DIECC
Diplomado Internacional de Endocannabinología, Cannabis y Cannabinoides

Drogas de abuso psicoestimulantes y potencial terapéutico de cannabidiol. ¿una opción terapéutica?

Psychostimulant drugs of abuse and therapeutic potential of cannabidiol. A therapeutic option?

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Departamento de Neurofarmacología Experimental

Instituto de Investigaciones Biológicas Clemente Estable

16 de octubre, 2024

Conflicto de interés

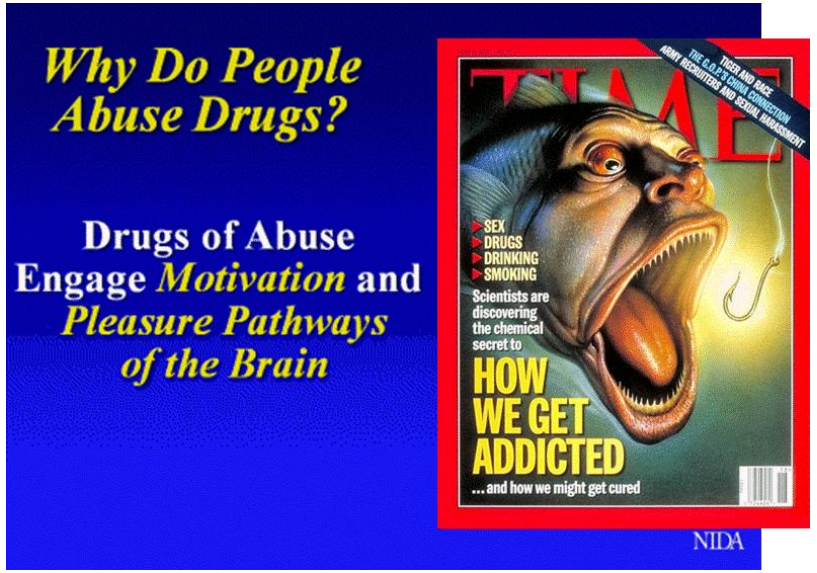
- **No tengo conflictos de interés para declarar**

Drugs of abuse and the endocannabinoid system

- **Drugs of abuse** are inherently rewarding, which is why they are consumed by humans or self-administered by animals (preclinical data).

- **More abused drugs**: alcohol; nicotine; amphetamines; cocaine; opium alkaloids; synthetic opioids; benzodiazepines; novel psychoactive substances (NPS), etc…

- Reward saliency, motivation, and memory/learned associations are relevant in maintaining addiction; these functions involved brain circuits (motivation circuit) which brain regions of it are **modulated by the endocannabinoid system (ECS)**



The manipulation of the ECS by administering cannabinoid compounds has raised much interest due to its close functional involvement in the regulation of emotion, cognition, and reward

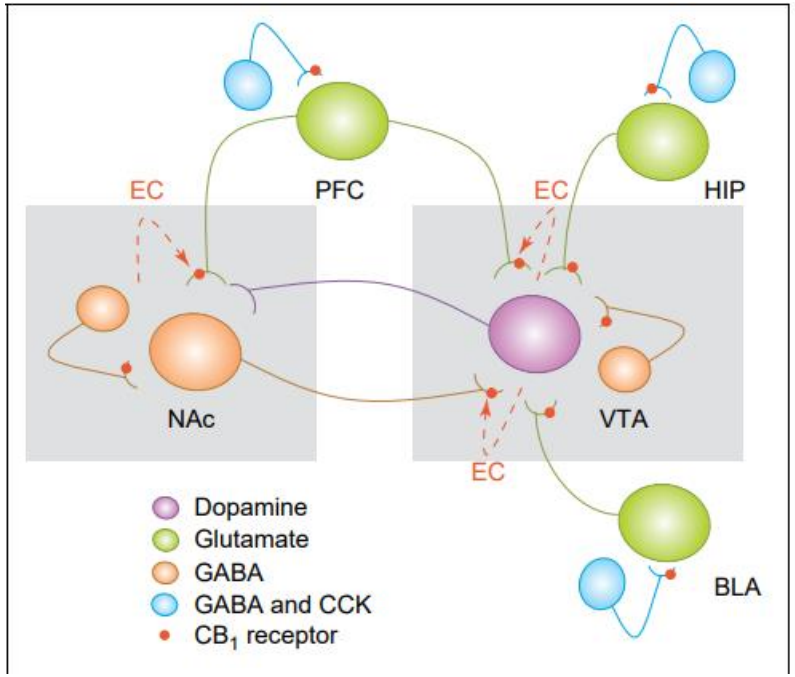
Drugs of abuse and the endocannabinoid system

Review TRENDS in Neurosciences Vol.29 No.4 April 2006
Full text provided by www.sciencedirect.com

Involvement of the endocannabinoid system in drug addiction

Rafael Maldonado, Olga Valverde and Fernando Berrendero

Laboratori de Neurofarmacologia, Facultat de Ciències de la Salut i de la Vida, Universitat Pompeu Fabra, Carrer Dr. Aiguader 80, 08003 Barcelona, Spain



Motivational circuit: PFC-VTA-NAc-HC-BLA

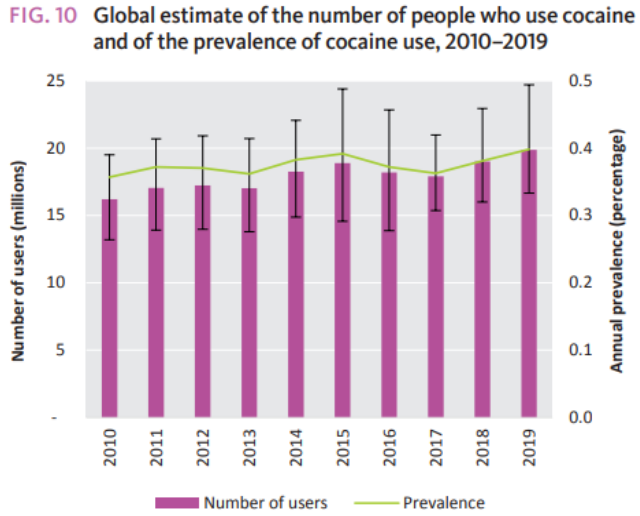
Drugs of abuse interact with these common brain circuits producing adaptive changes leading to a profound dysregulation of brain motivational and reward pathways and SEnC modulates it.

CB1 receptors are abundant in the brain reward circuitry and participate in the addictive properties induced by different drugs of abuse. The DAergic neurons of the mesocorticolimbic pathway are controlled by excitatory and inhibitory inputs that are modulated by CB1 receptors. Thus, endocannabinoids can be released following depolarization in the NAc and from DAergic neurons in the VTA, and they modulate GLUergic and GABAergic afferents by acting as retrograde messengers on CB1 receptors. The presence of CB1 receptors in other structures related to motivation and reward, such as the basolateral amygdala and the hippocampus, also contributes to this function of the endocannabinoid system.

Psychostimulants

- Cocaine is a powerfully addictive psychostimulant drug.
- Illicit drug of abuse; natural origin, from *Erythroxylon coca* bush.
- An estimated 0.4 % of the adult population worldwide has used cocaine in 2019.
- In South America, 1 % of adult population was estimated to be cocaine users in 2019.
- Cocaine use is associated with a range of severe health problems (addiction, cognitive impairments, cardiovascular disease, alterations during pregnancy, etc).
- There are no FDA-approved pharmacological treatments for psychostimulant use disorders.
- Further research is needed.

Erythroxylon coca



Degenhardt and Hall, *Lancet*, 2012

Source: UNODC, Report 2021

Cocaine forms

Our studies

- Different forms of cocaine: * hydrochloride salt (water-soluble), snorted or i.v. injection
  * cocaine base or freebase (water-insoluble), smoked

- CP is the earliest step in the purification process of cocaine hydrochloride. Cocaine, as a main alkaloid, is in its base form, **smokable**. Impurities and **adulterants**.

- Crack is prepared through heat evaporation of powdered cocaine with a base (sodium bicarbonate) to produce an alkaline cocaine product, which is typically inhaled (**smoked**).

CP and crack smoked forms of cocaine

Castagno Adicciones, 2000; Hatsukami and Fischman JAMA,1996; Lopez-Hill et al. Behav Brain Res. 2011.

Phenomenon of smoked cocaine

- Crack emerged as a sub-type in the 1980s, in the USA.
- CP is mainly consumed in South American countries (Argentina, Colombia, Chile, Perú, Paraguay, Uruguay). Crack (Brazil)
- Crack is the best-known smoked form of cocaine, but the social and economic crisis of 2002 (Argentina and Uruguay), led to the widespread use of CP.
- CP and crack use is prevalent mainly in socio-economically marginalized people.
- CP and crack's impact on health and specific brain effects are not systematically reviewed or studied.

Butler and Fisher *Drug and Alcohol Dependence, 2017.*
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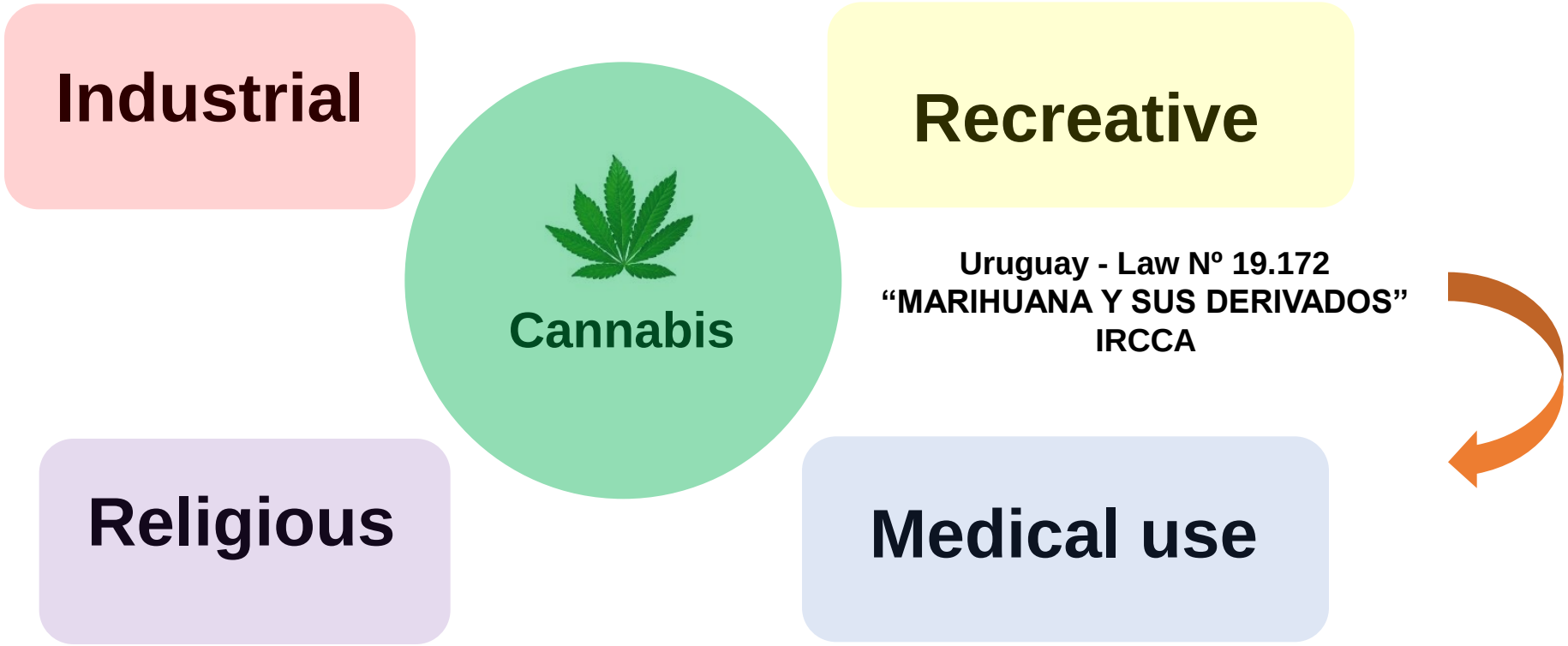
- CP and crack use is prevalent mainly in socio-economically marginalized people.
- CP and crack's impact on health and specific brain effects are not systematically reviewed or studied.
- **Clinical consensus**: smoked cocaine induces a prototypical clinical profile noticeably different from cocaine (hydrochloride): **high and fast dependence** (more addictive than cocaine hydrochloride).
- The **route of administration** could explain that profile, but we proposed chemical composition as another relevant factor.
- **No effective treatments** are available for CP dependence.

Butler and Fisher *Drug and Alcohol Dependence, 2017.*
Hatsukami and Fischman *JAMA,*1996.

Different uses of Cannabis

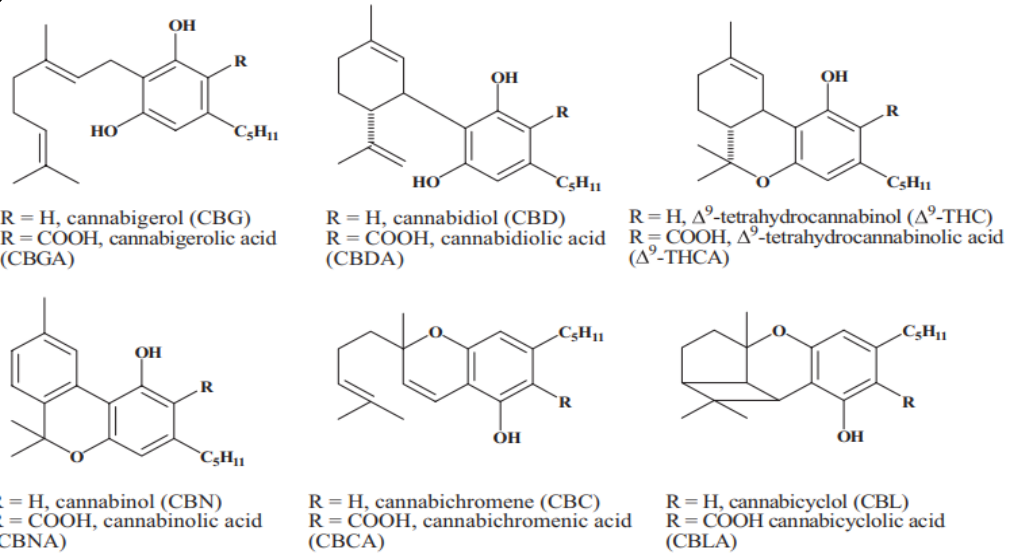


Clinical and preclínical research interest

IRCCA: Instituto de Regulación y Control de Cannabis

The main cannabinoids in Cannabis sativa

CBG: precursor



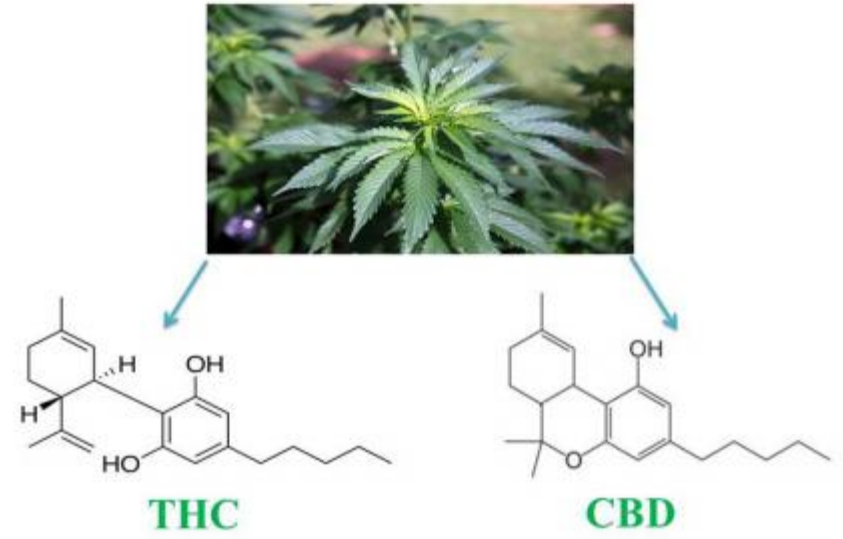


Fig. 3. Structure of cannabidiol (CBD) and delta–9–tetrahydrocannabinol (Δ^9–THC).

• THC is produced as an acid (Δ^9-Tetrahydrocannabinolic acid, Δ^9-THCA) in the glandular trichomes of the leaves and undergoes decarboxylation with age or heating to form Δ^9-THC. Cannabinoids are not the only active components of cannabis. Other constituents that might contribute in some way to the effects of cannabis include (terpens, flavonoids, alcaloids)

• Medicinal use of cannabis/cannabinoids: **CANNABIDIOL (CBD),** a non-psychotomimetic compound of cannabis. No rewarding properties.

Fraguas-Sánchez and Torres-Suárez, Drugs 2018
Majdi et al. Medical Hypotheses, 2019

Some therapeutic applications of cannabinoids or therapeutic potential

High quality evidence

- Pain (neuropathic pain): Δ^9-THC
- Multiple sclerosis (spasticity): Δ^9-THC
- Epilepsy: CBD
- Cancer (palliative treatments): Δ^9-THC
- Weight loss (AIDS): Δ^9-THC

CANNABINOIDS

Moderate-low quality evidence

- Parkinson´s disease
- Alzheimer´s disease
- Huntington's disease
- Addictions
- Glaucoma
- Post-traumatic stress syndrome
- Tourette syndrome: Δ^9-THC
- Anxiety: CBD
- Cancer: Δ^9-THC, CBD
- Antidepressant-like effects
- Antipsychotic-like effects

Fraguas-Sánchez and Torres-Suárez, Drugs 2018

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Therapeutic actions of CBD: anxiolytic, antipsychotic, antidepressant, anti-inflammatory, and anti-convulsivant effects; some of them are domains affected by cocaine abuse.

Fraguas-Sánchez and Torres-Suárez, Drugs 2018

Pharmacological and transgenic studies indicate that CB1, CB2, TRPV1 and 5-HT1A receptors are critically involved in CBD acts on *in vivo*

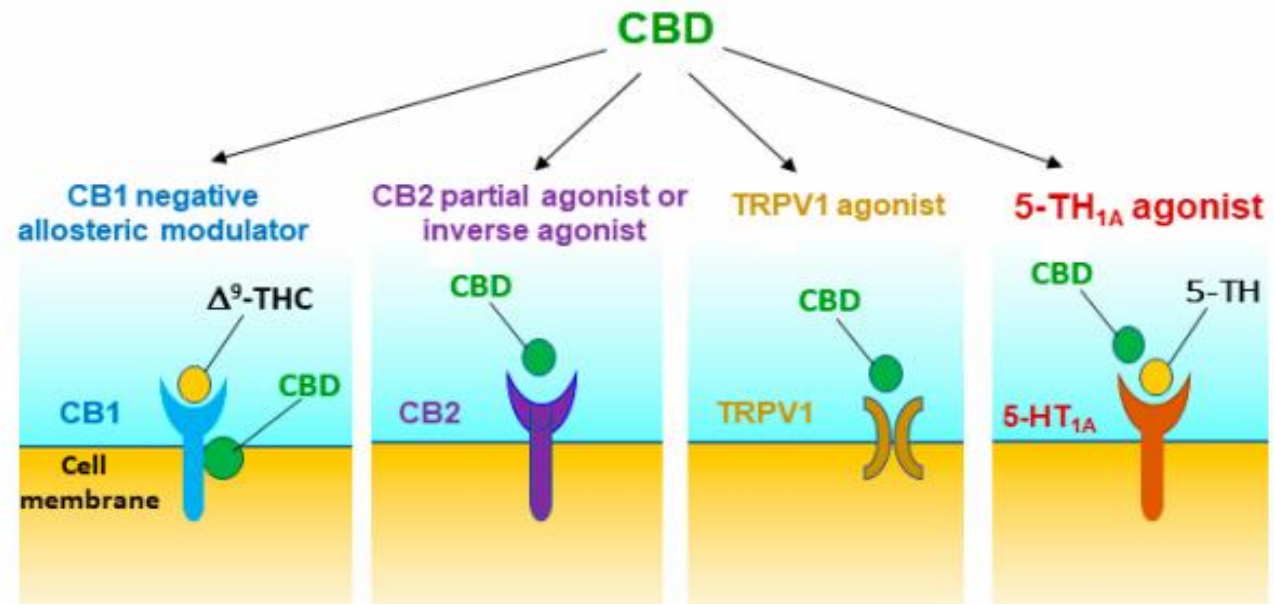

Figure 1. Potential receptor mechanisms associated to CBD in vivo actions. The results from *in vitro* receptor binding and functional intracellular signalling assays and *in vivo* behavioral studies with pharmacological and transgenic approaches suggest that CBD may act as a CB1 receptor negative allosteric modulator, a CB2 receptor partial agonist or antagonist/inverse agonist, and a TRPV1 and 5-HT1A receptor agonist. Multiple receptor mechanisms together produce several therapeutic effects.

- the anandamide (AEA) hydrolyzing enzyme (fatty acid amide hydrolase, FAAH) or the adenosine transporter (ENT-1).
- Positive allosteric modulator at 5HT1A receptors

Galaj and Xi, Int J of Molecular Sciences, 2020

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- Tourette syndrome: Δ^9-THC
- Anxiety: CBD
- Cancer: Δ^9-THC, CBD

* CBD as co-adjuvant treatment in ethanol and opioid abuse.

First reports were related with morphine and heroin, suggesting that CBD attenuates the rewarding effects of opioids and can serve as a preventive therapeutic.

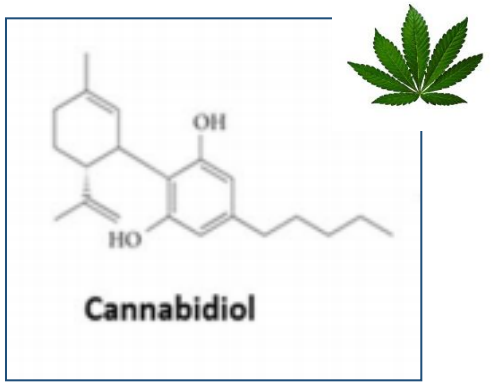
Galaj and Xi, Int J of Molecular Sciences, 2020

Evidence focused on treatment

- Medicinal use of cannabis/cannabinoids: **CANNABIDIOL (CBD),** non-psychotomimetic compound of cannabis. **No rewarding properties**.

- Clinical and preclinical studies indicate that CBD can be useful for cocaine-use disorder. **High degree of safety.**

- **Therapeutic actions**: anxiolytic, antipsychotic, antidepressant, anti-inflammatory, anti-convulsivant effect; some of them are domains affected by cocaine abuse.



Fraguas-Sánchez and Torres-Suárez, Drugs 2018
Majdi et al. Medical Hypotheses, 2019

molecules
MDPI
Molecules 2019, 24, 2583

Review

Cannabidiol Treatment Might Promote Resilience to Cocaine and Methamphetamine Use Disorders: A Review of Possible Mechanisms

Claudia Calpe-López [1], M. Pilar García-Pardo [2] and Maria A. Aguilar [1,*]

[1] Unit of Research "Neurobehavioural mechanisms and endophenotypes of addictive behavior", Department of Psychobiology, University of Valencia, Avda. Blasco Ibañez 21, 46010 Valencia, Spain
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Role of Cannabidiol in the Therapeutic Intervention for Substance Use Disorders

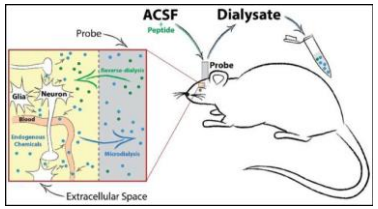
https://www.frontiersin.org/articles/10.3389/fphar.2021.626010/full

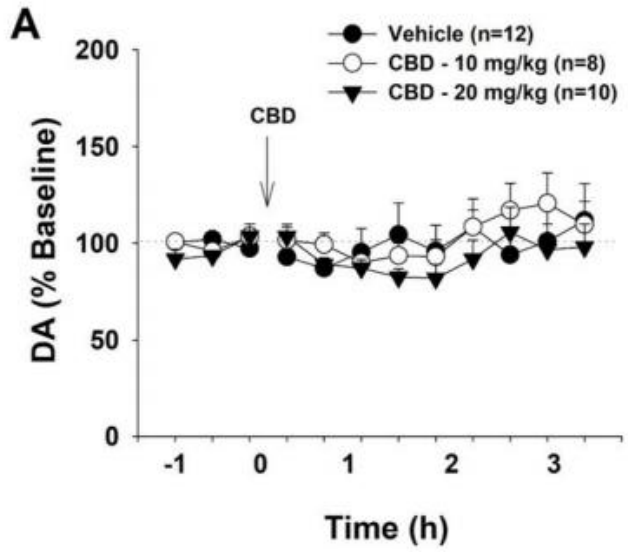
*Francisco Navarrete [1,2], María Salud García-Gutiérrez [1,2], Ani Gasparyan [1,2], Amaya Austrich-Olivares [1] and Jorge Manzanares [1,2]**

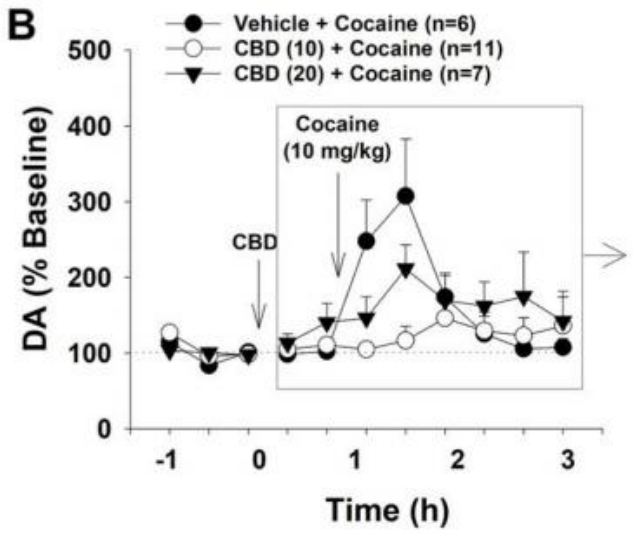
[1]Instituto de Neurociencias, Universidad Miguel Hernández-CSIC, San Juan de Alicante, Spain, [2]Red Temática de Investigación Cooperativa en Salud (RETICS), Red de Trastornos Adictivos, Instituto de Salud Carlos III, MICINN and FEDER, Madrid, Spain

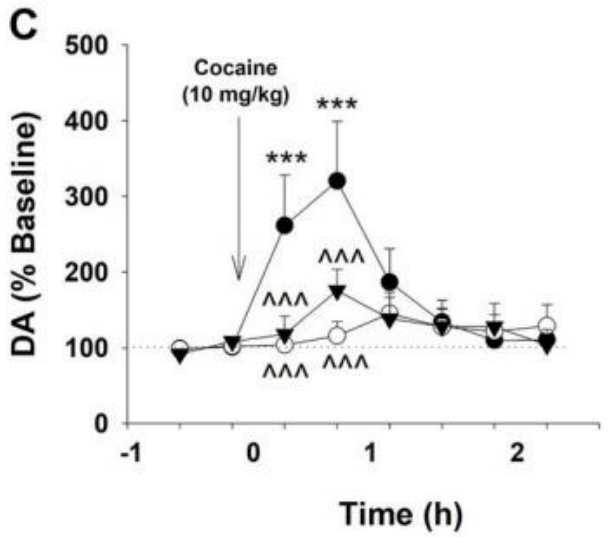
Preclinical data of CBD and psychostimulants

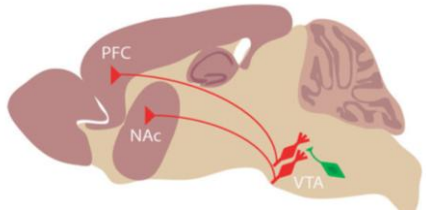
CBD attenuates cocaine-induced dopamine in the NAc



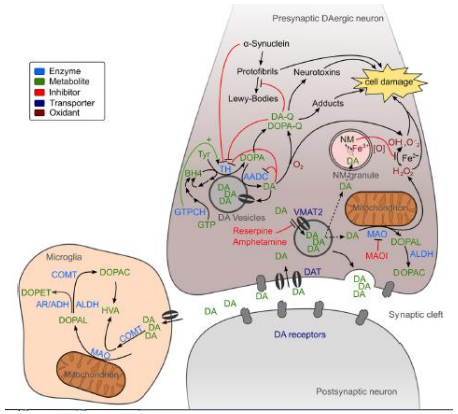








Mesolimbic and mesocortial systems and rewarding effect of drug of abuse

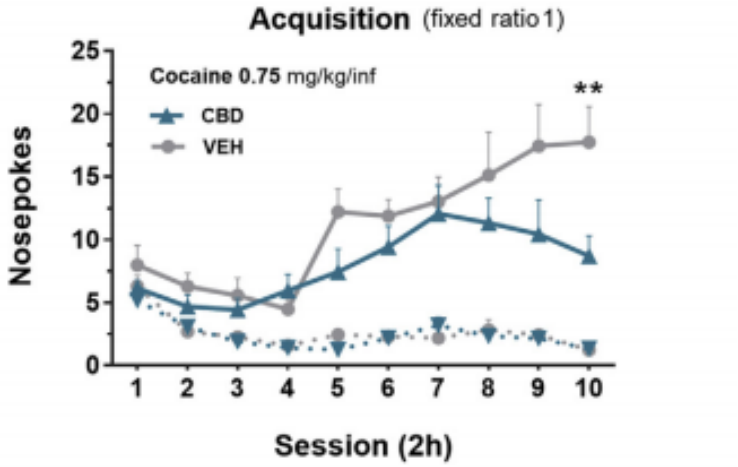


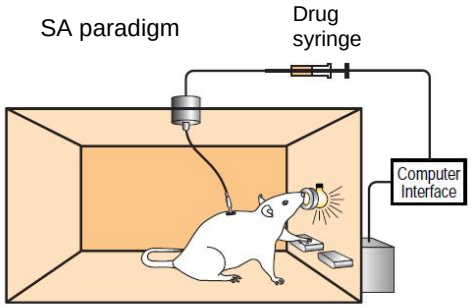
Luscher and Ungless, PLoS Med, 2006

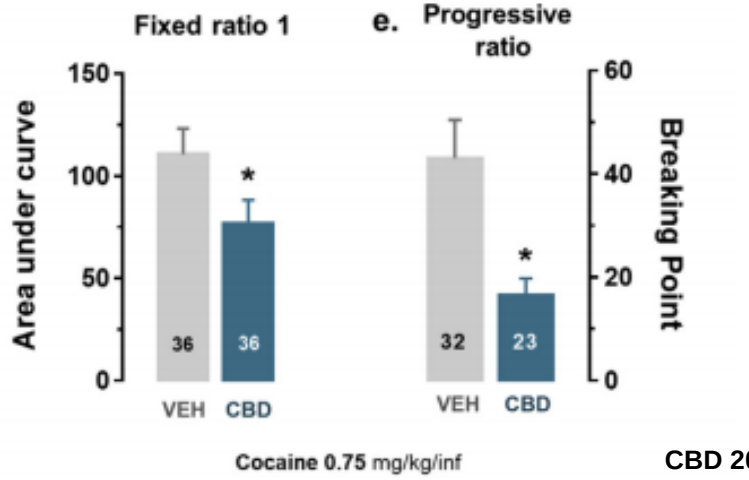
Galaj et al. Neuropharmacology. 2020

Preclinical data of CBD and psychostimulants

CBD reduces the cocaine reinforcing in self-administration paradigm but not ….





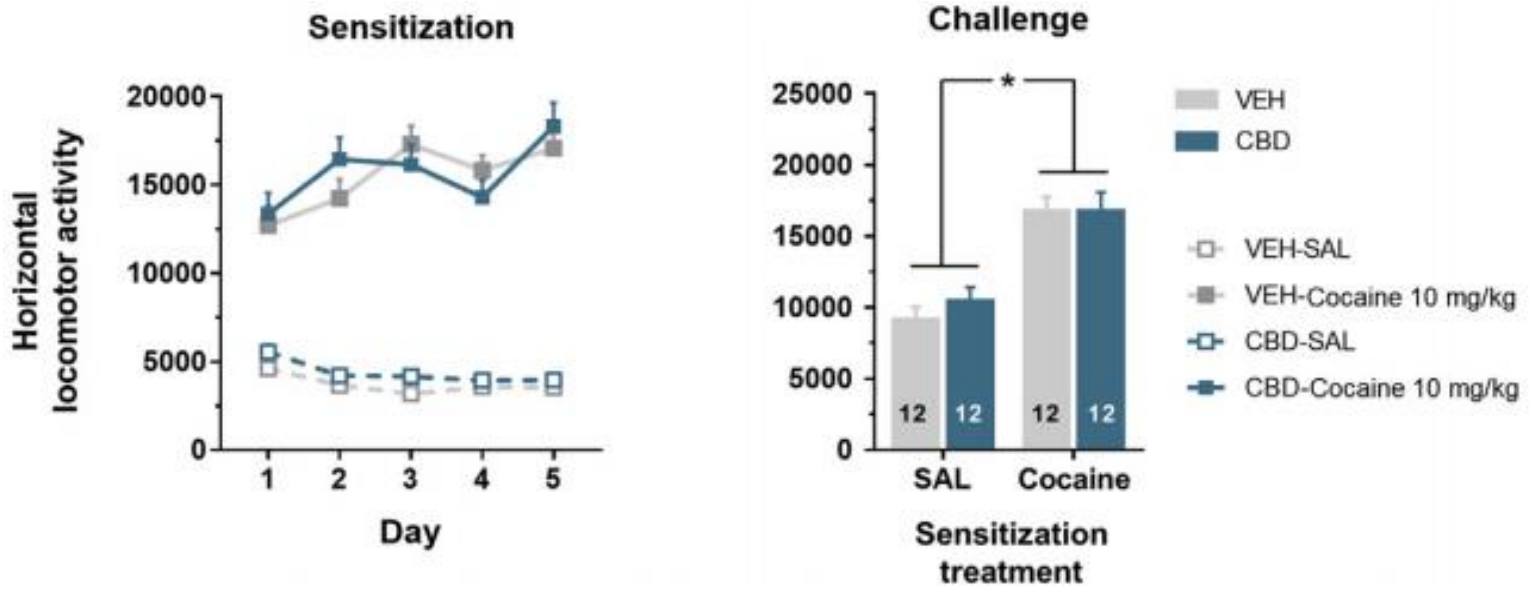


CBD 20 mg/kg/10 days

Luján et al Neuropharmacology 2018

Preclinical data of CBD and psychostimulants

CBD reduces the cocaine reinforcing in self-administration paradigm but not the behavioral sensitization induced by cocaine



CBD 20 mg/kg/10 days

Luján et al Neuropharmacology 2018

Some reviews of CBD and SUD...

frontiers in Psychiatry
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The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder

Yann Chye [1], Erynn Christensen [1], Nadia Solowij [2,3] and Murat Yücel [1]*

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molecules

Molecules 2019, 24, 2583

Review

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

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Cannabidiol and substance use disorder: Dream or reality

Saeideh Karimi-Haghighi [a,b], Yasaman Razavi [b], Daniela Iezzi [c,d], Andrew F. Scheyer [c,d], Olivier Manzoni [c,d], Abbas Haghparast [b,*]

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[c] INMED, INSERM U1249, Marseille, France
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REVIEW
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Role of Cannabidiol in the Therapeutic Intervention for Substance Use Disorders

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Despite the range of the psychosocial and pharmacological therapeutic approaches for substance use treatment, relapse prevalence into drug consumption is estimated between 40 and 75% (Sinha, 2011; Pasareanu et al., 2016; Andersson et al., 2019). This high rate of recurrence is largely due to the ineffectiveness of the available drugs or the lack of specific treatments (e.g., cannabis, cocaine, or amphetamine-type use disorders). Thus, there is a growing need to significantly improve our knowledge about the underlying mechanisms involved in the development of drug dependence to finally design new pharmacological tools with higher efficacy and safety. In this sense, the manipulation of the endocannabinoid system (ECS) by administering cannabinoid compounds has raised much interest due to its close functional involvement in the regulation of emotion, cognition, and reward…

Smokable form of cocaine: crack or cocaine paste

- Official permits were obtained from the Technical Forensic Institute (Montevideo-Uruguay) and the Uruguayan Drugs Board (Junta Nacional de Drogas)

- **These are seized samples that could be potentially smoked by drug users.**

- Route of administration and **chemical composition (active adulterants)**

The recreational drug illicit market

Dilution	Contamination	Adulteration
Inert subtances (diluents)	by-products of the drug manufacturing process (contaminants)	pharmacologically active substances (adulterants)
•To increase the bulk of the drug or to reduce the content of main drug in the final product	• No quality control or sanitary control (NPS)	• To mimic or boost the effects of the main drug
sugars (glucose, mannose, saccharose), starches, talc and quinine		

UNODC, 2015;
Cole et al. Drug Test Anal. 2011
Solimini et al. Curr Pharm Biotechnol. 2017

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UNODC, 2015;
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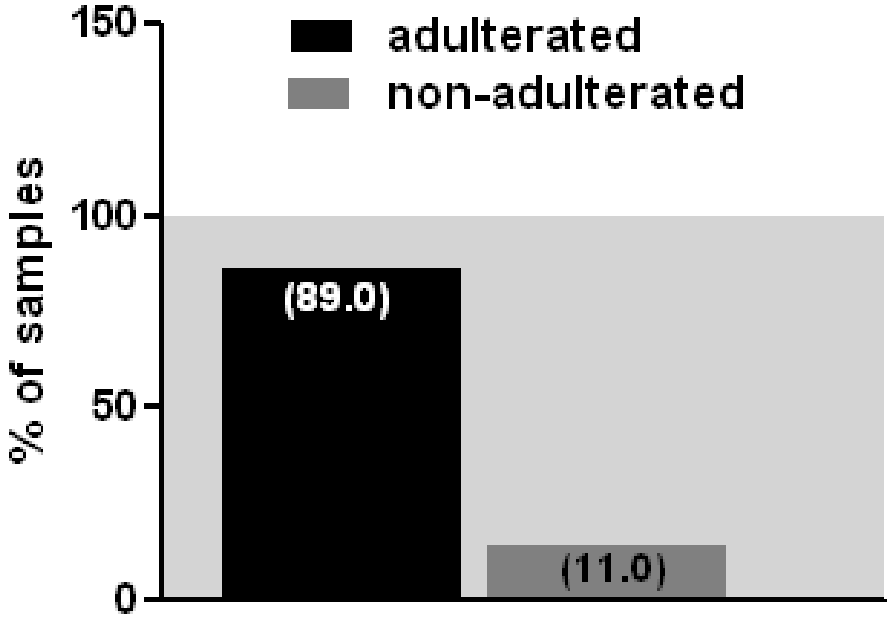
Chemical composition

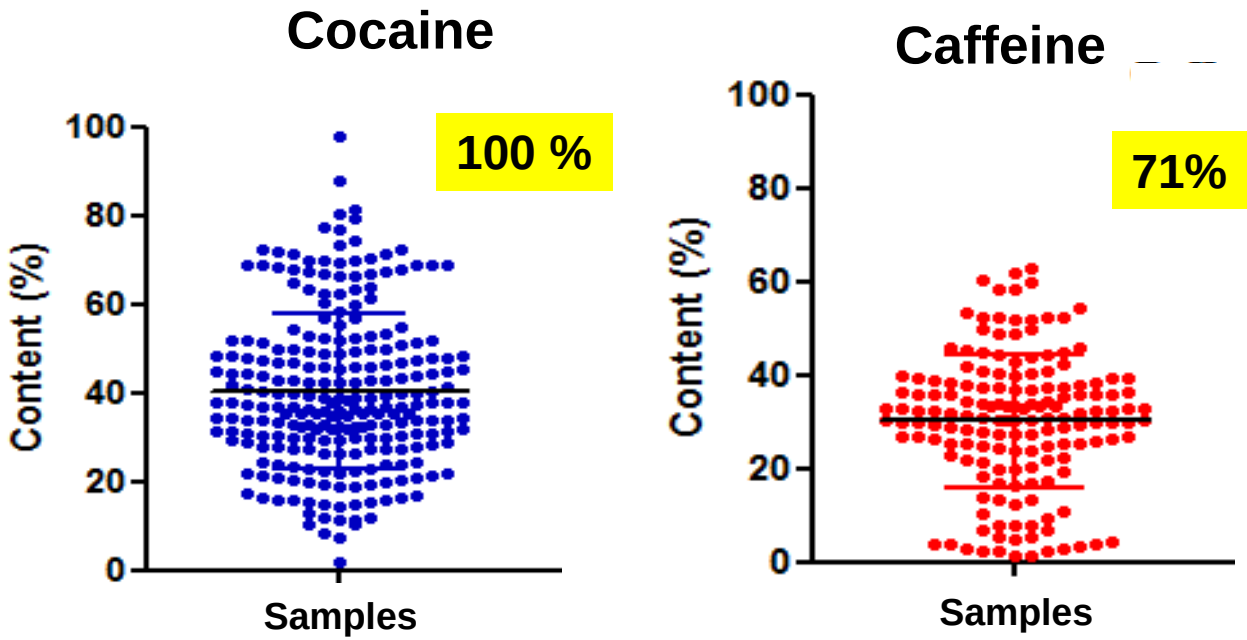
Frequency of cocaine ana caffeine in N = 306 seized-samples

Plataforma de Servicios Analíticos, IIBCE



HPLC-DAD analyses revealed that 89 % of CP samples were adulterated while 11% were not.

Caffeine and other adulterants were present.

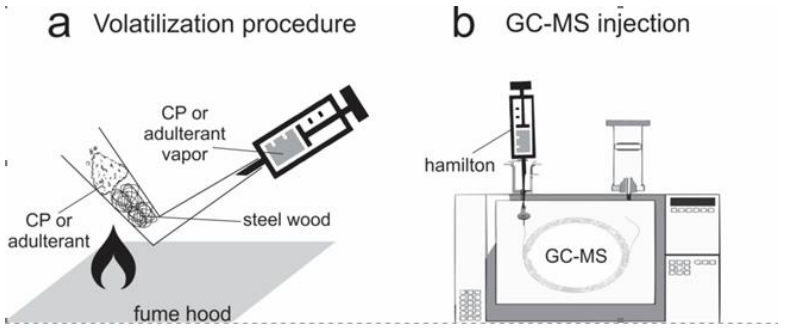


Abin Carriquiry et al. Neurotox. Res. 2018

Chemical composition

Caffeine:

- Active adulterant.
- Facilitates the volatilization of smoked drugs.
- Can be volatilized.



GC-MS analyses After CP volatilization, adulterants are preserved in the fume

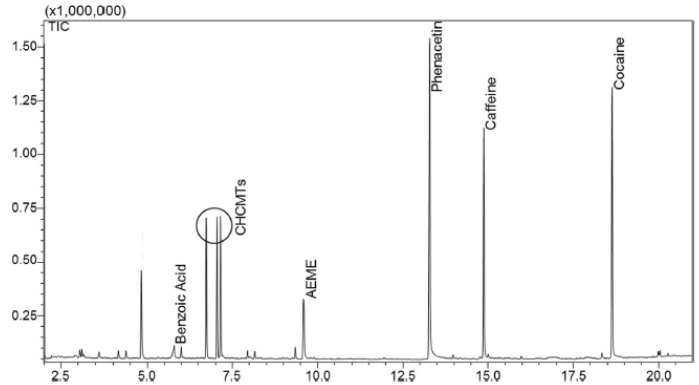


Fig. 4 Representative GC-MS chromatograms (TIC) of a CP volatilized seized sample adulterated with caffeine and phenacetin. To simplify, no mass spectrums were shown in this figure. Carbomethoxycycloheptatrienes (CMCHTs); anhydroecgonine methyl ester (AEME)

Non-pyrolysis compounds from caffeine volatilization were detected.

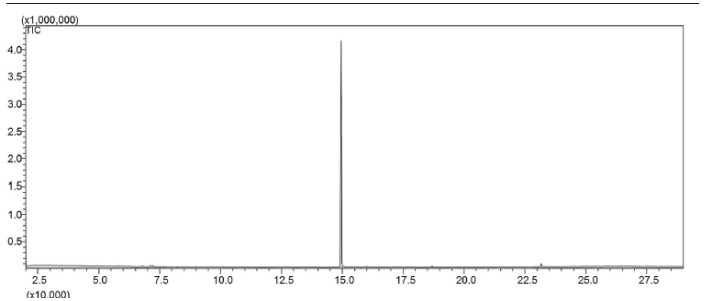


Fig. 6 Representative GC-MS chromatogram of caffeine isolated and volatilized. TIC chromatogram (upper), mass spectrum of the caffeine vapor sample (middle), and the reference mass spectrum of caffeine (lower)

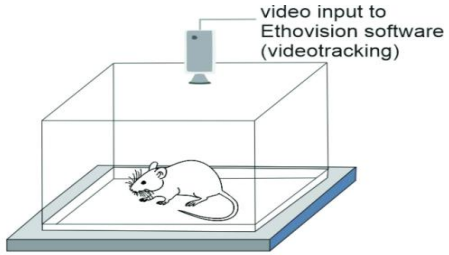
Galvalisi et al. Neurotox. Res. 2017; Abin Carriquiry et al. Neurotox. Res. 2018

Caffeine as an active adulterant in CP-seized samples

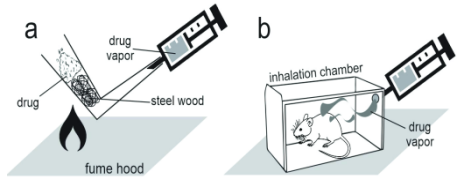
- Caffeine enhances the **acute stimulant effect** of cocaine in CP-seized samples after i.p. injection / pulmonary inhalation route of administration.

CP and subrogate CP

López-Hill et al. Behav Brain Res. 2011;
Prieto et al. Rev Psiquiat Uru. 2012;
Galvalisi et al. IBRO Congress, 2015;
Scorza et al. Neuromethods, 2023.



Open Field (OF)

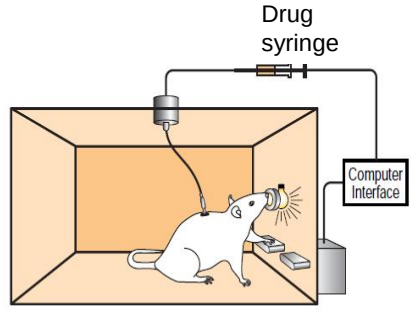


Passive pulmonary inhalation

- Caffeine enhances the **reinforcing** effect of cocaine and its **motivational** value. (significant increase in the breaking point) after i.v. injection.

Subrogate CP

Prieto et al. Psychopharmacology, 2016.

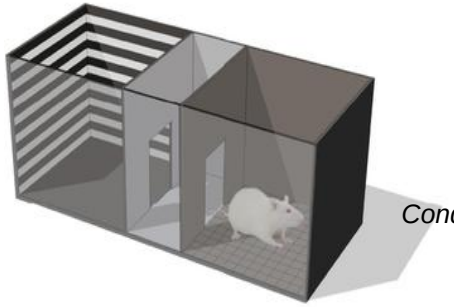


Self-administration paradigm (SA)

- Caffeine potenties **reward-associated memories** elicited by i.p. cocaine; associated with **changes in IEGs** expression in NAcc and mPFC.

Subrogate CP

Muñiz et al. Frontiers in Behav Neurosci. 2017.

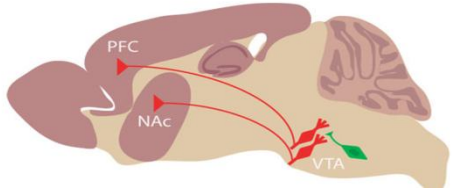


Conditioned Place Preference (CPP)

- Caffeine collaborates in the **acute rewarding effect** of CP samples determined by the DA release in NAc Shell.

CP and subrogate CP

Scorza et al. Neuromethods, 2023.



Mesolimbic system; microdialysis

A specific study…

Contents lists available at ScienceDirect

International Journal of Drug Policy

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

Addressing the stimulant treatment gap: A call to investigate the therapeutic benefits potential of cannabinoids for crack-cocaine use

Benedikt Fischer [a,b,c,1,*], Sharan Kuganesan [a], Andrea Gallassi [d], Renato Malcher-Lopes [e], Wim van den Brink [f,g], Evan Wood [h,i]

2015 - from Canada, The Netherlands, Brazil

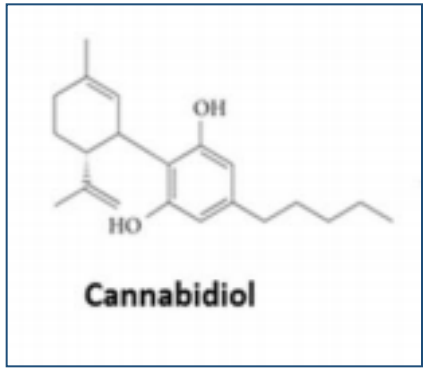
Abstract: Crack-cocaine use is prevalent in numerous countries, yet concentrated primarily – largely within urban contexts – in the Northern and Southern regions of the Americas. It is associated with a variety of behavioral, physical and mental health and social problems which gravely affect users and their environments. Few evidence-based treatments for crack-cocaine use exist and are available to users in the reality of street drug use… An important therapeutic potential for crack-cocaine use may rest in **cannabinoids**, which have recently seen a general resurgence for varied possible therapeutic usages for different neurological diseases. Distinct potential therapeutic benefits for crack-cocaine use and common related adverse symptoms may come specifically from cannabidiol (CBD)-one of the numerous cannabinoid components found in cannabis – with its demonstrated anxiolytic, antipsychotic, anti-convulsant effects and potential benefits for sleep and appetite problems. The possible therapeutic prospects of cannabinoids are corroborated by observational studies from different contexts documenting crack-cocaine users' 'self-medication' efforts towards coping with crack-cocaine-related problems, including withdrawal and craving, impulsivity and paranoia. Cannabinoid therapeutics offer further benefits of being available in multiple formulations…

Behavioral sensitization induced by psychostimulants

- Repeated non-contingent exposure to psychostimulant drugs produces **locomotor sensitization**, a progressive and enduring augmentation of locomotor responses to the drug after a withdrawal period and the re-exposure to the drug.
- This phenomenon implies **neuroplastic changes** in the brain (meso-cortico-limbic circuit).
- LS can be useful to better understand the **initial phases of drug intake that influence**, but does not provide a complete picture of SUD.
- LS phenomenon has been proposed to be useful to **drug-induced neuroadaptations related to drug craving** in rodents.

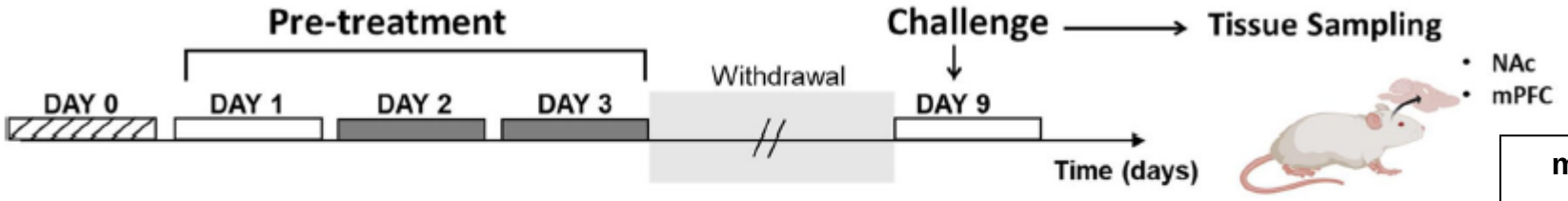
Robinson and Berridge, Brain Res Brain Res Rev.1993;
Pierce and Kalivas Brain Res Rev. 1997;
Kuhn, Kalivas, et al. Front Behav Neurosci. 2019.

• Can **Cannabidiol** attenuate some effects induced by the combined cocaine plus caffeine?



Locomotor sensitization + CBD

Behavioral assay



metabolic activity by CO-I

Pre-treatment			Challenge	Experimental group nomenclature
Vehicle (3% Tween 80)	30 min →	Saline	Coc (5 mg/kg) + Caf (2.5 mg/kg)	Veh-Sal
CBD (20 mg/kg)	30 min →	Saline	Coc (5 mg/kg) + Caf (2.5 mg/kg)	CBD-Sal
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CBD (20 mg/kg)	30 min →	Coc (5 mg/kg) + Caf (2.5 mg/kg)	Coc (5 mg/kg) + Caf (2.5 mg/kg)	CBD-Coc+Caf

Cocaine (5) + Caffeine (2.5) = subrogate CP

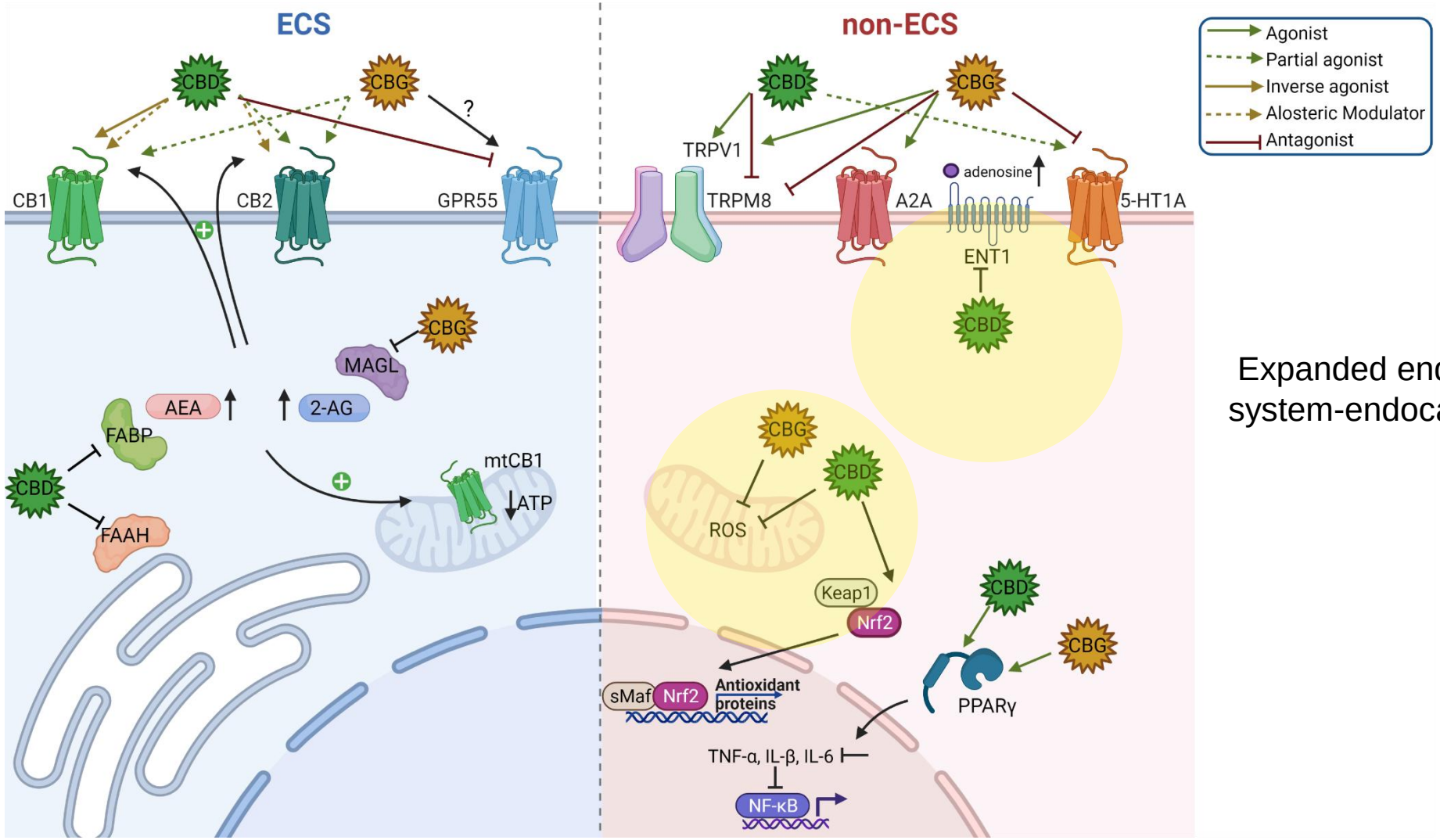
CBD 20 mg/kg

CBD purificado

PHYTOPLANT RESEARCH

Prieto et al. Neurotox. Research, 2020

Sites of action of CBD in the brain



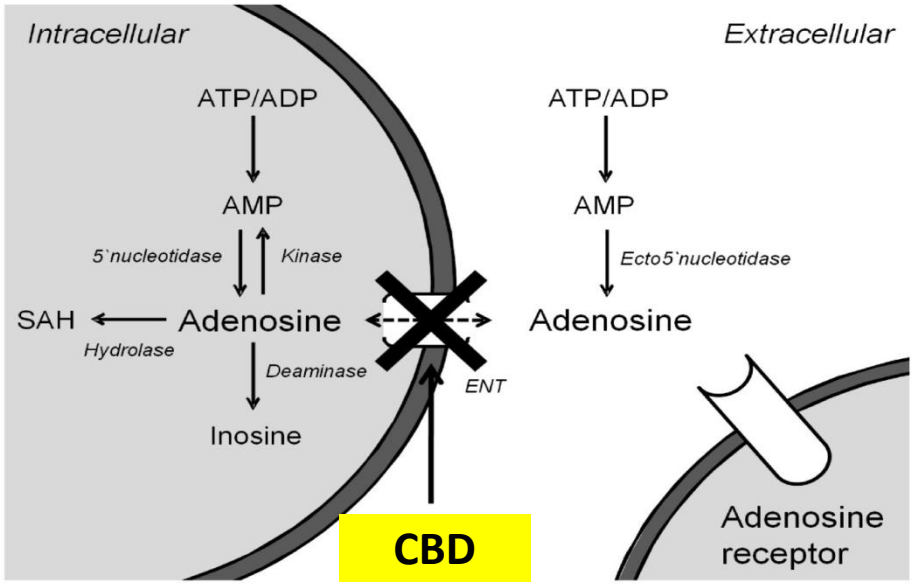
Expanded endocannabinoid system-endocannabinoidome.

Veilleux, Di Marzo, et al. Curr Diab Rep. 2019

TRPV: transient receptor potential channels vanilloid; FAAH: fatty acid amide hydrolase, FAAH, MAGL: monoacylglycerol lipase); AEA: anandamide; PPARs: peroxisome proliferator-activated receptors.

Echeverry et al., Medicinal Usage of Cannabis and Cannabinoids, Burlington: Academic Press, pp. 197-205, 2023

CBD increases adenosine levels by the blockage of ENT-1

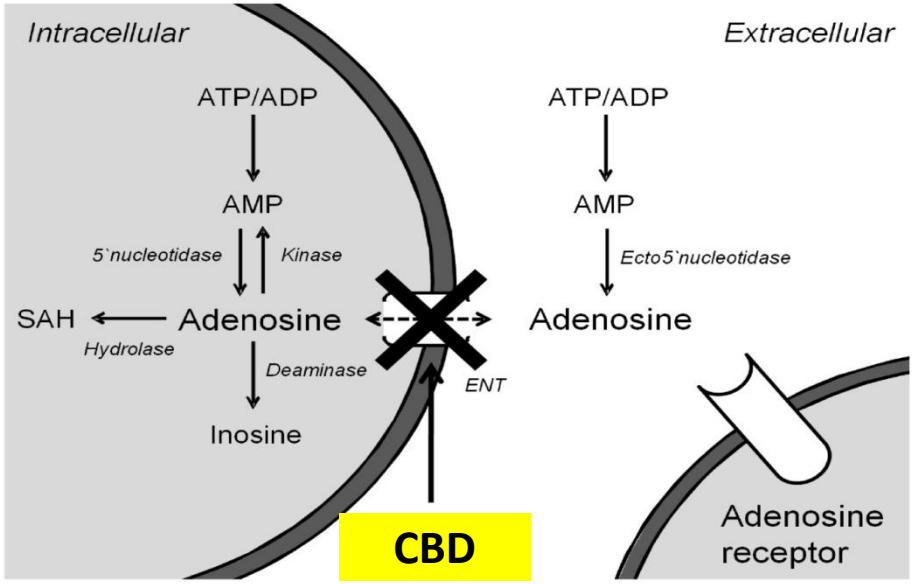


Carrier et al. PNAS, 2006

- Caffeine is a psychostimulant that promotes wakefulness by non-selectively antagonizing the adenosine A1 receptors (A1R) and A2 receptors (A2AR) in the nucleus accumbens (NAcc).
- A1 and A2A-Rs are expressed in brain motor and reward circuits.
- Caffeine potentiates the effect of cocaine.

- **Our hypothesis:** a competitive action between the increased levels of adenosine (evoked by CBD) and caffeine for the adenosine receptors binding site may result in an attenuation of caffeine action by CBD.

CBD increases adenosine levels by the blockage of ENT-1



Carrier et al. PNAS, 2006

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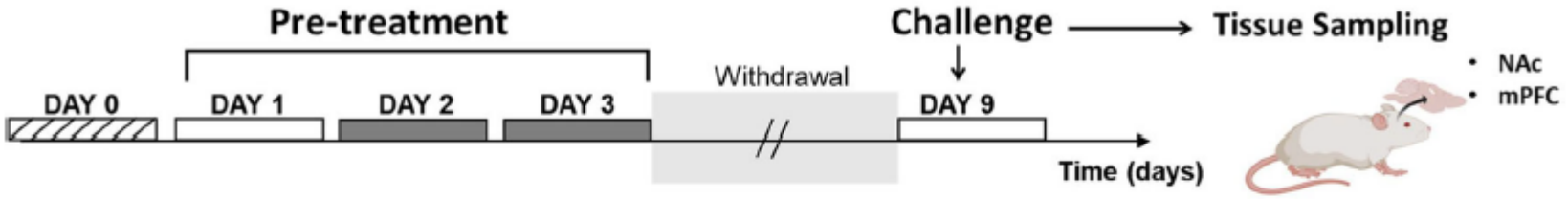
Can CBD attenuate the locomotor sensitization induced by cocaine + caffeine?

Locomotor sensitization protocol II + CBD



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CBD (20 mg/kg)	30 min →	Coc (5 mg/kg) + Caf (2.5 mg/kg)	Coc (5 mg/kg) + Caf (2.5 mg/kg)	CBD-Coc+Caf

Cocaine (5) + Caffeine (2.5) = subrogate CP

CBD 20 mg/kg

CBD purificado

PHYTOPLANT RESEARCH

Prieto et al. Neurotox. Research 2020

CBD attenuates the expression of the coc+caff locomotor sensitization but not the development

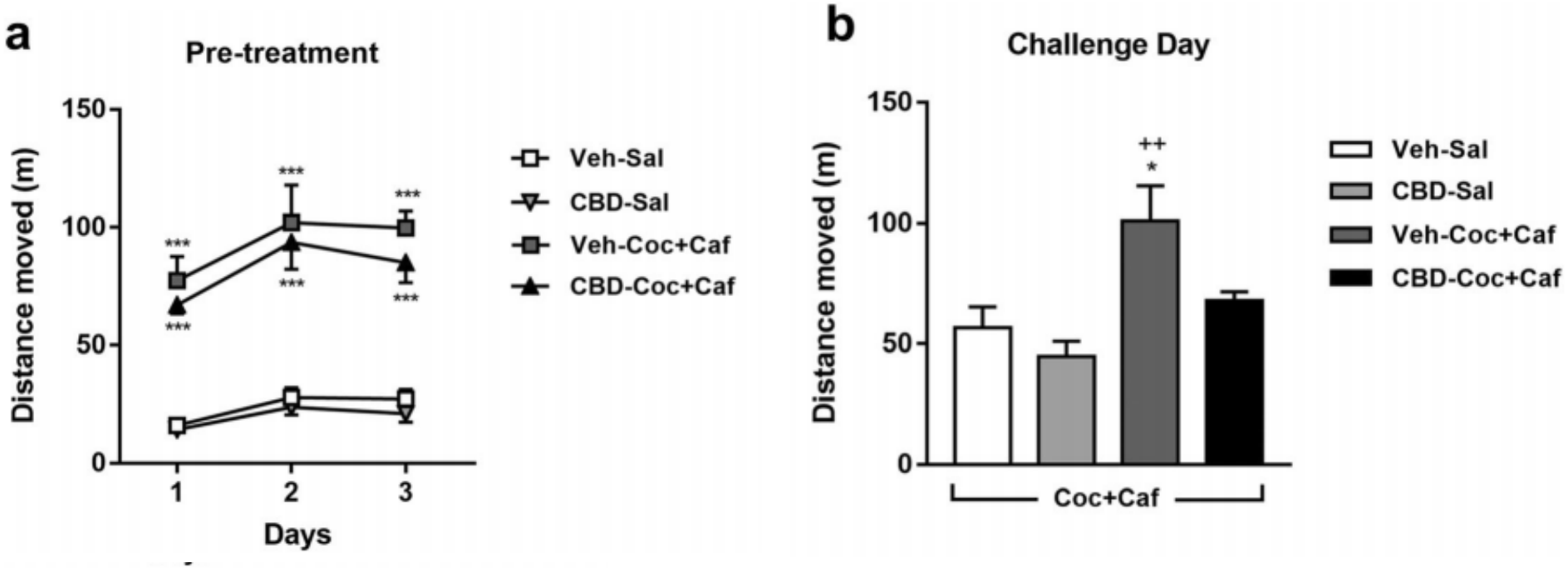
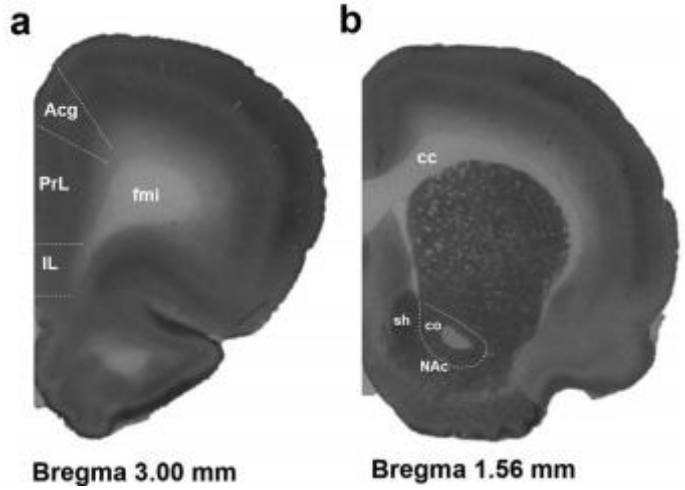
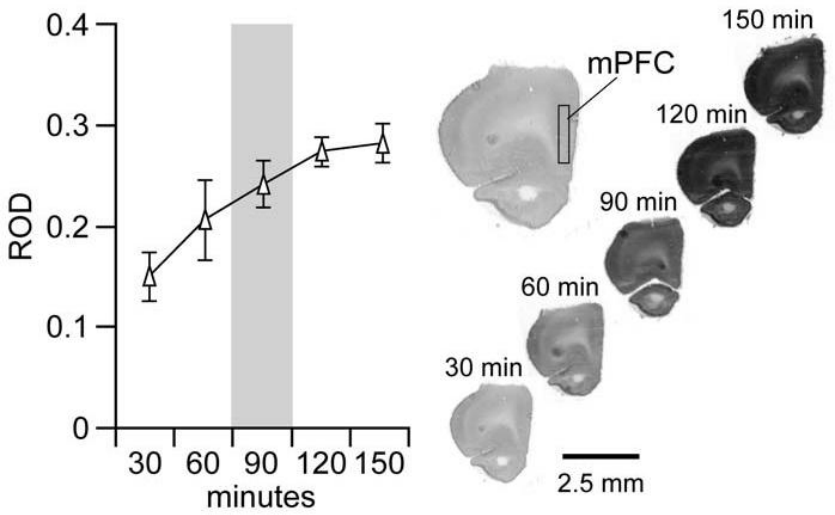


Fig. 3 Effect of CBD pretreatment on the pretreatment period (**a**), and the challenge day induced by Coc+Caf (**b**). Data are expressed as mean ± SEM. Two-way repeated measures ANOVA and one-way ANOVA followed by Tukey's post hoc test. $*p < 0.05$ and $***p < 0.001$ different from Veh-Sal; $++p < 0.01$ different from CBD-Sal. $N = 6–7$

Prieto et al. Neurotox. Research 2020

Cytochrome oxidase I (CO-I) histochemistry





- Cytochrome oxidase c is a mitochondrial enzyme associated with the energetic cellular metabolism.

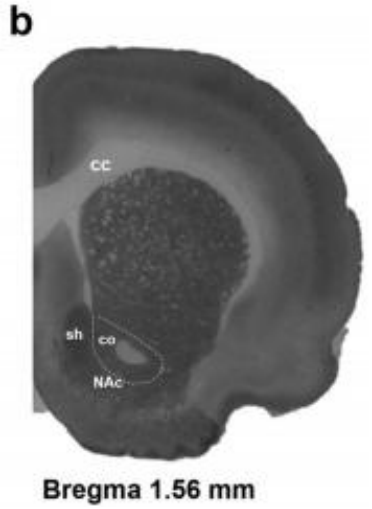
- CO-I activity is a **marker for the metabolic activity** of brain regions, and levels of cytochrome oxidase reaction are intimately associated with the neuron metabolic machinery, closely related to the levels of **neuronal activity.**

- Chronically, more active neuron would have greater energy demand and would be expected to have a more active cytochrome system**. Higher levels of functional activity demand oxidative metabolism.** A reduction in neuronal activity has presumably resulted in reduced energy demand.

- CO-I suggests the **functional state** of these brain regions involved in the behavioral sensitization

Wong-Riley, Brain Res 1979,
Tseng et al, Biol Psychiatry 2006

CBD attenuates the metabolic change induced by coc+caff in the NAc



CO-I staining in NAc

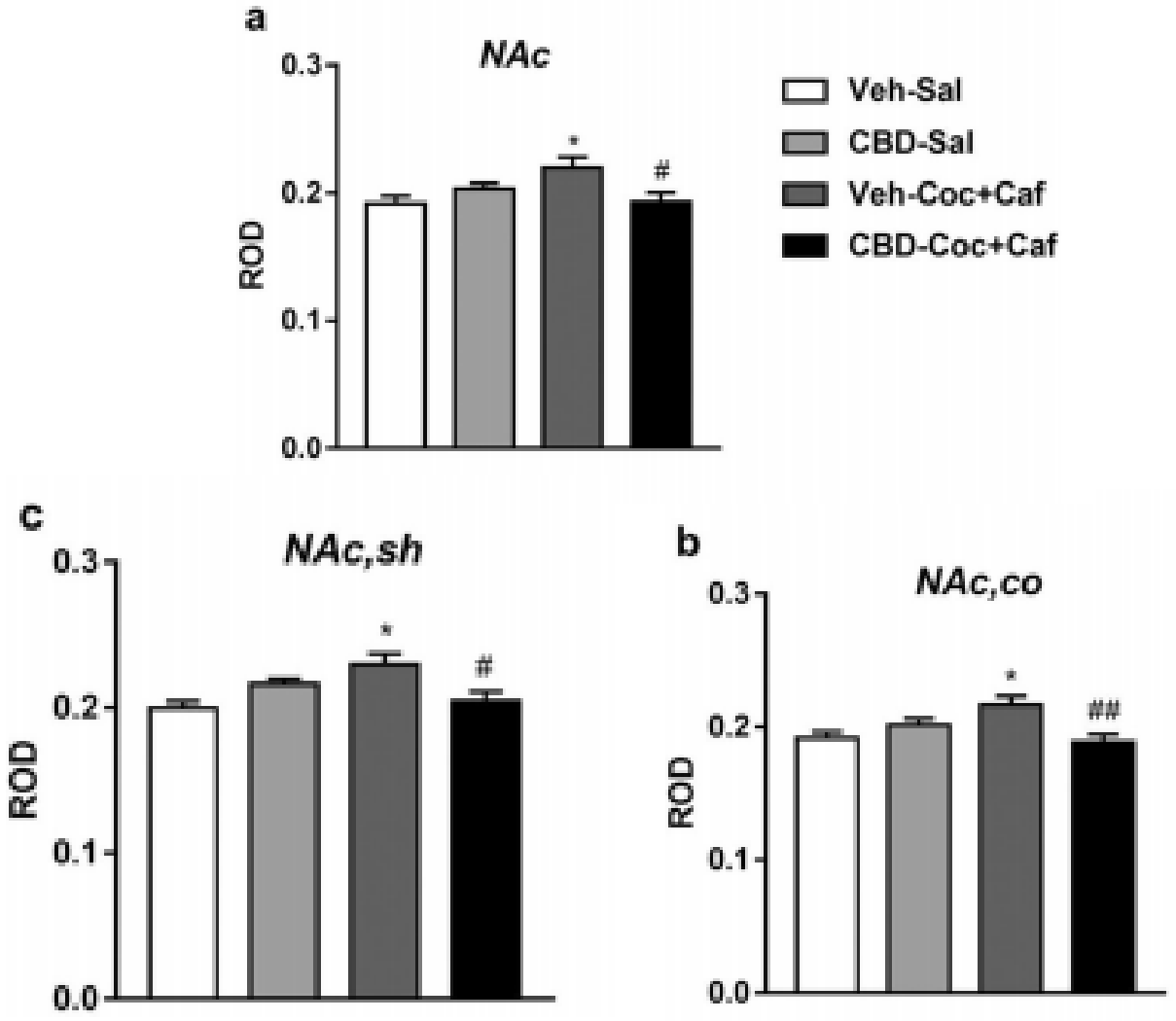
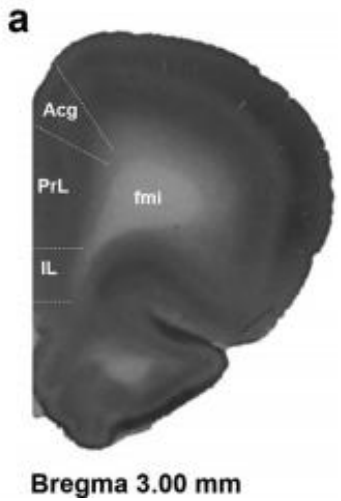


Fig. 5 CO-I activity after the Coc+Caf expression of locomotor sensitization and CBD pretreatment, in the total NAc (**a**), NAc core (NAc,co; **b**), and NAc shell (NAc,sh; **c**). Data of relative optical density (ROD) are expressed as mean ± SEM. One-way ANOVA followed by Tukey's post hoc test. $*p < 0.05$ different form Veh-Sal; $\#p < 0.05$ and $\#\#p < 0.01$ different from Veh-Coc+Caf. $N = 6–7$

Prieto et al. Neurotox. Research 2020

CBD attenuates the metabolic change induced by coc+caff in the PFC



CO-I staining in PFC

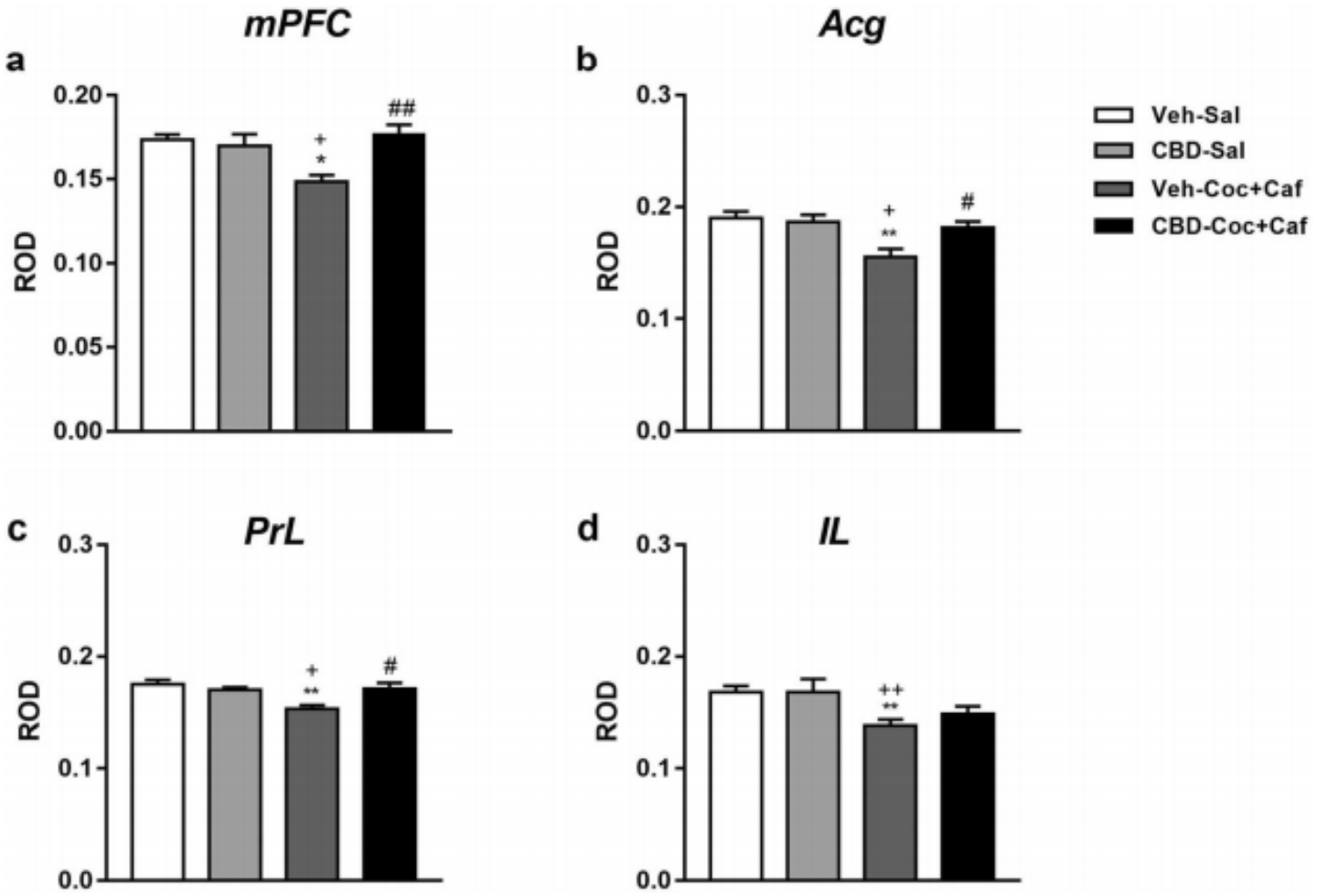
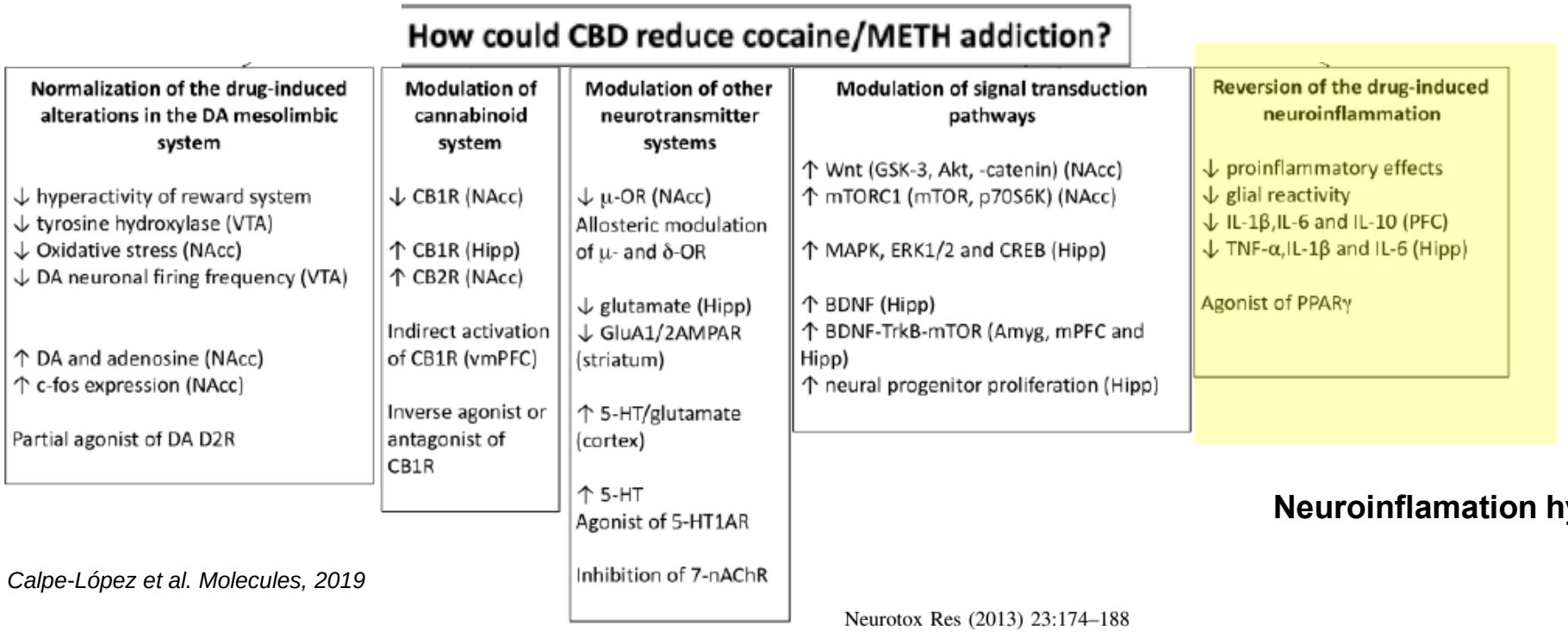


Fig. 4 CO-I activity after the Coc+Caf expression of locomotor sensitization and CBD pretreatment, in total mPFC (**a**), anterior cingular cortex (Acg; **b**), prelimbic cortex (PrL; **c**), and infralimbic cortex (IL; **d**). Data of relative optical density (ROD) are expressed as mean ± SEM. One-way ANOVA followed by Tukey's post hoc test. $*p < 0.05$ and $**p < 0.01$ different form Veh-Sal; $+p < 0.05$ and $++p < 0.01$ different from CBD-Sal; $\#p < 0.05$ and $\#\#p < 0.01$ different from Veh-Coc+Caf. $N = 6–7$

Prieto et al. Neurotox. Research 2020

Putative sites of action of CBD as “anti-addictive”



Calpe-López et al. Molecules, 2019

Neuroinflamation hypothesis…

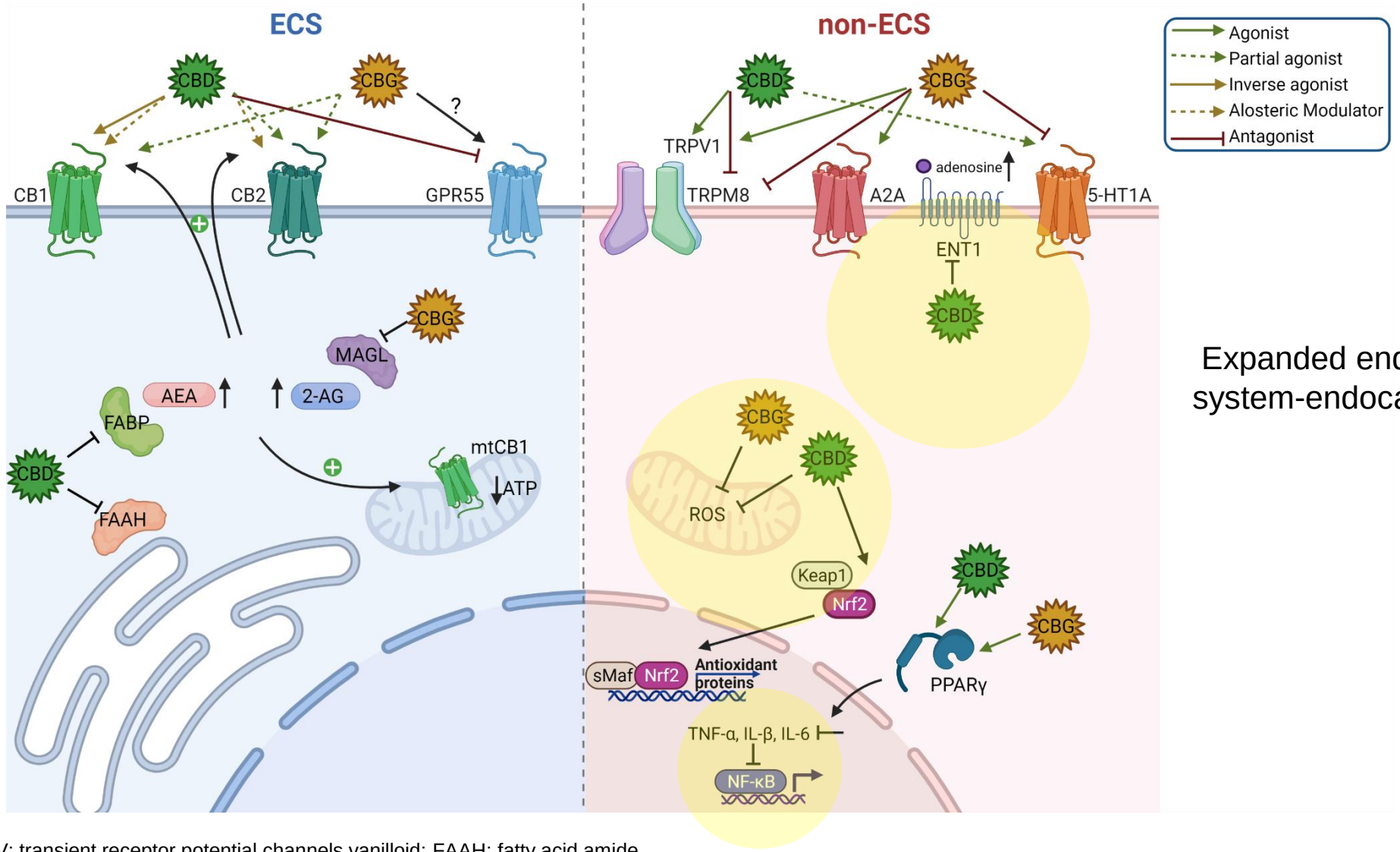
Neurotox Res (2013) 23:174–188
DOI 10.1007/s12640-012-9334-7

REVIEW ARTICLE

Psychostimulant Abuse and Neuroinflammation: Emerging Evidence of Their Interconnection

Kenneth H. Clark · Clayton A. Wiley · Charles W. Bradberry

Sites of action of CBD in the brain



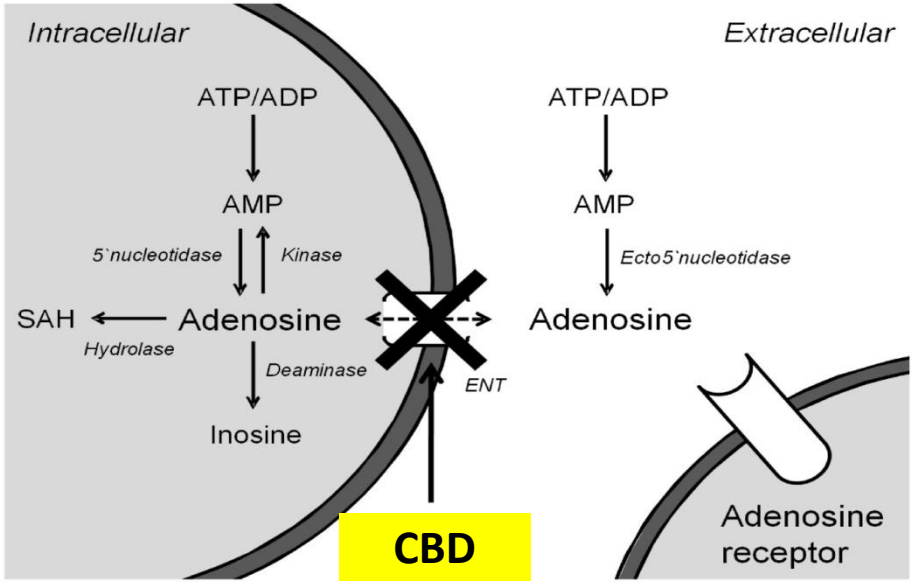
Expanded endocannabinoid system-endocannabinoidome.

Veilleux, Di Marzo, et al. Curr Diab Rep. 2019

TRPV: transient receptor potential channels vanilloid; FAAH: fatty acid amide hydrolase, FAAH, MAGL: monoacylglycerol lipase); AEA: anandamide; PPARs: peroxisome proliferator-activated receptors.

Echeverry et al., Medicinal Usage of Cannabis and Cannabinoids. Burlington: Academic Press, pp. 197-205, 2023.

CBD increases adenosine levels by the blockage of ENT-1



Carrier et al. PNAS, 2006

The equilibrative nucleotide transporter 1 (ENT-1; adenosine uptake protein) is the primary mechanism of adenosine reuptake. Adenosine is a purine nucleoside neurotransmitter. Release of adenosine is an endogenous mechanism to attenuate cellular stress and inflammation.

ENT1 was proposed to mediate the anti-inflammatory effect of CBD.

Carrier et al. PNAS, 2006

- **Can cocaine and caffeine induce neuroinflammatory processes?**

- Can CBD diminish the development of increased locomotor sensitivity caused by the combination of cocaine and caffeine through its anti-inflammatory properties?

2024; doi: 10.1038/s41380-024-02443-6.

Molecular Psychiatry

www.nature.com/mp

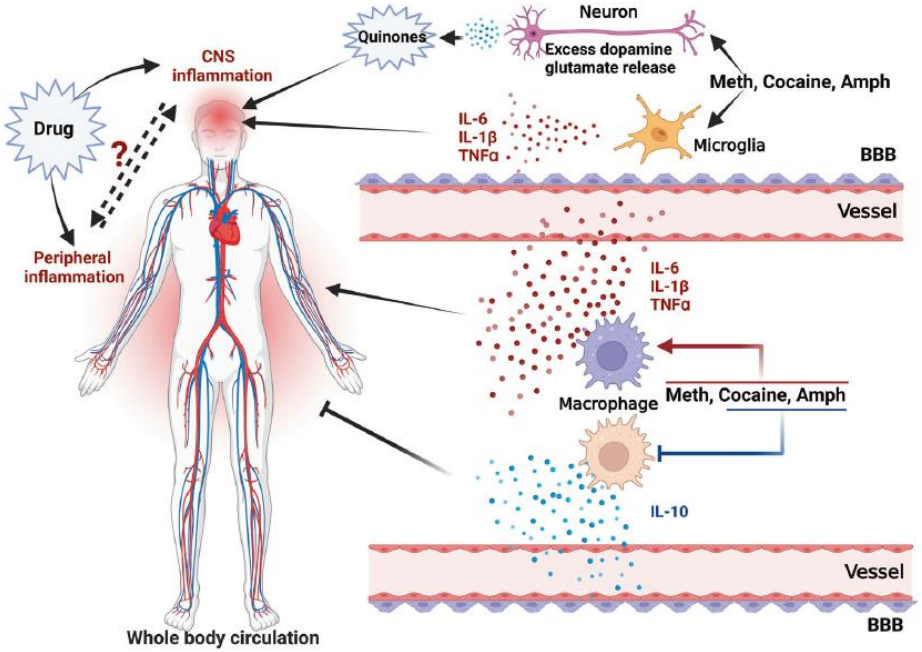
PERSPECTIVE

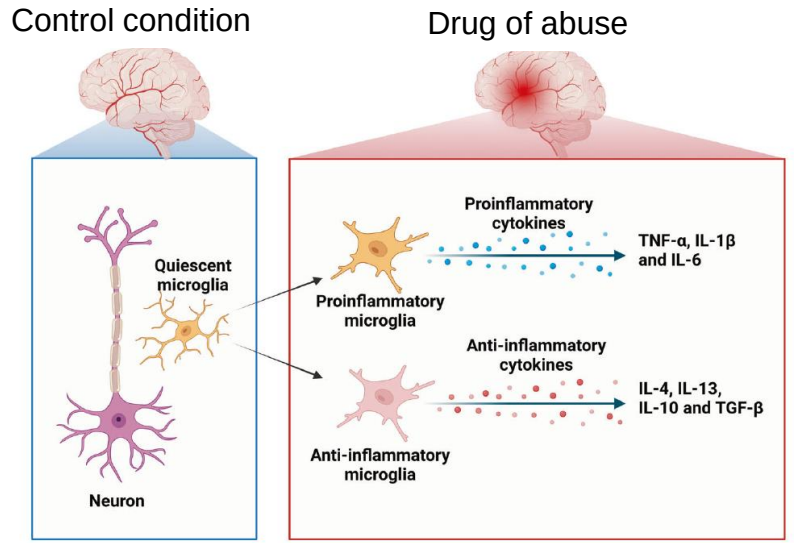
Microglia in neuroimmunopharmacology and drug addiction

Hongyuan Li[1], Linda R. Watkins[2] and Xiaohui Wang[1,3,4]✉

Drug addiction is a chronic and debilitating disease that is considered a global health problem. Various cell types in the brain are involved in the progression of drug addiction. Recently, the xenobiotic hypothesis has been proposed, which frames substances of abuse as exogenous molecules that are responded to by the immune system as foreign "invaders", thus triggering protective inflammatory responses. An emerging body of literature reveals that microglia, the primary resident immune cells in the brain, play an important role in the progression of addiction. Repeated cycles of drug administration cause a progressive, persistent induction of neuroinflammation by releasing microglial proinflammatory cytokines and their metabolic products. This contributes to drug addiction via modulation of neuronal function. In this review, we focus on the role of microglia in the etiology of drug addiction. Then, we discuss the dynamic states of microglia and the correlative and causal evidence linking microglia to drug addiction. Finally, possible mechanisms of how microglia sense drug-related stimuli and modulate the addiction state and how microglia-targeted anti-inflammation therapies affect addiction are reviewed. Understanding the role of microglia in drug addiction may help develop new treatment strategies to fight this devastating societal challenge.

Molecular Psychiatry; https://doi.org/10.1038/s41380-024-02443-6





- These cytokines may contribute to changes in synaptic plasticity, which can impact the availability and reuptake of neurotransmitters.
- Microglia undergo drastic morphological changes characterized by swollen soma and shortened processes and releases pro-inflammatory cytokines.

DIECC
Diplomado Internacional de Endocannabinología, Cannabis y Cannabinoides

uropsychopharmacology REVIEWS (2017) 42, 156–177
lege of Neuropsychopharmacology
www.neuropsychopharmacologyreviews.org

REVIEW

Glial and Neuroimmune Mechanisms as Critical Modulators of Drug Use and Abuse

Michael J Lacagnina[1], Phillip D Rivera[1] and Staci D Bilbo*[,1]
[1]Department of Psychology & Neuroscience, Duke University, Durham, NC, USA

Drugs of abuse cause persistent alterations in synaptic plasticity that may underlie addiction behaviors. Evidence suggests glial cells have an essential and underappreciated role in the development and maintenance of drug abuse by influencing neuronal and synaptic functions in multifaceted ways. Microglia and astrocytes perform critical functions in synapse formation and refinement in the developing brain, and there is growing evidence that disruptions in glial function may be implicated in numerous neurological disorders throughout the lifespan. Linking evidence of function in health and under pathological conditions, this review will outline the glial and neuroimmune mechanisms that may contribute to drug-abuse liability, exploring evidence from opioids, alcohol, and psychostimulants. Drugs of abuse can activate microglia and astrocytes through signaling at innate immune receptors, which in turn influence neuronal function not only through secretion of soluble factors (eg, cytokines and chemokines) but also potentially through direct remodeling of the synapses. In sum, this review will argue that neural–glial interactions represent an important avenue for advancing our understanding of substance abuse disorders.
Neuropsychopharmacology Reviews (2017) **42,** 156–177; doi:10.1038/npp.2016.121; published online 31 August 2016

Published in final edited form as:
Pharmacol Biochem Behav. 2019 April ; 179: 34–42. doi:10.1016/j.pbb.2019.01.007.

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INSTITUTO DE INVESTIGACIONES BIOLÓGICAS CLEMENTE ESTABLE

Neuroinflammation in addiction: A review of neuroimaging studies and potential immunotherapies

Milky Kohno[a,b,e], **Jeanne Link**[f], **Laura E. Dennis**[a,e], **Holly McCready**[a,e], **Marilyn Huckans**[b,d,e], **William F. Hoffman**[a,b,c,d,e], and **Jennifer M. Loftis**[a,b,e,*]

Abstract

Addiction is a worldwide public health problem and this article reviews scientific advances in identifying the role of neuroinflammation in the genesis, maintenance, and treatment of substance use disorders. With an emphasis on neuroimaging techniques, this review examines human studies of addiction using positron emission tomography to identify binding of translocator protein (TSPO), which is upregulated in reactive glial cells and activated microglia during pathological states. High TSPO levels have been shown in methamphetamine use but exhibits variable patterns in cocaine use. Alcohol and nicotine use, however, are associated with lower TSPO levels. We discuss how mechanistic differences at the neurotransmitter and circuit level in the neural effects of these agents and subsequent immune response may explain these observations. Finally, we review the potential of anti-inflammatory drugs, including ibudilast, minocycline, and pioglitazone, to ameliorate the behavioral and cognitive consequences of addiction.

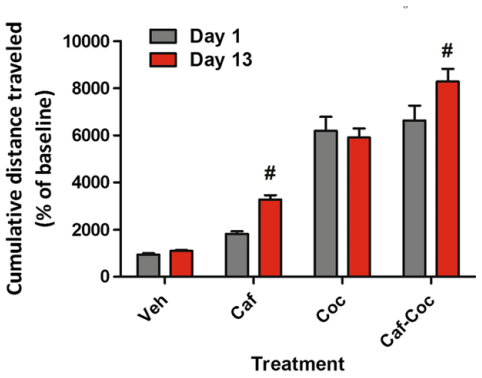
Published in final edited form as:
Neurotox Res. 2016 May ; 29(4): 525–538. doi:10.1007/s12640-016-9601-0.

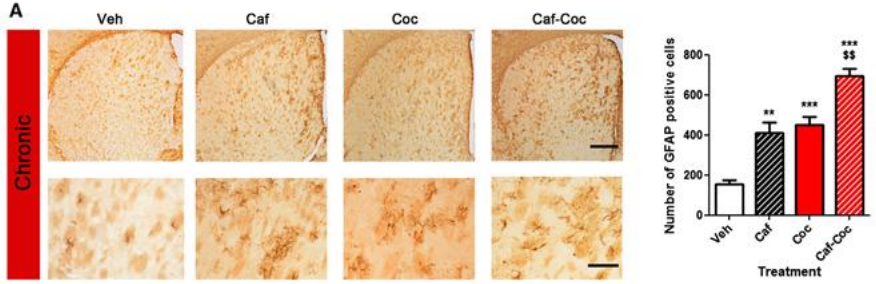
Combined Effects of Simultaneous Exposure to Caffeine and Cocaine in the Mouse Striatum

Javier A. Muñiz[1], **Gimena Gomez**[1], **Betina González**[1], **María Celeste Rivero-Echeto**[2], **Jean Lud Cadet**[3], **Edgar García-Rill**[4], **Francisco J. Urbano**[2], and **Veronica Bisagno**[1]

Glial Fibrillary Acidic Protein (GFAP)
Astroglyosis marker associated with glia inflammation process

Effect of caffeine, cocaine, and their combination on sensitization and striatal GFAP immunoreactivity after chronic treatment





Locomotor sensitization induced by coc+caf is associated with microglia activation

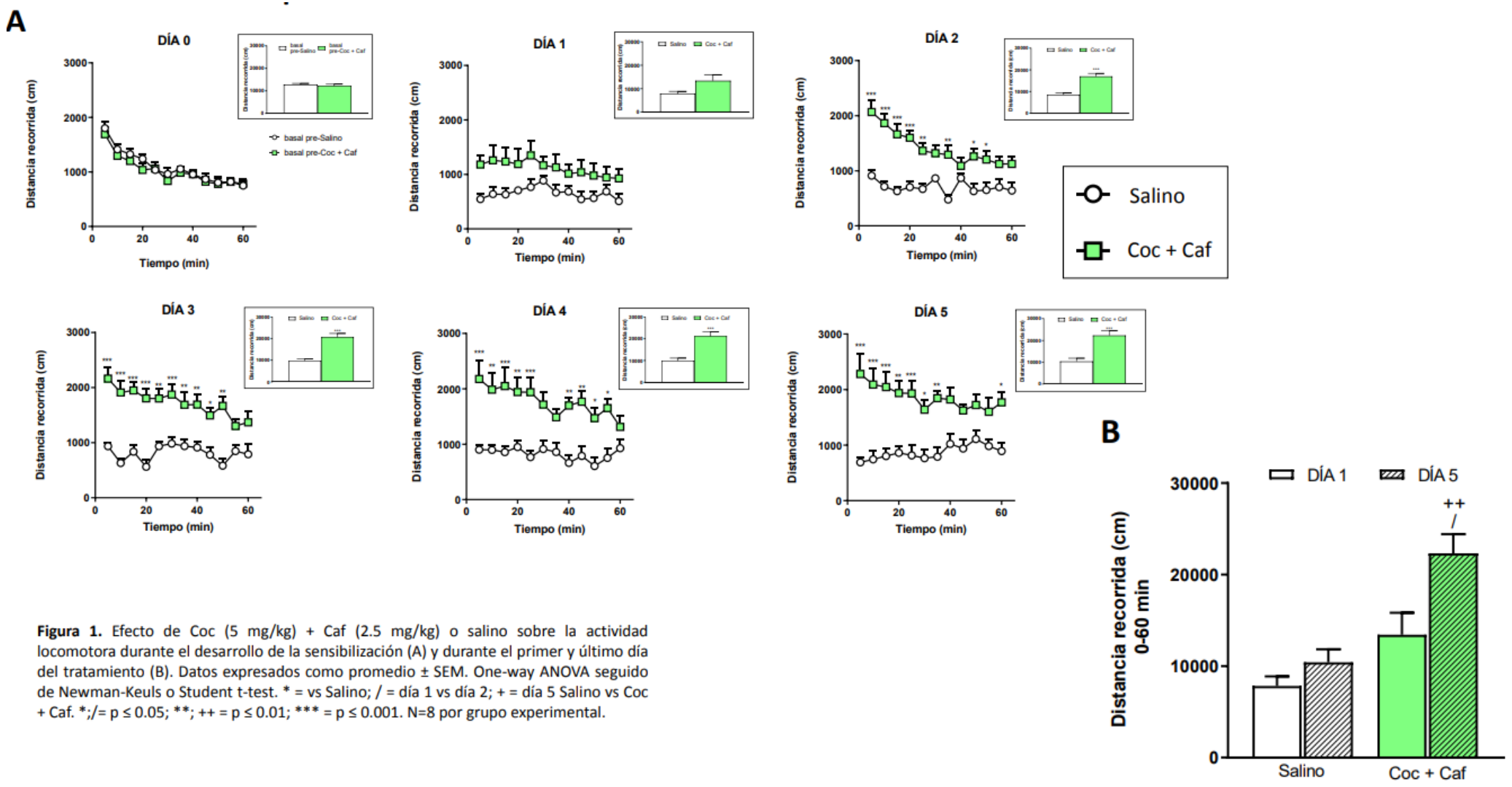
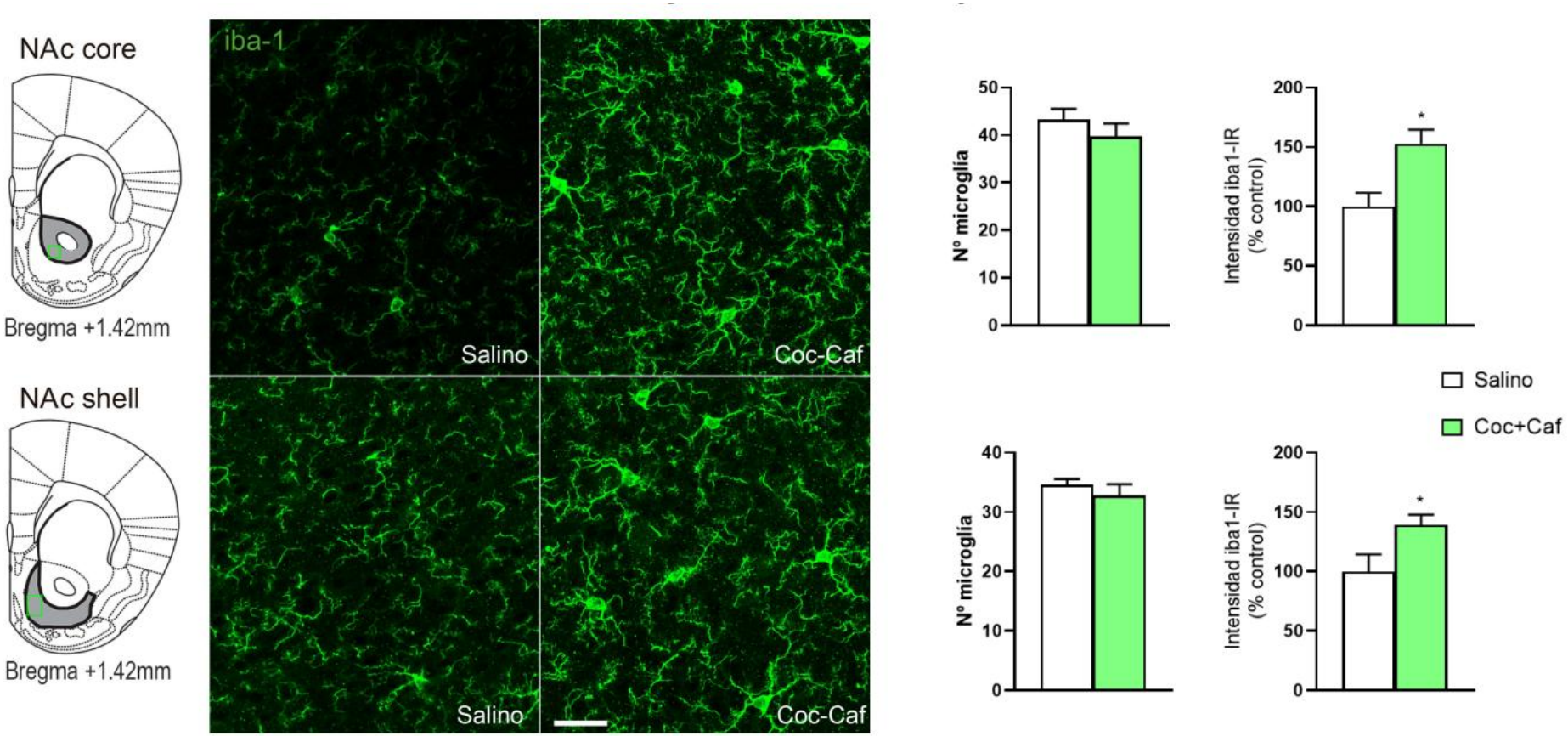


Figura 1. Efecto de Coc (5 mg/kg) + Caf (2.5 mg/kg) o salino sobre la actividad locomotora durante el desarrollo de la sensibilización (A) y durante el primer y último día del tratamiento (B). Datos expresados como promedio ± SEM. One-way ANOVA seguido de Newman-Keuls o Student t-test. * = vs Salino; / = día 1 vs día 2; + = día 5 Salino vs Coc + Caf. *;/= $p \leq 0.05$; **; ++ = $p \leq 0.01$; *** = $p \leq 0.001$. N=8 por grupo experimental.

Immunoreactivity for Iba-1 increased by coc+caf repeated treatment



Microglia, which have been estimated to comprise 10-15 % of all CNS cells, are thought to orchestrate the primary innate immune response within the brain. Cell-surface markers of microglia activation include Iba1 (ionized calcium-binding protein). Microglial activation is linked to the production of a number of pro-inflammatory molecules including cytokines (IL-1β), IL-6, and TNF-α)

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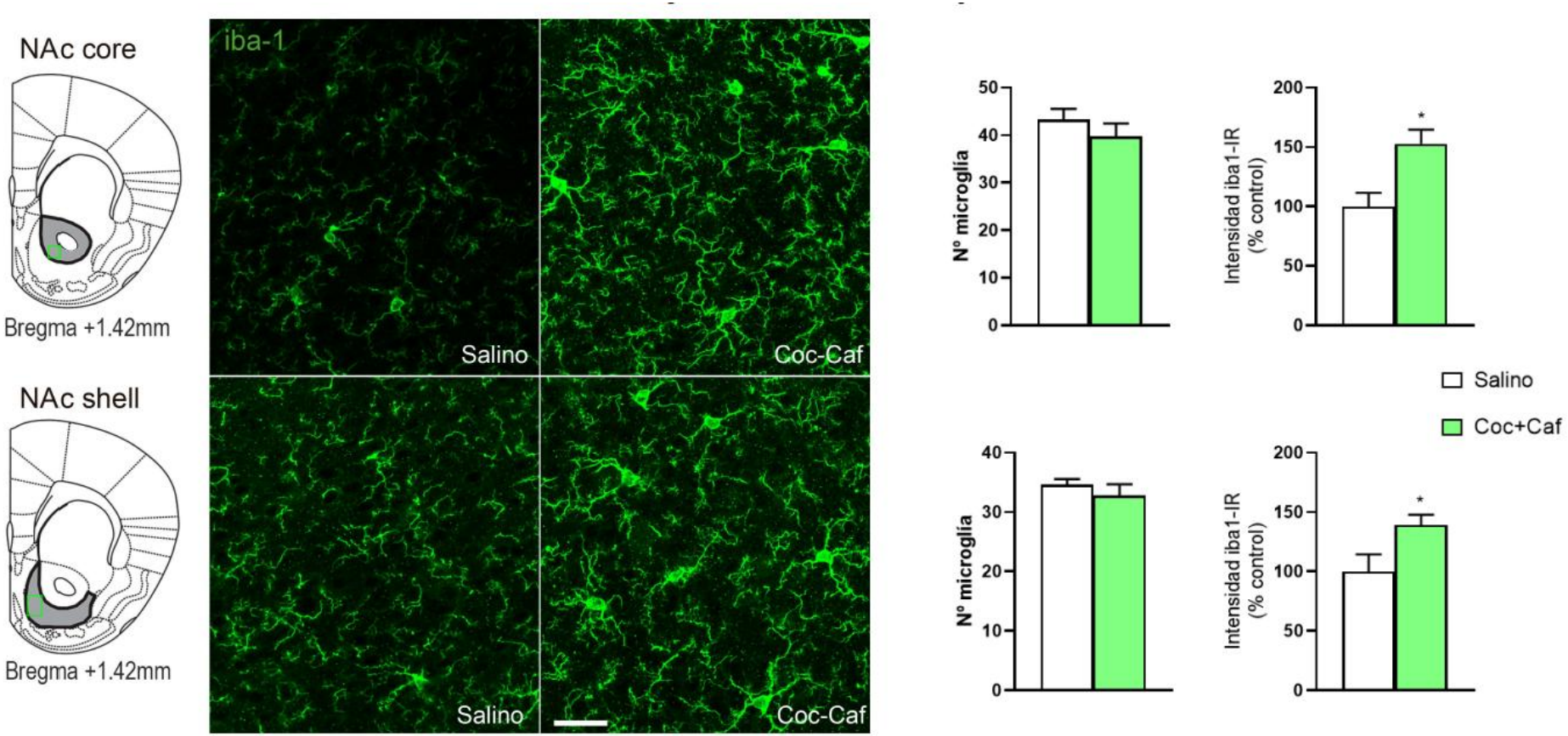

CBD?

- Iba-1
- Plasmatic cytokines

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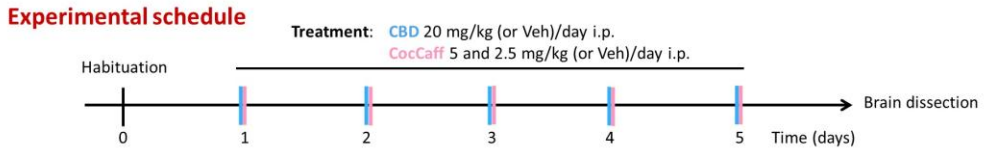

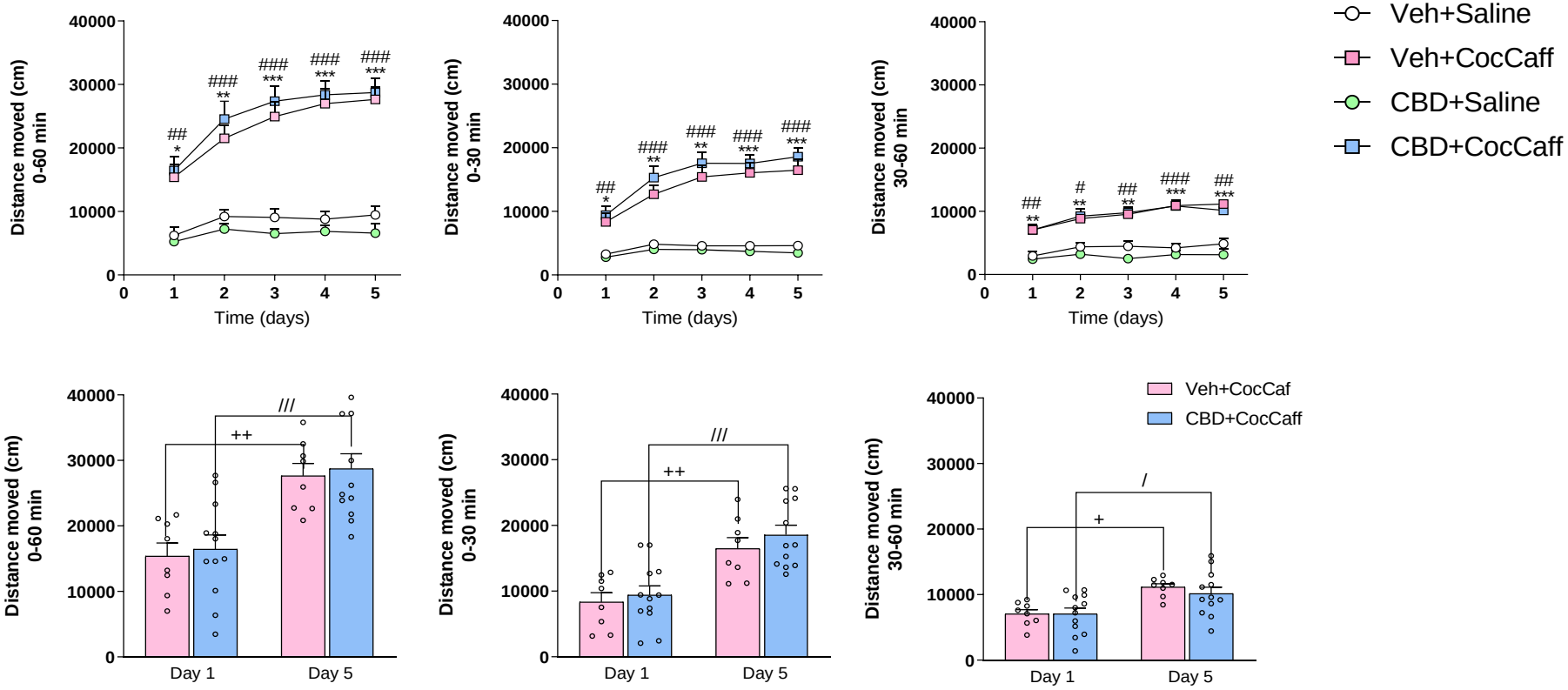

CocCaff significantly increased mice activity over the course of the 5-day treatment respect to control group. **CBD treatments failed to block CocCaff effect (A). CBD had no effect in the locomotor sensitization within the drug treated group (day 1 vs day 5; B).** Dots indicate individual subjects.

Take home message

- Our preclinical results contribute to identify the therapeutic potential of CBD in SUD field, specially in psychostimulants abuse (CUD).

- Remains to be confirmed if CBD prevents both neuroinflammation and sensitization processes induced by Coc+caff.

- More preclinical and clinical studies are necessary to further evaluate the role of CBD as a new therapeutic intervention for SUD.

Clinical data I

Table 2
Summary of clinical studies regarding CBD's effect on drug abuse.

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg; p.o)	Primary outcomes
Manini et al. (2015)	Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans	Healthy volunteers	Fentanyl	Double-blind, placebo-controlled cross-over	400 and 800	After low-dose CBD, tmax occurred at 3 and 1.5 h in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 h in sessions 1 and 2, respectively.
Hurd et al. (2019)	Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial	Men and women with heroin use disorder	Heroin	Double-blind randomized placebo-controlled trial	400 and 800	Acute CBD administration reduces cue-induced craving and anxiety in heroin-abstinent individuals. There no serious adverse effects.
Meneses-Gaya et al. (2020)	Cannabidiol for the treatment of crack-cocaine craving: an exploratory double-blind study	Men with a diagnosis of crack-cocaine dependence	Crack-cocaine	Craving	300	CBD had no effect on craving levels and indicators of anxiety, depression, and sleep alterations.
Mongeau-Pérusse et al. (2021)	Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial	Adult women with moderate to severe use disorder	Cocaine	Craving and relapse	800	Cocaine craving or relapse is unaffected by CBD among people being treated for cocaine abuse disorder.
Demirakca et al. (2011)	Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol	Male chronic recreational cannabis users	Cannabis			An inverse correlation of the ratio THC/CBD with the volume of the right HIP is observed. CBD positively correlates with gray matter concentration in the bilateral HIP.
Crippa et al. (2013)	Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report	19-year-old woman with cannabis withdrawal syndrome	Cannabis	Case report	300–600	CBD may have therapeutic effect in cannabis withdrawal syndrome, at least in patients with no psychiatric comorbidities.
Allsop et al. (2014)	Nabiximols as an agonist replacement therapy during cannabis withdrawal a randomized clinical trial	DSM-IV-TR cannabis dependence	Cannabis	A randomized clinical trial	Maximum daily dose 80	Nabiximols reduces the severity and duration of cannabis withdrawal and improves retention rates during inpatient treatment as well as cravings.
Trigo et al. (2016)	Sativex associated with behavioral-relapse prevention strategy as treatment for cannabis dependence: a case series	Cannabis dependence	Cannabis	Pilot phase of a double-blind placebo-controlled trial	Sativex (up to 105 mg of CBD)	Sativex is well tolerated by all participants. The amount of cannabis use decreases with no increases in withdrawal.
Haney et al. (2016)	Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis	Cannabis smokers	Cannabis	Multi-site, randomized, double-blind	200, 400, and 800	Cannabis SA and cannabis ratings did not vary as a function of CBD.

(continued on next page)

Clinical data II

Trigo et al. (2016)	Sativex associated with behavioral-relapse prevention strategy as treatment for cannabis dependence: a case series	Cannabis dependence	Cannabis	Pilot phase of a double-blind placebo-controlled trial	Sativex (up to 105 mg of CBD)	Sativex is well tolerated by all participants. The amount of cannabis use decreases with no increases in withdrawal.
Haney et al. (2016)	Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis	Cannabis smokers	Cannabis	Multi-site, randomized, double-blind	200, 400, and 800	Cannabis SA and cannabis ratings did not vary as a function of CBD.
Solowij et al. (2018)	Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial	Cannabis users	Cannabis	Pragmatic open-label clinical trial	200	CBD-treated participants report reduction in euphoria when smoking cannabis, fewer depressive and psychotic-like symptoms and improvements in attentional switching, verbal learning, and memory.
Beale et al. (2018)	Prolonged cannabidiol treatment effects on hippocampal subfield volumes in current cannabis users	Cannabis users	Cannabis	Open-label pragmatic trial	200.	Associations between greater right subicular complex and total HIP volume and higher plasma CBD concentration are evident, particularly in heavy users.
Morgan et al. (2013)	Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function	Cannabis users	Cannabis	A randomised, double-blind crossover	16; INH	CBD alone reduces PSI scores in light users only. Cannabis users may show a blunted anti-psychotic response to CBD.
Freeman et al. (2020)	Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial	DSM-5 cannabis users	Cannabis	Double-blind, placebo-controlled, randomised	200, 400, and 800	CBD exceeds the primary endpoint criterion for reducing cannabis use during treatment.
Consroe et al. (1979)	Interaction of cannabidiol and alcohol in humans	Healthy post graduate student volunteers	Alcohol	Double-blind, crossover, randomized design	200	Alcohol plus CBD produces decrements of motor and cognitive responses and subjective alteration. CBD decreases blood alcohol levels. .
Morgan et al. (2013)	Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings	Cigarette smokers	Tobacco	Double-blind placebo controlled	400 μg	CBD significantly reduces the number of cigarettes smoked by ~40% during treatment.
Hindocha et al. (2018)	Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal	Cigarette smokers	Tobacco	Randomized, double-blind crossover	800	CBD reverses automatic attentional bias is directed away from cigarette cues. CBD reduces explicit pleasantness of cigarette images. Craving and withdrawal are unaffected by CBD.
Hindocha et al. (2018)	The effects of cannabidiol on impulsivity and memory during abstinence in cigarette dependent smokers	Cigarette smokers	Tobacco	Double-blind placebo-controlled crossover	800	CBD does not improve verbal or spatial working memory, or impulsivity during tobacco abstinence.

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