CHAPTER 39

Reproductive Biology: From Gametogenesis to Hormonal Regulation

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SUMMARY

Reproductive biology is a complicated field that comprises the gametogenesis, fertilization as well as hormonal regulation. Gametogenesis is the mechanism through which gametes such as sperm as well as egg cells are produced, enabling sexual reproduction and the generation of offspring that are genetically different from each other. This process is indispensable for the survival as well as adaptation of species, as it facilitates the mixing of genetic information and the creation of new combinations of traits. Furthermore, gametogenesis also ensures the continuity of genetic material from one generation to the next, allowing species to evolve. Hormonal regulation serves as a fundamental component for the maintenance of homeostatic mechanisms as well as modulation of different physiological processes such as growth, development and metabolism. Moreover, the mechanism of hormone regulation is correlated with sleep, appetite as well as stress response, safeguarding normal physiological functions in the body. Any imbalance in hormonal regulation can lead to different disorders in the body, underscoring the importance of hormonal homeostasis. Effective hormonal modulation enables the body to respond to changing conditions, promoting resilience and adaptability. Therefore, in this chapter, we will explore the relationship between hormonal regulation and gametogenesis from the perspective of reproductive biology.

INTRODUCTION

The scientific study of the reproductive system is called reproductive biology. The field comprises a broad spectrum of research, including investigations concerning fertility and reproductive problems. The ultimate goal is to acquire an extensive understanding of human reproduction. Gametogenesis is complex and precise phenomenon in which mammalian germ cells undergo development that results in the production of sexually dimorphic gametes, spermatozoa and oocytes. Fusion of gametes produce new individuals, inherited with parents' genetic and epigenetic information (Saitou and Hayashi 2021).

SPERMATOGENESIS

Spermatogenesis is a phenomenal and intricate process that occurs inside the seminiferous tubules (STs) and produces mature male gametes (Neto et al., 2016). These testicular seminiferous tubules, which have a spiral in structure, are essential the progressive development of germ cells into haploid spermatozoa (de Kretser et al., 1998). This remarkable metamorphosis is made possible by the Sertoli cells as well as a wide variety of other cells, such as spermatogonia, primary and secondary spermatocytes, and spermatids (Holstein et al., 2003).

Leydig cells encircle the seminiferous tubules which are substantial for synthesis of testosterone. Once the spermatozoa are formed, they embark on a journey through the tubules and into the epididymis, where they undergo further maturation before being released during ejaculation (de Kretser et al., 1998). Previously, it was believed that the entire process of spermatogenesis took around 74 days (Heller and Clermont 1963; Heller and G 1964). However, a recent study on males with healthy reproductive systems revealed that the period for producing ejaculated sperm can vary from 42 to 76 days (Misell et al., 2006). On average, an individual produces a substantial quantity of 150-275 million spermatozoa per day (Heller and G 1964; Amann 2008).

Cellular events in spermatogenesis

During the early stages of puberty, spermatogenesis involves three complex and interrelated processes.

Meiosis: Male fertility relies on production of millions of gametes through meiosis, involving two successive divisions. This process halves the chromosome number, generating four haploid spermatids from a diploid spermatocyte. Spermatids are essential for the formation of functional male sex cells, ensuring fertility (White-Cooper et al., 2010; Nishimura & L'Hernault, 2017).

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Meiotic Cell Division I: Cell division initiates at leptotene stage in basal compartment of germinal epithelium. Spermatocytes traverse Sertoli cells barrier and enter luminal compartment. Thereafter, a sequence of events take place in the later prophase stages (zygotene, pachytene, and diplotene), including DNA duplication, chromosomal condensing, and homologous chromosome pairing by crossing over. After a complex process, the original diploid primary spermatocytes split into two haploid secondary spermatocytes, therefore halving the overall number of chromosomes (Holstein et al., 2003; Lancaster et al., 2014).

Meiotic Cell Division II: Each haploid secondary spermatocyte undergoes differentiation to yield two haploid spermatids, resulting in a total of tetrad of haploid cells. It is noteworthy that this process occurs rapidly, and there is no DNA replication taking place at this stage (Holstein et al., 2003).

Spermiogenesis: During the final stage of spermatogenesis, known as spermiogenesis, spermatids undergo a transformation that results in the formation of mature spermatozoa. As the process of spermatogonia maturation progresses, they migrate from the basement membrane to the inner side of seminiferous tubules. This crucial stage involves significant changes in spermatids, such as the condensation of the nucleus, the formation of the acrosome, and the development of the flagellum. To ensure the production of fully functional sperm, unnecessary cellular components are sorted and removed into residual body as spermatids align at the tubule's surface (Nishimura & L'Hernault, 2017).

Regulation by hormones

Spermatogenesis relay on hormonal interaction, involving endocrine and paracrine mechanisms, both in the body (in vivo) and in a controlled setting such as laboratory (in vitro). Sertoli cells play a critical role, facilitating the conversion of spermatogonia into spermatozoa via receptors of FSH and testosterone. Lack of these hormones, including LH, can result in the death of germ cells. Essential communication pathways, mediated by Bcl-2 family proteins, play a key role in maintaining the balance of germ cells. Paracrine signals and direct interactions between the membrane and Sertoli cells also impact the development of germ cells (Sofikitis et al., 2008).

GAMETE FORMATION IN FEMALE

Female gamete is vital for the reproduction and called as oocyte. Oocytes represent one of the largest cells in body, developing within ovary in specialized compartment known as ovarian follicle by the processes of oogenesis or folliculo-genesis. Oogenesis is a prolonged and intricate sequence which is characterized by birth, development and maturation, of a distinctive cell with potential to give rise to succeeding generations of organisms. Despite oogenesis is a complex process the ultimate goal remains unchanged, which is to generate proficient egg capable to producing viable offspring (Rodrigues et al., 2008).

Oogenesis

The critical stages of oogenesis transpire via three phases of development, staring from the onset of meiosis in fetal ovary, establishment of follicles in perinatal period followed by progression and development of ova in adult (Hunt & Hassold, 2008).

Formation of primary oocyte: During fetal development, oogonia multiply through division and enter preliminary phase of meiosis (meiosis I) to transform into diploid primary oocytes. However, these oocytes do not fully complete meiosis I and instead arrest at initial stages of prophase, known as dictyate. During this stage, the nucleus is called as germinal vesicle (GV). Germinal vesicle oocytes are restricted to primordial follicles. By the end of fetal period, all primary oocytes have been produced and have halted their growth at the dictyate stage (Johnson, 2018).

Follicle formation: Primordial follicles are formed when pregranulosa cells (somatic cells) envelop oocytes during the arresting phase. Only a small portion of the total number of oocytes that began meiosis in the fetus ovary remain in the newborn ovaries, since oocytes lost during follicle development (Da Silva et al., 2004). Despite primary oocytes meiosis ceases, their chromosomal structures keep synthesizing mRNA and rRNA, which are subsequently utilized to produce a large quantity of vital proteins required for the proliferation of any fertilized oocytes and embryos alongside for continued maturation of the oocyte. These primary oocytes persist for years until puberty. At onset of puberty only a small number (roughly 15 to 20) of primary oocytes, or follicles, appear in each period of menstruation. Out of them, the dominant follicle contains a single egg that matures and becomes ovulated and primordial follicles remained dormant for an extended period until they are activated to undergo the growth process.

Oocyte maturation: During this maturation process, the primary oocyte undergoes meiosis I, producing a pair of daughter cells: a secondary oocyte with half the normal number of chromosomes and a polar body that does not participate in fertilization. Meiosis is temporarily paused at the metaphase II stage until fertilization occurs and followed by the release of a second polar body. As the follicles progress from primordial to primary to secondary, the primary oocytes mature and grow, while the secondary oocytes develop in coordination with the tertiary and pre-ovulating Graafian follicle.

Role of oocyte in in late-stage maturation and granulosa cell interaction

The late phases of oocyte development are critical from a meiotic perspective, because the oocyte acquires the potential to resume and terminate the primary meiotic cell division gradually (Albertini et al., 2003). Granulosa cells were thought to be merely supporting the oocyte in a passive way. However, recent research has revealed that oocytes actively manipulate the development and differentiation of oocytes by secreting growth factors. Despite the fact that interaction is two-way, the

oocyte plays a major role in regulating its own developmental process (Hutt and Albertini 2007).

Molecular mechanism

In the female reproductive cycle, the hypothalamic-pituitary-ovarian axis is significant and releases Gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland for the production of luteinizing hormone (LH) and follicle-stimulating hormone [FSH (Saadia, 2020)]. The pre-ovulatory generation of LH promotes chromatin condensation, which completes meiosis I (Moghadam et al., 2022), moreover, it is essential for regulating meiosis completion, initiates follicular transformation, new blood vessel growth, and the development of granulosa (GC) and theca cells (TC). These cells break the follicle and release the egg by releasing inflammatory chemicals that trigger proteolytic processes (Duffy et al., 2019). FSH has a role in the formation of ovarian follicles, which results in the release of an egg during ovulation. The dominant follicle produces estradiol, which helps during this crucial stage. In addition, FSH regulates the production of estrogen by means of aromatase activity in granulosa cells and the corpus luteum (Stocco, 2008), where it plays a crucial role in the development of LH receptors.

FERTILIZATION: SPERM EGG INTERACTION

Fertilization constitutes an important phenomenon in sexual reproduction among heterogametic species. This biological process brings together two terminally differentiated cells, each harboring the genomes of two distinct individuals and resulting in a totipotent cell, known as zygote and this event gives rise to a genetically unique individual. Fertilization involves a sequence of well-coordinated steps that ultimately the union of the two cells. This union results from interactions between gametes, starting with cell adhesion and followed by the merging of the plasma membranes of the gamete (Evans, 2012).

Molecular mechanisms of fertilization

A potential mechanism governing directed sperm motility in the female reproductive tract involves the chemotactic response of sperm to factors secreted by the egg. The initial specific physical interaction between sperm and the zona pellucida is crucial in fertilization (Wassarman, 1988). The sperm's outer membrane contains the necessary molecules for interacting with the zona pellucida. The zp of mouse (glycoprotein) responsible for facilitating the binding is to proteins on the sperm plasma membrane is known as ZP3 (Bleil and Wassarman 1980). When the O-linked oligosaccharides of ZP3 are chemically removed its ability to bind to ligands is eliminated (Florman et al., 1985). The acrosome reaction, a mechanism also influenced by ZP3 sperm, continues to be associated with the zona pellucida (Bleil et al., 1988).

Fusion of the plasma and outer acrosomal membranes causes the sperm's acrosome reaction which is the exocytotic discharge of the acrosome's content (Roldan & Gomendio, 1992). In addition, the AR is necessary for fusion and is distinguished by an influx of Na+ and Ca*+ as well as an outflow of H+ across the plasma membrane. However, the exact molecular mechanisms behind this are yet unknown. It has been shown that the acrosomal regions of mouse and guinea pig sperm contain Gi protein subunits (Endo et al., 1987). Similar results for human sperm have recently been reported by Lee et al. (1992), indicating the involvement of a G-like protein in mediating the human zp-induced AR (Swann & Whitaker, 1990). Furthermore, Fig 1 illustrates the molecular mechanism of fertilizations in mammals.

Preventing polyspermy

Polyspermy is the process during which multiple sperms fuse with the single egg and causes the embryo death. To prohibit polyspermy, secondary sperm fusion exists across taxa blocked by several mechanisms (Jaffe, 1976; Stewart-Savage & Bavister, 1988; Bhakta et al., 2019). In mammals' cortical reaction block the polyspermy which causes the alternation of zona pellucida to stop entry of extra sperms (Sato, 1979). One alternation of cortical reaction in zone pellucida is the breaking of ZP2 and ZP3 through cortical granule ovastacin (Burkart et al., 2012). After sperm egg fusion in mammals, egg plasma membrane JUNO is discarded into the perivitelline space (Bianchi et al., 2014).

HORMONAL CONTROL OF REPRODUCTION: ENDOCRINE SYSTEM

The endocrine system comprises organs that play a key role in reproduction. Organs such as testis, ovary, corpus luteum, anterior pituitary, placenta, anterior pituitary, suprarenal, and thyroid are directly associated with reproductive functions. Some researchers also attribute sexual and reproductive roles to the pineal gland. The posterior pituitary has a minor role in reproduction. While the pancreas, thymus, and parathyroid are considered unrelated to reproduction, studies using birds as test subjects suggest evidence of their importance in regulating reproductive processes. The research challenges the conventional view and indicates that these seemingly unrelated organs may have a significant influence on reproduction (Riddle, 1929). Hormones of the endocrine being potent bioactive compounds play a key role in various reproductive processes, including development, behavior, puberty, gametogenesis and integrated sexual function.

Hormonal regulation in males

Numerous hormone messengers operating through endocrine, paracrine and autocrine routes are necessary for the mammalian testis to operate properly. The main messengers in the testis are the androgens, follicle stimulating hormone, luteinizing hormone, and gonadotrophins. Gonadotropins are essential for maintaining the health of testicular somatic cells, which produce testosterone. Testosterone, in turn, is crucial for germ cell development. Androgen signaling is unquestionably necessary for spermatogenesis at several distinct stages. This study aims to give a concise summary of recent developments in our knowledge of the hormonal regulation of spermatogenesis with a focus on the function of testosterone in the testis and to raise significant issues for further investigation in this area (Holdcraft et al., 2004).

Hormonal regulation in females

Peripheral organs and the nervous system must work to ensure healthy species development. Gonadotropin-releasing hormone (GnRH) is the primary signal which originates from the central nervous system. Estradiol secreted by the ovarian follicles which inhibits the release of FSH and GnRH in the future. Estradiol concentrations cause a surge in GnRH level which in turn causes an increase in LH level which induces ovulation. The central nervous system's release of gonadotropin-releasing hormone (GnRH) acts as a node to regulate reproductive activities (Christensen et al., 2012).

MENSTRUAL CYCLE AND HORMONAL CONTROL OF OVULATION

Menstruation is the orderly cyclical shedding of the uterine lining caused by the hypothalamus, pituitary and ovaries' interplay of hormone. The menstrual cycle consists of two phases: the follicular (proliferative) phase and the luteal (secretory) phase. Menstrual cycles typically last between 25 and 30 days with a median duration of 28 days. The synchronized actions of the pituitary, ovaries, endometrium, and hypothalamus control the menstrual cycle. The anterior pituitary secretes follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in response to the hypothalamus. This in turn, promotes the growth of ovarian follicles and the synthesis of ovarian steroids. A negative feedback system is significant for control and regulation.

Pregnancy and hormonal changes

In a study it was measured that how hormonal changes occurred during the pregnancy phase. While concentrations of sex hormones change from maternal ovaries, placenta and fetus. In respond to increasing concentrations of estrogen maternal tissues such as pituitary and liver secrete increasing amounts of prolactin and sex-hormone-binding globulin. A study revealed changes in circulating maternal hormones, we collected blood from sixty women during their pregnancies. They observed a 1.7-fold increase in testosterone concentration in serum; concentrations of sex-hormone-binding globulin in serum rose 5.6-fold (O'Leary et al., 1991).

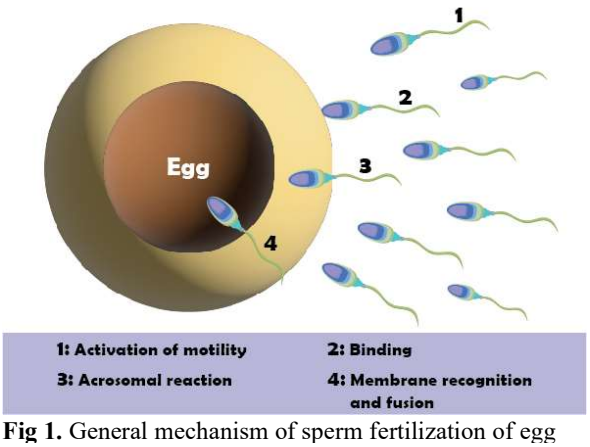

Fig 1. General mechanism of sperm fertilization of egg

REPRODUCTIVE ANATOMY AND PHYSIOLOGY

The male and female reproductive systems are vital systems of body responsible for the creation of new life. Both systems possess unique organs and functions which ultimately results in fertilization of an egg by a sperm to initiate the process of reproduction. Male reproductive system is responsible for the production and delivery of sperm. It comprises testes, located in the scrotum which help in the sperm production through a process called spermatogenesis. Testosterone, produced in the testes, regulates the development of secondary sexual characteristics. Sperm travel through the epididymis, vas deferens and ejaculatory duct, merge with seminal fluids from the seminal vesicles and prostate gland to form semen (Aumüller & Riva, 1992). During ejaculation, semen is expelled through the urethra in the penis (Giuliano & Clément, 2005).

Female reproductive system is responsible for the production of eggs, fertilization and nurturing a developing embryo. It includes ovaries that produce eggs and release them during ovulation (Gu et al., 2015).The fallopian tubes facilitate the movement of egg towards the uterus, where if fertilized by sperm, the zygote implants itself into the uterine lining (Mansour, 2023).The uterus, with its muscular walls and thick lining, supports embryonic and fetal development during pregnancy (Cramer et al., 2015).The vagina acts as the entrance to the reproductive system and the birth canal during delivery, while the cervix remain closed during pregnancy to protect the fetus (Yoshida, 2023).

Effect of hormones in reproductive organs

Hormones exert significant influence on the reproductive system and regulate the growth, function as well as coordination of reproductive organs in the body. In males, testosterone facilitates the development of primary sexual characteristics and secondary traits during puberty (Liew et al., 2021). Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland regulate sperm production and maintain testosterone levels (Oduwole et al., 2018). In females, estrogen and progesterone from the ovaries modulate the development of primary sexual organs and control the menstrual cycle as well as prepare the uterus for pregnancy (Wetendorf and DeMayo 2014). Pituitary hormones such as FSH and LH also play a major role in ovarian follicle growth, ovulation and menstrual cycle regulation (Kumari et al., 2023).

REPRODUCTIVE STRATEGIES

Living organisms, particularly animals, have evolved different reproductive strategies depending upon evolutionary pressure and environmental demands (Stockley and Bro-Jørgensen 2011). It is reported that R-selected species prefer to produce numerous offsprings while using significantly lower amount of parental contribution (Famoso et al., 2018). Different studies have been observed in a variety of insects as

well as a significant number of mammals that aim to increase the chances of survival in unpredictable or considerably harsh environmental conditions (Parsons, 2005).

Mating systems vary from monogamy to polygamy and promiscuity which reflect social structures and resource availability among different organisms (Boomsma, 2013). Reproductive timings also differ in different species, for instance some species breed continuously while others exhibit seasonal patterns influenced by environmental factors (Bronson, 2009). Furthermore, the spectrum of parental care ranges from minimal involvement such as egg-laying without further assistance to extensive care, where parents invest more time and resources in raising their young (Etxebarria et al., 2019).

Mating systems in animals include monogamy (long-term pair bond), polygyny (male mates with multiple females), polyandry (female mates with multiple males), and promiscuity [individuals' mate with multiple partners (Boomsma, 2013)]. Furthermore, behavioral manifestations span from intricate courtship rituals to direct competitive strategies such as physical combat or lekking displays. These diverse strategies evolve to maximize reproductive success in diverse ecological niches (Anholt, 2020).

REPRODUCTION CHALLENGES: INFERTILITY ISSUES AND CAUSES

Infertility is a widespread and emotionally challenging issue that influences the life of various individuals and couples globally. The causes of infertility are diverse and stems from both male and female factors. For men, problems such as low sperm count, poor sperm motility, and lifestyle factors such as smoking and excessive alcohol consumption can contribute to infertility (Inhorn and Patrizio, 2015). In women, problems including ovulatory disorders, hormonal imbalances, structural abnormalities, or conditions such as polycystic ovary syndrome (PCOS) may play a role. Age is also a critical factor that influence fertility index particularly in women. In certain instances, infertility may result from a combination of factors that affects individuals including genetic factors and certain infections (Olooto et al., 2012). Diagnostic tests are often employed to identify specific causes and advancements in assisted reproductive technologies such as *in-vitro* fertilization provide viable options for those facing infertility (Kafee & Parry, 2005).

Reproductive health concerns and assisted technologies

Reproductive health concerns encompass a wide range of issues that impact individuals' ability to maintain a healthy reproductive system (Glasier et al., 2006). Factors contributing to these concerns include sexually transmitted infections, hormonal imbalances, structural abnormalities and lifestyle choices. Comprehensive reproductive healthcare, involving preventive measures, education, and early detection, is crucial to tackle these issues, emphasizing the importance of regular check-ups, screenings, and open communication with healthcare professionals for men as well as women (Sharma et al., 2013).

Assisted reproductive technologies (ART) have become pivotal to overcome fertility challenges, providing hope to individuals and couples facing relative difficulties. Techniques such as in vitro fertilization (IVF), intrauterine insemination (IUI) and gamete intrafallopian transfer (GIFT) provide solutions for infertility due to factors such as advanced maternal age, genetic and disorders. However, the ethical framework surrounding ART remains complex, with considerations related to selective embryo implantation, surplus embryos and the potential for multiple pregnancies requiring careful regulation and ethical guidelines (Ziebe & Devroey, 2008).

Despite the positive impact of ART, challenges persist in terms of accessibility and affordability. Financial constraints and geographic disparities may limit access to these technologies for some individuals or couples. In addition to this, the psychological and emotional aspects of ART procedures are also significant, with stress, anxiety, and feelings of failure being common experiences (Tawfik et al., 2023).

SEXUAL SELECTION AND EVOLUTION OF TRAITS

Sexual selection is a pivotal force in evolutionary biology that influences the development and perpetuation of traits in a population (Cornwallis & Uller, 2010). This process involves individuals with certain traits having a higher likelihood of mating and passing those traits on to their offspring. There are two main mechanisms of sexual selection: intrasexual competition, where members of the same sex compete for mating opportunities, and intersexual selection, where individuals of one sex choose mates based on specific traits. Traits that evolve through sexual selection often prioritize reproductive success over immediate survival, leading to the development of characteristics that enhance an individual's attractiveness to potential mates (Miller & Svensson, 2014; Cornwallis & Uller, 2010).

Certain traits or behaviors, such as elaborate courtship displays or vibrant physical features, frequently emerge as outcomes of sexual selection. These traits serve as signals of genetic fitness and reproductive capability (Cornwallis & Uller, 2010). Despite their apparent impracticality or risks, the preference for such traits can lead to their amplification and persistence in a population over generations. Sexual selection thus contributes significantly to the diversity and complexity of traits observed in various species, playing a key role in the ongoing process of evolution and adaptation (Miller & Svensson, 2014).

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