Mechanism of Action

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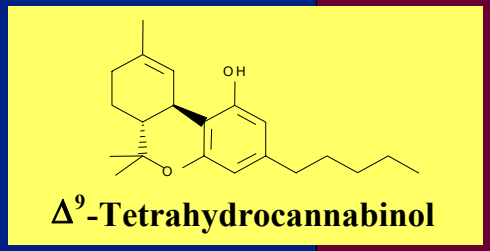
Overview

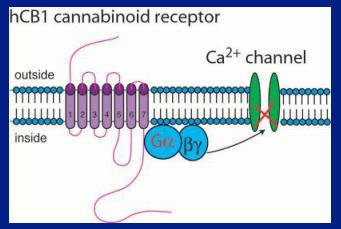
- Introduction to the endocannabinoid system (ECS)
- Pharmacological properties of rimonabant
- Hyperactivity of the ECS in obesity & type 2 diabetes
- Rationale for the therapeutic use of rimonabant in obesity and type 2 diabetes

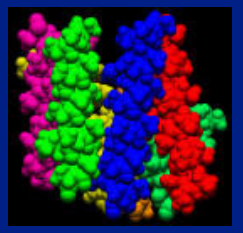
Historical Discovery of the Endocannabinoid System (ECS)

1964 – Isolation of Δ^9-THC, the active constituent of *Cannabis sativa*[1]

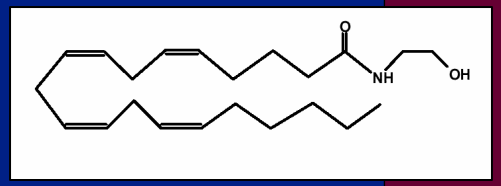


1991 – Cloning of the human CB_1 receptor[2]



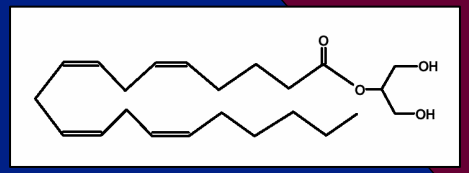


1992 – Discovery of anandamide, the first endogenous cannabinoid[3]



1994 – Characterization of the first selective CB_1 receptor blocker rimonabant

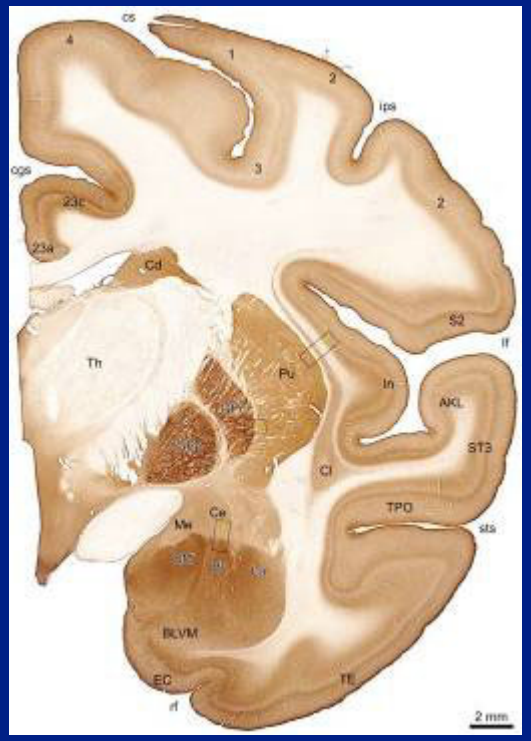
1995 – Isolation of a second endocannabinoid, 2-AG [4]



1. Gaoni Y, et al. *J Am Chem Soc*. 1964;86:1646-1647.
2. Gerard CM, et al. *Biochem J*. 1991;279(Pt 1):129-134.
3. Devane WA, et al. *Science*. 1992;258:1946-1949.
4. Sugiura T, et al. *Biochem Biophys Res Commun*. 1995;215:89-97.

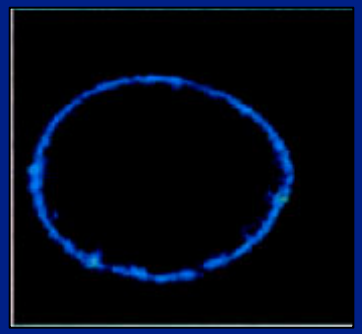
CB_1 Receptor Expression in Primate Brain and Peripheral Tissues

Monkey Brain



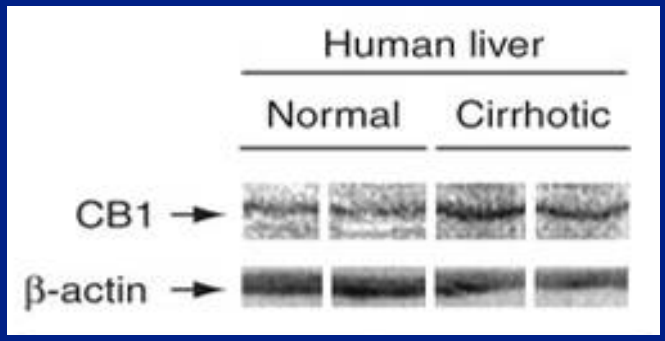
Eggan, S. and Lewis, D.
Cerebral Cortex 2007; 17:175.

Human Adipocyte



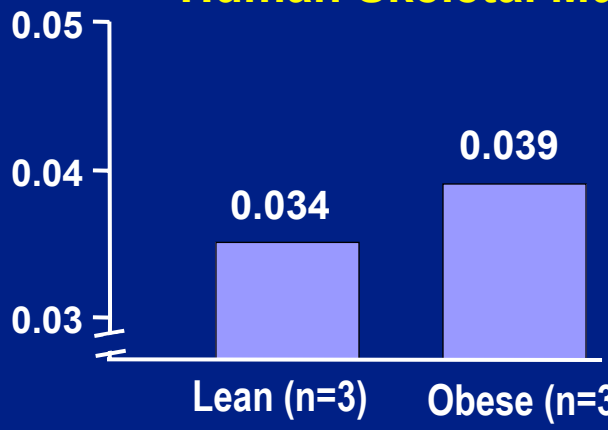
Engeli S. et al. *Diabetes* 2005; 54:2838

Human Liver



Teixeira-Clerc F. et al. *Nat Med.* Jun 2006;12(6):671.

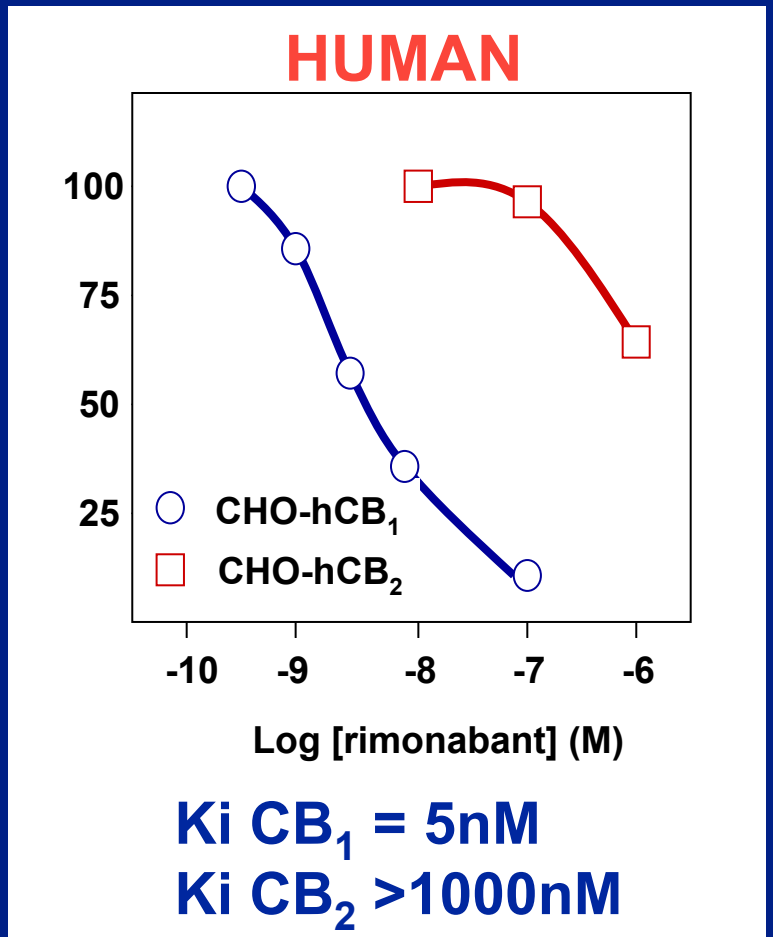
Human Skeletal Muscle



Cavuoto, P. et al. *Mol. Cell. Endocrinol*. 2007; 267: 63-69.

Rimonabant: High Affinity and Selectivity for the CB_1 Receptor

^{3}H-CP55,940 displacement

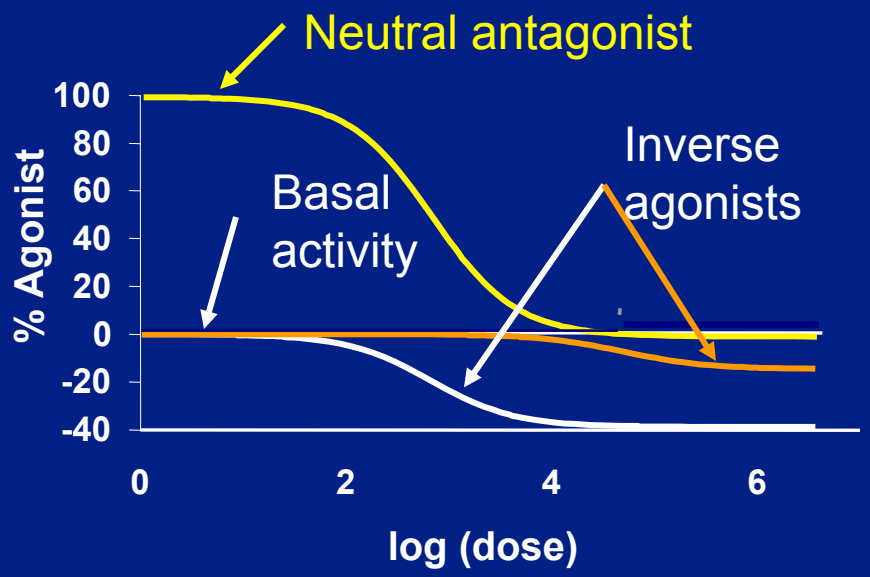


Ki CB_1 = 5nM

Ki CB_2 >1000nM

Receptor	IC_{50} (nM)
hCB1	5
hCB2	>1000
nonCB1/CB2	~1000
eCBx	~1000-5000
hGPR55	~30,000
hTRPV1	>10,000

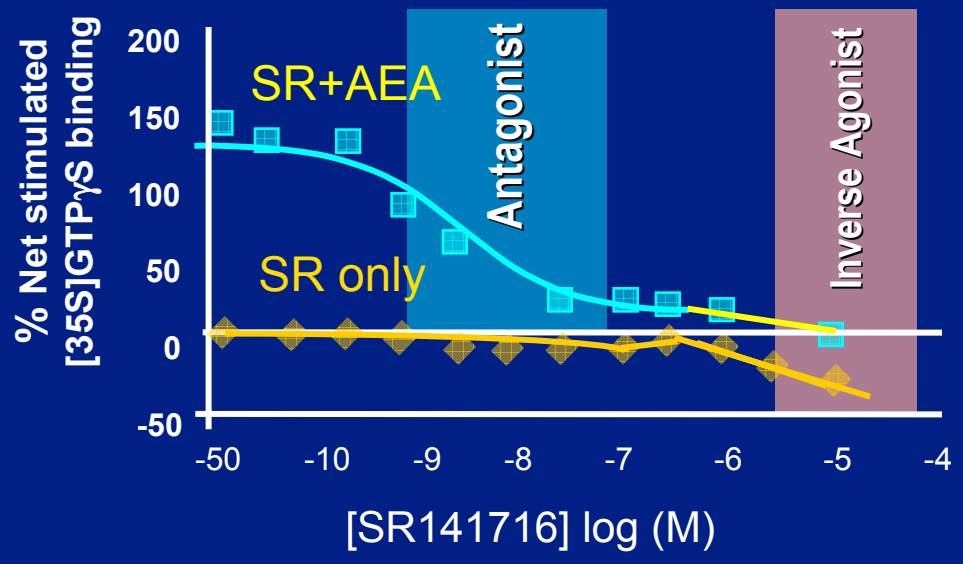
Neutral Antagonist versus Inverse Agonist



- Many antagonists are "inverse" agonists
- "Locks" receptor in inactive state
- Concern this may lead to negative consequences

An important distinction between antagonist and inverse agonist effects is that in the absence of agonist, an antagonist will have no effect; however, an inverse agonist would be active which could lead to effects opposite of an agonist's

Is Rimonabant an Inverse Agonist?



Rimonabant shows neutral antagonism at sub μM concentrations in CB_1 membranes whereas appreciable inverse agonism is only apparent at ~10 μM

Rimonabant human plasma steady state trough concentration: 190 nM (99.94% protein bound)

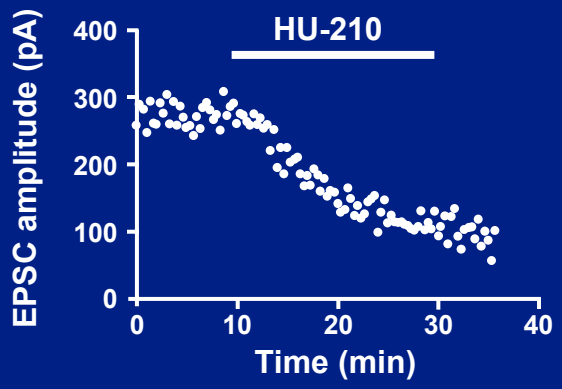
Rimonabant is a neutral CB_1 antagonist at clinically-encountered concentrations. Thus it will have an effect only in the presence of endogenous cannabinoid tone.

Adapted from, Breivogel et al. *Mol Pharm* 2001; 60: 155

In vitro Functional Effects of Rimonabant on Native CB_1 Receptors

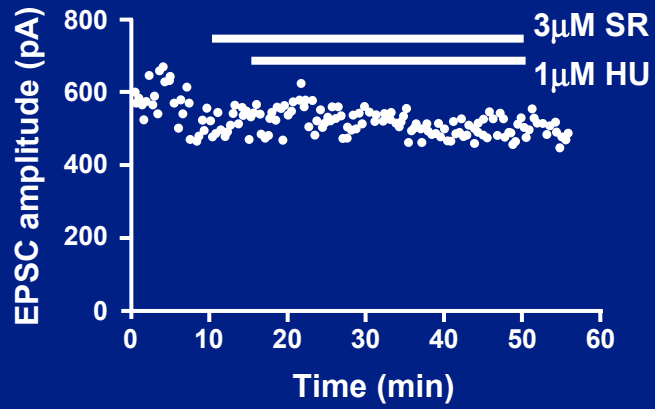
In vivo, it is impossible to distinguish between inverse agonism and antagonism of tonically-released endocannabinoids. Nonetheless:

CB_1 agonists decrease synaptic transmission



Gerdeman G and Lovinger D. *J. Neurophysiol*. 2001;85:468-471

Rimonabant doesn't increase synaptic transmission

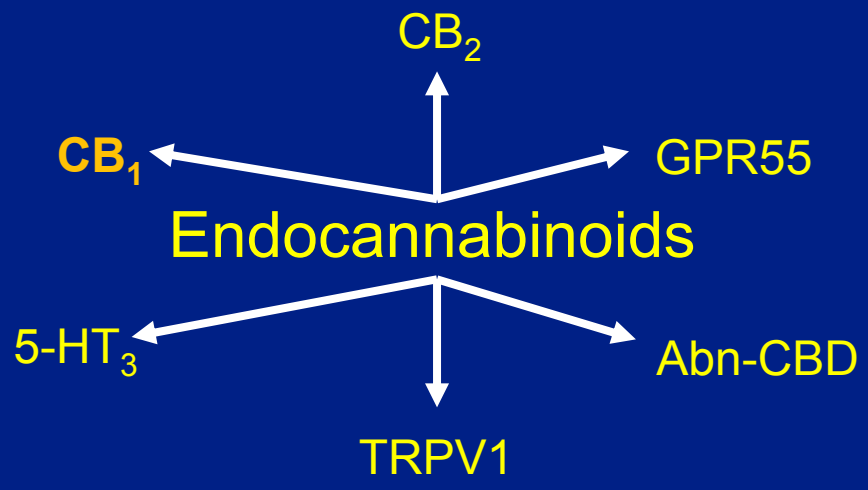


Gerdeman G and Lovinger D. *J. Neurophysiol*. 2001;85:468-471

While challenges remain to identify inverse agonist effects in biological systems, rimonabant at physiologic concentrations acts as a neutral antagonist at native CB_1 receptors

CB_1 Receptors are One of Many Mediators of Endocannabinoid Action

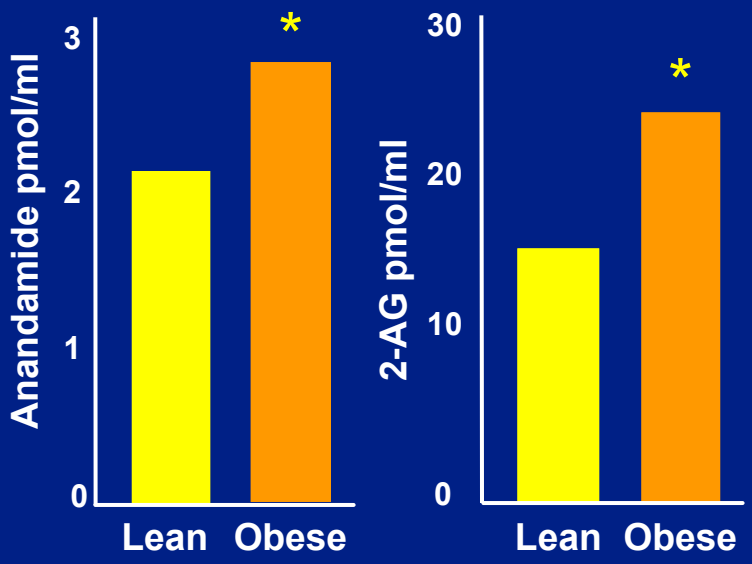
- The endocannabinoid system is involved in many processes. Several of these are mediated by non-CB_1 mechanisms.



- It doesn't follow automatically that if activating the endocannabinoid system attenuates a symptom or disorder that CB_1 blockade will produce the exact opposite effect.
- Chronic versus acute CB_1 blockade, different effects

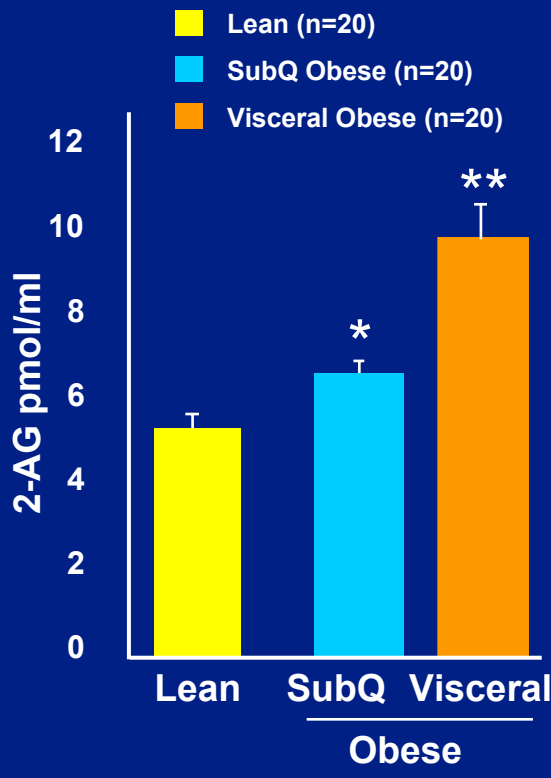
The Endocannabinoid System is Over-activated in Human Obesity and Type 2 Diabetes

Endocannabinoid Levels are Higher in Obese vs Lean Women



Engeli S, et al. *Diabetes* 2005; 54:2838–2843

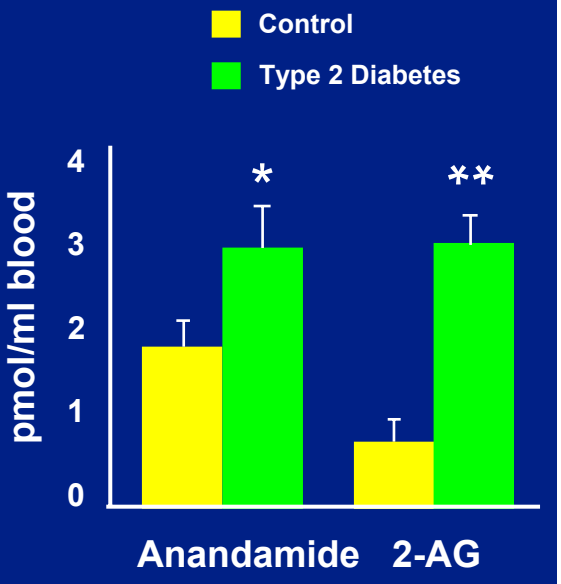
Predominance of Visceral vs Subcutaneous Obesity



Bluher M, et al. *Diabetes*. 2006;55:3053-3060

2-AG =2-Arachidonoylglycerol

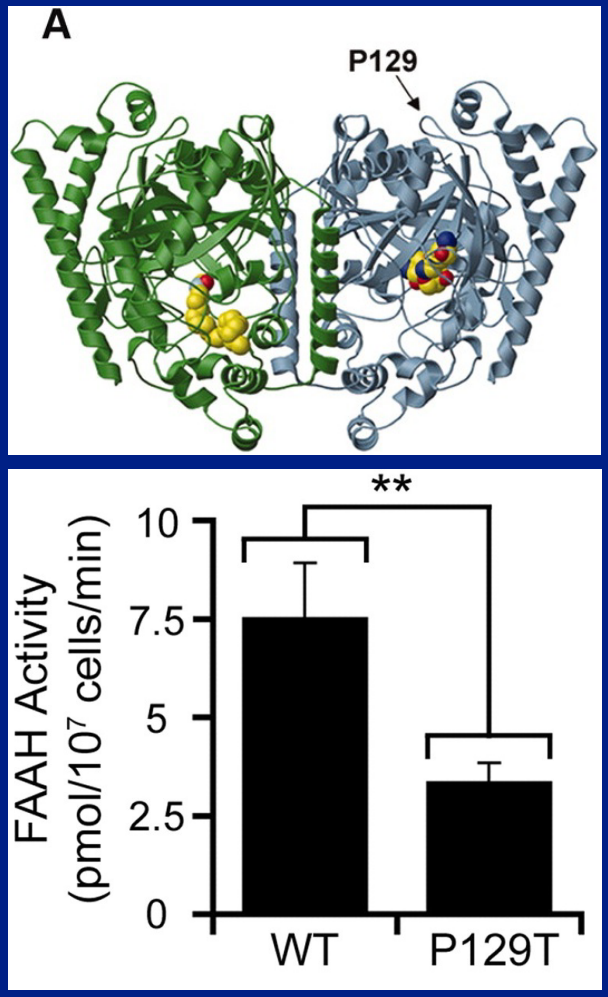
Endocannabinoid Levels are Higher in T2 Diabetes



Matias I, et al. *JCE&M*. 2006;91:3171–3180

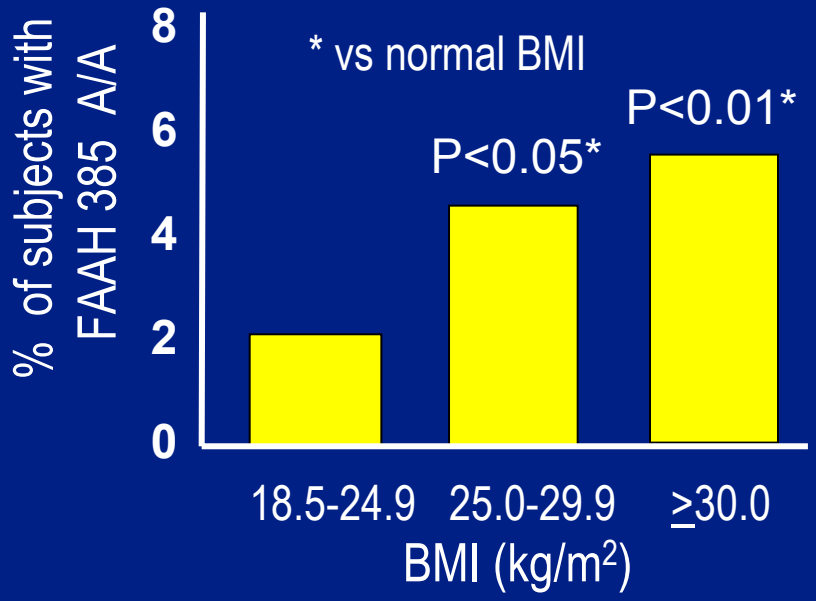
MM-28

A Mutation in an Anandamide Degrading Enzyme is Associated with Obesity



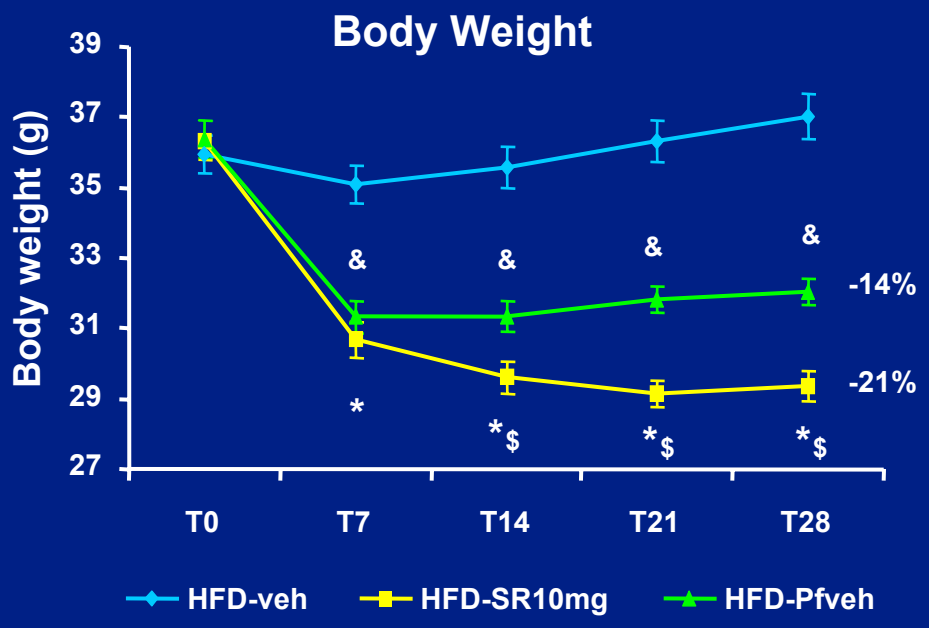
Chiang KP, et al. *Hum Mol Genet* 2004;13:2113-2119

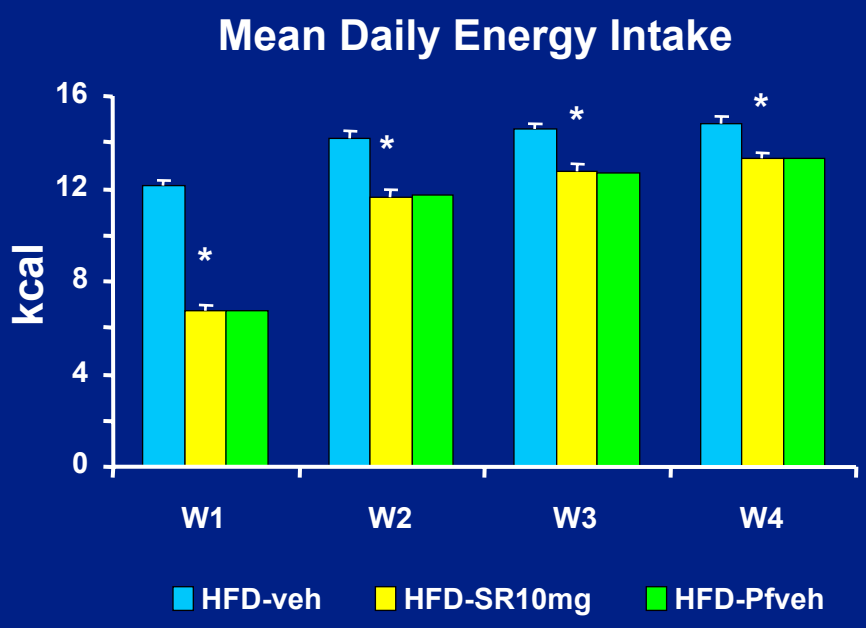
- FAAH degrades anandamide
- P129T mutation (385 A/A) reduces activity by decreasing enzyme levels
- Mutation associated with obesity



Sipe JC, et al. *Int J Obesity* 2005;29:755-759

Comparison of the Effects of Rimonabant and Food Restriction on Body Weight in DIO Mice





Pair fed DIO mice received the same amount of food as rimonabant treated animals

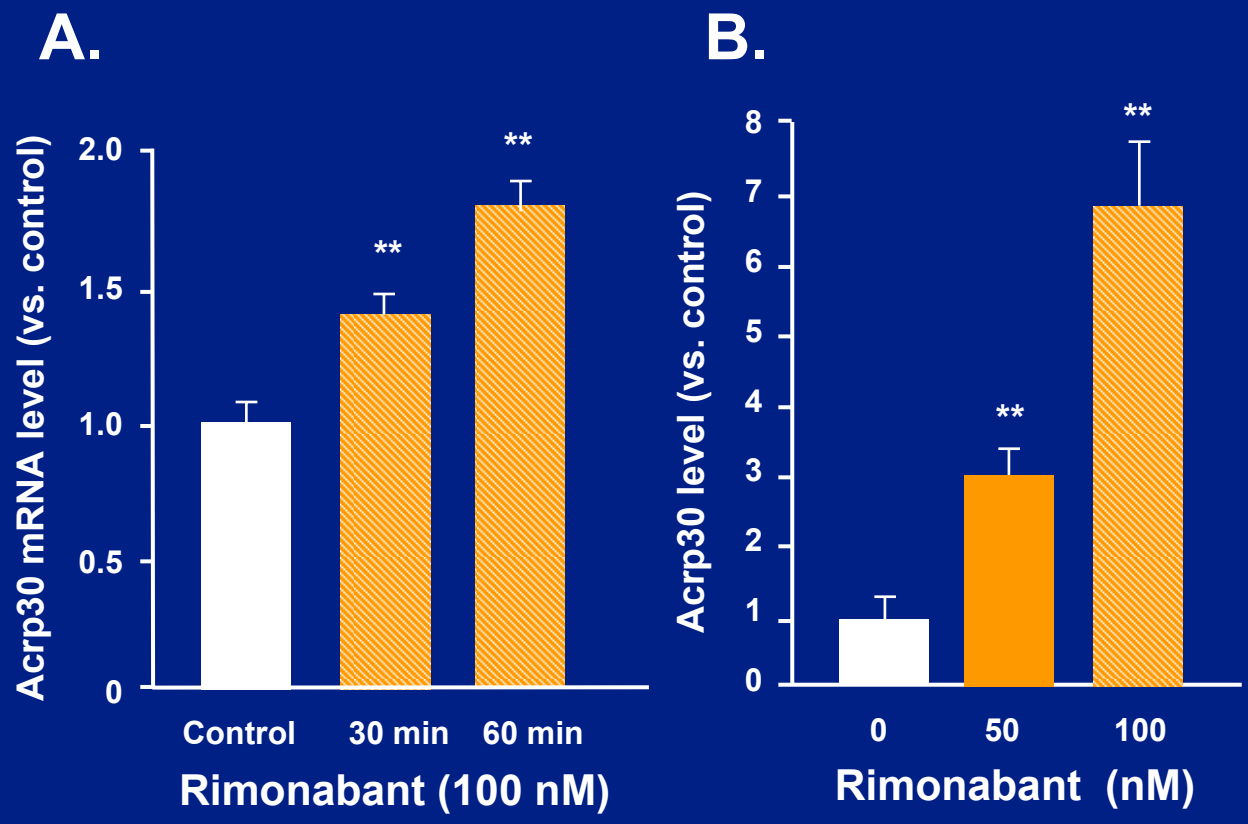
(Ravinet-Trillou et al, 2003 and unpublished data)

Rimonabant (10 mg/kg/d, for 4 weeks):

- **Induced a more pronounced body weight loss than pair feeding in DIO mice,**
- **suggesting an activation of metabolic processes independent of food intake reduction**

MM-30

Rimonabant Stimulates Adiponectin Expression (A) and Production (B) in Murine Adipocytes

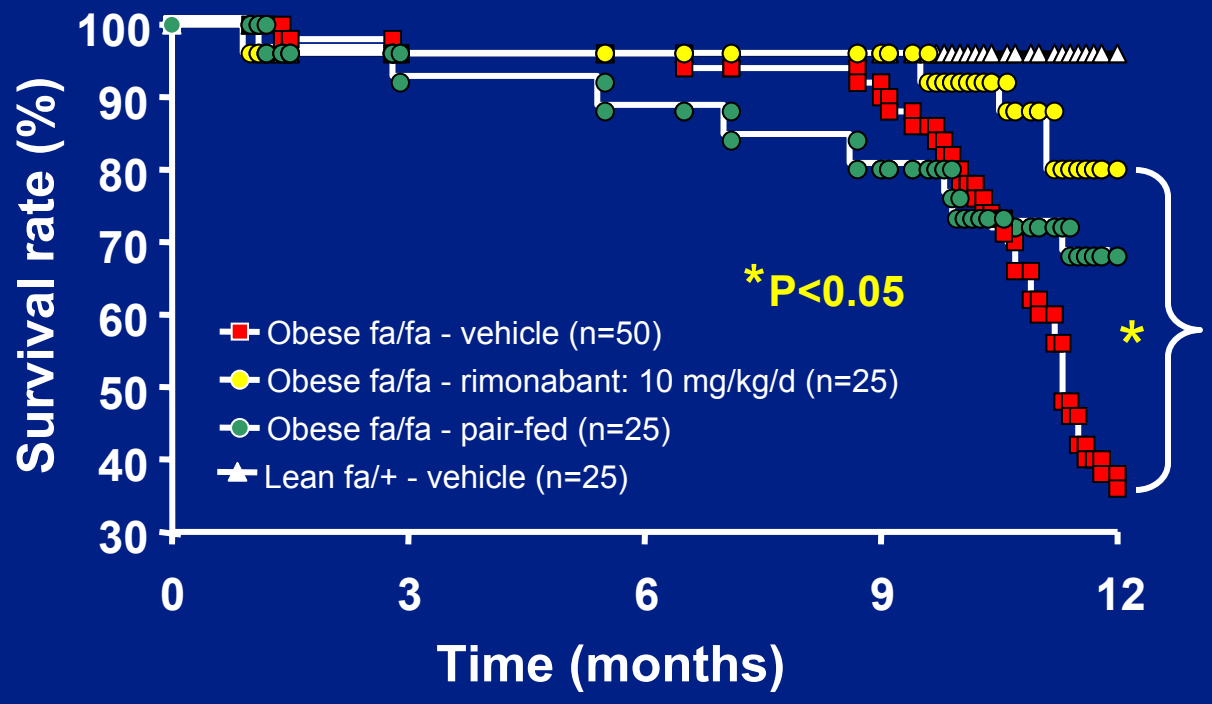


Adiponectin

- Adipokine synthesized and released by adipocytes
- Beneficial effects on glucose and lipid metabolism
- Improves insulin sensitivity
- Levels are low in obesity and type 2 diabetes
- Rimonabant increases adiponectin levels

Adapted from Bensaid M *et al*. *Mol Pharmacol*. 2003:63(4):908-914

Rimonabant Treatment Increases Survival in Obese Zucker Rats

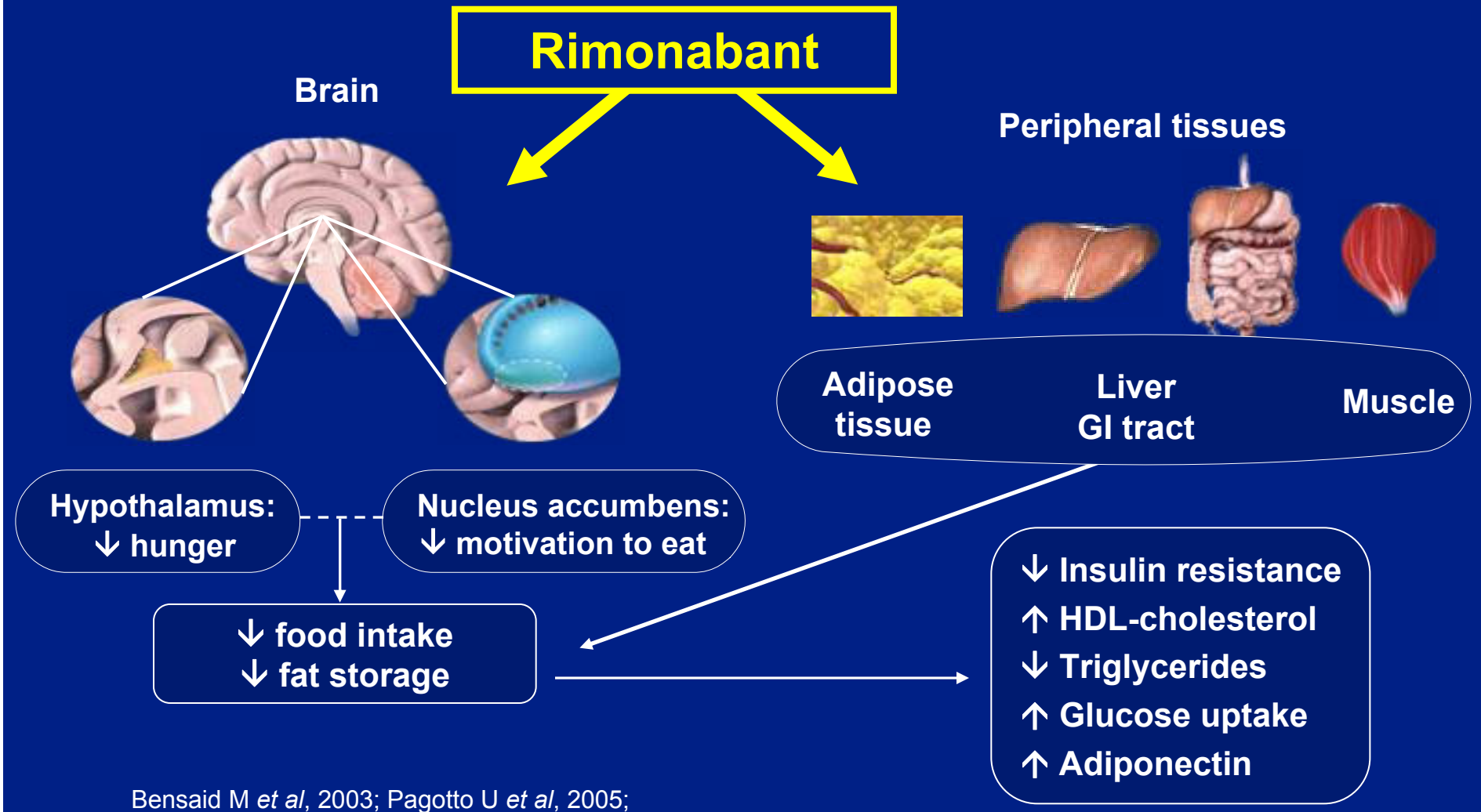


Obese Zucker Rats

- Genetically predisposed to obesity, treated with rimonabant starting at 12 wks
- Improvement in metabolic parameters
- Increased survival at 12 months

Adapted from Janiak Ph *et al*. *Kidney Int.* Under review.

CB_1 Blockade: Pathways and Metabolic Effects



Bensaid M *et al*, 2003; Pagotto U *et al*, 2005;
Osei-Hyiaman D *et al*, 2005;
Di Marzo V *et al*, 2005; Liu YL *et al*, 2005

Summary

- ECS is an endogenous physiological system which integrates nutrient intake, metabolism, and energy storage
- At clinically relevant concentrations rimonabant acts as a neutral antagonist of the CB_1 receptor
- A chronic over-activation of the ECS is associated with obesity and type 2 diabetes
- Rimonabant decreases body weight, an effect partially explained by reduced food intake, and increases adiponectin, suggesting an effect beyond food intake reduction
- Chronic rimonabant treatment improves metabolic parameters and survival in a rat model of obesity