



Kahverengi yağ dokusu: İnsan metabolizmasındaki rolünü arttırmak mümkün mü?

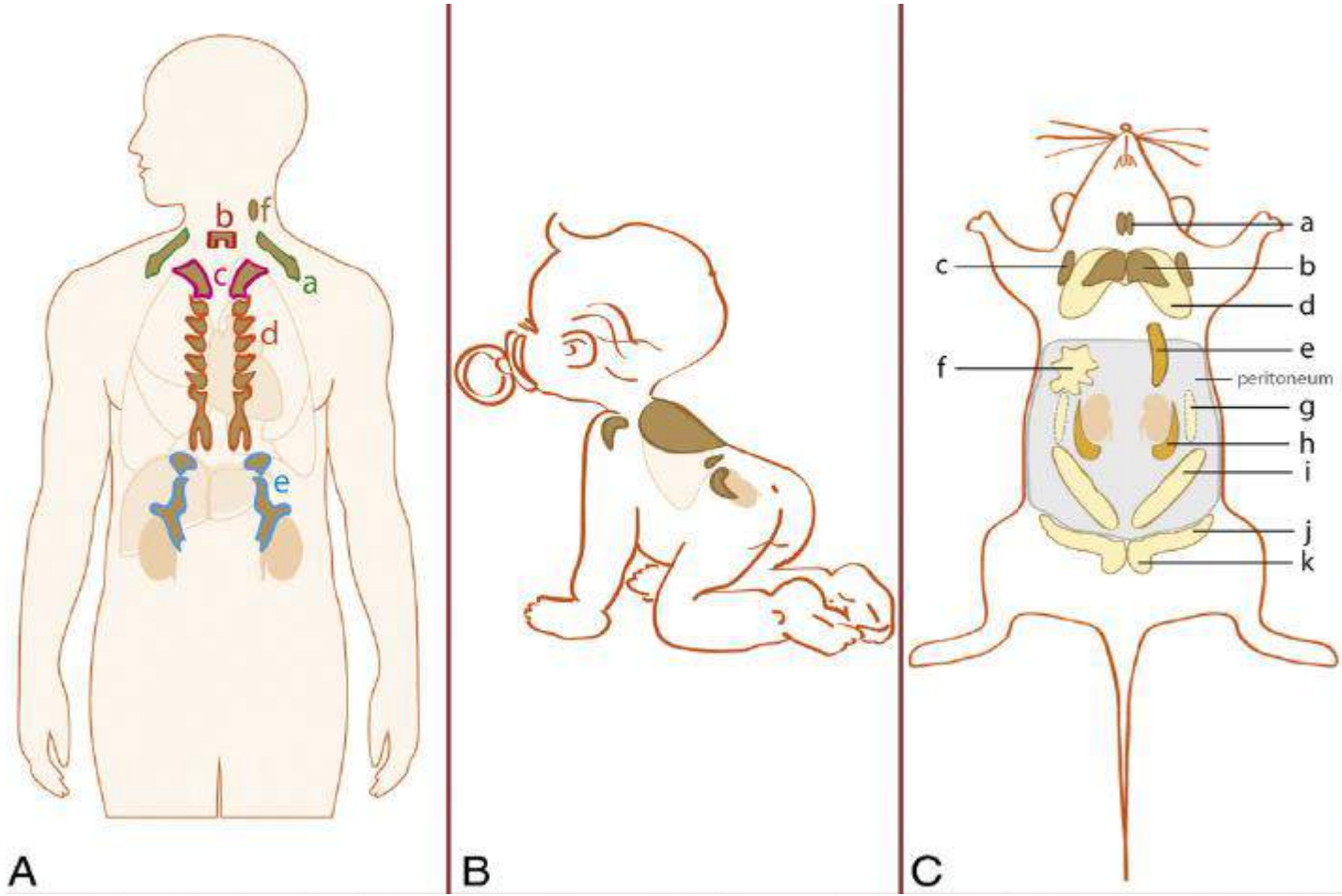
Prof. Dr. Volkan Demirhan Yumuk
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Endokrinoloji, Metabolizma ve Diyabet Bilim Dalı
Türkiye Obezite Araştırma Derneği
Avrupa Obezite Derneği

Yol haritası

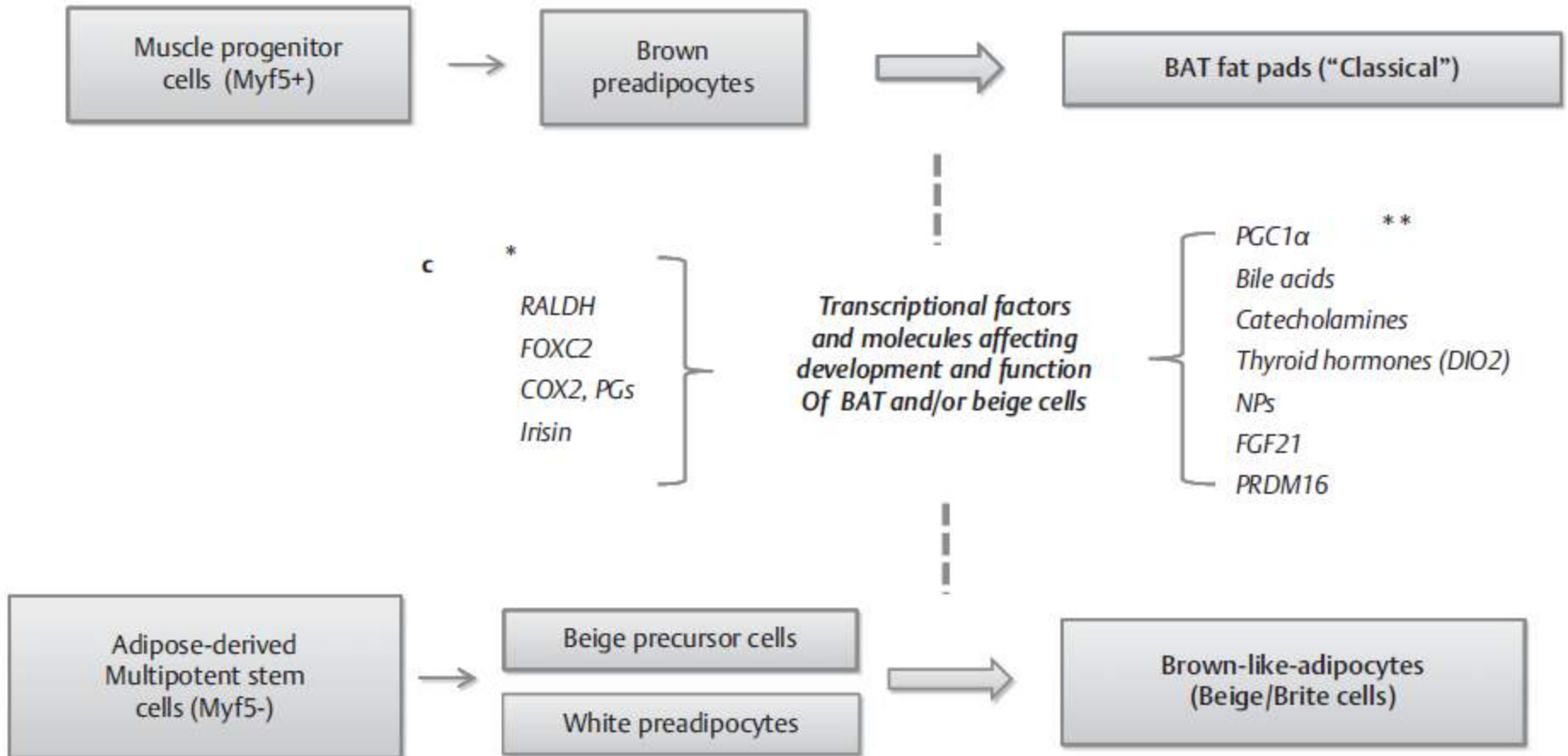
- Adipositler
- İnsanda kahverengi yağ dokusu (KYD)
- Bej mi KYD mu?
- KYD/BYD'nun metabolizmadaki yeri
- KYD/BYD'nun obezite tedavisindeki yeri



İnsan ve farede kahverengi yağ depoları



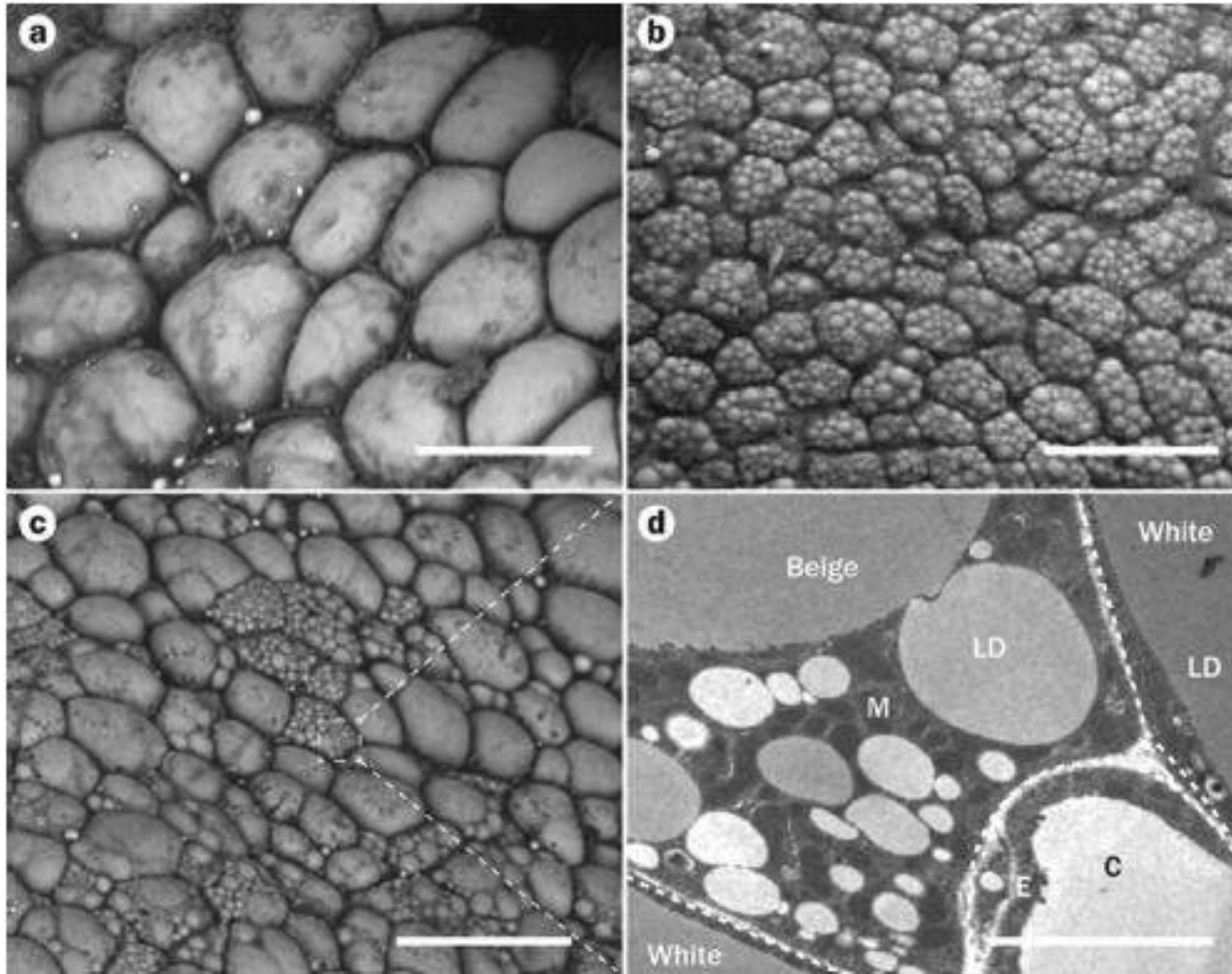
Adipositlerin farklılaşması



Beyaz-Kahverengi-Bej

	WAT	BAT	BeAT
Cell shape	Variable, but classically spherical	Polygonal	Resembles WAT
Cell size	Variable, but large (25-200 μm)	Comparatively small (15-60 μm)	Variable
Nucleus	Peripheral, flattened	Central, round or oval in shape	To be determined
Cytoplasm	Thin, peripheral rim	Large volume evenly distributed throughout cell	To be determined
Lipid content	Single large droplet occupying up to 90% of cell volume	Multiple small lipid droplets	To be determined
Mitochondria	Few	Abundant	Intermediate
Endoplasmic reticulum (ER)	Little, but recognizable as rough and smooth ER	Present, but poorly developed	To be determined
Tissue organization	Small lobules of densely packed cells	Lobular, gland-like	To be determined
Cell content	Multiple other cell types present	Few other cell types present	Few other cell types present
Vascularity	Adequate	Highly vascularised	To be determined
Gene expression	PPAR-gamma, aP2, Adiponectin, adipsin, perilipin	UCP-1, PGC-1alpha, β -3 adreno receptor (ARB3), PRDM16, de-iodinase type II (D2)	Low UCP1, but activated by cAMP stimulation
Cell markers	CD34, ABCG2, ALDH	EVA1, EBF3, FBXO31	CD137, TMEM26, TBX1

Fare adipositlerinin elektron mikroskopisi



High Incidence of Metabolically Active Brown Adipose Tissue in Healthy Adult Humans

Effects of Cold Exposure and Adiposity

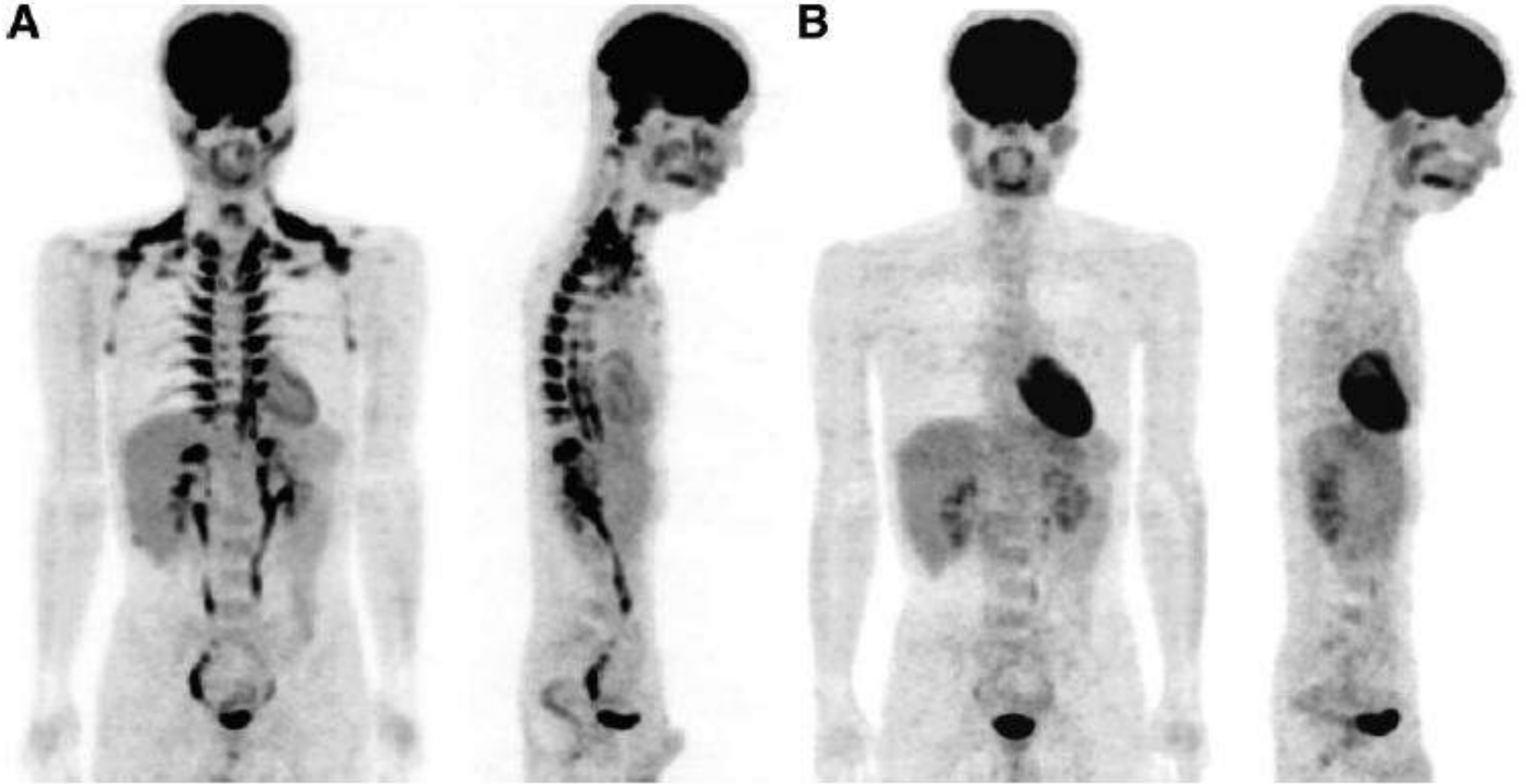
Masayuki Saito,¹ Yuko Okamatsu-Ogura,² Mami Matsushita,¹ Kumiko Watanabe,¹ Takeshi Yoneshiro,¹ Junko Nio-Kobayashi,² Toshihiko Iwanaga,³ Masao Miyagawa,⁴ Toshimitsu Kameya,⁵ Kunihiro Nakada,⁵ Yuko Kawai,⁵ and Masayuki Tsujisaki⁵

Diabetes 58:1526–1531, 2009

Materyal-Metod

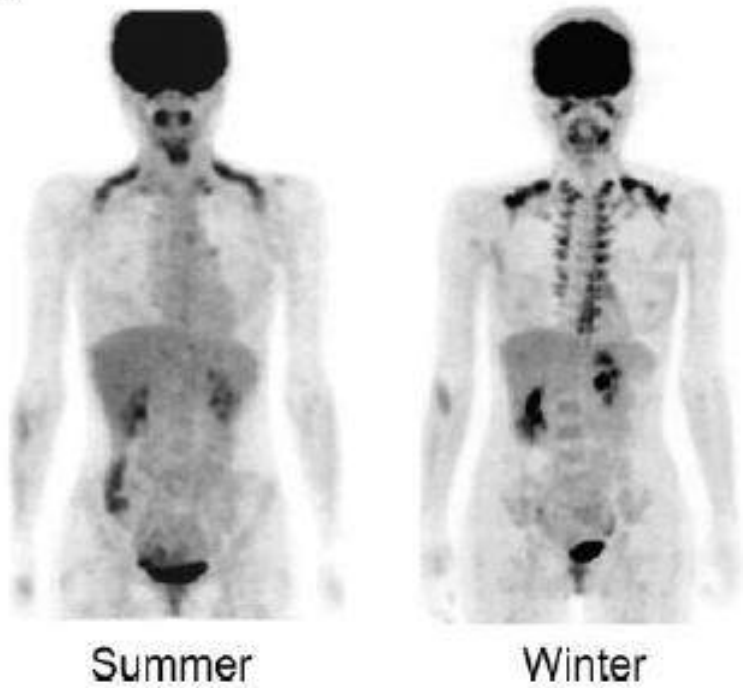
- 56 sađlıklı gönüllü (31 E, 25 K)
- 23-65 yař aralıđı
- Sođuk/sıcak uygulama
- PET-BT
- Histoloji

Tüm vücut FDG-PET/BT deęerlendirmesi

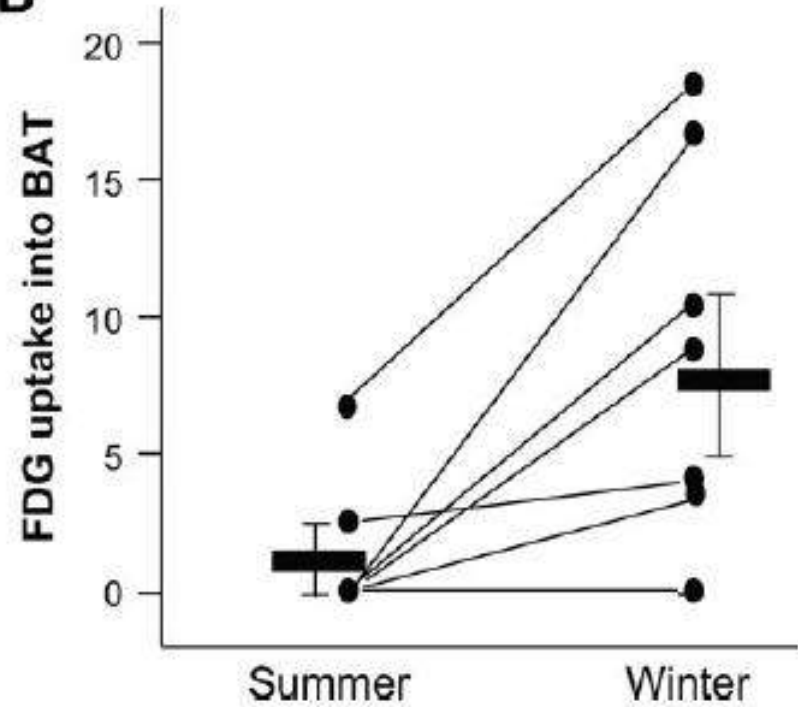


Yaz/Kış FDG “uptake”

A



B



KYD +/- deneklerin karşılaştırılması

BAT	Male subjects		Female subjects	
	-	+	-	+
<i>n</i>	21	10	16	9
Age (years)	38.4 ± 10.0	31.3 ± 6.7*	43.6 ± 8.6	30.3 ± 1.7*
Height (cm)	170 ± 6	170 ± 4	158 ± 5	159 ± 3
Body weight (kg)	71.3 ± 6.8	65.3 ± 6.6	54.5 ± 4.6	49.0 ± 5.7
BMI (kg/m ²)	24.4 ± 2.3	22.7 ± 2.8	22.0 ± 2.2	19.4 ± 2.1
Body fat (%)	24.5 ± 5.5	20.6 ± 5.0	29.4 ± 5.1	24.5 ± 5.4
Body fat (kg)	17.7 ± 4.8	13.8 ± 4.6	16.2 ± 3.6	12.5 ± 4.0
Fat area (cm ²)				
Total	236 ± 82	152 ± 87	222 ± 85	159 ± 76
Visceral	71 ± 27	47 ± 19	51 ± 24	30 ± 7
Subcutaneous	165 ± 64	104 ± 68	171 ± 67	129 ± 71

Data are means ± SD. **P* < 0.05 vs. BAT (-) by *t* test.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Identification and Importance of Brown Adipose Tissue in Adult Humans

Aaron M. Cypess, M.D., Ph.D., M.M.Sc., Sanaz Lehman, M.B., B.S.,
Gethin Williams, M.B., B.S., Ph.D., Ilan Tal, Ph.D., Dean Rodman, M.D.,
Allison B. Goldfine, M.D., Frank C. Kuo, M.D., Ph.D., Edwin L. Palmer, M.D.,
Yu-Hua Tseng, Ph.D., Alessandro Doria, M.D., Ph.D., M.P.H.,
Gerald M. Kolodny, M.D., and C. Ronald Kahn, M.D.

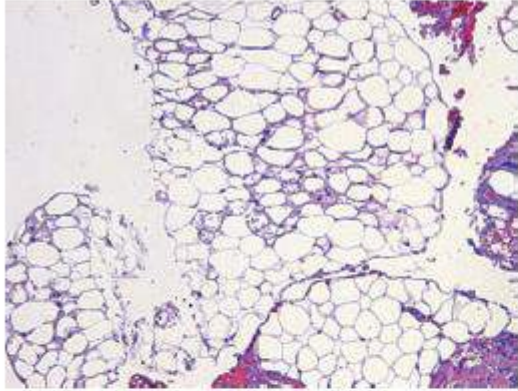
N Engl J Med 2009;360:1509-17.

Materyal-Metod

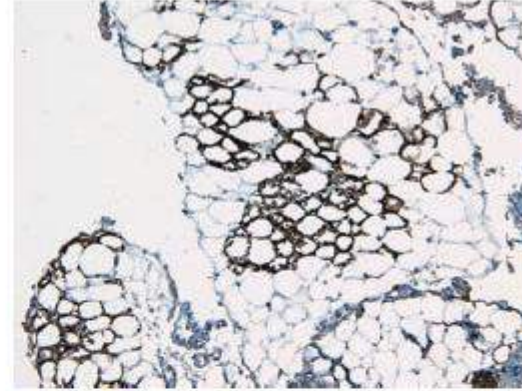
- Retrospektif
- 3640 PET/BT 1972 hasta
- Kadın %7.5 PET+, erkek %3.1 PET+
- Histoloji

Kahverengi yağ dokusu: Histoloji-PET/BT

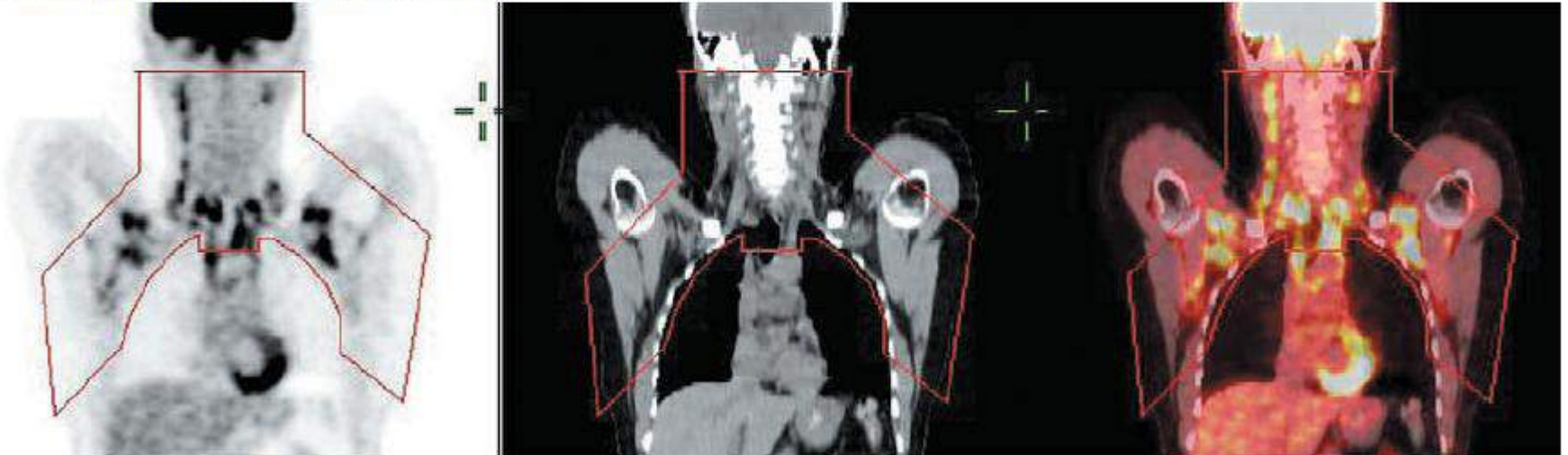
A



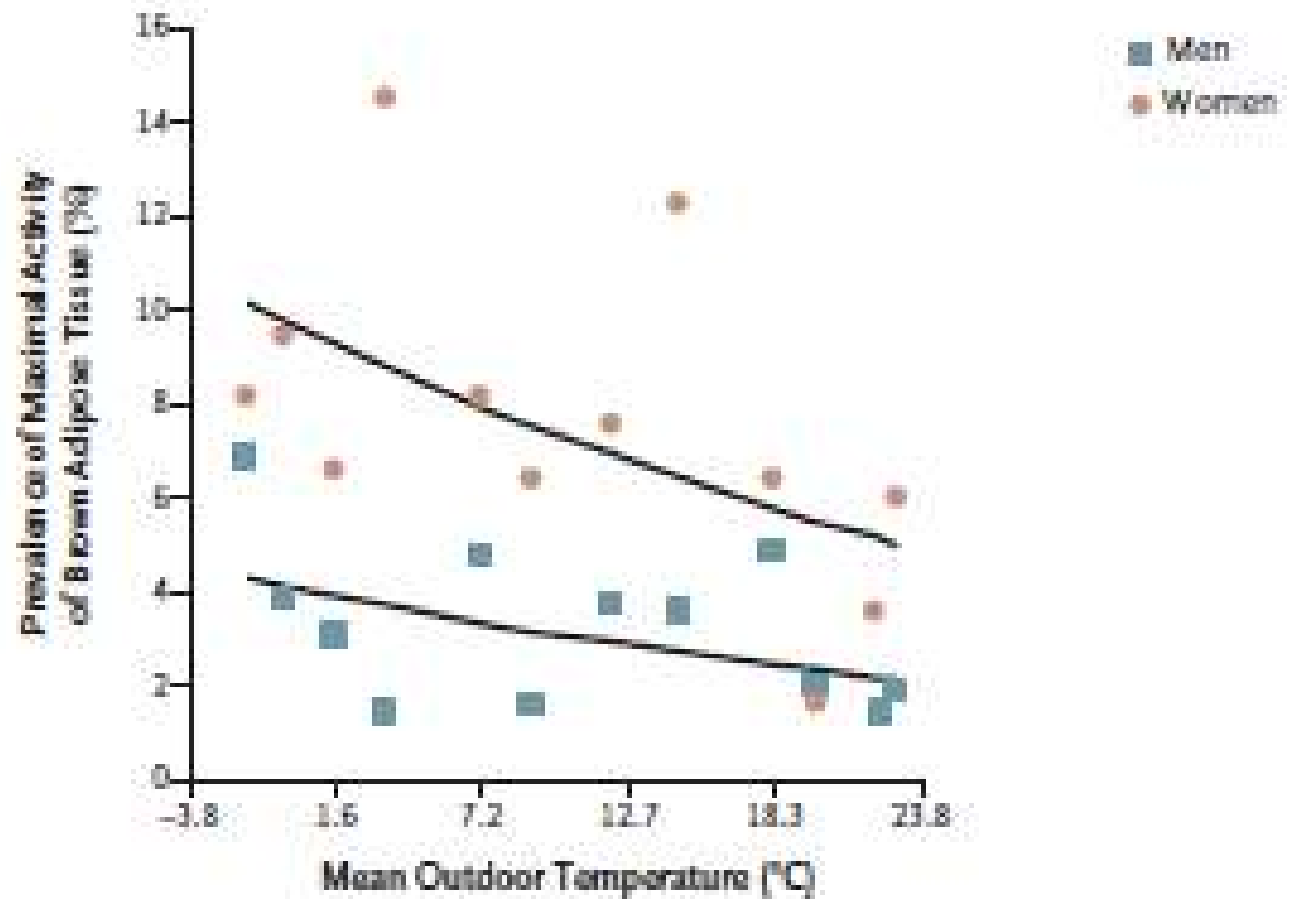
B



C Amount and Activity of Brown Adipose Tissue



KYD'nun maksimal aktivitesi



PET/BT taramasında KYD'nu belirleyen faktörler

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Sex				
Female vs. male	2.85 (1.72–4.72)	<0.001	3.07 (1.72–5.48)	<0.001
Years of age				
50–64 vs. <50	0.55 (0.31–0.96)		0.64 (0.33–1.21)	
>64 vs. <50	0.23 (0.12–0.43)	<0.001†	0.32 (0.15–0.67)	0.005†
Body-mass index‡				
23.5–27.8 vs. <23.5	0.81 (0.46–1.42)		1.32 (0.68–2.60)	
>27.8 vs. <23.5	0.54 (0.30–0.98)	0.04†	0.74 (0.38–1.44)	0.30†
Fasting plasma glucose level — mg/dl				
93–103 (5.2–5.7 mmol/liter) vs. <93	0.95 (0.54–1.67)		1.37 (0.70–2.68)	
>103 vs. <93	0.56 (0.31–1.01)	0.04†	0.97 (0.48–1.96)	0.77†
Cancer				
Lymphoma vs. no cancer	1.05 (0.41–2.67)		0.46 (0.14–1.46)	
Other cancers vs. no cancer	0.79 (0.31–2.02)	0.53§	0.47 (0.15–1.45)	0.40§
Smoking history				
Formerly vs. never	0.46 (0.26–0.81)		0.74 (0.38–1.44)	
Currently vs. never	0.58 (0.27–1.28)	0.02§	0.78 (0.32–1.93)	0.64§
Beta-blocker use				
Yes vs. no	0.06 (0.02–0.26)	<0.001	0.09 (0.02–0.38)	0.001
Benzodiazepine use				
Yes vs. no	1.74 (0.91–3.33)	0.09	0.99 (0.44–2.21)	0.98

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Functional Brown Adipose Tissue in Healthy Adults

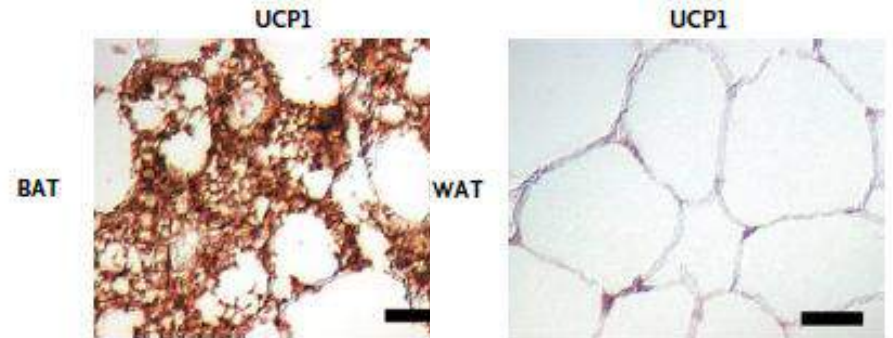
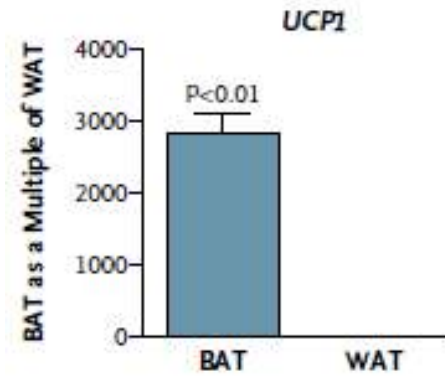
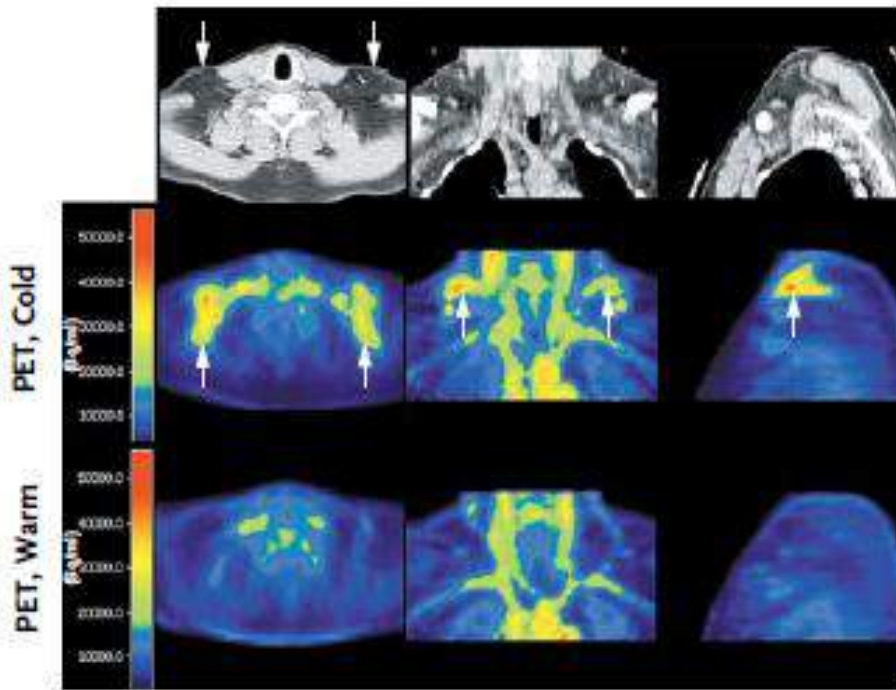
Kirsi A. Virtanen, M.D., Ph.D., Martin E. Lidell, Ph.D., Janne Orava, B.S.,
Mikael Heglind, M.S., Rickard Westergren, M.S., Tarja Niemi, M.D.,
Markku Taittonen, M.D., Ph.D., Jukka Laine, M.D., Ph.D., Nina-Johanna Savisto, M.S.,
Sven Enerbäck, M.D., Ph.D., and Pirjo Nuutila, M.D., Ph.D.

N Engl J Med 2009;360:1518-25.

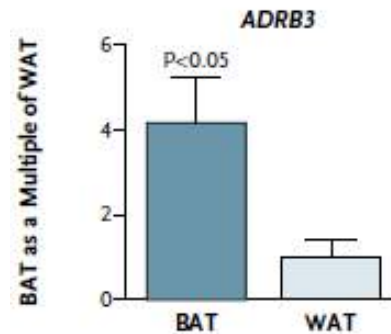
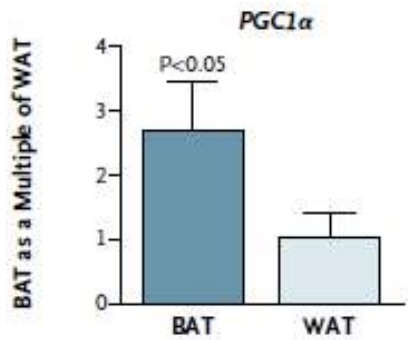
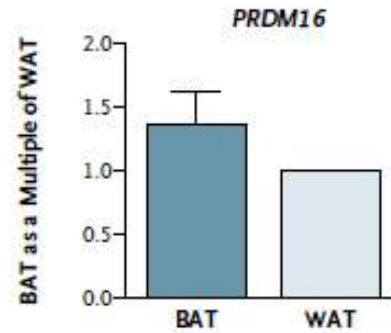
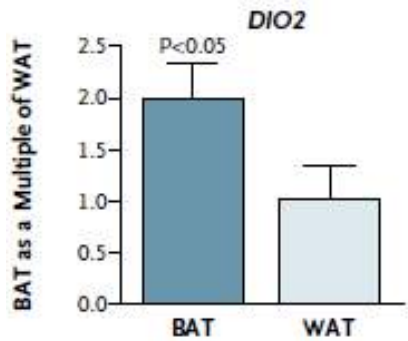
Materyal-Metod

- 5 gönüllü erkek
- 20-50 yaş
- Soğuk uygulama
- Histoloji
- UCP1, DIO2, PRDM16, ADRB3 mRNA

Sıcak ve soğuk farkı



KYD ve BYD: Gen ekspresyonları



The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Cold-Activated Brown Adipose Tissue in Healthy Men

Wouter D. van Marken Lichtenbelt, Ph.D., Joost W. Vanhommerig, M.S.,
Nanda M. Smulders, M.D., Jamie M.A.F.L. Drossaerts, B.S.,
Gerrit J. Kemerink, Ph.D., Nicole D. Bouvy, M.D., Ph.D.,
Patrick Schrauwen, Ph.D., and G.J. Jaap Teule, M.D., Ph.D.

N Engl J Med 2009;360:1500-8.

Materyal-Metod

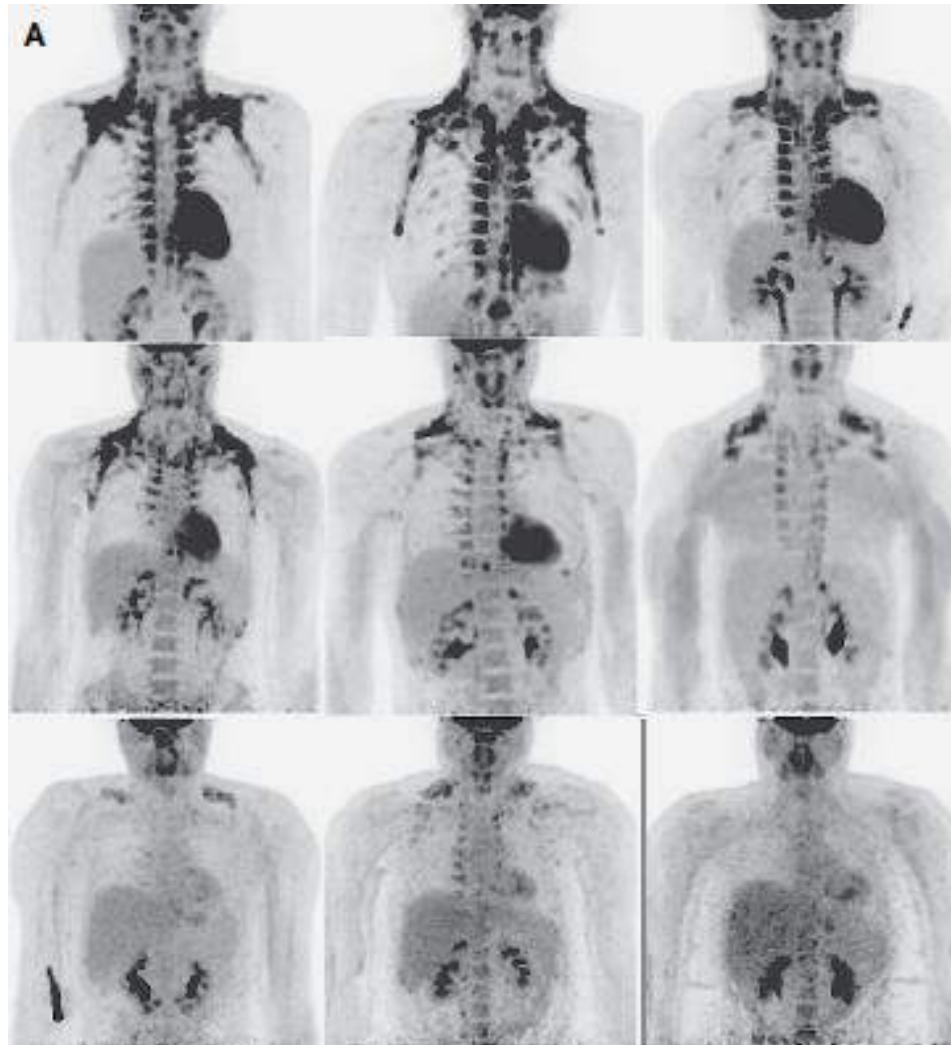
- 24 sađlıklı erkek
- Sođuk/sıcak uygulama
- PET-BT
- Histoloji

Denek profili

Characteristic	Lean Subjects (N=10)	Overweight or Obese Subjects (N=14)	P Value†
Age (yr)			0.58
Mean	24.3±3.6	23.5±3.4	
Range	20–32	18–30	
Body mass (kg)			<0.001
Mean	78.1±9.2	102.0±17.5	
Range	66.0–95.3	76.5–136.5	
Height (m)			0.99
Mean	1.83±0.09	1.83±0.06	
Range	1.75–2.02	1.74–1.94	
BMI			<0.001
Mean	23.2±1.2	30.3±4.2	
Range	21.3–24.5	25.4–38.7	
Body fat (%)‡			<0.001
Mean	16.2±5.1	27.3±7.4	
Range	9.4–25.1	16.9–41.8	

Kahverengi yağ aktivitesi

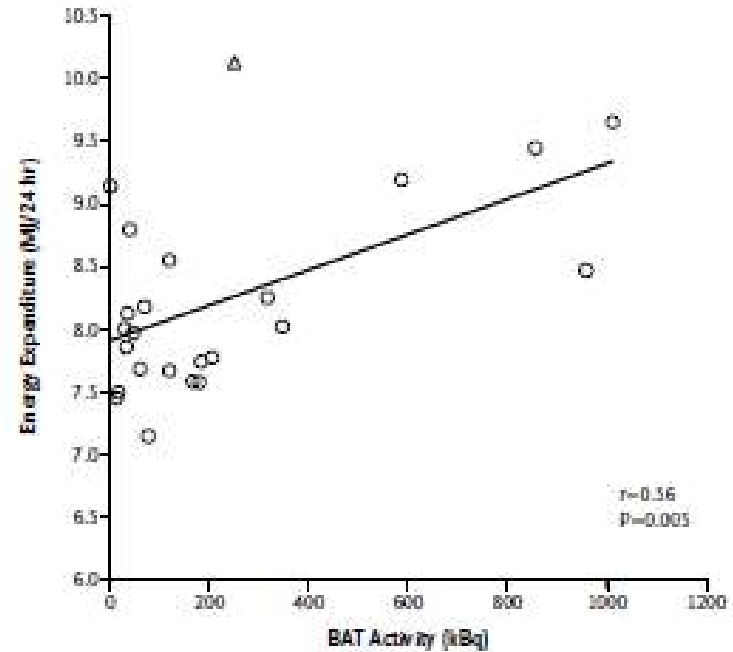
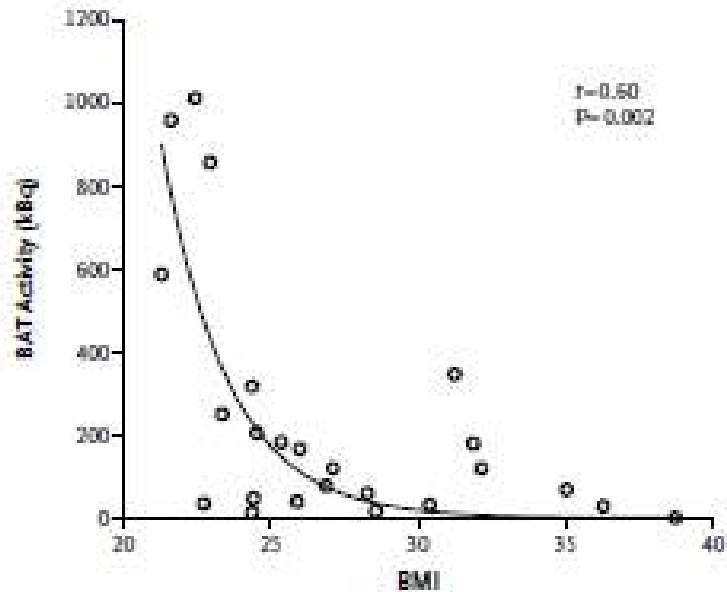
PET-BT ^{18}F -FDG



Kahverengi yağ dokusu aktivitesi

BKI-İstirahatte enerji sarfiyatı

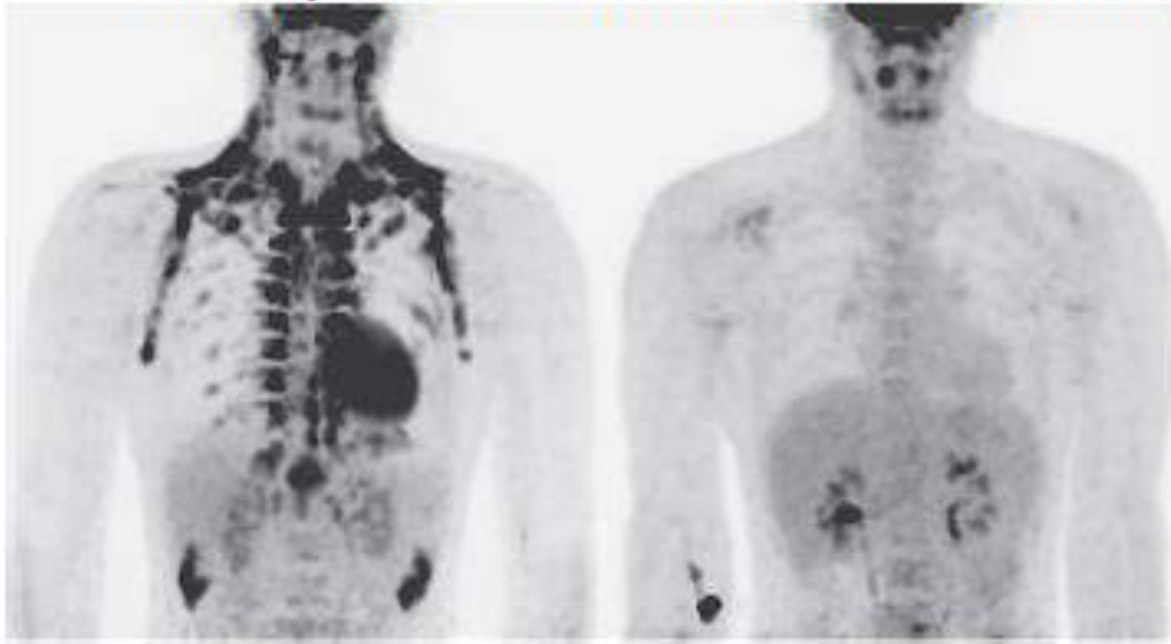
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Kahverengi yağ aktivitesi

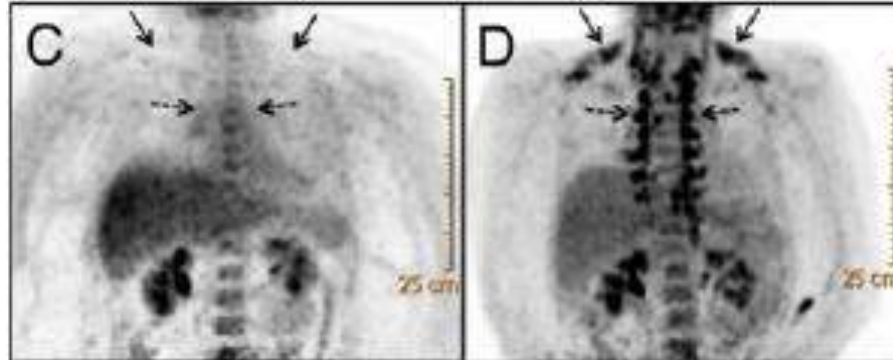
Cold Exposure

Thermoneutral Conditions



Bariyatrik cerrahi sonrası KYD artışı

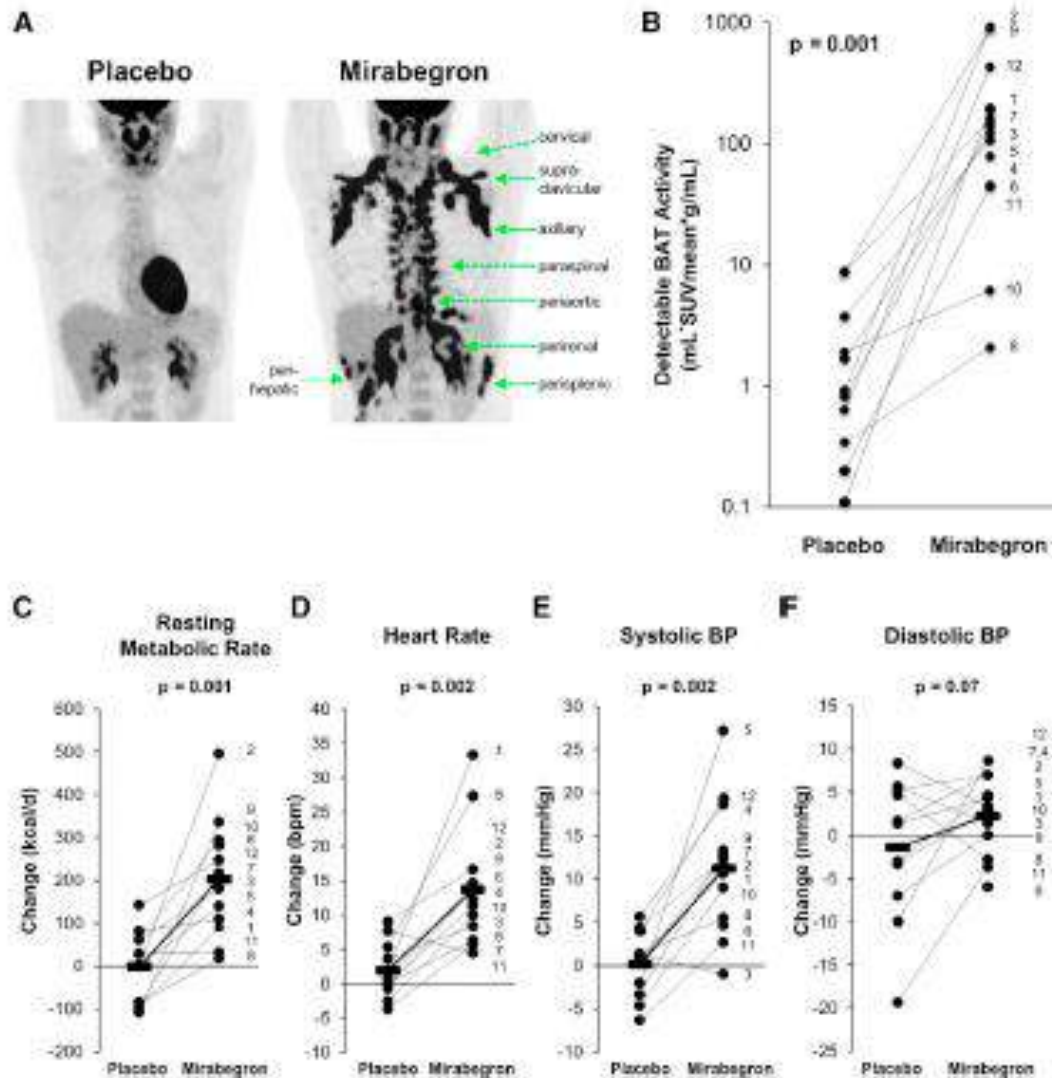
	Before	After	P value
Age (yr)	40 ± 9	41 ± 9	
BMI (kg/m ²)	41.7 ± 4.4	29.8 ± 4.2	<0.001
Body mass (kg)	127.0 ± 17.7	90.8 ± 16.7	<0.001
BF%	48.6 ± 5.2	34.8 ± 7.9	<0.001
Fat mass (kg)	62.1 ± 10.9	32.4 ± 10.5	<0.001
FFM (kg)	63.5 ± 11.7	57.7 ± 12.2	<0.001



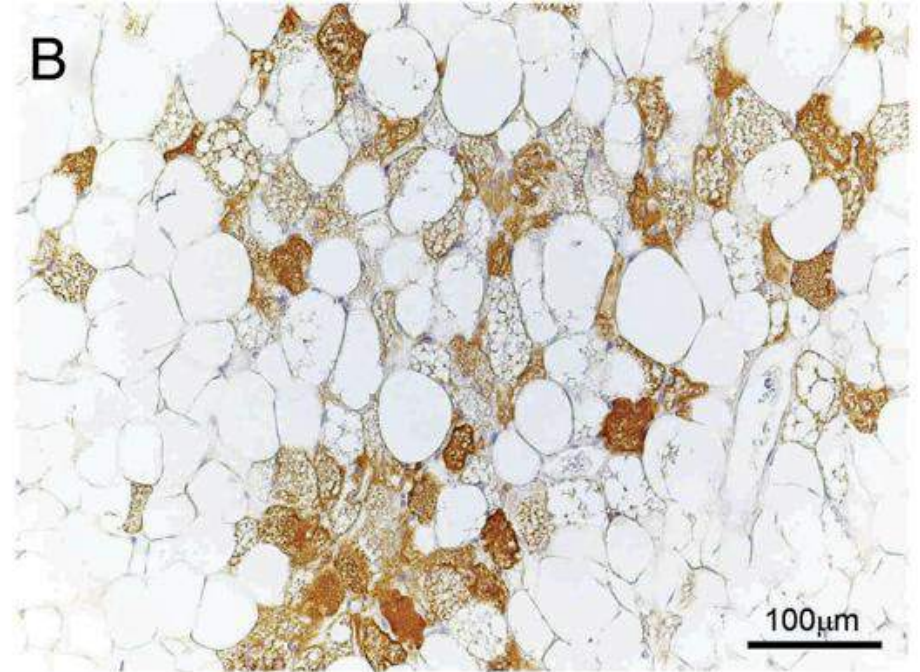
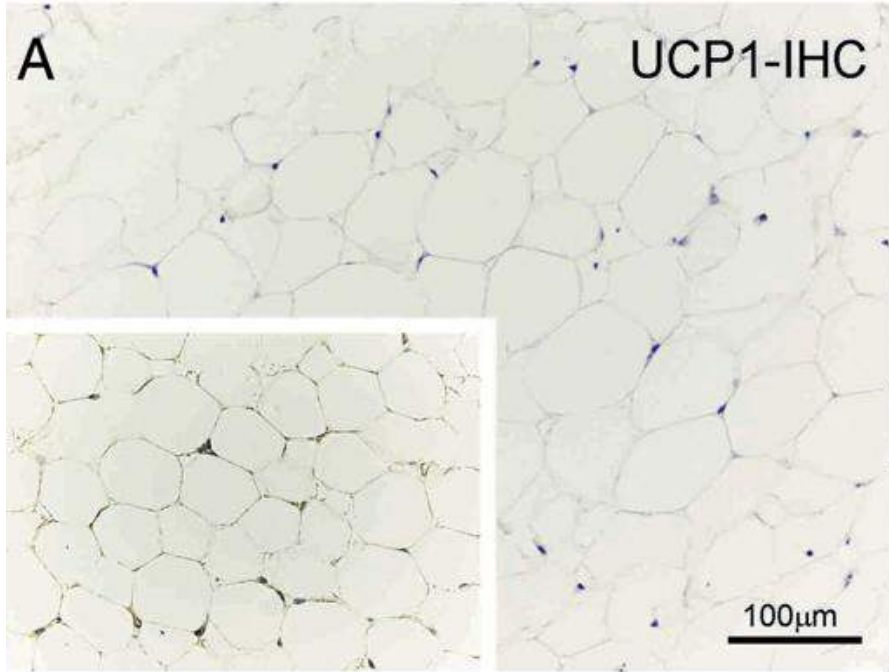
Hormonların KYD'na etkisi

Hormone	Influence on BAT	Probable BAT therapeutic suggestions
Epinephrine	+ve	Selective human β 3 receptor agonists
T3	+ve	TR β selective agonists- GC-40, KB-41
Testosterone	-ve	To be determined
Estradiol	+/- (? dual effect)	Selective estrogen receptor modulators (SERM)
Progesterone	+ve	To be determined
DHEA	+ve	To be determined
IGF-1	Probably +ve	Recombinant human IGF-1 or truncated IGF-1
GH	+ve at higher dose	To be determined
Insulin	Unclear	To be determined
Cortisol	-ve	To be determined
Prolactin	-ve	Bromocriptine, pure prolactin receptor antagonists eg., Δ 1-9-G129R- hPrI (Δ 1-9)
Aldosterone	-ve	Eplerenone, Spironolactone
Endocannabinoids	-ve	Peripheral CB1 antagonists

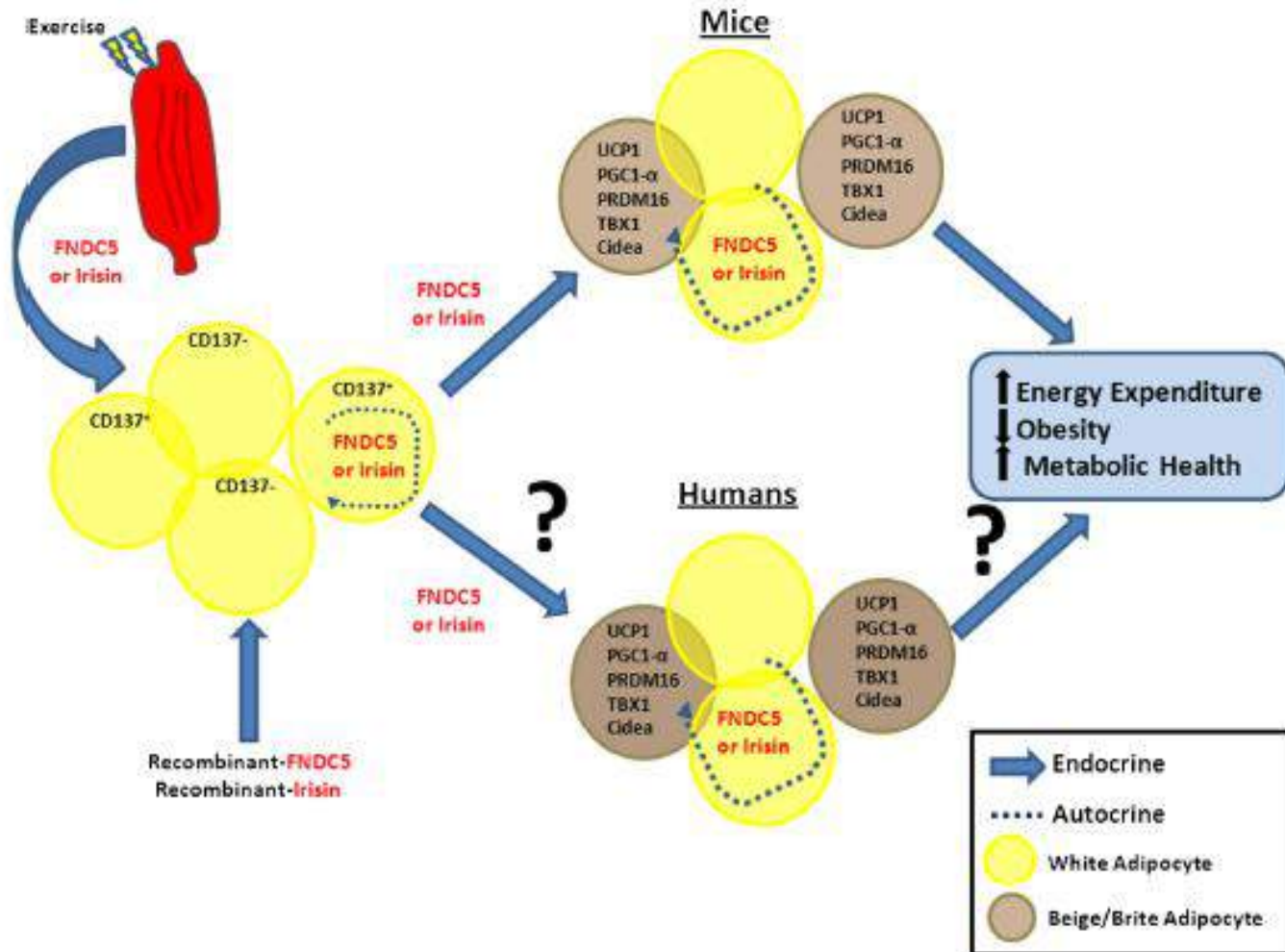
B3-AR agonisti mirabegron'un metabolik etkisi



Feokromositoma'da omental adipositler: Beyaz-Kahverengi dönüşümü



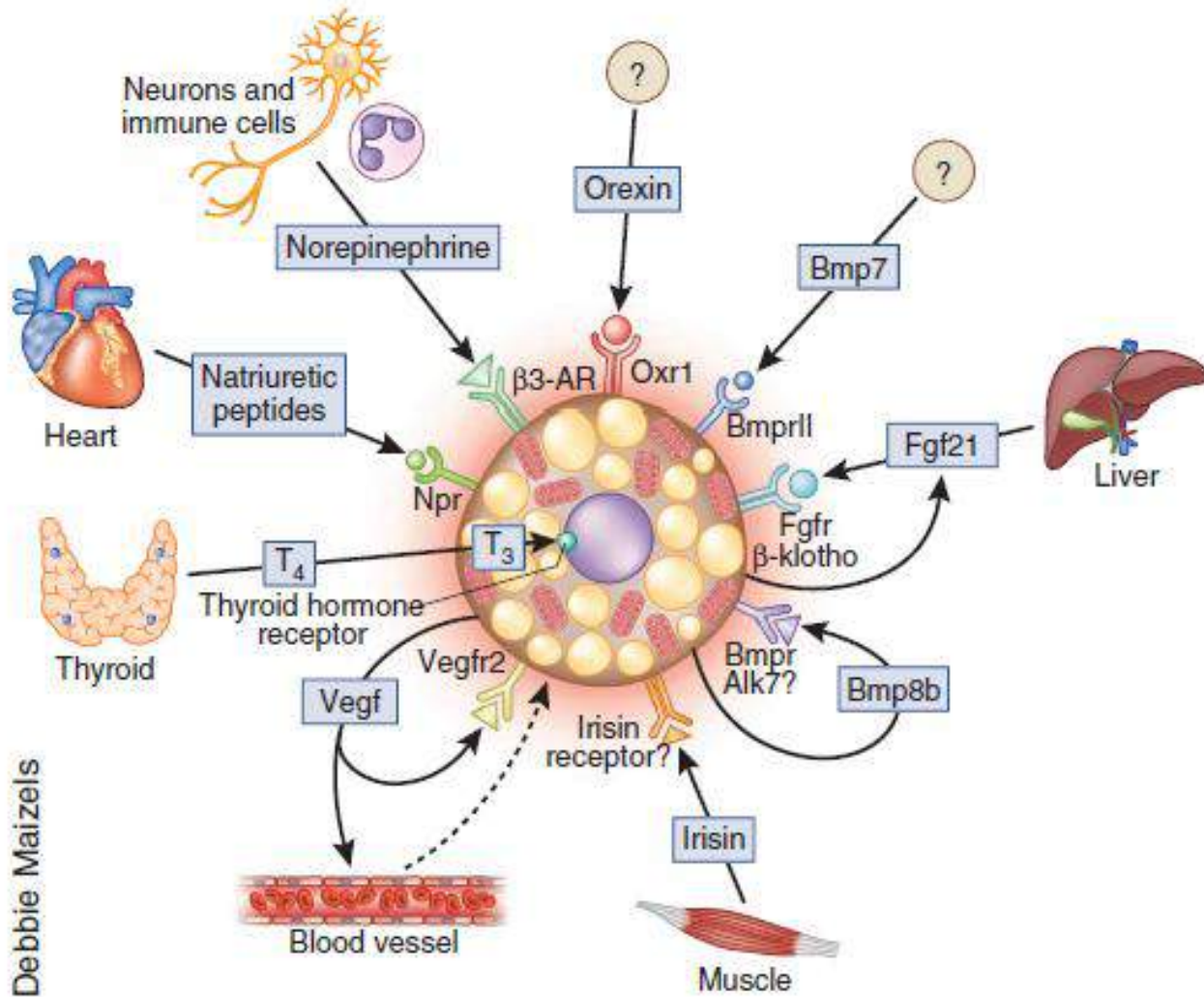
İrisin'in kahverengileşmede olası etkisi



İrisin insanda kahverengileşmede rol oynuyor mu?

Study (reference)	Patients/subjects	n	Exercise mode	Intervention	Main result
Boström <i>et al.</i> (2012a)	Healthy adults	8	A	10 weeks of supervised endurance training	WB with Abnova antibody – does not detect irisin
Hecksteden <i>et al.</i> (2013)	Healthy adults: Control	39	A	26 weeks of supervised aerobic endurance or strength endurance training	No change in circulating irisin levels between groups
	Aerobic training	23			
	Strength training	40			
Huh <i>et al.</i> (2012)	Young, moderately trained, healthy males	15	B	1 week of exercise (2–3 sets of two 80-m sprints)	Circulating irisin levels were significantly induced (18%) 30 min after the exercise
	Young, moderately trained, healthy males	15	A	8 weeks of exercise (three times a week, 2–3 sets of two 80-m sprints)	No change in circulating irisin levels
Kraemer <i>et al.</i> (2014)	Healthy, young male	7	B	90 min treadmill exercise	Circulating irisin levels were significantly induced (20%) by 54 min exercise
Kurdiova <i>et al.</i> (2014)	Sedentary vs trained	7 vs 8	B	1 h 75% of maximal capacity	No change in circulating irisin levels
Moraes <i>et al.</i> (2013)	Hemodialysis patients	26	A	6 months supervised resistance exercise	No change in circulating irisin levels
Nothelm <i>et al.</i> (2014)	Normoglycemic, sedentary men	13	A	12 weeks combined endurance and strength training	No change in circulating irisin levels
	Normoglycemic, sedentary men	13	B	45 min cycling at 70% VO _{2 max}	1.2-fold increase in circulating irisin levels directly after exercise
Pekkala <i>et al.</i> (2013)	Healthy, untrained male	17	B	1 h acute low-intensity aerobic exercise	No change in circulating irisin levels
	Healthy, young male	14	B	Single resistance exercise bout	No change in circulating irisin levels
	Healthy, young male	10	B	Single resistance exercise bout	No change in circulating irisin levels
	Healthy, untrained middle-aged male	9	A	21 weeks high-intensity endurance exercise	No change in circulating irisin levels
	Healthy, untrained middle-aged male	9	A	21 weeks combined endurance and resistance exercise	No change in circulating irisin levels
Aydin <i>et al.</i> (2013)	Obese males vs healthy males	7 vs 7	B	45 min of moderate outdoor running (5.5 km/45 min)	No change in circulating irisin levels

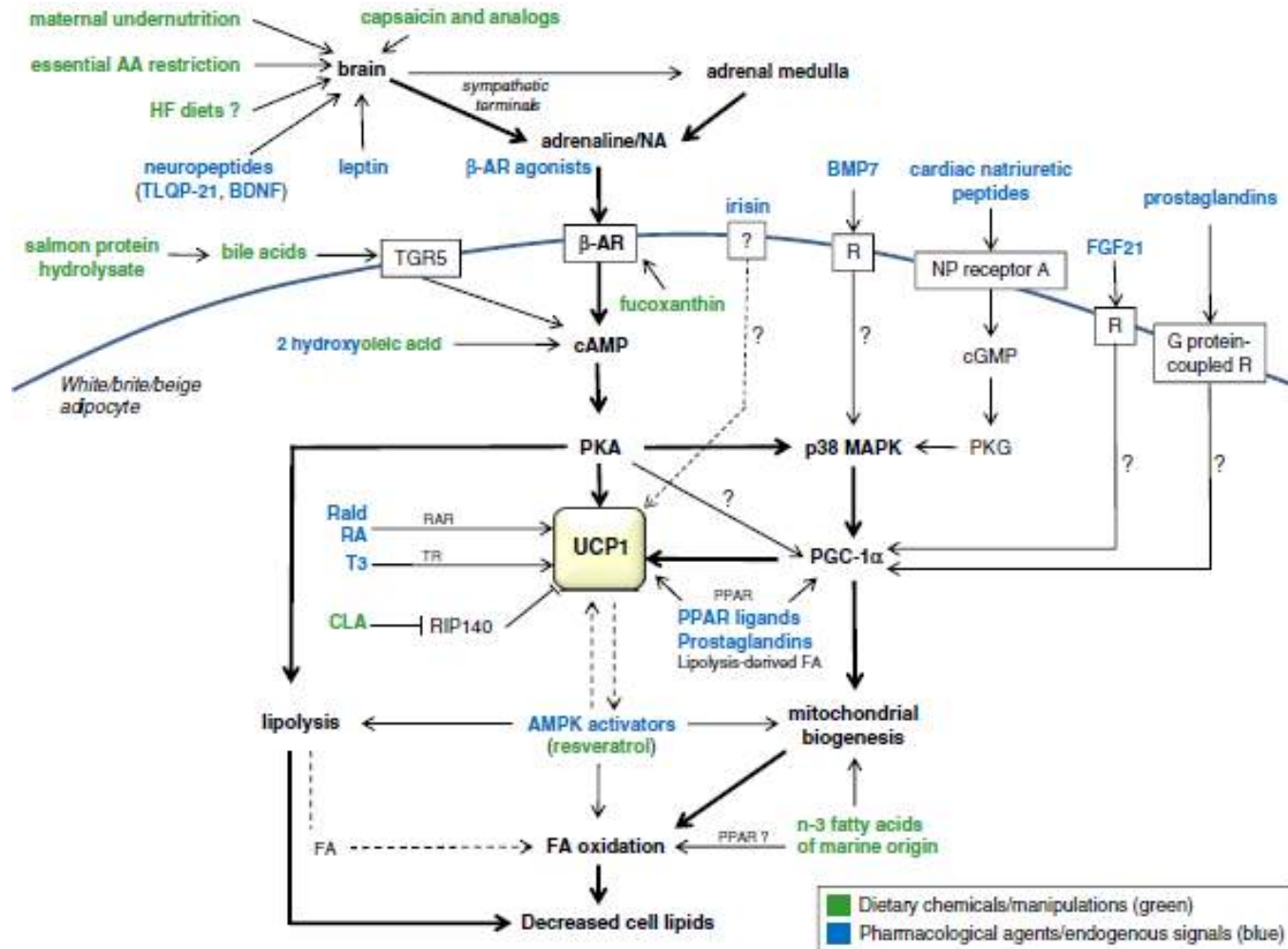
Kemirgenlerde KYD uyarıcıları



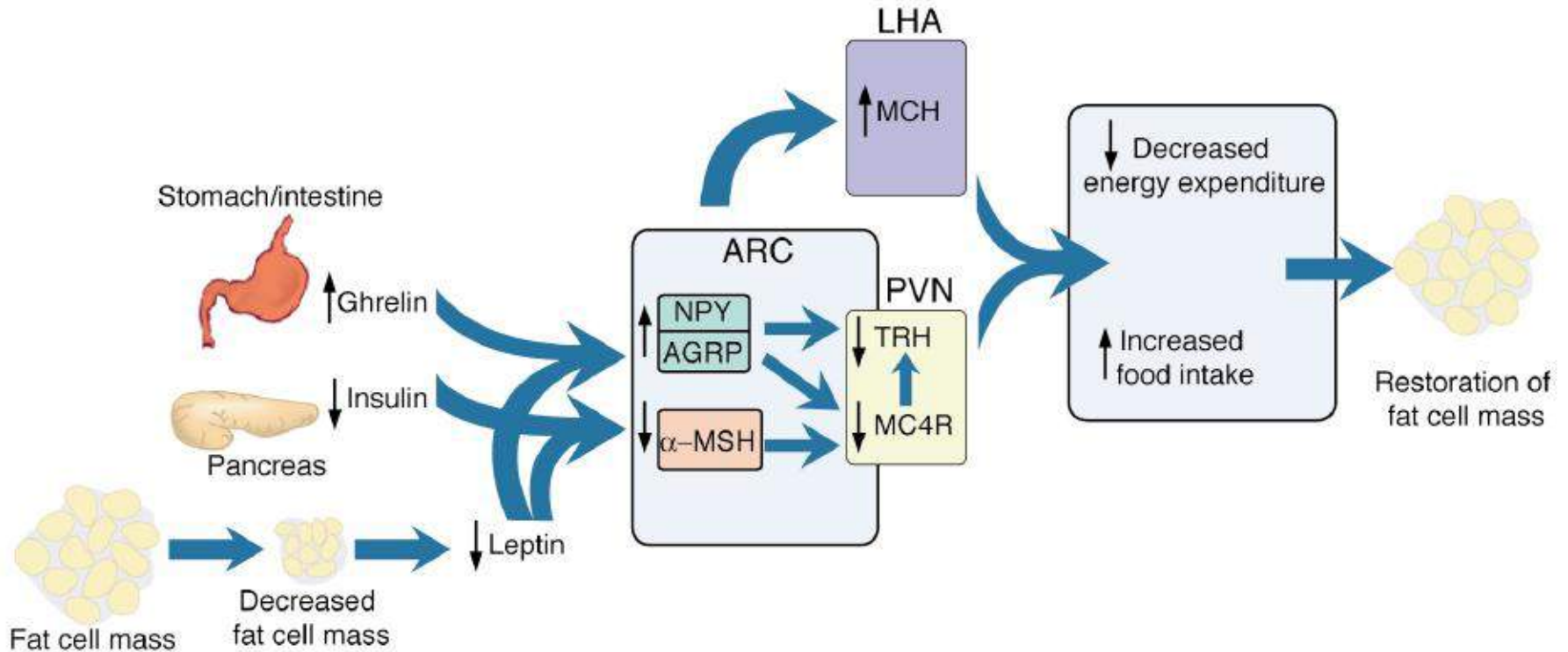
Endojen ve eksojen ajanlar ve sinyaller

Agent/signal	BAT activation	WAT browning
Beta-adrenergic agonists	+	+
Leptin	+	+
TLQP-21	+	++
Brain-derived neurotrophic factor	+	++
Prostaglandins	-	+
Cardiac natriuretic peptides	+	+
PPAR γ ligands	+	+
PPAR α ligands	+	+
Retinoids	+	+
Thyroid hormones	+	+
AMPK activators	-	?*
Irisin	-	+
Fibroblast growth factor 21	+	+++
Bone morphogenetic protein 7	+	?**

Endojen ve eksojen ajanlar ve sinyaller



Gıda alımını ve yağ kütleini regüle eden hormonal ve nöronal yollar



Tedaviye yansımalar

- Soğuk
- Fiziksel aktivite
- Adrenerjik sistem
- Tiroid aksı aktivitesi
- KYD transplantasyonu
- Kahverengileştirme
- İnsandaki transkripsiyon faktörleri?

Obezite tedavisinde enerji sarfiyatı mekanizmaları

