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

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Sustaining Life & Supporting all Reproductive Functions:

**FERTILITY IS LIFE!**

- **Brain**
  - Anxiety
  - Neuroprotection
  - Memory, learning

- **Eyes**
  - Vasorelaxant

- **Heart & Arteries**
  - Endothelial function
  - Anti-inflammatory

- **Stomach**
  - Anti-emetic
  - Appetite control

- **Intestines**
  - Antispasmodic
  - Reduces motility

- **Bones and Joints**
  - Maintains bone density
  - Reduces joint pain

- **Reproductive system**
  - Folliculogenesis
  - Oocyte maturation
  - Hormone secretion

**Role of the Endocannabinoid System**

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Fundamentals of the Endocannabinoid System: Arachidonic Acid Based Signaling System

1. Endocannabinoids
   1. Anandamide
   2. 2-Arachidonoylglycerol (2-AG)

2. Cannabinoid Receptors
   - CB₁
   - CB₂

3. Enzymes that control endocannabinoid levels

Acharya et al. PNAS. 2017. 114(19)5005-5010

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What do Endocannabinoids Look Like?

Fatty acid

Amine

or

Glycerol

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Introducing the Endocannabinoids

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

- Anandamide – N-arachidonoylethanolamine (AEA)
- 2-arachidonoylgllycerol (2-AG)
Endocannabinoid Synthesis & the Degradation Pathway

Biosynthetic Enzymes

Arachidonoyl-phosphatidylcholine (PC) → Nat (n-acyltransferase) → NAPE → NAPE-PLD → Anandamide (AEA)

Degradative Enzymes

Anandamide (AEA) → FAAH or COX2

Cleaves into Arachidonic Acid and Ethanolamine (FAAH); PGE2-ethanolamide (COX2)

Arachidonic acid and glycerol

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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

1. Excitatory neurotransmitters activate endocannabinoid synthesis and release.
2. Endocannabinoids activate CB₁ receptors, which are located on the presynaptic neuron.
3. Once activated, the CB1 receptor inhibits further release of the stimulating neurotransmitter, eliciting a relaxant effect.

Anandamide or 2-AG (endocannabinoids)
Excitatory neurotransmitter (e.g. glutamate)
The Endocannabinoid System in the Periphery

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

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

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Endocannabinoids: Mechanisms of Action: It’s Complex

- Neurotransmission (CB1)
- Immune modulation (CB2)

CB₁, CB₂ receptor activation

- 5HT₁A Serotonin receptor activation
  \( EC_{50} = 0.007 \, \mu M \)
  Anxiolysis

- TRPV1 Vanilloid receptor activation/
desensitization
  \( EC_{50} < 5\mu M \)
  Pain Perception

Pain Perception

- TRPV1 activation
  \( EC_{50} < 5\mu M \)

- GPR55 receptor inhibition
  \( IC_{50} < 0.5\mu M \)

- PPARγ activation
  \( EC_{50} = 5 \, \mu M \)

- Adenosine reuptake inhibition
  \( IC_{50} < 5\mu M \)

- Osteoclast Function

Legend

- Low affinity interaction supported by
  limited/inconclusive data

- Low to moderate affinity interaction
  supported by satisfactory data

- Potent interaction supported by
  satisfactory data

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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”
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 of 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

<table>
<thead>
<tr>
<th>Progesterone (PG) receptors on immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG suppresses immune responses by T-helper 1 (Th1) &amp; Th17</td>
</tr>
<tr>
<td>Promotes secretion of cytokines by Th2 lymphocytes</td>
</tr>
<tr>
<td>PG suppresses differentiation pathway of B lymphocytes</td>
</tr>
<tr>
<td>Induce immune tolerance against fetal antigens during pregnancy</td>
</tr>
<tr>
<td>PG &amp; Human lymphocytes – upregulates activity FAAH gene – decreases AEA plasma levels</td>
</tr>
<tr>
<td>Downregulates uterine NAPE-PLD expression in mice - lowers tissue AEA levels</td>
</tr>
</tbody>
</table>

Drehmer et al. Biochem Genetics. 2018;57:35-45

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REMINDER:
Prime Directive of Life:
Successful Reproduction

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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

Meccariellow et al. 2014
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-oxytoxin & 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

Sabatier et al. Am J Physiol Regul Integr Comp Physiol. 2006; 290:R577-R584
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


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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

Taylor et al. Histochem and Cell Bio. 2010a;133:557-565
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-ovulation 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
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


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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 (B).
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

Maccarone M. Progress in Lipid Research. 2009;48:344-354
Endocannabinoid System and Pregnancy

Schander et al. Mol Hum Reprod. 2016;22(11):800-808 © 2019 Dr. Felice Gersh
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-1alpha - 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

Basttista et al. J of Neuroendo. 2008;20:82-89
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

Contassot et al. Gynecol Oncol. 2004;93(1):182-8
Endocannabinoid System: Protection from Cancers!


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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

V Di Marzo. Diabetologia;51(8):1356
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Complex Interaction: Metabolic Health Linking to Reproductive Health
Brain

Liver

OEA

2-AG

AEA

Nodose ganglion

CB₁

CB₂

↑ Steatosis
↑ Fibrosis
↑ Hepatic apoptosis
↑ Hepatocyte proliferation

↓ Steatosis
↓ Fibrosis
↓ Hepatic apoptosis
↓ Hepatocyte proliferation

Long. Muscle
Myenteric plexus
Circ. Muscle
Submucosal plexus

Motility (CB₁ & CB₂)
↓ Inflammation (CB₁ & CB₂)
↑ Enhanced permeability (CB₁)
↓ Immune activation (CB₁ & CB₂)

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Effect of CB₁ activation</th>
<th>Effects of a HFD</th>
<th>Potential consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epididymal adipose tissue</td>
<td>Lipogenesis (LDL, FAS)</td>
<td>↑ 2-AG Sustained</td>
<td>Energy storage</td>
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<tr>
<td></td>
<td>PPAR-γ expression</td>
<td></td>
<td>Dyslipidaemia</td>
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<td></td>
<td>Glucose uptake</td>
<td></td>
<td>Insulin resistance</td>
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<td></td>
<td>AMPK activity</td>
<td></td>
<td>Excessive visceral fat</td>
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<td></td>
<td>Adiponectin</td>
<td></td>
<td></td>
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<tr>
<td>Subcutaneous adipose tissue</td>
<td>See above</td>
<td>↓ 2-AG, AEA Sustained</td>
<td>Subcutaneous fat</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin release?</td>
<td></td>
<td>Visceral and ectopic fat</td>
</tr>
<tr>
<td>Liver</td>
<td>Fatty acid synthesis</td>
<td>↑ AEA Early and sustained</td>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td></td>
<td>AMPK activity</td>
<td>↑ CB₁ Early</td>
<td>Dyslipoproteinaemia</td>
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<td></td>
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<td></td>
<td>Steatosis</td>
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<tr>
<td>Skeletal muscle</td>
<td>AMPK activity?</td>
<td>↑ 2-AG Early</td>
<td>Insulin resistance?</td>
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<tr>
<td></td>
<td>Glucose uptake?</td>
<td>↑ CB₁</td>
<td>Energy expenditure</td>
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<tr>
<td></td>
<td>Glucose oxidation?</td>
<td></td>
<td></td>
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<tr>
<td>Heart</td>
<td>↑ 2-AG, AEA Early and sustained</td>
<td></td>
<td>Cardiovascular fat?</td>
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<td>Pericardial fat?</td>
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<td></td>
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<td>Perirenal fat?</td>
</tr>
<tr>
<td>Kidneys</td>
<td>↓ Glomerular filtration</td>
<td>↑ 2-AG, AEA Late and sustained</td>
<td>Hypertrophy?</td>
</tr>
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<td></td>
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<td>Renal failure</td>
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</tbody>
</table>

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

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Plant Based Cannabinoids

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

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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 folliculo-genesis & 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 Heath: 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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