FFA Reseptör Agonistleri Adiponektin Agonistleri

Dr. Neşe Çınar

MSKÜ Tıp Fakültesi İç Hastalıkları AD

Endokrinoloji ve Metabolizma Hastalıkları BD

FFA Reseptör Agonistleri

Serbest Yağ Asitleri

- Non esterifiye yağ asitleri
- Majör enerji kaynağı (%6-9)
- **Sınıflama;**
  - Kısa zincir yağ asitleri (SCFAs; 1-6 karbon içeren),
  - Orta zincir yağ asitleri (MCFAs; 7-12 karbon)
  - Uzun zincir yağ asitleri (LCFAs, >12 karbon içeren)

Serbest Yağ Asitleri

- Reseptör sinyal iletiminde,
- Gen ekpresyonunda,
- Sistemik enerji homeostazının düzenlenmesinde görev alırlar
- Kimyasal iletici yada sinyal molekülü olarak fonksiyon gösterebilirler

Serbest Yağ Asitlerinin Metabolik Etkileri

› Diabetes. 1998 Oct;47(10):1613-8. doi: 10.2337/diabetes.47.10.1613.

Circulating fatty acids are essential for efficient glucose–stimulated insulin secretion after prolonged fasting in humans

R L Dobbins [1], M W Chester, M B Daniels, J D McGarry, D T Stein

Affiliations + expand

PMID: 9753300 DOI: 10.2337/diabetes.47.10.1613

Abstract

In the fasted rat, efficient glucose-stimulated insulin secretion (GSIS) is absolutely dependent on an elevated level of circulating free fatty acids (FFAs). To determine if this is also true in humans, nonobese volunteers were fasted for 24 h (n = 5) or 48 h (n = 5), after which they received an infusion of either saline or nicotinic acid (NA) to deplete their plasma FFA pool, followed by an intravenous bolus of glucose. NA treatment resulted in a fall in basal insulin concentrations of 35 and 45% and in the area under the insulin response curve (area under the curve [AUC]) to glucose of 47 and 42% in the 24- and 48-h fasted individuals, respectively. The 48-h fasted subjects underwent the same procedure with the addition of a coinfusion of Intralipid plus heparin (together with NA) to maintain a high concentration of plasma FFAs throughout the study. The basal level and AUC for insulin were now completely normalized (C-peptide profiles paralleled those for insulin). To assess the effect of an overnight fast, nonobese (n = 6) and obese (n = 6) subjects received an infusion of either saline or NA, followed by a hyperglycemic clamp (200 mg/dl). The insulin AUC in response to glucose was unaffected by lowering of the FFA level in nonobese subjects, but fell by 29% in the obese group. The data clearly demonstrate that in humans, the rise in circulating FFA levels after 24 and 48 h of food deprivation is critically important for pancreatic beta-cell function both basally and during subsequent glucose loading. They also suggest that the enhancement of GSIS by FFAs in obese individuals is more prominent than that seen in their nonobese counterparts.

› J Clin Invest. 1969 Oct;48(10):1934-43. doi: 10.1172/JCI106160.

Stimulation of insulin secretion by infusion of free fatty acids

S R Crespin, W B Greenough 3rd, D Steinberg

PMID: 5822597 PMCID: PMC322430 DOI: 10.1172/JCI106160

Free PMC article

Abstract

The acute elevation of plasma free fatty acid (FFA) levels by direct infusion of sodium oleate into the plasma of conscious dogs was accompanied by the rapid onset of a 2- to 12-fold increase in plasma immunoreactive insulin, and, subsequently, a marked fall in plasma glucose, even in dogs receiving intravenous glucose throughout the infusion. The magnitude of both the insulin and glucose responses correlated with the mean FFA level during infusion. A large increase in plasma insulin and fall in glucose also occurred when glycerol was infused with oleate in order to simulate endogenous lipolysis more closely. Insulin levels in pancreaticoduodenal vein blood rose markedly during oleate infusion, while plasma ketone levels rose only slightly. In contrast to the effects of oleate infusion, elevation of plasma FFA to correspondingly high levels by triolein ingestion and intravenous heparin produced only small increases in plasma insulin, which did not correlate well with the FFA level reached, and small increases in plasma glucose.The results indicate that under certain conditions elevated FFA levels may be a potent stimulus of insulin secretion. This response is modified under other conditions such as during chylomicron removal under the influence of heparin. This effect may play a role in the regulation of lipolysis and ketone formation, but determination of the exact mechanism of FFA stimulation of the pancreas and its physiological significance will require further investigation.

› J Clin Invest. 1996 Jun 15;97(12):2728-35. doi: 10.1172/JCI118727.

Essentiality of circulating fatty acids for glucose–stimulated insulin secretion in the fasted rat

D T Stein [1], V Esser, B E Stevenson, K E Lane, J H Whiteside, M B Daniels, S Chen, J D McGarry

Affiliations + expand

PMID: 8675683 PMCID: PMC507365 DOI: 10.1172/JCI118727

Free PMC article

Abstract

We asked whether the well known starvation-induced impairment of glucose-stimulated insulin secretion (GSIS) seen in isolated rat pancreas preparations also applies in vivo. Accordingly, fed and 18-24-h-fasted rats were subjected to an intravenous glucose challenge followed by a hyperglycemic clamp protocol, during which the plasma-insulin concentration was measured. Surprisingly, the acute (5 min) insulin response was equally robust in the two groups. However, after infusion of the antilipolytic agent, nicotinic acid, to ensure low levels of plasma FFA before the glucose load, GSIS was essentially ablated in fasted rats, but unaffected in fed animals. Maintenance of a high plasma FFA concentration by coadministration of Intralipid plus heparin to nicotinic acid-treated rats (fed or fasted), or further elevation of the endogenous FFA level in nonnicotinic acid-treated fasted animals by infusion of etomoxir (to block hepatic fatty acid oxidation), resulted in supranormal GSIS. The in vivo findings were reproduced in studies with the perfused pancreas from fed and fasted rats in which GSIS was examined in the absence and presence of palmitate. The results establish that in the rat, the high circulating concentration of FFA that accompanies food deprivation is a sine qua non for efficient GSIS when a fast is terminated. They also serve to underscore the powerful interaction between glucose and fatty acids in normal beta cell function and raise the possibility that imbalances between the two fuels in vivo could have pathological consequences.

Dobbins et al., Diabetes, 1998

Crespin et al., J Clin Invest, 1969

Stein et al., J Clin. Invest, 1996

Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40

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Diabetes, a disease in which carbohydrate and lipid metabolism are regulated improperly by insulin, is a serious worldwide health issue[1,2]. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose, with various factors modifying its secretion[3]. Free fatty acids (FFAs) provide an important energy source as nutrients, and they also act as signalling molecules in various cellular processes, including insulin secretion[4,5]. Although FFAs are thought to promote insulin secretion in an acute phase, this mechanism is not clearly understood[6]. Here we show that a G-protein-coupled receptor, GPR40,

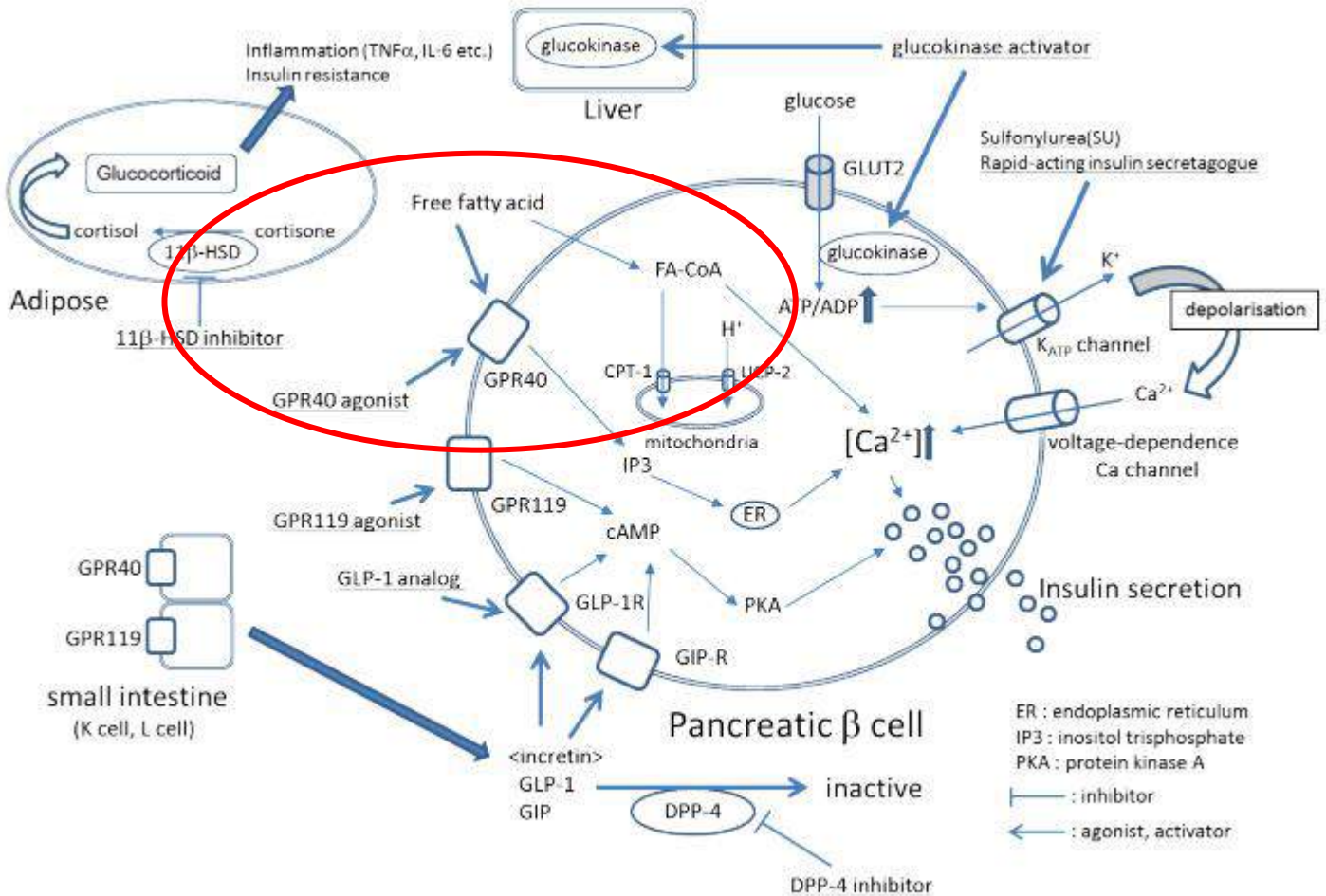
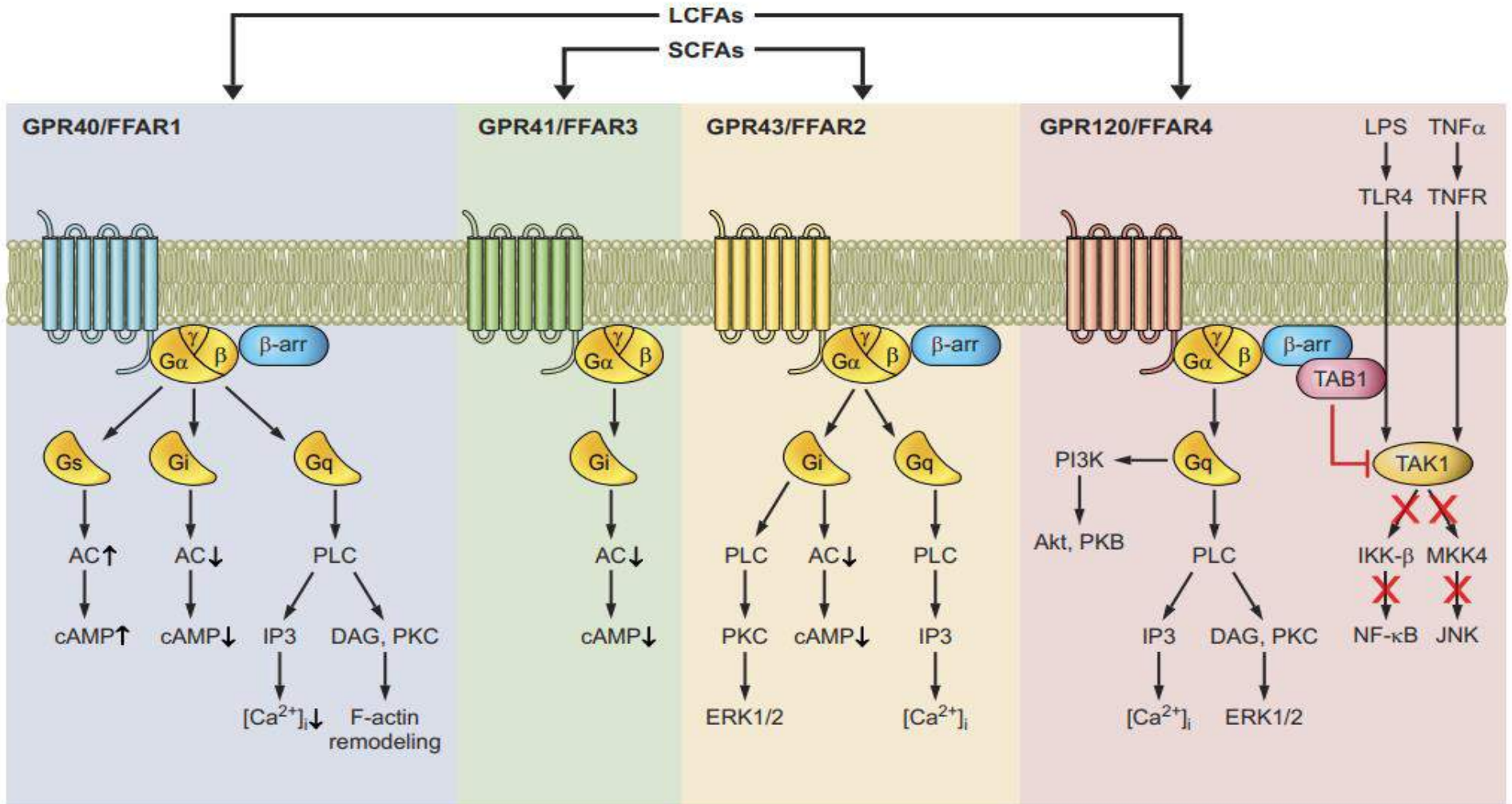


Figure 1. The mechanisms of major diabetes drugs.

Itoh et al., Nature, 2003

Serbest Yağ Asidi Reseptörleri

- G protein-kenetli reseptörler

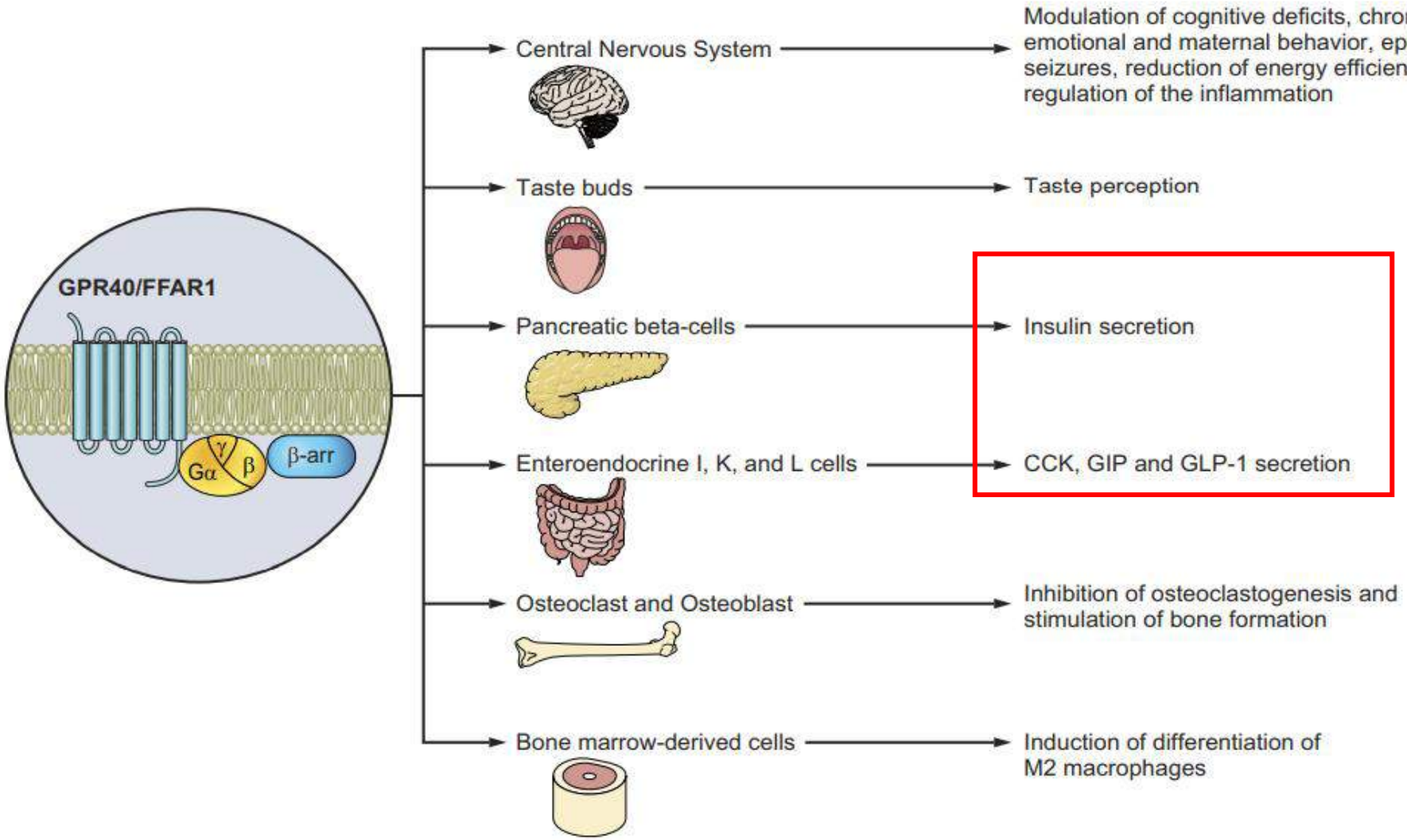


Serbest Yağ Asidi Reseptörleri

Table 1. Summary of free fatty acid (FFA) receptor expression profile and biological functions.

Receptor	Major Coupling Proteins	Major Expression Sites	Main Function
FFAR1	Gαq/11 Gαi/o Gαs Gα12/13 β-arrestin	Pancreas (β-cells) Intestine (L, K, I cells) Bone Central nervous system Immune cells (Monocytes)	Insulin secretion Gut hormone secretion Bone remodeling Pain perception Macrophage M2 differentiation
FFAR2	Gαq/11 Gαi/o Gα12/13 β-arrestin	PMNs (Neutrophils, Eosinophils) Lymphocytes Monocytes Pancreas (β-cells) Intestine (L cells, IECs) White adipose tissue	Immune cell activation T_{reg} expansion Cytokine secretion Insulin release Gut hormone secretion, immune-modulatory Reduction in lipolysis, lipid accumulation, and insulin resistance
FFAR3	Gαi/o β-arrestin	Peripheral nervous system Pancreas (β-cell) Intestine (L, K cells) Immune tissue (DCs, thymus)	Increase in heart rate, energy expenditure, reduction of gut motility Inhibition of insulin secretion Gut hormone release Decrease Th2 response, increase T_{reg} differentiation
FFAR4	Gαq/11 Gαi/o β-arrestin	Adipose tissue Macrophages Lung Intestine (K, I cells) Bone	Differentiation, browning Anti-inflammatory Epithelial repair Gut hormone release Bone formation

FFAR1/GPR40 reseptörü



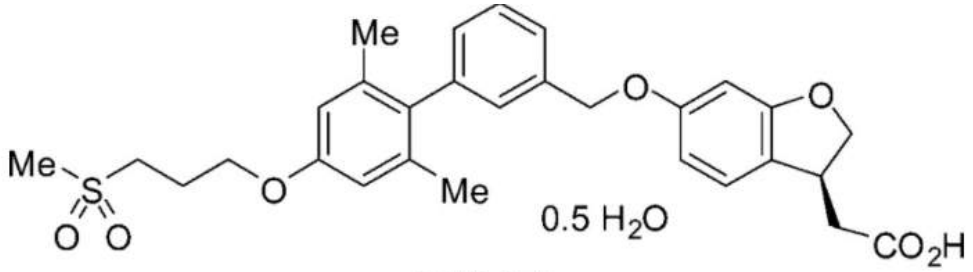
FFAR1 Reseptör Agonistleri

Table 4. *Summary of synthetic ligands for FFARs*

Ligands	Action	Half-Maximal Activities, μM	Therapeutic Target
GPR40/FFAR1			
Rosiglitazone	Full agonist	2.8[a]	Type 2 diabetes
MEDICA 16	Full agonist	1.22[a]	Type 2 diabetes
GW9508	Partial agonist	0.048[b]	Type 2 diabetes
GW1100	Antagonist	1[b]	Type 2 diabetes
AMG-837	Allosteric partial agonist	0.0015–0.12[c]	Type 2 diabetes
TUG424	Partial agonist	0.032[d]	Type 2 diabetes
TUG-770	Agonist	0.006[b]	Type 2 diabetes
DS-1558	Agonist	0.0038[c]	Type 2 diabetes
Compound 40	Full agonist	0.02[b]	Type 2 diabetes
NCG21	Agonist	20[b]	Type 2 diabetes
Compound 43	Agonist	65[g]	Type 2 diabetes
TUG891	Orthosteric agonist	5.011[b], 0.064[g]	Metabolic and inflammatory processes, type 2 diabetes
TAK-875	Agonist	0.014[c]	Type 2 diabetes
Compound 1	Partial agonist (for G_q), full agonist (for G_s)	0.072[b], 0.1258[j]	Type 2 diabetes
Compound 9	Agonist	0.38[b]	Type 2 diabetes

TAK-875/Fasiglifam

- Potent, selektif, oral FFAR1 reseptör agonisti



TAK-875

GPR40–induced insulin secretion by the novel agonist TAK–875: first clinical findings in patients with type 2 diabetes

T Araki [1], M Hirayama, S Hiroi, K Kaku

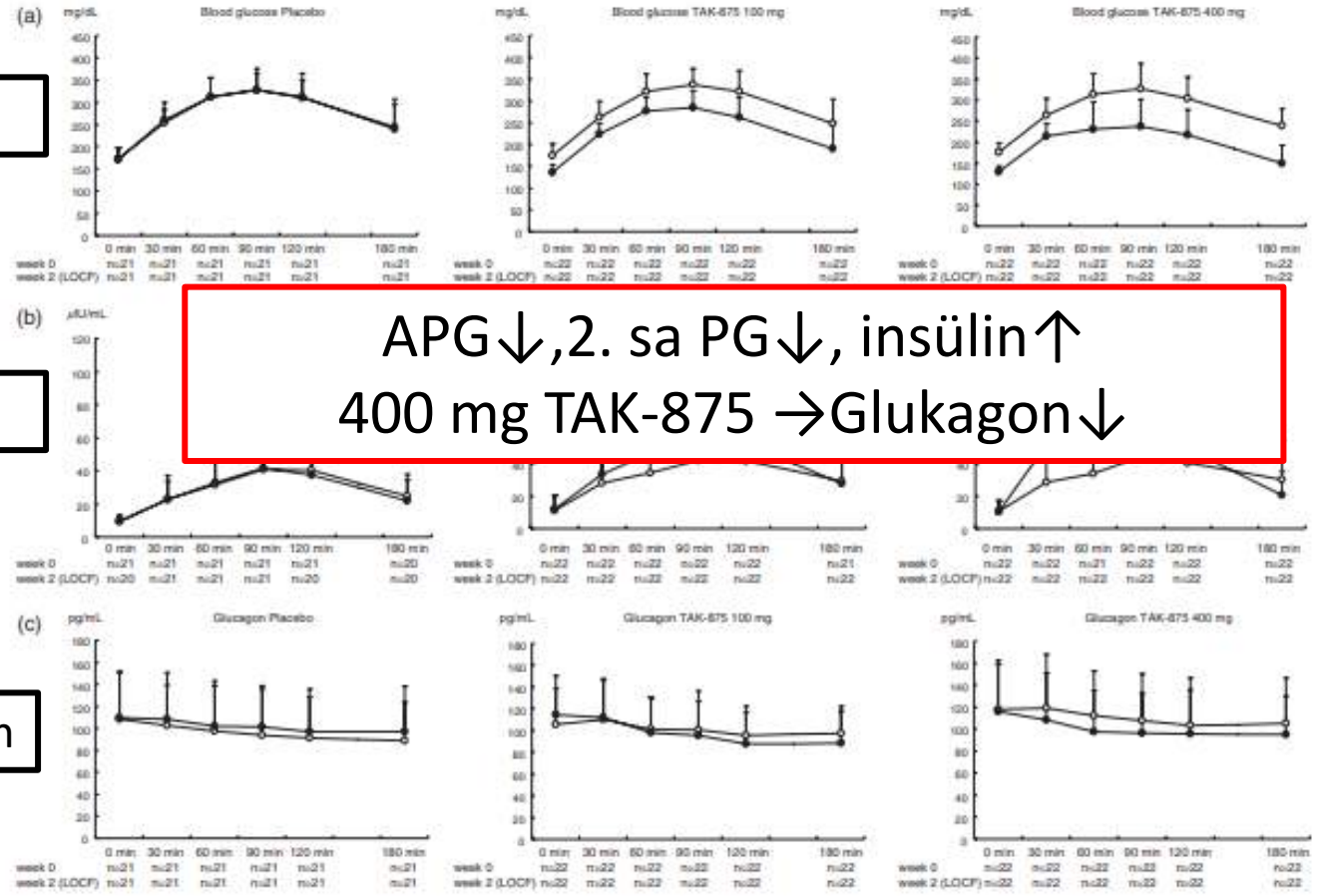
- Faz 2, multisenter, çift-kör, plasebo kontrollü
- 20-75 y, tip 2 DM ve APG 140-199 mg/dl arasında
- N: 21→ Plasebo
- N: 22→100 mg TAK-875
- N: 22 →400 mg TAK-875
- 2 haftalık takip

Plasebo | TAK-875 100 mg | TAK-875 400 mg

Glukoz

İnsülin

Glukagon



APG↓,2. sa PG↓, insülin↑
400 mg TAK-875 →Glukagon↓

Figure 2. Mean ± standard deviation (SD) plasma concentration-time profiles for glucose (a), insulin (b) and glucagon (c) during 75 g oral glucose tolerance tests after 2 weeks' treatment (● — ●) with placebo, TAK-875 100 mg and TAK-875 400 mg compared with baseline value (○ — ○).

Araki et al., DOM, 2012

TAK–875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double–blind, placebo–controlled trial

Charles F Burant [1], Prabhakar Viswanathan, John Marcinak, Charlie Cao, Majid Vakilynejad, Benhuai Xie, Eckhard Leifke

- Faz 2, multisenter, çift-kör, plasebo kontrollü
- Diyet ya da metformin tedavisine yanıt vermeyen tip 2 DM hastaları
- 4 mg glimeprid
- 12 haftalık takip

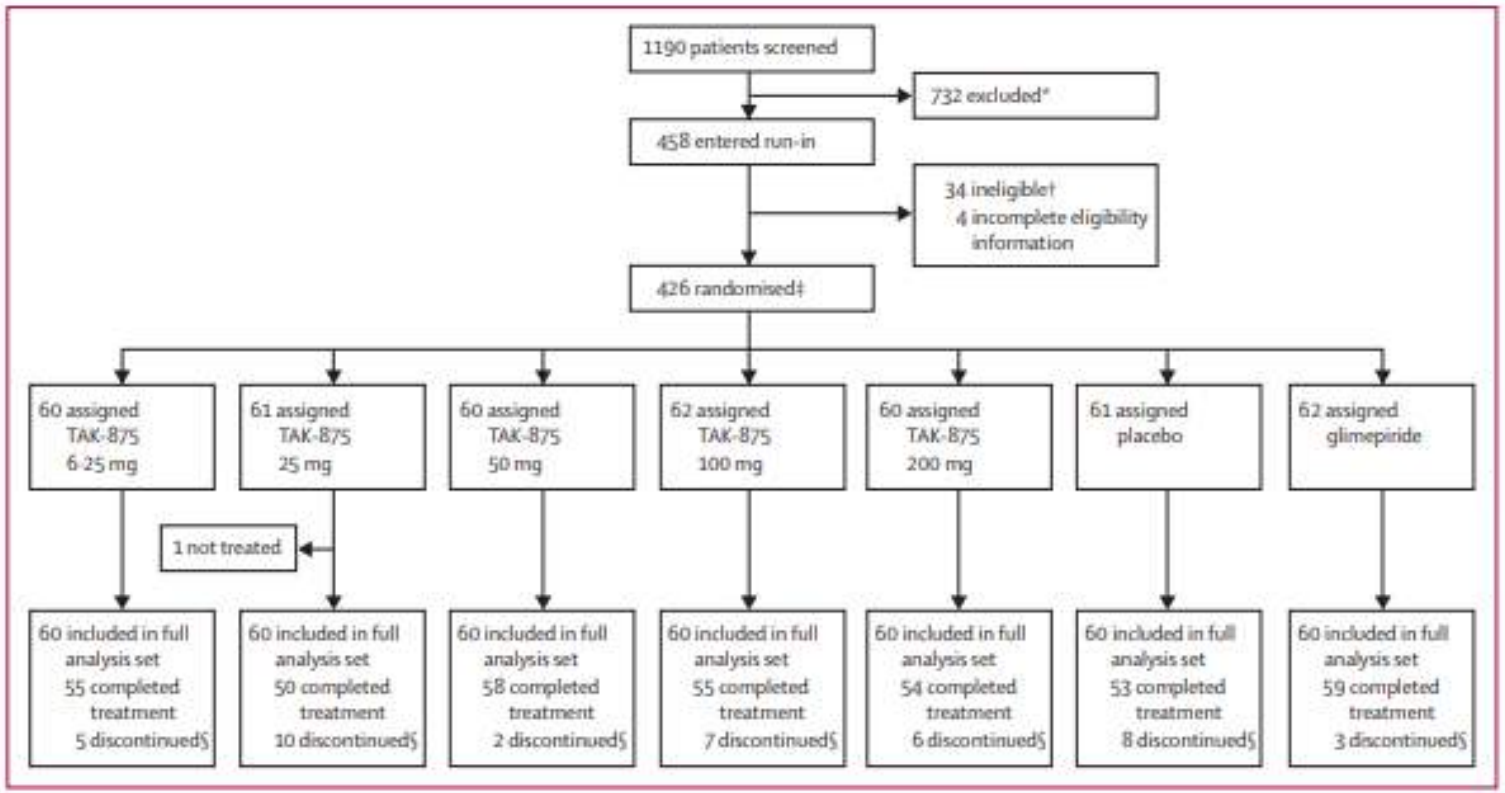


Figure 1: Trial profile

Burant et al., Lancet, 2012

TAK–875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double–blind, placebo–controlled trial

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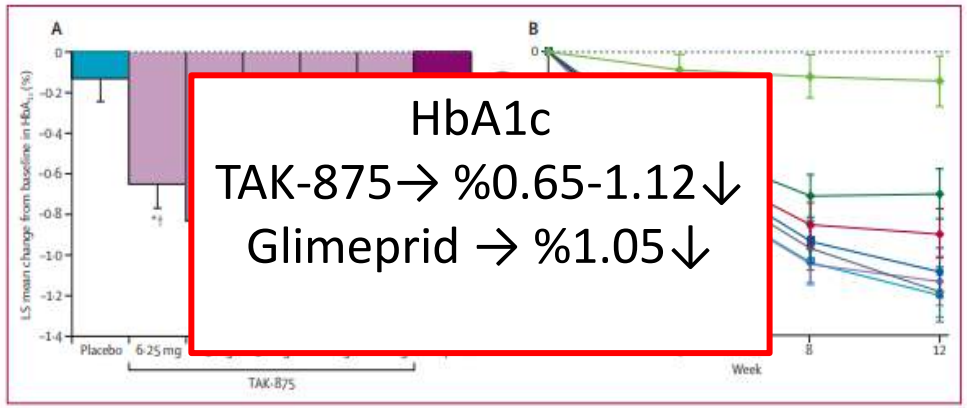
HbA1c



HbA1c
TAK-875→ %0.65-1.12↓
Glimeprid → %1.05↓

Figure 2: LS mean change from baseline in HbA_{1c}

	TAK-875					Placebo (n=51)	Glimepiride§ (n=57)
	6·25 mg*† (n=52)	25 mg‡ (n=46)	50 mg‡ (n=55)	100 mg‡ (n=52)	200 mg‡ (n=48)		
Baseline	1 (2%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)	4 (8%)	0
Week 12	10 (19%)	20 (43%)	21 (38%)	17 (33%)	23 (48%)	9 (18%)	23 (40%)

Data are n (%). Only patients who had values at both baseline and week 12 were included in the analysis. HbA_{1c}=glycated haemoglobin. *p=0·491 versus placebo. †p=0·015 versus glimepiride. ‡p value range 0·035 to <0·0001 versus placebo. §p=0·002 versus placebo.

Table 2: Patients reaching the American Diabetes Association target of HbA_{1c} less than 7% at week 12

AUCglukoz

AUCinsülin

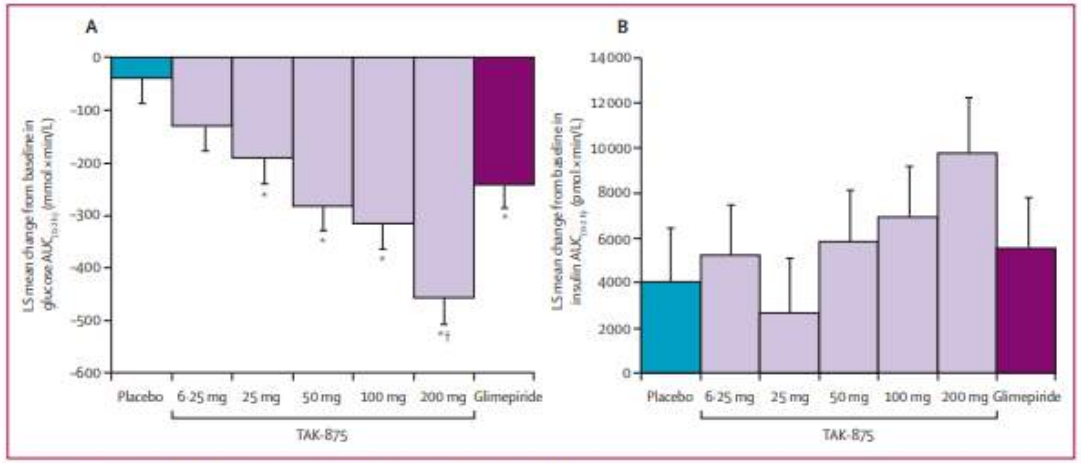


Figure 3: LS mean changes from baseline in glucose AUC and insulin AUC at week 12

Cpeptid/Glukoz

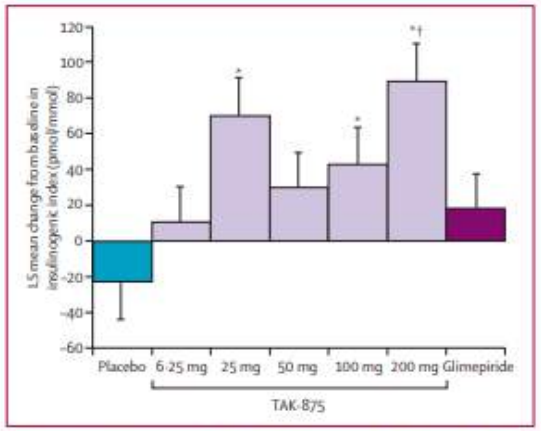


Figure 4: LS mean change in insulinogenic index (C-peptide:glucose ratio) during the first 30 min of the oral glucose tolerance test at week 12
Error bars show SE. LS=least-squares. *p value range 0·027–0·002 versus placebo. †p=0·016 versus glimepiride.

Kilo

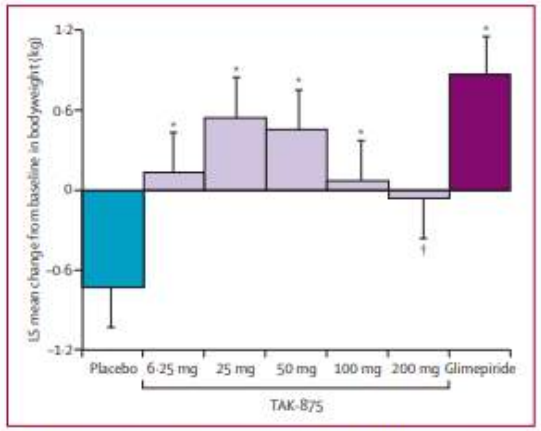


Figure 5: LS mean change from baseline in bodyweight at week 12
Error bars show SE. LS=least-squares. *p value range 0·046 to 0·0002 versus placebo. †p=0·0298 versus glimepiride.

Burant et al., Lancet, 2012

TAK–875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double–blind, placebo–controlled trial

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Hipoglisemi

- Hipoglisemi riski
  - Plasebo →%3
  - TAK-875 →%2
  - Glimeprid →%19*
- İlaç ilişkili acil yan etki profili benzer

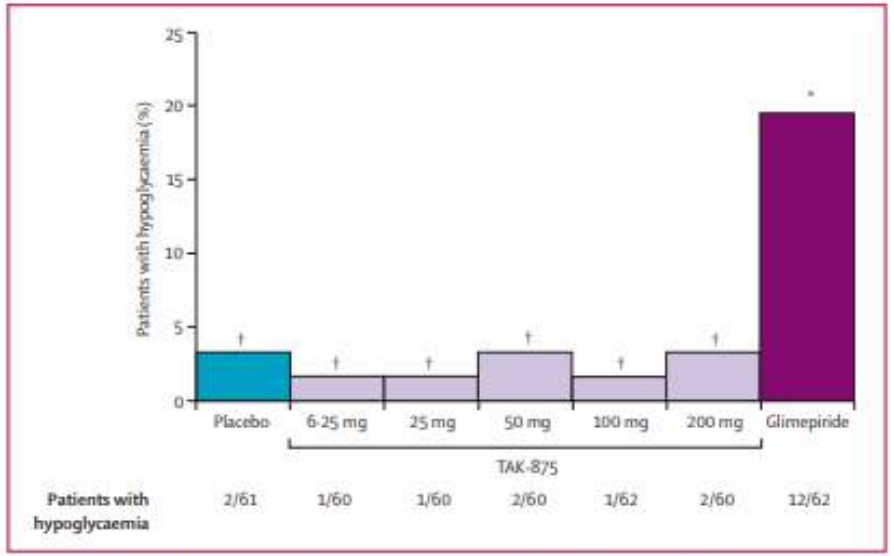


Figure 6: Percentage of patients with hypoglycaemia during the 12-week double-blind period
*p=0·009 versus placebo. †p value range 0·010–0·002 for all TAK-875 groups versus glimepiride.

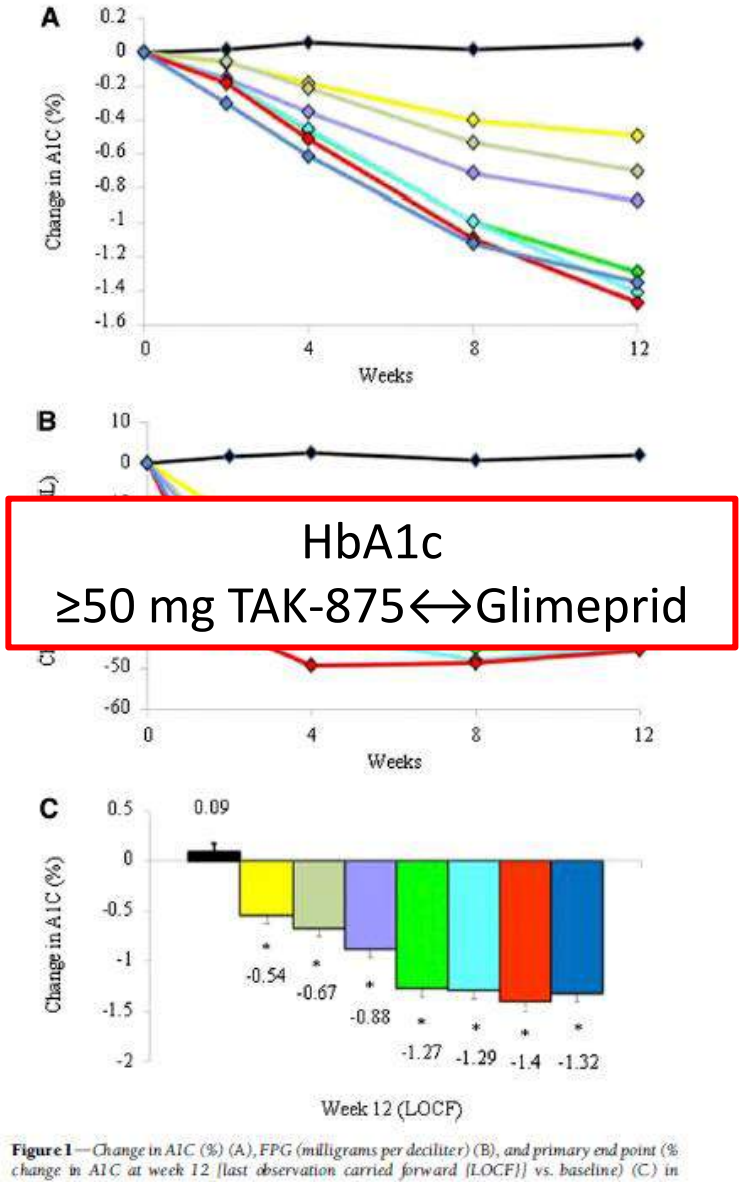
Burant et al., Lancet, 2012

Randomized, double-blind, dose-ranging study of TAK-875, a novel GPR40 agonist, in Japanese patients with inadequately controlled type 2 diabetes

Kohei Kaku [1], Takahiro Araki, Ryoji Yoshinaka

- Faz 2, multisenter, çift-kör, plasebo kontrollü
- Diyet/egzersiz ile kontrol sağlanamayan Tip 2 DM
- N: 299→ TAK-875 (Subgruplar 6.25, 12.5, 25, 50, 100, 200 mg)
- N: 48→ Plasebo
- N: 49 → 1 mg Glimeprid
- 12 haftalık takip

ΔHbA1c ve APG



HbA1c
≥50 mg TAK-875↔Glimeprid

Figure 1—*Change in A1C (%) (A), FPG (milligrams per deciliter) (B), and primary end point (% change in A1C at week 12 [last observation carried forward {LOCF}] vs. baseline) (C) in*

Kaku et al., Diabetes Care, 2013

Randomized, double-blind, dose-ranging study of TAK-875, a novel GPR40 agonist, in Japanese patients with inadequately controlled type 2 diabetes

Kohei Kaku [1], Takahiro Araki, Ryoji Yoshinaka

- Öğün tolerans testi sonrası
  - 2. sa PG↓, AUC $_{0\text{-}2.sa}$ Glukoz↓
  - İnsülin salınımı ↑ (Glimeprid ile daha belirgin)
  - AUC $_{0\text{-}2.sa}$ total GLP-1↑ (Glimeprid↔)

Table 2—Change in key glycemic efficacy end points after 12 weeks' treatment (last observation carried forward) versus baseline

		TAK-875 (mg)						
	Placebo	6.25	12.5	25	50	100	200	1 mg Glimepiride
ΔA1C (%)	0.08 ± 0.65, n = 48	−0.49 ± 0.49, n = 48*	−0.68 ± 0.67, n = 53*	−0.86 ± 0.59, n = 52*	−1.25 ± 0.74, n = 51*	−1.30 ± 0.78, n = 52*	−1.43 ± 0.78, n = 42*	−1.35 ± 0.58, n = 49
ΔFPG (mg/dL)	3.2 ± 24.7, n = 48	−16.0 ± 25.5, n = 48*	−25.3 ± 33.1, n = 53*	−28.7 ± 21.5, n = 52*	−43.3 ± 28.2, n = 51*	−42.8 ± 28.0, n = 52*	−45.1 ± 31.3, n = 42*	−35.2 ± 29.0, n = 49*
Δ1,5-AG (μg/dL)	−0.15 ± 2.28, n = 48	1.40 ± 1.66, n = 48*	2.02 ± 3.21, n = 53*	3.65 ± 2.77, n = 52*	4.63 ± 3.22, n = 51*	5.19 ± 3.24, n = 52*	6.43 ± 4.53, n = 42*	4.19 ± 2.94, n = 49
ΔFasting insulin (μU/mL)	−0.54 ± 2.97, n = 47	−0.08 ± 3.04, n = 47	0.47 ± 4.95, n = 53	0.82 ± 3.15, n = 51*	0.71 ± 3.87, n = 51	0.17 ± 3.44, n = 52	0.99 ± 4.43, n = 42	1.33 ± 2.85, n = 49
ΔFasting C-peptide (ng/mL)	−0.12 ± 0.35, n = 48	−0.05 ± 0.44, n = 48	−0.04 ± 0.66, n = 53	0.11 ± 0.39, n = 52*	−0.06 ± 0.44, n = 51	0.09 ± 0.47, n = 52*	−0.04 ± 0.30, n = 42	0.02 ± 0.38, n = 49
ΔFasting glucagon (pg/mL)	1.6 ± 15.4, n = 48	4.3 ± 13.9, n = 48	1.4 ± 12.1, n = 53	5.9 ± 15.1, n = 52	4.4 ± 10.8, n = 51	4.1 ± 15.7, n = 52	7.9 ± 11.6, n = 42*	1.6 ± 14.0, n = 49
ΔProinsulin/insulin	0.033 ± 0.196, n = 47	−0.014 ± 0.173, n = 47	0.010 ± 0.156, n = 53	0.058 ± 0.307, n = 51	−0.041 ± 0.243, n = 51	−0.021 ± 0.240, n = 52	−0.075 ± 0.215, n = 42*	−0.058 ± 0.202, n = 49
Meal tolerance test								
Δ2-h PG (mg/dL)	6.2 ± 37.6, n = 46	−29.9 ± 37.7, n = 48*	−45.3 ± 53.8, n = 52*	−57.4 ± 44.3, n = 50*	−68.6 ± 40.4, n = 48*	−72.7 ± 37.8, n = 49*	−79.6 ± 49.3, n = 41*	−73.0 ± 51.5, n = 49
ΔPG $AUC_{0\text{-}2\,h}$ (mg · h/dL)	0.9 ± 60.4, n = 46	−56.8 ± 59.7, n = 48*	−84.8 ± 88.3, n = 52*	−91.9 ± 61.6, n = 50*	−122.2 ± 58.1, n = 48*	−129.2 ± 63.0, n = 49*	−139.3 ± 71.1, n = 41*	−107.5 ± 77.2, n = 49*
ΔInsulin $AUC_{0\text{-}2\,h}$ (μU · h/mL)	−5.94 ± 18.25, n = 46	−0.36 ± 10.98, n = 47	8.54 ± 17.74, n = 52*	7.22 ± 17.38, n = 48*	12.56 ± 18.31, n = 47*	10.90 ± 18.09, n = 49*	11.33 ± 21.58, n = 40*	25.22 ± 41.04, n = 48
ΔC-peptide $AUC_{0\text{-}2\,h}$ (ng · h/mL)	−0.61 ± 1.25, n = 46	−0.05 ± 1.09, n = 48*	0.38 ± 1.25, n = 52*	0.81 ± 1.46, n = 50*	0.87 ± 1.38, n = 48*	0.99 ± 1.32, n = 49*	0.81 ± 1.29, n = 41*	1.50 ± 1.81, n = 49
ΔGlucagon $AUC_{0\text{-}2\,h}$ (pg · h/mL)	−2.7 ± 29.3, n = 46	8.5 ± 24.8, n = 48*	1.7 ± 22.7, n = 52	6.4 ± 23.4, n = 50	5.0 ± 23.4, n = 48	3.5 ± 22.2, n = 49	−4.2 ± 23.2, n = 41	−3.5 ± 27.3, n = 49
ΔTotal GLP-1 $AUC_{0\text{-}2\,h}$ (pmol · h/L)	−0.019 ± 13.745, n = 46	5.806 ± 15.092, n = 48	2.076 ± 15.446, n = 52	5.045 ± 18.842, n = 50	3.961 ± 14.858, n = 48	3.747 ± 14.911, n = 49	9.143 ± 15.912, n = 41*	−3.267 ± 13.937 n = 49*
ΔActive GLP-1 $AUC_{0\text{-}2\,h}$ (pmol · h/L)	−1.521 ± 2.252, n = 46	−0.656 ± 2.880, n = 48	−1.090 ± 4.265, n = 51	−0.666 ± 2.930, n = 50	−0.232 ± 2.145, n = 48*	−0.399 ± 2.745, n = 48*	−0.072 ± 2.668, n = 41*	−1.780 ± 2.633, n = 49

Data are means ± SD unless otherwise indicated. PG, plasma glucose. *P < 0.05 vs. placebo. Parameters in glimepiride group were not compared with placebo.

Kaku et al., Diabetes Care, 2013

Randomized, double-blind, dose-ranging study of TAK-875, a novel GPR40 agonist, in Japanese patients with inadequately controlled type 2 diabetes

Kohei Kaku [1], Takahiro Araki, Ryoji Yoshinaka

- Yan etki profili gruplar arası benzer
- Doza bağlı intolerans ve ilaç değişikliği görülmemiş
- En sık yan etki nazofarinjit
- Hipoglisemi
  - 2 Glimeprid (%4.1)
  - 2 TAK-875 (%0.7)
- Kilo alımı
  - Glimeprid (0.96 ±1.70 kg)*
  - 200 mg TAK-875 (0.76 ±1.74 kg)
  - 100 mg TAK-875 (0.62 ±1.79kg)
  - 50 mg TAK-875 (0.26 ±1.94 kg)

Table 3—*Treatment-emergent adverse events reported during 12-week study, including those with an incidence of ≥5%*

		TAK-875 mg						
	Placebo	6.25	12.5	25	50	100	200	1 mg Glimepiride
Subjects	48	48	53	52	51	52	43	49
Patients with at least 1 AE (%)	31 (64.6)	24 (50.0)	27 (50.9)	28 (53.8)	25 (49.0)	28 (53.8)	23 (53.5)	30 (61.2)
Events	53	34	50	40	45	61	40	56
Serious AEs (%)	0	0	1 (1.9)	0	2 (3.9)	2 (3.8)	0	0
Serious AEs related to treatment	0	0	0	0	0	0	0	0
Subjects with an AE who discontinued treatment	0	0	2 (3.8)	3 (5.8)	2 (3.9)	1(1.9)	0	0
TEAEs reported in ≥5% of subjects by preferred term								
Nasopharyngitis	8 (16.7)	5 (10.4)	11 (20.8)	5 (9.6)	6 (11.8)	5 (9.6)	7 (16.3)	3 (6.1)
Upper-respiratory tract inflammation	2 (4.2)	4 (8.3)	1 (1.9)	0	3 (5.9)	2 (3.8)	0	1 (2.0)
Contusion	3 (6.3)	1 (2.1)	3 (5.7)	0	0	2 (3.8)	0	0
Back pain	0	0	0	0	2 (3.9)	2 (3.8)	1 (2.3)	3 (6.1)
Constipation	0	0	3 (5.7)	1 (1.9)	1 (2.0)	0	1 (2.3)	1 (2.0)
Blood uric acid increased	1 (2.1)	0	0	1 (1.9)	3 (5.9)	0	0	1 (2.0)
Headache	0	0	1 (1.9)	1 (1.9)	1 (2.0)	3 (5.8)	0	0

Data are n or n (%). AE, adverse event.

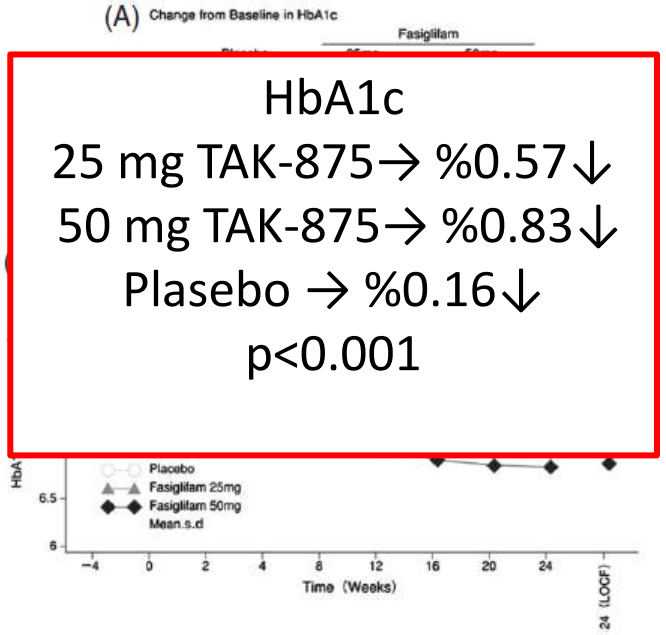
Kaku et al., Diabetes Care, 2013

Efficacy and safety of fasiglifam (TAK-875), a G protein-coupled receptor 40 agonist, in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial

K Kaku,[1] K Enya,[2] R Nakaya,[2] T Ohira,[2] and R Matsuno[2]

- Faz 3 multisenter, çift-kör, plasebo kontrollü
- Diyet/egzersiz ile kontrol sağlanamayan Tip 2 DM
- N: 192
- N: 63→ 25 mg TAK-875
- N: 62→ 50 mg TAK-875
- N: 67→ Plasebo
- 24 haftalık takip

HbA1c



HbA1c
25 mg TAK-875→ %0.57↓
50 mg TAK-875→ %0.83↓
Plasebo → %0.16↓
p<0.001

Figure 2. Change in glycated haemoglobin (HbA1c; %). (A) Primary end-

APG

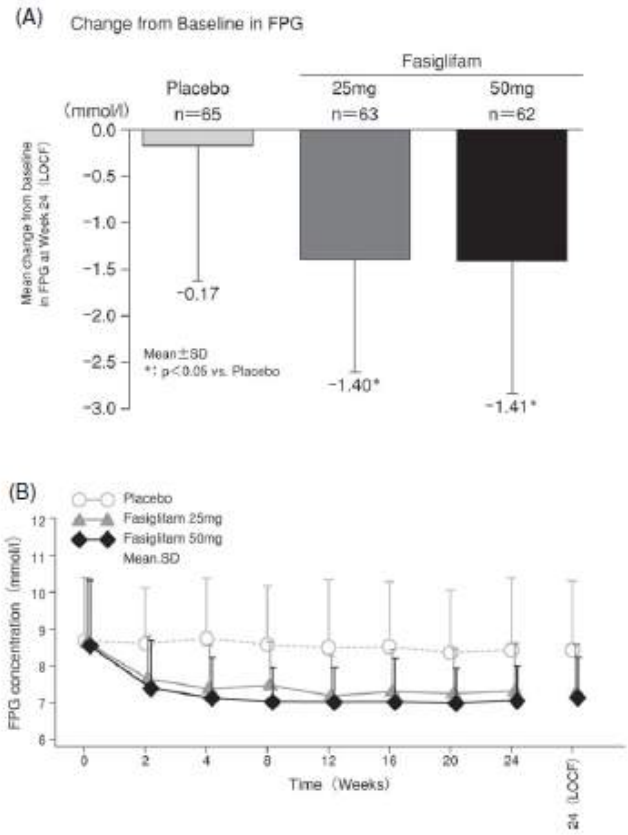


Figure 3. Change in fasting plasma glucose (FPG, mmol/l). (A)

Kaku et al., DOM, 2015

Efficacy and safety of fasiglifam (TAK-875), a G protein-coupled receptor 40 agonist, in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial

K Kaku,[1] K Enya,[2] R Nakaya,[2] T Ohira,[2] and R Matsuno[2]

- Yan etki profili plasebo ile benzer
- TAK-875→1 kişide hipoglisemi
- Kilo alımı↔
- ALT≥3X yükselme TAK-875 grubunda hf yüksek (n: 7 vs. 1)
- ALT≥5X fark yok (n: 1 vs. 1)
- 1 hastada 25 mg TAK-875 mg alan hastada ilaç ilişkili ciddi hepatik fonksiyonlarda bozulma

Table 2. Summary of treatment-emergent adverse events.

		Fasiglifam, n (%)	
	Placebo, n (%)	25 mg	50 mg
Number of participants	67	63	62
Patients with any TEAEs	40 (59.7)	37 (58.7)	35 (56.5)
Patients with any TEAEs: mild	35 (52.2)	31 (49.2)	35 (56.5)
Patients with any TEAEs: moderate	5 (7.5)	6 (9.5)	0
Patients with any TEAEs: severe	0	0	0
Patients with any treatment-related TEAEs	4 (6.0)	4 (6.3)	9 (14.5)
Patients with any TEAEs leading to drug discontinuation	3 (4.5)	2 (3.2)	1 (1.6)
Patients with any treatment-emergent serious AEs	1 (1.5)	2 (3.2)	0
Deaths	0	0	0
Patients with any TEAEs and a frequency of at least 5% in any group			
Nasopharyngitis	11 (16.4)	11 (17.5)	9 (14.5)
Upper respiratory tract inflammation	1 (1.5)	5 (7.9)	5 (8.1)
Patients with any treatment-related TEAEs			
Lymphadenopathy	1 (1.5)	0	0
Constipation	1 (1.5)	0	0
Feeling abnormal	0	0	1 (1.6)
Hepatic function abnormal	0	1 (1.6)	1 (1.6)
Cholelithiasis	0	0	1 (1.6)
Bronchitis	0	0	1 (1.6)
Increased alanine aminotransferase	0	1 (1.6)	3 (4.8)
Increased aspartate aminotransferase	0	1 (1.6)	0
Blood creatine phosphokinase increased	0	1 (1.6)	0

TEAEs are listed in order of severity. Each participant was counted only once by maximum severity of Preferred Term or System Organ Class. AE, adverse event; TEAE, treatment-emergent AE.

Kaku et al., DOM, 2015

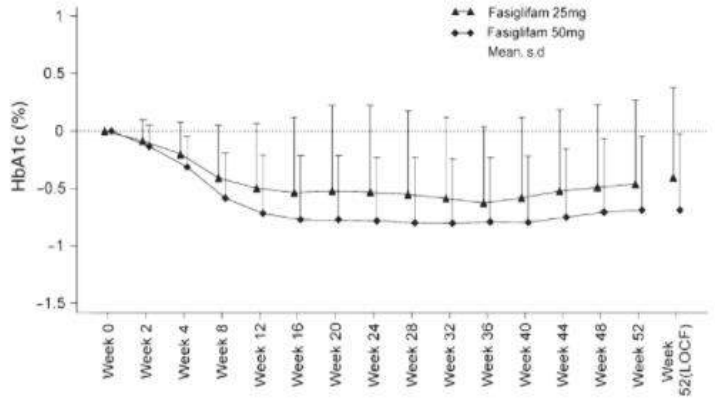
Clinical Trial > Diabetes Obes Metab. 2016 Sep;18(9):925-9. doi: 10.1111/dom.12693. Epub 2016 Jun 29.

Long-term safety and efficacy of fasiglifam (TAK-875), a G-protein-coupled receptor 40 agonist, as monotherapy and combination therapy in Japanese patients with type 2 diabetes: a 52-week open-label phase III study

K Kaku [1], K Enya [2], R Nakaya [2], T Ohira [2], R Matsuno [2]

- Faz 3 multisenter, çift-kör, plasebo kontrollü
- Diyet/egzersiz ile kontrol sağlanamayan ve en az 10 haftadır bir OAD alan Tip 2 DM
- 262 SU, 124 hızlı etkili insülin sekretagog, 141 α-glukosidaz inhibitörü, 136 biguanid, 139 TZD, 138 DPP4 inhibitörü
- N: 282 → 25/50mg Fasiglifam
- N: 261→ SU+ 25/50mg Fasiglifam

- N: 124→ IS+ Fasiglifam
- N: 124→ α-glukosidaz inhibitörü + Fasiglifam
- N: 136→ Biguanid + Fasiglifam
- N: 138→ TZD + Fasiglifam
- N: 138→ DPP4 inhibitörü + Fasiglifam
- 52 haftalık takip



HbA1c
25 mg TAK-875→ %0.42-0.83↓
50 mg TAK-875→ %0.67-1.11↓

Kaku et al., DOM, 2016

Clinical Trial > Diabetes Obes Metab. 2016 Sep;18(9):925-9. doi: 10.1111/dom.12693. Epub 2016 Jun 29.

Long-term safety and efficacy of fasiglifam (TAK-875), a G-protein-coupled receptor 40 agonist, as monotherapy and combination therapy in Japanese patients with type 2 diabetes: a 52-week open-label phase III study

K Kaku [1], K Enya [2], R Nakaya [2], T Ohira [2], R Matsuno [2]

52 hafta sonunda HbA1c<6.9%

- 25 mg fasiglifam →%32.6
- 50 mg fasiglifam →%40.4
- 25 mg fasiglifam+SU →%24
- 50 mg fasiglifam+SU →%22.1
- 25 mg fasiglifam+İS →%27.4
- 50 mg fasiglifam+İS →%30

52 hafta sonunda HbA1c<6.9%

- 25 mg fasiglifam+ α-glukosidaz inhibitörü →%22.9
- 50 mg fasiglifam+ α-glukosidaz inhibitörü →%35.2
- 25 mg fasiglifam+biguanid →%42.6
- 50 mg fasiglifam+biguanid →%52.9
- 25 mg fasiglifam+TZD→%31.9
- 50 mg fasiglifam+TZD →%42
- 25 mg fasiglifam+DPP4-I→%26.9
- 50 mg fasiglifam+DPP4-I→%45.6

Kaku et al., DOM, 2016

Table 1. Summary of treatment-emergent adverse events in the safety analysis set[a].

	Fasiglifam monotherapy		Fasiglifam combination therapy							
							Thiazolidine-dione		+ DPP-IV inhibitor	
	25 mg	50 mg	25				mg	50 mg	25 mg	50 mg
Number of patients	141	141	129					69	69	69
Number of events	449	443	397				5	204	164	191
Patients with any TEAE, n (%)	120 (85.1)	114 (80.9)	107 (82				.1)	62 (89.9)	52 (75.4)	58 (84.1)
Mild, n (%)	104 (73.8)	95 (67.4)	97 (75				.0)	53 (76.8)	44 (63.8)	51 (73.9)
Moderate, n (%)	14 (9.9)	17 (12.1)	8 (				7.2)	8 (11.6)	8 (11.6)	7 (10.1)
Severe, n (%)	2 (1.4)	2 (1.4)	2 (				5.8)	1 (1.4)	0 (0.0)	0 (0.0)
Patients with treatment-related TEAE, n (%)	12 (8.5)	11 (7.8)	18 (14				7.2)	8 (11.6)	3 (4.3)	9 (13.0)
TEAE leading to drug discontinuation, n (%)	13 (9.2)	8 (5.7)	5 (				8.7)	2 (2.9)	6 (8.7)	2 (2.9)
Serious TEAE, n (%)	10 (7.1)	10 (7.1)	9 (				10.1)	4 (5.8)	5 (7.2)	2 (2.9)
Deaths, n (%)	0	0	0				1.4%)	0	0	0
Hepatic function abnormal, n (%)	2 (1.4)	1 (0.7)	2 (					1 (1.4)	4 (5.8)	2 (2.9)
TEAEs reported at a frequency of at least 10% in any										
Nasopharyngitis	53 (37.6)	47 (33.3)	43 (33				7.5)	21 (30.4)	26 (37.7)	32 (46.4)
Fall	7 (5.0)	4 (2.8)	4 (				7.2)	8 (11.6)	2 (2.9)	1 (1.4)
Hypoglycaemia	1 (0.7)	3 (2.1)	16 (12				4.3)	3 (4.3)	0	0
Arthralgia	2 (1.4)	7 (5.0)	7 (				4.3)	2 (2.9)	3 (4.3)	2 (2.9)
Upper respiratory tract inflammation	6 (4.3)	9 (6.4)	8 (				10.1)	6 (8.7)	3 (4.3)	2 (2.9)

DPP-IV, dipeptidyl peptidase-IV; TEAE, treatment-emergent adverse event.

[a] All patients who received at least one dose of study medication during the treatment period (n=1220).

Ciddi yan etki

25 mg fasiglifam →%7.1 (2.9–10.1)

50 mg fasiglifam →%5.9 (2.9–8.5)

ALT >3xULN

25 mg fasiglifam →% 1.6 (10/608)

50 mg fasiglifam →% 2.9 (18/612)

ALT>5× ULN

25 mg fasiglifam →% 0.2 (1/608)

50 mg fasiglifam →% 0.8 (5/612)

Hipoglisemi

25 mg fasiglifam →% 0.7

50 mg fasiglifam →% 2.1

25 mg fasiglifam+SU →% 12.4

50 mg fasiglifam+SU →% 9.1

Kaku et al., DOM, 2016

Randomized Controlled Trial > Drug Saf. 2018 Jun;41(6):625-640.
doi: 10.1007/s40264-018-0642-6.

Liver Safety of Fasiglifam (TAK-875) in Patients with Type 2 Diabetes: Review of the Global Clinical Trial Experience

John F Marcinak [1], Melvin S Munsaka [2], Paul B Watkins [3], Takashi Ohira [4], Neila Smith [2]

- 15 çift kör çalışma
- 9139 Tip 2 dm hastası
- N: 5350 → Fasiglifam
- N: 123→Fasiglifam +Sitagliptin
- N: 3657 →Plasebo+ Diğer antidiyabetik ajanlar
- Fasiglifam'ın KC üzerindeki güvenliği

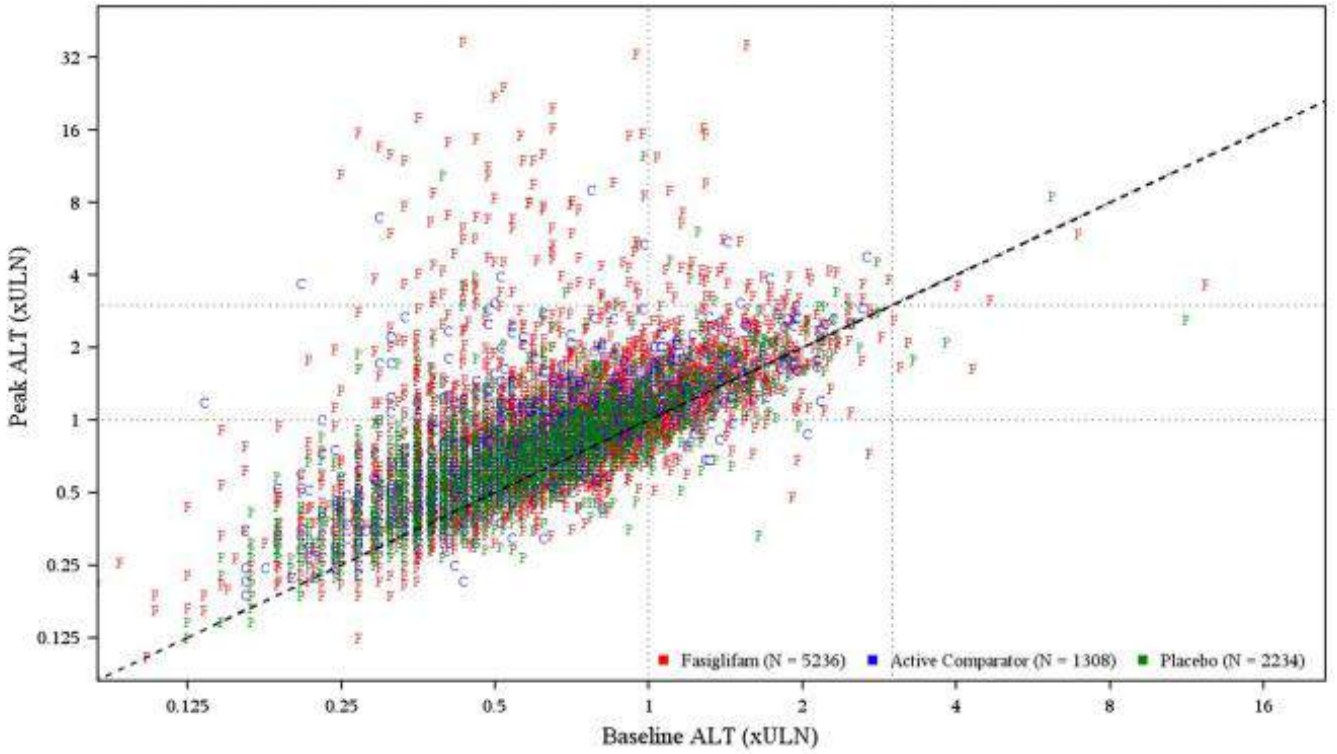


Fig. 3 Shifts from baseline, color coded by treatment group. *ALT* alanine aminotransferase, *ULN* upper limit of normal

Marcinak et al., Drug Saf, 2018

- ALT ≥3 ULN
  - Fasiglifam %2.7
  - Diğer antidiyabetik %0.8
  - Plasebo %0.5
- Fasiglifam 25-50 mg arasında fark yok
- ALT ≥3 ULN ilk 6 ayda belirgin
- Predispozan faktör: -
- İlaç kesildiğinde KCFT'de düzelme
- 3 hastada ilaca bağlı ciddi KC hasarı

Table 2 Liver test elevations for fasiglifam 25 and 50 mg doses, placebo, and active comparators

	Placebo [$N = 2336$] (%)	Fasiglifam				Active comparator [$N = 1321$] (%)
		25 mg [$N = 1637$] (%)	50 mg [$N = 3300$] (%)	25/50 mg [$N = 4937$] (%)	Total [$N = 5359$] (%)	
ALT > 3 × ULN	12/2234 (0.5)	45/1624 (2.8)	89/3195 (2.8)	134/4819 (2.8)	140/5236 (2.7)	10/1308 (0.8)
ALT > 5 × ULN	4/2234 (0.2)	17/1624 (1.0)	43/3195 (1.3)	60/4819 (1.2)	63/5236 (1.2)	4/1308 (0.3)
ALT > 10 × ULN	2/2234 (0.1)	6/1624 (0.4)	19/3195 (0.6)	25/4819 (0.5)	26/5236 (0.5)	0/1308
ALT > 3 × ULN, and TBIL > 2 × ULN	1/2234 (< 0.1)	2/1624 (0.1)	4/3195 (0.1)	6/4819 (0.1)	6/5236 (0.1)	2/1308 (0.2)
AST > 3 × ULN	9/2234 (0.4)	23/1624 (1.4)	53/3194 (1.7)	76/4818 (1.6)	79/5235 (1.5)	7/1307 (0.5)
AST > 5 × ULN	4/2234 (0.2)	7/1624 (0.4)	28/3194 (0.9)	35/4818 (0.7)	36/5235 (0.7)	3/1307 (0.2)
AST > 10 × ULN	1/2234 (< 0.1)	3/1624 (0.2)	11/3194 (0.3)	14/4818 (0.3)	15/5235 (0.3)	1/1307 (0.1)
AST > 3 × ULN, and TBIL > 2 × ULN	1/2234 (< 0.1)	1/1624 (0.1)	4/3194 (0.1)	5/4818 (0.1)	5/5235 (0.1)	1/1307 (0.1)
ALT or AST > 3 × ULN, and TBIL > 2 × ULN	1/2234 (< 0.1)	2/1624 (0.1)	5/3195 (0.2)	7/4819 (0.1)	7/5236 (0.1)	2/1308 (0.2)

ALT alanine aminotransferase, *ULN* upper limit of normal, *TBIL* total bilirubin, *AST* aspartate aminotransferase

Marcinak et al., Drug Saf, 2018

Takeda Announces Termination of Fasiglifam (TAK-875) Development

Category: Small Molecules | Published on Friday, 27 December 2013 08:43 | Hits: 1267

OSAKA, Japan I December 27, 2013 I Takeda Pharmaceutical Company Limited (Takeda) announced today that it has decided voluntarily to terminate the development activities for fasiglifam (TAK-875), an investigational treatment for type 2 diabetes, due to concerns about liver safety.

Patient safety is Takeda's highest priority. The company has worked with three independent panels of experts to provide for the safety of trial participants and ensure independent safety oversight for the clinical trials throughout the duration of the fasiglifam (TAK-875) Phase 3 development program.

The expert panels include the independent Data Monitoring Committee (DMC), a committee that oversees the fasiglifam global clinical development program, reviews the unblinded clinical data from program trials and provides continual safety oversight of trial subjects and recommendations. The DMC is comprised of clinical experts in endocrinology, cardiology and hepatology as well as a statistician. The independent Liver Safety Evaluation Committee (LSEC) is comprised of five hepatologists with expertise in drug-induced liver injury. While remaining blinded to treatment information, the LSEC regularly evaluates data on liver enzymes elevations and adjudicates cases that impacted the liver. In addition, an independent Executive Committee (EC) provides additional oversight for the fasiglifam (TAK-875) cardiovascular outcomes trial.

After careful consideration of the data emerging from all the clinical trials and in consultation with these panels, the company has reached the conclusion that, on balance, the benefits of treating patients with fasiglifam (TAK-875) do not outweigh the potential risks. For this reason, Takeda has decided voluntarily to terminate the development activities for fasiglifam.

HWL-088-Compound 7

- Yüksek potent FFAR1 agonisti
- Orta derece PPARδ aktivitesi
- Glukoz bağımlı insülin sekresyonu↑
- TAK-875'ten daha iyi glukoz kontrolü

Bioorg Chem. 2019 Nov;92:103209. doi: 10.1016/j.bioorg.2019.103209. Epub 2019 Aug 16.

Discovery of HWL-088: A highly potent FFA1/GPR40 agonist bearing a phenoxyacetic acid scaffold

Zheng Li [1], Qiang Ren [1], Xuekun Wang [2], Zongtao Zhou [1], Lijun Hu [1], Liming Deng [1], Li Guan [3], Qianqian Qiu [4]

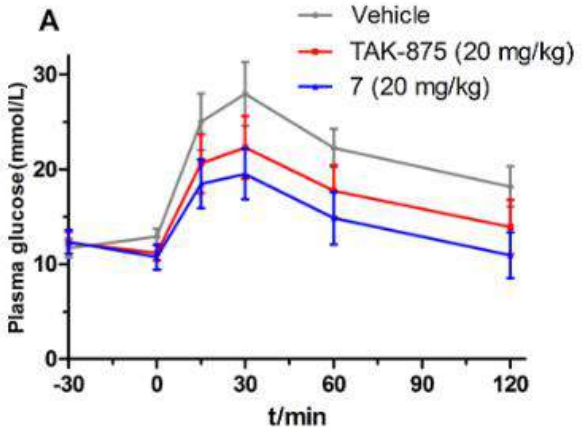
Affiliations + expand

PMID: 31487621 DOI: 10.1016/j.bioorg.2019.103209

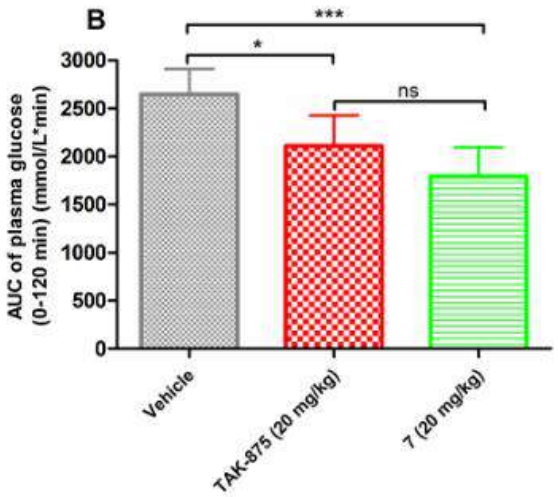
Abstract

Based on a previously reported phenoxyacetic acid scaffold, compound 7 (HWL-088) has been identified as a superior free fatty acid receptor 1 (FFA1) agonist by comprehensive structure-activity relationship study. Our results indicated that the introduction of ortho-fluoro greatly increased the activity of phenoxyacetic acid series, and the unique structure-activity relationship in biphenyl moiety is different from previously reported FFA1 agonists. Moreover, the modeling study was also performed to better understand the binding mode of present series. Compound 7 significantly improved glucose tolerance both in normal and diabetic models, and even exerted greater potential on glucose control than that of TAK-875. These findings provided a novel candidate HWL-088, which is currently in preclinical study to evaluate its potential for the treatment of diabetes.

Glukoz



AUCglukoz



Li et al., Bioorg Chem, 2019

Br J Pharmacol. 2020 May;177(10):2286-2302. doi: 10.1111/bph.14980. Epub 2020 Feb 8.

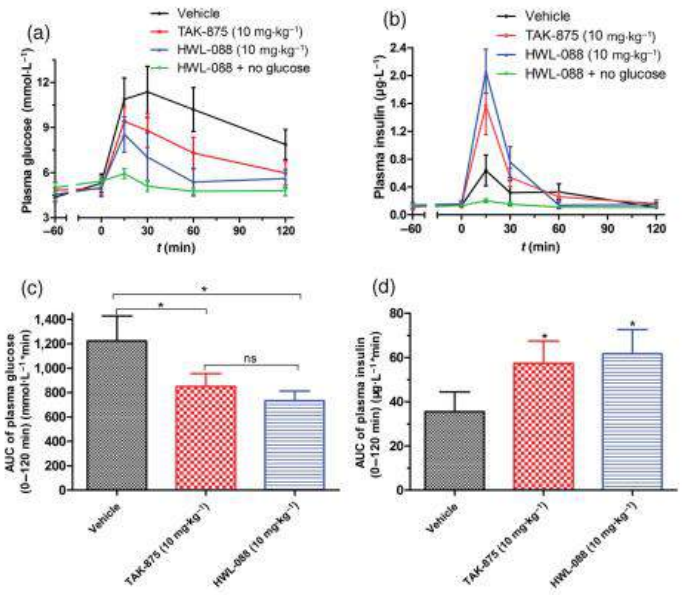
HWL-088, a new potent free fatty acid receptor 1 (FFAR1) agonist, improves glucolipid metabolism and acts additively with metformin in ob/ob diabetic mice

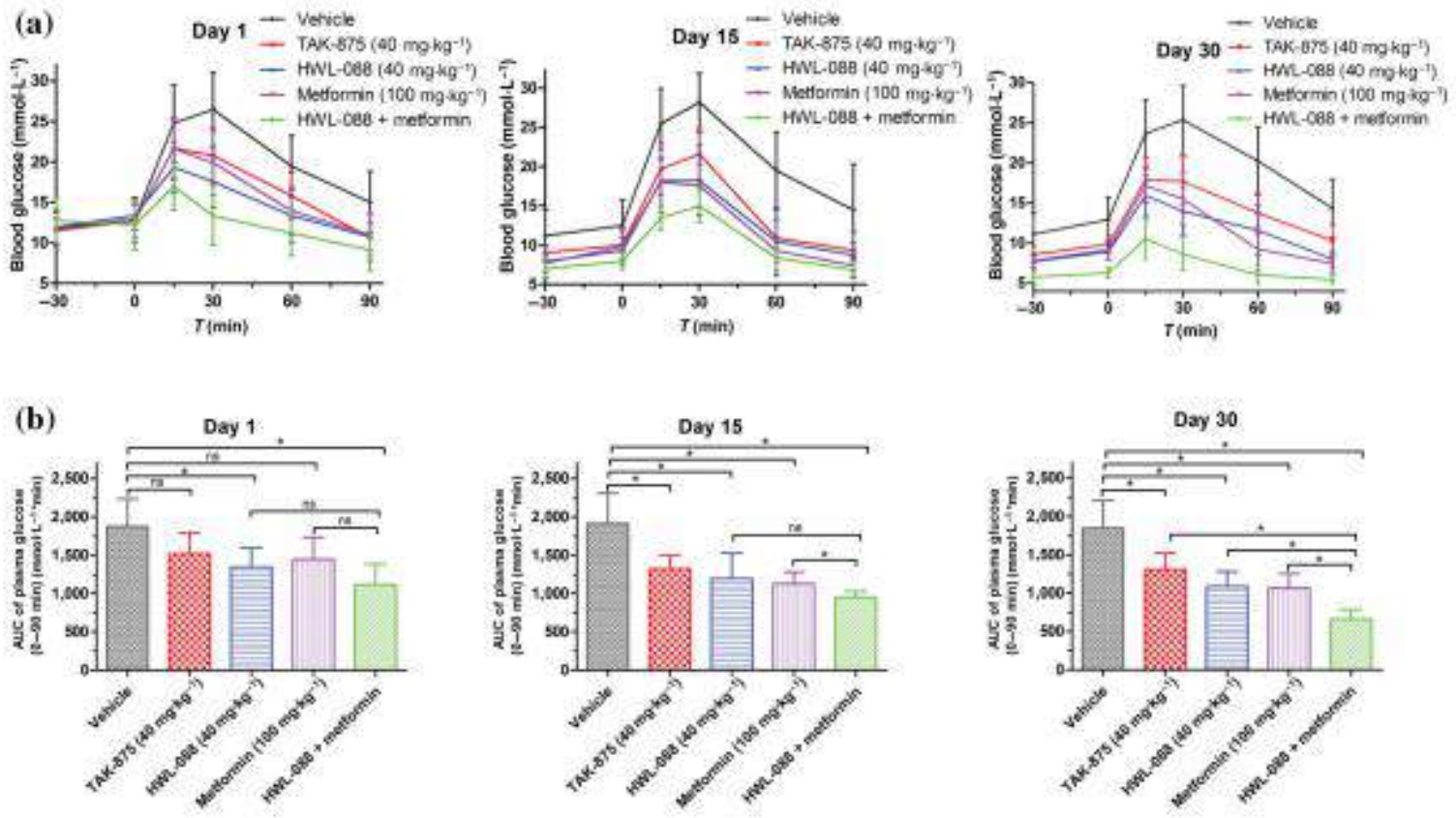
Yueming Chen [1 2], Qiang Ren [1], Zongtao Zhou [1], Liming Deng [1], Lijun Hu [1], Luyong Zhang [1 2 3 4], Zheng Li [1 2]

Glukoz

Glukoz

İnsülin





Li et al., Bioorg Chem, 2019

Br J Pharmacol. 2020 May;177(10):2286-2302. doi: 10.1111/bph.14980. Epub 2020 Feb 8.

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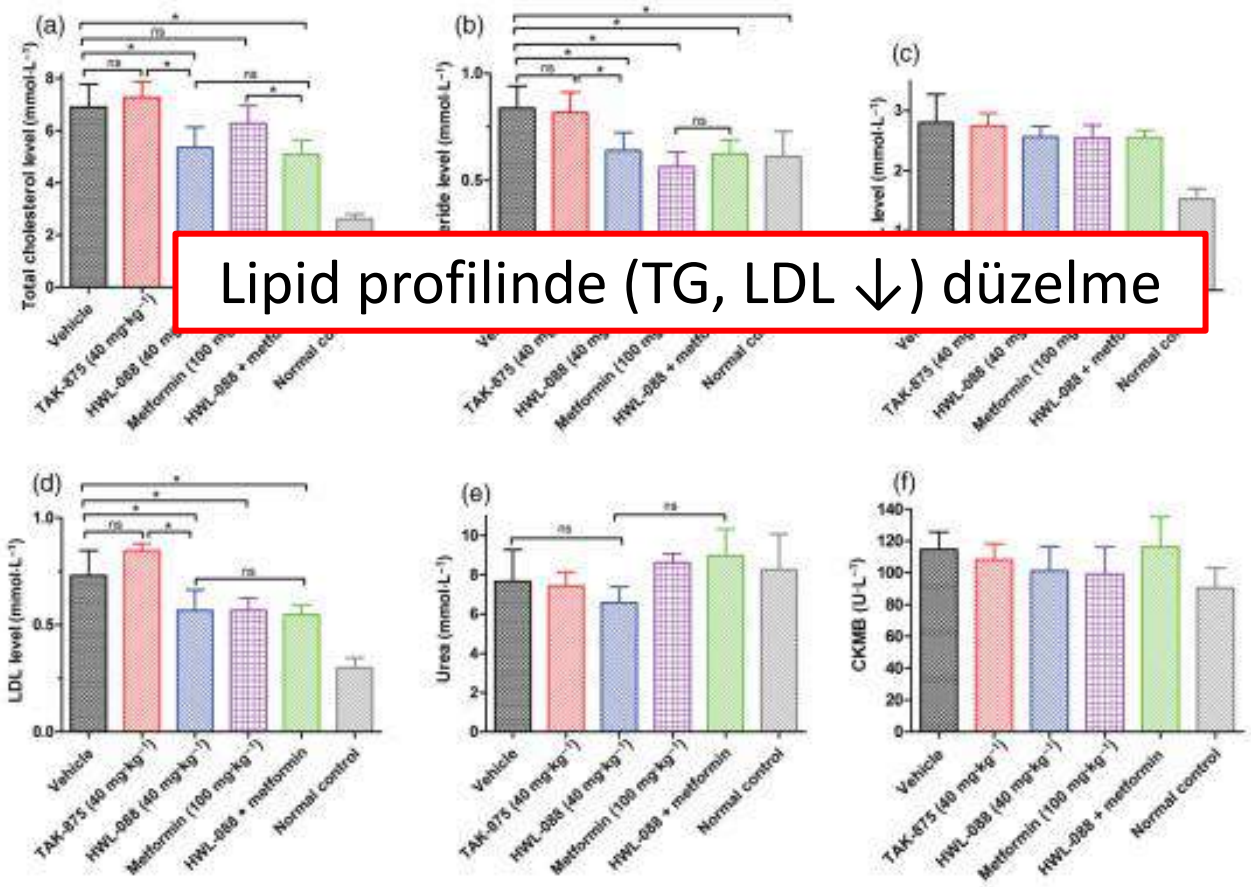
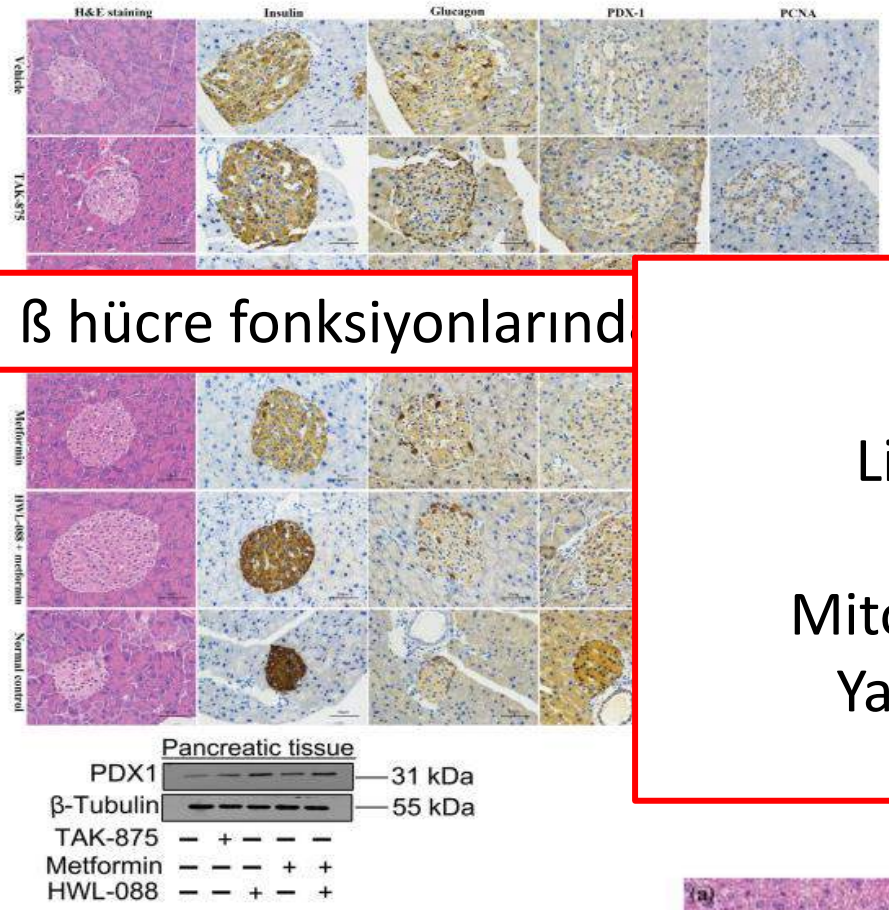
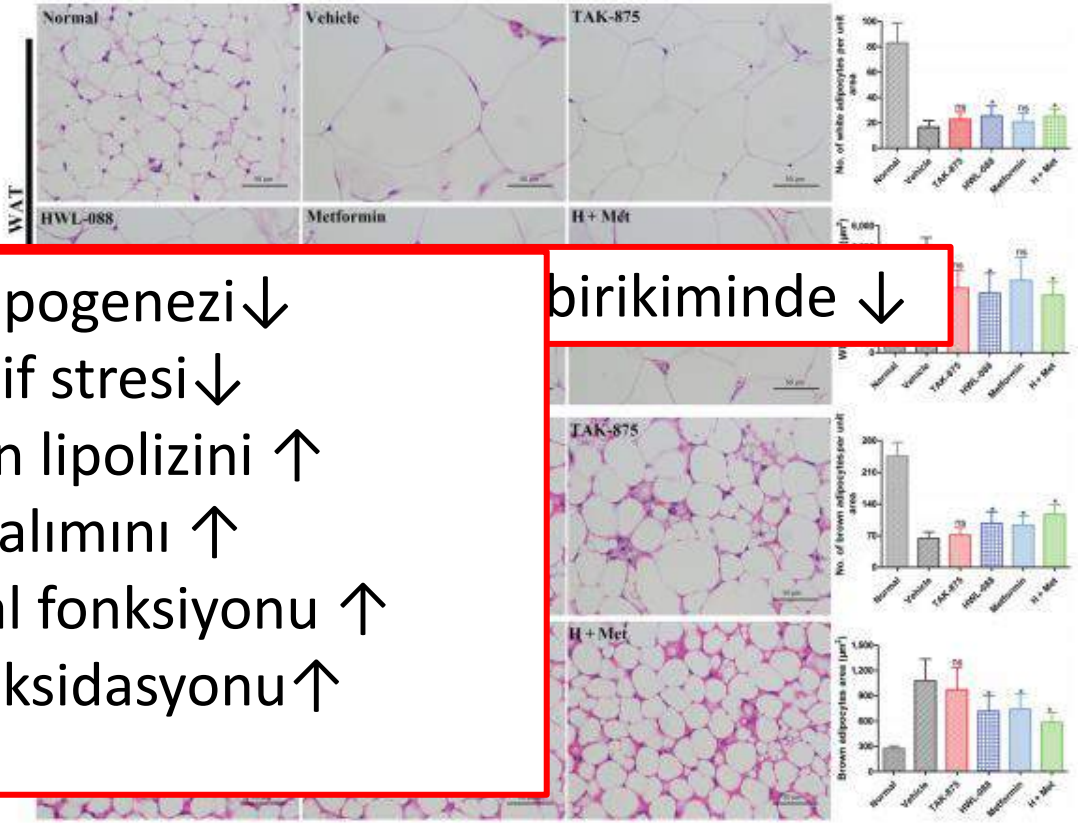


Lipid profilinde (TG, LDL ↓) düzelme

Li et al., Bioorg Chem, 2019



ß hücre fonksiyonlarınd



birikiminde ↓

Hepatik lipogenezi↓
Oksidatif stresi↓
Lipoprotein lipolizini ↑
Glukoz alımını ↑
Mitokondriyal fonksiyonu ↑
Yağ asit ß-oksidasyonu↑

Hepatik yağ birikiminde ↓

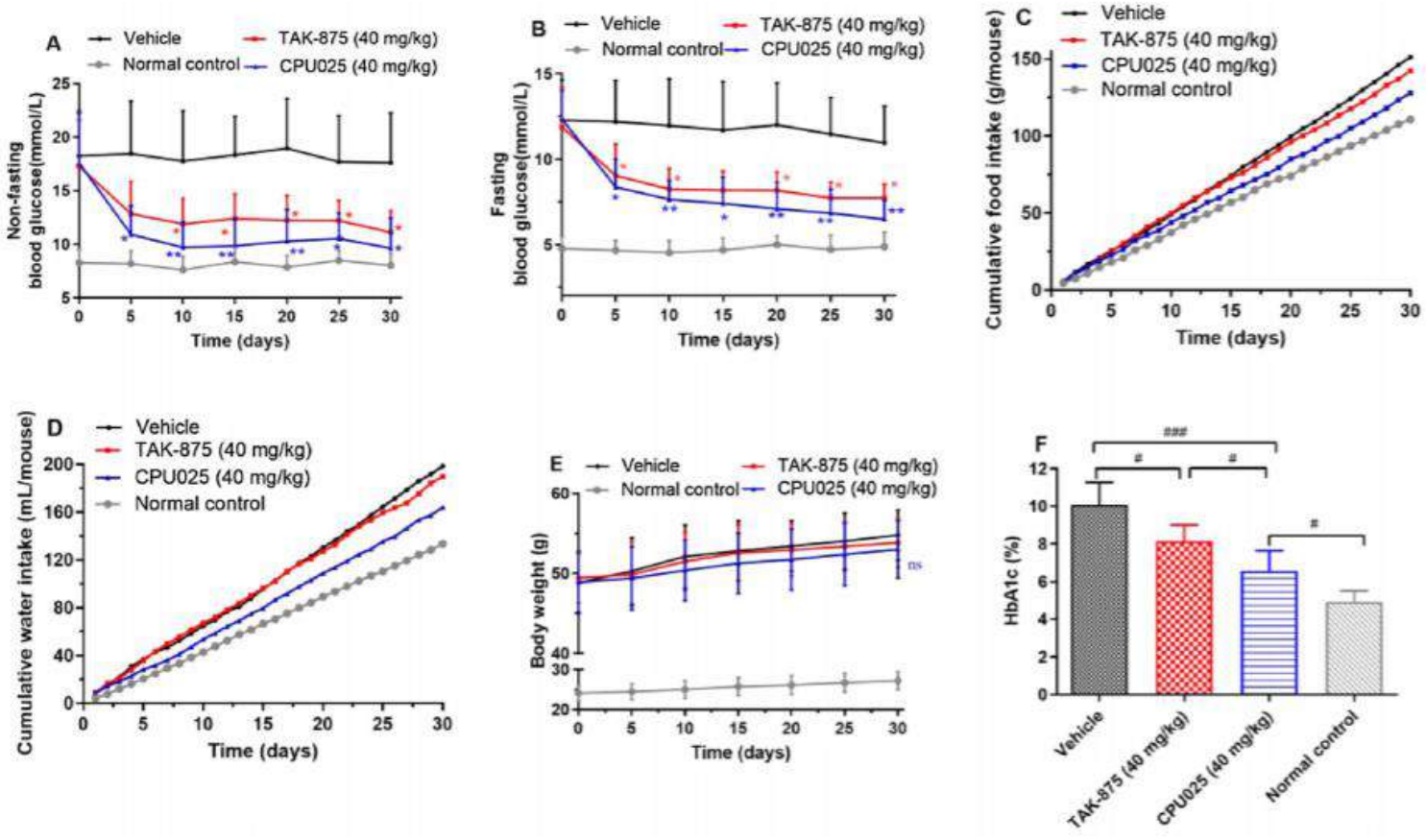
Li et al., Bioorg Chem, 2019

Pharmacol Res. 2020 Mar;153:104679. doi: 10.1016/j.phrs.2020.104679. Epub 2020 Jan 31.

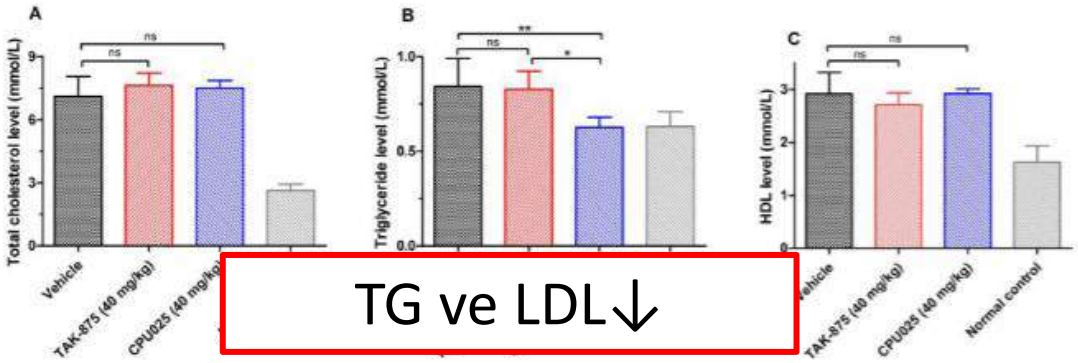
A novel FFA1 agonist, CPU025, improves glucose–lipid metabolism and alleviates fatty liver in obese–diabetic (ob/ob) mice

Zheng Li [1], Chunxia Liu [2], Zongtao Zhou [3], Lijun Hu [3], Liming Deng [3], Qiang Ren [3], Hai Qian [4]

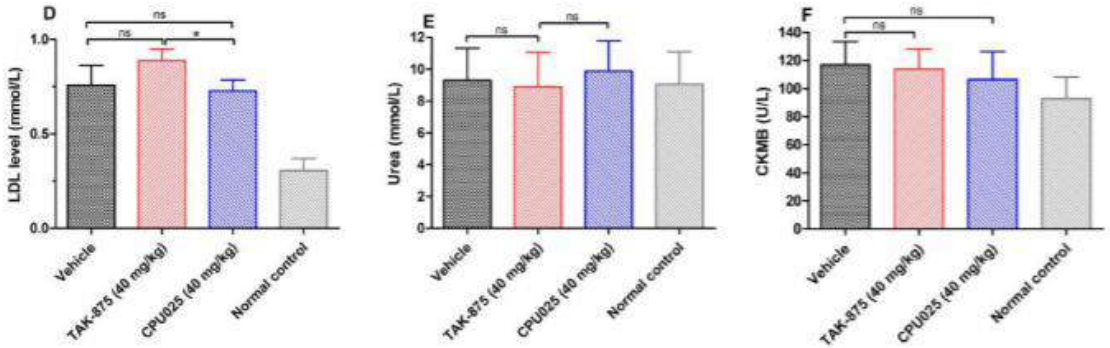
- Yüksek potent FFAR1 agonisti
- Orta derece PPARδ aktivitesi
- Glukoz bağımlı insülin sekresyonu↑
- TAK-875'ten daha iyi glukoz kontrolü

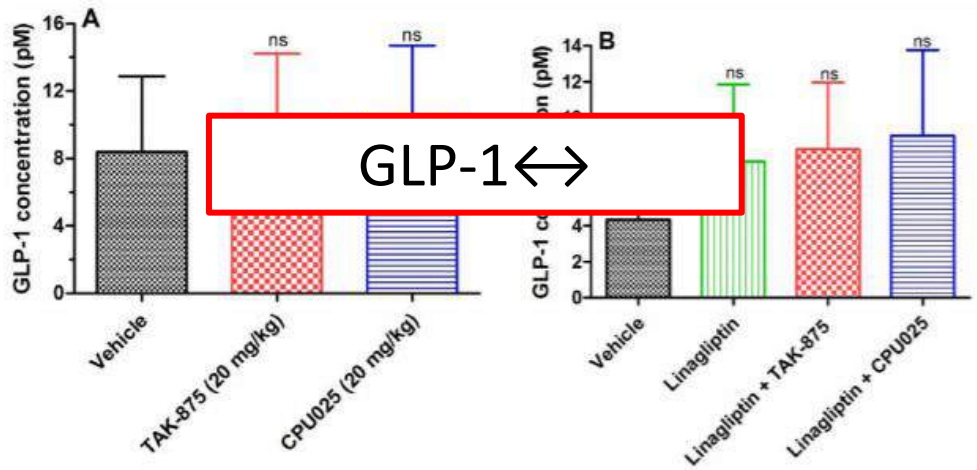


Li et al., Pharmacol Res, 2020

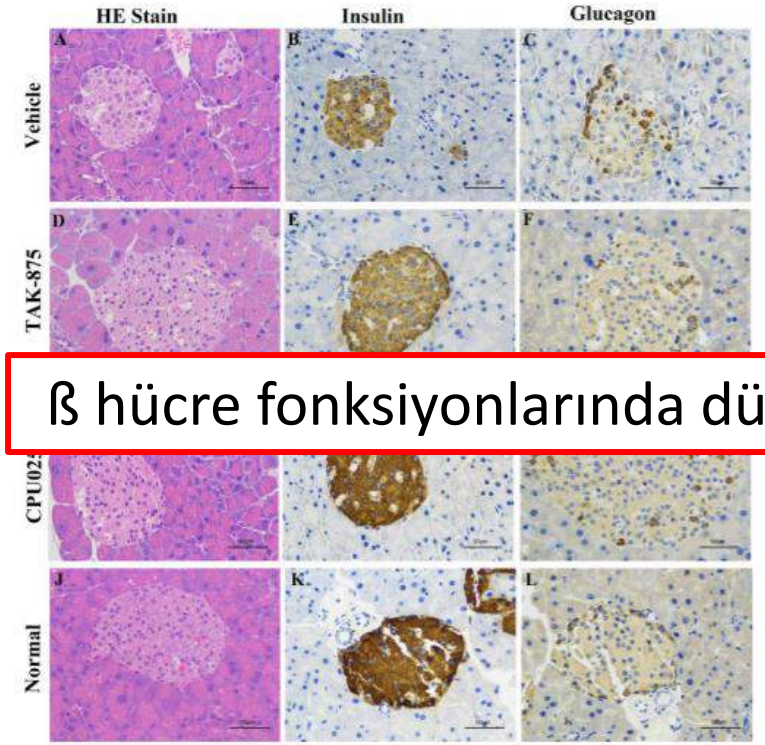


TG ve LDL↓

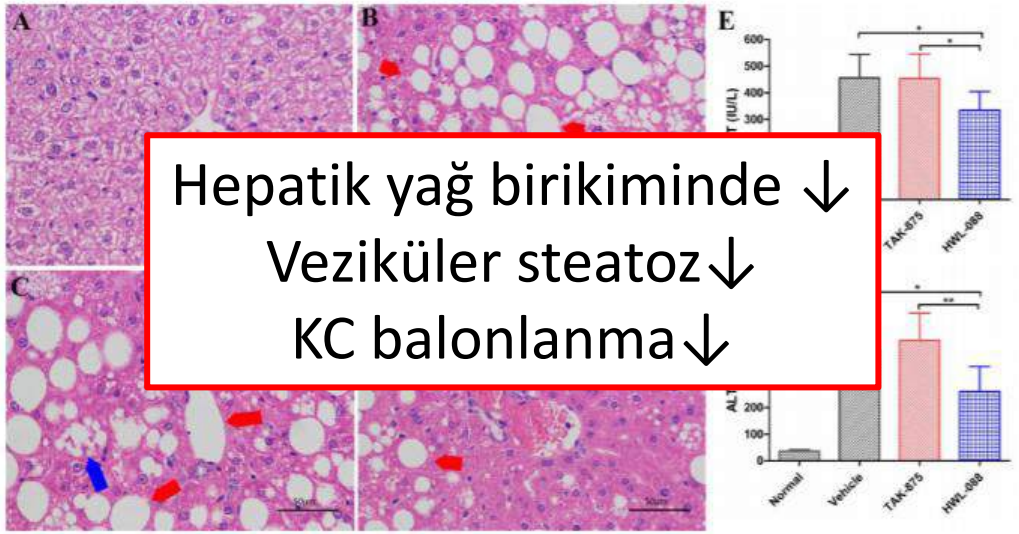




GLP-1↔

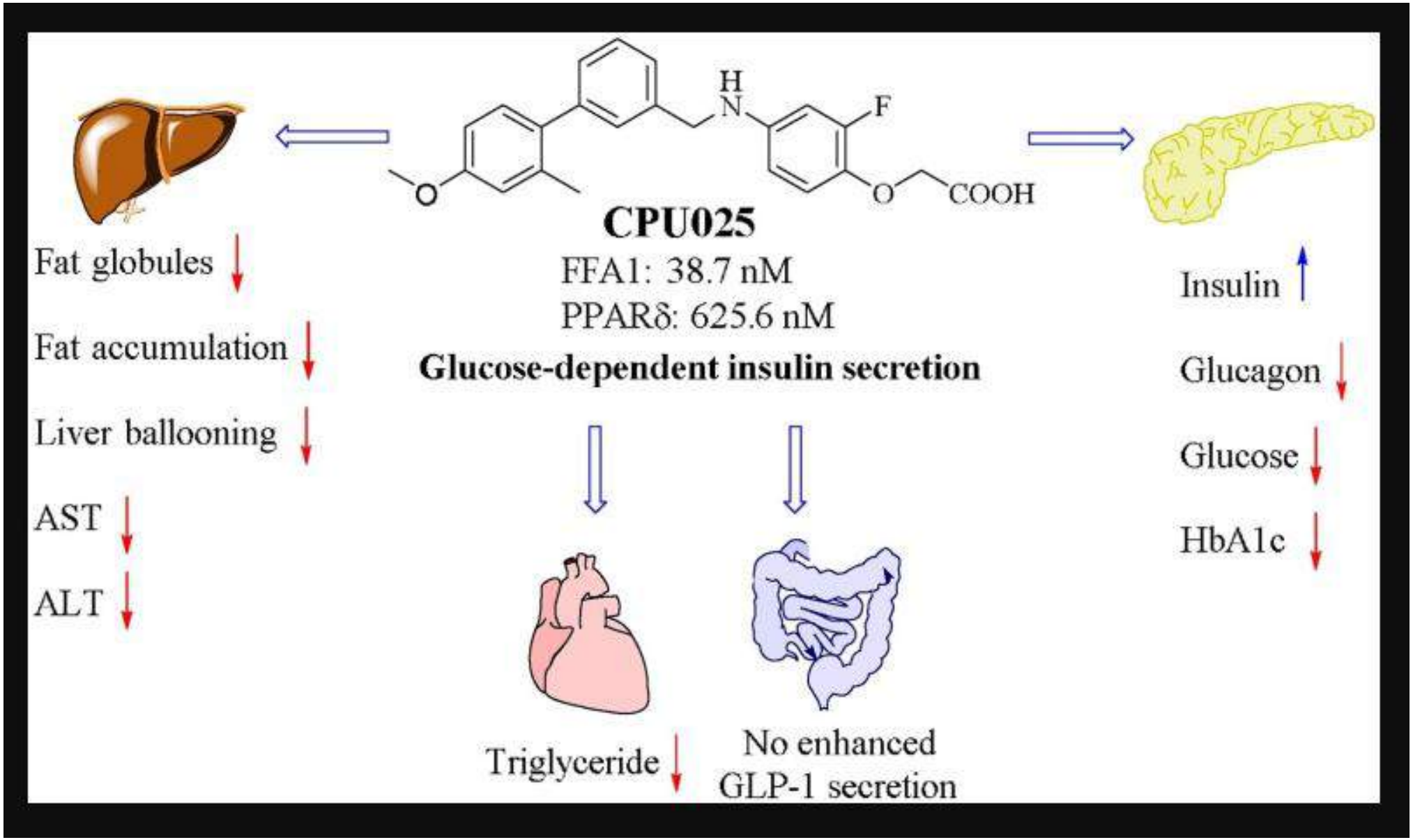


ß hücre fonksiyonlarında düzelme



Hepatik yağ birikiminde ↓
Veziküler steatoz↓
KC balonlanma↓

Li et al., Pharmacol Res, 2020



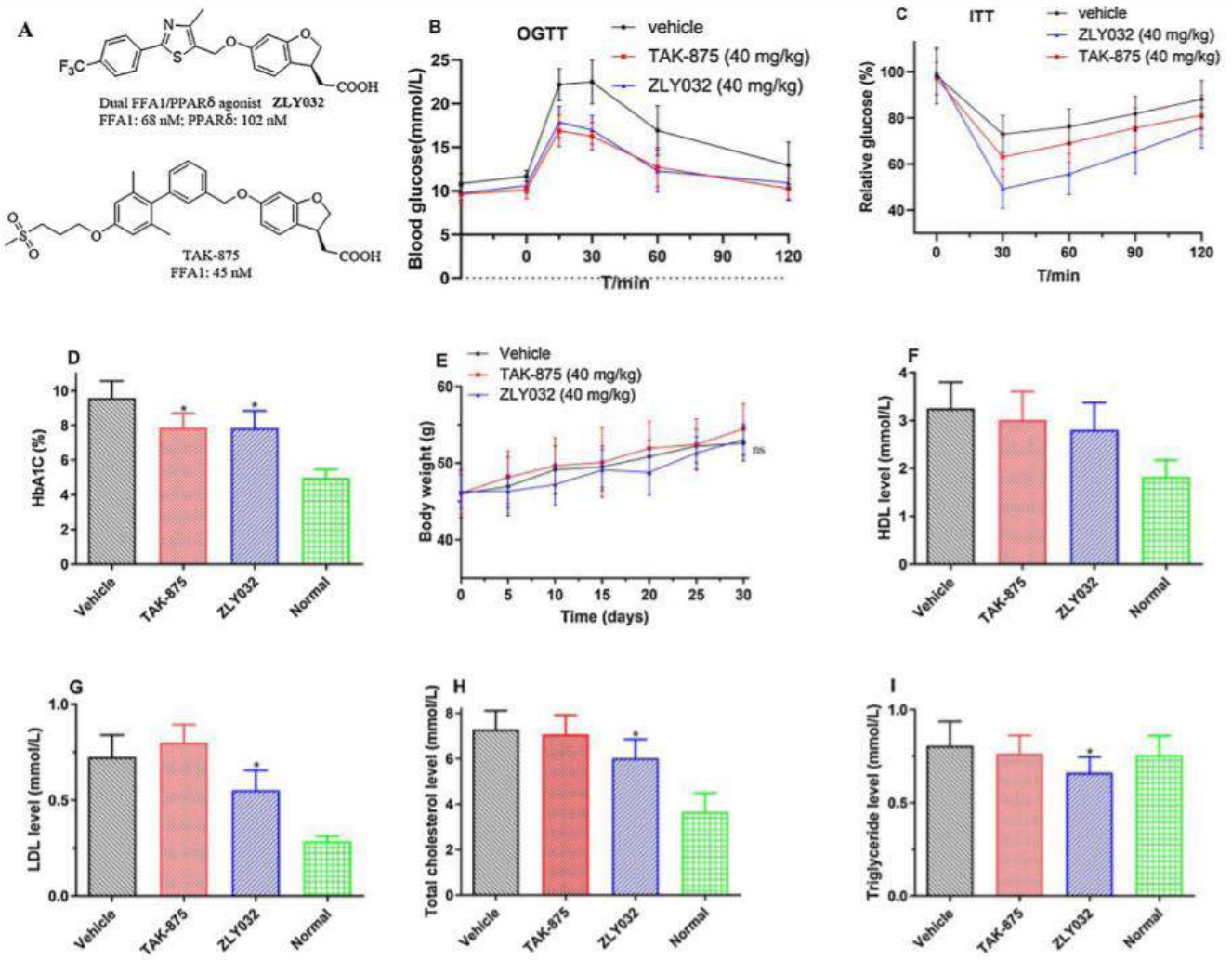
Li et al., Pharmacol Res, 2020

Pharmacol Res. 2020 Sep;159:105035. doi: 10.1016/j.phrs.2020.105035. Epub 2020 Jun 17.

ZLY032, the first-in-class dual FFA1/PPARδ agonist, improves glucolipid metabolism and alleviates hepatic fibrosis

Zheng Li [1], Zongtao Zhou [2], Lijun Hu [2], Liming Deng [2], Qiang Ren [2], Luyong Zhang [3]

- Dual FFAR1/ PPARδ agonisti
- 40 mg/kg
- Daha iyi insülin duyarlılığı (PPARδ agonistik etkisi)
- Kilo ↔
- TG ve LDL↓



Li et al., Pharmacol Res, 2020

Pharmacol Res. 2020 Sep;159:105035. doi: 10.1016/j.phrs.2020.105035. Epub 2020 Jun 17.

ZLY032, the first-in-class dual FFA1/PPARδ agonist, improves glucolipid metabolism and alleviates hepatic fibrosis

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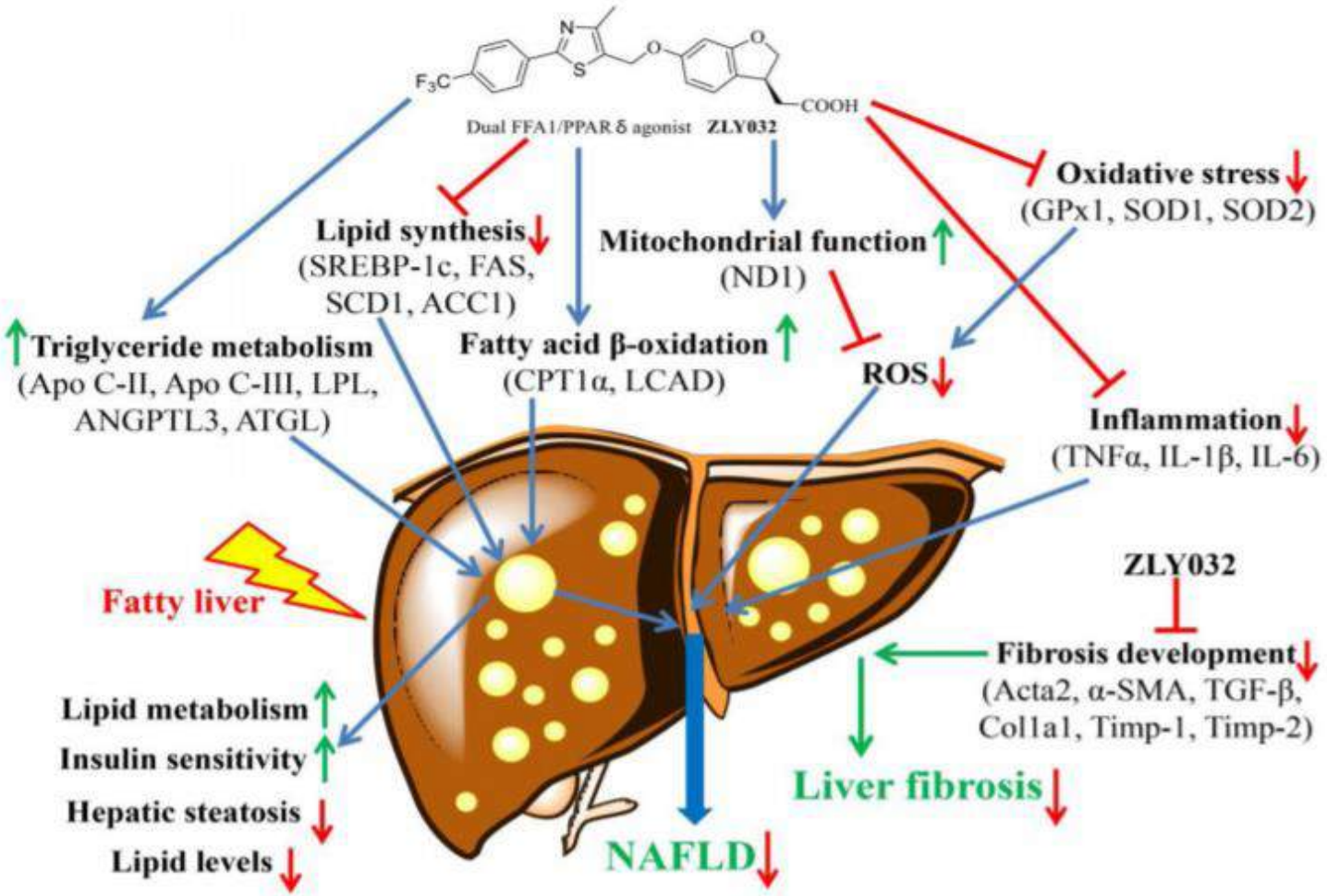


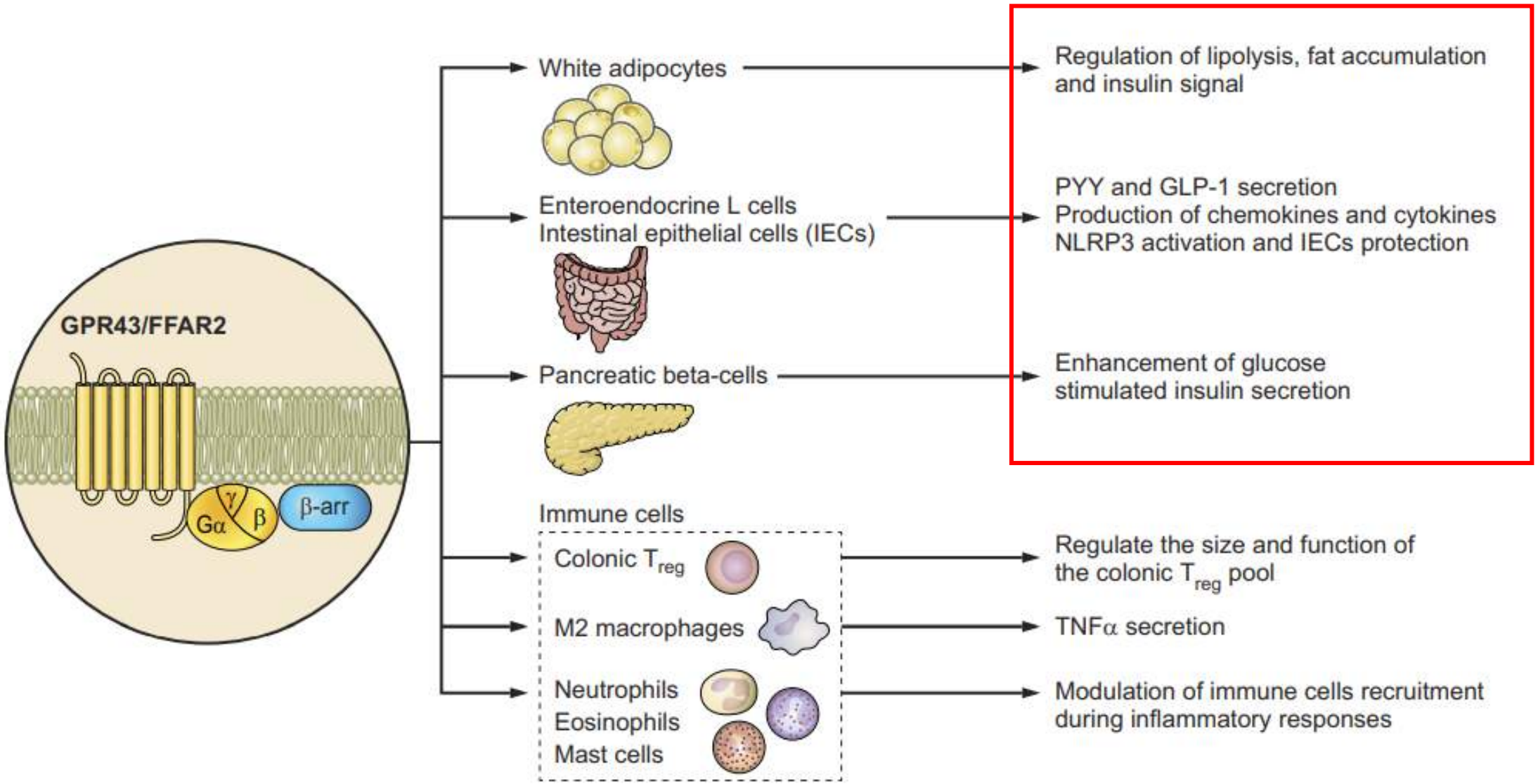
Li et al., Pharmacol Res, 2020

FFAR1 Reseptör Agonistleri

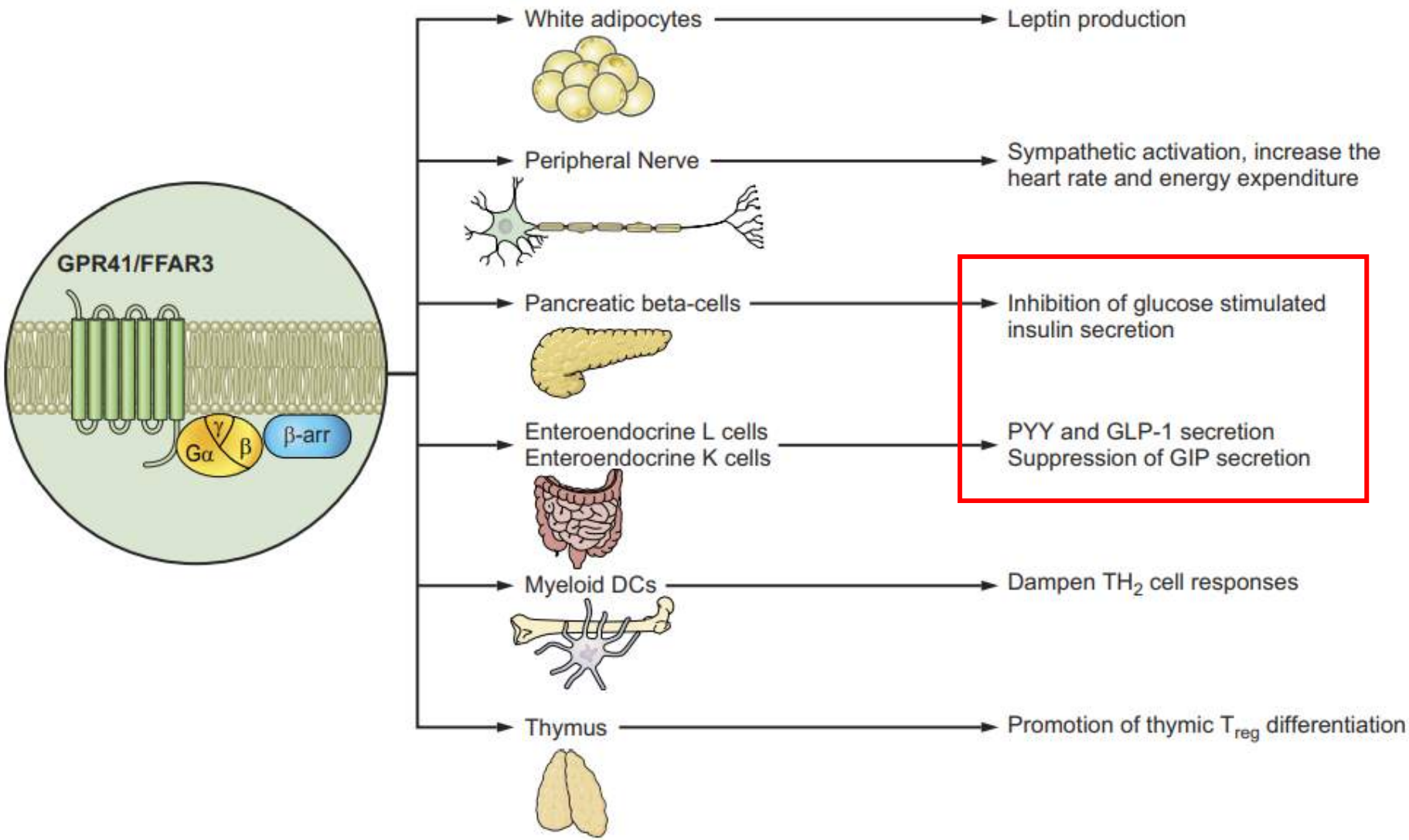
- Yüksek lipofilisite, büyük moleküler boyut
- Kötü metabolik stabilite
- Düşük suda çözünürlük
- Yüksek SSS penetrasyonu
- Hedef dışı toksisite
- Kompleks sinyal yolağı

Medikal tedavi??

FFAR2/GPR43 reseptörü



FFAR3/GPR41 reseptörü



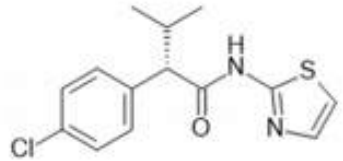
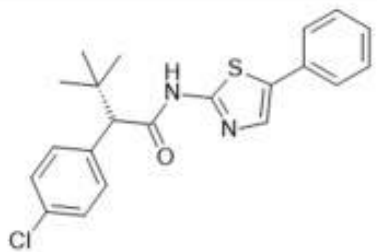
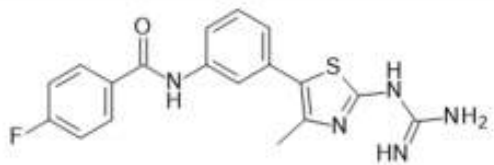
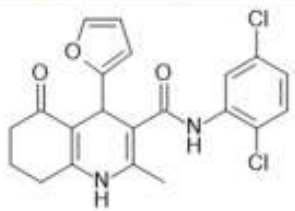
FFAR2 ve 3 Reseptör Agonistleri

Table 4. *Summary of synthetic ligands for FFARs*

Ligands	Action	Half-Maximal Activities, μM	Therapeutic Target
GPR41/FFAR3			
AR420626	Agonist	0.27[i], 0.117[j]	Type 2 diabetes, GLP-1 secretion, ghrelin secretion
Compund 3	Positive allosteric modular agonist	3.47[h]	Inflammatory processes
GPR43/FFAR2			
Compound 1	Orthosteric agonist	0.072[b]	Metabolic and inflammatory conditions
4-CMTB	Ago-allosteric modulator	6.38[h]	Inflammation
CFMB	Allosteric agonist	0.7[j]	Immune and inflammatory responses
Compound 58/PA	Allosteric modulator	0.7[m]	Obesity, insulin resistance, and diabetes
SCA14	Orthosteric agonist	3.2[c]	Hyperglycemia and type 2 diabetes
SCA15	Orthosteric agonist	2.7[c]	Hyperglycemia and type 2 diabetes
AMG-7703	Allosteric agonist	0.45[c]	Inflammation and metabolic disorders
Euroscreen compound series	Orthosteric agonist	0.013–0.06[e]	Inflammatory, gastrointestinal, and/or metabolic disorders
Euroscreen compound series	Antagonist	0.006–0.02[e]	Metabolic disorders and inflammatory diseases
Galapagos compounds	Antagonist	<0.01[c]	Metabolic disorders and inflammatory diseases

FFAR2 ve 3 Reseptör Agonistleri

Table 3. Selection of FFAR2 and FFAR3 allosteric ligands.

Name	Structure	References
FFA2 allosteric agonists		
AMG 7703/4-CMTB		Amgen [88,91,92,105,107]
Compound 58		Amgen [89,141]
AZ1729		AstraZeneca [145]
FFA3 allosteric agonist		
AR420626		Arena Pharmaceuticals [146,147]

Compound 58

- FFAR2 agonisti
- İnsülin salınımı↑
- ß-hücre proliferasyonunu ↑
- ß-hücre gen ekspresyonunu ↑

› Diabetes. 2015 Sep;64(9):3203-17. doi: 10.2337/db14-1938. Epub 2015 May 28.

GPR43 Potentiates β-Cell Function in Obesity

Joanne C McNelis [1], Yun Sok Lee [1], Rafael Mayoral [1], Rik van der Kant [2], Andrew M F Johnson [1], Joshua Wollam [1], Jerrold M Olefsky [3]

Affiliations + expand

PMID: 26023106 PMCID: PMC4542437 DOI: 10.2337/db14-1938

Free PMC article

Abstract

The intestinal microbiome can regulate host energy homeostasis and the development of metabolic disease. Here we identify GPR43, a receptor for bacterially produced short-chain fatty acids (SCFAs), as a modulator of microbiota-host interaction. β-Cell expression of GPR43 and serum levels of acetate, an endogenous SCFA, are increased with a high-fat diet (HFD). HFD-fed GPR43 knockout (KO) mice develop glucose intolerance due to a defect in insulin secretion. In vitro treatment of isolated murine islets, human islets, and Min6 cells with (S)-2-(4-chlorophenyl)-3,3-dimethyl-N-(5-phenylthiazol-2-yl)butanamide (PA), a specific agonist of GPR43, increased intracellular inositol triphosphate and Ca(2+) levels, and potentiated insulin secretion in a GPR43-, Gαq-, and phospholipase C-dependent manner. In addition, KO mice fed an HFD displayed reduced β-cell mass and expression of differentiation genes, and the treatment of Min6 cells with PA increased β-cell proliferation and gene expression. Together these findings identify GPR43 as a potential target for therapeutic intervention.

McNeils et al., Diabetes, 2015

AR420626

- FFAR3 agonisti
- FFAR-3 →CCK, GIP, GLP-1, PYY sekrete eden hücrelerin üzerinde
- FFAR2→ Enterik lökosit üzerinde
- AR420626→ GLP-1↑

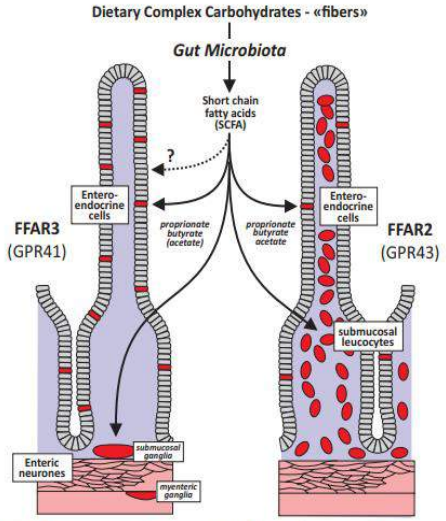


Figure 7. Schematic overview of the expression and function of FFAR3/GPR41 and FFAR2/GPR43 in the intestine based on the analysis of the FFAR3-mRFP and FFAR2-mRFP reporter mice of the present study and information available in the literature. FFAR3 (GPR41) and FFAR2 (GPR43) appear to be coexpressed and cofunction as sensors for SCFAs in the enteroendocrine cells (here indicted in the small intestine), whereas FFAR3 is expressed alone in enteric neurons of both the submucosal and myenteric ganglia and FFAR2 is expressed alone in enteric leukocytes.

GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes

Mark K Nøhr [1], Maria H Pedersen, Andreas Gille, Kristoffer L Egerod, Maja S Engelstoft, Anna Sofie Husted, Rasmus M Sichlau, Kaare V Grunddal, Steen Seier Poulsen, Sangdon Han, Robert M Jones, Stefan Offermanns, Thue W Schwartz

Affiliations + expand

PMID: 23885020 DOI: 10.1210/en.2013-1142

Abstract

The expression of short-chain fatty acid receptors GPR41/FFAR3 and GPR43/ free fatty acid receptor 2 (FFAR2) was studied in the gastrointestinal tract of transgenic monomeric red fluorescent protein (mRFP) reporter mice. In the stomach free fatty acid receptor 3 (FFAR3)-mRFP was expressed in a subpopulation of ghrelin and gastrin cells. In contrast, strong expression of FFAR3-mRFP was observed in all cholecystokinin, glucose-dependent insulinotropic peptide (GIP), and secretin cells of the proximal small intestine and in all glucagon-like peptide-1 (GLP-1), peptide YY, and neurotensin cells of the distal small intestine. Throughout the colon and rectum, FFAR3-mRFP was strongly expressed in the large population of peptide YY and GLP-1 cells and in the neurotensin cells of the proximal colon. A gradient of expression of FFAR3-mRFP was observed in the somatostatin cells from less than 5% in the stomach to more than 95% in the rectum. Substance P-containing enterochromaffin cells displayed a similar gradient of FFAR3-mRFP expression throughout the small intestine. Surprisingly, FFAR3-mRFP was also expressed in the neuronal cells of the submucosal and myenteric ganglia. Quantitative PCR analysis of fluorescence-activated cell sorting (FACS) purified FFAR3-mRFP positive cells confirmed the coexpression with the various peptide hormones as well as key neuronal marker proteins. The FFAR2-mRFP reporter was strongly expressed in a large population of leukocytes in the lamina propria of in particular the small intestine but surprisingly only weakly in a subpopulation of enteroendocrine cells. Nevertheless, synthetic ligands specific for either FFAR3 or FFAR2 each released GLP-1 from colonic crypt cultures and the FFAR2 agonist mobilized intracellular Ca^{2+} in FFAR2 positive enteroendocrine cells. It is concluded that FFAR3-mRFP serves as a useful marker for the majority of enteroendocrine cells of the small and large intestine and that FFAR3 and FFAR2 both act as sensors for short-chain fatty acids in enteroendocrine cells, whereas FFAR3 apparently has this role alone in enteric neurons and FFAR2 in enteric leukocytes.

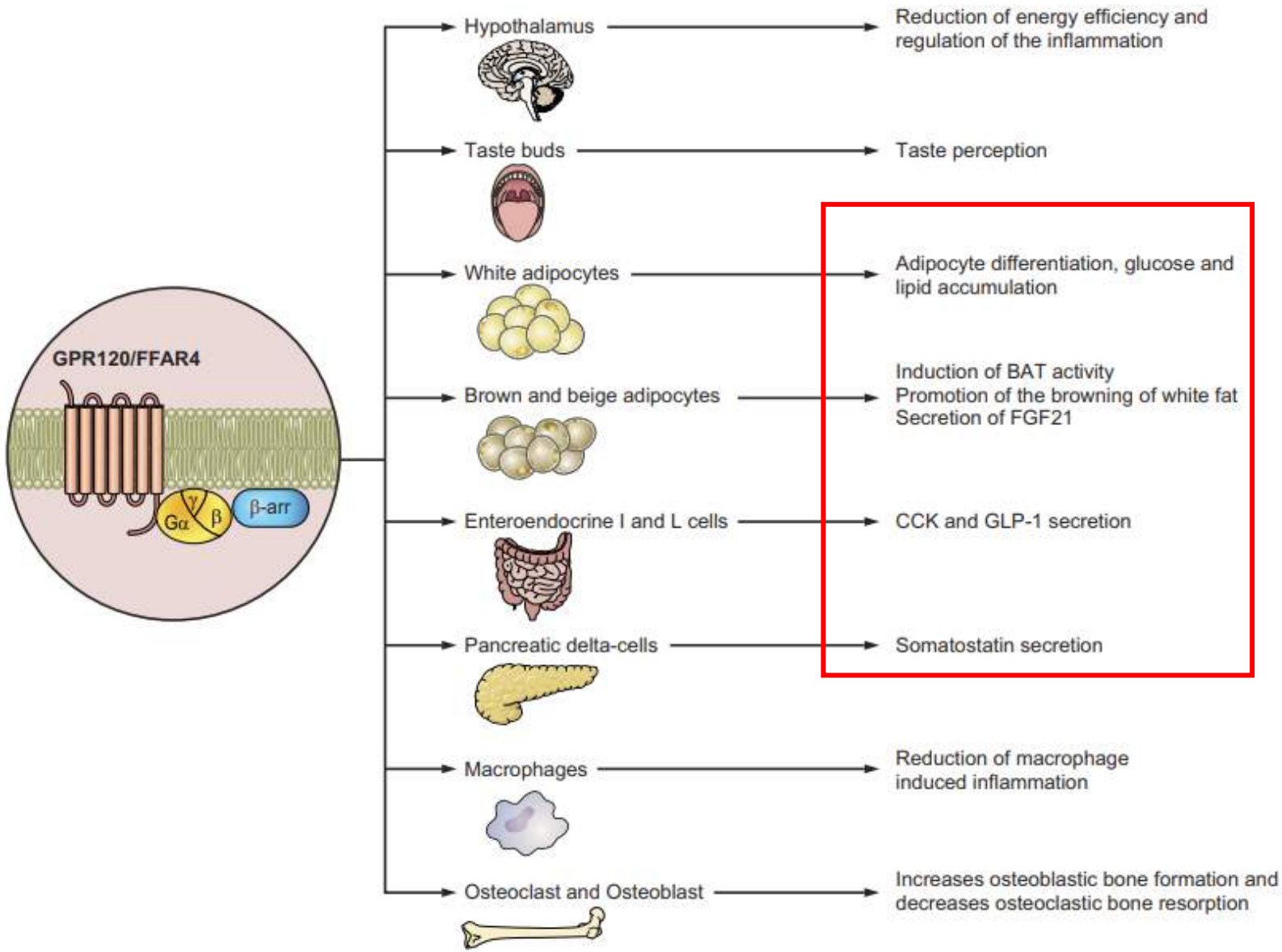
Nohr et al., Endocrinology, 2013

FFAR2 ve 3 Reseptör Agonistleri

- Hidrofobik özellik
- Kompleks farmakolojik özellikler
- Ligand selektivitesinin yetersiz olması
- Selektif ligand azlığı
- Hayvan ve insan reseptör etkinliklerinin farklılık göstermesi

Medikal tedavi??

FFAR4/GPR120 reseptörü



FFAR4 Reseptör Agonistleri

Table 4. *Summary of synthetic ligands for FFARs*

Ligands	Action	Half-Maximal Activities, μM	Therapeutic Target
GPR120/FFAR4			
GW9508	Full agonist	3.5[b]	Type 2 diabetes
GSK137647A	Full agonist	0.5[f]	Mitigating excess food intake and limiting obesity risk
Compound 40	Full agonist	4.8[b]	Type 2 diabetes
NCG21	Agonist	1.3[b]	Type 2 diabetes
Compound 43	Agonist	0.044[g]	Metabolic and inflammatory processes, type 2 diabetes
TUG891	Orthosteric agonist	0.093[b], 0.044–0.065[g]	Metabolic and inflammatory processes, type 2 diabetes and/or obesity
AH-7614	Negative allosteric modulator	0.00751[b]	Type 2 diabetes
cpdA	Agonist	0.024[b], 0.347[g]	Type 2 diabetes and other human insulin-resistant states
Phytosphingosine	Agonist	33.4[k]	Type 2 diabetes
GPU-028	Agonist	0.0631[l]	Type 2 diabetes
Compound 14	Agonist	0.066[g]	Type 2 diabetes

TUG-891

- Farelerde;
- Lipid oksidasyonu↑
- Kilo kaybı sağladığı
- Yağ kitlesini azalttığı
- Kahverengi yağ dokusunu aktive ettiği gösterilmiş

EMBO Mol Med. 2018 Mar;10(3):e8047. doi: 10.15252/emmm.201708047.

The GPR120 agonist TUG-891 promotes metabolic health by stimulating mitochondrial respiration in brown fat

Maaike Schilperoort [1 2 3], Andrea D van Dam [2 3], Geerte Hoeke [2 3], Irina G Shabalina [4], Anthony Okolo [5], Aylin C Hanyaloglu [5], Lea H Dib [6], Isabel M Mol [2 3], Natarin Caengprasath [5], Yi-Wah Chan [7], Sami Damak [8], Anne Reifel Miller [9], Tamer Coskun [9], Bharat Shimpukade [10], Trond Ulven [10], Sander Kooijman [2 3], Patrick Cn Rensen [2 3], Mark Christian [1]

Affiliations + expand

PMID: 29343498 PMCID: PMC5840546 DOI: 10.15252/emmm.201708047

Free PMC article

Abstract

Brown adipose tissue (BAT) activation stimulates energy expenditure in human adults, which makes it an attractive target to combat obesity and related disorders. Recent studies demonstrated a role for G protein-coupled receptor 120 (GPR120) in BAT thermogenesis. Here, we investigated the therapeutic potential of GPR120 agonism and addressed GPR120-mediated signaling in BAT We found that activation of GPR120 by the selective agonist TUG-891 acutely increases fat oxidation and reduces body weight and fat mass in C57Bl/6J mice. These effects coincided with decreased brown adipocyte lipid content and increased nutrient uptake by BAT, confirming increased BAT activity. Consistent with these observations, GPR120 deficiency reduced expression of genes involved in nutrient handling in BAT Stimulation of brown adipocytes *in vitro* with TUG-891 acutely induced O_2 consumption, through GPR120-dependent and GPR120-independent mechanisms. TUG-891 not only stimulated GPR120 signaling resulting in intracellular calcium release, mitochondrial depolarization, and mitochondrial fission, but also activated UCP1. Collectively, these data suggest that activation of brown adipocytes with the GPR120 agonist TUG-891 is a promising strategy to increase lipid combustion and reduce obesity.

Keywords: Ca2+; GPR120; brown adipose tissue; lipid metabolism; mitochondria.

Schilperoort et al., Embo Mol Med, 2018

GSK17647

- Reseptöre 50 kat daha selektif bir FFA4R agonisti
- Sıçanlarda;
- İnsülin salınımı↑
- Postprandiyal hiperglisemiyi düzelttiği gösterilmiş

Clin Sci (Lond). 2017 Feb 1;131(3):247-260. doi: 10.1042/CS20160545. Epub 2016 Dec 15.

Insulinotropic effects of GPR120 agonists are altered in obese diabetic and obese non-diabetic states

Dan Zhang [1], Wing Yan So [1], Yi Wang [1], Shang Ying Wu [1], Qianni Cheng [1], Po Sing Leung [2]

Affiliations + expand

PMID: 27980130 DOI: 10.1042/CS20160545

Abstract

G-protein-coupled receptor 120 (GPR120) is a putative target for obesity and diabetes therapies. However, it remains controversial whether resident GPR120 plays a direct regulatory role in islet β-cell insulin secretion. The present study examined this issue in isolated rodent islets and rat β-cell line INS-1E, and assessed the role of GPR120 in islet insulin secretion in obese non-diabetic (OND) and diabetic states. GPR120 expression was detected in rodent islet β-cells. Docosahexaenoic acid (DHA) and synthetic GPR120 agonist GSK137647 (GSK) augmented insulin release from rat/mouse islets and INS-1E; DHA effects were partially mediated by GPR40. GPR120 knockdown and overexpression attenuated and enhanced DHA effects in INS-1E respectively. DHA and GSK improved postprandial hyperglycaemia of diabetic mice. Inhibition of calcium signalling in INS-1E reduced GPR120 activation-induced insulinotropic effects. The insulinotropic effects of DHA/GSK were amplified in OND rat islets, but diminished in diabetic rat islets. GPR120 and peroxisome proliferator-activated receptor γ (PPARγ) expression were elevated in OND islets and palmitic acid (PA)-treated INS-1E, but reduced in diabetic islets and high glucose-treated INS-1E. PPARγ activation increased GPR120 expression in rat islets and INS-1E. DHA and GSK induced protein kinase B (Akt)/extracellular signal-regulated kinase (ERK) phosphorylation in rodent islets and INS-1E, and these effects were altered in OND and diabetic states. Taken together, the present study indicates that (i) GPR120 activation has an insulinotropic influence on β-cells with the involvement of calcium signalling; (ii) GPR120 expression in β-cells and GPR120-mediated insulinotropic effects are altered in OND and diabetic states in distinct ways, and these alterations may be mediated by PPARγ.

Keywords: Type 2 diabetes mellitus (T2DM); calcium signalling; insulin secretion; non-diabetic obesity; peroxisome proliferator-activated receptor γ (PPARγ).

Zhang et al., Clin Sci, 2017

cpdA

- Selektif, yüksek affiniteli oral FFA4R agonisti
- Sıçanlarda;
- Kas ve KC'de insülin aktivitesini arttırarak insülin duyarlılığı↑
- Hepatosteatozu ↓ Trigliserid ↓
- Anti-inflammatuvar etkiler

Nat Med. 2014 Aug;20(8):942-7. doi: 10.1038/nm.3614. Epub 2014 Jul 6.

A Gpr120–selective agonist improves insulin resistance and chronic inflammation in obese mice

Da Young Oh [1], Evelyn Walenta [1], Taro E Akiyama [2], William S Lagakos [1], Denise Lackey [1], Ariane R Pessentheiner [3], Roman Sasik [1], Nasun Hah [4], Tyler J Chi [1], Jason M Cox [2], Mary Ann Powels [2], Jerry Di Salvo [2], Christopher Sinz [2], Steven M Watkins [5], Aaron M Armando [6], Heekyung Chung [1], Ronald M Evans [7], Oswald Quehenberger [8], Joanne McNelis [1], Juliane G Bogner-Strauss [9], Jerrold M Olefsky [1]

Affiliations + expand

PMID: 24997608 PMCID: PMC4126875 DOI: 10.1038/nm.3614

Free PMC article

Abstract

It is well known that the ω-3 fatty acids (ω-3-FAs; also known as n-3 fatty acids) can exert potent anti-inflammatory effects. Commonly consumed as fish products, dietary supplements and pharmaceuticals, ω-3-FAs have a number of health benefits ascribed to them, including reduced plasma triglyceride levels, amelioration of atherosclerosis and increased insulin sensitivity. We reported that Gpr120 is the functional receptor for these fatty acids and that ω-3-FAs produce robust anti-inflammatory, insulin-sensitizing effects, both in vivo and in vitro, in a Gpr120-dependent manner. Indeed, genetic variants that predispose to obesity and diabetes have been described in the gene encoding GPR120 in humans (FFAR4). However, the amount of fish oils that would have to be consumed to sustain chronic agonism of Gpr120 is too high to be practical, and, thus, a high-affinity small-molecule Gpr120 agonist would be of potential clinical benefit. Accordingly, Gpr120 is a widely studied drug discovery target within the pharmaceutical industry. Gpr40 is another lipid-sensing G protein-coupled receptor, and it has been difficult to identify compounds with a high degree of selectivity for Gpr120 over Gpr40 (ref. 11). Here we report that a selective high-affinity, orally available, small-molecule Gpr120 agonist (cpdA) exerts potent anti-inflammatory effects on macrophages in vitro and in obese mice in vivo. Gpr120 agonist treatment of high-fat diet-fed obese mice causes improved glucose tolerance, decreased hyperinsulinemia, increased insulin sensitivity and decreased hepatic steatosis. This suggests that Gpr120 agonists could become new insulin-sensitizing drugs for the treatment of type 2 diabetes and other human insulin-resistant states in the future.

De Young Oh et al., Nat Med, 2014

FFAR4 Reseptör Agonistleri

- Biyolojisi ve farmakolojik özellikleri net bilinmiyor
- Mekanizmaları net değil
- Tekrarlayan maruziyette desensitizasyon riski

Medikal tedavi??

FFA Reseptör Agonistleri Özetle..

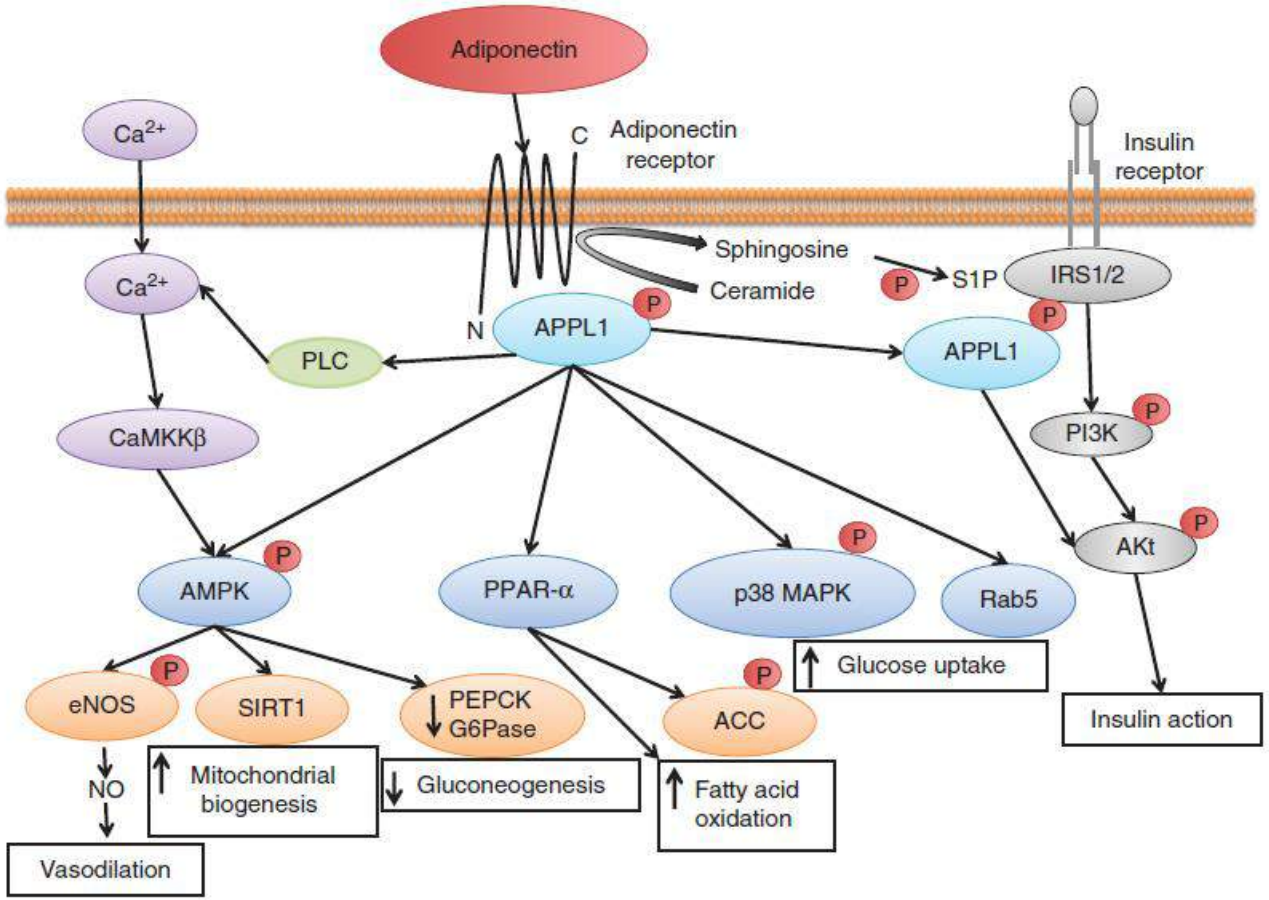
- APG, PPPG, HbA1c↓
- Glukoz bağımlı insülin sekresyonu↑
- İnkretin sekresyonu ↑
- Hipoglisemi↔
- Kilo alımı↔
- Oral kullanılabilir

FFA reseptör	Agonistler	Klinik çalışma durumu
FFA1	Natürel ligandlar: palmitik acid, oleik acid, linoleik acid Sentetik ligandlar: GW9508, TAK-875/Fasiglifam, AMG-837, AM-1638, AM-5262, LY2881835, JTT-851, P11187, TUG-469, TUG-424, TUG-770, AS2575959, DS-1558	AK-875/Fasiglifam (Takeda): Faz I/II çalışmaları APG ↓, insülin↑, HbA1c % 1.2–1.4% ↓ -Hipoglisemi/kilo alımı- KC toksisitesinden dolayı Faz III'de kaldırıldı AMG-837 (Amgen) and LY2881835 (Eli Lilly): Toksisiteden dolayı Faz I'de kaldırıldı JTT-851 (Japan Tobacco): Faz II devam ediyor P11187 (Piramal): Faz I devam ediyor
FFA2	Natürel ligandlar: acetate (tercih edilen), propionate, butyrate Sentetik ligandlar: AMG7703/ 4-CMTB, Euroscreen compounds, compounds 1 and 2	Klinik çalışma mevcut değil
FFA3	Natürel ligandlar: propionate (tercih edilen), butyrate, acetate Sentetik ligandlar: Arena Pharmaceuticals series	Klinik çalışma mevcut değil
FFA4	Natürel ligandlar: α-linolenic acid (αLA), docosahexanoic acid (DHA) Sentetik ligandlar: GW9508, NCG21, NCG46, TUG-891	Klinik çalışma mevcut değil

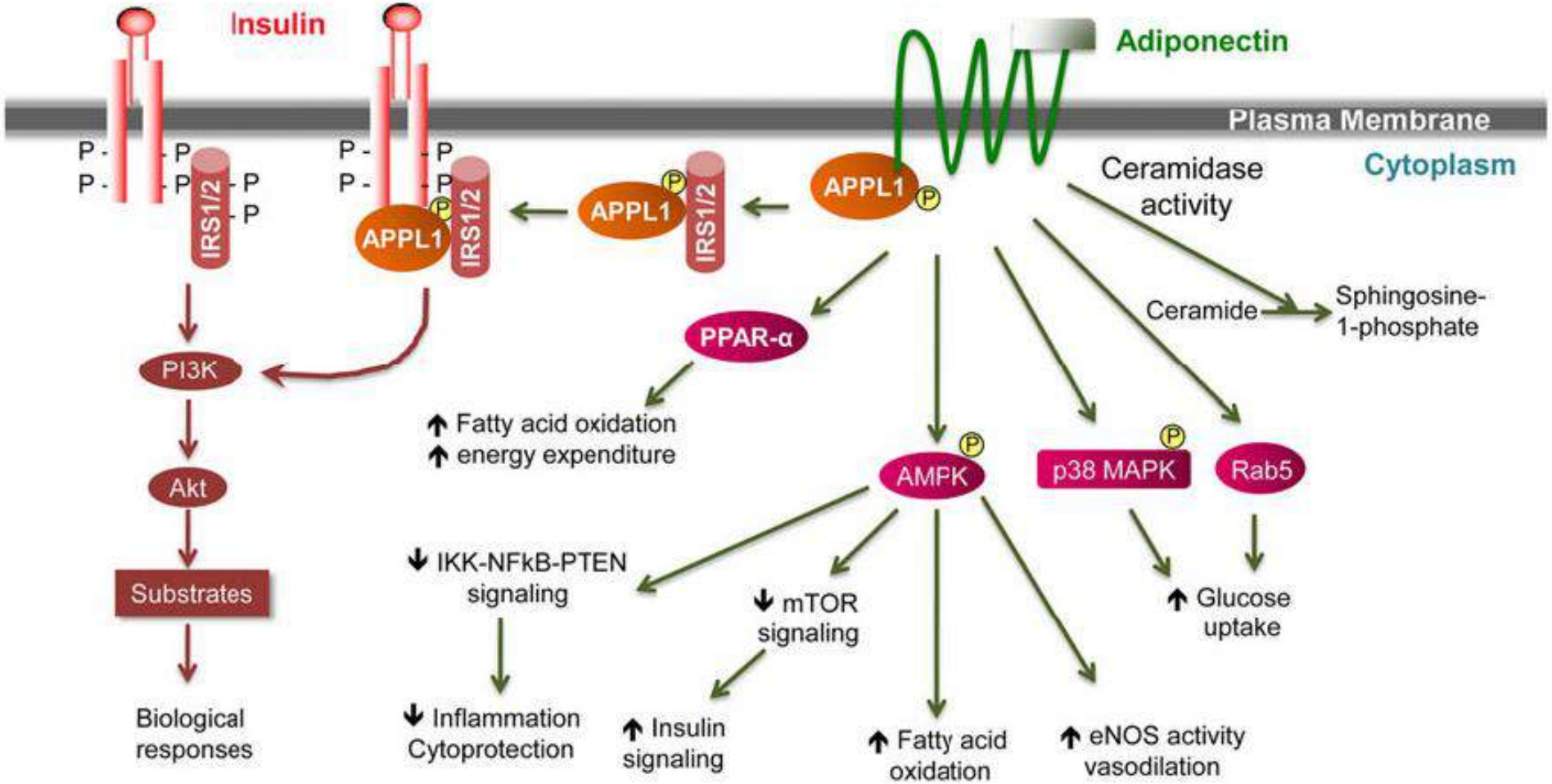
Adiponektin Reseptör Agonistleri

Adiponektin

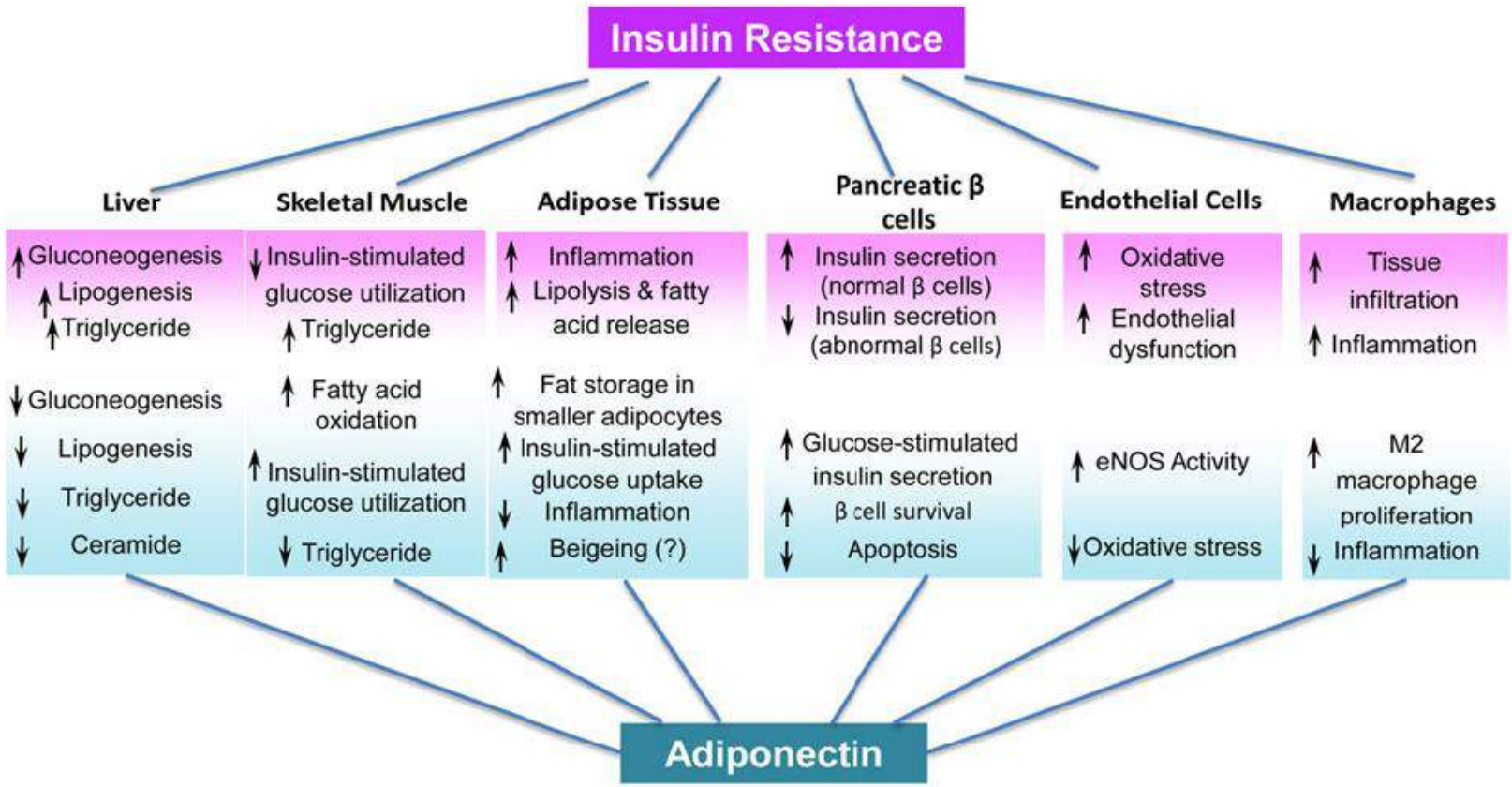
- Adiponektin (Acrp 30, AdipoQ, GBP-28, apM1)
- 244 aa içeren glikoprotein
- Adiposit spesifik faktör
- AdipoR1→ İskelet kası
- AdipoR2→ Karaciğer
- T-kadherin→ Endotel ve düz kas hücresi



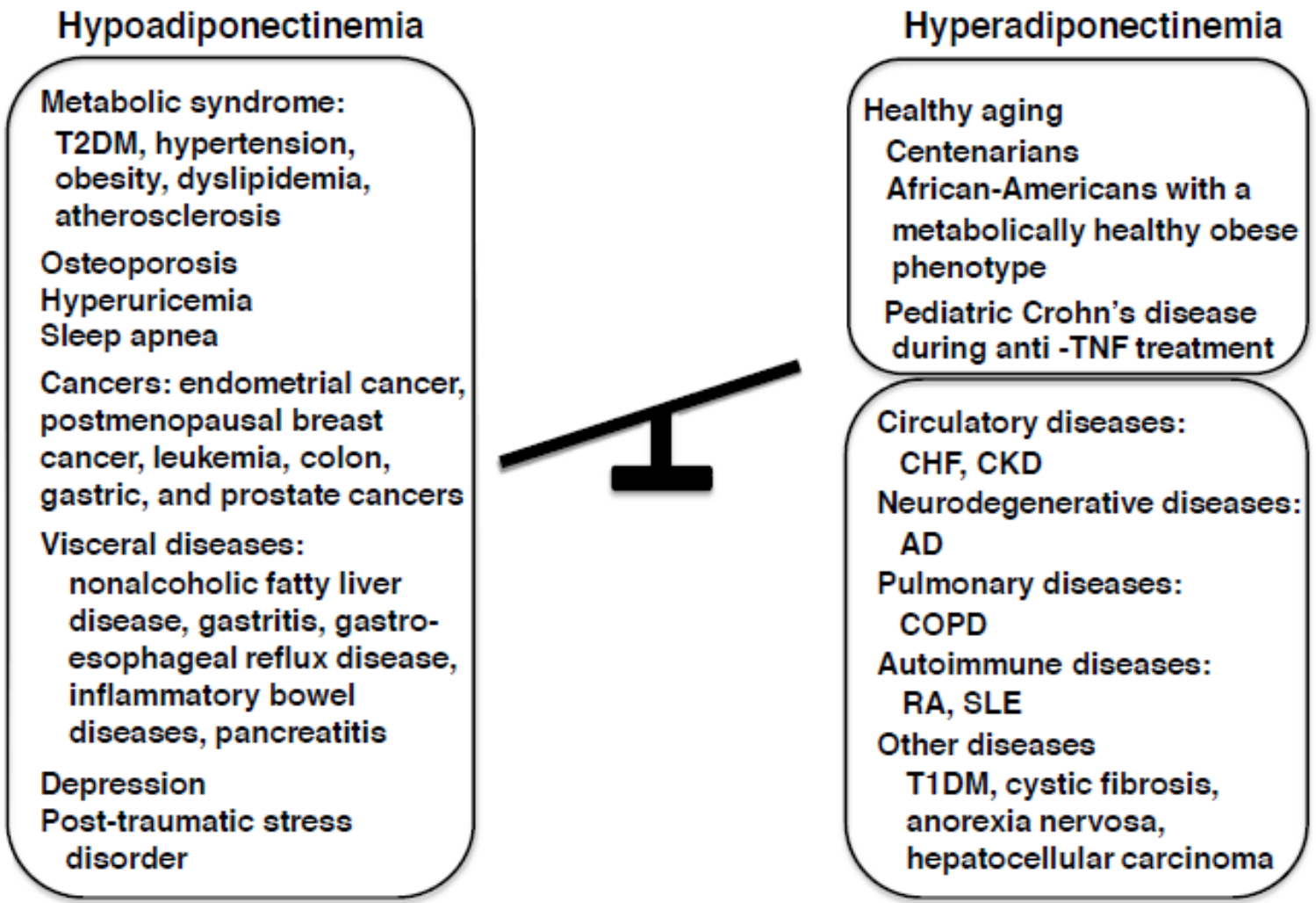
Adiponektin



Adiponektin



Adiponektin



Adiponectin

- Plazma konsantrasyonu 2-20 µg/ml (plazma insülin X1000)
- Dolaşımda farklı oligomerler halinde bulunuyor
- Her birinin spesifik hedef ve sinyal yolağı mevcut
- Yarılanma ömrü kısa (trimer: 38 dk, HMW ve MMW: 83 dk)- multipl doz ihtiyacı

?

Adiponektin Reseptör Agonistleri

TABLE 2 | Published activities of adiponectin receptor response modifiers.

Molecule	*in vitro* activity approx. IC_{50}
AdipoRon	Activation of LDLR 5 μM
GTDF	Enhanced of glucose uptake Activity observed at 10 nM
ADP355	Activation of LDLR 25 nM
ADP399	Cancer cell proliferation inhibition 10 nM
Pep70	HSC proliferation inhibition 10 μM
BHD-1028	AMPK activation <800 nM
ADP400	900 (EC_{50})

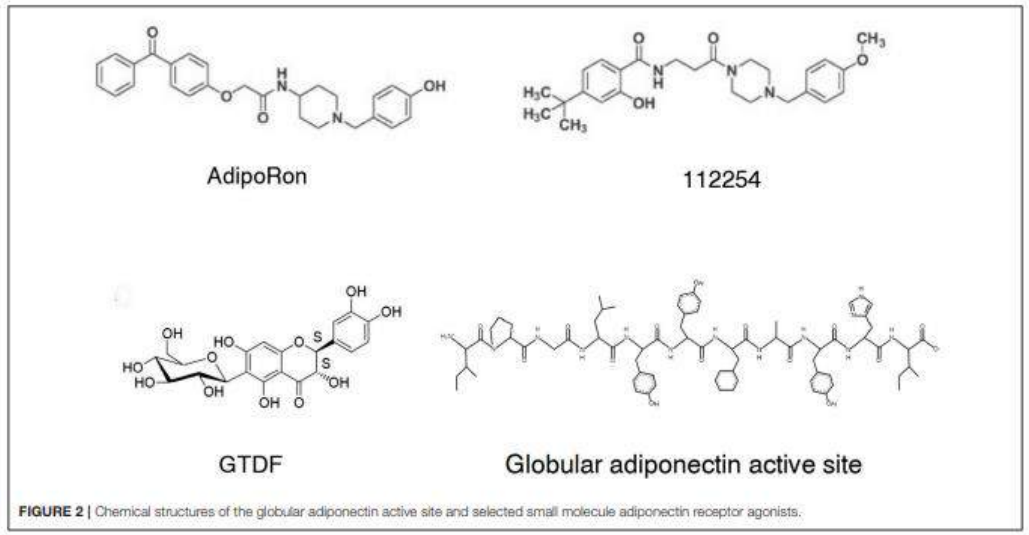


FIGURE 2 | Chemical structures of the globular adiponectin active site and selected small molecule adiponectin receptor agonists.

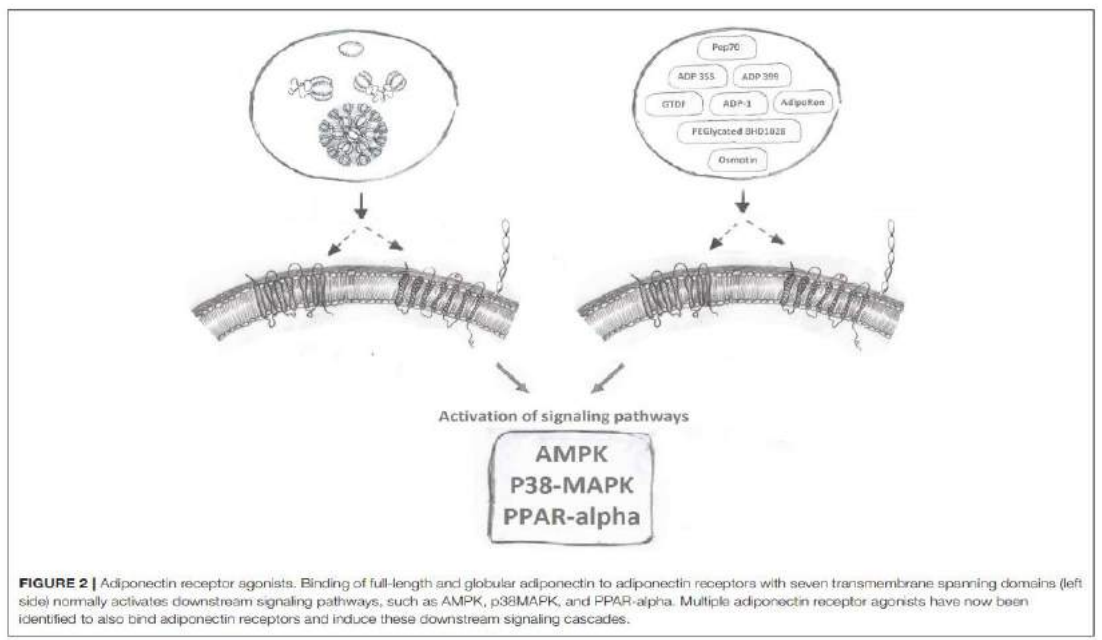
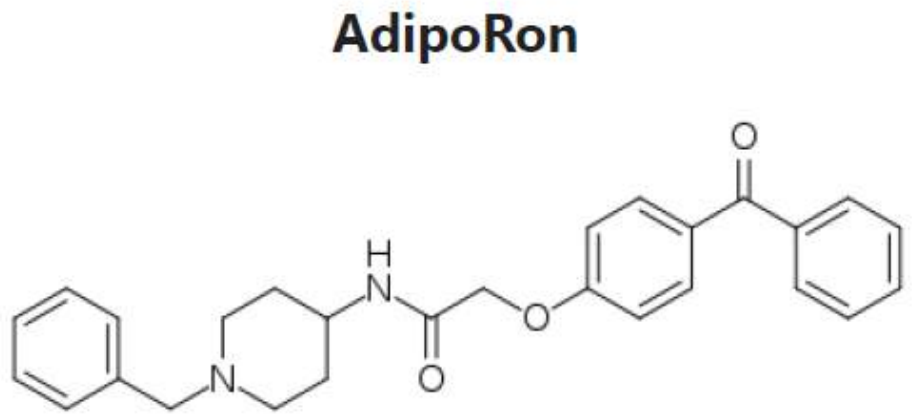


FIGURE 2 | Adiponectin receptor agonists. Binding of full-length and globular adiponectin to adiponectin receptors with seven transmembrane spanning domains (left side) normally activates downstream signaling pathways, such as AMPK, p38MAPK, and PPAR-alpha. Multiple adiponectin receptor agonists have now been identified to also bind adiponectin receptors and induce these downstream signaling cascades.

AdipoRon

- Tokyo Üniversitesi'nde geliştirilmiş bir ajan (2013)
- İlk oral selektif, sentetik, küçük-molekül AdipoR1 ve AdipoR2 agonisti
- AMPK, PPARα, PGC1α üzerinden etki gösterir

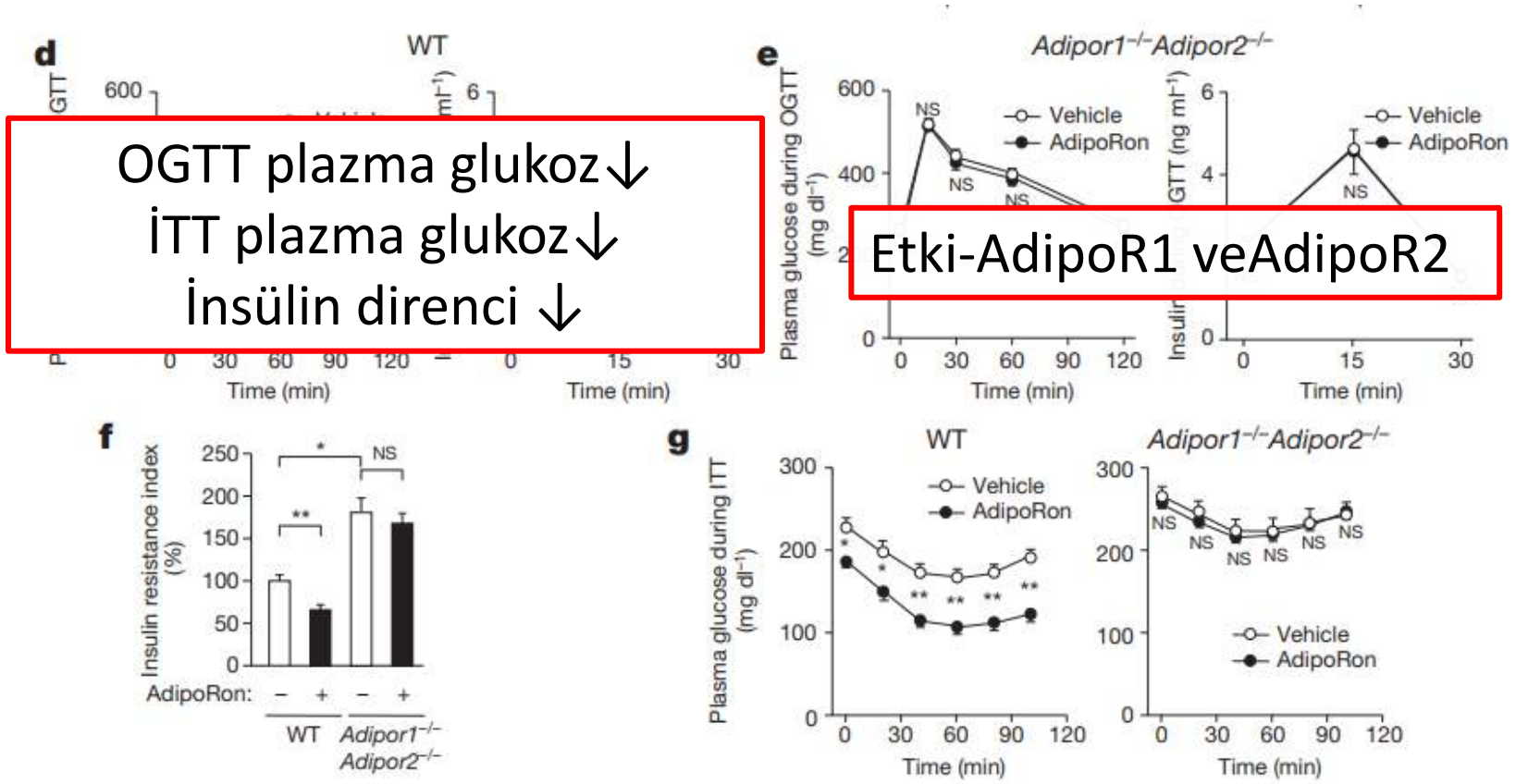


A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity

Miki Okada-Iwabu[1,2,3]*, Toshimasa Yamauchi[1,2,3]*, Masato Iwabu[1,2]*, Teruki Honma[4], Ken-ichi Hamagami[1], Koichi Matsuda[1], Mamiko Yamaguchi[1], Hiroaki Tanabe[4], Tomomi Kimura-Someya[4], Mikako Shirouzu[4], Hitomi Ogata[5], Kumpei Tokuyama[5], Kohjiro Ueki[1], Tetsuo Nagano[6], Akiko Tanaka[4,6], Shigeyuki Yokoyama[4,7] & Takashi Kadowaki[1,2,3]

- AdipoRon (50 mg/kg) po
- Yüksek yağla beslenmiş obez fareler
- 10 gün
- Kilo↔
- Besin tüketimi↔

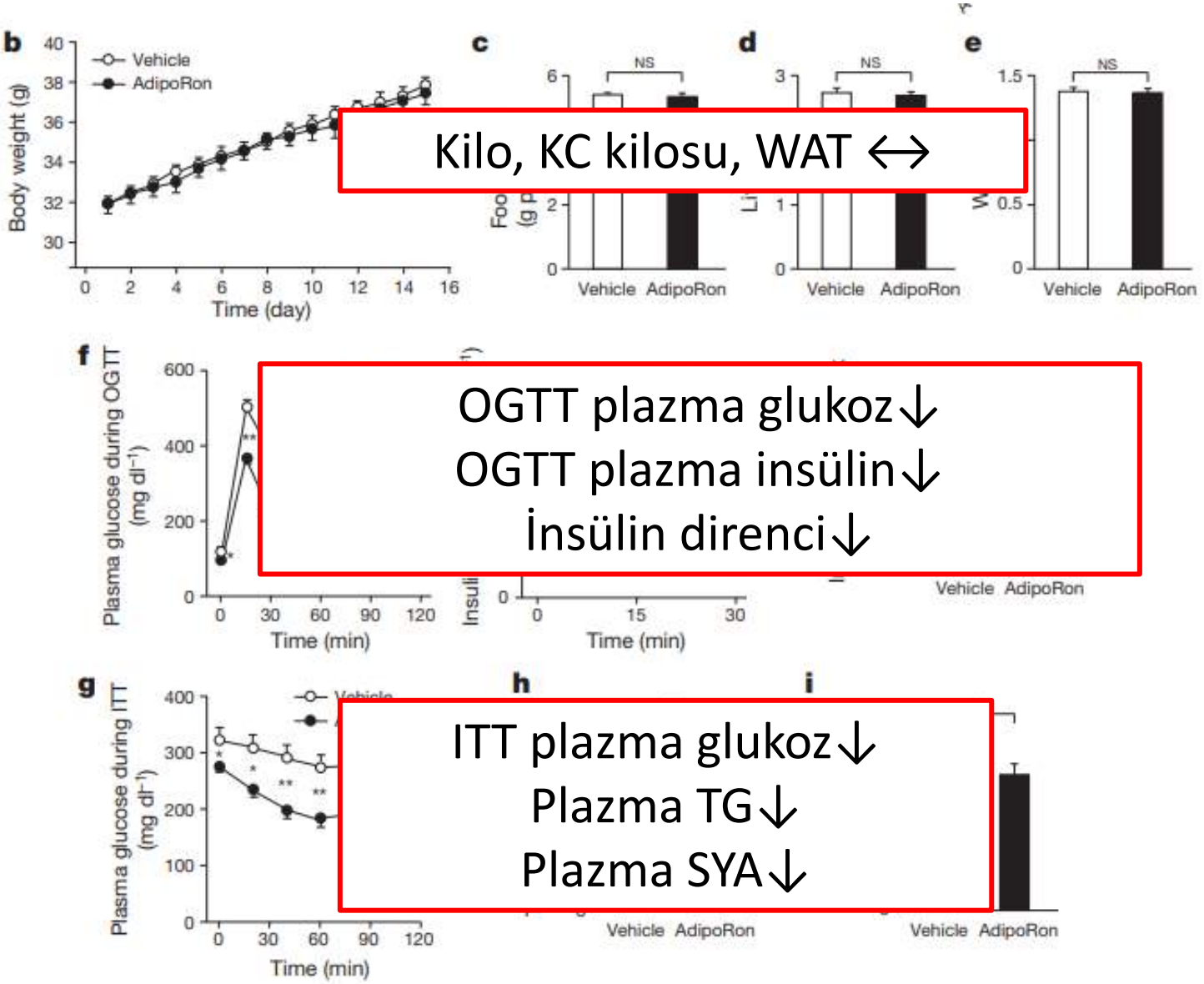
OGTT plazma glukoz↓
İTT plazma glukoz↓
İnsülin direnci ↓



Etki-AdipoR1 veAdipoR2

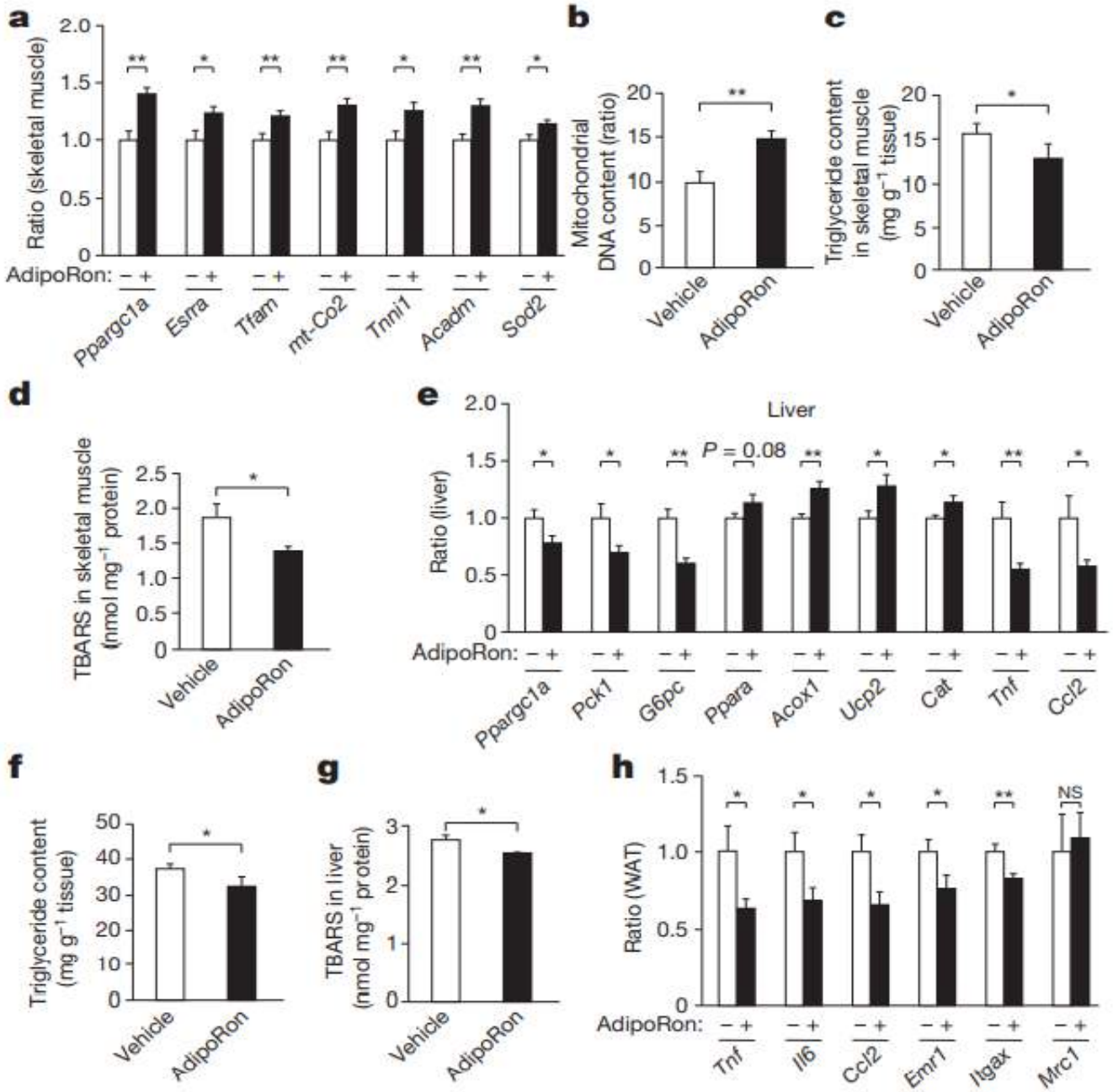
Okada-Iwabu et al., Nature, 2013

- AdipoRon (50 mg/kg) po
- *db/db (leptin-, obez diyabetik) fareler*
- 14 gün



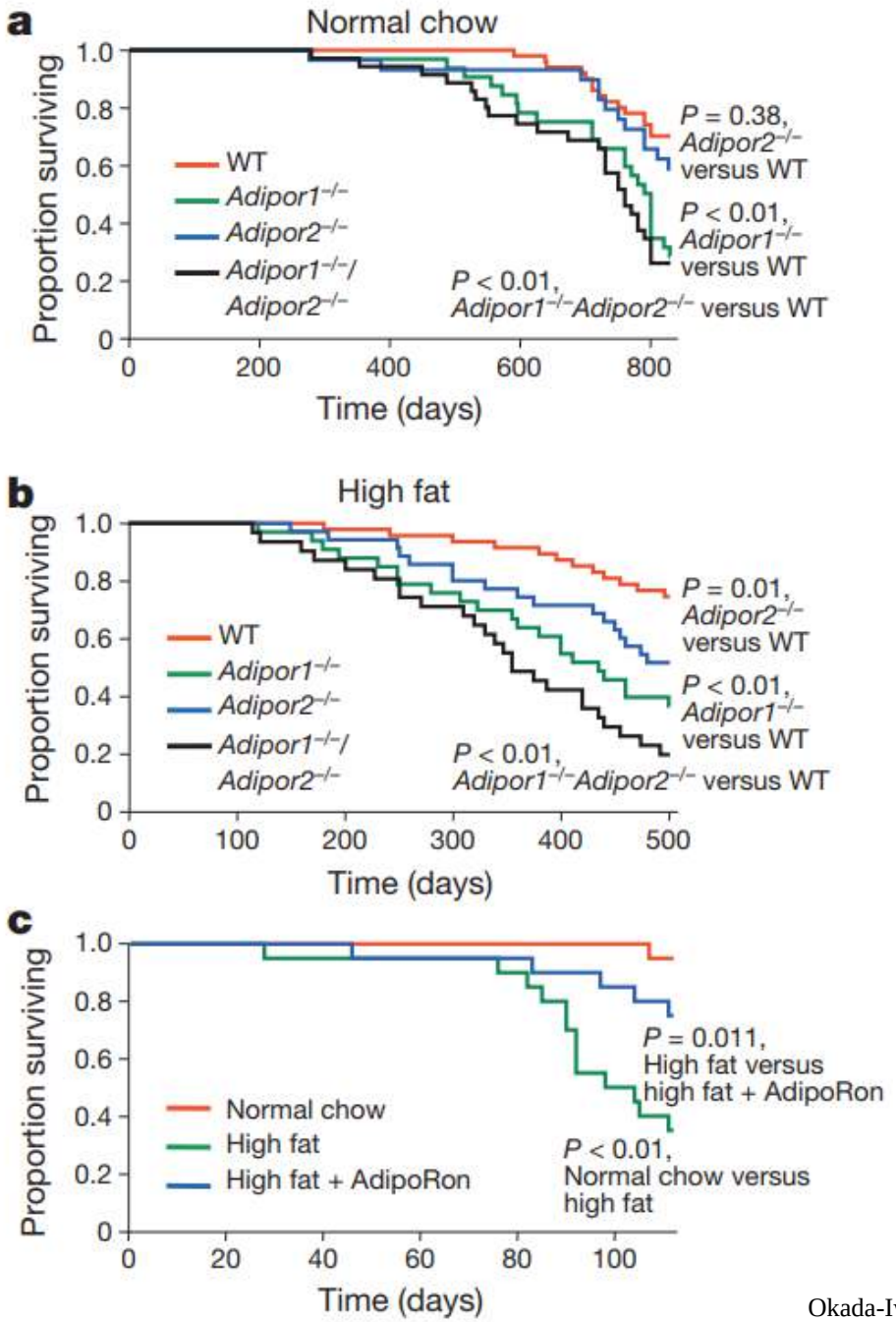
Okada-Iwabu et al., Nature, 2013

- İskelet kasında mitokondriyal biogenez↑
- KC'de ve iskelet kasında doku TG miktarını↓
- KC, İK ve WAT'de oksidatif stres ve inflamasyonu↓
- Proinflammatuvar sitokinlerin gen ekspresyonunu↓

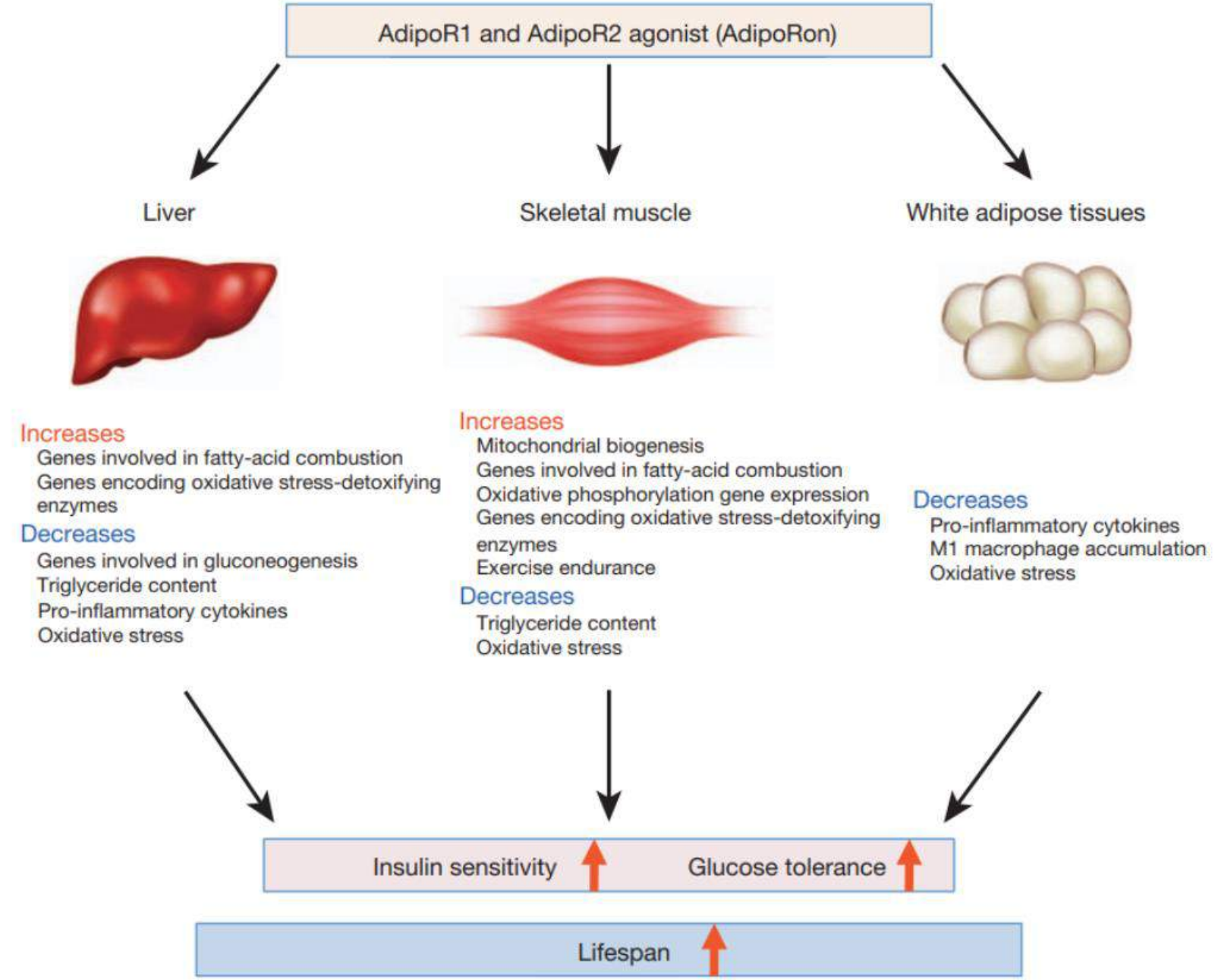


Okada-Iwabu et al., Nature, 2013

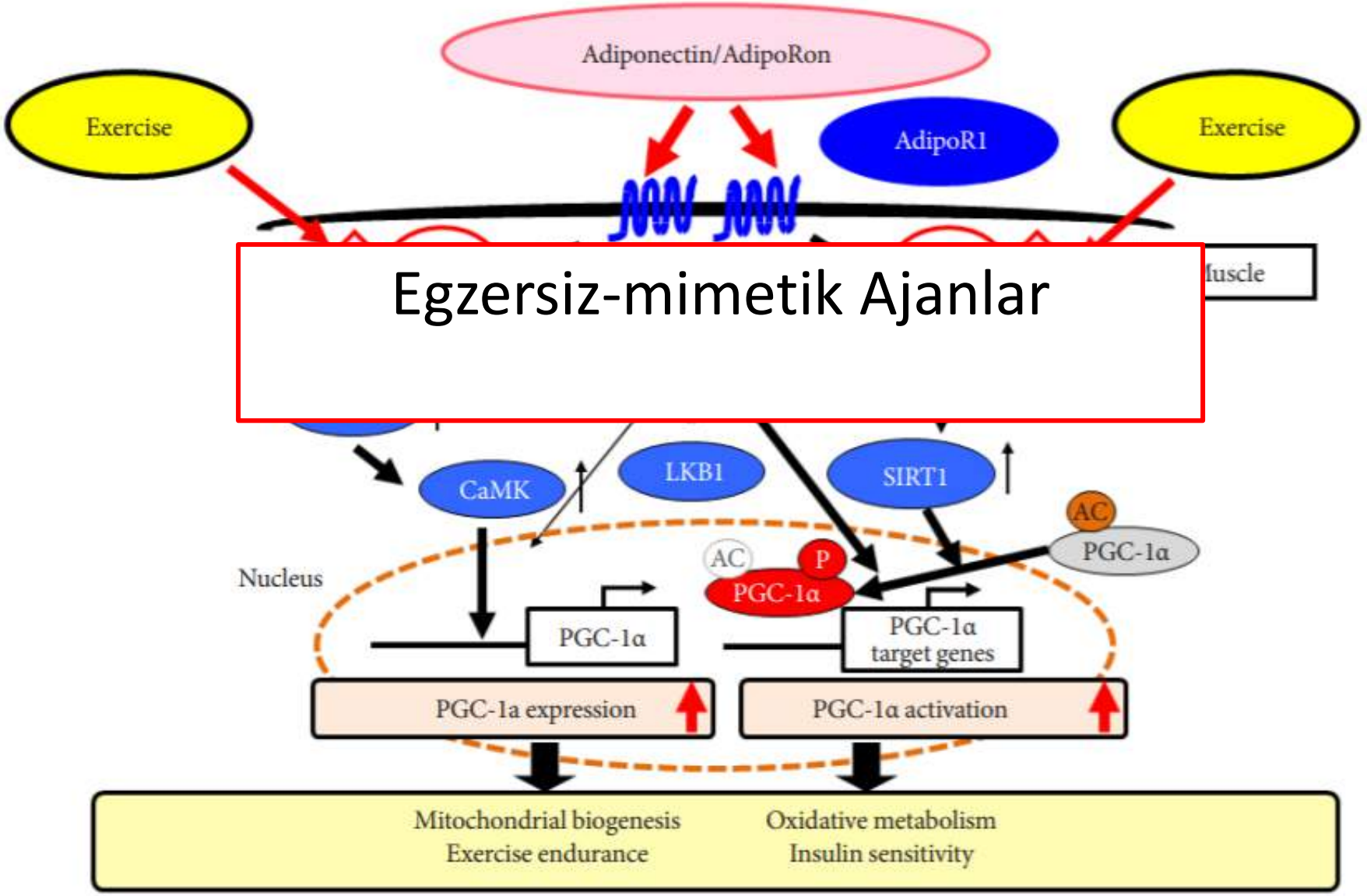
- AdipoR1 $^{-/-}$ ve AdipoR2$^{-/-}$ yaşam süresi↓
- Yüksek yağla beslenen farelerin yaşam süresi normal beslenen farelere göre daha kısa
- AdipoRon→ *db/db* farelerin yaşam süresini uzatmış



Okada-Iwabu et al., Nature, 2013



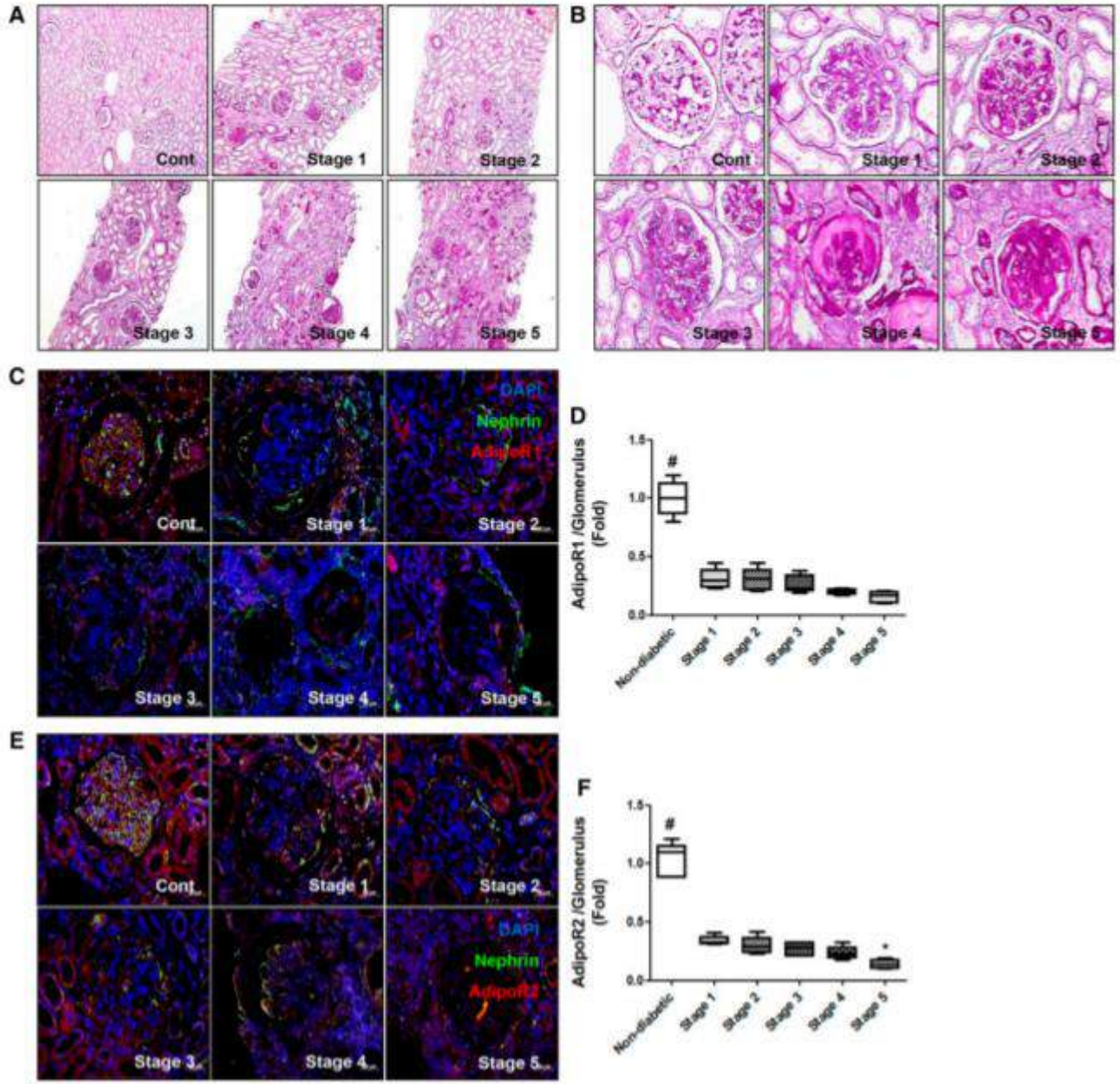
Okada-Iwabu et al., Nature, 2013


Adiponectin/AdipoRon
Exercise
AdipoR1
Exercise
Egzersiz-mimetik Ajanlar
CaMK
LKB1
SIRT1
AC
PGC-1α
AC
P
PGC-1α
Nucleus
PGC-1α
PGC-1α
target genes
PGC-1a expression
PGC-1α activation
Mitochondrial biogenesis
Exercise endurance
Oxidative metabolism
Insulin sensitivity

The Adiponectin Receptor Agonist AdipoRon Ameliorates Diabetic Nephropathy in a Model of Type 2 Diabetes

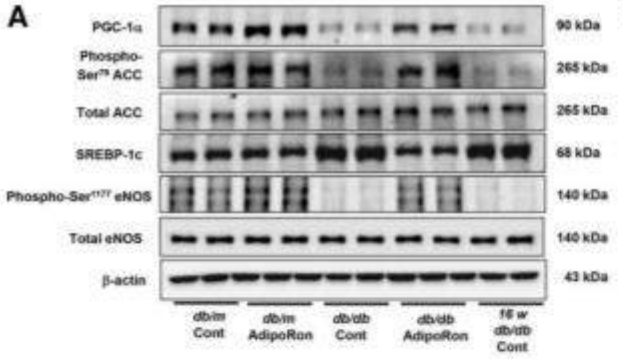
Yaeni Kim [1 2], Ji Hee Lim [1 3], Min Young Kim [1 3], Eun Nim Kim [1 3], Hye Eun Yoon [1 2], Seok Joon Shin [1 2], Bum Soon Choi [1 3], Yong-Soo Kim [1 3], Yoon Sik Chang [1 4], Cheol Whee Park [5 3]

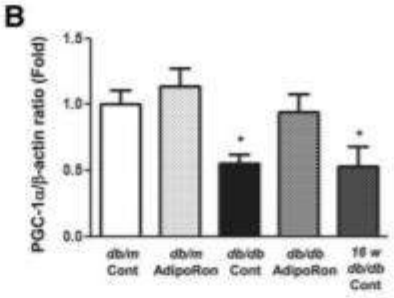
- Diyabetik insan böbrek dokusunda azalmış intraglomerular AdipoR1/AdipoR2 ekspresyonu saptanmış

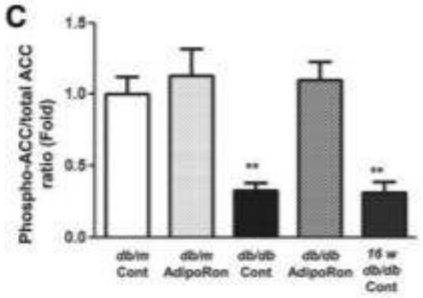


Kim et al., Nature, 2013

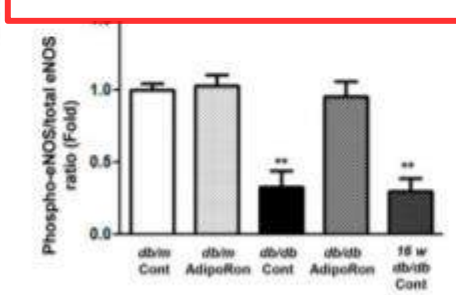
- AdipoRon *db/db* farelerde intrarenal AdipoR1/AdipoR2 ekspresyonunu arttırdığı gösterilmiş

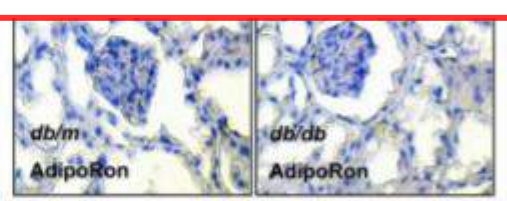


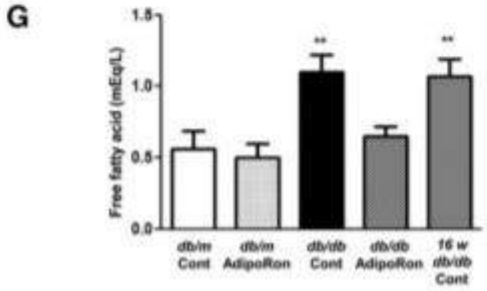


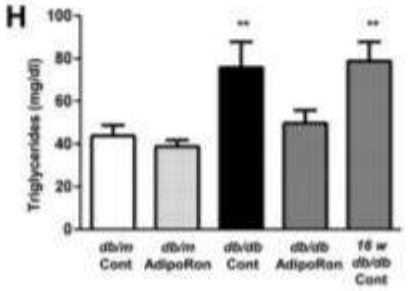


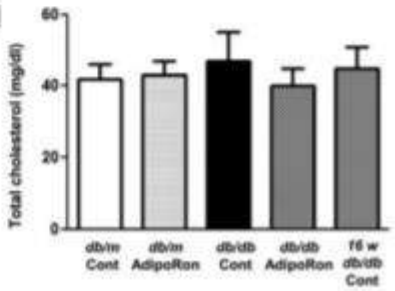
- İntrarenal triasilgliserol ve SYA azalma
- İdrar oksidatif stres belirteçlerinde azalma
- Lipotoksiteyi, oksidatif stresi ve apoptozisi azaltarak DN 'de geri dönüş





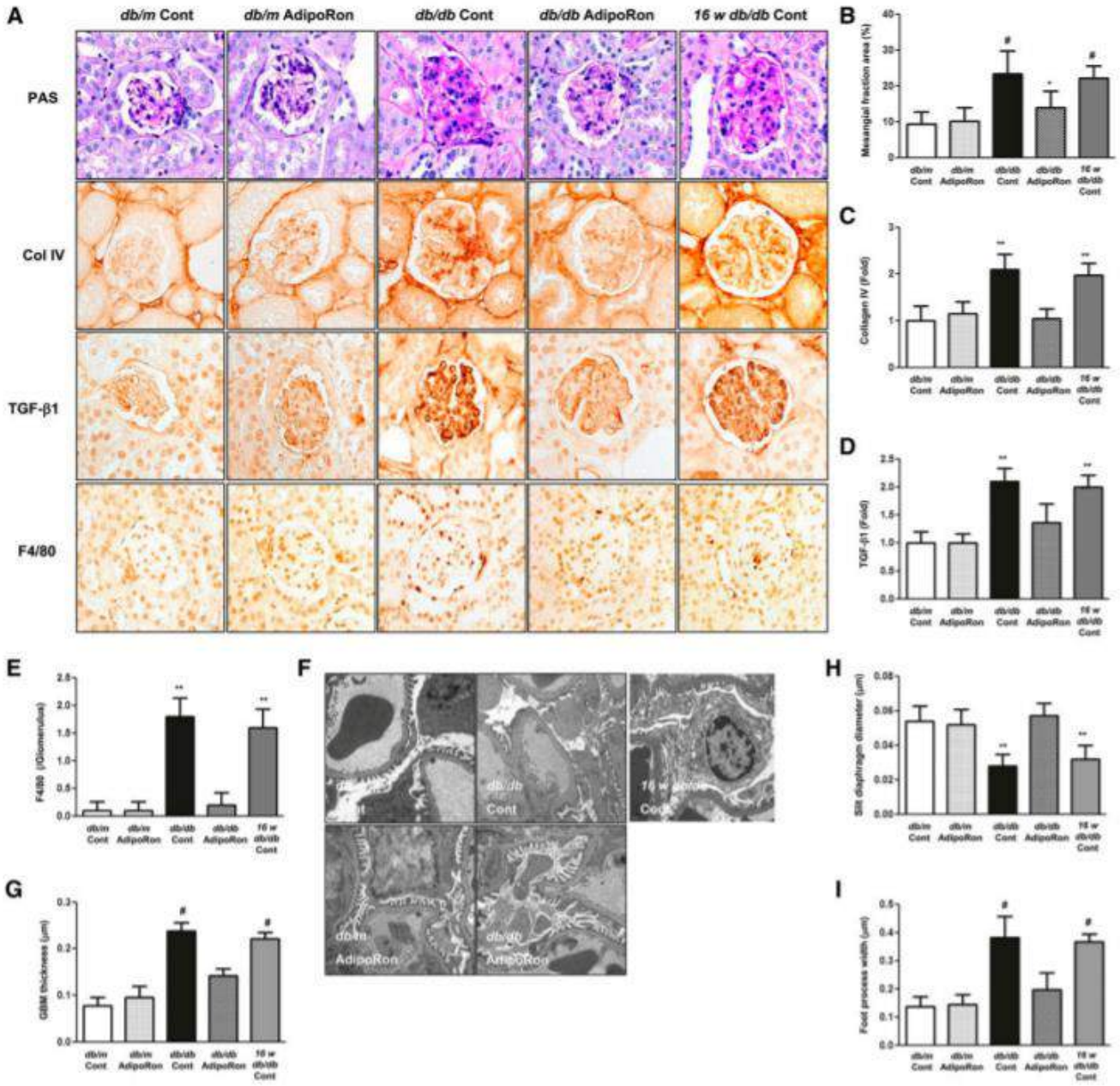






Kim et al., Nature, 2013

- AdipoRon ile intrarenal fibrozis, inflamasyon ve apoptoziste azalma
- Podosit hasarında ve GBM kalınlığında geri dönüş



Kim et al., Nature, 2013

Table 1. Biochemical and physical characteristics of mice in the four groups before and after 4 weeks of AdipoRon treatment

Characteristics	*db/m* Cont	*db/m* AdipoRon	*db/db* Cont	*db/db* AdipoRon	*16 w db/db* Cont
Body weight, g	36.2±1.7	37.2±1.8	53.0±7.3[a]	51.1±4.8[a]	49.9±3.4[a]
Kidney weight, g	0.20±0.04	0.21±0.03	0.21±0.04	0.21±0.01	0.22±0.01
Heart weight, g	0.18±0.02	0.18±0.02	0.18±0.04	0.17±0.02	0.17±0.03
FBS, mg/dl	152±14	138±7	534±89[a]	532±93[a]	640±150[a]
HbA1c, %	4.0±0.2	3.9±0.2	10.5±0.49[a]	11.5±0.8[a]	8.8±0.7[b]
$HOMA_{IR}$	0.06±0.01	0.06±0.01	2.37±0.02[a]	0.21±0.01[b]	2.11±0.11[a]
Total cholesterol, mmol/L	2.70±0.41	2.65±0.51	3.51±0.42[c]	3.39±0.55[c]	3.80±0.50[c]
Triacylglycerols, mmol/L	1.21±0.21	1.32±0.19	2.18±0.33[a]	1.60±0.22[c]	1.96±0.29[a]
Nonesterified fatty acid, mmol/L	0.62±0.22	0.67±0.19	1.42±0.20[c]	1.21±0.15[c]	1.41±0.21[c]
24-h albuminuria, μg/d	10.0±2.0	8.2±2.8	223.0±51.9[a]	100.0±18.8[b]	163.2±30.3[a]
Urine volume, ml	0.8±0.2	1.0±0.2	14.5±4.5[a]	10.3±3.4[a,c]	11.4±4.3[a,c]
Serum Cr, μmol/L	17.1±3.1	17.3±1.7	19.3±3.7	17.5±3.9	18.3±3.1
Ccr, ml/min	0.36±0.11	0.32±0.23	1.13±0.34[a]	0.74±0.25[c]	1.15±0.33[a]
Mean systolic BP, mm Hg	101±7	102±5	106±7	103±4	105±4
Serum adiponectin, μg/ml	10.6±1.2	10.8±1.4	4.6±0.5[a]	4.7±0.9[a]	4.5±0.7[a]

Data are mean±SD. Cont, control; FBS, fasting blood sugar; HbA1c, Hemoglobin A1c; $HOMA_{IR}$, homeostatic model assessment of insulin resistance; Cr, Creatinine; Ccr, creatinine clearance.

[a] $P<0.001$ compared with other groups.

[b] $P<0.01$ compared with other groups.

[c] $P<0.05$ compared with other groups.

Kim et al., Nature, 2013

Adiponectin receptor agonist AdipoRon decreased ceramide, and lipotoxicity, and ameliorated diabetic nephropathy

Sun Ryoung Choi [1], Ji Hee Lim [2], Min Young Kim [2], Eun Nim Kim [2], Yaeni Kim [2], Beom Soon Choi [2], Yong-Soo Kim [2], Hye Won Kim [3], Kyung-Min Lim [4], Min Jeong Kim [4], Cheol Whee Park [5]

- AdipoRon (30 mg/kg)
- Normal beslenen ve *db/db* farelere (n 8/8)
- 17 hafta

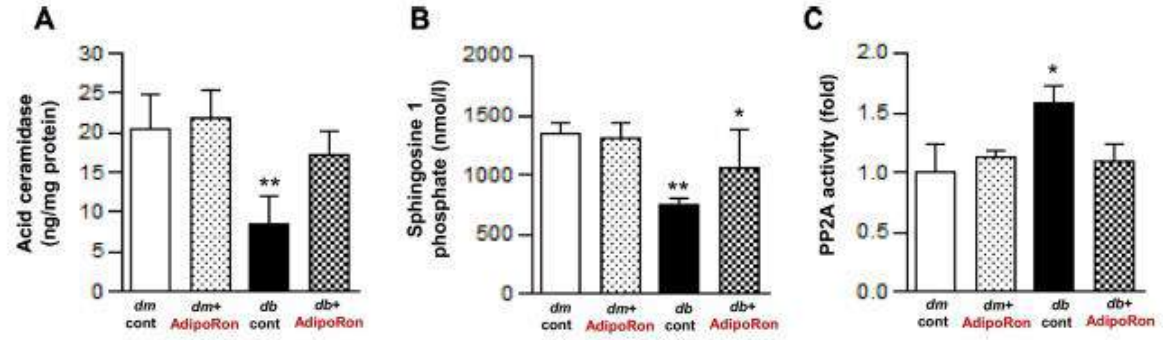
Table 1.Biochemical and physical characteristics of the four groups at the end of the 4 weeks period.

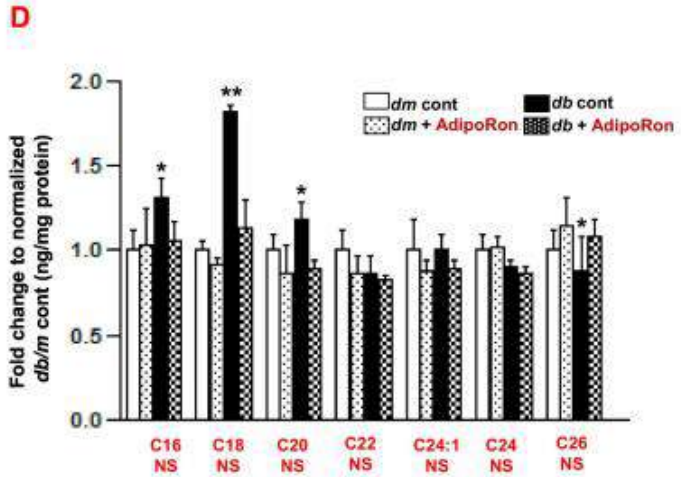
Characteristics	*dm* cont	*dm*+AdipoRon	*db* cont	*db*+AdipoRon
Body weight (g)	30.2±2.1	31.1±2.0	52.3±5.1***	50.1±4.3***
Kidney weight (g)	0.19±0.03	0.2±0.03	0.21±0.04	0.2±0.02
FBS (mmol/l)	7.99±0.83	7.49±0.5	29.03±4.27***	27.69±4.22***
Hb A_{1c} (%)	4.1±0.17	4±0.19	11.5±0.44***	10.9±0.64***
Total cholesterol (mmol/l)	2.72±0.41	2.80±0.47	3.42±0.49*	3.34±0.54*
Triacylglycerols (mmol/l)	1.19±0.24	1.21±0.26	2.00±0.26***	1.53±0.21*
Non-esterified fatty acid (mmol/l)	0.65±0.21	0.71±0.14	1.32±0.19*	1.10±0.19*
24 hr albuminuria (μg/day)	9.2±2	9±2.1	241±44.4***	122±15.5**
Urine volume (ml)	1.0±0.2	0.9±0.2	15.5±5.3***	10.3±5.4***
Serum Cr (μmol/l)	16.77±3.05	17.54±3.05	19.06±3.81	18.30±3.81
Serum adiponectin (μg/ml)	10.03±0.56	9.87±0.67	4.20±0.42***	4.11±0.59***

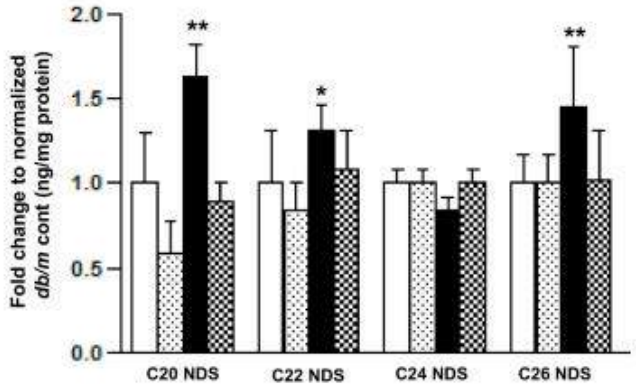
- Albuminüri ve böbrekte lipid birikiminde ↓
- Serum adiponektin↔
- APG ve kilo ↔

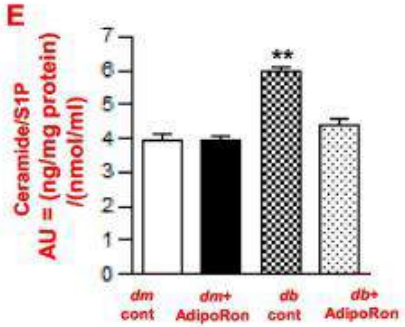
Choi et al., Metabolism, 2018

- AdipoRon hücre seramid düzeylerini asid seramidaz enzimini aktive ederek düşürür.
- Oksidatif stres ve apoptozis↓

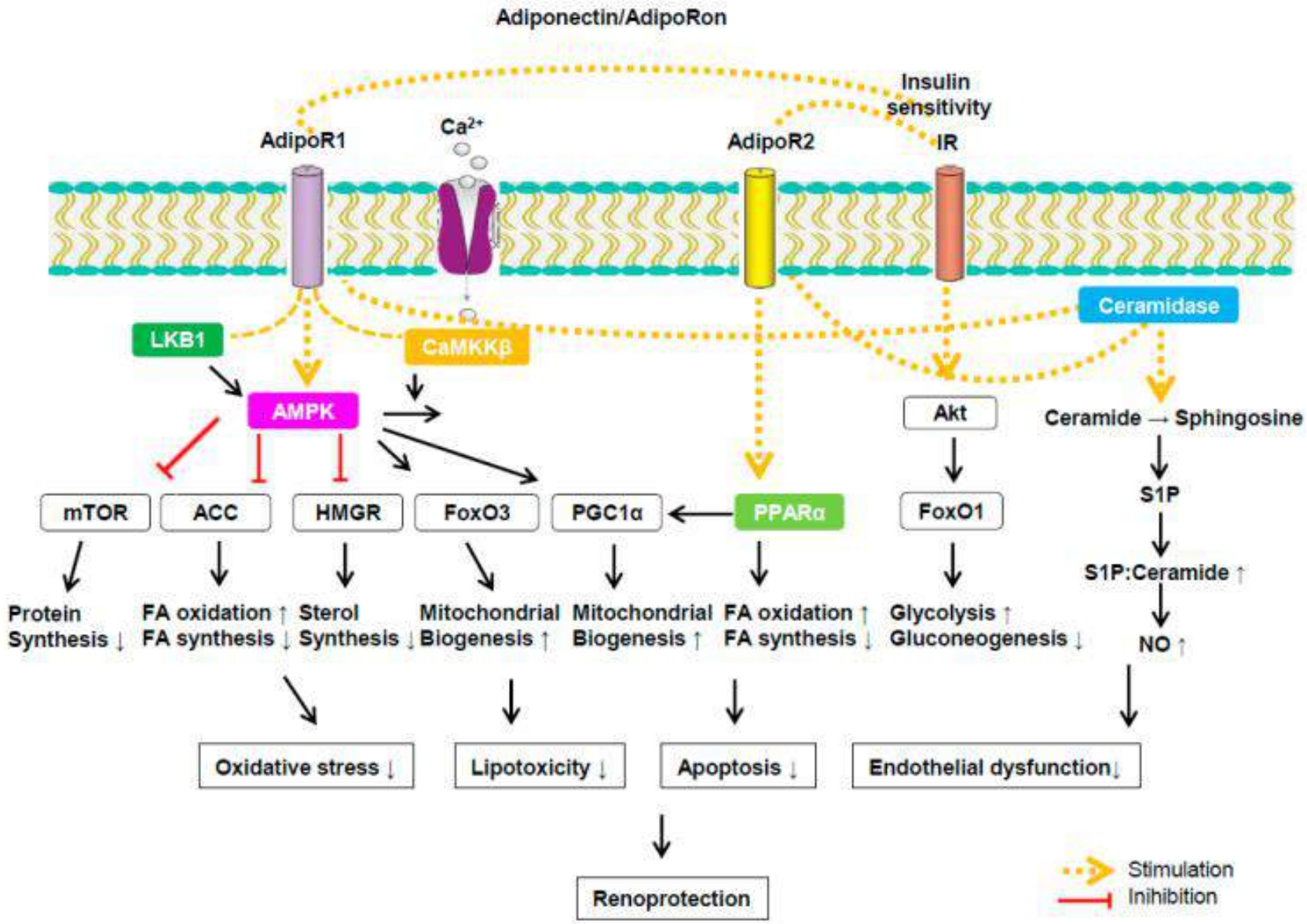








Choi et al., Metabolism, 2018



Choi et al., Metabolism, 2018

- AdipoRon (50 mg/kg)
- Deneysel periodontit geliştirilen farelere
- 2 hafta
- Diyabetik farelerde APG ↓
- Osteoklast sayısında ve alveolar kemik kaybı ↓
- Gingival dokulardaki proinflammatuvar moleküller CC kemokin ligand 2 and interlökin 6 ↓
- Osteojenik differensiyasyonu arttırarak alveolar kemik rejenerasyonu ↑
- Osteoanabolik etkiler

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An Adiponectin Receptor Agonist Reduces Type 2 Diabetic Periodontitis

X. Wu[1,2], W. Qiu[2], Z. Hu[2], J. Lian[2], Y. Liu[2], X. Zhu[2], M. Tu[2], F. Fang[2], Y. Yu[2], P. Valverde[2], Q. Tu[2], Y. Yu[1], and J. Chen[2,3]

Abstract

Periodontitis is twice as prevalent in diabetics as in nondiabetics, and type 2 diabetes (T2D)–associated periodontitis is severe in many cases due to the altered and aberrant functions of bone cells in hyperglycemic conditions. Therefore, developing an effective method to halt the disease process, as well as restore and regenerate lost alveolar bone to reserve the natural teeth in diabetics, is critically important. In the current study, we applied a newly discovered adiponectin receptor agonist AdipoRon (APR) in experimental periodontitis in diabetic animal models and demonstrated the underlying molecular mechanisms. We found that when APR systemically quenched the blood sugar level in diet-induced obesity (DIO) diabetic mice, it reduced osteoclast numbers and alveolar bone loss significantly due to APR's inhibition on osteoclast differentiation shown in our in vitro studies. APR also decreased the production of proinflammatory molecules CC chemokine ligand 2 and interleukin 6 in diseased gingival tissues. On the other hand, APR promoted alveolar bone regeneration through enhancing osteogenic differentiation and decreasing stromal cell–derived factor 1 in the bone marrow that facilitates stem cell migration. Same results were achieved by APR treatment of periodontitis induced in adiponectin (APN) knockout mice, indicating the ability of APR to activate the endogenous APN receptors to exert osteoanabolic effects. In summary, our study supports the notion that APR could be used as an effective multipronged approach to target T2D-associated periodontitis.

Keywords: AdipoRon, alveolar bone loss, type 2 diabetes mellitus, osteoclast, osteogenesis, animal disease model

Wu et al., JDR, 2019

Diğer Adiponektin Reseptör Agonistleri

- **Osmontin**
  - Amyloid betanın sebeb olduğu sinaptik eksikliklerde↓
  - Aβ birikimi ↓,
  - Nöroinflamasyonda ↓
  - Kognitif bozukluklarda, hafıza kaybında ve uzun süreli potansiyel artışında düzelme

› Mol Psychiatry. 2017 Mar;22(3):407-416. doi: 10.1038/mp.2016.23. Epub 2016 Mar 22.

Novel osmotin inhibits SREBP2 via the AdipoR1/AMPK/SIRT1 pathway to improve Alzheimer's disease neuropathological deficits

S A Shah [1], G H Yoon [1], S S Chung [2], M N Abid [1], T H Kim [1], H Y Lee [1], M O Kim [1]

› Mol Psychiatry. 2017 Feb;22(3):323. doi: 10.1038/mp.2017.12.

Osmotin reduced amyloid beta (Aβ) burden by inhibiting SREBP2 expression in APP/PS1 mice

S A Shah [1], G H Yoon [1], S S Chung [2], M N Abid [1], T H Kim [1], H Y Lee [1], M O Kim [1]

› Mol Neurobiol. 2018 Aug;55(8):6673-6686. doi: 10.1007/s12035-017-0847-1. Epub 2018 Jan 15.

The Adiponectin Homolog Osmotin Enhances Neurite Outgrowth and Synaptic Complexity via AdipoR1/NgR1 Signaling in Alzheimer's Disease

Gwangho Yoon [1], Shahid Ali Shah [1], Tahir Ali [1], Myeong Ok Kim [2]

Shah et al., Mol Psychiatry, 2017

Yoon et al., Mol Neurobiol ,2018

GTDF

- Daha çok AdipoR1 bağlanmakla beraber her iki AdipoR bağlanır
- Glukoz alımını↑
- Lipid profilini düzelttiği
- Beta hücre yaşam süresini uzattığı
- Steatohepatit ↓

Diabetes. 2014 Oct;63(10):3530-44. doi: 10.2337/db13-1619. Epub 2014 May 21.

Orally active osteoanabolic agent GTDF binds to adiponectin receptors, with a preference for AdipoR1, induces adiponectin–associated signaling, and improves metabolic health in a rodent model of diabetes

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Free article

Abstract

Adiponectin is an adipocytokine that signals through plasma membrane-bound adiponectin receptors 1 and 2 (AdipoR1 and -2). Plasma adiponectin depletion is associated with type 2 diabetes, obesity, and cardiovascular diseases. Adiponectin therapy, however, is yet unavailable owing to its large size, complex multimerization, and functional differences of the multimers. We report discovery and characterization of 6-C-β-D-glucopyranosyl-(2S,3S)-(+)-5,7,3',4'-tetrahydroxydihydroflavonol (GTDF) as an orally active adiponectin mimetic. GTDF interacted with both AdipoRs, with a preference for AdipoR1. It induced adiponectin-associated signaling and enhanced glucose uptake and fatty acid oxidation in vitro, which were augmented or abolished by AdipoR1 overexpression or silencing, respectively. GTDF improved metabolic health, characterized by elevated glucose clearance, β-cell survival, reduced steatohepatitis, browning of white adipose tissue, and improved lipid profile in an AdipoR1-expressing but not an AdipoR1-depleted strain of diabetic mice. The discovery of GTDF as an adiponectin mimetic provides a promising therapeutic tool for the treatment of metabolic diseases.

Singh et al., Diabetes, 2014

Tilirosid

- Glikozidik flavonoid
- 100 mg/kg/g
- 21 gün
- Her iki AdipoR’e bağlanır

Tiliroside, a glycosidic flavonoid, ameliorates obesity-induced metabolic disorders via activation of adiponectin signaling followed by enhancement of fatty acid oxidation in liver and skeletal muscle in obese-diabetic mice

Tsuyoshi Goto [1], Aki Teraminami, Joo-Young Lee, Kana Ohyama, Kozue Funakoshi, Young-Il Kim, Shizuka Hirai, Taku Uemura, Rina Yu, Nobuyuki Takahashi, Teruo Kawada

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PMID: 21889885 DOI: 10.1016/j.jnutbio.2011.04.001

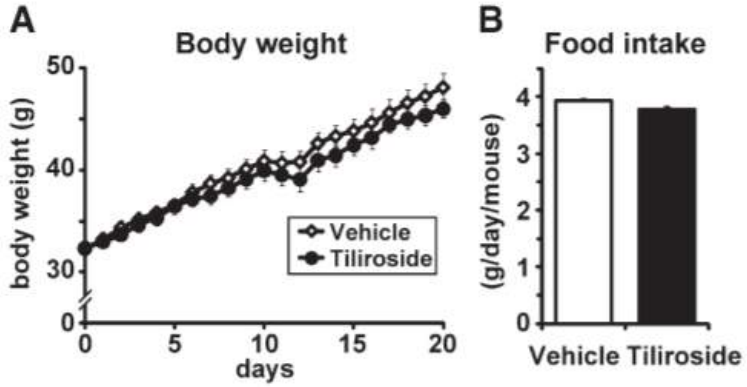
Abstract

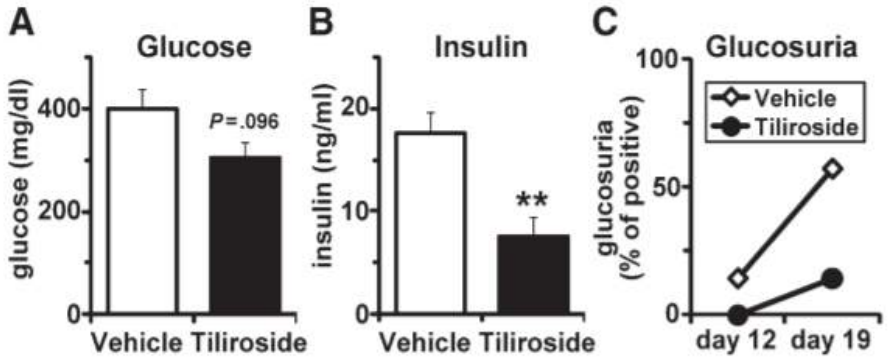
Tiliroside contained in several dietary plants, such as rose hips, strawberry and raspberry, is a glycosidic flavonoid and possesses anti-inflammatory, antioxidant, anticarcinogenic and hepatoprotective activities. Recently, it has been reported that the administration of tiliroside significantly inhibited body weight gain and visceral fat accumulation in normal mice. In this study, we evaluated the effects of tiliroside on obesity-induced metabolic disorders in obese-diabetic KK-A(y) mice. In KK-A(y) mice, the administration of tiliroside (100 mg/kg body weight/day) for 21 days failed to suppress body weight gain and visceral fat accumulation. Although tiliroside did not affect oxygen consumption, respiratory exchange ratio was significantly decreased in mice treated with tiliroside. In the analysis of metabolic characteristics, it was shown that plasma insulin, free fatty acid and triglyceride levels were decreased, and plasma adiponectin levels were increased in mice administered tiliroside. The messenger RNA expression levels of hepatic adiponectin receptor (AdipoR)-1 and AdipoR2 and skeletal muscular AdipoR1 were up-regulated by tiliroside treatment. Furthermore, it was indicated that tiliroside treatment activated AMP-activated protein kinase in both the liver and skeletal muscle and peroxisome proliferator-activated receptor α in the liver. Finally, tiliroside inhibited obesity-induced hepatic and muscular triglyceride accumulation. These findings suggest that tiliroside enhances fatty acid oxidation via the enhancement adiponectin signaling associated with the activation of both AMP-activated protein kinase and peroxisome proliferator-activated receptor α and ameliorates obesity-induced metabolic disorders, such as hyperinsulinemia and hyperlipidemia, although it does not suppress body weight gain and visceral fat accumulation in obese-diabetic model mice.

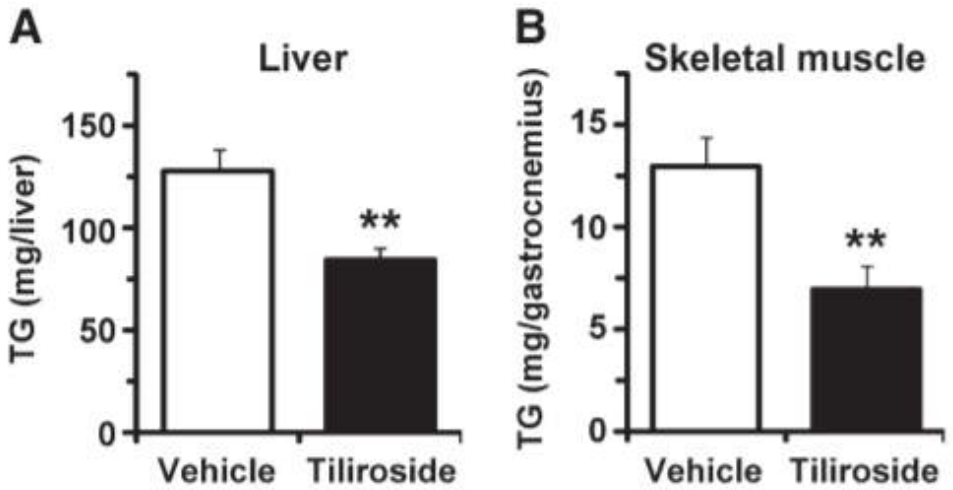
Goto et al., J Nutr Biochem, 2012

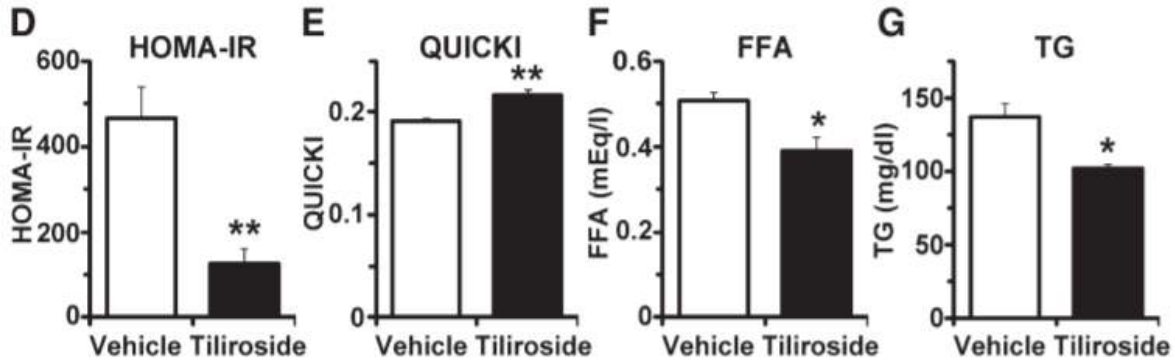
Tiliroside, a glycosidic flavonoid, ameliorates obesity-induced metabolic disorders via activation of adiponectin signaling followed by enhancement of fatty acid oxidation in liver and skeletal muscle in obese–diabetic mice

Tsuyoshi Goto[a,b], Aki Teraminami[a], Joo-Young Lee[a], Kana Ohyama[a], Kozue Funakoshi[a], Young-Il Kim[a], Shizuka Hirai[a], Taku Uemura[a], Rina Yu[c], Nobuyuki Takahashi[a,b], Teruo Kawada[a,b,*]

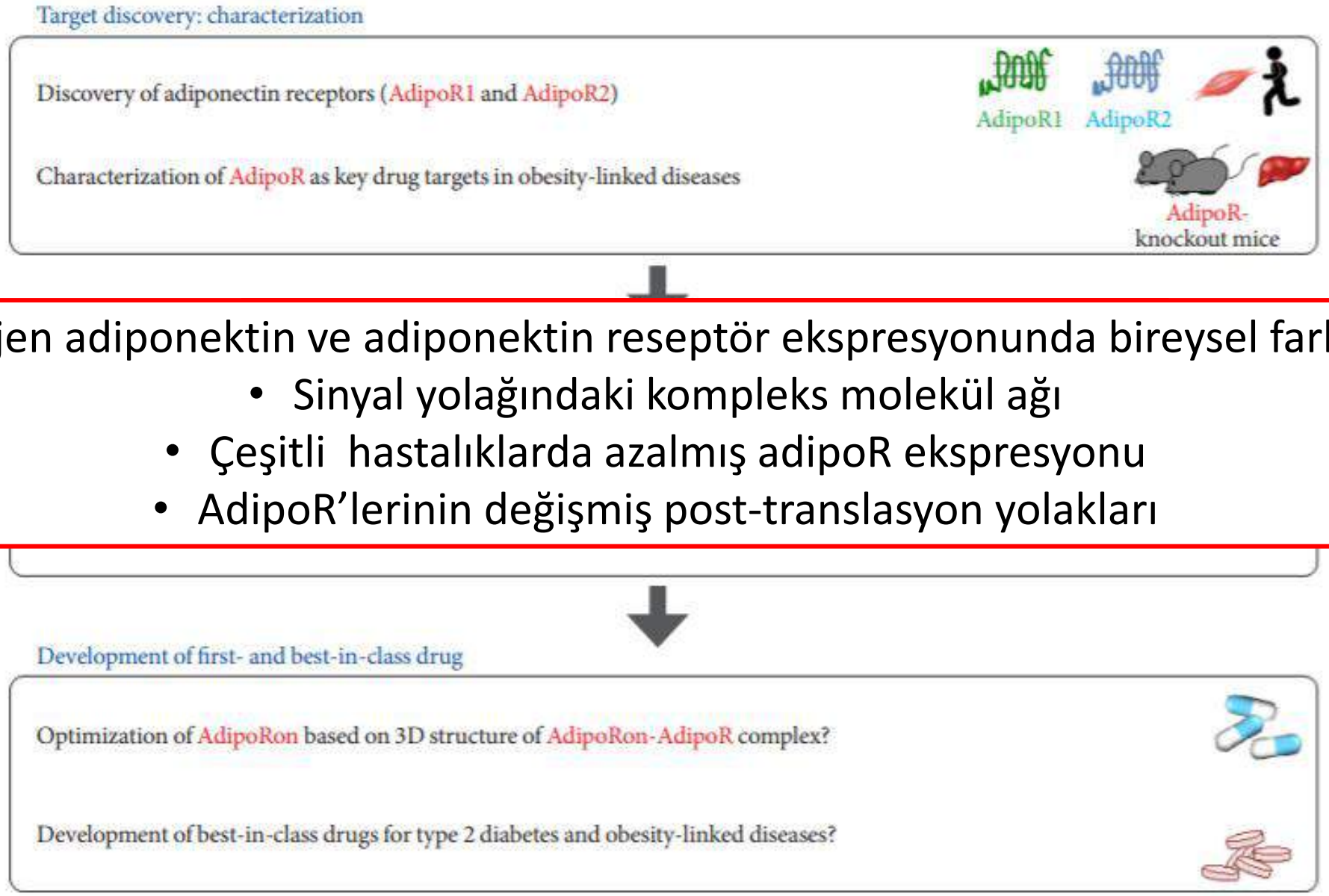








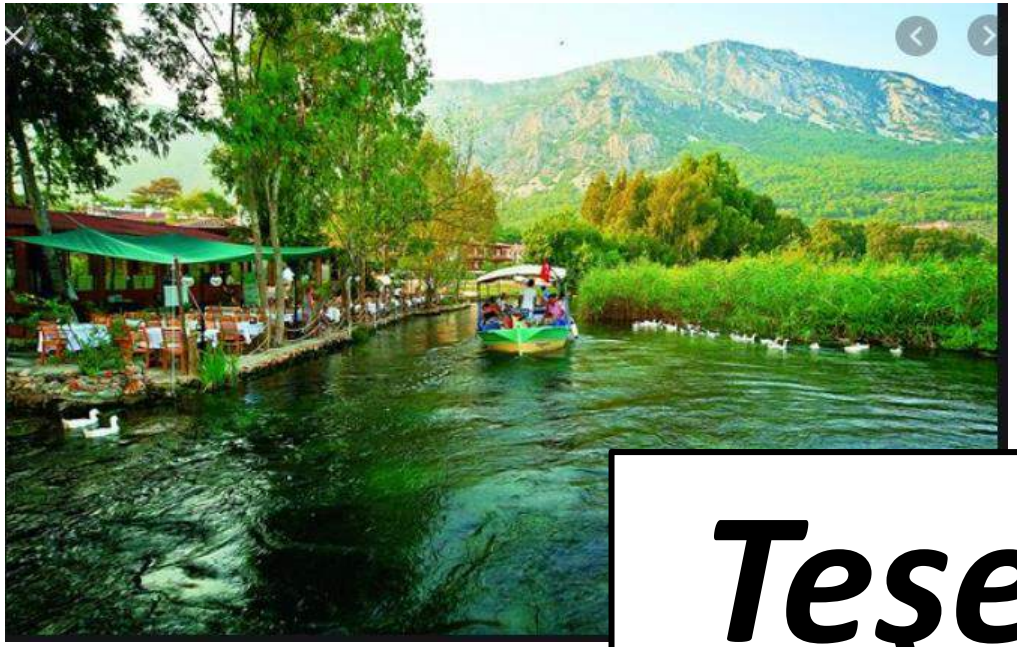
Goto et al., J Nutr Biochem, 2012

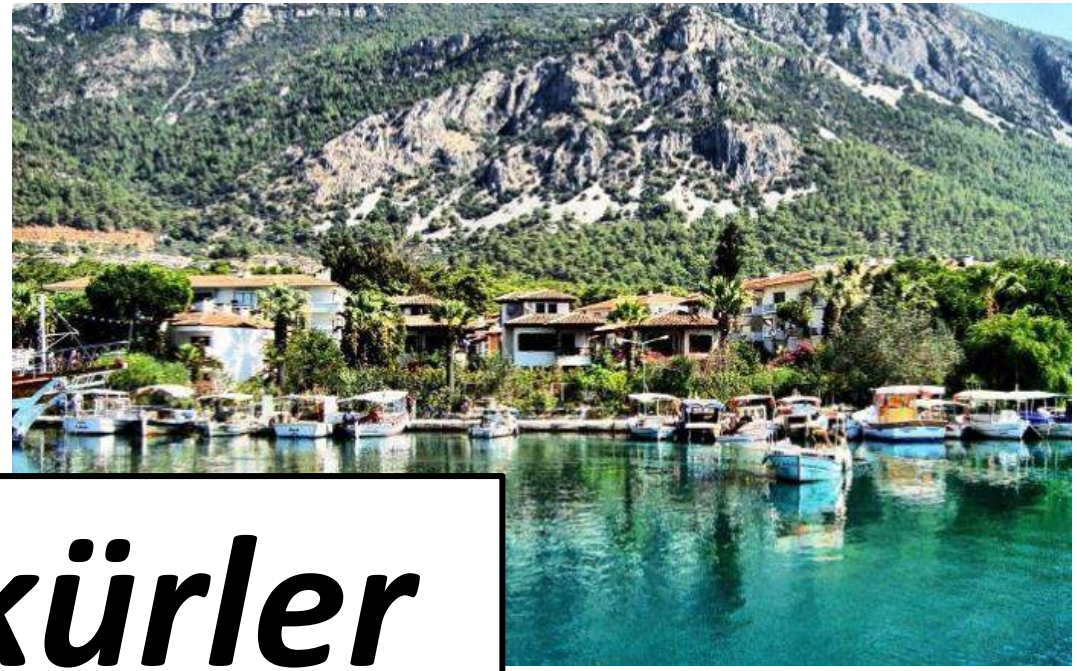


- Endojen adiponektin ve adiponektin reseptör ekspresyonunda bireysel farklılıklar
  - Sinyal yolağındaki kompleks molekül ağı
  - Çeşitli hastalıklarda azalmış adipoR ekspresyonu
  - AdipoR'lerinin değişmiş post-translasyon yolakları

Sonuç olarak..

- Gelecekte umut vadeden ajanlar
- Gelecekte farmakokinetikleri geliştirilmiş, daha yüksek affinite gösteren, doku- ya da hücre- spesifik ajanlara yönelik çalışmalar yapılmalı





Teşekkürler