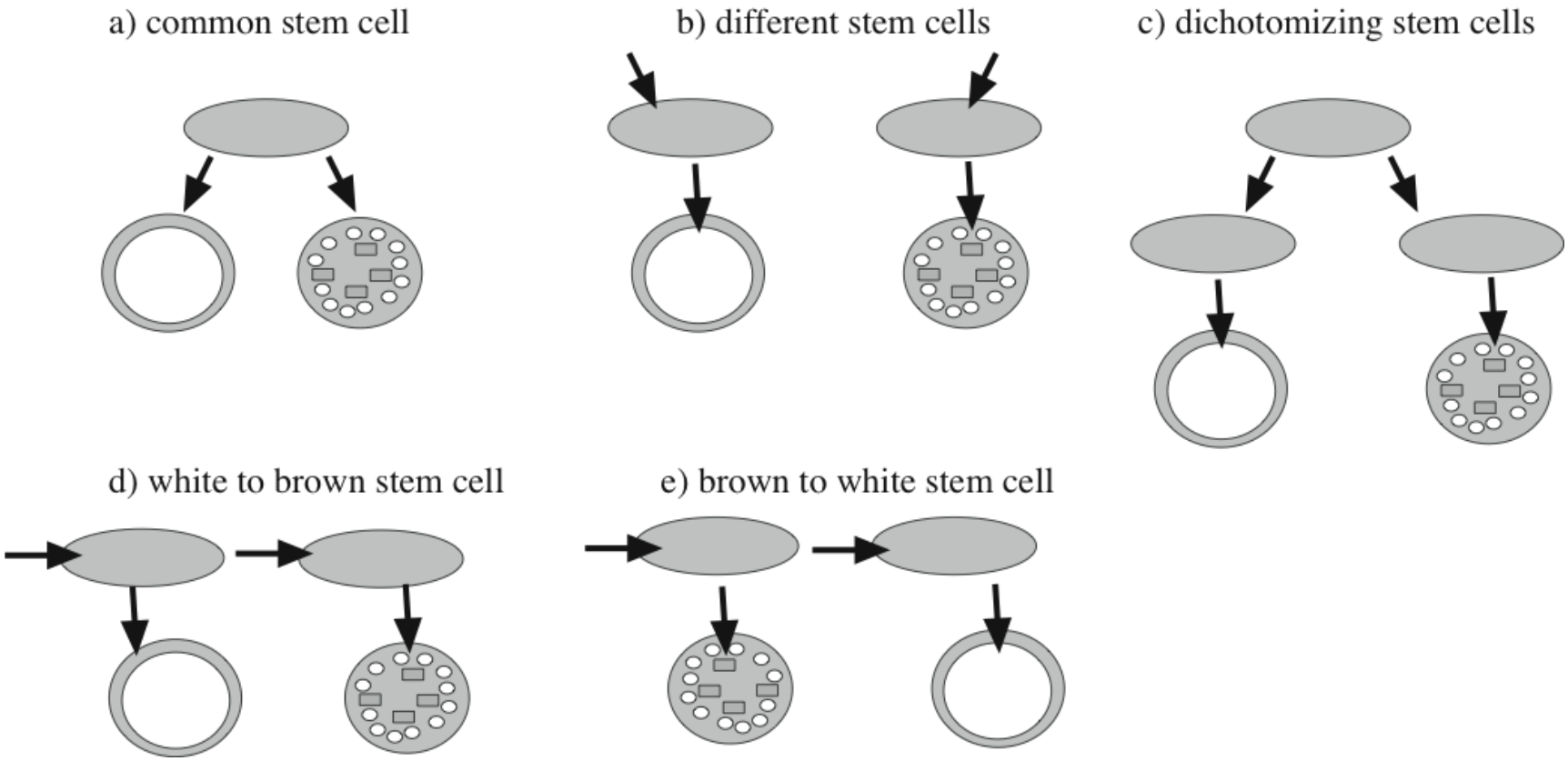
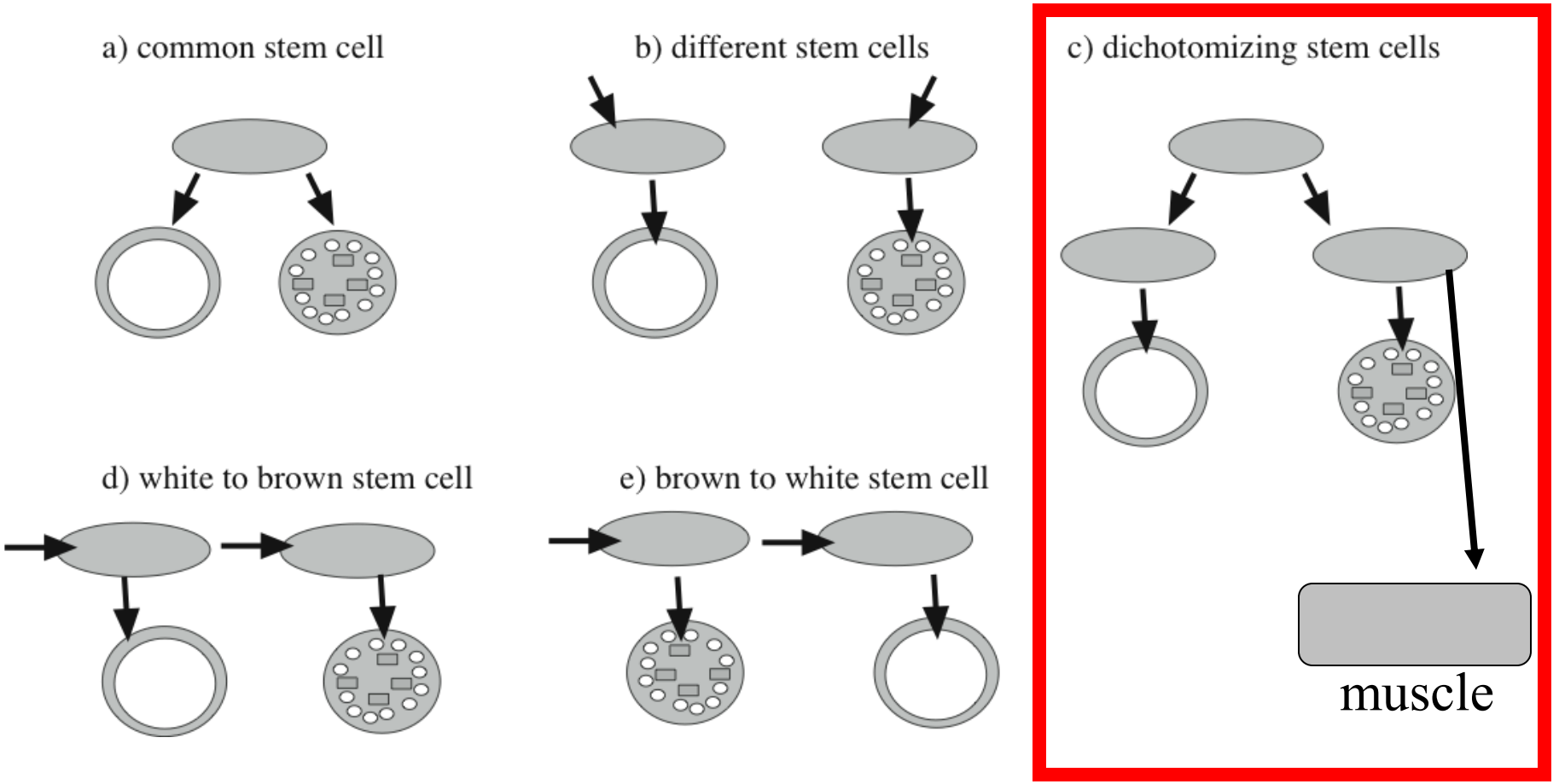

Myogenin
MyoD
Myf5
Myf6

A myogenic gene expression signature establishes that brown and white adipocytes originate from distinct cell lineages



A myogenic gene expression signature establishes
that brown and white adipocytes originate from distinct cell lineages

Timmons et al. (2007) PNAS

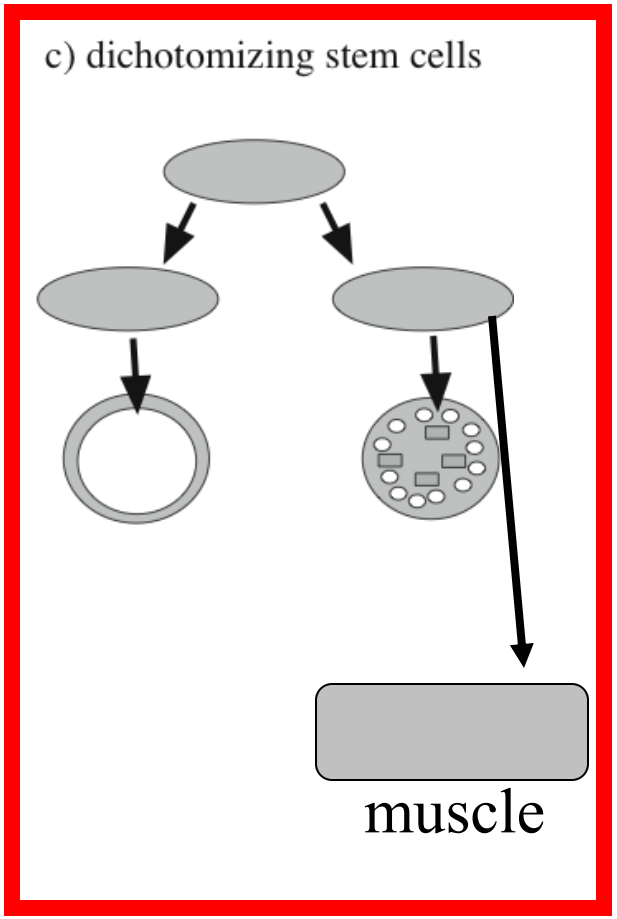


A myogenic gene expression signature establishes
that brown and white adipocytes originate from distinct cell lineages

Timmons et al. (2007) PNAS

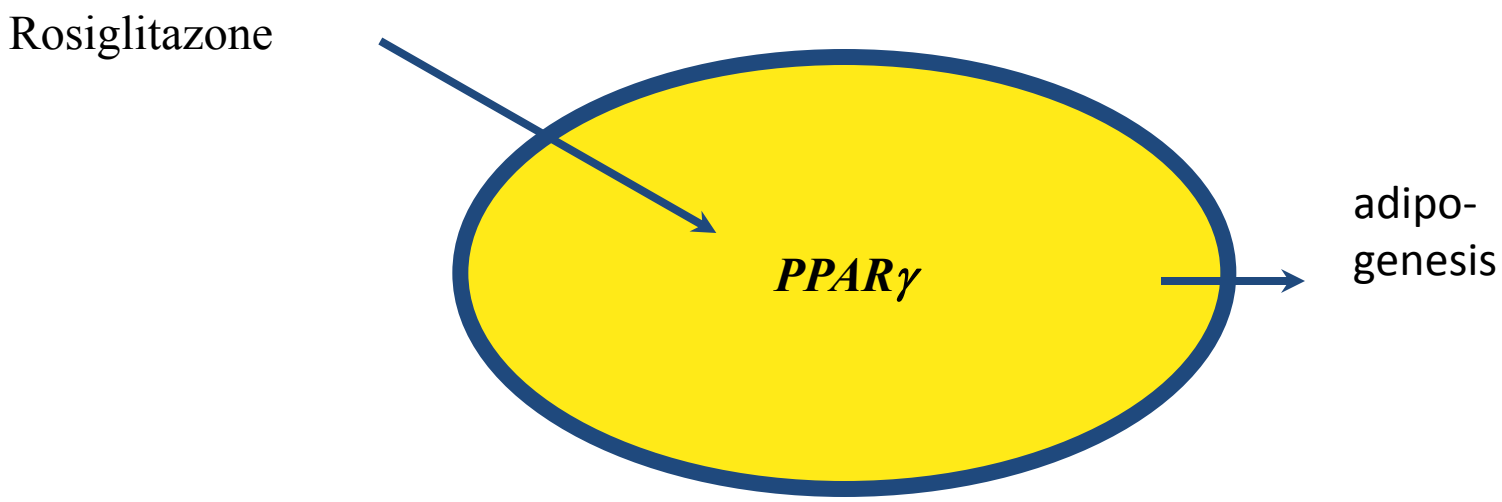
Brown fat cells are “adipomyocytes”

-



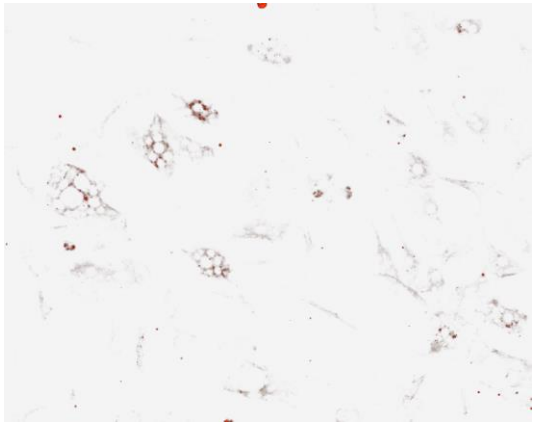
Are all UCP1-containing cells brown adipocytes?

Treatment of *white* adipocytes



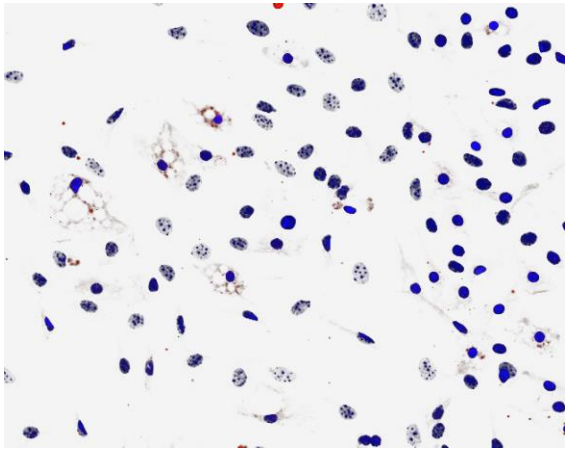
White adipocytes

VDAC



UCP1

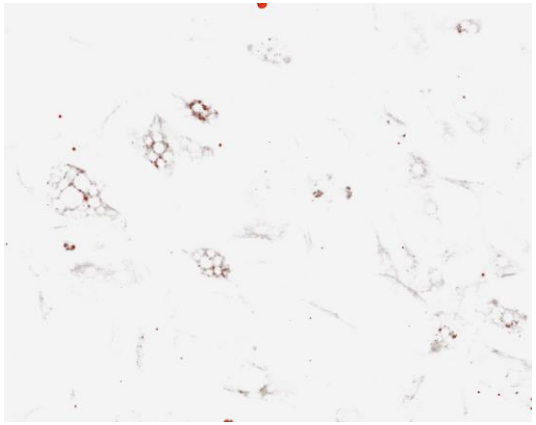
VDAC
UCP1
nuclei



Do all white fat cells become "brown"?
(i.e. express UCP1)?

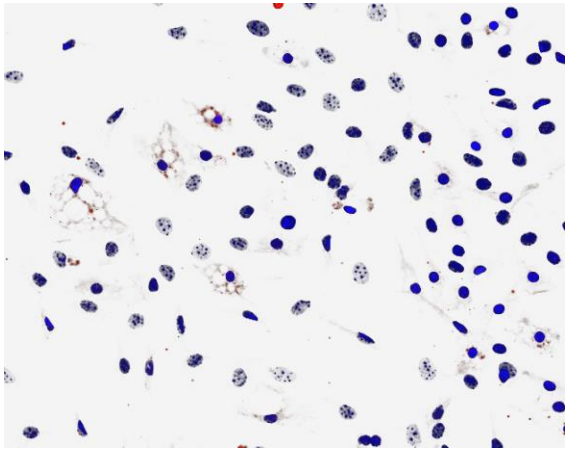
White adipocytes

VDAC

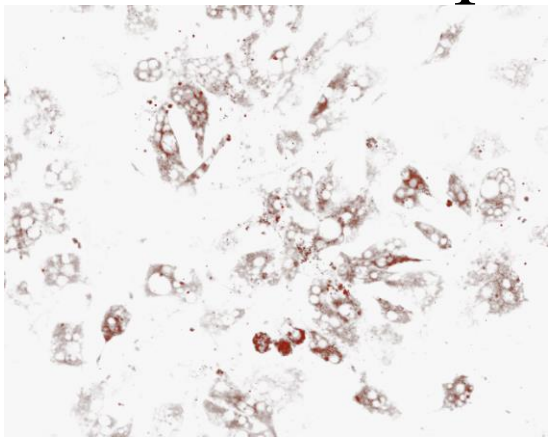


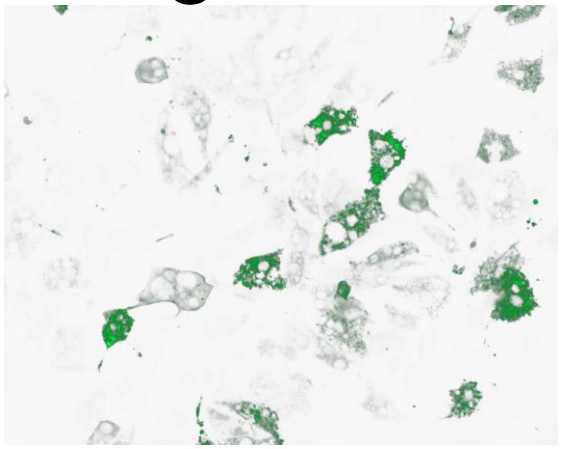
UCP1

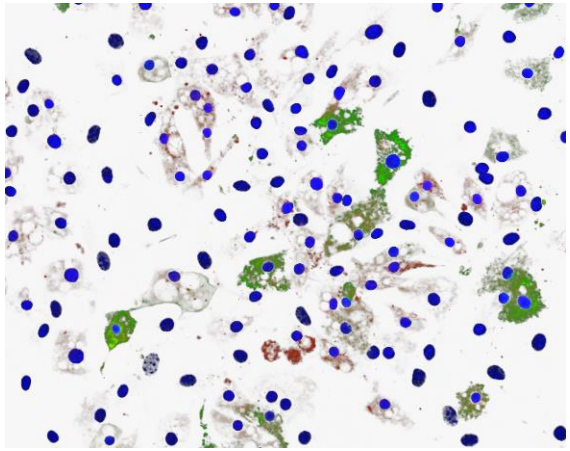
VDAC
UCP1
nuclei

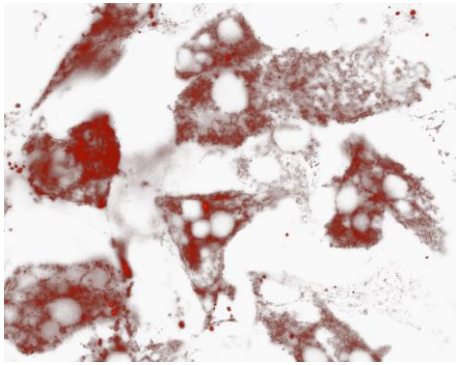
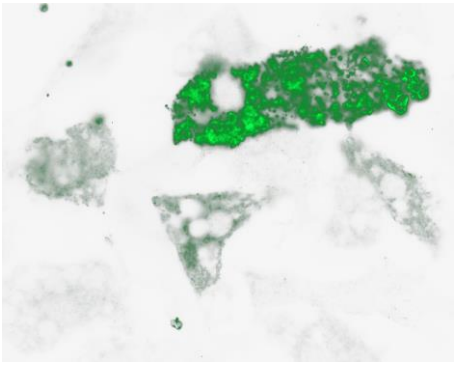
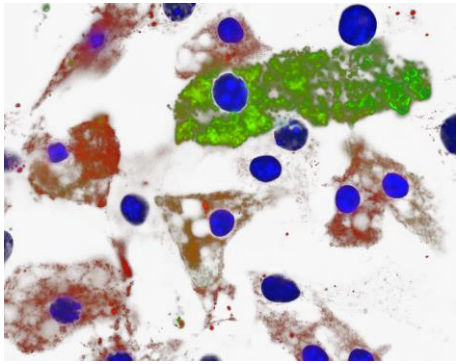


plus rosiglitazone



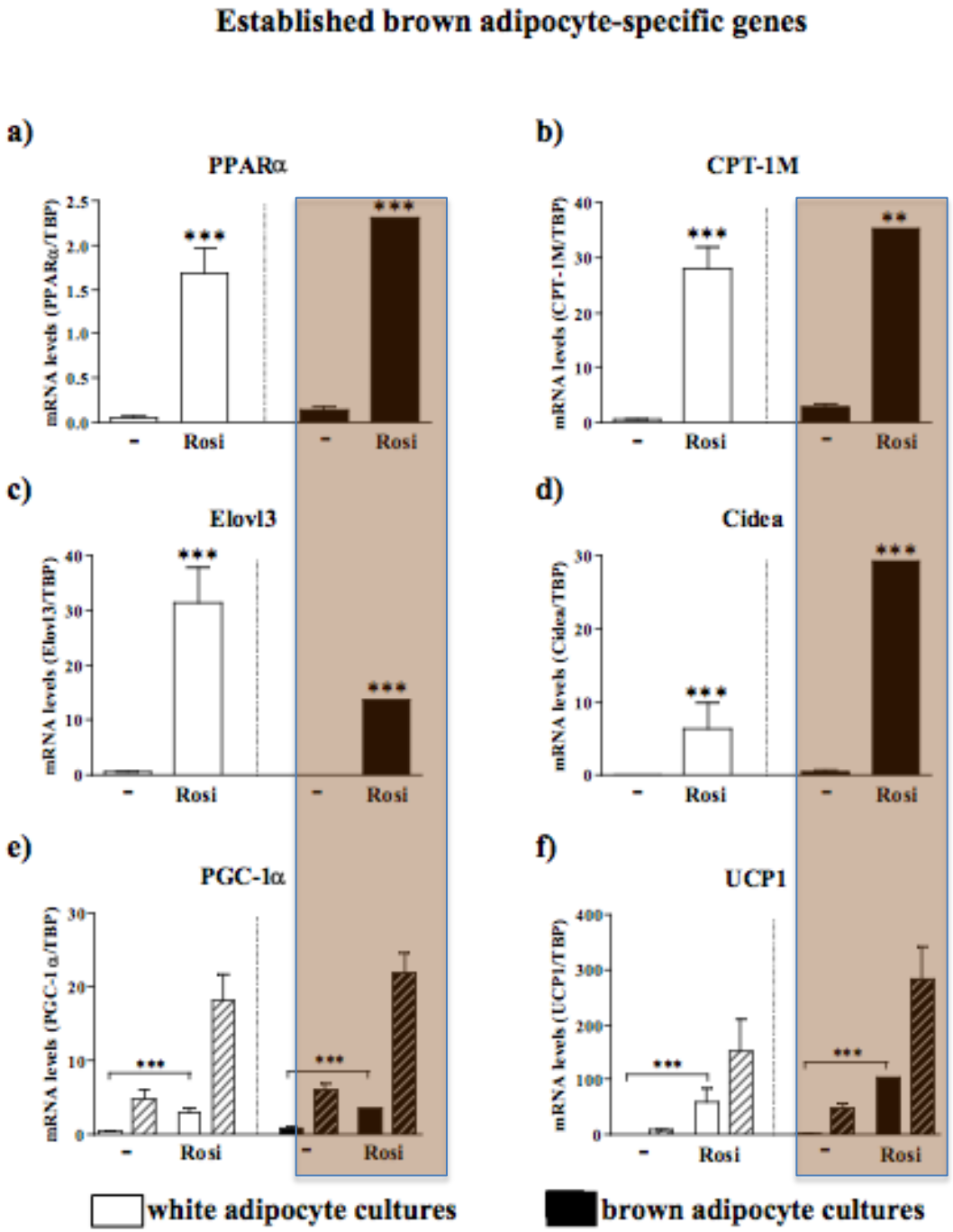




	VDAC	UCP1	VDAC UCP1 nuclei
White adipocytes Rosiglitazone			

Are the UCP1-expressing cells
"true" brown adipocytes?

They express UCP1 - but is that sufficient?



Established brown adipocyte genes are induced in white adipocytes

Are the UCP1-expressing cells
"true" brown adipocytes?

They express UCP1 - but is that sufficient?

What characterizes a "true" brown adipocyte?

Genes enriched >5 fold
in brown versus white undifferentiated pre-adipocytes

Gene Symbol	Gene Title
Acta1	**actin, alpha 1, skeletal muscle**
Actc1	**actin, alpha, cardiac**
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Chrna1	**cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)**
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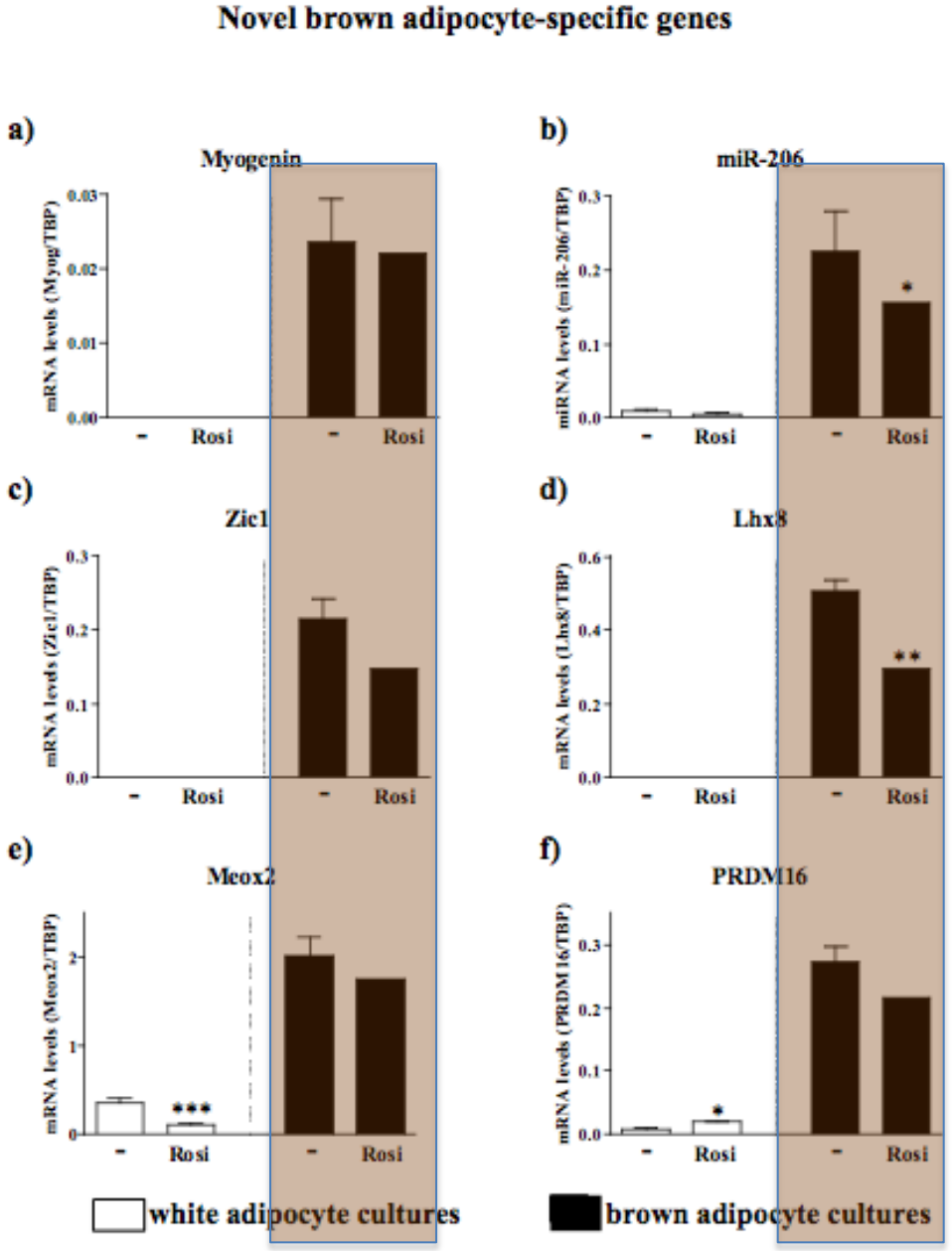
Lhx8

Zic1

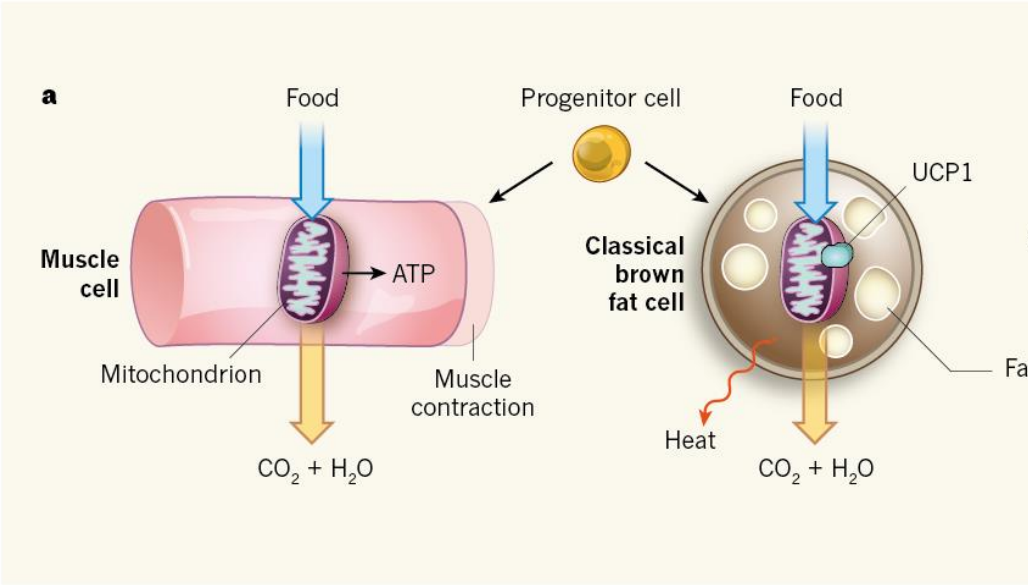


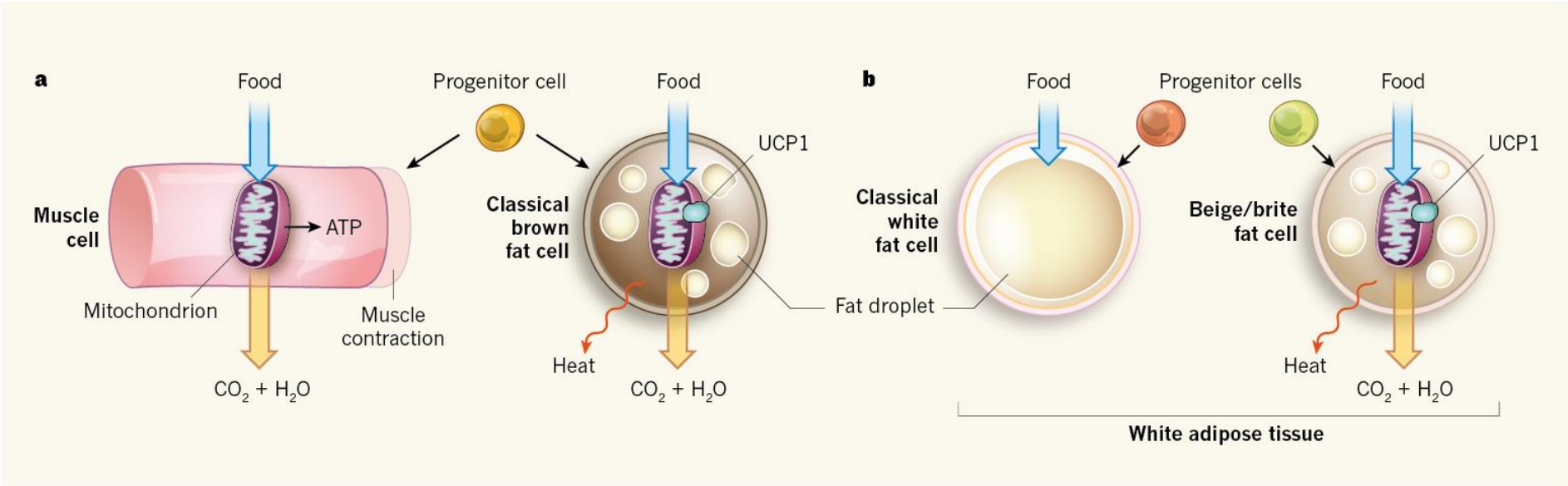
Novel brown adipocyte genes are *not* induced in white adipocytes

Thus, these cells are neither brown, nor white,
but they are **BR**own-like in wh**ITE** cultures:

thus they are **BRITE!**

or beige or induced or ectopic


a
Food
Progenitor cell
Food
UCP1
Muscle cell
ATP
Classical brown fat cell
Mitochondrion
Muscle contraction
Fa
Heat
$CO_2 + H_2O$
$CO_2 + H_2O$


a
Food
Progenitor cell
Food
UCP1
Muscle cell
ATP
Classical brown fat cell
Mitochondrion
Muscle contraction
Fat droplet
Heat
$CO_2 + H_2O$
$CO_2 + H_2O$
b
Food
Progenitor cells
Food
UCP1
Classical white fat cell
Beige/brite fat cell
Heat
$CO_2 + H_2O$
White adipose tissue

What is the point of brite/beige adipose tissue?

Heat production as in brown fat?

Yes, but capacity only 0-20 % of that of brown fat (in mice)

Only form in humans?

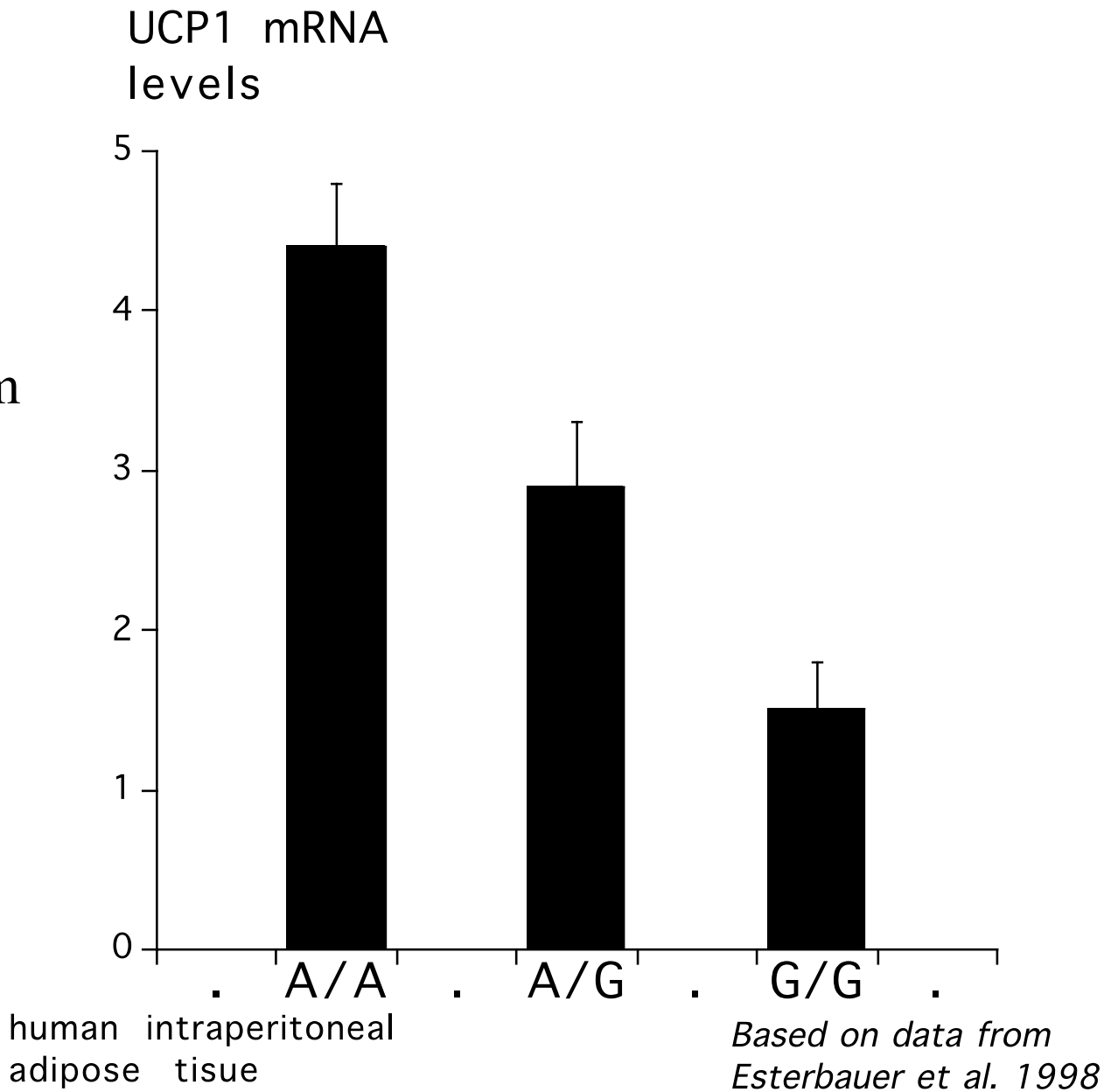
Probably not, humans have both, just like mice

Doing something else?

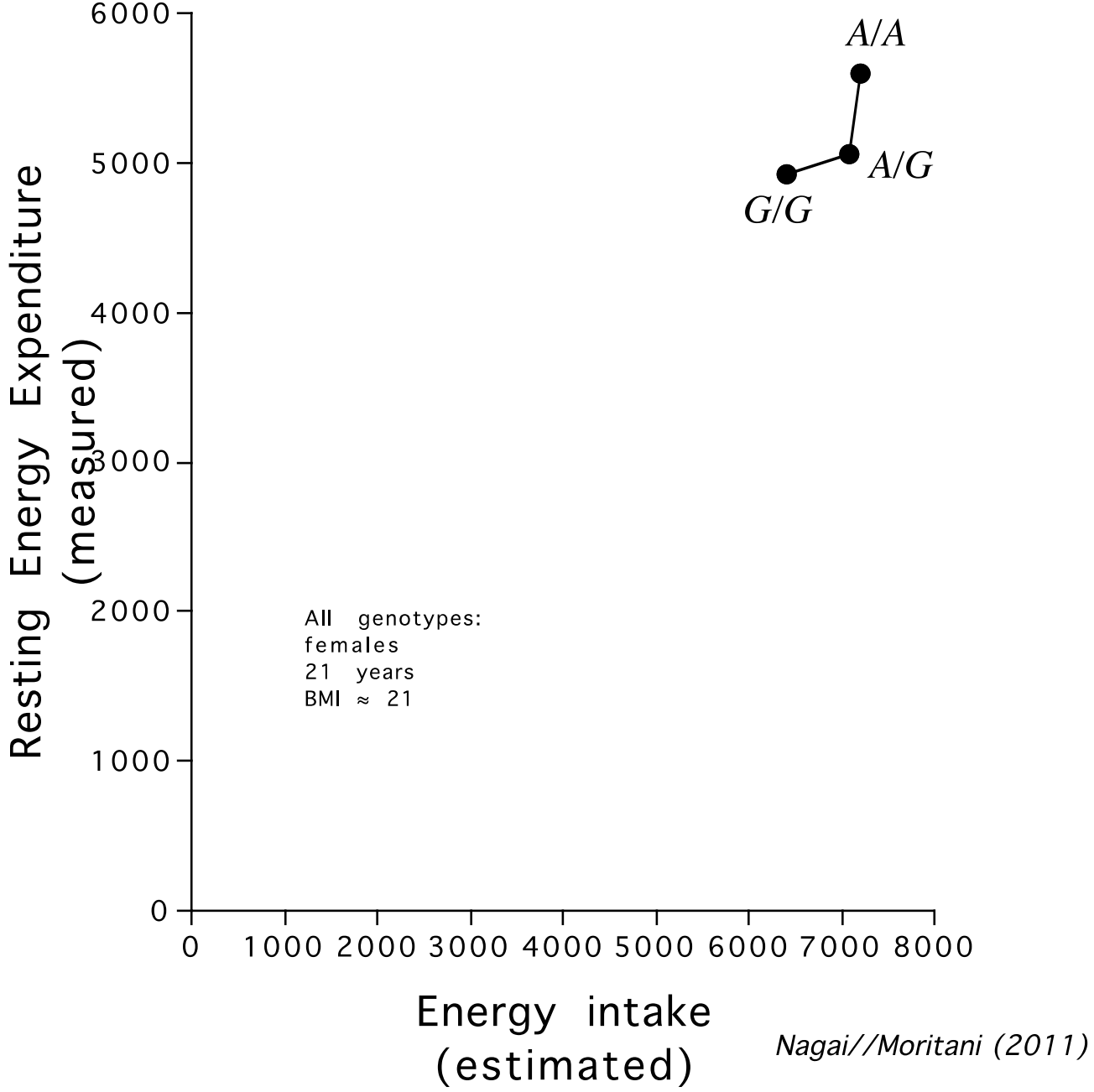
Could be so, but nothing firmly demonstrated

The only “functional” evidence for possible significance of brown fat and brite/beige fat in humans is genetic

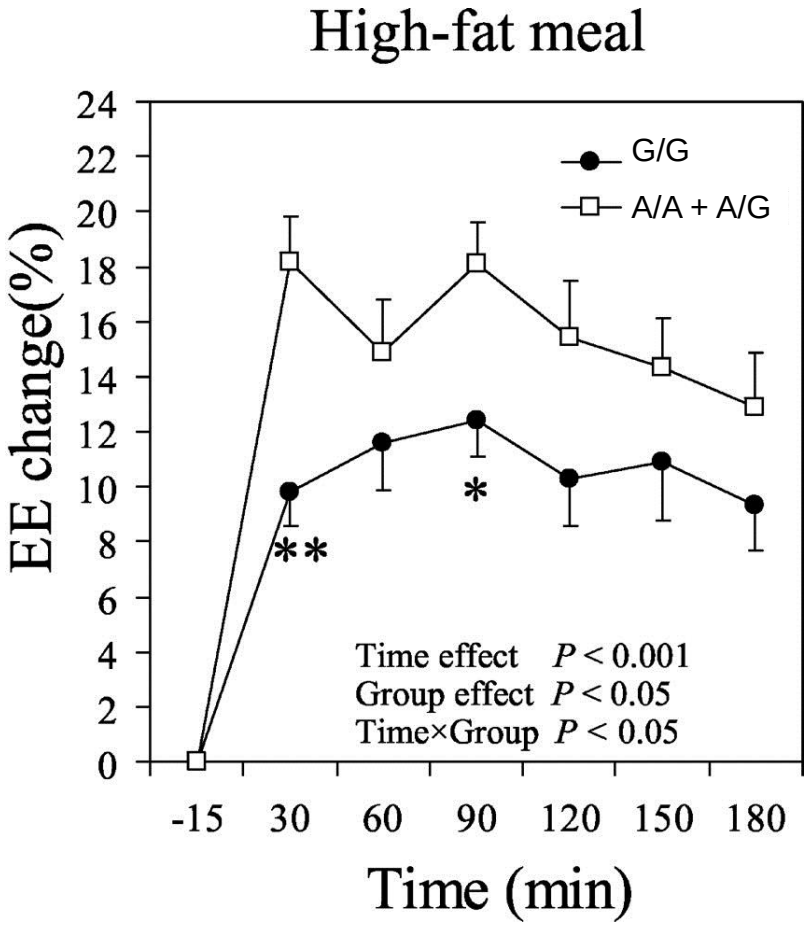
The -3826 polymorphism



Based on data from Esterbauer et al. 1998



Nagai//Moritani (2011)

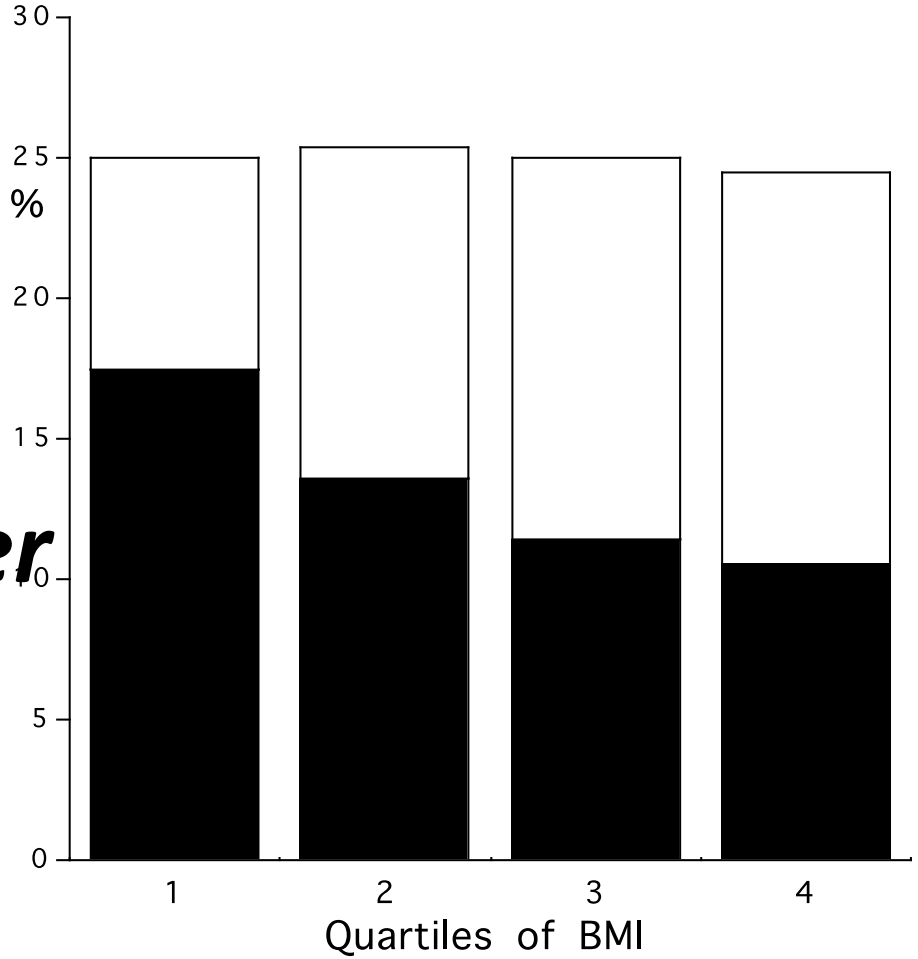


Nagai et al. 2003

And as time goes by

Evidence from man

Correlation of UCP1 genotype with obesity

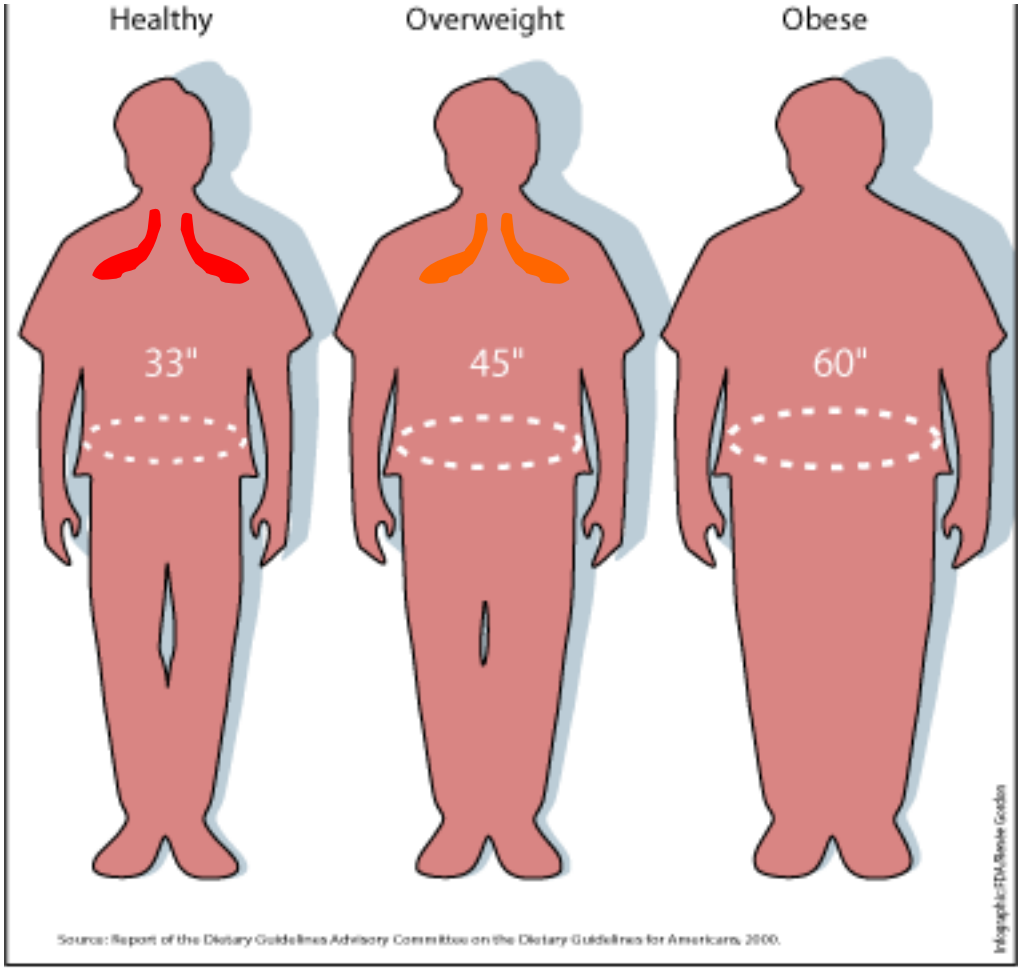


slimmer

obese

Sramkova et al. 2007

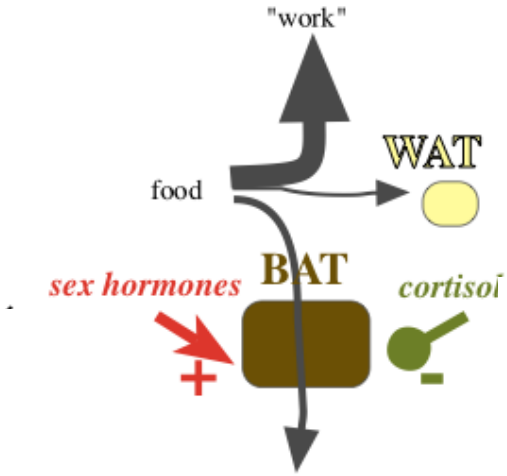
Thus,
the A's can both eat more than the G's
– and stay slim…



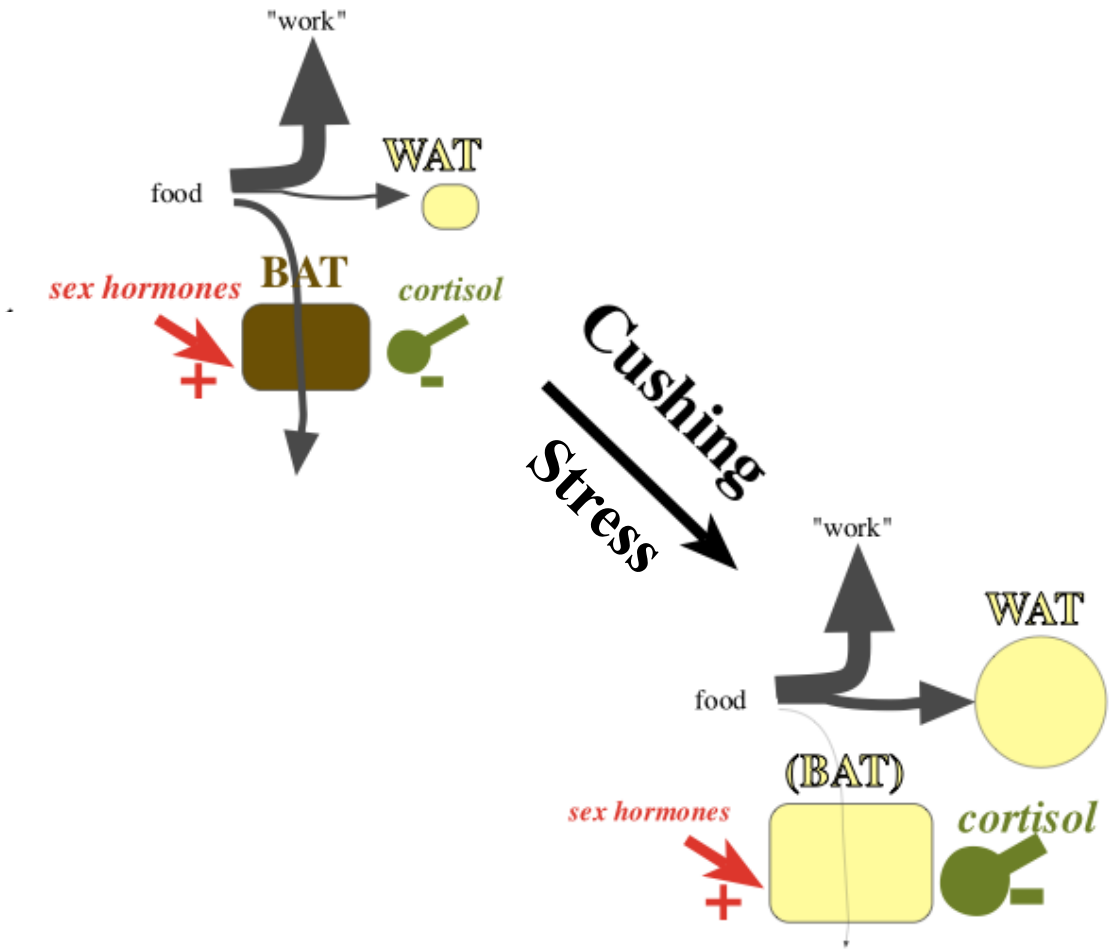
In our opinion,
extrapolation from
mouse data
to humans
(now allowed)
implies that even in humans
the absence of brown fat
***causes* obesity**

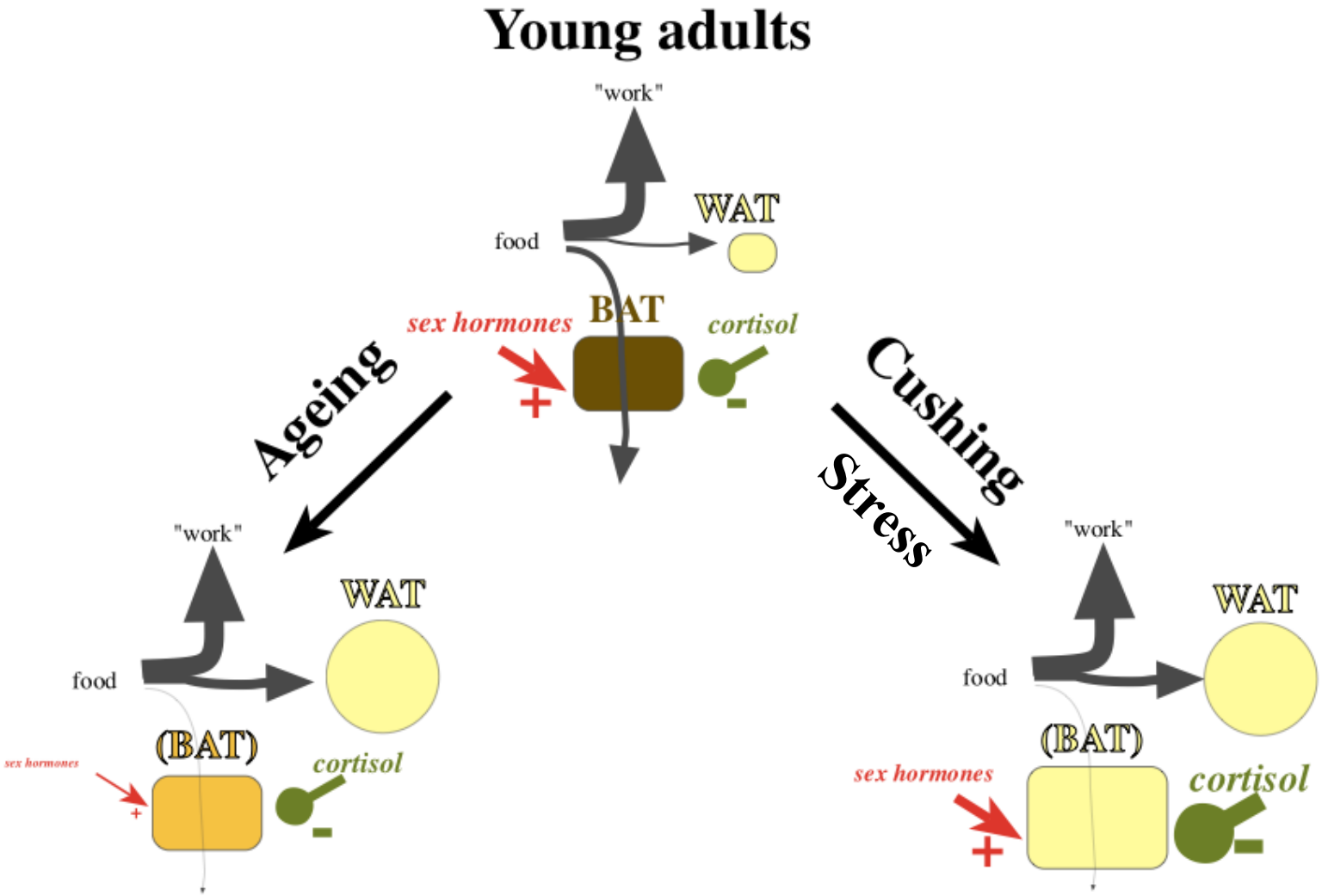
- **but why do we lose it with age?**

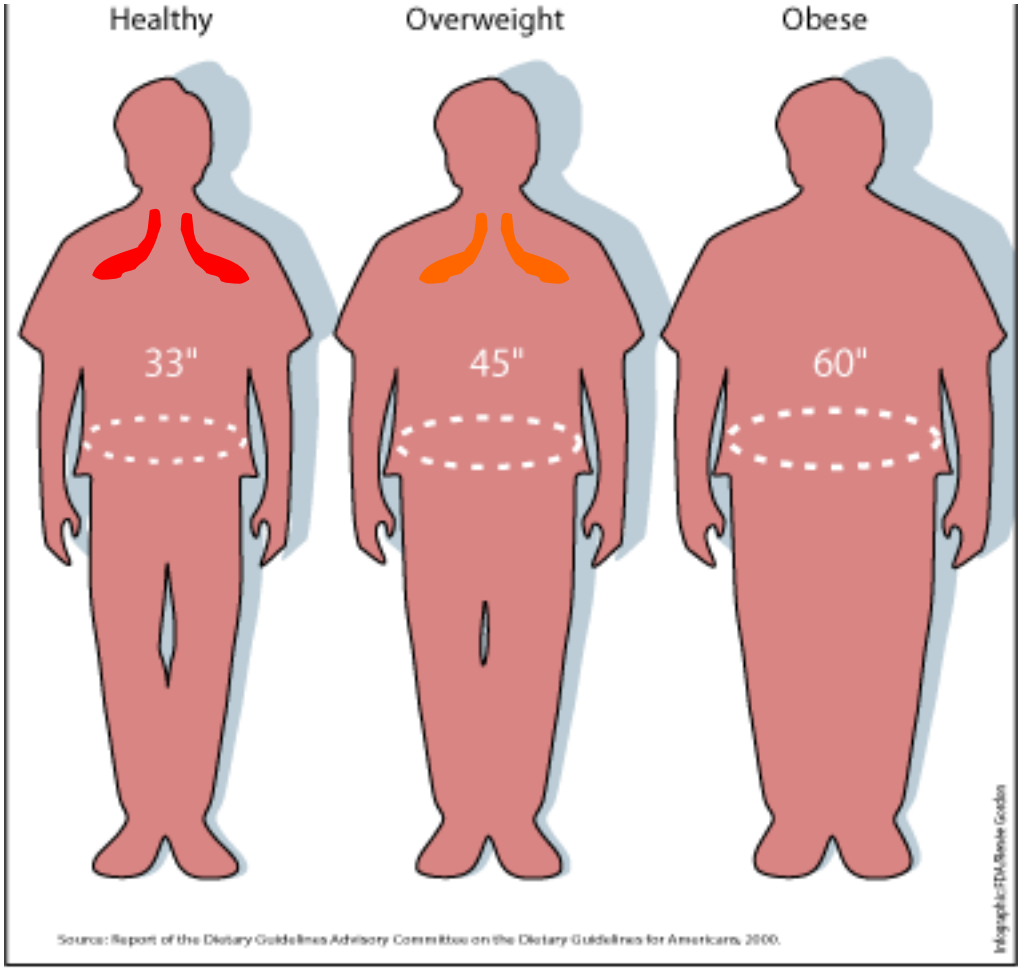
Young adults



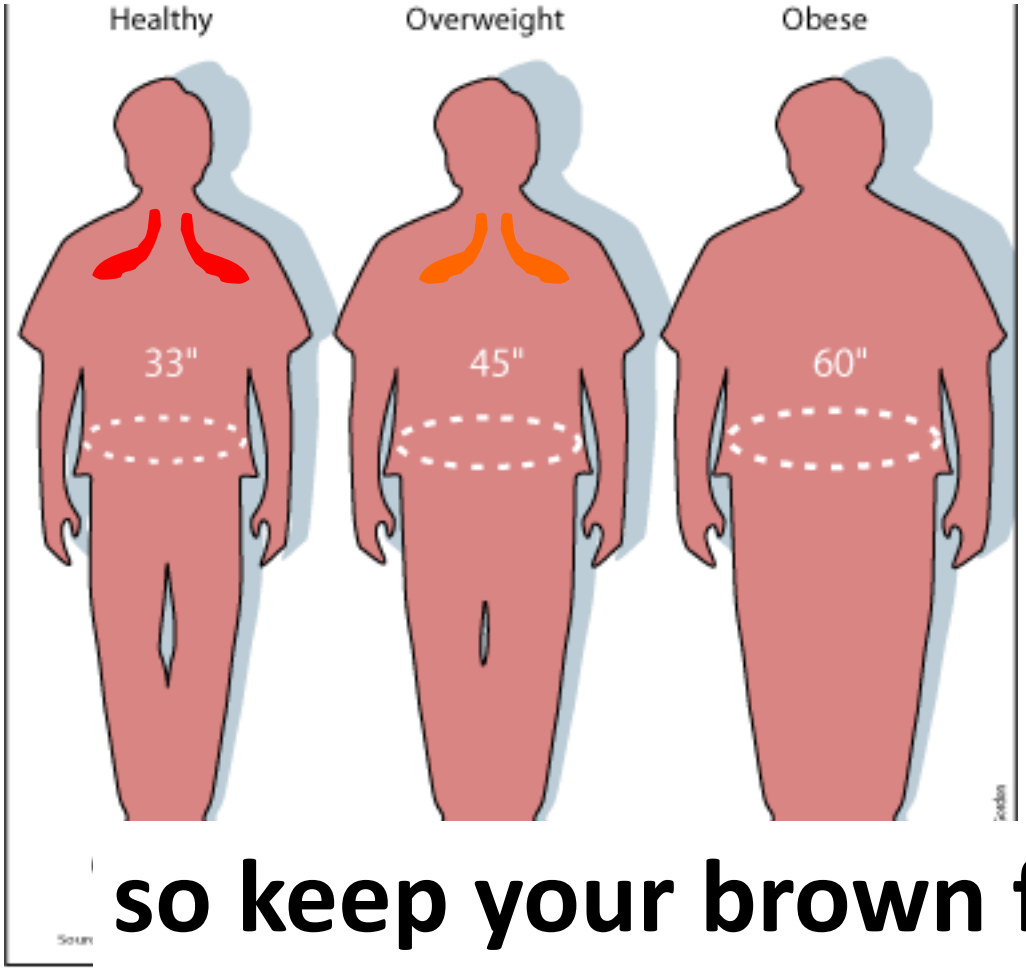
Young adults




Young adults
"work"
food
WAT
sex hormones
BAT
cortisol
+
-
Ageing
Cushing
Stress
"work"
food
WAT
(BAT)
sex hormones
cortisol
+
-
"work"
food
WAT
(BAT)
sex hormones
cortisol
+
-



In our opinion,
extrapolation from
mouse data
to humans
(now allowed)
implies that even in humans
successive diminishment
or absence of brown fat
causes obesity,
worsens triglyceridemia
and disposes to diabetes



In our opinion,
extrapolation from
mouse data
to humans
(now allowed)
implies that even in humans
successive diminishment
or absence of brown fat
causes obesity,
worsens triglyceridemia
and disposes to diabetes

so keep your brown fat active!

Worldwide increasing metabolic problems

Metabolic syndrome*:

- **Central obesity**

plus any two of the following four factors:

- **raised triglycerides level in blood**
- **reduced HDL cholesterol in blood**
- **raised blood pressure**
- **raised fasting plasma glucose or type 2 diabetes (insulin resistance)**

Active brown adipose tissue has the capacity to modulate most of above parameters

* newest IDF definition

Brown Adipose Tissue panacea

Jan Nedergaard

Department of Molecular Biosciences

The Wenner-Gren Institute,

Stockholm University

Professor at

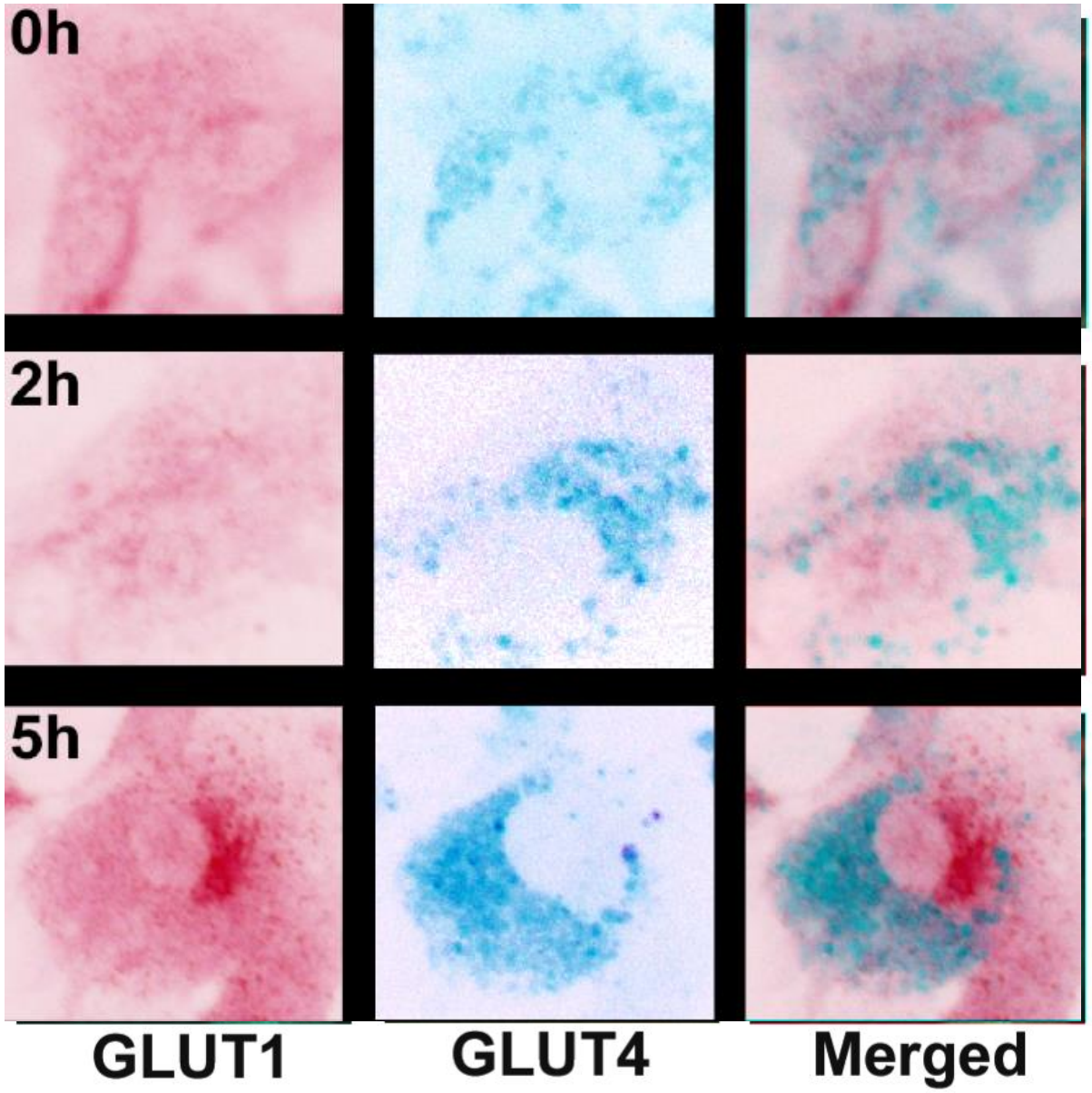
Stockholm University

Fellow of the Nobel-prize awarding

KUNGL. VETENSKAPS AKADEMIEN

THE ROYAL SWEDISH ACADEMY OF SCIENCES

Hours of adrenergic stimulation



Results in collaboration with
(among others)

The Cannon/Nedergaard lab:
Gustavo Abreu de Vieira
Tore Bengtsson
Helena Feldmann
Valeria Golozoubova
Anders Jacobsson
Elaina Maldonado
Natasa Petrovic
Tomas Waldén
and
Jan Nedergaard

RVC London
Valentina Gburcik
James A. Timmons

University of Copenhagen
Naja Zenius Jespersen
Camilla Scheele
Bente Klarlund Pedersen
Therese Juhlin

University of Ancona
Marie Cristina Zingaretti
Saverio Cinti

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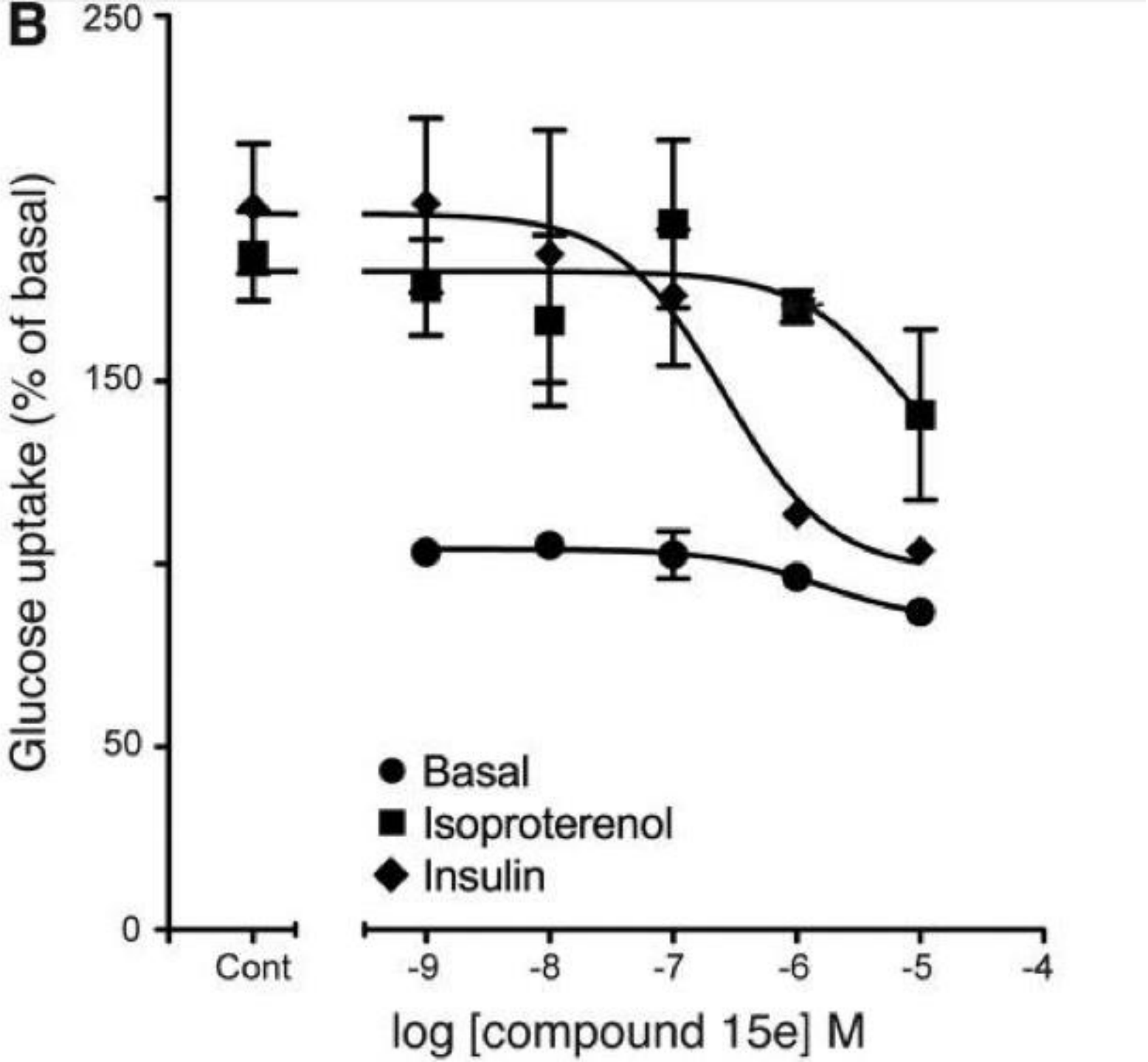
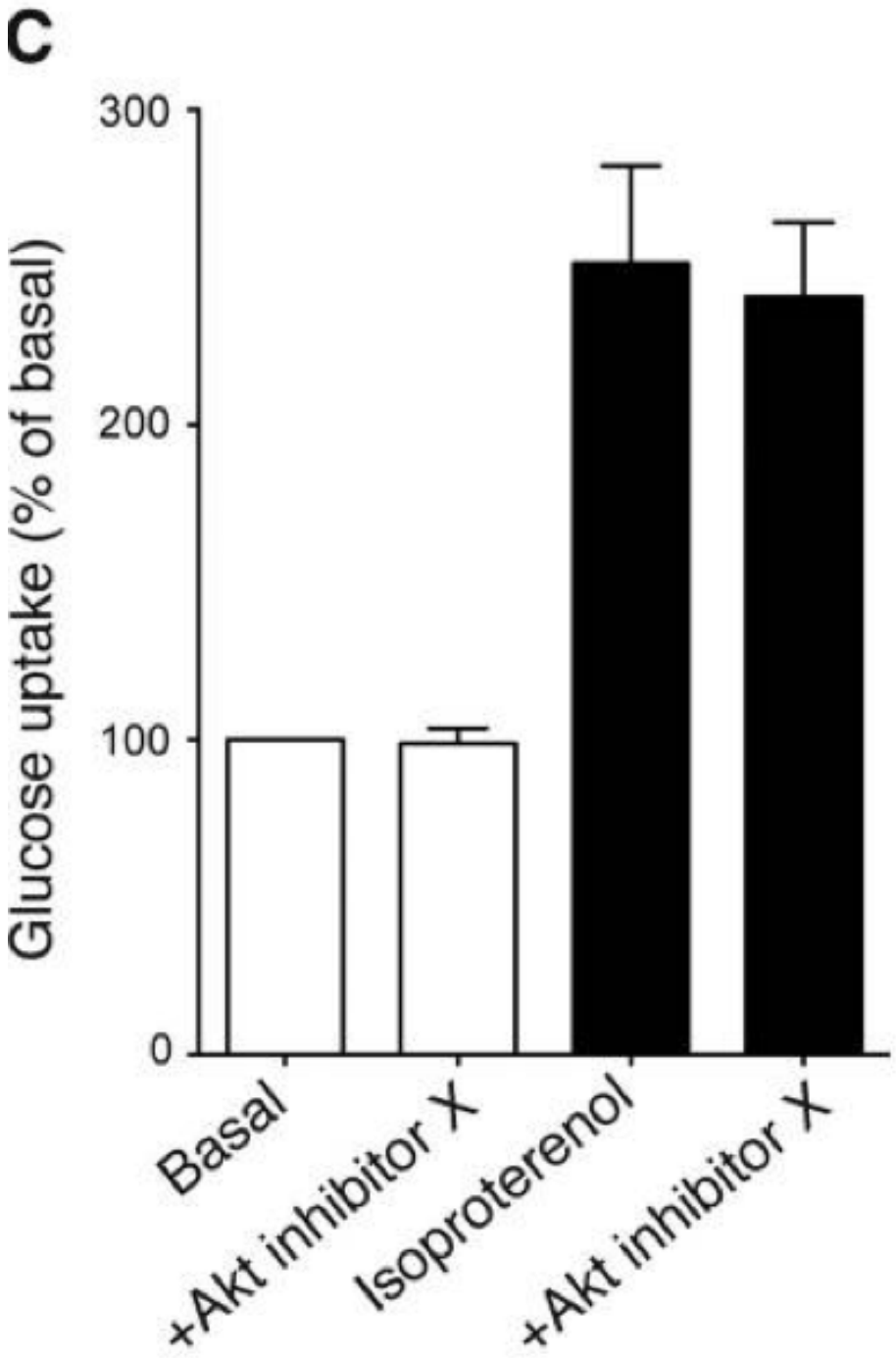
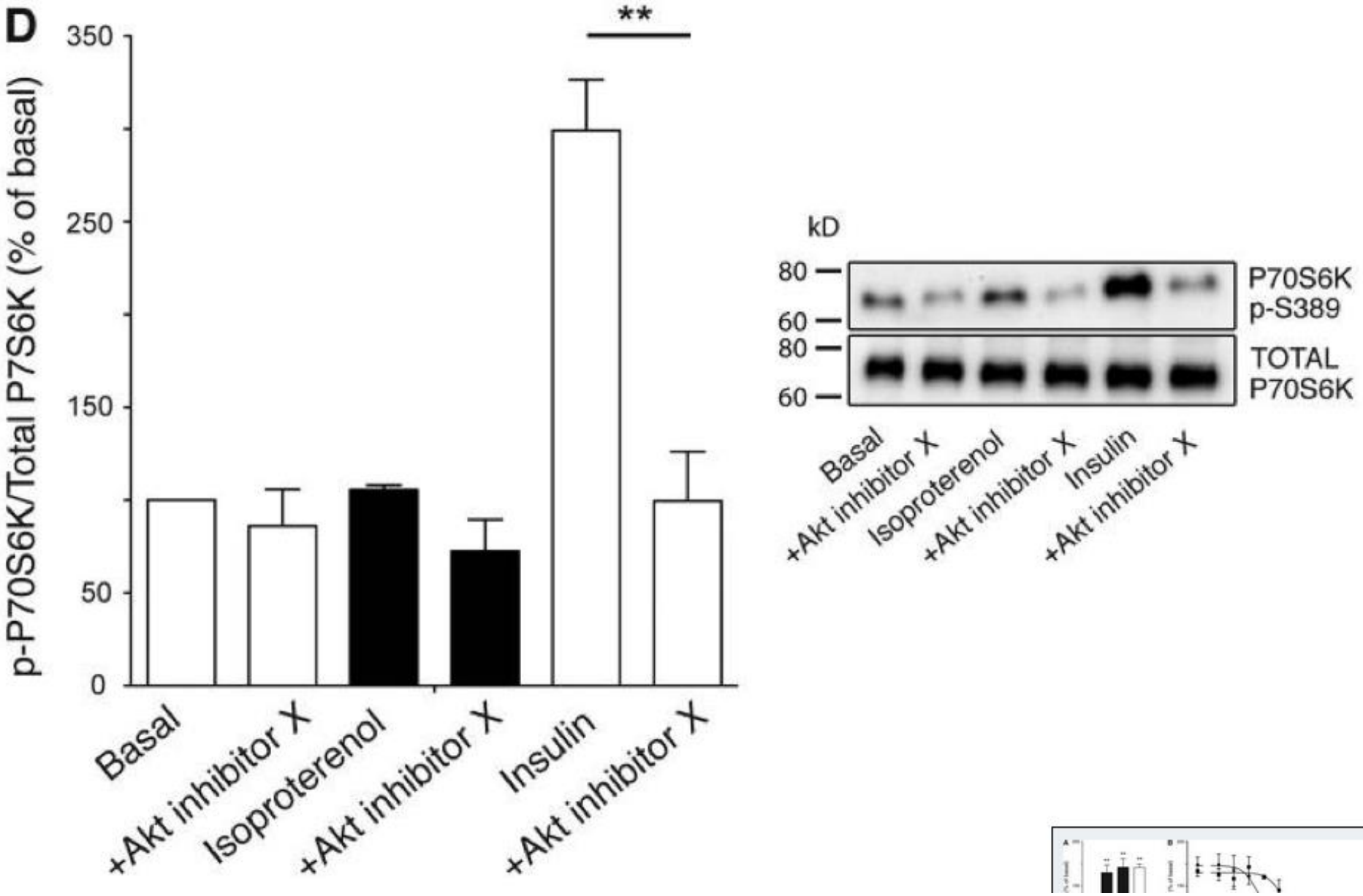
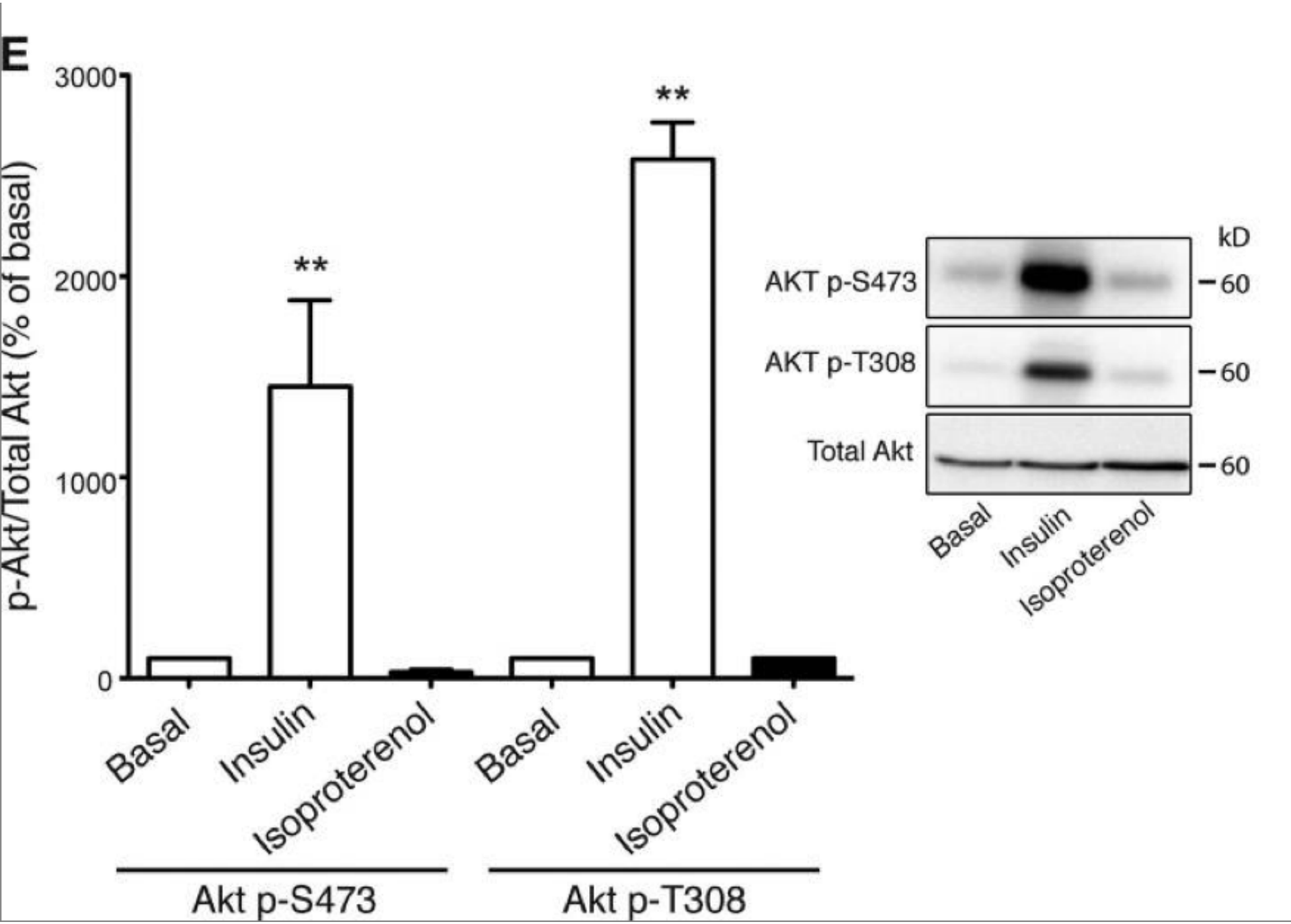
Elaina Maldonado
Natasa Petrovic
Tomas Waldén

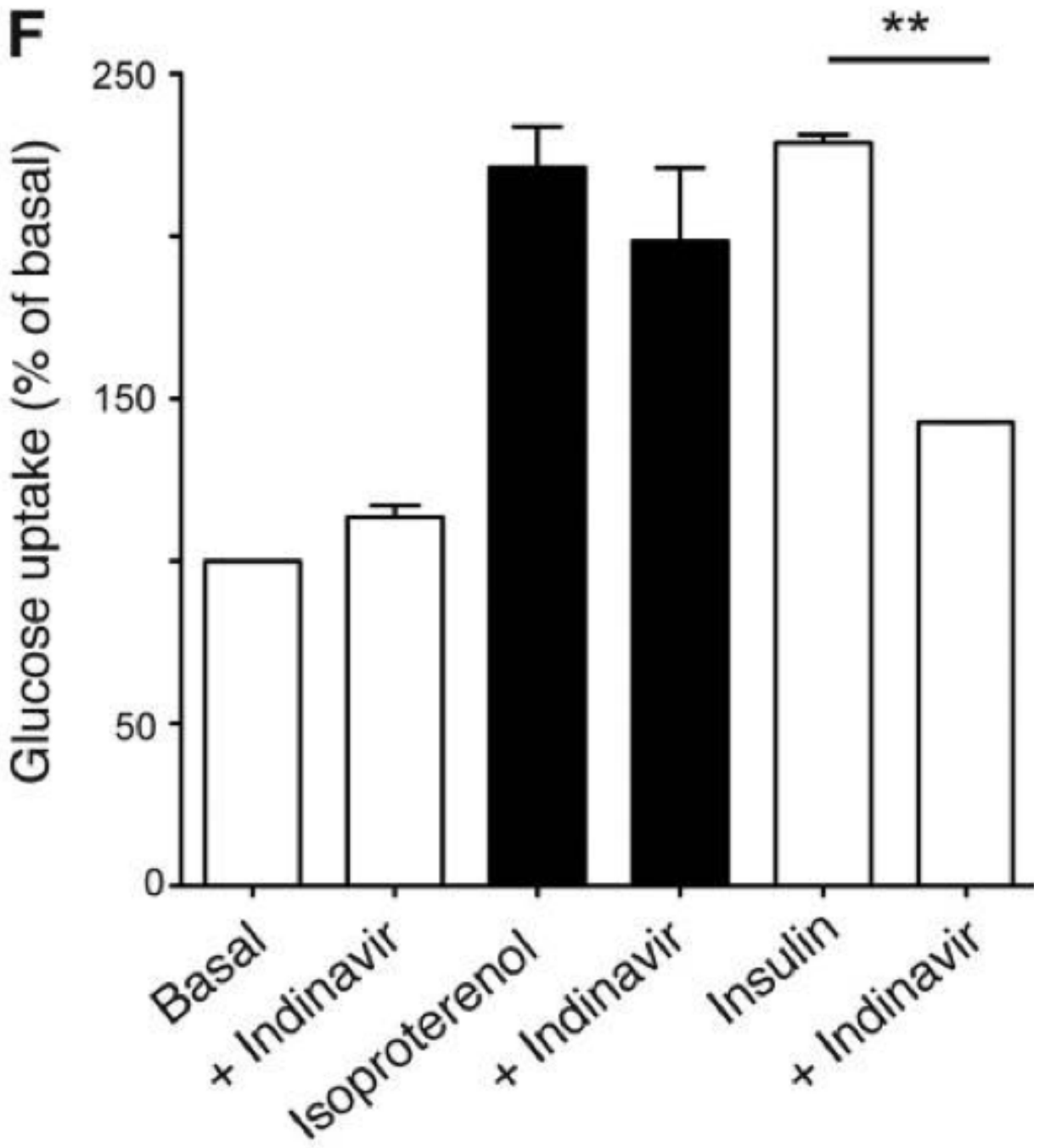
The Bengtsson lab:
Jessica Olsen
Gu

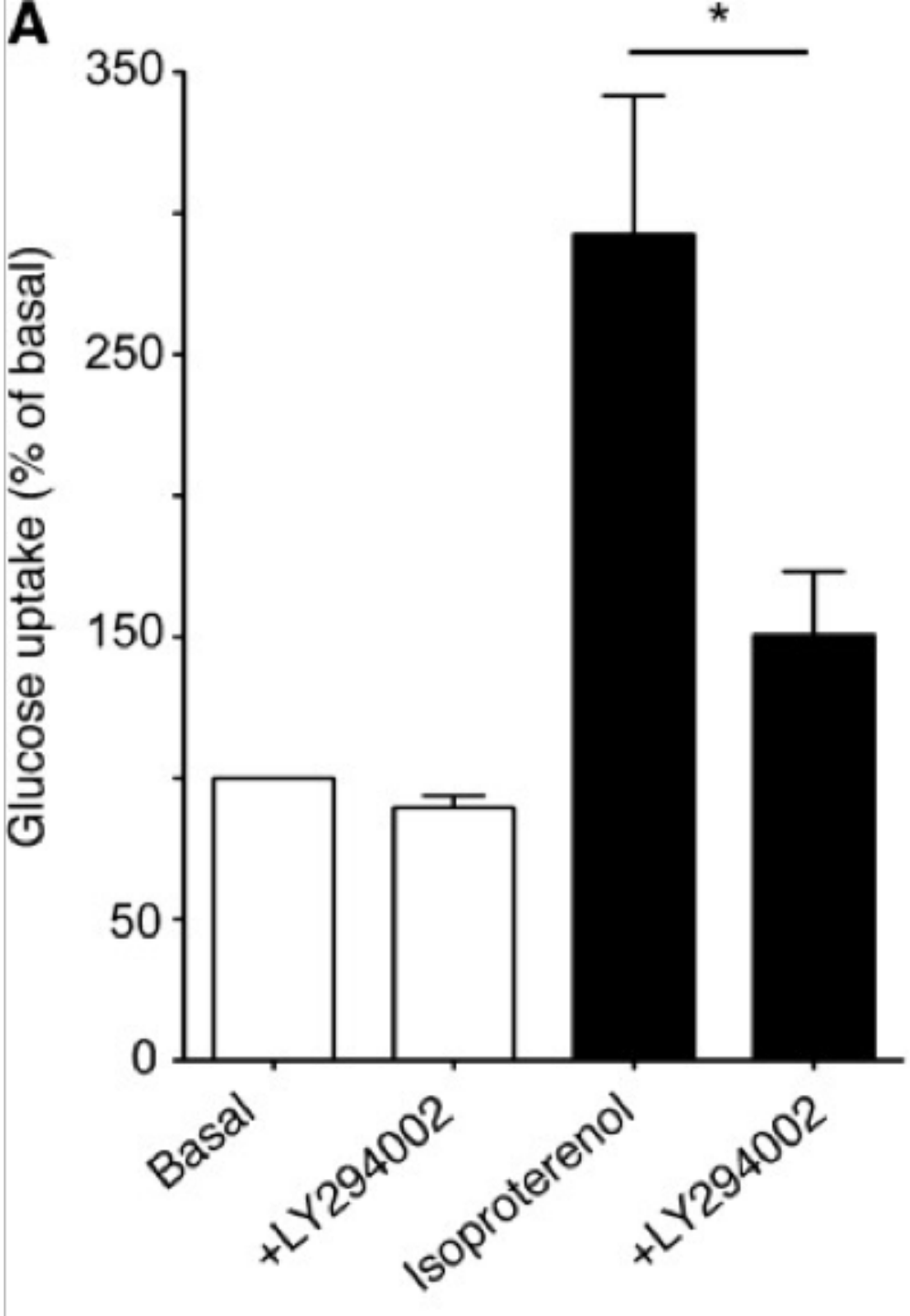

B
250
150
50
0
Glucose uptake (% of basal)
Basal
Isoproterenol
Insulin
Cont
-9
-8
-7
-6
-5
-4
log [compound 15e] M

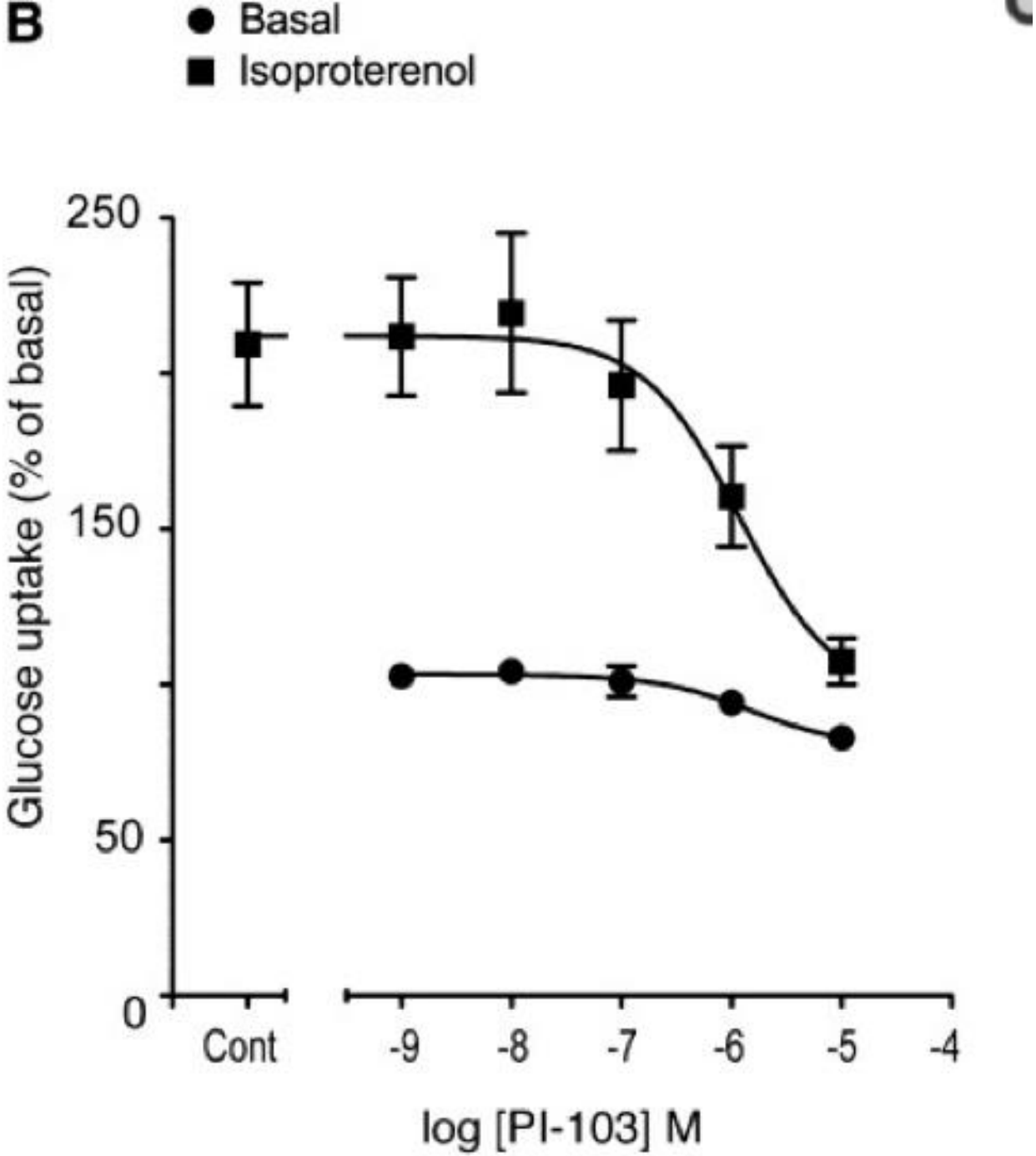

C
300
200
100
0
Glucose uptake (% of basal)
Basal
+Akt inhibitor X
Isoproterenol
+Akt inhibitor X

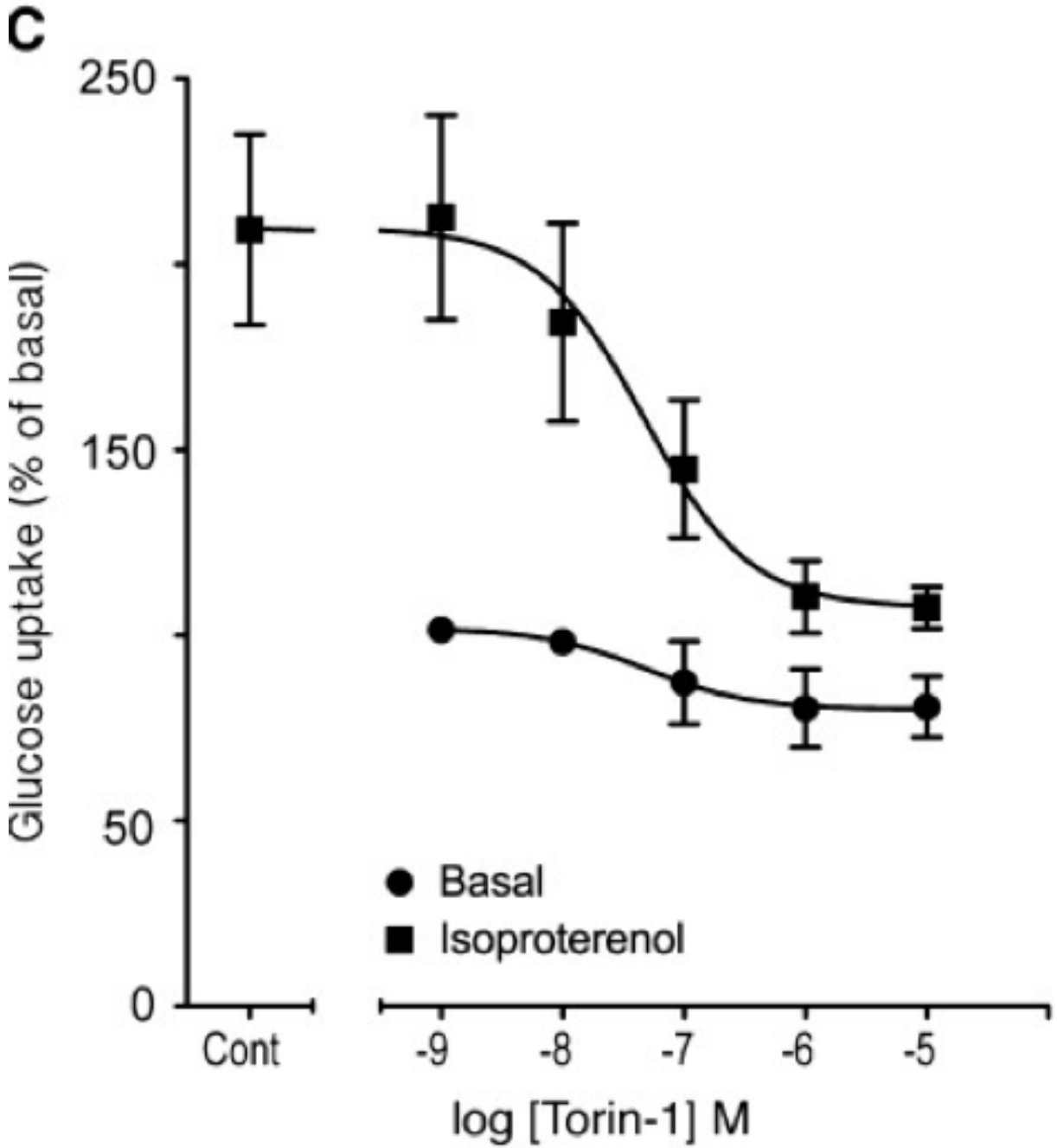

D
**
350
250
150
50
0
p-P70S6K/Total P7S6K (% of basal)
Basal
+Akt inhibitor X
Isoproterenol
+Akt inhibitor X
Insulin
+Akt inhibitor X
kD
80
60
80
60
P70S6K
p-S389
TOTAL
P70S6K
Basal
+Akt inhibitor X
Isoproterenol
+Akt inhibitor X
Insulin
+Akt inhibitor X

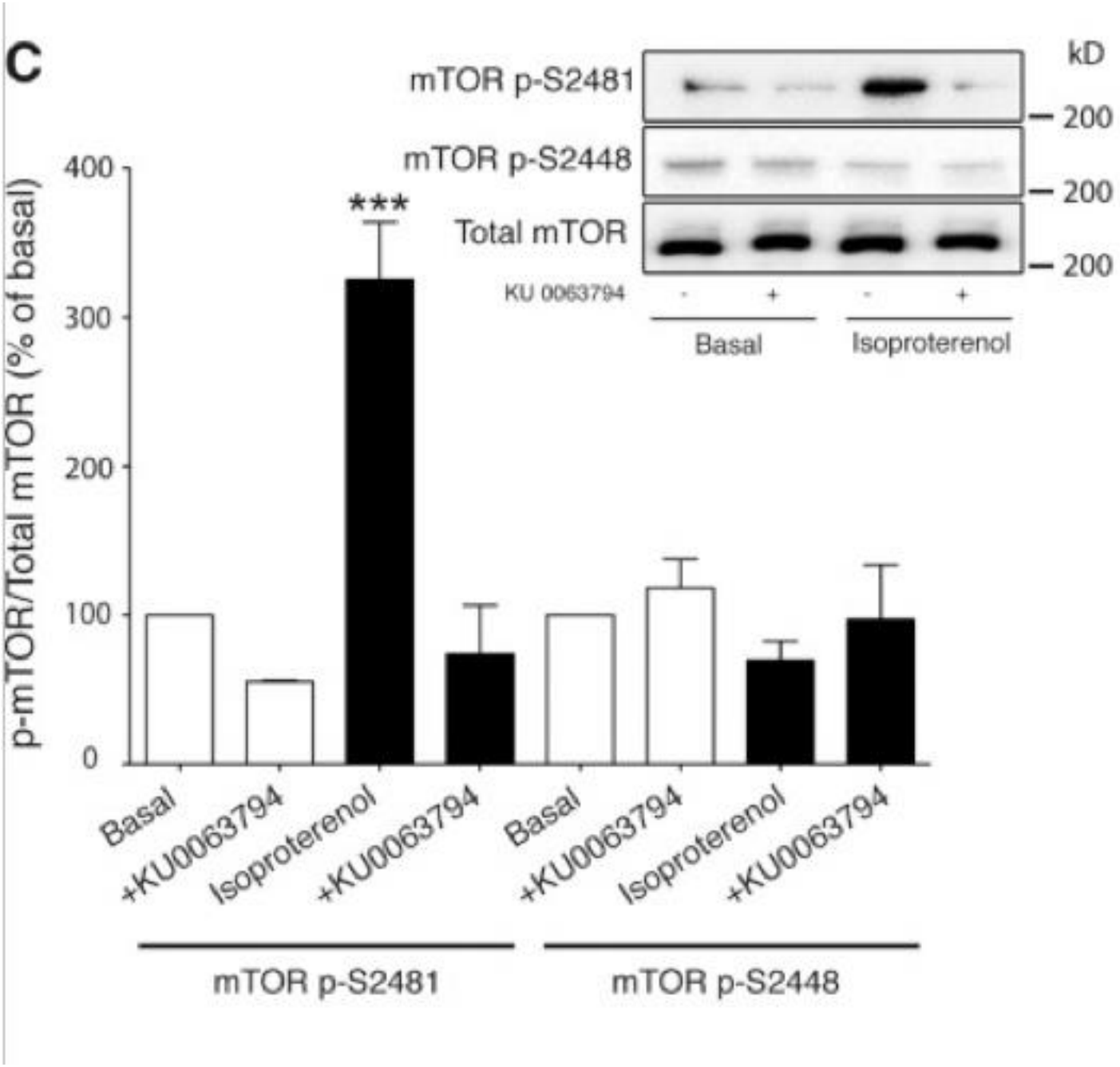

m
p-Akt/Total Akt (% of basal)
3000
2000
1000
0
**
**
Basal
Insulin
Isoproterenol
Basal
Insulin
Isoproterenol
Akt p-S473
Akt p-T308
kD
AKT p-S473
AKT p-T308
Total Akt
60
60
60
Basal
Insulin
Isoproterenol

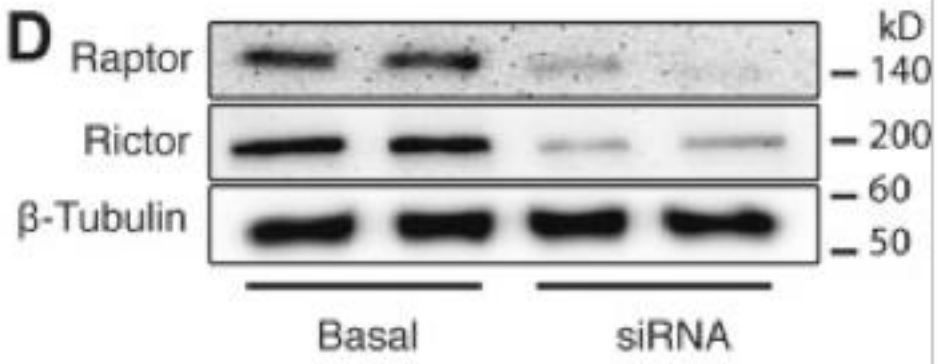

F
**
250
150
50
0
Glucose uptake (% of basal)
Basal
+ Indinavir
Isoproterenol
+ Indinavir
Insulin
+ Indinavir

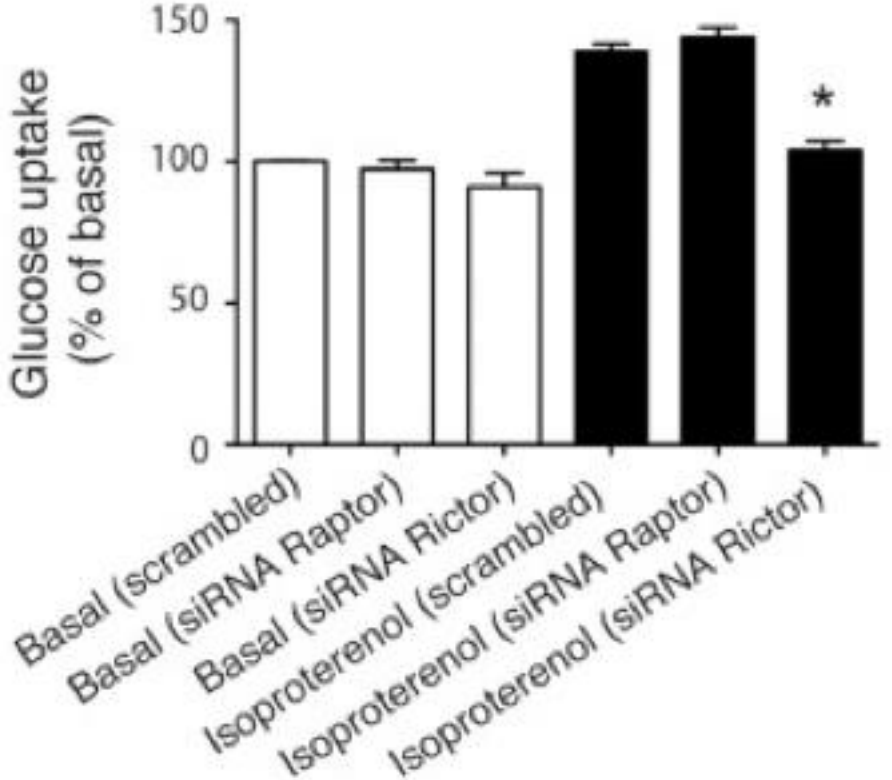

A
*
350
250
150
50
0
Glucose uptake (% of basal)
Basal
+LY294002
Isoproterenol
+LY294002

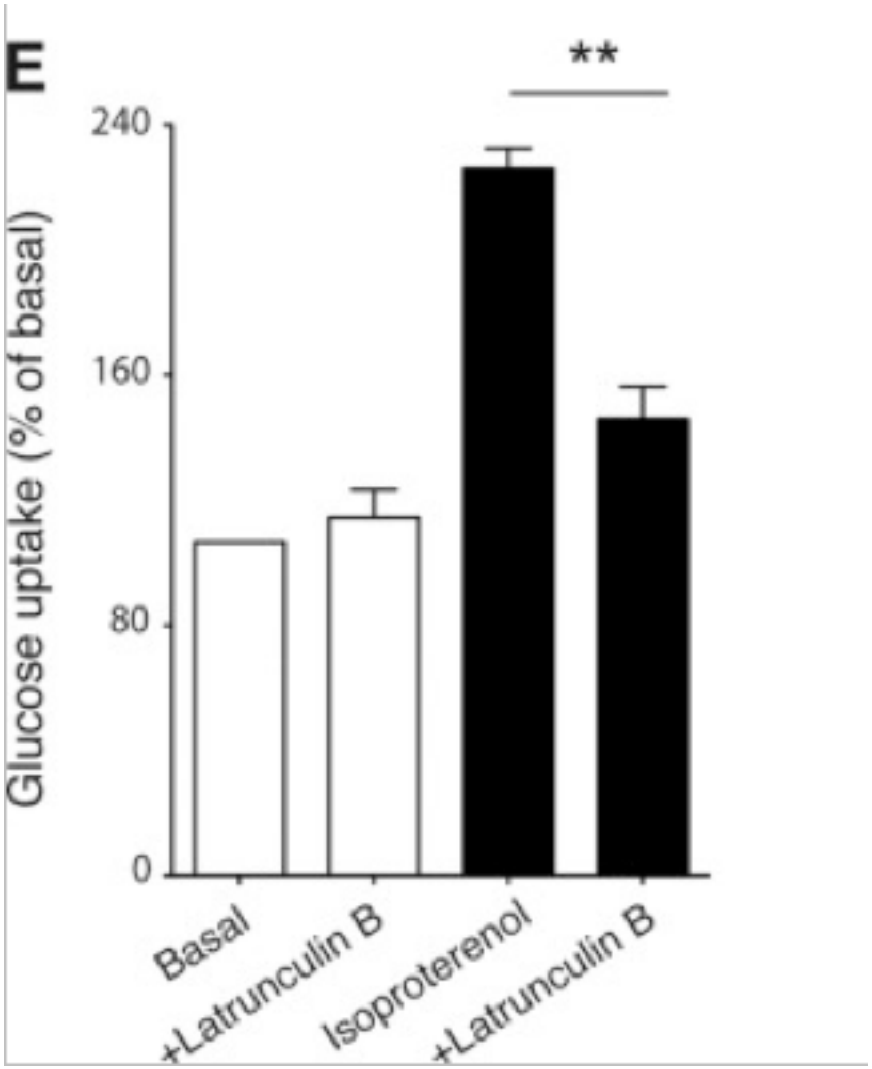

B
Basal
Isoproterenol
250
150
50
0
Glucose uptake (% of basal)
Cont
-9
-8
-7
-6
-5
-4
log [PI-103] M

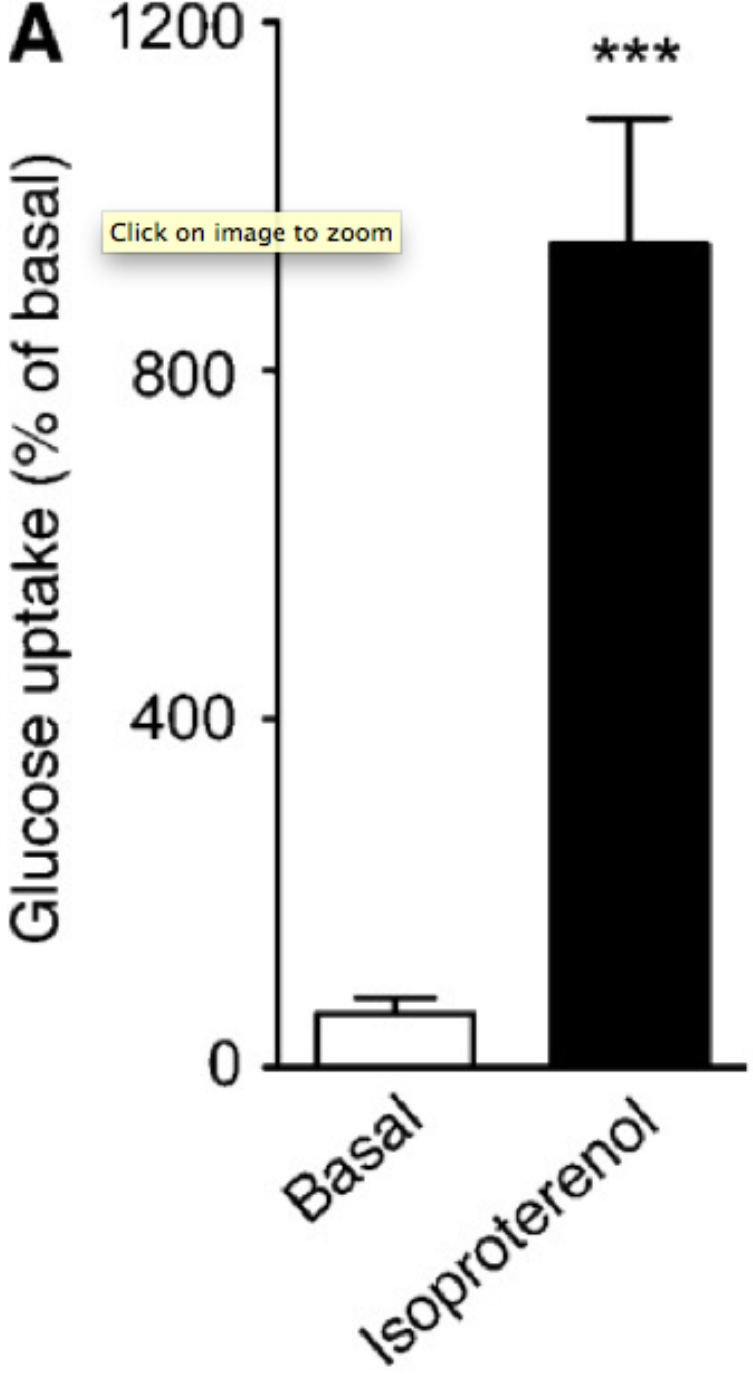

C
250
150
50
0
Glucose uptake (% of basal)
Basal
Isoproterenol
Cont
-9
-8
-7
-6
-5
log [Torin-1] M

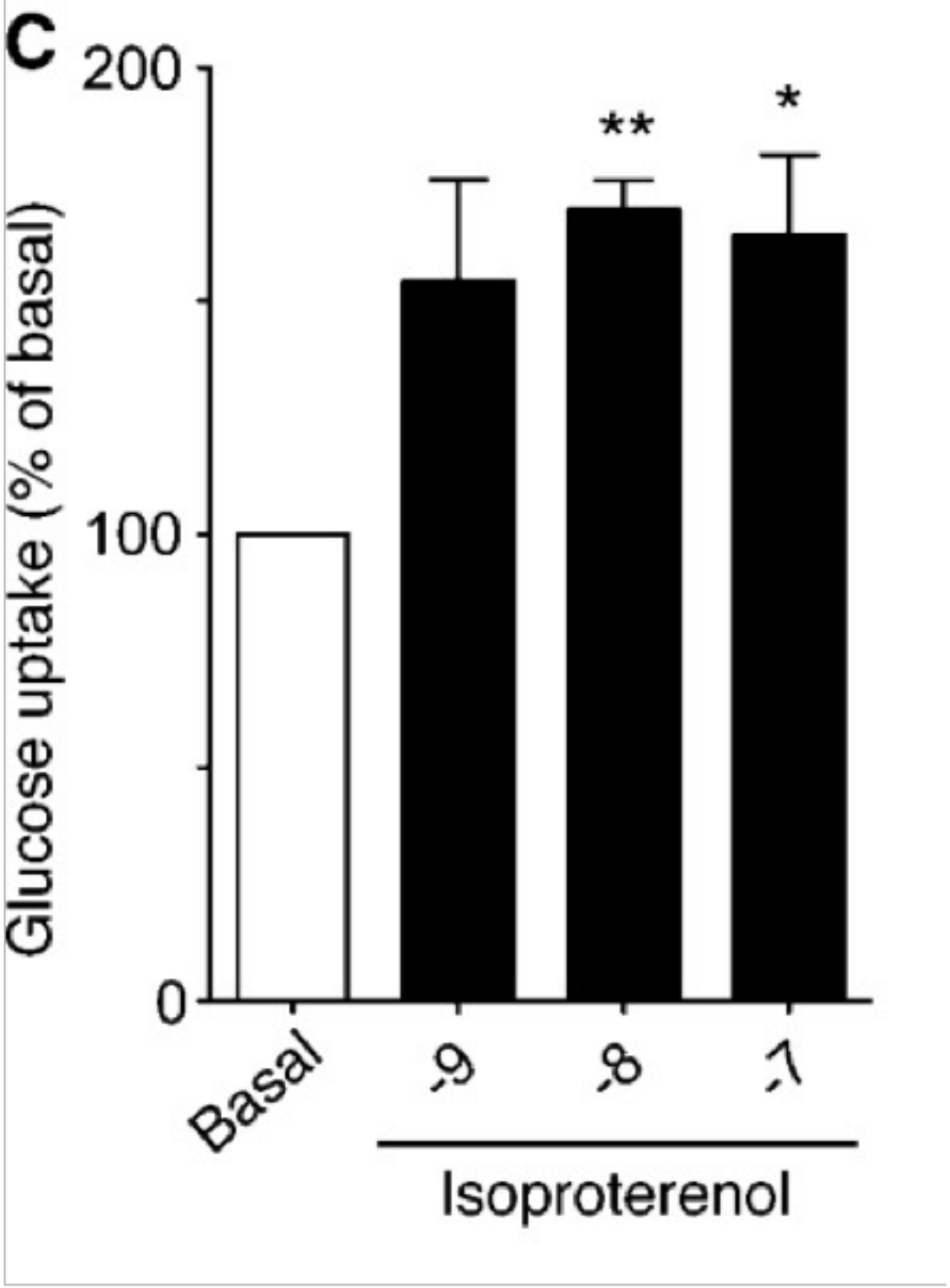

C
mTOR p-S2481
mTOR p-S2448
Total mTOR
kD
200
200
200
KU 0063794
-
+
-
+
Basal
Isoproterenol
p-mTOR/Total mTOR (% of basal)
400
300
200
100
0
***
Basal
+KU0063794
Isoproterenol
+KU0063794
Basal
+KU0063794
Isoproterenol
+KU0063794
mTOR p-S2481
mTOR p-S2448


D
Raptor
Rictor
β-Tubulin
kD
140
200
60
50
Basal
siRNA

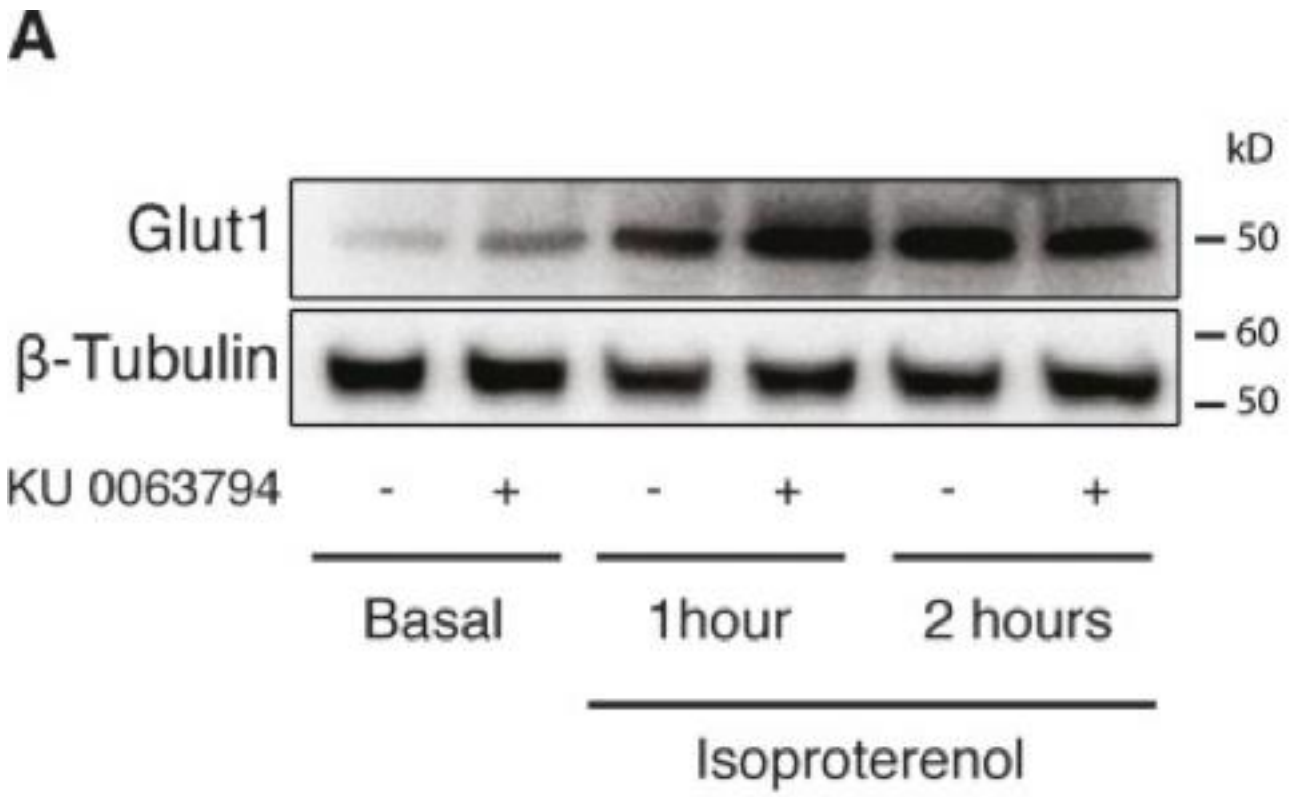

Glucose uptake
(% of basal)
150
100
50
0
*
Basal (scrambled)
Basal (siRNA Raptor)
Basal (siRNA Rictor)
Isoproterenol (scrambled)
Isoproterenol (siRNA Raptor)
Isoproterenol (siRNA Rictor)


m
**
240
160
80
0
Glucose uptake (% of basal)
Basal
+Latrunculin B
Isoproterenol
+Latrunculin B

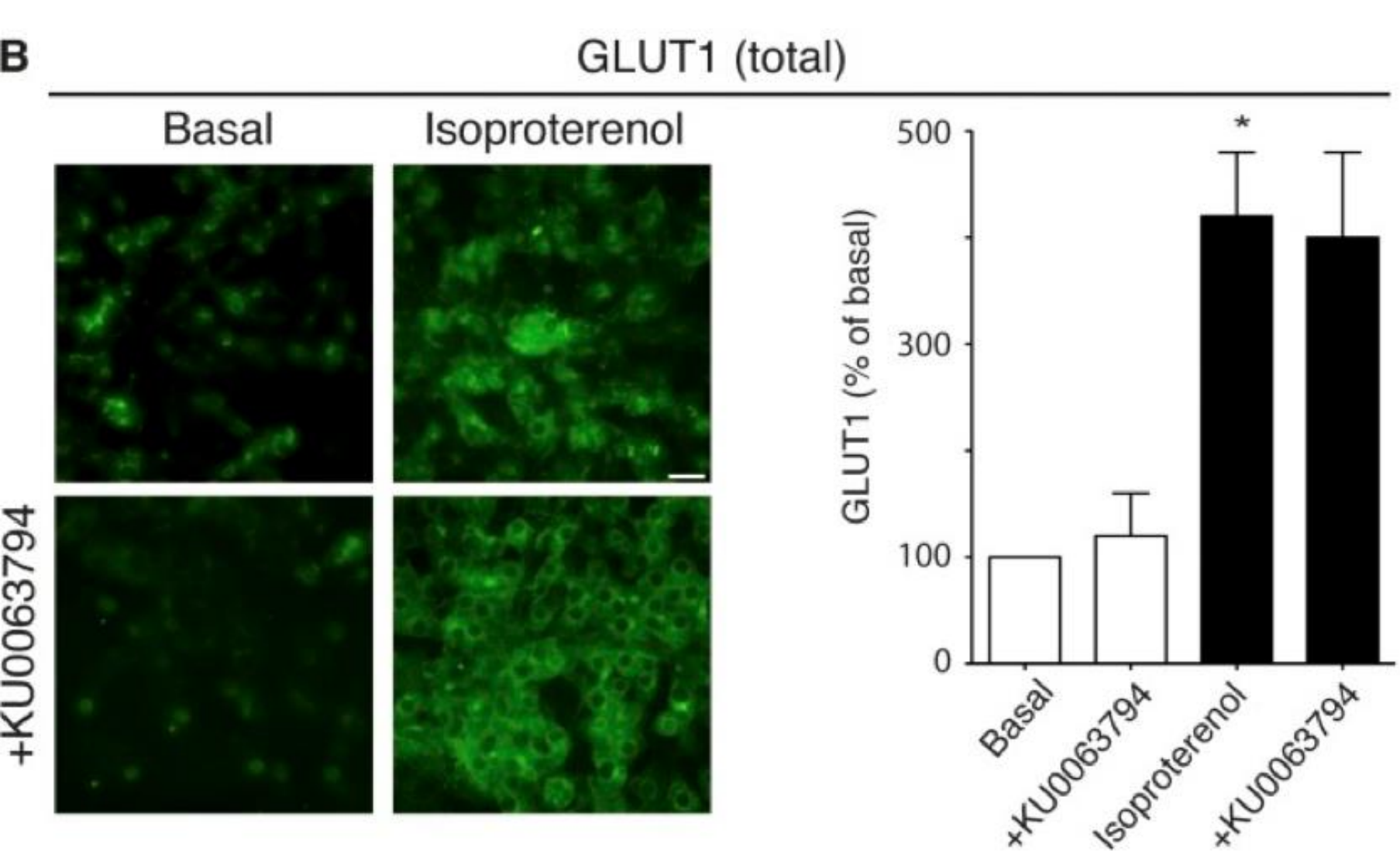


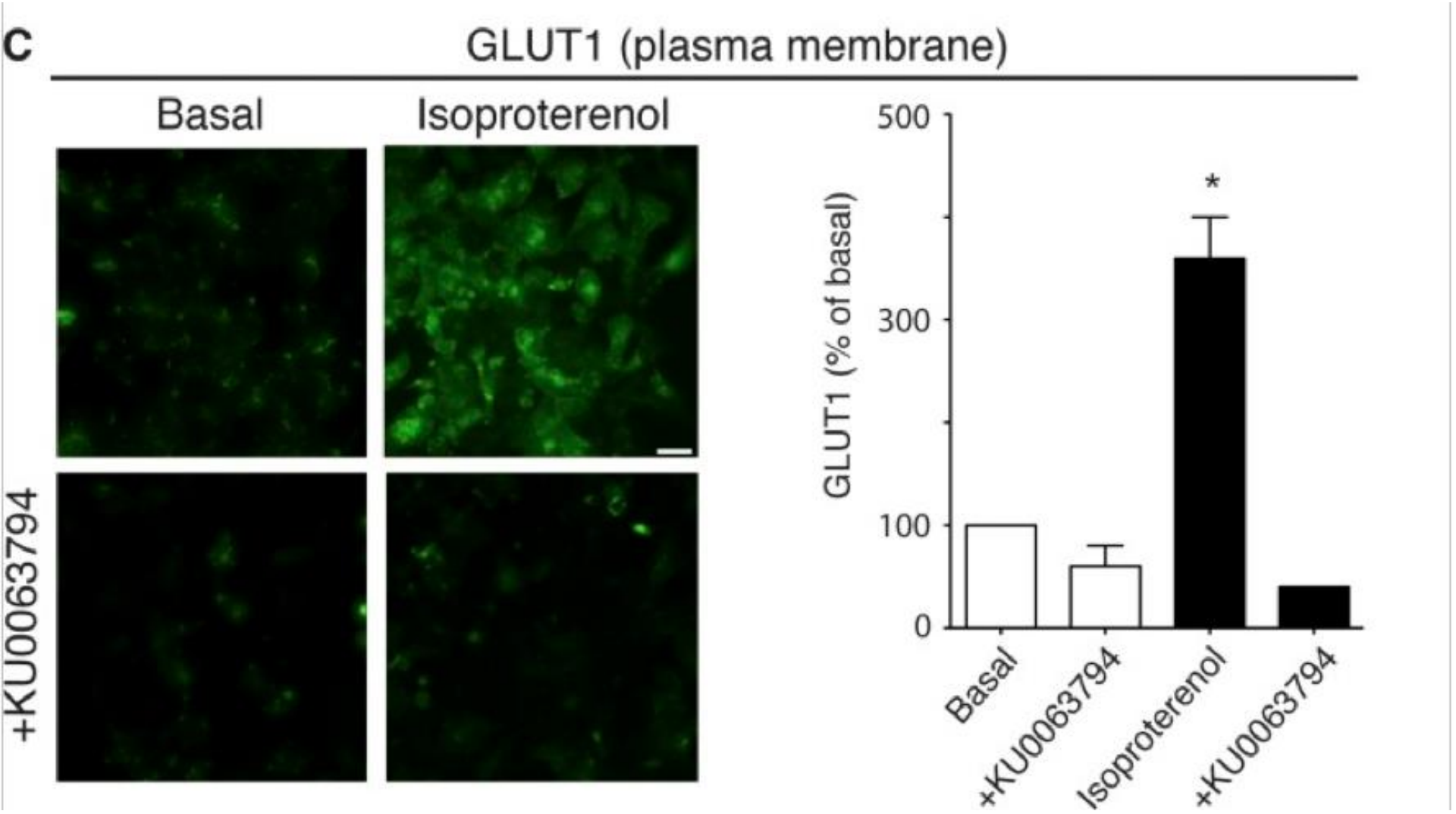

C
200
100
0
Glucose uptake (% of basal)
**
*
Basal
-9
-8
-7
Isoproterenol

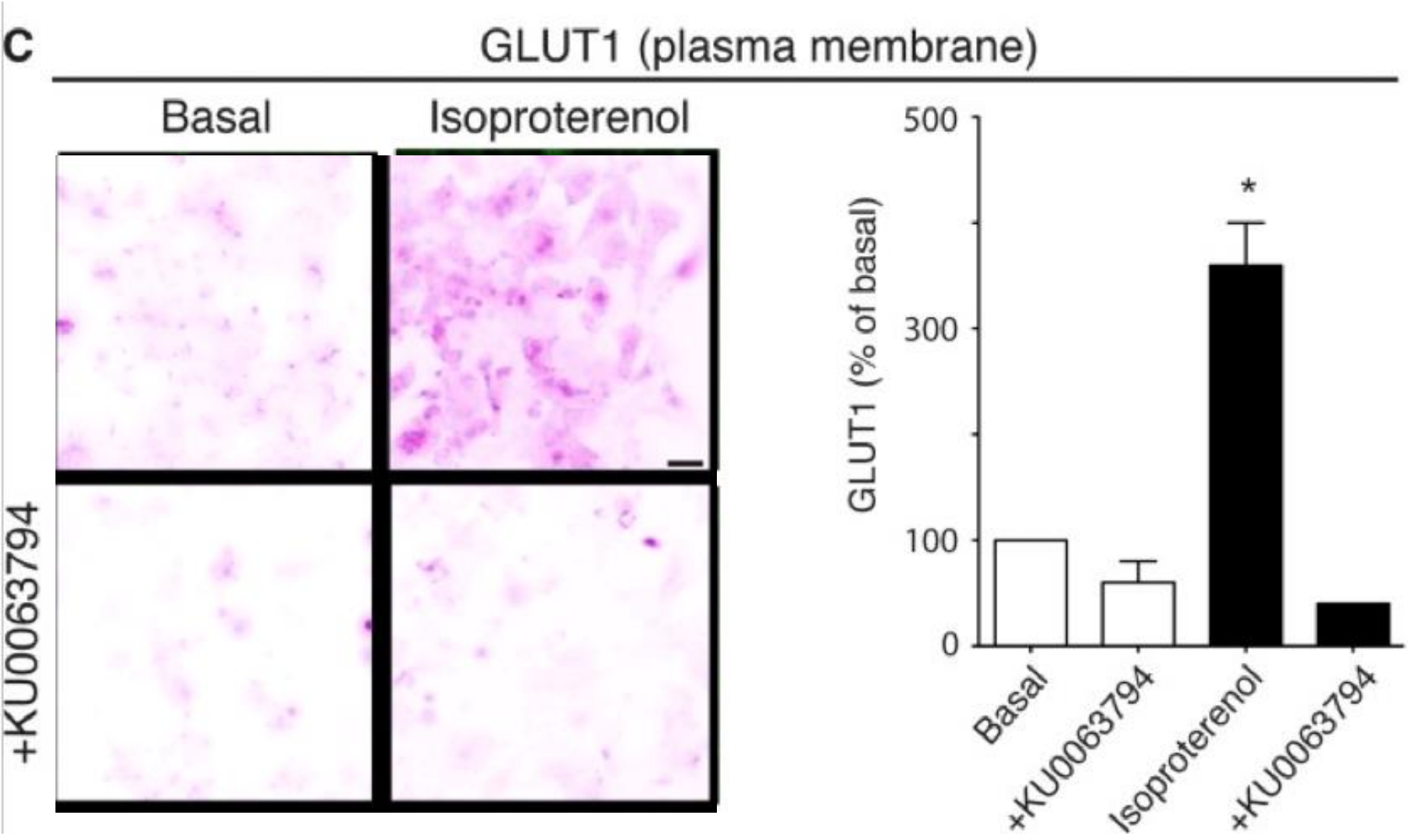
D
**
150
50
0
Glucose uptake (% of basal)
Basal
+KU0063794
Isoproterenol
+KU0063794
Human MADS cells

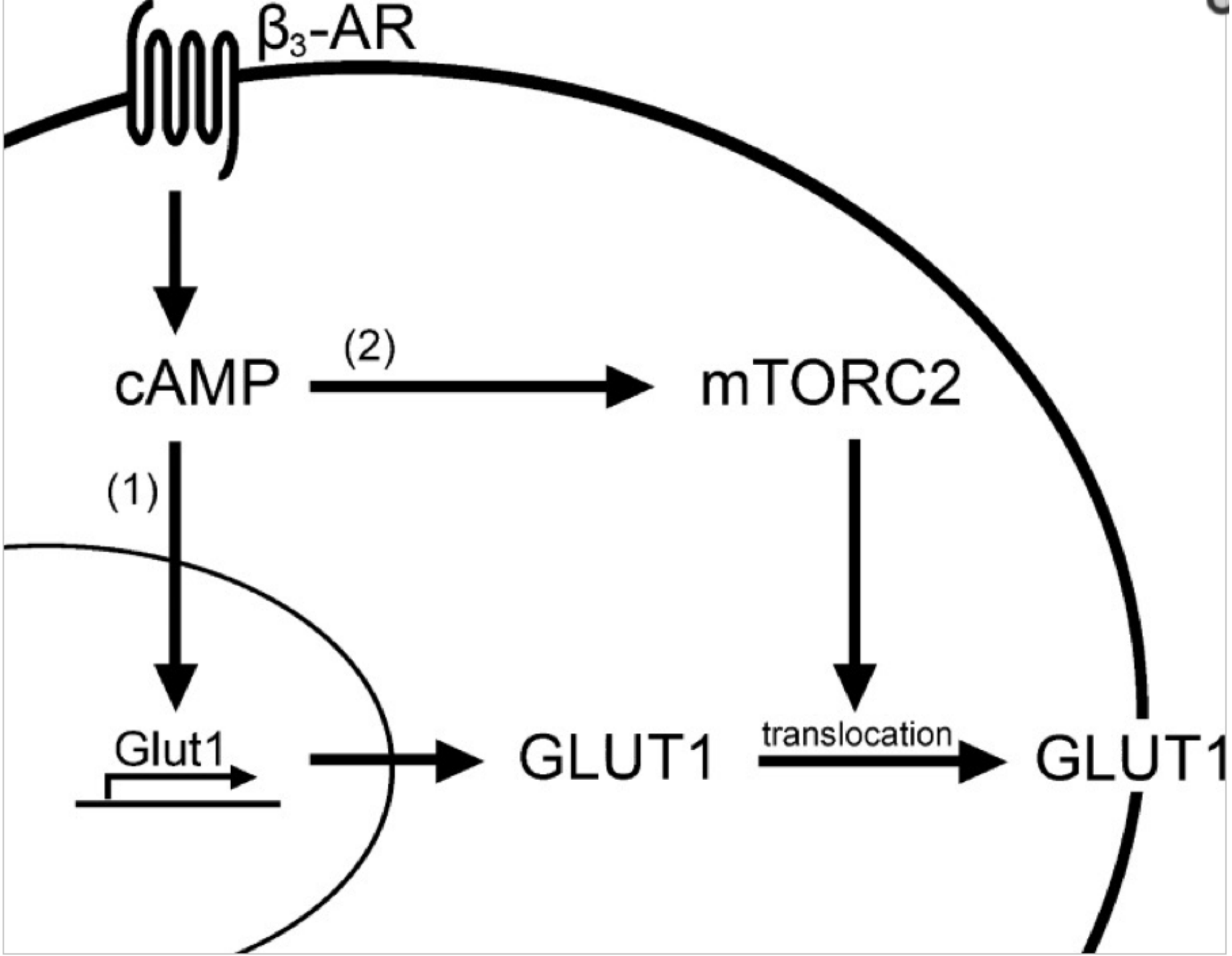

A
kD
Glut1
50
β-Tubulin
60
50
KU 0063794
-
+
-
+
-
+
Basal
1hour
2 hours
Isoproterenol

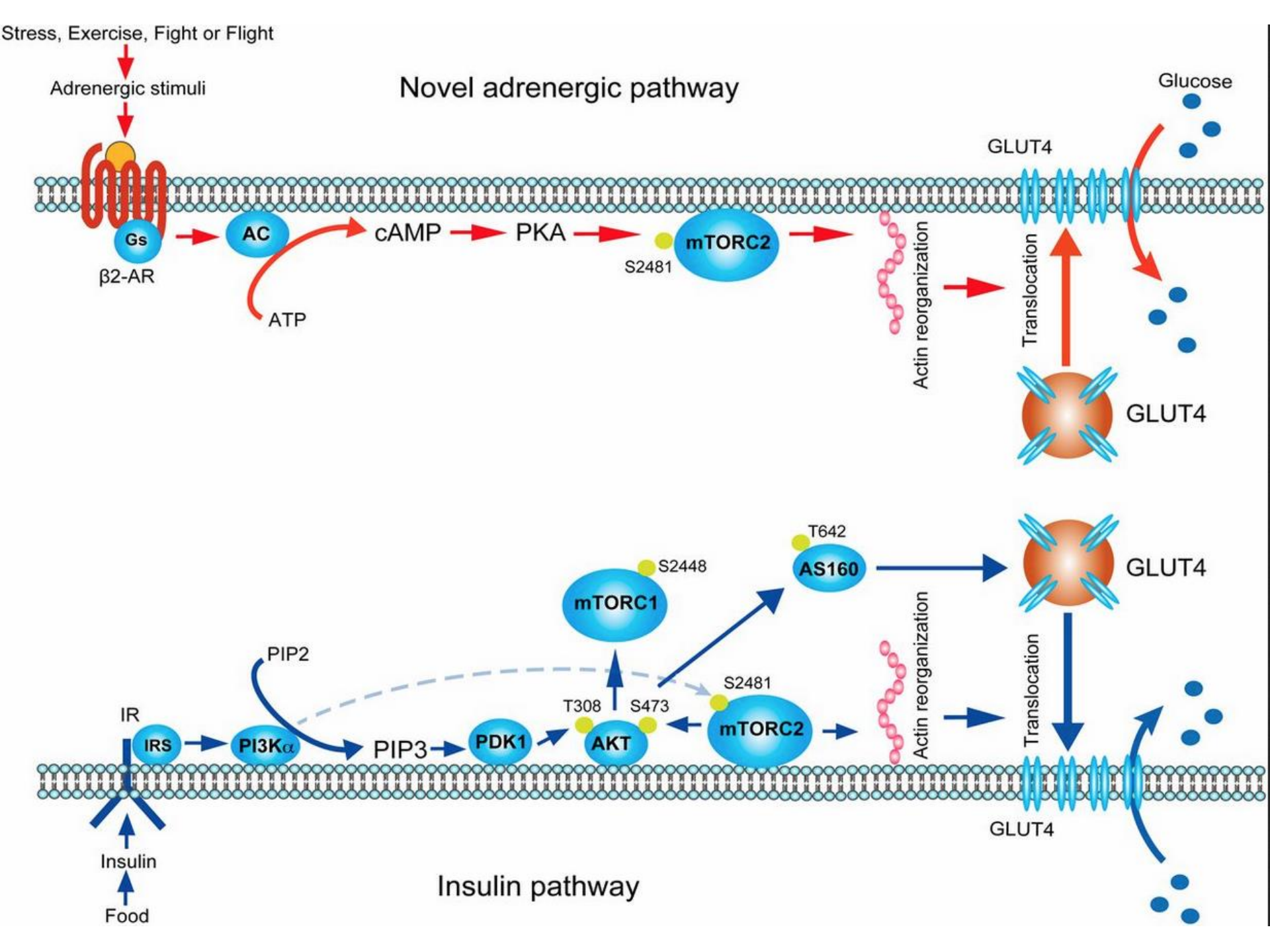
GLUT1/β-Tubulin (% of basal)
400
300
200
100
0
**
***
Basal
+KU0063794
Isoproterenol 1h
+KU0063794
Isoproterenol 2h
+KU0063794

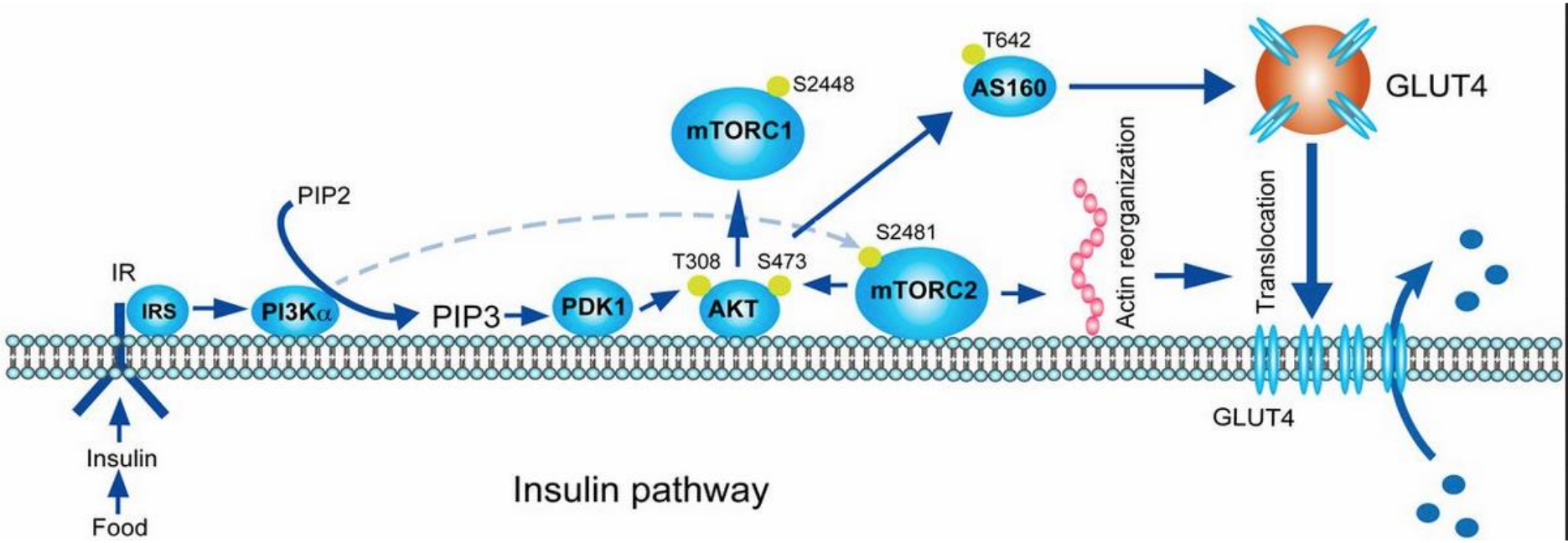

B
GLUT1 (total)
Basal
Isoproterenol
+KU0063794
GLUT1 (% of basal)
500
300
100
0
*
Basal
+KU0063794
Isoproterenol
+KU0063794


c
GLUT1 (plasma membrane)
Basal
Isoproterenol
+KU0063794
GLUT1 (% of basal)
500
300
100
0
*
Basal
+KU0063794
Isoproterenol
+KU0063794

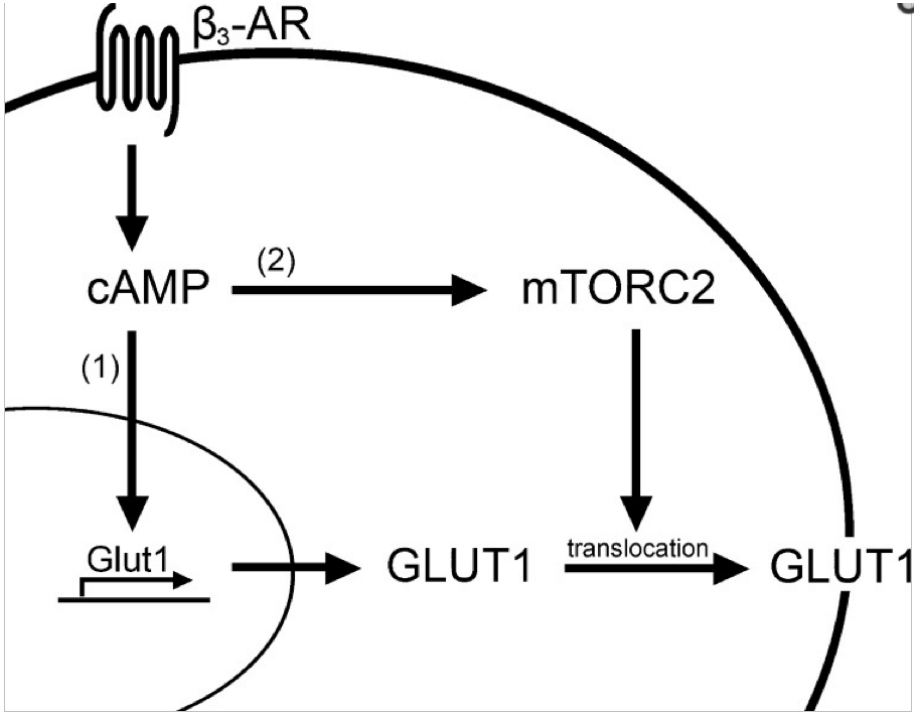

c
GLUT1 (plasma membrane)
Basal
Isoproterenol
+KU0063794
GLUT1 (% of basal)
500
300
100
0
*
Basal
+KU0063794
Isoproterenol
+KU0063794

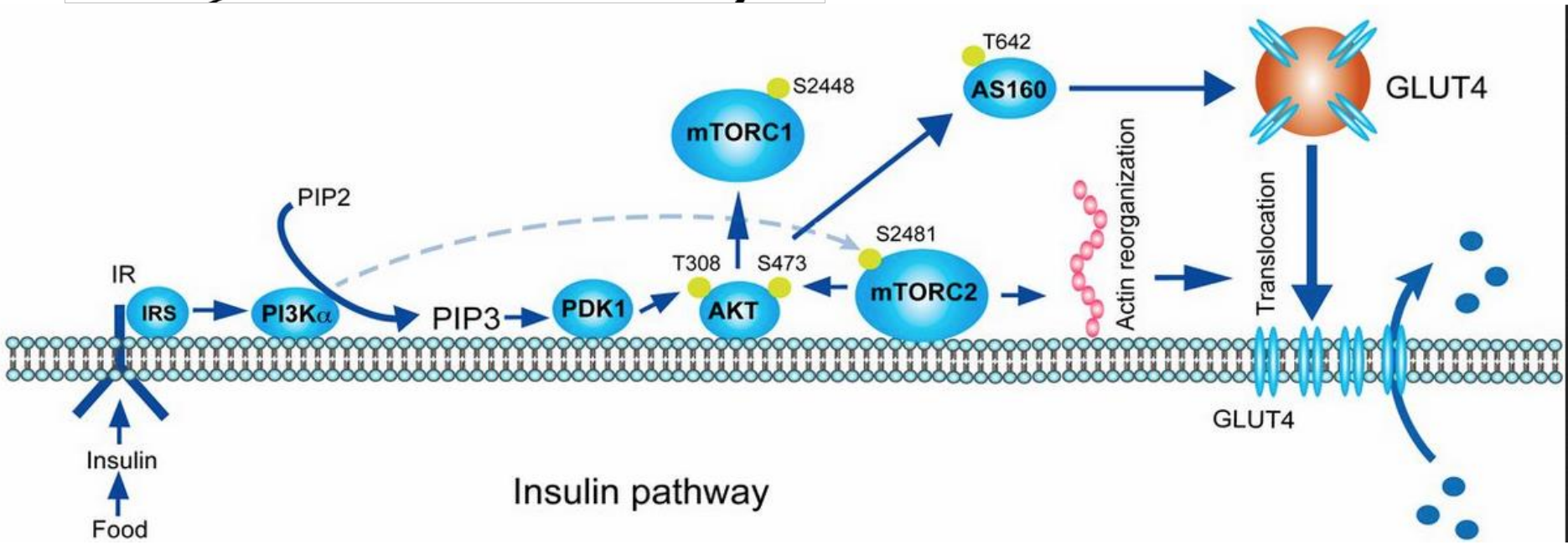

β3-AR
cAMP
(2)
mTORC2
(1)
Glut1
GLUT1
translocation
GLUT1


Stress, Exercise, Fight or Flight
Adrenergic stimuli
Novel adrenergic pathway
Glucose
GLUT4
Gs
AC
cAMP
PKA
mTORC2
S2481
β2-AR
ATP
Actin reorganization
Translocation
GLUT4
T642
AS160
S2448
mTORC1
GLUT4
PIP2
S2481
IR
T308
S473
IRS
PI3Kα
PIP3
PDK1
AKT
mTORC2
Actin reorganization
Translocation
GLUT4
Insulin
Food
Insulin pathway



Insulin pathway


β3-AR
cAMP
(2)
mTORC2
(1)
Glut1
GLUT1
translocation
GLUT1


T642
AS160
GLUT4
S2448
mTORC1
PIP2
S2481
T308
S473
IR
IRS
PI3Kα
PIP3
PDK1
AKT
mTORC2
Actin reorganization
Translocation
GLUT4
Insulin
Food
Insulin pathway

These SNPs
accelerate age-related decrease in BAT activity,
and thereby may associate with
visceral fat accumulation with age.

Yoneshiro//Saito, 2013)