INTRODUCCIÓN A LA FISIOLOGÍA Y FARMACOLOGÍA DEL SISTEMA ENDOCANNABINOIDE

FORO FARMACÉUTICO DE LAS AMERICAS WEBINAR 24 DE JUNIO

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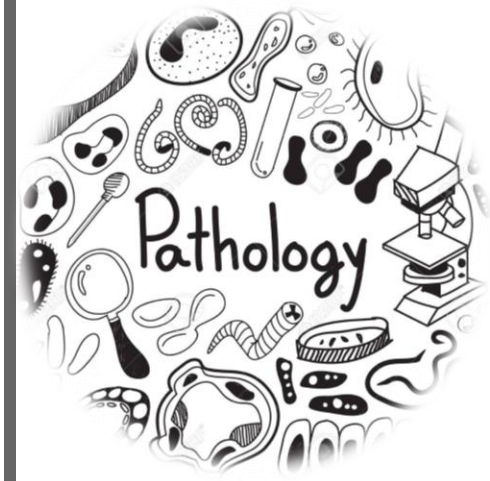
UNIVERSIDAD DE LA REPÚBLICA URUGUAY

90 AÑOS Fq 1929 2019 Facultad de Química Año Internacional de la Tabla Periódica

SISTEMA ENDOCANNABINOIDE

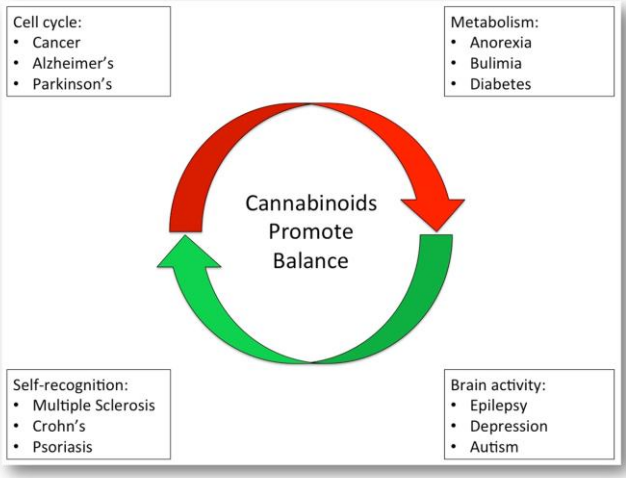
MECANISMO DE ACCIÓN EN DIFERENTES PATOLOGÍAS

SEC



El reino animal posee un sistema endocannabinoide

ROL DE SISTEMA ENDOCANNABINOIDE



Apetito

Sueño

Relax: físico y mental

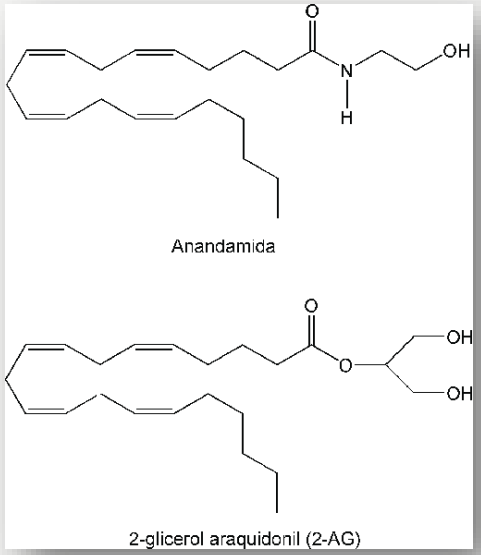
Protección

inmunomodulación,

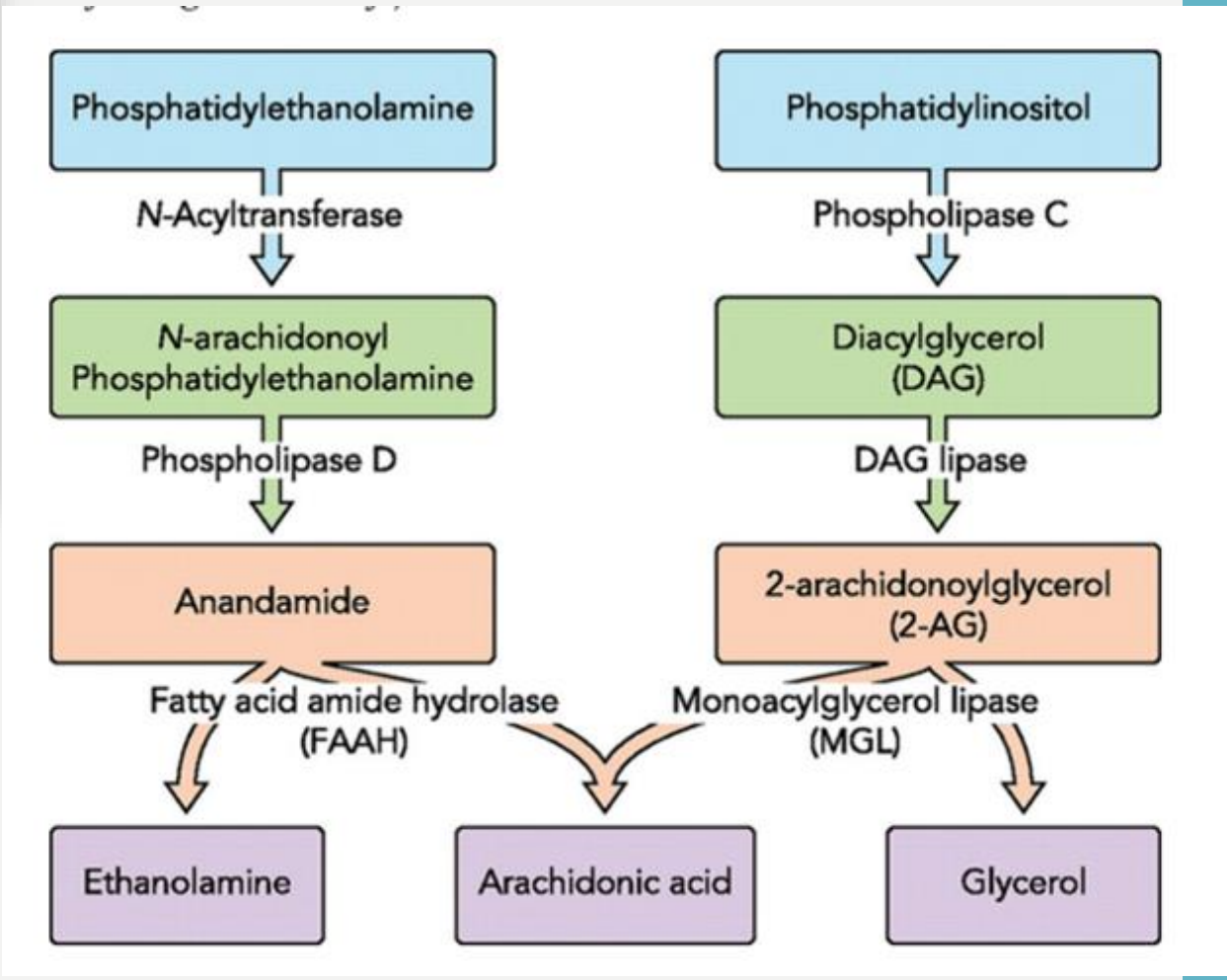
citoprotección

neuroprotección,

regulación metabólica,



TRANSMISORES DE SEÑALES…..



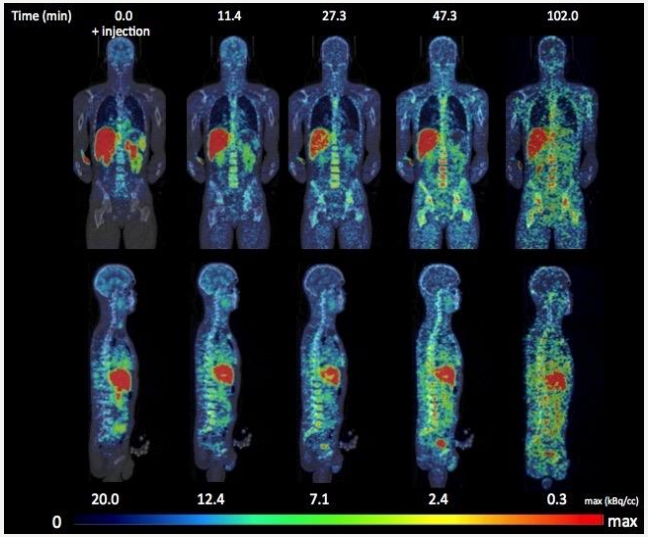
311
NRC Research Press
REVIEW

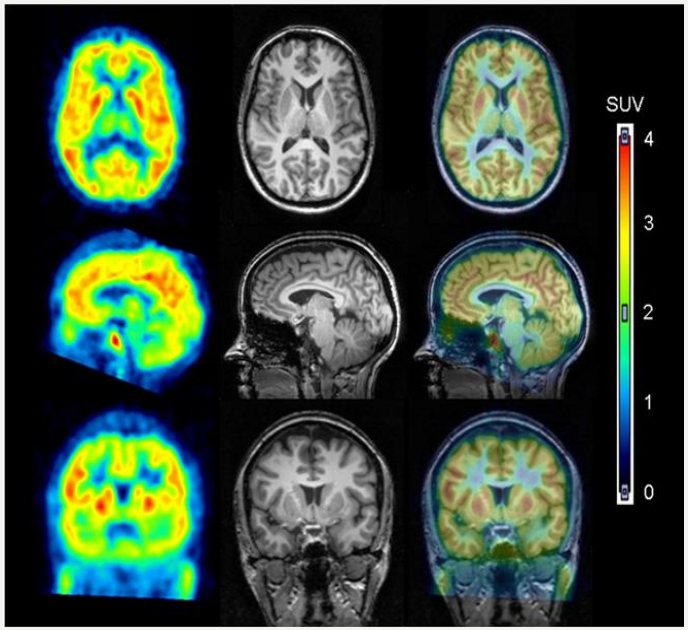
Cannabinoid signaling in health and disease

Yan Lu and Hope D. Anderson

Distribución de los receptores CB2

(Ahmad, 2015)



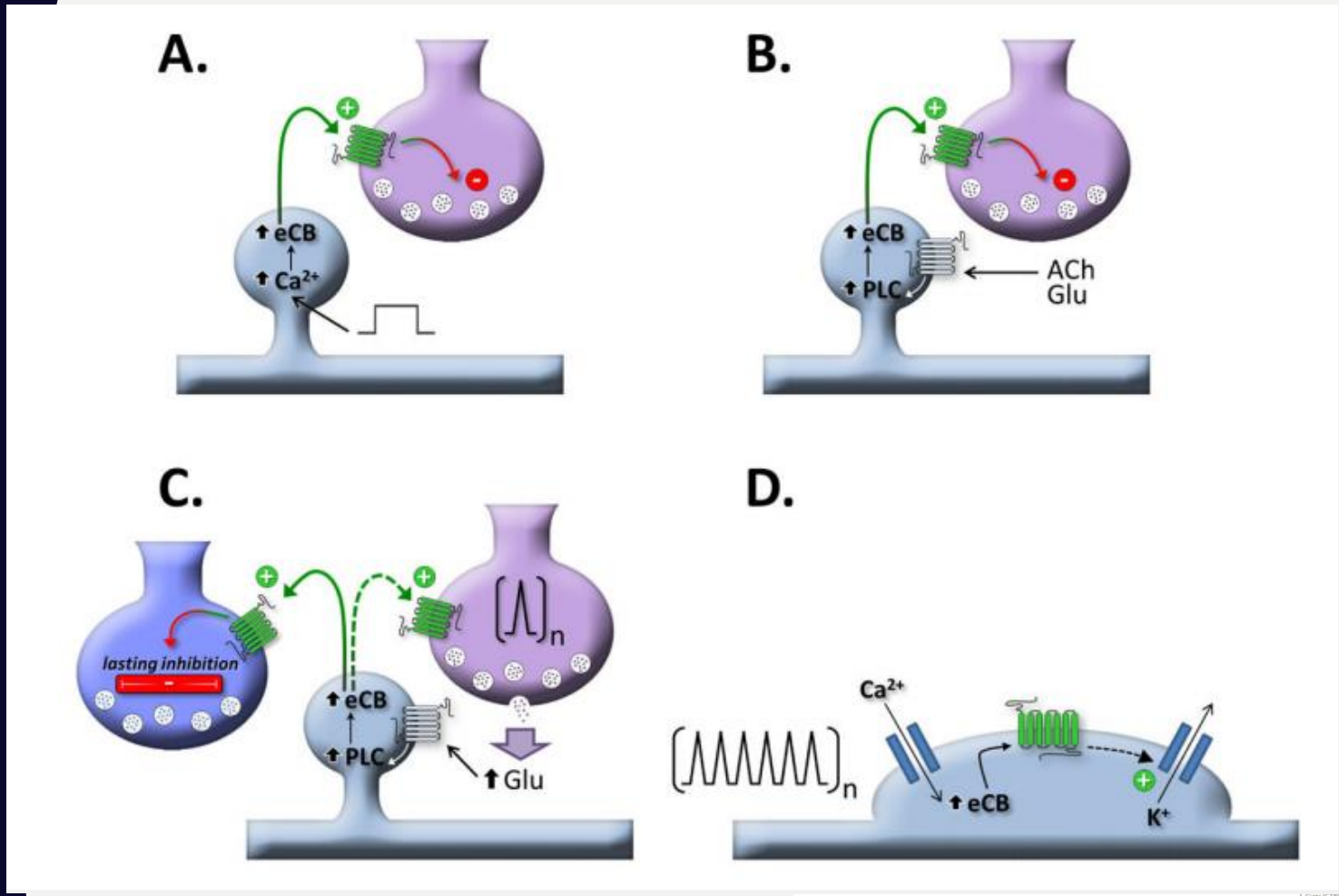


Distribución de los receptores CB1

(Terry, 2010)

SITIO ORTOSTÉRICO - SITIO ALOSTÉRICO

CÓMO ACTÚAN?

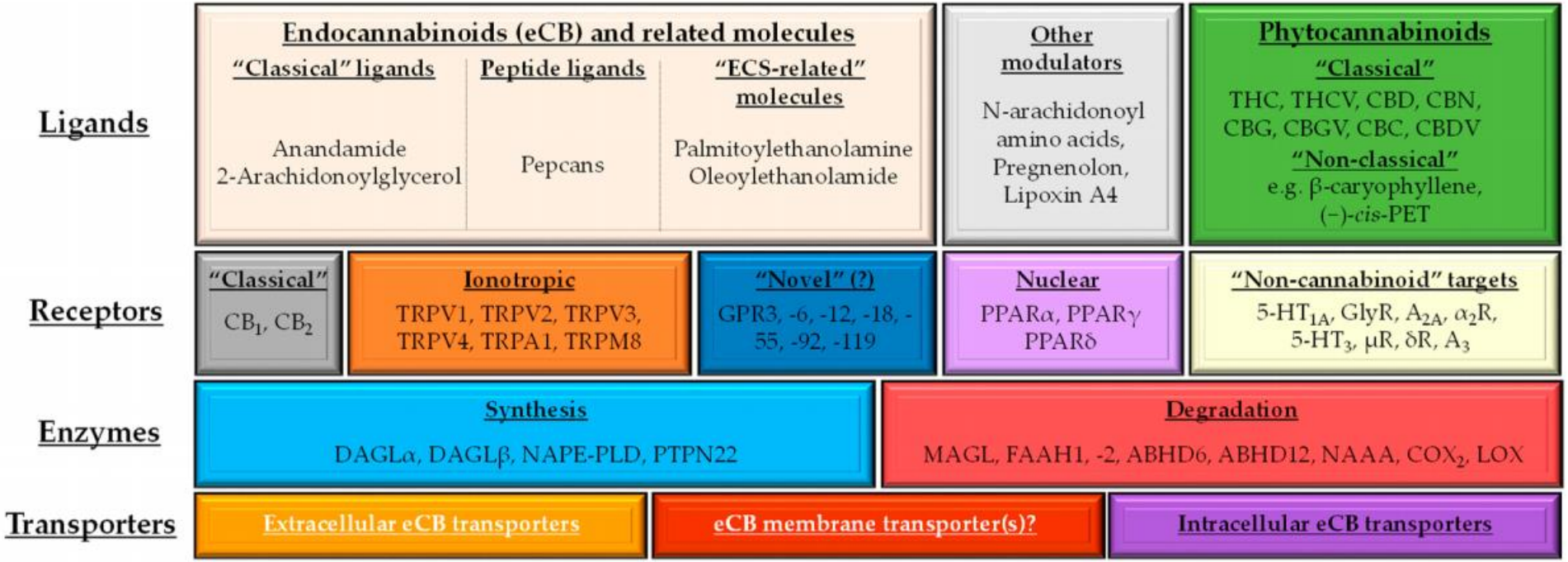


Published in final edited form as:
Biol Psychiatry. 2016 April 1; 79(7): 516–525. doi:10.1016/j.biopsych.2015.07.028.

An introduction to the endogenous cannabinoid system

Hui-Chen Lu[1,2] and **Ken Mackie**[1,2,*]

SEC tiene características muy particulares …..

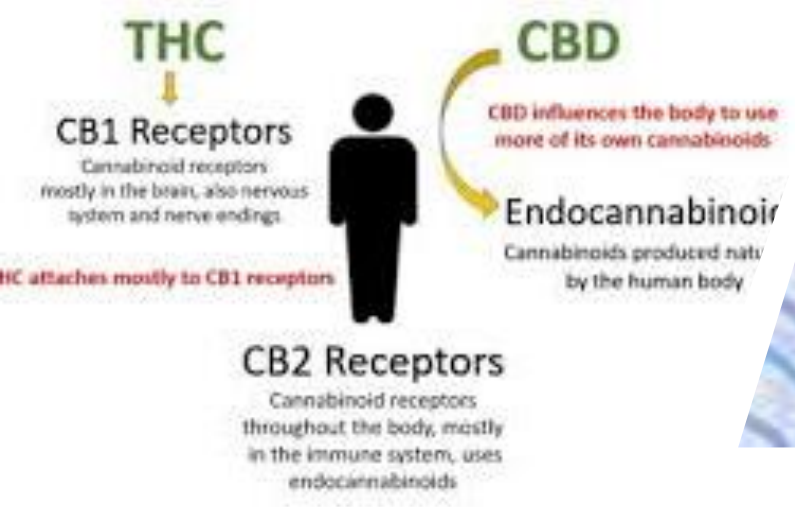


Published in final edited form as:
Trends Pharmacol Sci. 2009 August ; 30(8): 411–420. doi:10.1016/j.tips.2009.05.004.

The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities

Tamás Bíró[1], Balázs I. Tóth[1], György Haskó[2], Ralf Paus[3,4], and Pál Pacher[5]

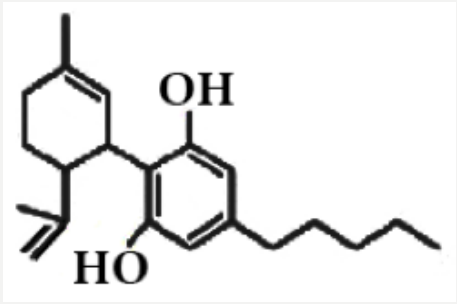
CUÁLES PUEDEN SER LOS EFECTOS DEL CANNABIS DE USO MÉDICO?



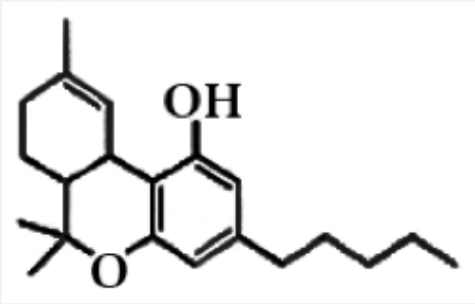
Cannabis sativa

FITOCANNABINOIDES

- CBD
  - Regulador alostérico CB1
  - Reduce la recaptación e hidrólisis de anandamida
  - Agonismo 5-HT1A
  - Activación de TRPV1 y 2

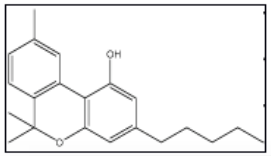


- THC
  - Agonista parcial CB1 y CB2
  - Antagonista 5-HT3
  - Inhibición de la recaptación NA y 5-HT

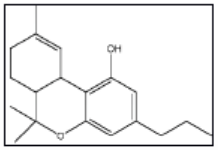


OTROS CANNABINOIDES

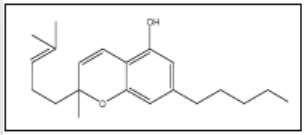
Cannabinol (CBN)



Tetrahydrocannabivarin (THCV)



Cannabigerol (CBG)



- GABA uptake inhibitor (more potent than THC or CBD)
- Modest antifungal activity
- Antidepressant tumors.
- Anti-hypertensive
- Next most effective phytocannabinoid vs. breast cancer after CBD
- Inhibits keratinocyte proliferation (anti-psoriasis?)
- Powerful activity against MRSA
- Analgesic?
- Inhibits anandamide reuptake.
- TRPM8 antagonist (application in prostate cancer?)

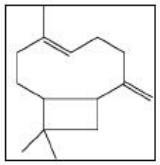
TERPENOS

Linalool (also found in lavender)

Limonene (also found in lemon)

- Antidepressant and immune stimulator in humans —CBD
- Anti-anxiety, antidepressant in mice via serotonin receptor. CBD
- Apoptosis of breast cancer cells

Beta-caryophyllene (also found in Echinacea)

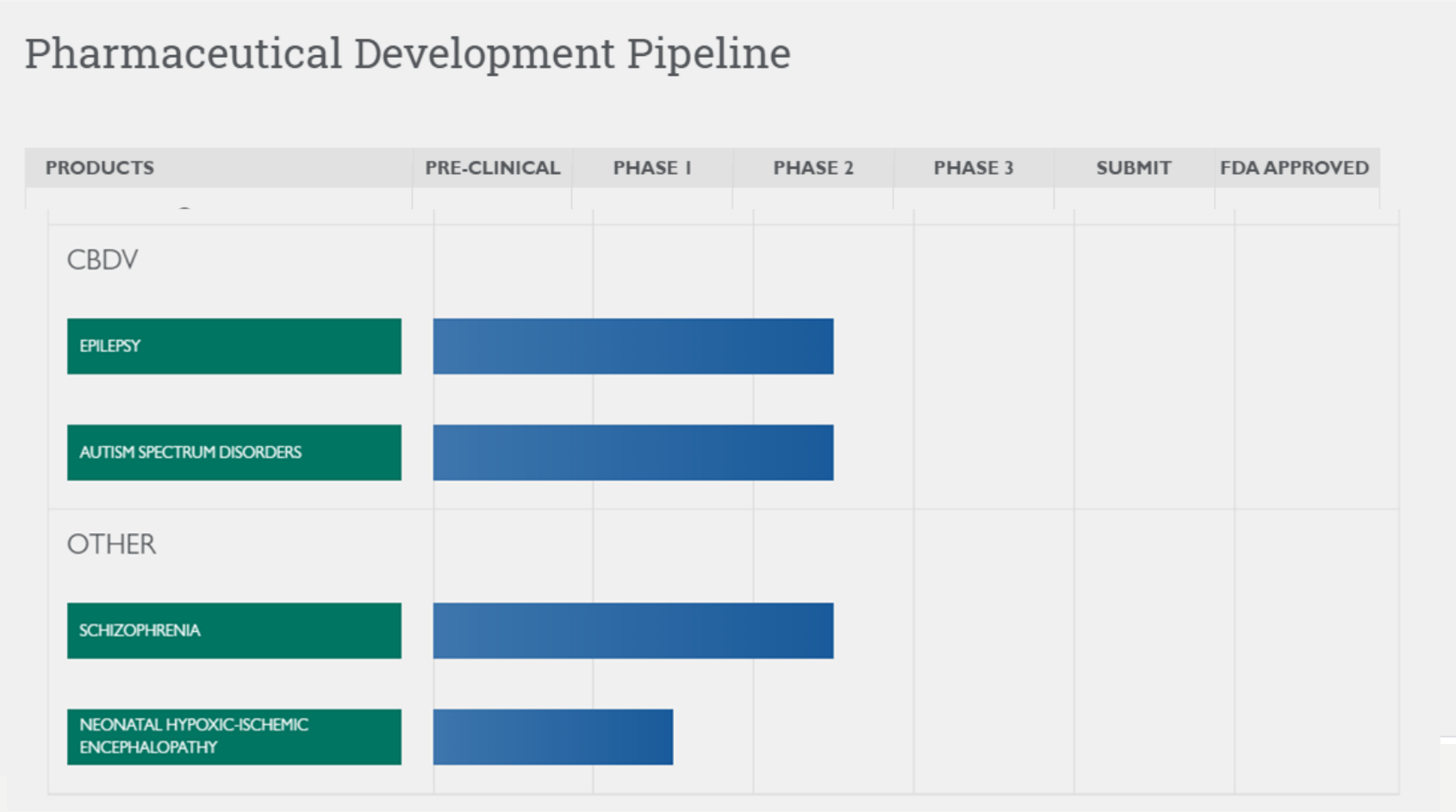


- Anti-inflammatory via PGE-1 —CBD
- Gastric cytoprotective —THC
- Selective CB2 full agonist (anti-inflammatory, analgesic) —THC
- Treatment of pruritus? —THC
- Treatment of addiction? —CBD

Myrcene (also found in hops)

- Blocks inflammation via prostaglandin E2 —CBD
- Analgesic in mice, antagonized by naloxone —CBD, THC
- Sedating; muscle relaxant; potentiated sleep time —THC
- Blocks hepatic carcinogenesis by aflatoxin —CBD, CBG

CBD •Antibacterial •Inhibits cancer cell growth •Neuro-protective •Promotes bone growth •Reduces seizures and convulsions •Reduces blood sugar levels •Reduces function in the immune system •Reduces inflammation •Reduces risk of artery blockage •Reduces small intestine contractions •Reduces vomiting and nausea •Relieves pain •Relieves anxiety •Slows bacterial growth •Suppresses muscle spasms •Tranquilizing •Treats psoriasis •Vasorelaxant	**CBDA** •Reduces inflammation •Inhibits cancer cell growth **CBGA** •Reduces inflammation •Relieves Pain •Slows bacterial growth **CBCA** •Reduces inflammation •Treats fungal infection **CBC** •Inhibits cancer cell growth •Promotes bone growth •Reduces inflammation •Relieves Pain **Δ8-THC** • Relieves pain	**THCV** •Reduces seizures and convulsions •Promotes bone growth **Δ9-THCA** •Aids sleep •Inhibits cancer cell growth •Suppresses muscle spasms **Δ9-THC** •Reduces vomiting and nausea •Relieves pain •Stimulates appetite •Suppresses muscle spasms **CBG** •Aids sleep •Inhibits cancer cell growth •Promotes bone growth •Slows bacterial growth

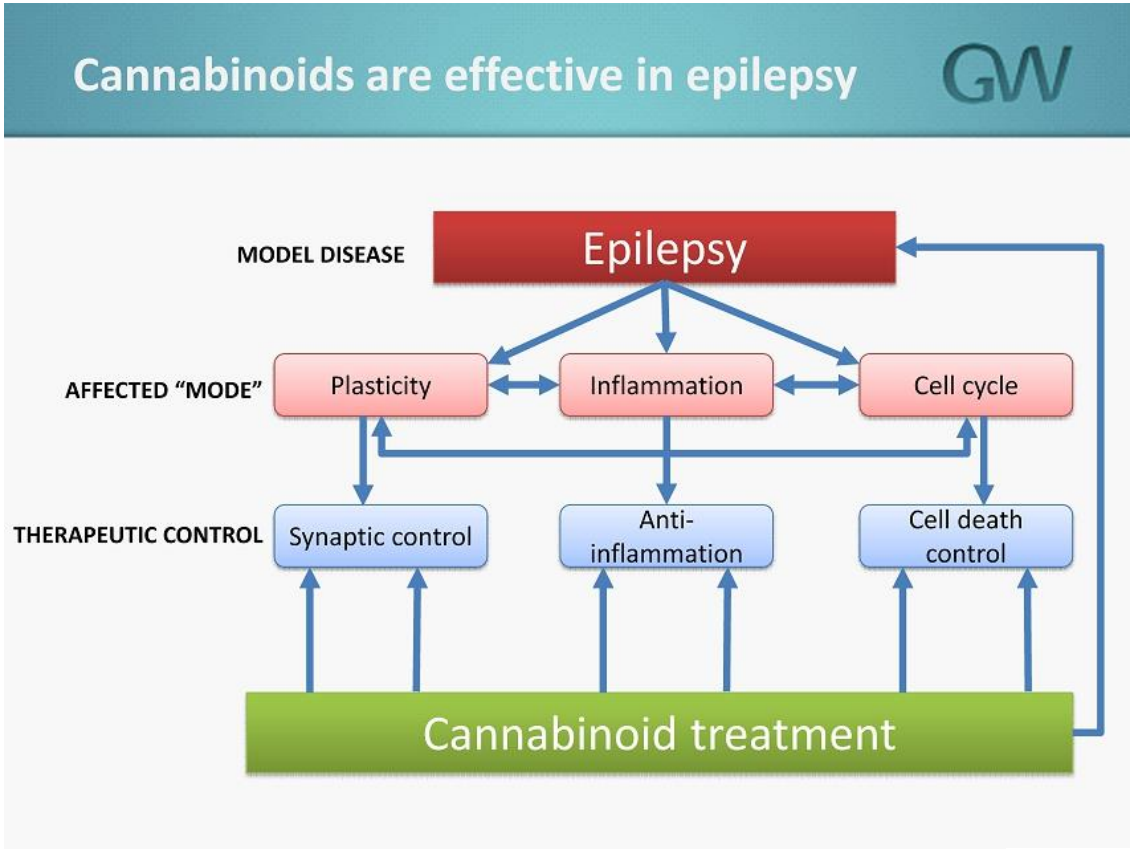


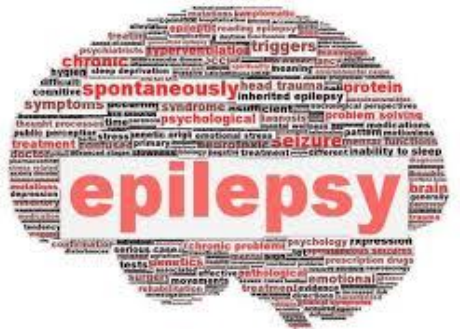
- GW Pharmaceutical Pipeline

Nombre comercial	Principio activo y forma farmacéutica	Usos terapéuticos Aprobados	Países donde está Aprobado y/o Comercializado
CESAMET® (1, 9, 27, 28)	Cápsulas de 1 mg de nabilona (un análogo sintético del THC)	- Tratamiento de náuseas y vómitos asociados a la quimioterapia, en pacientes adultos que no han respondido satisfactoriamente a los tratamientos antieméticos convencionales.	Estados Unidos, Canadá, Reino Unido, Irlanda, Gran Bretaña, Australia, México, Argentina.
MARINOL® (1, 9, 27, 29)	Cápsulas de 2,5 mg, 5 mg o 10 mg de dronabinol (THC sintético) disuelto en aceite de sésamo.	- Tratamiento de náuseas y vómitos asociados a la quimioterapia, en pacientes adultos y pediátricos que no han respondido satisfactoriamente a los tratamientos antieméticos convencionales. - Tratamiento de la anorexia/caquexia en pacientes adultos con SIDA o cáncer terminal.	Estados Unidos, Canadá, Sudáfrica, Dinamarca.
SATIVEX® (1, 9, 27, 30)	Spray oromucosal o sublingual de un extracto estandarizado de Cannabis. Cada pulverización libera una dosis fija de 2,7 mg de THC y 2,5 mg de CBD.	- Tratamiento coadyuvante en pacientes adultos con espasticidad moderada o grave debida a Esclerosis Múltiple (EM) que no han respondido de forma adecuada a otros medicamentos antiespásticos. - Tratamiento coadyuvante para el alivio sintomático del dolor neuropático en pacientes adultos con EM. * - Tratamiento coadyuvante en pacientes adultos con cáncer avanzado que sufren de dolor moderado a severo a pesar de un tratamiento con medicamentos opiáceos a dosis máxima. *	Aprobado para su uso en 27 países (entre ellos España, Canadá, Países Bajos, Reino Unido, Australia, Dinamarca, Suecia, Suiza, Bélgica, Alemania, Italia, Francia, Israel).

** Estos usos terapéuticos solo están aprobados en Canadá e Israel.*

PRESENTACIONES CONTENIENDO CANNABINOIDES NATURALES O SINTÉTICOS

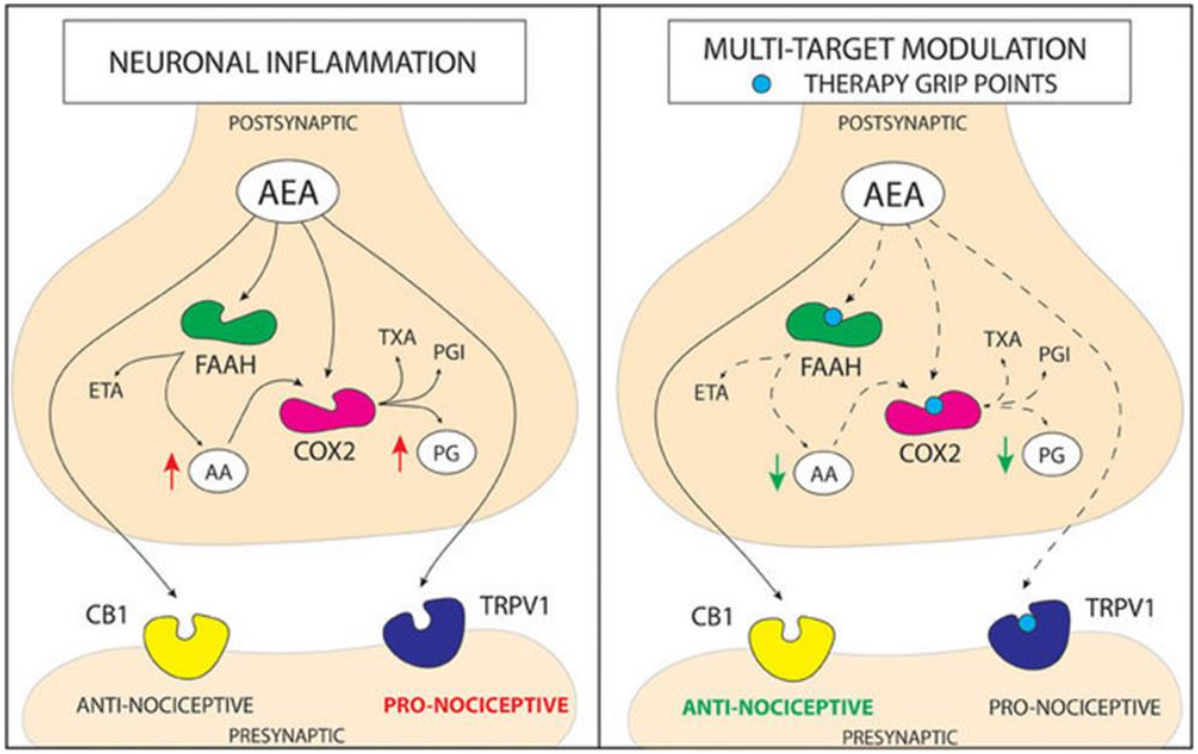

Cannabinoids are effective in epilepsy
GW
MODEL DISEASE
Epilepsy
AFFECTED "MODE"
Plasticity
Inflammation
Cell cycle
THERAPEUTIC CONTROL
Synaptic control
Anti-inflammation
Cell death control
Cannabinoid treatment


epilepsy
spontaneously
seizure
triggers
protein
psychological
brain

CBD

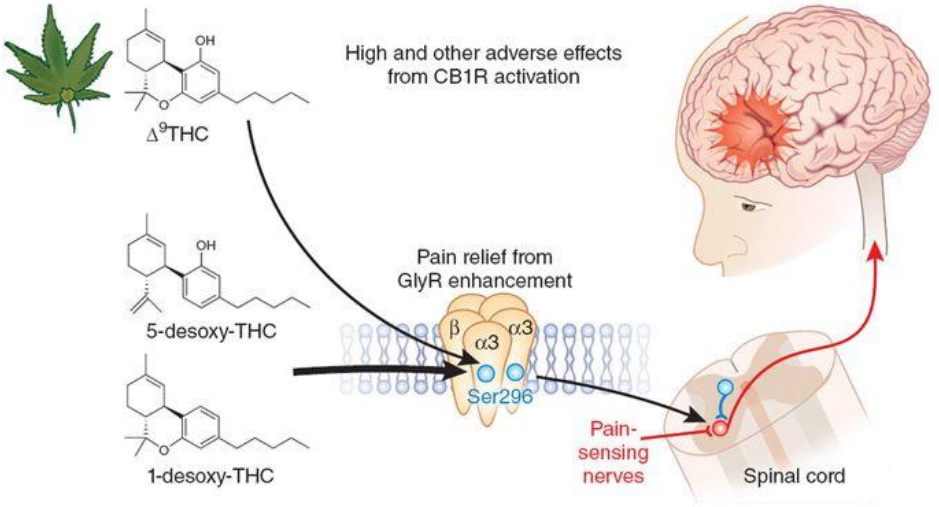
CBDV?


tratamiento de la epilepsia
neuropediatra.org
70%
fármacos
30%
©mimas 2016
éxito
responde a fármacos.
Retirará el tratamiento
sin recaídas.
resistente
NO responde.
Necesita asociar
otros tratamientos.


NEURONAL INFLAMMATION
POSTSYNAPTIC
AEA
FAAH
ETA
TXA
PGI
COX2
AA
PG
CB1
TRPV1
ANTI-NOCICEPTIVE
PRO-NOCICEPTIVE
PRESYNAPTIC
MULTI-TARGET MODULATION
THERAPY GRIP POINTS
POSTSYNAPTIC
AEA
FAAH
ETA
TXA
PGI
COX2
AA
PG
CB1
TRPV1
ANTI-NOCICEPTIVE
PRO-NOCICEPTIVE
PRESYNAPTIC


pain
medicine
day
feels
Pain
burning
lasts
sharp
gets
support
treatment
working
joints
worse
aches
sleep
knees
better
when
bending
head
night
worried
walking
bothering
dull

CBD y THC


High and other adverse effects from CB1R activation
Δ9THC
5-desoxy-THC
1-desoxy-THC
Pain relief from GlyR enhancement
β
α3
α3
Ser296
Pain-sensing nerves
Spinal cord

POTENCIA ANALGÉSICA

- Escalón 2
- 10 mg vo – 60 mg codeína
- Dosis mayores a 20 mg efectos no deseados
- Tratamiento coadyuvante

Tipos de Dolor

Oncológico

Neuropático

Esclerosos múltiple

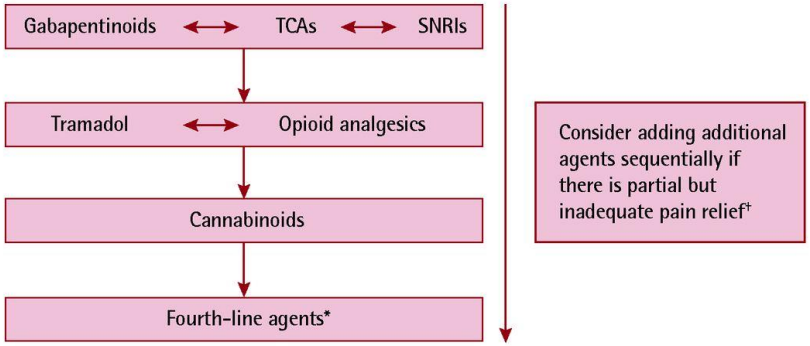
Parkinson

Fibromialgia

Artritis

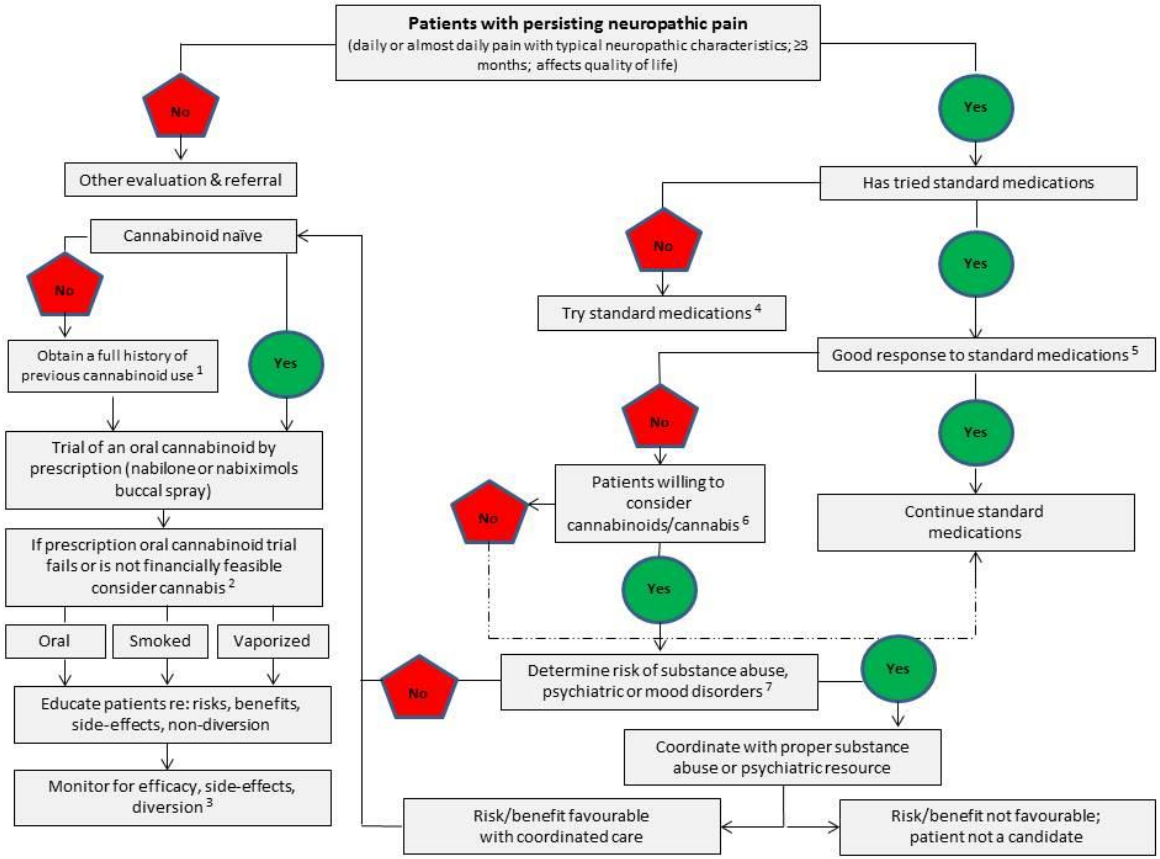
VIH

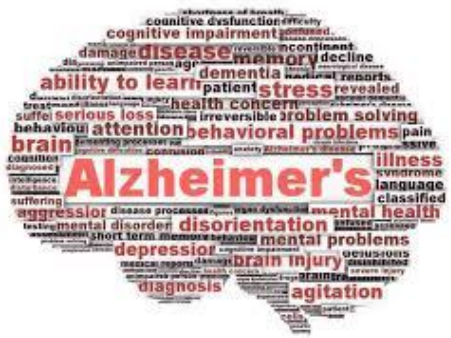
Figure 1. Algorithm for the pharmacologic management of neuropathic pain



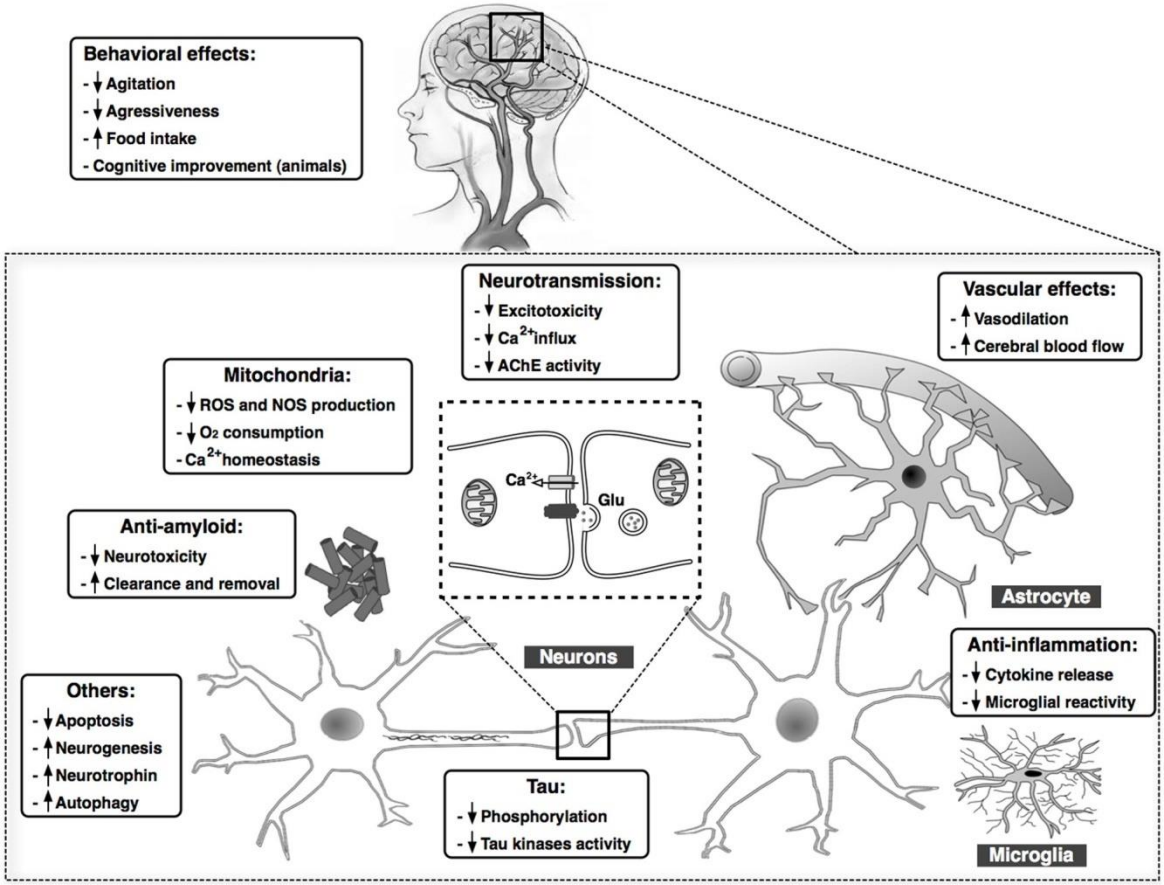
SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant.
*Fourth-line agents include topical lidocaine (second-line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, and botulinum toxin.
†There is limited randomized controlled trial evidence to support add-on combination therapy.
Adapted from Moulin et al.[7]

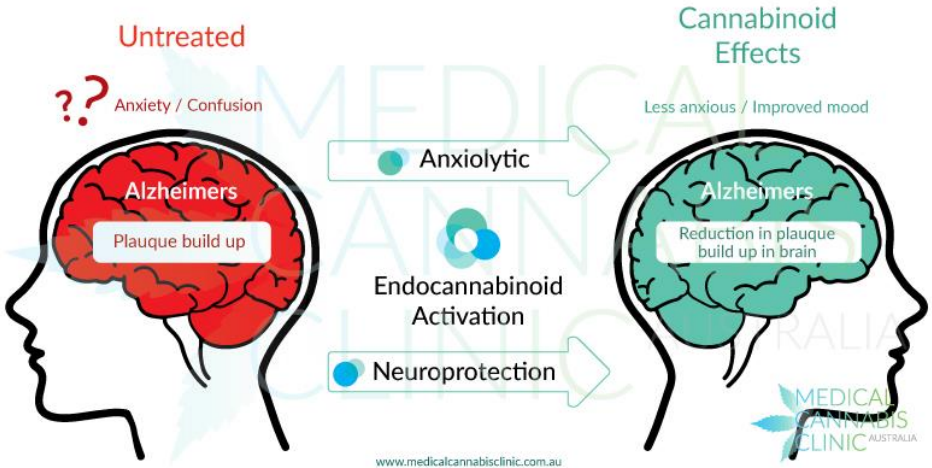
Algoritmo para el tratamiento del dolor Neuropático - Canadá




cognitive dysfunction
cognitive impairment
damage
disease
memory
decline
incontinent
dementia
ability to learn
patient
stress
revealed
health concern
serious loss
problem solving
behaviou
attention
behavioral problems
brain
Alzheimer's
illness
syndrome
language
classified
aggressior
mental health
disorientation
mental problems
depressior
brain injury
diagnosis
agitation

CBD y THC


Behavioral effects:
- ↓ Agitation
- ↓ Agressiveness
- ↑ Food intake
- Cognitive improvement (animals)
Neurotransmission:
- ↓ Excitotoxicity
- ↓ Ca2+influx
- ↓ AChE activity
Vascular effects:
- ↑ Vasodilation
- ↑ Cerebral blood flow
Mitochondria:
- ↓ ROS and NOS production
- ↓ O2 consumption
- Ca2+homeostasis
Ca2+
Glu
Anti-amyloid:
- ↓ Neurotoxicity
- ↑ Clearance and removal
Astrocyte
Neurons
Anti-inflammation:
- ↓ Cytokine release
- ↓ Microglial reactivity
Others:
- ↓ Apoptosis
- ↑ Neurogenesis
- ↑ Neurotrophin
- ↑ Autophagy
Tau:
- ↓ Phosphorylation
- ↓ Tau kinases activity
Microglia


Untreated
Anxiety / Confusion
Alzheimers
Plauque build up
Anxiolytic
Endocannabinoid Activation
Neuroprotection
Cannabinoid Effects
Less anxious / Improved mood
Alzheimers
Reduction in plauque build up in brain
www.medicalcannabisclinic.com.au

More and Choi *Molecular Neurodegeneration* (2015) 10:17
DOI 10.1186/s13024-015-0012-0

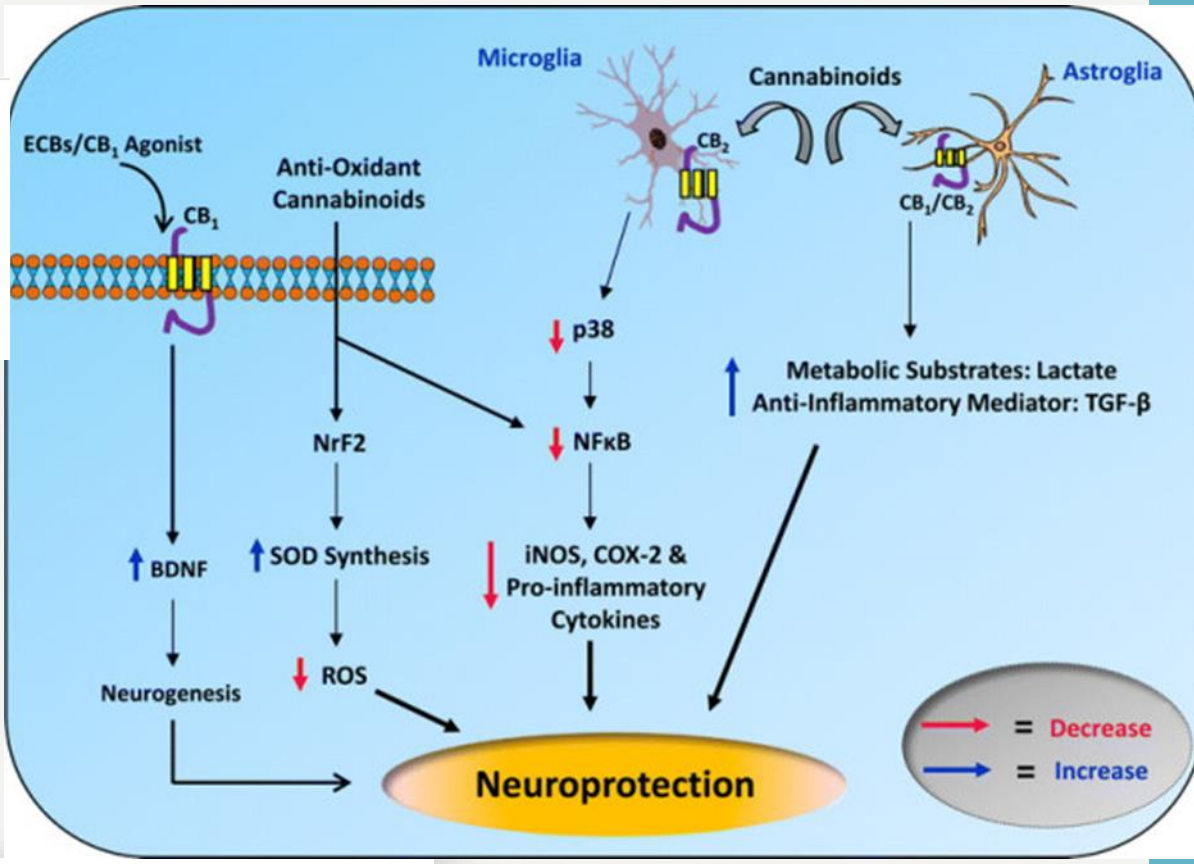
MOLECULAR NEURODEGENERATION

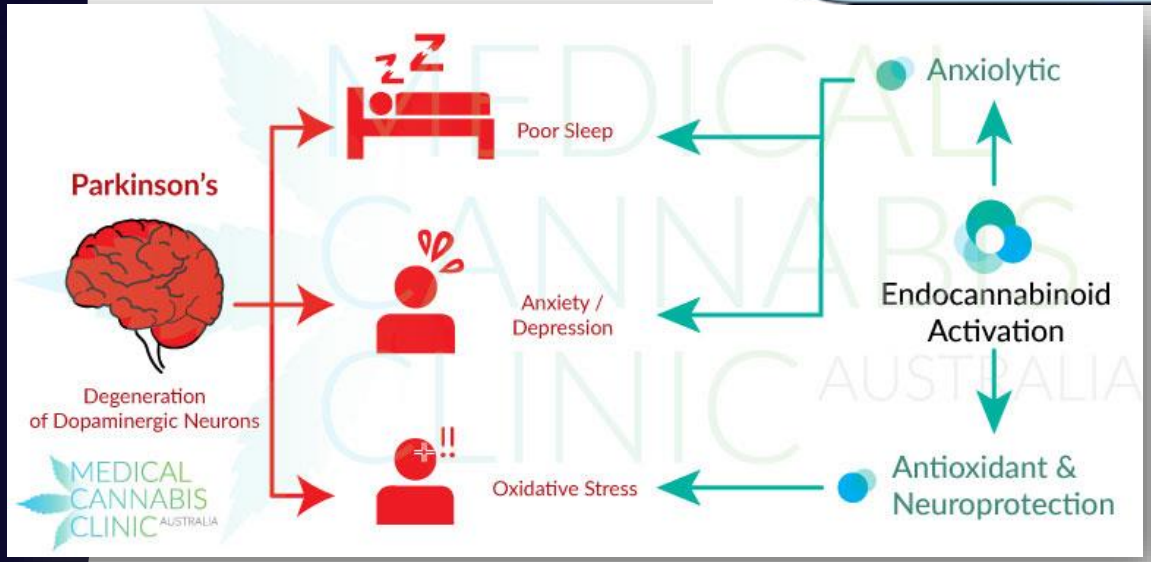
REVIEW Open Access

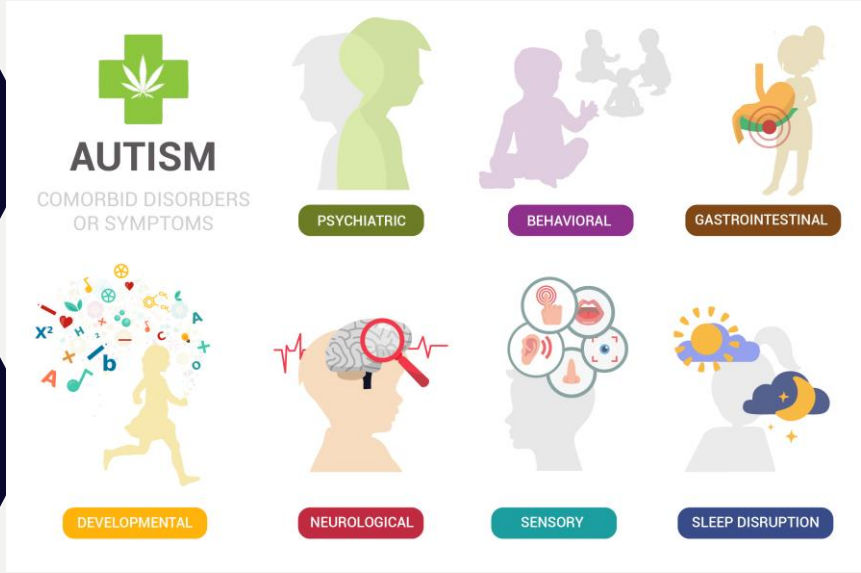
Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection

Sandeep Vasant More and Dong-Kug Choi*

CBD y THC

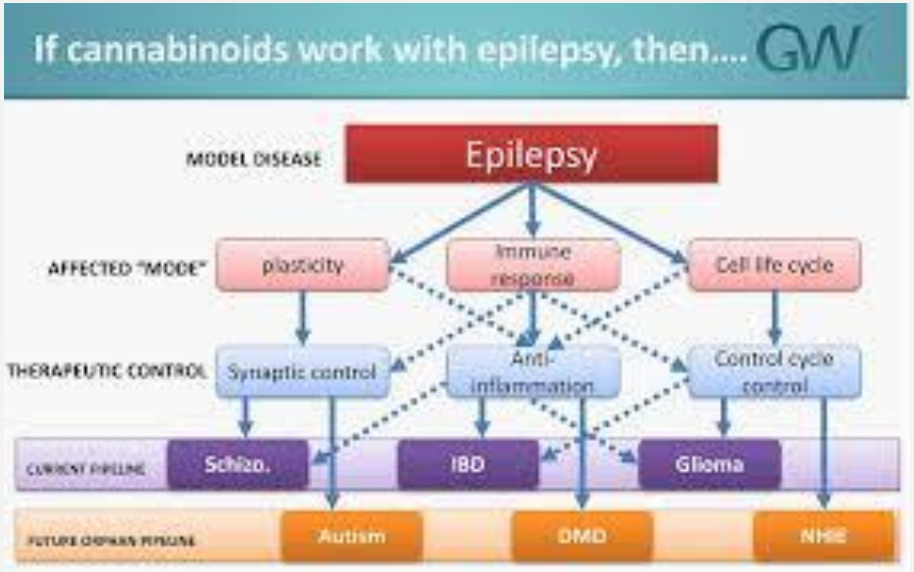






CBDV

CBDV+CBD



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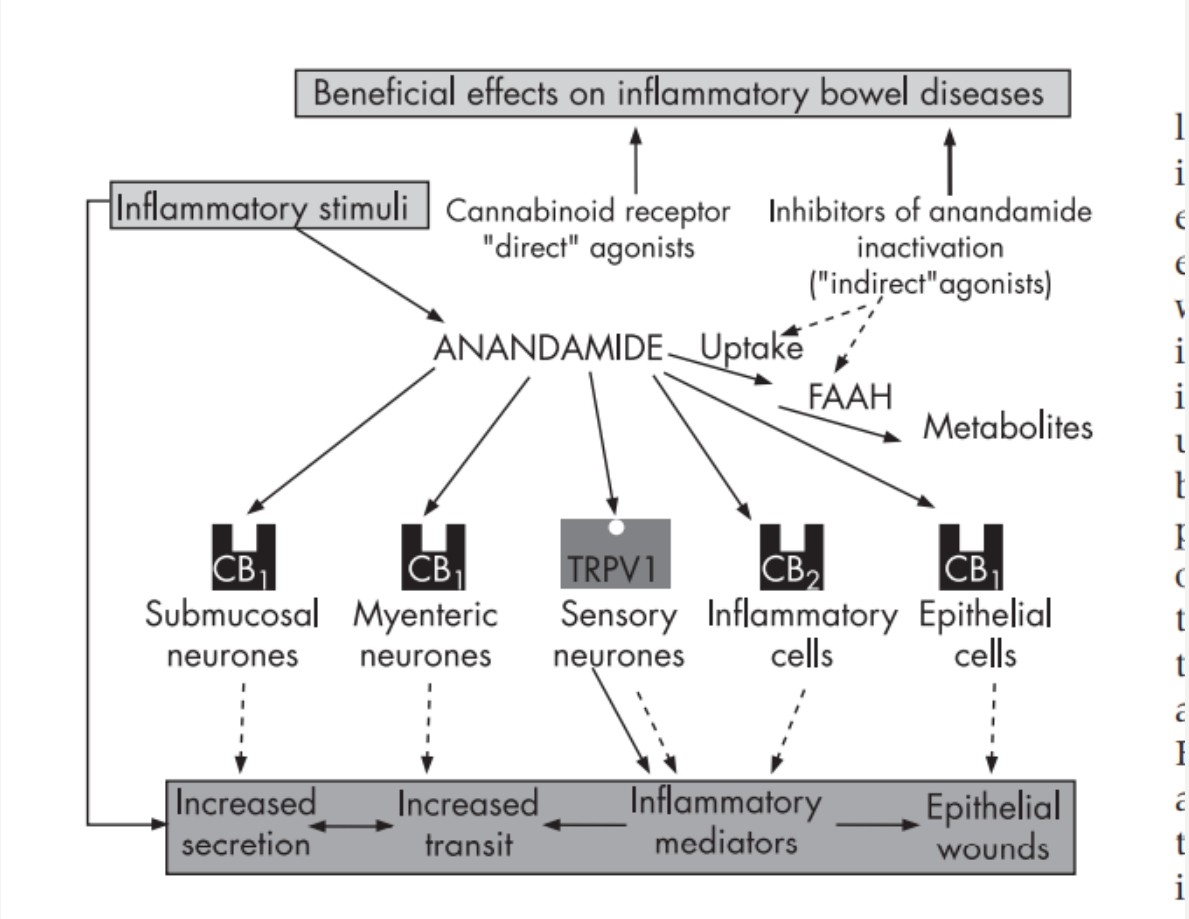
Cannabidivarin (CBDV) vs. Placebo in Children With Autism Spectrum Disorder (ASD)

ENFERMEDADES INFLAMATORIAS DEL TGI

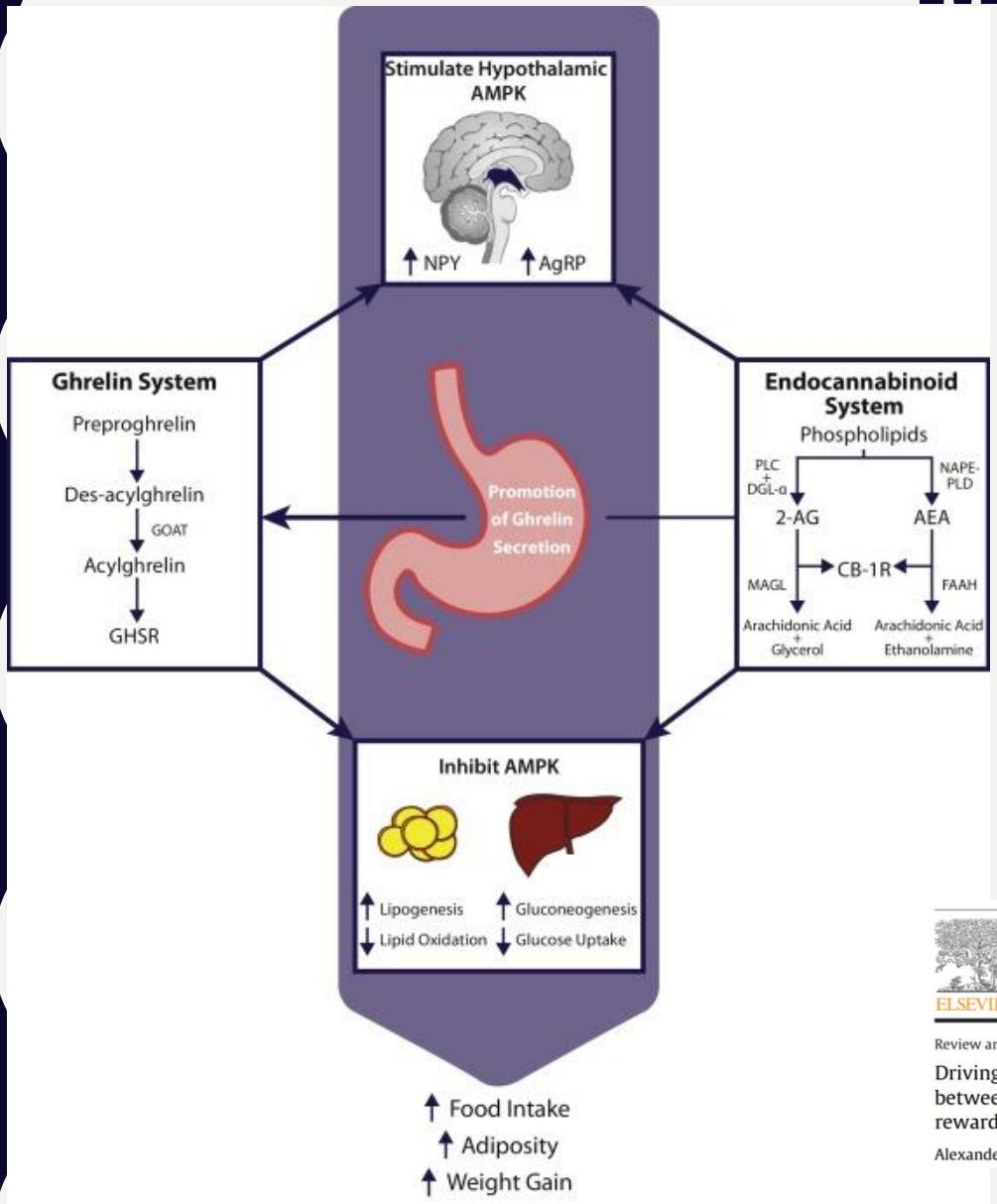


LEADING ARTICLE

Endocannabinoid overactivity and intestinal inflammation

V Di Marzo, A A Izzo

METABOLISMO



Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

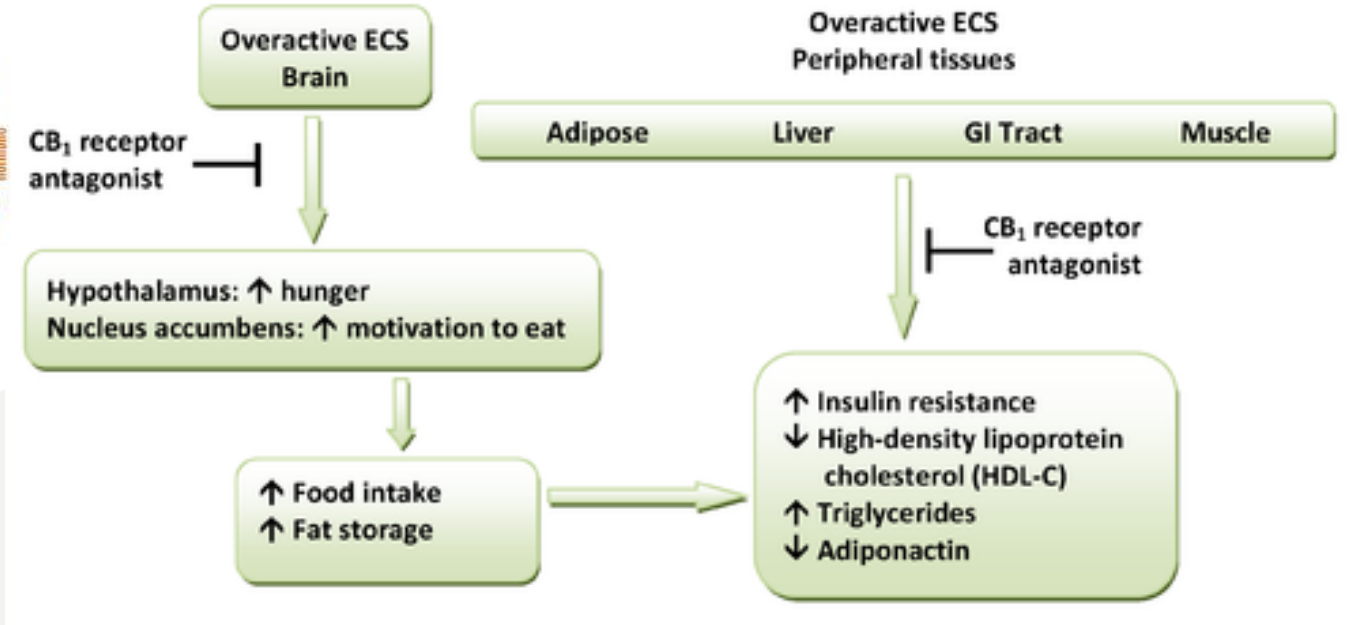
journal homepage: www.elsevier.com/locate/neubiorev

ELSEVIER

Review article

Driving the need to feed: Insight into the collaborative interaction between ghrelin and endocannabinoid systems in modulating brain reward systems

Alexander Edwards, Alfonso Abizaid *



ANTAGONISTAS

CBD

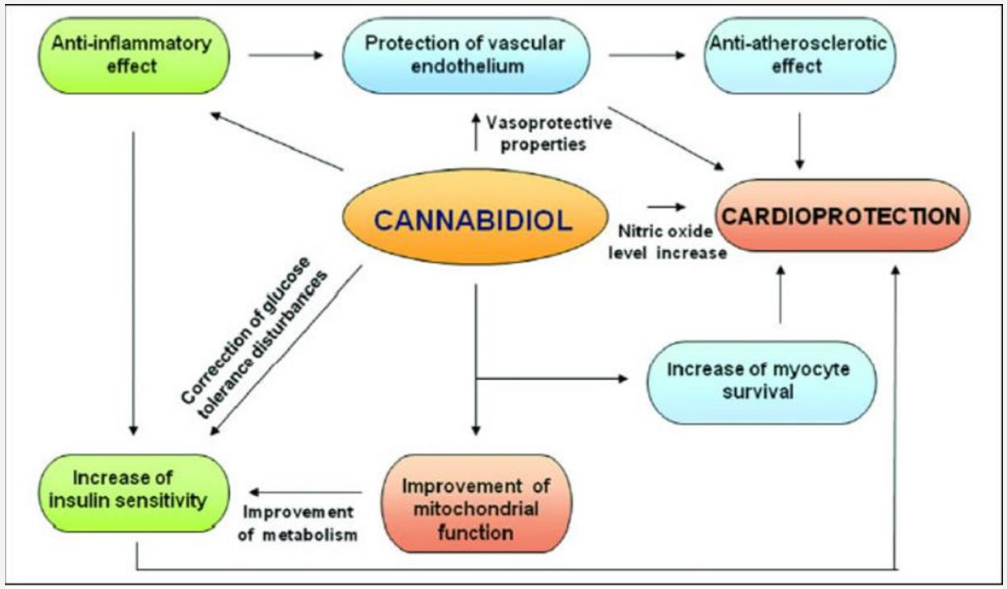


Fig. 3. Therapeutic potential targets of cannabidiol (CBD) in diabetes. CBD may exert beneficial effects against various diabetic complications by attenuating high glucose (inducing endothelial cell activation and inflammatory response), cardioprotection, increasing sensitivity to insulin, protection of vascular endothelium, improvement of metabolism, anti-inflammatory and anti-atherosclerotic effects.

MUCHAS GRACIAS

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