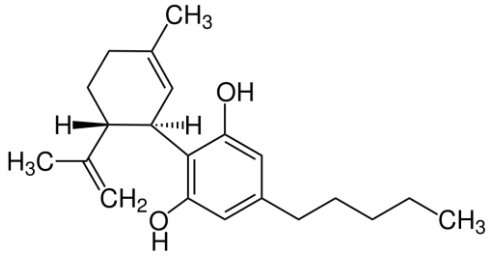
Cannabidiol, nuevo Fármaco Antiepiléptico. ¿Podría jugar un papel como agente Neuroprotector en los Trastornos del Neurodesarrollo?



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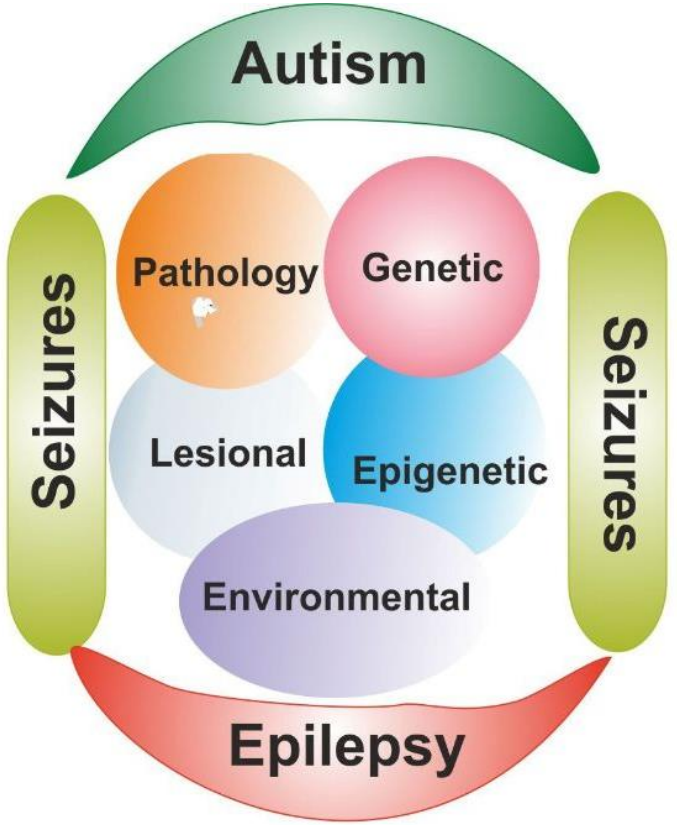
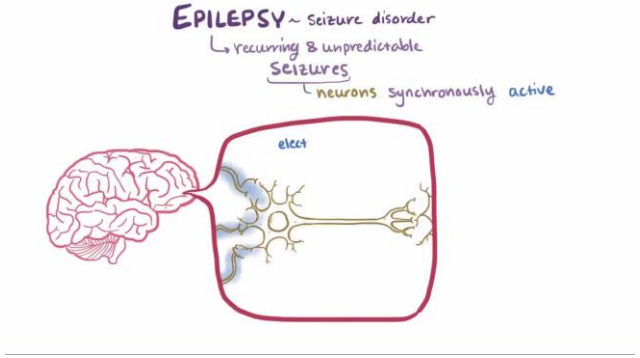
ABORDAJE MULTIDISCIPLINAR DE LOS TRASTORNOS DEL NEURODESARROLLO EN LA INFANCIA (XVI CURSO).
Madrid, 04/11/2022

ASD and Epilepsy

- **Sharing etiologies.**
- **Excitation-Inhibition imbalance.**
- **Abnormal neural network development.**
- **Sharing pathogenesis.**
  - Neuronal Migration.
  - Neuronal Differentiation.
  - Synaptogenesis.
  - Neuronal plasticity.
  - Apoptosis.
  - Neurotransmitters dysfunction.
  - Ionotropic and metabotropic receptors.
  - Mitochondrial oxidative metabolism.
  - Neuroinflammation.
  - Nuclear signaling transcription.



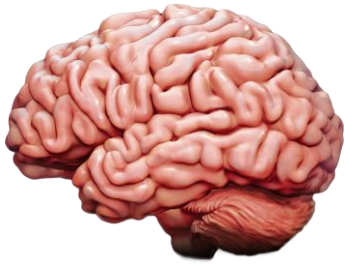
Lee-2015, Frye-2016, Richard-2016

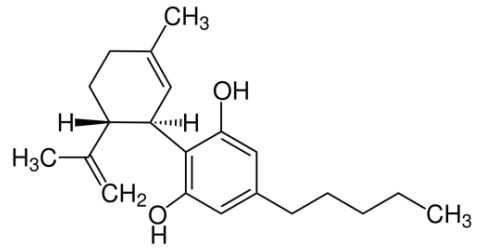


- **<u>Cannabidiol (CBD)</u> (Epidiolex®)** has been FDA- and EMA-approved **for two epilepsy syndromes associated with ASD**: <u>Dravet Syndrome</u> and <u>Lennox-Gastaut Syndrome</u> (Devinsky et al., 2017; Devinsky et al., 2016; Devinsky et al., 2018; Thiele et al., 2018); and for **Tuberous Sclerosis Complex (TSC)**, a well-defined etiology of refractory epilepsy that associates both epilepsy and ASD (Thiele et al. 2021).

- **Another non-psychoactive phytocannabinoid drug, <u>Cannabidivarin (CBDV)</u>,** is under clinical trial to assess its efficacy in people suffering from <u>ASD</u> (ClinicalTrials.gov Identifier: NCT03849456; NCT03202303).

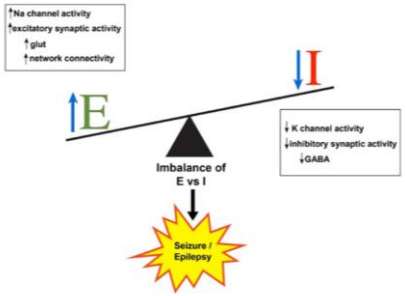
CBD and CNS





- **CBD is the non-psychotropic component of Cannabis**, and there are numerous therapeutic effects of this drug including treatment of epilepsy, anxiety, pain, nausea, and motor deficits including the tremor in Parkinson's disease.

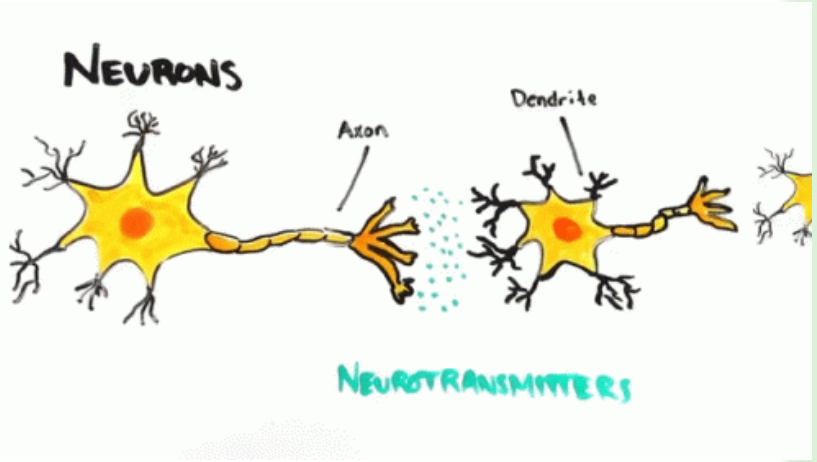
- **CBD has both Neuromodulatory and Neuroprotective effects:**
  1. Blocking neuroinfammation and potentiating anti-infammatory pathways.
  2. Improving mitochondrial function / redox.
  3. GABA-A-R agonist potentiation (inhibition!!!).
  4. Stimulation of 5HT1A receptors.
  5. Enhancing levels of endocannabinoid anandamide (AEA).



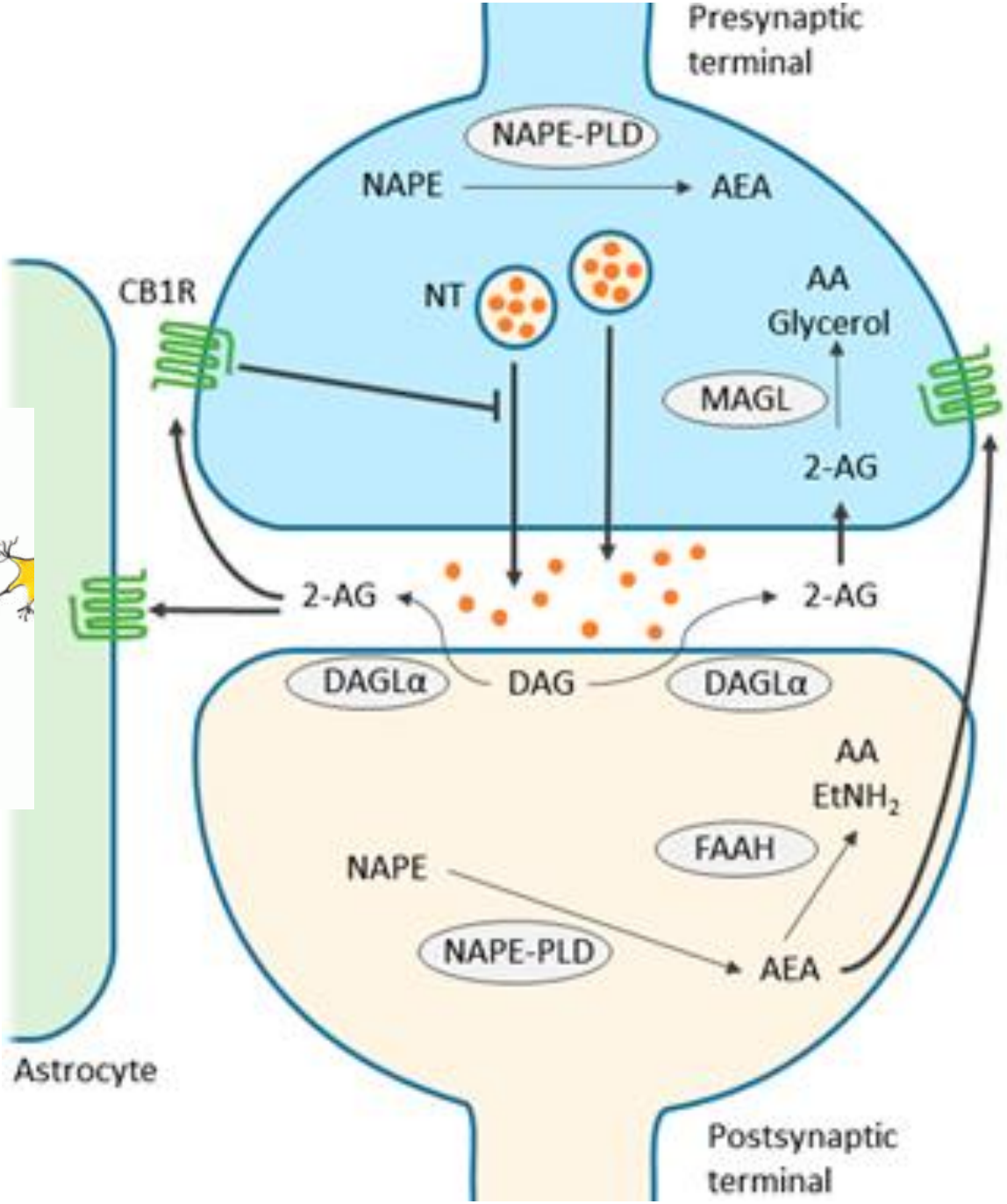
- CBD could **improve the balance in inhibitory and excitatory transmission** and help restore neuronal function and synaptic plasticity in patients with ASD and FXS **even when there is no epilepsy**.

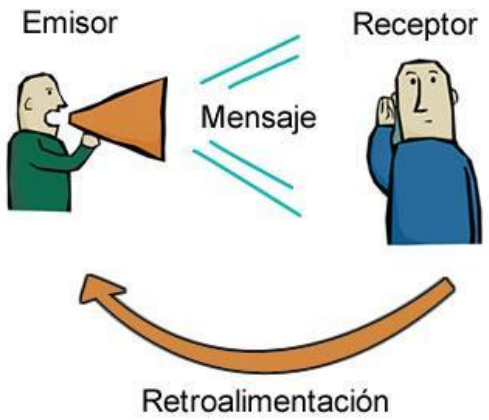
Patricio-2020, Aishworiya-2022, Bakas-2017, Leweke-2012, Russo-2005

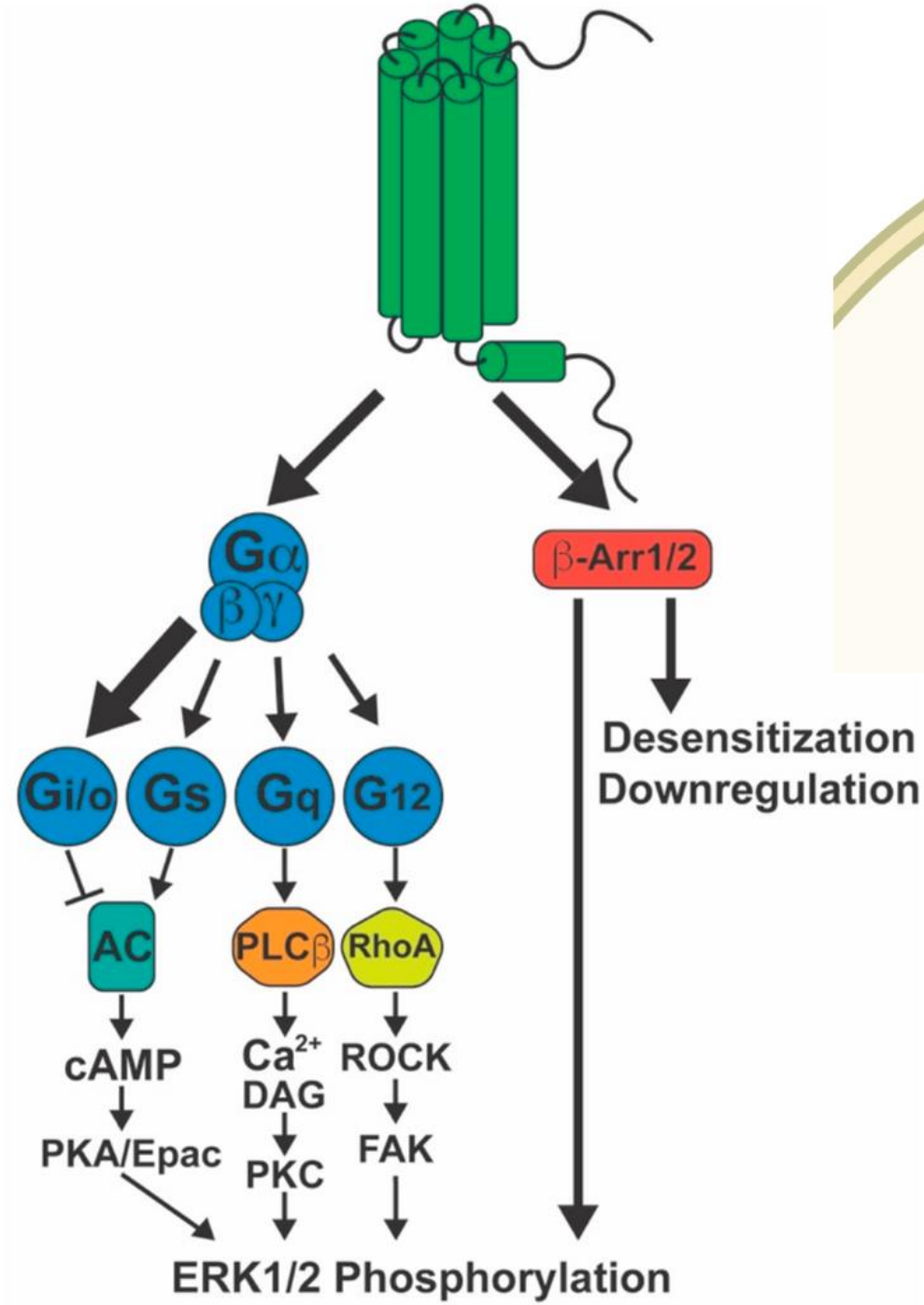
ENDOCANNABINOID SIGNALING SYSTEM

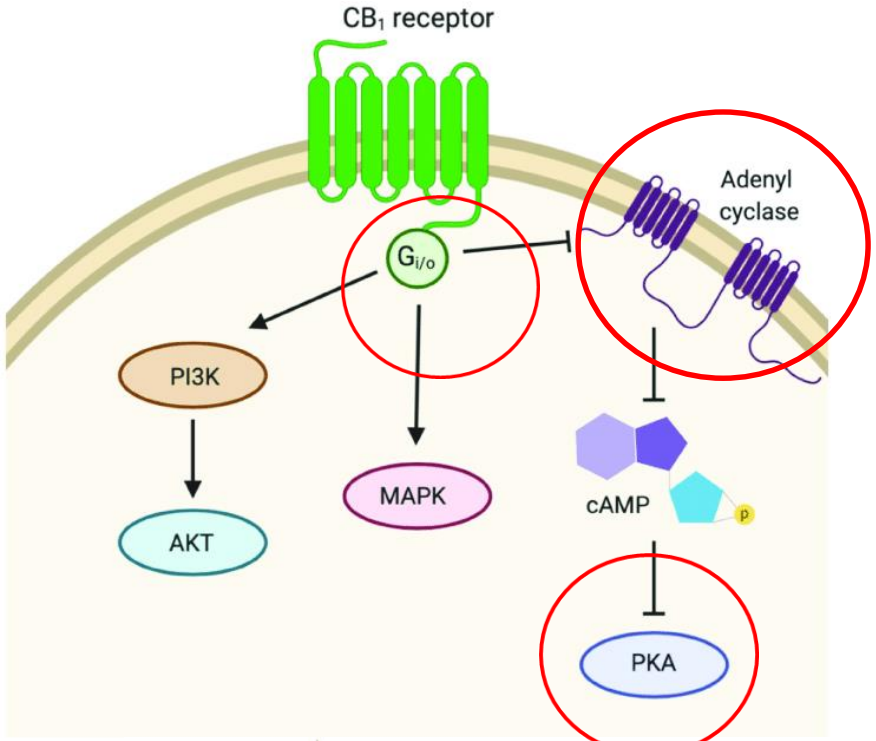


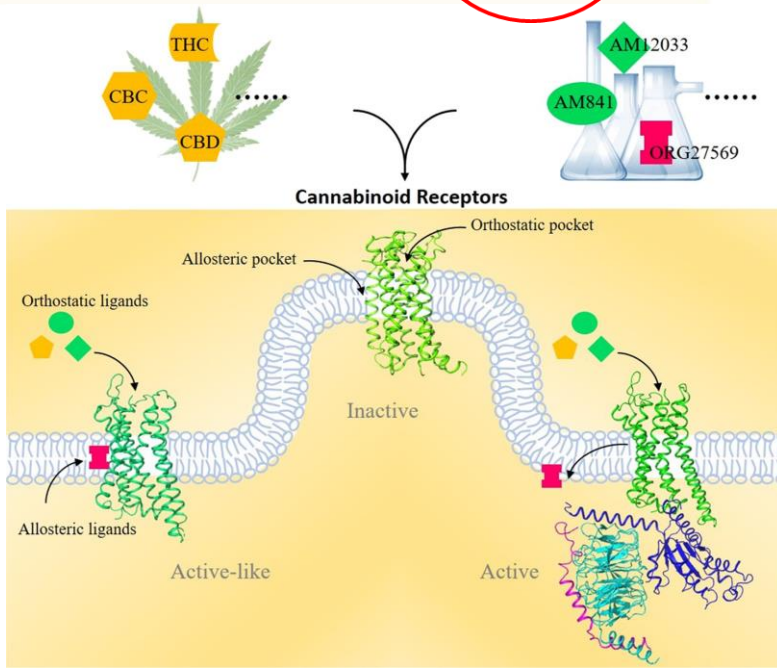
AEA: Anandamida.
2-AG: 2-arachidonoylglycerol.



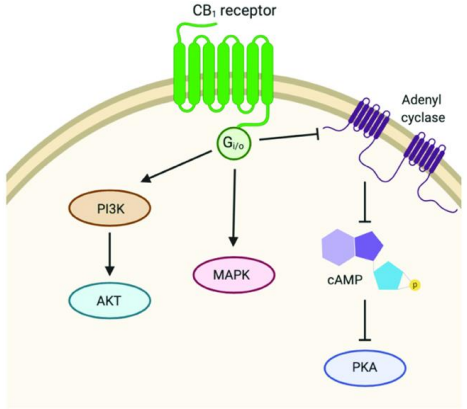



Gα
βγ
β-Arr1/2
Gi/o
Gs
Gq
G12
AC
PLCβ
RhoA
cAMP
Ca2+
DAG
ROCK
PKA/Epac
PKC
FAK
Desensitization
Downregulation
ERK1/2 Phosphorylation


CB1 receptor
Adenyl cyclase
Gi/o
PI3K
MAPK
cAMP
AKT
PKA


THC
CBC
CBD
AM12033
AM841
ORG27569
Cannabinoid Receptors
Orthostatic pocket
Allosteric pocket
Orthostatic ligands
Inactive
Allosteric ligands
Active-like
Active

ENDOCANNABINOID SIGNALING: EFFECTORS IN NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL DISORDERS



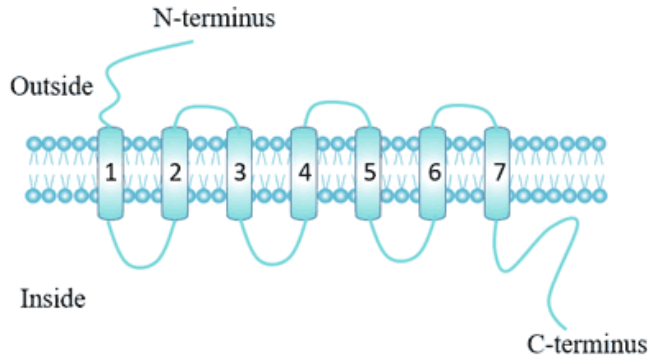
1. Basic in regulation of ion channels.

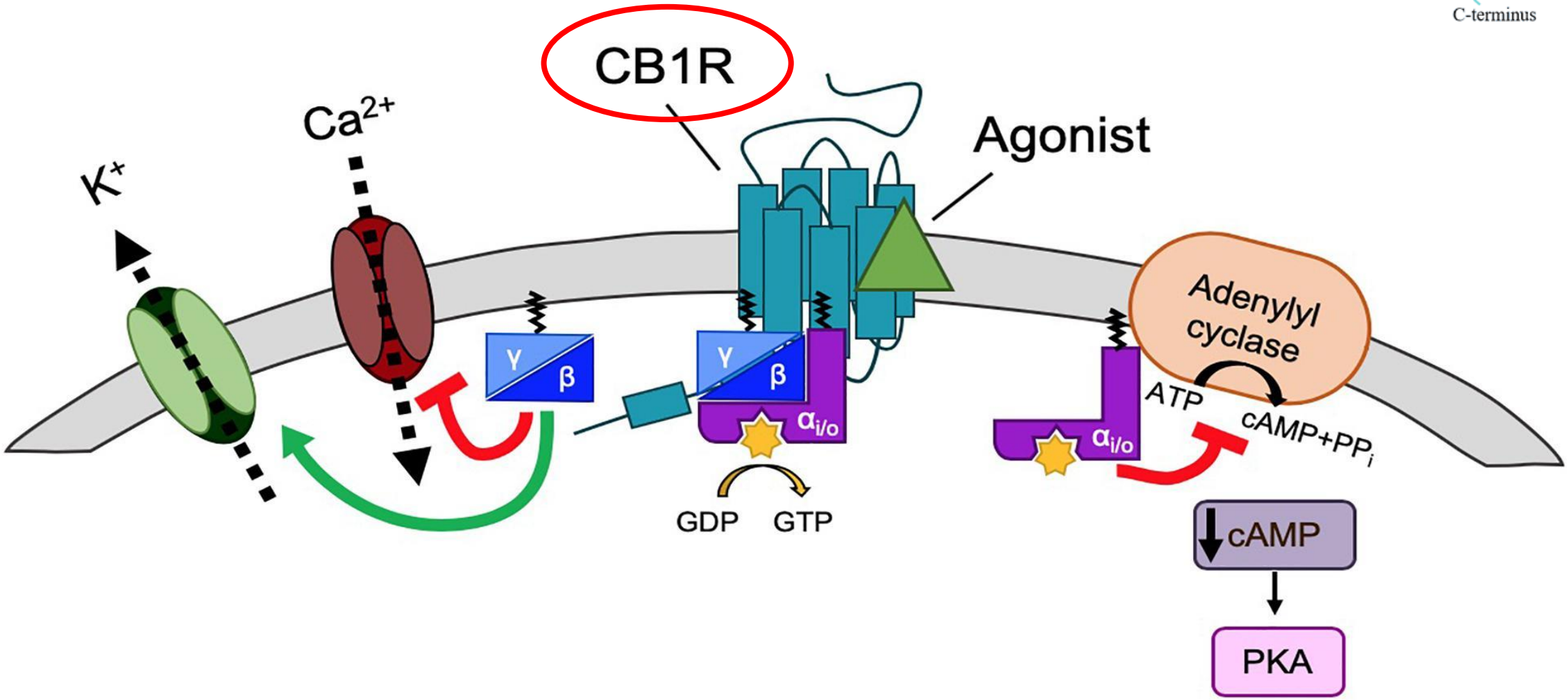
2. Inhibit adenylyl cyclase, which through downstream signaling increase cyclic AMP in the modulation of neurotransmission.

3. Activate protein kinase A (PKA) to govern cellular function; and regulate **mitogen-activated protein kinases (MAPK)** in control of transcriptional factors.

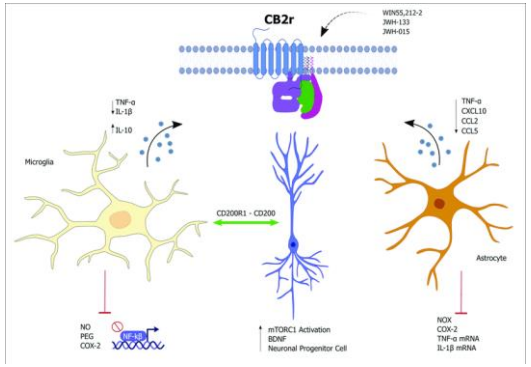
Castillo-2012, Mechoulan-2013, Kahrson-2016

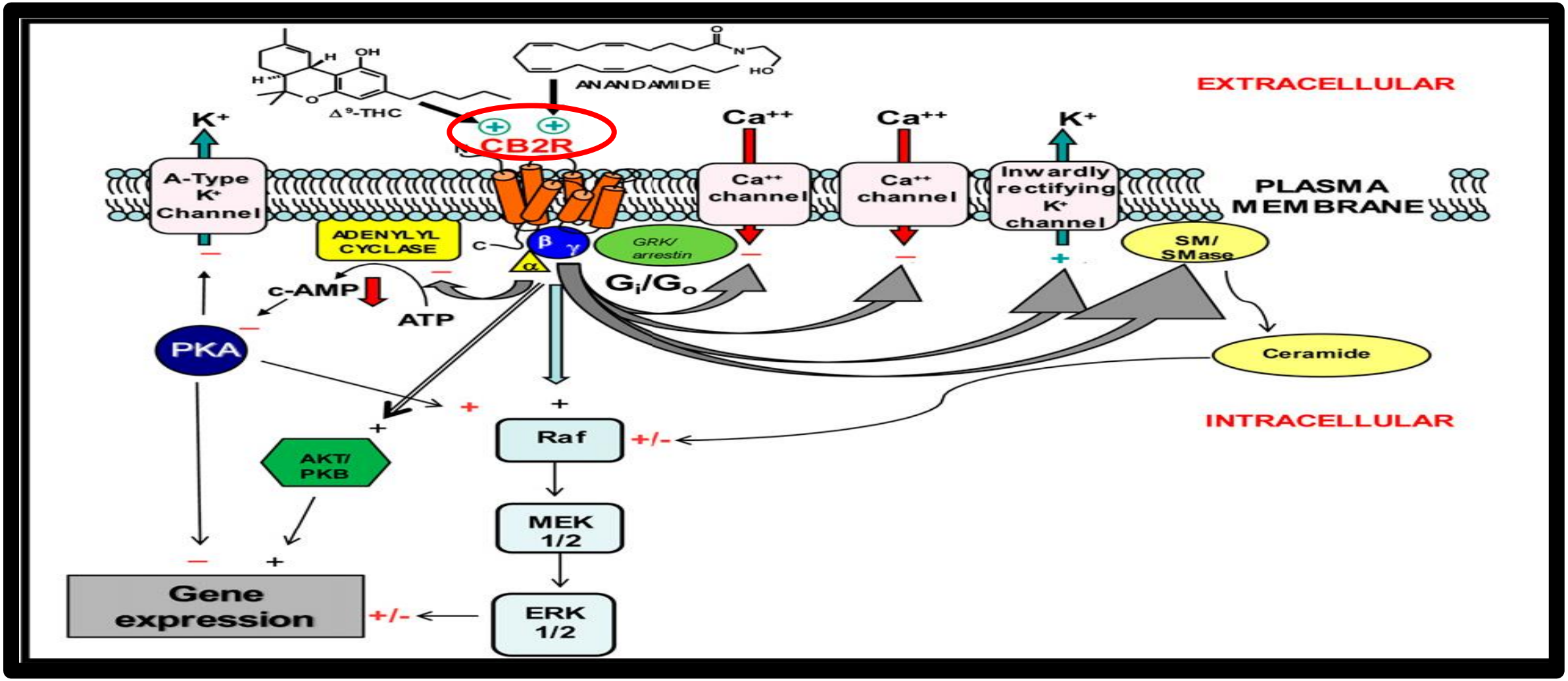
ENDOCANNABINOID SIGNALING: EFFECTORS IN NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL DISORDERS

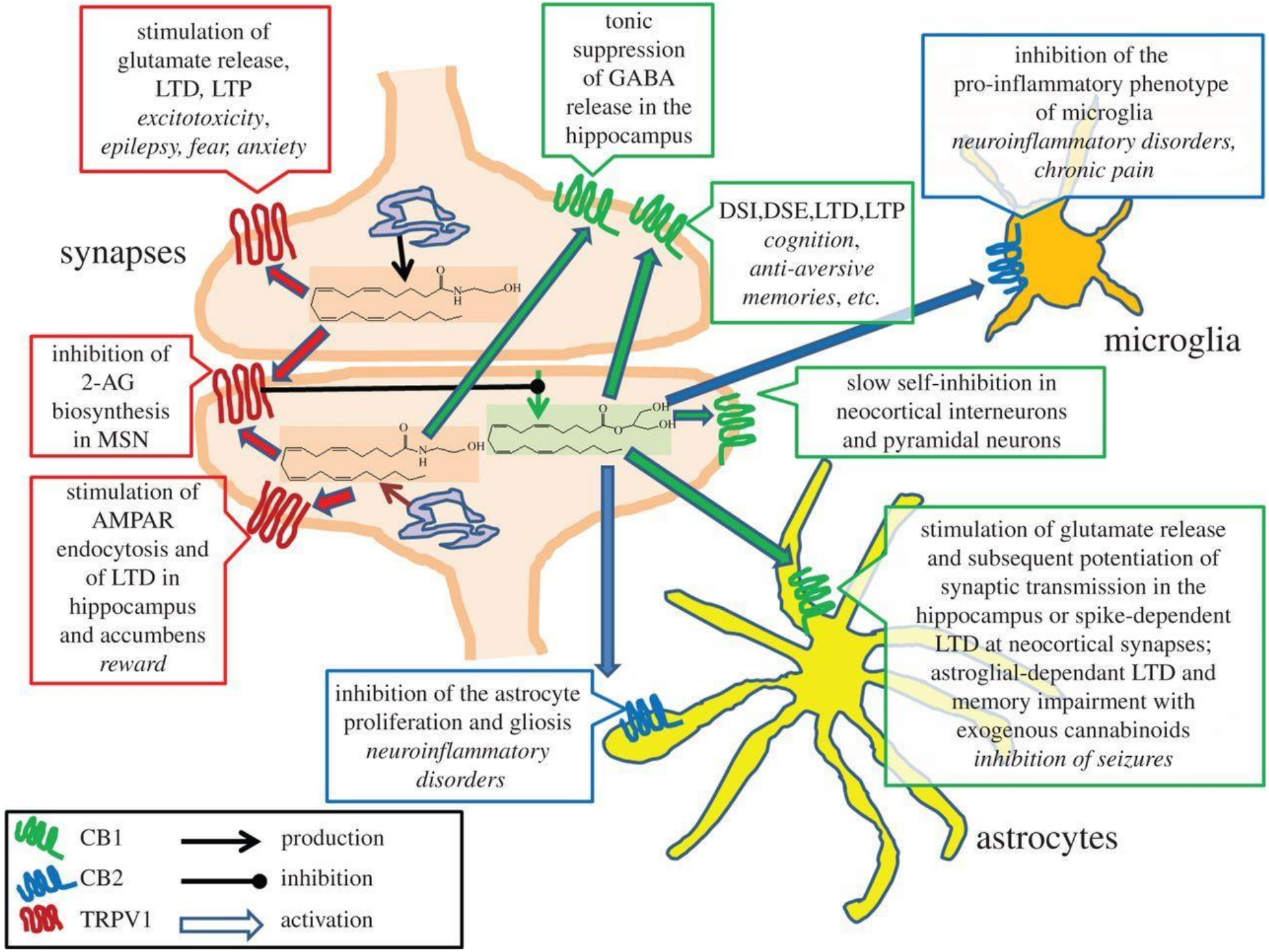


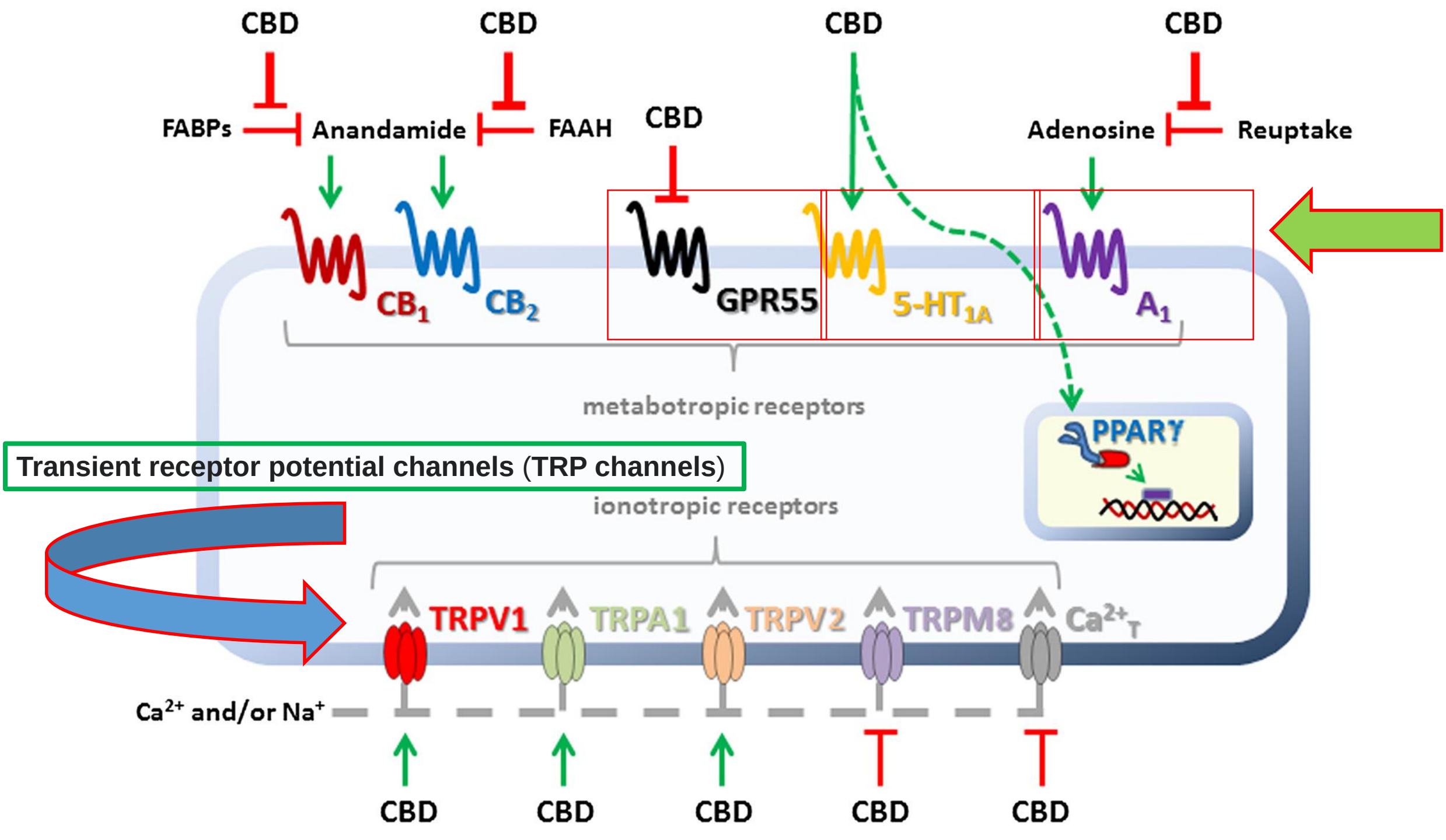


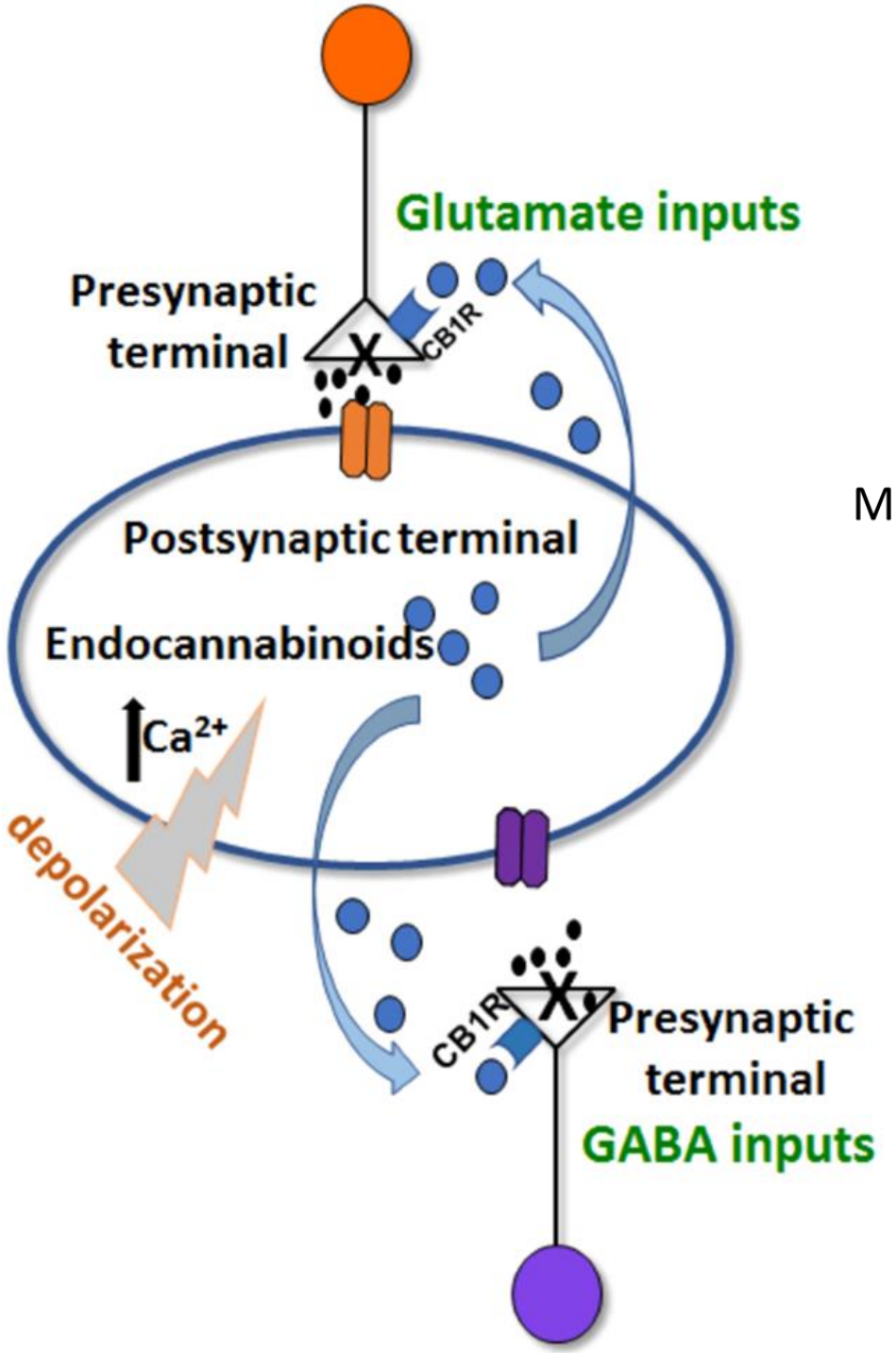
ENDOCANNABINOID SIGNALING: EFFECTORS IN NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL DISORDERS

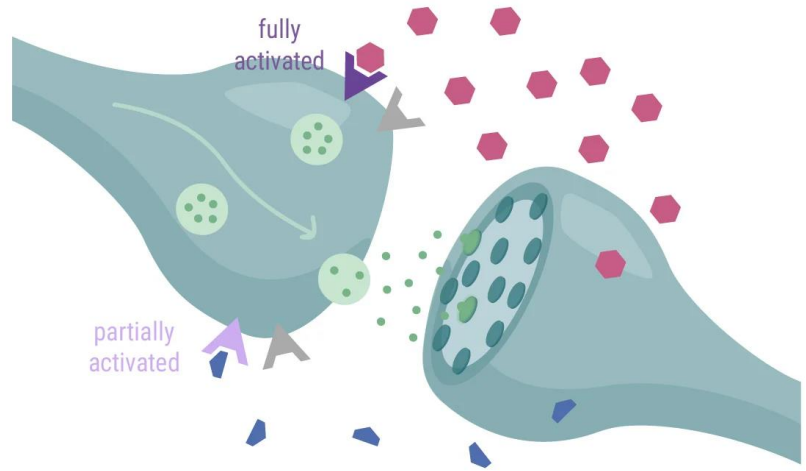


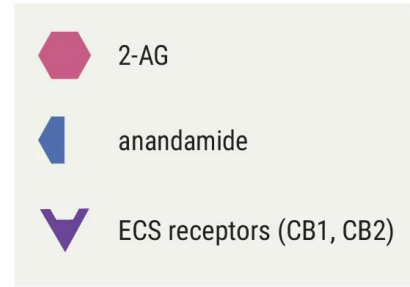



stimulation of glutamate release, LTD, LTP *excitotoxicity, epilepsy, fear, anxiety*
tonic suppression of GABA release in the hippocampus
inhibition of the pro-inflammatory phenotype of microglia *neuroinflammatory disorders, chronic pain*
synapses
DSI,DSE,LTD,LTP *cognition, anti-aversive memories, etc.*
microglia
inhibition of 2-AG biosynthesis in MSN
slow self-inhibition in neocortical interneurons and pyramidal neurons
stimulation of AMPAR endocytosis and of LTD in hippocampus and accumbens *reward*
stimulation of glutamate release and subsequent potentiation of synaptic transmission in the hippocampus or spike-dependent LTD at neocortical synapses; astroglial-dependant LTD and memory impairment with exogenous cannabinoids *inhibition of seizures*
inhibition of the astrocyte proliferation and gliosis *neuroinflammatory disorders*
astrocytes
CB1
CB2
TRPV1
production
inhibition
activation

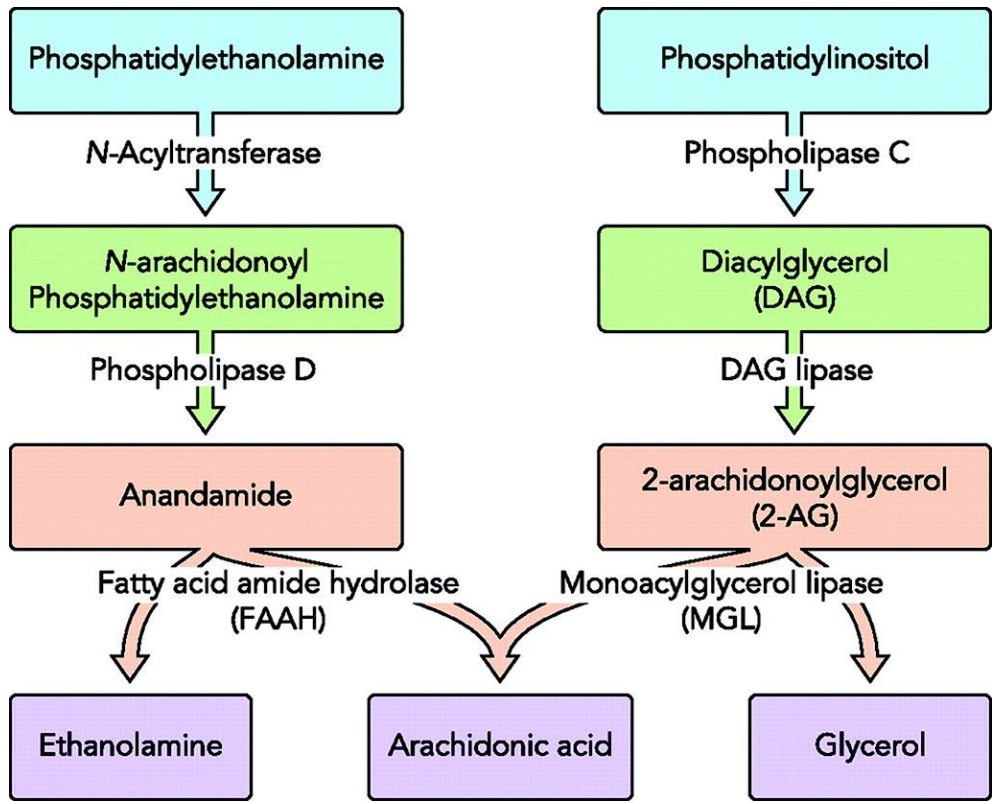

CBD
CBD
CBD
CBD
FABPs
Anandamide
FAAH
CBD
Adenosine
Reuptake
CB1
CB2
GPR55
5-HT1A
A1
metabotropic receptors
PPARγ
Transient receptor potential channels (TRP channels)
ionotropic receptors
TRPV1
TRPA1
TRPV2
TRPM8
Ca2+T
Ca2+ and/or Na+
CBD
CBD
CBD
CBD
CBD



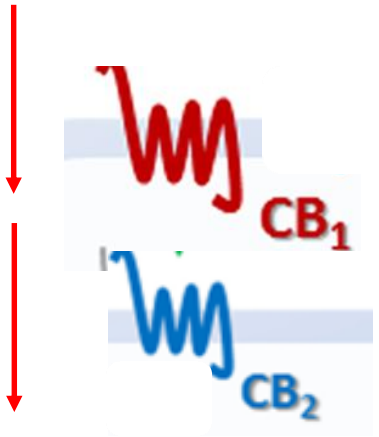


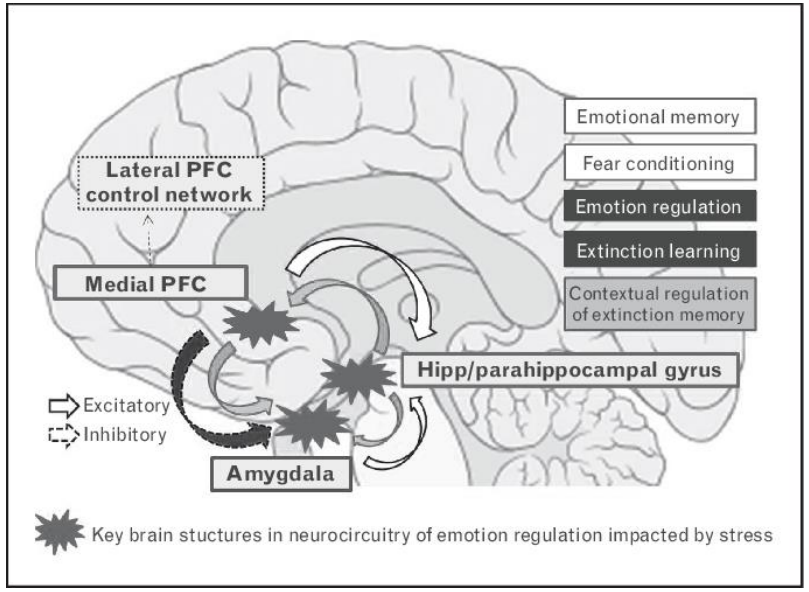


Metabolic pathways of the ligands of eCB system



ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





❖**eCB SIGNALING AND NEGATIVE VALENCE SYSTEMS:**

➢ Anxiety.

❑ **Major components of the neurocircuitry mediating anxiety**, such as the prefrontal cortex (PFC), hippocampus, amygdala and hypothalamus are **rich in CB1R and CB2R expression.**

➢ **In animal models, genetic deletion of CB1R increases anxiety-like behaviors.**

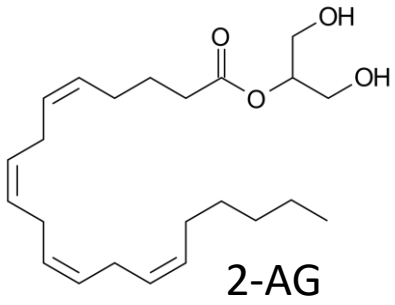
➢ **In animal models, genetic deletion of CB2R modulate vulnerability to anxiogenesis.**

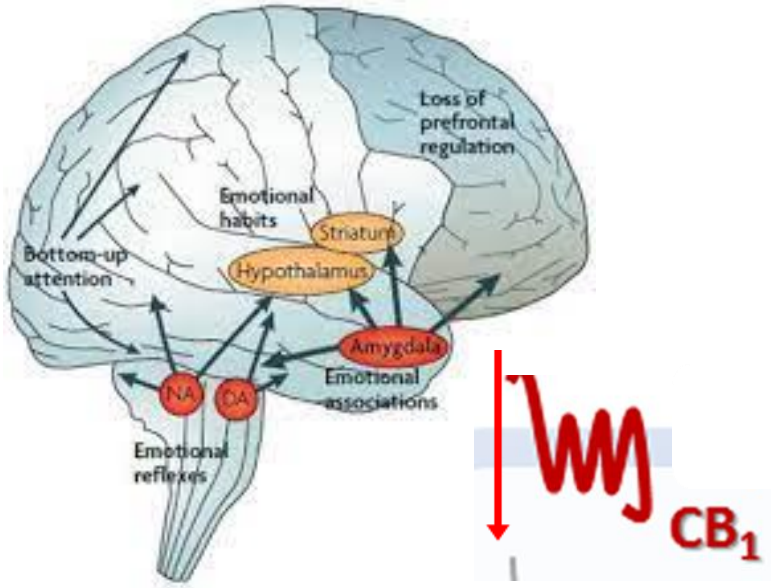
✓ Overexpression of CB2Rs in mouse models increases resistance to anxiogenic stimuli, mediated by increased 2-AG and GABA signaling.

❑**Acute administration of THC and CBD commonly produces an anxiolytic response**, likely due to inhibition of the glutamatergic firing.

Castillo-2012, Mechoulan-2013, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





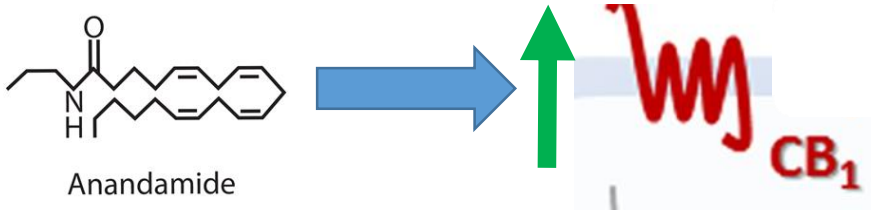
❖**eCB SIGNALING AND NEGATIVE VALENCE SYSTEMS:**

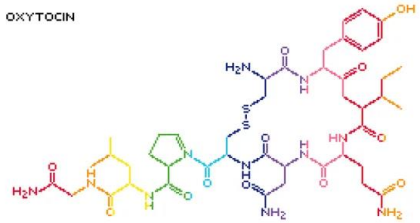
➢Chronic stress.

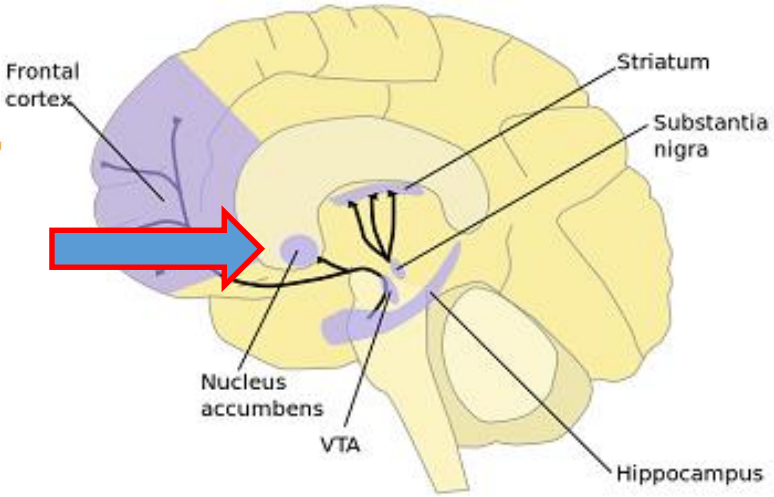
- **Persistent activation of stress neurocircuitry** breaks down homeostatic balance and creates a **"hypocannabinergic state"'** through **downregulation of CB1R expression** in the hippocampus, hypothalamus, striatum and dorsal root ganglion. Otherwise, **no significant change in CB2R expression was observed.**
- **Chronic stressor exposure impairs AEA signalling and elevates 2-AG content within the amygdala** (and increases glucocorticoid hormone secretion); and in hippocampus, hypothalamus and PFC, likely due to altered FAAH and monoacylglycerol lipase-mediated hydrolysis, as the synthesis of these eCBs is unimpaired.
- **The enhancement of 2-AG signaling → attempt to habituate to the chronic stress exposure →** eCB signaling is basic in the modulation of the hypothalamus-adrenal (HPA) axis to guarantee a positive adaptive response.

Castillo-2012, Mechoulan-2013, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE







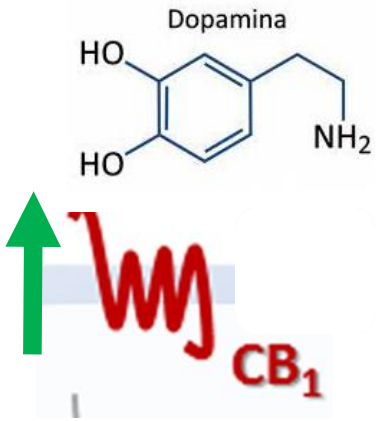
❖**eCB SIGNALING AND POSITIVE VALENCE SYSTEMS:**

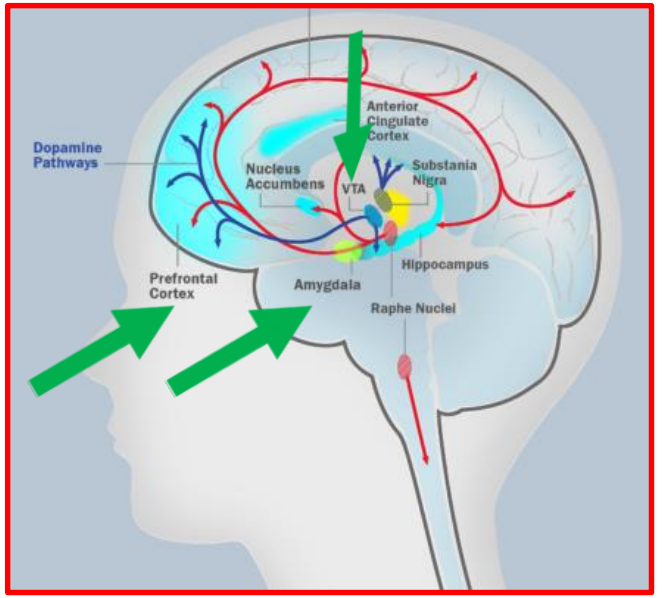
➢<u>Reward Learning.</u>

- ❑ **Adaptive reinforcement of social interactions** requires **long-term synaptic plasticity** <u>at excitatory synapses of the nucleus accumbens</u> (Nac) and is **dependent on <u>oxytocin</u>**, a neuropeptide that regulates prosocial behavior.
- ❑**<u>Oxytocin (OT)</u> → social reinforcement signal** to induce long-term depression in medium spiny neurons and **requires specific activation of CB1Rs by AEA** to regulate social incentive salience.
- ❑**Researchers have advocated that these findings are of particular relevance to ASD,** although these results can also be broadly applied to neuropsychiatric disorders characterized by dysregulated OT and impaired social functioning.

Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





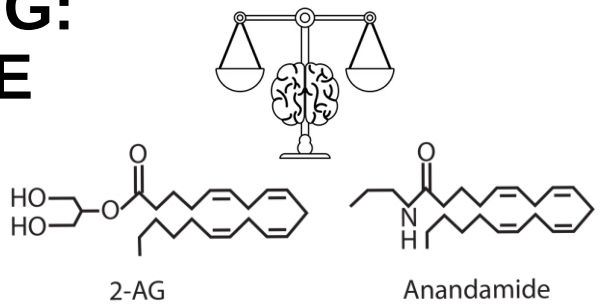
❖**eCB SIGNALING AND POSITIVE VALENCE SYSTEMS:**

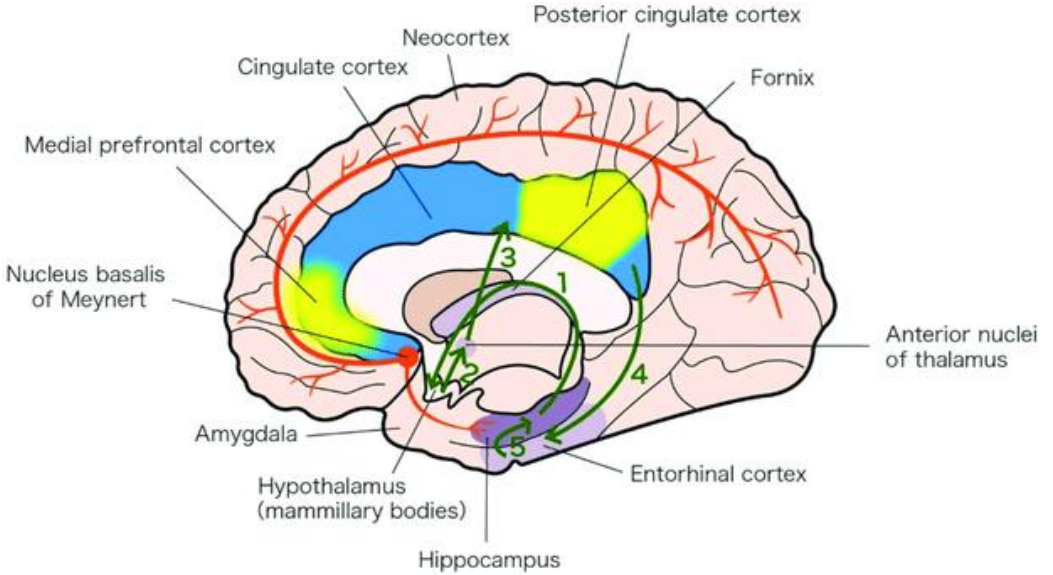
➢Social motivation.

- **Individual differences in social motivation are associated with alterations in the activity of neurocircuitry that overlap with reward learning**; **high social motivation** is correlated with enhanced activation of the amygdala and orbital frontal cortex, whereas weaker activation is related to lower social motivation.
- **Opioid and dopaminergic neurons in the ventral tegmental area have complementary roles in motivated behaviors and require eCB signaling** to **fine-tune dopamine release** in incentive-related reward learning.
- **Enhanced motivation is observed following CB1R stimulation and with increased AEA signaling in the amygdala, NAc and dorsal striatum and 2-AG in the NAc**. Diminished motivation is associated with CB1R blockade.

Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





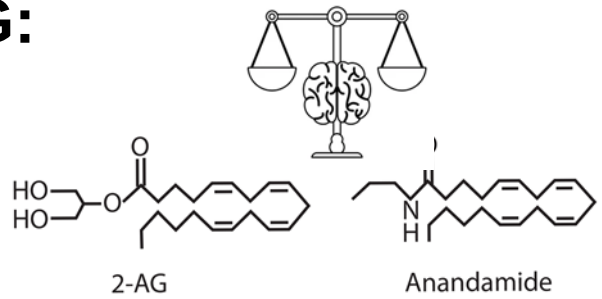
❖**eCB SIGNALING AND COGNITIVE SYSTEM:**

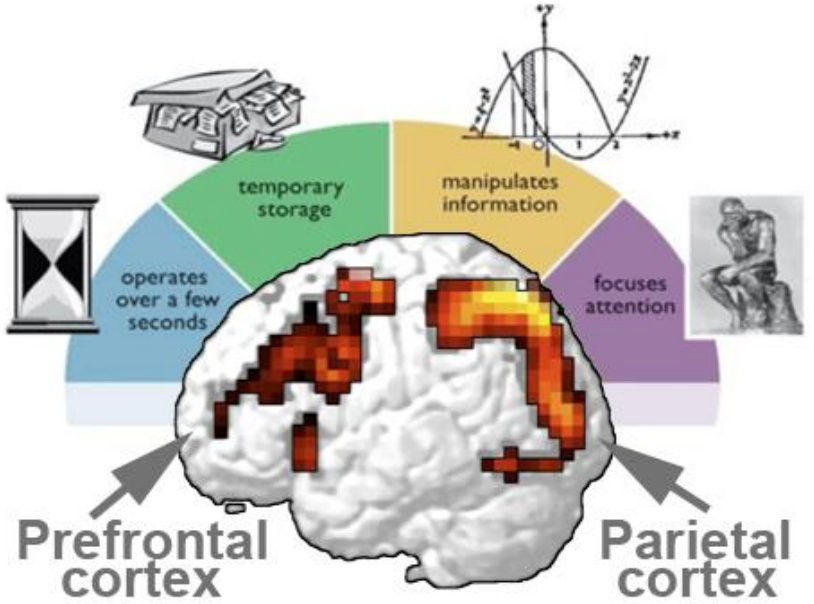
➢<u>Declarative Memory / Long Term Memory.</u>

- ❑ Declarative memory (that is, encoding, consolidation, storage and retrieval of factual information) <u>supports social interactions by providing biographical and episodic recall</u>.
- ❑**AEA and 2-AG are both modulators** of early-stage acquisition, consolidation and extinction.
- ❑**Enhancement of 2-AG** that is <u>correlated with disrupted encoding in spatial memory</u>.
- ❑**Evidence demonstrates transient, <u>dose-dependent THC-induced memory impairments</u>** (with a tolerance effect in heavy users) and the contrasting **<u>absence of memory deficits following CBD administration</u>** → <u>CBD is protective against THC-induced impairments in episodic and spatial memory</u>.

Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





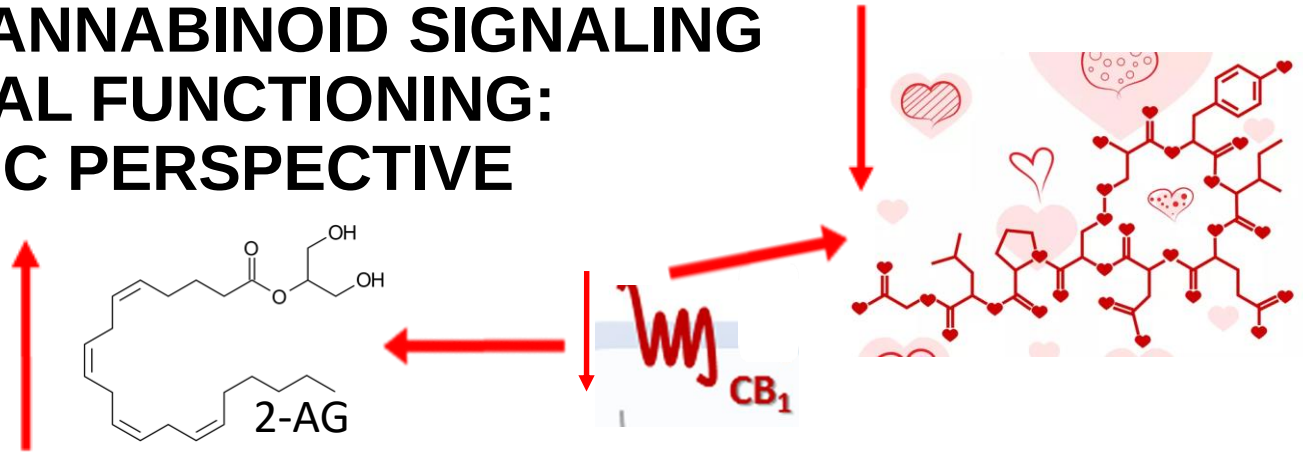
❖**eCB SIGNALING AND COGNITIVE SYSTEM:**

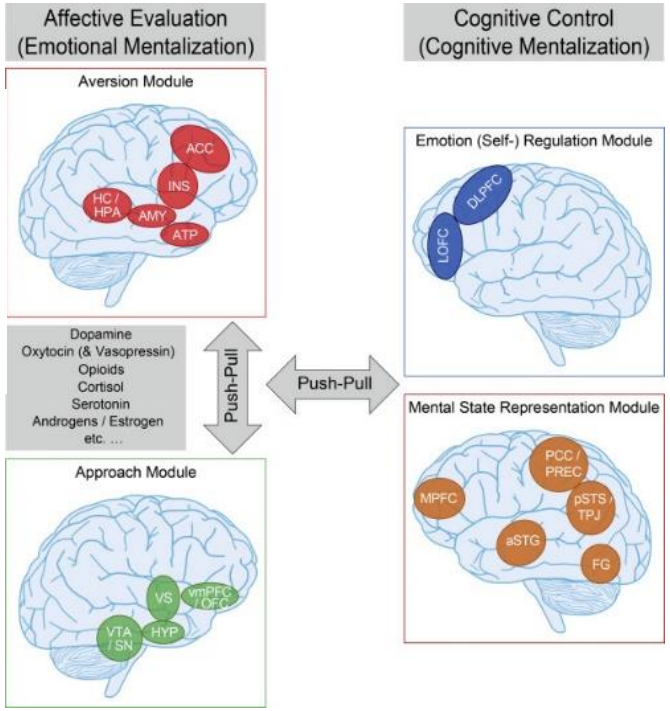
➢**Working Memory.**

- More immediate information processing involves working memory, which actively maintains and updates relevant information, but is capacity-limited.
- In social interactions, **working memory tracks / regulates social information**, like the characteristics of, or relationships among, people necessary to competently socially interact.
- **THC exposure in humans negatively impacts working memory** via CB1R activation and inhibition of AEA reuptake → **changing cognitive flexibility**.
- Data in FAAH knockout mice demonstrate that **AEA-biased tone improves acquisition in working memory tasks**, but the effects are transient and do not persist into later trials.
- **Control of AEA tone and local modulation of 2-AG signaling** → improves working memory.

Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE





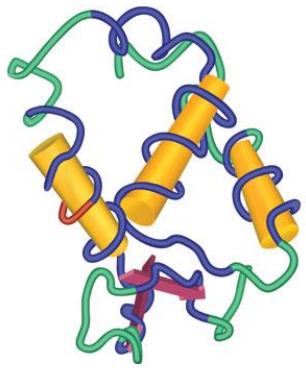
❖**eCB SIGNALING AND SOCIAL PROCESSING SYSTEMS:**

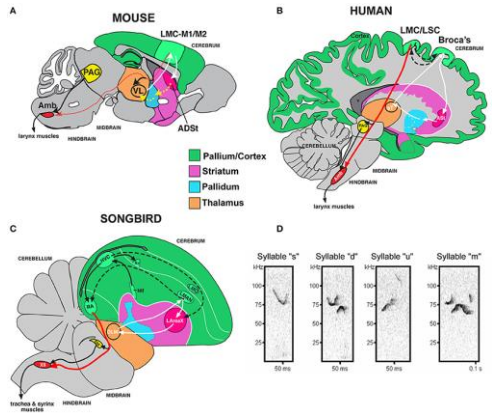
➢ <u>Affiliation and Attachment.</u>

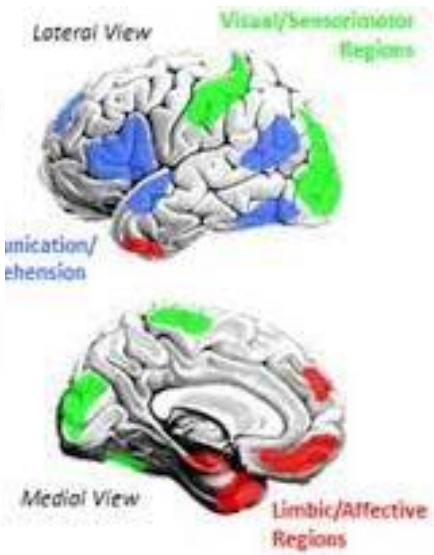
- ❑**OT is a primary regulator of social behavior**, particularly in maternal care, **and is associated with eCB signaling.**
- ❑**Genetic ablation of CB1R** negatively affected maternal care. This impairment correlated with <u>decreased hippocampal OT receptor expression and increased hippocampal levels of 2-AG</u> → consistent with observations from socially isolated animals.
- ❑**Changes in CB1R density → affect GABAergic and glutamatergic input to OT-synthesizing neurons for mobilization of OT release**, which is necessary for social interaction.

Schechter-2012, Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE







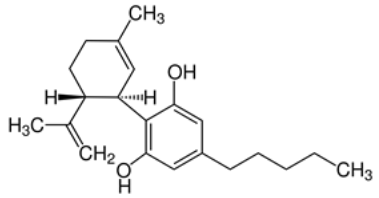
❖**eCB SIGNALING AND SOCIAL PROCESSING SYSTEMS:**

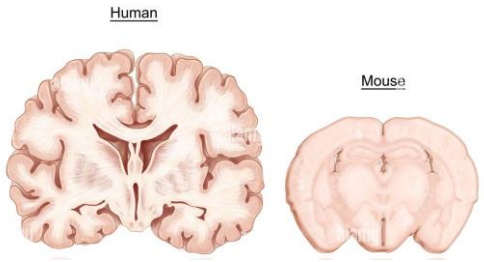
➢<u>Social Communication.</u>

- ❑In humans, <u>high concentrations of cannabinoid receptors are found in the left hemisphere</u> cortical regions that are associated with **verbal language function**, which suggests <u>a role for eCB signaling in social communication</u>.
- ❑**However, current findings only supports** a **role for eCB signaling in <u>nonverbal motor-related aspects of social communication</u>** (that is, eye-gaze or body language).
- ❑**Animal models of social communication impairments** demonstrate a **direct connection to cannabinergic function → interacts with the forkhead box (FOXP) protein family**.
- ❖**FOXP are instrumental in ultrasonic vocalizations (USVs) production and vocal learning →** in rodents, USVs serve a communicatory function to elicit social interaction or to share socially relevant information with known conspecifics. **FOXP2 !!!!!!**

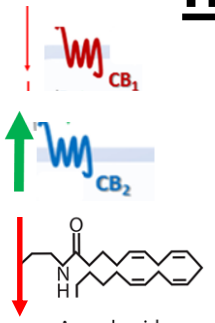
Schechter-2012, Castillo-2012, Mechoulan-2013, Wei-2015, Kahrson-2016

Role of the eCB system in ASD: focus on CBD

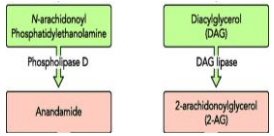




➢ **Evidence for the involvement of the eCB-S in ASD comes from both human and animal studies:**



- ❖ **Reduced CB1R expression was found in postmortem brains of ASD.**
- ❖ **Up-regulation of CB2R but not CB1R gene expression was detected in** PBMC of blood of ASD individuals compared to healthy controls.
- ❖ **Lower circulating endocannabinoid levels** (including **AEA** but not 2-AG) have been detected in children with ASD.

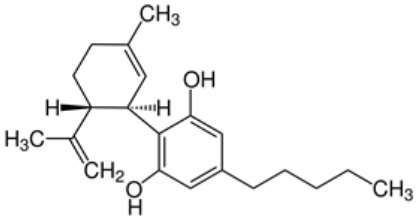


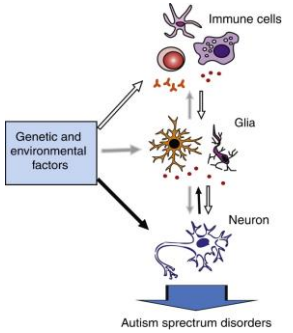
- ❖ **Heterozygous rare variants in diacylglycerol lipase α (DAGL-α),** the major enzyme involved in 2-AG biosynthesis, have been found associated with ASD.
- ❖ **ASD patients** → Lower gene expression for **NAPE-hydrolyzing phospholipase D (NAPE-PLD),** one of the enzymes responsible for the synthesis of AEA.

- ➢ **CBD has beneficial effects on the seizures and social deficits observed in a mouse model of Dravet Syndrome.**
- ➢ **CBD and CBDV improves behavioral and functional deficits in a mouse model of Rett syndrome.**
- ➢ **CBD and CBDV improves behavioral and functional deficits in an environmental rat model of ASD / prenatal exposure to VPA.**

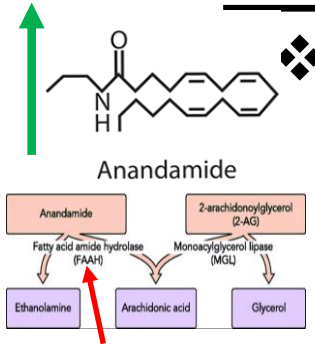
Purcel-2001, Siniscalco-2013, Aran-2019, Leweke-2012, Smith-2017, Kaplan-2017, Zamberletti-2019, Carbone-2020

Role of the eCB system in ASD: focus on CBD





➢ **Evidence for the involvement of the eCB-S in ASD comes from both human and animal studies:**

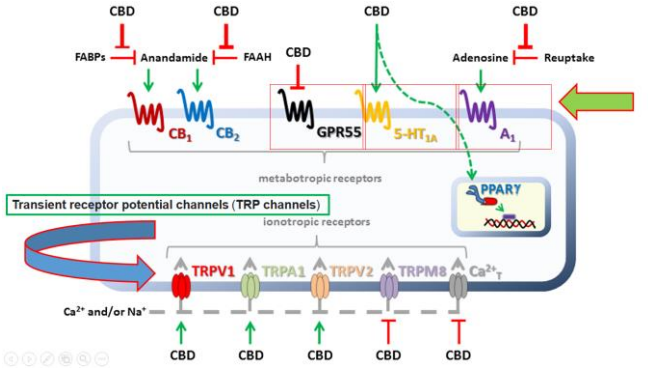


❖ **CBD increases the serum levels of AEA in schizophrenic and ASD subjects,** by inhibiting the action of the enzyme FAAH, responsible for AEA degradation → **thereby normalizing the depletion of AEA tone observed in these patients.**

❖ **Decreased AEA tone observed in ASD** → compensatory increase in CB2R and a decrease in plasma pro-inflammatory cytokines, thereby supporting the efficacy of CBD in the treatment for ASD → CBD has a great potential as anti-inflammatory agents and specific targeting of CB2R → well-defined **immunosuppressive effects without exerting psychotropic side effects.**

Purcel-2001, Siniscalco-2013, Aran-2019, Leweke-2012, Smith-2017, Kaplan-2017, Zamberletti-2019, Carbone-2020

Role of the eCB system in ASD: focus on CBD



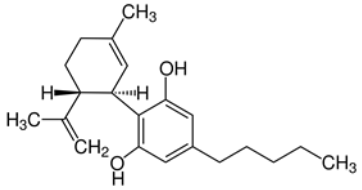
➢ **<u>The exact mechanism of action of eCB-S in ASD remains unclear:</u>**

1. <u>Not related to eCB-R</u> due to the <u>low affinity</u> of CBD for both CB1 and CB2 receptors.
2. <u>Potential regulation of both glutamatergic and GABAergic neurotransmission</u>.

3. <u>Potential modulation of other receptors</u> → including the G protein-coupled receptor GPR55, the 5-HT1a receptor, the α3 and α1 glycine receptors, and the transient receptor potential of ankyrin type 1 channel.
4. <u>CBD may also indirectly act through neuropeptides</u> such as <u>oxytocin</u> and v<u>asopressin</u> which are involved in modulating social reward.

Purcel-2001, Siniscalco-2013, Aran-2019, Leweke-2012, Smith-2017, Kaplan-2017, Zamberletti-2019, Carbone-2020

Role of the eCB system in ASD: focus on CBD

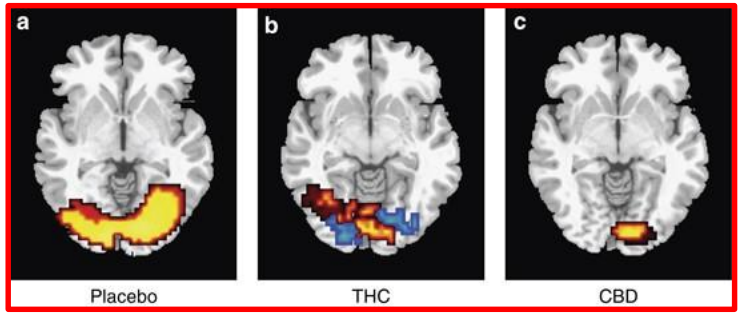


- **CBD may alleviate many conditions co-occurring with ASD**, such as seizures / epilepsy, gastrointestinal problems, anxiety and depression, ADHD, and sleep disturbances.

  This evidence leads to the hypothesis that targeting the eCB-S may contribute to normalize different behavioral patterns compromised in ASD, such as social reward responsiveness, neuronal development, circadian rhythms, and anxiety-related symptoms → even focus on ASD-core????

Purcel-2001, Siniscalco-2013, Aran-2019, Leweke-2012, Smith-2017, Kaplan-2017, Zamberletti-2019, Carbone-2020

The Impact of CBD on Human Brain Function

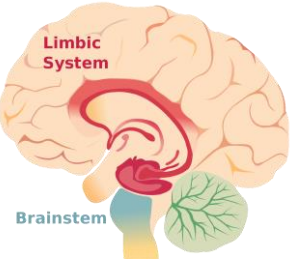


- Nearly 200 studies investigated the **acute effects of CBD on brain function during <u>resting state</u> or in the context of <u>cognitive tasks</u>**.
- **Neuroimaging studies (PET, MRI-S)** → <u>acute CBD induces significant alterations in brain activity and connectivity patterns</u> during <u>resting state and performance of cognitive tasks</u> in **<u>both healthy volunteers and patients with a psychiatric disorder</u>**.

❖ **In healthy volunteers, <u>acute CBD enhanced fronto-striatal RESTING STATE CONNECTIVITY</u>, both compared to placebo and THC.**

❖ **CBD modulated brain activity and had <u>opposite effects when compared to THC</u> following <u>TASK-SPECIFIC PATTERNS</u>** → improving <u>emotional processing</u> (fronto-temporal), <u>verbal memory</u> (fronto-striatal), <u>response inhibition</u> (fronto-limbic-striatal), and <u>auditory/visual processing</u> (temporo-occipital).

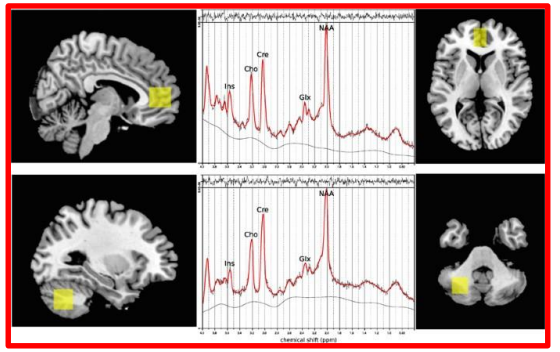
➢ **CBD modulates <u>RESTING LIMBIC ACTIVITY</u> in ASD subjects with anxiety.**



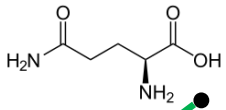
Batalla-2021

The Impact of CBD on Human Brain Function

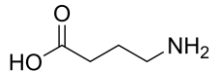
MRI-S



- Pretsch et al. (2019) investigated the acute effects of **600 mg PO CBD** on 17 patients with ASD and 17 healthy controls (17 / 17).
- **MRI-S** was used to measure glutamate and glutamine (Glx) and GABA and macromolecules (GABA+) levels in two voxels placed in the basal ganglia and dorsomedial prefrontal cortex.

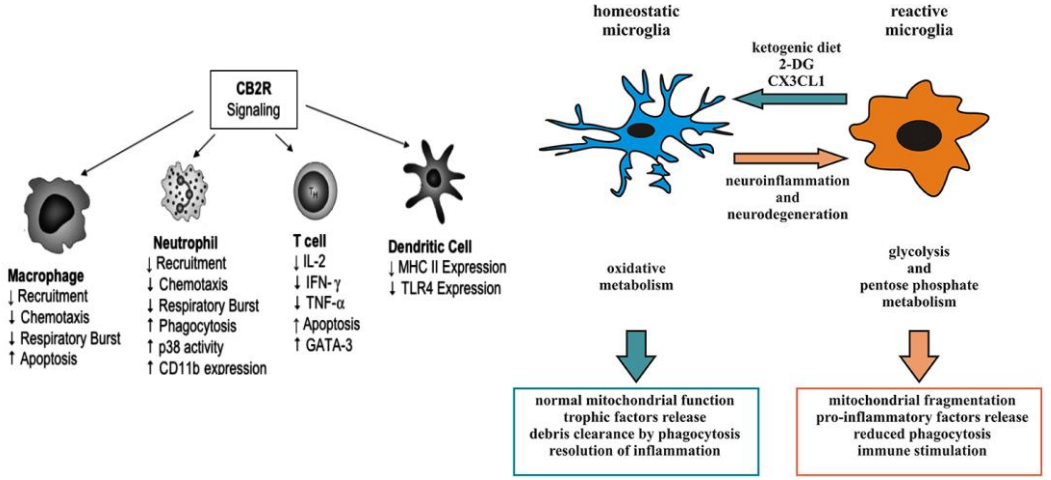


- **The effect of CBD on Glx levels** showed the **same pattern in both patients and controls:** CBD increased Glx levels relative to baseline in the *basal ganglia* and CBD decreased Glx levels in the *prefrontal cortex*.
- **Effects of CBD on GABA+ levels** showed an **opposite pattern between groups:** GABA+ levels in both the basal ganglia and prefrontal cortex increased in the control group after CBD administration but decreased in the patients with ASD.



Pretsch-2019, Batalla-2021

The eCB system as anti-inflammatory mediator



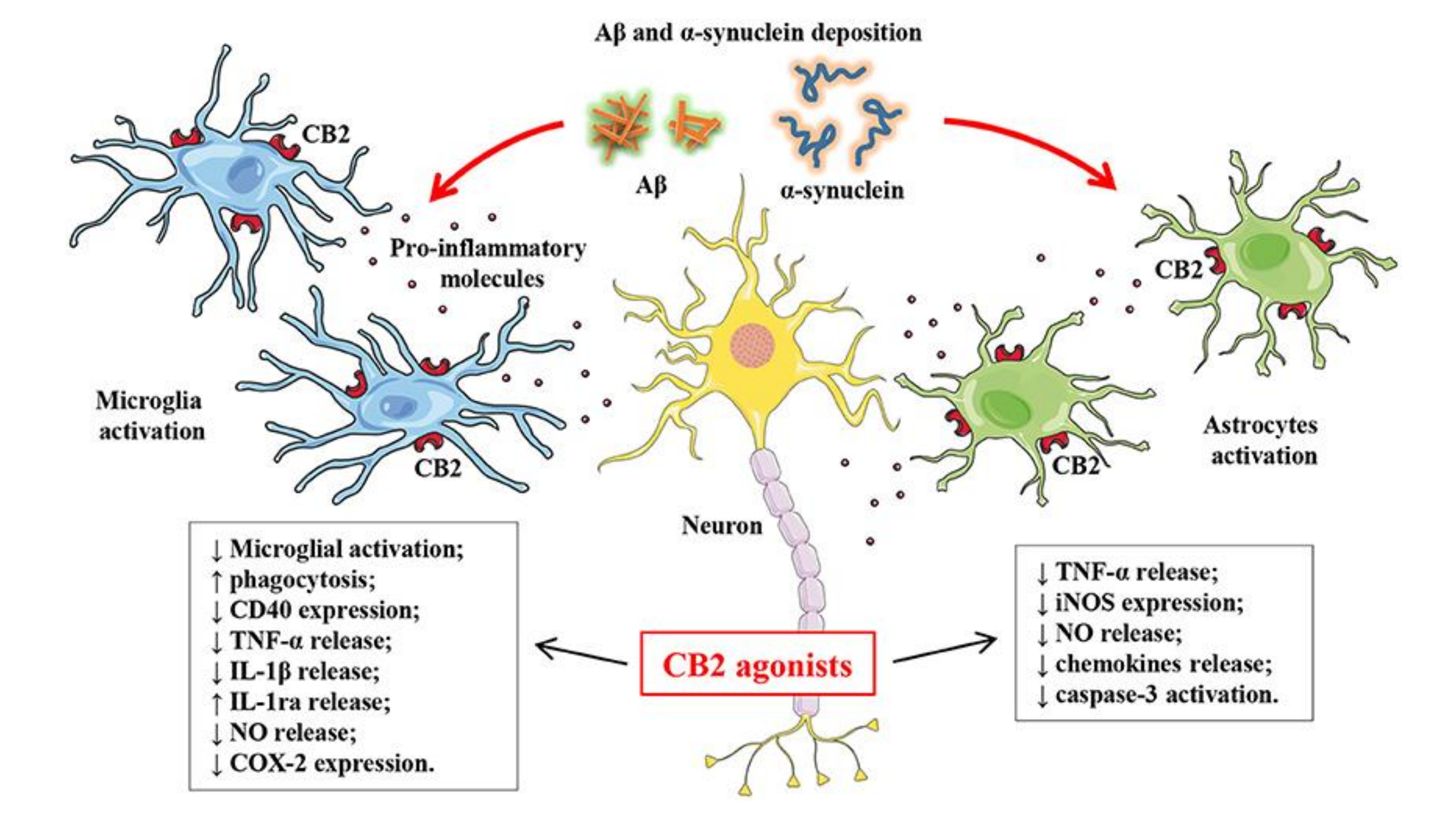
- Microglia have a complete and functional ECB system → **regulatory role of eCBS for patterns of microglial maturation, differentiation and activation.**
- CB2R are highly expressed in immune cells in the PNS and **mainly in microglia** at the CNS level, controlling immunomodulatory functions.

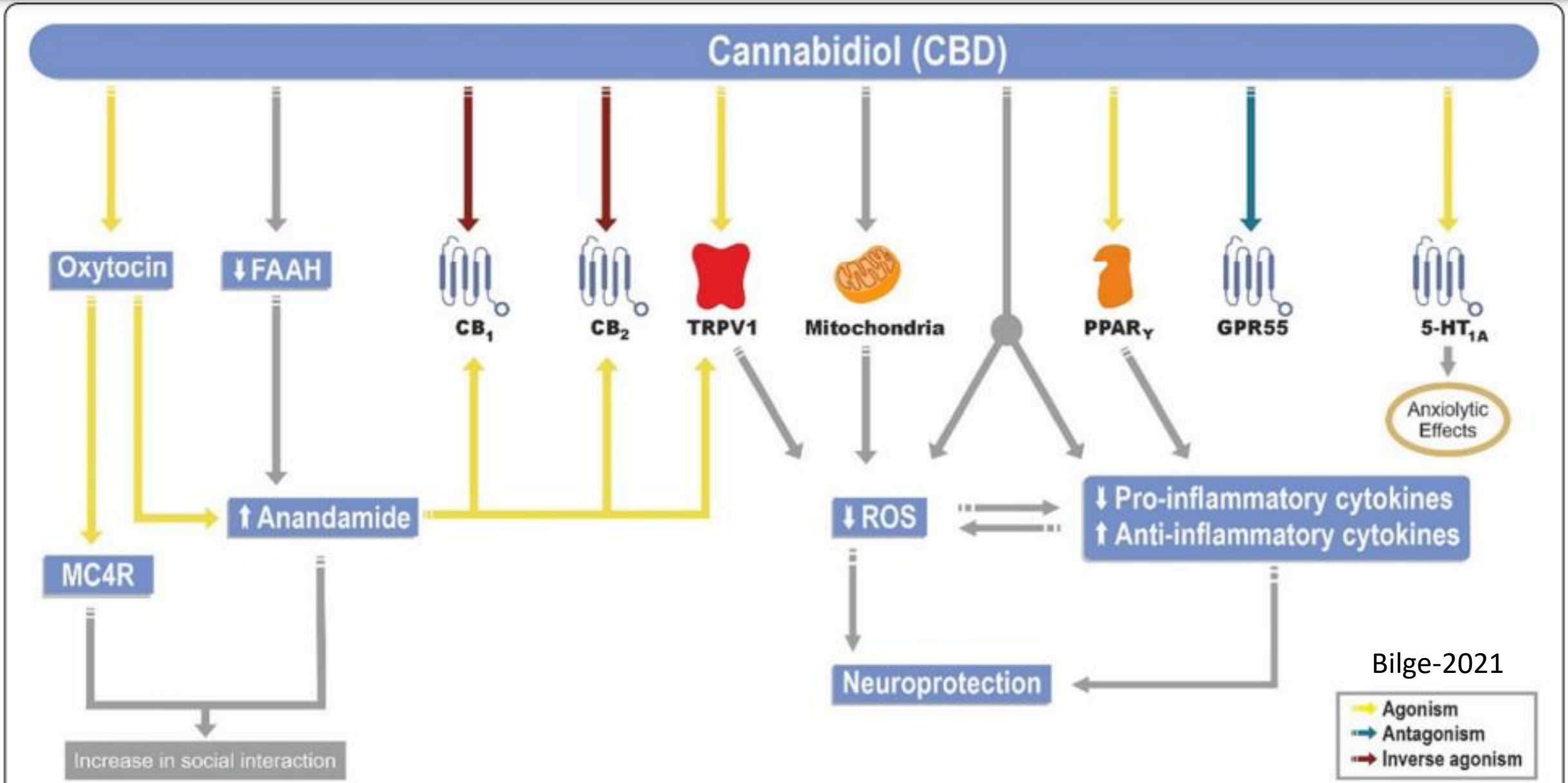
➢ **Immunomodulatory and neuroprotective effects of the eCBS on microglia.**

- **Up-regulation described in microglia alternative states aimed at restoring physiological conditions.**
- **CB2R can promote essential neuroprotective functions but……**

- **Their activation triggers some specific pathways** such as the activation of phospholipase C with subsequent calcium release, the activation of phosphatidylinositol 3-kinase (PI3K), the induction of apoptosis and suppression of cell proliferation, the increase of anti-inflammatory cytokine production and the inhibition of pro-inflammatory agents production, or the modulation of microglial cell migration → **microglia up-regulation**.

Carbone-2020, Tanaka-2020, Stella-2009


Aβ and α-synuclein deposition
Aβ
α-synuclein
CB2
Pro-inflammatory molecules
Microglia activation
CB2
CB2
CB2
Astrocytes activation
Neuron
CB2 agonists
↓ Microglial activation;
↑ phagocytosis;
↓ CD40 expression;
↓ TNF-α release;
↓ IL-1β release;
↑ IL-1ra release;
↓ NO release;
↓ COX-2 expression.
↓ TNF-α release;
↓ iNOS expression;
↓ NO release;
↓ chemokines release;
↓ caspase-3 activation.



Bilge-2021

Fig. 1 CBD and mechanism of action. CBD, cannabidiol; FAAH, fatty acid amide hydrolase CB, cannabinoid receptor; TRPV1, transient receptor potential cation channel subfamily V member 1; PPAR-γ, peroxisome proliferator-activated receptor-gamma; GPR, G protein-coupled receptor; GPR55, G protein-coupled receptor 55; 5-HT_{1A}, serotonin 5HT receptor; MC4R, melanocortin 4 receptor; ROS, reactive oxygen species

CBD and MENTAL HEALTH

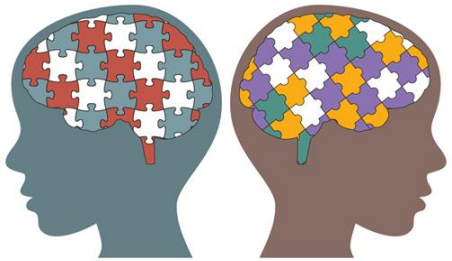
- **There is Grade B recommendation** supporting the use of CBD: for the treatment of schizophrenia, social anxiety disorder and autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD).

- **There is Grade C recommendation for** insomnia, anxiety, bipolar disorder, posttraumatic stress disorder, and Tourette syndrome.

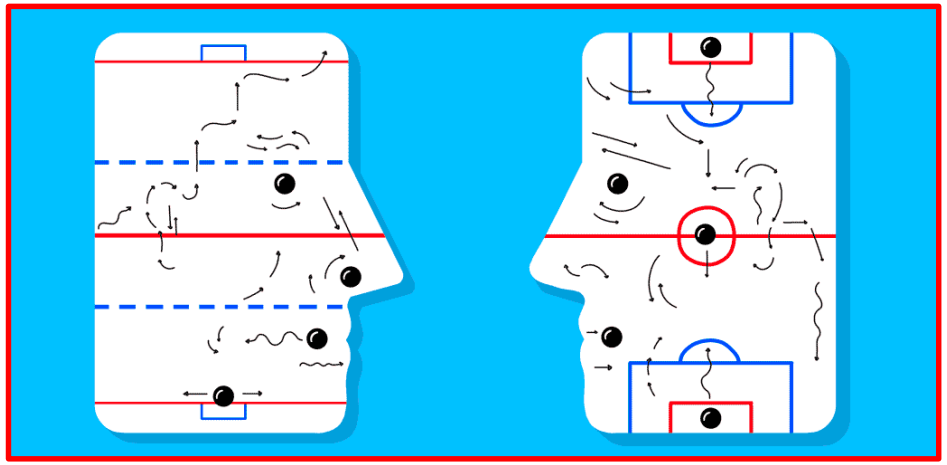
- These recommendations should be considered in the context of limited number of available studies.

Khan-2020, Poleg-2018

CBD AND ASD
Systematic Review

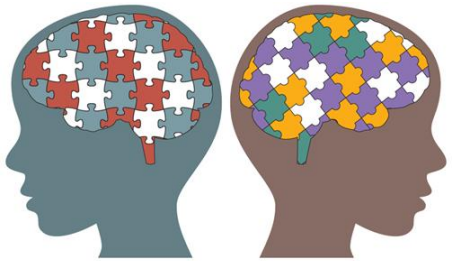


- **This systematic review sought to investigate whether cannabis-based products could bring any benefit to patients with ASD.**
- **From the nine studies evaluated, it was possible to observe that the cannabis products used were able to improve some symptoms related to ASD**:
  - Self-mutilation.
  - Anger bouts.
  - Hyperactivity.
  - Sleep problems.
  - Anxiety.
  - Depression.
  - Psychomotor agitation.
  - Restlessness.
  - Irritability.
  - Aggressiveness.
  - Sensory sensitivity.
  - Seizures.
  - Cognition, attention / social interaction / language.



Da Silva-2022, Pedrazzi-2022, Poleg-2018

Systematic Review



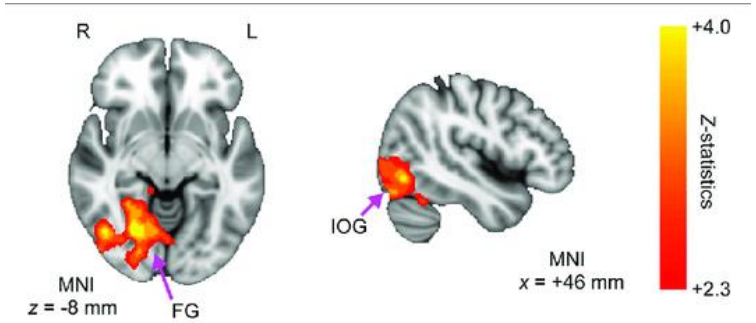
- ***<u>WHAT ABOUT SIDE EFFECTS OF CBD TREATMENT IN ASD PATIENTS??</u>***
- The use of CBD in patients with ASD showed <u>mild or moderate transient side effects</u>, such as sleep disturbances, restlessness, moderate irritability, diarrhea, increased appetite, behavioural problems, decreased cognition, fatigue, and aggression/agitation.

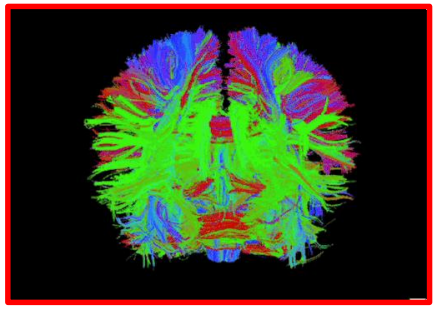
  <u>Few participants had to interrupt treatment before the end of the first month</u>, due to adverse effects such as insomnia, irritability, rapid heartbeat, and worsening of the psychobehavioral crisis.

  <u>The patients who had relevant side effects were all taking several medications, including at least one antipsychotic</u>.

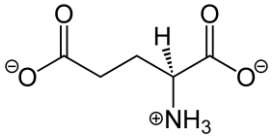
  <u>These adverse effects of CBD were not as severe as those observed with classic drugs for symptomatic treatment of ASD</u>. No hepatotoxicity linked to CBD + VPA (epilepsy).

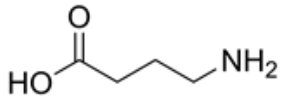
Systematic Review





- **fMRI pattern after using CBD:**
  - **A 600 mg CBD oral solution** was used in individuals with ASD who underwent fMRI to assess the effects of this treatment on their central nervous system.
  - All those studies were carried out by the same team of researchers; 17 neurotypical adults and 17 adults with autism were administered a 600 mg CBD oral solution at one occasion, and a placebo substance at another occasion (randomized order); patients were then examined using fMRI.





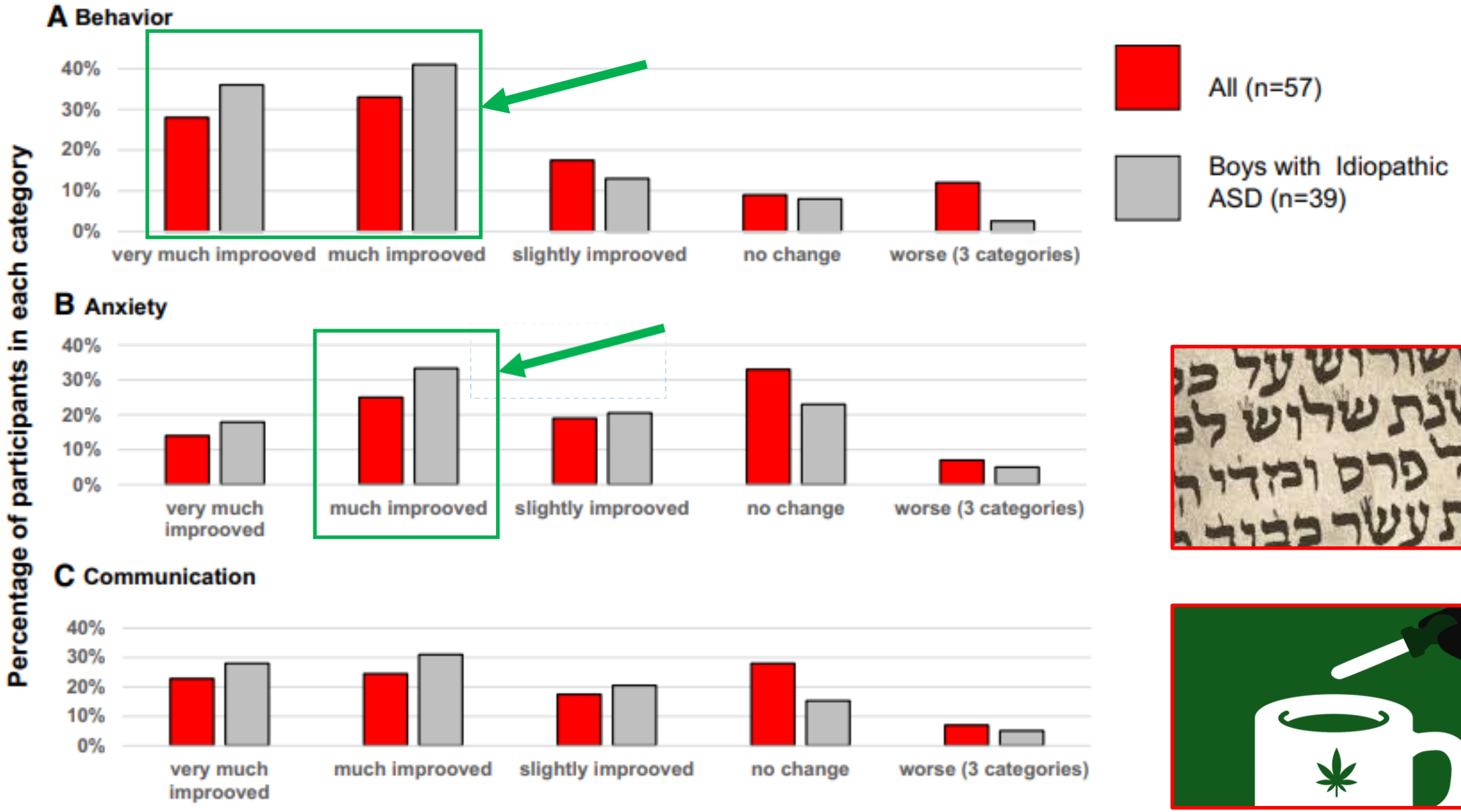
  - **The excitatory mechanisms of response to glutamate did not differ between the two groups, however the inhibitory response mediated by GABA was different in people with ASD**, indicating that the brain of an autistic individual has a distinct GABAergic system from that of neurotypical individuals.
  - **In addition, CBD was able to change the fractional low-frequency oscillation amplitude and functional connectivity in the adult brain in key regions commonly associated with the ASD condition.**

Da Silva-2022, Pretzsch-2019,

Systematic Review

- **Clinical results of using cannabis to treat ASD symptoms without MRI data:**
  - Improvements in several behavioral aspects, regardless of the substance or composition employed.
  - The problem is that the authors used different designs to measure and present the results.
  - Most of the studies evaluated in this systematic review measured the evolution of symptoms through the **perception of improvement by parents/caregivers** of symptoms secondary to ASD, using questionnaires or scales developed by the authors themselves. None of the articles mentioned the use of neuropsychological assessments to investigate cognitive aspects
  - ➢ **It was possible to observe an improvement in the following symptoms associated with ASD:** decreased bouts of self-mutilation and anger, hyperactivity, sleep problems, anxiety, restlessness, psychomotor agitation, irritability, perseverance, aggressiveness, and depression.
  - ➢ **Improvement in sensory sensitivity, cognition, attention, social interaction, and language were also reported (+/-).**

Pedrazzi-2022, Da Silva-2022, Pretzsch-2019, Khalil-2012



Aran-2018: Israel. N=60 children with ASD, 5–18 years old. All children were prescribed **whole plant extracts** that contain CBD and THC in a 20:1 ratio. Retrospective study. 7–13 months of treatment.

CBD and Core Symptoms of ASD

- **Bar-Lev Schleider-2019 → N=188 patients with ASD** who were treated with **Medical Cannabis** between 2015 and 2017 to assess the efficacy and safety of therapy. Of the 188 children, the mean age was 12.9 years. **Cannabis oil containing 30% CBD and 1.5% THC**.
  - After 6 months of treatment, 28 patients (30.1%) reported a significant behavioral improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their symptoms.

- **Aran-2021. Research group at Shaare Zedek Medical Center (Israel) → N=150 persons with ASD,** ages ranging from 5 to 21 years. The trial was a DBRPC with crossover to assess the potential therapeutic effects of cannabinoids on **behavioral problems**.
  - After 3 months of treatment, Median Social Responsiveness Scale (SRS) Total Score **improved by 14.9 on whole-plant extract** (n = 34) **versus 3.6 points after placebo** (n = 36); (p = 0.009).

Mostafavi-2020, Fusar-Poli-2020, Aran-2021, Bar-Lev Schleider-2019

CBD and Core Symptoms of ASD

- **Mostafavi-2020 → N=32 patients with ASD**, who used cannabis-based products. Retrospective analysis.
  - Overall, 20 out of 22 patients with **epilepsy (91%)** reported some improvement in seizure control. And 12 out of 20 patients treated for **aggression (60%)** reported improvement.

- **Fleury-Teixeira-2019 → N=18 patients with ASD in Brazil.** Prospective cohort study. Mean age 10,9 years. **Cannabis Sativa extract containing a 75:1 CBD: THC ratio.**
  - Communication and social interaction deficits (CSID): median perception of improvement **25%**
  - Epilepsy: three participants (16%) reported ≥50% of improvement; two participants (11%) reported 100% of improvement. **RR → 27% SF → 11%**

Mostafavi-2020, Fusar-Poli-2020, Fleury-Teixeira-2018

CBD and Core Symptoms of ASD

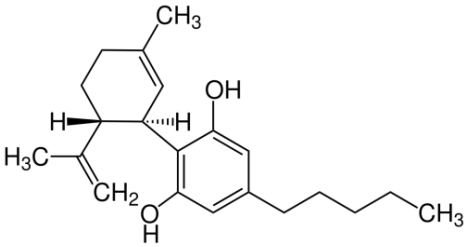
- **Bilge 2021. Turkey → N=33 children with ASD.** Followed up between January 2018 and August 2020. The mean age was 7.7 ± 5.5 years. The **average daily dosage of CBD was *0.7 mg/kg/day*** (0.3–2 mg/kg/day). The median duration of treatment was 6.5 months (3–28 months). The preparations used in this study contained **full-spectrum CBD** and trace elements tetrahydrocannabinol (THC) of less than 3%
  - A decrease in behavioral problems was reported in 10 patients (32.2%), an increase in expressive language was reported in 7 patients (22.5%), improved cognition was reported in 4 patients (12,9%), an increase in social interaction was reported in 3 patients (9.6%), and a decrease in stereotypes was reported in 1 patient (3.2%).

➢ **Dosage for CBD in ASD (review / different trials)** → the average dose of CBD was 3.8 ± 2.6 mg/kg/day. **The median ratio of CBD to THC in the used preparations is 20:1**. **Lower doses than the one we use for Epilepsy.**

Bilge-2021

CBD and ASD

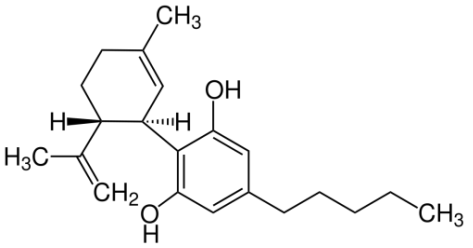
ASD



- **Animal models of both FXS and ASD** have shown benefits when treated with CBD → behavior and social interaction.
- **Studies of individuals with ASD treated with CBD** and open label trials of CBD are **reviewed by Nezgovorva et al. in 2022**; however, the **preparations studied have both CBD and variable levels of THC**, although in general, benefits were seen in irritability, sleep disorders, tantrums, and anxiety.
- **Currently, studies of cannabidavarin (CBDV)** are taking place in ASD and **CBDV has also been helpful in animal models of ASD** [Nezgovorva et al. 2022].
- Recently, the development of a **topical / transdermal CBD** that is manufactured so that there is no THC has facilitated studies in both **ASD and in FXS.**

Nezgovorva-2022, Quin-2015, Wei-2016, Patricio-2020, Aishworiya-2022, Bakas-2007, Leweke-2012, Russo-2005

CBD and ASD



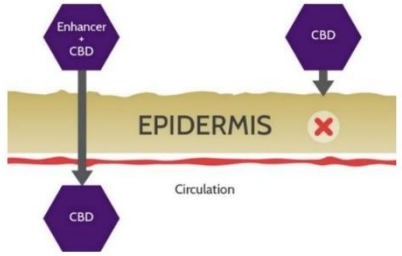
- **The BRIGHT study** was an open label study of children ages 3 to 17 years with ASD treated with an **oral preparation of CBD** lasting 14 weeks, and benefits were seen in most outcome measures including the ABC and measures of anxiety (Heussler-2021).

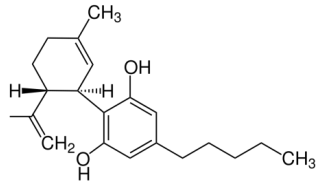
- A RCT study looking at an **oral preparation of CBD in children and young adults with ASD** demonstrated positive improvements in behavior and social communication with CBD (Aran-2021).

- Currently, a **controlled trial of a topical CBD called Zyn002** is taking place in children with ASD.

Heussler-2019, Heussler-2021, Aran-2021, Nezgovorva-2022, Aishworiya-2022

CBD and ASD





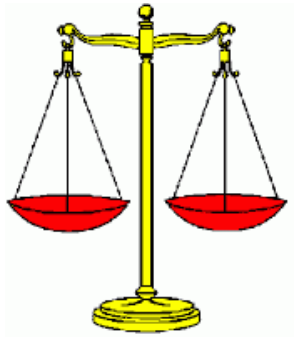
- **Heussler et al. (Heussler-2019)** carried out an **open label trial of Zyn002** in Australia for **children with FXS** of ages 3–17 years old with doses of the **transdermal CBD** at doses 250 mg bi-daily for 12 weeks (ACTRN12617000150347). Both the primary outcome, the Anxiety Mood and Depression (ADAMS) scale and the secondary measures including the ABC, demonstrated efficacy.
- **Subsequently, a multicenter controlled trial of over 200 children with FXS** was carried out and efficacy was seen in only those children with >90% methylation with FXS on the primary outcome measure of the Social Avoidance subscale of the ABCFX, a scale that has been developed for FXS modified from the ABC (Berry Kravis et al. 2022).

- Currently, the FDA has not approved Zyn002 for general use, but an additional multicenter controlled trial is now taking place to win this approval.
- It is very likely that the current controlled trials taking place for ASD and FXS will show efficacy for subgroups for both disorders, and subsequently, CBD will be more broadly utilized for this population.

Heussler-2019, Heussler-2021, Aran-2021, Nezgovorva-2022, Aishworiya-2022, Berry Kravis-2022

Autism Spectrum Disorder and Cannabidiol: Have We Seen This Movie Before?

ASD and Cannabidiol: Have We Seen This Movie Before?



- **There is a paucity of literature** supporting the clinical evidence for use of CBD in ASD.
- **CBD and similar products remain a promising yet unproven** intervention in the treatment of children with ASD.
- **Many questions remain unanswered.**
  1. Will CBD be effective in the treatment of certain target symptoms in children with ASD?
  2. Will the selection of individuals who are candidates for this treatment be an important factor?
  3. What is the most appropriate ratio of CBD to THC for the beneficial effects, if any?
  4. What happens if we only use purified-CBD alone?
- **There would still be a need for confirmation studies.**
- **We urge physicians to be familiar with the current state of the evidence**, be able to have conversations with families and patients about the level of support, and be aware of the limitations that exist if choosing to recommend CBD as a treatment for children with ASD.

Salgado-2018

Drawing My Own Conclusions

Conclusions

- **CBD interact with the eCB system** and can modulate different aspects related to cognition, socioemotional responses, susceptibility to seizures, nociception and neuronal plasticity, which are often altered in ASD.
- CBD can also change the levels of glutamate, glutamine and GABA, substances that contribute to the regulation of excitatory and inhibitory neurotransmission in ASD → **potential neuroprotective effect.**
- **CBD has very promising effects in the treatment of ASD symptoms** and can be used in the future as an important therapeutic alternative to relieve those symptoms, especially bouts of self-mutilation and anger, hyperactivity, sleep problems, epilepsy, anxiety, restlessness, psychomotor agitation, irritability, and aggressiveness; as well as improve sensory sensitivity, cognition, attention, social interaction, language, perseverance, and depression.
- **However, randomized, blind, placebo-controlled clinical trials are necessary to clarify findings on the effects of CBD in individuals with ASD.**