We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 1

Introductory Chapter: The Endocannabinoid System in Human Physiology

Rosanna Chianese and Rosaria Meccariello

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63818

1. Endocannabinoid system (ECS)

The identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) in 1964 by Gaoni and Mechoulam [1] as the principal biologically active component of *Cannabis sativa* has implicated the indispensable need to unveil the pharmacology of such a molecule and the correlated mechanisms of action. Since then, the subsequent identification of two G-protein-coupled cannabinoid receptors, CB1 [2] and CB2 [3], able to mediate Δ^9-THC effects. The existence of endogenous ligands that share many effects of the Δ^9-THC allows to formulate the attractive hypothesis that an endocannabinoid system (ECS) may play a pivotal role in a variety of centrally and peripherally regulated physiological processes. A plethora of endocannabinoids has been discovered starting from the anandamide [AEA, 4] and 2-arachidonoylglycerol [2-AG, 5] toward; they bind to CB1, CB2, or other cannabinoid receptors. In this regard, a role of GPR119 [6] and GPR55 [7] in endocannabinoid signal transduction has been suggested a long time ago; intriguingly, some endocannabinoids—such as the AEA—also bind to type 1 vanilloid receptor [TRPV1, 8] and to peroxisome proliferator-activated receptor γ [PPARγ, 9], as well as 2-AG binds to specific γ-aminobutyric acid (GABA) receptor (A) subtypes in neuronal cells [10], thus making more intricate the network of the endocannabinoid activated pathways.

Endocannabinoid tone is finely regulated by a highly organized system of biosynthesis and degradation enzymes that are integral part of ECS. The main pathways of AEA biosynthesis and degradation depend on the activity of the N-arachidonoyl-phosphatidylethanolamine phospholipase D (Nape-PLD) [11] and the fatty acid amide hydrolase (FAAH) [12], respectively. Two diacylglycerol lipases (DAGLα and DAGLβ) enzymes are involved in 2-AG biosynthesis [13], whereas monoacylglycerol lipase (MAGL) and to a lesser extend FAAH metabolizes it [14]. The biological activity of endocannabinoids is finely regulated by mechanisms of intracellular uptake. In this respect, many doubts still exist and several hypotheses have been formulated. AEA transport, for instance, may occur by passive and/or facilitated diffusion, this last by an hypothetical endocannabinoid membrane transporter whose chemical identity

remains as yet unknown [15], by endocytosis [16], through fatty acid binding protein (FABP) proteins [17] or a FAAH-like AEA transporter protein (FLAT), a cytosolic variant of FAAH that lacks amidase activity, but bounding AEA, facilitates its translocation into cells [18].

2. Endocannabinoid activity in biological systems

Endocannabinoid biosynthesis, uptake, degradation, and activity have been largely reported in the central nervous system (CNS) and in a wide set of peripheral tissues in vertebrates—from fish to mammals, humans included [19]—but also in invertebrates [20]. Thus, this phylogenetically and onthogenetically conserved system is involved in the central and local control of many biological functions.

At cellular level, cell proliferation, differentiation, survival, and apoptotic rate—with different outcomes depending on the molecular targets and cellular context involved—have been reported to be under ECS control in tissues such as gonads, adipose tissues, bone, blood, epithelial cells, and also in the brain [21].

ECS activity is critical in CNS, as elsewhere properly reviewed [22]. In general, physiological functions of ECS in CNS include: pain perception, motor functions, control of tremor, and spasticity, cognitive functions (i.e. learning and memory), thermogenesis, regulation of weak/sleep cycles, axonal pathfinding, synaptic plasticity and adult neurogenesis, emotional behavior, stress response *via* modulation of hypothalamus-pituitary-adrenal gland axis (HPA), feeding and appetite, reproductive functions *via* modulation of hypothalamus-pituitary-gonad axis (HPG) and sex behavior, retinal neurotransmission from the retina to the primary visual cortex [properly reviewed in the following books: 23, 24]. Classically, 2-AG is released in the brain by postsynaptic neurons and acts as rapid retrograde signal to target presynaptic neurons in order to inhibit neurotransmitter release, whereas AEA may function as slow retrograde signal, non-retrograde signal or as TRPV1 agonist [25]. Dopaminergic, glutamatergic, GABA and N-methyl-D-aspartate (NMDA) transmission, and the secretion of neurohormones such as the gonadotropin-releasing hormone (GnRH) are all controlled by endocannabinoids [26, 27]. Direct involvement in the control of pituitary hormone release has also been provided [28].

Besides the brain, endocannabinoid biosynthesis and activity occur in peripheral tissues, such as blood cells, heart, intestine, liver, adipose tissue, muscle, and pancreas, where it seems to be involved in the regulation of inflammation, platelet aggregation, blood pressure, heart rate, vasodilatation, modulation of peristalsis, energy balance *via* lipid and glucose homeostasis and so on [properly reviewed in the following book: 23, 29–32]. However, most studies concern the activity of ECS in the control of reproduction in both sexes, as summarized in **Table 1**. In fact, besides the activity exerted at hypothalamic and pituitary level in order to regulate GnRH release and the discharge of pituitary gonadotropins which in turns sustain sex steroid biosynthesis, direct ECS activity has been reported in both testis and ovary, in male and female reproductive tracts, in gametes and also in reproductive fluids. Functions related to the production of high-quality gametes, fertilization, embryo implantation, embryo growth, and

delivery have excellently been reviewed elsewhere, with evidence that the maintenance of gradients of endocannabinoids in reproductive tracts is required to modulate step-by-step several events, from the acquisition of sperm motility to a successful embryo implantation (details and references in **Table 1**).

Female Reproduction	**References**
Folliculogenesis	[35, 36]
Oocyte maturation	[35]
Embryo transport	[37]
Embryo implantation/pregnancy	[38–41]
Endometrial plasticity	[42]
Delivery	[34, 43]
Male reproduction	**References**
Spermatogenesis progression	[44–50]
Sperm motility	[51, 52]
Chromatin remodelling	[53–55]
Sperm fertilizing ability	[34, 56, 57]
Leydig cell functions	[58–60]
Sertoli cell apoptosis	[44, 61]
Sperm capacitation, ZP-induced acrosomal reaction (AR)	[57, 62–64]

Table 1. Main biological activities of ECS in both female and male reproduction.

Thus, the modulation of endocannabinoid tone by FAAH is the main gatekeeper in the control of many physiological functions, from the formation of specialized tissues to neurotransmitter release, neuroprotection of circuit integrity and neuroplasticity, central pain perception, neuroendocrine functions, food intake, energy balance, reproduction, pregnancy, delivery, cardioprotection, inflammatory response, and so on [33].

As a consequence, alterations of ECS activity have been correlated to many diseases such as neurodegenerative disorders and motor dysfunctions, mood disorders as well as psychosis (schizophrenia) and autism, retinopathy, neuroendocrine dysfunctions, obesity, diabetes and metabolic syndrome, cardiovascular disorders and cardiac pathologies, gastrointestinal and urogenital diseases, sepsis, cancer and related inflammation processes, infertility, but also to miscarriage and preterm birth.

Consistently, alteration of the physiological endocannabinoid tone by the occasional use or abuse of phytocannabinoids has been reported to deeply impact human health [34].

3. Conclusions

Due to the above considerations, ECS has emerged as important regulator of both physiological and pathological processes. Considerable attention has been focused on the targeting of the endocannabinoid receptors and of endocannabinoid byosinthetic/hydrolizing enzymes for the treatment of a variety of disorders with high impact on human health. Thus, in the future, the administration of specific cannabinoid receptor agonists/antagonists or the inhibition of endocannabinoid degradation might represent a promising therapeutic strategy for the maintenance/restore of human health and the cure of human diseases such as neurological and cardiovascular diseases, diabetes and obesity, as well as infertility and cancer.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgements

Work incorporated in this paper was partially supported by Prin MIUR 2010–2011 (Rosaria Meccariello).

The authors apologize for unintended omission of any relevant references.

Author details

Rosanna Chianese[1] and Rosaria Meccariello[2*]

*Address all correspondence to: rosaria.meccariello@uniparthenope.it

1 Dipartimento di Medicina Sperimentale sez "F. Bottazzi", Seconda Università di Napoli, Napoli, Italy

2 Dipartimento di Scienze Motorie e del Benessere, Università di Napoli Parthenope, Napoli, Italy

References

[1] Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964;86:1646.

[2] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–564.

[3] Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61–65.

[4] Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946–1949.

[5] Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995;50:83–90.

[6] Fredriksson R, Hoglund PJ, Gloriam DE, Lagerstrom MC, Schioth HB. Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives. FEBS Lett 2003;554:381–388.

[7] Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K. GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci USA 2008;105:2699–2704.

[8] Starowicz K, Nigam S, Di Marzo V. Biochemistry and pharmacology of endovanilloids. Pharmacol Ther 2007;114:13–33.

[9] Gasperi V, Fezza F, Pasquariello N, Bari M, Oddi S, Agrò AF, Maccarrone M. Endocannabinoids in adipocytes during differentiation and their role in glucose uptake. Cell Mol Life Sci 2007;64:219–229.

[10] Sigel E, Baur R, Rácz I, Marazzi J, Smart TG, Zimmer A, Gertsch J. The major central endocannabinoid directly acts at GABA(A) receptors. Proc Natl Acad Sci USA 2011; 108:18150–18155.

[11] Okamoto Y, Morishita J, Tsuboi K, Tonai T, Ueda N. Molecular characterization of a phospholipase d generating anandamide and its congeners. J Biol Chem 2004;279:5298–5305.

[12] McKinney MK, Cravatt BF. Structure and function of fatty acid amide hydrolase. Annu Rev Biochem 2005;74:411–432.

[13] Stella N, Schweitzer P, Piomelli DA, second endogenous cannabinoid that modulates longterm potentiation. Nature 1997;388:773–778.

[14] Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. Chem Phys Lipids 2002;121:149–158.

[15] Ligresti A, Morera E, van der Stelt M, Monory K, Lutz B, Ortar G, Di Marzo V. Further evidence for the existence of a specific process for the membrane transport of anandamide. Biochem J 2004;380:265–272.

[16] McFarland MJ, Porter AC, Rakhshan FR, Rawat DS, Gibbs RA, Barker EL. A role for caveolae/lipid rafts in the uptake and recycling of the endogenous cannabinoid anandamide. J Biol Chem 2004;279:41991–41997.

[17] Kaczocha M, Glaser ST, Deutsch DG. Identification of intracellular carriers for the endocannabinoid anandamide. Proc Natl Acad Sci USA 2009;106:6375–6380.

[18] Fu J, Bottegoni G, Sasso O, Bertorelli R, Rocchia W, Masetti M, Guijarro A, Lodola A, Armirotti A, Garau G, Bandiera T, Reggiani A, Mor M, Cavalli A, Piomelli D. A catalytically silent FAAH-1 variant drives anandamide transport in neurons. Nat Neurosci 2011;15:64–69.

[19] Cacciola G, Chianese R, Chioccarelli T, Ciaramella V, Fasano S, Pierantoni R, Meccariello R, Cobellis G. Cannabinoids and reproduction: a lasting and intriguing history. Pharmaceuticals 2010;3:3275–3323

[20] Elphick MR, Egertová M. The neurobiology and evolution of cannabinoid signalling. Philos Trans R Soc Lond B Biol Sci. 2001;356:381–408.

[21] Galve-Roperh I, Chiurchiù V, Díaz-Alonso J, Bari M, Guzmán M, Maccarrone M. Cannabinoid receptor signaling in progenitor/stem cell proliferation and differentiation. Prog Lipid Res. 2013;52:633–650.

[22] Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu Rev Psychol 2013;64:21–47.

[23] Pertwee RG (editor). Endocannabinoids. in Handbook of experimental pharmacology. Springer International Publisher Science, Technology, Medicine, Germany. 2015. 231 p. doi:10.1007/978-3-319-20825-1_2.

[24] Litwack G (editor). Anandamide an endogenous cannabinoid. in Vitamins & Hormones. Elsevier Science Publishing Co Inc, United States (2009). 2009. 81 p. ISBN: 978-0-12-374782-2.

[25] Ohno-Shosaku T, Kano M. Endocannabinoid-mediated retrograde modulation of synaptic transmission. Curr Opin Neurobiol 2014;29:1–8.

[26] van der Stelt M, Di Marzo V. The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. Eur J Pharmacol 2003;480:133–150.

[27] Meccariello R, Battista N, Bradshaw HB, Wang H. Endocannabinoids and reproduction. Int J Endocrinol 2014;378069.

[28] Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: an overview. Front Behav Neurosci 2012;6:9.

[29] Watkins BA, Hutchins H, Li Y, Seifert MF. The endocannabinoid signaling system: a marriage of PUFA and musculoskeletal health. J Nutr Biochem 2010;21:1141–1152.

[30] Bab I, Zimmer A. Cannabinoid receptors and the regulation of bone mass. Br J Pharmacol 2008;153:182–188.

[31] Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 2005;5:400–411.

[32] Pacher P, Gao B. Endocannabinoids and liver disease. III. Endocannabinoid effects on immune cells: implications for inflammatory liver diseases. Am J Physiol Gastrointest Liver Physiol 2008;294:G850–854.

[33] Katona I, Freund TF. Multiple functions of endocannabinoid signaling in the brain. Annu Rev Neurosci 2012;35:529–558.

[34] Wang H, Xie H, Guo Y, Zhang H, Takahashi T, Kingsley PJ, Marnett LJ, Das SK, Cravatt BF, Dey SK. Fatty acid amide hydrolase deficiency limits early pregnancy events. J Clin Invest 2006;116:2122–2131.

[35] El-Talatini MR, Taylor AH, Elson JC, Brown L, Davidson AC, Konje JC. Localisation and function of the endocannabinoid system in the human ovary. PLoS One 2009;4:e4579.

[36] Cecconi S, Rossi G, Castellucci A, D'Andrea G, Maccarrone M. Endocannabinoid signaling in mammalian ovary. Eur J Obstet Gynecol Reprod Biol 2014;178:6–11.

[37] Maccarrone M. Endocannabinoids: friends and foes of reproduction. Prog Lipid Res 2009;48:344–354.

[38] Sun X, Dey SK. Aspects of endocannabinoid signaling in periimplantation biology. Mol Cell Endocrinol 2008;286:S3–11.

[39] Taylor AH, Ang C, Bell SC, Konje JC. The role of the endocannabinoid system in gametogenesis, implantation and early pregnancy. Hum Reprod Update 2007;13:501–513.

[40] 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.

[41] Trabucco E, Acone G, Marenna A, Pierantoni R, Cacciola G, Chioccarelli T, Mackie K, Fasano S, Colacurci N, Meccariello R, Cobellis G, Cobellis L. Endocannabinoid system in first trimester placenta: low FAAH and high CB1 expression characterize spontaneous miscarriage. Placenta 2009;30:516–522.

[42] Di Blasio AM, Vignali M, Gentilini D. The endocannabinoid pathway and the female reproductive organs. J Mol Endocrinol 2013;50:R1–9.

[43] Melford SE, Taylor AH, Konje JC. Of mice and (wo)men: factors influencing successful implantation including endocannabinoids. Hum Reprod Update 2014;20:415–428.

[44] Maccarrone M, Cecconi S, Rossi G, Battista N, Pauselli R, Finazzi-Agrò A. Anandamide activity and degradation are regulated by early postnatal aging and follicle-stimulating hormone in mouse Sertoli cells. Endocrinology 2003;144:20–28.

[45] Grimaldi P, Orlando P, Di Siena S, Lolicato F, Petrosino S, Bisogno T, Geremia R, De Petrocellis L, Di Marzo V. The endocannabinoid system and pivotal role of the CB2 receptor in mouse spermatogenesis. Proc Natl Acad Sci USA 2009;106:11131–11136.

[46] Cacciola G, Chioccarelli T, Fasano S, Pierantoni R, Cobellis G. Estrogens and spermiogenesis: new insights from type1 cannabinoid receptor knockout mice. Int J Endocrinol 2013;2013:501350.

[47] Chianese R, Ciaramella V, Scarpa D, Fasano S, Pierantoni R, Meccariello R. Anandamide regulates the expression of GnRH1, GnRH2, and GnRH-Rs in frog testis. Am J Physiol Endocrinol Metab 2012;303:E475–487.

[48] Chianese R, Ciaramella V, Scarpa D, Fasano S, Pierantoni R, Meccariello R. Endocannabinoids and endovanilloids: a possible balance in the regulation of the testicular GnRH signalling. Int J Endocrinol 2013;2013:904748.

[49] Meccariello R, Chianese R, Chioccarelli T, Ciaramella V, Fasano S, Pierantoni R, Cobellis G. Intra-testicular signals regulate germ cell progression and production of qualitatively mature spermatozoa in vertebrates. Front Endocrinol (Lausanne) 2014;5:69.

[50] Di Giacomo D, De Domenico E, Sette C, Geremia R, Grimaldi P. Type 2 cannabinoid receptor contributes to the physiological regulation of spermatogenesis. FASEB J 2016;30:1453–1463.

[51] Ricci G, Cacciola G, Altucci L, Meccariello R, Pierantoni R, Fasano S, Cobellis G. Endocannabinoid control of sperm motility: the role of epididymus. Gen Comp Endocrinol 2007;153:320–322.

[52] Cobellis G, Ricci G, Cacciola G, Orlando P, Petrosino S, Cascio MG, et al. A gradient of 2-arachidonoylglycerol regulates mouse epididymal sperm cell start-up. Biol Reprod 2010;82:451–458.

[53] Chioccarelli T, Cacciola G, Altucci L, Lewis SE, Simon L, Ricci G, Ledent C, Meccariello R, Fasano S, Pierantoni R, Cobellis G. Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement. Endocrinology 2010;151:5563.

[54] Battista N, Meccariello R, Cobellis G, Fasano S, Di Tommaso M, Pirazzi V, Konje JC, Pierantoni R, Maccarrone M. The role of endocannabinoids in gonadal function and fertility along the evolutionary axis. Mol Cell Endocrinol 2012;355:1–14.

[55] Cacciola G, Chioccarelli T, Altucci L, Ledent C, Mason JI, Fasano S, et al. Low 17beta-estradiol levels in Cnr1knock-out mice affect spermatid chromatin remodeling by interfering with chromatin reorganization. Biol Reprod 2013;88:152.

[56] Sun X, Wang H, Okabe M, Mackie K, Kingsley PJ, Marnett LJ, Cravatt BF, Dey SK. Genetic loss of Faah compromises male fertility in mice. Biol Reprod 2009;80:235–242.

[57] Rossato M. Endocannabinoids, sperm functions and energy metabolism. Mol Cell Endocrinol. 2008;286:S31–35.

[58] Wenger T, Ledent C, Csernus V, Gerendai I. The central cannabinoid receptor inactivation suppresses endocrine reproductive functions. Biochem Biophys Res Commun 2001;284:363–368.

[59] Chianese R, Ciaramella V, Fasano S, Pierantoni R, Meccariello R. Hypothalamus–pituitaryaxis: an obligatory target for endocannabinoids to inhibit steroidogenesis in frog testis. Gen Comp Endocrinol 2014;205:88–93.

[60] Cacciola G, Chioccarelli T, Mackie K, Meccariello R, Ledent C, Fasano S, Pierantoni R, Cobellis G. Expression of type-1 cannabinoid receptor during rat postnatal testicular development: possible involvement in adult leydig cell differentiation. Biol Reprod 2008;79:758–765.

[61] Rossi G, Gasperi V, Paro R, Barsacchi D, Cecconi S, Maccarrone M. Follicle-stimulating hormone activates fatty acid amide hydrolase by protein kinase A and aromatase-dependent pathways in mouse primary Sertoli cells. Endocrinology 2007;148:1431–1439.

[62] Bernabò N, Barboni B, Maccarrone M. The biological networks in studying cell signal transduction complexity: The examples of sperm capacitation and of endocannabinoid system. Comput Struct Biotechnol J 2014;11:11–21.

[63] Lewis SE, Maccarrone M. Endocannabinoids, sperm biology and human fertility. Pharmacol Res 2009;60:126–131.

[64] Schuel H, Burkman LJ. A tale of two cells: endocannabinoid-signaling regulates functions of neurons and sperm. Biol Reprod 2005;73:1078–1086.

IntechOpen