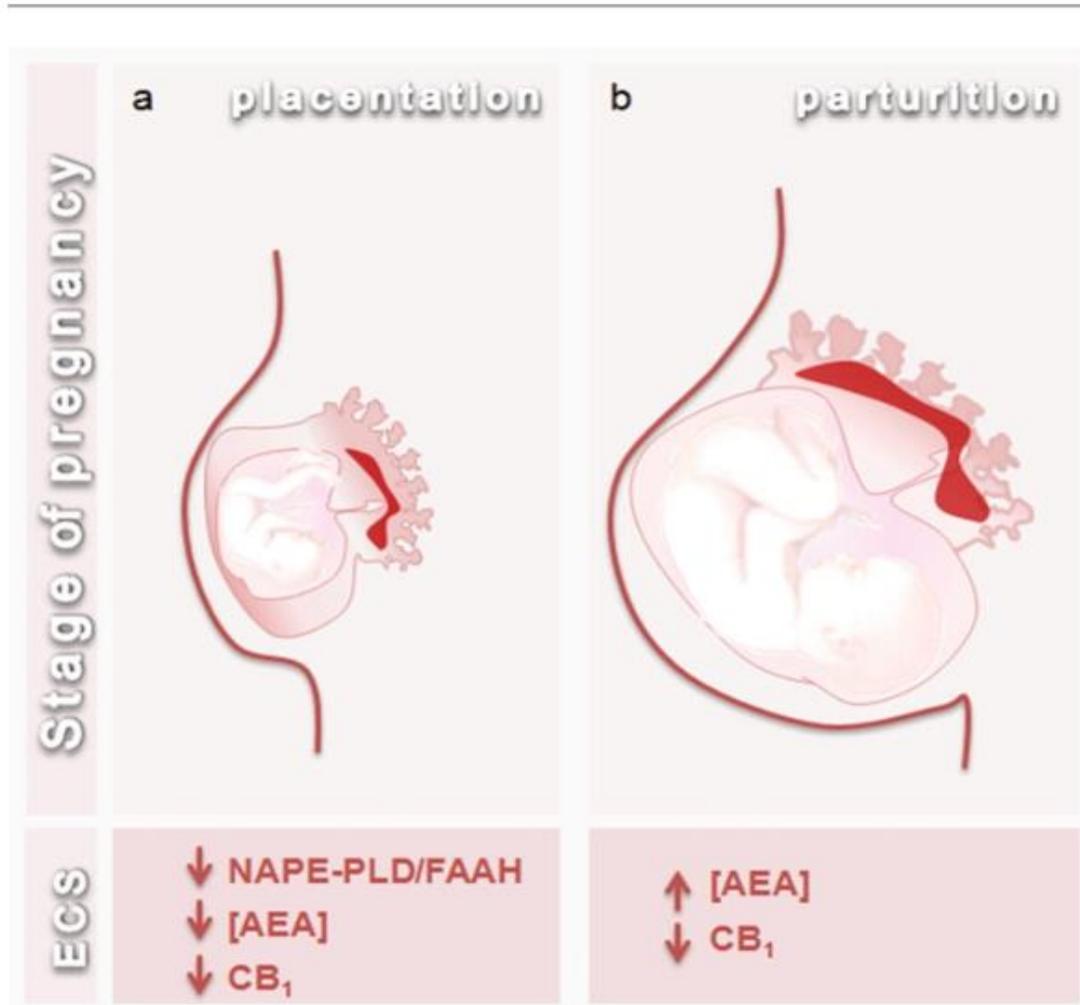


NEW UNDERSTANDINGS OF THE ENDOCANNABINOID SYSTEM & WOMEN'S HEALTH



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Prime Directive of Life:

Health

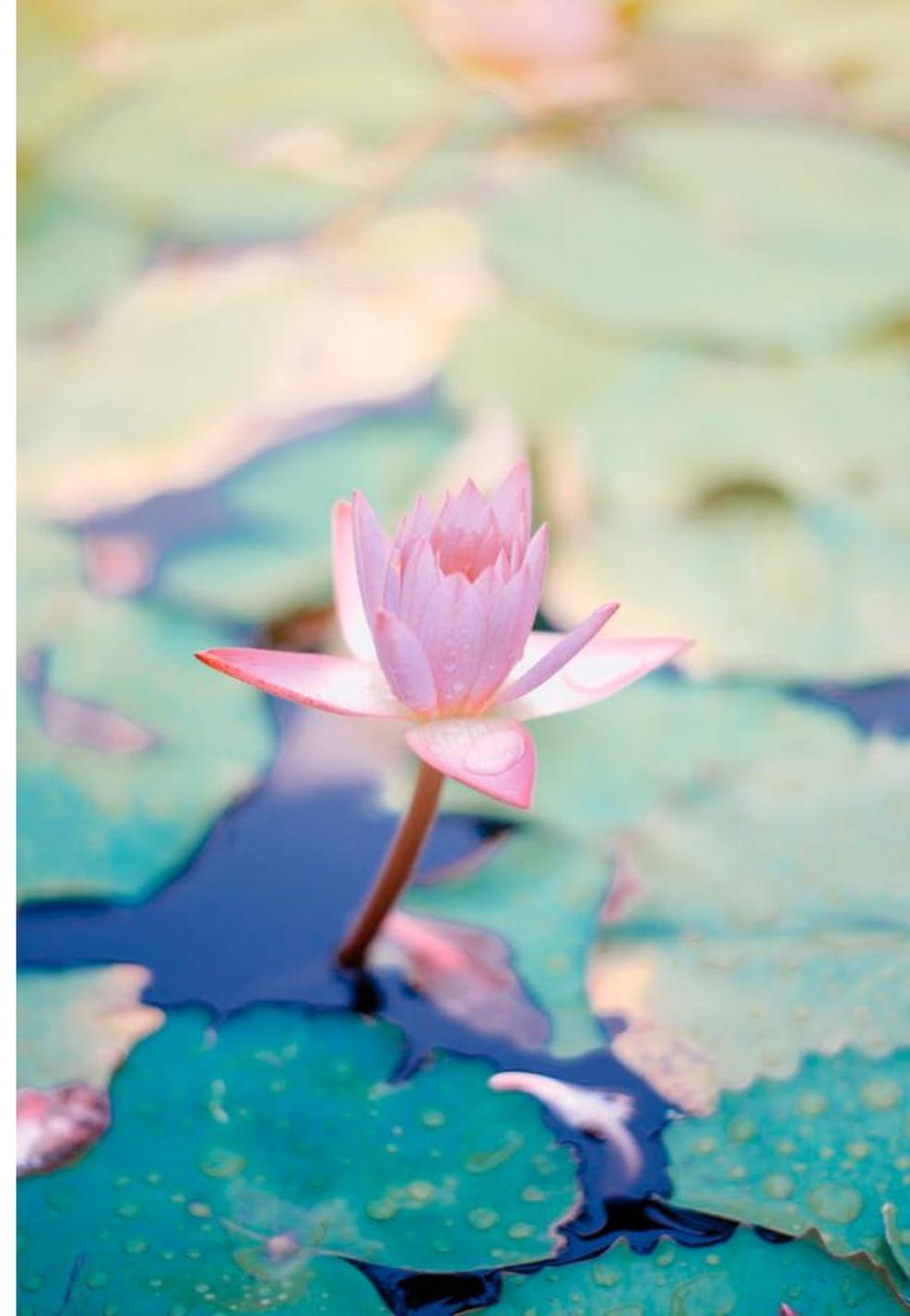
to ensure

reproductive success

*it's all about the process of making
and raising babies!*

Learning Objectives

- 1. Learn the fundamentals of the Endocannabinoid System**
- 2. Understand the myriad roles played by endogenous endocannabinoids in the female body**
- 3. Recognize how the endocannabinoid system impacts all reproductive, emotional, cognitive, and immune functions of women**
- 4. Acquire basic knowledge of exogenous endocannabinoid receptor agonists – the cannabinoids – and how to advise your patients on their use**



Introducing the Endocannabinoid System (ECS) A Key Physiological System

Highly conserved in evolution – dating
back over 600 million years

Implicated in regulating wide range of
physiological processes & pathologies –
energy homeostasis, immune modulation,
cardiovascular disease, cancer,
neurodegeneration

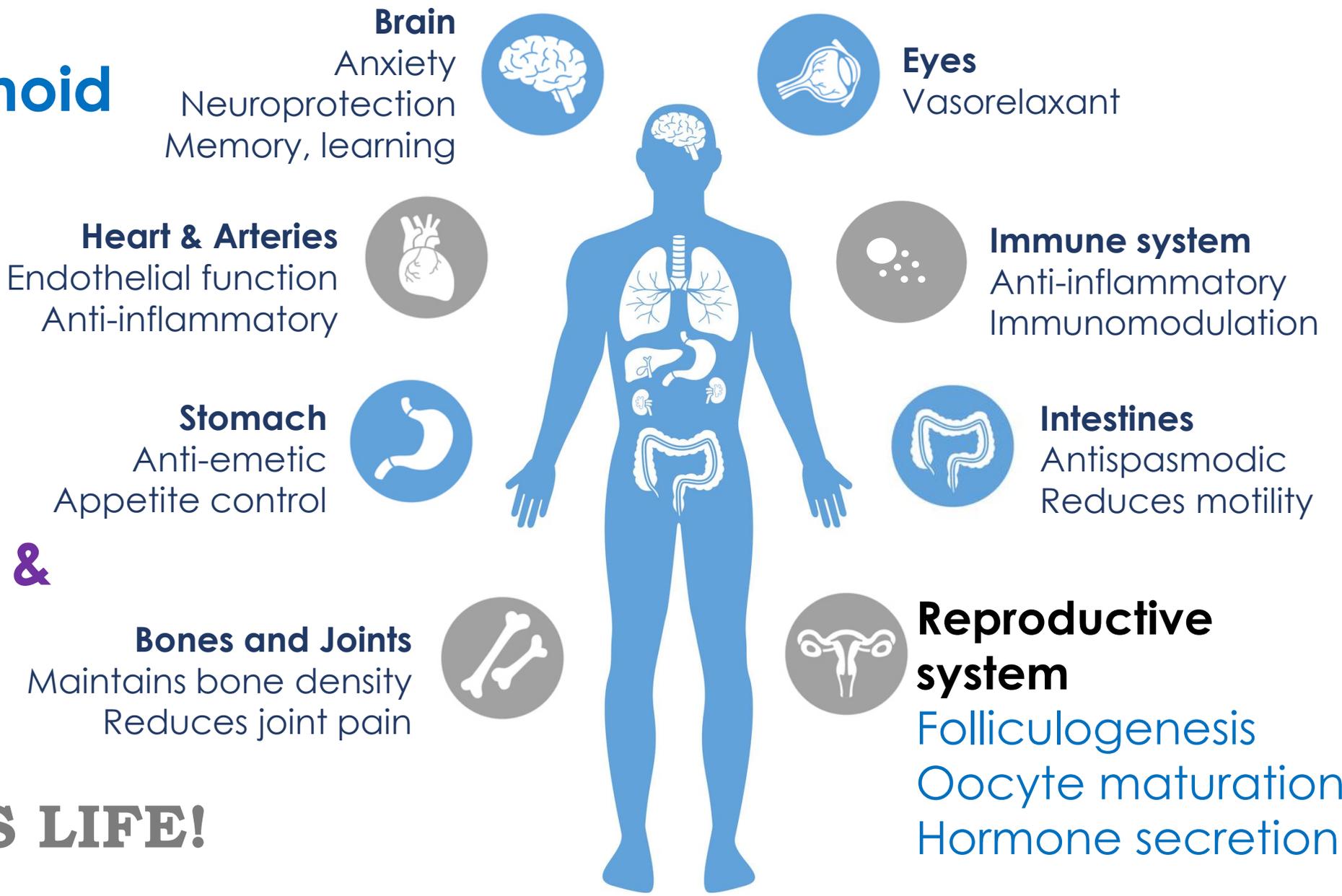
and

REPRODUCTION

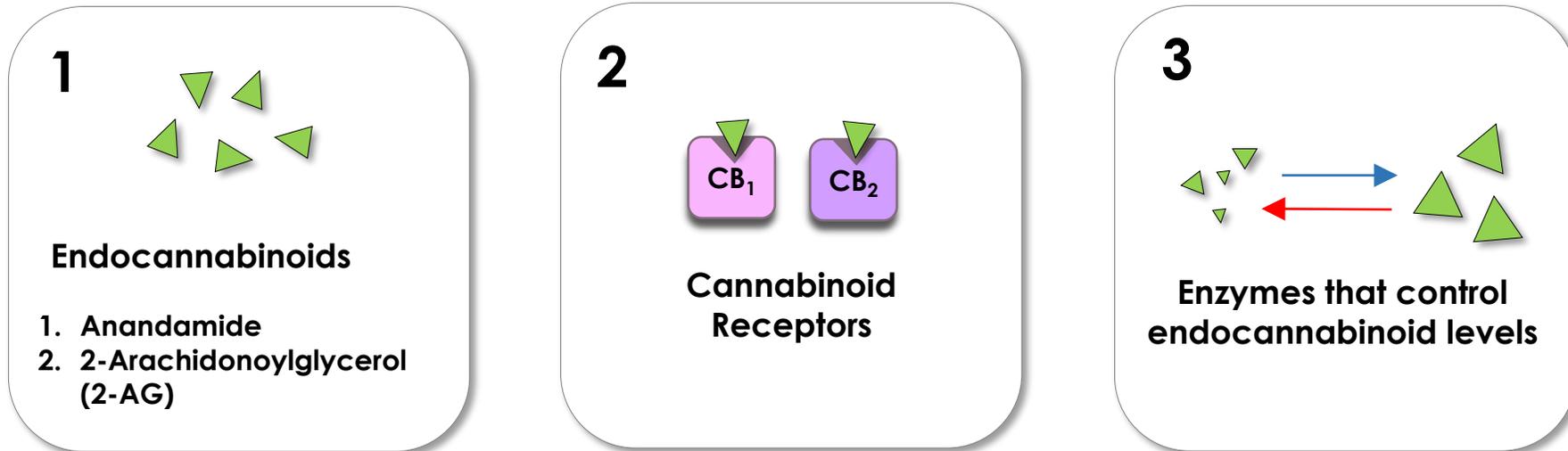


Role of the Endocannabinoid System

Sustaining Life & Supporting all Reproductive Functions:
FERTILITY IS LIFE!



Fundamentals of the Endocannabinoid System: Arachidonic Acid Based Signaling System



What do Endocannabinoids Look Like?

Fatty acid

Amine

or

Glycerol

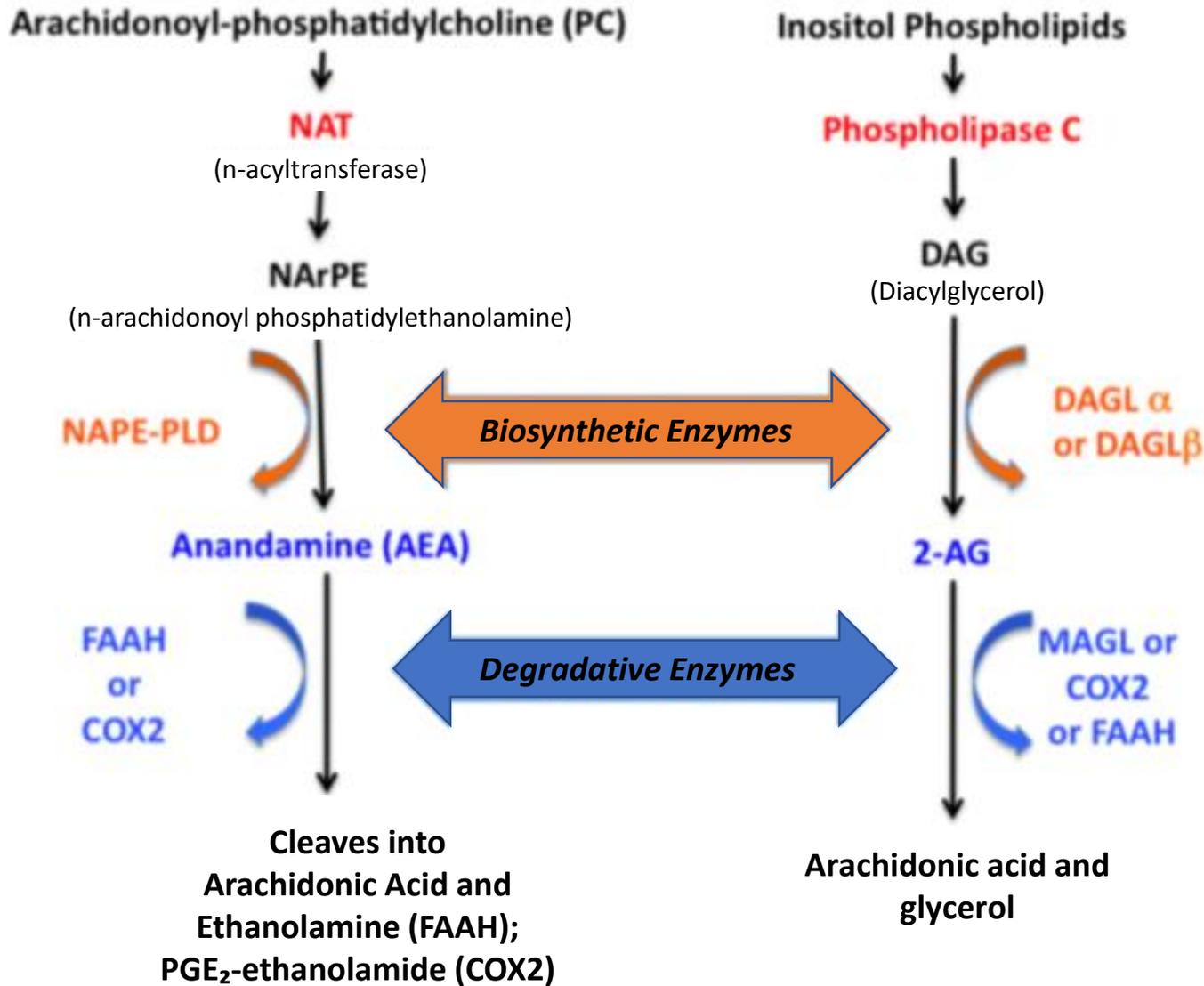




Introducing the Endocannabinoids

2 key lipid-derived molecules
bioactive lipids –
Endogenous ligands:

- **Anandamide – N-arachidonylethanolamine (AEA)**
- **2-arachidonoylglycerol (2-AG)**



Endocannabinoid Synthesis & the Degradation Pathway

Biological Activity of Endocannabinoids

Several oxidative enzymes can metabolize endocannabinoids into bioactive derivatives

1. **Lipoxygenases**
2. **Cytochrome P450 monooxygenases**
3. **Cyclooxygenase-2 (COX-2)**

Diaz-Laviada et al. Mini Reviews in Medicinal Chemistry. 2005;5:619-630



Endocannabinoid Receptors: CB 1 and CB 2

**CB1 and CB2 are 7
transmembrane G-protein-
coupled receptors**

**Both present in the CNS
and peripheral tissues**



The Endocannabinoid System in the CNS

2

Endocannabinoids activate CB₁ receptors, which are located on the presynaptic neuron



Anandamide or 2-AG (endocannabinoids)



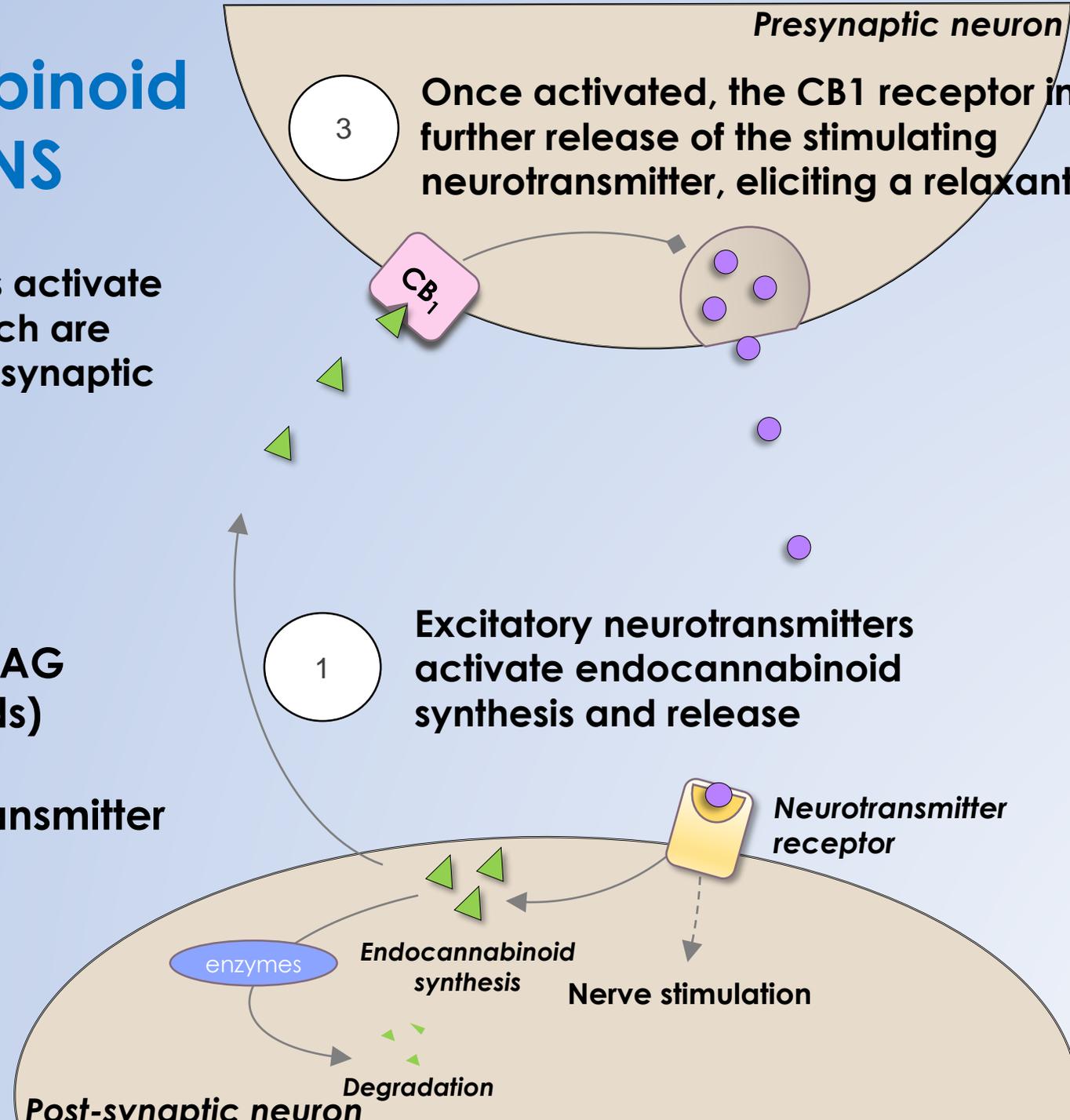
Excitatory neurotransmitter (e.g. glutamate)

3

Once activated, the CB₁ receptor inhibits further release of the stimulating neurotransmitter, eliciting a relaxant effect

1

Excitatory neurotransmitters activate endocannabinoid synthesis and release



The Endocannabinoid System in the Periphery

▲ Anandamide or 2-AG
(Mostly 2-AG)

● Inflammatory cytokines
(e.g. TNF-alpha, IL-6, IFN-gamma)

1

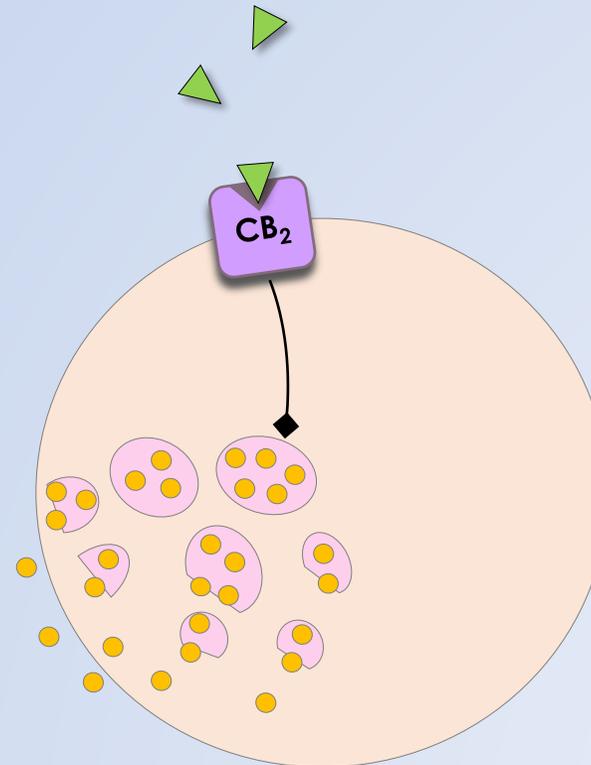
In cells of the immune system, GI tract, and other peripheral tissues, endocannabinoids (primarily 2-AG) activate CB₂ receptors

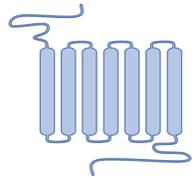
2

Once activated, CB₂ receptors elicit many immunomodulating effects, which depend on the cell type and its environment

3

CB₂ activation inhibits inflammatory cytokine production, which has broad clinical implications

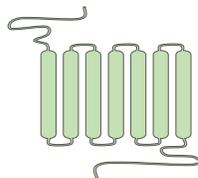




CB₁, CB₂
receptor
activation

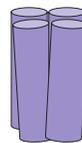
- **Neurotransmission (CB1)**
- **Immune modulation (CB2)**

Endocannabinoids: Mechanisms of Action: It's Complex



5HT_{1A}
Serotonin receptor
activation
EC₅₀ = 0.007 μM

Anxiolysis

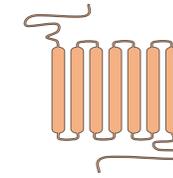


TRPV1
Vanilloid receptor
activation/
desensitization
EC₅₀ < 5 μM

Pain Perception

**Adenosine
reuptake inhibition**
IC₅₀ < 5 μM

**Immune
Modulation**



GPR55
receptor inhibition
IC₅₀ < 0.5 μM

Osteoclast Function



PPAR γ
activation
EC₅₀ = 5 μM

**Metabolic Health
Neuroprotection**

Legend	
-----	Low affinity interaction supported by limited/inconclusive data
————	Low to moderate affinity interaction supported by satisfactory data
————	Potent interaction supported by satisfactory data

OEA and PEA – Entourage Effect

N-oleoylethanolamine (OEA) N-palmitoylethanolamine (PEA) – a Mast Cell stabilizer!

- Structurally related to eCBs – “eCB-like” substances
- Competitively inhibit eCB degradation or modulates receptor binding
- Potentiates effect of genuine eCBs by **“entourage effect”**



ESTROGEN

A huge and unappreciated connection to the endocannabinoid system



Complex Interrelationship: Endocannabinoids & Estradiol

Central CB1 receptor expression
modulated by E2

**STUDY: Ovariectomized rats given E2
increase production anandamide**

- E2 decreases FAAH activity -
increases amount AEA
- Increased AEA decreases GnRH –
less FSH and LH release
- Less FSH & LH – reduced amount of
ovarian estrogen

**E2 down-regulates FAAH
activity centrally & peripherally**



Estradiol Impacts Levels of eCBs

- E2 stimulates transcription N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) – catalyzes formation of NAEs – AEA
- E2 directly stimulates release of AEA from endothelial cells
- E2 increases ABHD6 mRNA levels in uterine cells – breaks down 2-AG



Let's not forget Progesterone! Immunomodulatory Function with the ECS



Progesterone (PG) receptors on immune cells

PG suppresses immune responses by T-helper 1 (Th1) & Th17

Promotes secretion of cytokines by Th2 lymphocytes

PG suppresses differentiation pathway of B lymphocytes

Induce immune tolerance against fetal antigens during pregnancy

PG & Human lymphocytes – upregulates activity FAAH gene – decreases AEA plasma levels

Downregulates uterine NAPE-PLD expression in mice - lowers tissue AEA levels

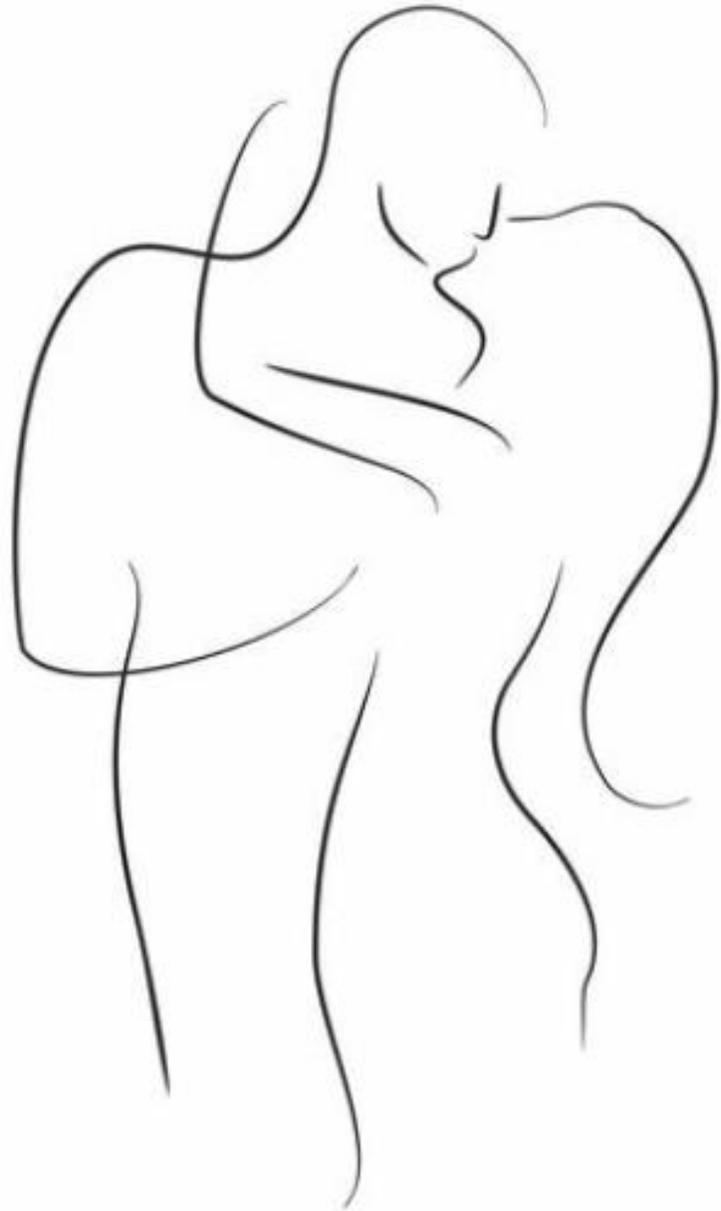


REMINDER:
Prime Directive of Life:
Successful Reproduction



The Beginning of a New Life Always Involves the ECS

- Endocannabinoids affect reproductive events from gametogenesis to fertilization - from embryo implantation to final outcome of pregnancy
- Endocannabinoid signaling modulates reproductive events - under healthy & pathological conditions



Let's Start with Sexual Desire and Orgasms – Where it all begins!

- Alpha MSH switch - turns off systemic oxytocin release & turns on CNS dendritic release
- Centrally-oxytocin & alpha MSH inhibit feeding & stimulate sexual behaviors
- Peripherally-oxytocin stimulates natriuresis + food intake
- Presynaptic action endocannabinoids mediate alpha MSH-induced inhibition of oxytocin cells
- Sexual arousal + inhibited appetite requires stimulation central oxytocin release & inhibition peripheral release
- Oxytocin released into circulation at orgasm – burst firing



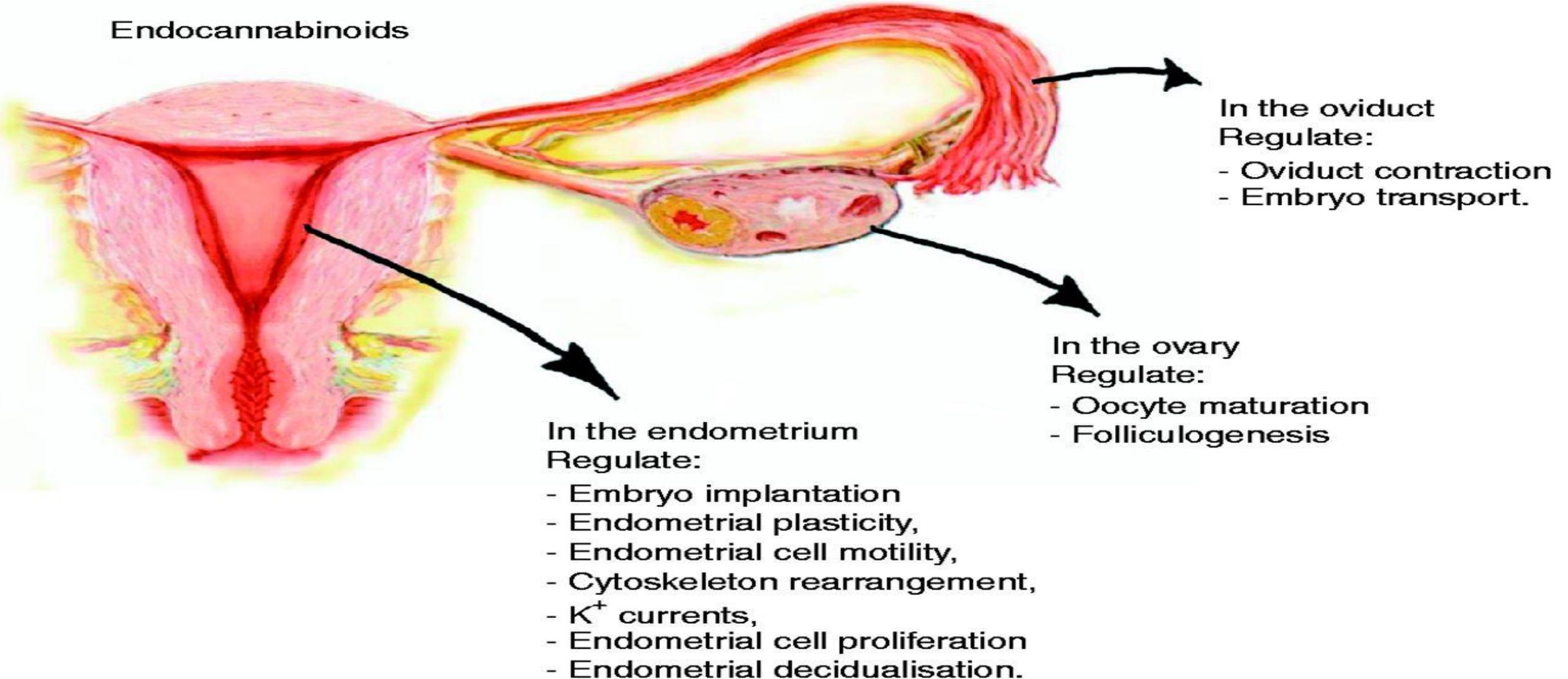
Moving on from Coitus: Overview of Endocannabinoid System & the Making of a New Life

Biological
activities:

regulation of oocyte,
follicle maturation,
embryo transport
through oviduct,
implantation of
blastocyst, endometrial
plasticity, endometrial
cell migration &
proliferation

Overview of the Endocannabinoid System and Reproduction

Endocannabinoids



Endocannabinoid System - Role in Regulation of the Menstrual Cycle

Endocannabinoid activity & CB1 receptor function fluctuates through the menstrual cycle

- Amount anandamide circulating - higher during follicular phase & highest during ovulation
- Anandamide lower during luteal phase

Bidirectional relationship between endocannabinoid system and gonadal hormones



Endocannabinoids and the Ovary: Endocannabinoid System Active at the Ovarian Level

- CB1R, CB2R, AEA , NAPE-PLD – all in ovarian tissue
- CB1R and CB2R expression in medulla and cortex of ovary
- CB1R and CB2R expression in corpus luteum and corpus albicans
- AEA mainly produced from granulosa of growing follicles



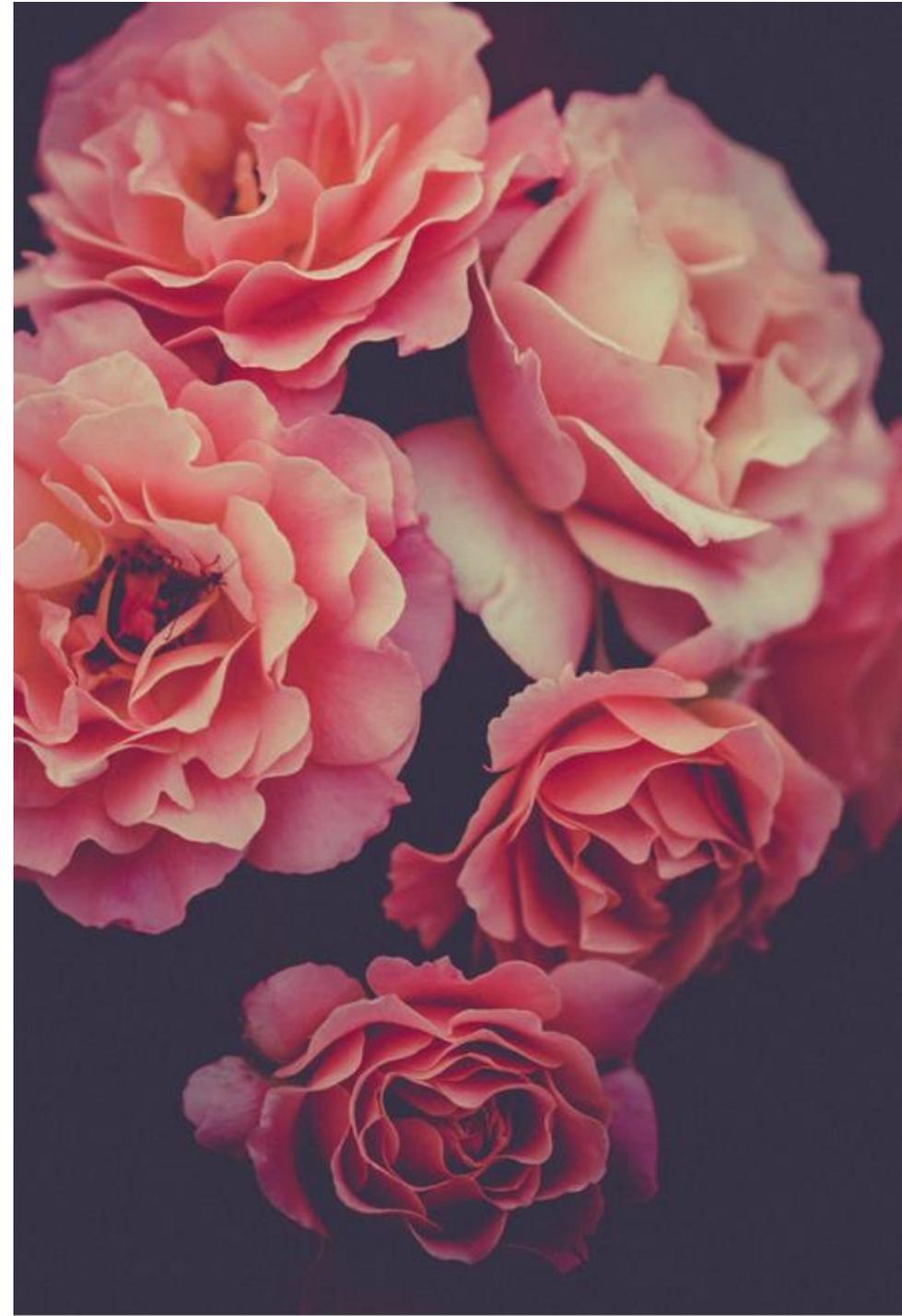
Energy Balance & Metabolism of Ovaries

- ECS interacts with ovarian function through modulation of pathways involved in energy balance and metabolism control
- Obesity associated with menstrual irregularities, chronic oligo-anovulation and infertility
- Regular ovulation often restored after weight reduction – improved natural conception

Pagotto et al. Endo Reviews.2006;27:73-100

Zain et al. 2008; Women's Health

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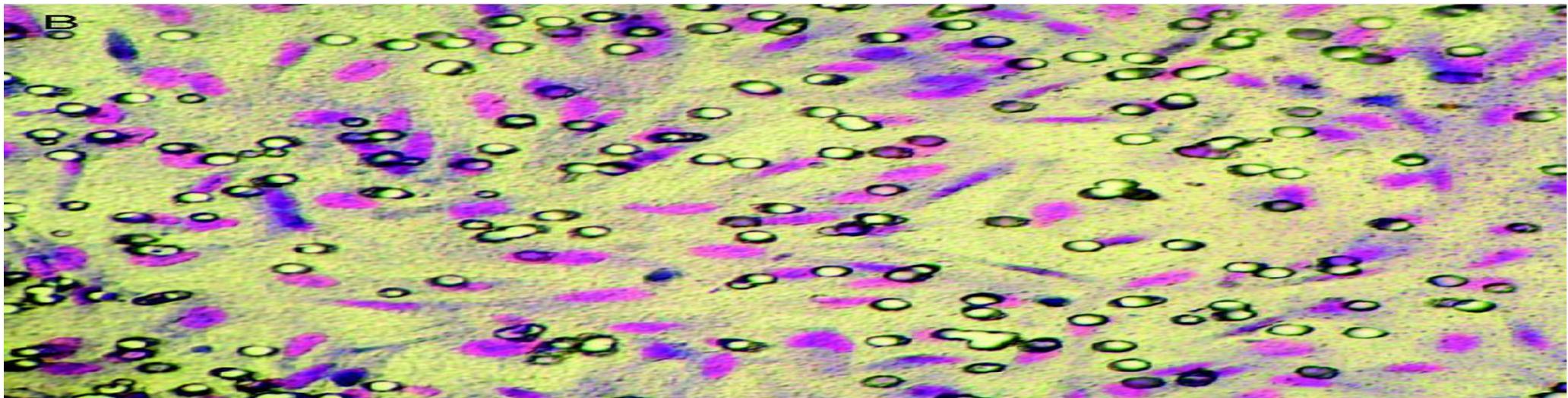
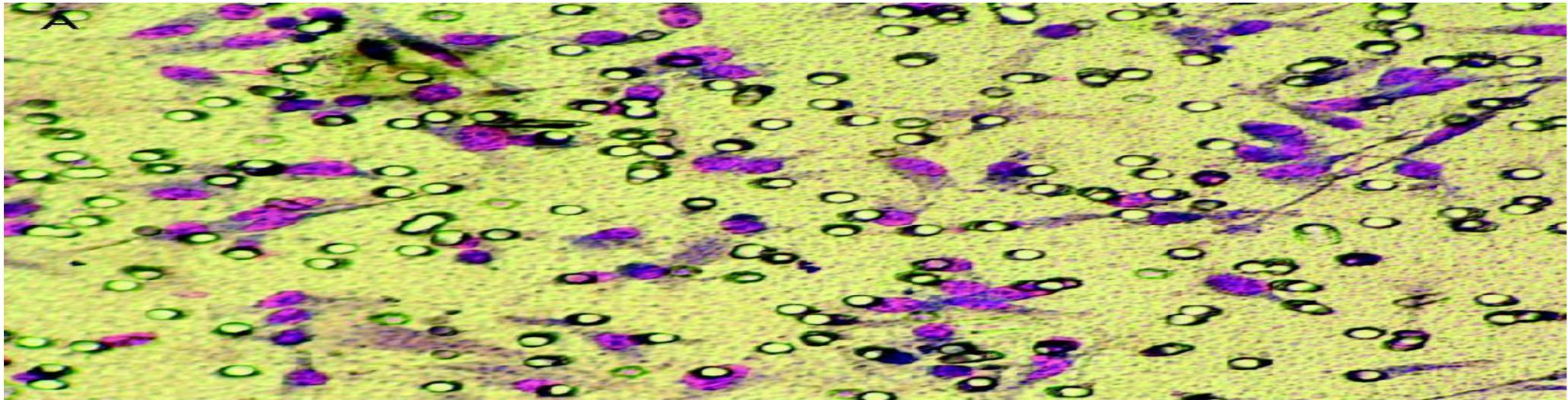


Endocannabinoid System and the Uterus

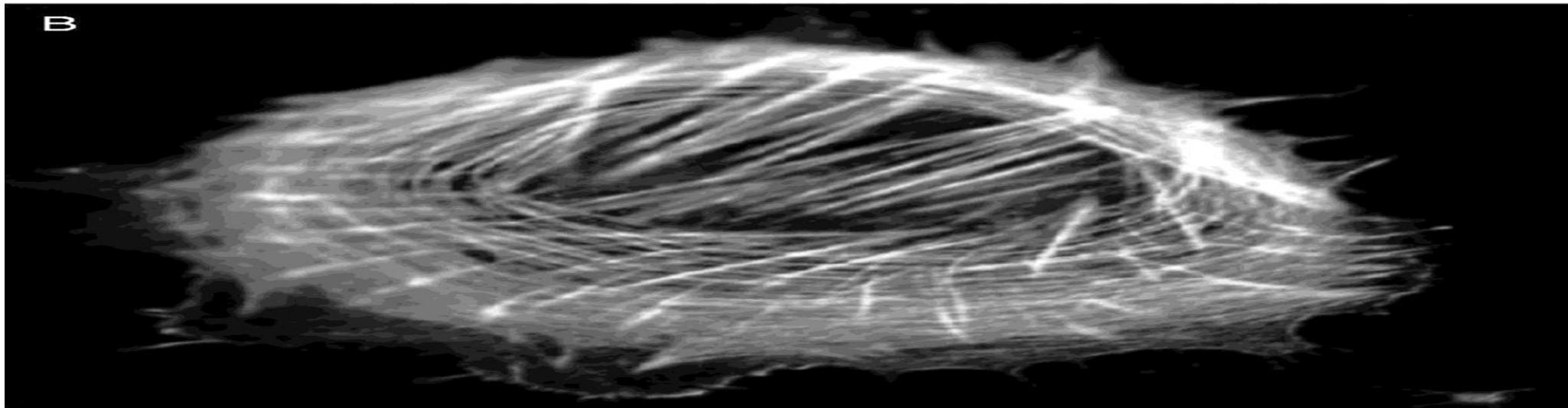
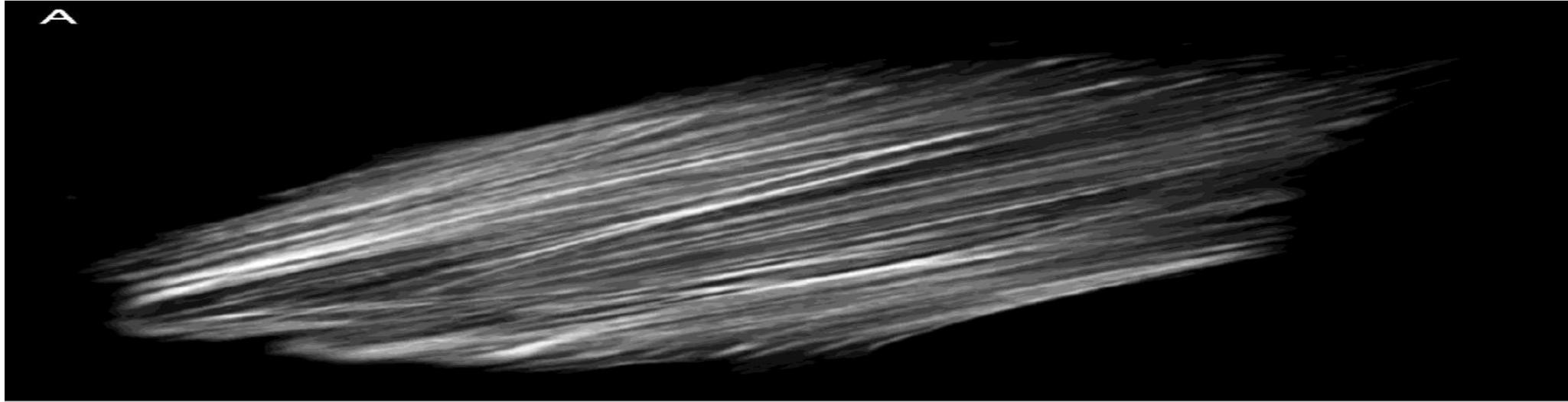
- Endometrial plasticity- adaptation response to physiological changes that occur during menstrual cycle & embryo implantation
- ECS system – control endometrial cell motility & migratory behavior – balance created between endometrial growth & transformation – works through CB1R only



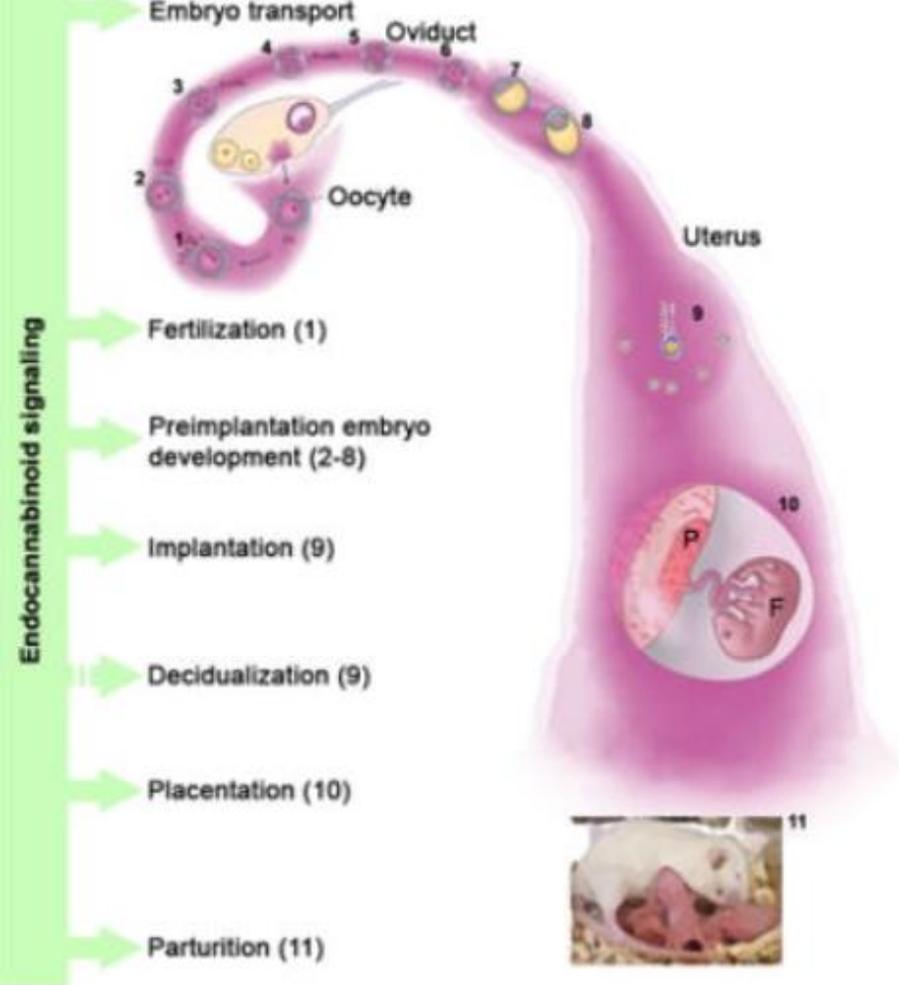
Migration of Endometrial Cells – Induced by Cannabinoid Agonist



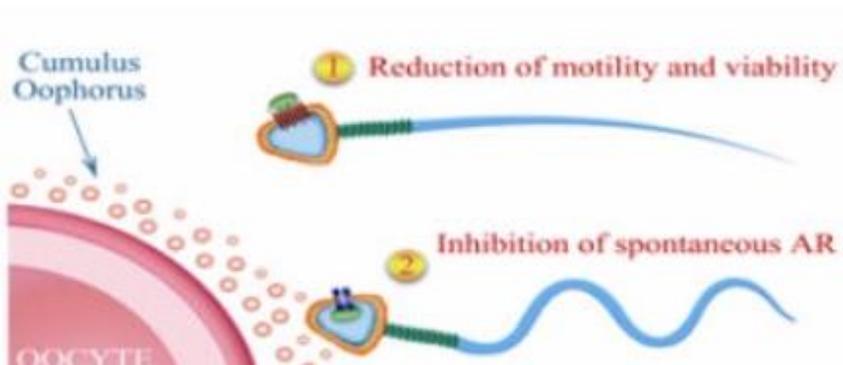
Effects of methanandamide (10^{-5}M) on actin cytoskeleton pattern of endometrial stromal cells. Untreated cells show a classic static phenotype (A). Treatment with methanandamide induces cytoskeleton rearrangements and a migratory phenotype



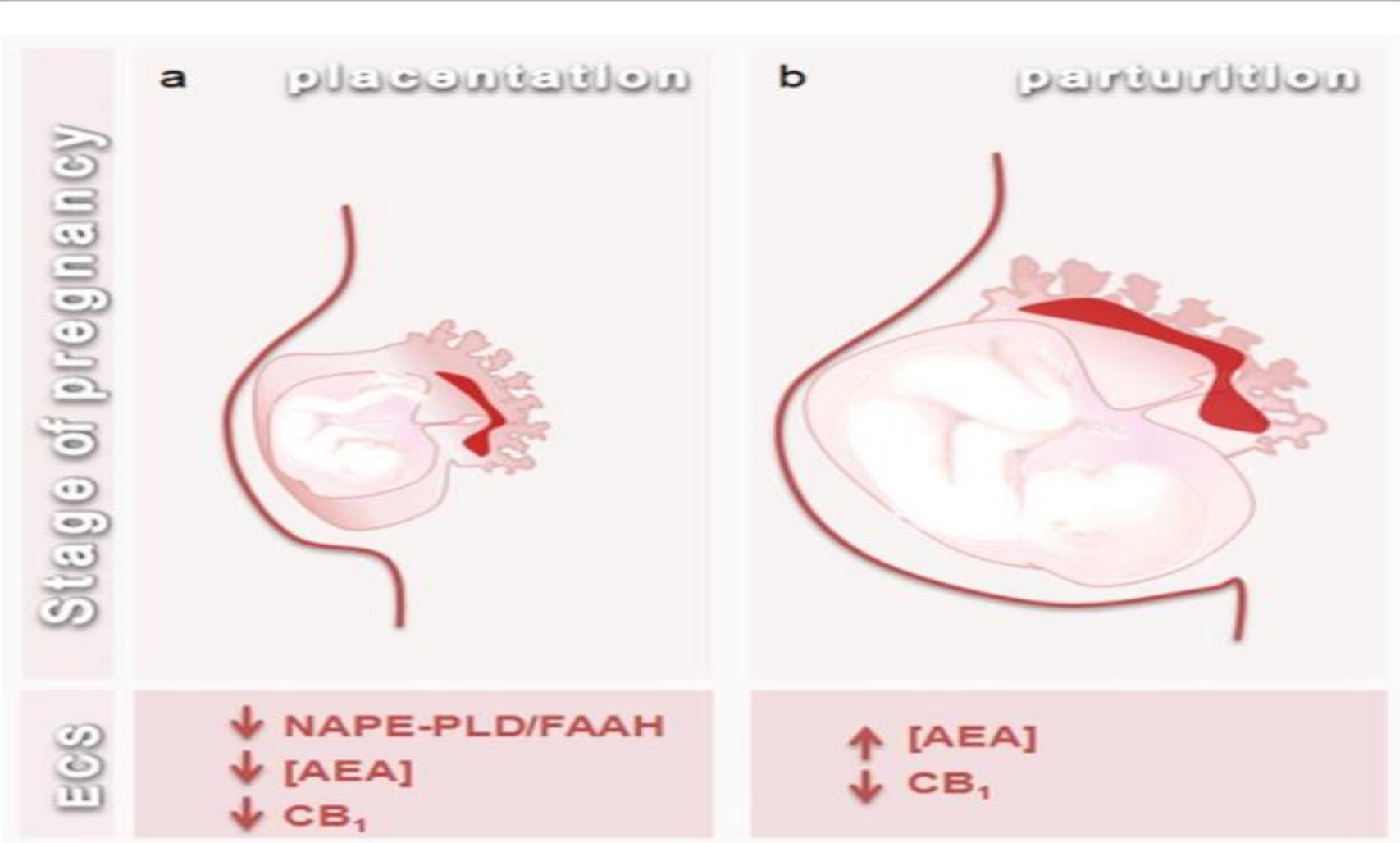
ECS – Role Played in Every Aspect of the Reproductive Process



- Levels vary in set manner during embryo implantation
- Low levels anandamide needed for implantation & carrying pregnancy to term
- During pregnancy - low levels anandamide present - surge occurs near labor onset
- High anandamide facilitates labor process
- If increased anandamide or agonist in early pregnancy – higher rate of miscarriage



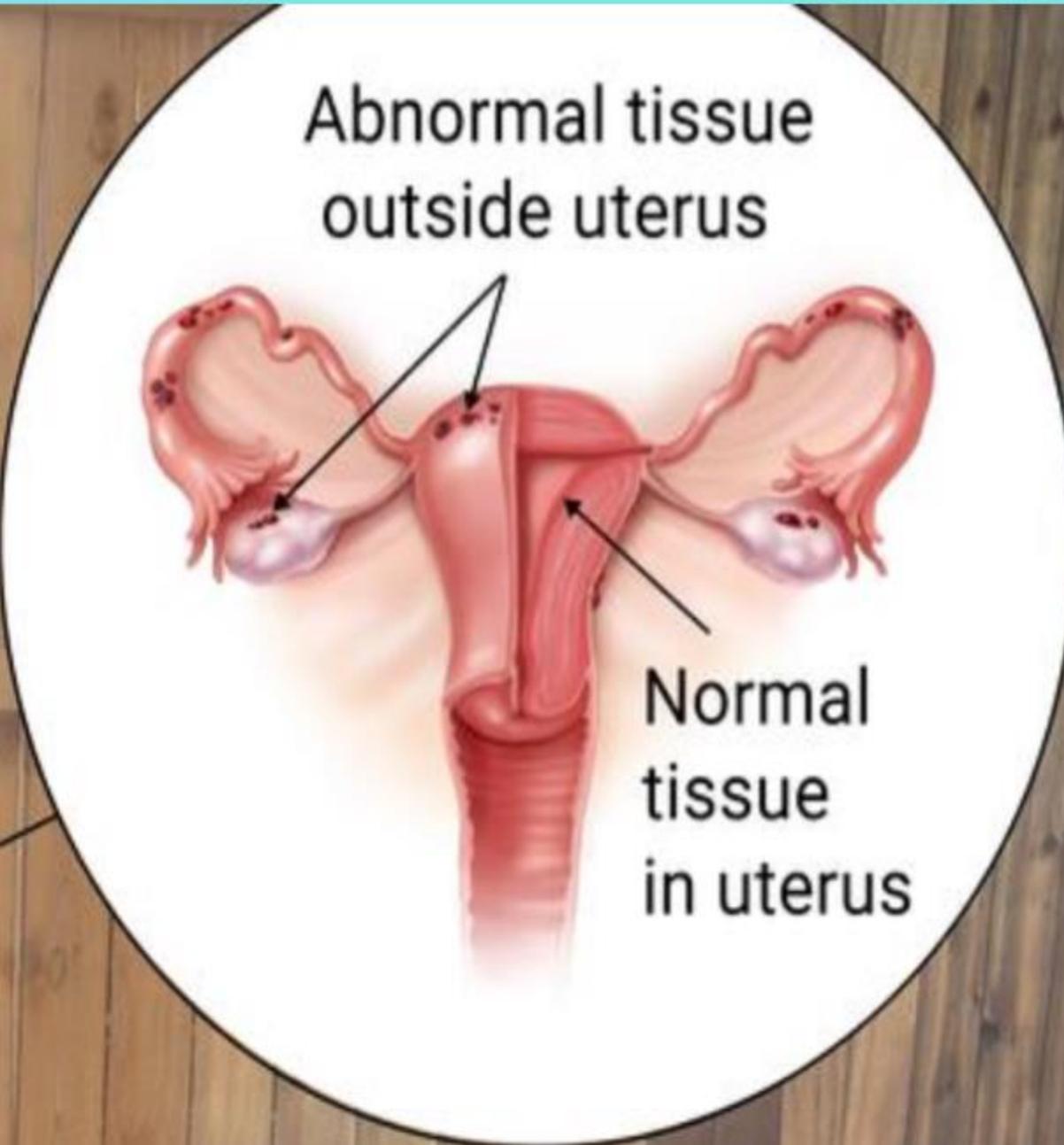
Endocannabinoid System and Pregnancy



The Endocannabinoid System & Relationship to Medical Dysfunctions



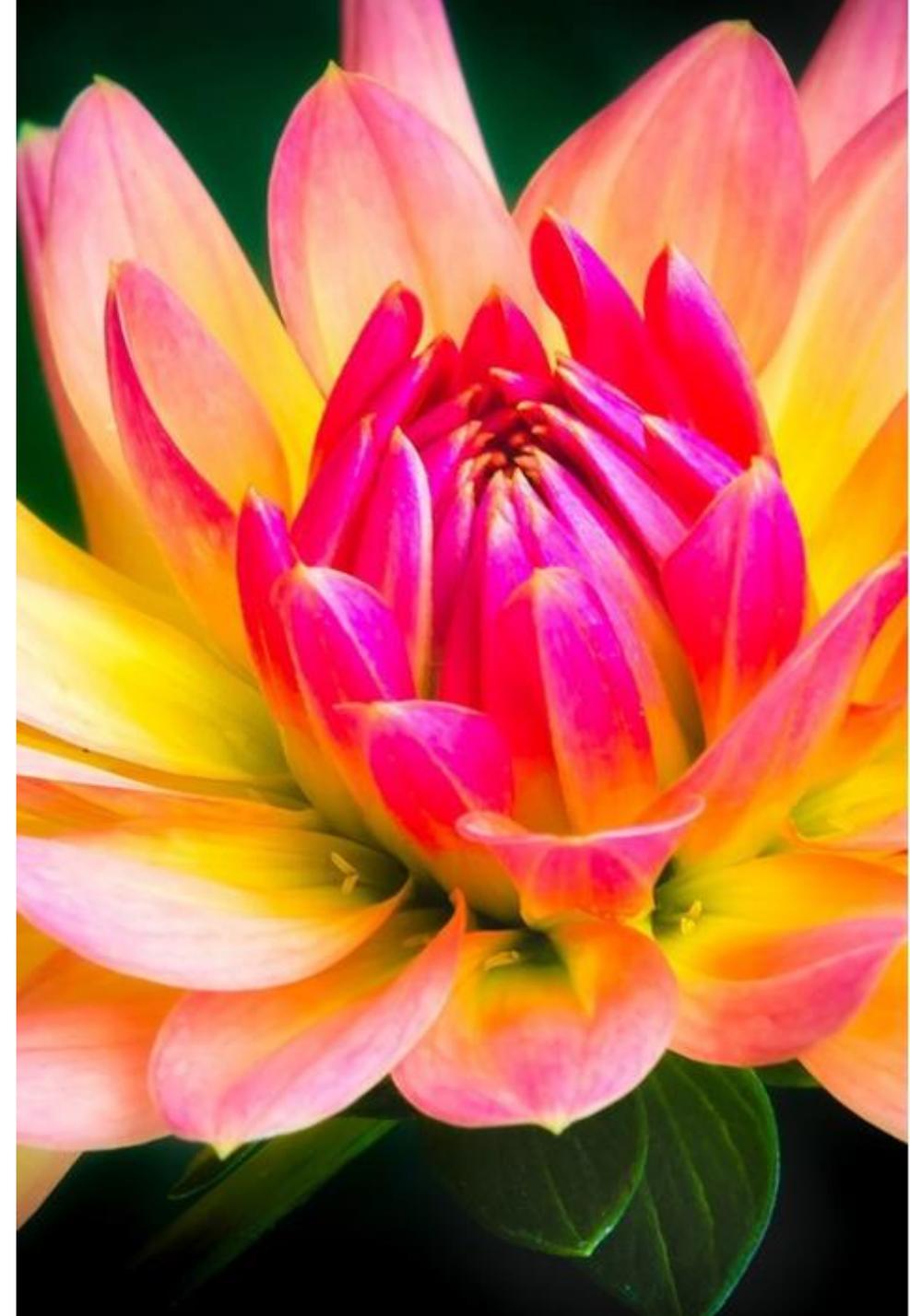
Endocannabinoid System & Endometriosis



- Reduced expression CB1R in ectopic endometrium in endometriosis pts compared with healthy controls
- Reduced CB1R expression attributed to effects of persistent environmental toxicants and interleukin-1 alpha - induce progesterone resistance phenotype
- Reduced cannabinoid signaling might underlie enhanced proliferative capacity of endometriotic lesions

Endocannabinoid System and PCOS

- Insulin resistance, androgen hypersecretion, and obesity influenced by ECS
- In rats – AEA activation of CB1R pancreatic Beta cells induces insulin hypersecretion & resistance
- Local effect endocannabinoid signaling in pancreas – possible role in PCOS-associated insulin resistance
- Anovulation possibly result complex interplay of endocannabinoids, leptin production, and obesity

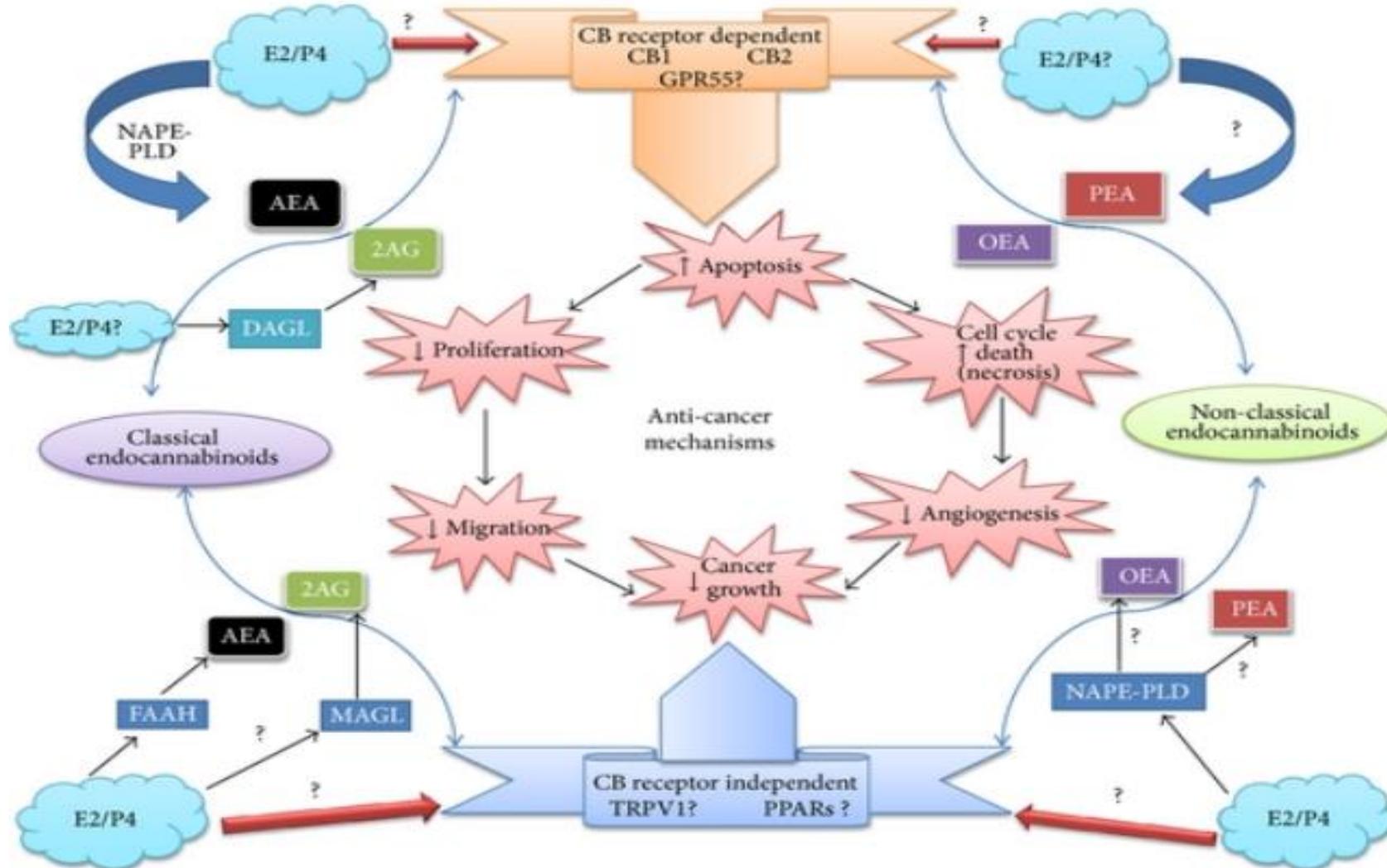


Effect of AEA on Cervical Carcinoma Cell Lines

- AEA induced apoptosis of cervical cancer cell lines
- Mechanism: vanilloid receptor-1
- Binding to CB1 and CB2 mediates protective effect

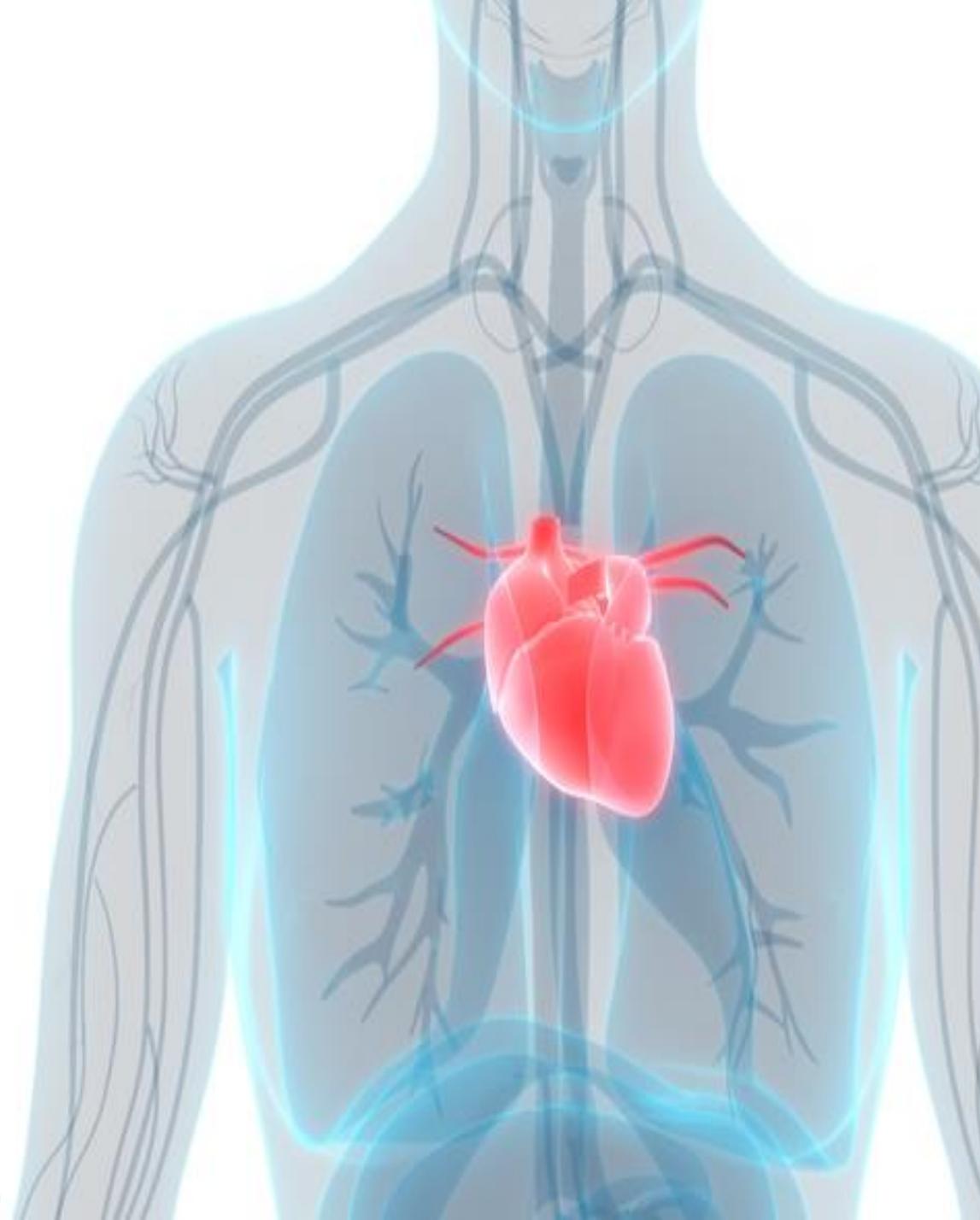


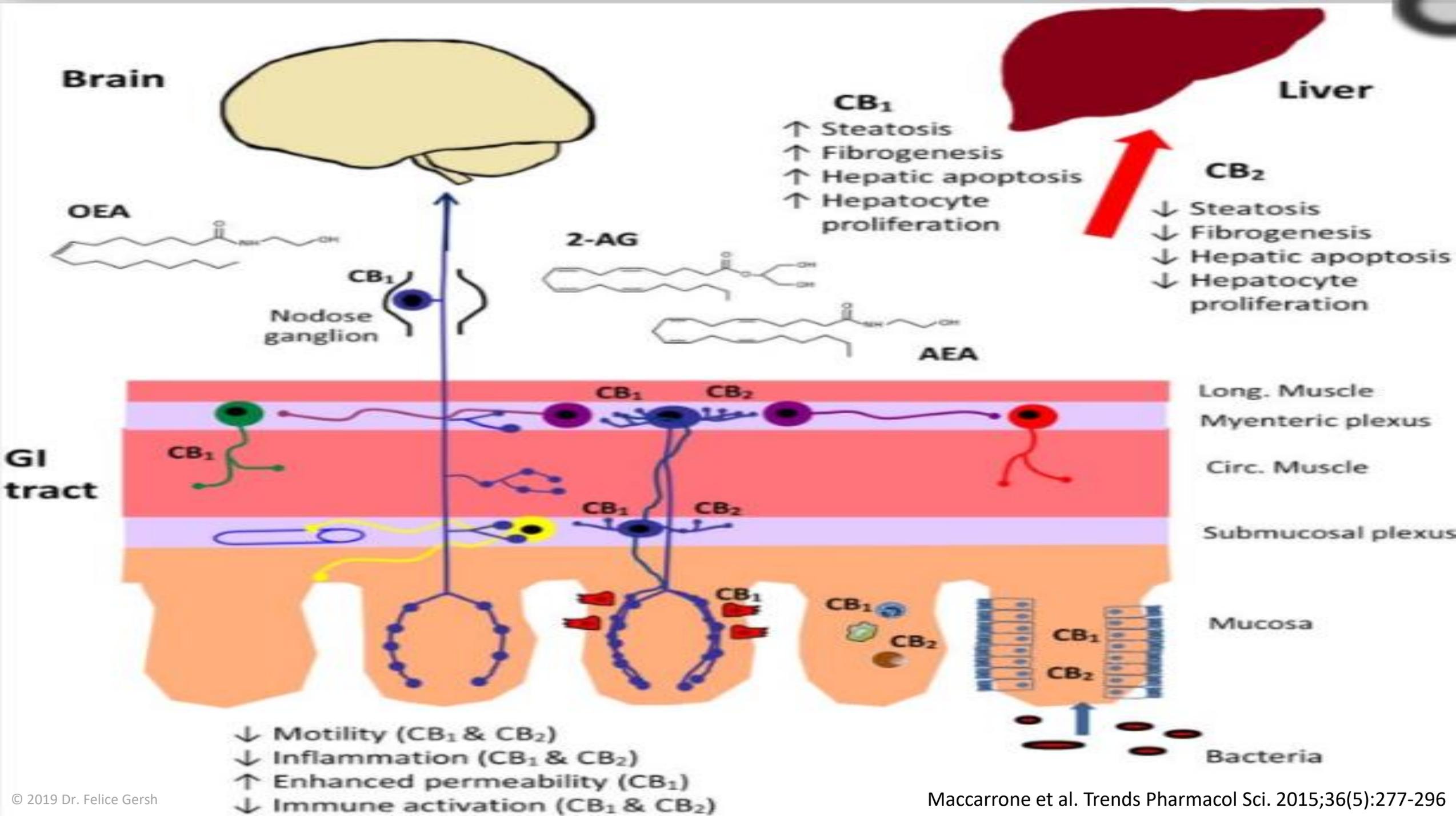
Endocannabinoid System: Protection from Cancers!



Endocannabinoid System: Metabolic Health Key to Reproductive Health

- Regulates energy balance & appetite
- Modulates inflammation
- Blood pressure & arterial health
- Adipose tissue & energy homeostasis – dysregulation – excessive visceral fat and reduced adiponectin – obesity and Type 2 DM





Dysregulation of the peripheral endocannabinoid system in high-fat diet-induced hyperglycaemia and obesity

	Site of action	Effect of CB ₁ activation	Effects of a HFD	Potential consequences
	Epididymal adipose tissue	<ul style="list-style-type: none"> ↑ Lipogenesis (LDL, FAS) ↑ PPAR-γ expression ↑ Glucose uptake ↓ AMPK activity ↓ Adiponectin 	<ul style="list-style-type: none"> ↑ 2-AG Sustained 	<ul style="list-style-type: none"> ↑ Energy storage ↑ Dyslipidaemia ↑ Insulin resistance ↑ Excessive visceral fat
	Subcutaneous adipose tissue	See above	<ul style="list-style-type: none"> ↓ 2-AG, AEA Sustained 	<ul style="list-style-type: none"> ↓ Subcutaneous fat ↑ Visceral and ectopic fat
	Pancreas	<ul style="list-style-type: none"> ↑ Insulin release? 	<ul style="list-style-type: none"> ↑ 2-AG, AEA Early and sustained 	<ul style="list-style-type: none"> ↑ Hyperinsulinaemia?
	Liver	<ul style="list-style-type: none"> ↑ Fatty acid synthesis ↓ AMPK activity 	<ul style="list-style-type: none"> ↑ AEA ↑ CB₁ Early 	<ul style="list-style-type: none"> ↑ Dyslipidaemia ↑ Dyslipoproteinaemia ↑ Steatosis
	Skeletal muscle	<ul style="list-style-type: none"> ↓ AMPK activity? ↓ Glucose uptake? ↓ Glucose oxidation? 	<ul style="list-style-type: none"> ↑ 2-AG Early ↑ CB₁ 	<ul style="list-style-type: none"> ↑ Insulin resistance? ↓ Energy expenditure
	Heart		<ul style="list-style-type: none"> ↑ 2-AG, AEA Early and sustained 	<ul style="list-style-type: none"> ↑ Pericardial fat? ↑ Cardiovascular risk?
	Kidneys	<ul style="list-style-type: none"> ↓ Glomerular filtration 	<ul style="list-style-type: none"> ↑ 2-AG, AEA Late and sustained 	<ul style="list-style-type: none"> ↑ Hypertrophy? ↑ Perirenal fat? ↑ Renal failure

The possible (and, in some cases, just hypothesised) consequences of CB₁ activation and over-activation are also shown. Note how the upregulation of endocannabinoid tone can have different effects on AEA and 2-AG (with subsequent differential impact on the activity of cannabinoid and TRPV1 receptors, as suggested in Fig. 3), and in a time-dependent way ('early' is usually associated with HFD-induced hyperglycaemia; 'sustained', with overt HFD-induced obesity). AEA, anandamide; HFD, high-fat diet

Nurturing the Endocannabinoid System

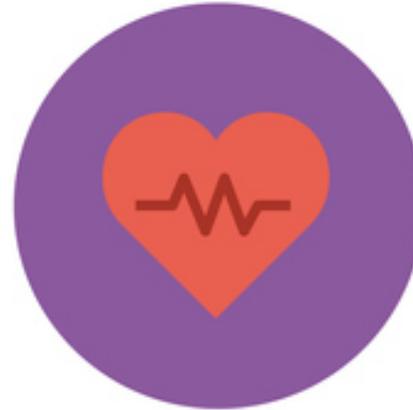


Exercise



Control your weight

**Nutrition as
Medicine**



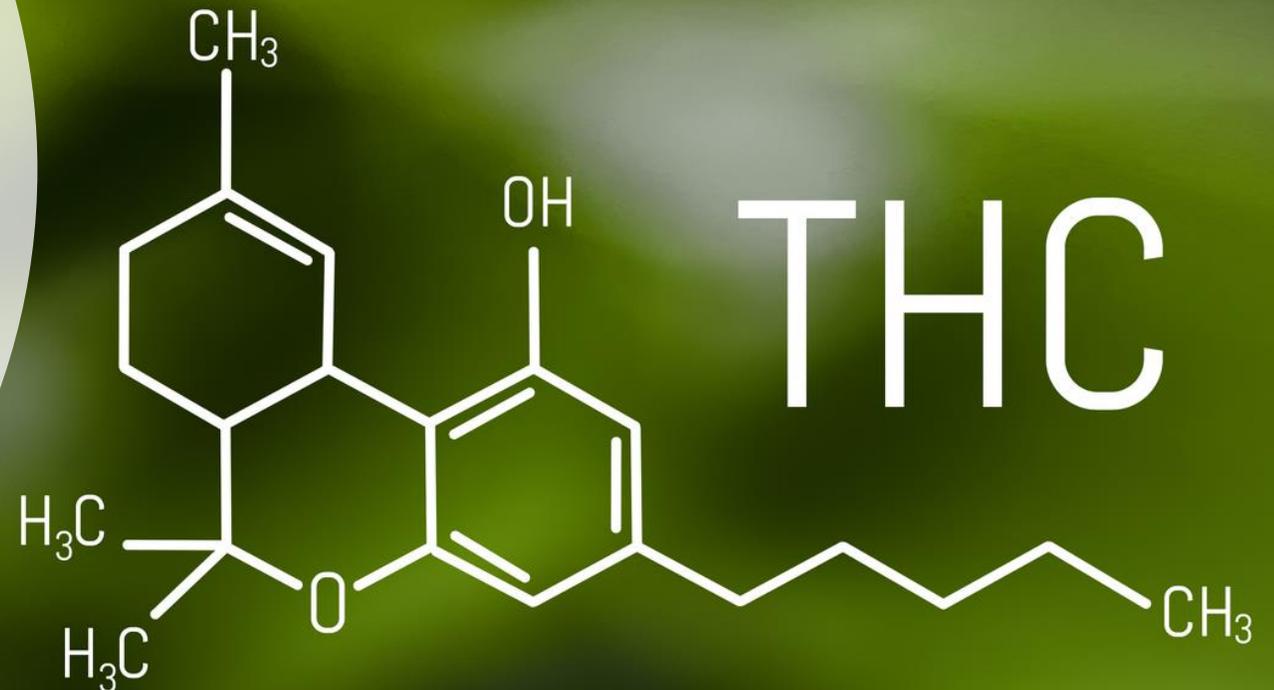
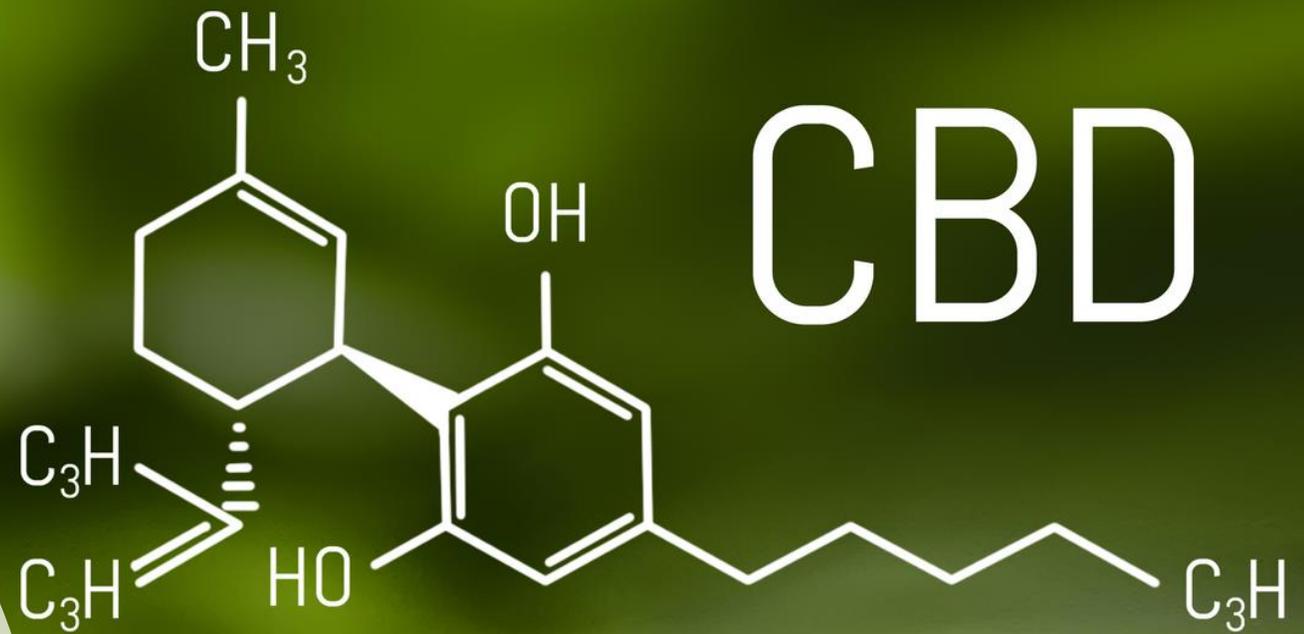
Manage stress



**Manage
environmental
exposures**

Plant Based Cannabinoids

Cannabinoid compounds:
THC, cannabidiol,
tetrahydrocannabivarin,
cannabichromene,
cannabigerol, others



Cannabis: Impact on Women vs. Men

Marijuana commonly used & increasing rates among women

- More impacted – altered functioning on tasks
- More susceptible to abuse - more prone to develop dependence
- Experience more severe withdrawal symptoms & relapse more than men
- In adolescents – females more adversely affected by cannabinoids than males



Complex Interaction: Estrogen - ECS - Cannabis

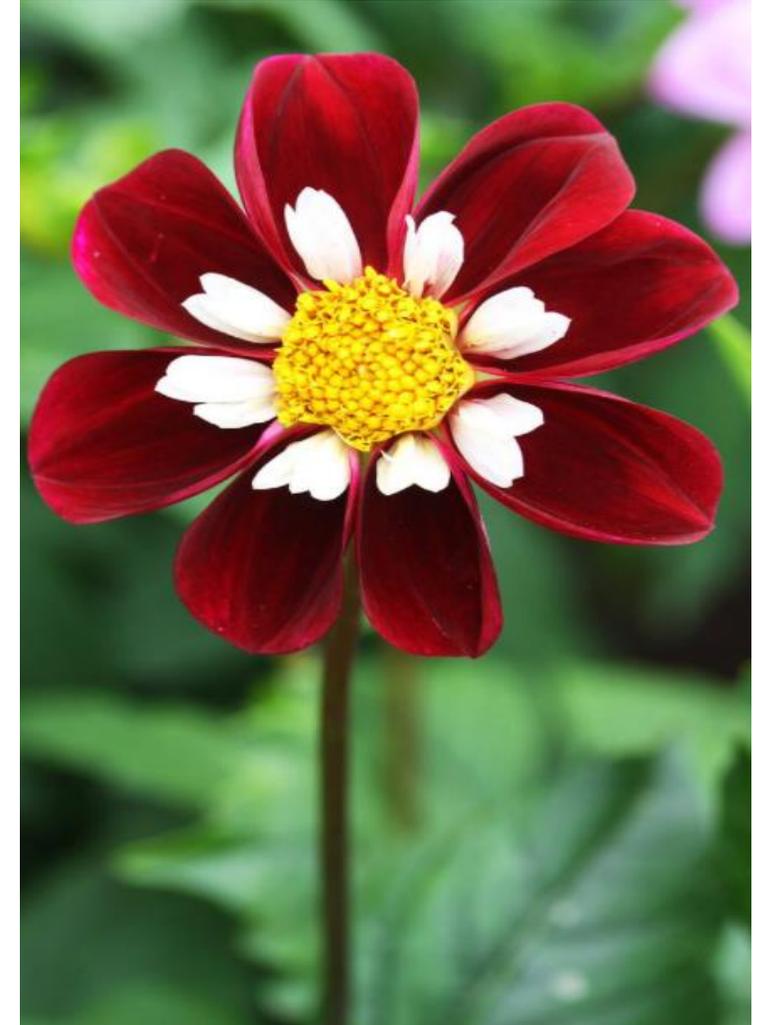
- Lowers release estrogens through central down-regulation of LH & GnRH
- THC - decreases serum LH & pulsatile nature of LH
- GnRH given to female rats - effects of THC reversed
- Suppression of LH release by THC demonstrated in monkey & rats
- Pituitary gland remains sensitive to stimulation – impact of cannabinoids through effects on central neurotransmission - suppressing LH release

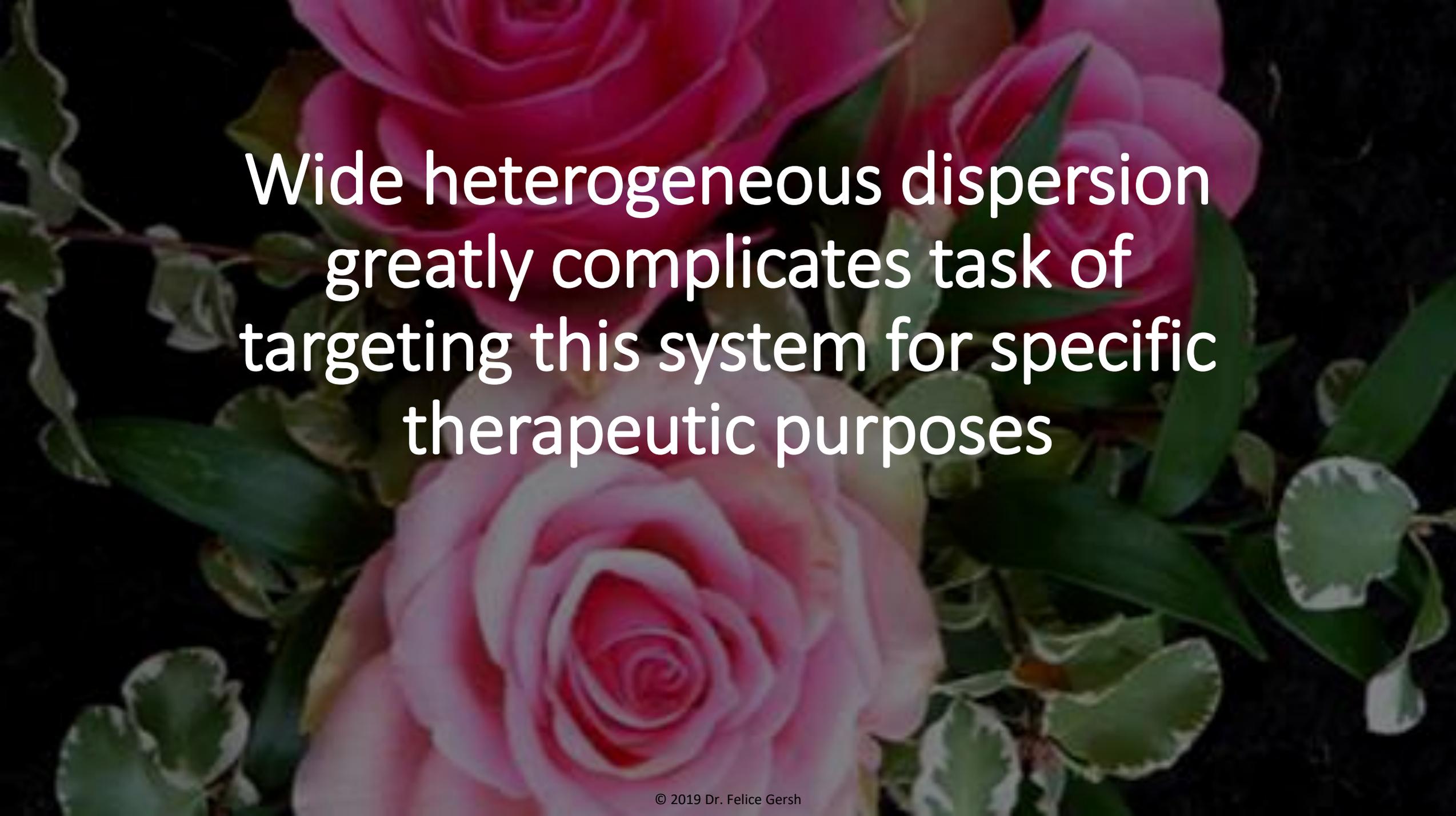


Effect of THC on the Maturation of Follicles & Oocytes

- THC - direct inhibitory effect on folliculogenesis & ovulation
- Cannabis users higher risk primary infertility due to anovulation
- IVF treatment – Cannabis (Marijuana) users poor-quality oocytes & lower pregnancy rates compared with non-users
- Follicular fluid AEA concentrations correlate with follicle size - lower in follicles from which oocytes not retrieved

Klonoff-Cohen et al. 2006; Amer J of Obstet and Gyn; 194:369-376
El-Talatini et al. PLoS ONE 4 e4579.

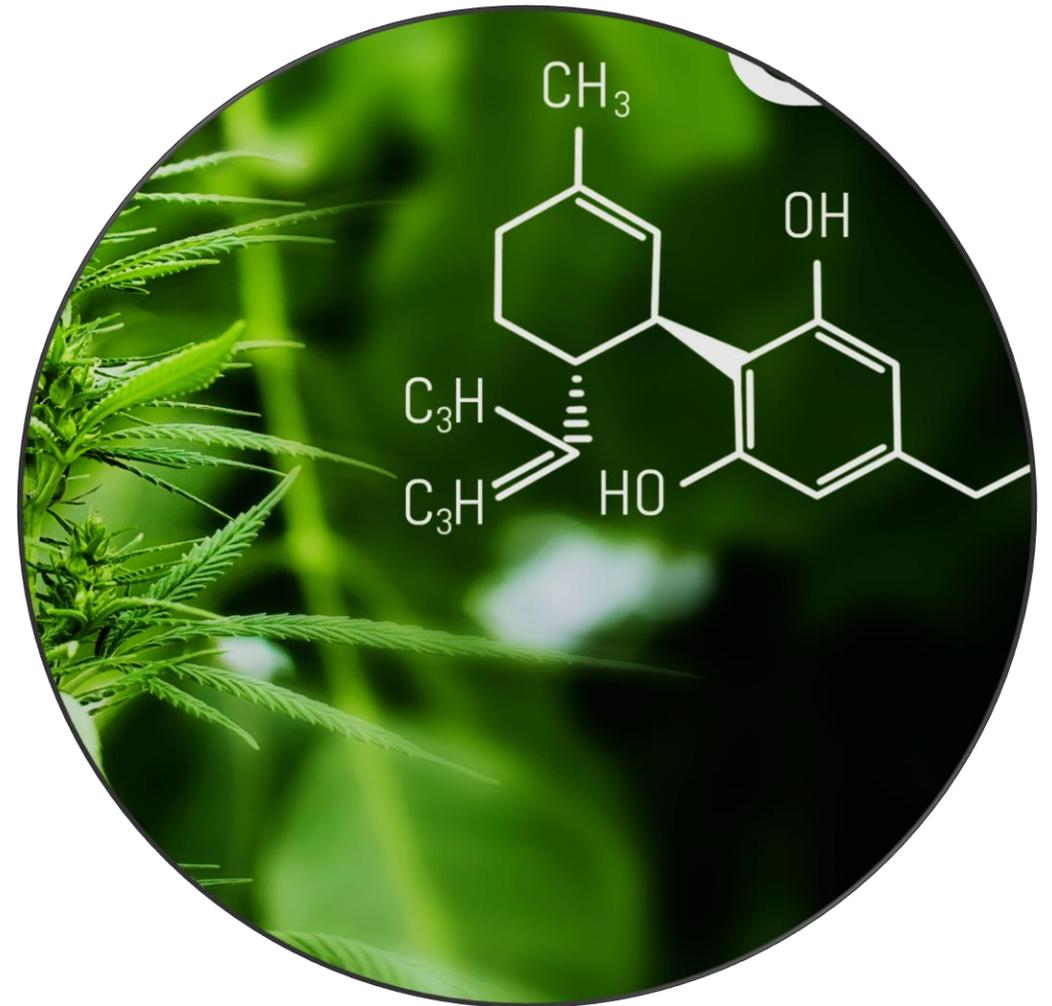




Wide heterogeneous dispersion
greatly complicates task of
targeting this system for specific
therapeutic purposes

Selecting Hemp Extracts: Consider the Following

- Potency: *Read labels carefully*
- THC content – undetectable or <0.3%
- “Broad spectrum”
- Purity:
Solvents, Pesticides
- Bioavailability



Endocannabinoid System & Female Health: An Incredible Connection



When all is in balance

The Prime Directive can be Realized:

Fertility and Metabolic Health

**Thank You
for Your Kind Attention**



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