



# The Endocannabinoid System: Deep Dive



Lex Pelger

Scientist, Educator + Host of Psymposia  
[psymposia.com](https://psymposia.com)



SUPPORT US  
ON PATREON



**holisticcannabis**  
ACADEMY



# The Endocannabinoid System: Widespread + Influential

- The old debate of information flow through neurons – soup + spark
- In classic neurotransmission theory:
  - Step #1: Electricity within the neurons rockets down to the end of the axon to tell the synapses to release the neurotransmitter
  - Step #2: Neurotransmitters pass across the synapse + deliver the message from the upstream (pre-synaptic neuron) to the downstream (post-synaptic) neuron





# Neuronal Architecture, or: To Fire or Not to Fire?

- Dendrites – information collectors + collators
- Central cell body chemical messengers work to determination if + what to release
- When released, a chain reaction starts – similar to water flowing, information passes down through the axons



# Retrograde Signaling: Natural-calming CB1 Receptors

- If activated, CB1 receptors inhibit cyclic adenosine monophosphate (cAMP) – the most common “second messenger”
- Endocannabinoid molecules act as mediators of retrograde transmission
- When detecting information sent downstream, send calming message back upstream at the pre-synaptic connection





# Retrograde Signaling: Vital for Regulating Synaptic Homeostasis

- Endocannabinoids can retrograde, or go backwards, in this signaling process to calm
- Produce long-term + short-term inhibitory + excitatory plasticity
- Endocannabinoid lipid messengers can change ion channels (the electricity of the cell) + impact various receptors



# Genetic Polymorphisms: New, Contradictory yet Vital + Fascinating

- CB1 receptors are widespread in the brain's higher areas
- Density + variation helps explain variation of action/reaction among individuals
- Associated with systems affecting stress, energy balance + immune function





# Genetic Polymorphisms: Types of CB1 Receptors

- As individuals are different, so is the coding of CB1 protein embedded into the cell membranes among individuals
- Coding – 4 exons, 3 introns + 2 promoters
- DNA turned into MRNA
- MRNA (working blueprint making the actual protein) contains the exons
- Promoters help decide how much will be produced + used
- Introns have historically been called “junk DNA”



# Genetic Polymorphisms: The Importance of Exons, Introns + Promotors

- Nature is conservative
- Translation of exons is of high-functional importance
- These different splice variants, seem to change how receptor binding occurs
- 1995: first tri-nucleotide repeat of the AAT pattern was found in an untranslated region of the DNA (an intron) with functional changes downstream







# Genetic Polymorphisms: Importance of SNPs

- Single Nucleotide Polymorphism, or SNP
- SNP – one letter in the genetic code is different
- First SNP found in CB1 changed the common nucleotide G to the rarer one, A
- Should not have occurred because the same amino acid is coming out of the code
- Does change how the MNRA passes on, but we do not know why
- SNPs linked to phenotypes – how this can alter transcription factor binding of MNRA + change the quantity



# Genetic Polymorphisms: The effects of SNPs

- Can affect reactivity + impulsivity
- CA or AA genotypes have significantly reduced activation in the medulla compared with those with the CC genotype when faced with a threat
- Impulsivity + reactivity changes in accordance with the length of the AAT repeat
- SNPs + genetic variations also appear to be racially segregated
- Endocannabinoid polymorphism linkages may be found anorexia, substance abuse, depression, autism, learning, memory + individual reaction to amphetamines





# Endocannabinoid Systems: Gender Differences

- Males tend to be researched more often + use grey matter versus white matter
- Endocannabinoids affect males + females differently
- Men – elevated food intake, differences in energy homeostasis, less sexual behavior
- Females – pain relief, increased motor activity effects, depression relief, more sexual behavior



# Metabolites + Clinical Endocannabinoid Deficiency

- Making adjustments to neurotransmitter levels is common practice in medicine for many ailments
- Does a clinical endocannabinoid deficiency help explain the ambiguous + seemingly inexplicable pain disorders such as migraine, fibromyalgia, irritable bowel syndrome (IBS) plus other autoimmune disorders?





# Drug Interactions + Endocannabinoid Systems Interaction

- Anticholinergics: atropine + scopolamine may increase tachycardia of THC
- Anticholinesterases: physostigmine antagonizes psychotropic + tachycardia effects of THC
- Antidepressants (SSRIs): THC may increase fluoxetine effect  
Antidepressants (tricyclic): amitriptyline's tachycardic, hypotensive + sedation may be enhanced
- Barbiturates: CNS depression enhanced - may reinforce tachycardic effects - clearance of barbiturates may be severely decreased



# Drug Interactions + Endocannabinoid Systems Interaction (continued)

- Benzos: CNS + respiratory depression may be increased - antiepileptic effect may be enhanced
- Beta-blockers: reduce THC tachycardia
- Cocaine: nasal absorption + tachycardia may be enhanced
- Dopamine agonists: D2 receptor agonists might increase analgesia of THC







# Drug Interactions + Endocannabinoid Systems Interaction (continued)

- Ethanol: CNS impairment enhanced
- Glaucoma: additive for IOP decrease
- Ketamine: possible additive CNS depression
- Neuroleptics: THC may antagonize antipsychotic actions – may improve clinical response in motor disorders
- NSAIDs: antagonize THC effects – indomethacin reduces high + tachycardia





# Drug Interactions + Endocannabinoid Systems Interaction (continued)

- Opiates: enhances sedation + analgesia
- Phenothiazines: prochlorperazine attenuates THC psychotropic + increases antiemetic
- Reserpine: THC increases reserpine hyperkinesia
- Sympathomimetics: additive tachycardia + hypotension with amphetamines + epinephrine

