Università degli Studi di Padova
Dipartimento di salute della donna e del bambino – SDB
U.O.C. Clinica Ginecologica ed Ostetrica
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

Cannabis and Female Fertility

Simone Fagherazzi, MD

Cannabis, the beginning

«Viaggiare era sempre stato per me un modo di vivere
e ora avevo preso la malattia come un altro viaggio:
un viaggio involontario,
non previsto,
per il quale non avevo carte geografiche,
per il quale non mi ero in alcun modo preparato,
ma che di tutti i viaggi fatti fino ad allora era il più impegnativo, il più intenso.»

[T. Terzani]

- Pacher, P.; Bátkai, S; Kunos, G (2006). "The Endocannabinoid System as an Emerging Target of Pharmacotherapy". Pharmacological Reviews 58 (3): 389–462.doi:10.1124/pr.58.3.2. PMC 2241751. PMID 16968947
- Pertwee, Roger, ed. (2005). Cannabinoids. Springer-Verlag. p. 2. ISBN 3-540-22565-X.

Cannabis, Current Classification

Schedule I

no currently accepted medical use and a high potential for abuse. Schedule I drugs are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence

Schedule II

high potential for abuse, less abuse potential than Schedule I drugs, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous

Schedule III

moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV.

Schedule IV

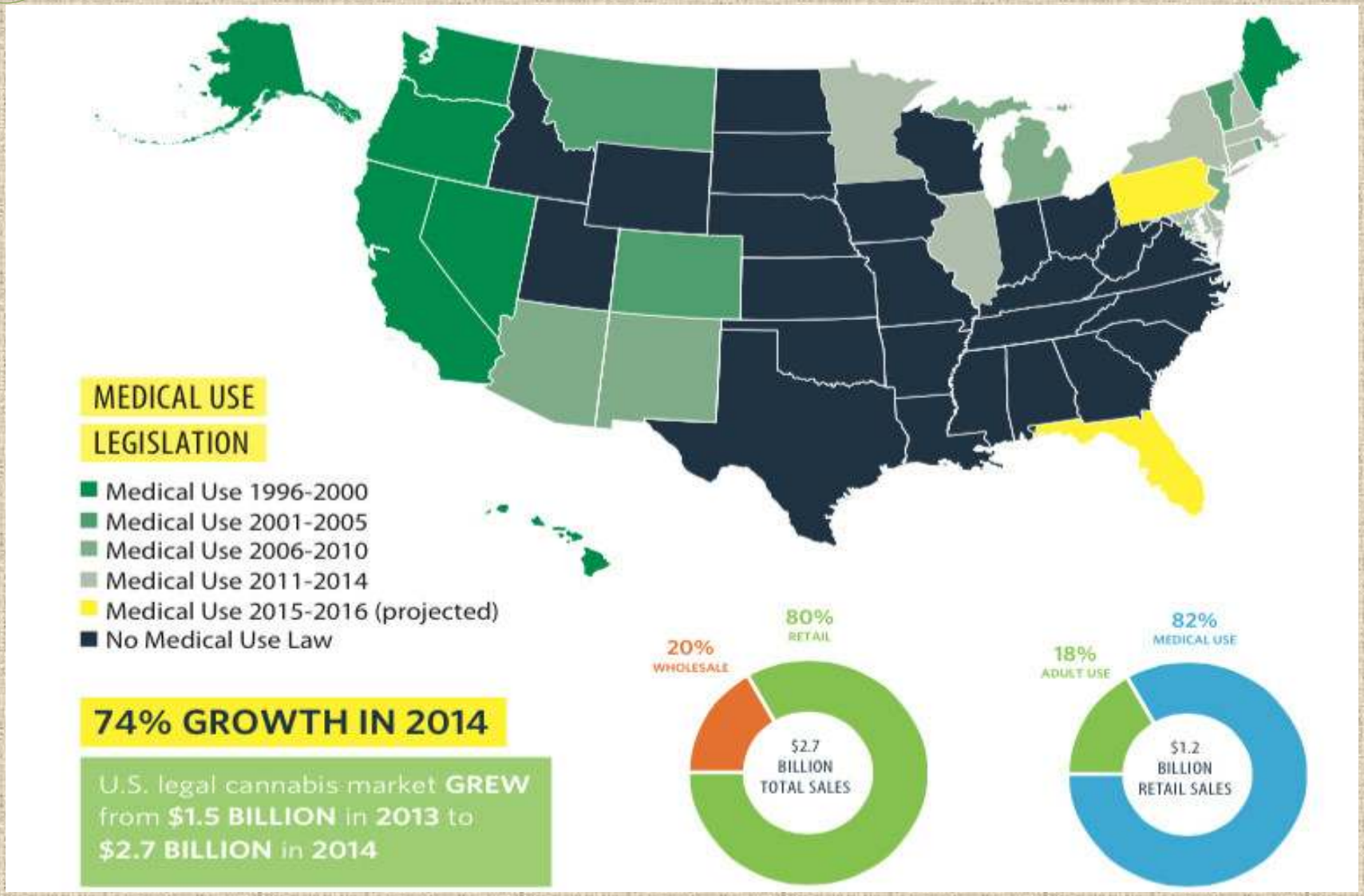
ow potential for abuse and low risk of dependence

Schedule V

lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes.

- USA, Drug Enforcement Administration – DEA – http://www.dea.gov/druginfo/ds.shtml

Cannabis, the impulse of United States



- http://www.huffingtonpost.com/2015/01/26/marijuana-industry-fastest-growing_n_6540166.html

Cannabis, Italian Asset

Nessun protocollo attuativo è stato emesso, le leggi, pertanto non sono attive

ABRUZZO: Legge Regionale n. 4 del 4/1/2014

EMILIA ROMAGNA: Legge Regionale n. 11 del 17/7/2014

FRIULI VENEZIA GIULIA: Legge Regionale n. 213 del 30/1/2013

LIGURIA: Legge Regionale n. 26 del 3/8/2013

LOMBARDIA: progetto di legge

MARCHE: Legge Regionale n. 1 del 22/1/2013

PUGLIA: Legge Regionale n. 2 del 12/2/2014

SICILIA: delibera regionale n. 83 del 26/03/2014

UMBRIA: Legge Regionale n. 7 del 17/4/2014

DM 18/04/2007 (GU 28/04/2007)

inserisce i principi attivi cannabinoidi **Δ9-THC, Dronabinolo e Nabilone** all'interno della **Tabella II, sezione B**

DM 23/01/2013 (GU n. 33 del 08/02/2013)

inserisce nella **Tabella II sezione B** anche **i medicinali di origine vegetale a base di Cannabis (sostanze e preparazioni vegetali, inclusi estratti e tinture)**, *rendendo prescrivibile anche la Cannabis Flos*

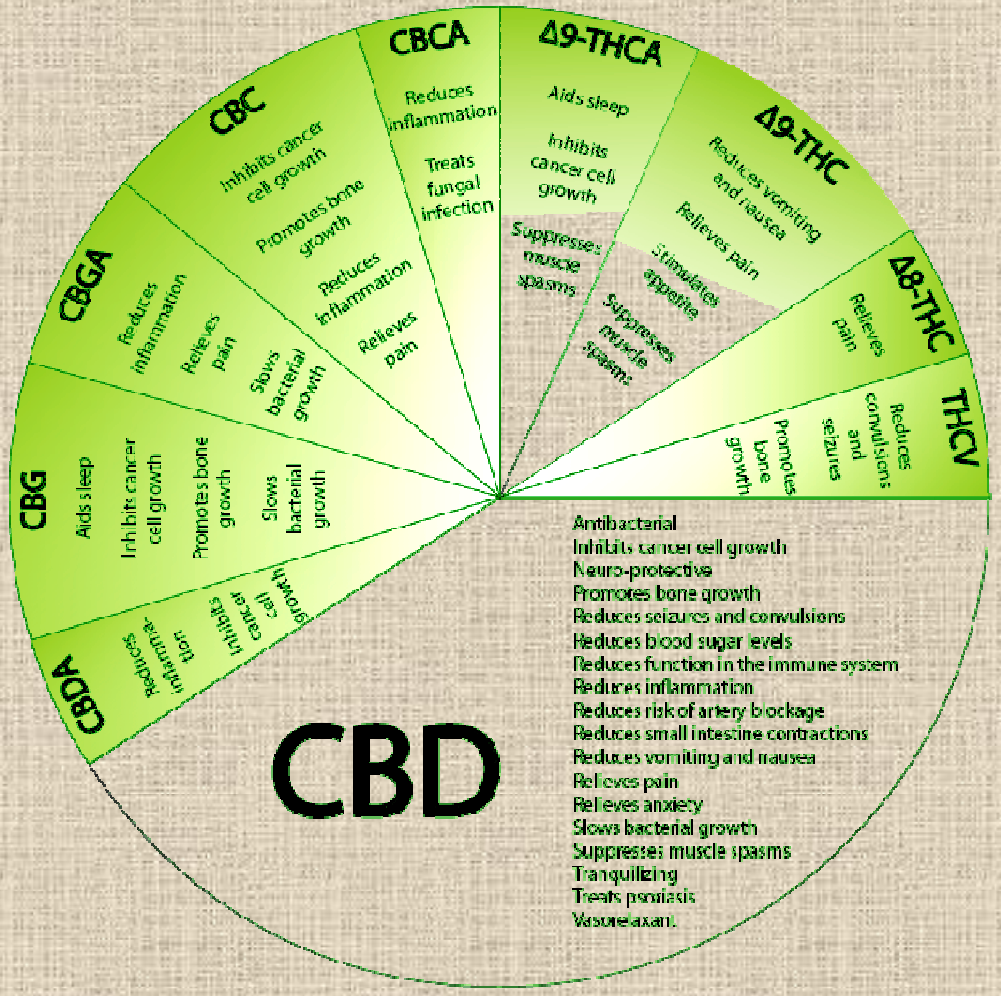
Cannabis, the plant

Cannabis is a genus of flowering plants that includes three different species,

- *Cannabis Sativa*
- *Cannabis Indica*
- *Cannabis Ruderalis*

These species are indigenous to Central Asia and the Indian Subcontinent.

Different types of Cannabinoids founded in the plant and their actions.



- Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011 Aug;163(7):1344-64. doi: 10.1111/j.1476-5381.2011.01238.x. Review.

Cannabis, the plant

- **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)

- GW pharmaceuticals official presentation downloadable by: videocast.**nih**.gov/**ppt**/nida_042105.**ppt**

Cannabis, role in Human Fertility

2003

Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Prostaglandins, Leukotrienes and Essential Fatty Acids 70 (2004) 189–197
Prostaglandins Leukotrienes Essential Fatty Acids
www.elsevier.com/locate/plefa

Cannabis, cannabinoids and reproduction

Boram Park[a], John M. McPartland[b], Michelle Glass[a,*]

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Received 1 April 2003; accepted 1 April 2003

2010

Human Reproduction Update, Vol.17, No.3 pp. 347–361, 2011
Advanced Access publication on January 12, 2011 doi:10.1093/humupd/dmq058
human reproduction update

The role of sex steroid hormones, cytokines and the endocannabinoid system in female fertility

T. Karasu [1], T.H. Marczylo [1], M. Maccarrone [2,3†], and J.C. Konje [1,*†]

2012

ACS Chemical Neuroscience
Review
pubs.acs.org/acschemicalneuroscience

Endocannabinoid Signaling in Female Reproduction

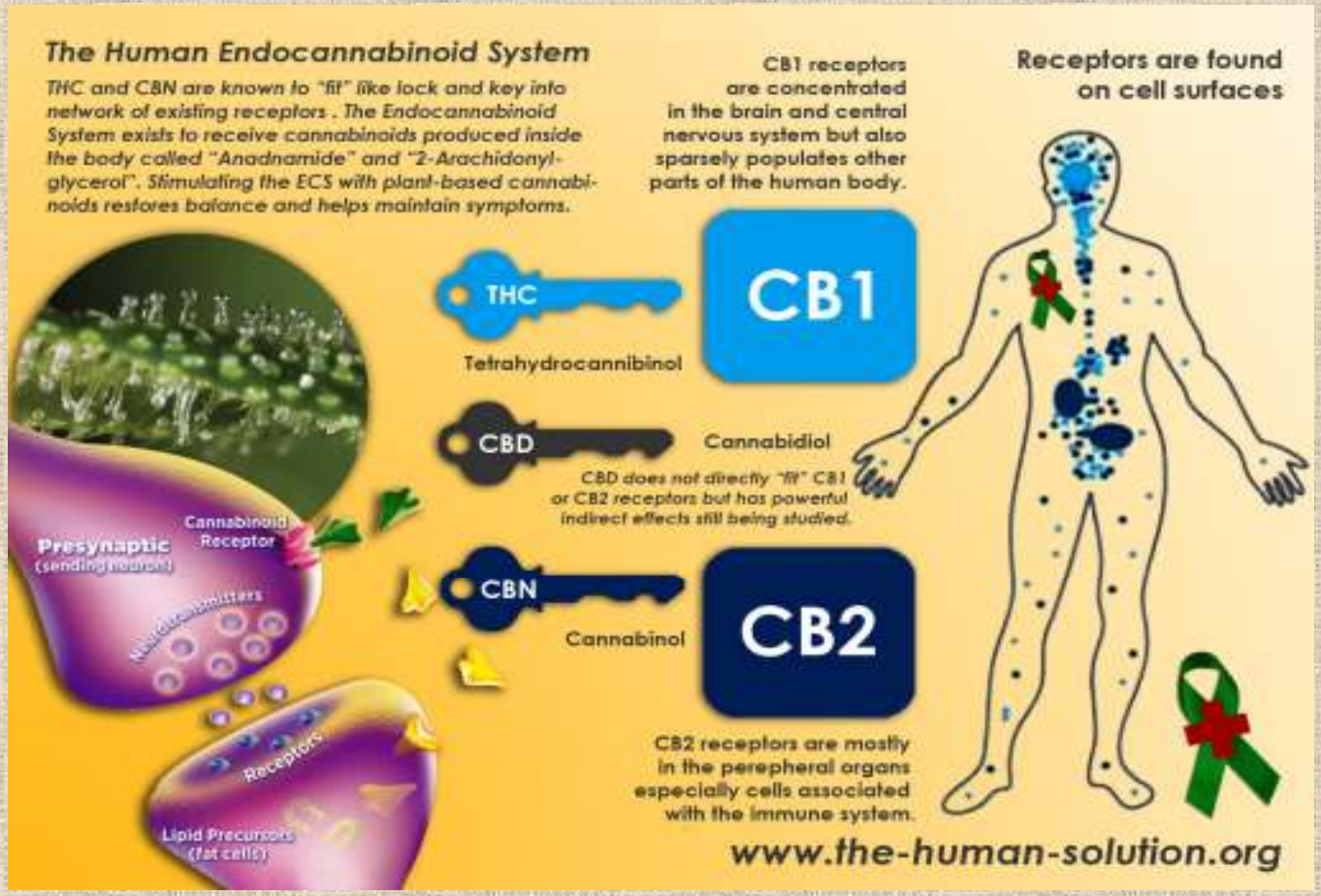
Xiaofei Sun and Sudhansu K. Dey*

Division of Reproductive Sciences, Perinatal Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio 45229, United States

The Endocannabinoid System (ECS)

We naturally produce the endogenous cannabinoids **Anandamide** and **2-Arachidonyl-glycerol** (2AG).

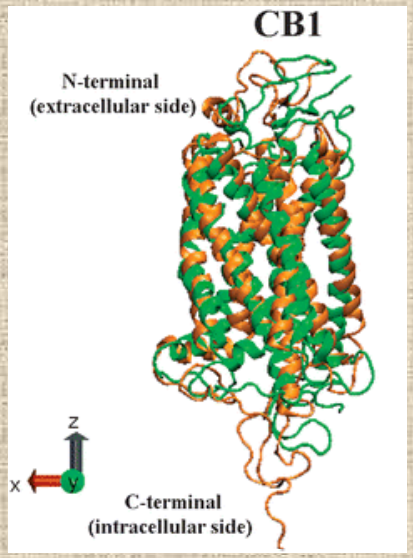
These compounds are found to naturally occur in mother's breast-milk to help stimulate the infant's appetite.



The Endocannabinoid System is currently the topic of some studies, mostly outside of the US, aimed at unlocking the mystery of overwhelming world-wide anecdotal reports of cannabis cures.

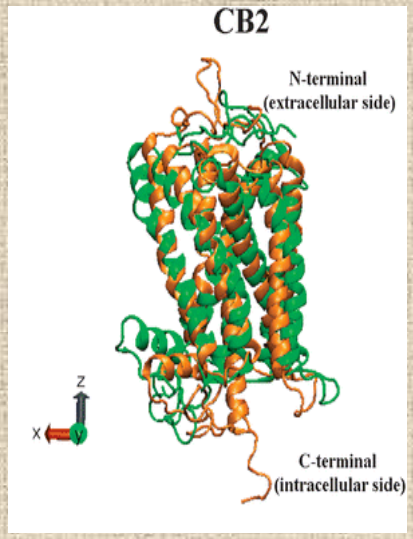
- Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. Drug Test Anal. 2014 Jan-Feb;6(1-2):7-16. doi: 10.1002/dta.1574. Epub 2013 Nov 11. Review.

Cannabinoid receptors distribution



- **ovary**
- **uterine endometrium**
- **testis**
- liver
- heart
- small intestine
- urinary bladder
- peripheral cells (lymphocytes)

- **embryonic stem cells**
- **human placenta**
- **Myometrium**
- immune cells
- central neurons
- Gastrointestinum
- heart



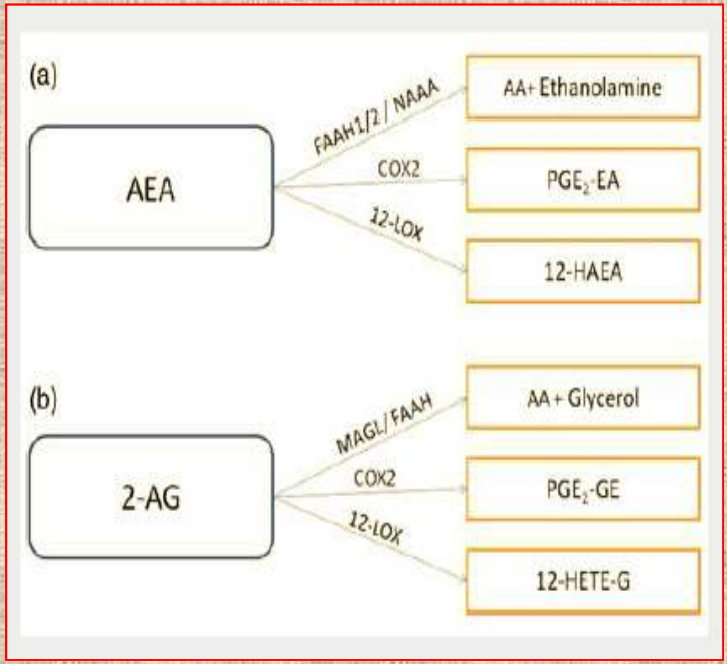
CB2 activation inhibits nitric oxide synthase, whereas CB1 activates it

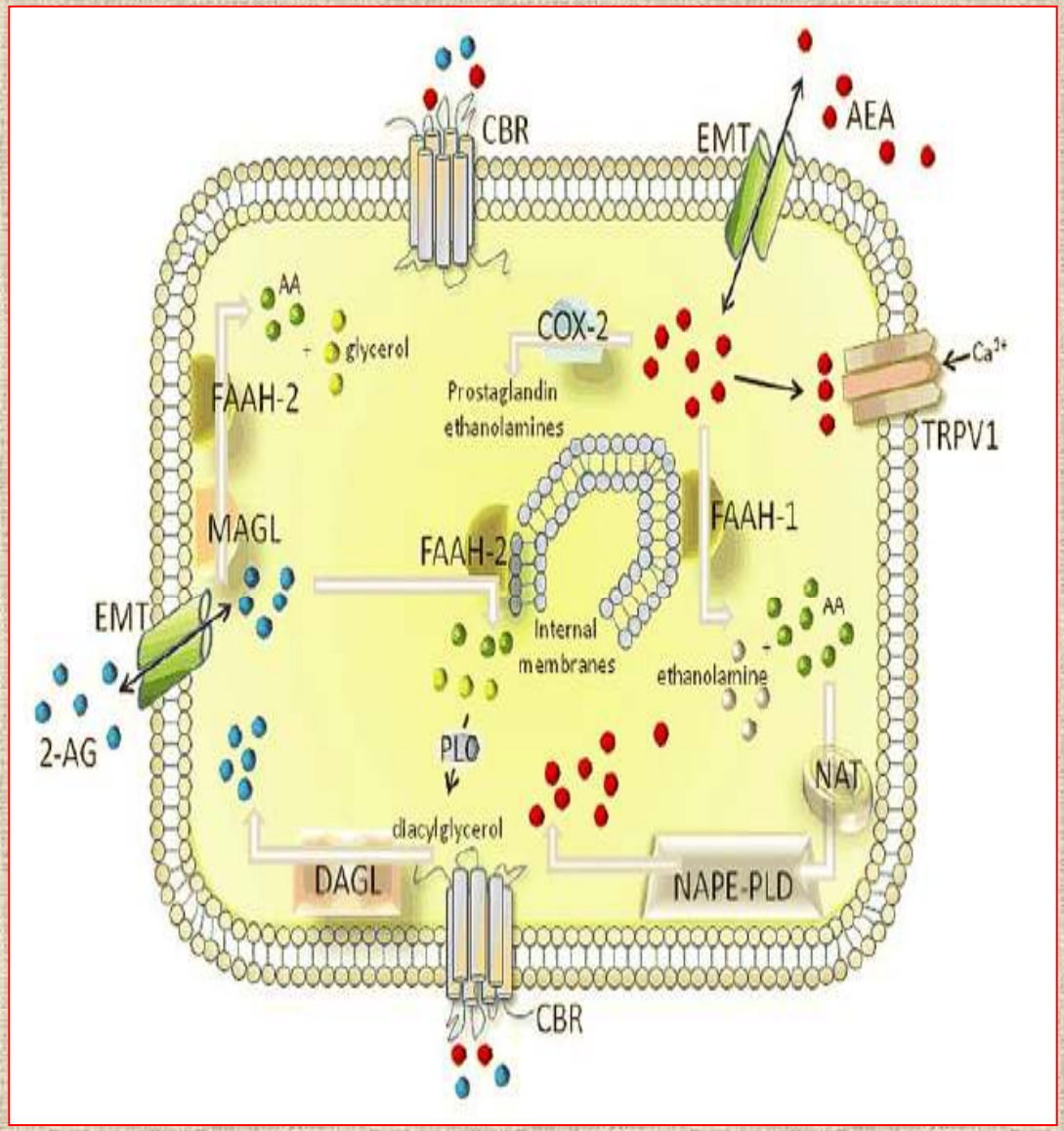
Nitric oxide has been shown to play an important role in several critical processes in female reproduction, including ovulation, implantation, pregnancy maintenance, labour and delivery

- Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. Neuropharmacology 2004;47:345–358.
- Demuth DG, Molleman A. Cannabinoid signalling. Life Sci 2006;78:549–563.
- Maul H, Longo M, Saade GR, Garfield RE. Nitric oxide and its role during pregnancy: from ovulation to delivery. Curr Pharm Des 2003;9:359–380.

The ECS: synthesis and degradation of AEA and 2-AG

The biosynthesis of AEA occurs on demand





- Taylor AH, Amoako AA, Bambang K, Karasu T, Gebeh A, Lam PM, Marzcylo TH, Konje JC. Endocannabinoids and pregnancy. Clin Chim Acta 2010;411:921–930.

ECS in reproduction

In animal studies, it has been shown that the **ECS plays a pivotal role in reproduction**.

Endocannabinoid signalling pathways are involved in:

- *Fertilization*
- *Oviductal transport*
- *Implantation*
- *Embryo Development*
- *Maintenance of early pregnancy*

AEA is now thought to be the **key link between the developing embryo and the endometrium**, ensuring synchronous development of the preimplantation embryo and the endometrium, thereby facilitating to permit embryo implantation during the 'implantation window'.

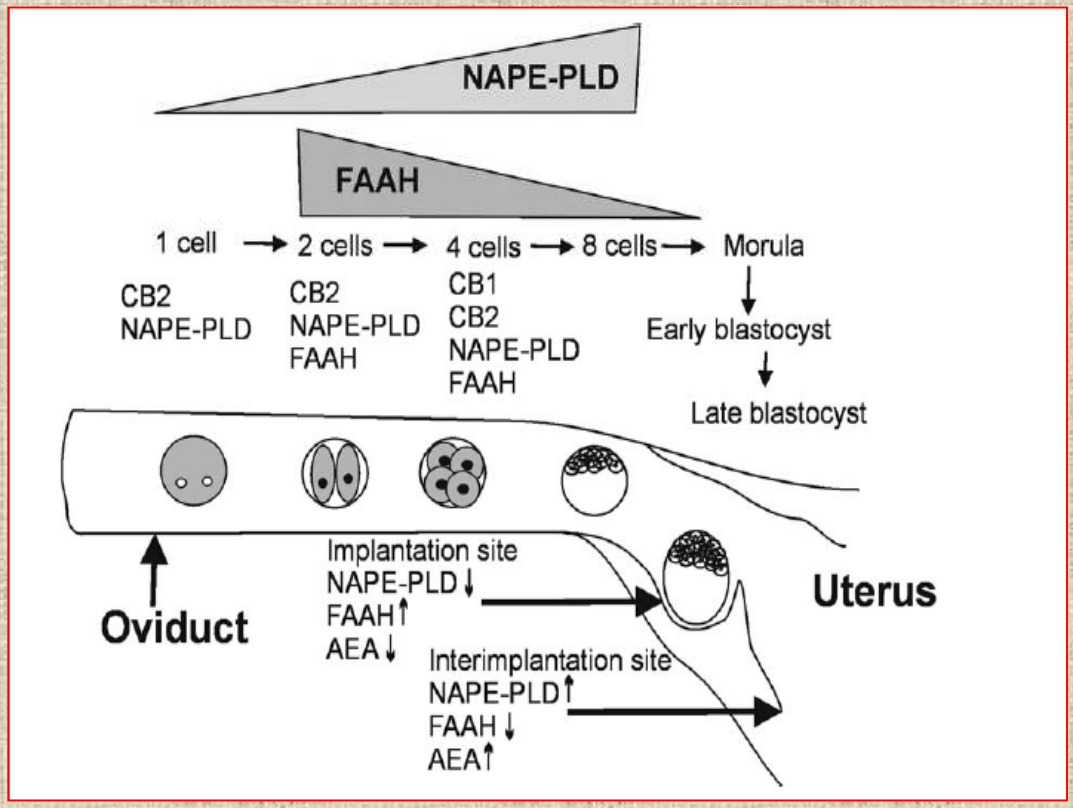
- Battista et al., 2007, 2008a;
- Taylor et al., 2007)

Tubaric AEA gradient and it's importance

NAPE-PLD is also found in the oviduct, with **higher levels at the isthmus** and **lower levels in the ampullary region**, whereas the expression of *FAAH is higher in the ampulla*.

The AEA gradient is important for:

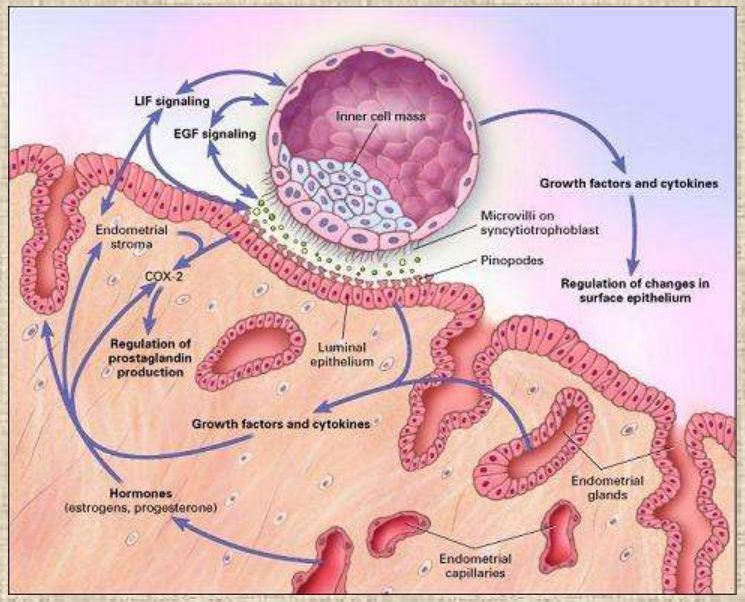
- Normal embryo development,
- Oviductal transport
- Implantation
- Successful pregnancy

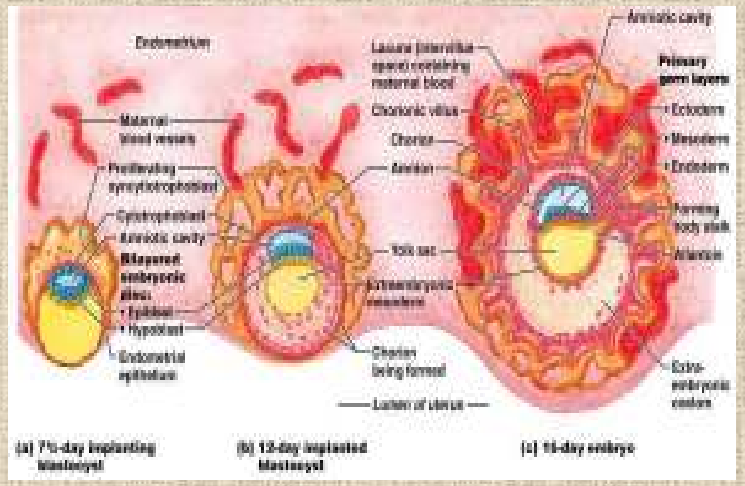


- Wang et al., 2006

Blastocyst implantation

- **AEA 7 nM** activate the ERK signalling pathway via CB1 and make the blastocyst competent for implantation.
- **AEA 28 nM** cannot activate ERK but inhibit calcium mobilization.
- Clinical relevance as reduced peripheral levels of AEA hydrolase in women have been shown to be associated with spontaneous miscarriage.
- A pilot study of women with threatened miscarriage showed that all women who subsequently miscarried had high peripheral AEA levels (> 2.0 nM)





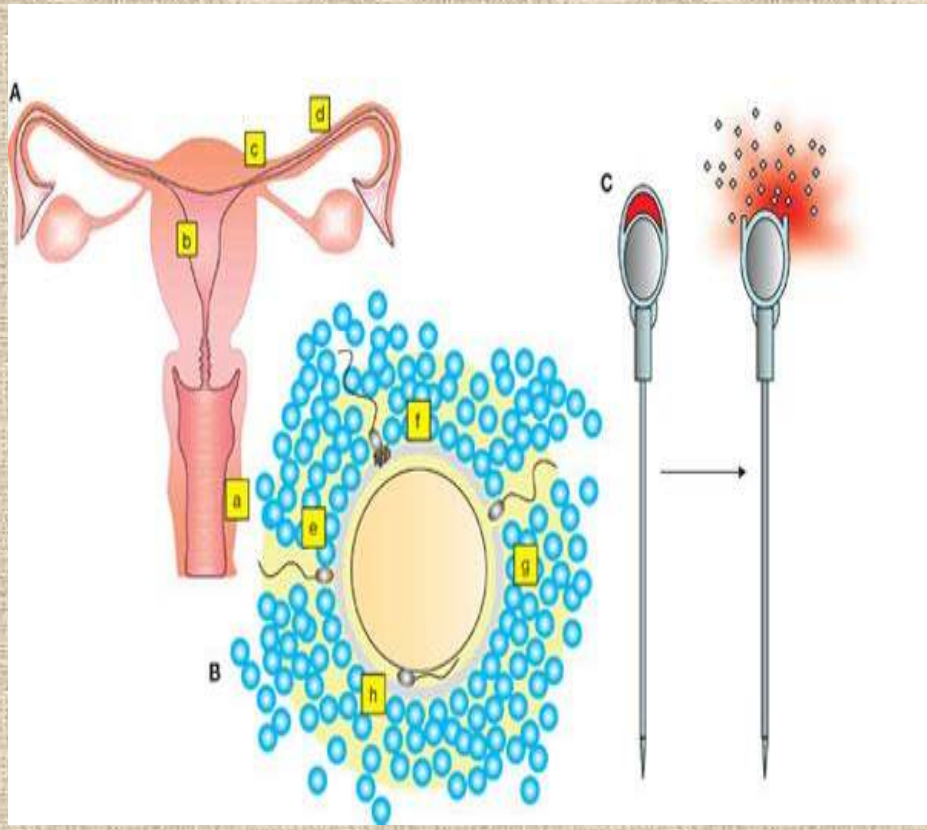
- J. Wang, B.C. Paria, S.K. Dey, D.R. Armant, Stage-specific excitation of cannabinoid receptor exhibits differential effects on mouse embryonic development, Biol. Reprod. 60 (1999) 839–844.
- W.M. Liu, E.K. Duan, Y.J. Cao, Effects of anandamide on embryo implantation in the mouse, Life Sci. 71 (2002) 1623–1632.

ECS in reproduction, the male

The metabolically stable AEA-analogue (R-methanandamide) stimulates **hyperactive motility of human sperm** during in vitro capacitation at 0.25 nM, and **inhibits hyperactivated motility** at 2.5 nM.

These findings suggest that localized differences in AEA concentration may *modulate sperm capacitation* within the human oviduct.

Influence occur in attachment of sperm to epithelial cells by activating CB1 receptors, which suggests an important role of endocannabinoid-signalling in regulating the migration of sperm to the site of fertilization within the oviduct.



- Schuel et al.,2002
- Gervasi et al., 2009

ECS in Assisted Reproduction

- **IVF pregnancies** that high plasma levels of AEA were associated with failure to achieve an ongoing pregnancy after embryo transfer.
- **IVF/ICSI** required low AEA levels at the time of implantation for a successful pregnancy.

*Taken together, the results suggest that **FAAH activity** as well as **AEA content in blood** could perhaps be used for the monitoring of early pregnancies.*

In addition to the direct effects proposed for endocannabinoids on reproduction, the ECS also interacts with sex steroid hormones and cytokines to <u>regulate reproduction indirectly</u>

- (El-Talatini et al., 2009a, b) (Table I)

ECS and Progesterone

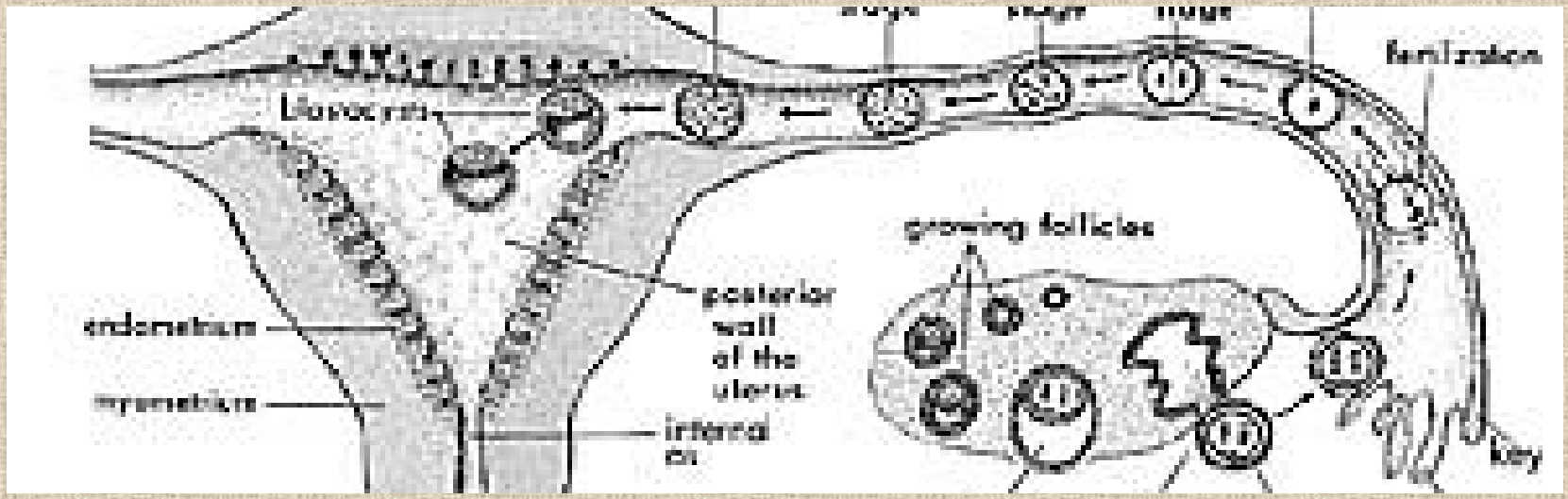


Table II Effects of progesterone and oestrogen on ECS in female fertility.

Hormone/ cytokine	Reproductive process	Effect on ECS
Progesterone	Implantation	Increases FAAH through transcription factor Ikaros and reduces AEA
	Pregnancy maintenance	Increases LIF via IL4
		Promotes pro-fertility Th2 cytokines
Oestrogen	Folliculogenesis	Stimulates NAPE-PLD and increases AEA from endothelial cells
	Implantation	Inhibits FAAH activity and increases AEA content in endothelial cells
		Down-regulates NAPE-PLD and inhibits FAAH in uterine epithelium

Progesterone:

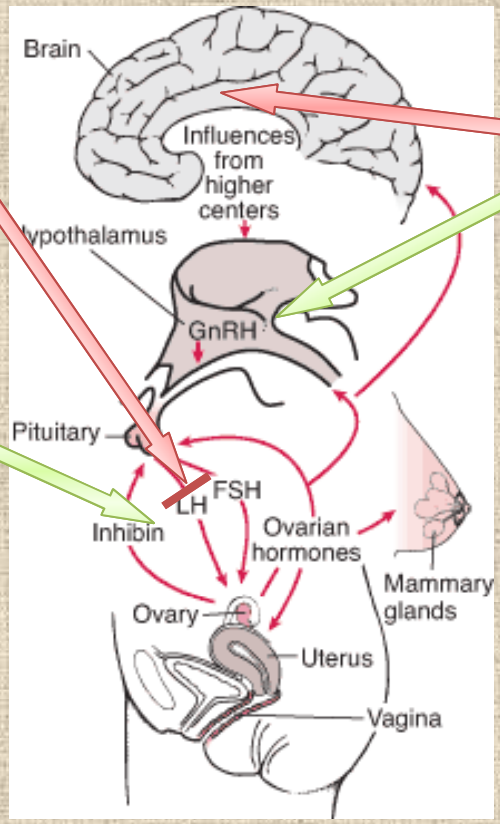
- creates a suitable endometrial environment for implantation and maintains pregnancy by contributing to a protective immune milieu.
- induces, also, the production of the pro-fertility Th2 cytokines and inhibits the anti-fertility Th1 cytokines

Maccarrone M, Di Rienzo M, Finazzi-Agro` A, Rossi A. Leptin activates the anandamide hydrolase promoter in human T lymphocytes through STAT3. J Biol Chem 2003a;278:13318–13324.
Maccarrone M, Valensise H, Bari M, Lazzarin N, Romanini C, Finazzi-Agro` A. Progesterone up-regulates anandamide hydrolase in human lymphocytes: role of cytokines and implications for fertility. J Immunol 2001;166:7183–7189.
Guo Y,Wang H, Okamoto Y, Ueda N, Kingsley PJ, Marnett LJ, Schmid HH, Das SK, Dey SK. N-acylphosphatidylethanolamine-hydrolyzing phospholipase D is an important determinant of uterine anandamide levels during implantation. J Biol Chem 2005;280:23429–23432.

Endocannabinoid control in Endocrine Regulation

THC inhibits ovulation by potent antigonadotropic activity

LH release could be induced by exogenous gonadotropins or gonadotropin-releasing hormone, even in the presence of high concentrations of THC



cannabinoids do not directly block the basal GnRH secretion from hypothalmi in vitro, rather they may produce this effect through modulation of neuronal systems known to inhibit GnRH

Direct intracerebro ventricular administrati on of THC

decreased plasma LH levels

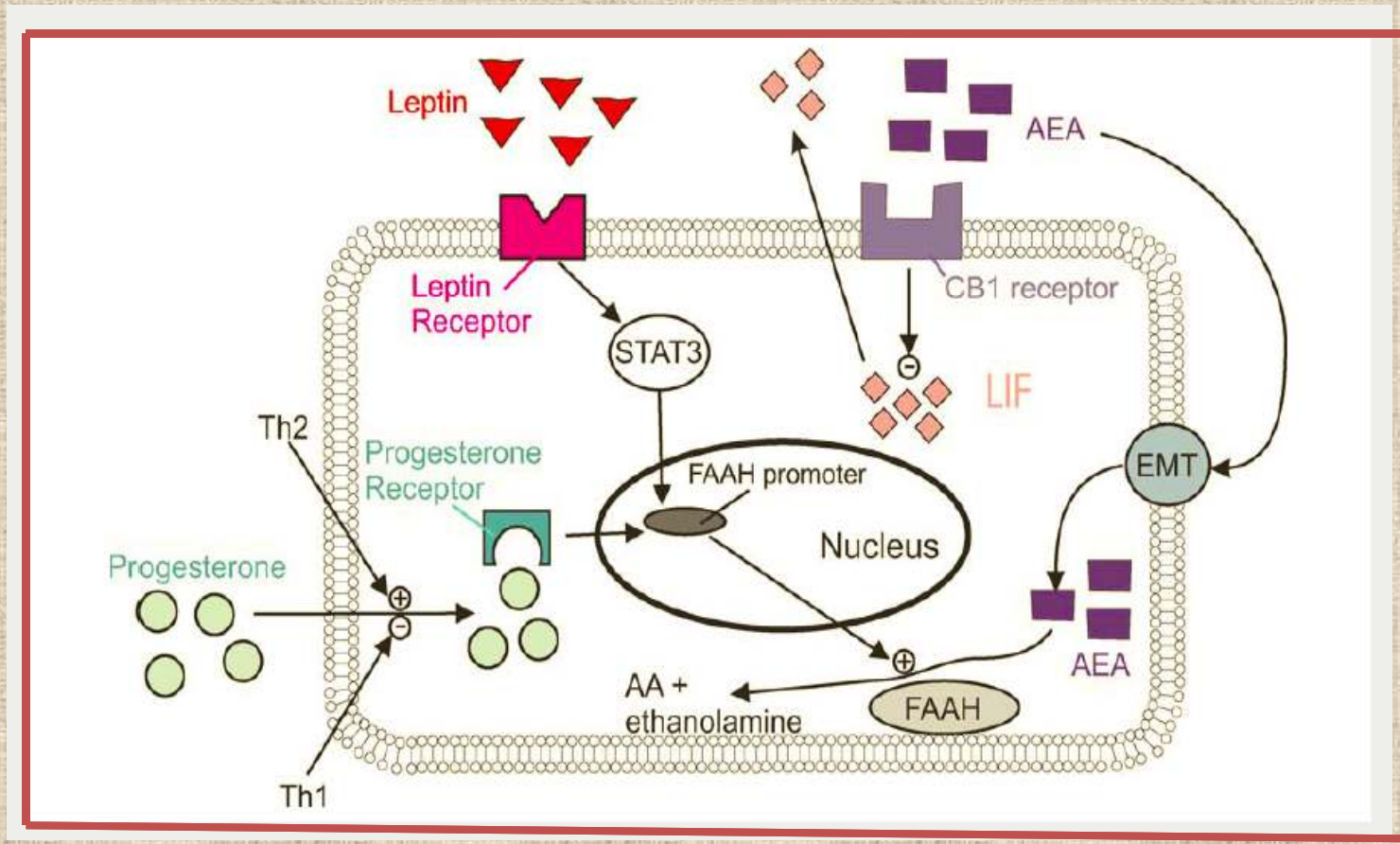
increased hypothalamic levels of GnRH

decreased release of GnRH into the pituitary portal vasculature is responsible for the suppressed levels of LH that follow THC exposure

- J.H. Mendelson, N.K. Mello, J. Ellingboe, A.S. Skupny, B.W. Lex, M. Griffin, Marihuana smoking suppresses luteinizing hormone in women, J. Pharmacol. Exp. Ther. 237 (1986) 862–866.
- J.H. Mendelson, P. Cristofaro, J. Ellingboe, R. Benedikt, N.K. Mello, Acute effects of marihuana on luteinizing hormone in menopausal women, Pharmacol. Biochem. Behav. 23 (1985) 765–768.
- J.H. Mendelson, N.K. Mello, Effects of marijuana on neuroendocrine hormones in human males and females, NIDA Res. Monogr. 44 (1984) 97–114.

Key Factors in Implantation

Overall, **LIF**, **Th1/Th2 cytokines** and **leptin** are all essential for implantation.
It seems, therefore, that a fundamental interaction exists between these substances and the ECS, which ultimately impacts on implantation.



LIF

Th1/ Th2

Ob

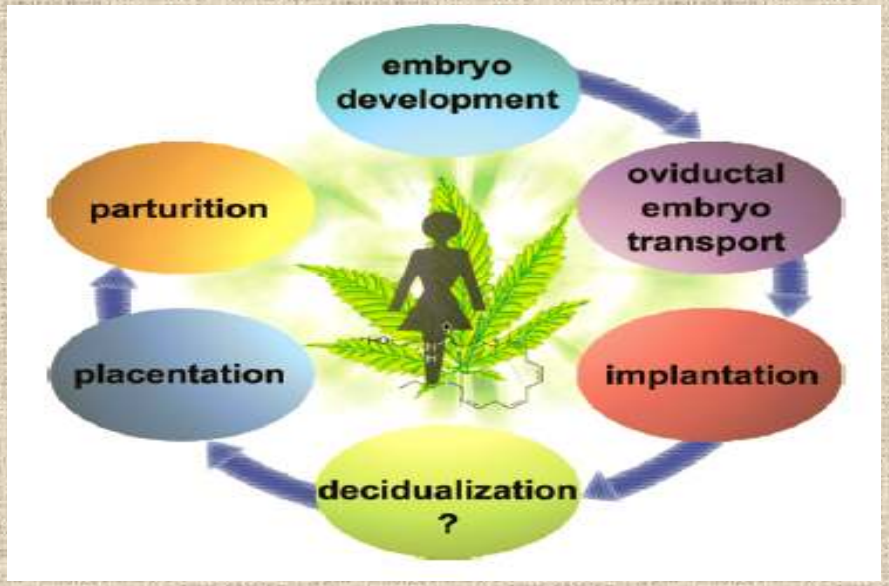
- Di Marzo V, Goparaju SK, Wang L, Liu J, Batkai S, Jarai Z, Fezza F, Miura GI, Palmiter RD, Sugiura T. et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001b;410:822–825.

New perspectives

Studies have shown that:

- **Low plasma AEA levels** are **required** for successful implantation and maintenance of pregnancy
- **FAAH is the key regulator** of AEA levels, which directs various preimplantation events.
- AEA levels in humans inversely correlate with FAAH activity in peripheral lymphocytes
- FAAH is also under the control of Th1/Th2 cytokines, Progesterone and leptin

Tight control of this network is required for successful implantation and maintenance of early pregnancy.



Taken together, **<u>FAAH and AEA assays might be useful in predicting the outcome of assisted reproduction and natural pregnancy</u>** in women with threatened miscarriage.

Internationa Cannabis Conference, Prague 2015

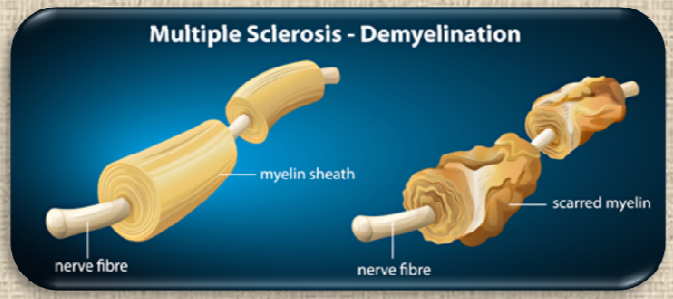
"Prague Resolution of the International Medical Cannabis Patient Coalition on the Rights of people suffering with conditions treatable with Medical Cannabis and products made of it."

Prague 8-03-2015

medical cannabis

IMCPC
INTERNATIONAL MEDICAL CANNABIS PATIENTS COALITION

Multiple Sclerosis



Chronic, progressive, degenerative disorder of the CNS characterized by disseminated demyelination of nerve fibers of the brain and spinal cord

Sexual dysfunction

- Erectile dysfunction
- Decreased libido
- Difficulty with orgasmic response
- Painful intercourse
- Decreased lubrication

- Pacher, P.; Bátkai, S; Kunos, G (2006). "The Endocannabinoid System as an Emerging Target of Pharmacotherapy". Pharmacological Reviews 58 (3): 389–462.doi:10.1124/pr.58.3.2. PMC 2241751. PMID 16968947
- Pertwee, Roger, ed. (2005). Cannabinoids. Springer-Verlag. p. 2. ISBN 3-540-22565-X.

Cannabis, the plant

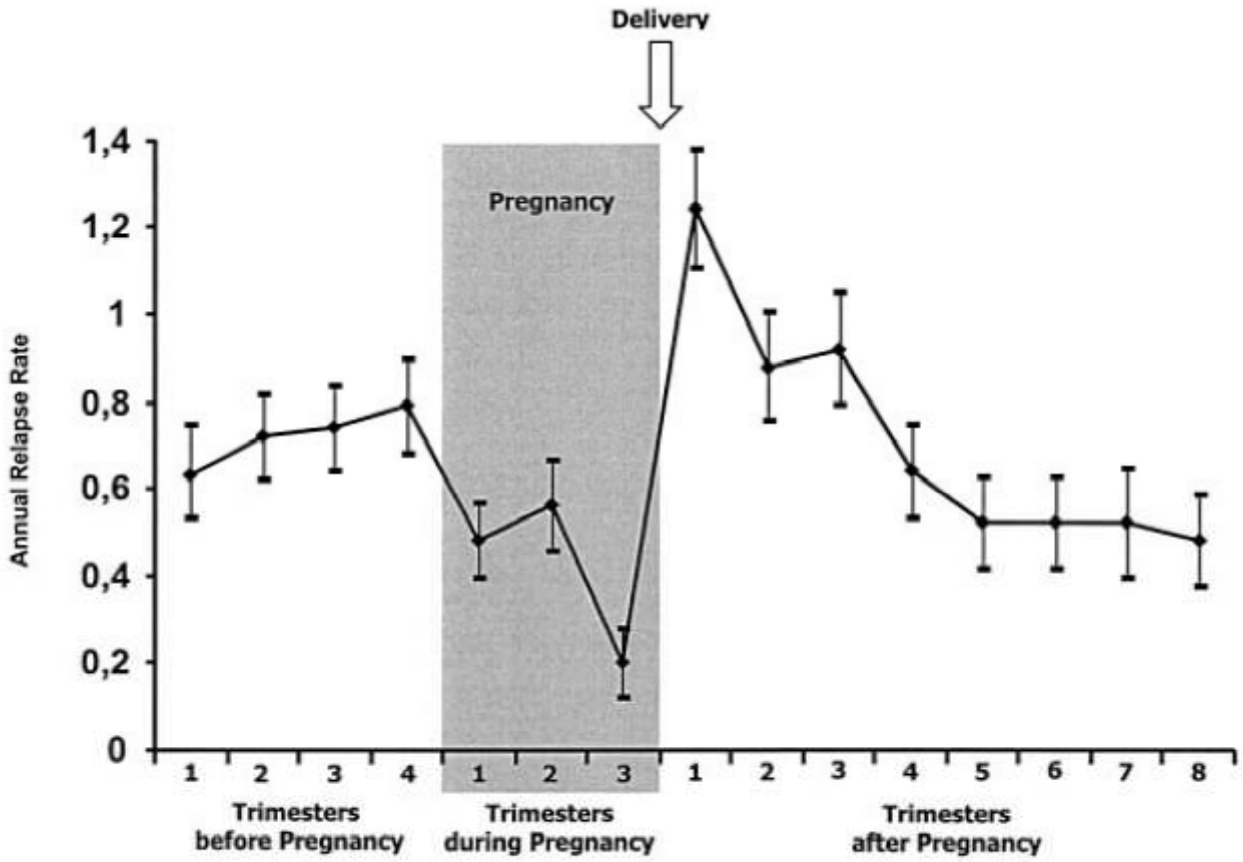


Fig. 1 Annualized relapse rate in the year before pregnancy, during pregnancy and in the two years after delivery among 227 women with MS (vertical bars represent means and 95% confidence intervals).

- Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998 Jul 30;339(5):285-91.

Raw cannabis and other complementary and alternative medicine in relapsing-remitting multiple sclerosis. a pilot, randomized, double-blind, crossover trial

Current therapies have a poor efficacy.

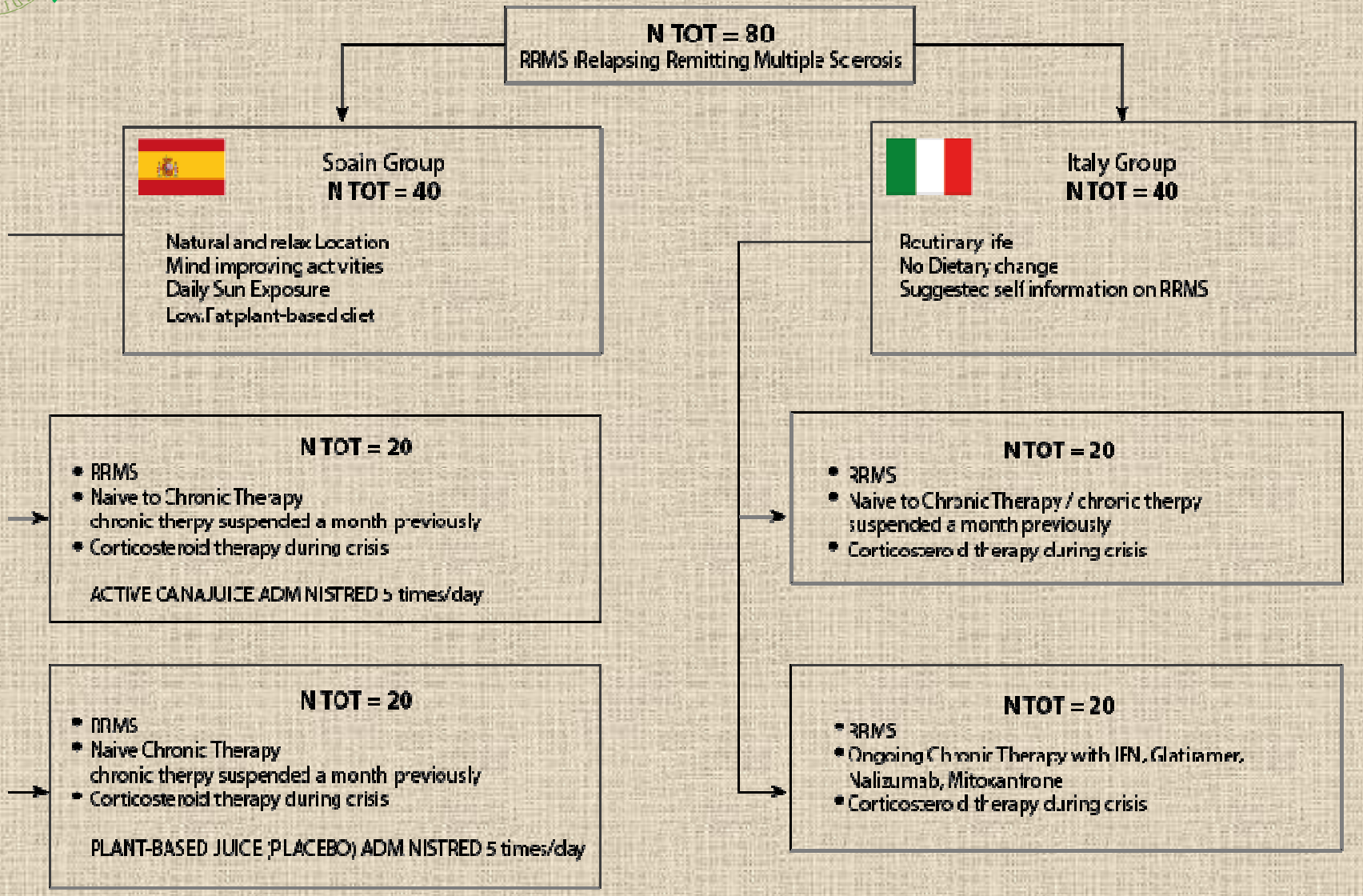
In MS there is percieved a poor quality of life

RAW
the study

Up to 80% take in consideration Complementary Alternative Medicines

Starting in March 2016

Raw, Study Design



- Pacher, P.; Bátkai, S; Kunos, G (2006). "The Endocannabinoid System as an Emerging Target of Pharmacotherapy". Pharmacological Reviews 58 (3): 389–462.doi:10.1124/pr.58.3.2. PMC 2241751. PMID 16968947
- Pertwee, Roger, ed. (2005). Cannabinoids. Springer-Verlag. p. 2. ISBN 3-540-22565-X.