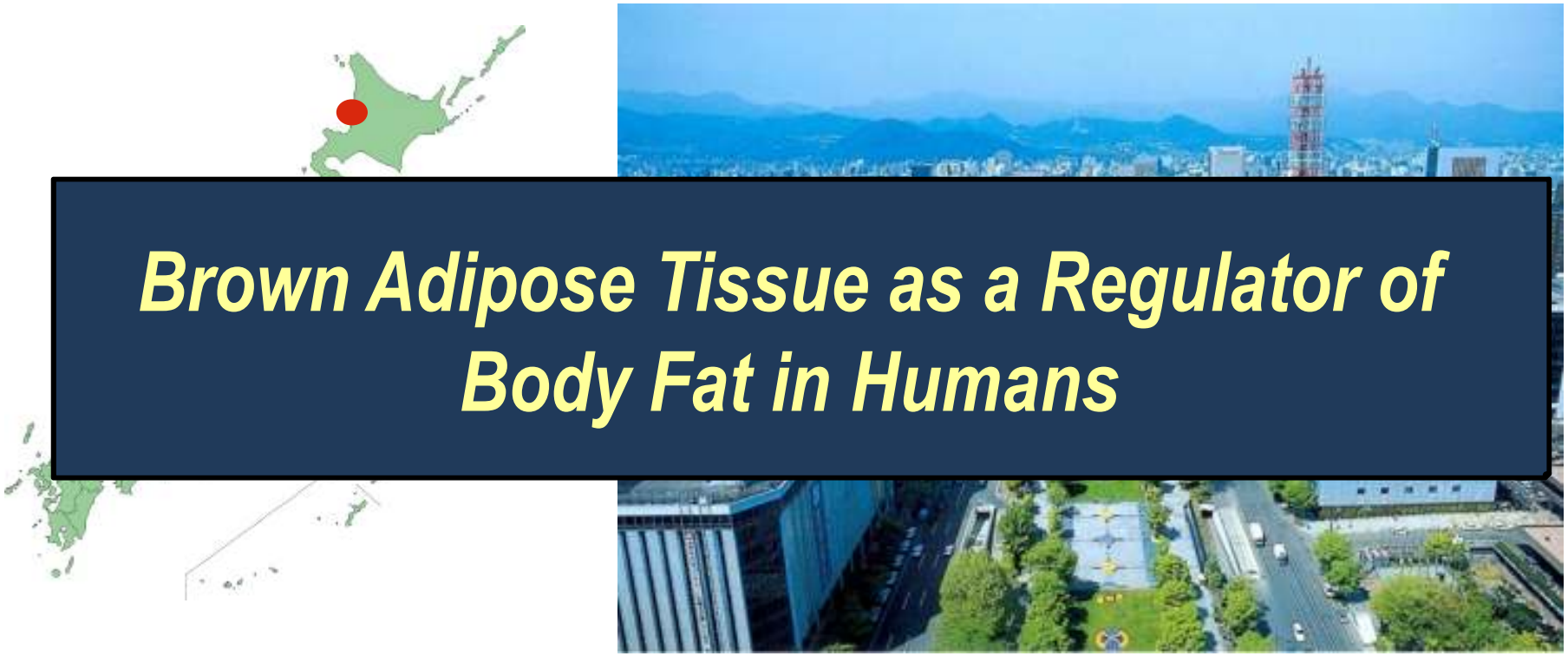
2012 International Conference of Diabetes and Metabolism

Symposium 3: Obesity November 9, 2012, Seoul , Korea



Brown Adipose Tissue as a Regulator of Body Fat in Humans

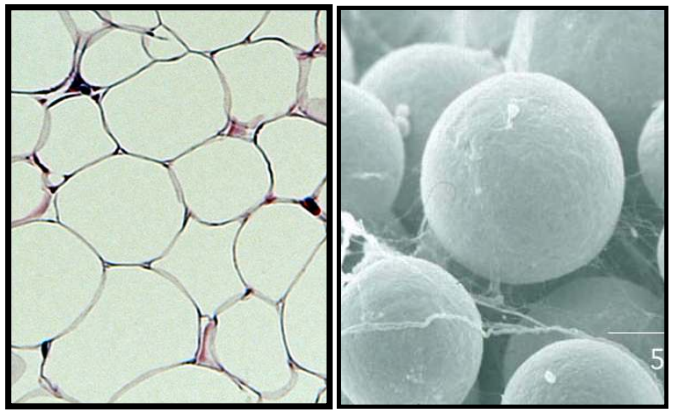
Masayuki Saito

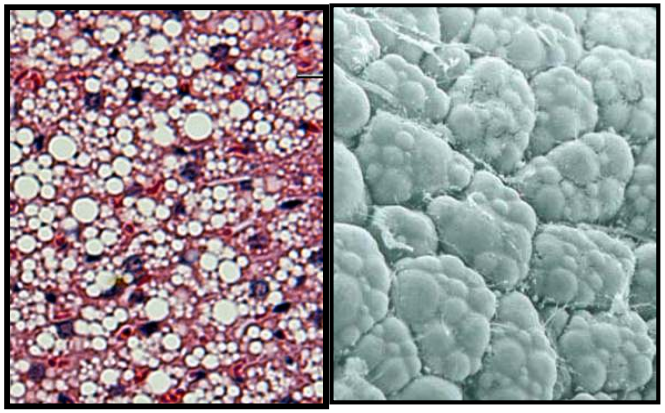
Department of Nutrition, Tenshi College, Sapporo, Japan

Two types of adipose tissue in mammals

White fat

Brown fat

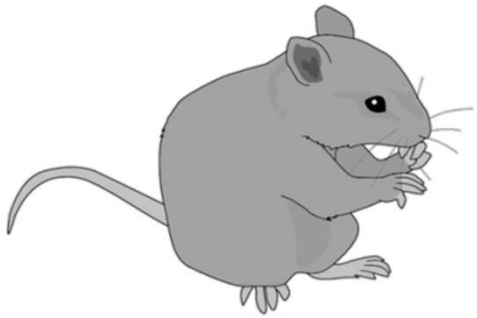




Energy storage

Energy dissipation
Thermogenesis

Brown adipose tissue in small rodents and humans



In small rodents, brown adipose tissue (BAT) is the major site of metabolic thermogenesis during cold exposure and overfeeding, and significantly contributes to the control of body temperature, whole body energy balance and adiposity.

In humans, brown adipocytes/UCP1 can be detected in neonates and also in patients with pheochromocytoma. But, in normal adults, this is rather difficult to be detected by the conventional anatomical methods.

⇩

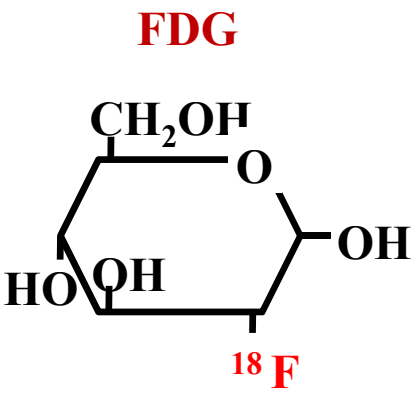
BAT is absent (or of minute amounts) and plays negligible roles for energy metabolism in adult humans.

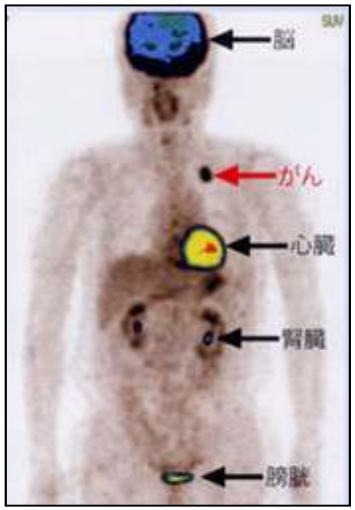
^{18}F-2-deoxyglucose-positron emissiontomography computed tomography （^{18}F-FDG-PET/CT）

Tissue metabolic activity can be assessed from PET image of the uptake of isotope-labeled fluoro-2-deoxyglucose (FDG).

High FDG uptake is found in cancer tissues, and also in some normal tissues, such as the brain and heart.

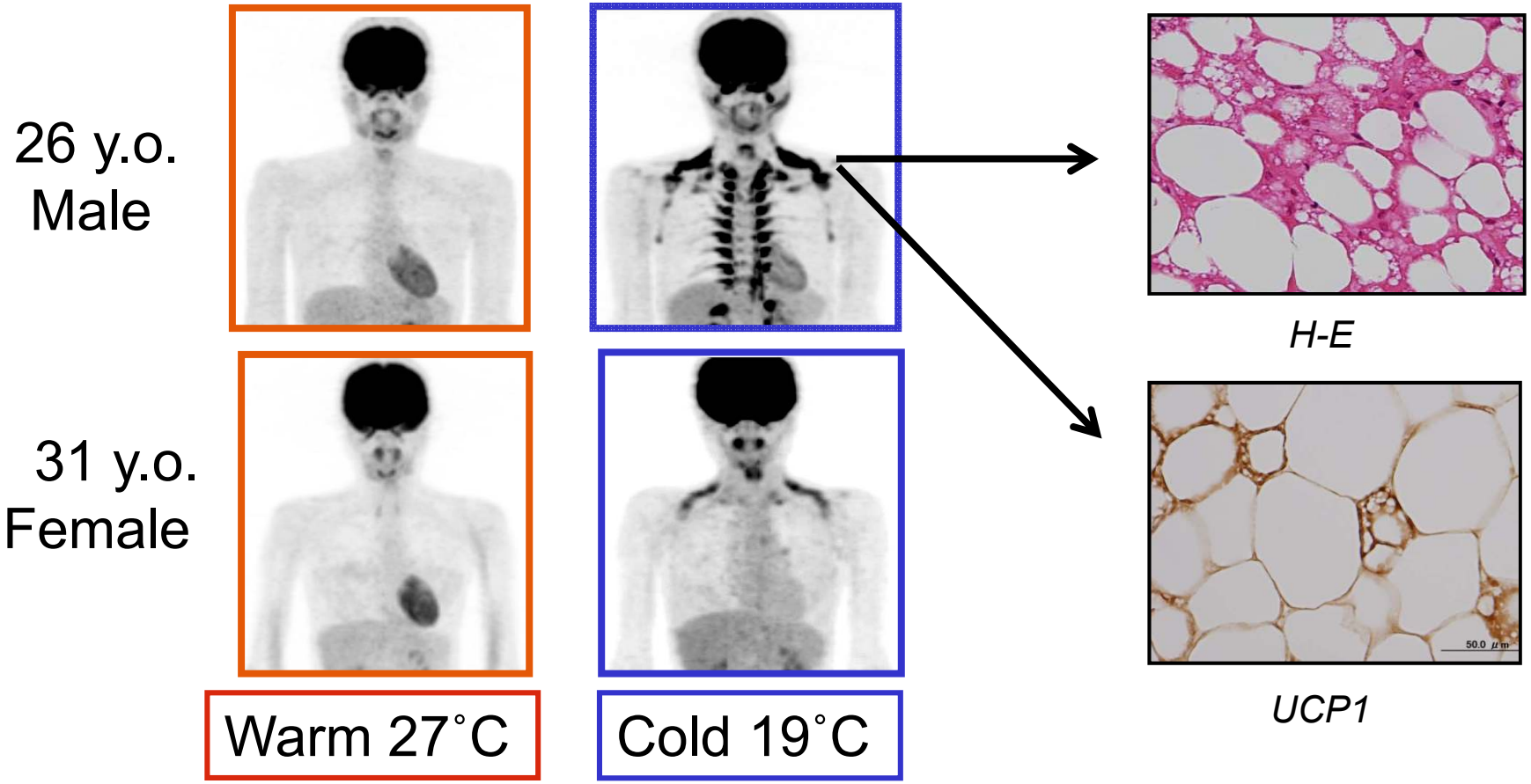
Sometimes, significant FDG uptake is also found in adipose tissue in the supraclavicular and paraspinal regions.





BAT activated by acute cold exposure

Overnight fasted healthy subjects were kept in warm (27˚C), or in cold (light clothing in a room at 19˚C, intermittent ice-cooling of legs), and after 2 h, 40-min FDG uptake was examined by PET.



Saito et al, Int J Obesity 2007

Saito et al, Diabetes 2009

Human brown adipose tissue evaluated by FDG-PET/CT

1. It is activated by acute cold exposure.
2. The activity/prevalence is higher in winter.
3. The activity/prevalence decrease with age.
4. The activity is inversely related to adiposity.

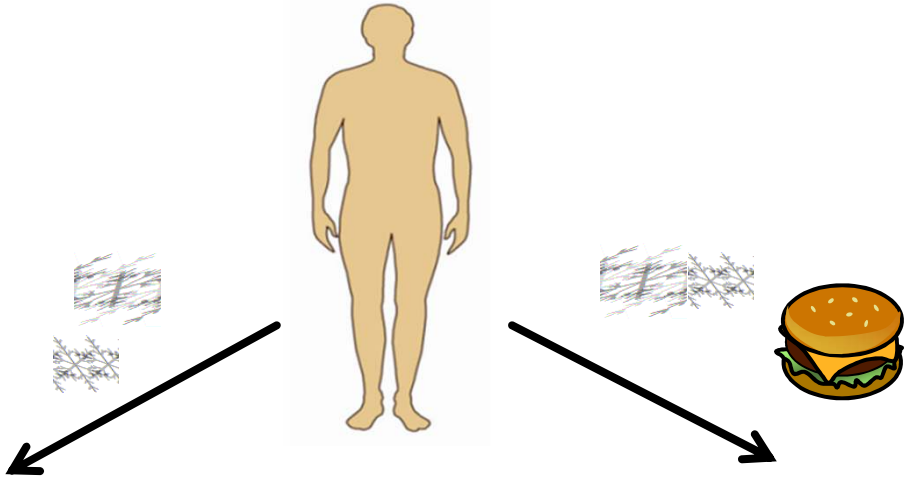
Adult human has metabolically active brown adipose tissue

Does brown fat contribute to the control of whole body energy expenditure and adiposity?

sm1

Contribution of BAT to thermogenesis induced by cold exposure or food intake

Forty-two healthy male subjects aged 20-30 years.



FDG-PET/CT after 2-hr cold

BAT (SUV>2)

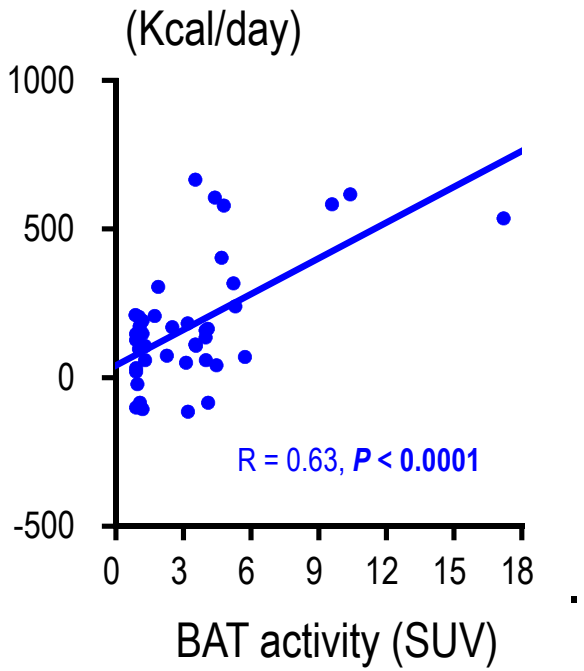
Indirect calorimetry

sm1 saito masayuki, 2012-11-04

Cold-induced thermogenesis (CIT) and BAT

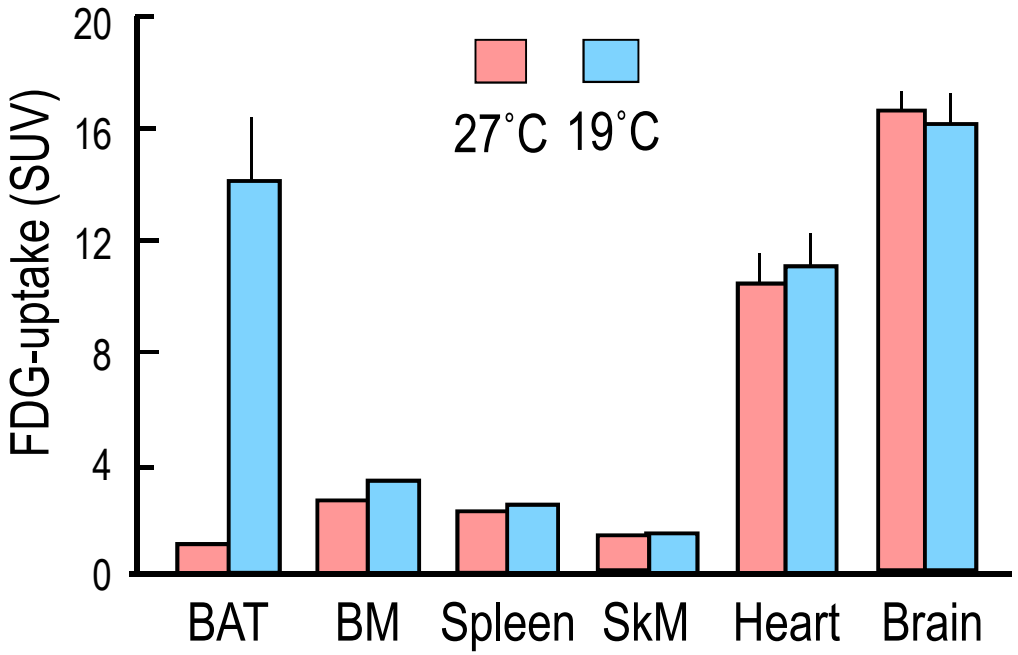
Energy expenditure was measured at 27˚C ( ) and after 2hr-cold exposure at 19˚C ( ).

⊿ Energy expenditure
(Cold-induced thermogenesis)



Yoneshiro et al, Obesity 2011a

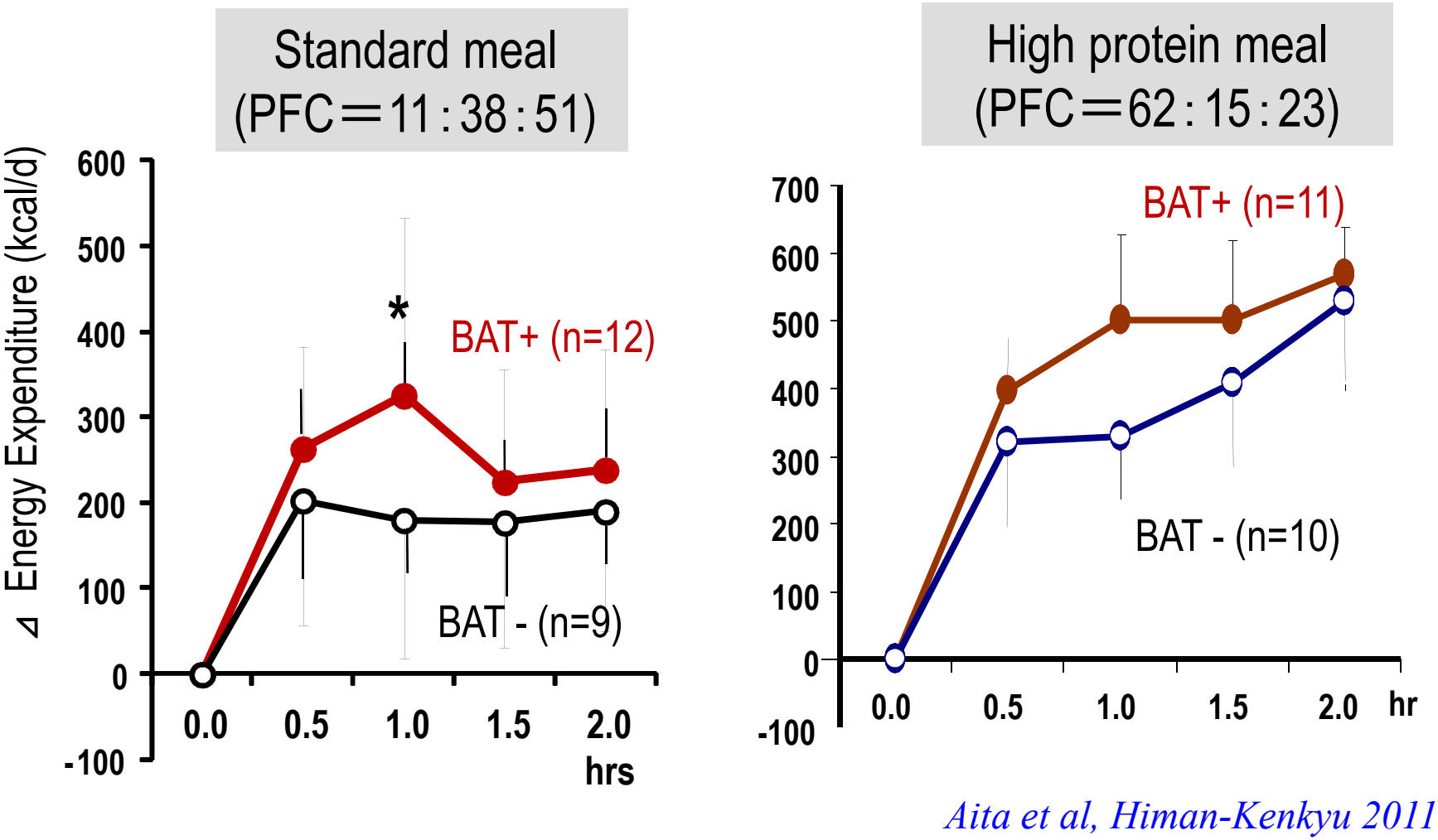
FDG-uptake



Nishio et al, Cell Metab 2012

Postprandial thermogenesis (DIT) and BAT

Energy expenditure was measured after intake of a standard or high protein meal (500kcal/63kg) in BAT-positive and -negative subjects.



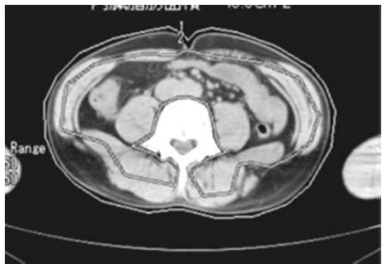
Aita et al, Himan-Kenkyu 2011

Brown adipose tissue and body fat accumulation

FDG-PET

Brown adipose tissue
（SUV)

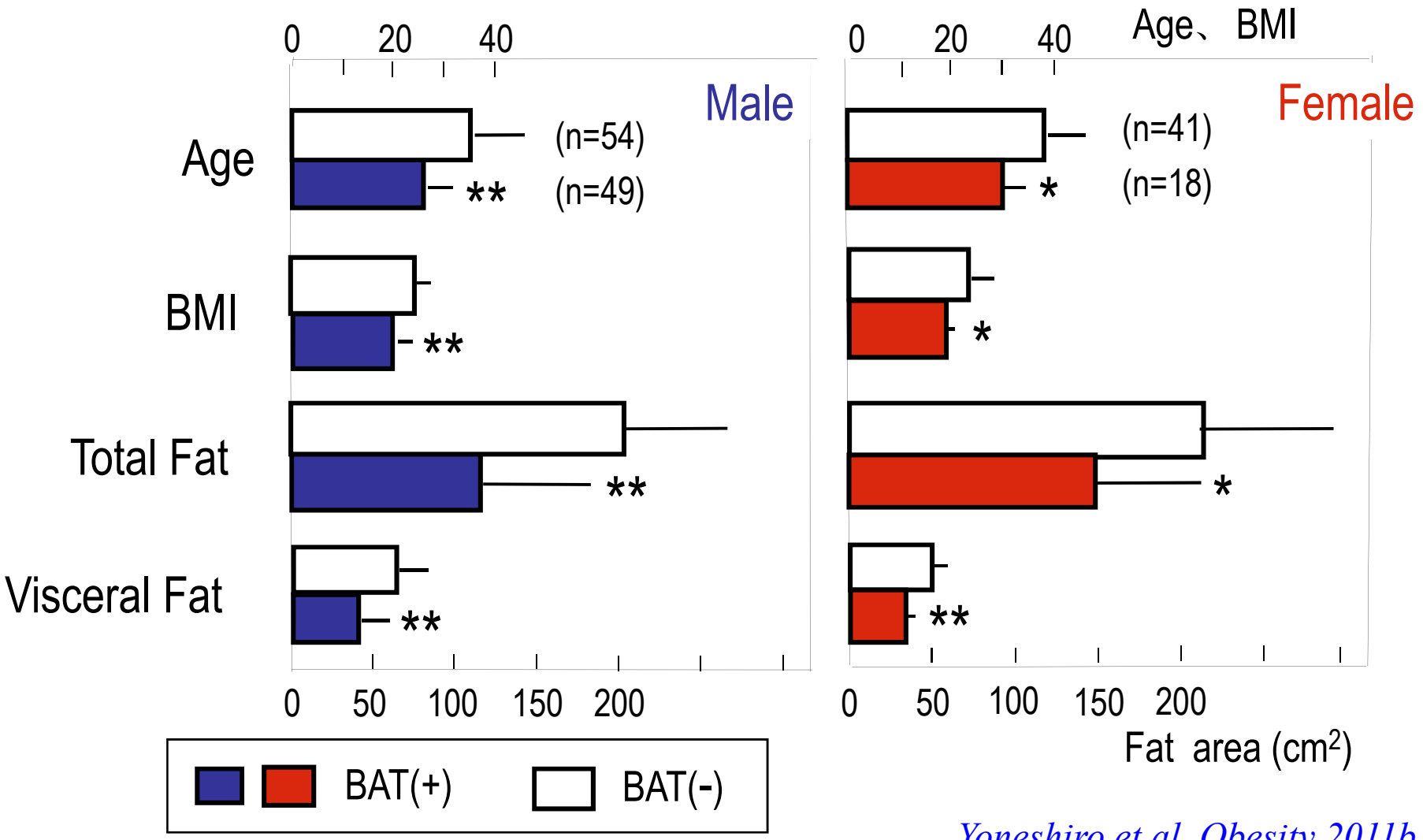
CT



Body fat
Visceral fat
Subcutaneous fat

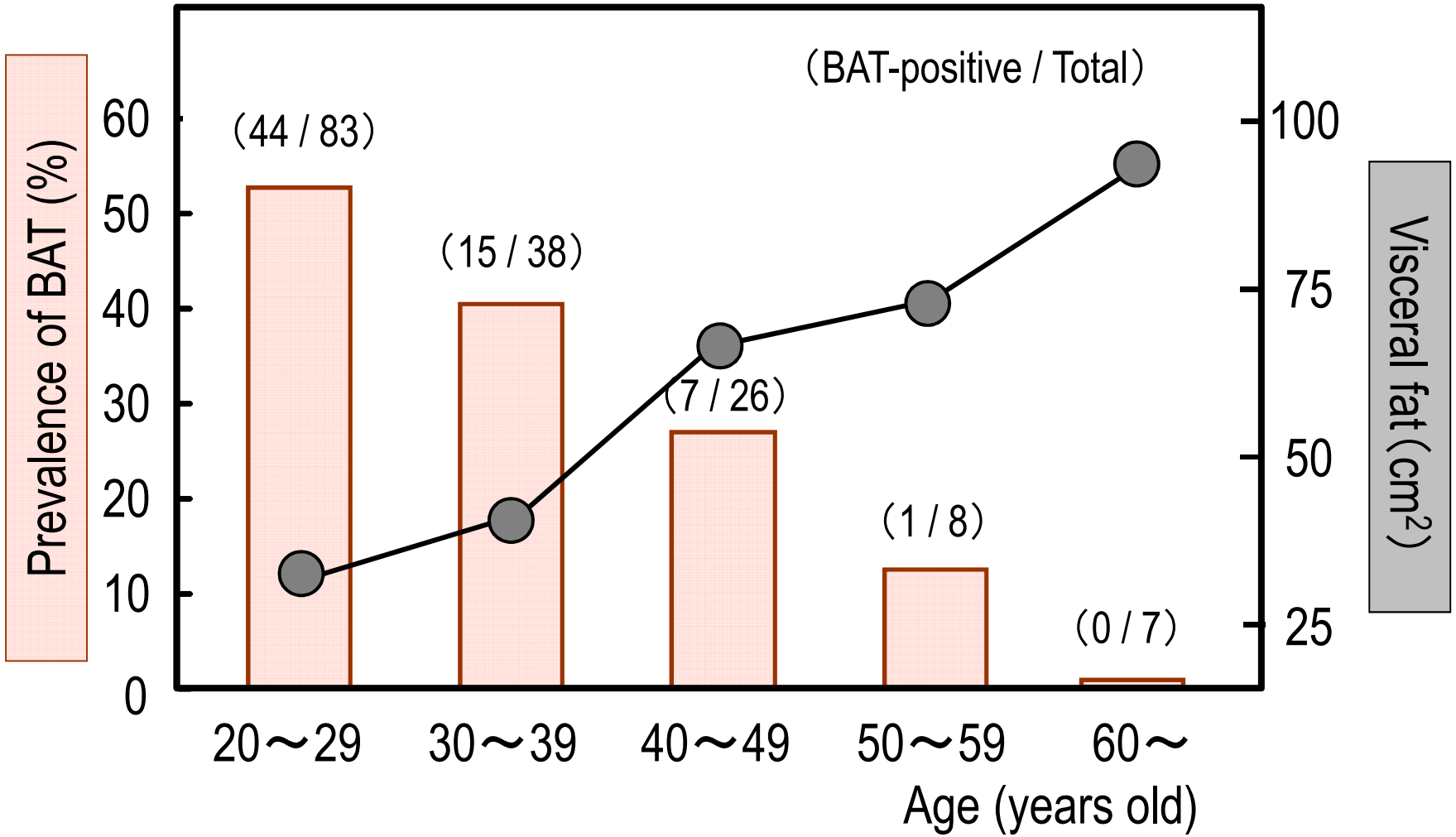
Adiposity of BAT-positive and -negative subjects

（20-72 years old、N=162）



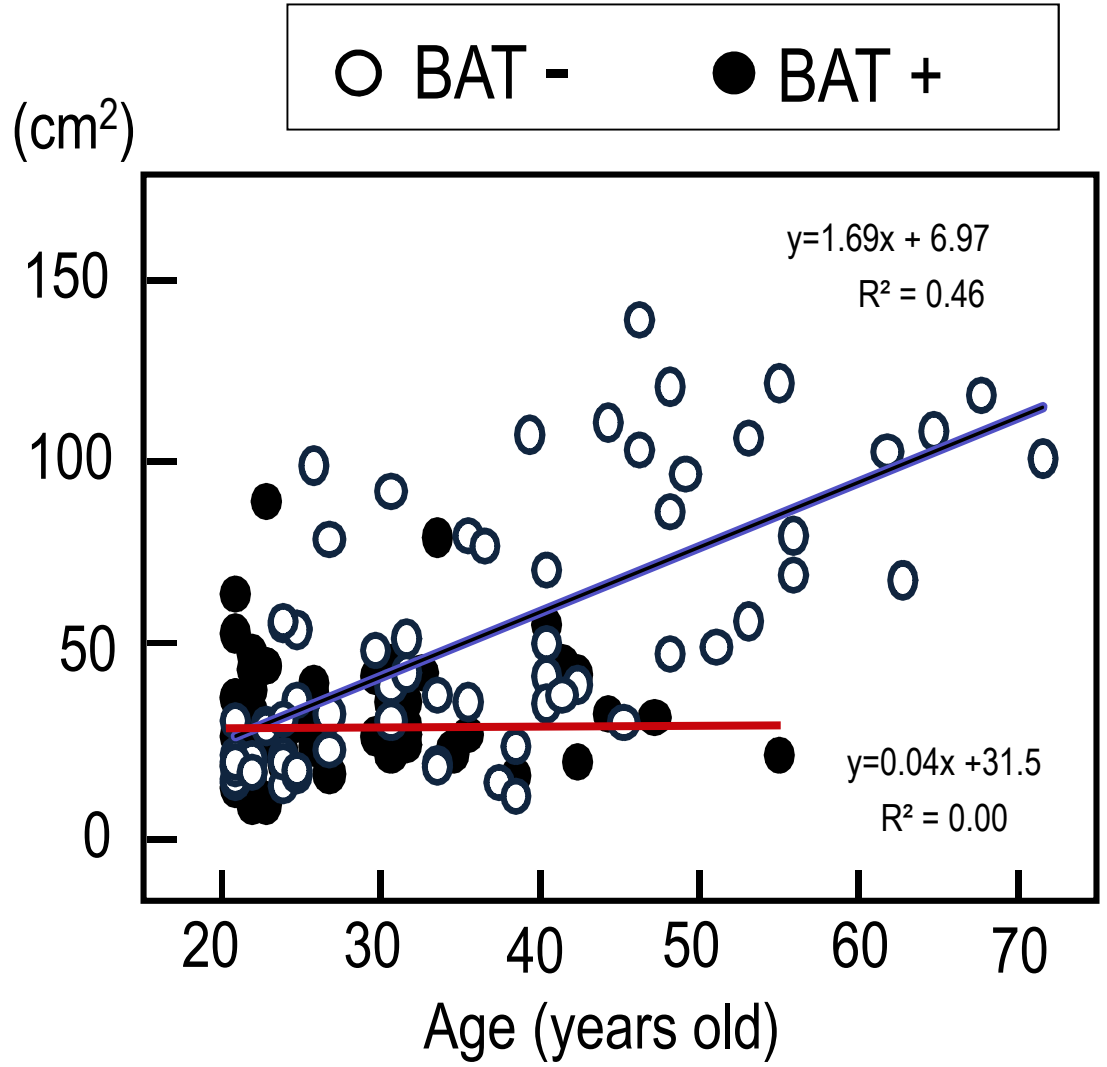
Yoneshiro et al, Obesity 2011b

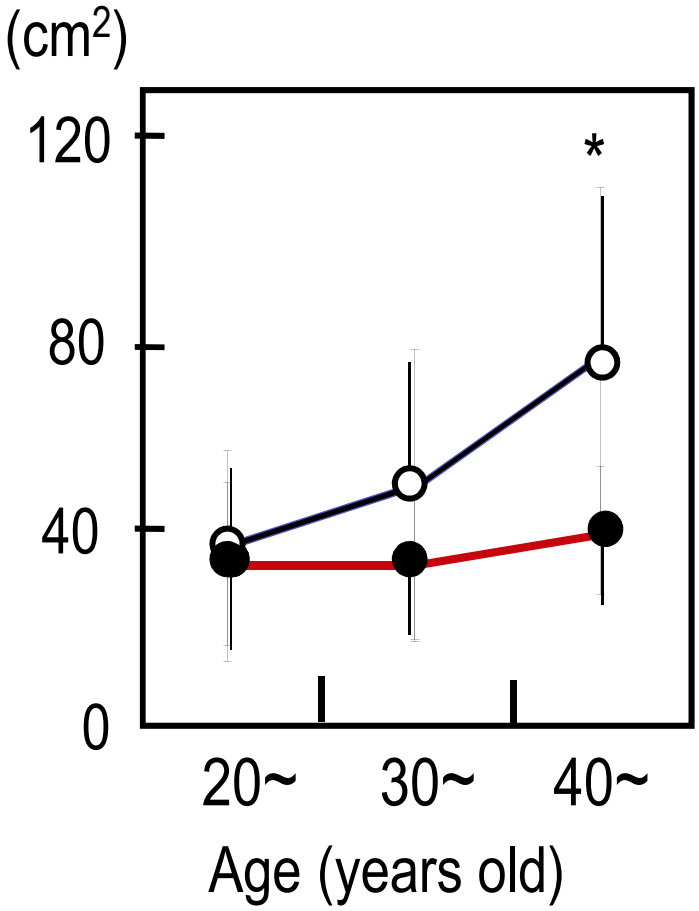
Age-related accumulation of visceral fat and decrease in BAT



Yoneshiro et al, Obesity 2011b

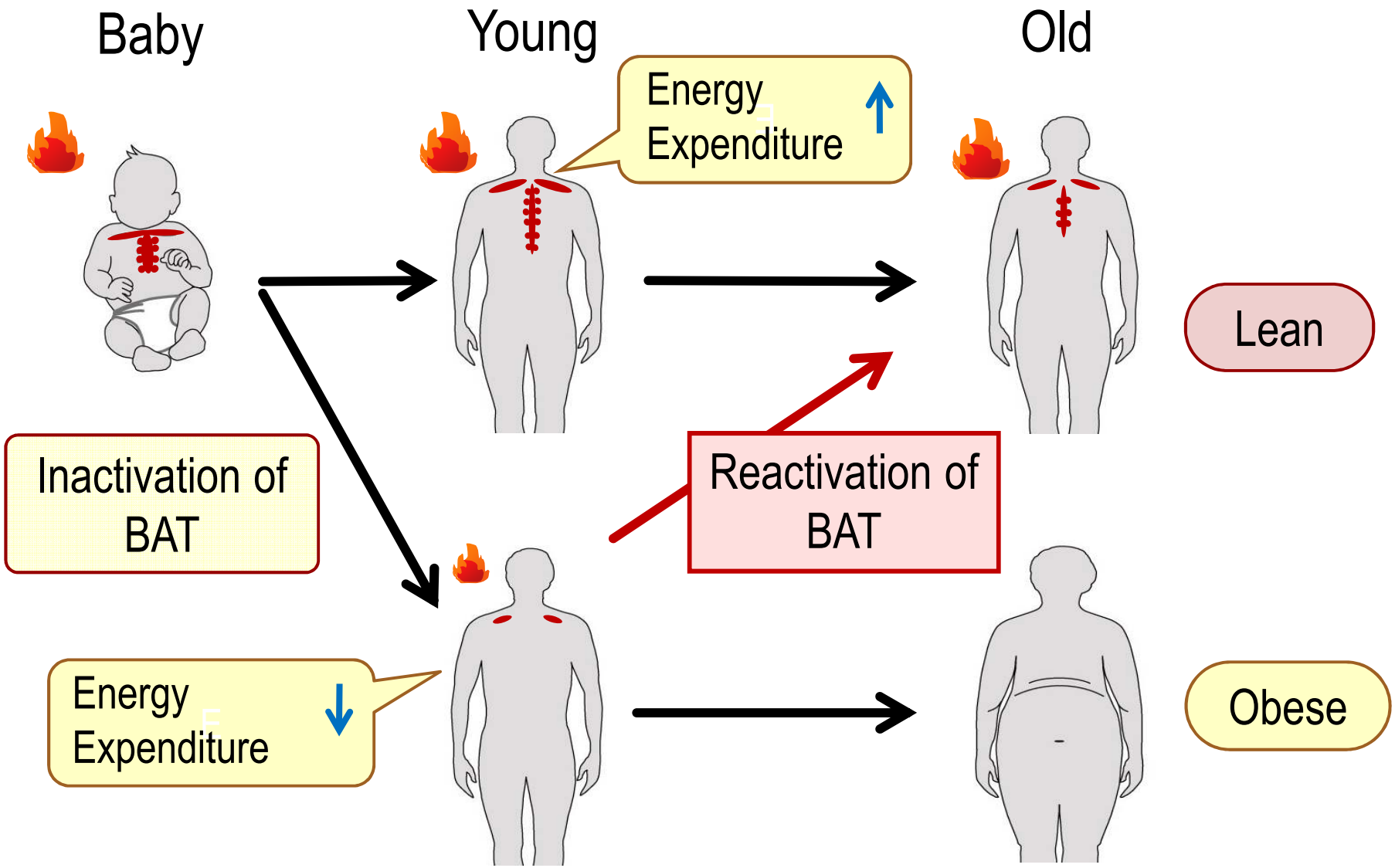
Age-related accumulation of visceral fat in BAT-negative and –positive subjects



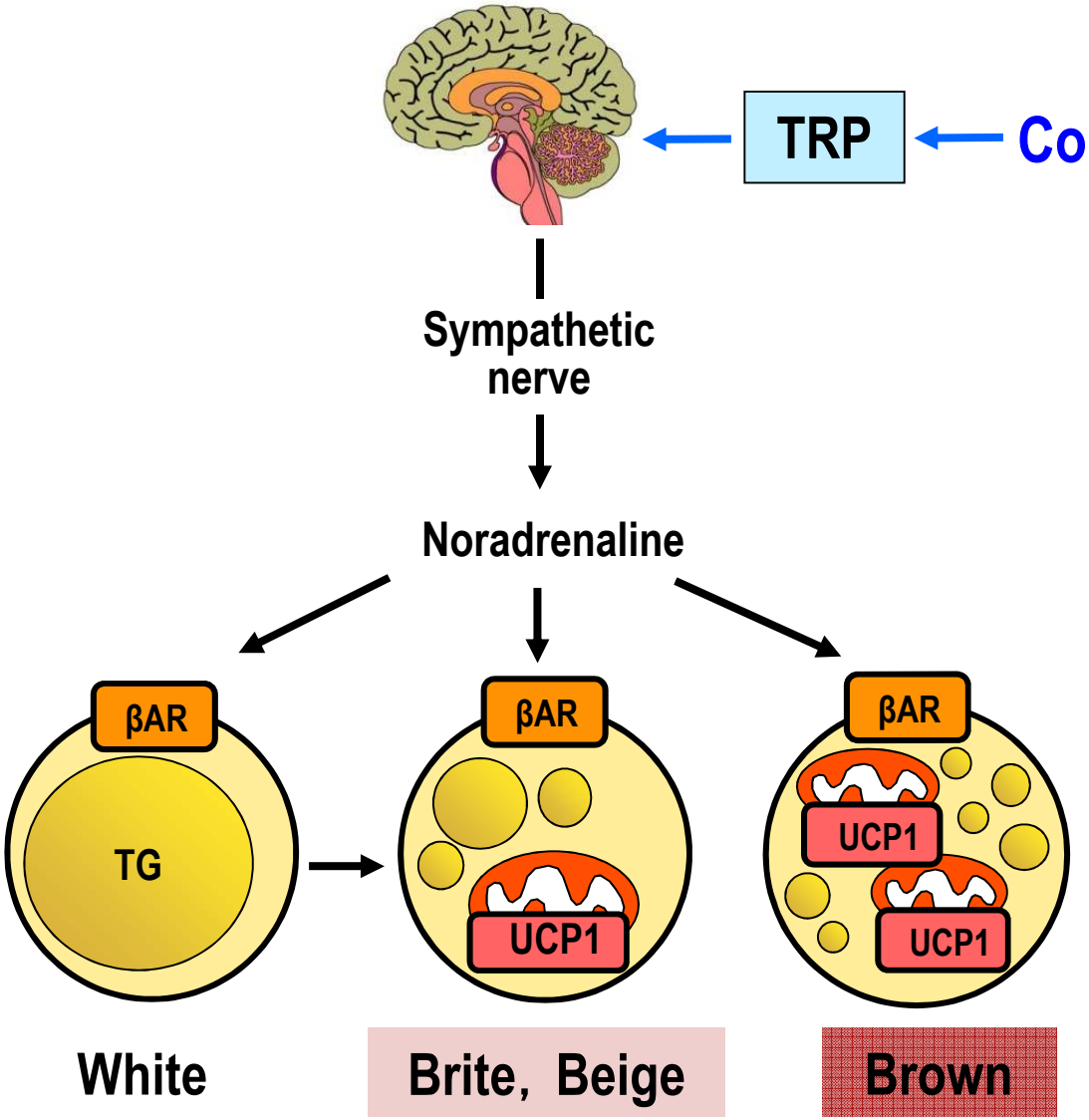


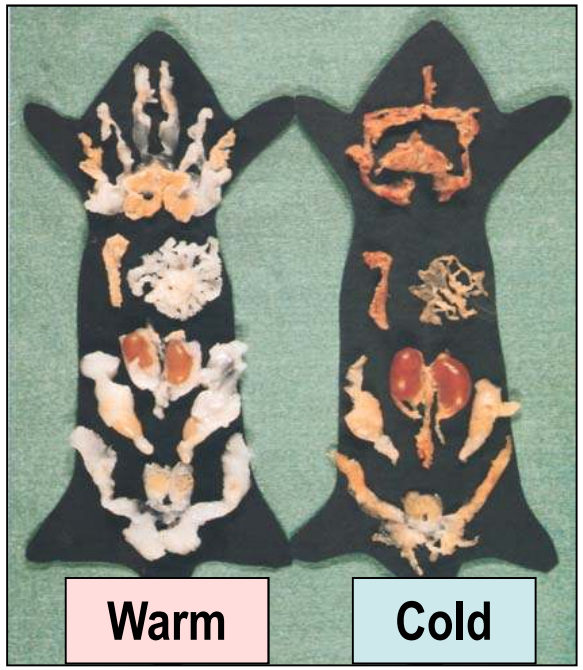
Yoneshiro et al, Obesity 2011b

Age-related decrease in BAT and accumulation of body fat



Cold-induced activation and recruitment of BAT



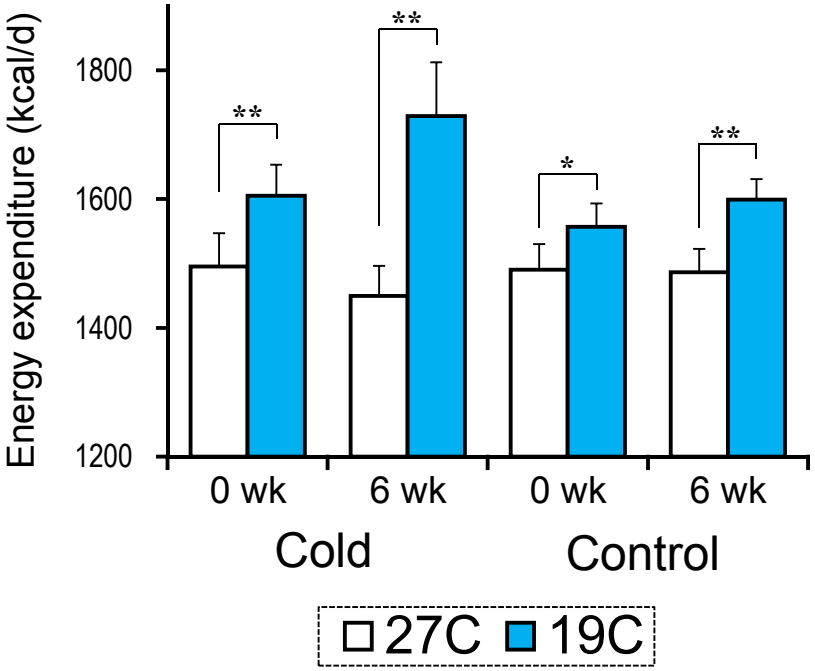


Cinti S, 1999
The Adipose Organ

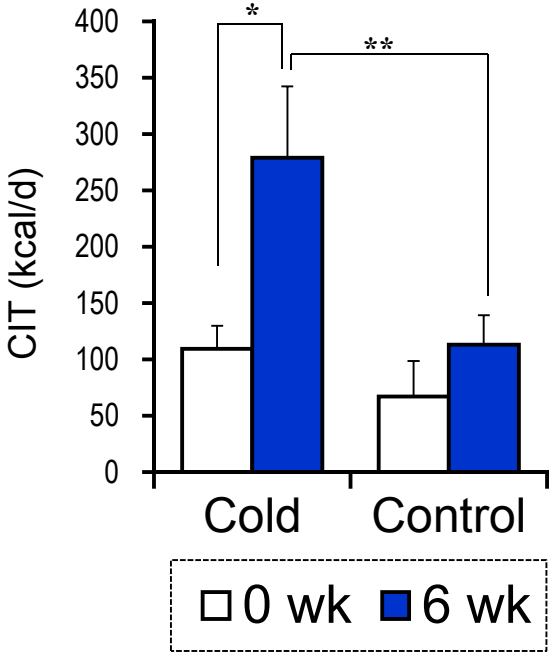
BAT is recruited after repeated cold exposure

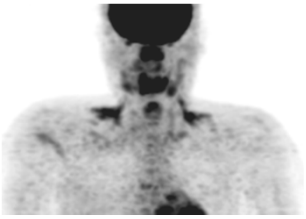
Healthy male subjects were exposed to cold at 17˚C for 2h every day for 6 weeks or kept at room temperature (Control), and energy expenditure was measured at 27˚C and again at 19˚C to estimate cold-induced thermogenesis (CIT), an index of BAT activity. Some subjects underwent FDG-PET before and after the 6-wk period.

Energy expenditure at 27˚C and 19˚C before and after daily cold exposure for 6 wk

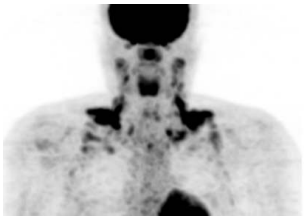


Cold-induced thermogenesis and FDG-uptake before and after daily cold exposure for 6 wk





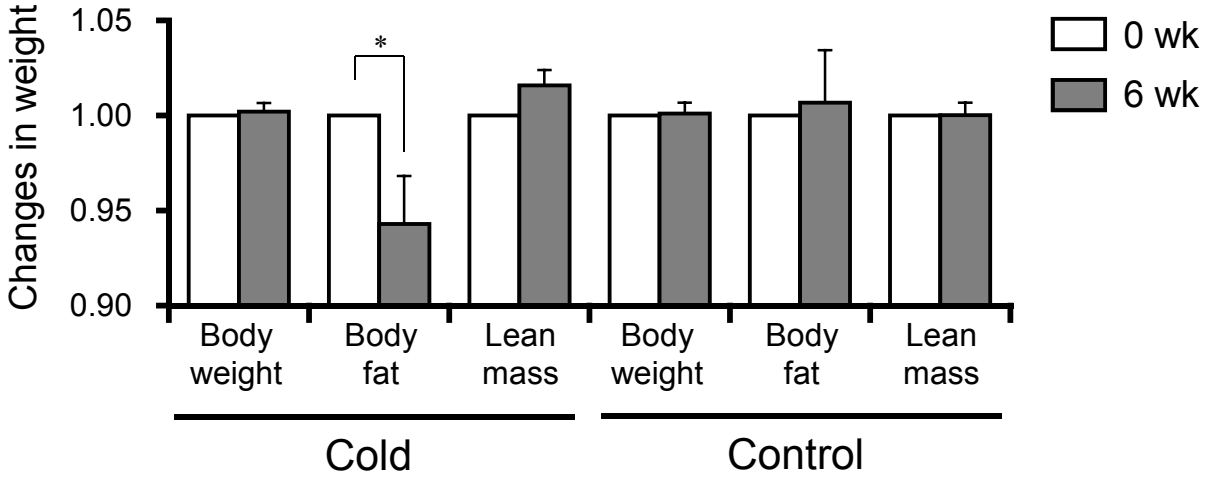
0 wk

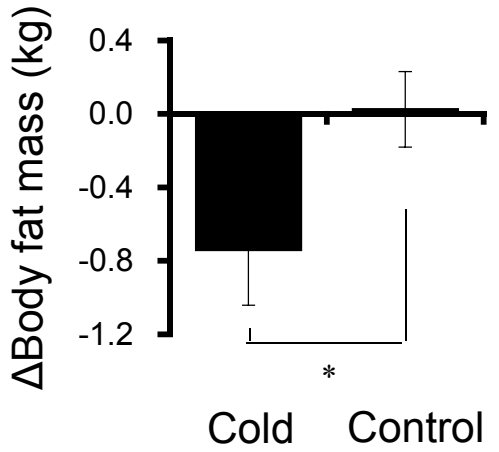


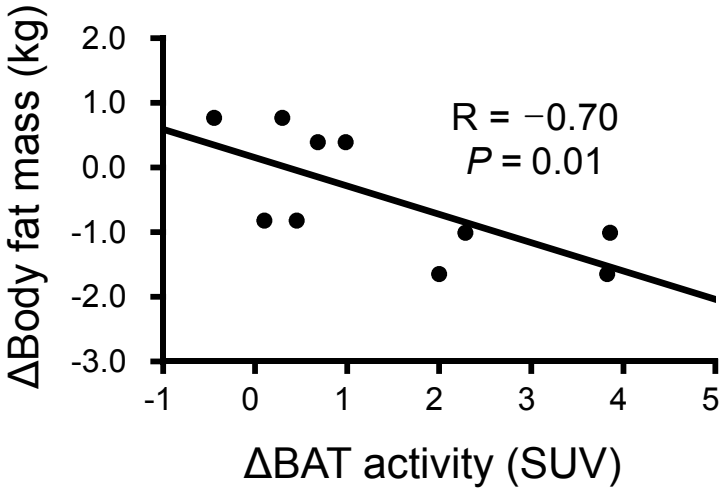
6 wk

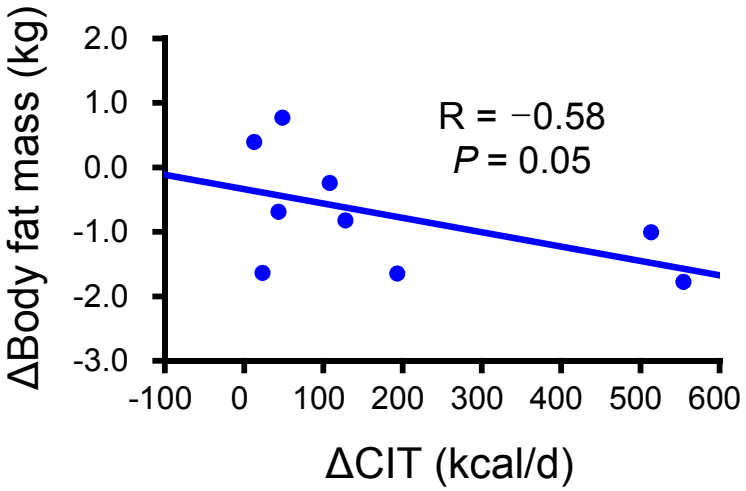
Body fat is reduced as BAT is recruited

Healthy male subjects were exposed to cold at 17˚C for 2h every day for 6 weeks or kept at room temperature (Control), and body composition was measured.



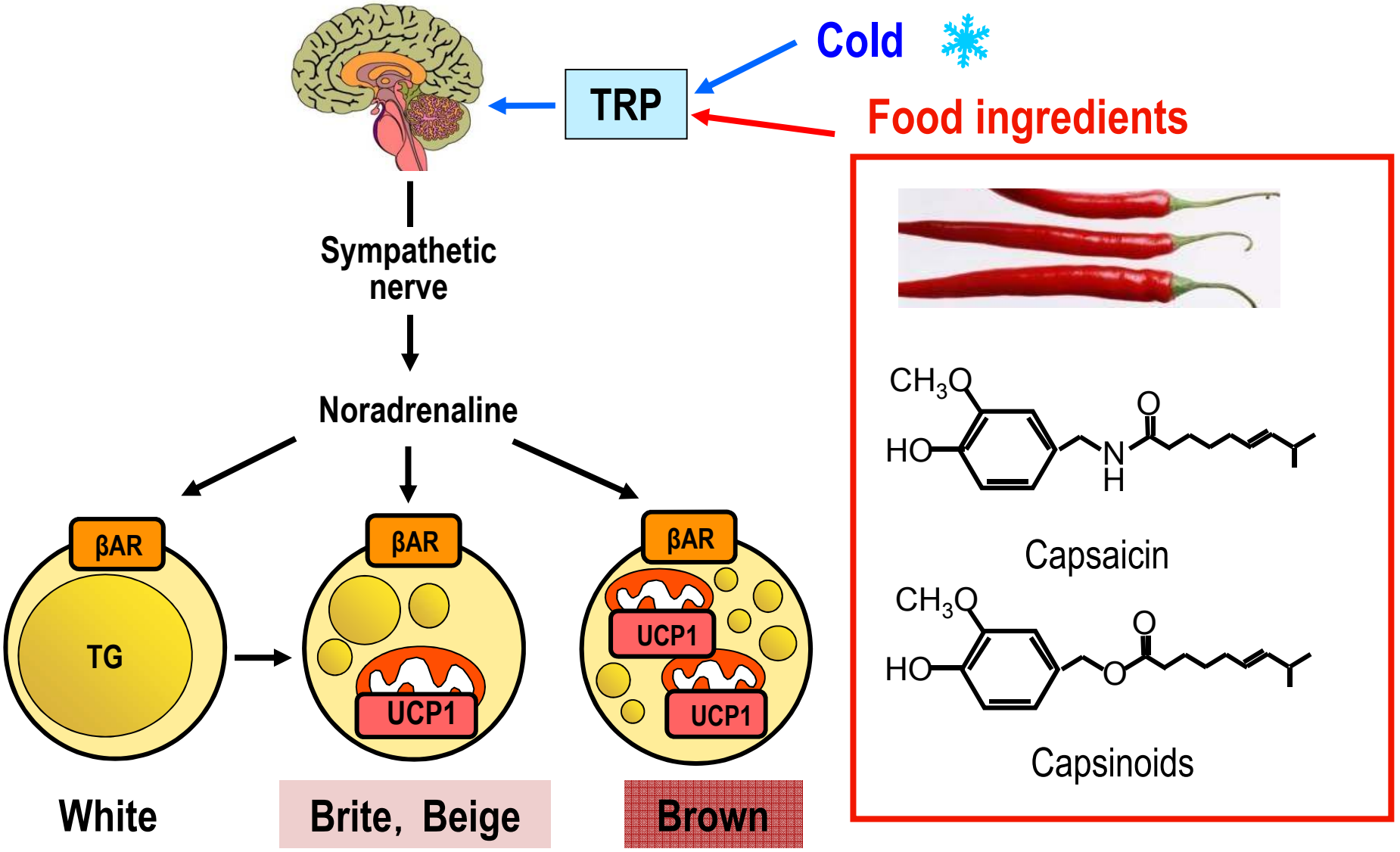






Yoneshiro et al, submitted

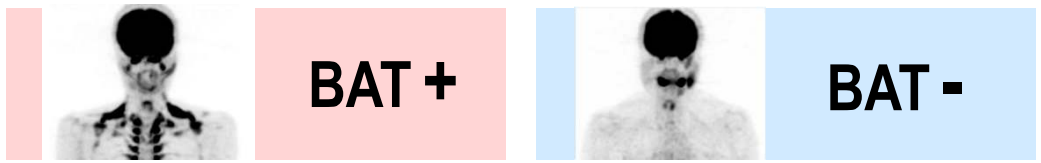
TRP-mediated activation and recruitment of BAT

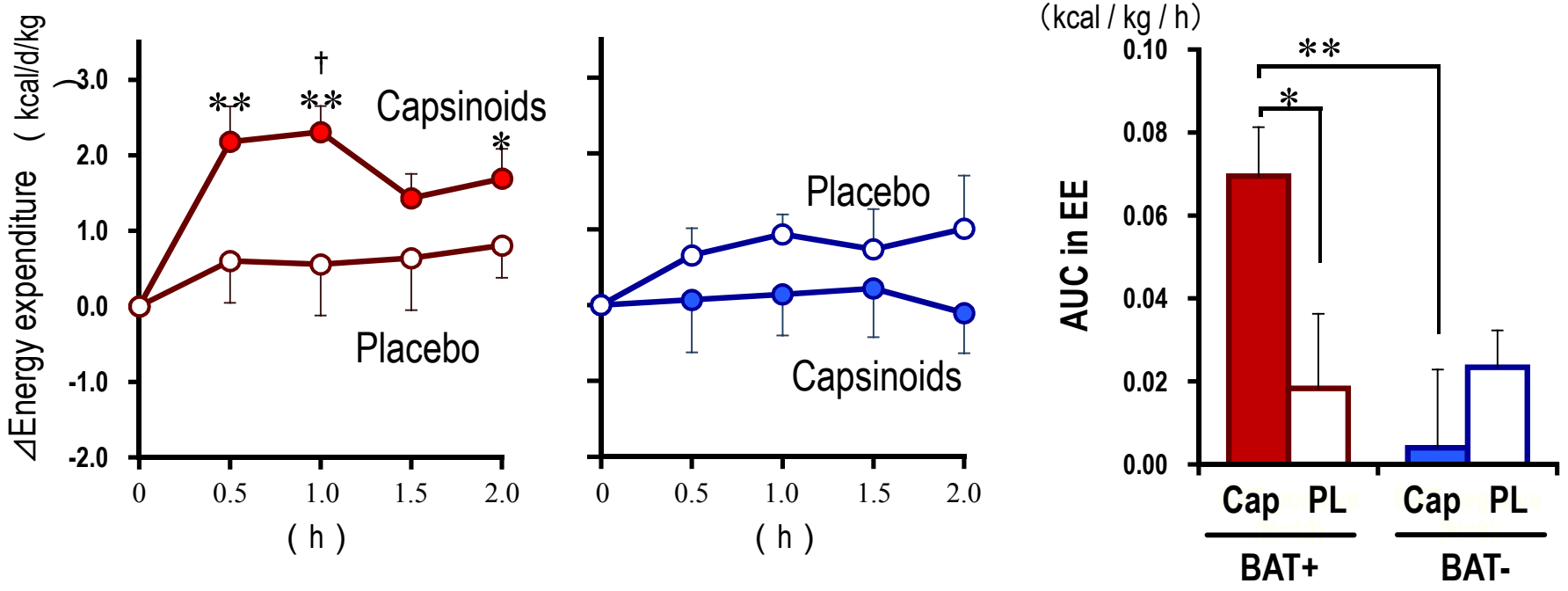


Saito et al, Curr Opin Lipidol 2012

Energy expenditure after oral ingestion of capsinoids

Capsules containing 9mg capsinoids or placebo were given to healthy male subjects with high or no BAT activity, and their energy expenditure was monitored for 2h.

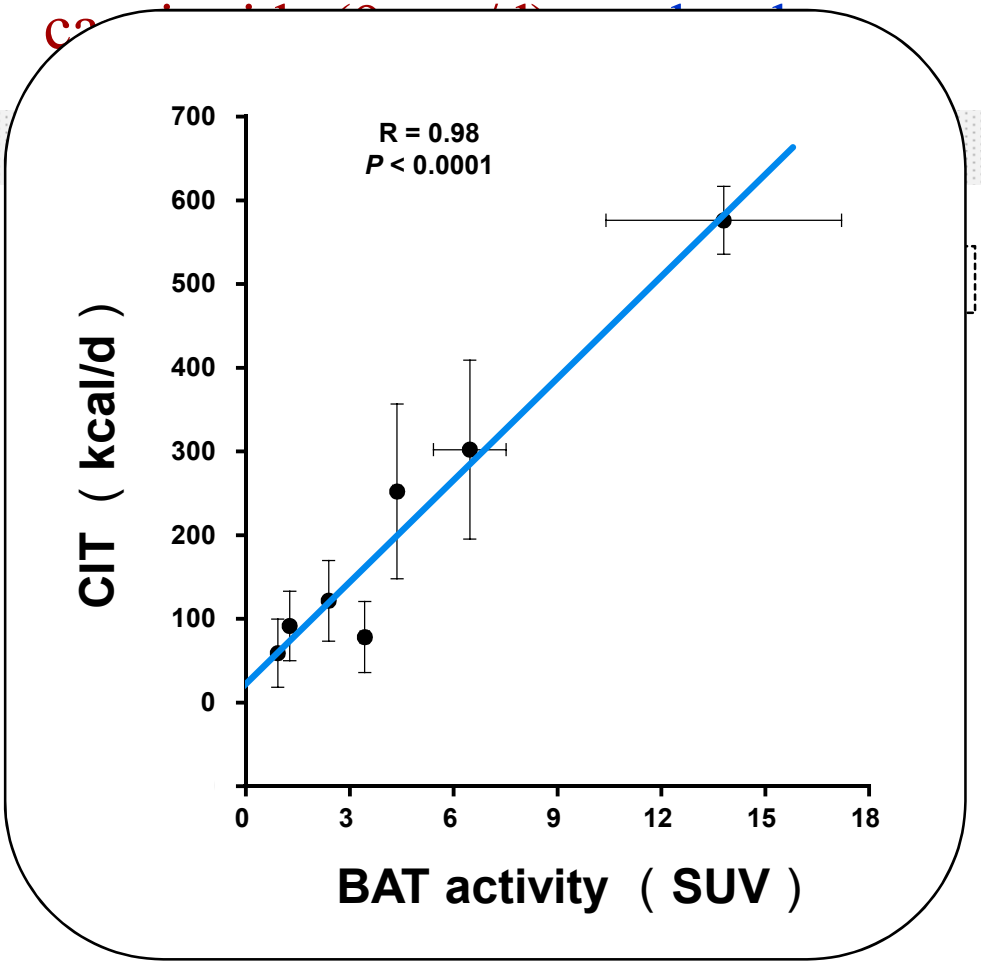




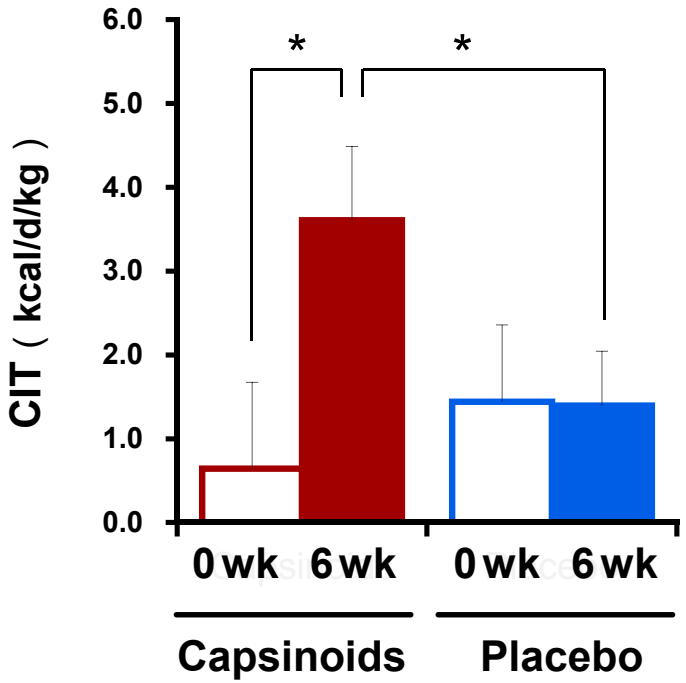
Yoneshiro et al, Am J Clin Nutr 2012

Daily ingestion of capsinoids recruits BAT

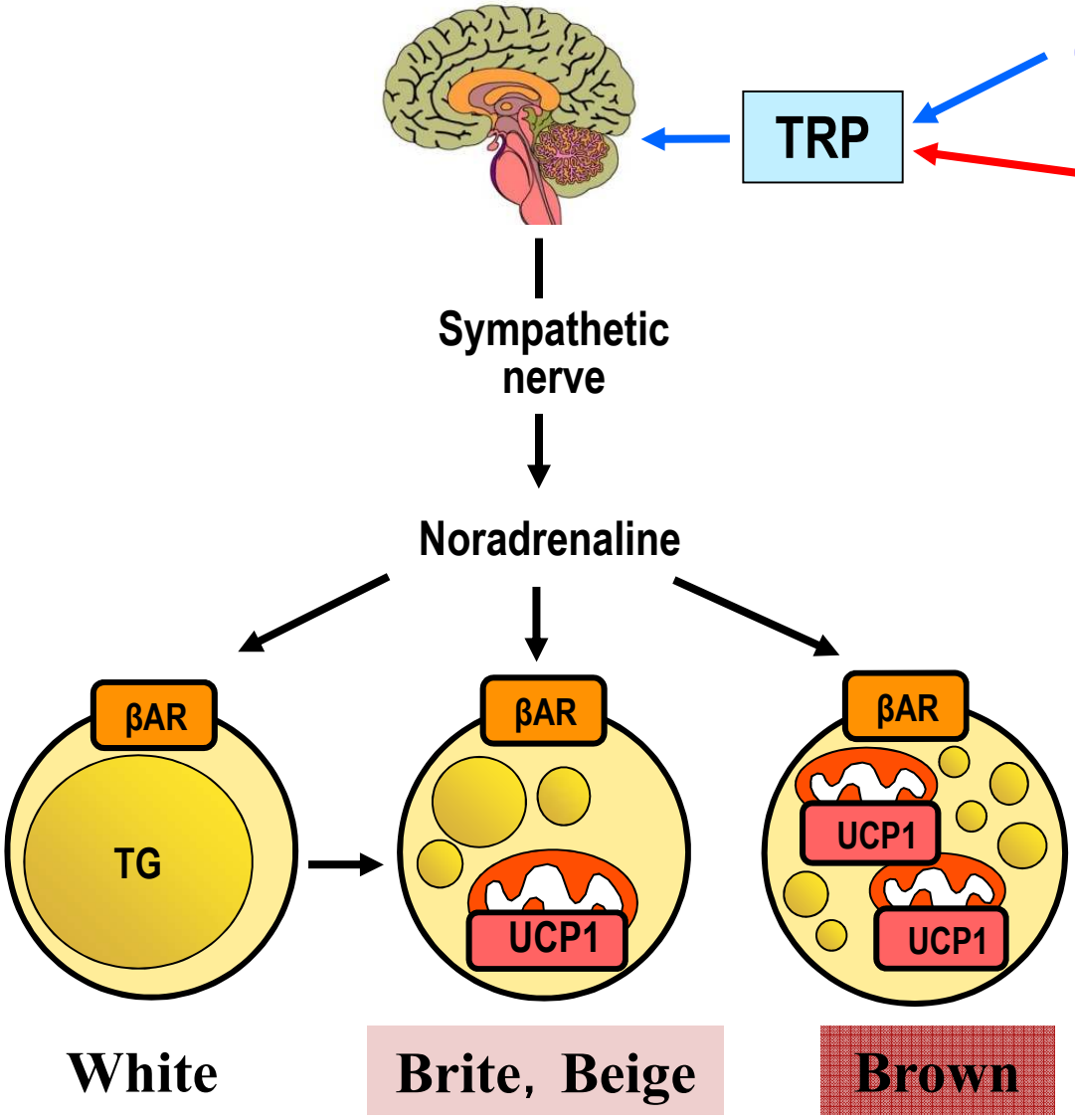
Cold-induced thermogenesis (CIT), an index of BAT activity, was measured before (0 wk) and 6 wk after daily oral ingestion of



Cold-induced thermogenesis



TRP-mediated activation and recruitment of BAT



Saito et al, Curr Opin Lipidol 2012

Brown adipose tissue in humans

1. **Human adults, as well as small rodents, have significant amounts of BAT, which is activated by acute cold exposure, and can be recruited by repeated cold exposure and some TRP agonists.**

2. **BAT is involved in cold- and diet-induced thermogenesis.**

3. **BAT correlates negatively to adiposity, and protects against age-related accumulation of body fat.**

4. **BAT significantly contributes to the control of whole-body energy expenditure and body fat, thereby being a hopeful target to combat obesity.**

Acknowledgements

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LSI Sapporo Clinic

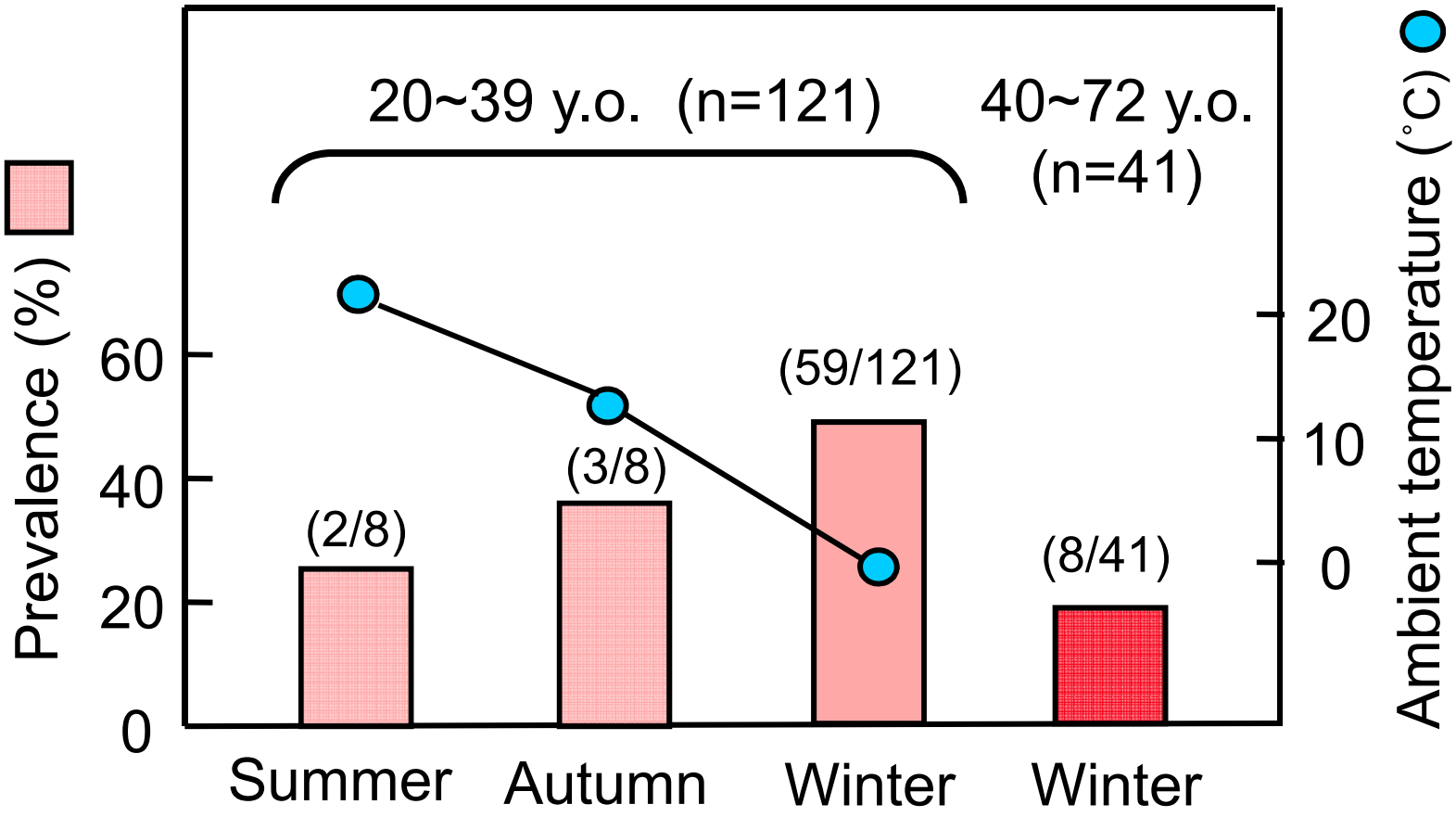
Yuko Kawai

Toshimitsu Kameya

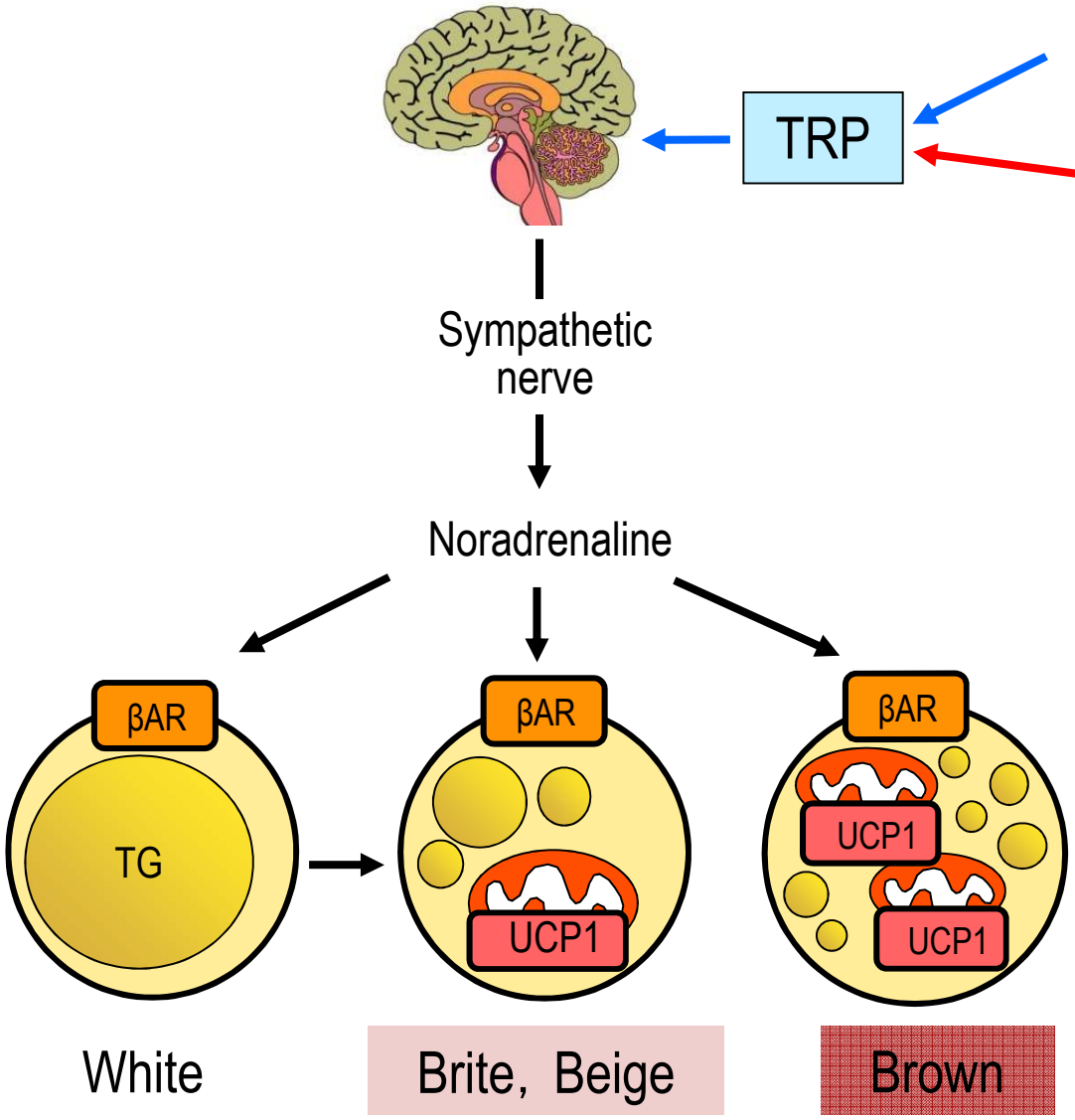
Masayuki Tsujisaki

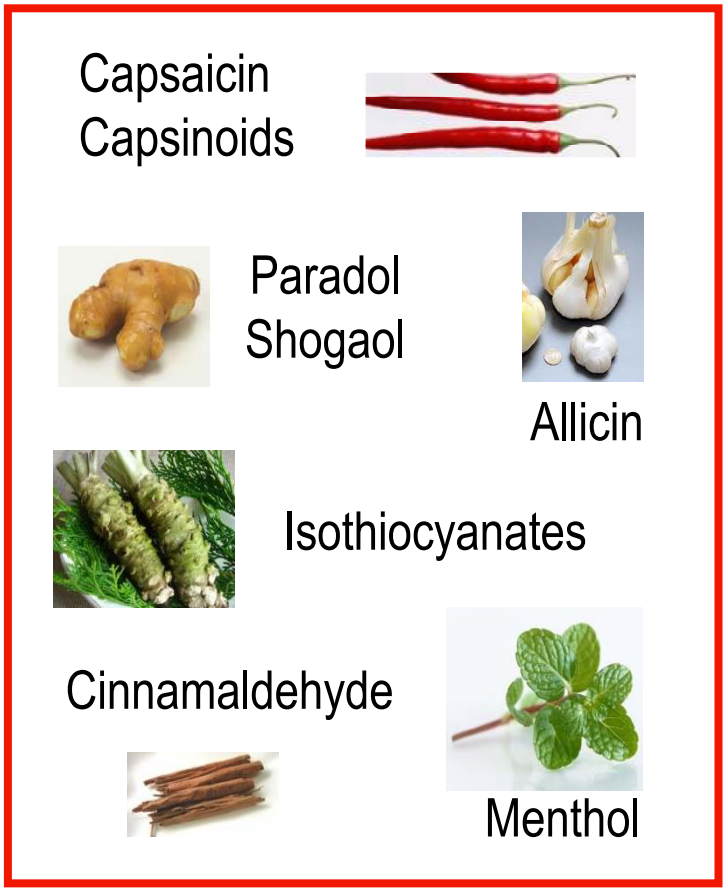
Prevalence of cold-activated BAT in adult humans

From February 2006 to March 2010, a total of 184 FDG-PET/CT examinations were conducted under a 2-hr cold condition (19 ˚C) for 162 healthy volunteers. None of them showed detectable BAT under a warm condition at 27 ˚C.



TRP-mediated activation and recruitment of BAT

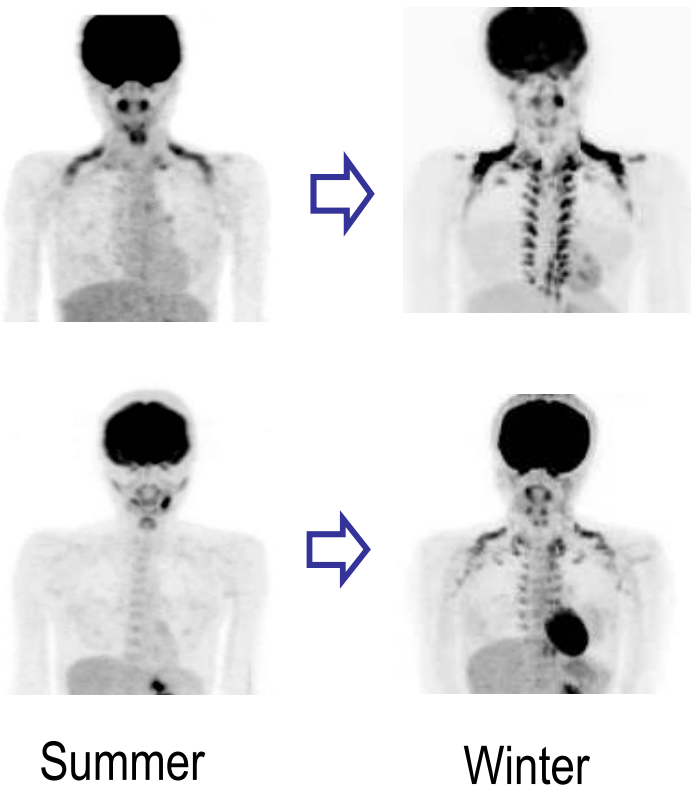


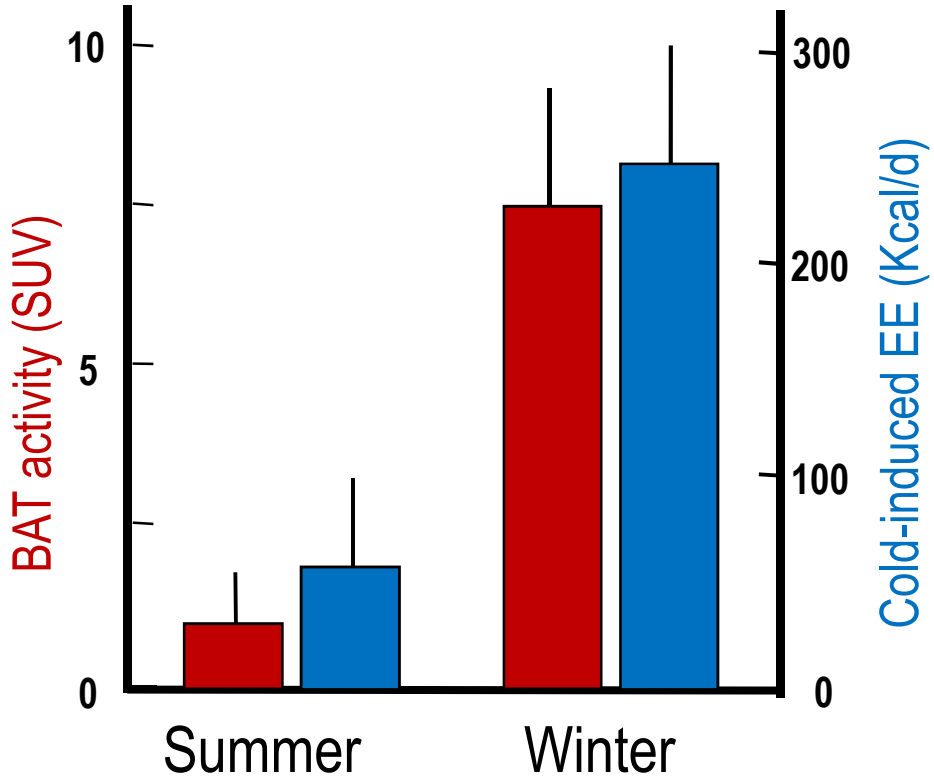


Saito et al, Curr Opin Lipidol 2012

Seasonal variations of BAT and CIT

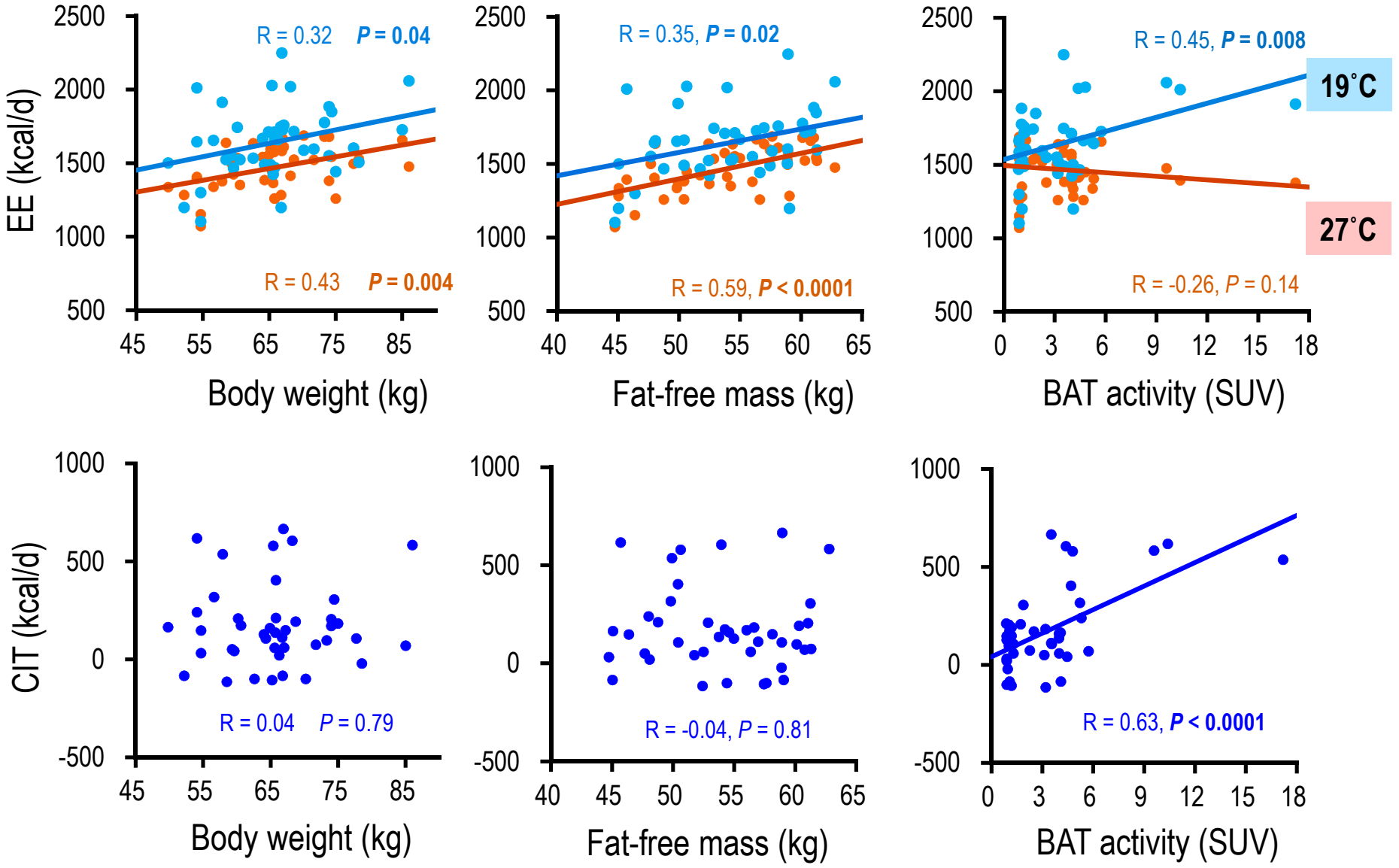
BAT activity and energy expenditure were measured after 2-hr cold exposure in summer, and again in winter.





Saito et al, Diabetes 2009

Contribution of BAT to whole-body EE and CIT



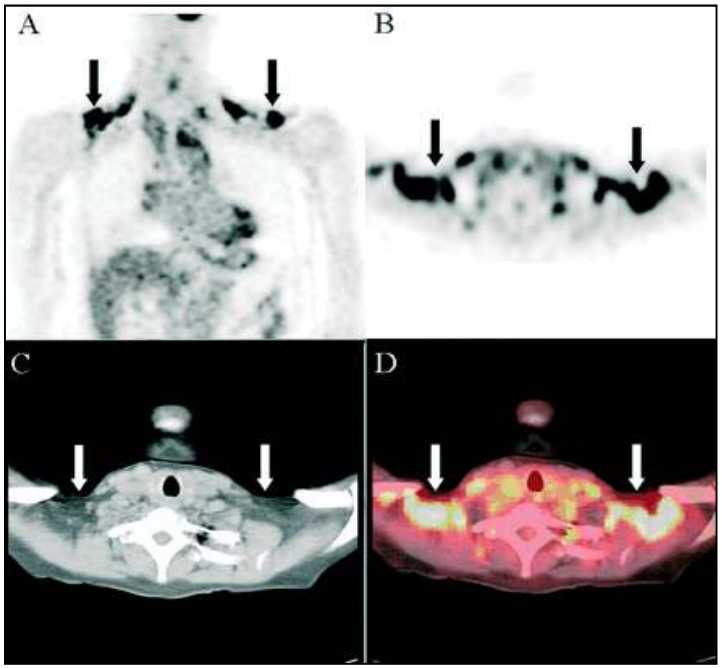
Detection of human BAT by FDG-PET/CT

170 THE JOURNAL OF NUCLEAR MEDICINE • Vol. 44 • No. 2 • February 2003

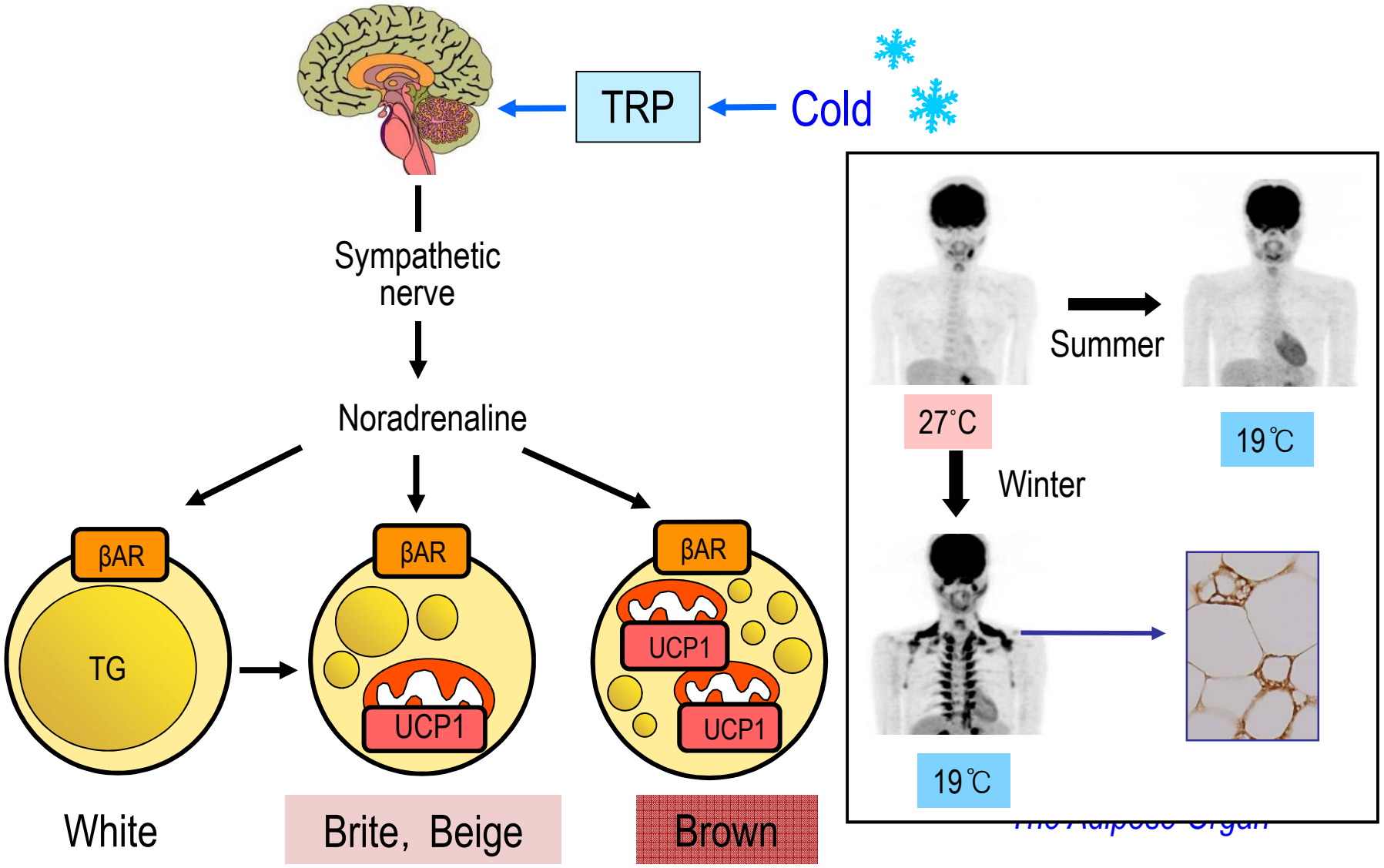
Uptake in Supraclavicular Area Fat ("USA-Fat"): Description on ^{18}F-FDG PET/CT

Christian Cohade, MD[1]; Medhat Osman, MD, PhD[1]; Harpreet K. Pannu, MD[2]; and Richard L. Wahl, MD[1]

[1]Division of Nuclear Medicine, The Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore, Maryland; and [2]Division of Body CT, The Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore, Maryland

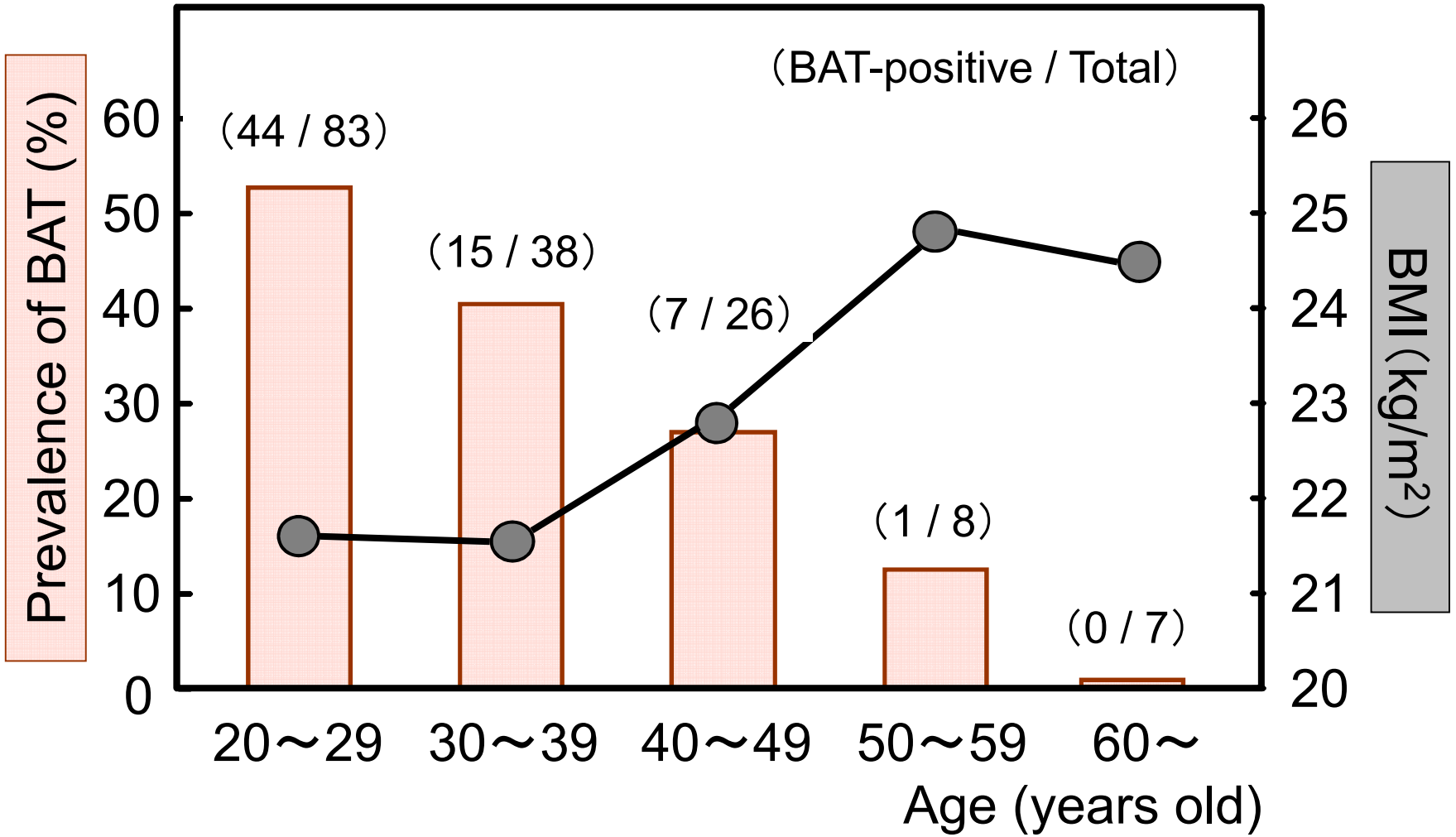


Cold-induced activation and recruitment of BAT



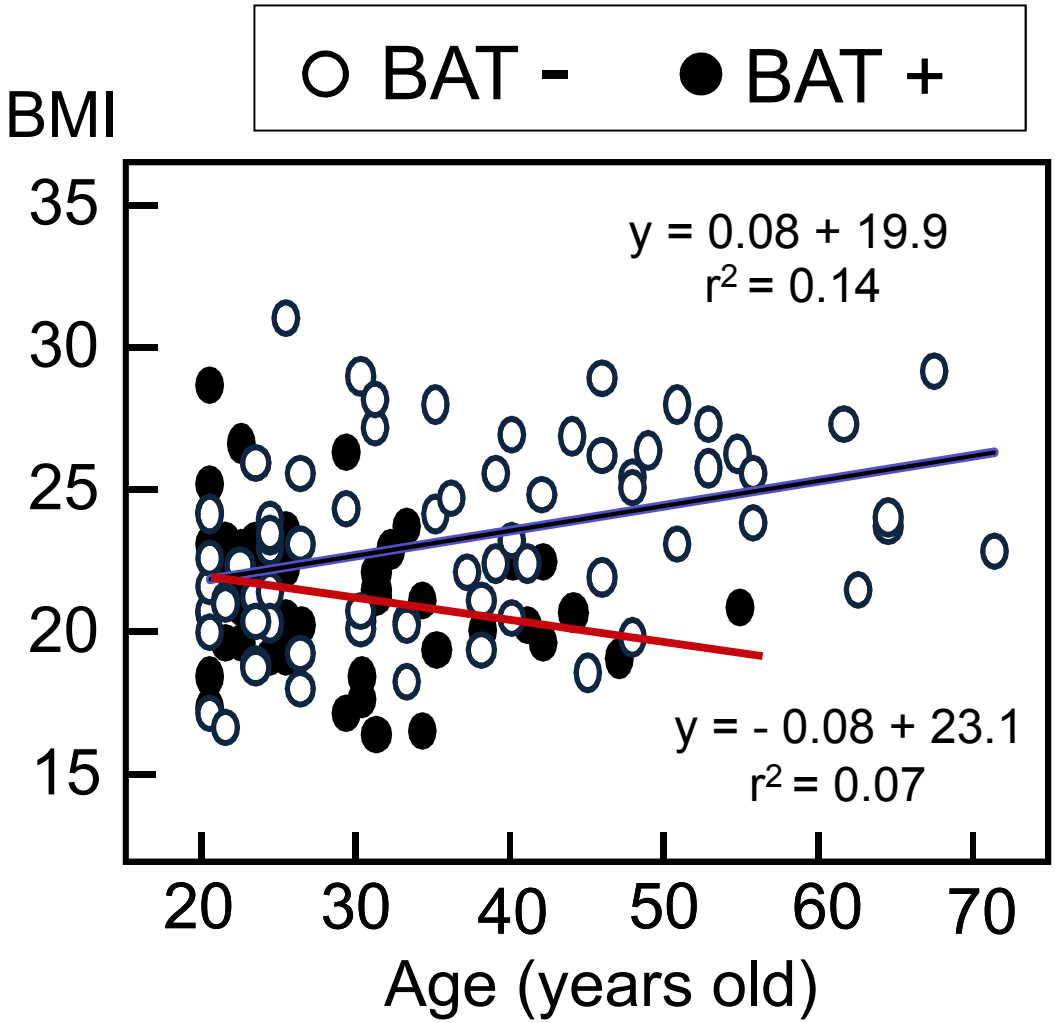
Age-related changes in BMI and BAT prevalence

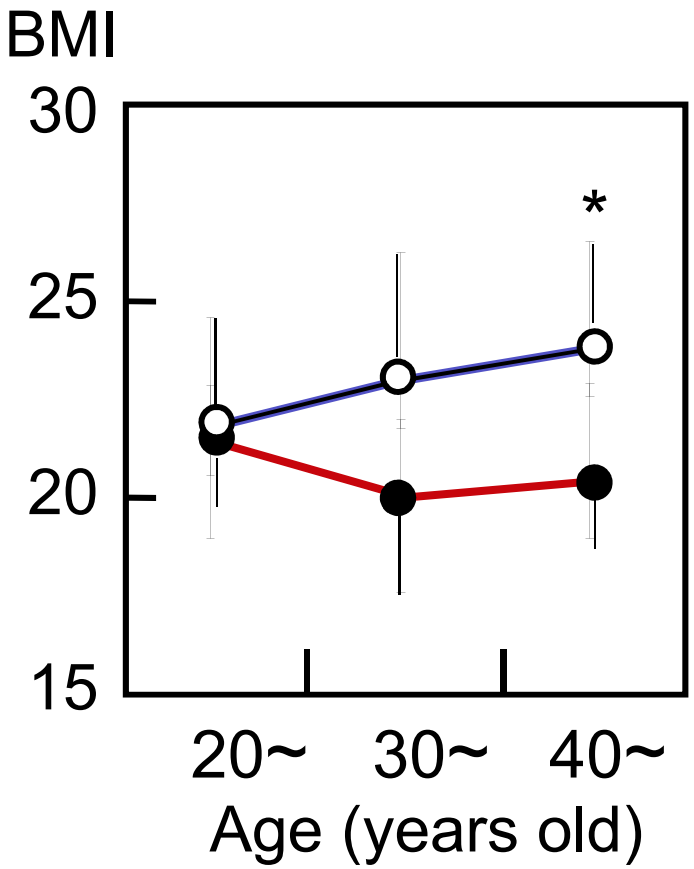
（20-72 years old、N=162）



Yoneshiro et al, Obesity 2011b

Age-related change in BMI of BAT-negative and –positive subjects



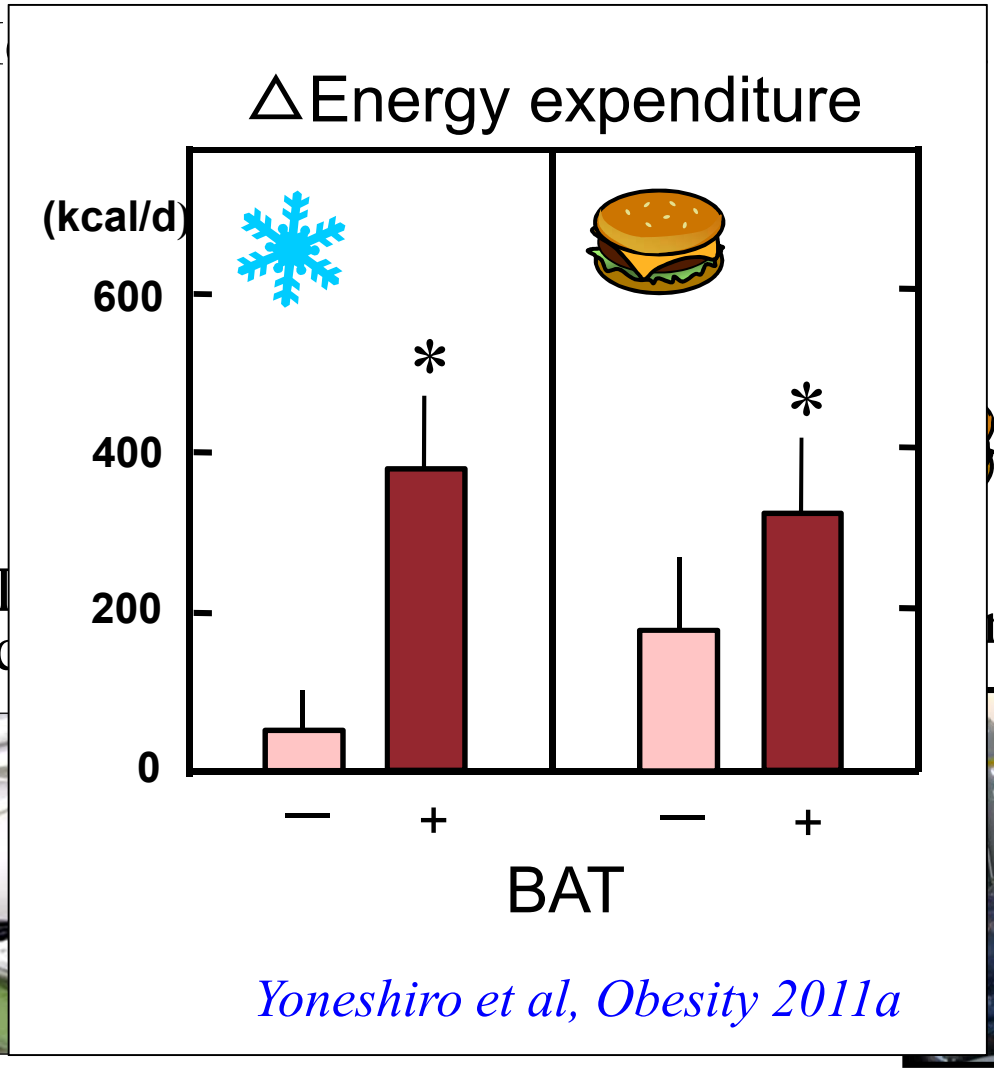


Yoneshiro et al, Obesity 2011b

Contribution of brown fat to thermogenesis induced by cold exposure and food intake

H

FDG-PET/CT
after 2-hr cold



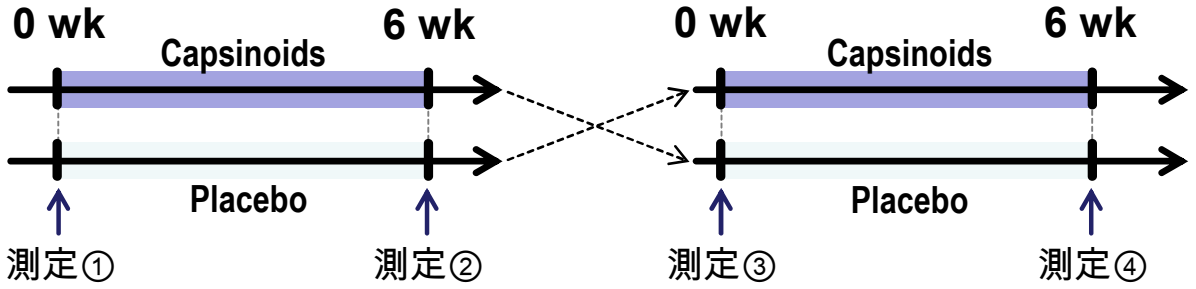
Yoneshiro et al, Obesity 2011a

rect calorimetry

Clinical and experimental studies on human BAT

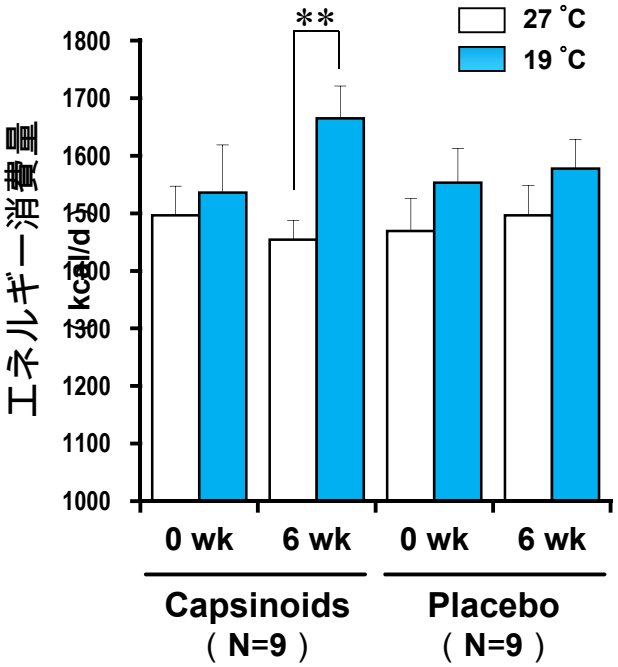
	City, Country	N	Age	Incidence (%)
Experimental prospective studies)				
Lichtenbelt et al (2009)	Maastricht, Netherland	24	24 (18-32)	95
Orava et al (2011)	Turku, Finland	27	40	70
Yoneshiro et al (2011)	Sapporo, Japan	162	32 (20-73)	59
Clinical retrospective studies)				
Cohade et al (2003)	Baltimore, USA	905	58 (1-93)	7
Cypess et al (2009)	Boston, USA	1972	59	5
Stefan et al (2009)	Tubingen, Germany	3604	48 (11-82)	5
Au-Yong et al (2009)	Nottingham, UK	3614	52 (13-88)	5
Lee et al (2010)	Sydney, Australia	2934	36 (18-87)	9
Quellet V et al (2011)	Quebec, Canada	4842	58 (2-94)	7
Gilsanz et al (2011)	Los Angeles, USA	71	15 (6-20)	42
Zukotynski et al (2010)	Boston, USA	168	14 (21>)	27

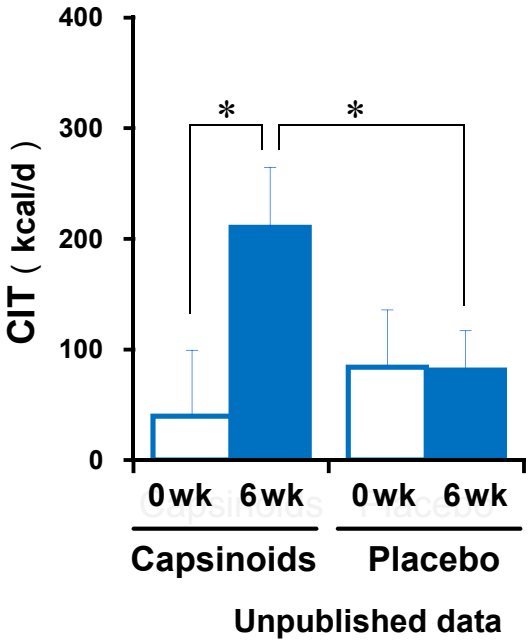
カプシノイド慢性摂取による BAT熱産生能力の上昇



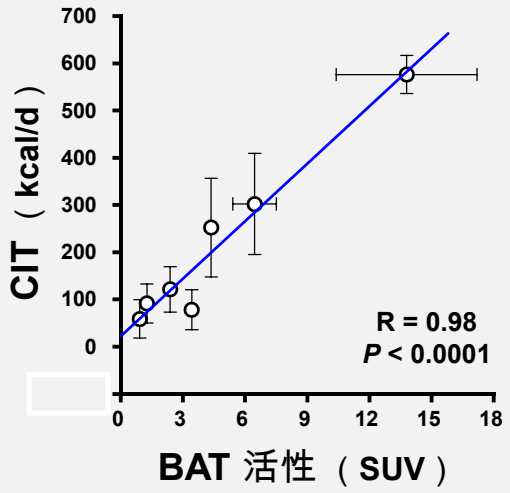
□対象： **BAT低活性者 （ N=9 ）**　□容量： カプシノイド **9 mg/day** または プラセボ　□摂取期間： 約**6** 週間

□測定項目： **CIT**　□摂取： 起床時（**4.5 mg**）と 就寝前（**4.5 mg**）





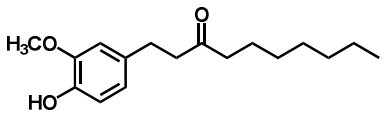
再掲載



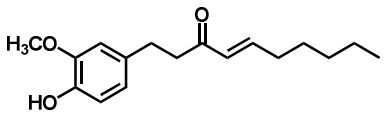
CITはBAT活性の指標になる

GP単回 および 慢性摂取による BAT熱産生の応答

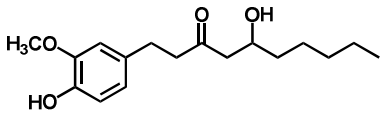
Grains of Paradise 含有 成分 （ TRPV1, TRPA1刺激物質 ）



6-paradol

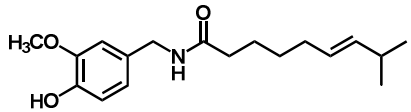


6-shogaol



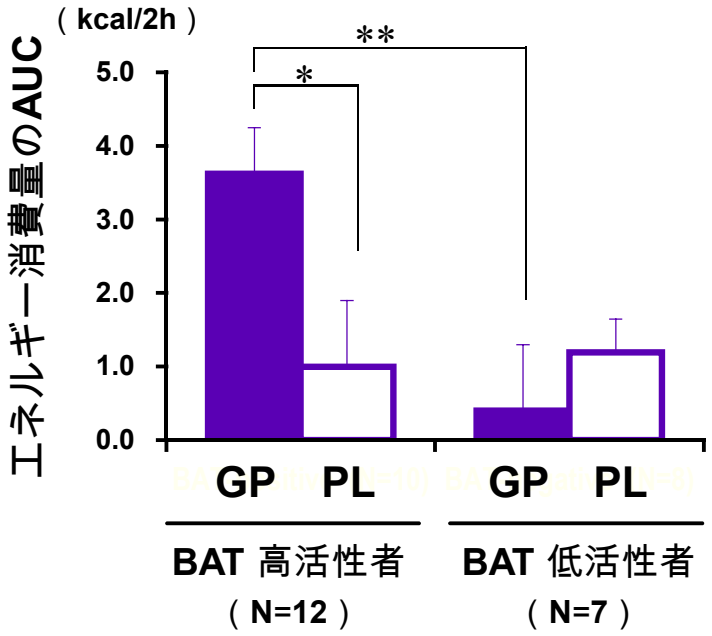
6-gingerol

トウガラシ 含有



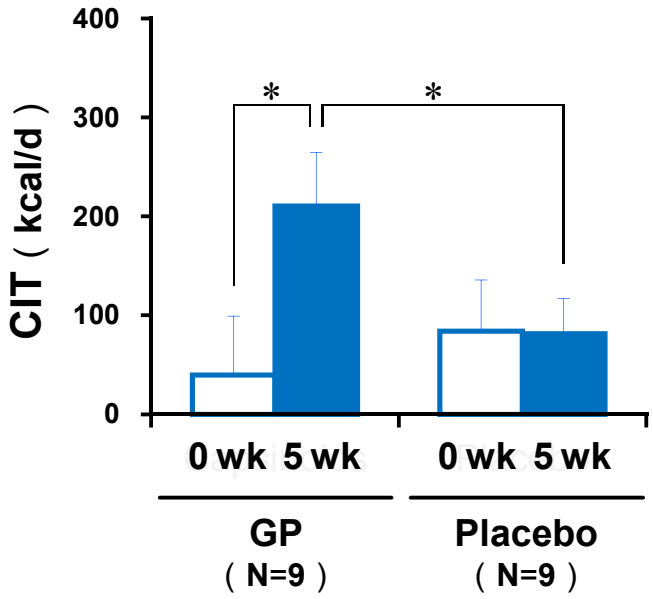
Capsaicin

GP 40mg 単回摂取の影響



Submitted

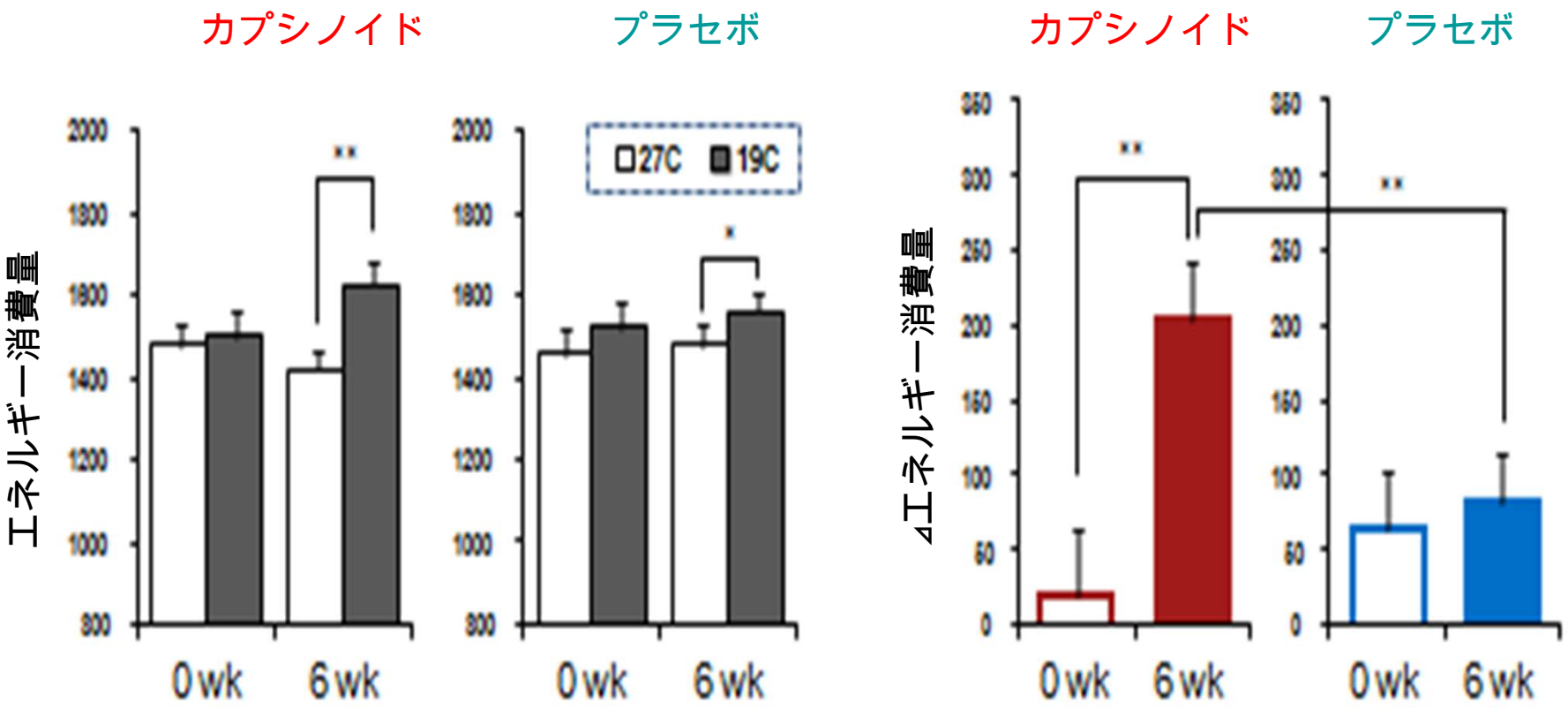
GP 40mg/day, 5 wk 継続摂取の影響



Unpublished data

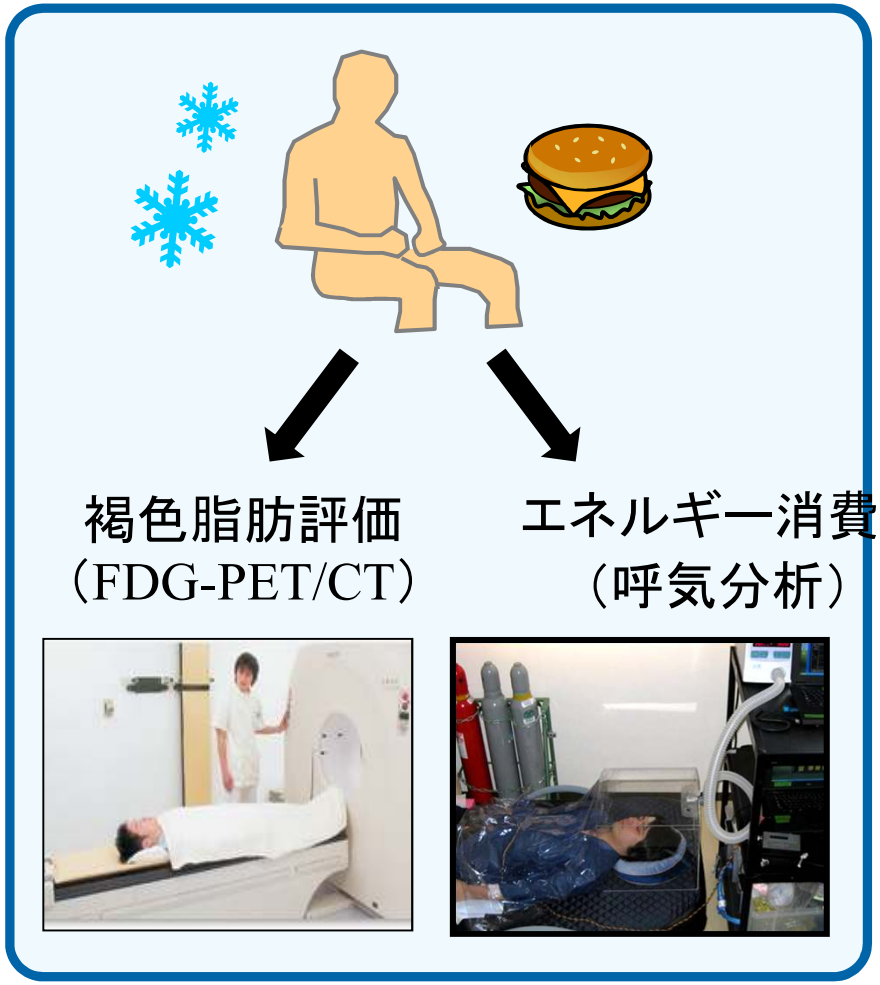
TRPチャネル長期刺激と褐色脂肪熱産生能

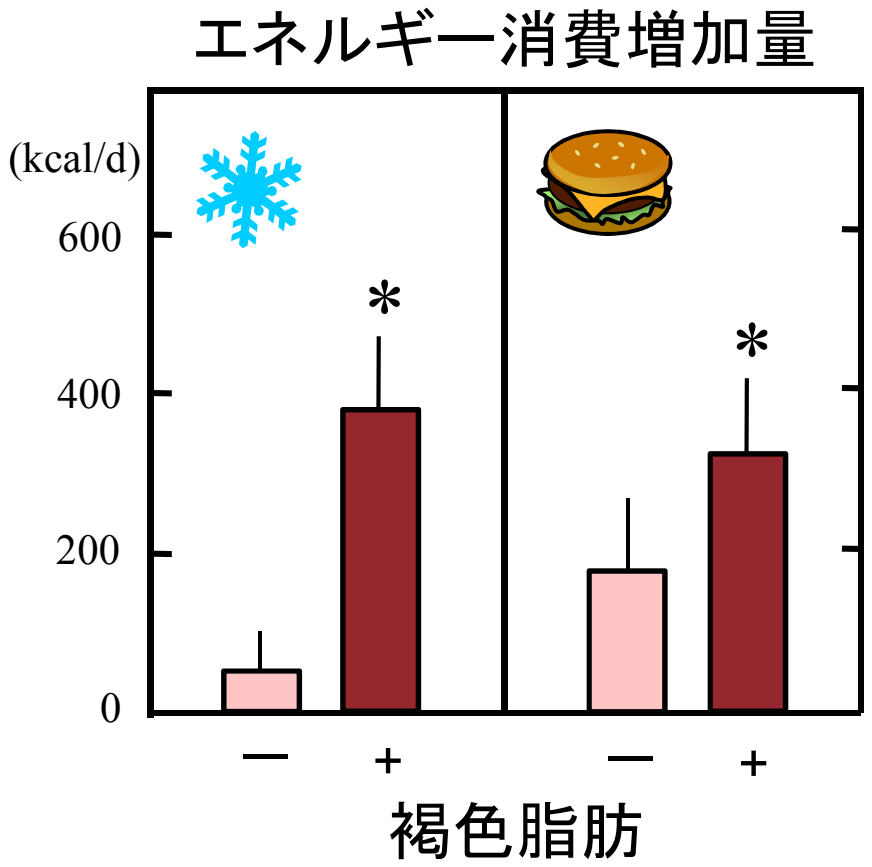
褐色脂肪が非検出あるいは低活性な20才代男性10名を被験者として、カプシノイド（9mg）または0mg（プラセボ）を含んだソフトカプセルを、毎日摂取させ、6週間後に27℃と19℃でエネルギー消費量を測定して、寒冷誘導熱産生（褐色脂肪の指標）を算出した。



褐色脂肪と寒冷・食事誘導熱産生

寒冷刺激19 ℃（2時間）又は食事摂取（500kcal)後のエネルギー消費量を褐色脂肪保有者（＋）と消失者（－）で比較した



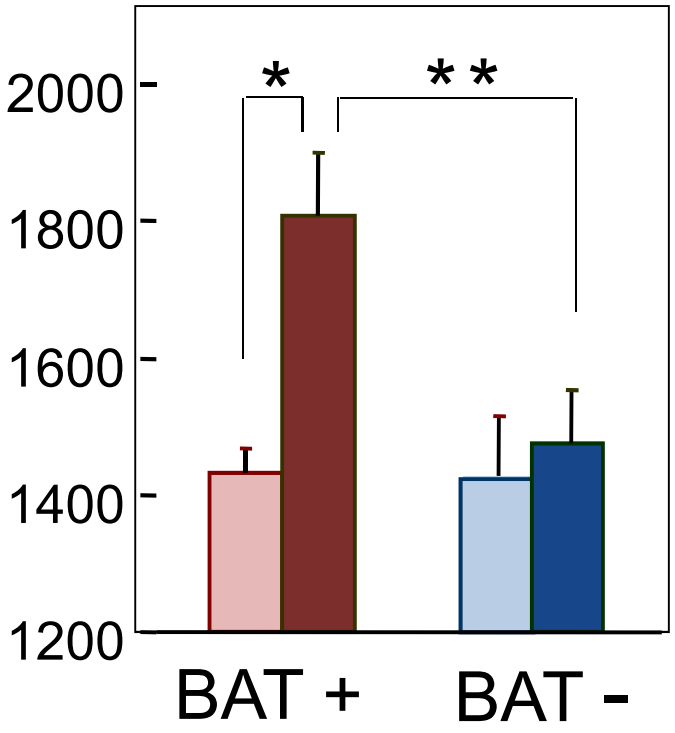


Yoneshiro et al, Obesity 2011a

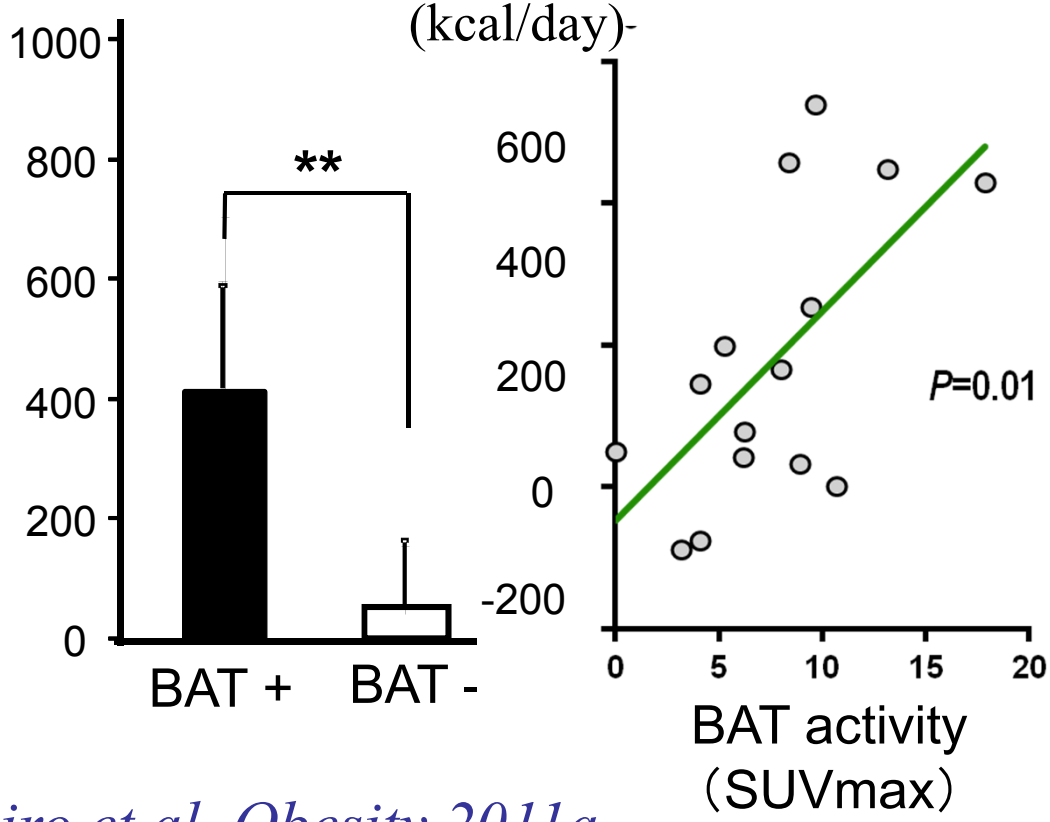
Energy expenditure after cold exposure

Energy expenditure was measured at 27˚C ( ) and after 2hr-cold exposure at 19˚C ( )

Energy expenditure
(kcal/day)

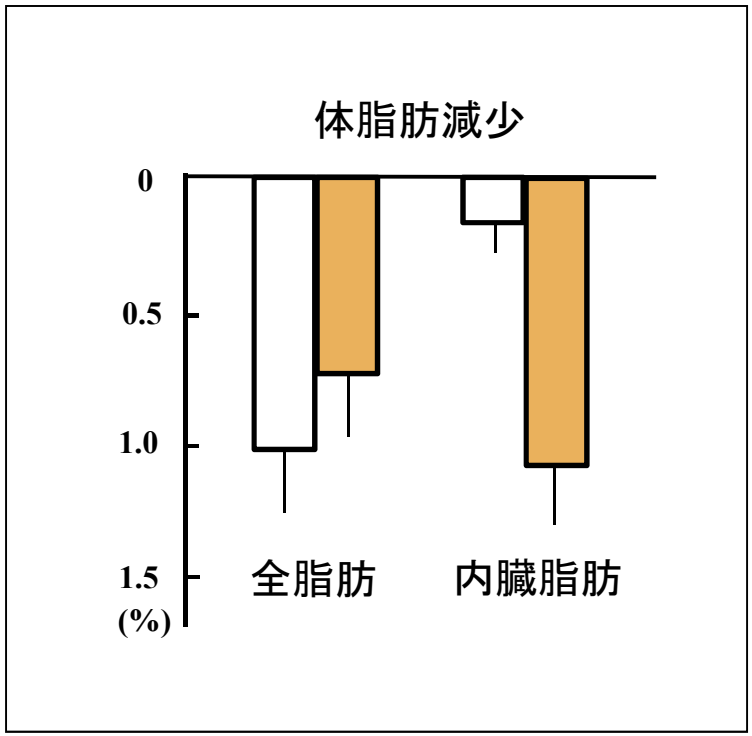


⊿ Energy expenditure
(Cold-induced thermogenesis)

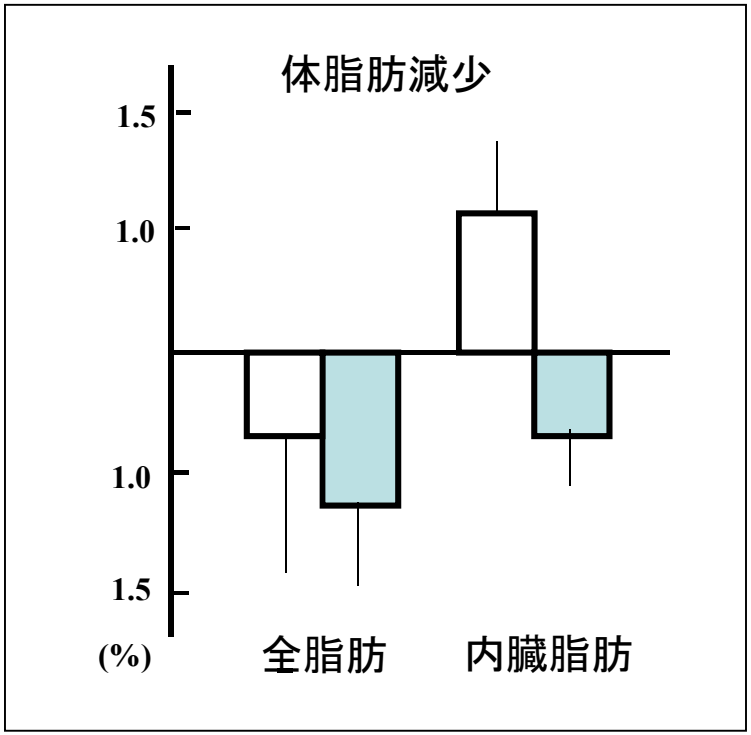


Yoneshiro et al, Obesity 2011a

唐辛子“CH-19甘”



ショウガ科の植物マニゲット



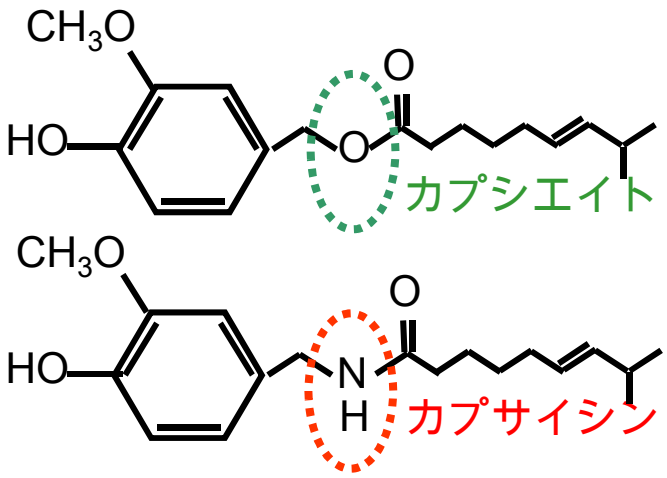
辛くない唐辛子“CH–19甘”

□ 矢澤（京都大学）らによって、*C.annuum* の辛味品種CH-19から、辛味を持たない品種CH-19甘が単離。

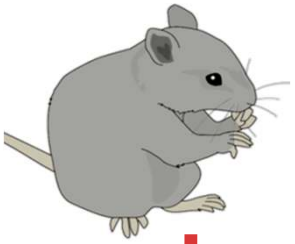
□ CH-19甘はカプサイシンをほとんど含まず、カプシエイト類を多量に含有。

□ CH-19甘からは3種類のカプシエイト類が同定。

□ カプシエイト類の辛味はカプサイシンの1/1000。



辛味刺激による褐色脂肪活性化、エネルギー消費亢進、体脂肪減少



辛味物質
（カプサイシンなど）

TRPV1
Channel

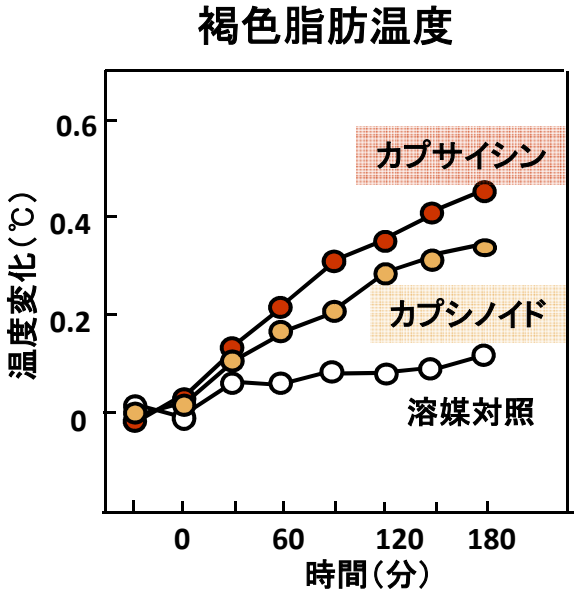
交感神経

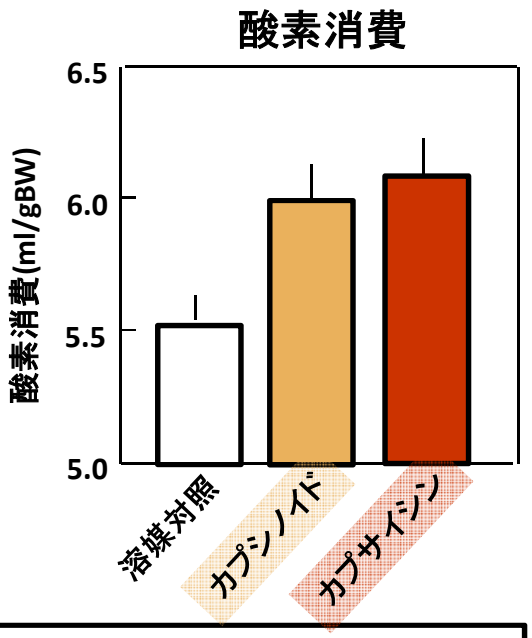
β受容体

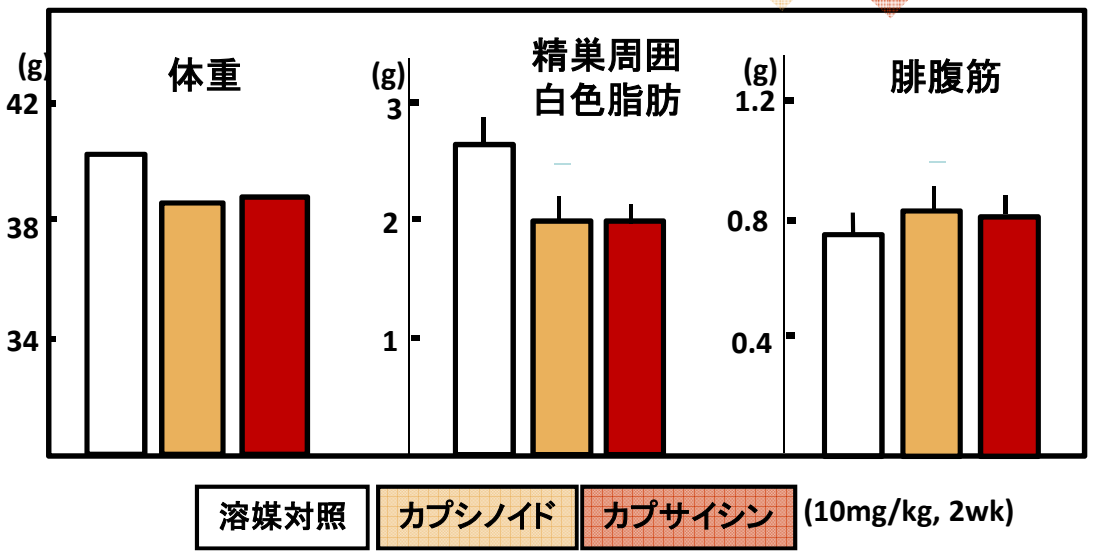
褐色脂肪

UCP1

熱

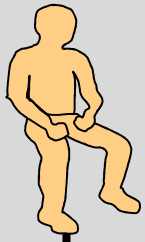






Ohnuki K et al. BBB 2001, Kawabata F et al. BBB 2009

健常な若年男性 18名
12 時間 絶食



FDG-PET/CT

寒冷刺激 2時間

活性評価

褐色脂肪
検出者

褐色脂肪
非検出者

エネルギー消費
測定

カプシノイド 9mg
経口投与

プラセボ
経口投与

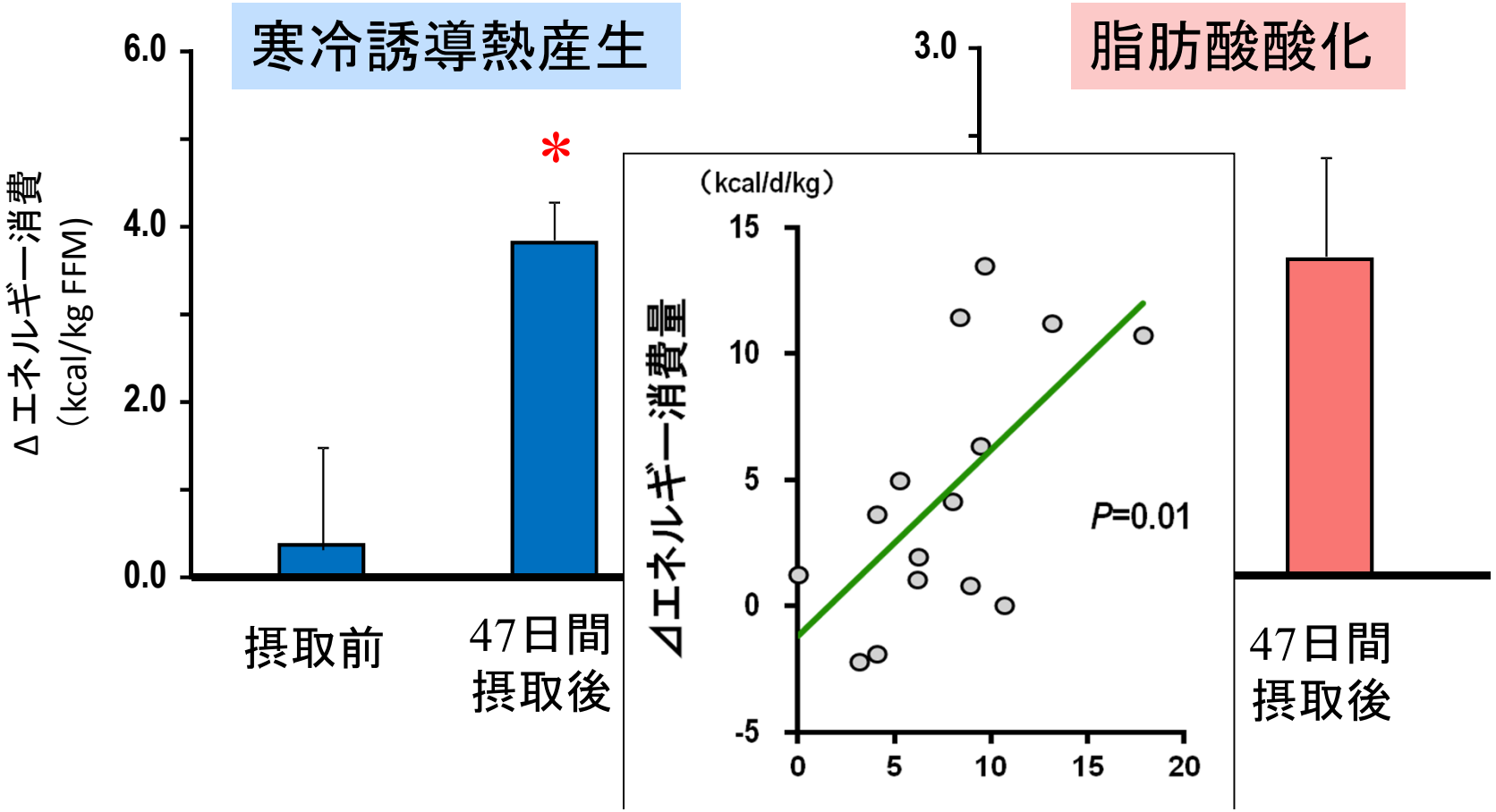
プラセボ
経口投与

カプシノイド 9mg
経口投与

エネルギー消費量と
褐色脂肪活性の関係を解析

カプシノイドの長期摂取と褐色脂肪

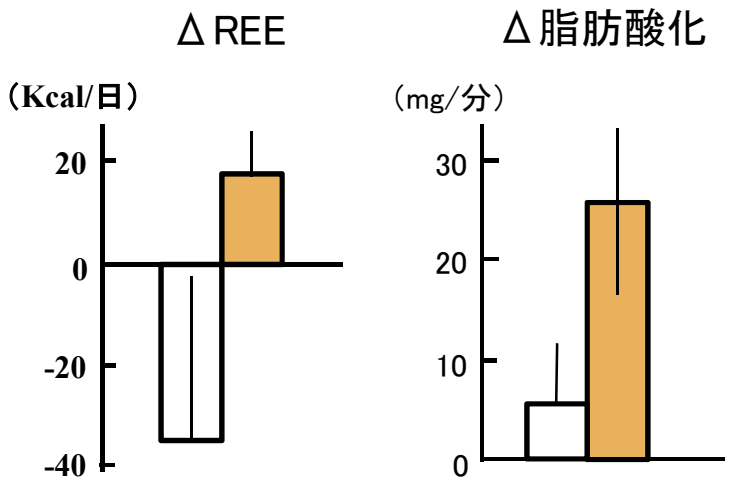
褐色脂肪の活性が低い、あるいは検出できない若年男性を被験者として、カプシノイド（9mg/日）を47日間摂取させ、前後で寒冷誘導熱産生（CIT）を測定して褐色脂肪の増減を評価した。呼吸商から脂肪酸酸化も算出した。

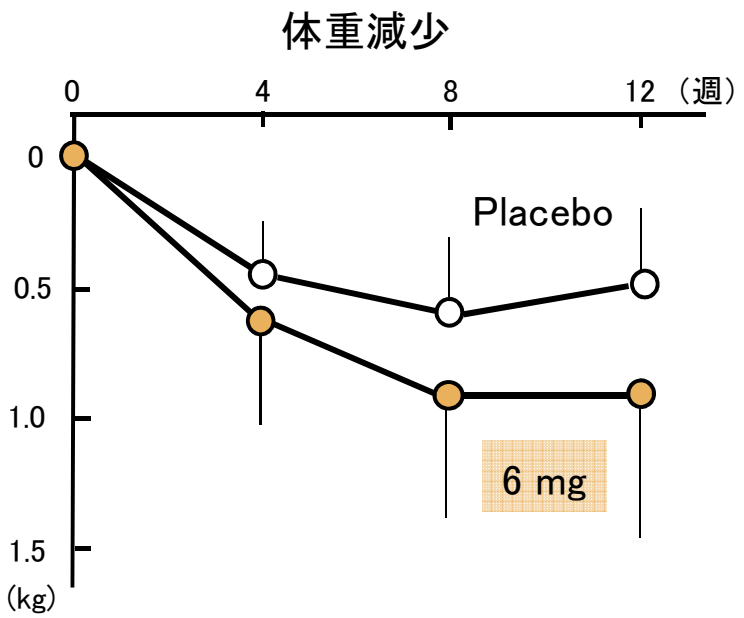


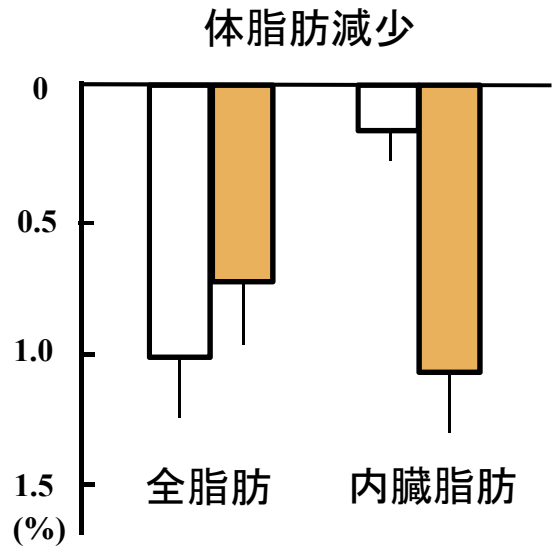
カプシノイド長期摂取とエネルギー消費・体脂肪

Baseline characteristics of all dosed subjects[1]

	Capsinoids (n = 37)	Placebo (n = 38)
Age (y)	43 ± 8[2]	41 ± 8
Females (%)	51.4	52.6
Body weight (kg)	88.9 ± 13.3	84.7 ± 12.5
BMI (kg/m^2)	30.6 ± 2.4	30.3 ± 2.4
Waist girth (cm)	104 ± 7	101 ± 8
Total fat (%)	37.1 ± 7.4	36.8 ± 7.4
Abdominal fat (%)	41.9 ± 6.3	39.6 ± 6.7
REE (kcal/d)	1811 ± 216	1753 ± 172
Fat oxidation (mg/min)	59 ± 40	53 ± 24



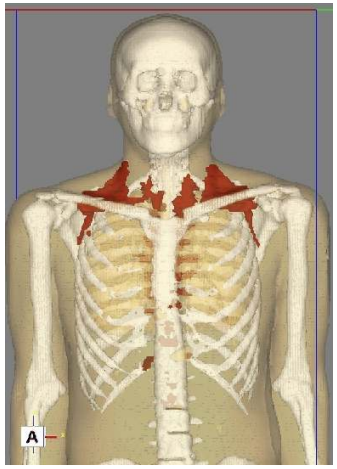




Snitker S et al. Am J Clin Nutr 2009

Human brown adipose tissue

1. Can be evaluated by FDG-PET/CT.
2. Is found in the supraclavicular and paravertebral regions.
3. Is undetectable under warm conditions.
4. Is activated by acute cold exposure.
5. The activity
   - shows seasonal variations,
     - (low in summer and high in winter)
   - is lower in more obese subjects,
   - decreases with age.
   - shows individual variations.



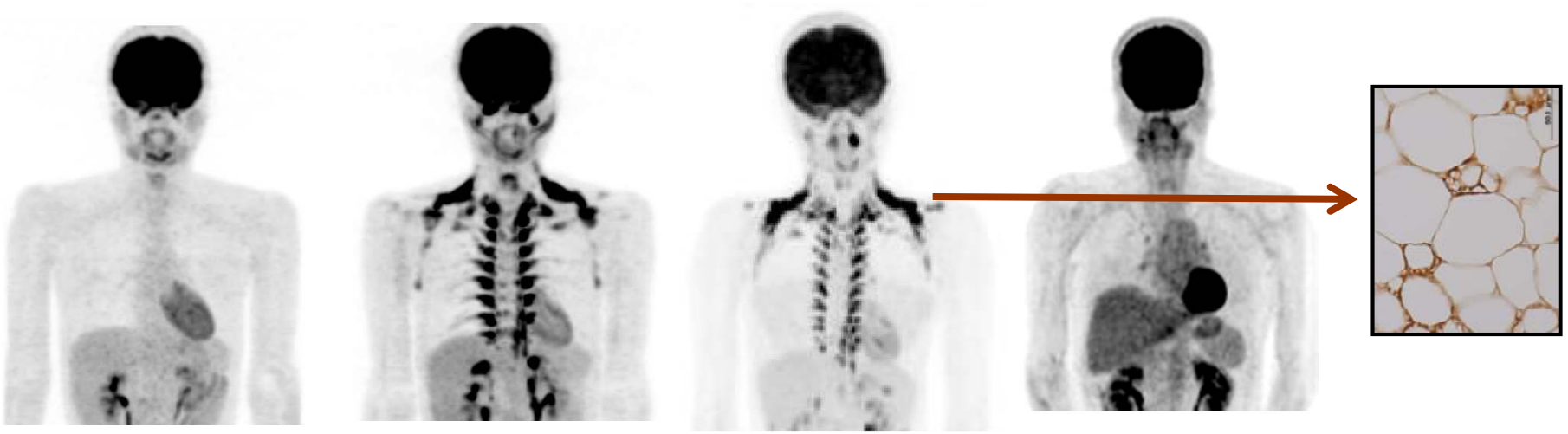
Saito M et al, Diabetes2009

Profile of healthy male subjects

	BAT (+) n=23	BAT (-) n=19
SUV	5.2 ± 0.7	1.2 ± 0.1
Age	24.9 ± 0.9	23.7 ± 0.8
Height (cm)	171.9 ± 1.2	174.3 ± 1.1
Weight (kg)	64.3 ± 2.0	67.2 ± 1.5
BMI (kg/m^2)	21.8 ± 0.7	22.1 ± 0.4
Body Fat (%)	17.8 ± 1.2	16.8 ± 1.1
Lean mass (kg)	52.4 ± 1.0	55.7 ± 1.1

Human BAT activated by acute cold exposure

On February 22, 2006, 3 healthy subjects were fasted overnight, and underwent FDG-PET/CT in either warm (27˚C) or cold (at 19˚C, light clothing, intermittent ice-cooling of legs).



Saito et al, Int J Obesity 2007

Saito et al, Diabetes 2009