G.U.I.D.A.
IV CONGRESSO NAZIONALE
Torino 11 maggio 2023

DIPARTIMENTO DI NEUROSCIENZE
UNIVERSITÀ DI TORINO

Il sistema cannabinoide nel dolore muscolo-scheletrico

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Dipartimento di Neuroscienze
Università degli Studi di Torino

Disclosures

Participation as speacker at congresses or scientific boards

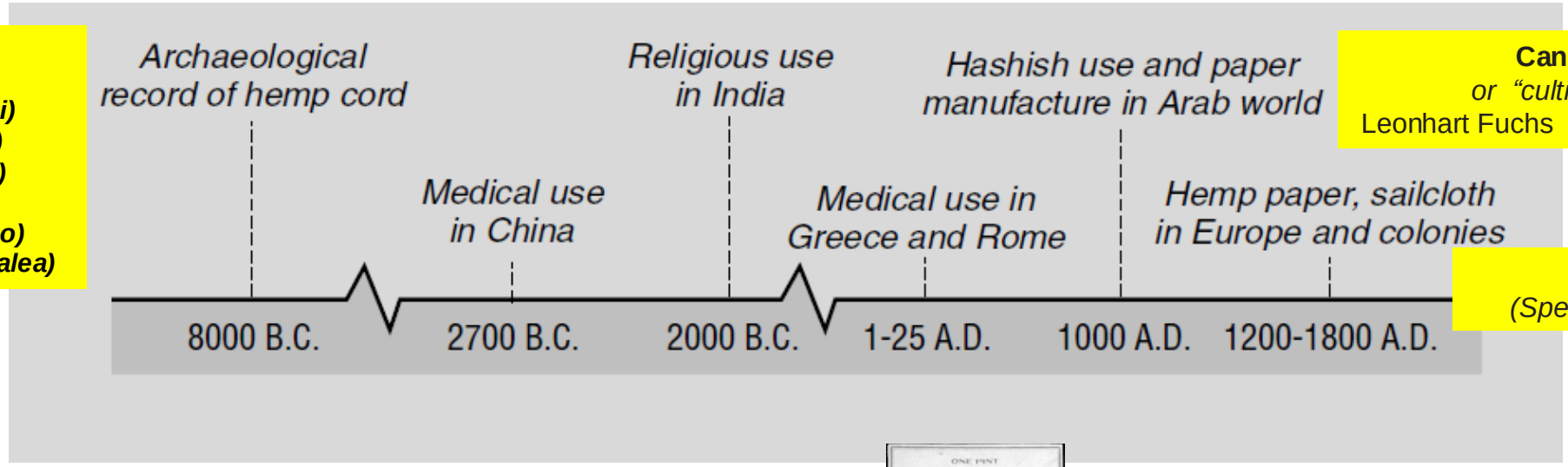
Grants from:

Viatris
Jannsen
Roche
Admiral
Pfeizer

Topics

cannabinoids science and clinic
the endocannabinoids system
cannabinoids and bone pain
cannabinoids and muscle pain

Analgesia
Dermatologia (lebbra)
Inflammologia (reumatismi)
Ostetricia (dolori da parto)
Ginecologia (dismenorrea)
Anti-emetico
Astenia (agente oressigeno)
Neurologia (epilessia,, cefalea)

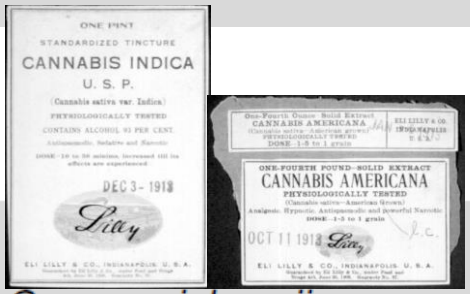


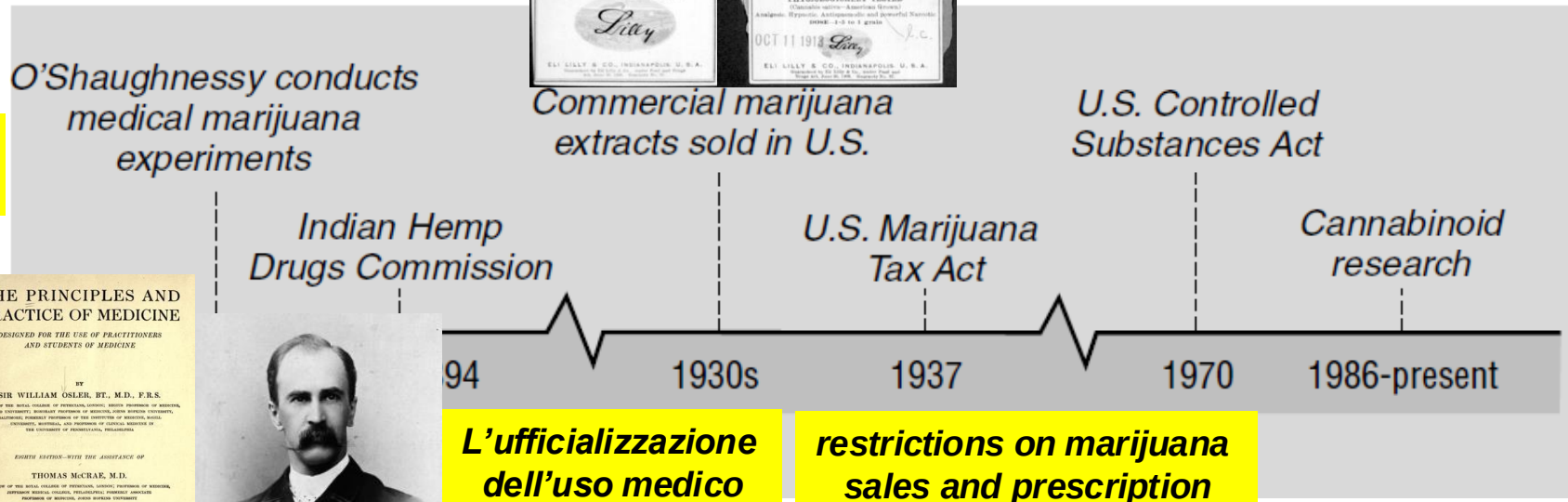
Cannabis sativa
or "cultivated Cannabis"
Leonhart Fuchs *(Neue Kreüterbuch,1542)*

Linnaeus
(Species Plantarum ,1753)

Medical marijuana timelines.

la riscoperta coloniale





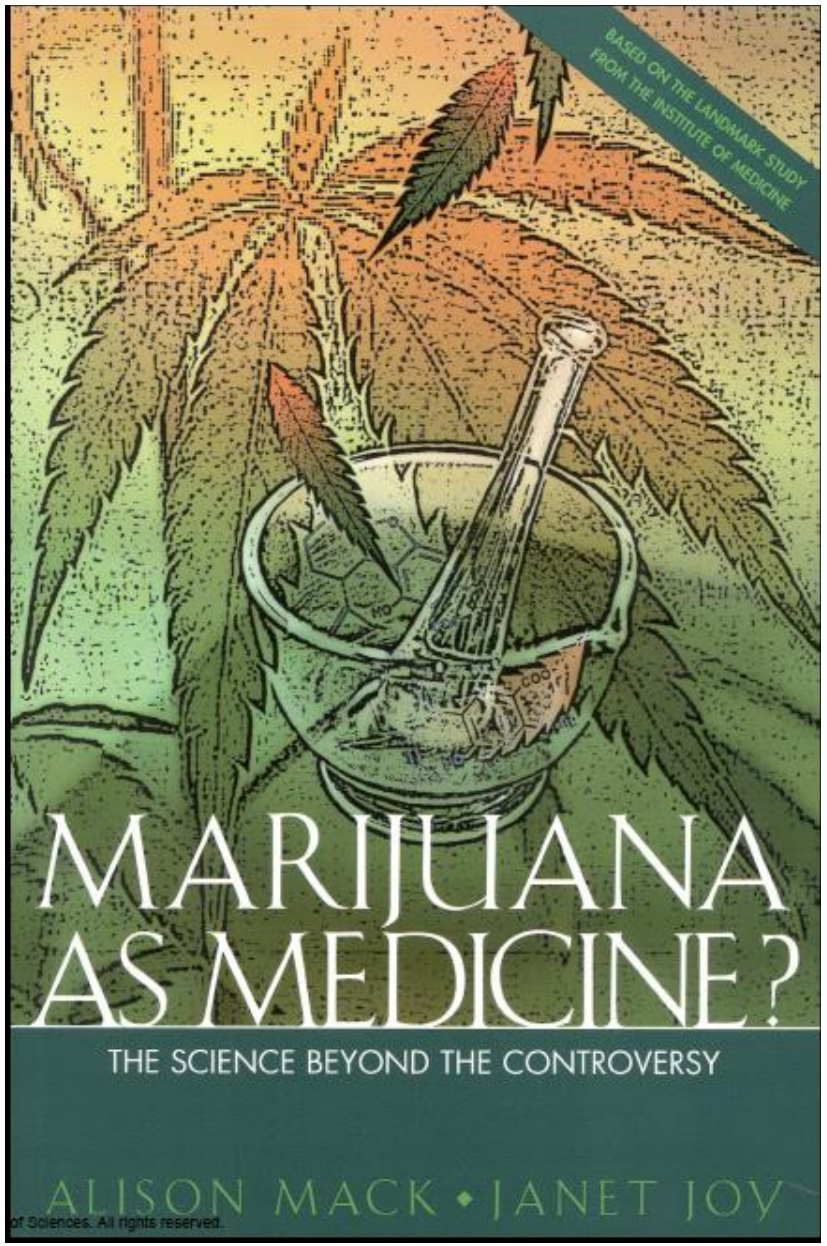
THE PRINCIPLES AND PRACTICE OF MEDICINE
DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE
BY
SIR WILLIAM OSLER, BT., M.D., F.R.S.
EIGHTH EDITION—WITH THE ASSISTANCE OF
THOMAS McCRAE, M.D.
NEW YORK AND LONDON
D. APPLETON AND COMPANY
1919

L'ufficializzazione dell'uso medico

restrictions on marijuana sales and prescription

1942 marijuana removed from the United States Pharmacopoeia

Mack and Joy, 2000



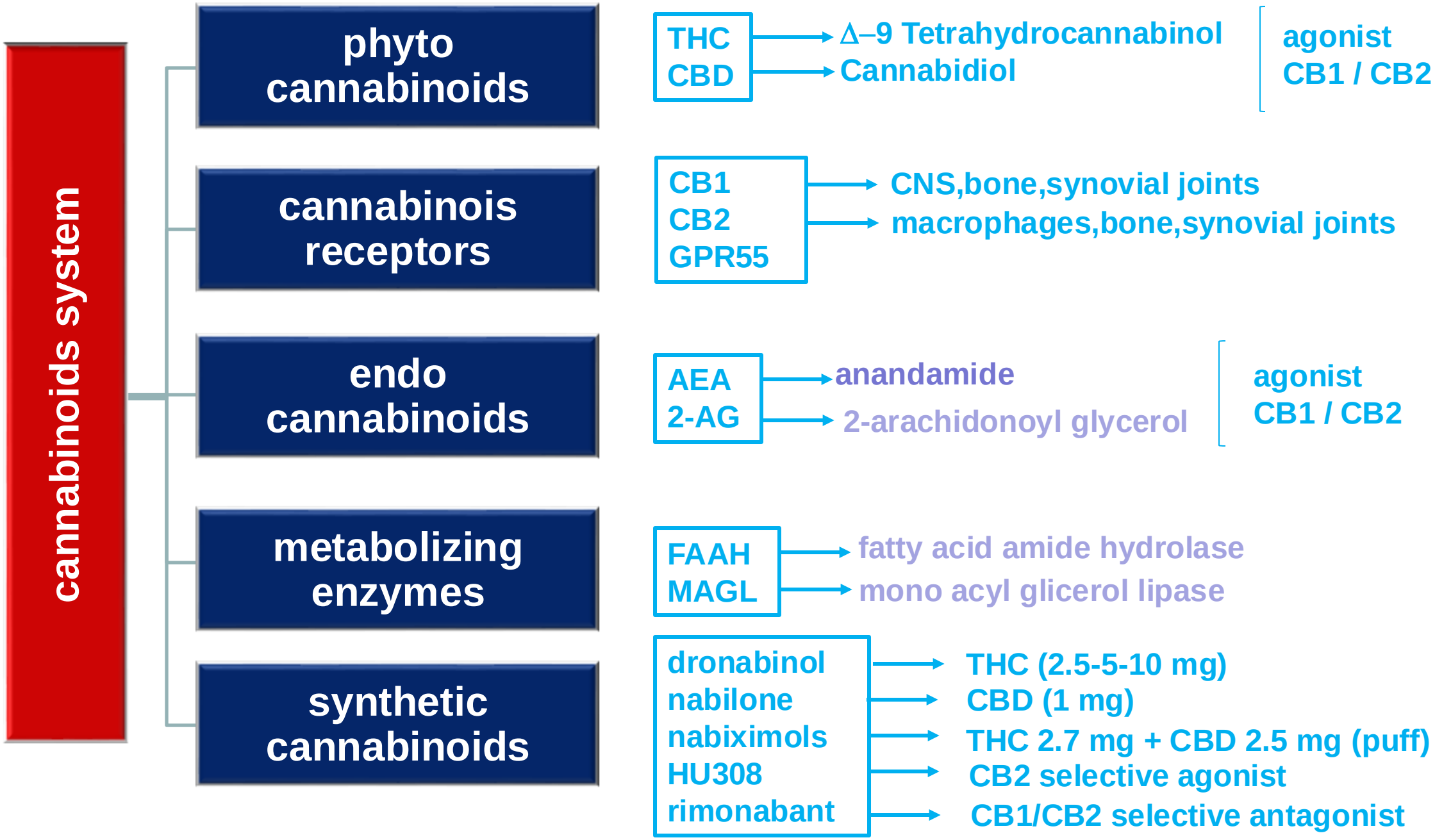
1997: the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to review the evidence for the potential benefits and risks associated with the use of marijuana.

Not long ago most medical treatment was based on anecdotal evidence.

Only recently, in the world's wealthiest societies, have scientific standards replaced the oral traditions of folk medicine.

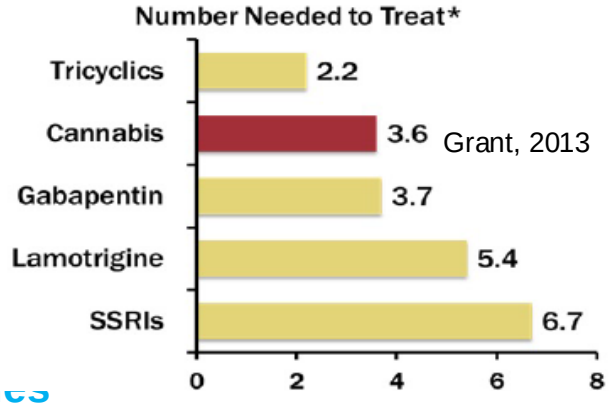
CANNABINOID SCIENCE

- biological knowledge
- scientific proofs
- effectiveness and safety

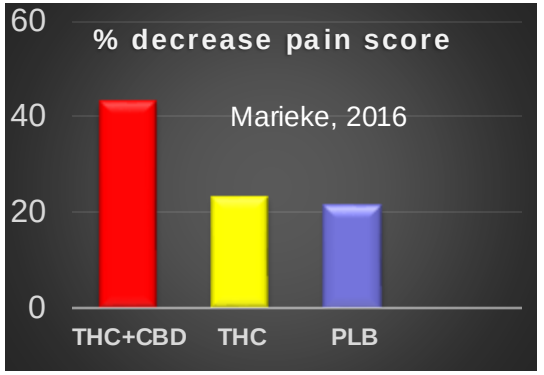

cannabinoids system
phyto cannabinoids
cannabinois receptors
endo cannabinoids
metabolizing enzymes
synthetic cannabinoids
THC
CBD
Δ–9 Tetrahydrocannabinol
Cannabidiol
agonist
CB1 / CB2
CB1
CB2
GPR55
CNS,bone,synovial joints
macrophages,bone,synovial joints
AEA
2-AG
anandamide
2-arachidonoyl glycerol
agonist
CB1 / CB2
FAAH
MAGL
fatty acid amide hydrolase
mono acyl glicerol lipase
dronabinol
nabilone
nabiximols
HU308
rimonabant
THC (2.5-5-10 mg)
CBD (1 mg)
THC 2.7 mg + CBD 2.5 mg (puff)
CB2 selective agonist
CB1/CB2 selective antagonist

cannabinoids therapeutics

- **pain** → chronic pain (neuropathic),fibromyalgia, arthritis, headache, etc
- **inflammation** → flogistic diseases
- **seizures** → epilepsy
- **appetite** → oncology, chemotherapies
- **spasticity** → multiple sclerosis. amyotrophic lateral sclerosis
- **nausea** → oncology, cytostatic-induced nausea and vomiting
- **neuropsych.** → depression, anxiety, insomia, PTSD, autism, Alzheimer, Parkinson,etc.



Grant, 2013



Analgesic potency as codeine

E.P. Baron, Headache 2015
Can Marijuana help ?

695 references

Pubmed *cannabinoids therapy*

12.004 references

Eur J Pain 2022
Long term study chronic non cancer pain Biales et al.

2686 participants,
duration 26-52 weeks.

EFFECTIVENESS

Pain relief of 50% or greater : **20.8 %**

Pain relief of 30% or greater : **38.3 %**

Drop-out lack efficacy : **7.4 %**

DECRETO 9 novembre 2015.

Funzioni di Organismo statale per la *cannabis* previsto dagli articoli 23 e 28 della convenzione unica sugli stupefacenti del 1961, come modificata nel 1972.

Deliberazione della Giunta Regionale 15 febbraio 2016, n. 24-2920

Indirizzi procedurali ed organizzativi per l'attuazione della Legge Regionale n. 11 del 15 giugno 2015 - Uso terapeutico della canapa.

INDICAZIONI TERAPEUTICHE

a) analgesia in patologie che implicano spasticità associata a dolore (sclerosi multipla, lesioni del midollo spinale) resistente alle terapie convenzionali;

b) **analgesia nel dolore cronico** (con particolare riferimento al dolore neurogeno) in cui il trattamento con antinfiammatori non steroidei o con farmaci cortisonici o oppioidi si sia rivelato inefficace;

c) **effetto anticinetosico ed antiemetico nella nausea e vomito**, causati da chemioterapia, radioterapia, terapie per HIV, che non può essere ottenuto con trattamenti tradizionali;

d) **effetto stimolante l'appetito** nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici o affetti da AIDS e nell'anoressia nervosa, che non può essere ottenuto con trattamenti standard;

e) **effetto ipotensivo nel glaucoma** resistente alle terapie convenzionali;

f) **riduzione dei movimenti involontari** del corpo e facciali nella sindrome di *Gilles de la Tourette* che non può essere ottenuta con trattamenti standard.

cannabinoids adverse effects

- **sedative** → CNS depression, somnolence, amotivational syndrome,
- **emotional** → euphoria, dysphoria, anxiety, induced psychoses
- **perception** → heightened sensory perception, misperception, hallucinations, etc.
- **cognition** → impaired memory, reduce cognitive performance, mental clouding,etc
- **dependence** → physical and psychological (chronic and heavy use)
- **vascular** → heart rate, arrhytmia, vasodilatation, risk of MI (smoking)
- **respiratory** → lung cancer (?), lung inflammatory disease, (smoking), etc

E.P. Baron, Headache 2015
Can Marijuana help ?

695 references

Pubmed *«cannabinoids adverse events»*

6247 references

interactions

Cannabinoids	CYP P450 isoenzymes
CBD	Inhibition of CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2B6, CYP3A4, and CYP2D6
THC	Inhibition of CYP3A4, CYP2D6, and CYP2C9
CBN	Inhibition of CYP3A4, CYP2D6, and CYP2C9

Eur J Pain 2022 Long term study chronic non cancer pain Biales et al.

SAFETY

Drop-out for side effects: **6.8 %.**

Serious adverse events : **3 %**

Inadequate response to analgesics in chronic pain

← treatment resistence, inadequate drug inadequate dosages

↓

Other underevaluated components ?

emotional ← mood depression, anxiety, stress, etc

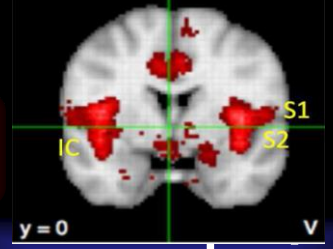
cognitive ← fear, alexythymia, catastrophizing, etc

social ← low perceived support, etc

↓

interference with:
quality of life
pain intensity
pain chronification
drug treatments

acute pain



sensory brain regions activity

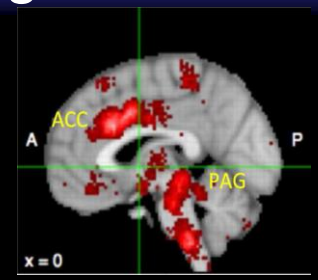
↓

transition

↓

chronic pain

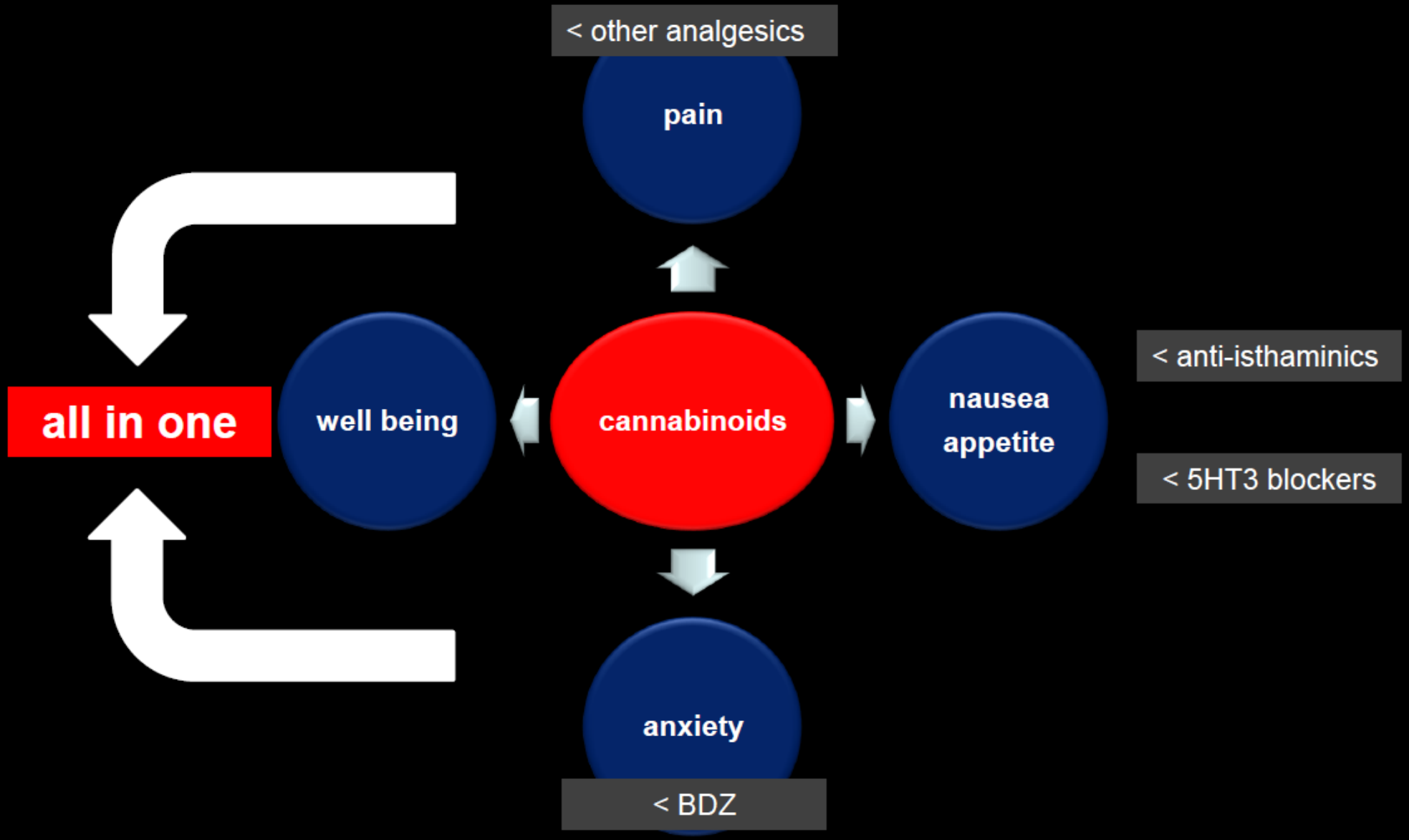
emotional brain regions activity



from comorbility

depression → **pain**

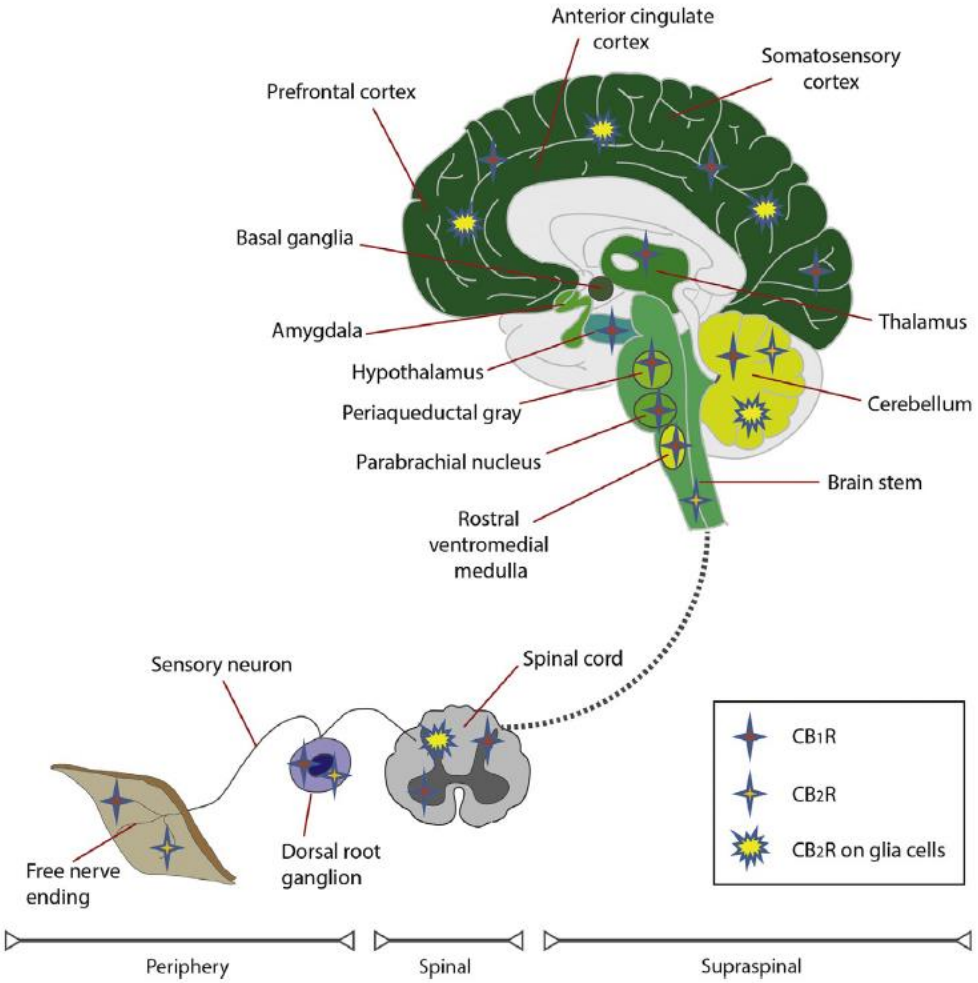
to copathogenesis


< other analgesics
pain
all in one
well being
cannabinoids
nausea
appetite
< anti-isthaminics
< 5HT3 blockers
anxiety
< BDZ

Advances in Pharmacology, 2017

Cannabinoids and Pain: Sites and Mechanisms of Action

Katarzyna Starowicz, David P. Finn,1



Analgesic effects mechanisms :

inhibition of presynaptic neurotransmitter and neuropeptide release

modulation of postsynaptic neuronal excitability

activation of the descending inhibitory pain pathway

reductions in neuroinflammatory signaling

modulation of nuclear factor kappa B

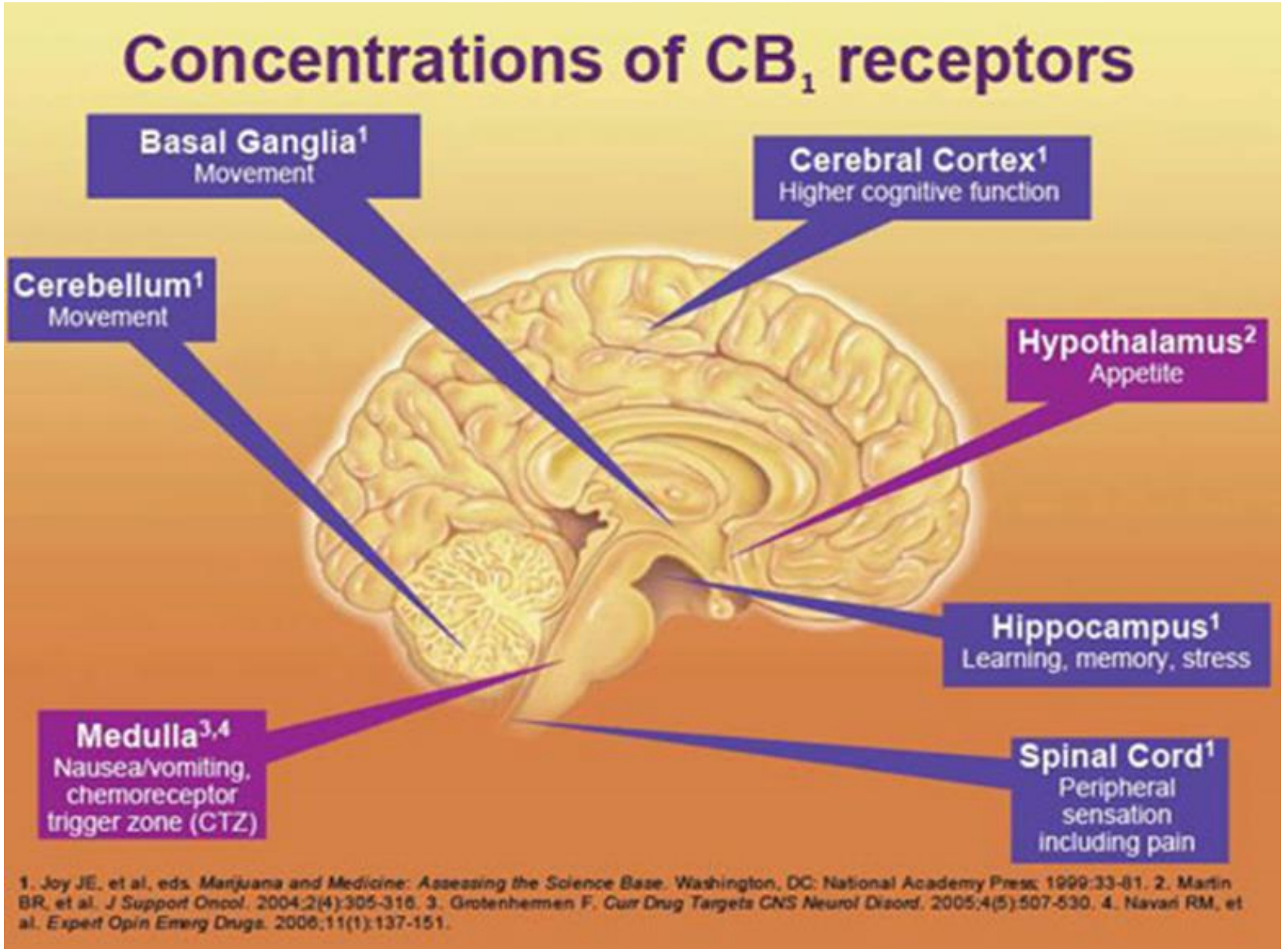
agonist CB1 inhibit calcium channels
(release of proinflammatory cytokines)

The Human Endocannabinoid System

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

Activation of CB1 receptors
alleviation of nausea and vomiting also to to an antagonistic action on the 5-HT3 receptors

Activation of CB1 receptors
involves memory, perception, movement, mood-enhancing and detrimental effects

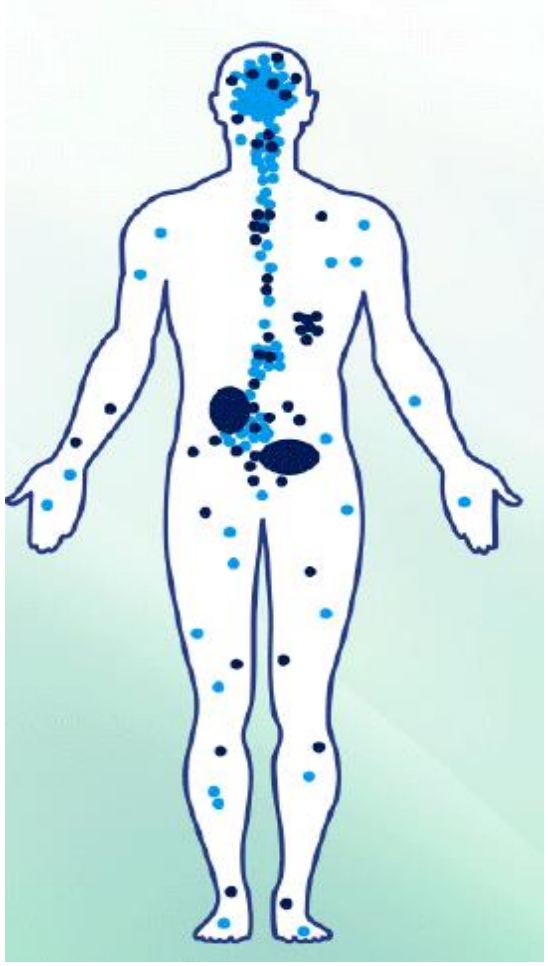


The Human Endocannabinoid System

CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

Activation of CB2 receptors
induces a pain modulation
and has an important role
in immune function and inflammation

the presence of CB2 receptors on **microglia**
explains the putative benefits of cannabinoids
in reducing cytokine-mediated
neuroinflammation

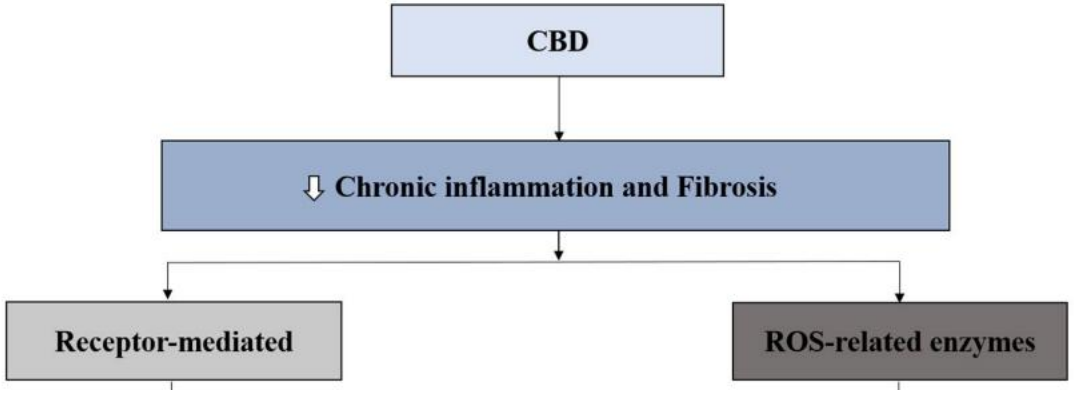


CBD acts on CB2 > CB1
CBD mitigates the psychomimetic activity of THC

CB2

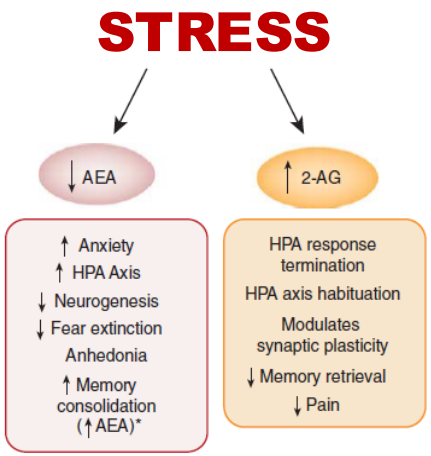
CBD
Cannabidiol

A molecular basis for the anti-inflammatory and anti-fibrosis properties of cannabidiol Sunda & Arovolo, Faseb Journal 2020



Neuropsychopharmacology Reviews (2016)

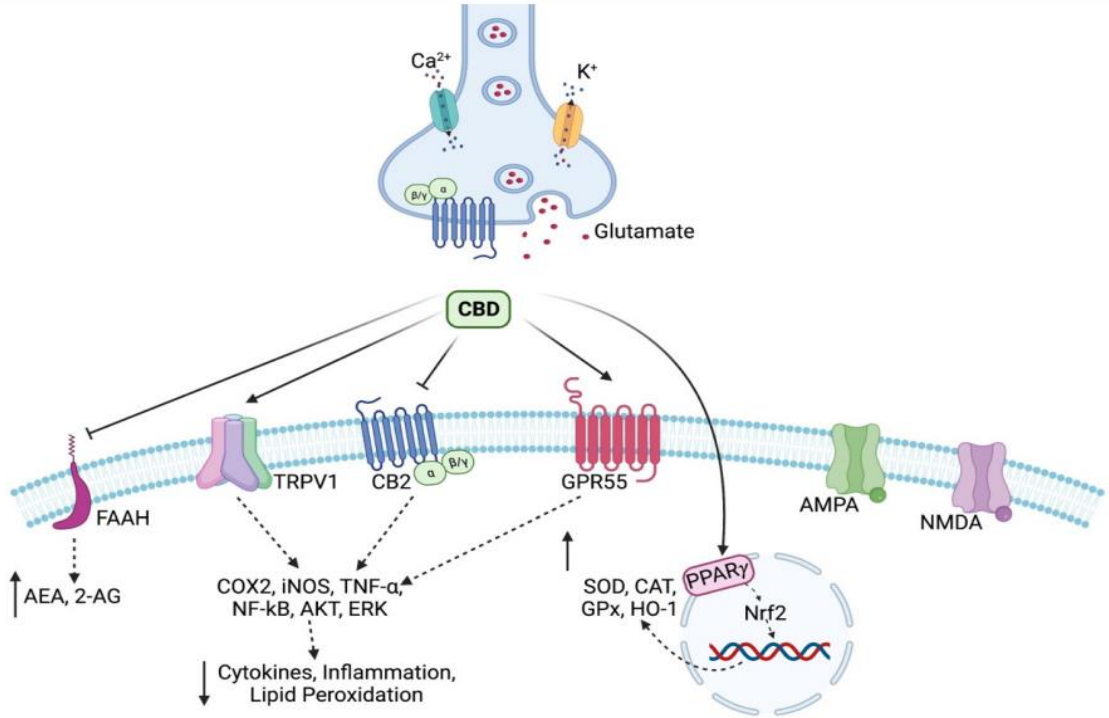
Neurobiological Interactions Between Stress and the Endocannabinoid System **Maria Morena et al.**



eCB signaling in humans is critical in stress regulation

Cannabidiol: Bridge between Antioxidant Effect, Cellular Protection, and Cognitive and Physical Performance

George Jîtcă et al. Antioxidants,2023



cannabinoids and bone pain

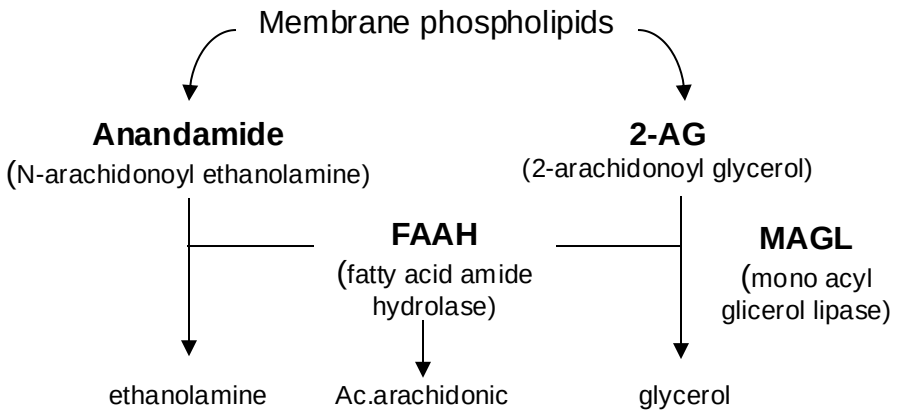
The discovery of the skeletal EC system

endocannabinoids and their receptors play important roles in regulating bone → **bone mass, bone loss, bone cell function**

associated with other factors
(geneticS, sex, age, hormonal status**)**

Bab IA.
The skeleton: stone bones and stoned heads?
Springer; 2005

endocannabinoids are produced in bone and in synovial joints



CB1r →
- Osteoblasts, osteoclasts and adipocytes differentiation
- Osteoclasts inhibition
- Expresseed by sympatetic neurones (inhibition of NE release)
- Deletion : osteoporosis, reduced bone formation, adipocytes accumulation

CB2r →
- Osteoblasts, osteoclasts and adipocytes differentiation
- Osteoclasts inhibition, stimulate osteoblasts and bone formation

GPR55r →
- expressed by osteoclasts
- regulates osteoclasts activity and bone resorption
- CBD GPR55r antagonist enhanced osteoclasts formation

conflicting results
(but promising therapeutic options in addition to analgesic and anti-inflammatory effects)

THC
CBD → **stimulate bone formation**
collagen production
osteoporosis prevention

(Idris and Ralston, 2010; Raphael-Mizrahi and Gabet, 2020)

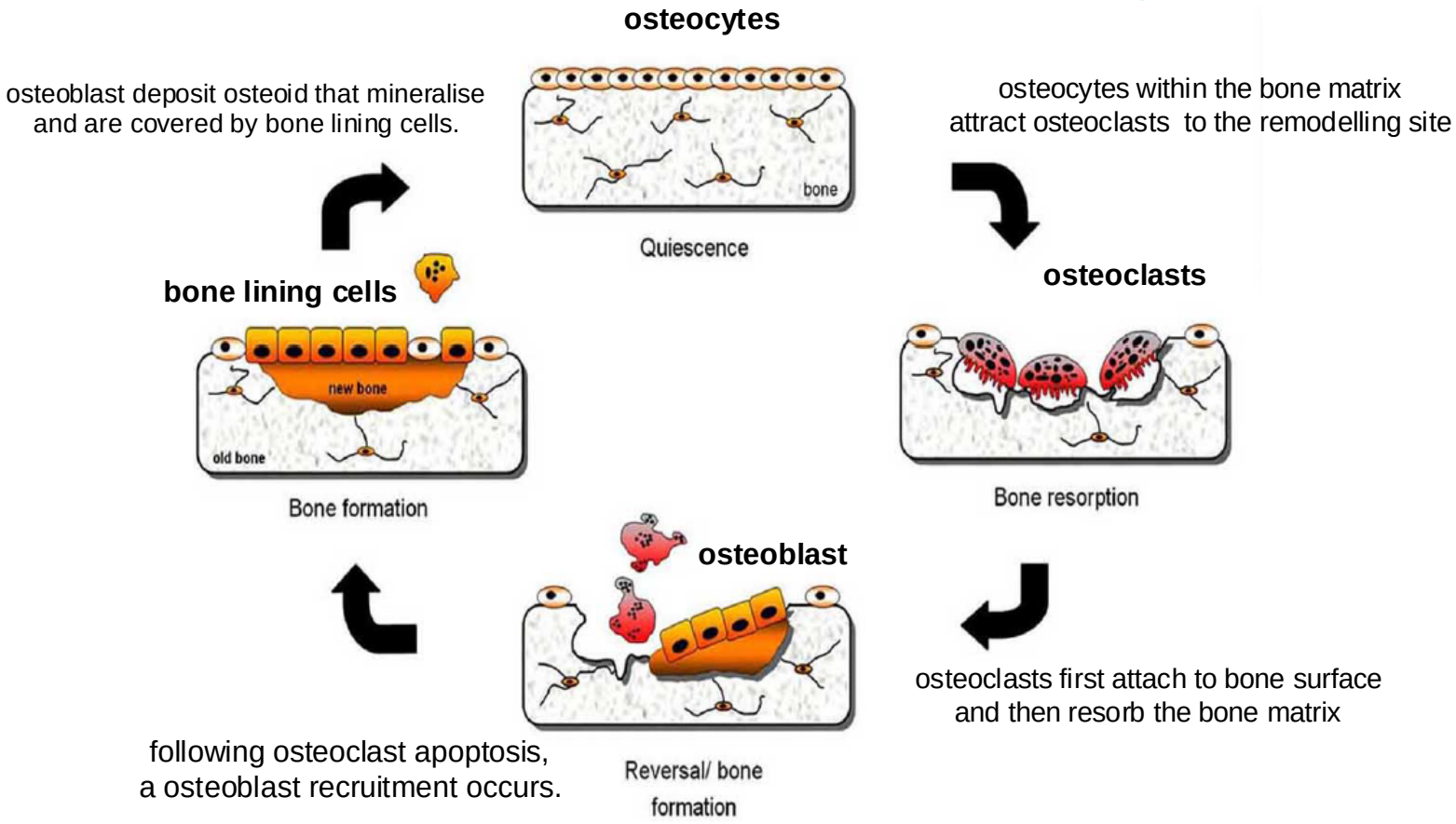
Current Neuropharmacology, 2010, *8*, 243-253

Cannabinoid Receptors as Target for Treatment of Osteoporosis

Aymen I. Idris

CB1

Osteoblasts, osteoclasts and adipocytes differentiation
Osteoclasts inhibition
Expresseed by sympatetic neurones (inhibition of NE release)
Deletion : osteoporosis, reduced bone formation, adipocytes accumulation



CB2

Osteoblasts, osteoclasts and adipocytes differentiation
Osteoclasts inhibition, stimulate osteoblasts and bone formation

THC
CBD
→ **stimulate bone formation**
collagen production
osteoporosis prevention

Calcif Tissue Int (2010) 87:285–297

Cannabinoids and Bone: Friend or Foe?

Aymen I. Idris · Stuart H. Ralston

cannabinoids play a key role in the regulation of bone metabolism.

Mice with CB_1 deficiency
have high peak bone mass because of an osteoclast defect
but develop age-related osteoporosis because of impaired bone formation
and accumulation of bone marrow fat.

Mice with CB_2 deficiency
have relatively normal peak bone mass
but develop age-related osteoporosis because of increased bone turnover
with uncoupling of bone resorption from bone formation.

CANNABINOIDS AND INFLAMMATORY JOINT DISEASE PAIN

CANNABINOIDS AND CANCER-INDUCED BONE DISEASE

CANNABINOIDS AND INFLAMMATORY JOINT DISEASE PAIN

Pertwee RG
Cannabinoid pharmacology
Br J Pharmacol (2006)

Cannabis-based medicines as treatments for inflammatory conditions and pain

Lowin, Schneider, & Pongratz
Joints for joints.
Current Opinion in Rheumatology, 2019

CB2 activation mediates anti-inflammatory effects in RA by decreasing immune cell migration and cytokine production.
CB1 antagonists provide anti-inflammatory effects by enhancing beta2-adrenergic signaling in arthritis.
CBD is effective in reducing inflammation and pain and might enhance the efficacy of therapeutic drugs

Aymen I. Idris
Cannabinoid Receptors as Target for Treatment of Osteoporosis
***Current Neuropharmacology*, 2010**

CB1 and CB2 are expressed in synovial tissue from pts with osteoarthritis and rheumatoid arthritis and represent a therapy target

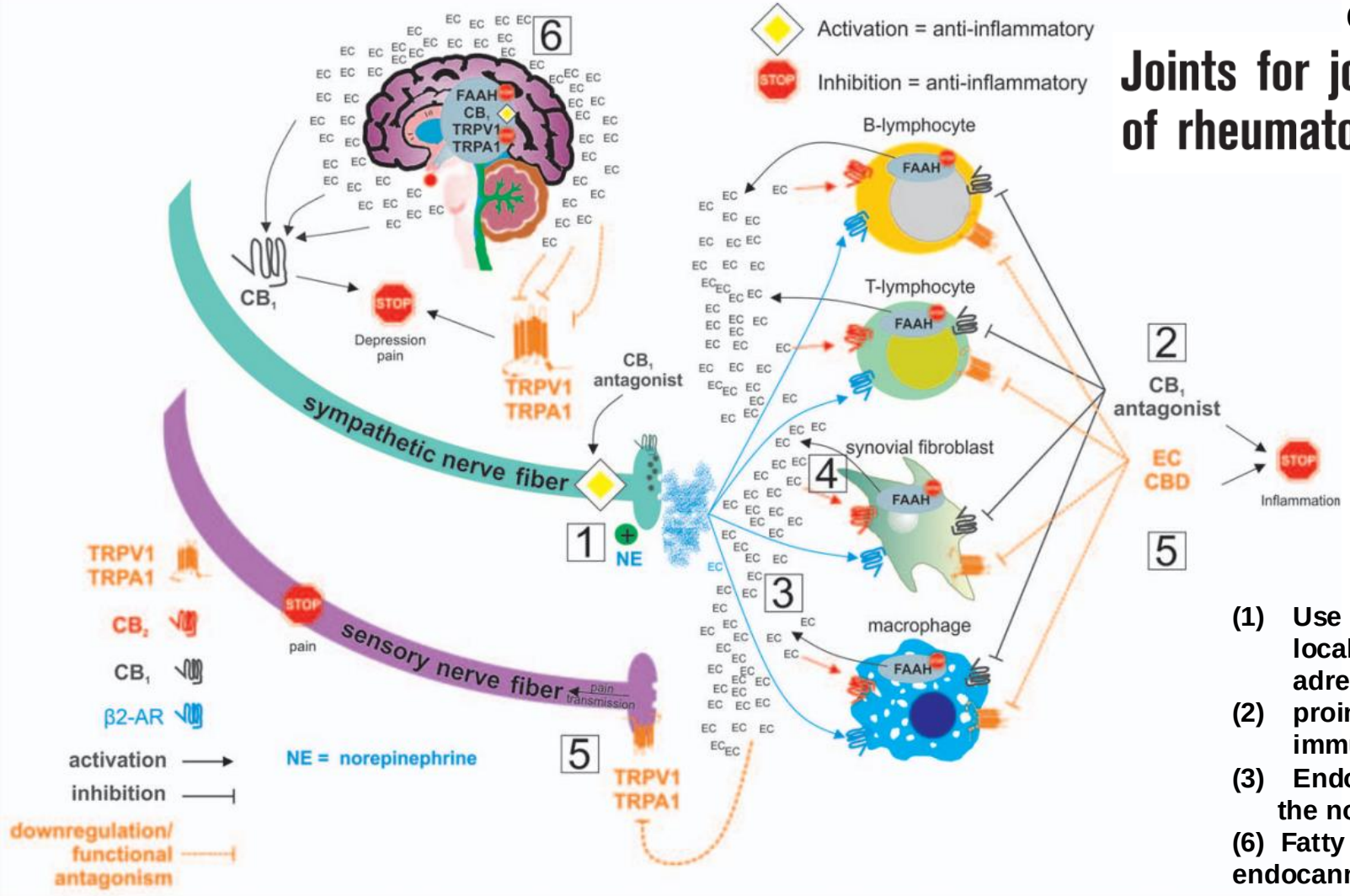
Bryk and Starowicz
Cannabinoid-based therapy as a future for joint degeneration. Focus on the role of CB2 receptor in the arthritis progression and pain
Pharmacological Reports (2021)

role of the CB2 receptor in arthritis-related pain and the suppression of infammation

Curr Opin Rheumatol 2019

Joints for joints: cannabinoids in the treatment of rheumatoid arthritis

Lowin, Schneider, and Pongratz



(1) Use of a peripherally restricted CB1r antagonist increases local NE release and promotes anti-inflammatory beta 2-adrenergic signaling

(2) proinflammatory cannabinoid type 1 receptor signaling on immune cells is inhibited

(3) Endocannabinoids and cannabidiol inhibit the nociceptors TRP vanilloid 1 (TRPV1)

(6) Fatty acid amide hydrolase inhibition increases central endocannabinoid levels.

CANNABINOIDS AND CANCER-INDUCED BONE DISEASE

Ramer et al.
Cannabidiol inhibits cancer cell invasion
Biochem Pharmacol (2010)

Cannabinoid receptor agonists reduce cancer cell invasion by inhibiting matrix metalloproteinases

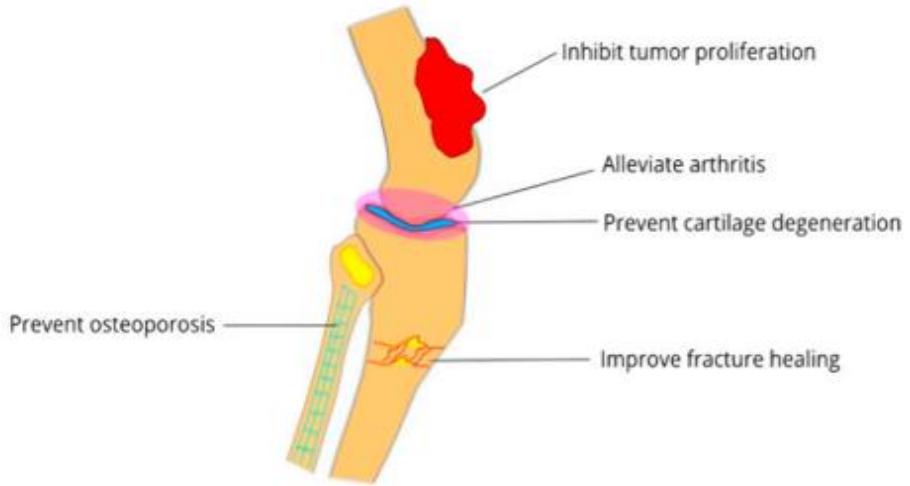
Ellingson and Vanderah
Potential Therapeutic Treatments of Cancer Induced Bone Pain.
Curr Opin Support Palliat Care. 2020

Peripherally restricted cannabinoid 2 (CB2) and kappa opioid receptor agonists have been shown to reduce cancer-induced bone pain

Qamri Zett et al
cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer.
Mol Cancer Ther (2009)

inhibit the development of metastases in preclinical models of glioma, lymphoma, lung cancer and breast cancer

Xin, Tang, Pan and Zhang
Components of the Endocannabinoid System and Effects of Cannabinoids Against Bone Diseases
Front. Pharmacol.2021

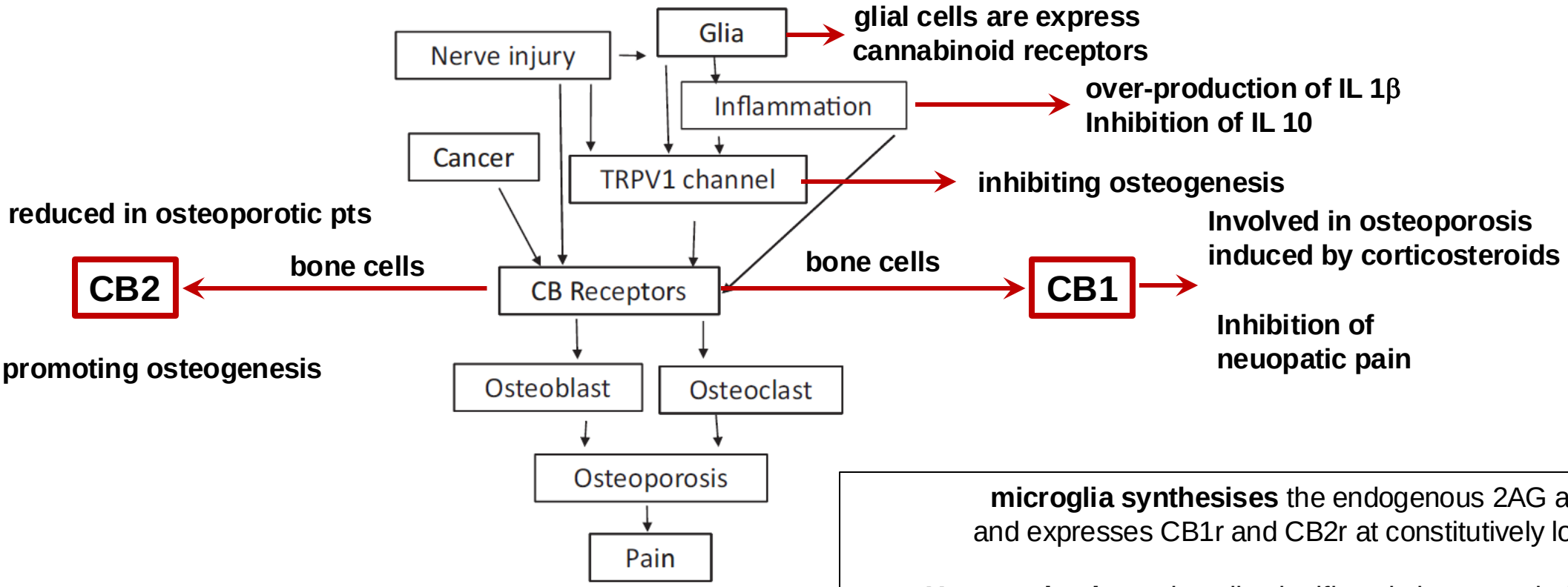


Journal of Pharmacy and Pharmacology, **71** (2019)

Cannabinoid receptors in osteoporosis and osteoporotic pain: a narrative update of review

Jing Wang, Hong-xia Lu and Jing Wang

j.neuropharm.2021
The cannabinoid system and microglia in health and disease
Duffy,Hayes, Fiore, and Moalem-Taylor



microglia synthesises the endogenous 2AG and ANA
and expresses CB1r and CB2r at constitutively low levels.

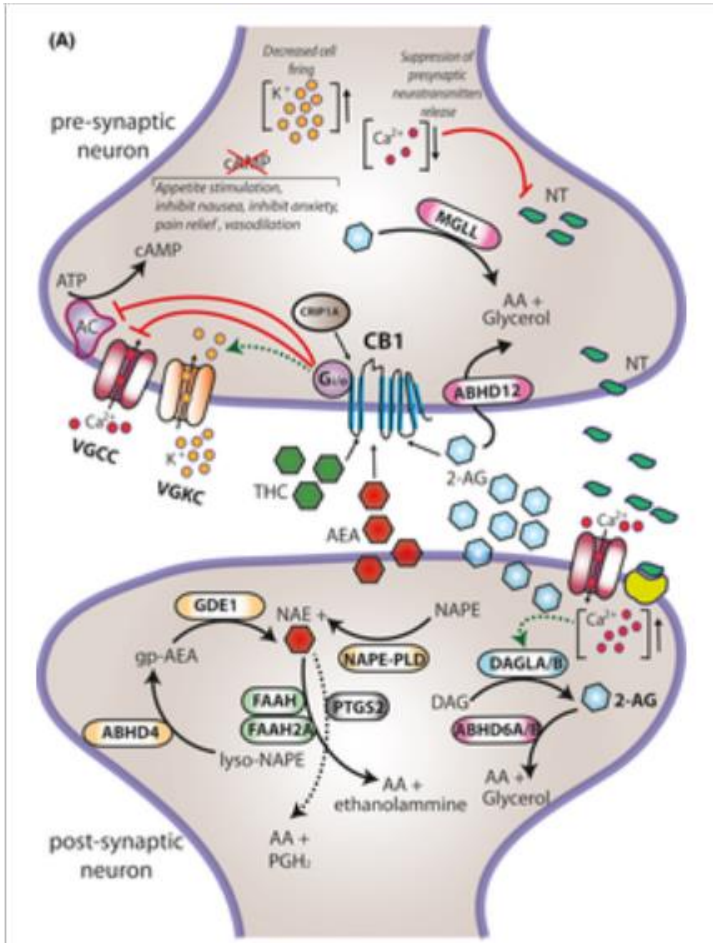
Upon activation, microglia significantly increase their synthesis of endocannabinoids and upregulate their expression of CB2 receptors, which enhancing their production of neuroprotective factors
and reducing their production of pro-inflammatory factors.

cannabinoids
and muscle pain

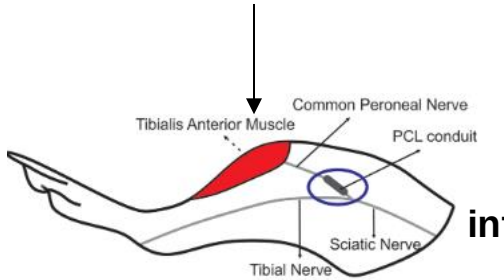
European Journal of Pharmacology 901 (2021)

Endogenous opioid and cannabinoid systems modulate the muscle pain: A pharmacological study into the peripheral site

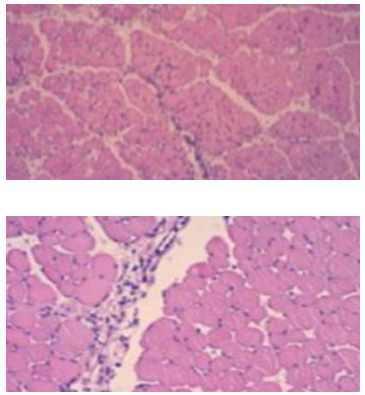
Gonçalves WA, Ferreira RCM, TRL Romero et al.



carrageenan injection



→ **inflammation**



→ **Pain leg withdraw**

opioid receptor antagonist naloxone
MOP antagonist clocinnamox
KOP antagonist *nor*-binaltorphimine
aminopeptidase inhibitor bestatin,
CB1 receptor antagonist AM251

hyperalgesia

MAFP inhibitor of anandamide hydrolysis
JZL184 inhibitor of [2-AG] hydrolysis
VDM11 inhibitor of the anandamide transporter

decreased hyperalgesia

DOP antagonist naltrindole
CB2 cannabinoid antagonist AM630

any effect

endogenous activation of peripheral MOP, KOP and CB1 receptors mediates the control of muscular hyperalgesia induced by inflammation

European Journal of Pharmacology 745 (2014) 69–75

Involvement of central and peripheral cannabinoid receptors on antinociceptive effect of tetrahydrocannabinol in muscle pain

Ana Bagüés, M. Isabel Martín, Eva M. Sánchez-Robles

Response data heterogeneity

CB_1 / CB_2 → The antinociceptive effect of cannabinoids is different depending on the **type of pain**

CB2 agonists → algesic effects in models of both **acute and chronic pain**

CB2 analgesia → is related to **peripheral mechanisms** without CNS effects

antinociceptive activity of THC →
- in **acute pain** is mediated only by the CB_1 receptor
- in **chronic pain** is mediated by both CB_1 and CB_2 receptor

different intensity of THC analgesia → is related to a different proportion of cannabinoid receptors within **different muscles** (eg masseter > gastrocnemius)

sex differences → female rodents being more sensitive to THC related to
- differences in metabolism,
- differences in receptor expression
- influence of ovarian hormones

Pharmacol Biochem Behav. 2021
SEX DIFFERENCES AND THE ENDOCANNABINOID SYSTEM IN PAIN Henry L. Blantonet al.

Planta Med 2018; 84: 225–233

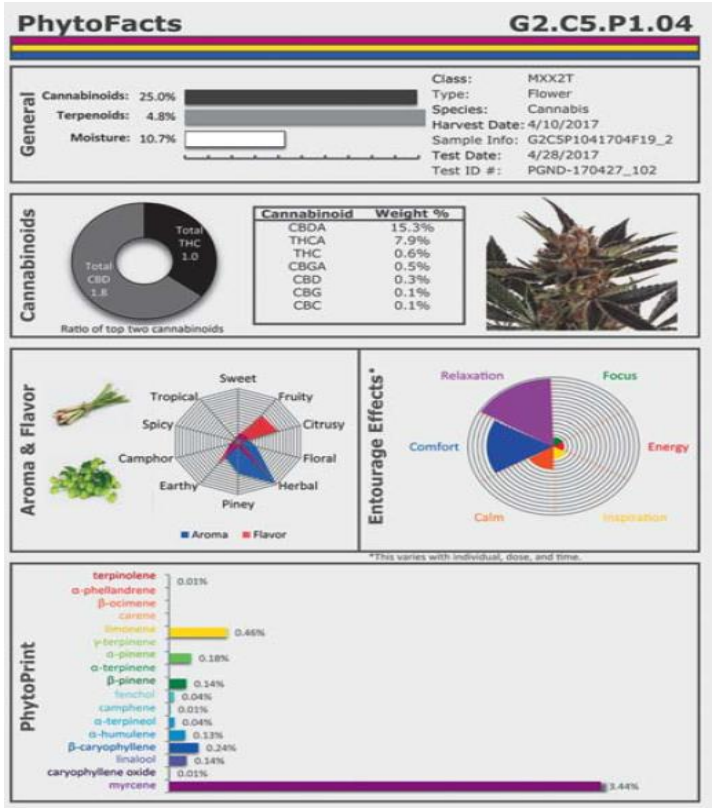
Pharmacological Foundations of Cannabis Chemovars

Mark A. Lewis[1], Ethan B. Russo[2], Kevin M. Smith[1]

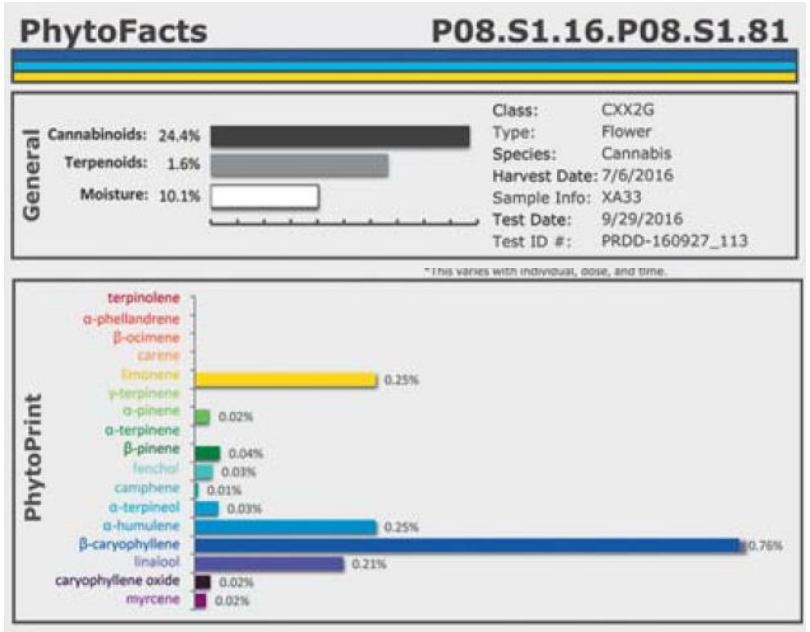
Type I : 9 THC predominant
Type II : 9-THC + CBD
Type III : CBD predominant

the term “chemovars” forchemical varieties, emphasizes the unique biochemical attributes of particular Cannabis plants

terpenoid-rich profiles can improve both efficacy and minimize adverse events of cannabis



PhytoFacts of a Type II, **high-myrcene** chemovar
(sedative effects : (termed “couch-lock”)



Another example is P08.S1.16.P08.S1.81, displaying a high CBD and **Caryophyllene** profile acting on pain and inflammation through agonism on CB2 insula receptors

PhytoFacts of a Type II, **α-Pinene** chemovar
(cognitive effects : inhibition of acetylcholinesterase)

prescrizione di cannabis terapeutica

Ricetta : codice del P.te, motivazioni prescrizione, tipo di cannabis, posologia, validità 30 giorni
consenso informato, scheda P.te (per il Medico o ISS)

preparazioni di cannabis

Decotto : cartine; preparazione ministeriale: scarsa efficacia ed indaginosità
Olio: variabilità di THC/CBD, capsule
Resina : siringhe preriempite
Spray : nabiximol
Inalazione : utilizzo con vaporizzatore

posologia

personalizzata (su paziente e patologia)
necessaria titolazione
dosaggio massimo : differenziato per composto
(es. THC 30 mg/die; CBD 15 mg/kg/die)

Pharmaceuticals **2021**, *14*, 171.

Cannabis-Based Oral Formulations for Medical Purposes: Preparation, Quality and Stability

Francesca Baratta, Riccardo Torta, Massimo Collino, Paola Brusa et al.

In 2018, our group developed an improved **Cannabis oil** extraction technique. In order to facilitate the consumption of the prescribed medical Cannabis therapy by patients, a standard procedure was defined for the preparation of a **single-dose preparation for oral use (hard capsules**) containing the oil extract. The capsule dosage form is easily transported and administered, has pleasant organoleptic properties and is stable at room temperature for extended periods of time, this would **facilitates the adherence to therapy by patients**

Take home messages

I dati attuali sull'efficacia e tollerabilità dei cannabinoidi
nella pratica clinica sono contrastanti
e suggeriscono un loro impiego in specifici cluster sintomatologici
come farmaci di seconda –terza linea

Tali incertezze derivano:
dalla complessità del sistema endocannabinoide
dalle molteplici azioni farmacologiche dei cannabinoidi
dalla eterogeneità dei vari composti
dalle loro interazioni farmacodinamiche e farmacocinetiche
dalle variabili patogenetiche delle patologie studiate
dalla disomogenità dei gruppi di pazienti
dalla modalità di valutazione degli outcome clinici
dalla interferenza di fattori ideologici nella valutazione del problema