Sistema Endocannabinoide e Sistema Nervoso Centrale

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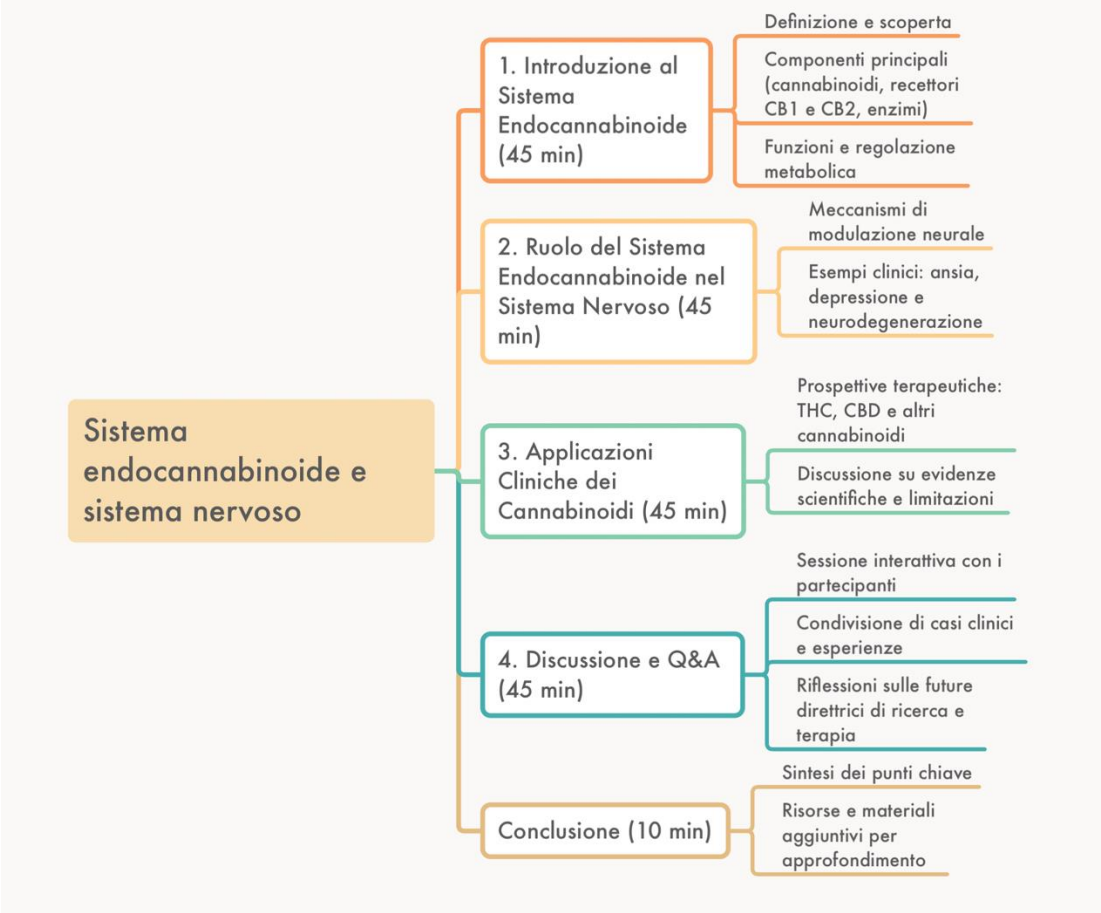
Obiettivi del Seminario

- Spiegare la struttura e la funzione del sistema endocannabinoide
- Analizzarne il ruolo nel sistema nervoso
- Discutere l’applicazione clinica dei farmaci cannabinoidi-relati nella pratica medica

Organizzazione del seminario



1. Introduzione al Sistema Endocannabinoide

Cannabinoidi: Glossario di base

Cannabis sativa: basso contenuto di THC e CBD – uso industriale

Cannabis indica: alto contenuto di THC e CDB: uso ricreazionale e terapeutico

Ibridi e cannabis geneticamente modificate per variare i contenuti dei principi attivi.

THC = tetraidrocannabinolo
CDB = cannabidiolo

Marijuana: infiorescenze essiccate
Hashish: resina estratta dalla cannabis

BREVE STORIA DELLA CANNABIS

- Periodo Neolitico (7000-5000 a.C.) Semi fossilizzati di cannabis trovati in Romania

- 2700 a.C. Cina - Il Grande Erbario dell'Imperatore Shen Neng

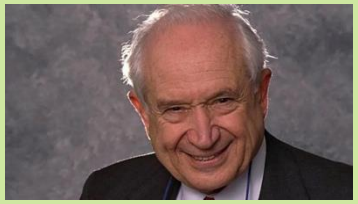
- V sec. a.C. **Erodoto -** Le Storie IV, 72-75
- […] gli Sciti prendono i semi di canapa,
- si infilano sotto la tenda fatta di coperte
- e li gettano sulle pietre roventi, i semi
- bruciati producendo fumo. […] Gli Sciti
- urlano di gioia per il fumo […]

- I sec. d.C. **Plinio il Vecchio -** Historia Naturalis Libro XX

- XIX Sec. **Jacques Joseph Moreau -** *Du Hachisch Et de L'Alienation Mentale: Etudes Psychologiques*

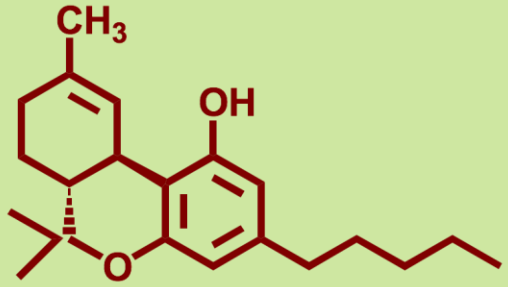
La scoperta degli (endo)cannabinoidi

HERBAL CANNABIS



Raphael Mechoulam

1964: Mechoulam and colleagues elucidate the structure of Δ^9-tetrahydrocannabinol (THC)



THC

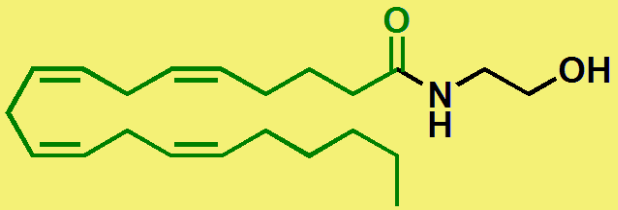
CANNABINOID RECEPTORS

1990: Matsuda and colleagues clone the **CB_1 receptor**

1992: Mechoulam's group in collaboration with Pertwee's group identifies the first endocannabinoid: *N*-arachidonoylethanolamine or **anandamide (AEA)**

Roger G. Pertwee

1993: Munro and colleagues clone the **CB_2 receptor**



AEA

ENDOCANNABINOID SYSTEM

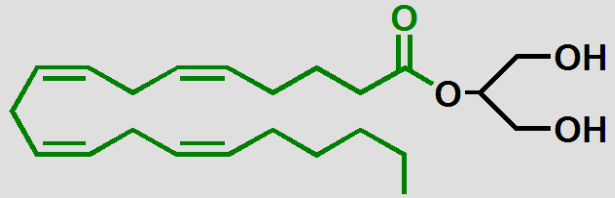
1995: Mechoulam's group and Sugiura's group identify the second endocannabinoid: 2-arachidonoylglycerol (2-AG)

1996: Cravatt and colleagues clone FAAH, the first endocannabinoid-degrading enzyme

Benjamin F. Cravatt

2003: Di Marzo and colleagues clone DAGL, the first 2-AG-biosynthesizing enzyme

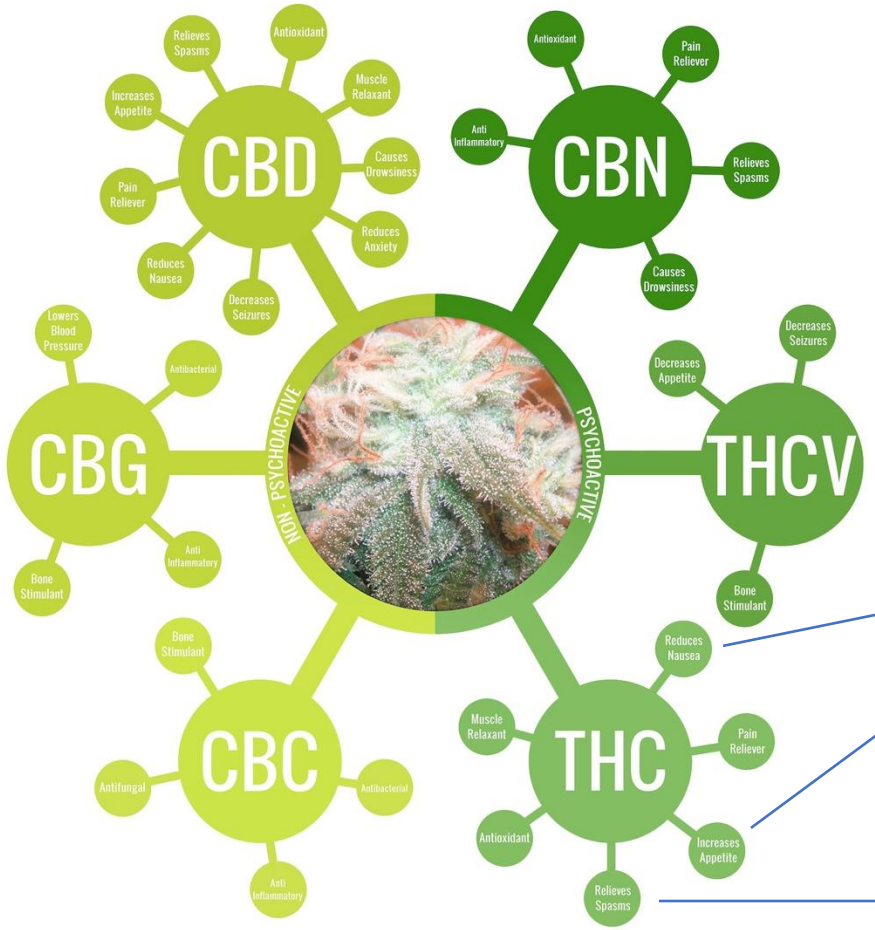
Vincenzo di Marzo

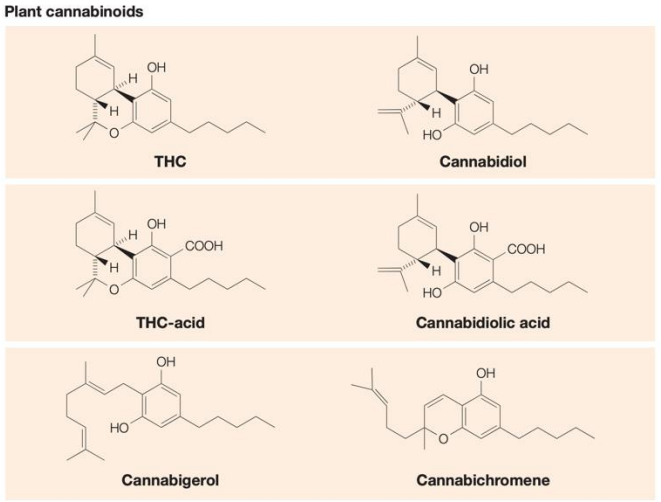


2-AG

Fitocannabinoidi

- Il **tetraidrocannabinolo** (THC), il principale principio psicoattivo estratto dalla *Cannabis indica,* è attualmente impiegato come anti-emetico, oressìgeno, anti-spasmodico in un'ampia varietà di condizioni patologiche
- Non tutti i fitocannabinoidi sono psicoattivi (p.e., il **cannabidiolo**, CBD)
- Le proprietà farmacologiche dei fitocannabinoidi devono essere ancora studiate e valorizzate (la pianta della cannabis contiene circa 150 fitocannabinoidi, oltre a 500 altri composti potenzialmente attivi da un punto di vista farmacologico)



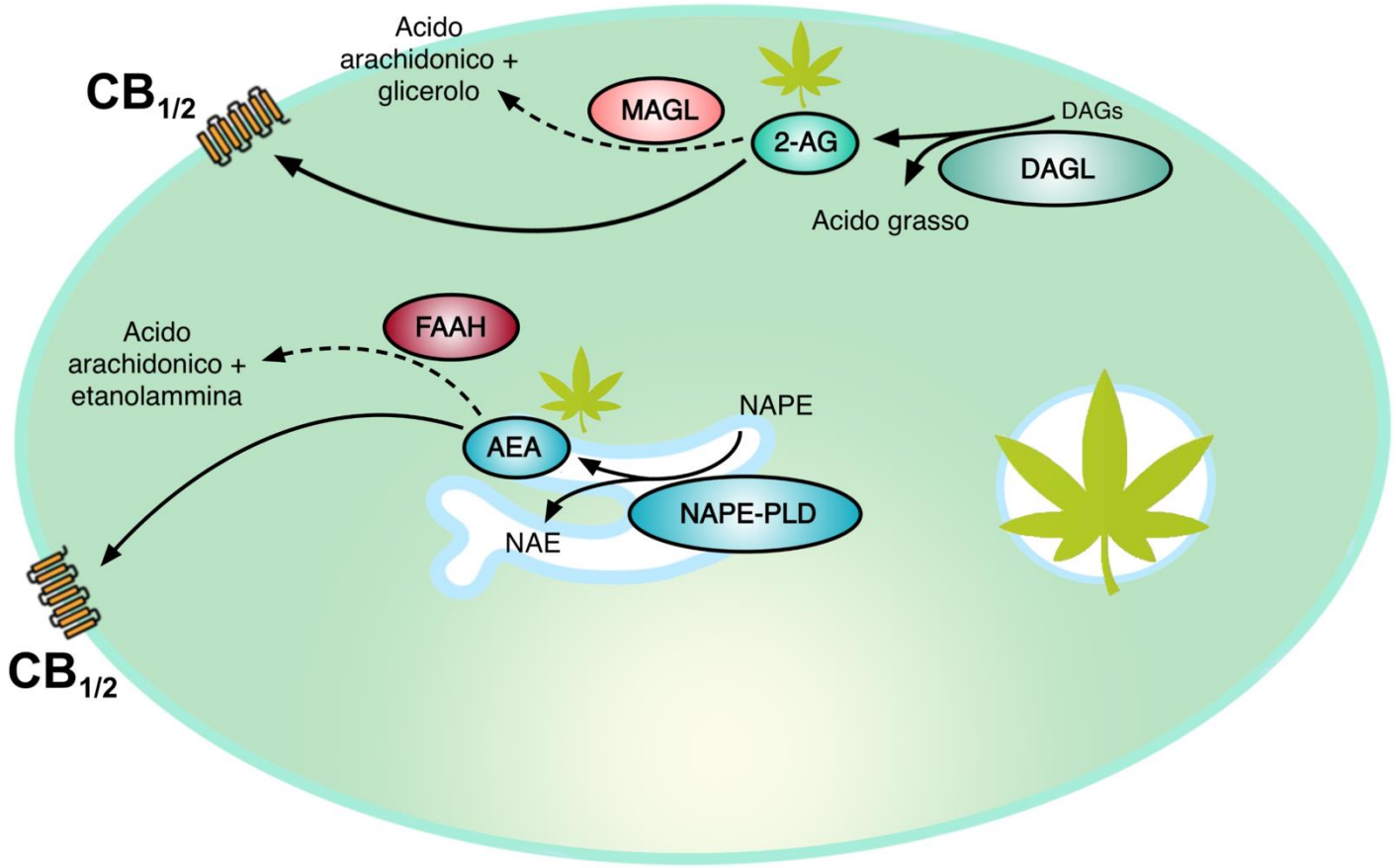


Chemoterapia
Radio-terapia
AIDS

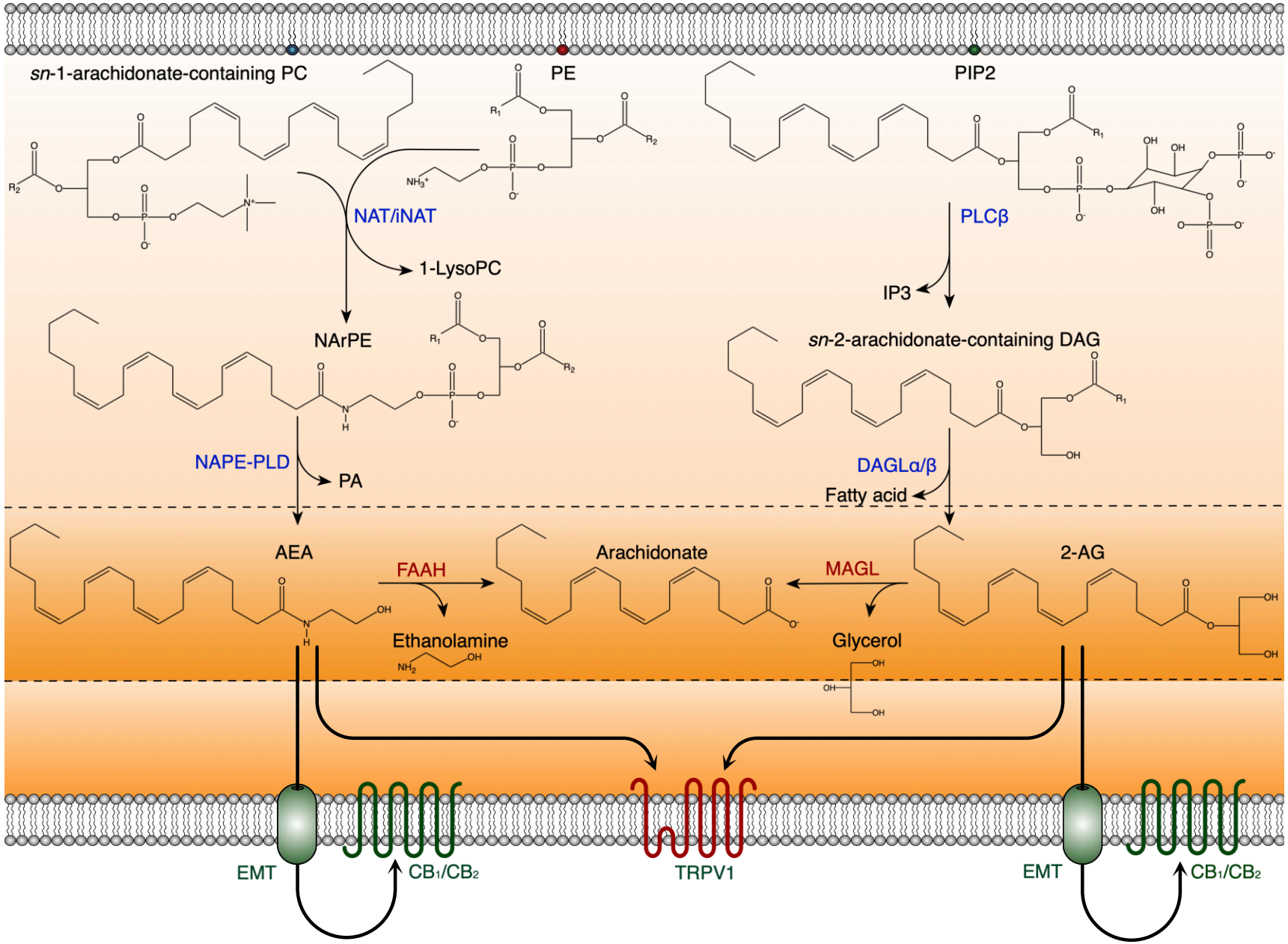
Sclerosi multipla

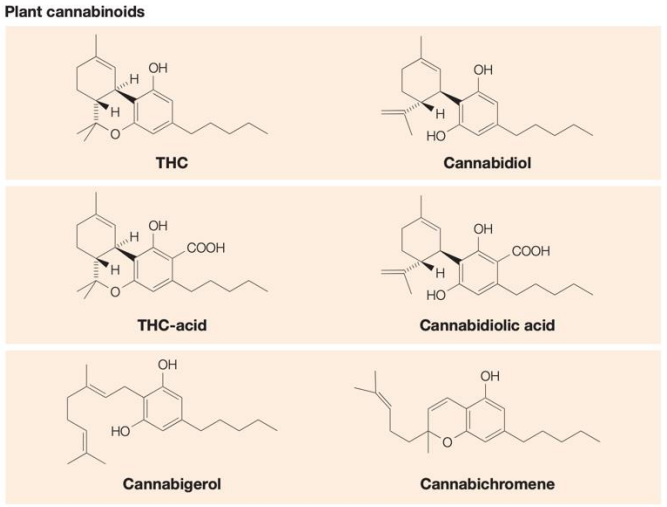
Il Sistema Endocannabinoide

- Il sistema endocannabinoide (eCB) è un sistema biochimico che si attiva nelle cellule come risposta adattativa allo stress
- Comprende un gruppo di «lipidi segnale» derivati da fosfolipidi di membrana: in particolare, *N*-arachidoniletanolamina (AEA o anandamide) e 2-arachidonilglicerolo (2-AG); che si legano ad almeno due recettori cannabici accoppiati a proteine G: CB_1 e CB_2; due principali enzimi biosintetici: NAPE-PLD e DAGL, rispettivamente per AEA e 2-AG; e due principali enzimi degradativi: acido grasso ammide idrolasi (FAAH) e monoacilglicerolo-lipasi (MAGL), rispettivamente per AEA e 2-AG

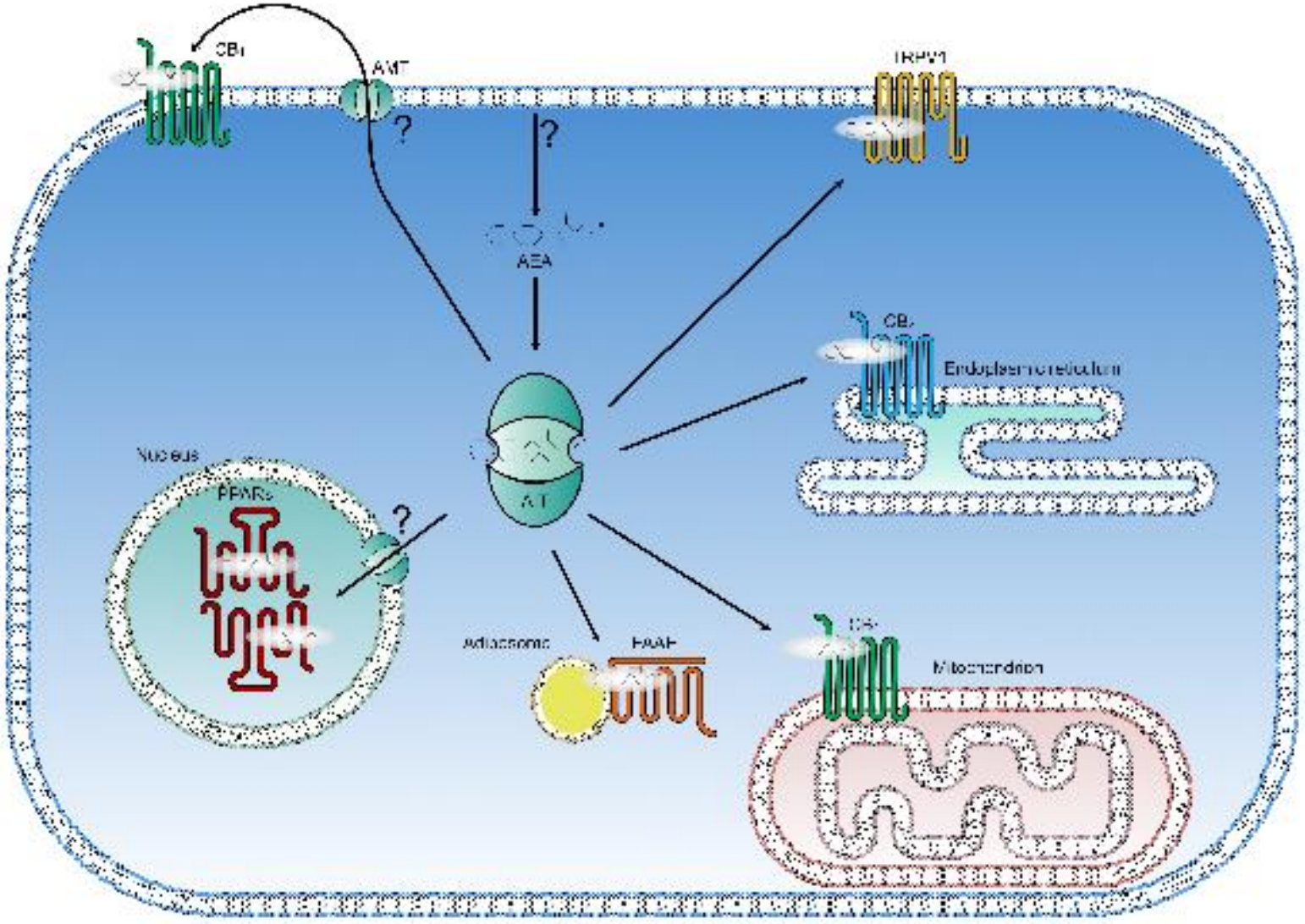


Biochimica del sistema endocannabinoide





Trasporto intracellulare dell'AEA



AITs:

Albumin

Hsp70

FABP5

AMT: ?

Fezza F et al, J Lipid Res 2008;49:1216–1223.
Oddi S et al, Cell Mol Life Sci 2008;65:840–850.
Oddi S et al, Chem Biol 2009;16:624–632.
Maccarrone M et al, Trends Biochem Sci 2010;35:601–608.

Complessità biochimica del sistema endocannabinoide

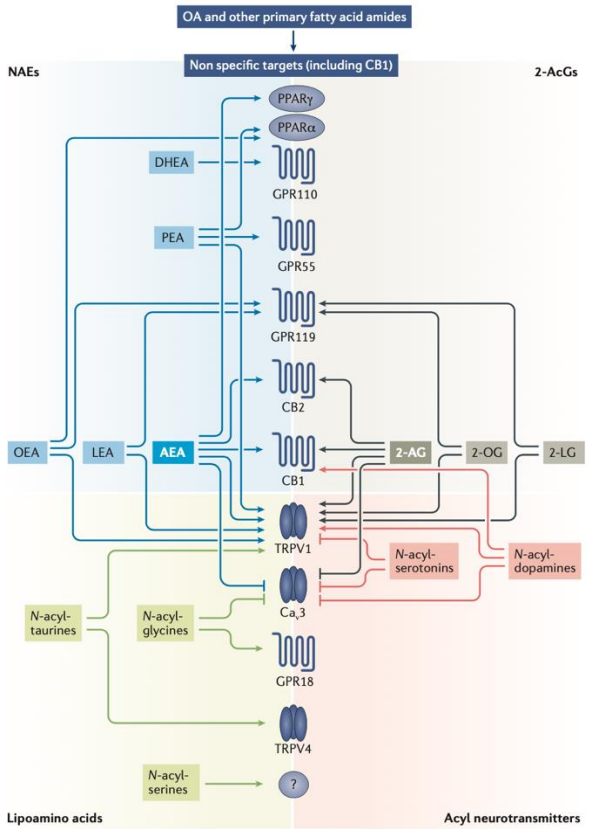


Figure 1 | **Endocannabinoidome mediators and receptors.** The main endocannabinoids, *N*-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), are part of larger families of lipids, the *N*-acylethanolamines (NAEs) and the 2-acylglycerols (2-AcGs), respectively. Numerous other members of these families signal through other G protein-coupled receptors (GPCRs), ion channels and nuclear receptors, as shown. In addition, long-chain primary fatty acid amides, lipoamino acids and acyl neurotransmitters signal through some of the receptors used by NAEs and 2-AcGs. 2-LG, 2-linoleoyl glycerol; 2-OG, 2-oleoyl glycerol; Ca_v3, T-type Ca^{2+} channel; CB, cannabinoid receptor; DHEA, *N*-docosahexaenoyl ethanolamine; GPR18, G protein-coupled receptor 18; LEA, *N*-linoleoyl ethanolamine; OA, oleamide; OEA, *N*-oleoylethanolamine; PEA, *N*-palmitoylethanolamine; PPAR, peroxisome proliferator-activated receptor; TRPV1, transient receptor potential cation channel subfamily V member 1.

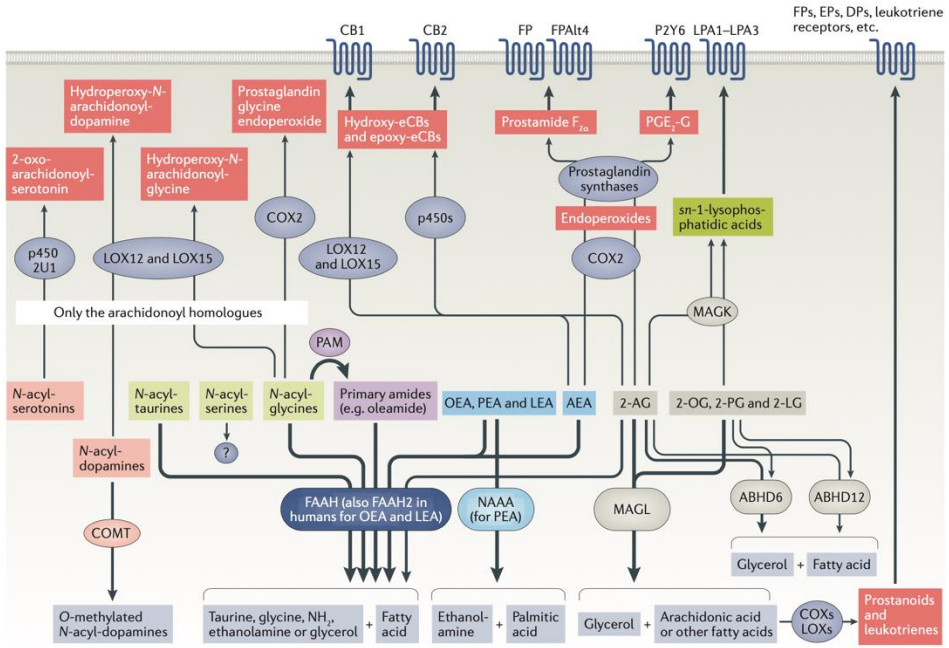


Figure 3 | **Catabolism of the endocannabinoidome mediators.** Oxidizing enzymes (indicated in medium blue) and more pathway-specific serine hydrolases are primarily responsible for the catabolism of endocannabinoidome signalling molecules. Fatty acid amide hydrolase 1 (FAAH) and monoacylglycerol lipase (MAGL) are thought to be the primary enzymes responsible for the catabolism of *N*-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) respectively. Products of oxidation (indicated in red) often signal through G protein-coupled receptors (GPCRs), as shown. The thickness of the arrows indicates the importance of the pathway in metabolite degradation. *N*-Acylethanolamines (NAEs) are shown in light blue, 2-acylglycerols (2-AcGs) are shown in grey, lipoamino acids are shown in light green, and the acyl neurotransmitters are shown in pink. FAAH (dark blue) catabolizes multiple endocannabinoidome signalling molecules. The receptor for prostamide $F_{2\alpha}$ has been suggested to be a heterodimer between the prostaglandin $F_{2\alpha}$ receptor (FP) and its splicing variant 4 (FPAlt4)[239]. Several NAEs, including AEA, as well as 2-AG have also been suggested to have non-specific intracellular carriers (not shown in the figure) such as fatty-acid-binding proteins[240] and heat shock 70 kDa protein (HSP70) (REF.[241]), which seem to be important for their inactivation. 2-LG, 2-linoleoyl glycerol; 2-OG, 2-oleoyl glycerol; 2-PG, 2-palmitoyl glycerol; ABHD, α/β-hydrolase; CB, cannabinoid receptor; COMT, catechol-*O*-methyltransferase; COX, cyclooxygenase; DPs, prostaglandin D_2 receptors; eCBs, endocannabinoids; EPs, prostaglandin E_2 receptors; LEA, *N*-linoleoyl ethanolamine; LOX, arachidonate lipoxygenase; LPA1, lysophosphatidic acid receptor 1; MAGK, monoacylglycerol kinase; NAAA, *N*-acylethanolamine-hydrolyzing acid amidase; OEA, *N*-oleoylethanolamine; P2Y6, P2Y purinoceptor 6; p450 2U1, cytochrome p450 2U1; PAM, peptidyl-glycine α-amidating monooxygenase; PEA, *N*-palmitoylethanolamine; PGE_2-G, prostaglandin E_2-glycerol.

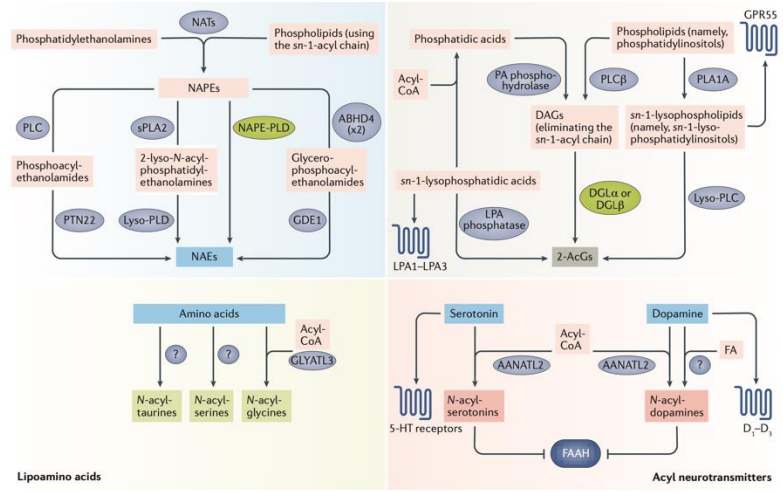
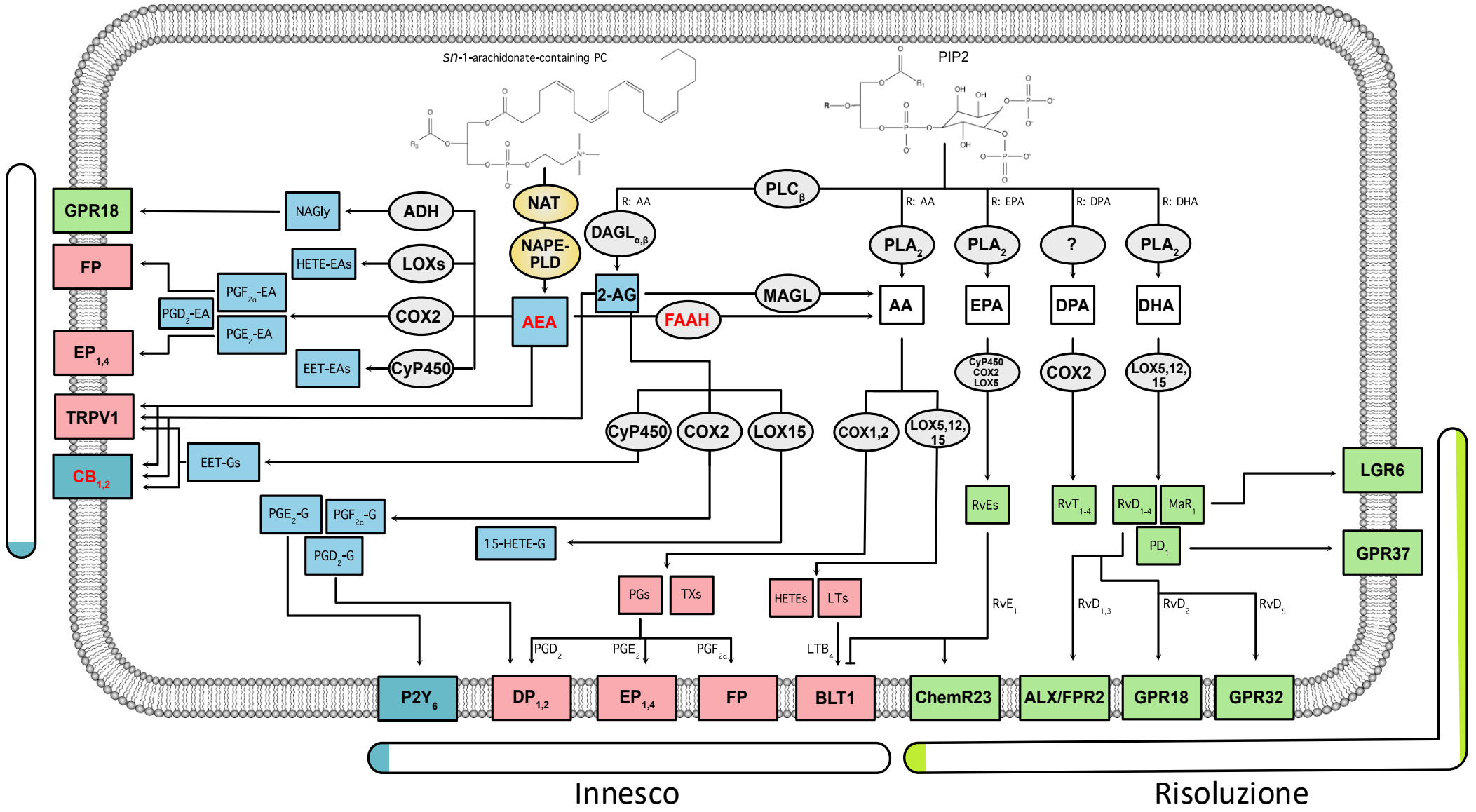


Figure 2 | **Synthesis of the endocannabinoidome mediators.** Although *N*-acyl-phosphatidylethanolamine-hydrolysing phospholipase D (NAPE-PLD) and *sn*-1-specific diacylglycerol lipase-α (DGLα) or DGLβ are considered to be the main enzymes involved in the biosynthesis of the *N*-acylethanolamines (NAEs) and 2-acylglycerols (2-AcGs), respectively, numerous other potential biosynthetic pathways exist. In addition, some of the precursors are signalling lipids themselves. Among the *sn*-1-lysophospholipids, only lysophosphatidylinositols have been shown to activate G protein-coupled receptor 55 (GPR55)[10]. Limited knowledge is available regarding the biosynthesis of *N*-acyl neurotransmitters, and this has only been studied in *Drosophila melanogaster*, in which the corresponding neurotransmitters play important roles. Similarly, little is known about the biosynthesis of lipoamino acids, except for *N*-acyl-glycines, for which the anabolic processes and their role as biosynthetic precursors of primary amides are well understood. 5-HT, 5-hydroxytryptamine; AANATL2, arylalkylamine *N*-acyltransferase-like 2, isoform A; ABHD4, α/β-hydrolase 4; D_1, dopamine receptor 1; DAGs, diacylglycerols; DHEA, *N*-docosahexaenoyl ethanolamine; FA, fatty acid; FAAH, fatty acid amide hydrolase 1; GDE1, glycerophosphodiester phosphodiesterase 1; GLYATL3, glycine *N*-acyltransferase-like protein 3; LPA, lysophosphatidic acid; LPA1, LPA receptor 1; NAPEs, *N*-acyl-phosphatidylethanolamines; NATs, *N*-acyltransferases (including phospholipase A2 group IVE and phospholipase A/acyltransferase 1); PA, phosphatidic acid; PLA1A, phospholipase A1 member A; PLC, phospholipase C; PTPN22, tyrosine-protein phosphatase non-receptor type 22; sPLA2, soluble phospholipase A2.

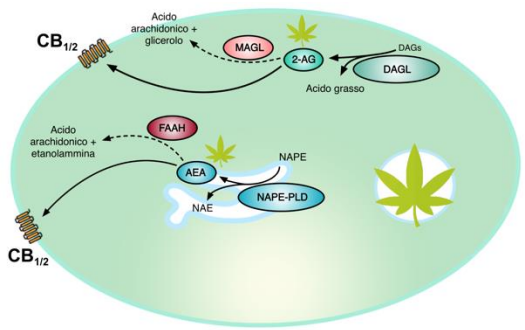
Lipidi bioattivi e infiammazione

Modulazione?

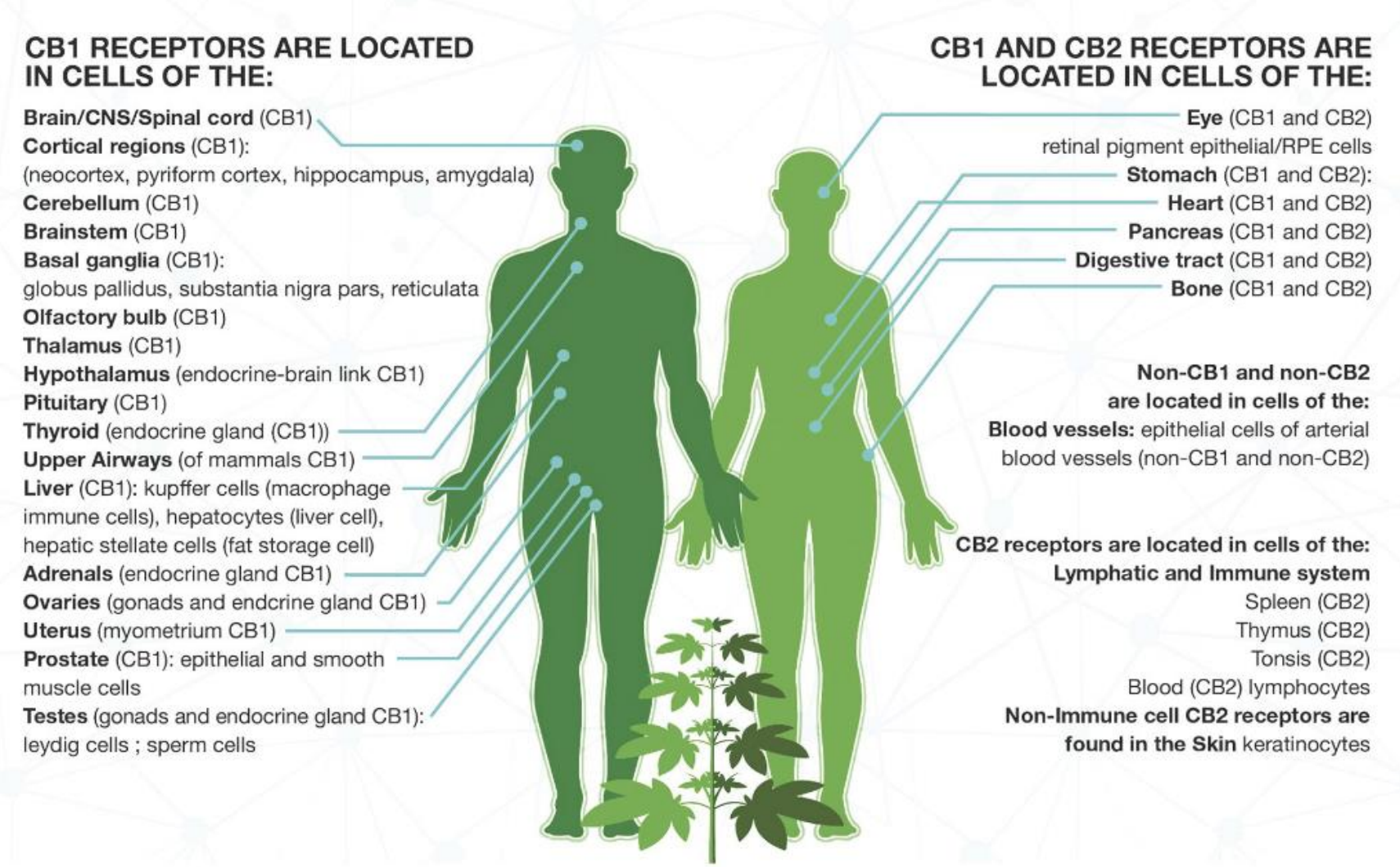


Leuti A et al, *FASEB Journal.* **2024;** 38(10):e23675. doi: 10.1096/fj.202301325R

Complessità di segnaletica



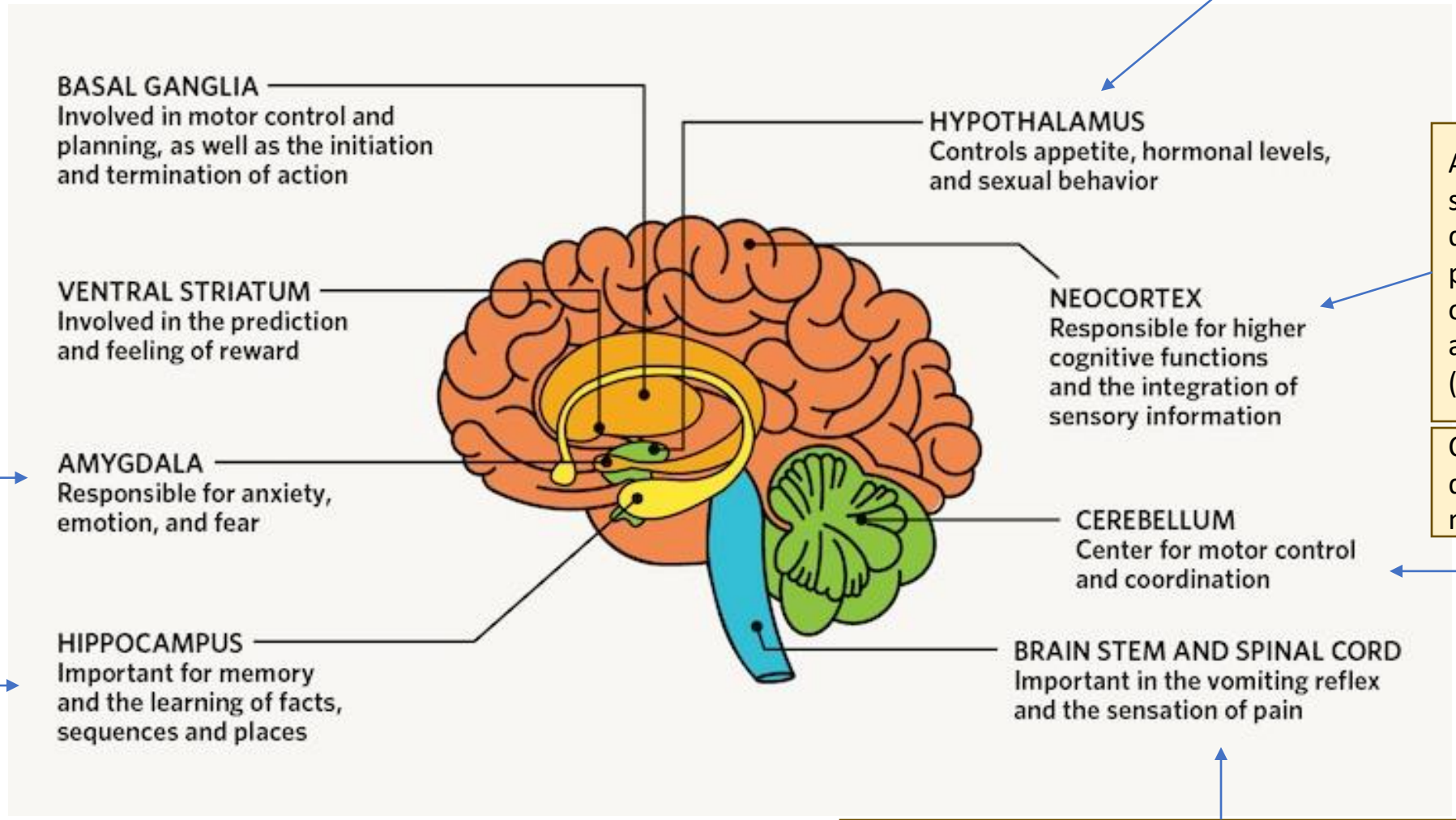
Distribuzione del Sistema Endocannabinoide



- **Il sistema eCB è ubiquitariamente distribuito nel corpo, con i recettori CB_1 prevalentemente espressi nel cervello (effetti psicotropici del THC) e i recettori CB_2 presenti in periferia e soprattutto nel sistema immunitario (effetti immunosoppressivi del THC)**

Effetti del consumo di cannabis sul cervello umano
Ruolo del recettore CB1

Aumento appetito (a. oressigenica)



Aumento o riduzione di ansia/panico (a. ansiogenica/ansiolitica)

Alterazione degli stati di coscienza, distorsioni percettive, occasionali deliri e allucinazioni (psicosi)

Compromissione della coordinazione motoria

Compromissione della formazione e del consolidamento della memoria

Riduzione di vomito o nausea (a. antiemetica), riduzione del dolore (a. antinocicettiva, analgesica), aumento della frequenza del battito cardiaco (a. cronotropica positiva), diminuzione della pressione sanguigna (a. ipotensiva)

Architettura Molecolare del Sistema Endocannabinoide nella Sinapsi Chimica

Produzione degli Endocannabinoidi (eCB):

- Sintetizzati nei terminali **post-sinaptici (2-AG) o pre-sinaptici (AEA)** in risposta all'attivazione neuronale.
- **AEA** e **2-AG** derivano da precursori di membrana tramite specifiche enzimi (NAPE-PLD e DAGLα/β). Si noti che l'azione **retrograda** è quella del 2-AG, mentre l'AEA sembra agire in modo anterogrado

Meccanismo di Azione:

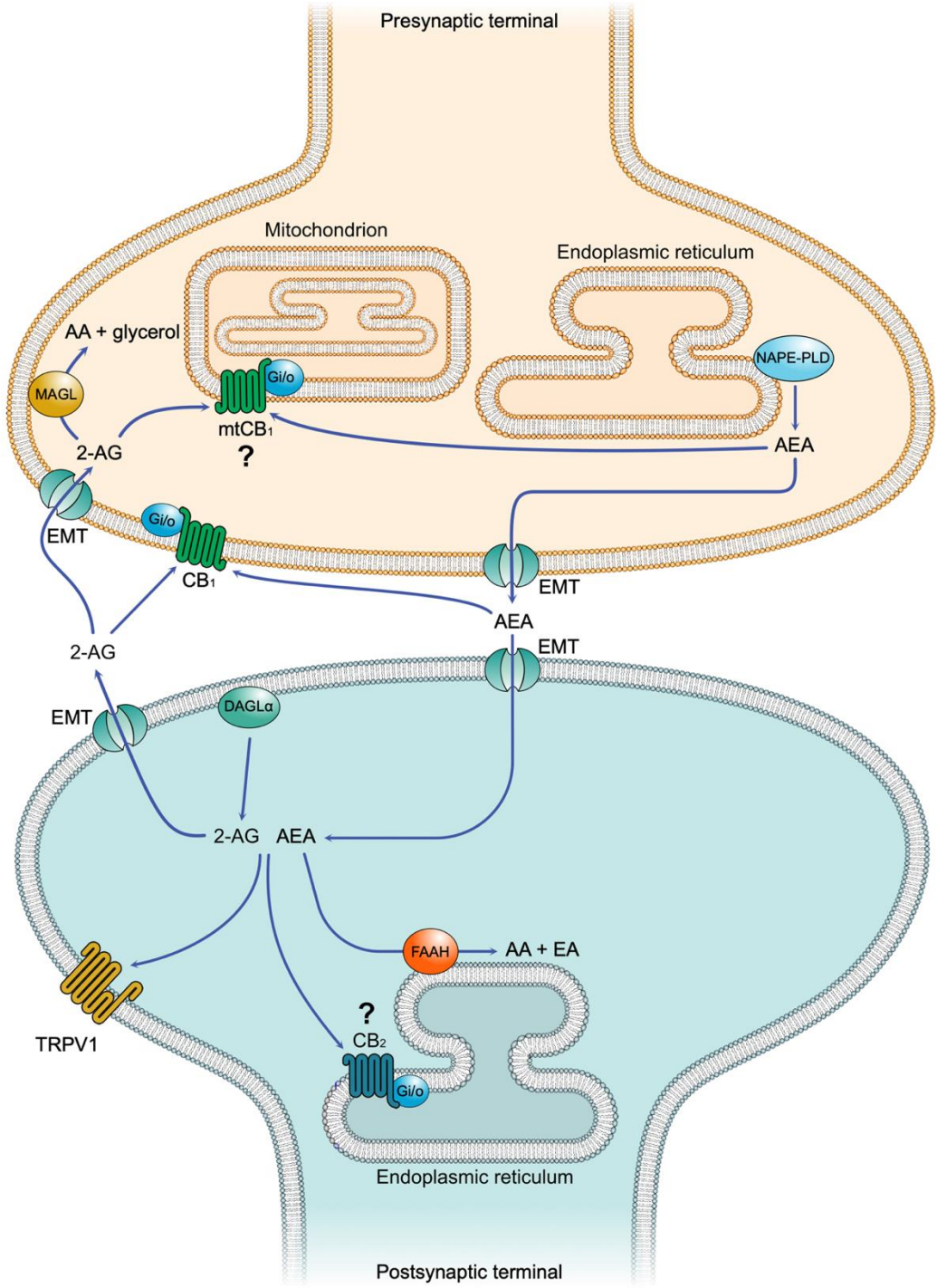
- Attraversano la membrana (forse tramite un trasportatore EMT).
- Il 2-AG viaggia **retrogradamente** per attivare i recettori CB1 nei **terminali presinaptici**, inibendo il rilascio di neurotrasmettitori.
- I recettori CB1 mitocondriali (mtCB1) regolano ulteriormente la neuromodulazione.

Azione Autocrina e Regolazione Sinaptica:

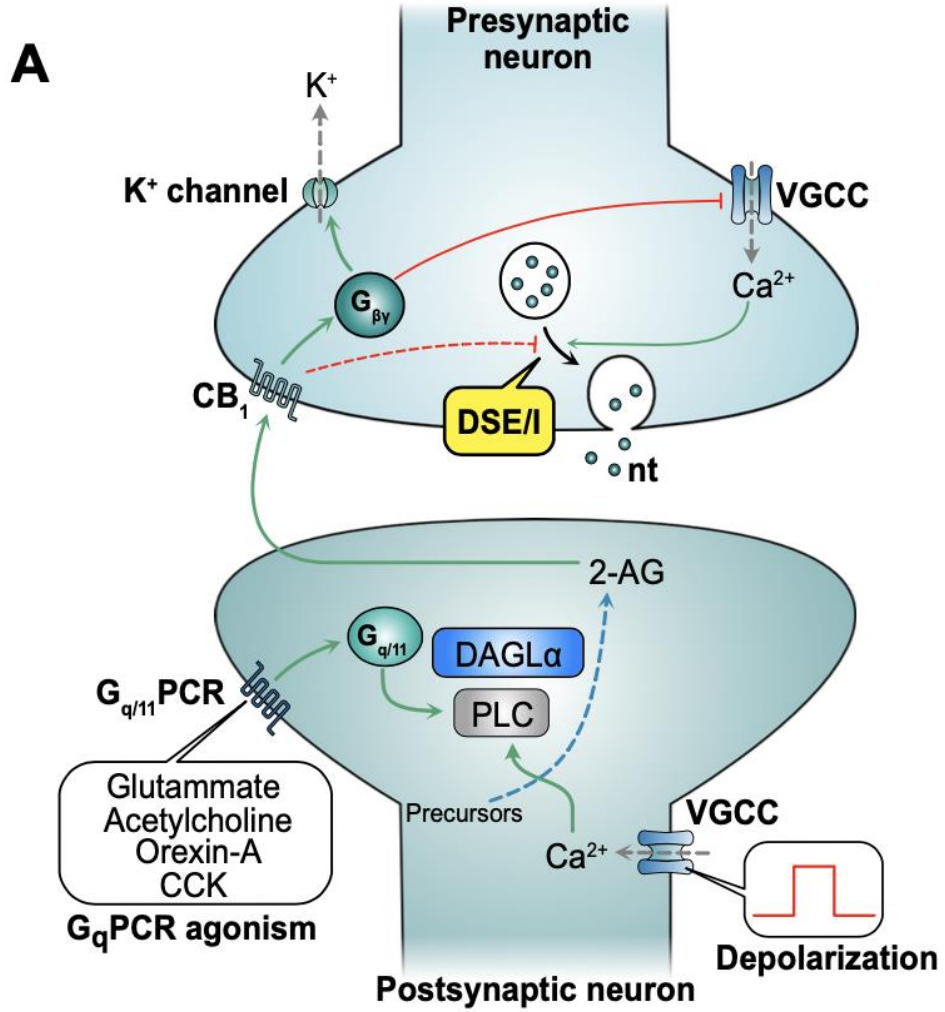
- Gli eCB possono anche attivare recettori **postsinaptici**, come **TRPV1** e **CB2**, modulando la trasmissione sinaptica.

Degradazione degli eCB:

- **MAGL** degrada **2-AG** nel terminale **presinaptico**.
- **FAAH** degrada **AEA** nel terminale **postsinaptico**.
- La distribuzione di questi enzimi conferma una possibile funzione **anterograda** per l'AEA.



Neuromodulazione Endocannabinoide-mediata



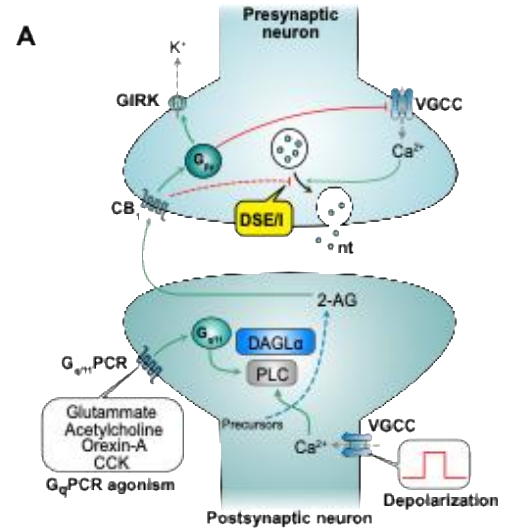
All'interno del cervello, gli eCB agiscono come **neuromodulatori** coinvolti in modo cruciale nella comunicazione neuronale, regolando l'efficacia e la **plasticità sinaptica**. A seconda del tipo e della localizzazione del recettore coinvolto, questi messaggeri innescano una varietà di meccanismi pre- o post-sinaptici in grado di modificare la trasmissione sinaptica sia a livello delle sinapsi eccitatorie che di quelle inibitorie, normalmente **attenuandole** su tempi che possono essere transitori (su scala di secondi) o di lunga durata (su scala di minuti o più).

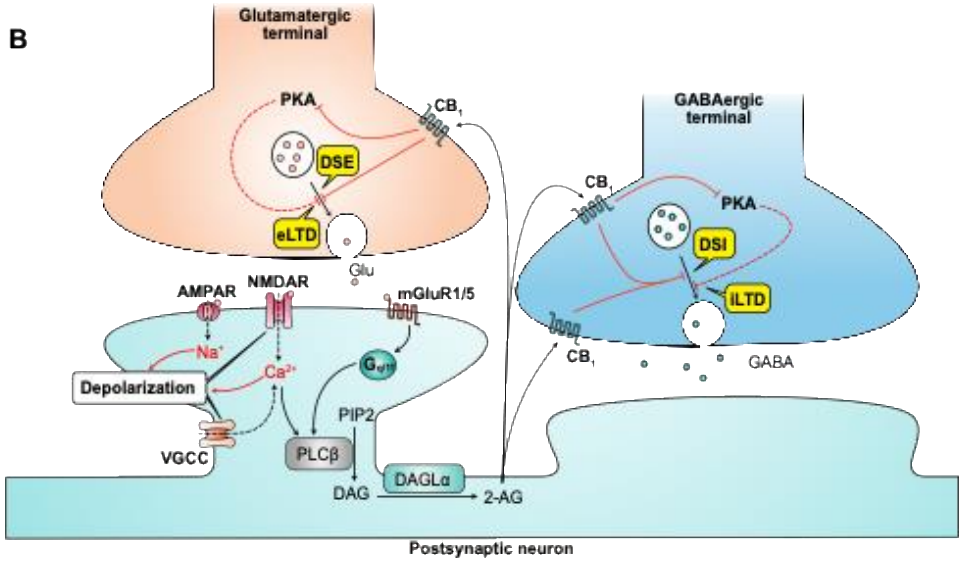
Una volta prodotti a livello postsinaptico (2-AG), in risposta a una breve **depolarizzazione** della membrana neuronale, all'innalzamento del Ca2+ intracellulare e/o all'attivazione di alcuni recettori metabotropici accoppiati a Gq/11, gli eCB attraversano la fessura sinaptica e attivano i recettori CB1 presinaptici per sopprimere il rilascio di neurotrasmettitori inibitori o eccitatori (ad esempio, GABA o glutammato). Questo tipo di attività viene definita "**segnalazione retrograda**", poiché il segnale viaggia in direzione retrograda, dal neurone postsinaptico a quello presinaptico.

DSE/DSI: Depolarization-stimulated Suppression of Excitation/Inhibition

Depressione Sinaptica a Breve Termine (DSE/DSI) tramite Segnalazione Retrograda

- Attivazione di **recettori metabotropici Gq/11** o **canali Ca2+** postsinaptici → produzione di **2-AG**.
- Gli **eCBs attraversano retrogradamente** la fessura sinaptica e attivano **CB1 presinaptico**, modulando:
  - **Canali GIRK** (attivati, favorendo iperpolarizzazione).
  - **Canali VGCC** (inibiti, riducendo il rilascio di neurotrasmettitori).
- A seconda del neurotrasmettitore inibito:
  - **DSE** (soppressione depolarizzazione-dipendente dell'eccitazione glutamatergica).
  - **DSI** (soppressione depolarizzazione-dipendente dell'inibizione GABAergica).

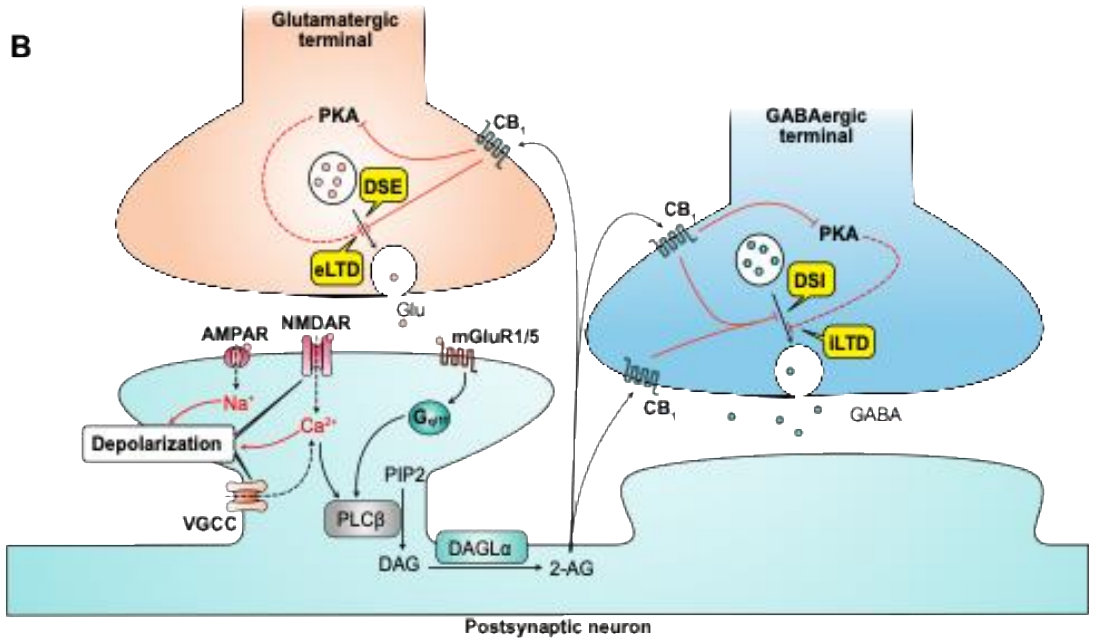


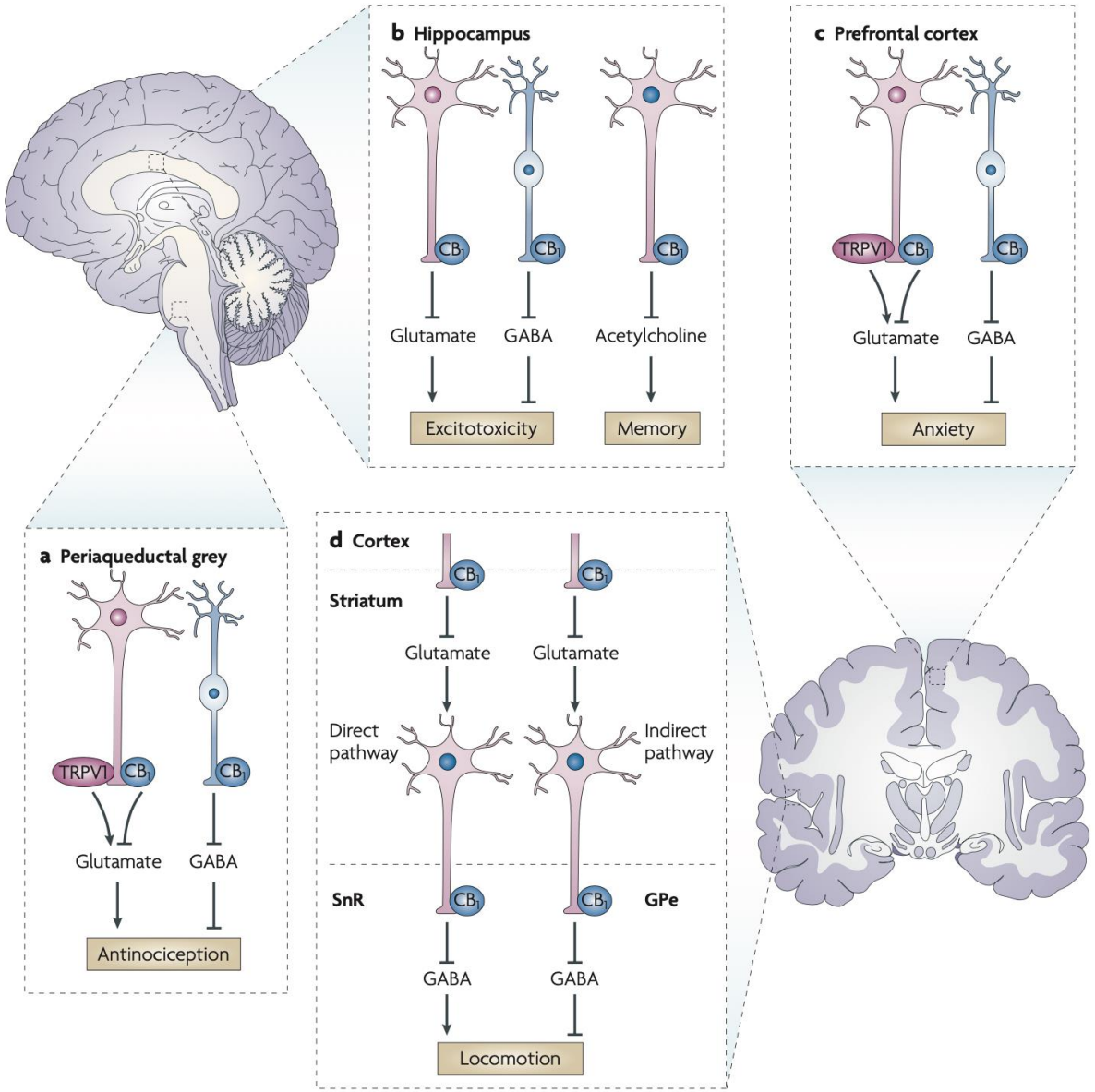


GIRK: canali del potassio attivati da proteine G (**canali** del **potassio rettificanti** verso l'**interno** attivati dalla **proteina G**)
VGCC: Canali del calcio voltaggio-dipendenti

Depressione della trasmissione sinaptica (eccitatoria o inibitoria) a lungo termine (LTD)

eCB-LTD coinvolge l'inibizione della trasmissione sinaptica via **cAMP/PKA**, essenziale per la plasticità a lungo termine sia nelle sinapsi eccitatorie (eLTD) che in quelle inibitorie (iLTD).

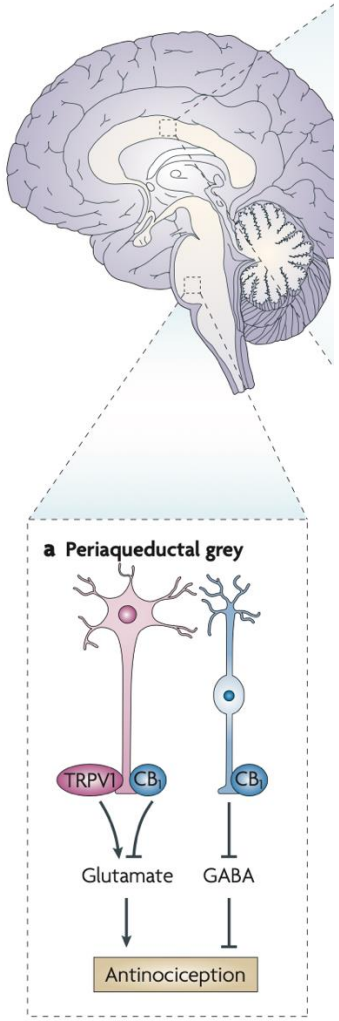




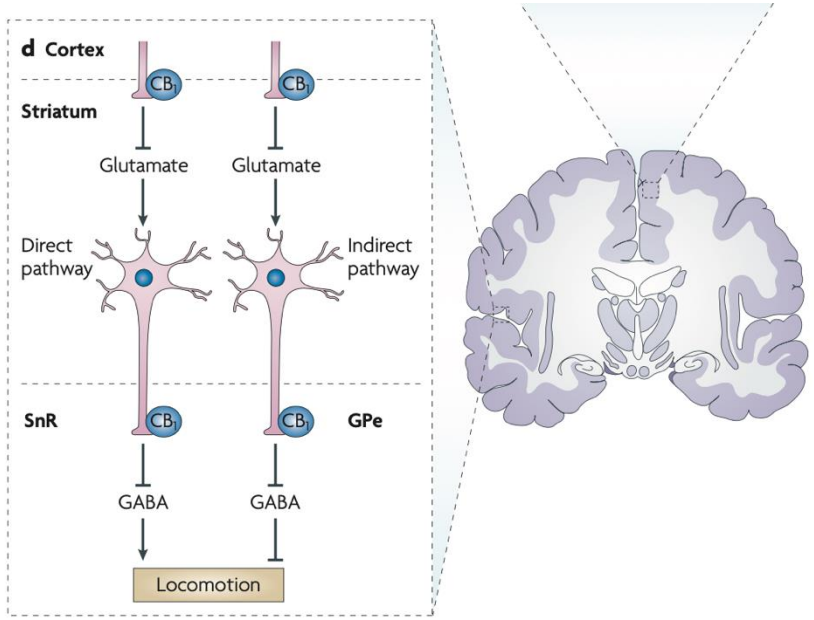
Regolazione retrograda della neurotrasmissione
Gli eCB inibiscono il rilascio di neurotrasmettitori (glutammato, GABA, acetilcolina). Questo meccanismo di feedback contribuisce a mantenere l'equilibrio tra eccitazione e inibizione neuronale.

Protezione da eccitotossicità
Nel contesto dell'ippocampo, l'attivazione dei recettori CB1 può ridurre il rilascio di glutammato e limitare il danno da **eccitotossicità**. Un corretto funzionamento degli eCB in quest'area è inoltre cruciale per i processi di memoria e apprendimento.

Modulazione dell'ansia (corteccia prefrontale)
Nel corteccia prefrontale, gli eCB possono regolare l'equilibrio tra neurotrasmettitori eccitatori e inibitori, contribuendo a modulare risposte di tipo ansioso. Alterazioni di questo sistema possono favorire condizioni di iperattivazione e ansia patologica.



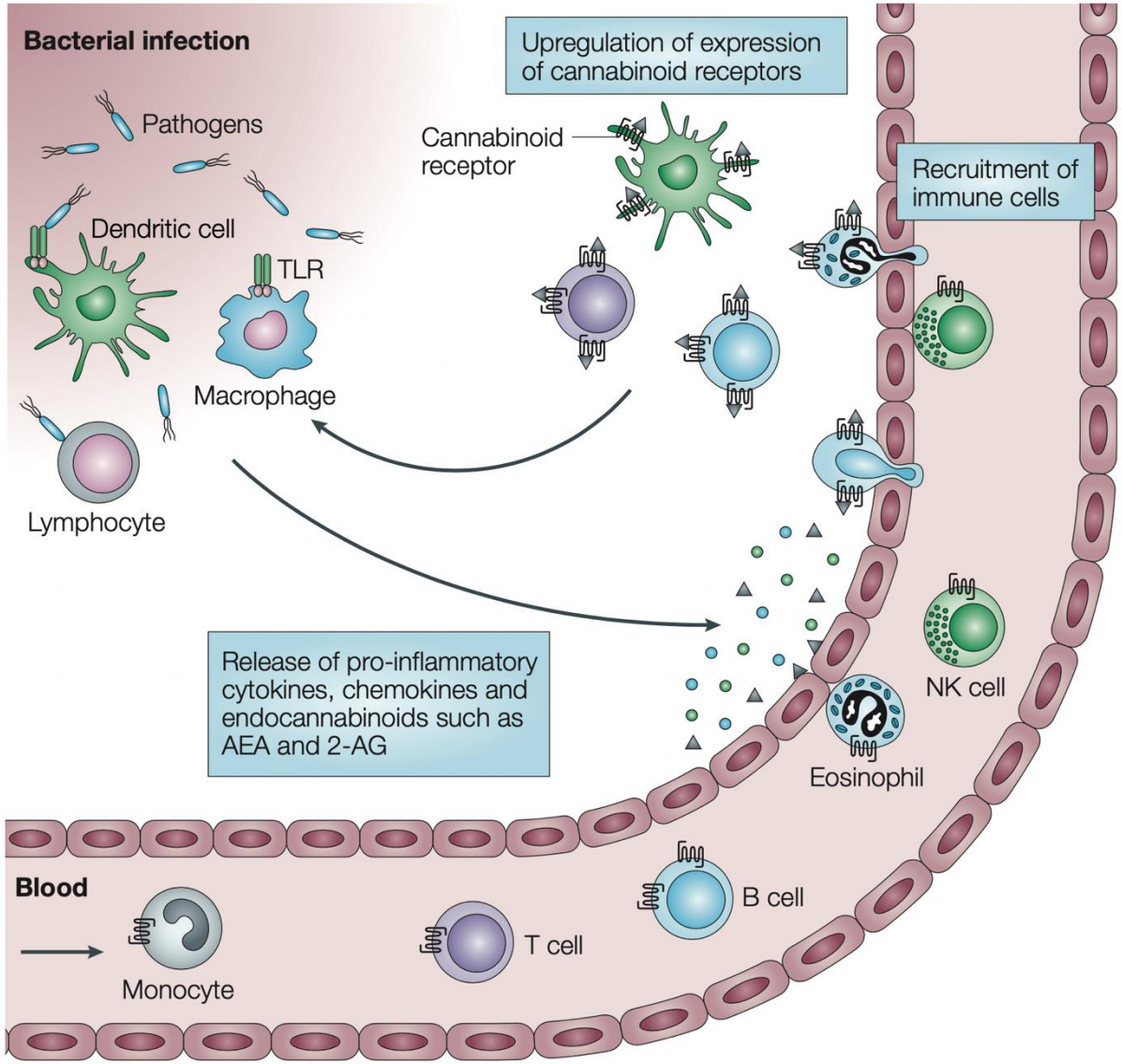
Controllo del dolore (area grigia periacqueduttale)
Nell'area grigia periacqueduttale (PAG), gli eCB interagiscono anche con il canale **TRPV1**, influenzando i circuiti del dolore. L'effetto antinocicettivo (riduzione del dolore) dipende sia dalla modulazione del rilascio di neurotrasmettitori sia dall'azione diretta sui recettori coinvolti nella percezione nocicettiva.

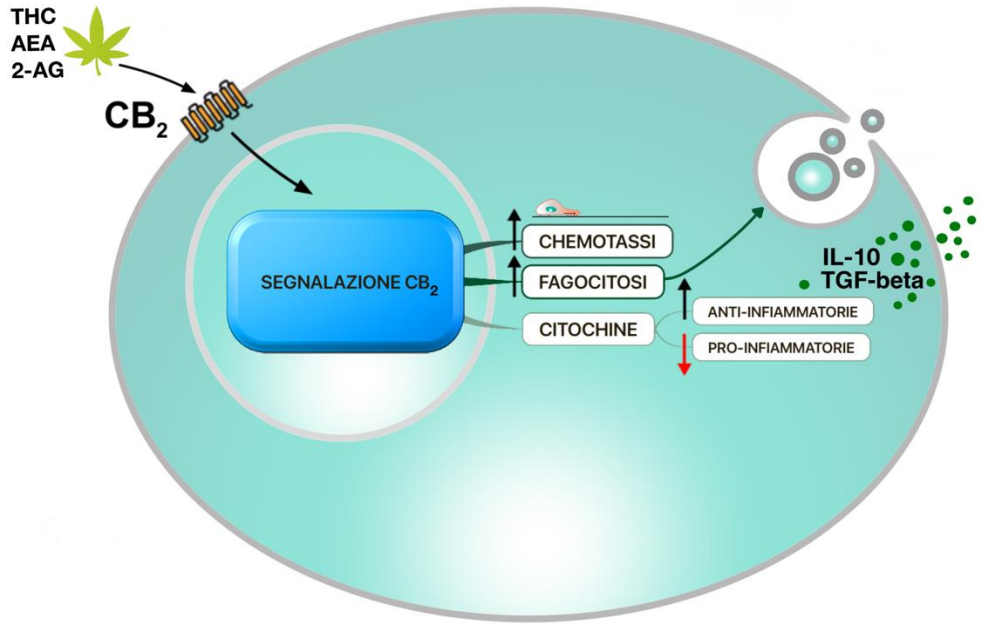


Regolazione del movimento (striato e circuiti motori)
Nei terminali GABAergici e glutammatergici dello striato, l'azione degli eCB influenza i pathway motori diretto e indiretto, contribuendo a modulare la locomozione. Una disfunzione del segnale endocannabinoide in questa regione è stata associata a disturbi del movimento, come nel Parkinson.

- **Implicazioni terapeutiche**
  In condizioni patologiche (ad esempio, dolore cronico, ansia persistente, disturbi neurodegenerativi), un'alterazione del sistema endocannabinoide può amplificare i sintomi. La modulazione farmacologica dei recettori CB1/CB2 o dei livelli di endocannabinoidi (ad es. tramite inibitori di FAAH o MAGL) rappresenta una potenziale strategia terapeutica.
- **Equilibrio fine tra effetti benefici e rischi**
  Sebbene l'attivazione del sistema eCB possa fornire effetti neuroprotettivi e antinfiammatori, un suo eccesso o una sua carenza possono causare conseguenze negative (ad esempio, alterazioni cognitive, dipendenza, peggioramento di stati d'ansia). È quindi fondamentale un'azione selettiva e ben regolata.

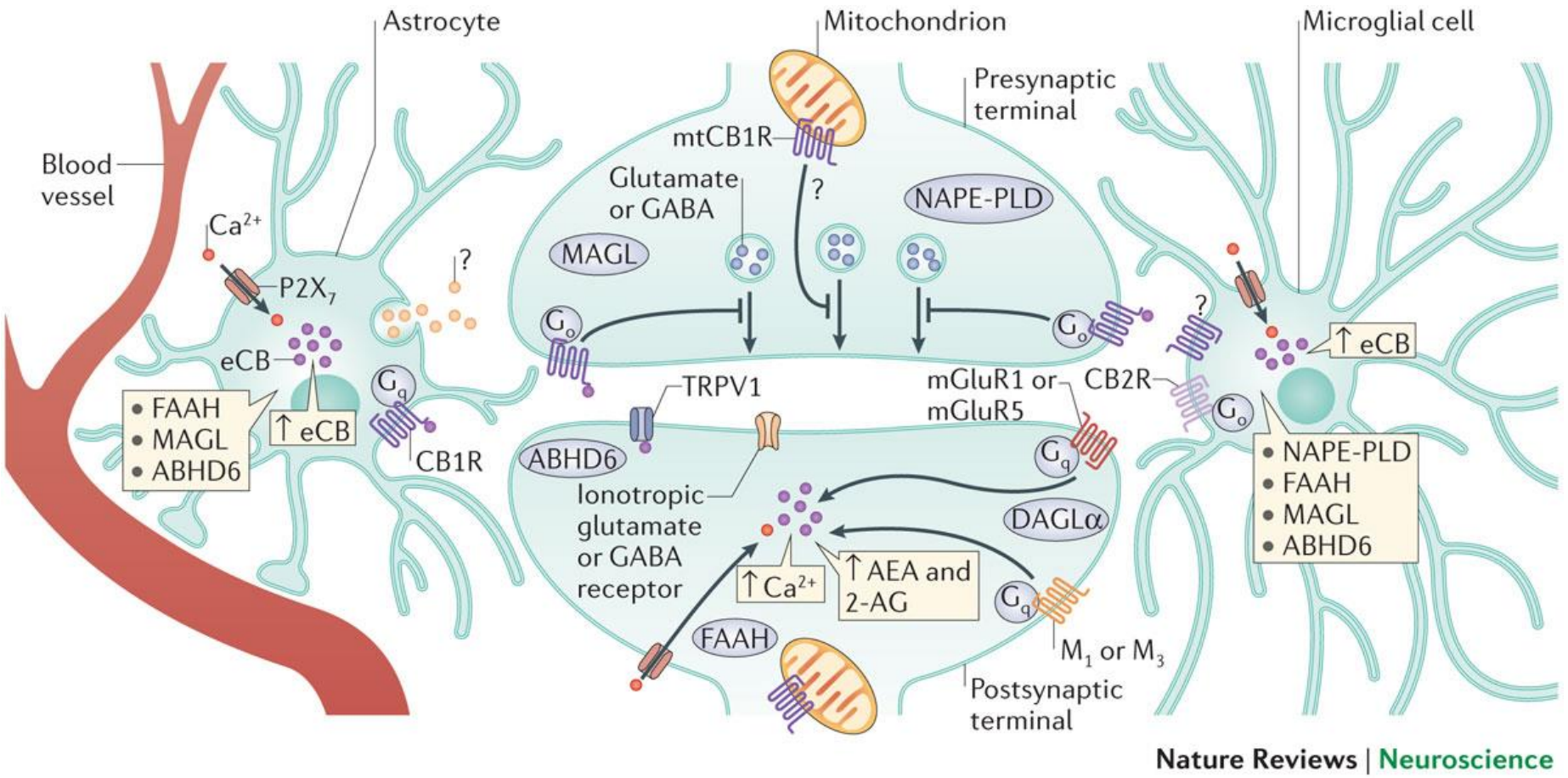
Ruolo immunomodulatorio (recettore CB2)





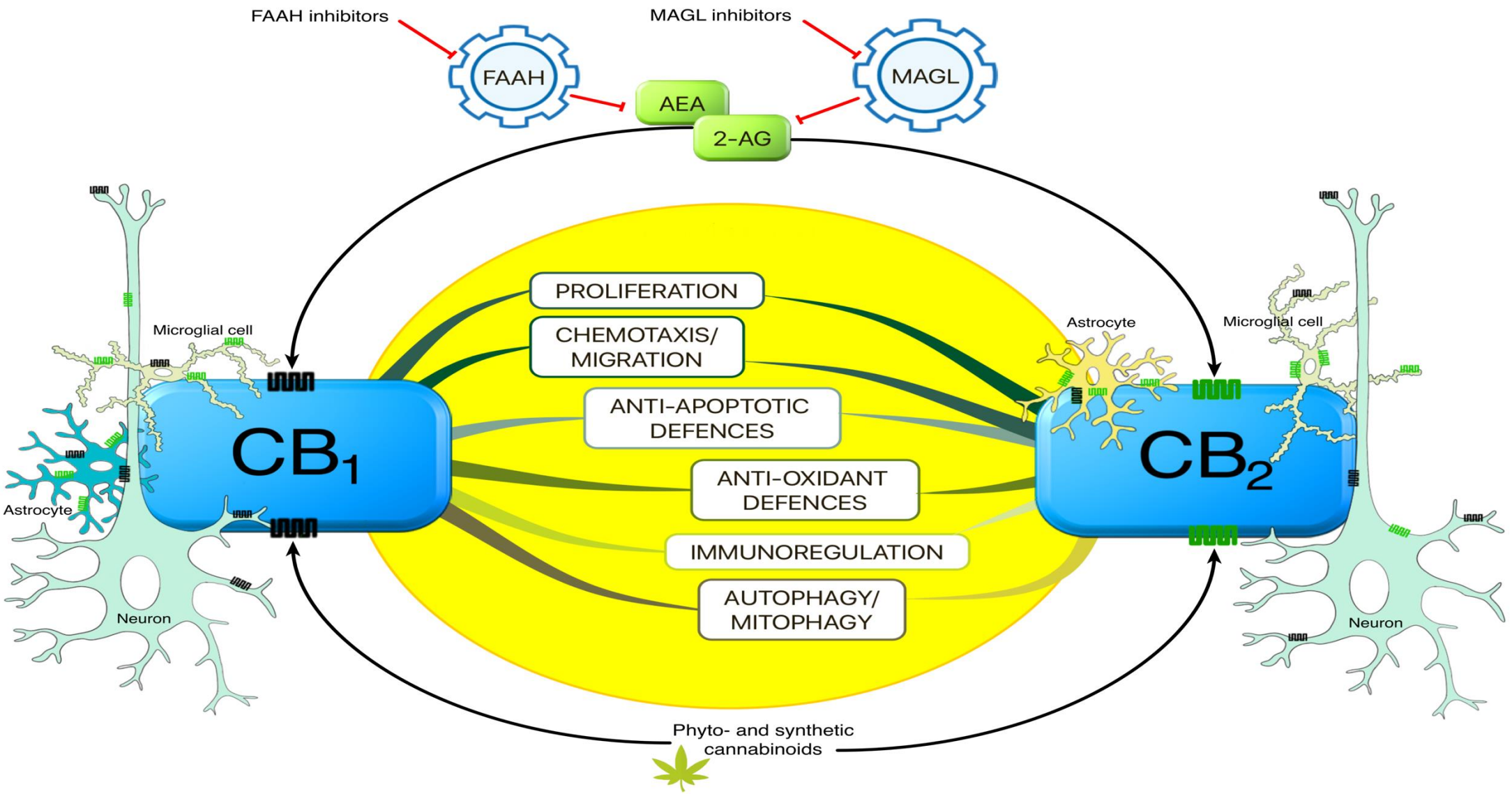
Il sistema è estesamente espresso sia nelle cellule dell'immunità innata che di quella acquisita ed esercita un ruolo estremamente complesso nella modulazione della risposta immunitaria

Co-espressione dell'ECS nelle cellule cerebrali



Nel cervello, l'ECS fa parte dell'apparato biochimico complesso attraverso cui neuroni e cellule gliali reagiscono a varie perturbazioni/insulti provenienti dall'ambiente esterno e interno, integrando reciprocamente le loro attività per (i) adattarsi in modo plastico (plasticità), (ii) ripristinare condizioni fisiologiche (omeostasi) e/o (iii) riparare e affrontare eventuali danni (resilienza).

The endocannabinoid signaling in the brain



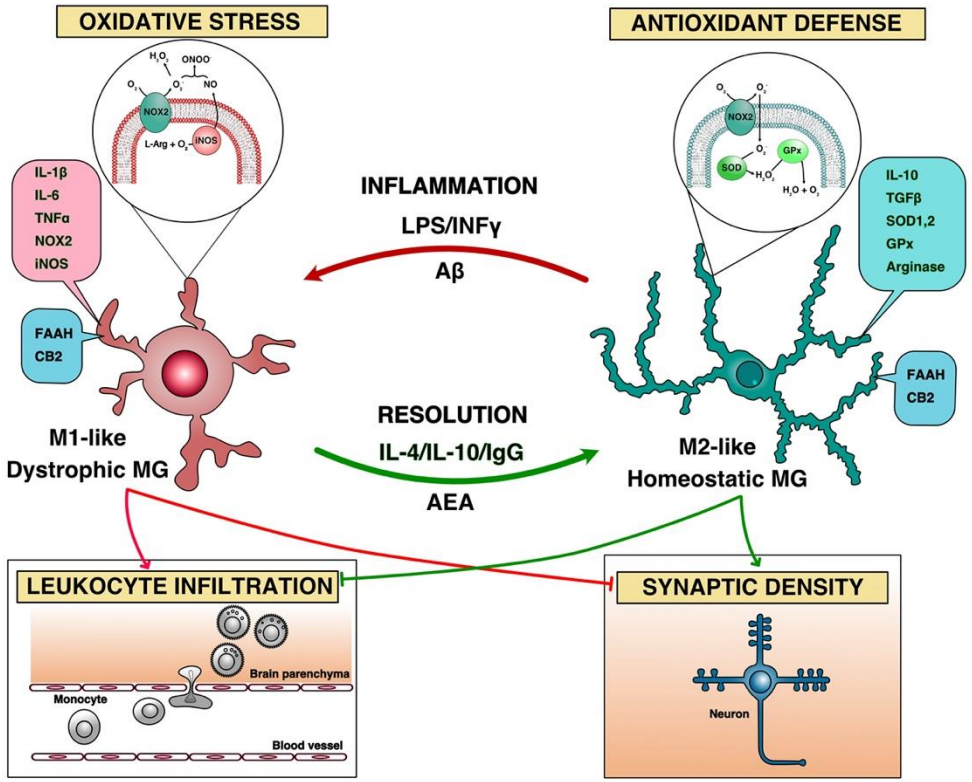


Figure 2. Possible impact of AEA signalling on to the multifaceted roles of microglia (MG) in neuroinflammation and its resolution

Upon different physiological and pathological stimuli, MG may switch to complementary activated phenotypes, referred to as M1-like and M2-like state. The former is a "proinflammatory phenotype" —committed by Aβ, LPS and INFγ— that is associated with the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNFα and cytotoxic substances like RNS and ROS. M1-like phenotype in sustained inflammation can cause leakage across the BBB and leukocyte infiltration in the brain parenchyma. In contrast, the M2-like phenotype — driven by anti-inflammatory cytokines, such as IL-4 and IL-10, and possibly by anti-inflammatory lipid mediators such as AEA — promotes tissue repair and resolution of inflammation, by promoting: i) release of anti-inflammatory cytokines, such as IL-10 and TGFβ, ii) activity of antioxidant defense (SOD1 and 2, GPx, arginase) and iii) neuronal homeostasis. Thus, inactivation of FAAH, and hence enhancement of AEA tone and signalling, may exert its beneficial anti-inflammatory effects by polarizing MG towards the pro-resolutory M2-like phenotype.

Abbreviations: Aβ, amyloid β; AEA, *N*-arachidonoylethanolamine; BBB, blood brain barrier; CB_2, type-2 cannabinoid receptor; FAAH, fatty acid amide hydrolase; GPx, glutathione peroxidase; IFNγ, interferon γ; IL, interleukin; iNOS, inducibile nitric oxide synthase; LPS, lipopolysaccharide; NO, nitric oxide; NOX2, NADPH oxidase 2; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD1,2, superoxide dismutase 1 and 2; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α.

Table 1 | **Possible endocannabinoid-system-based approaches for the treatment of neurodegenerative disorders.**

eCB-system-based drugs	Rationale	Advantages	Disadvantages	Disease	Refs*
Inhibitors of eCB cellular reuptake and enzymatic hydrolysis (by FAAH, MAGL, ABHD6)	Mimic the beneficial neuromodulatory effects of CB1 activation and the anti-inflammatory effects of CB2 activation in a time- and tissue-selective manner	Activity-dependent control of therapeutic effect, and fewer side effects	• Indirect activation of non-CB1, non-CB2 receptors (with FAAH inhibitors) • Possible receptor desensitization at high dose (MAGL inhibitors)	• Multiple sclerosis • Alzheimer's disease (depending on model and disease phase) • Parkinson's disease	116, 136, 147, 150
Inhibitors of MAGL	Inhibition of 2-AG-derived inflammatory prostaglandins	Activity-dependent control of therapeutic effect, fewer side effects	Inhibition of beneficial effects of prostaglandins in other tissues or organs	• Alzheimer's disease • Parkinson's disease	126–128
CB2 agonists	Reduction of inflammatory component of disease	Relative lack of psychotropic effects compared to CB1 agonists	• Possible receptor desensitization at high dose • May favour leukocyte infiltration due to chemotaxis	• Huntington's disease • Amyotrophic lateral sclerosis • Multiple sclerosis	145, 151–153
CB1 antagonists or inverse agonists	Reduction of the neurochemical imbalance due to prolonged alterations of eCB signalling	Already tested in humans	Potential psychiatric adverse events (anxiety, depression)	Parkinson's disease and Alzheimer's disease (depending on model and disease phase)	141, 142, 154

2-AG, 2-arachidonoyl-glycerol; ABHD6, α,β hydrolase 6; CB1, cannabinoid receptor 1; eCB, endocannabinoid; FAAH, fatty acid amide hydrolase 1; MAGL, monoacylglycerol lipase. *Selected references.

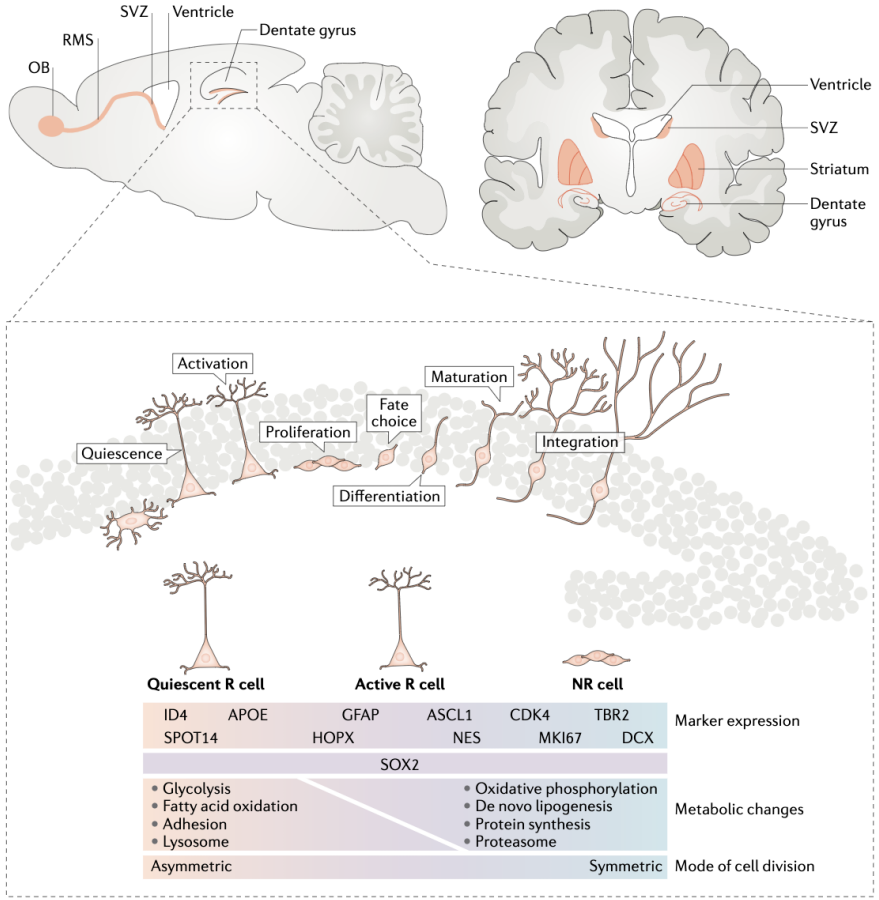
Contents

- Brief introduction to hippocampus adult **neurogenesis (gross anatomy, neurogenic niche)**
- Brief introduction to the endocannabinoid system
- Molecular mechanisms involved in modulating adult neurogenesis

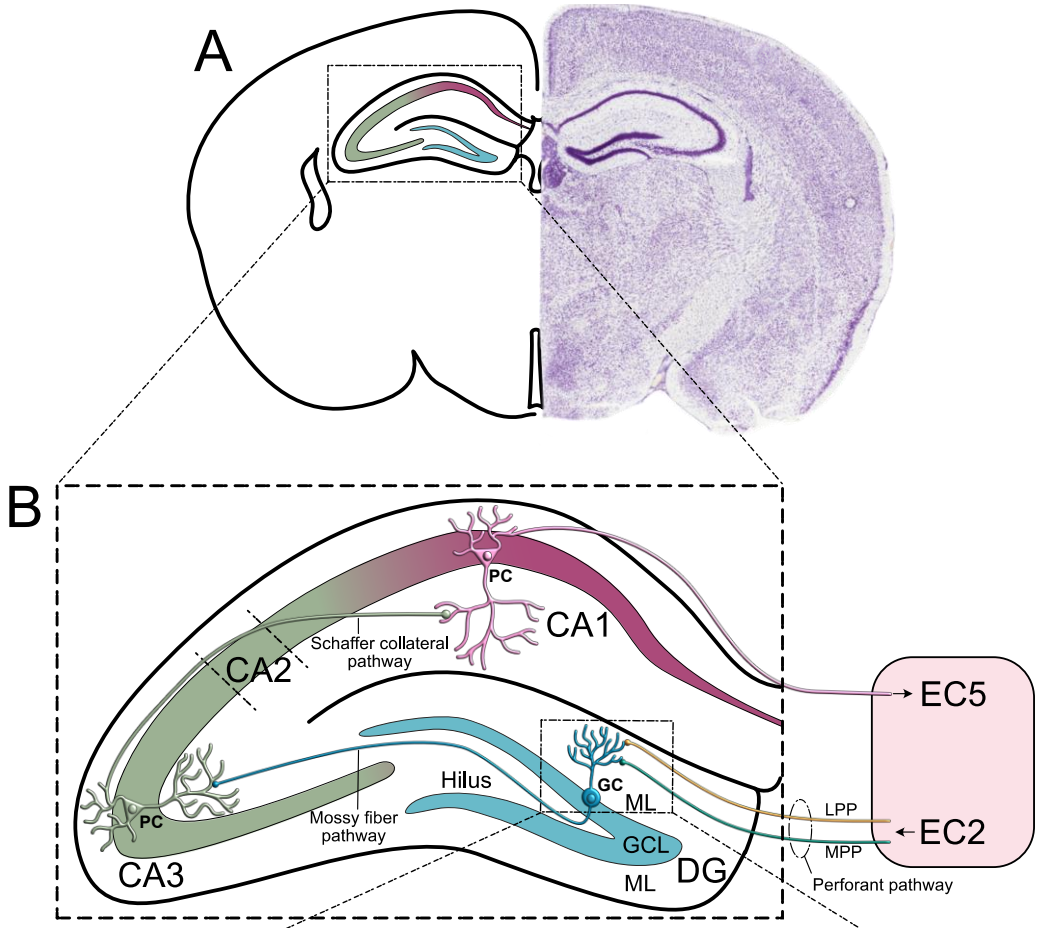
The adult hippocampal neurogenesis

Adult hippocampal neurogenesis is the process by which new functional neurons are continuously generated and integrated into the DG of the hippocampus, after embryonic development and throughout adulthood.

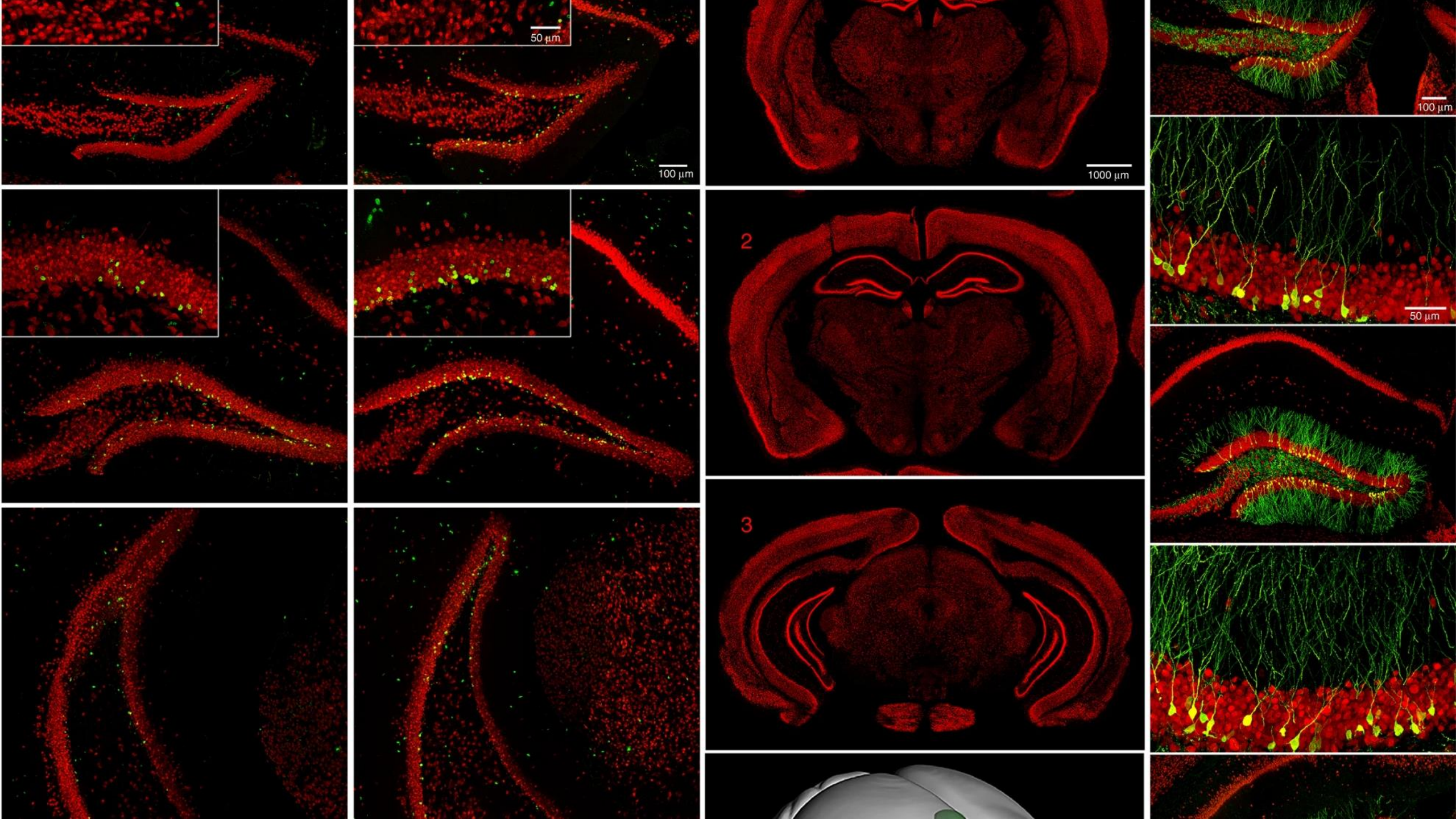
These new neurons impose a substantial remodeling of pre-existing circuits, involving the formation, competition and elimination of synaptic inputs and outputs in the DG, thus profoundly affecting different hippocampus-mediated functions, including **learning**, **memory** and **emotional behavior**.



Neuroanatomy of the dentate gyrus



- The **hippocampus (archicortex)** is an essential part of the **brain's limbic system**
- DG forms a V-shaped structure embedded into the curved cornu ammonis (CA), which itself is composed of CA1, CA2 and CA3 areas. Histologically, the DG is divided into three layers: (i) the molecular layer (ML), (ii) the granule cell layer (GCL), and (iii) the hilus.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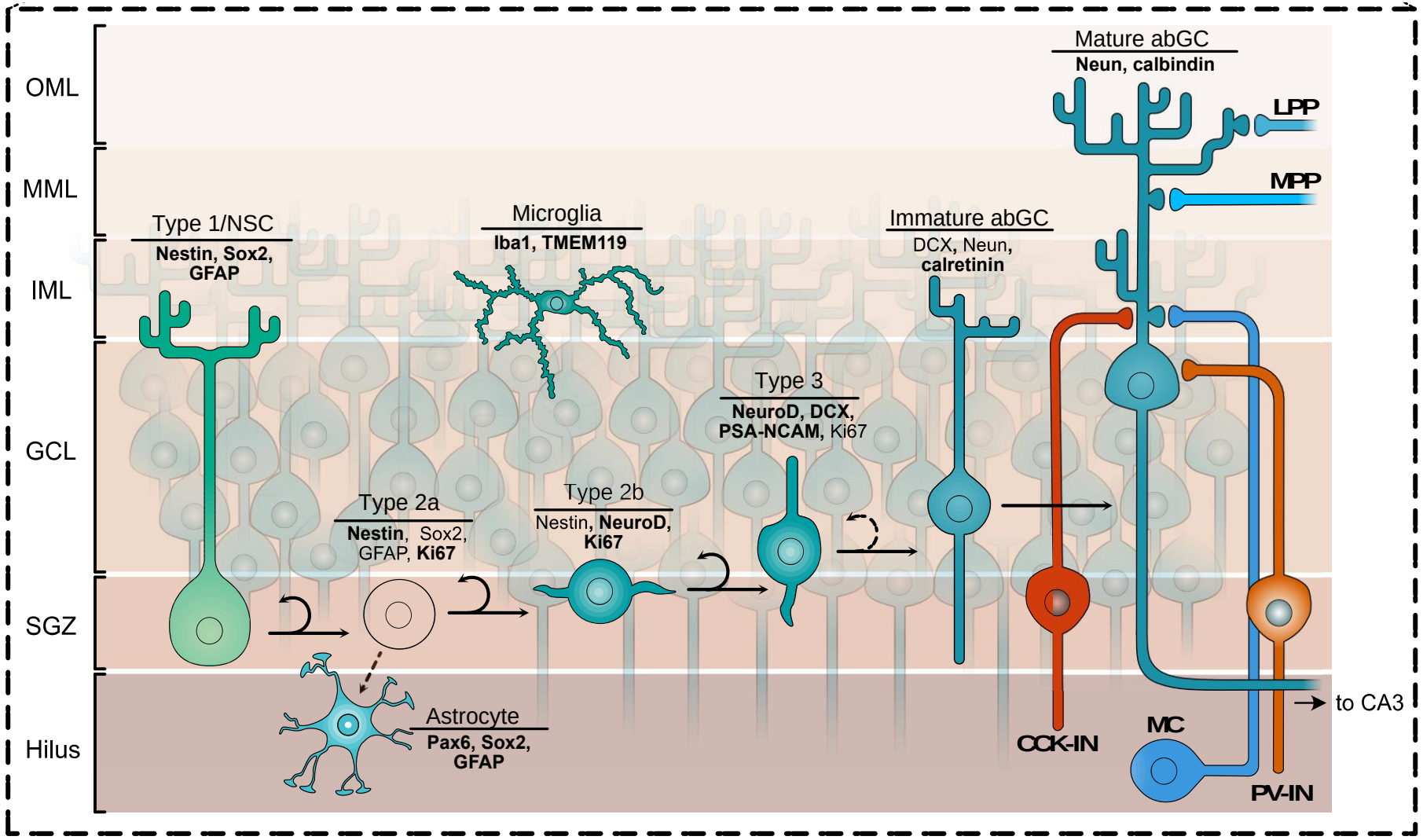
The hippocampal neurogenic niche



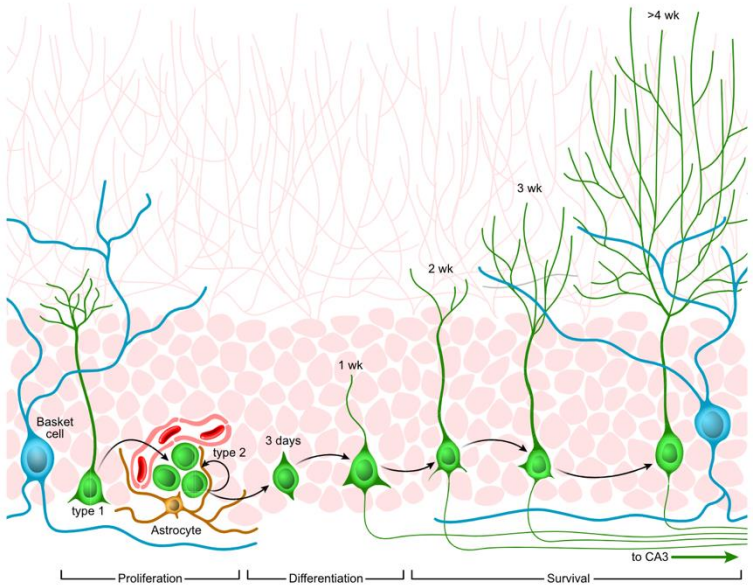
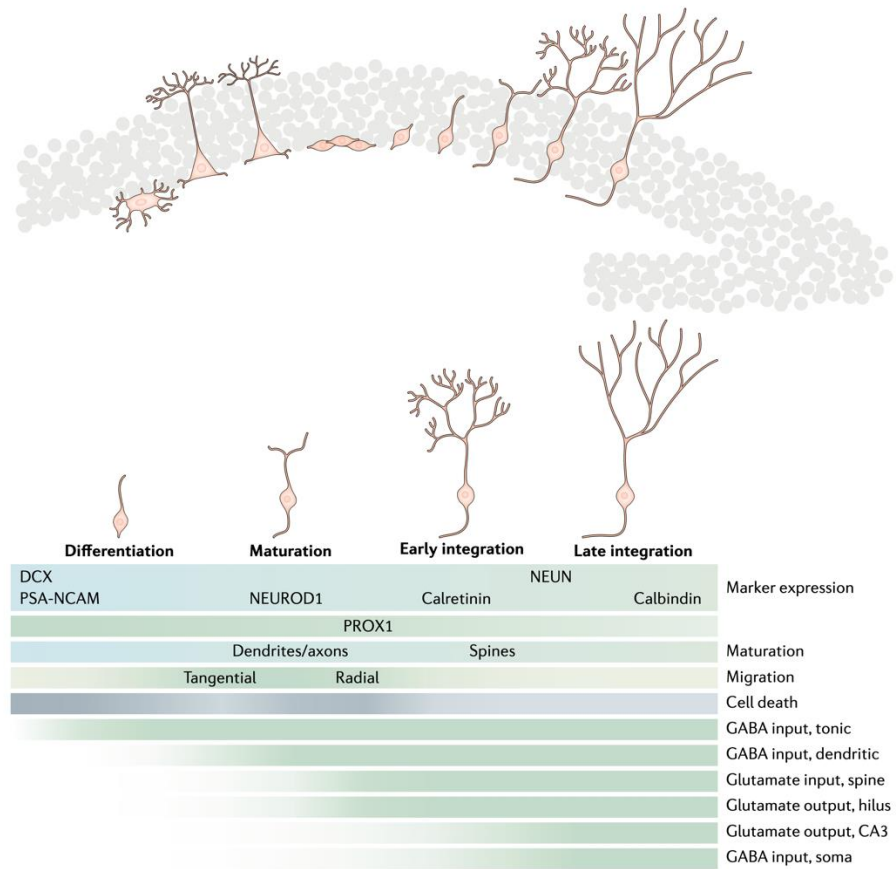
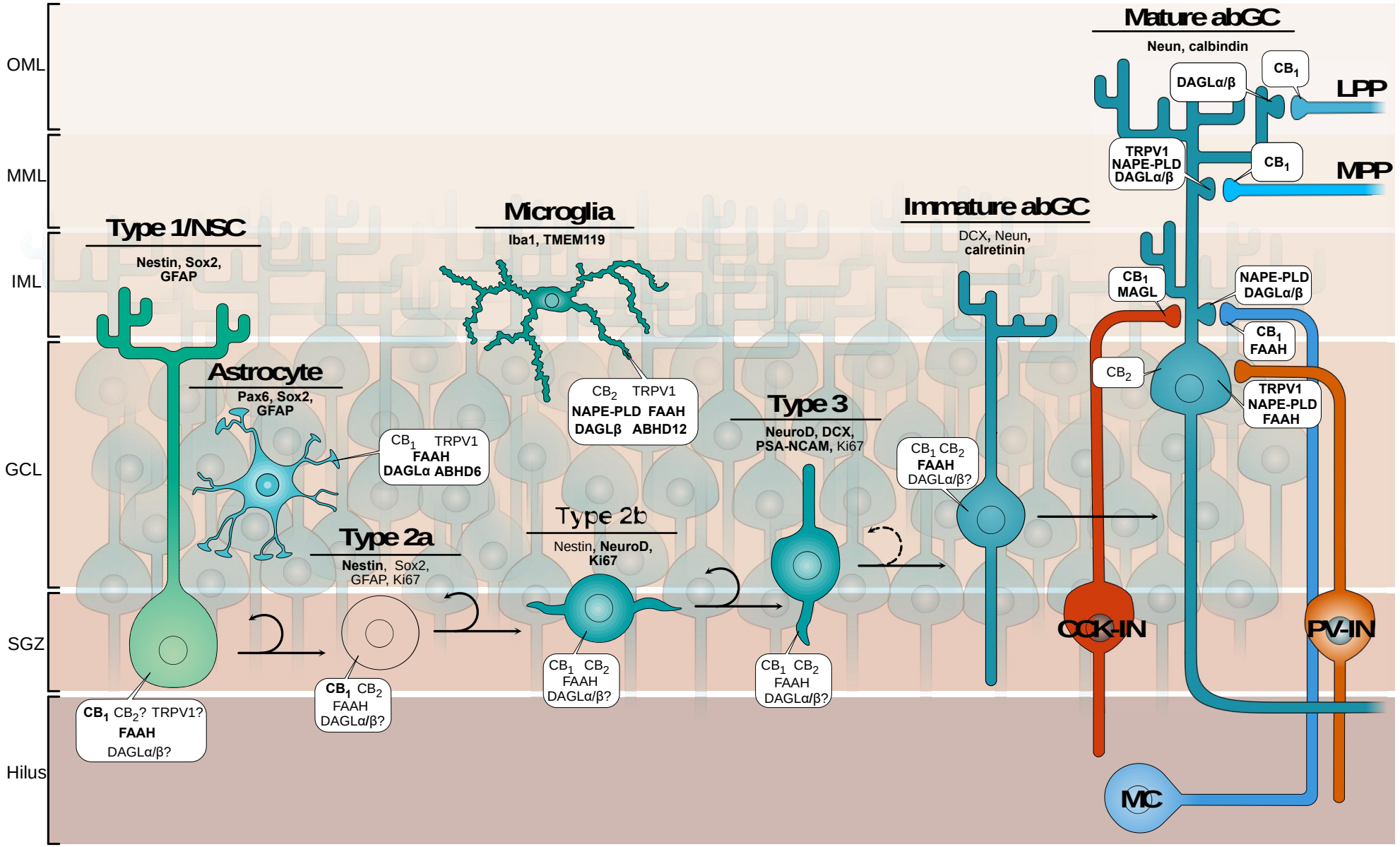


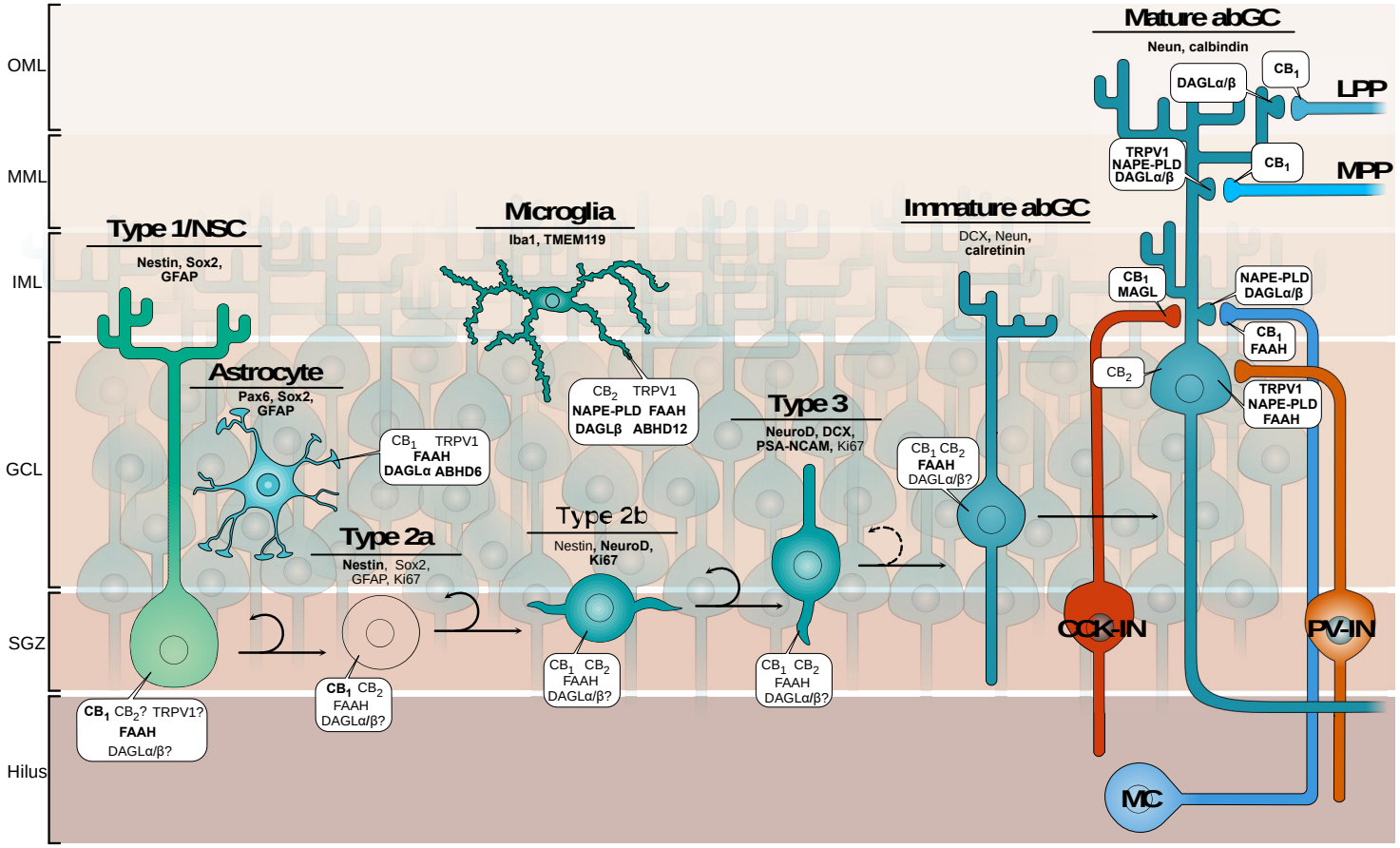
FIGURE 1. Illustration of the development of dentate gyrus granule cells from stem cells to fully mature neurons. New neurons arise from two populations of primitive cells, the slowly dividing type 1 cells, also known as radial glial cells, and the more rapidly amplifying type 2 neural progenitor cells. Over the next few weeks, cells differentiate into neurons, slowly developing dendritic arborizations and axonal projections. Between 2 and 3 wk of age, new neurons begin to receive excitatory input from cortical perforant path axons, and by 4–8 wk, their physiology and anatomy begin to approach those of fully mature neurons.

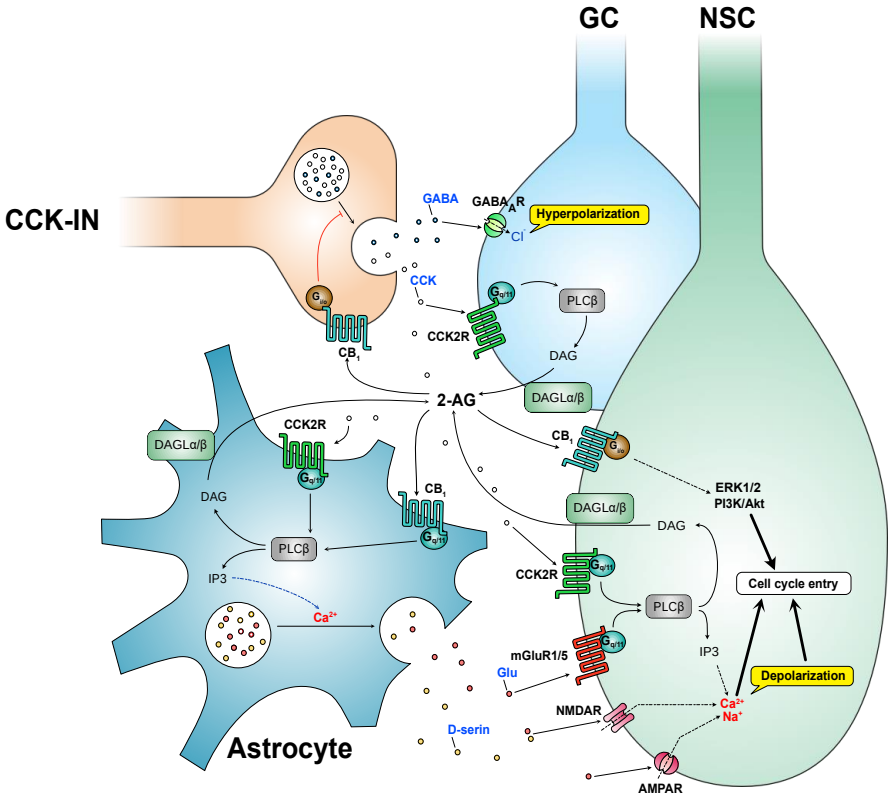


The ECS in the hippocampal neurogenic niche

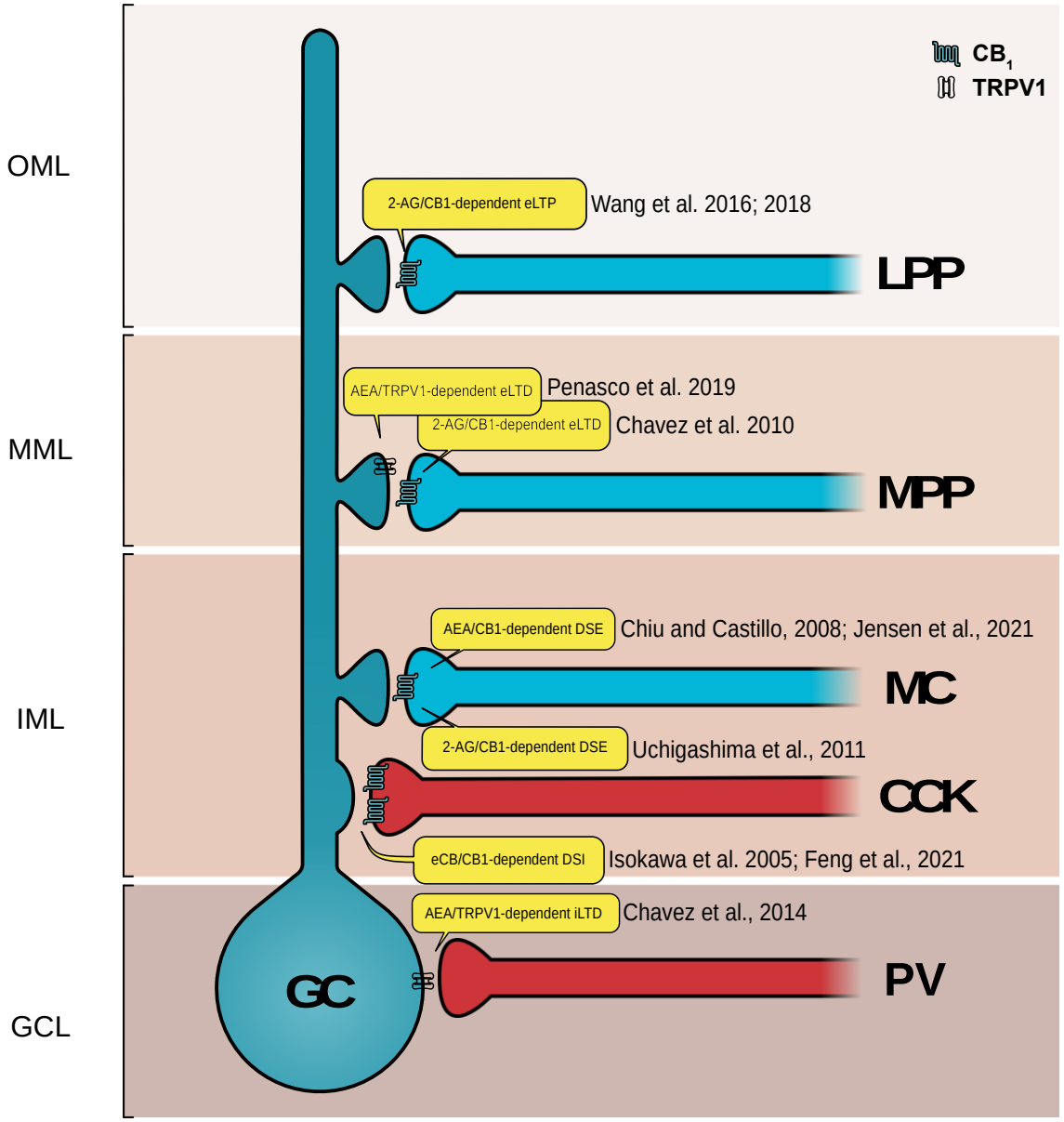


Indirect effects

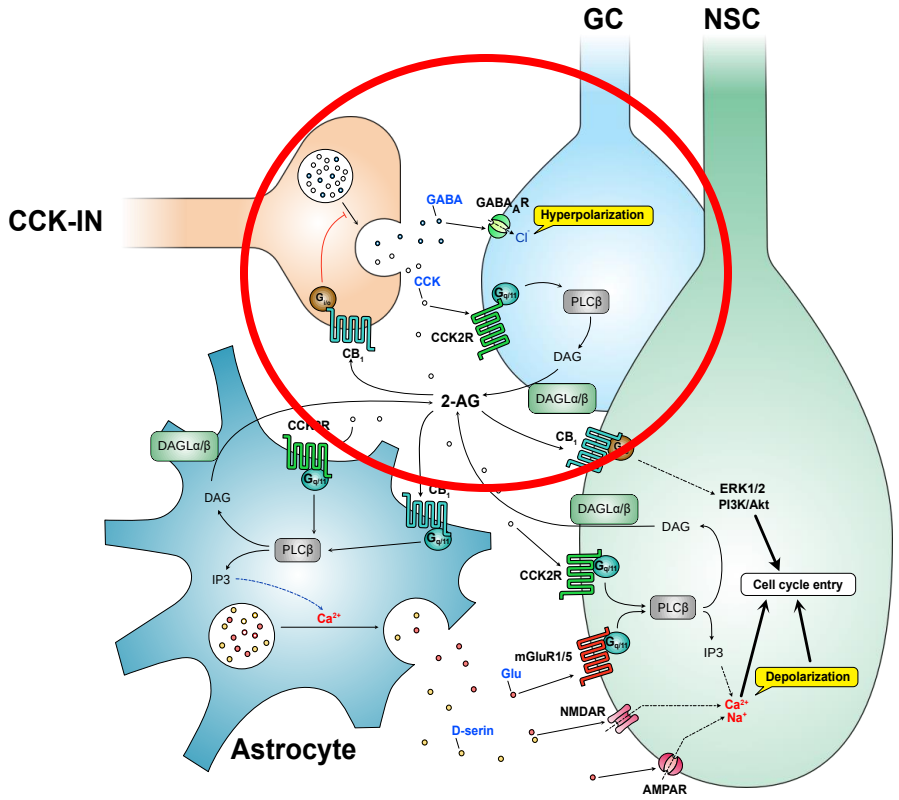




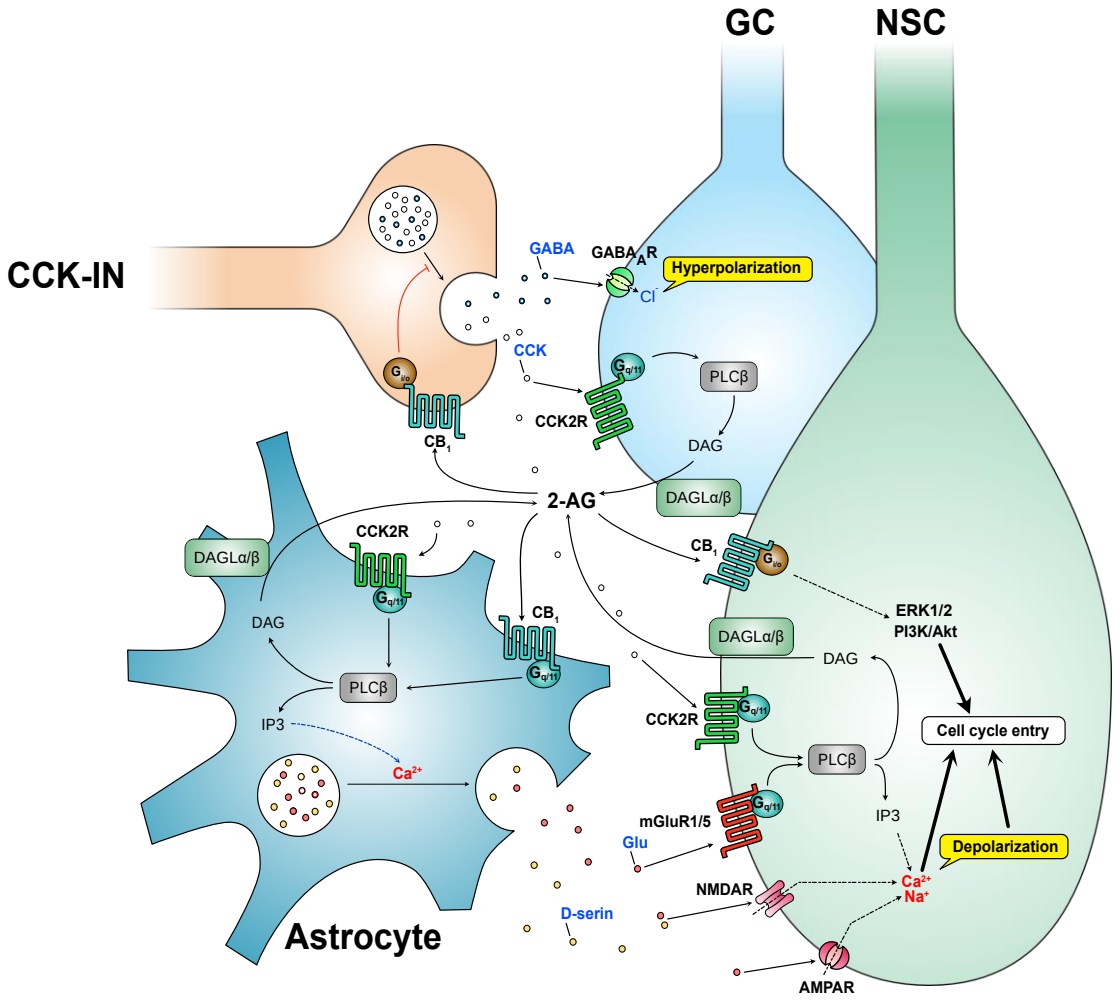
Impact of endocannabinoids in neuronal activity-dependent control of neurogenesis



Neuronal ECS may influence **neurogenesis** by regulating the balance between the tonic levels of GABA and glutamate derived from the synaptic spillover in the neurogenic niche



Impact of the endocannabinoid system in glial activity-dependent control of neurogenesis



Physiological relevance

- The hippocampal ECS may be influenced by exercise and learning and in turn it influences the effects of these physiological experiences on mood and cognition, at least in part, by regulating AHN
- There is a close relationship between ECS, stress, and AHN

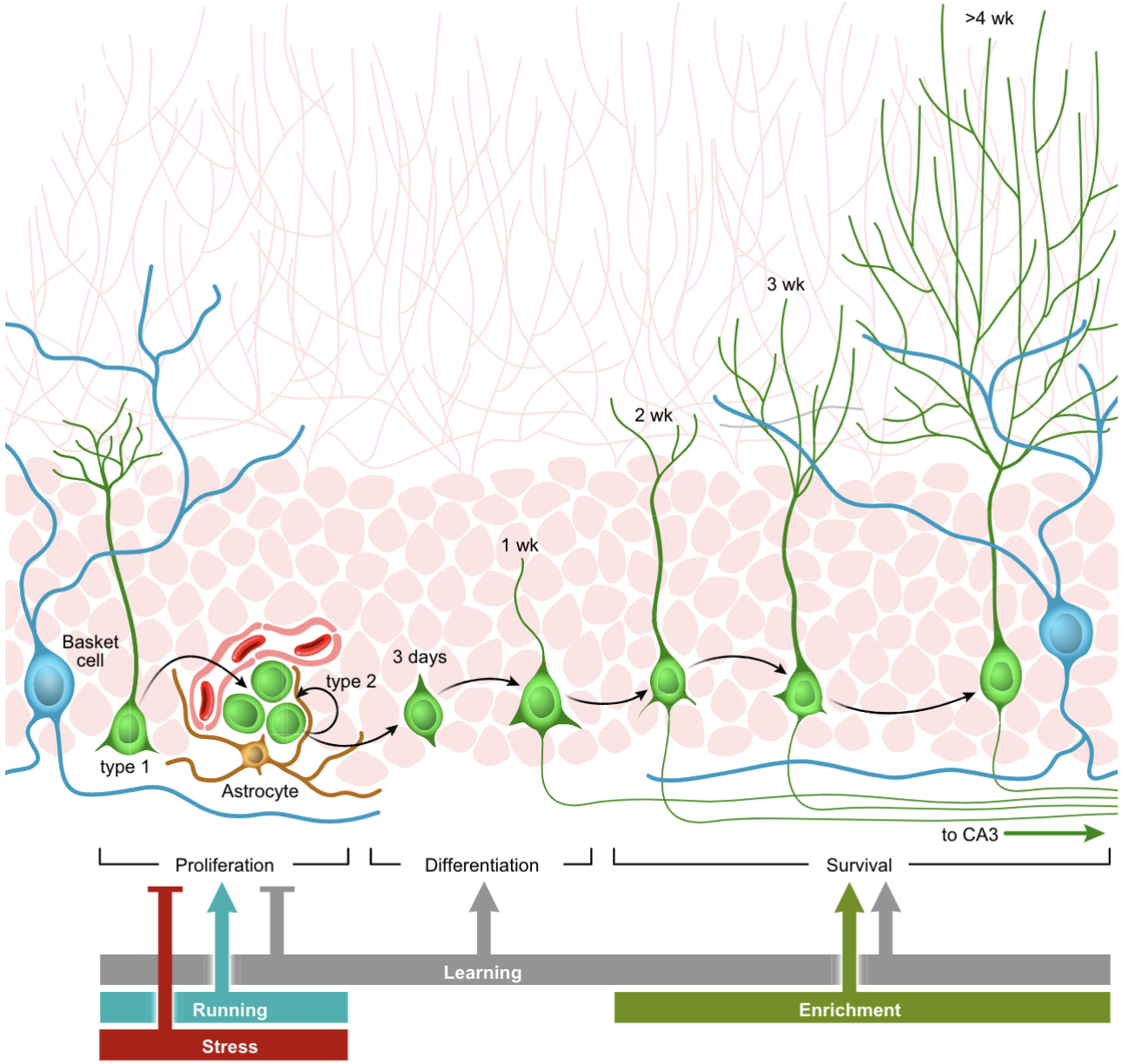


FIGURE 4. Regulation of neurogenesis by behaviors. Neurogenesis is regulated by many behavioral factors as well. Running is one of the most potent inducers of neurogenesis, targeting the proliferation of neural progenitor cells. Enrichment has a complementary effect, increasing the survival of neurons at a critical stage of their maturation. In contrast, stress is a severe negative regulator of new neuron birth, suppressing proliferation. The effects of learning are more complex, suppressing the neurogenesis process at some stages while increasing it at other stages.

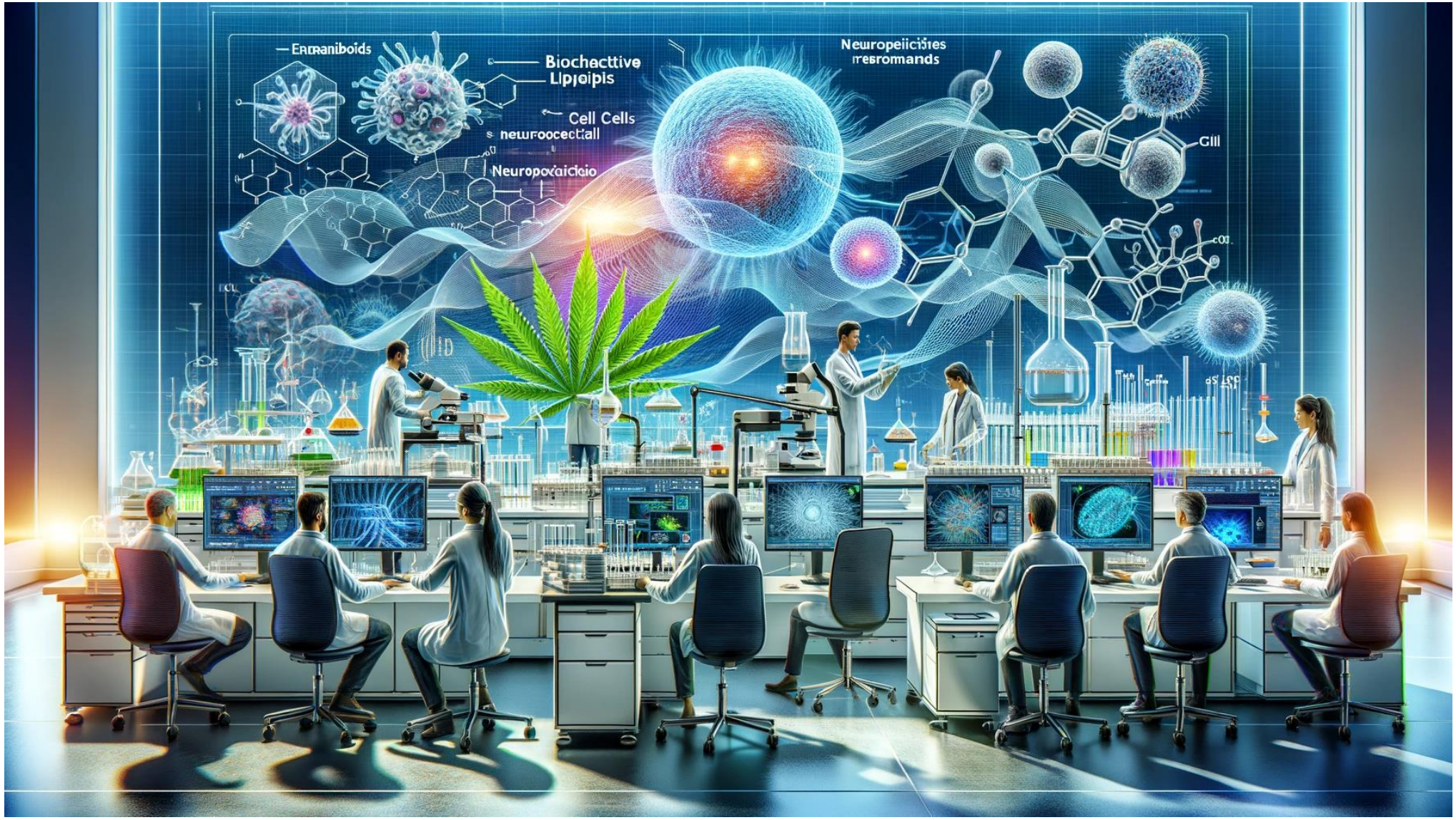
Unità di Biochimica

Laboratorio convenzionato

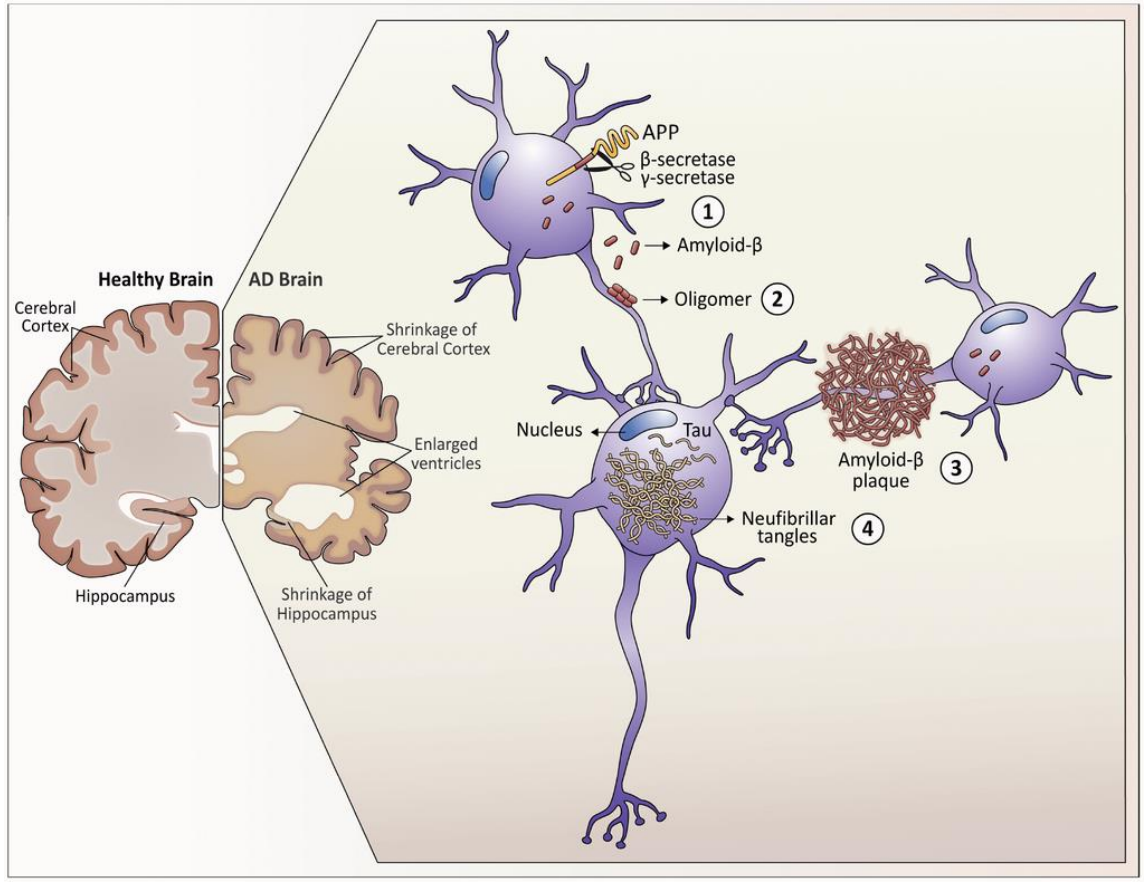
SANTA LUCIA
NEUROSCIENZE E RIABILITAZIONE

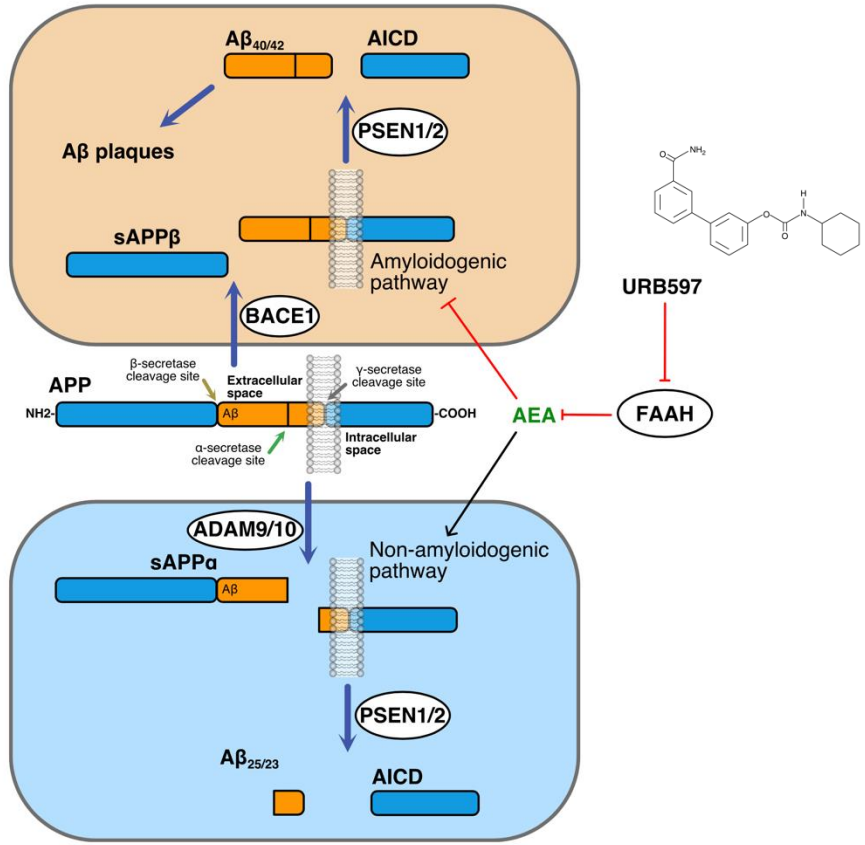
Principali tematiche

- (i) Meccanismi cellulari e molecolari coinvolti nel trasporto e nella segnalatica dei lipidi bioattivi nei processi fisiologici e infiammatori;
- (ii) dinamica spaziotemporale dei recettori dei lipidi bioattivi all'interno del loro ambiente di membrana;
- (iii) i meccanismi cellulari e molecolari alla base del ruolo neuroprotettivo degli endocannabinoidi in modelli preclinici di patologie;
- (iv) nuove sonde per la visualizzazione dei lipidi e delle loro cascata di segnalazione attraverso tecniche avanzate di imaging cellulare in tempo reale;
- (v) effetti dei nutraceutici sulle cascata di segnalazione lipidiche clinicamente rilevanti.

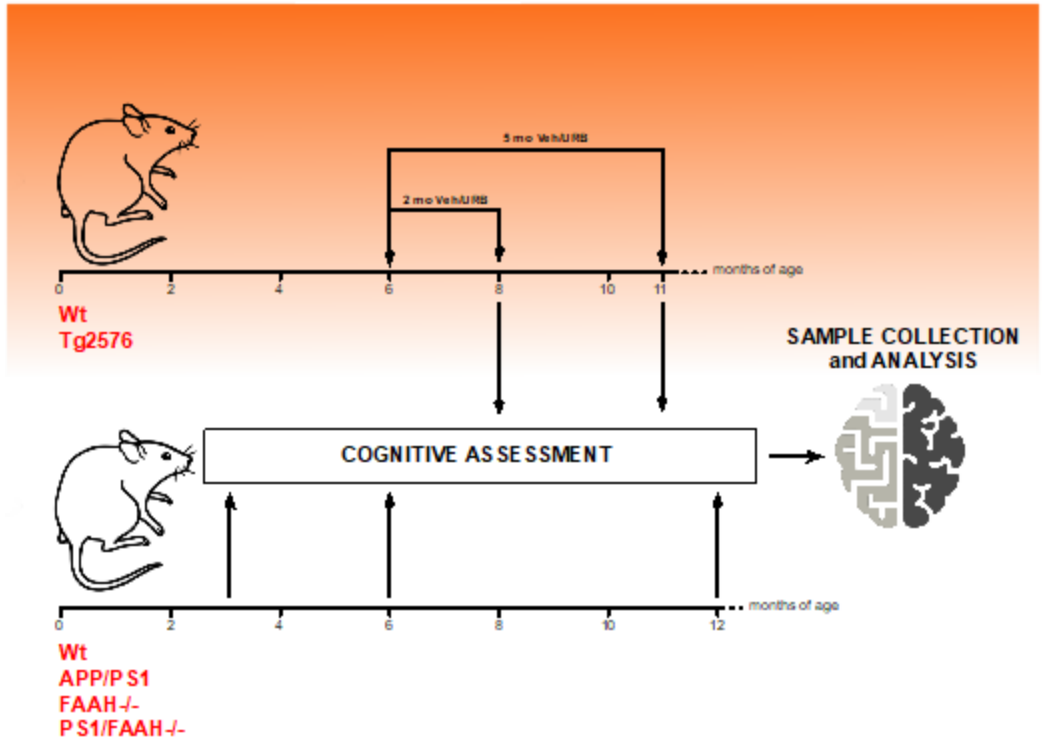


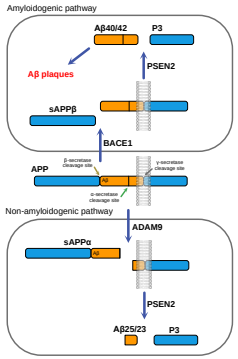
AEA signaling e AD



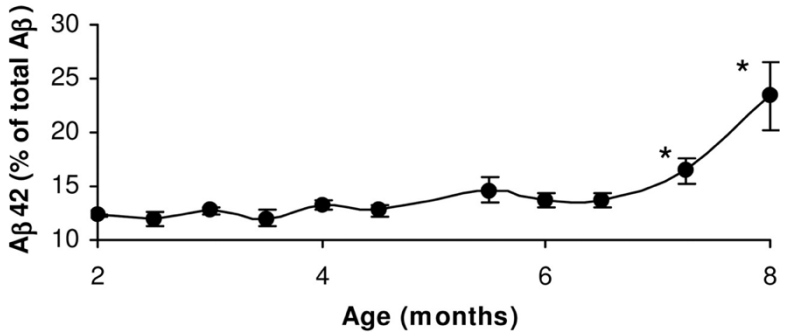


Experimental models

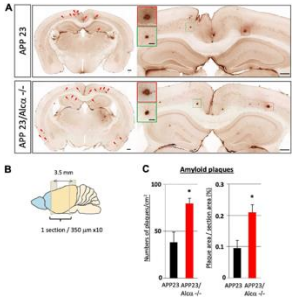




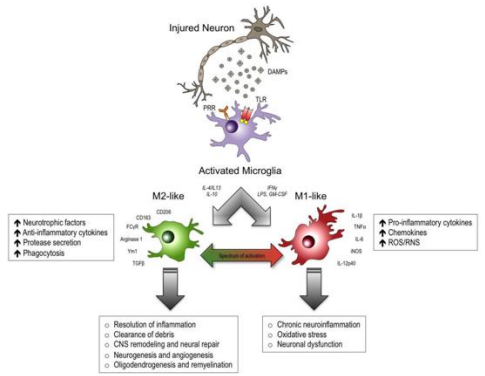
• Amiloidogenesi



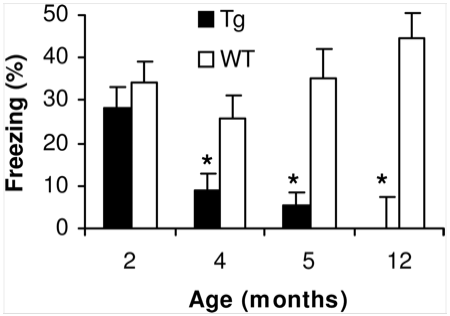
• Formazione placche amiloidi



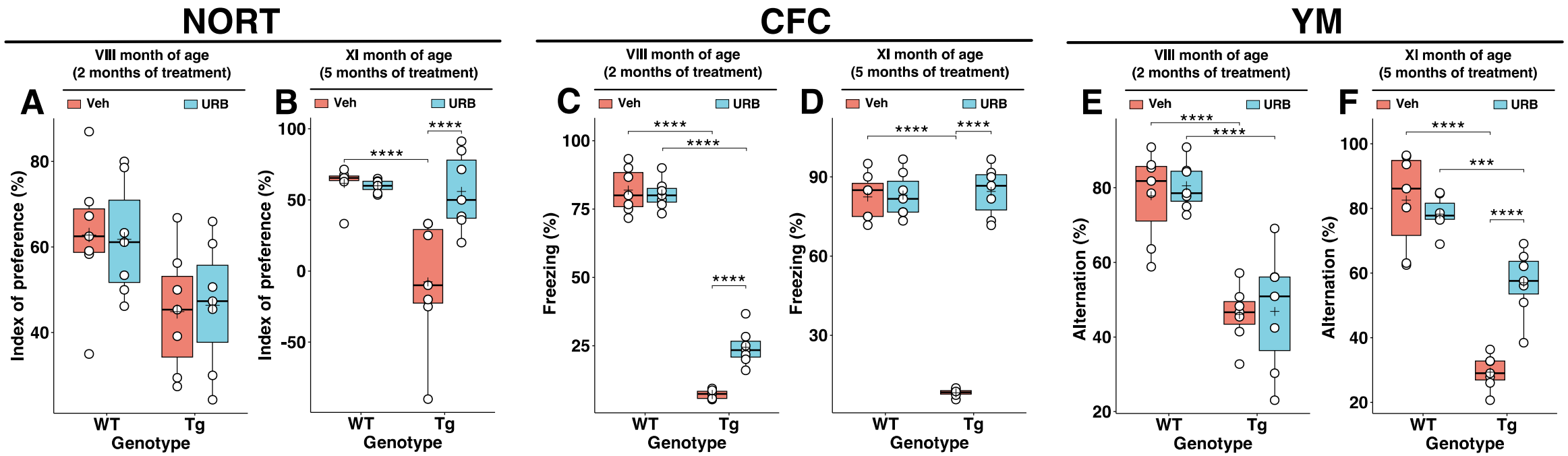
• Neuroinfiammazione



• Deficit cognitivi



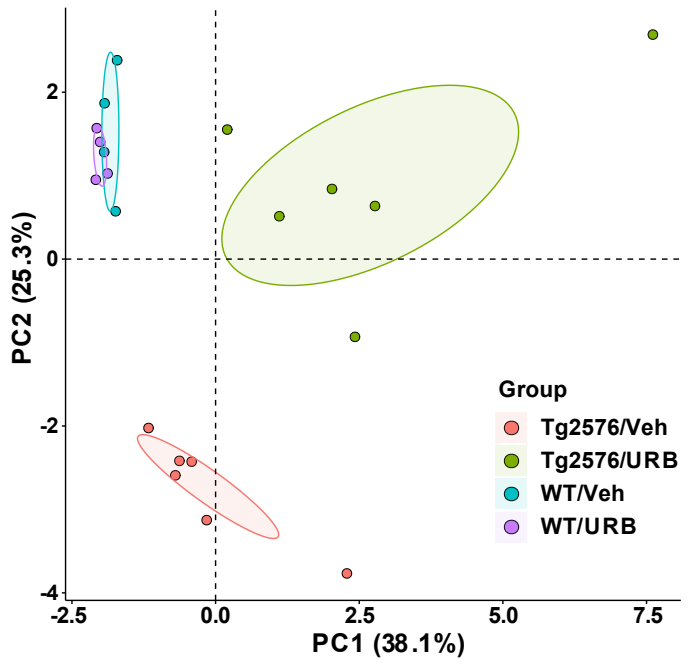
Inhibiting FAAH reverts the memory deficits in Tg2576 mice



Extended treatment periods led to more pronounced cognitive improvements and molecular changes, suggesting a dose-dependent efficacy.

Inhibiting FAAH significantly affects gene expression patterns

A



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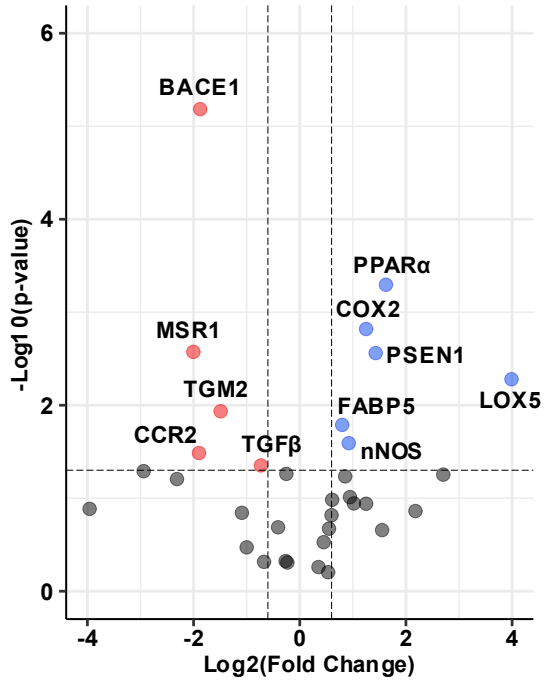


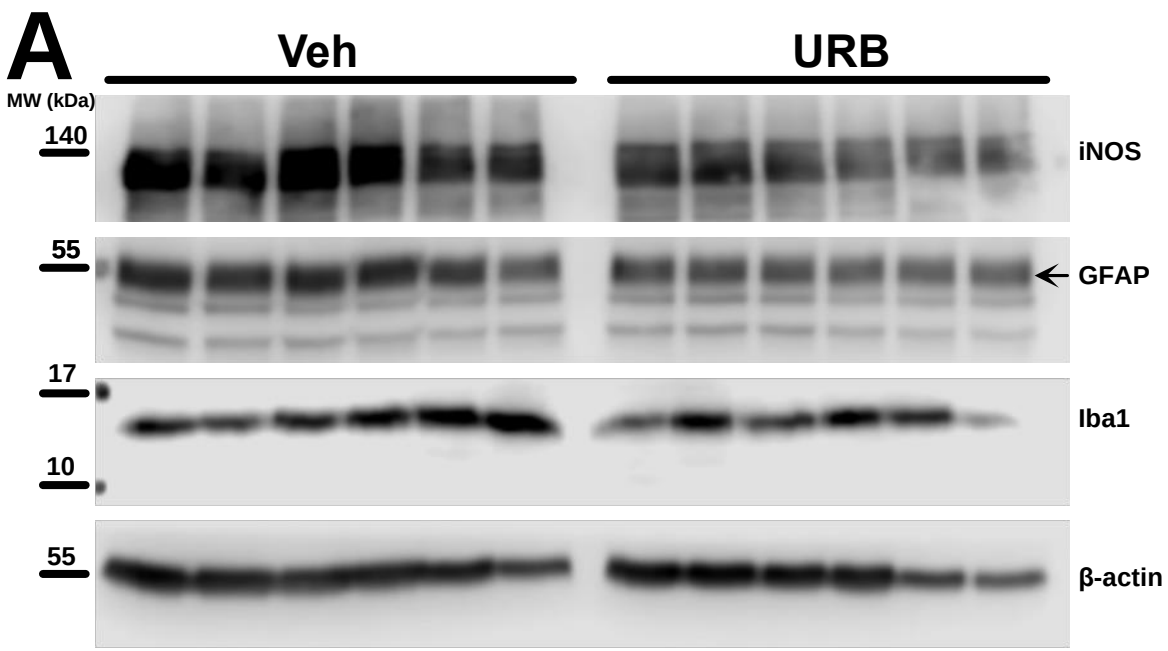
PPARα/γ: AEA-binding transcription factor

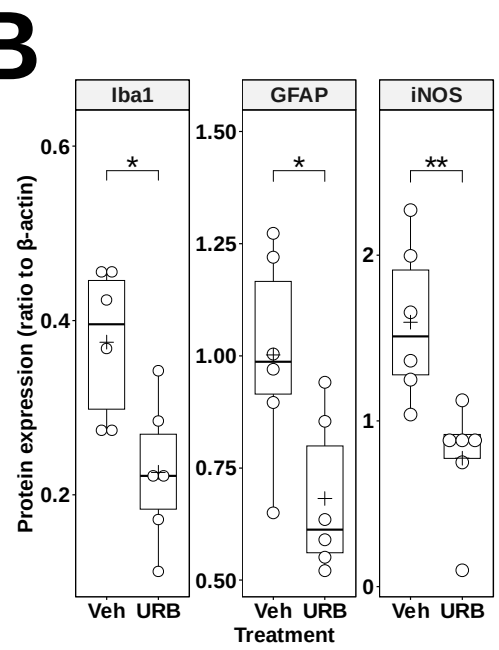
COX2: AEA-oxidizing enzyme (PG-EAs)

LOX5: AEA-oxidizing enzyme (hydroxy-AEAs)

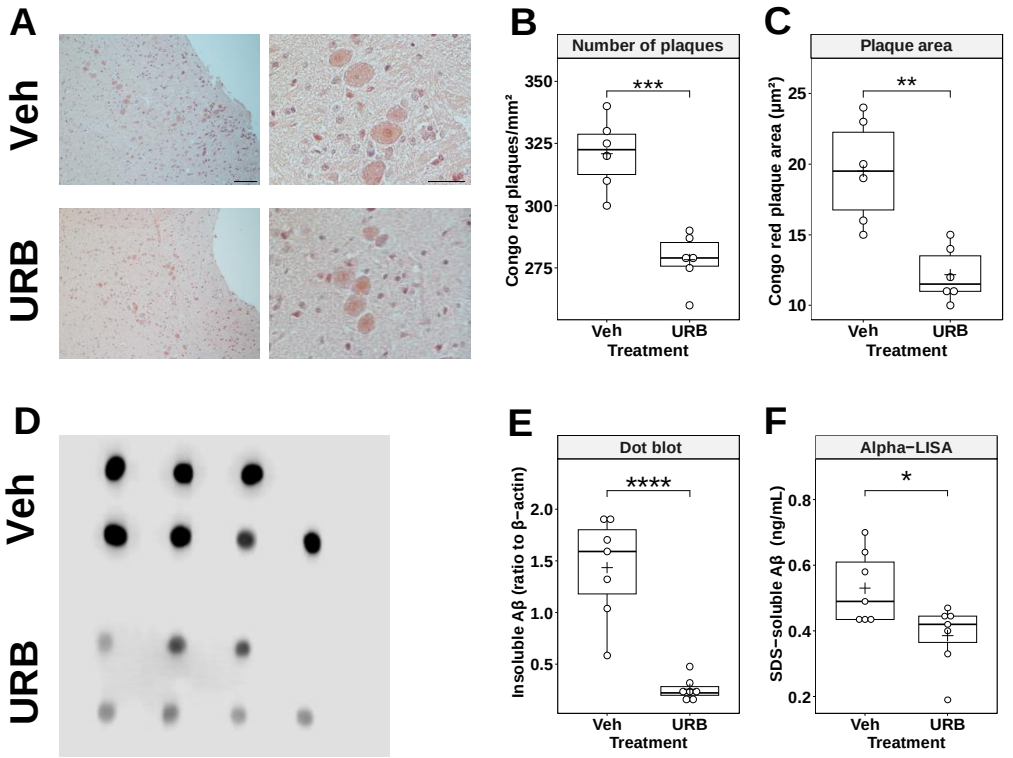
FABP5: AEA intracellular transporter

Inhibiting FAAH reduces neuroinflammation

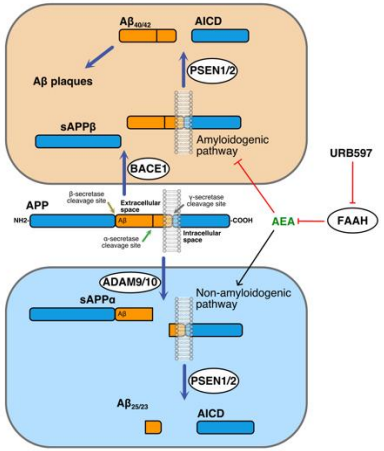


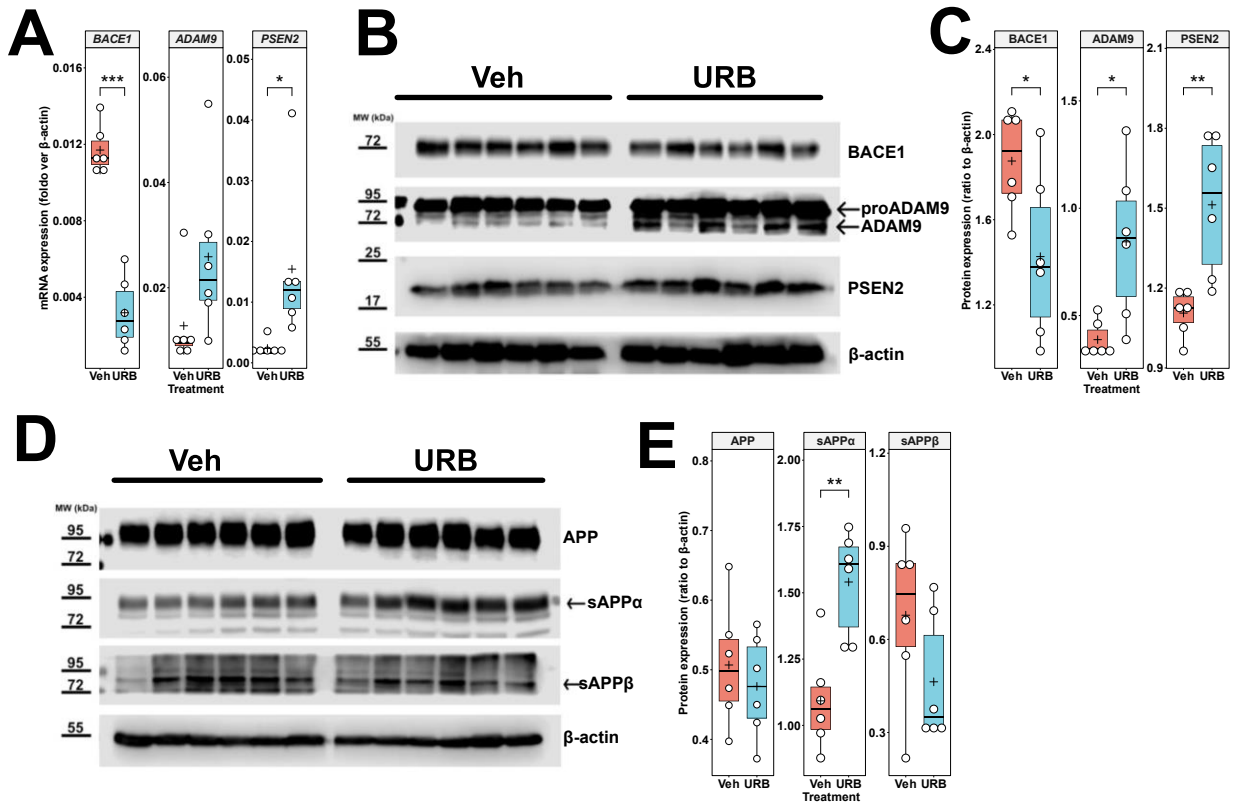


Inhibiting FAAH reduces β-amyloid production and aggregation in Tg2576 mice

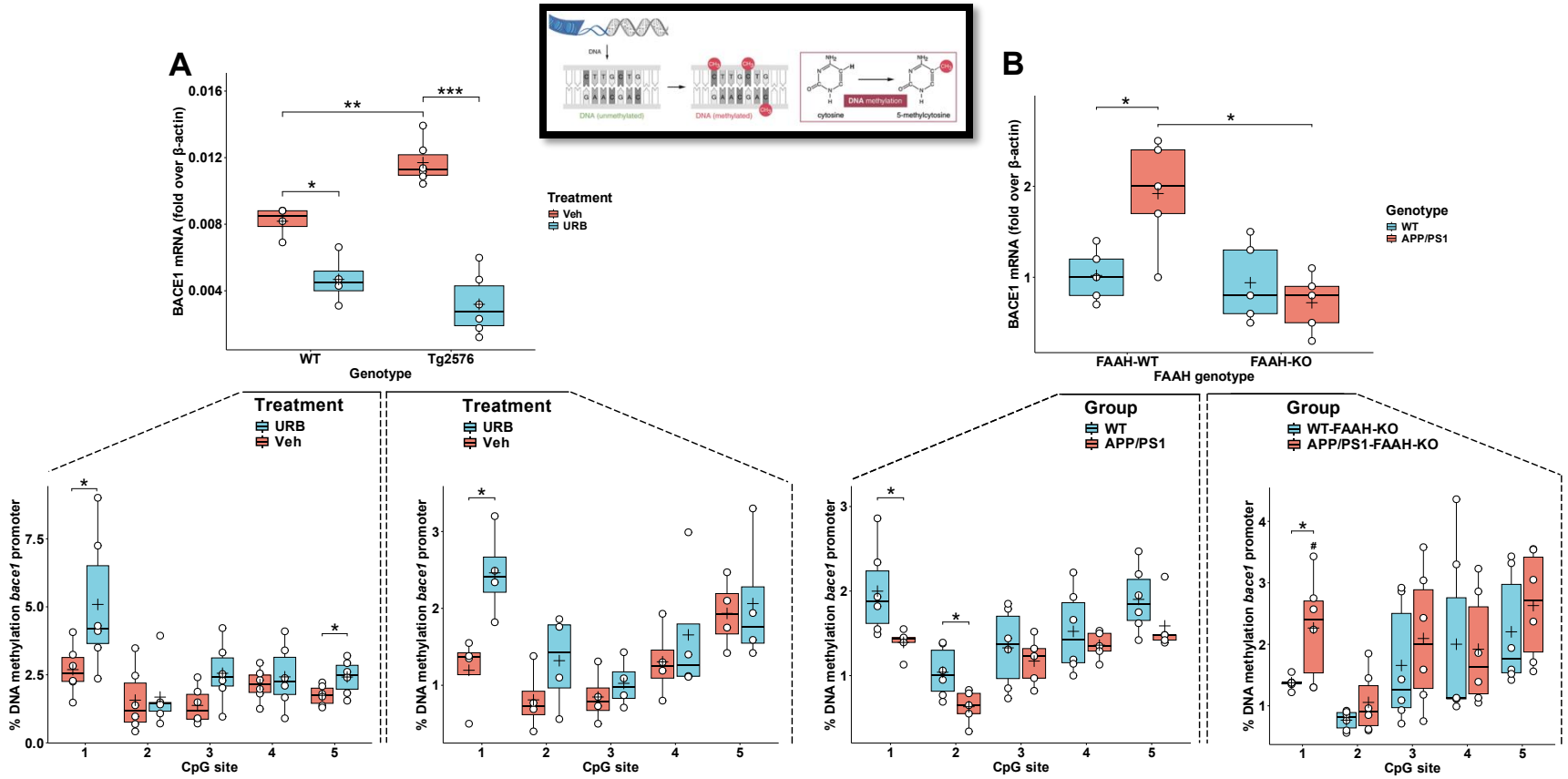


Inhibiting FAAH promotes the nonamyloidogenic cleavage of APP

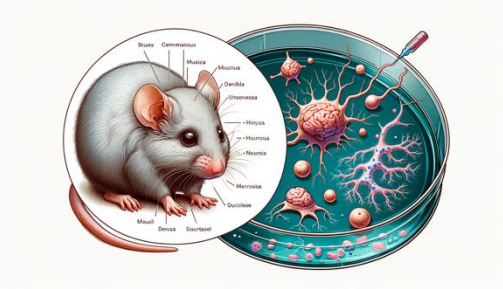


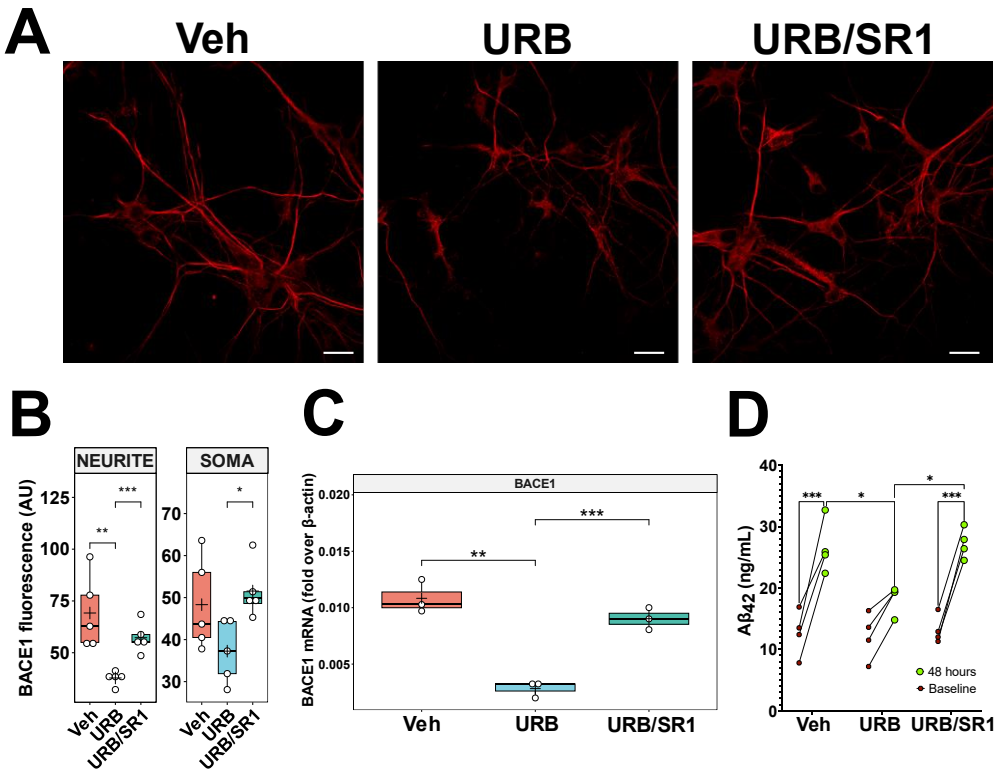


Inhibiting FAAH curtails the overexpression of the *bace1* gene in transgenic mice through promotion of promoter hypermethylation



Inhibiting FAAH promotes decreases BACE1 expression and Aβ42 production in primary Tg2576 neurons via CB_1-dependent pathway





Summary of the study

- Enhancing endocannabinoid signaling by targeting FAAH effectively mitigates cognitive deficits, reduces amyloid pathology, and modulates neuroinflammatory responses in a preclinical model of Alzheimer's disease. This effect is potentially mediated by attenuating the Aβ-induced overexpression of *bace1* gene through CB_1-dependent hypermetilation of its promoter region.

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Original Article | Open Access

Fatty-acid amide hydrolase inhibition mitigates Alzheimer's disease progression in mouse models of amyloidosis

Sergio Oddi, Lucia Scipioni, Antonio Totaro, Giacomo Giacovazzo, Francesca Ciaramellano, Daniel Tortolani, Alessandro Leuti, Rita Businaro, Federica Armeli ... See all authors

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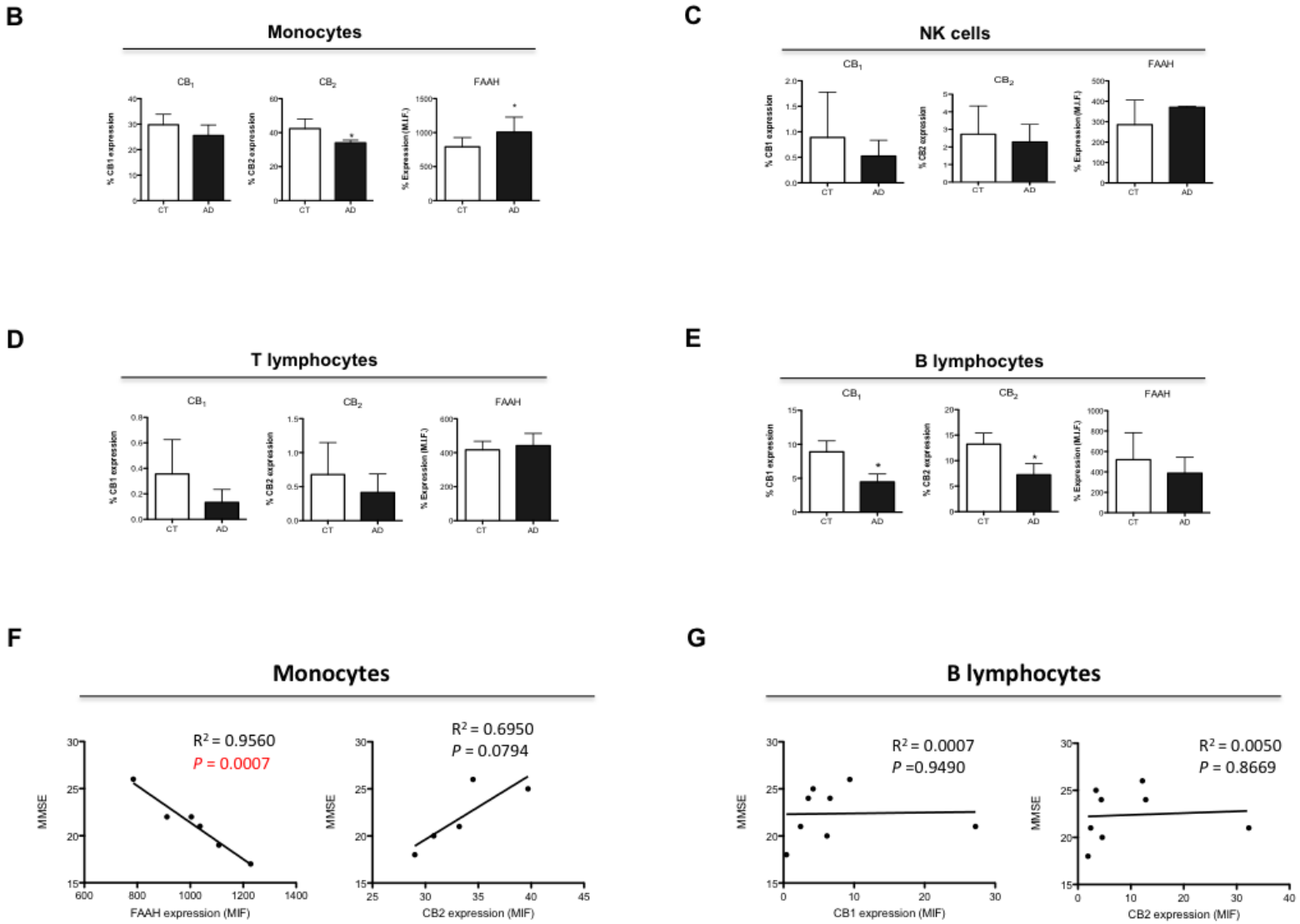
Alterazione dei livelli di FAAH e $CB_{1/2}$ in alcune popolazioni di leucociti circolanti di pazienti AD

- FAAH e recettori cannabici sono espressi in modo differente nelle cellule immunitarie di soggetti sani e pazienti AD.
- L'espressione della FAAH nei monociti circolanti è direttamente correlata alla severità della malattia.



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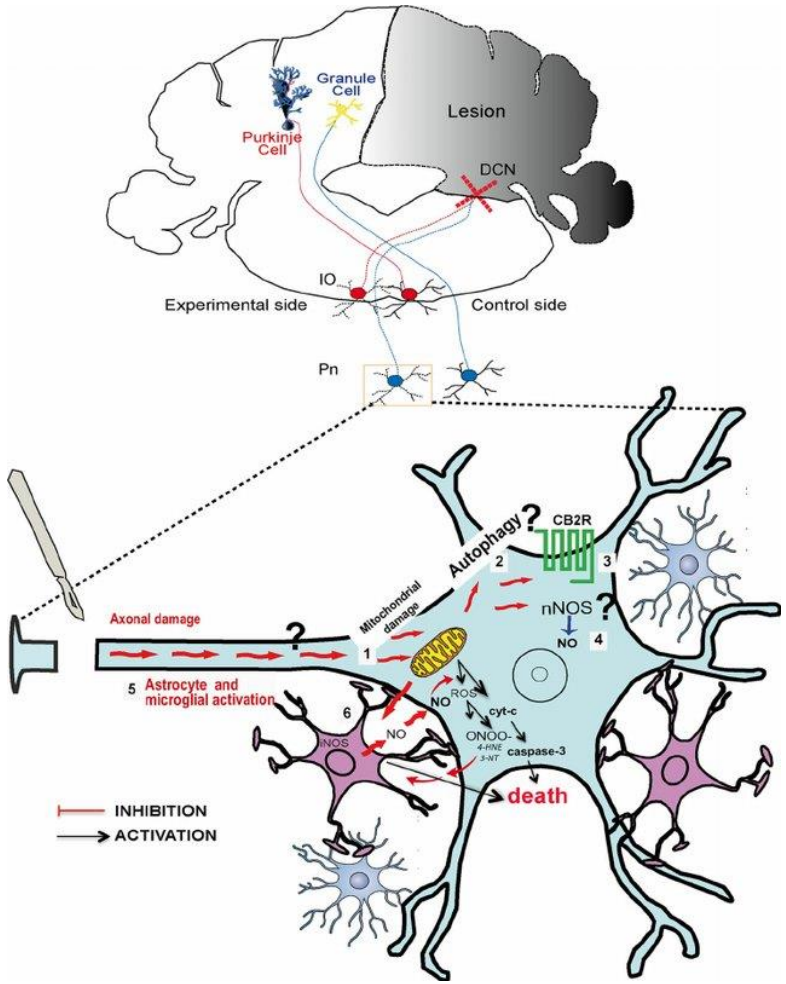
What about the neuroprotective potential of neuronal CB_2 signaling?

Hemicerebellectomized rats: a model for damage and remote cell death of neurons

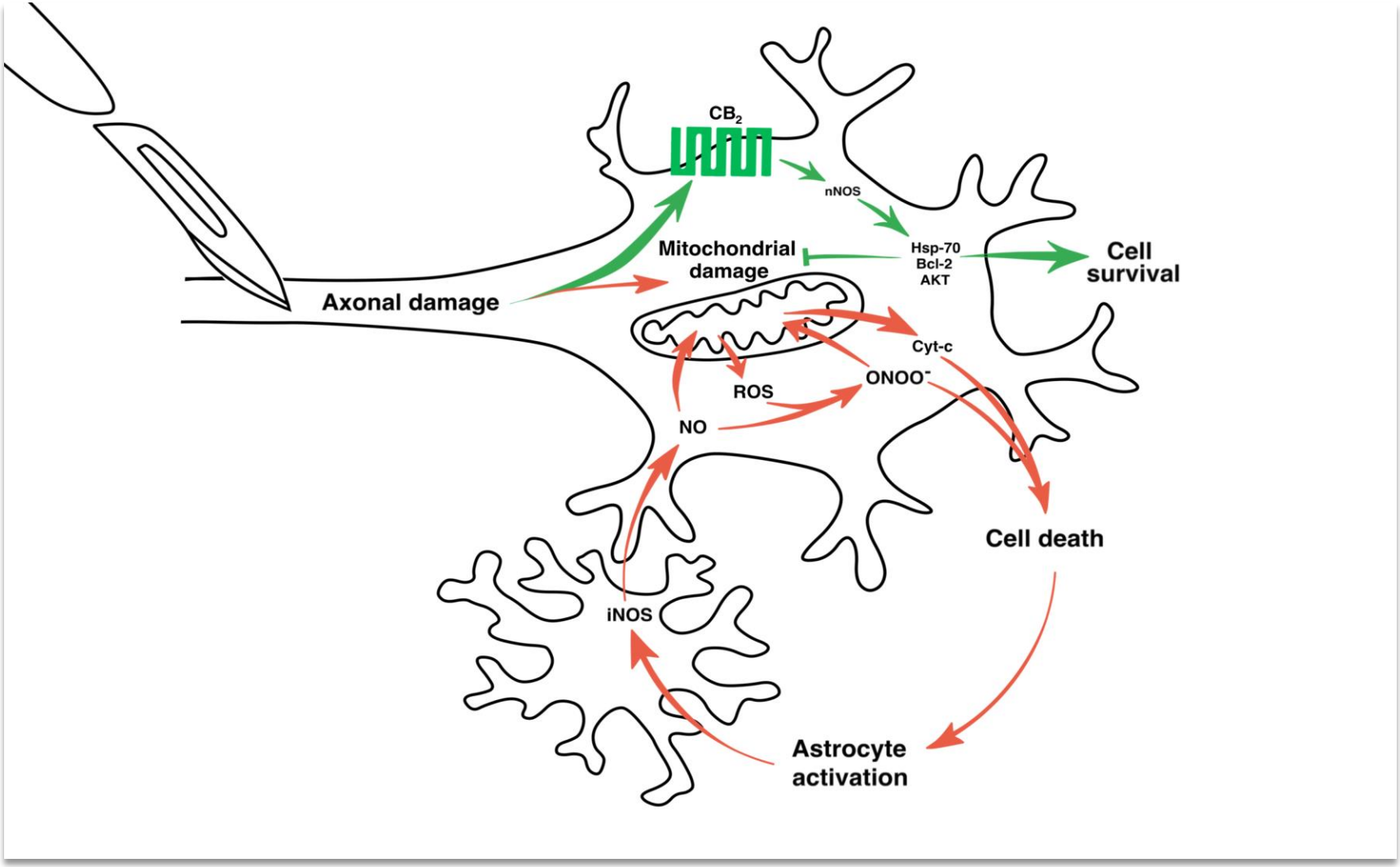


Delayed cell death (even 7-14 days) of remotely damaged neurons

- Glial activation
- Inflammation
- Oxidative/nitrative stress
- Apoptosis

Possible role of CB_2 signaling in modulating axotomy-induced neurodegeneration

- **Neuronal CB_2 is induced by neuron damage (i.e., axotomy)**
- **CB_2 agonists exert beneficial effects (improvement in motor function, attenuation of neuroinflammation and neurodegeneration)**
- **CB_2 has an opposing regulatory role on nNOS and iNOS which can determine survival or death of neurons**
- **CB_2 may be part of a protective mechanism that is both acutely and chronically expressed and/or activated upon brain damage, and operates at once and at multiple levels to orchestrate a series of pro-homeostatic responses**



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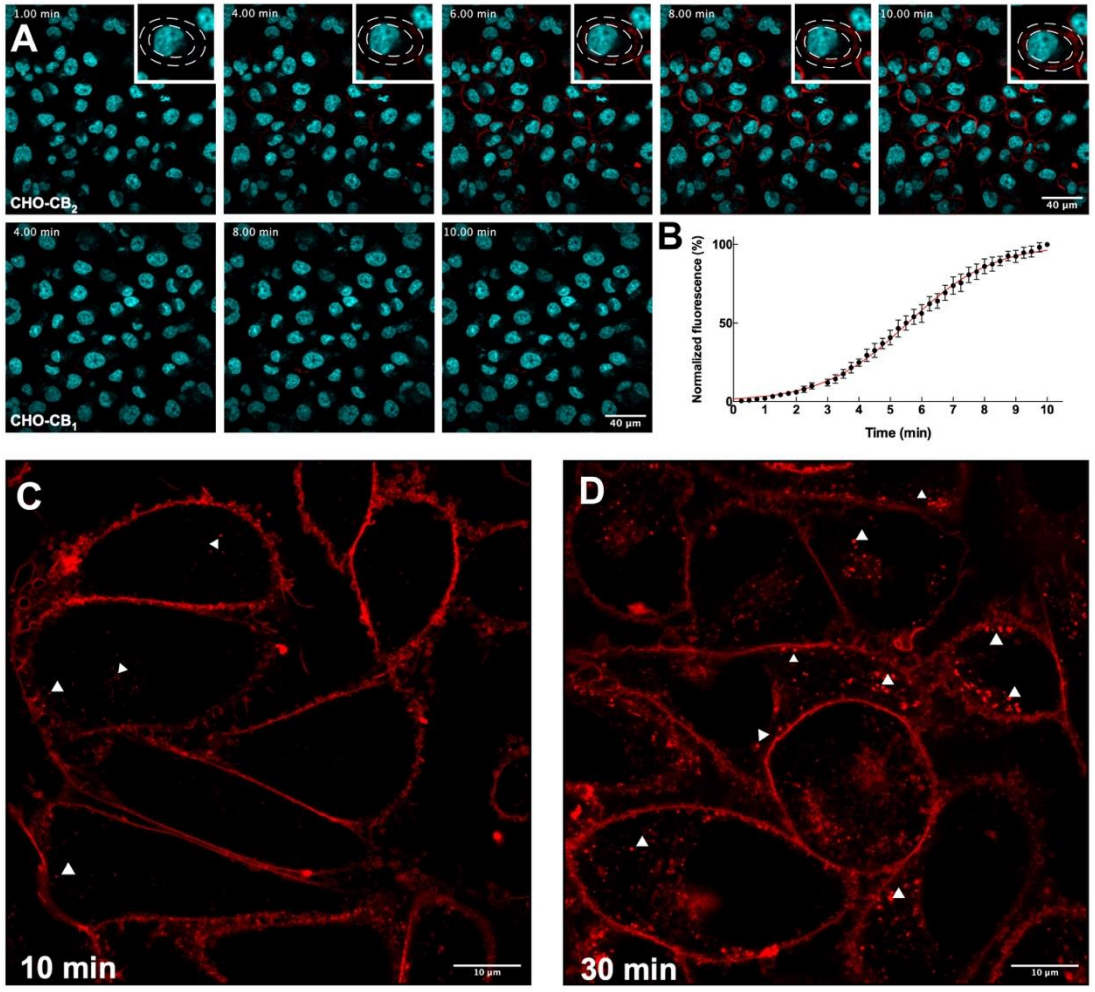
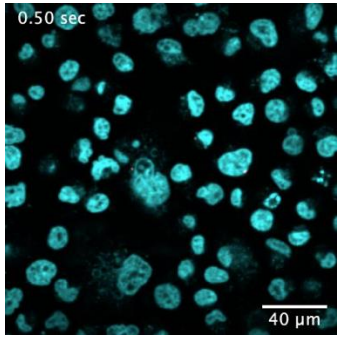
Live imaging of CB_2 receptors by new fluorescent probes

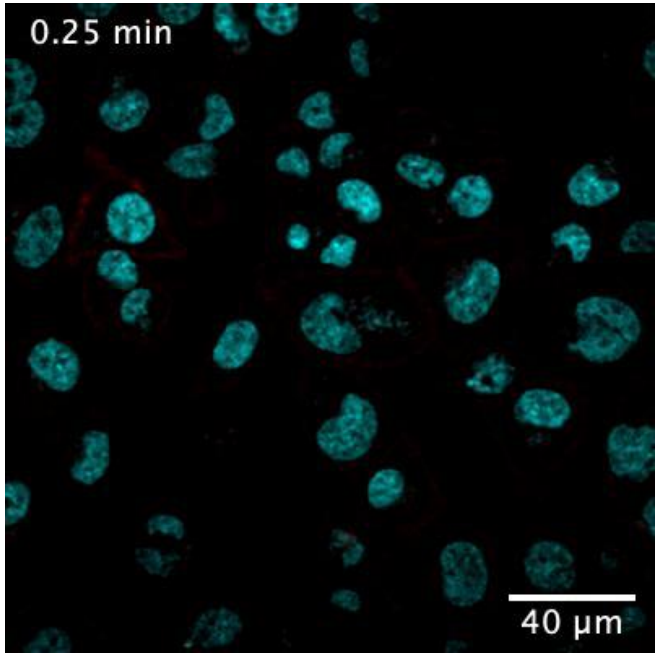


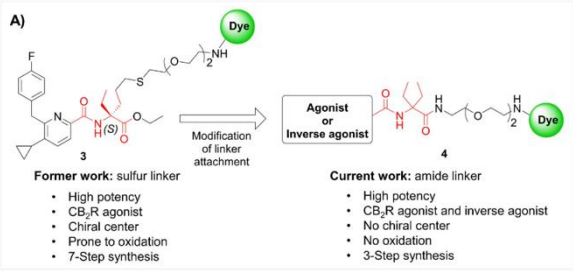
Video

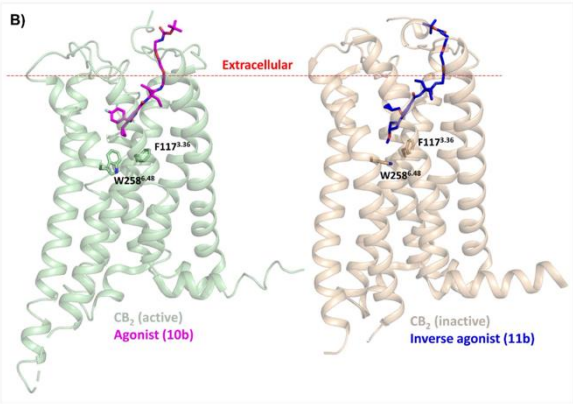
Cellule CB1



Cellule CB2







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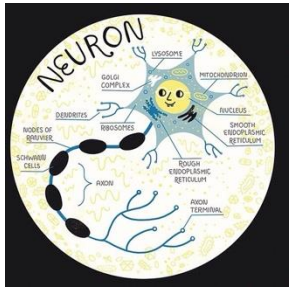
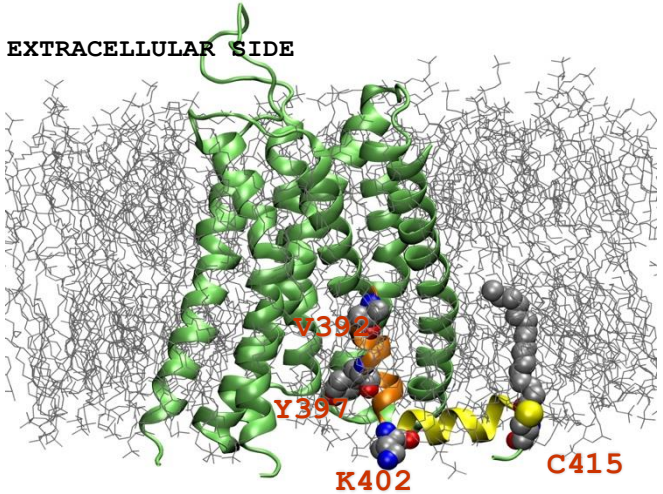


Interazioni dei recettori cannabici nel loro ambiente di membrana (CRAC, colesterolo, palmitoile)

- Simulazione *in silico* di interazioni proteina-proteina e proteina-lipide
- Studio di distribuzione subcellulare e co-localizzazione
- Dinamica molecolare: time- lapse imaging e saggi FRAP.



CB_1 NSTVNPIIYALRSKDLRHAFRSMFPSCEGTA
CB_2 NSMVNPVIYALRSGEIRSSAHHCLAHWKKCV
$A_{2A}AR$ NSVVNPFIYAYRIREFRQTFRKIIRSHVLRQ
β_2AR NSGFNPLIYCRSPDFRIAFQELLCLRRSSLK

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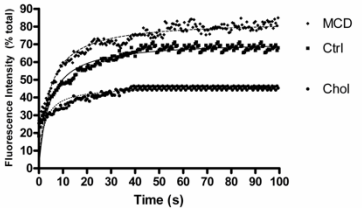
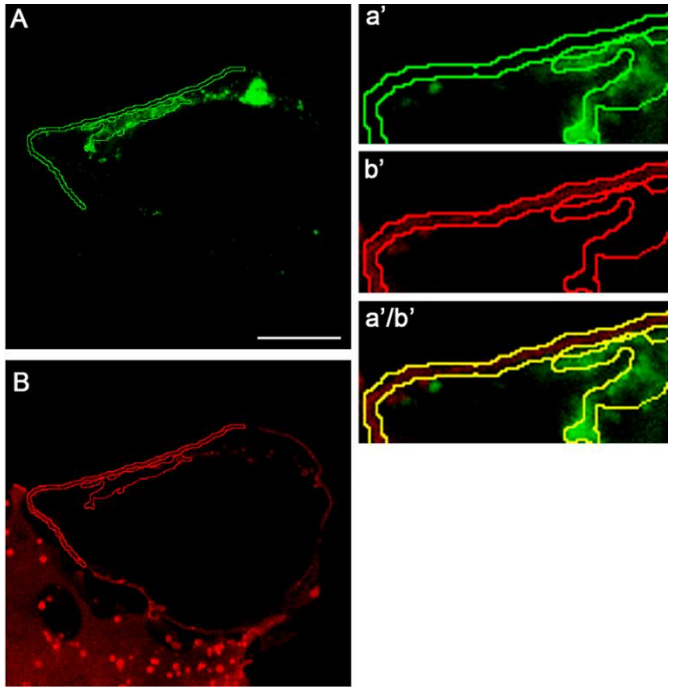
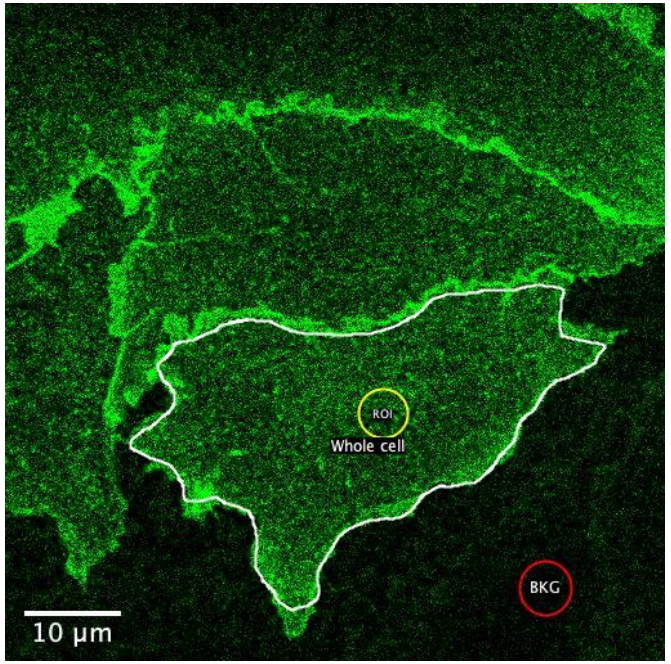


Colocalizzazione



Video FRAP



Conclusions

- The endocannabinoids, the type-1 and type-2 cannabinoid receptors (CB1 and CB2), and the transient receptor potential vanilloid 1 (TRPV1) channel, along with the enzymes and proteins for eCB synthesis, degradation, and transport, constitute a widespread endogenous signaling system termed the “endocannabinoid system” (ECS)

- In determining temporally and spatially precise control of neuronal and glial activity, the ECS is part of a widely distributed and multimodal signaling network involved in modulating every step of adult hippocampal neurogenesis

- The anxiolytic and anti-depressant effects of endocannabinoid-based drugs could be partly attributable to the ECS’s ability to counteract alterations in adult hippocampal neurogenesis induced by chronic stressors

Grazie per l’attenzione!