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# Introductory Chapter: The Endocannabinoid System in Human Physiology

Rosanna Chianese and Rosaria Meccariello

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## 1. Endocannabinoid system (ECS)

The identification of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -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  $\Delta^9$ -THC effects. The existence of endogenous ligands that share many effects of the  $\Delta^9$ -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  $\gamma$  [PPAR $\gamma$ , 9], as well as 2-AG binds to specific  $\gamma$ -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 (DAGL $\alpha$  and DAGL $\beta$ ) enzymes are involved in 2-AG biosynthesis [13], whereas monoacylglycerol lipase (MAGL) and to a lesser extent 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 neuro-hormones 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 biosynthetic/hydrolyzing 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/restoration 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.

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### Author details

Rosanna Chianese<sup>1</sup> and Rosaria Meccariello<sup>2\*</sup>

\*Address all correspondence to: [rosaria.meccariello@uniparthenope.it](mailto:rosaria.meccariello@uniparthenope.it)

<sup>1</sup> Dipartimento di Medicina Sperimentale sez “F. Bottazzi”, Seconda Università di Napoli, Napoli, Italy

<sup>2</sup> Dipartimento di Scienze Motorie e del Benessere, Università di Napoli Parthenope, Napoli, Italy

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