The Endocannabinoid System

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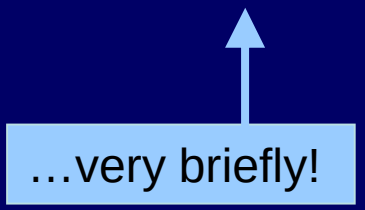
The Endocannabinoid System

Discovery of the endocannabinoid system

The endocannabinoid system and schizophrenia

- the impact of schizophrenia on the endocannabinoid system
- targeting the endocannabinoid system in schizophrenia

Cannabinoids and schizophrenia…beyond the endocannabinoid system



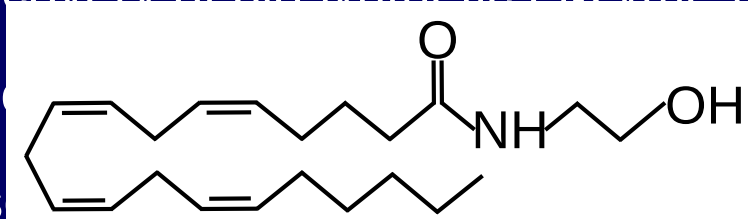
The Endocannabinoid System

- Discovery of CB_1 & CB_2 cannabinoid receptors (cloned in 1990 & 1993)
- Discovery of CB_1- & CB_2-selective agonists & antagonists
- Discovery tha
- Discovery of
- Dis
- Dis
- Discovery of potential strategies

• G protein coupled receptors (GPCRs)
• signal mainly through $G_{i/o}$ protein
• CB_1/CB_2 homology = ca 44%

for example:
- the CB_1-selective antagonist, rimonabant
- the CB_2-selective antagonist AM630

mains)



anandamide

OH

OH

2-arachidonoyl glycerol

ase

lipase

autoprotective examples: pain, multiple sclerosis, cancer…
autoimpairing examples: obesity etc, drug dependence…

Devane WA, Ha
Gibson D, Manc
and structure of a brain constituent which acts on the cannabinoid receptor. Science 258: 1946-1949

tegies that exploit either

via changes in endocannabinoid levels
&/or in CB_1/CB_2 expression/signalling
e.g. rimonabant for obesity etc

Mechoulam
Almog S, M
(1995) Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 50: 83-90

ki NE, Schatz AR, Gopher A,
yewitch M, Barg J & Vogel Z

or
t

CBR Agonists *Now* Licensed for Clinical Use

	Nabilone	THC	Sativex
Country	UK, Can, USA	USA	Can
Anti-emetic	Yes	Yes	No
Appetite stimulant	No	Yes	No
Neuropathic & cancer pain	No	No	Yes
First licensed	1982	1986	2005

- Nabilone = Cesamet®, a synthetic analogue of Δ^9-THC (1 mg capsules by mouth)
- Δ^9-THC = dronabinol = Marinol® (2.5, 5 or 10 mg capsules by mouth)
- Sativex® = cannabis extract: mainly Δ^9-THC & cannabidiol (oromucosal spray)

The Endocannabinoid System and Schizophrenia

The impact of schizophrenia on the endocannabinoid system

- cannabinoid receptors in schizophrenia
- endocannabinoid levels in schizophrenia
- effects of antipsychotics on the endocannabinoid system

Schizophrenia and the Cannabinoid CB_1 Receptor

Human data

Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, Fujiwara Y, Sakai A, Kuroda S (2002). CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Molecular Psychiatry* 7: 515-518.

Koethe D, Llenos IC, Dulay JR, Hoyer C, Torrey EF, Leweke FM, Weis S (2007). Expression of CB_1 cannabinoid receptor in the anterior cingulate cortex in schizophrenia, bipolar disorder, and major depression. *Journal of Neural Transmission* 114: 1055-1063.

Zavitsanou K, Garrick T, Huang XF (2004). Selective antagonist [3H]SR141716A binding to cannabinoid CB_1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 28: 355-360.

Newell KA, Deng C, Huang XF (2006). Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. *Experimental Brain Research* 172: 556-560.

Dean B, Sundram S, Bradbury R, Scarr E, Copolov D (2001). Studies on [^{3}H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience* 103: 9-15.

Eggan SM, Hashimoto T, Lewis DA (2008). Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Archives of General Psychiatry* 65: 772-784.

Animal data

Malone DT, Kearn CS, Chongue L, Mackie K, Taylor DA (2008). Effect of social isolation on CB_1 and D_2 receptor and fatty acid amide hydrolase expression in rats. *Neuroscience* 152: 265-272.

Haller J, Szirmai M, Varga B, Ledent C, Freund TF (2005). Cannabinoid CB1 receptor dependent effects of the NMDA antagonist phencyclidine in the social withdrawal model of schizophrenia. *Behavioural Pharmacology* 16: 415-422.

The Impact of Schizophrenia on the Endocannabinoid System

- cannabinoid CB_1 receptor and schizophrenia in man

  - triplet repeat CNR1 polymorphism has been detected in schizophrenics

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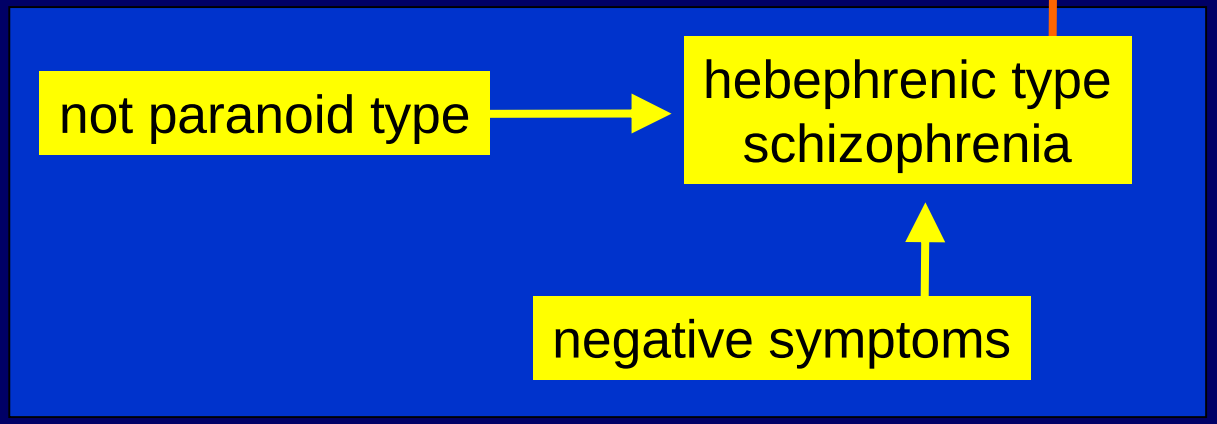
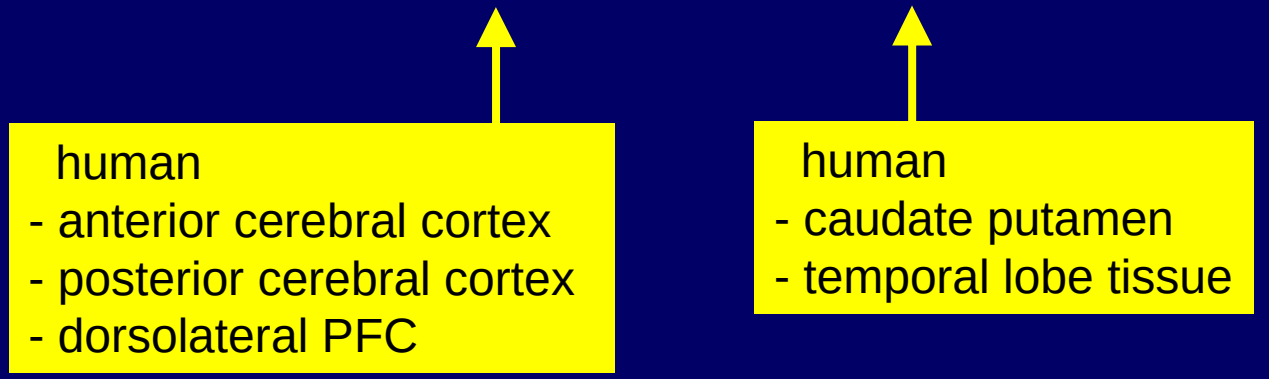


The Impact of Schizophrenia on the Endocannabinoid System

- cannabinoid CB_1 receptor and schizophrenia in man
  - triplet repeat CNR1 polymorphism has been detected in schizophrenics
  - CB_1 protein decreases in man in dorsolateral PFC but not in anterior cingulate cortex
  - [^{3}H]CP55940 or [^{3}H]SR141716A binding increases in some but not other brain areas



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- anandamide (AEA) and schizophrenia in man
  - csf levels of AEA but not of PEA or OEA are elevated in paranoid schizophrenia
  - plasma levels of AEA are not elevated in paranoid schizophrenia
  - plasma levels of AEA but not of 2-AG, PEA or OEA are elevated in schizophrenia

Potvin S, Kouassi E, Lipp O, Bouchard RH, Roy MA, Demers MF, Gendron A, Astarita G, Piomelli D, Stip E (2008). Endogenous cannabinoids in patients with schizophrenia and substance use disorder during quetiapine therapy. *Journal of Psychopharmacology* 22: 262-269.

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De Marchi et al. (2003)
Lipids in Health and Disease 2: 1-9.

- effects of antipsychotics on the endocannabinoid system in man & rat
  - olanzepine decreases plasma levels of AEA in patients with schizophrenia
  - [^{3}H]CP55940 binding increased in some but not other rat brain areas

olanzepine & aripiprazole but not haloperidol

dorsal vagal complex

cerebellum

Weston-Green et al. (2008)
Int J Neuropsychopharmacology 11: 827-835

also decreases FAAH mRNA CB_2 mRNA but not CB_1 mRNA in mononuclear cells

The Endocannabinoid System and Schizophrenia

The impact of schizophrenia on the endocannabinoid system ✓

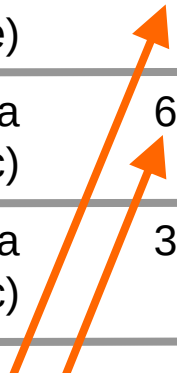
- cannabinoid receptors in schizophrenia
- endocannabinoid levels in schizophrenia
- effects of antipsychotics on the endocannabinoid system

Targeting the endocannabinoid system in schizophrenia

- cannabinoid CB_1 receptor activation versus schizophrenia ←
- cannabinoid CB_1 receptor blockade versus schizophrenia

Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms

Subject type (all cannabis experienced)	Anandamide in csf (fmol ml^{-1} ± sem)	n
Healthy controls	7 ± 2	81
Paranoid schizophrenia (antipsychotic-free)	57 ± 11†	47
Paranoid schizophrenia (plus "atypical" antipsychotic)	62 ± 16†	31
Paranoid schizophrenia (plus "typical" antipsychotic)	31 ± 12	36

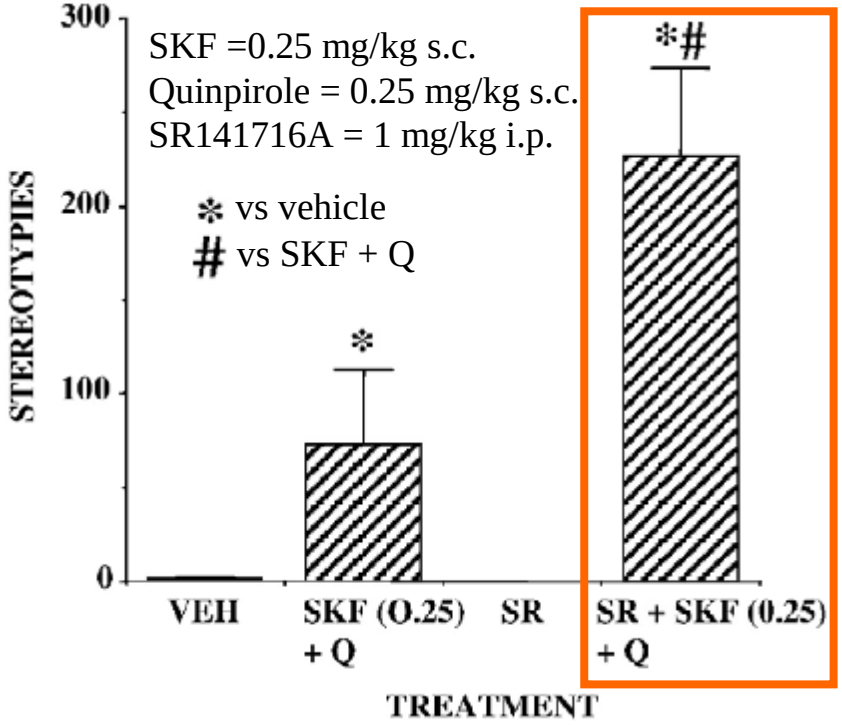


There was an inverse correlation between csf levels of anandamide and psychotic symptoms in antipsychotic-free (first-episode) paranoid schizophrenics

Not increased in schizophrenia:
- csf levels of oleoylethanolamide …or of palmitoylethanolamide
- serum levels of anandamide

Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, Klosterkötter J, Piomelli D (2004). Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology* 29: 2108-2114.

CB_1 receptors appear to modulate stereotyped behaviour in rats that follows dopamine D_1 plus D_2 receptor activation



SKF 38393 = a selective dopamine D_1 agonist
Quinpirole (Q) = a selective dopamine D_2 agonist
SR141716A = selective cannabinoid CB_1 antagonist

Cannabinoid CB_1 receptor blockade augments stereotypies induced in rats by the activation of dopamine D_1 receptors plus dopamine D_2 receptors

Postulate that "the endocannabinoid system acts as a brake for abnormal behaviour associated with dopaminergic overactivation"

Ferrer, B., Gorriti, M.A., Palomino, A., Gornemann, I., de Diego, Y., Bermudez-Silva, F.J., Bilbao, A., Fernandez-Espejo, E., Moratalla, R., Navarro, M. & de Fonseca, F.R. (2007). Cannabinoid CB_1 receptor antagonism markedly increases dopamine receptor-mediated stereotypies. *European Journal of Pharmacology* 559: 180-183.

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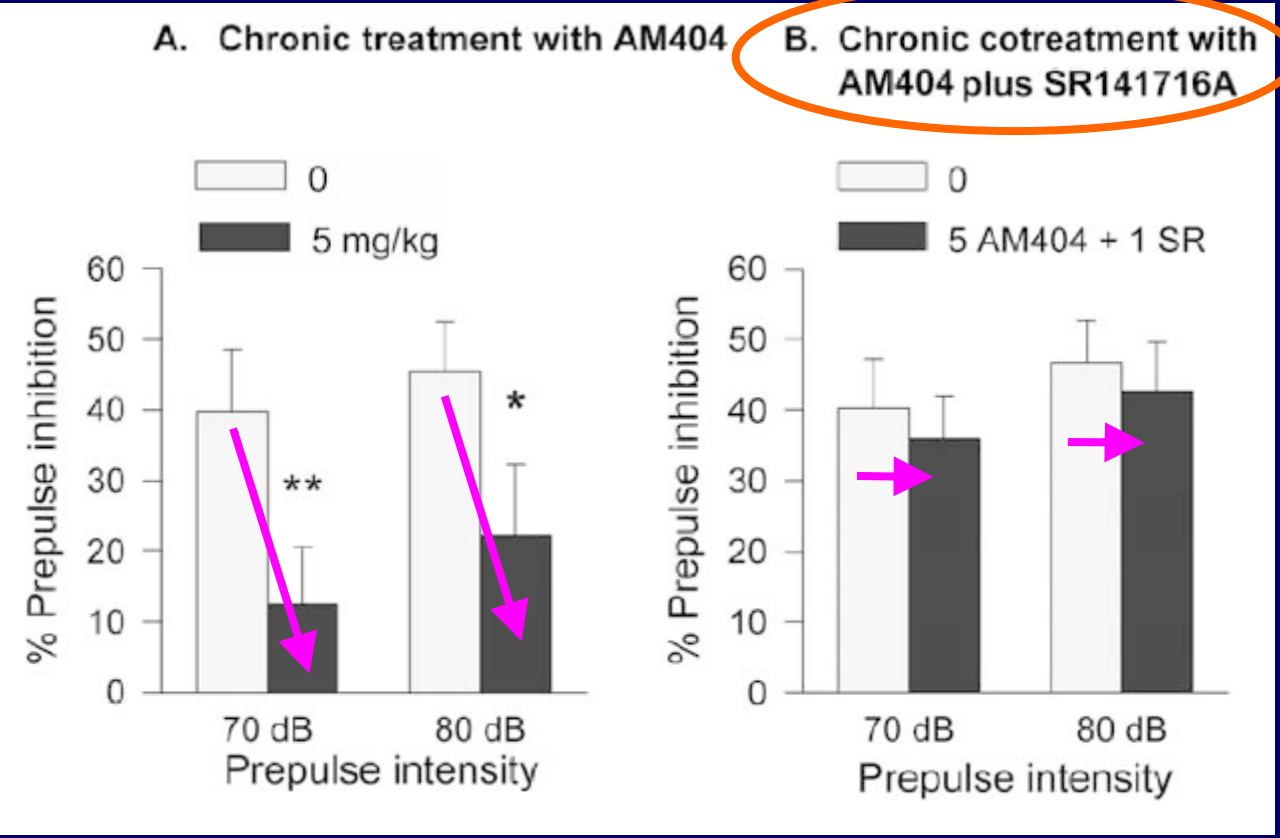
Targeting the endocannabinoid system in schizophrenia

- cannabinoid CB_1 receptor **activation** versus schizophrenia ←
- cannabinoid CB_1 receptor **blockade** versus schizophrenia ←

AM404, an inhibitor of anandamide cellular uptake & enzymatic hydrolysis, reduces prepulse inhibition in grouped mice in a manner that appears to involve CB_1 receptor activation

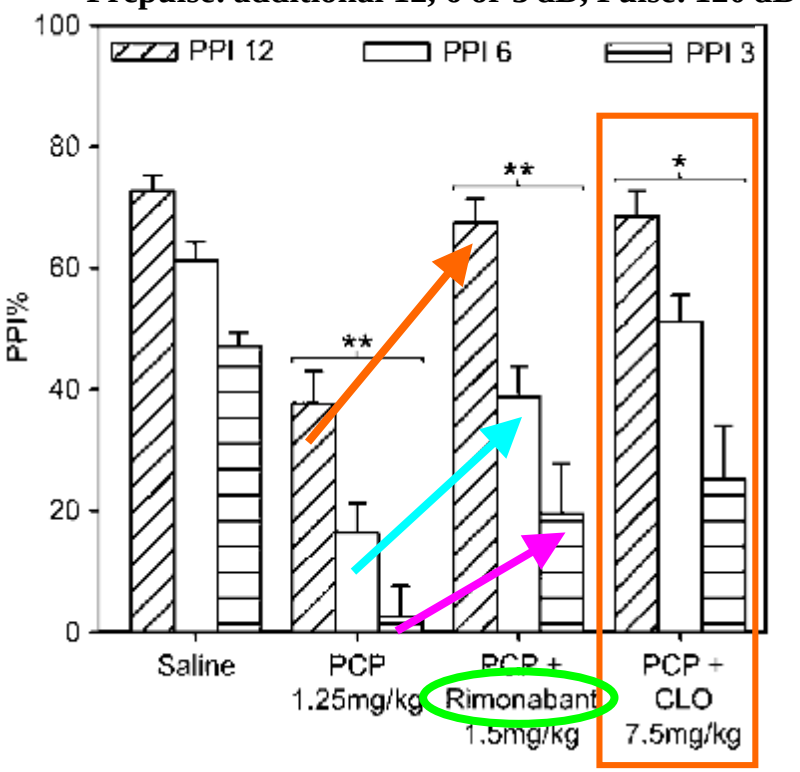


- Acute AM404 also inhibited PPI (70 dB but not 80 dB)
- SR141716A by itself did not affect PPI
- SR141716A & chronic AM404 did not affect the startle response

Postulate that "dyregulation of the endogenous cannabinoid system could participate in the emergence of some schizophrenic symptoms"

Fernandez-Espejo, E. & Galan-Rodriguez, B. (2004). Sensorimotor gating in mice is disrupted after AM404, an anandamide reuptake and degradation inhibitor. *Psychopharmacology* 175: 220-224.

Rimonabant behaves as an atypical antipsychotic agent in rats in the phencyclidine prepulse inhibition model of psychosis via blockade of cannabinoid CB_1 receptors



- AM251 also active *vs* PCP
- rimonabant also active *vs* dizocilpine
- rimonabant also active *vs* apomorphine
- no effects on startle amplitude

Martin RS *et al* (2003)
Psychopharmacology **165:** 128-135

- rimonabant had no effect on disruption of PPI induced in rats by
  - MK-801,
  - apomorphine or
  - amphetamine
- clozapine, olanzepine & haloperidol were all active in these assays

…rimonabant also lacked antipsychotic activity in a clinical trial…

Ballmaier M, Bortolato M, Rizzetti C, Zoli M, Gessa G, Heinz A, Spano P (2007). Cannabinoid receptor antagonists counteract sensorimotor gating deficits in the phencyclidine model of psychosis. *Neuropsychopharmacology* **32:** 2098-2107

Placebo-controlled evaluation of the CB_1 receptor antagonist, SR141716A (rimonabant; Acomplia®)

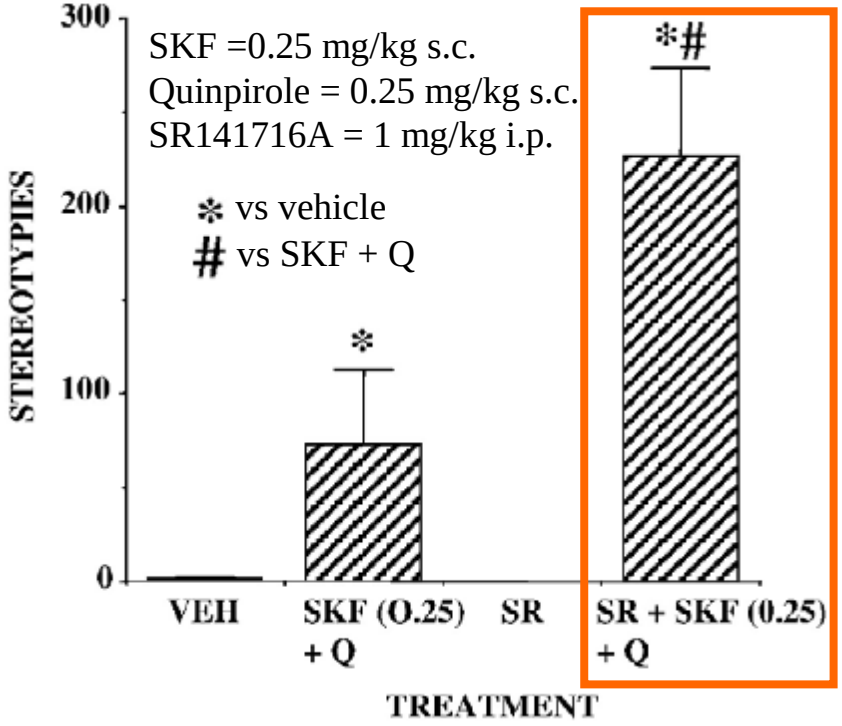
- Adult patients with moderate to severe symptoms of schizophrenia or schizoaffective disorder (n = 69 to 98 per treatment group)
- Double blind, randomly assigned, parallel-group, placebo-controlled study
  - placebo
  - SR141716A at 20 mg/day p.o. (20 days)
  - one of 3 other test drugs
  - haloperidol

...but SR141716A does seem to cause anxiety, depression and suicidality in some obese patients

- SR141716A produced no statistically significant amelioration (n = 72)

Meltzer HY, Arvanitis L, Bauer D, Rein W (2004). Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and Schizoaffective disorder. *American Journal of Psychiatry* 161: 975-984.

CB_1 receptors appear to modulate stereotyped behaviour in rats that follows dopamine D_1 plus D_2 receptor activation



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CB_1 gene deletion modulates "schizophrenia-relevant" behaviour in mice

Haller J, Szirmai M, Varga B, Ledent C, Freund TF (2005). Cannabinoid CB_1 receptor dependent effects of the NMDA antagonist phencyclidine in the social withdrawal model of schizophrenia. *Behav Pharmacol* 16: 415-422.

positive symptom model:
CB_1 deletion
à more stereotypy

negative symptom model:
CB_1 deletion
à less social withdrawal

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Targeting the endocannabinoid system in schizophrenia ✓

- cannabinoid CB_1 receptor activation versus schizophrenia
- cannabinoid CB_1 receptor blockade versus schizophrenia

selective activation of just *some* CB_1 receptors

Treat some type(s) of schizophrenia by boosting

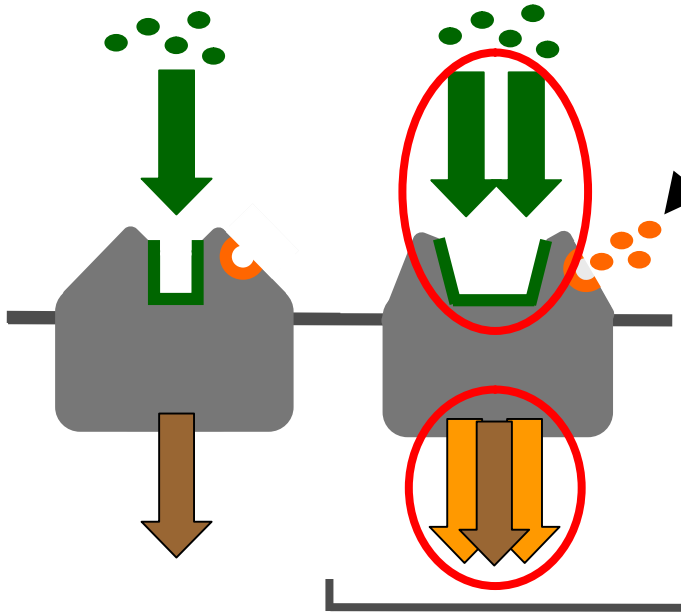
- endocannabinoid levels?
  - e.g. with a FAAH or MAG lipase inhibitor
- endocannabinoid-induced CB_1 receptor activation?
  - e.g. with an allosteric enhancer

CB_1 Allosteric Enhancement: Summary

endocannabinoid

allosteric enhancer

such allosteric enhancers have been discovered

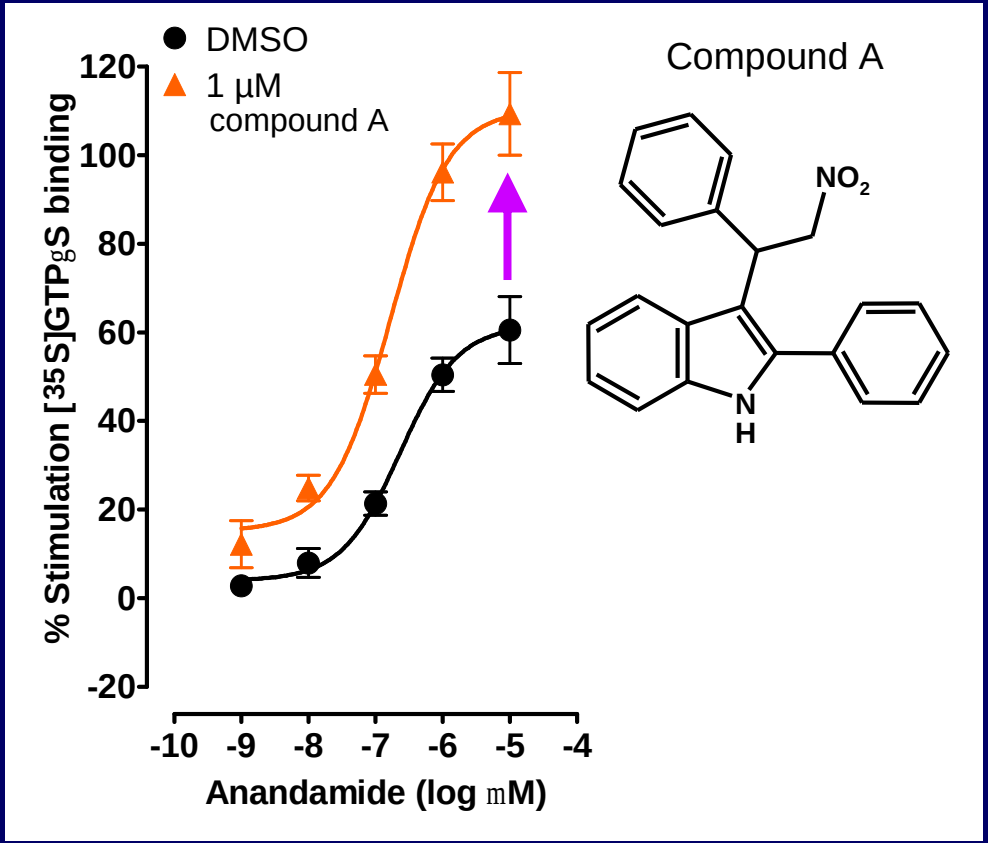


amelioration of schizophrenia etc?

CB_1 Orthosteric site | **Allosteric site**

Price et al (2005) *Mol Pharmacol* 68: 1484-1495

CB_1 allosteric enhancement …of CP55940-induced stimulation of $[^{35}S]GTP\gamma S$ binding to mouse brain membranes



Adam L, Salois D, Rihakova Baillie, Ross & Pertwee (2009) cque J, Payza K (2007) Positive allosteric modulators of CB_1 receptors. In: *17th Annual Symposium of the Cannabinoids*. p. 86

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Cannabinoids and schizophrenia

selective activation of just *some* CB_1 receptors

- beyond the cannabinoid CB_1 receptor
- beyond the endocannabinoid system

Treat some type(s) of schizophrenia by boosting

- endocannabinoid levels?
  - e.g. with a FAAH or MAG lipase inhibitor
- endocannabinoid-mediated
  - e.g. with an allosteric enhancer

e.g. the plant cannabinoid, cannabidiol

British Journal of Pharmacology (2005) 146, 913–915 © 2005 Nature Publishing Group All rights reserved 0007–1188/05 $30.00

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COMMENTARY

Plant cannabinoids: a neglected pharmacological treasure trove

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[1]Department of Medicinal Chemistry and Natural Products, Faculty of Medicine, Hebrew University, Ein Kerem Campus, Jerusalem 91120, Israel

Most of the cannabinoids in *Cannabis sativa* L. have not been fully evaluated for their pharmacological activity. A publication in this issue presents evidence that a plant cannabinoid, Δ^9-tetrahydrocannabivarin is a potent antagonist of anandamide, a major endogenous cannabinoid. It seems possible that many of the non-psychoactive constituents of this plant will be of biological interest.

British Journal of Pharmacology (2005) **146**, 913–915. doi:10.1038/sj.bjp.0706415;
published online 3 October 2005

Keywords: Anandamide; CB1 receptor antagonist; CB2 receptor antagonist; mouse vas deferens; Δ^9-tetrahydrocannabinol; Δ^9-tetrahydrocannabivarin; -(−)-(*R*)- WIN55212

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Evidence that the plant cannabinoid Δ^9-tetrahydrocannabivarin is a cannabinoid CB_1 and CB_2 receptor antagonist

[1]Adèle Thomas, [1]Lesley A. Stevenson, [1]Kerrie N. Wease, [1]Martin R. Price, [1]Gemma Baillie, [1]Ruth A. Ross & *,[1]Roger G. Pertwee

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Gernot Riedel *et al*
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Lynda Williams
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Any Questions or Comments?