DBPR211

A Peripheral CB1 Antagonist for the Treatment of Type 2 Diabetes

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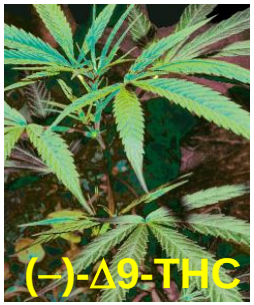
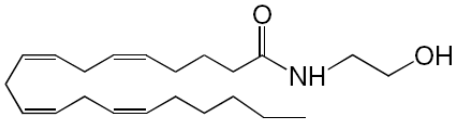
Cannabinoid Central Action on Appetite via Cannabinoid Receptor 1 (CB1)

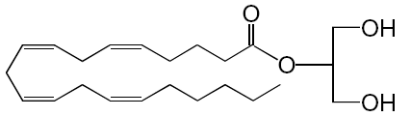


Cannabis sativa

Endocannabinoids

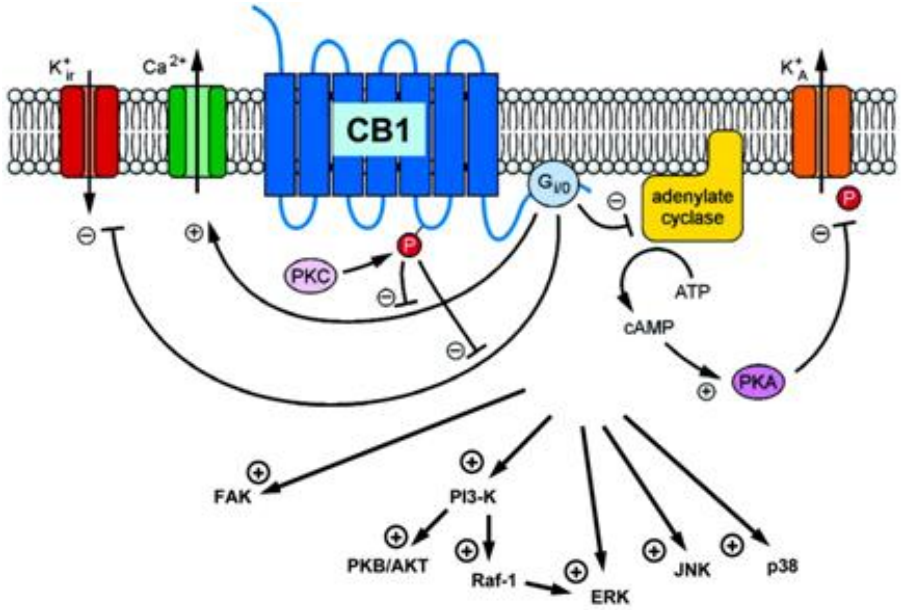


Anandamide (AEA)



2-arachidonoyl-glycerol (2-AG)

- (–)-Δ9-THC and endocannabinoids stimulate food intake.
- Cannabinoids induce over-consumption by amplifying the palatability.
- These effects are mediated by cannabinoid receptor 1 (CB1) in the brain.



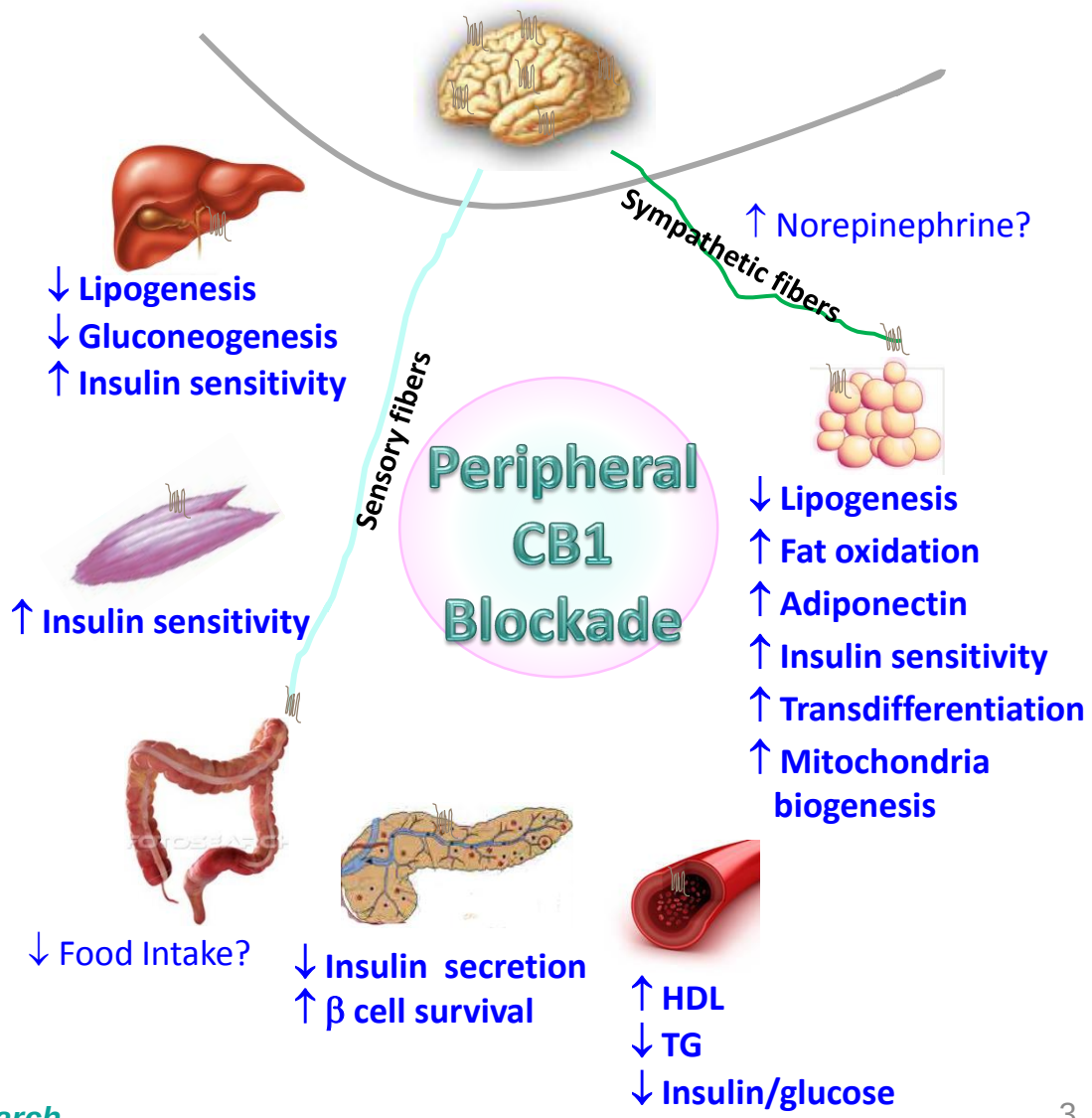
Pagotto, U. et al. Endocr Rev (2006)

Peripheral CB1 and Type 2 Diabetes

Pooled analysis of the 1-year data of the four trials of the RIO programme (Rimonabant 20 mg)

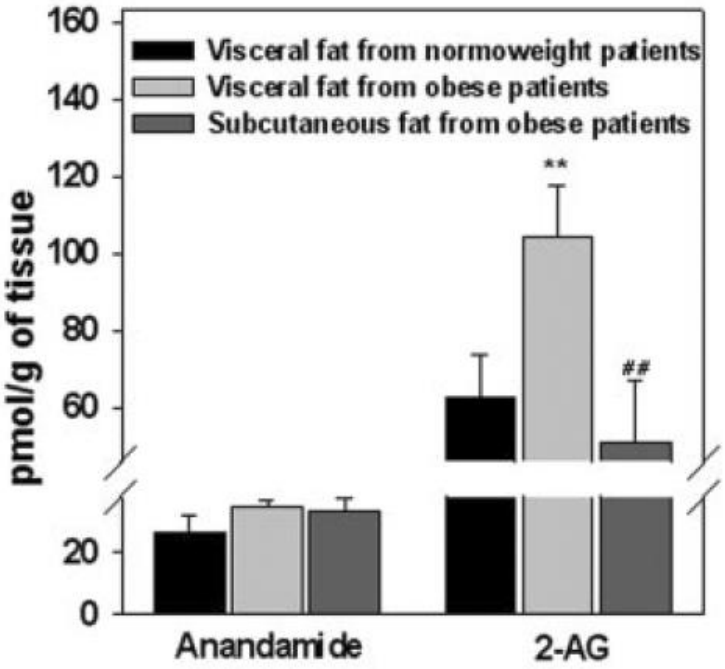
variables	Overall Effects	% of the overall effect not attributable to WL alone
HDL-Cholesterol (%)	+ 8.0	45%
Triglycerides (%)	- 14.0	46%
Fasting Insulin (μIU/ml)	- 2.74	49%
Adiponectin (μg/ml)	+ 1.5	57%
HbA1c (%)	- 0.67	55%

Adapted fromScheen (2008)

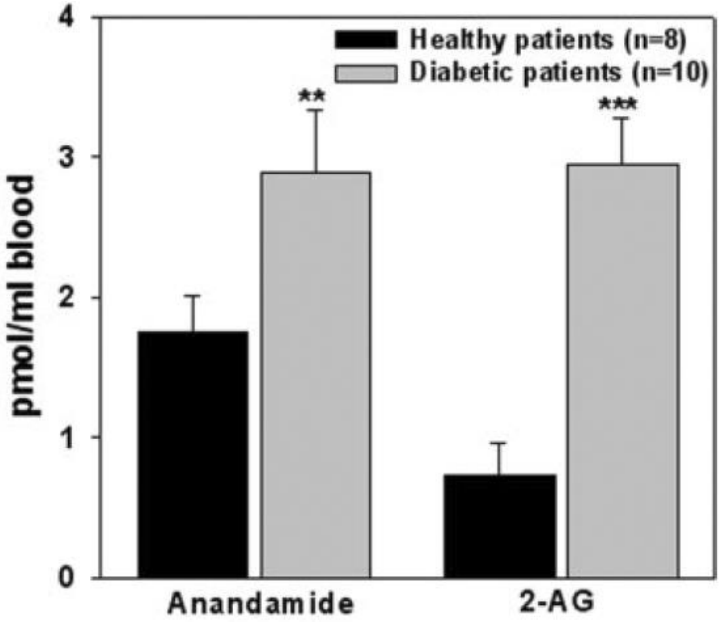


Overactivation of Endocannabinoid Tone in Obese and Diabetic Patients

Tissue levels in obese patients



Plasma levels in diabetic patients



Matias et al. (2006)

Endocannabinoids:
anandamide and 2-arachidonoyl glycerol (2-AG)

Structure-BBB Penetration Relationships

Physicochemical properties greatly affect the passive transcellular BBB permeation of compounds.

The following key structural features are suggested for discovery of CNS drugs.

Physicochemical properties	Rule (Pardridge)	Rule (Clark)
Hydrogen bonds	**H- bonds < 8-10**	**N +O < 6**
Lipophilicity	**Higher Log P**	**CLog P- (N+O) > 0; Log D=1-3**
Polar surface area (PSA)	**lower**	**< 60~70 $Å^2$**
Molecular weight (MW)	**< 400-500**	**< 450**
Acidity	**No acids**	

* To obtain P-glycoprotein Efflux compounds is another alternative.

Profiles of DBPR211

	Profiles	DBPR211	Note
In vitro	K_i (nM)	1.6	*In vitro* Safety Pharmacology: Off-target profiling: 163 No hERG activity (IC_{50} > 30 μM)
	EC_{50} (nM)	3.0	
	Selectivity (CB2/CB1)	7	
In vivo	C_{max} (ng/mL)	358	PK dose (PO, rat): Low brain level at 24 hr after single dosing at 10 mg/kg
	AUC ((ng/mL)x hr)	3824	
	$T_{1/2}$ (h)	5.9	
	BA (%)	14.7 %	

Limited Brain Penetration of DBPR211

Study	Desirable effect	DBPR211
Brain to plasma (B/P) ratio	Low B/P ratio (<1/30)	1/64
In vivo occupancy	Limited binding to the brain regions	√
PET imaging	Limited brain distribution of ^{18}F-DBPR211	√
Tetrad response	No reversing effects in CB1 agonist-induced tetrad response at a high dose (hypolocomotion, analgesia, hypothermia and catalepsy)	√
Food intake	No acute effect in food intake suppression in normal rats or mice	√
Gastrointestinal transit	Reversing effects in CB1 agonist-induced delay in gastrointestinal transit at a low dose	√

In Vivo Efficacy of DBPR211

db/db diabetic mice

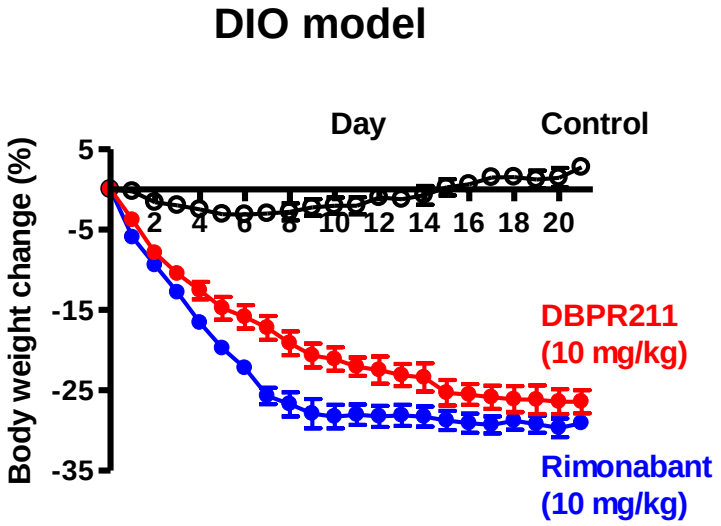
- Amelioration of insulin resistance

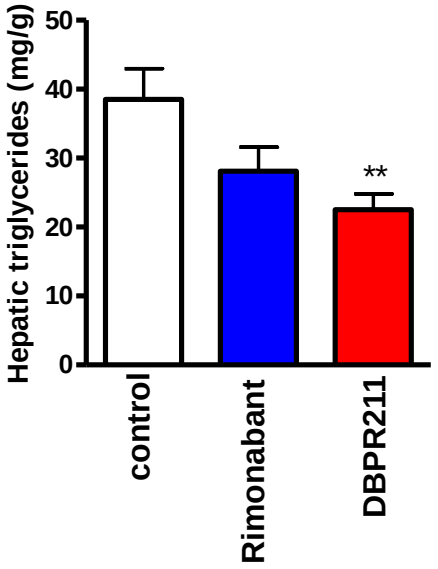
Diet-induced obese (DIO) mice

- Weight loss
- Reduction in fasting glucose and insulin
- Amelioration of insulin resistance
- Decrease in plasma ALT level and hepatic triglycerides

Zucker diabetic *fa/fa* (ZDF) rats

- Amelioration of insulin resistance
- Decrease in HbA1c





Major Advantages and Differentiation of DBPR211

- Potent and highly selective antagonist of peripheral CB1 receptor
- Minimum penetration into brain with no central effects (supported by direct drug exposure measurement and ^{18}F-labelled PET imaging studies) – does not compete with the centrally mediated CB1 agonist (CP55940)
- Chronic treatment (oral administration) effectively ameliorates insulin resistance in diabetic rodents and DIO mice. HbA1c was reduced in ZDF rat model. Weight loss and reduction in hepatic steatosis in DIO mice was also observed.
- Orally bioavailable with acceptable DMPK profile
- A novel and patentable lipid-based formulation has been successfully developed for GLP and phase I/II studies.
- Potential First-in-Class asset for T2DM, obesity and non-alcoholic fatty liver disease