Role of the expanded endocannabinoid system in cardiometabolic risk

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Outline

-Brief introduction to the endocannabinoid (eCB) system and its role in lipogenesis and lipolysis

-Obesity – associated dysregulation of the eCB system in different white adipose depots and its role in ectopic fat formation, inflammation and atherosclerosis, in both animal models and patients

-The endocannabinoidome and its emerging role in cardiometabolic risk and atherosclerosis

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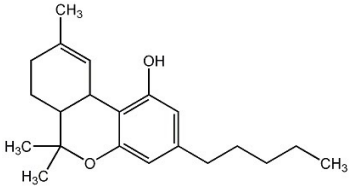
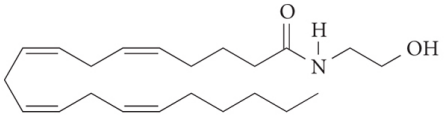
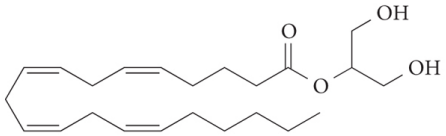
Cannabinoid receptors



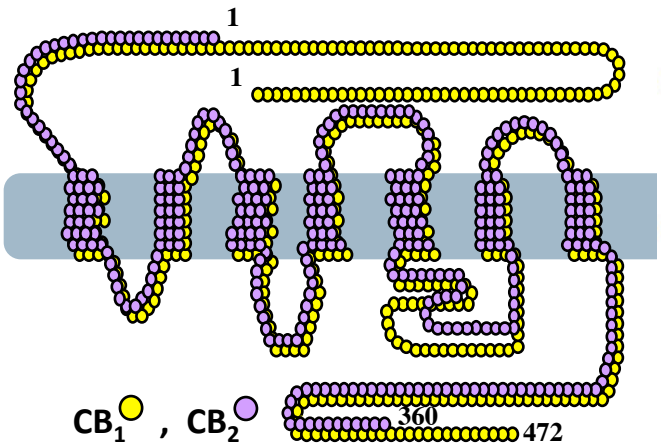
d9-tetrahydrocannabinol

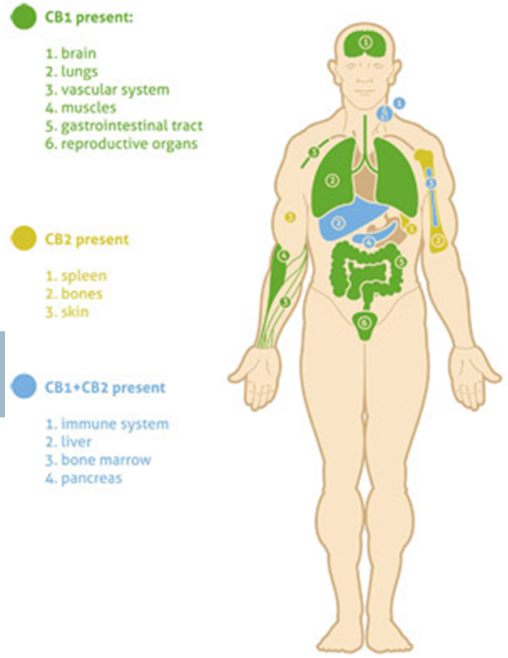


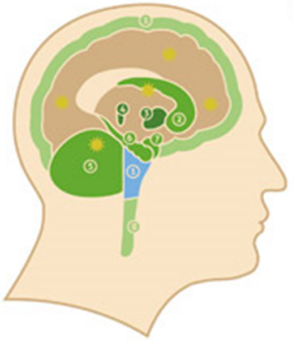
Arachidonoyl ethanlolamide
(AEA; anandamide)



2-arachidonoyl glycerol
(2-AG)







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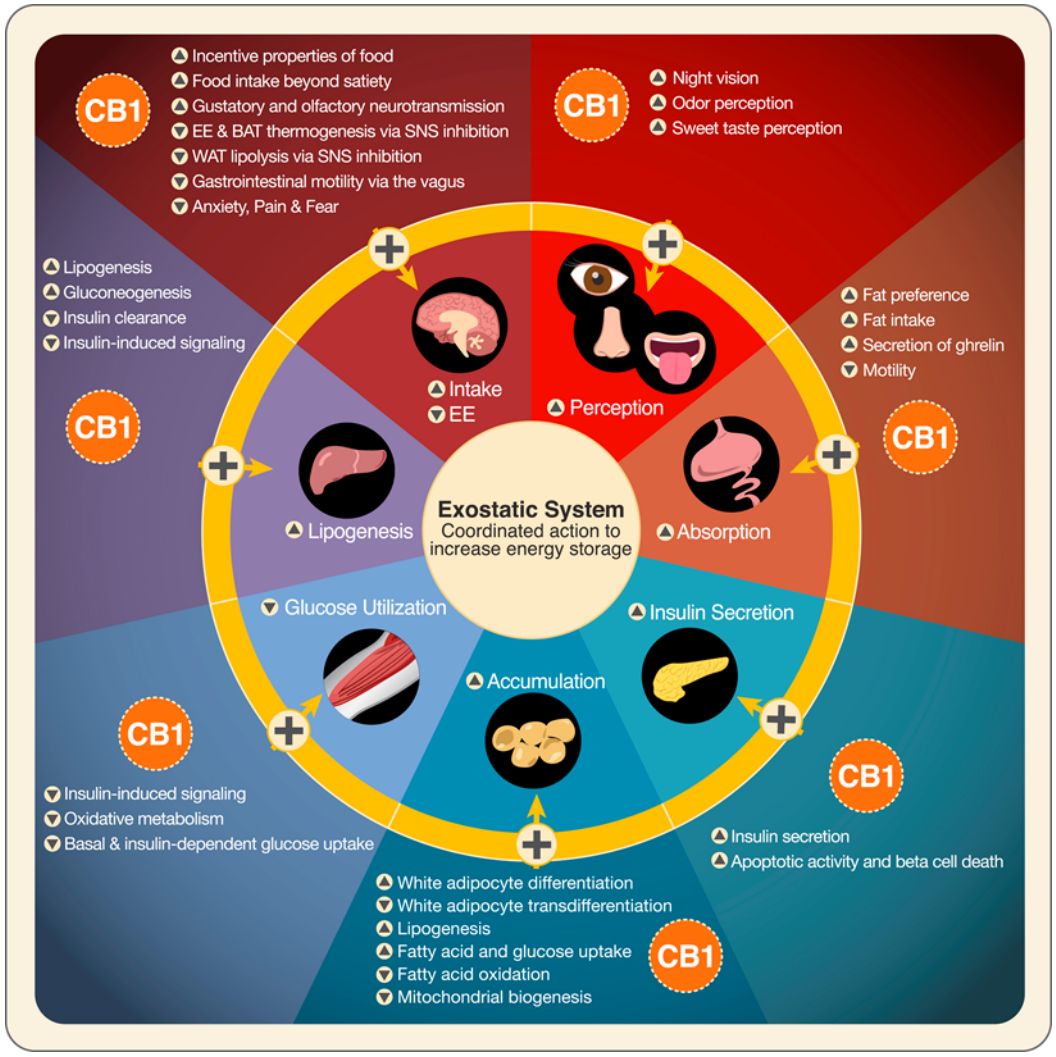
The eCB system: a pleiotropic «thrifty» system controlling all aspects of metabolism, at both central and peripheral levels



Piazza et al, Neuron 2017

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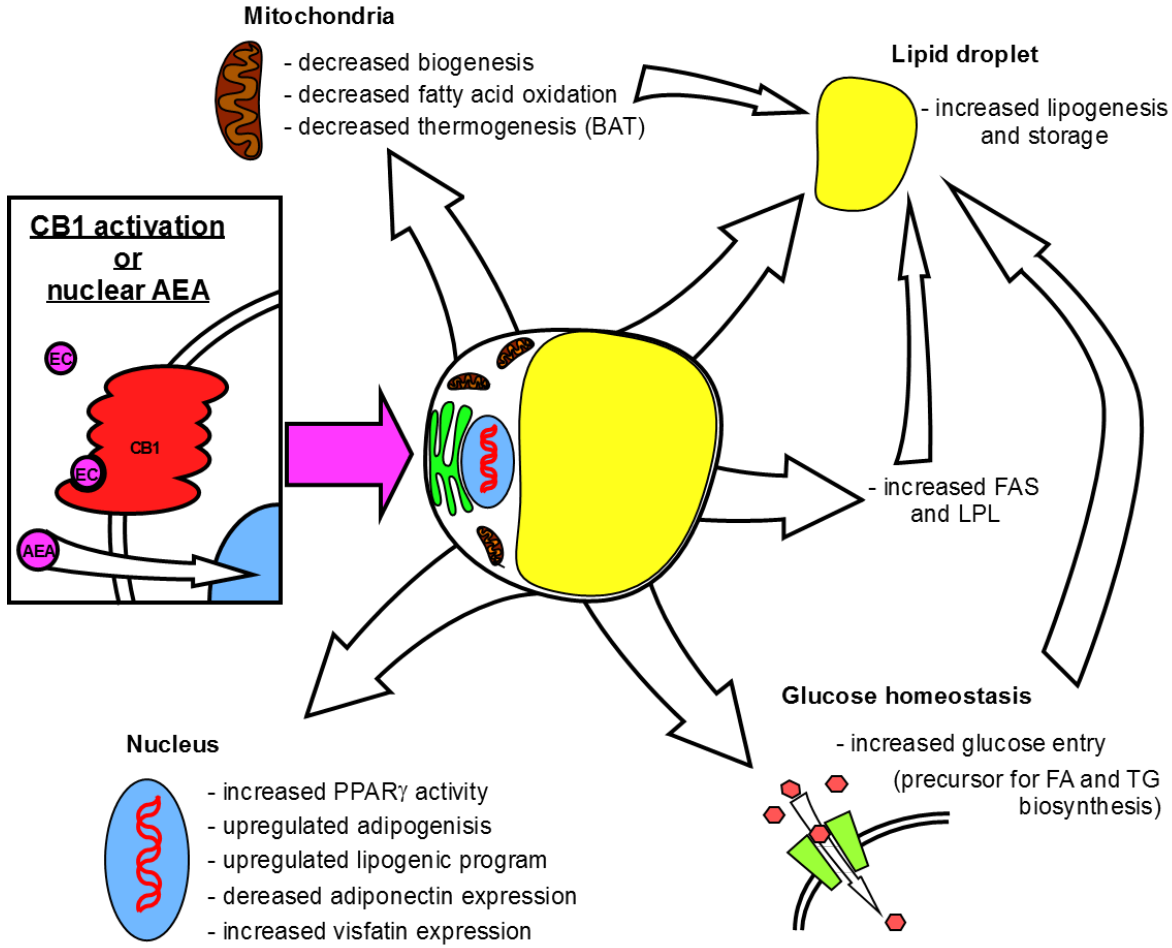
CB1 receptors play a crucial role in adipogenesis and adipose tissue metabolism



Silvestri, Cell Metab. 2013

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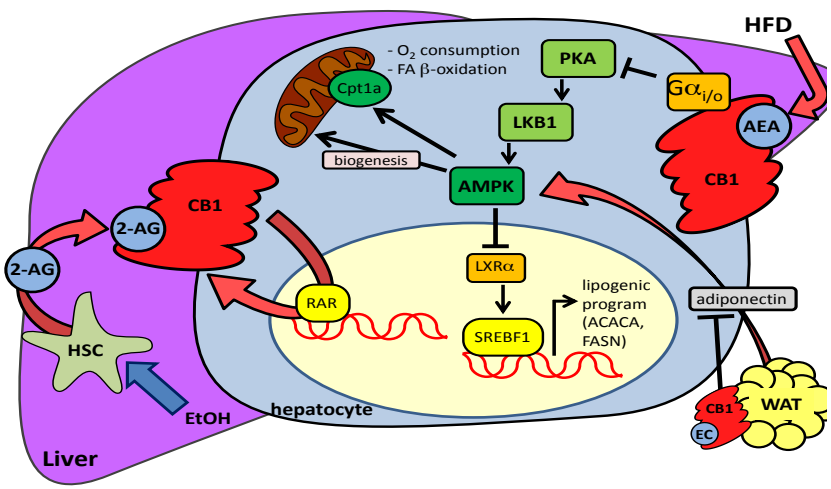
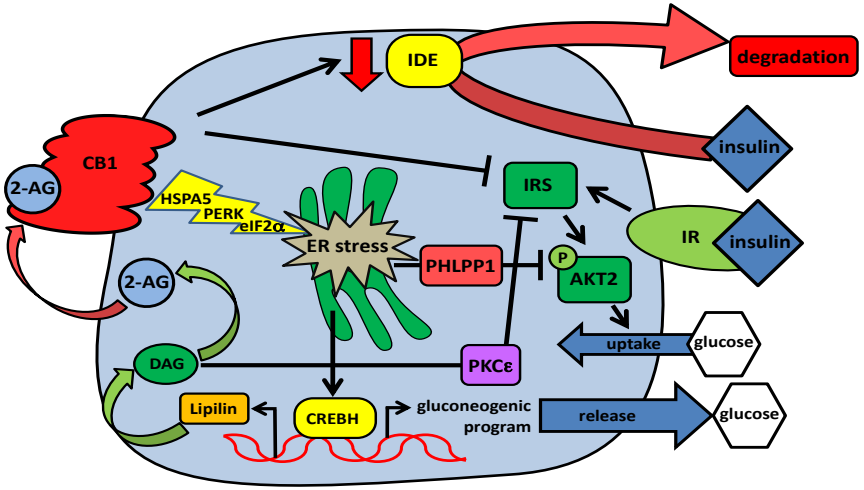
The eCB system in hepatocytes reduces insulin sensitivity and stimulates glucose production and de novo lipogenesis





Silvestri, Cell Metab. 2013

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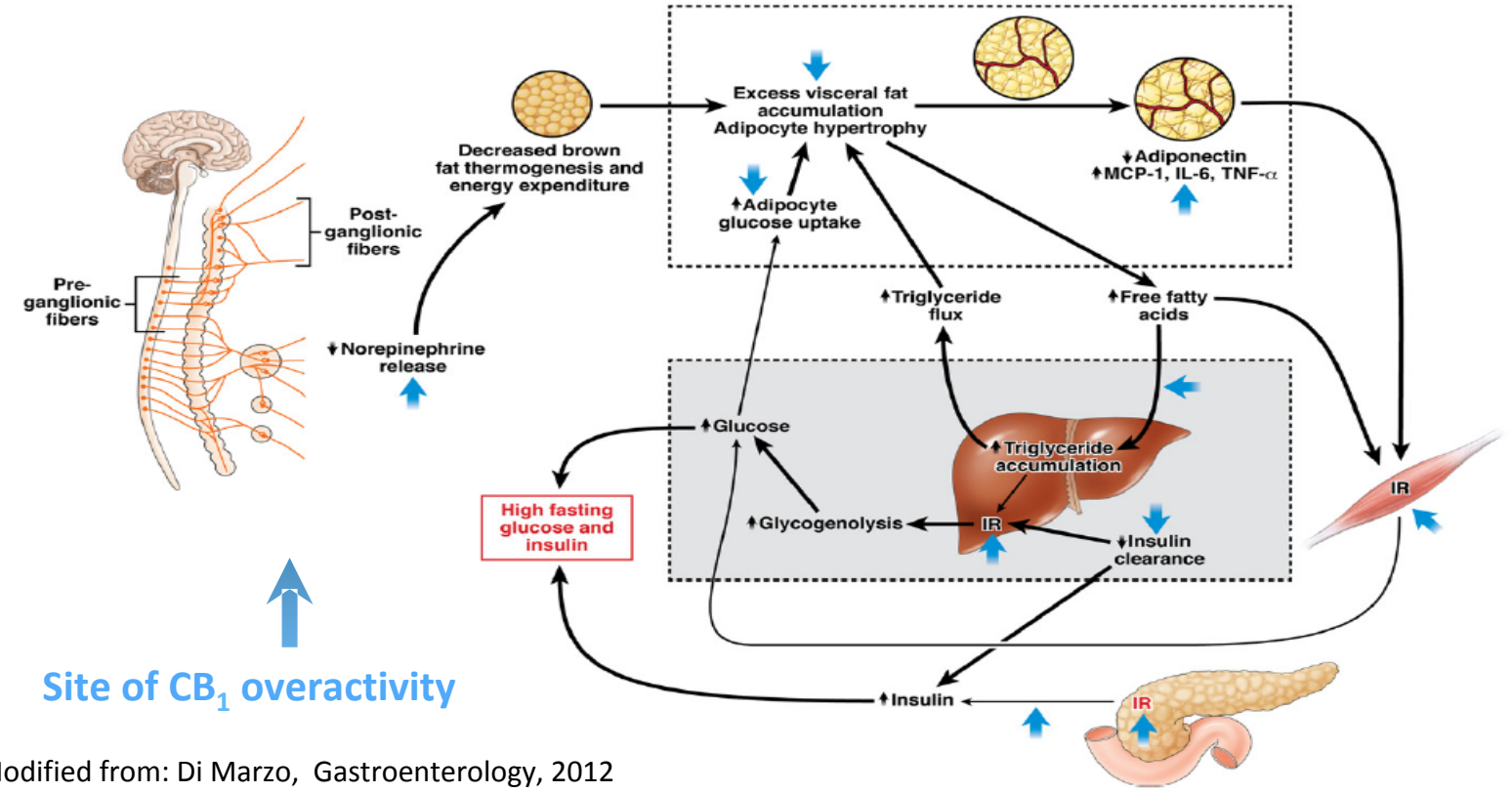
Dysregulation of peripheral control of energy balance by the eCB system in obesity and insulin or leptin resistance



Site of CB_1 overactivity

Modified from: Di Marzo, Gastroenterology, 2012

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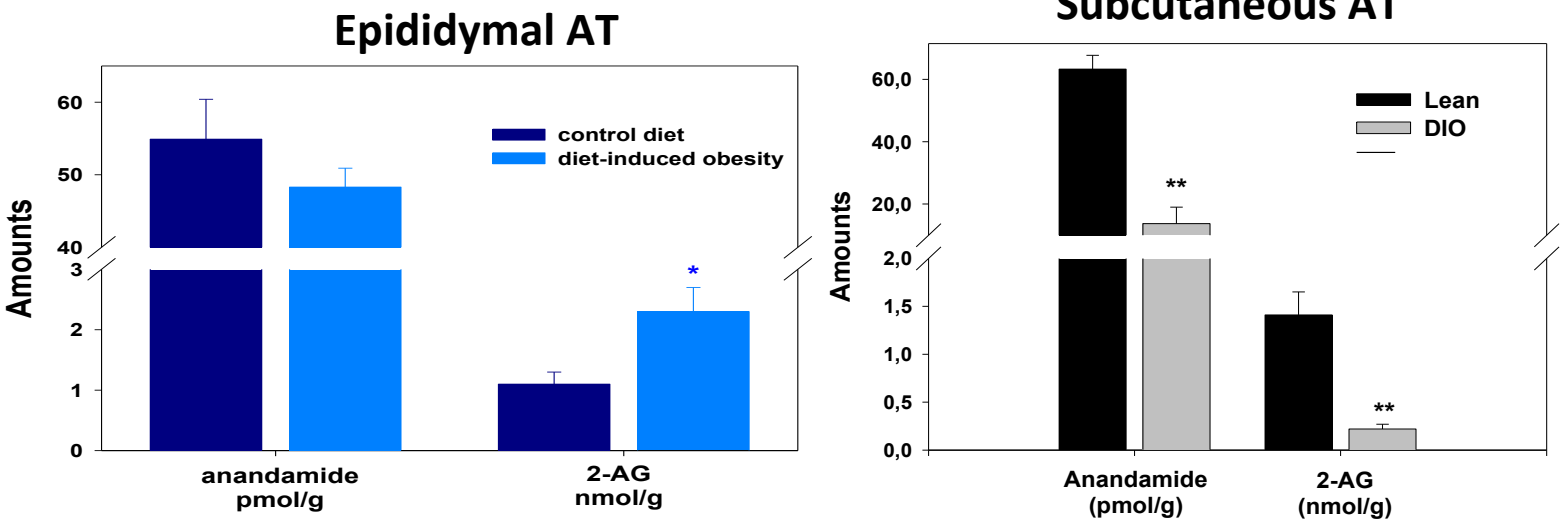
Aberrant eCB levels in the epididymal and subcutaneous adipose tissue of mice with high fat diet-induced obesity (DIO)



Matias et al. J. Clin. Endocrinol. Metab. 2006;
Starowicz et al., Obesity, 2008

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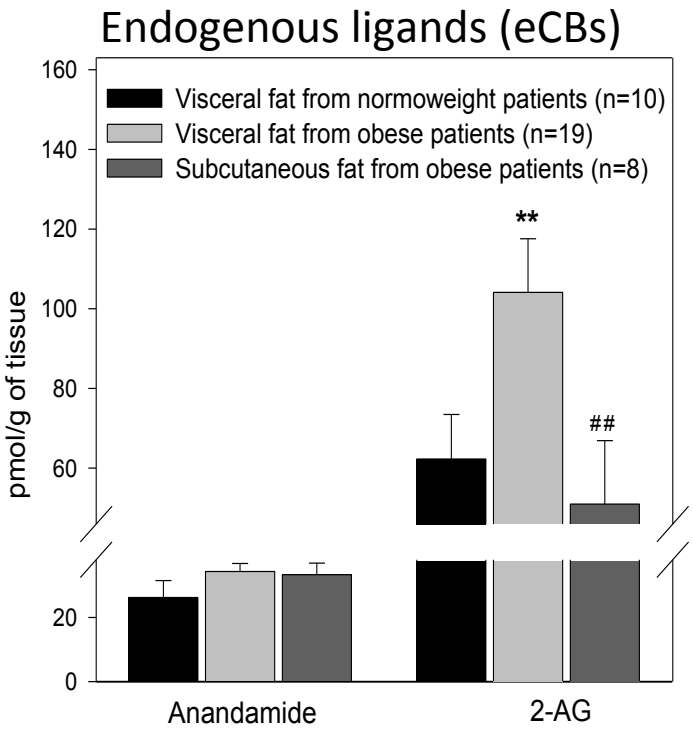
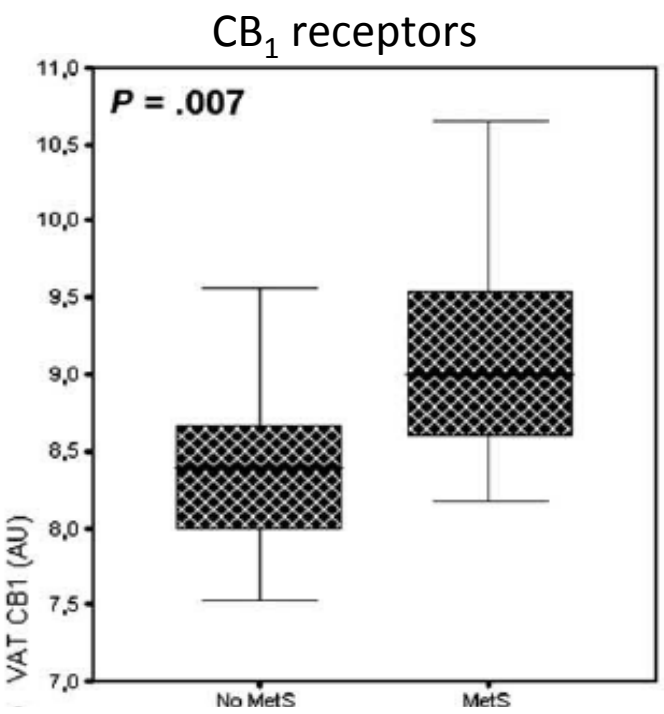
Elevated eCB/CB1 tone in human visceral adiposity and metabolic syndrome



Matias et al. *J. Clin.Endocrinol. Metab.* 2006



(Sarzani et al., Metabolism, 2009)

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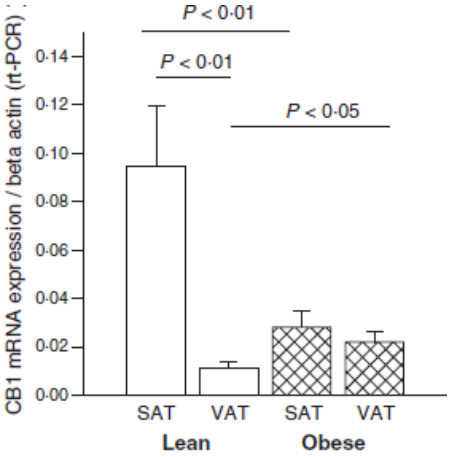
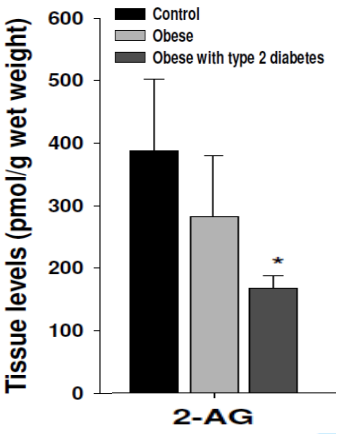
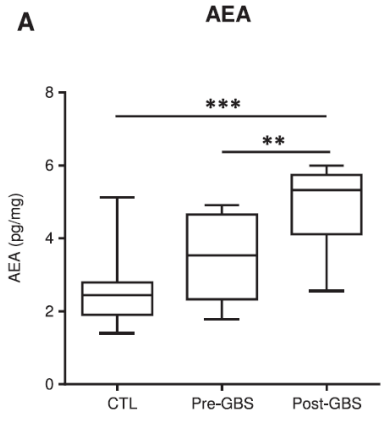
The eCB system is down-regulated in the subcutaneous adipose tissue of obese/OW/T2D subjects and up-regulated following bariatric surgery

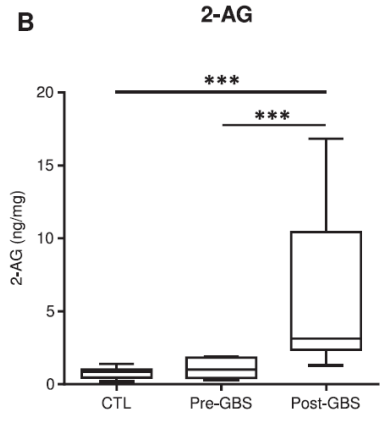
Receptor



Endogenous ligands







Bennetzen et al., Eur. J. Clin. Invest., 2009
Annuzzi et al., Lipids Health Dis 2010
Montecucco et al., Thrombosis and Haemostasis 2015

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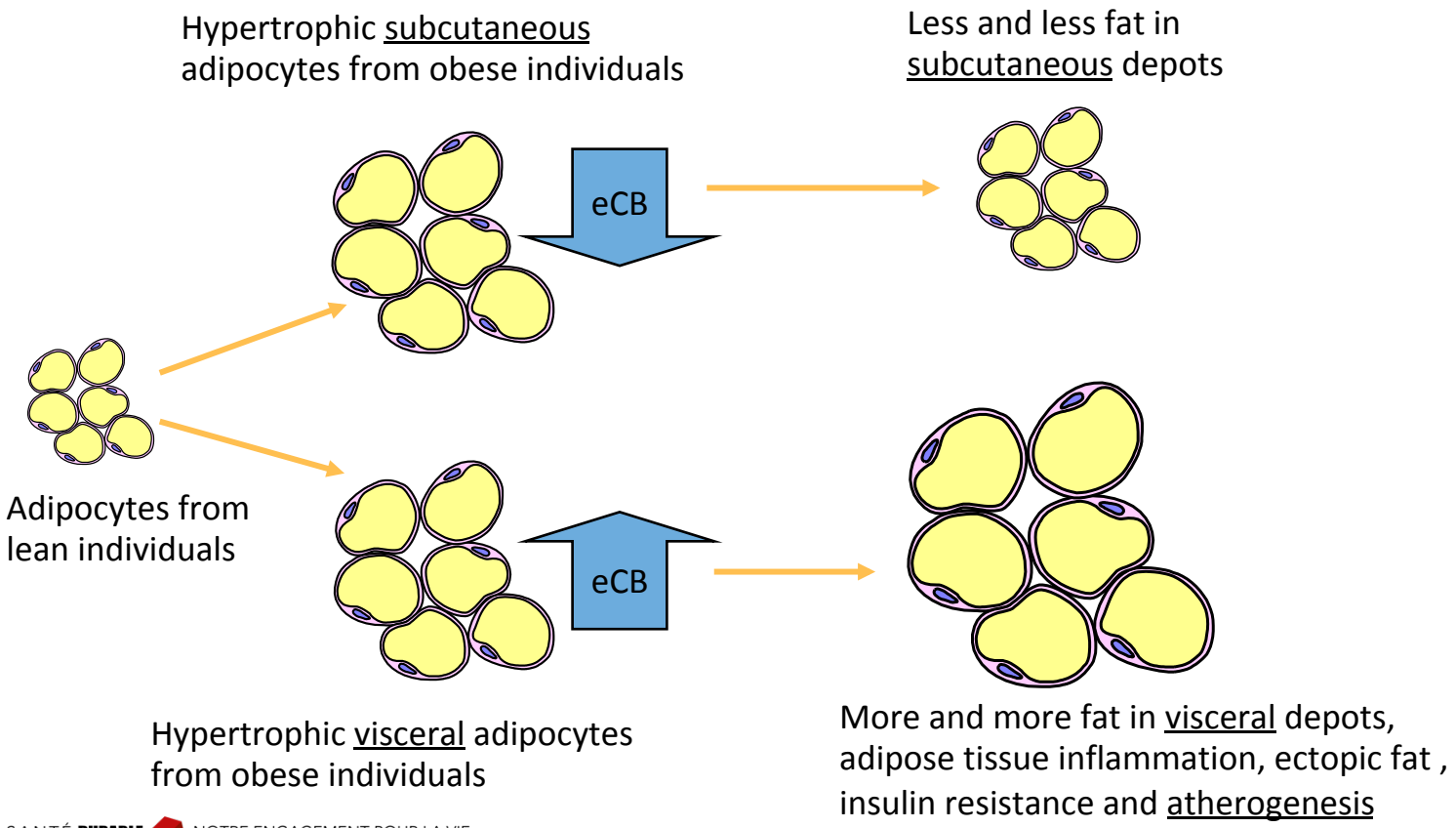
eCB dysregulation might contribute to fat redistribution and ectopic (liver) fat formation



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Correlations between plasma 2-AG levels and cardio-metabolic risk factors in abdominally obese male subjects

Variables	2-AG
Body mass index (kg/m^2)	r=0.30, p<0.02
Waist circumference (cm)	r=0.31, p<0.02
Intra-abdominal AT (cm^2)	r=0.45, p<0.0003
Subcutaneous AT (cm^2)	r=0.07, NS
HDL cholesterol (mmol/L)	r=-0.25, p<0.04
Triglycerides (mmol/L)	r=0.35, p<0.005
Fasting insulin (pmol/L)	r=0.35, p<0.005
Fasting glucose (mmol/L)	r=0.16, NS
Insulin area ($pmol/Lx10^{-3}$)	r=0.35, p<0.006
Glucose area ($mmol/Lx10^{-3}$)	r=0.36, p<0.005
Adiponectin ($\mu g/ml$)	r=-0.30, p<0.02

Côté et al., *Int. J. Obes.*, 2007

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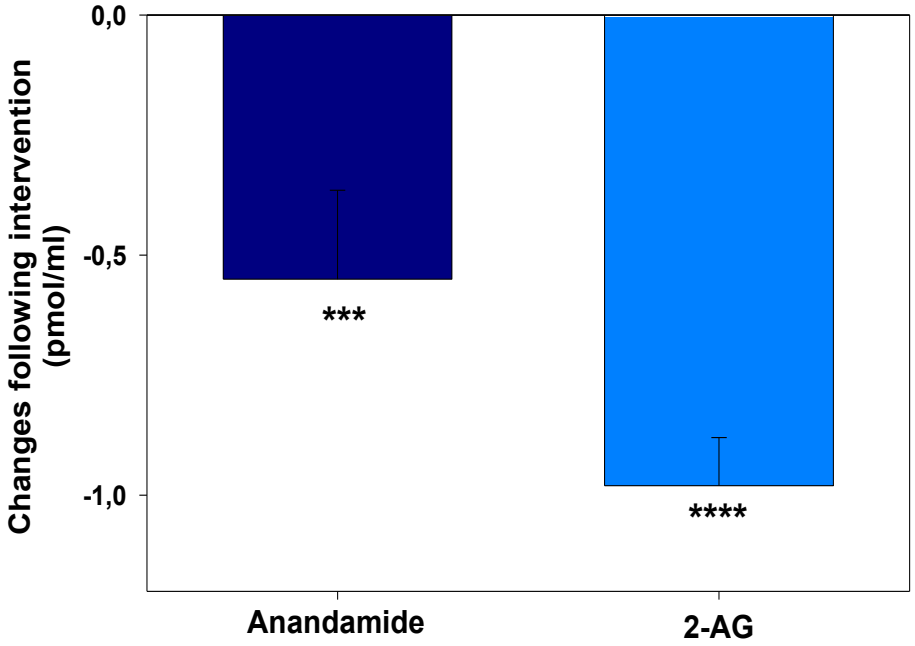
One year lifestyle modification inducing a 8 cm reduction in waist circumference reduces plasma eCB levels in abdominally obese males



Positive correlations between

↓ 2-AG levels with:

↓ visceral adipose tissue (VAT);

↓ Free TG and TG in HDL, LDL and VLDL cholesterol;

↑ HDL_3-cholesterol;

↓ insulin resistance

Di Marzo, *Diabetologia, 2009*

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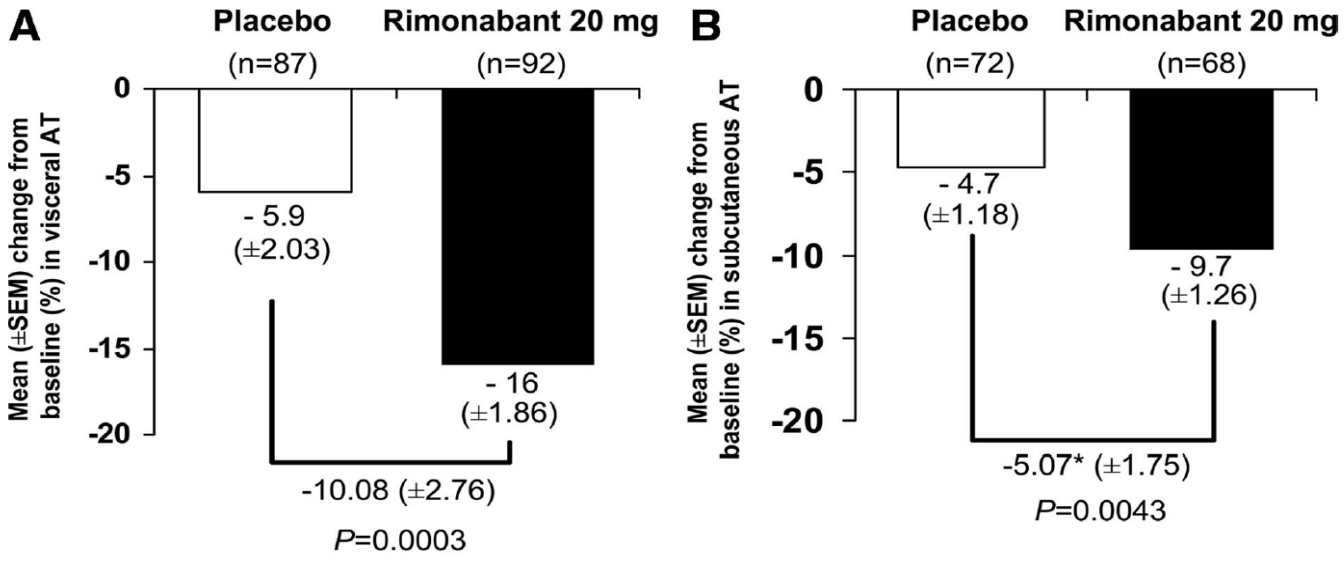
CB1 antagonism preferentially reduces visceral adiposity in abdominally obese individuals



ADAGIO-Lipids study: Després et al, ATVB, 2009

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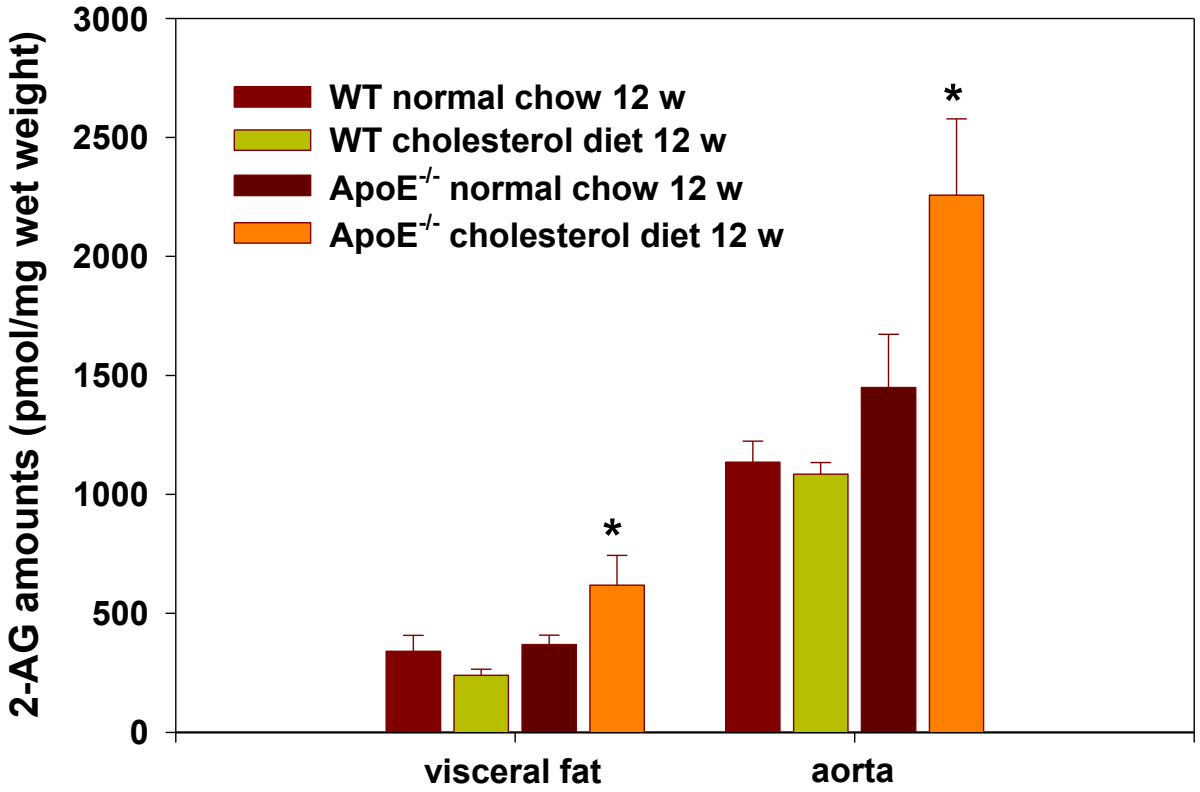
eCB overactivity in an animal model of atherosclerosis

Higher 2-AG levels were only observed in ApoE$^{-/-}$ mice fed a high cholesterol diet for 12 weeks (when the mutants develop plaques). No differences were found after 8 weeks



Montecucco et al., Atherosclerosis, 2009

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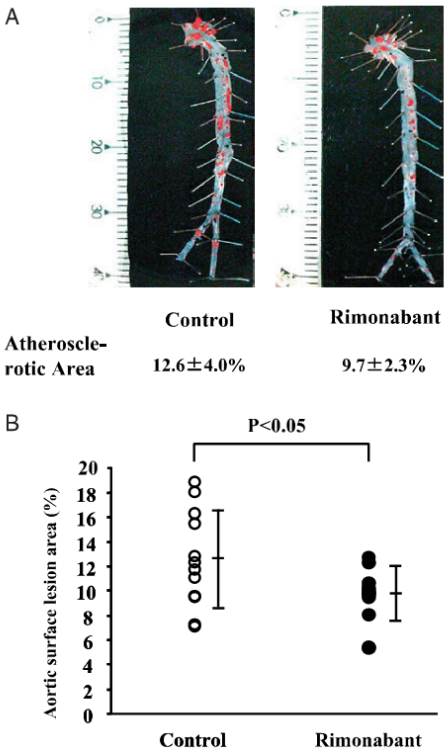
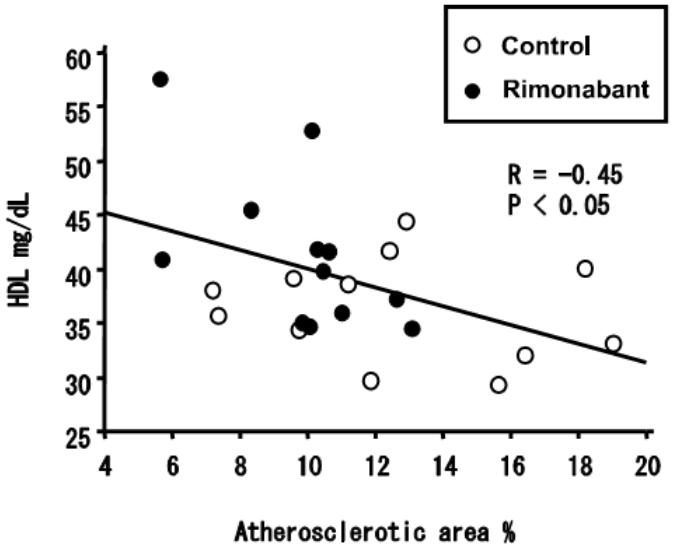
CB1 blockade with rimonabant (8 mg/kg, oral, 3 months) reduces atherosclerosis in ApoE-/- mice





Sugamura et al., J Atheroscler Thromb. 2010

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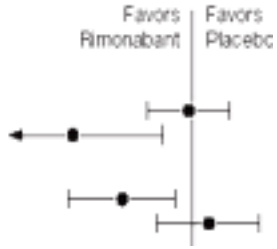
Rimonabant improves some, but not all, markers of atherosclerosis in obese patients, and it works better in hypertrigliceridemic patients: the STRADIVARIUS trial

Parameter	Placebo (n = 341) No.	Placebo (n = 341) Value	Rimonabant (n = 335) No.	Rimonabant (n = 335) Value	*P* Value
		Baseline Values			
Body weight, mean (SD), kg		103.4 (21.7)		103.2 (20.3)	.89
Waist circumference, mean (SD), cm	340	117.3 (14.3)	335	116.9 (13.3)	.71

	LS Mean (SE) [95% CI]	*P* Value (Change From Baseline)	LS Mean (SE) [95% CI]	*P* Value (Change From Baseline)	*P* Value[c]
Nominal change from baseline					
PAV[a]	0.51 (0.15) [0.22 to 0.80]	<.001	0.25 (0.15) [−0.04 to 0.54]	.09	.22
TAV,[b] mm³	0.88 (0.97) [−1.03 to 2.79]	.37	−2.2 (0.96) [−4.09 to −0.24]	.03	.03

Baseline Characteristics	No. of Patients Placebo	No. of Patients Rimonabant	Percentage Atheroma Volume Mean LS Change From Baseline, % (SE) Placebo	Percentage Atheroma Volume Mean LS Change From Baseline, % (SE) Rimonabant	Treatment Difference, % (95% CI)	*P* Value
Statin therapy						
Yes	287	273	0.29 (0.16)	0.23 (0.16)	−0.06 (−0.51 to 0.39)	.03
No	54	62	1.66 (0.36)	0.35 (0.34)	−1.31 (−2.29 to −0.33)	
Baseline triglycerides						
≥Median (140 mg/dL)	169	169	1.07 (0.21)	0.30 (0.21)	−0.77 (−1.35 to −0.16)	.03
<Median	168	163	0.01 (0.20)	0.17 (0.20)	0.16 (−0.40 to 0.72)	



PAV, percent atheroma volume; TAV, total atheroma volume

Nissen et al., JAMA, 2008

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"Global" CB1 receptor antagonists are no longer in clinical development for the metabolic syndrome: what's next?

Most Common Treatment-Emergent Adverse Events (Safety Population, n = 838)

No.	416	422	
Psychiatric disorders	118 (28.4)	183 (43.4)	<.001
Anxiety	49 (11.8)	76 (18.0)	.01
Depression	47 (11.3)	71 (16.8)	.02
Insomnia	38 (9.1)	52 (12.3)	.14
Depressed mood	20 (4.8)	29 (6.9)	.20
Major depression	9 (2.2)	13 (3.1)	.41
Suicidal ideation	10 (2.4)	7 (1.7)	.44
Suicide attempt	1 (0.2)	0	.50
Completed suicide	0	1 (0.2)	.50
Severe psychiatric disorders[b]	16 (3.8)	20 (4.7)	.52

Nissen et al., JAMA, 2008

- CB_1 receptors and their dysregulation due to unbalanced eCB levels play a key role in the pathophysiology of abdominal obesity, type 2 diabetes and atherogenesis

- There are several alternative strategies to counteract CB_1 dysregulation (peripherally restricted antagonists, allosteric CB1 inhibitors, inhibitors of eCB biosynthesis and w-3 PUFAs)

- Any such strategy will have to be investigated in abdominally obese subjects with pre-diabetes or atherosclerosis rather than in otherwise healthy, globally obese subjects

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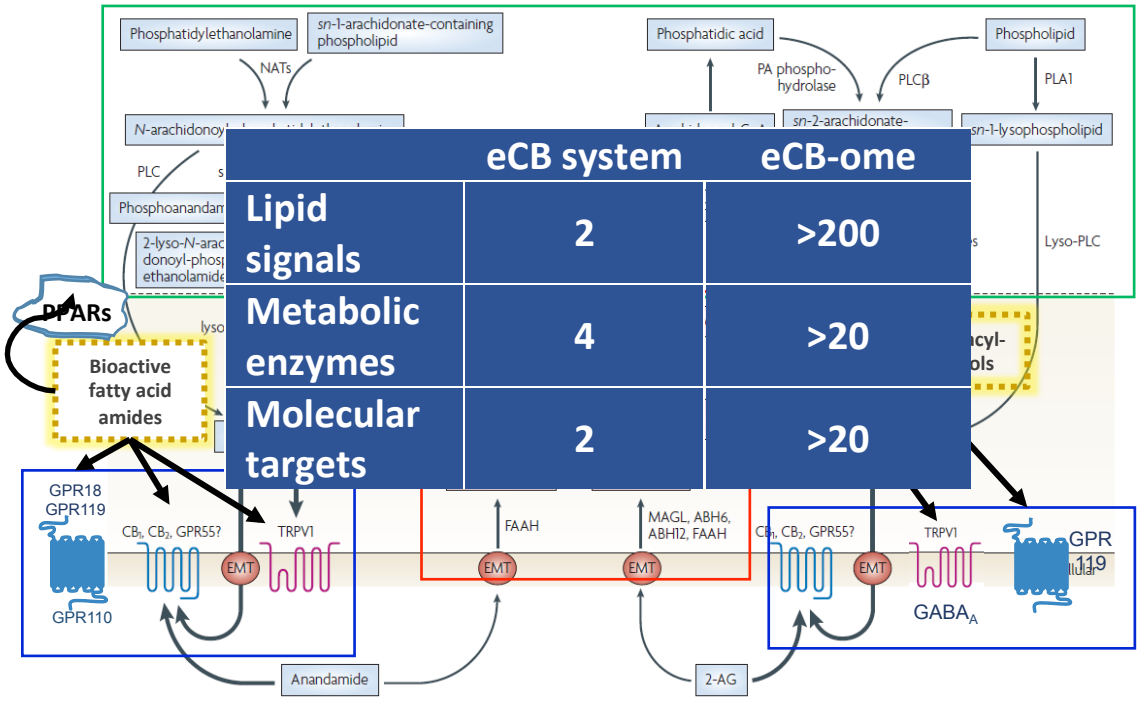
The endocannabinoidome: the expanded endocannabinoid system

	eCB system	eCB-ome
Lipid signals	2	>200
Metabolic enzymes	4	>20
Molecular targets	2	>20



Adapted from:
Di Marzo, 2008, Nature Reviews Drug Discovery

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Targeting CB2 for cardiometabolic risk and atherosclerosis?

Cannabinoid CB2 receptor potentiates obesity-associated inflammation, insulin resistance and hepatic steatosis. Deveaux et al. PLoS One. 2009;4(6):e5844

Deficiency of CB2 cannabinoid receptor in mice improves insulin sensitivity but increases food intake and obesity with age. Agudo et al. Diabetologia. 2010; 3(12):2629-40.

Pro-inflammatory obesity in aged cannabinoid-2 receptor-deficient mice. Schmitz et al. Int J Obes 2016;40(2):366-79.

Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice

Sabine Steffens[1], Niels R. Veillard[1]*, Claire Arnaud[1]*, Graziano Pelli[1], Fabienne Burger[1], Christian Staub[3], Andreas Zimmer[4], Jean-Louis Frossard[2] & François Mach[1]

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[2]*Division of Gastroenterology and* [3]*Institute of Legal Medicine, University Hospital, Faculty of Medicine, 1211 Geneva, Switzerland*
[4]*Laboratory for Molecular Neurobiology, Department of Psychiatry, University of Bonn, 53105 Bonn, Germany*

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European Heart Journal (2012) 33, 846–856
doi:10.1093/eurheartj/ehr449

FASTTRACK CLINICAL

The activation of the cannabinoid receptor type 2 reduces neutrophilic protease-mediated vulnerability in atherosclerotic plaques

Fabrizio Montecucco[1*†], Vincenzo Di Marzo[2†], Rafaela F. da Silva[3], Nicolas Vuilleumier[4], Luciano Capettini[3], Sébastien Lenglet[1], Sabrina Pagano[4], Fabiana Piscitelli[2], Silvia Quintao[3], Maria Bertolotto[5], Graziano Pelli[1], Katia Galan[1], Lucie Pilet[1], Kristina Kuzmanovic[1], Fabienne Burger[1], Bianca Pane[6], Giovanni Spinella[6], Vincent Braunersreuther[1], Angèle Gayet-Ageron[7], Aldo Pende[5], Giorgio Luciano Viviani[8], Domenico Palombo[6], Franco Dallegri[5], Pascale Roux-Lombard[4,9], Robson A.S. Santos[10], Nikos Stergiopulos[3], Sabine Steffens[1‡], and François Mach[1‡]

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Pharmacological and genetic manipulation of eCB levels affects experimental atherosclerosis

Inhibition of endocannabinoid-degrading enzyme fatty acid amide hydrolase increases atherosclerotic plaque vulnerability in mice. Hoyer et al. J Mol Cell Cardiol. 2014; 66:126-32

Fatty acid amide hydrolase deficiency enhances intraplaque neutrophil recruitment in atherosclerotic mice. Lenglet et al. Arterioscler Thromb Vasc Biol. 2013; 33(2): 215-23.

Myeloid-Specific Deletion of Diacylglycerol Lipase α Inhibits Atherogenesis in ApoE-Deficient Mice. Jehle et al. PLoS One 2016;11(1):e0146267.

Monoglyceride lipase deficiency modulates endocannabinoid signaling and improves plaque stability in ApoE-knockout mice. Vujic et al. Atherosclerosis 2016; 244:9-21.

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eCB-derived prostamides as negative feedback regulators of adipogenesis

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 288, NO. 32, pp. 23307–23321, August 9, 2013

Anandamide-derived Prostamide $F_{2\alpha}$ Negatively Regulates Adipogenesis[S]

Received for publication, May 31, 2013 Published, JBC Papers in Press, June 25, 2013, DOI 10.1074/jbc.M113.489906

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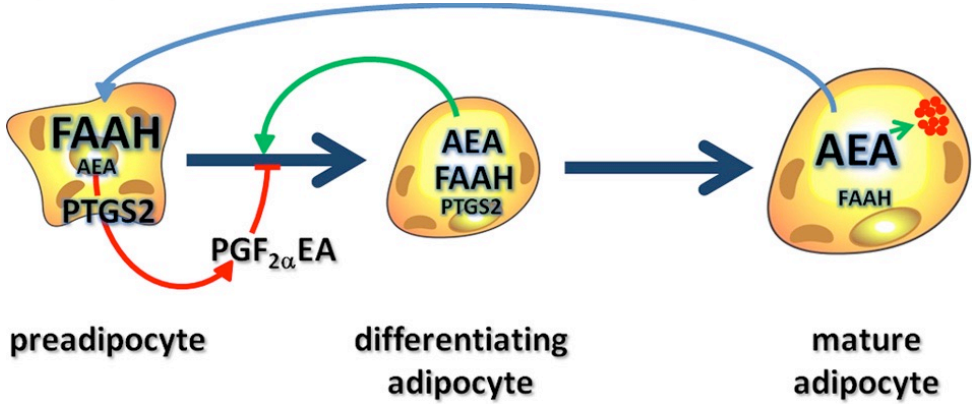
From the [‡]Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, 80078 Pozzuoli, Italy, [§]Allergan, Inc., Irvine, California 92612, and the [¶]Endocannabinoid Research Group, Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy



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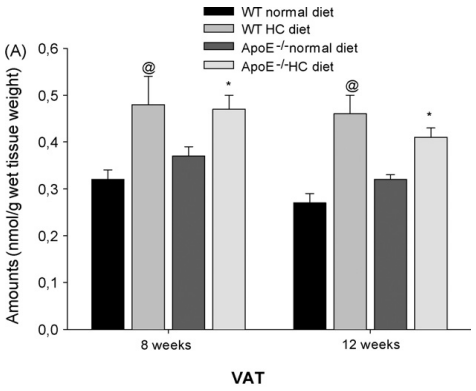
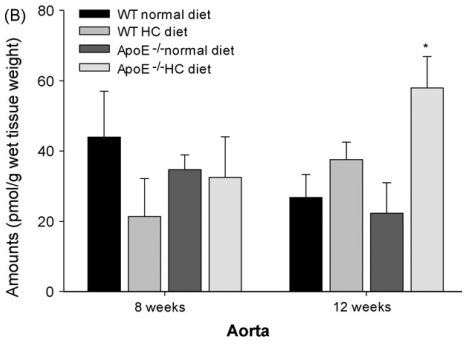
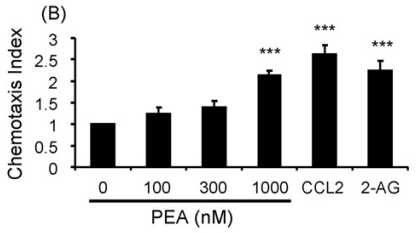
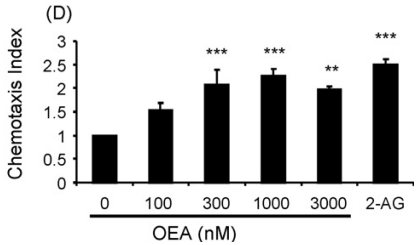
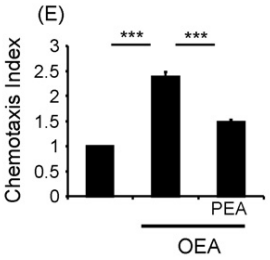
Dysregulation of eCB-related N-acylethanolamines in atherosclerosis and their role in mouse monocyte chemotaxis and adipocyte inflammation

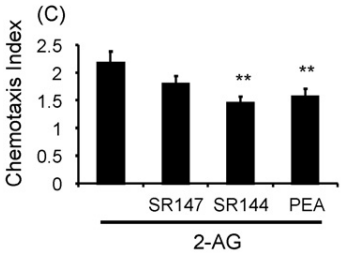


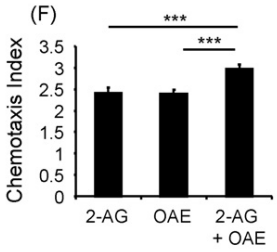


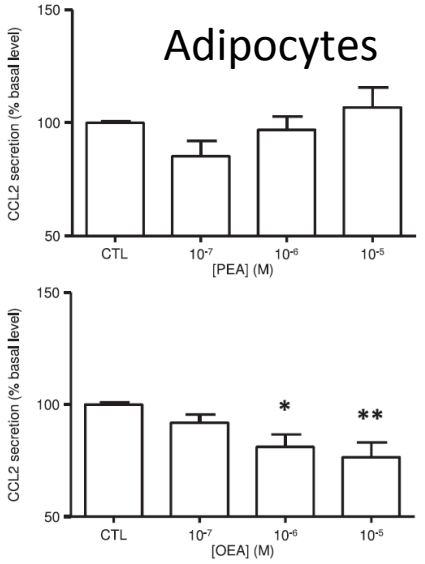












In morbid obese SAT, inverse correlations were found between PEA/OEA levels and inflammatory mediators

Montecucco et al., Atherosclerosis, 2009
Montecucco et al., Thromb Haemost 2015

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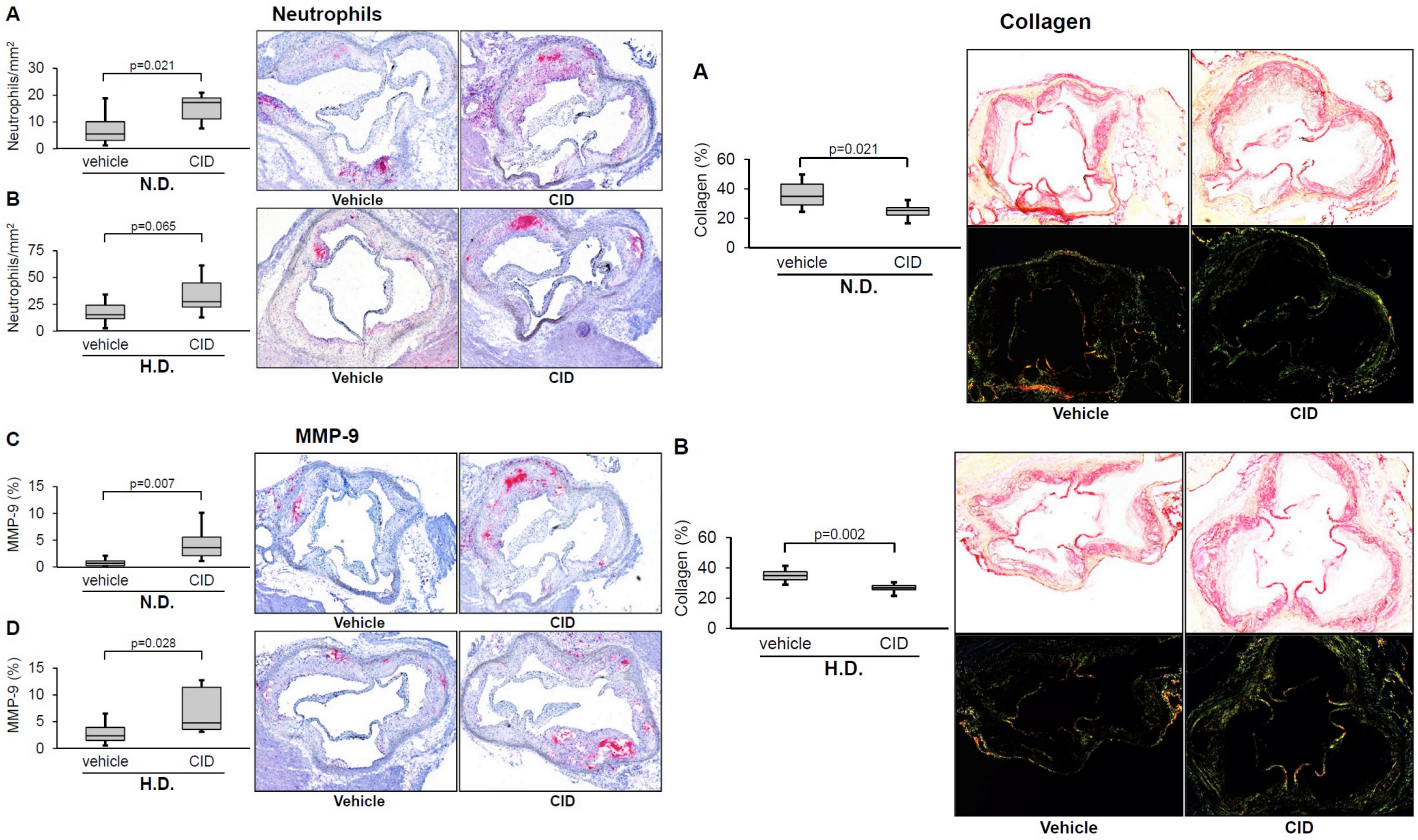
Antagonism of one of PEA proposed targets, GPR55, increases neutrophil activation and plaque instability in mouse atherogenesis



Montecucco et al Thromb Haemost. 2016

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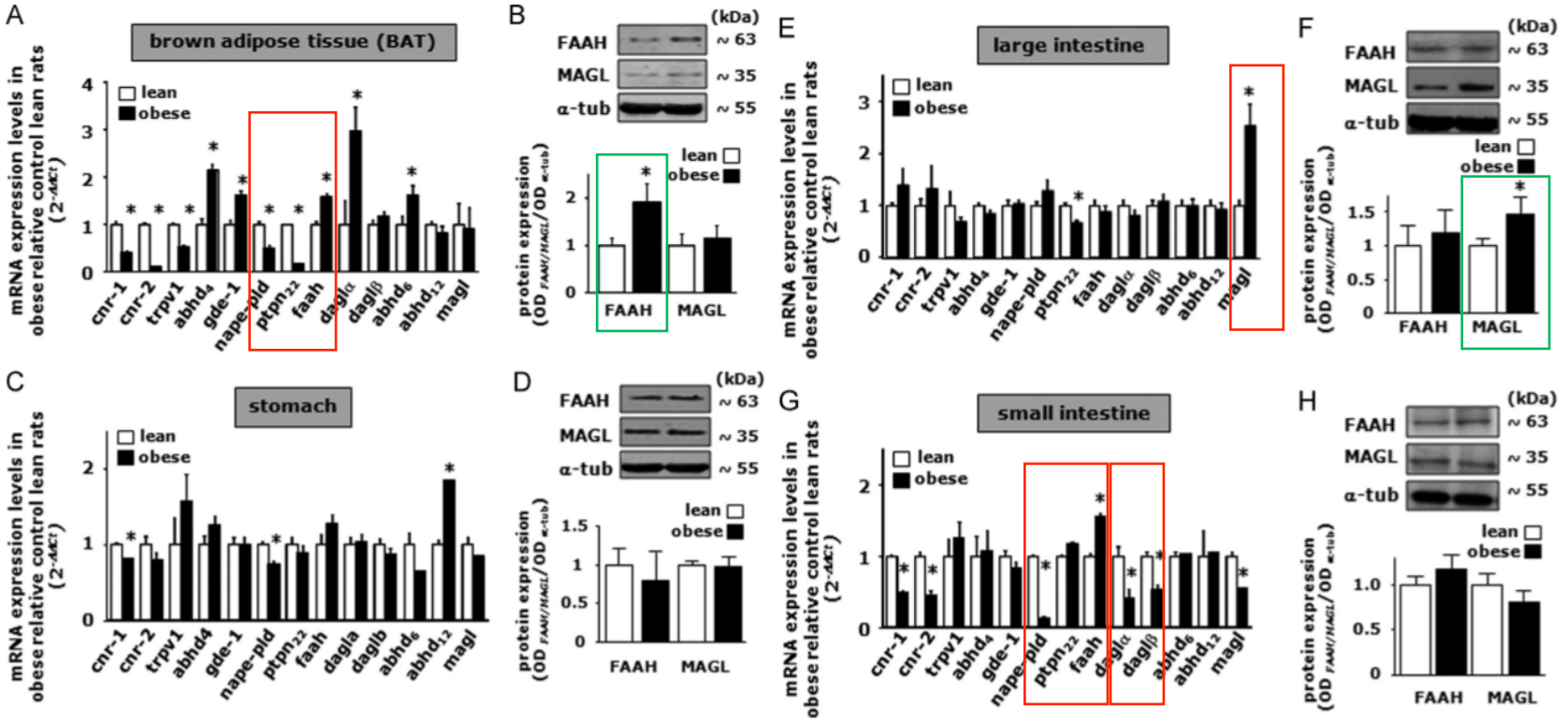
Endocannabinoidome profiling of young Zucker rats



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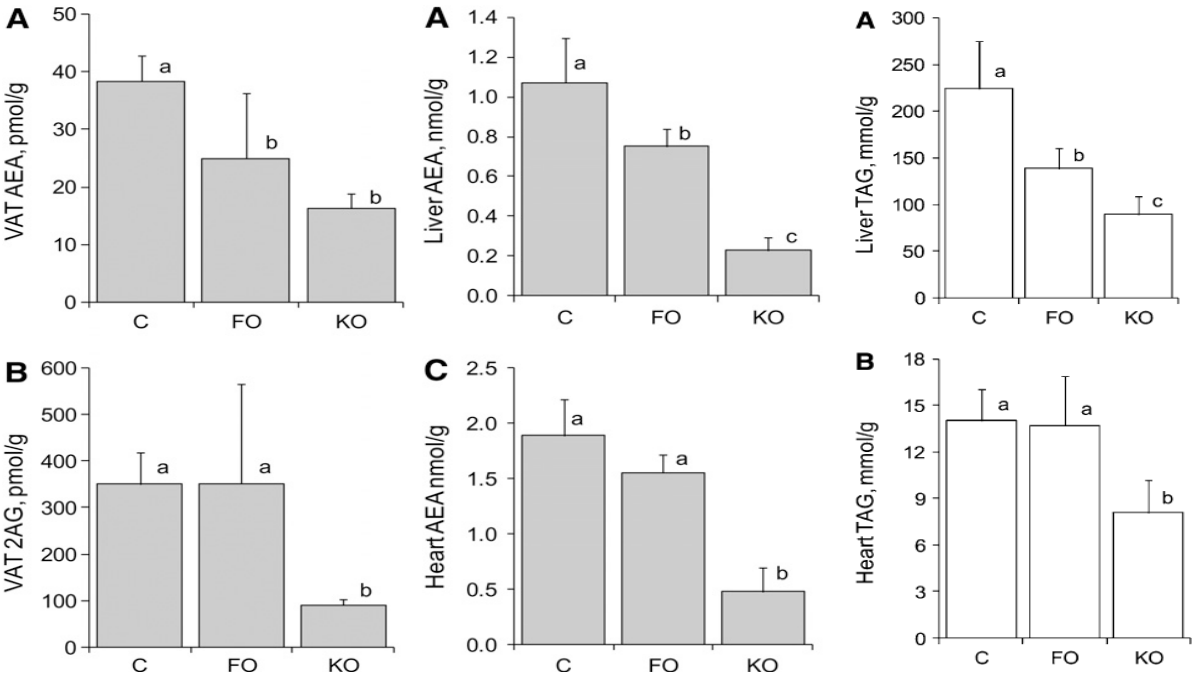
Dietary n-3 PUFAs as selective inhibitors of peripheral eCB overactivity and ectopic fat deposition in obese rats

Four week administration in Zucker *fa/fa* rats of 0.5 g EPA + DHA/100 g of diet (corresponding to 1.8 g/d in an 8.4-MJ/d diet in humans)



The effects were stronger with krill oil (KO) than fish oil (FO) and were accompanied by reduction of the phospholipid biosynthetic precursors of eCBs

There was no effect on food intake and body weight

Batetta et al., J Nutr 2009

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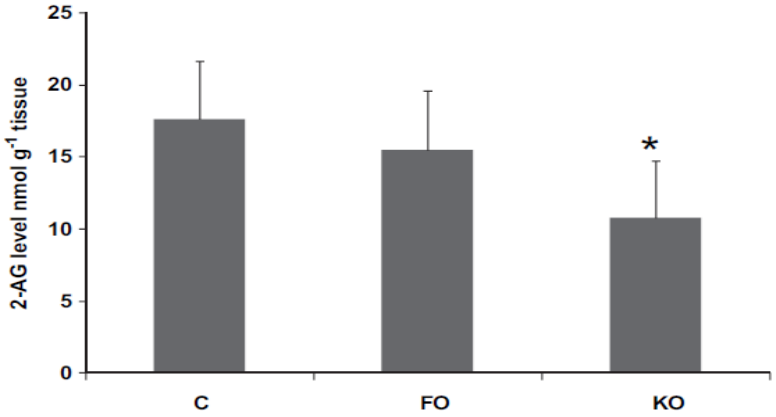
Dietary n-3 fatty acids reduce eCB levels in the brain less than peripheral tissues: less central side effects than CB1 antagonists?



Effect of 4 weeks administration of krill oil (KO) vs. fish oil (FO)

No effect on anandamide levels (Di Marzo et al., Int Dairy J, 2010)

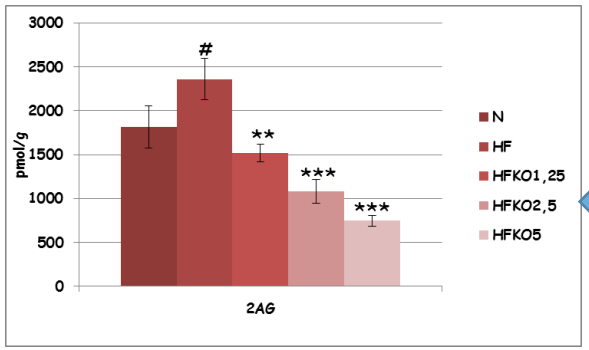
Two weeks of DHA-supplemented diet in lean mice

	Brain				Plasma			
AEA	1.88 ± 0.46	1.47 ± 0.42	-22%	*0.0324*	0.55 ± 0.38	0.38 ± 0.26	-32%	0.1757
AG	5,700 ± 2,100	5,480 ± 1,950	-4%	0.8164	1,570 ± 750	876 ± 442	-44%	*0.0227*

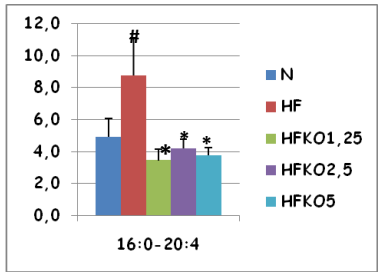
Di Marzo et al., Int Dairy J, 2010
Woods et al., J Lipid Res, 2010

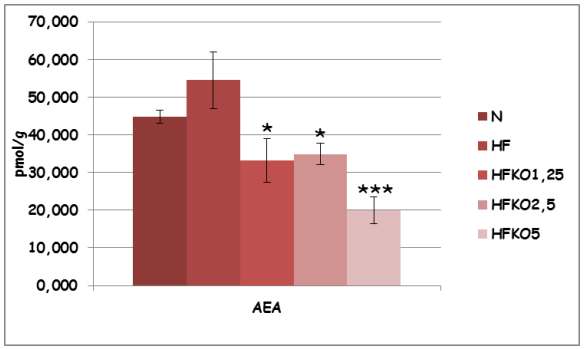
Endocannabinoidome profiling of DIO mice following krill oil treatment

Gastrocnemius muscle

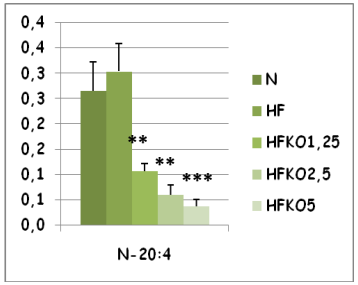


major AA-containing DAG





***N*-arachidonoyl-PE**



-N Normal diet

-HF High-fat diet

-HFKO High-fat diet supplemented with increasing doses of krill oil (1.25, 2.5, 5 KO)

Piscitelli et al, Nut. & Met., 2011

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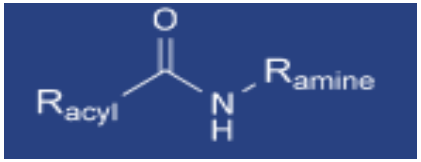
Are the effects of dietary n-3 PUFAs also due to the direct formation of n-3 endocannabinoidome mediators?



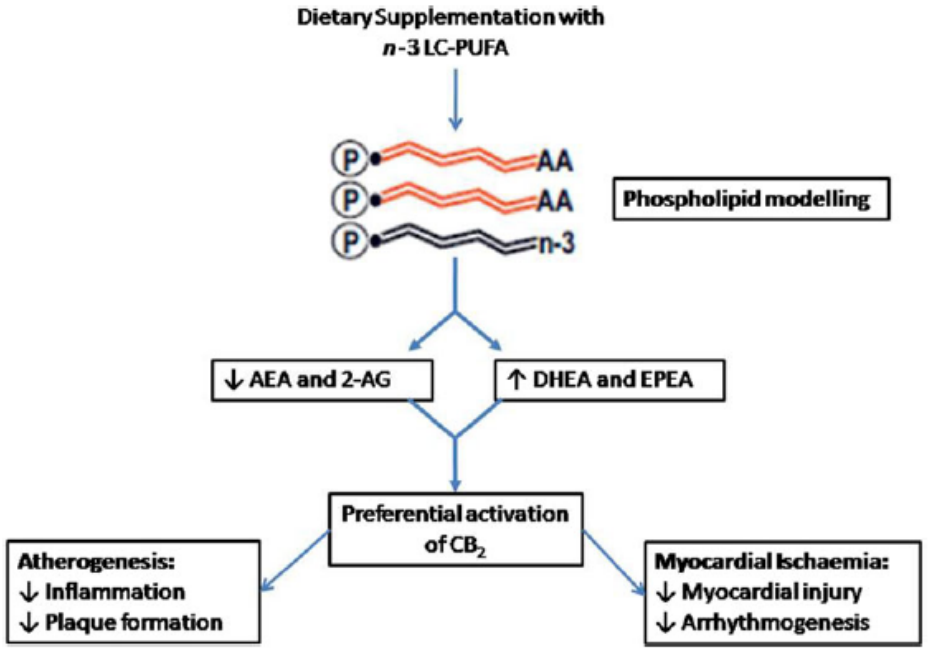


Fig. 3. (colour online) Proposed mechanism of *n*-3 LC-PUFA–endocannabinoid interaction in atherogenesis and myocardial ischaemia. AEA, anandamide; 2-AG, 2-arachidonyl glycerol; DHEA, docosahexaenoyl ethanolamide; EPEA, eicosapentaenoyl ethanolamine; CB_2, cannabinoid receptor type 2.

Meijerink et al., Br. J. Pharmacol. 2013
Wainright et al., P. Nut. Soc. 2013

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Pilot study in diabetic non-human primates with dyslipidemia

Endocannabinoid-type compound	Group		Baseline	Week after start of treatment									
				2	4	6	8	10	12	14	16	18	20
Anandamide ↓	Control	Mean	4,24	4,80	5,60	4,31	4,82	4,66	6,02	6,19	2,82	5,19	5,15
		SEM	2,00	1,18	2,17	0,93	0,80	0,91	3,84	2,65	0,77	1,38	1,67
	Treated	Mean	3,07	3,40	2,86	2,98	2,86	3,34	2,28	3,64	4,25	4,05	4,44
		SEM	0,52	1,54	0,93	0,56	0,92	1,35	0,97	1,35	1,69	1,53	0,43
2-arachidonoylglycerol ↓	Control	Mean	14,3	21,0	23,1	21,9	27,8	20,7	28,6	22,7	19,0	18,6	22,4
		SEM	5,5	13,8	15,9	11,1	19,2	15,2	20,6	12,3	11,8	11,3	15,5
	Treated	Mean	16,8	19,2	13,3	9,14	11,7	4,42	8,48	15,0	26,5	16,5	26,4
		SEM	6,4	9,2	7,9	1,12	3,3	1,60	4,20	10,0	19,1	9,1	11,3
EPA ethanolamide ↑	Control	Mean	1,36	1,45	0,91	1,25	0,22	0,57	1,00	1,07	2,07	2,04	2,84
		SEM	0,49	0,29	0,16	0,31	0,07	0,20	0,07	0,71	0,84	0,62	1,06
	Treated	Mean	0,47	1,04	1,05	1,13	0,85	1,00	1,07	0,58	1,34	1,55	0,63
		SEM	0,13	0,48	0,34	0,26	0,24	0,17	0,26	0,22	0,93	0,51	0,35
DHA ethanolamide ↔	Control	Mean	1,23	4,67	5,17	6,64	4,95	4,63	4,61	2,28	3,89	5,82	4,80
		SEM	0,29	1,35	2,09	1,95	2,45	2,03	2,06	1,10	1,45	2,49	1,91
	Treated	Mean	3,06	6,63	8,03	7,24	6,60	7,41	4,96	3,49	5,57	5,97	6,76
		SEM	1,68	3,17	2,34	1,52	1,59	1,12	0,89	0,39	1,30	2,83	2,93
Palmitoyl ethanolamide	Control	Mean	54,7	64,7	58,3	94,7	53,5	71,9	89,9	30,8	24,7	59,3	120
		SEM	4,7	10,3	15,3	30,5	12,7	11,2	7,8	4,7	1,5	20,8	36,3
	Treated	Mean	66,2	62,5	65,6	86,1	58,6	48,4	69,1	78,8	39,5	92,0	120
		SEM	19,2	11,9	14,7	17,3	13,9	9,2	2,4	23,7	8,3	31,5	47,9
Oleoyl ethanolamide	Control	Mean	24,2	24,3	19,0	20,3	30,5	28,5	14,0	29,1	17,6	29,3	31,0
		SEM	4,44	1,50	2,25	2,23	1,55	2,65	1,35	5,26	4,10	4,60	2,28
	Treated	Mean	24,2	22,3	16,0	20,3	24,8	29,9	14,4	36,9	18,0	39,7	45,5
		SEM	3,63	6,86	2,05	2,49	6,63	7,76	2,54	15,01	3,03	14,54	9,89
Dose (mg phospholipids/kg bw/day)				50		150		450		0			
Dose (mg [EPA/DHA]/kg bw/day)				9.35/5.48		28.0/16.4		84.1/49.3		0/0			

Hals et al., Lipids Health Dis 2017

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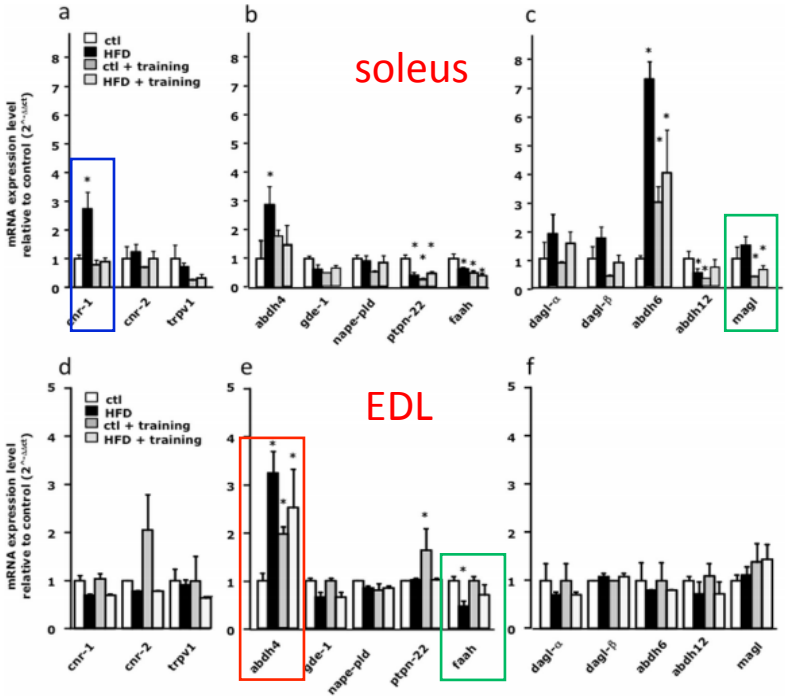
Effects of exercise on the skelatal muscle endocannabinoidome in DIO rats

	Ctl	HFD	Ctl + training	HFD + training	Main effects by ANOVA Diet × Ex, NS
Soleus					
AEA (pmol g^{-1})	18.21 ± 2.98	38.60 ± 10.84	30.96 ± 18.29	35.71 ± 15.28	Diet, $p < 0.02$ Ex, NS Diet × Ex, NS
2-AG (pmol mg^{-1})	2.74 ± 0.80	1.74 ± 0.40*	2.21 ± 0.65	2.28 ± 0.60	Diet, NS Ex, NS Diet × Ex, $p < 0.04$
PEA (pmol mg^{-1})	0.86 ± 0.33	0.70 ± 0.23	0.60 ± 0.14	0.61 ± 0.15	Diet, NS Ex, NS Diet × Ex, NS
OEA (pmol mg^{-1})	0.21 ± 0.02	0.28 ± 0.05	0.22 ± 0.06	0.26 ± 0.05	Diet, $p < 0.006$ Ex, NS Diet × Ex, NS
EDL					
AEA (pmol g^{-1})	8.15 ± 1.81	18.45 ± 4.35**	6.73 ± 2.05	11.34 ± 4.15	Diet, $p < 0.00002$ Ex, $p < 0.005$ Diet × Ex, $p < 0.05$
2-AG (pmol mg^{-1})	0.68 ± 0.15	0.85 ± 0.21	0.73 ± 0.29	0.91 ± 0.16	Diet, $p < 0.04$ Ex, NS Diet × Ex, NS
PEA (pmol mg^{-1})	0.56 ± 0.24	0.76 ± 0.42	0.54 ± 0.24	0.44 ± 0.18	Diet, NS Ex, NS Diet × Ex, NS
OEA (pmol mg^{-1})	0.24 ± 0.10	0.42 ± 0.17	0.27 ± 0.14	0.25 ± 0.06	Diet, NS Ex, NS Diet × Ex, NS

Data are means ± SD

*Significantly different from Ctl group, $p < 0.05$

**Significantly different from all the groups, $p < 0.05$



Gamelin et al., J Physiol Biochem 2016

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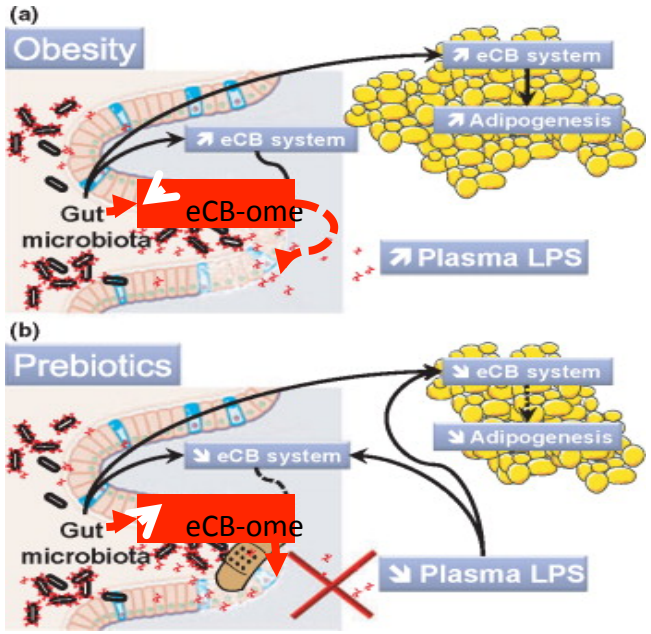
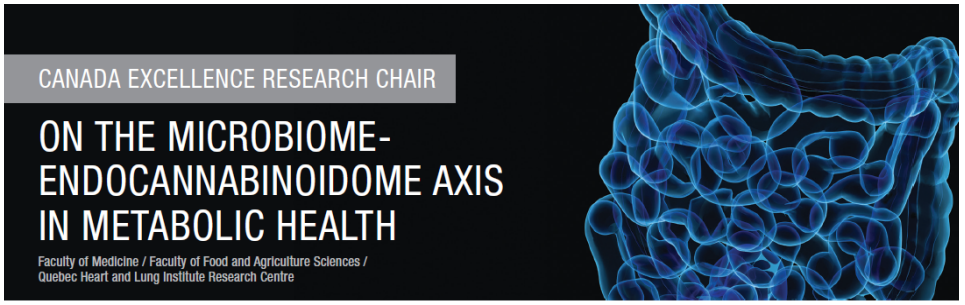
The gut microbiome-endocannabinoidome axis



Adapted from Cani et al. Nat Rev Endocrinol 2016



BACKGROUND

According to the World Health Organization, more than 1.9 billion adults were overweight in 2014, including 600 million who were obese. This pandemic, which also affects children and adolescents, is one of the century's leading worldwide health challenges. Obesity increases the prevalence of many diseases, including diabetes, cardiometabolic disease, certain cancers, and inflammatory diseases, placing a major financial burden on society. In 2015 Statistics Canada estimated that 3.5 million Canadians suffered from Type 2 diabetes and that metabolic disease directly linked to obesity had cost the country more than $14 billion. The latest discoveries in human health increasingly reveal the urgency of understanding the composition and function of the human intestinal microbiome in promoting health in order to put a halt to this scourge.

MISSION

The Canada Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health is the first chair in the world dedicated to the integrated study of the intestinal microbiome and its impairments in order to understand its influence on the molecular mechanisms underlying obesity, as well as the development of Type 2 diabetes, cardiometabolic disease, and other associated health issues. The chair's mission consists of identifying new therapeutic targets and designing innovative medical and nutritional strategies to maintain health and prevent certain illnesses.

http://www.cerc.gc.ca/chairholders-titulaires/di_marzo-eng.aspx

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Take home messages

The eCB system and CB_1 receptors control energy homeostasis at all levels investigated thus far

This control becomes dysfunctional under conditions leading to insulin and leptin resistance and obesity, such as those produced by chronic high (calory) fat diets, thereby contributing to increased cardiometabolic risk

The dysregulation of eCB tone in select regions of the brain and certain peripheral organs is a feature of, and contributes to, the metabolic syndrome, and can be counteracted by CB1 receptor antagonists, eCB biosynthesis inhibitors and dietary n-3 PUFAs, though the potential for unpredictable results due to the existence of a complex «endocannabinoidome» must be examined

eCB-related mediators such as prostamides and non-eCB mono-acyl-glycerols and *N*-acyl-ethanolamines, may play different roles in cardiometabolic risk via non-cannabinoid receptors (e.g. GPR55, GPR119, TRPV1, PPARs, and receptors yet to be discovered) and by being differently regulated by the gut microbiome

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Thank You