The future of cannabis-based therapeutics

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Cannabis: a short history

1845  Cannabis is introduced in modern science

1854-1942  Cannabis is listed in the USP as analgesic, antispasmodic

1937  Marihuana Tax Act: Cannabis becomes illegal

1944-1964  Discovery of THC

1970  Controlled Substance Act: Illegality is confirmed

1988-1990  Discovery of cannabinoid receptors

1992-1999  Discovery of the brain endocannabinoid system

2018  Medical use of cannabis legal in 30 States and DC
How does cannabis work?

Cannabis sativa L.

Δ⁹-THC

Cannabinoid receptors
Brain, peripheral neurons, adipocytes, hepatocytes, etc.

Innate and adaptive immune cells (B lymphocytes, macrophages)

Two cannabinoid receptors

CB₁

CB₂
CB₁: main cannabinoid receptor in the human brain
Cannabinoid receptors outside the brain
Two subtypes: CB₁ and CB₂

CB₁
Blood vessels: vascular resistance and blood pressure

CB₁
Kidney: vascular resistance

CB₁ and CB₂
White blood cells: Immune response

CB₁
Lungs: bronchial reactivity

Small intestine: hunger

Large intestine: contractility

Peripheral nerve terminals: Pain control
The body’s own cannabis

Cannabinoid receptors

Endocannabinoids

Δ⁹-THC

feeding
emotion
pain
memory
reward
First known lipid-based neurotransmitters
Produced upon demand, rapidly destroyed
Functionally different, but in subtle ways

Anandamide and 2-AG

2-AG
Point-to-point retrograde messenger

Anandamide
Modulatory transmitter
2-AG mediates point-to-point ‘retrograde signaling’ at CNS synapses

The enzyme DGL forms 2-AG when there is need for it
Stopping retrograde signals

The enzyme MGL degrades 2-AG when it is no longer needed.
Anandamide acts as a ‘local modulatory signal’

Social contact

Hypothalamus (PVN)

Oxytocin neuron

Anandamide

CB₁

Oxytocin receptor

Nucleus accumbens
Formation and deactivation of anandamide

The enzyme NAPE-PLD forms anandamide when there is need for it.

The enzyme FAAH degrades anandamide when it is no longer needed.
Anandamide and 2-AG

First known lipid-based neurotransmitters
Produced upon demand, rapidly destroyed
Functionally different, but in subtle ways

2-AG
Point-to-point retrograde messenger
Many functions in CNS and periphery...

Anandamide
Modulatory transmitter
CNS: social behavior, stress response
Periphery: pain

Many functions in CNS and periphery...
The endocannabinoid system is the port of entry for THC into the body.

- Lipid precursors in cell membranes
- Biologically active endocannabinoids
- Metabolites, some inactive, some active via non-CB mechanisms

Δ⁹-THC

CBR
Can we use endocannabinoid signals for therapy?

Lipid precursors in cell membranes

Biologically active endocannabinoids

Metabolites, Some inactive, some active via non-CB mechanisms

Cannabidiol?

Blocking ECB degradation enhances the system’s intrinsic regulatory functions

Greater selectivity, safety than direct CBR activation
Thank you!

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