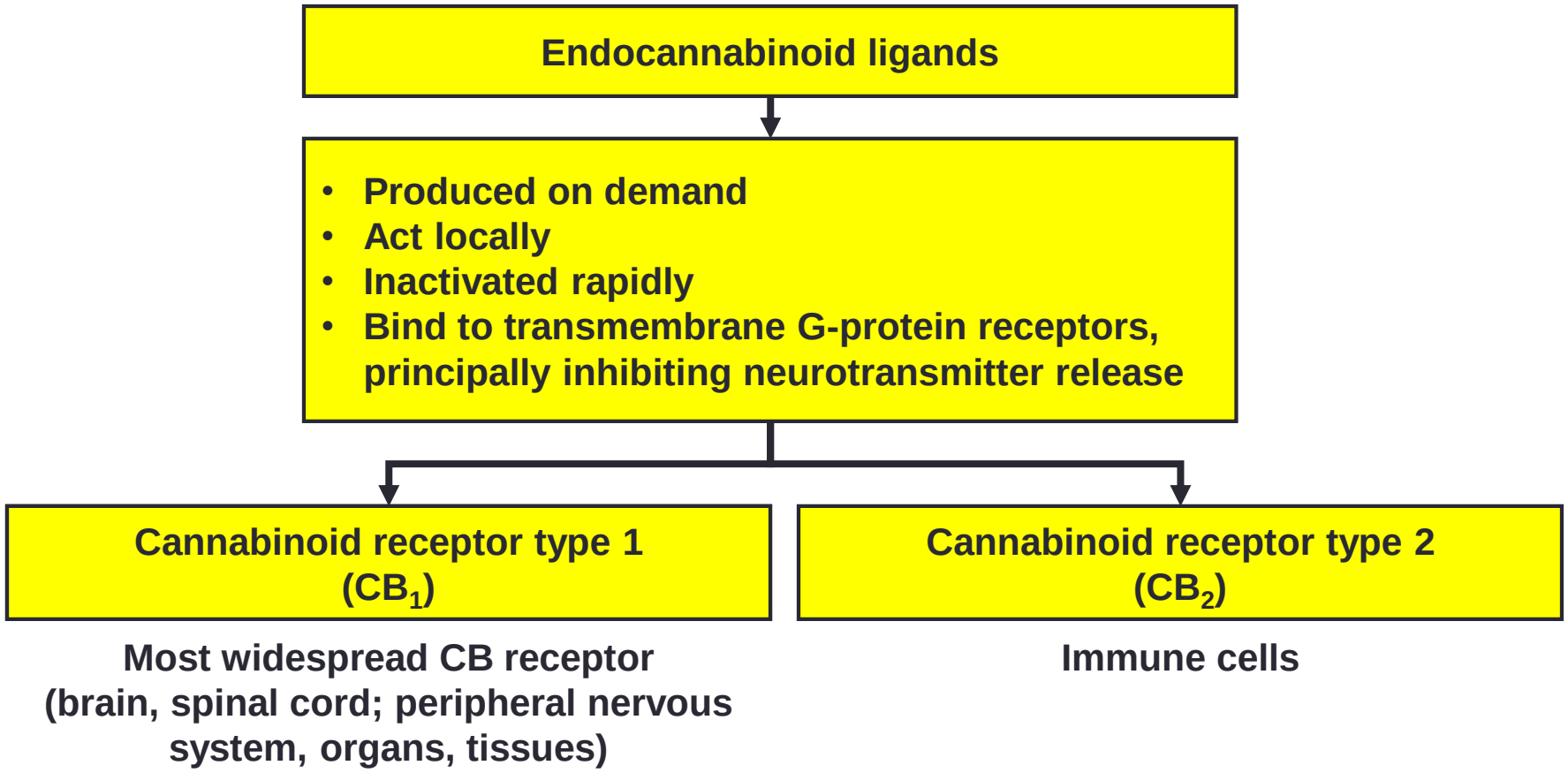
Endocannabinoid system (ECS): Overview

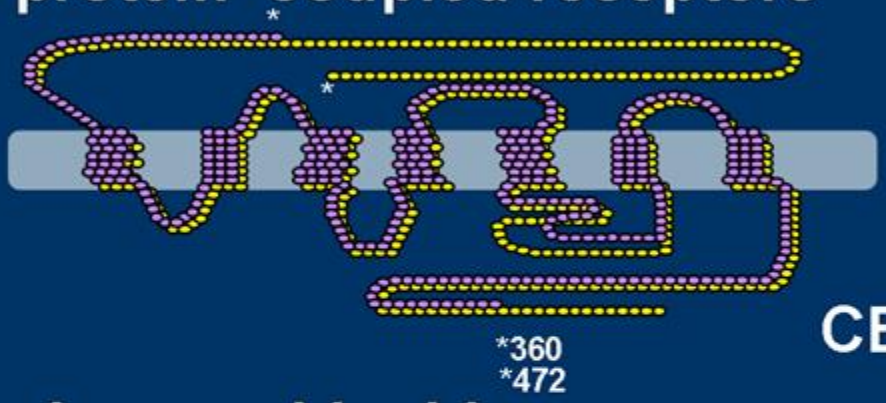


Gelfand EV, Cannon CP. *J Am Coll Cardiol*. 2006;47:1919-26.
Pagotto U et al. *Ann Med.* 2005;37:270-5.

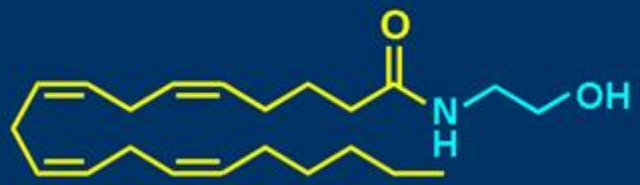
AEA also an endovanalloid at TRPV1 (with 5-20-fold lower affinity cf with CB1); also PPARγ

Key ECS Elements

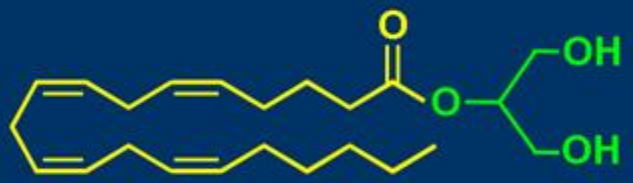
Cannabinoid receptors are G-protein–coupled receptors



Endocannabinoids



Anandamide



2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors

CB_1 receptor

- Central nervous system
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α-cells)

CB_2 receptor

- Immune cells and tissues
  - T cells, B cells
  - Macrophages
  - Dendritic cells
  - Spleen, tonsils
  - Adipose tissue

De Petrocellis et al. *Br J Pharmacol*. 2004;;141:765-774.
Pertwee et al. *Pharmacol Ther*. 1997;74:129-180.
Roche R et al. *Histochem Cell Biol*. 2006;126(2):177-187.

Cannabinoid System

- **CB1 and CB2 receptors**
- **Pain, movement, neuromodulation, smooth muscle, inflammation, cytoprotection, feeding, perception, reward, cognition**
- **Pre-synaptic at Dopamine, GABA, Glutamate, 5HT, NA, ACH…**
- **Cross-talk – endorphine, vanilloid - organs**
- **Effects – TNF, ILs, NO, oxygen radicals, anti-oxidant**
- **Endocannabinoids:**

Homeostatic super-modulatory system

Brain cannabinoids in chocolate

SIR — Chocolate craving, common in western societies, is still incompletely understood. Although sensory components of the nervous system are likely to be essential[1], the association of chocolate craving with certain drug-induced psychoses[2] suggests that pharmacologically active substances could also be involved. Attention in this respect has been focused primarily on the methylxanthines[3], which are thought to act as competitive antagonists at adenosine receptors[4]. We report here on a novel group of pharmacological constituents of chocolate, whose main target may be the endogenous cannabinoid system of the brain.

Anandamide (*N*-arachidonoylethanolamine) is a brain lipid that binds to cannabinoid receptors with high affinity and mimics the psychoactive effects of plant-derived cannabinoid drugs[5]. It is released from neurons[6] and is rapidly broken down by a selective enzyme activity[7], suggesting that it may be an endogenous cannabinoid neurotransmitter or neuromodulator. We considered that chocolate, which is rich in fat, might contain lipids chemically and pharmacologically

coylethanolamine inhibit anandamide hydrolysis in rat brain microsomes, a reaction catalysed by anandamide amidohydrolase activity[7] (Fig. 2*a*). Moreover, *N*-linoleoylethanolamine produces a similar inhibitory effect in intact cells. Rat cortical astrocytes in culture hydrolyse

order is *N*-oleoylethanolamine> *N*-linoleoylethanolamine >anandamide = 0.05–57 μg

Further experiments are necessary to determine whether the concentrations of

- Chocolate may inhibit the natural breakdown of anadamide. This means that natural anandamide (or introduced anandamide) may stick around longer, making us feel good longer, when we eat chocolate.

Nature **382** (6593): 677–8

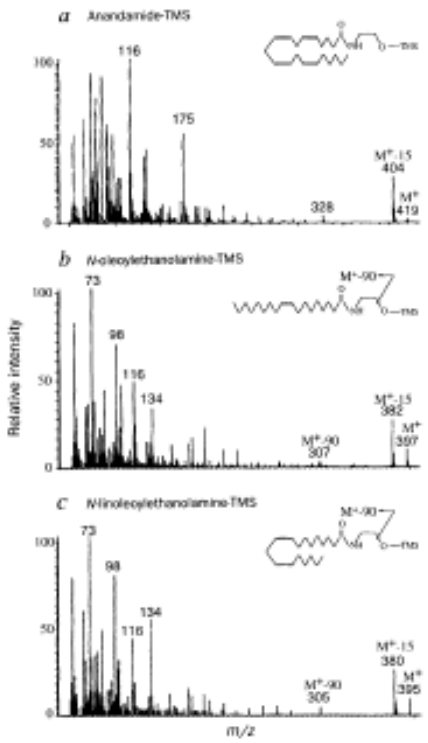
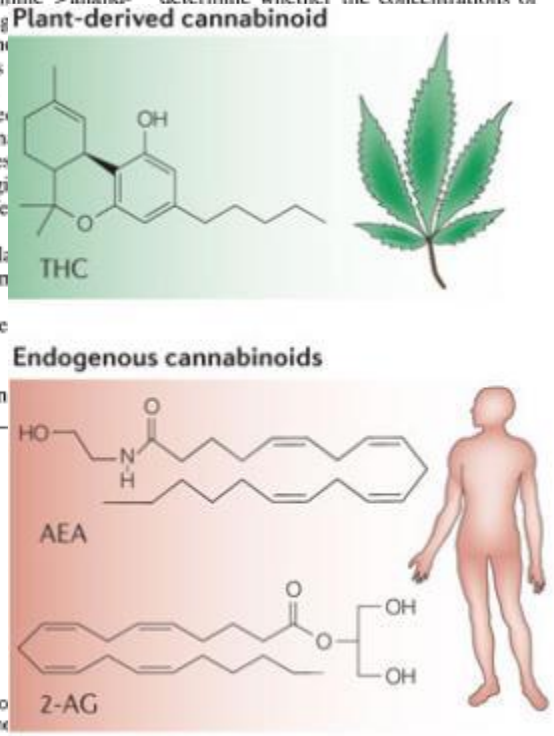
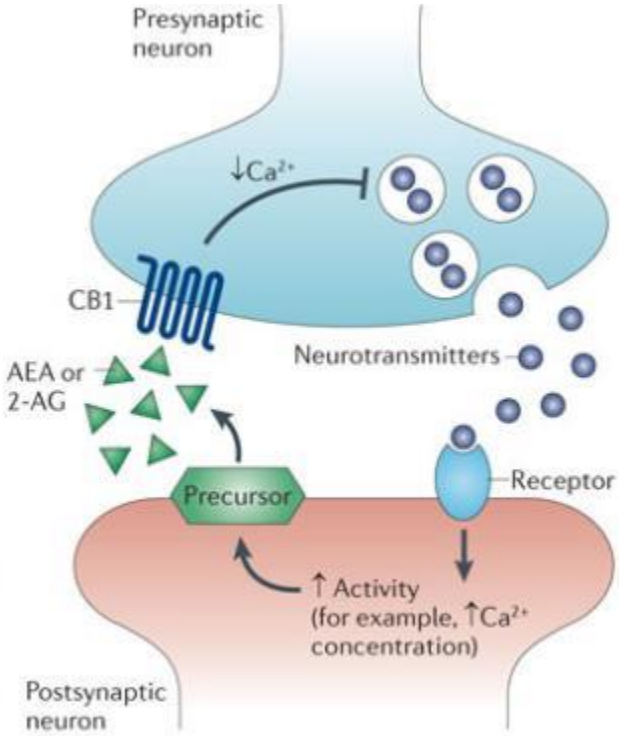
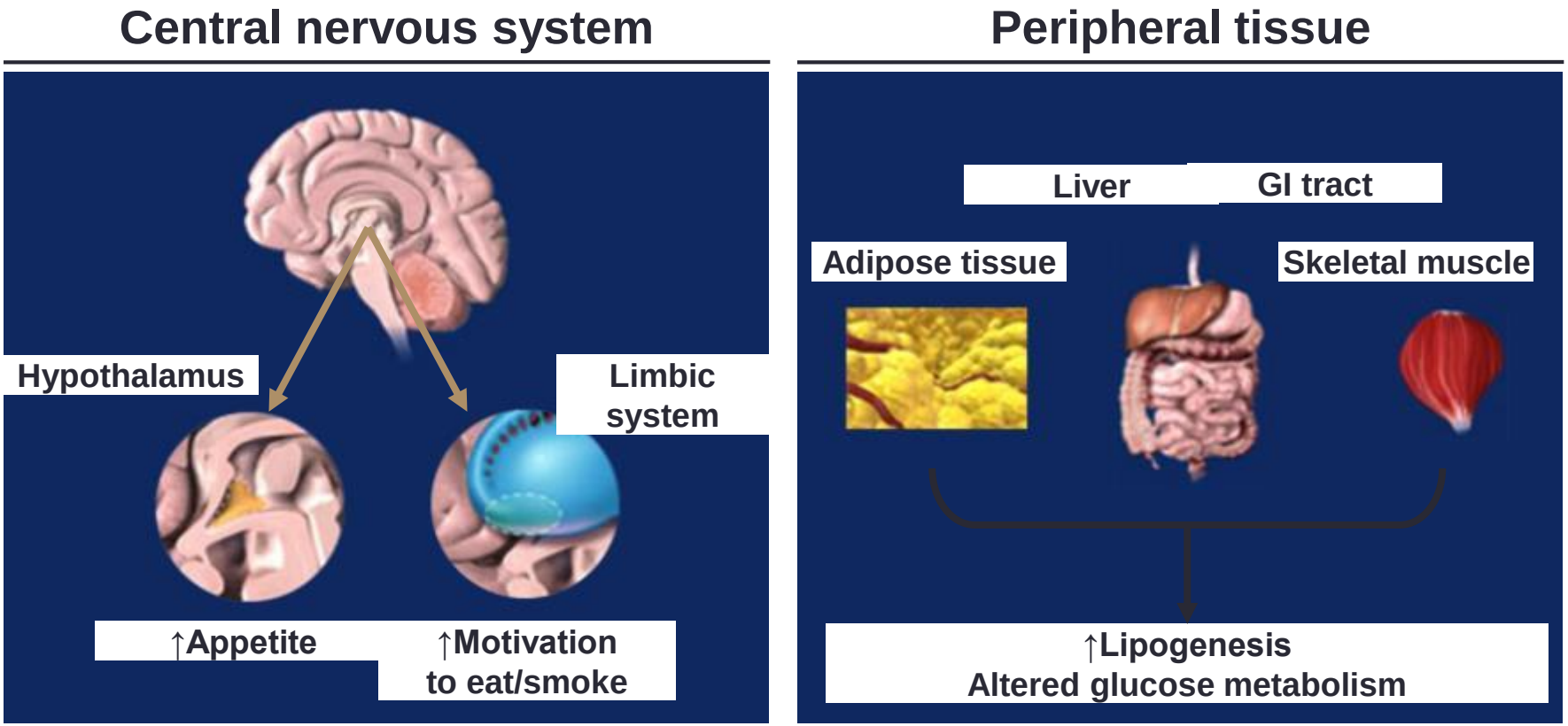


FIG. 2 *a*, Effects of *N*-oleoylethanolamine (circles) and *N*-linoleoylethanolamine (squares) on rat brain microsome anandamide amidohydrolase activity. *b*, Effect of *N*-linoleoylethanolamine on [^{3}H]anandamide degradation by rat co
linoleoylethanolamin
of *N*-linoleoylethanola
microsomes (0.2 mg
containing 100 nM [



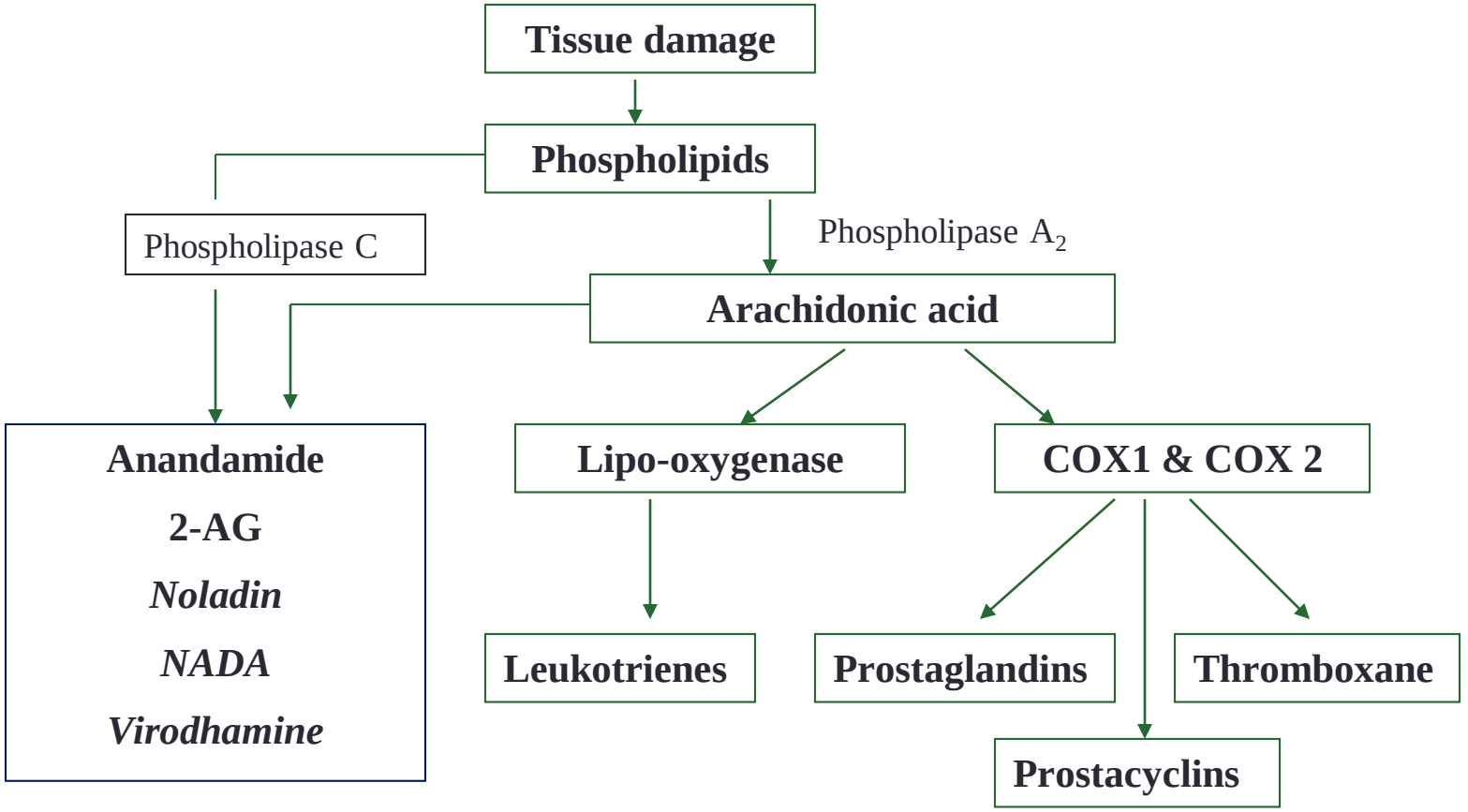


Implications of CB_1 receptor activation



Gelfand EV, Cannon CP. *J Am Coll Cardiol*. 2006;47:1919-26.
Pagotto U et al. *Ann Med.* 2005;37:270-5.

Biosynthesis of endocannabinoids and the arachidonic acid pathway



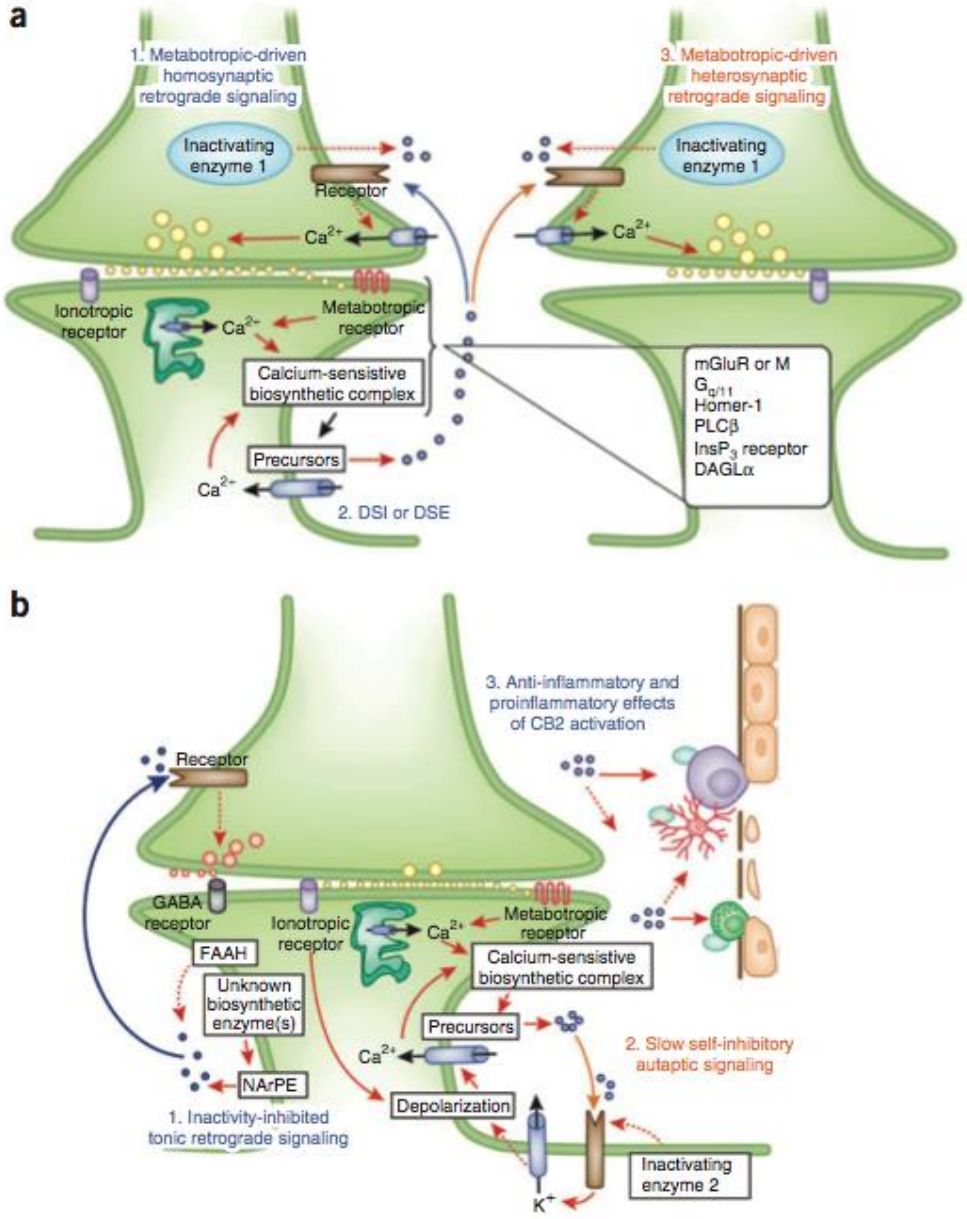
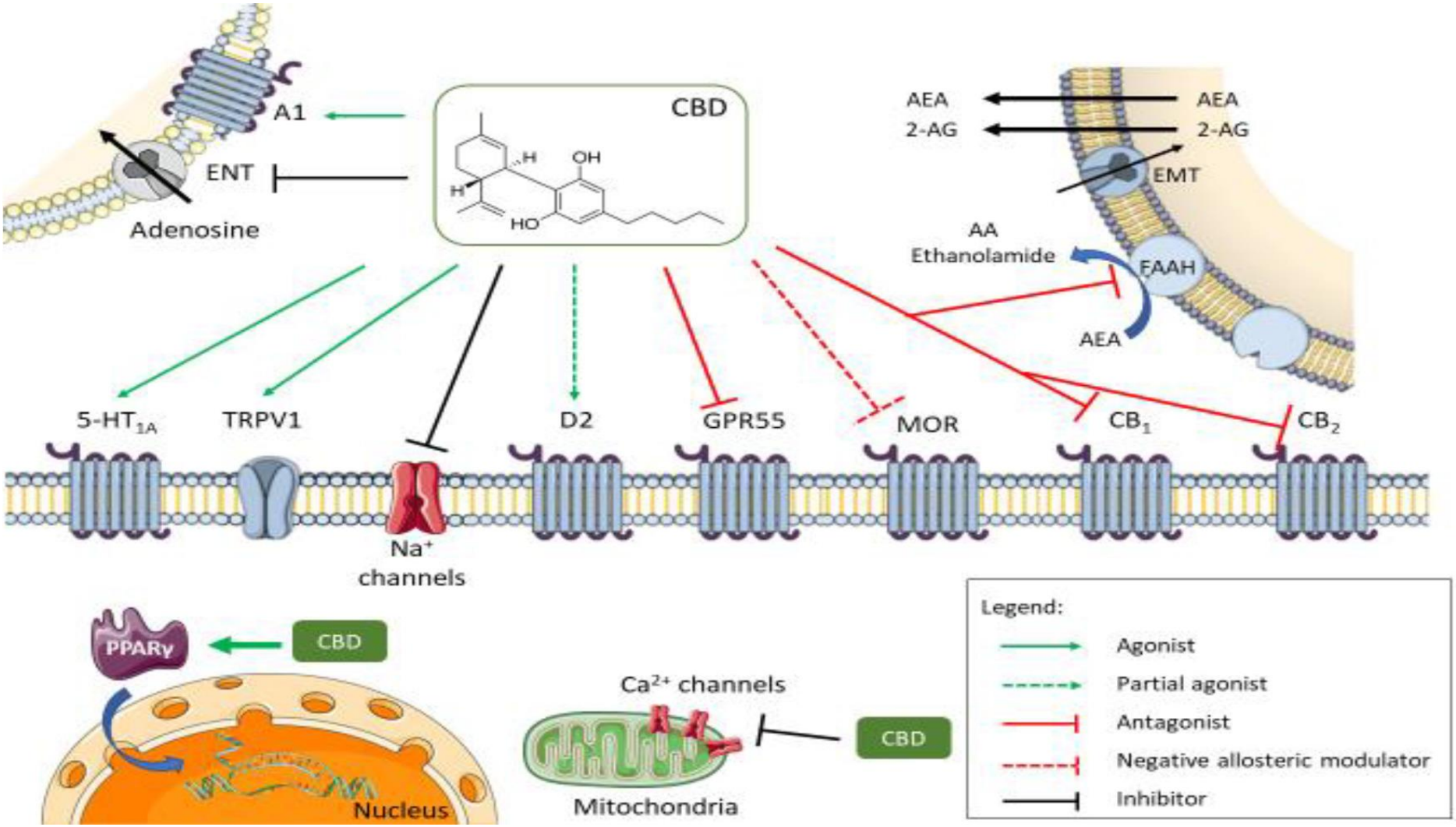


Figure 1 Endocannabinoid metabolism in synaptic plasticity and neuroinflammation. (**a**) When their receptor is presynaptic (as is often the case of CB_1 receptors), signals produced postsynaptically might act retrogradely to reduce neurotransmitter release in a way that is either 'homosynaptic metabotropic-driven' (1) or 'depolarization-driven' (that is, DSE or DSI) (2). One such signal is 2-arachidonoylglycerol (2-AG), as its Ca^{2+}-sensitive biosynthetic machinery, comprising phospholipase Cβ (PLCβ) and diacylglycerol lipase-α (DAGLα), is located on the somatodendritic membrane near metabotropic receptors (for example, mGluR1, mGluR5 or M1 receptors), $G_{q/11}$ and Homer-1, as well as inositol trisphosphate ($InsP_3$) receptors on the endoplasmic reticulum. In retrograde signaling, the enzyme responsible for inactivation of the signal ('inactivating enzyme 1') should be presynaptic, as is the case of monoacylglycerol lipase (MAGL) for 2-AG. In 'heterosynaptic metabotropic-driven' retrograde signaling (3), endocannabinoids act at synapses near (usually within 20 μm) those from whose activity they are generated. (**b**) In some pyramidal neurons of the CA1 region of the hippocampus, anandamide acts as a 'tonic' (that is, driven by neither depolarization nor metabotropic receptor activation) retrograde inhibitor of the release of GABA from certain inhibitory interneurons (1). In this case, chronic inactivity of interneurons results, through an unknown mechanism, in upregulation of postsynaptic fatty acid amide hydrolase (FAAH), enhanced degradation of anandamide and inhibition of this tonic neuromodulatory effect, with subsequent disinhibition of some neurons[46]. 2-AG can also act on the same postsynaptic neuron by which it has been generated and inhibit the activity of the latter through postsynaptic CB_1 activation and subsequent stimulation of G protein–coupled inward rectifier K^+ channels, leading to hyperpolarization. This mechanism, known as 'long-lasting somatodendritic slow self-inhibition' (2), is triggered by excessive postsynaptic activity[22] and terminated by postsynaptic inactivating enzymes ('inactivating enzyme 2'), such as α,β-hydrolase-6 (ref. 20) or FAAH. It is not clear whether 2-AG involved in SSI is of extracellular or intracellular origin. Finally, via CB_2 receptors, endocannabinoids can downregulate astrocyte and microglial cell overactivation during neuroinflammatory disorders, thus protecting them (3). However, endocannabinoids might also attract macrophages and T-lymphocytes into the brain after disruption of the blood brain barrier and contribute to sustained neuroinflammation[2]. Blue dots, neuromodulatory mediator (for example, 2-AG); yellow dots, excitatory or inhibitory neurotransmitters; dark blue dots, anandamide; green ovals, CB_2 receptors; solid arrows, activation or movement; broken arrows, inhibition or inactivation; large yellow circles, secretory vesicles.

Phyto-Cannabinoids

- **Cannabinoids - molecules unique to the cannabis plant**
- **Initial focus on two principal cannabinoids:**
  THC (Tetrahydrocannabinol) **and CBD** (Cannabidiol)
  - **THC** **Analgesic, Anti-spasmodic, Anti-tremor, Anti-inflammatory, Appetite stimulant, Anti-emetic**
  - **CBD** **Anti-inflammatory, Anti-convulsant, Anti-psychotic Anti-oxidant, Neuroprotective, Immunomodulator**
- **Other Cannabinoids**
  - **CBC** (Cannabichromene)
  - **CBG** (Cannabigerol)
  - **CBN** (Cannabinol)
  - **THC-V / CBC-V** (Propyl derivatives)

Diversity of molecular targets and signaling pathways for CBD



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Endocannabinoids & AED properties

- Several cannabinoids (Δ^9-tetrahydrocannabinol: Δ^9-THC, cannabidiol: CBD, Δ^9-tetrahydrocannabivarin: Δ^9-THCV and cannabidivarin: CBDV) are anticonvulsant in a variety of animal models of seizure and epilepsy (Consroe & Wolkin, 1977; Hill et al., 2012a; Hill et al., 2010; Jones et al., 2010).
- CB_1 cannabinoid receptor (CB_1R) agonism is anti-epileptiform and anticonvulsant (Chesher & Jackson, 1974; Deshpande et al., 2007b; Wallace et al., 2003; Wallace et al., 2001)
- The notable psychoactivity associated with CB_1R activation hinders the prospective clinical utility of this target.
- CBD, which exerts effects via, as yet unknown, non- CB_1R mechanisms *in vitro*, *in vivo* and in humans (Consroe et al., 1982; Cunha et al., 1980; Jones et al., 2010; Wallace et al., 2001).
- CBD has low affinity for CB1 and CB2 receptors (Pertwee, 2008)

Endocannabinoids & neuroprotection

- Anandamide (arachidonoyl-ethanolamide) and 2-arachidonoyl glycerol (2-AG).
- Both anandamide and 2-AG bind to the cannabinoid receptors CB_1 (present principally in the central nervous system and to a lesser extent in the peripheral nervous system) and CB_2 (present almost exclusively in the peripheral nervous system).
- These receptors are activated by THC, accounting for the effects of cannabis on the nervous system.
- A nonpsychotropic constituent of cannabis, cannabidiol, effectively treats major seizures in animals, and HU-211 (**Dexanabinol®**) is neuroprotective during brain trauma.
- Paradoxically, neither cannabidiol nor HU-211 binds to CB_1 or CB_2 receptors.

Science 3 October 2003:
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DOI: 10.1126/science.1088208

RESEARCH ARTICLE

CB1 Cannabinoid Receptors and On-Demand Defense Against Excitotoxicity

Giovanni Marsicano[1,*], Sharon Goodenough[2,4,*], Krisztina Monory[1,*], Heike Hermann[1], Matthias Eder[3], Astrid Cannich[1], Shahnaz C. Azad[3,5], Maria Grazia Cascio[6], Silvia Ortega Gutiérrez[7], Mario van der Stelt[6], Maria Luz López-Rodríguez[7], Emilio Casanova[8], Günther Schütz[8], Walter Zieglgänsberger[3], Vincenzo Di Marzo[6], Christian Behl[2,4,†], Beat Lutz[1,†‡]

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* These authors contributed equally to this work.

† These authors share senior authorship.

ABSTRACT

Abnormally high spiking activity can damage neurons. Signaling systems to protect neurons from the consequences of abnormal discharge activity have been postulated. We generated conditional mutant mice that lack expression of the cannabinoid receptor type 1 in principal forebrain neurons but not in adjacent inhibitory interneurons. In mutant mice,the excitotoxin kainic acid (KA) induced excessive seizures in vivo. The threshold to KA-induced neuronal excitation in vitro was severely reduced in hippocampal pyramidal neurons of mutants. KA administration rapidly raised hippocampal levels of anandamide and induced protective mechanisms in wild-type principal hippocampal neurons. These protective mechanisms could not be triggered in mutant mice. The endogenous cannabinoid system thus provides on-demand protection against acute excitotoxicity in central nervous system neurons.

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An endogenous cannabinoid (2-AG) is neuroprotective after brain injury

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Traumatic brain injury triggers the accumulation of harmful mediators that may lead to secondary damage[1, 2]. Protective mechanisms to attenuate damage are also set in motion[2]. 2-Arachidonoyl glycerol (2-AG) is an endogenous cannabinoid, identified both in the periphery[3] and in the brain[4], but its physiological roles have been only partially clarified[5, 6, 7]. Here we show that, after injury to the mouse brain, 2-AG may have a neuroprotective role in which the cannabinoid system is involved. After closed head injury (CHI) in mice, the level of endogenous 2-AG was significantly elevated. We administered synthetic 2-AG to mice after CHI and found significant reduction of brain oedema, better clinical recovery, reduced infarct volume and reduced hippocampal cell death compared with controls. When 2-AG was administered together with additional inactive 2-acyl-glycerols that are normally present in the brain, functional recovery was significantly enhanced. The beneficial effect of 2-AG was dose-dependently attenuated by SR-141761A, an antagonist of the CB_1 cannabinoid receptor.

OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

Modulation of Pilocarpine-Induced Seizures by Cannabinoid Receptor 1

Rebecca L. Kow, Kelly Jiang, Alipi V. Naydenov, Joshua H. Le, Nephi Stella, Neil M. Nathanson

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Abstract

Administration of the muscarinic agonist pilocarpine is commonly used to induce seizures in rodents for the study of epilepsy. Activation of muscarinic receptors has been previously shown to increase the production of endocannabinoids in the brain. Endocannabinoids act at the cannabinoid CB_1 receptors to reduce neurotransmitter release and the severity of seizures in several models of epilepsy. In this study, we determined the effect of CB_1 receptor activity on the induction in mice of seizures by pilocarpine. We found that decreased activation of the CB_1 receptor, either through genetic deletion of the receptor or treatment with a CB_1 antagonist, increased pilocarpine seizure severity without modifying seizure-induced cell proliferation and cell death. These results indicate that endocannabinoids act at the CB_1 receptor to modulate the severity of pilocarpine-induced seizures. Administration of a CB_1 agonist produced characteristic CB_1-dependent behavioral responses, but did not affect pilocarpine seizure severity. A possible explanation for the lack of effect of CB_1 agonist administration on pilocarpine seizures, despite the effects of CB_1 antagonist administration and CB_1 gene deletion, is that muscarinic receptor-stimulated endocannabinoid production is acting maximally at CB_1 receptors to modulate sensitivity to pilocarpine seizures.