European Journal of Obstetrics & Gynecology and Reproductive Biology 178 (2014) 6–11

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Endocannabinoid signaling in mammalian ovary

Sandra Cecconi [a,*], Gianna Rossi [a], Annalisa Castellucci [a], Gabriele D'Andrea [b], Mauro Maccarrone [c,d,*]

[a] Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[b] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[c] Center of Integrated Research, Campus Bio-Medico University of Rome, Rome, Italy
[d] European Center for Brain Research (CERC)/Santa Lucia Foundation, Rome, Italy

ARTICLE INFO

Article history:
Received 19 December 2013
Received in revised form 17 March 2014
Accepted 8 April 2014

In the memory of Riccardo Del Gratta (1966–2013).

Keywords:
Endocannabinoid
Ovary
Reproduction

ABSTRACT

The role of the endocannabinoid system (ECS) in mammalian reproduction is a rather active field of research, due to its potential exploitation to combat human infertility. Available data shows that the aberrant endocannabinoid signaling negatively affects embryo development, implantation and pregnancy. Although many efforts have been devoted to a better understanding of the ECS in these steps of female reproduction, very little is known about its role in regulating ovarian follicle development and production of mature oocytes. This is the subject of the present review where we discuss current knowledge about the impact and potential exploitation of the ECS and endocannabinoid signaling in mammalian ovary and folliculogenesis.

Introduction

Since 1990, the number of couples affected by infertility has increased to about 48 millions, which means that approximately 10% of couples worldwide have faced fertility problems during their reproductive life [1]. Such a figure will increase in the next few years by about 15%, and by 2025 the number of women facing infertility problems will increase by about 7 millions.

Behind the reduced female reproductive performances there are the social and economical reasons, both in developed (Western Europe, USA) and developing countries. As a matter of fact, more and more women are postponing childbearing to older ages. In contrast with the physiological fertile lifespan, that declines rapidly from 35 years onward, the number of first births among women aged 30–39 has doubled in the past 15 years, and among women aged 40 or older has increased by 50% [2].

Additionally, lifestyle and environmental pollution have negative impact on female fertility. The continuous exposure to harmful toxicants in the environment, as those derived from industrial pollutants (*e.g.*, dioxins) and plastic components (*e.g.*, phthalates), has a negative impact on human health. Since the majority of these chemicals mimic steroid hormones, they have been collectively termed "endocrine disruptors" (EDs). It is likely that the EDs, by affecting estrogen and steroid receptors, induce endocrine disorders with consequences on fertility, especially in women [3,4]. In this context, the most common cause of female subfertility linked to endocrine disorders is the polycystic ovarian syndrome (PCOS), a pathological condition characterized by excessive amounts of androgens, that affects about 5–10% of fertile women worldwide [5].

Epidemiological data demonstrate that PCOS frequently affects obese women, and is a risk factor associated with type 2 diabetes. The increased levels of serum leptin present in obese women could explain infertility and anovulation [6], because this hormone is considered a permissive signal for puberty and a metabolic controller of neuroendocrine regulation of reproduction [7,8]. Leptin receptors have been identified in both granulosa cells (GCs) and theca cells (TCs) of mammalian follicles, and their activation interferes with steroidogenesis via cAMP signaling [9]. The use of mutant animal models has allowed to identify the existence of an inverse relationship between leptin and the hypothalamic endocannabinoids (eCBs) [7]. Indeed, leptin participates in the regulation of eCBs levels, that are dysregulated in obese women. In this context, Iannotti et al. [10] have recently shown significant differences in the expression of the ECS genes between normal and obese rats.

* Corresponding authors. Tel.: +39 06 225419169; fax: +39 06 22541456.
E-mail addresses: sandra.cecconi@univaq.it (S. Cecconi), m.maccarrone@unicampus.it (M. Maccarrone).

http://dx.doi.org/10.1016/j.ejogrb.2014.04.011
0301-2115/

The emerging picture is that the ECS plays a central role in mammalian reproductive organs, probably by modulating their homeostasis via autocrine/paracrine loops. This view is supported by the observation that the use of cannabis-derived recreational drugs (*e.g.*, marijuana) increases the chances of infertility by reducing sperm count in males and the risk of abnormal ovulation, conception and miscarriage in females [11]. Even women who are occasional users of marijuana may experience a delay in getting pregnant [12]. Despite Δ^9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, has no estrogenic effects but its acute intake suppresses secretion of the luteinizing hormone (LH) during the luteal phase [12]. To date, no conclusive data has been obtained on the effects on THC on pregnancy, birth and newborn health, an issue that remains highly debated [13].

The available evidence supports the concept that distinct ECS components (*i.e.*, eCBs, their metabolic enzymes and receptors) can respond to fertility signals by cooperating with hormones, cytokines and other signaling molecules, and that the dysregulated (decreased or increased) eCBs signaling adversely affects reproduction [14]. In this review we shall discuss the potential role of ECS in the mammalian ovary. Other aspects of the regulation of reproductive events by ECS have been extensively reviewed in recent papers [14,15].

The mammalian folliculogenesis

The ovary has two main functions: the production of female gametes (oocytes) and the release of a number of paracrine factors (*e.g.*, estrogens, activin, insulin-like growth factors), which collaborate with gonadotropins such as the follicle stimulating hormone (FSH), and LH to assure fertilization and a positive pregnancy outcome [16,17].

The basic unit of the ovary is the follicle, formed by the germ cell and surrounding somatic cells, like the GCs and TCs. The development of both the oocyte and the follicle is highly coordinated to warrant a correct oocyte maturation and subsequent embryo development (Fig. 1). Indeed, oocyte and somatic cells exert a reciprocal influence through the transfer of nutrients, regulatory factors and signals, via either gap junctions or paracrine pathways. Folliculogenesis is a process occurring during reproductive life, until exhaustion of follicle endowment that coincides with menopause. In humans, about 7 million of the germ cells are present at 20 weeks of gestation, and by month 7 the presence of primordial follicles has been described in the fetal ovary. From this point of time, a massive apoptotic process called “atresia” occurs, so that at birth about 1 million of follicles remains for the whole fertile lifespan. Among these follicles, only a few hundreds are rescued from atresia, and undergo final maturation and ovulation under the effects of gonadotropins, steroid hormones and paracrine factors. The close feedback between hypothalamus/pituitary and the ovary is strictly influenced by the input and output signals produced by both tissues, and any alteration to disruption of this fine balance, caused by internal and/or external factors, can impair the follicular development and ovarian function in adulthood [3,4,16,17].

The formation of the ovarian follicle, and its development from the primordial to the preovulatory stage, are sequential crucial steps for the production of a mature egg [18]. As reported above, during fetal life, the number of primordial germ cells (PGCs) increases, because of the intense mitotic proliferation; yet, after

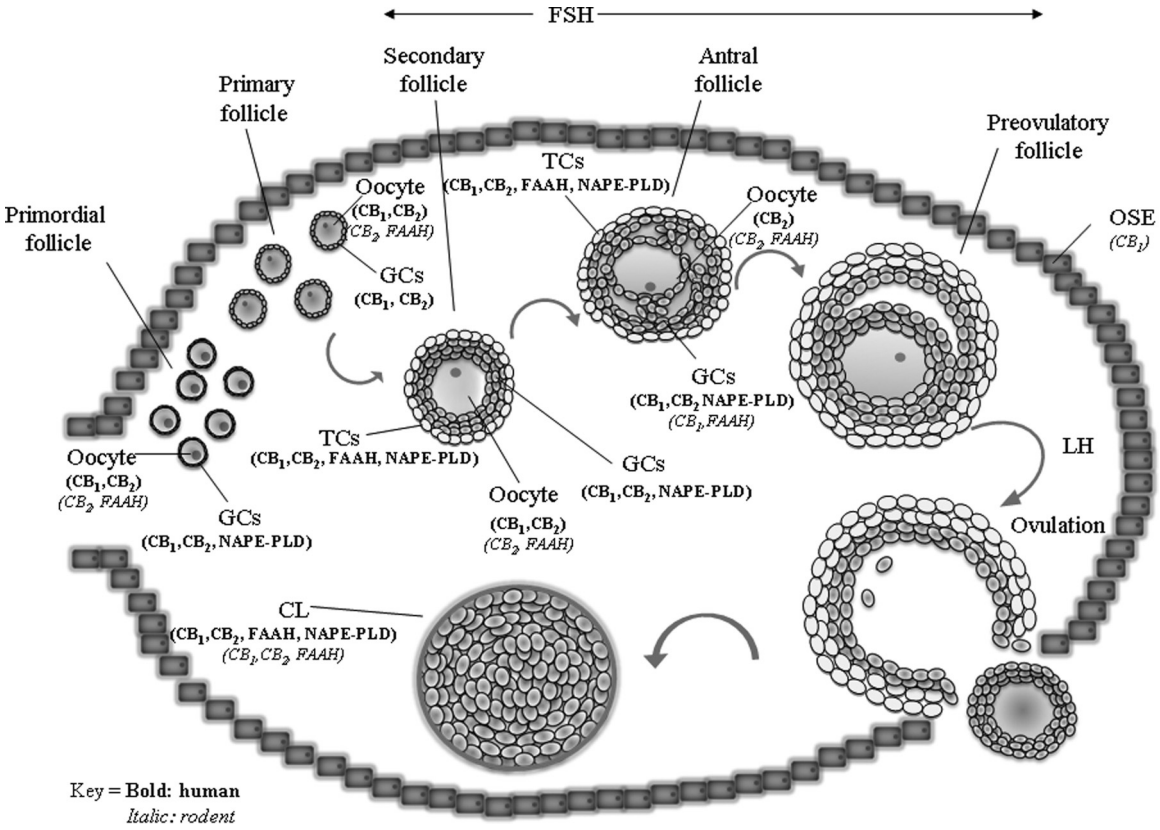

Fig. 1. Schematic representation of ECS distribution along mammalian folliculogenesis.
A follicle is formed by the oocyte and surrounding GCs. TC layers are formed at the secondary stage. From secondary stage onward FSH is necessary to promote follicle terminal differentiation to preovulatory stage. LH-dependent ovulation of dominant follicle(s) results in *corpus luteum* formation. CL, *corpus luteum*; GCs, granulosa cells; OSE, ovarian surface epithelium. See text for further abbreviations.