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REPRODUCTIVE BIOLOGY: REVIEW

The Mongolian Gerbil as a Useful Experimental Model in Reproductive Biology

Thalles Fernando Rocha Ruiz[1,4] · Patricia Simone Leite Vilamaior[1] · Vitor Grigio[1] · Simone Jacovaci Colleta[1] · Mariele Ilario Zucão[1] · Silvana Gisele Pegorin de Campos[1] · Fernanda Cristina Alcântara dos Santos[2] · Manoel Francisco Biancardi[2] · Ana Paula Silva Perez[3] · Sebastião Roberto Taboga[1] · Ellen Cristina Rivas Leonel[2]

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Abstract

Ultimately, the Mongolian gerbils (*Meriones unguiculatus*) have acquired a relevant role in biological and biomedical experiments alongside other rodents. The use of gerbils in research has been mainly oriented to physiological and pharmacological studies, with special attention to nervous, digestive, and auditory systems as well as microbiology and parasitology. Ultimately, gerbils have also been applied for studying carcinogenesis in different organs and systems, since these animals show a natural propensity to develop spontaneous proliferative lesions, especially in steroid-responsive organs. This characteristic shed light on the reproductive aspects of this rodent model regarding morphological features in male and female individuals. This review of literature summarizes the significance of this model as an alternative to the use of inbred mice and rats in reproductive experimental research, highlighting recent findings. Gerbils have contributed to the expansion of knowledge in prostate biology in male and female individuals, providing studies related to prostatic morphogenesis and neoplasia. In the testes, spermiogenesis occurs in 15 steps, differently from other experimental models. Also, the complete maturation of the testis-epididymal complex occurs between the second and third months. Mammary gland alterations related to the estrous cycle and pregnancy were described, as well as its modulation under endogenous and exogenous estrogenic compounds. The ovaries frequently present ovarian cysts. Furthermore, this organ shows predominantly interstitial steroidogenic glands in the stroma, especially at aging. Adrenal gland shows a large size compared to other animals, presenting three distinct zones with a remarkable role in steroidogenesis.

Keywords Animal experimentation · Morphology · Rodent · Reproduction

Introduction

The Mongolian gerbil (*Meriones unguiculatus*), also known as the Mongolian squirrel (Fig. 1), is a murine rodent of the Gerbillinae subfamily, naturally found in arid regions of Russia, China, and Mongolia [1]. In recent years, it has acquired a relevant role in biological and biomedical experiments alongside other rodents, such as rats (*Rattus norvegicus*) and mice (*Mus musculus*). Its use in research has been oriented to physiological and pharmacological studies, mainly those related to the nervous [2] and digestive systems [3] and auditory structures [4], as well as microbiology [5] and parasitology [6]. Other groups have also utilized gerbils for studying carcinogenesis in different organs and systems [7, 8].

Interest has been directed to the reproductive aspects of these rodents, especially because some characteristics of

✉ Ellen Cristina Rivas Leonel
ellenleonel@ufg.br

1 Department of Biology, Institute of Biosciences, Humanities and Exact Sciences, São Paulo State University, Rua Cristóvão Colombo, 2265 Jardim Nazareth, São José Do Rio Preto, SP 15054-000, Brazil

2 Department of Histology, Embryology and Cell Biology, Institute of Biological Sciences, Federal University of Goiás, Avenida Esperança, S/N, Câmpus Samambaia, Goiânia, Goiás 74690-900, Brazil

3 Academic Unit of Health Sciences, Medicine Course, Federal University of Jataí, BR 36, Km 195, Jataí, Goiás 75801-615, Brazil

4 Institute of Biology, University of Campinas (UNICAMP), Campinas, Brazil

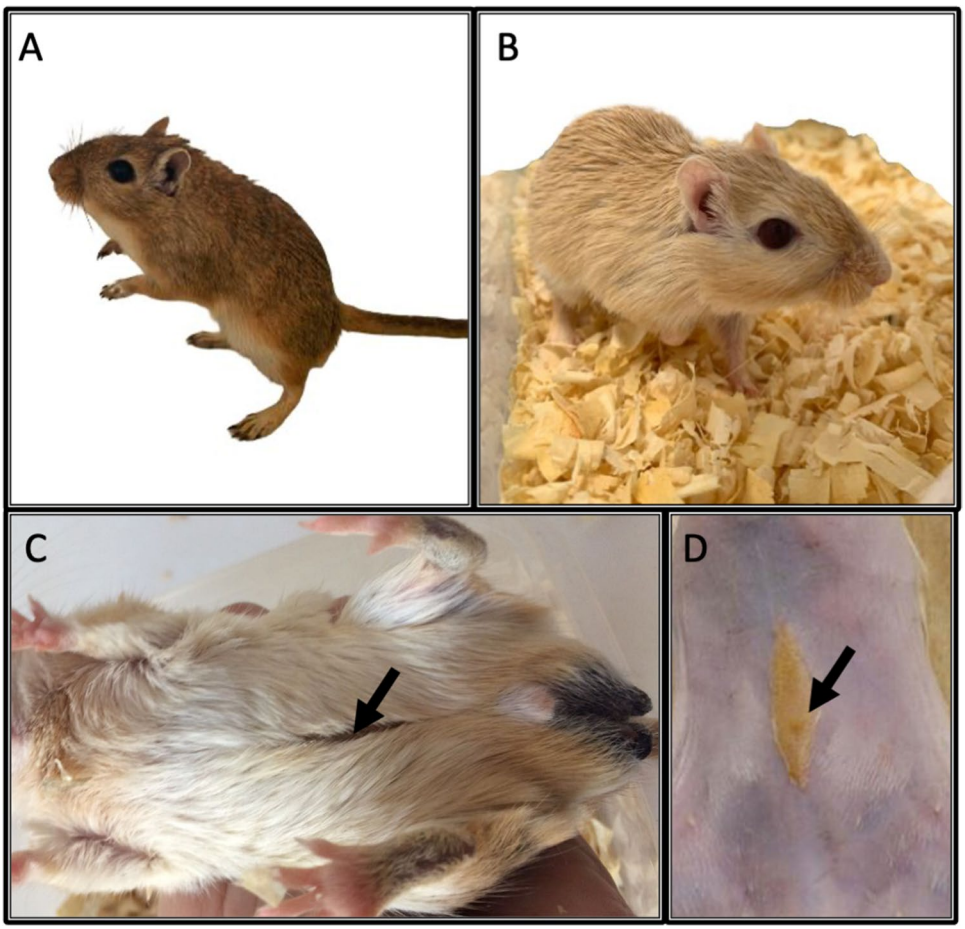


Fig. 1 Representative pictures of male (**A**, **C**) and female (**B**) Mongolian gerbils (*Meriones unguiculatus*). The most common fur is the golden agouti (**A**) and yellow (**B**). A prominent abdominal sebaceous gland (arrows) is present in both male and female ventral surfaces and has the function of scent marking

their prostatic biology and morphology correspond to those of humans [9]. Interestingly, female gerbils show a well-developed prostate gland similar to that found in women (paraurethral Skene's gland), and its morphology and pathology have been widely studied since 2003 [10]. Furthermore, the endocrine aspects of Mongolian gerbils, described by Santos et al., suggest that their high serum levels of testosterone exert a stimulatory effect for the development of the prostate and polycystic ovaries [11]. The discovery of such a hyperandrogenic condition has paved the way for the development of further studies on female reproductive organs in this species.

Yet, for reproduction, special behavioral and morphological conditions were observed in male and female individuals being relevant and useful to transgenerational studies. Females present short estrous, lasting 4–6 days [12] and normally accept mating after some hours of giving birth [13]. Thus, pregnancy and lactation are concomitant events in natural situations [14], allowing females to provide serial multiple pregnancies. In addition, pregnancy and weaning of pups occurs shortly: 24–26 days of pregnancy and 21 days for lactation [15]. Such a short physiological period for reproduction is a positive aspect when performing experiments and analysis.

Considering the above, the current work offers an overview of the literature, assembling studies published until 2022, thus including the most recent findings, in which both male and female Mongolian gerbils were applied as an animal model for experiments related to the reproductive and endocrine systems, and discussing the experiments in which this animal model was adopted. Jointly, we provide an illustrative description of the morphological aspects of their reproductive and endocrine organs, complementing information recently published in a series of chapters [16].

Testes

The microscopic aspects of the Mongolian gerbil testicular tissue have been described [17] and present a structure very similar to that observed in other rodents. Seminiferous tubules are composed of germinal epithelium basally limited by a myoid cell layer and organized by a loose connective tissue that connects to the tunica albuginea (Fig. 2).

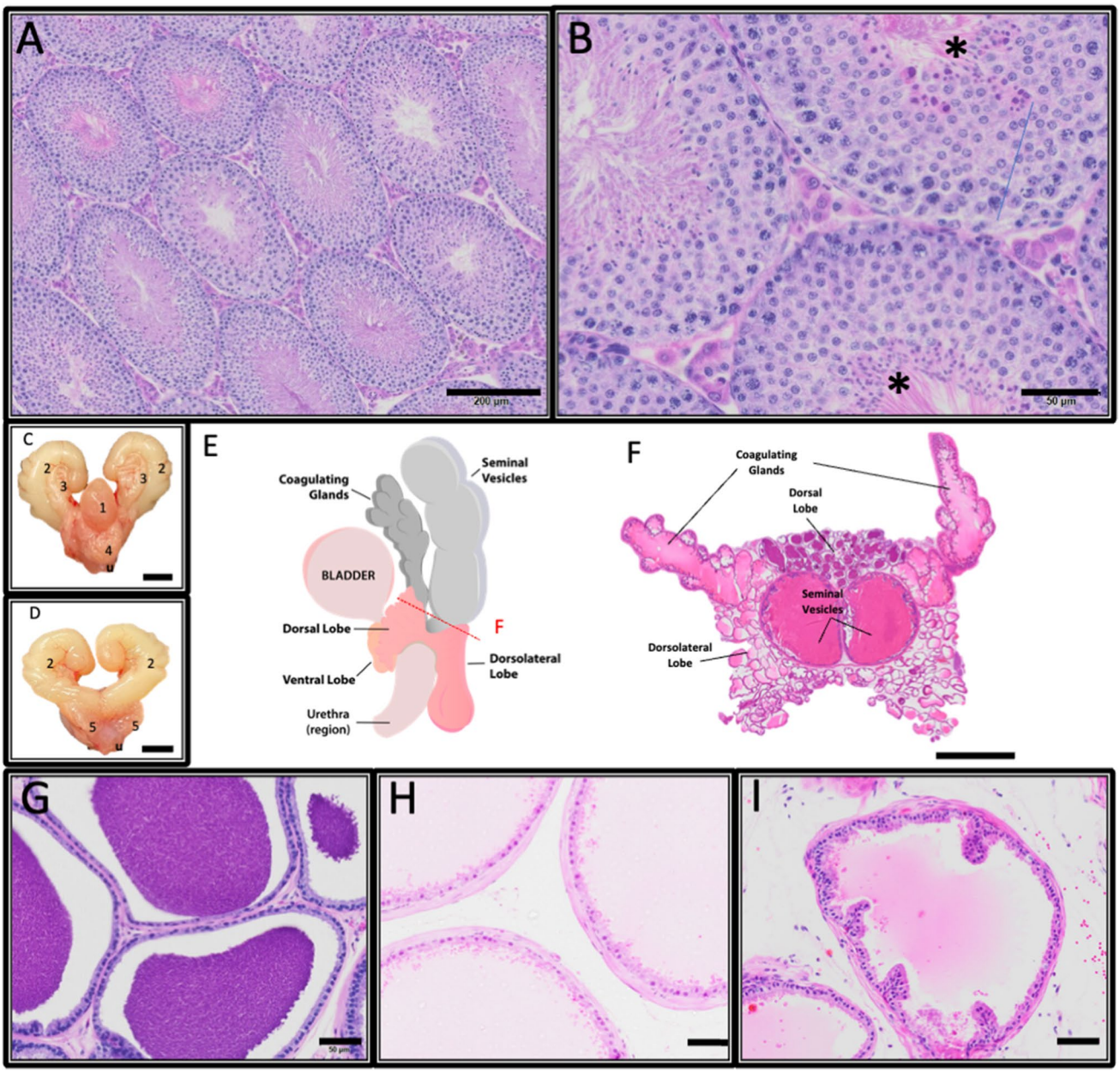


Fig. 2 The morphological aspects of testes and male prostate of Mongolian gerbils (*Meriones unguiculatus*). **A** and **B** The pictures show a clear delimitation of the basal limits in the seminiferous tubules and the interstitial compartment with characteristic Leydig cells. Asterisk shows sperm cells in the lumen of seminiferous tubules. **C** and **D** Representative pictures of the ventral (**C**) and dorsal (**D**) view of the seminal glandular complex of male Mongolian gerbils: 1, urinary bladder; 2, seminal vesicle; 3, coagulating gland; 4, ventral prostate lobe; 5, dorsal prostate lobe; u, urethra. **E** Schematic figure depicting the regions of the gland for this species in a lateral view. **F** Panoramic view. **G** Dorsal lobe. **H** Ventral lobe. **I** Dorsolateral lobe. Staining: hematoxylin and eosin. Scale bars: **A** 200 µm; **B**, **G**, **H**, and **I** 50 µm; **C** and **D** 5 mm; **F** 2 mm

The early development of gerbil gonocytes was first depicted in 1987 [18]. In 2010, Pinto et al. published a descriptive work focusing on the relocation, apoptosis, and post-relocation of gonocytes to the basement membrane of seminiferous cords and on the distribution of cells expressing androgen receptors (AR) [19]. In 2016, an integrative analysis of the testicular and epididymal morphology [20] revealed that the gerbil's testicular weight increases until the 60th postnatal day, remaining stable after that age. On the other hand, the epididymis maintains its growth until the 90th postnatal day. In the seminiferous cords, a lumen remains absent until the 14th postnatal day, with the majority of gonocytes being localized in this region during this period. Although mitotic activity is observed in

spermatogonia by the 2nd postnatal week [18], meiosis only starts by the 21st postnatal day, and the onset of puberty is present on the 42nd day, when mature Leydig cells expressing 17β-HSD are present. However, full spermatogenesis does not take place before the 60th day [20].

Spermiogenesis and formation of the acrosome were detailed in a work published in 2000, where the authors described the changes in spermatids through transmission electron microscopy [21]. Based on the acrosomal and spermatid development, spermiogenesis of Mongolian gerbils is divided into 15 steps, being shorter than in rats (19 steps) and mice (16 steps) [21]. This feature confers a shorter time for sperm formation and renewal, as well as a high availability of this gamete. Also, the main difference between spermiogenesis in gerbils and other rodents takes place during its final formation, when the sperm acquires its specific hook shape [22]. The presence of chromatoid bodies was related to the assembly of mitochondrial sheath organization and formation of the sperm tail and acrosome during spermiogenesis; its association with lipid droplets suggests that this structure may have other unknown functions during spermatogenesis [23].

The impacts of endocrine disrupting chemicals (EDC) in the gerbil's testis were evaluated during perinatal development [24]. After daily in utero exposure to di-n-butyl phthalate, an additive used in the manufacture of plastic and personal care products, the authors evidenced that early testis differentiation was more impaired than the pubertal developmental process. On the 7th postnatal day, a higher proliferation rate of gonocytes and increased serum concentration of testosterone were observed in exposed, compared to non-exposed animals [24]. Similarly, gestational exposure to this phthalate caused long-term negative impacts in adult male reproduction, including reduced sperm production and altered testicular levels of androgens [25]. Other compounds, such as quinestrol, a synthetic estrogen used in some prostate cancer treatment protocols, have also been demonstrated to impair spermatogenesis and to increase oxidative stress in testicular cells of sexually mature gerbils [26]. This exposure induced a reduction in testicular weight and rarefied germ cells, with high rates of apoptosis in spermatocytes and spermatids [26].

Mongolian gerbils were also utilized in studies on the impact of experimental inoculation of hepatitis E virus in the testicular tissue. Histopathological analysis revealed that viral proteins induce structural and molecular alterations that disrupt the blood–testis barrier, inducing germ cell apoptosis [27].

The long-term use of gerbils as laboratory animals, however, has induced some adaptation of this species in terms of reproductive function. Their testicular activity, for example, has been assumed to be higher in a laboratory established strain in comparison to wild animals [28]. These alterations might be because in the wild, gerbils are subjected to variations in the light/dark cycle, demonstrating a natural period of sexual inactivity, which does not occur in the laboratory environment. Indeed, a study in which the pineal gland was excised showed that it exerts a substantial effect on the size and activity of their testes and, consequently, on the reproductive system [29].

Male Prostate

The prostate is an exocrine gland that secretes seminal fluid components. Essentially, it contributes to the nutritional maintenance of sperm cells and its viability in the female reproductive tract, since it produces an alkaline secretion that represents 70% of the total seminal content. Morphologically, the rodent prostate is divided into four lobes: anterior, dorsal, lateral, and ventral [30], differently from the human prostate structure, which is a single organ formed by the anterior fibromuscular stroma and three zones: central, peripheral, and transitional [31]. However, morphology [32] and physiology [33, 34] of male gerbil prostate present similarities to human prostate, mainly due to structural and ultrastructural aspects, making this a relevant model for prostatic biology studies. Mongolian gerbils can thus respond to potential therapeutic approaches and environmental conditions, to unveil at some degree the prostatic microenvironment of health and disease.

Although the prostate presents different morphologies between species, its developmental process is similar. Briefly, the prostate gland differentiates from the urogenital sinus, a cloaca-derived structure originating from the endoderm and mesoderm. As most of the knowledge regarding prostate organogenesis has been elucidated in rodent models, such as rats, the use of Mongolian gerbils has provided novel sources of data for understanding this process. Sanches et al. and collaborators carried out a study to characterize the organogenesis of the ventral prostate lobe in gerbils [32]. In this species, the first ventral buds emerge from the ventral urethral epithelium between embryonic days 20 and 21. The characteristic "V" shape acquired by the budding structure suggests an important signaling role of the smooth muscle during this stage of development [32].

Different mammalian animal models have been applied to study the mechanisms that orchestrate prostatic diseases. The gerbil prostate (Fig. 2) particularly has a similar morphology to that of the human gland, with respect to the partial fusion of its lobes in a more compacted structure, unlike that of mice and rats [35]. However, the main reason for adopting the Mongolian gerbil as an experimental model for prostatic diseases is that it develops spontaneous lesions with age; furthermore, stimuli such as steroidal hormones, chemical carcinogens, environmental EDCs, and a high-fat

diet contribute to this process and boost knowledge about its pathophysiology [34, 36, 37]. It is worth mentioning that although development of induced lesions usually requires a long period of exposure, gerbils are resistant to different experimental protocols and develop a substantial number of neoplasms.

Despite some variations among species, the prostatic stroma in mammals is composed of smooth muscle cells and fibroblasts spread among elements of the extracellular matrix [38]. The stromal compartment of the gerbil prostate responds to steroidal ablation with a particular pattern of phenotypic alterations: extracellular matrix elements basally to the epithelium, with smooth muscle cells and fibroblasts exhibiting secretory phenotypes [39]. This ablation also causes an increase in collagen deposits, accompanied by a thickening of reticular fibers [40]. Some smooth muscle cells acquire an irregular wrinkled contour, contributing to the loose rearrangement of this layer [41, 42]. In addition, the telocyte population in the gerbil's prostate was described by Sanches et al. (2020) [43]. These are interstitial cells that diverge morphologically from fibroblasts and are associated with several functions, such as tissue regeneration, muscle contraction, and prevention of fibrosis [44]. During the physiological aging process of gerbil prostate, telocytes form a network around smooth muscle cells, demonstrating a significant role in maintaining the integrity of the alveolar structure; however, evidence suggests that they might be related to angiogenic and proinflammatory processes [43].

Endogenous hormones, such as testosterone, induced prostatic intraepithelial neoplasia and increased inflammatory foci in the gerbil adult prostate [45], as well as disrupting prostate postnatal organogenesis [46]. Prenatal exposure to estradiol reduced the rates of epithelial proliferation and hypomorphic growth of the mesenchymal compound of the gland in the neonatal phase of development [47]. During the neonatal window of susceptibility, exposure to ethinylestradiol, an estrogenic compound present in many contraceptive pills, causes a higher incidence of epithelial hyperplasia and inflammation [48].

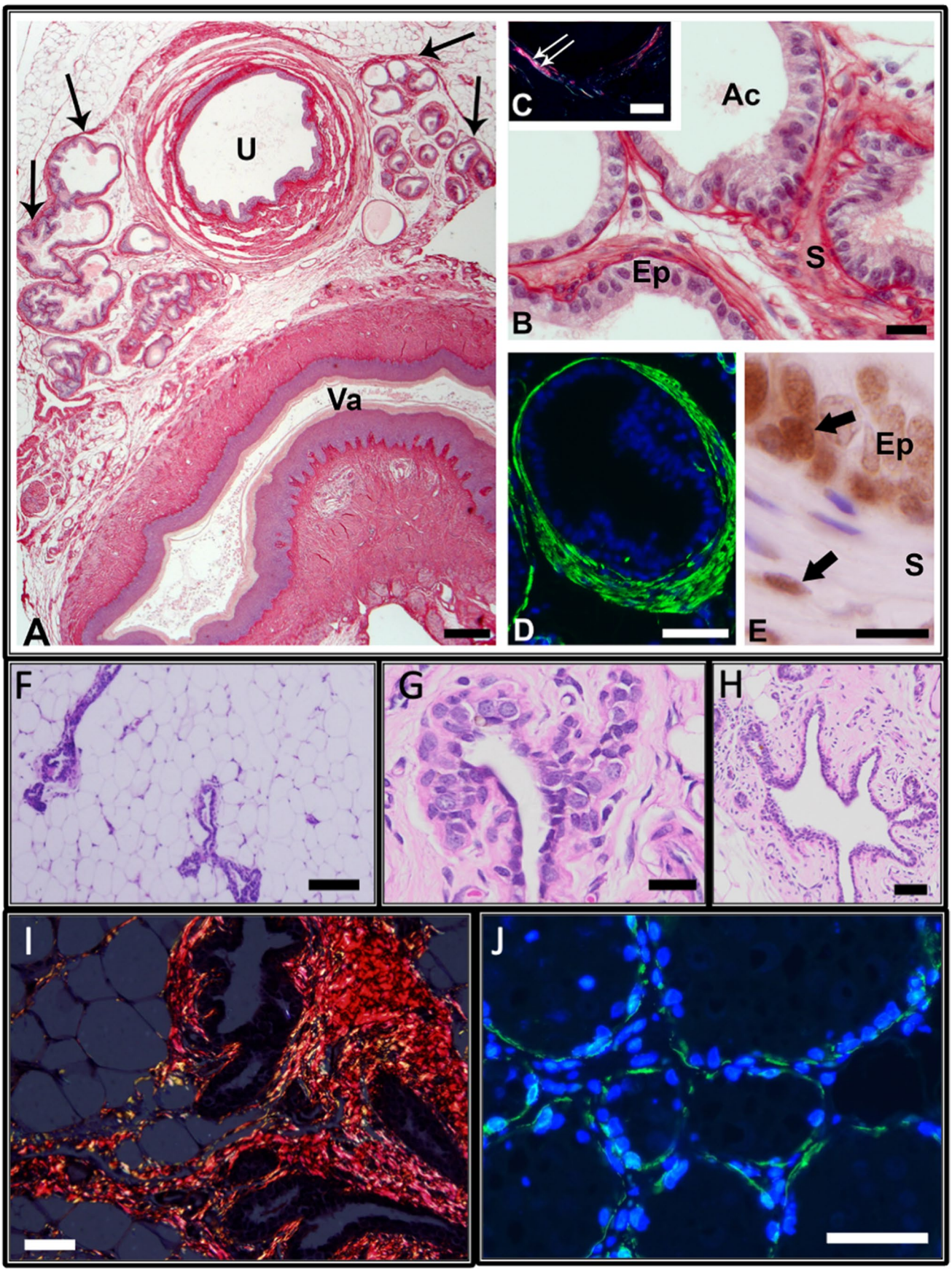
Mongolian gerbils have been applied as a model for therapies against prostatic diseases commonly seen in humans, such as prostate cancer, benign prostatic hyperplasia, and prostatitis [49]. Among these therapies, inhibition of hormonal pathways, surgically and/or chemically, is the first measure to prevent further injury [50]. In adult and old gerbils, orchiectomy and antiandrogenic/antiestrogenic drugs promote regression of the epithelial layer thickness [33, 39, 40, 42]. In old animals, there is a rapid increase in glandular apoptotic rates 1 day after castration, followed by decreased androgen receptor expression [36, 51]; in these experiments, the epithelial cells remaining after the apoptotic peak are differentiated and maintain a secretory activity, as indicated by CK8/18 expression and the presence of secretory content in the lumen [36, 51]. Ultrastructural analyses showed that these remaining epithelial cells demonstrate evidence of oxidative stress, such as the presence of lipofuscin-like deposits, ceramide bodies, and lipid droplets [36, 51]. Results recently published indicated that under androgenic ablation, the proteoglycans and perlecan, compounds of the extracellular matrix, are temporally and dynamically modulated in the prostatic stroma [52]. Thus, the prostate secretes glycoproteins of all types by an androgen-dependent modulation. These studies in gerbils demonstrated that the prostate involutes and regresses by steroid ablation. On the other hand, when the steroid-metabolizing enzymes 5-alpha reductase and aromatase were inhibited intraprostatically by finasteride and/or letrozole, substantial and persistent alterations were present in the prostate gland [42]. The morphological feature did not return to a normal histological pattern post-treatment, it being evident that the prostate is primarily influenced by local hormone steroid synthesis during postnatal development [42].

A particularity of the gerbil prostate is that basal cells express AR in all postnatal phases, with the greatest expression in young animals [33]. Basal cells are p63 positive and form an important subpopulation, surviving long periods of castration and flutamide (non-steroidal antiandrogen) and/or tamoxifen (antiestrogen) therapies [51].

As a hormone-responsive organ, the prostate is particularly sensitive to EDCs, and the Mongolian gerbil has been applied as a model for studies with EDCs [53–55], as their prostate is particularly sensitive to these chemicals. Oral exposure to doses of bisphenol A (BPA) considered safe [37] or high [53] causes a high incidence of prostatic lesions. Cadmium also showed a potential to cause changes in the morphology of the gerbil ventral prostate [53]. Exposure to EDCs during the intrauterine life in the gerbil also induced changes in prostatic development and the budding process during the embryonic [56] and first postnatal stages [57]. Neonatal exposure to aluminum disrupts the expression of androgen and estrogen receptors, impacting the branching process [58]. In adults, aluminum caused alterations such as increased cell proliferation and hyperplasia after 30 days of exposure [54]. Even the impacts of commonly applied vehicles for exposure experiments, such as mineral or corn oil, altered the expression of androgen and estrogen receptors in Mongolian gerbils, in addition to causing morphological alterations [55].

Female Prostate

The female prostate (Skene's paraurethral gland) is present in several mammals, such as rodents [59, 60], bats [61], dogs [62], and women [63]. Zaviačič's studies on the female human prostate shed light on important morphological and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◂**Fig. 3** The morphological aspects of the Mongolian gerbil (*Meriones unguiculatus*) female prostate and mammary gland. **A** An overview picture where the prostatic tissue is present on both sides of the urethra (picrosirius). **B** The gland shows acini immersed in a fibrous stroma (picrosirius). **C** Collagen fibers (arrows) are easily seen by polarized microscopy in picrosirius-stained sections. **D** The prostate acini are surrounded by a layer of smooth muscle as seen in green (α-actin). **E** AR-positive cells are present in both compartments of the prostate gland (i.e., epithelium and stroma). **F** The resting adult mammary gland of gerbils is very similar to that of mice, showing a wide area of adipose tissue with few sparse epithelial structures (hematoxylin and eosin). **G** Terminal end buds. **H** Mammary ducts confluencing to lactiferous sinus. **I** A rich collagen framework supports the ductal epithelium as seen by polarized microscopy in picrosirius-stained sections. **J** In the active gland, the smooth muscle layer surrounding the mammary epithelial structures is thin (green, α-actin). U, urethra; black arrows, female prostatic tissue; Va, vagina; Ac, acini; Ep, epithelium; S, stroma; white arrows, collagen fibers seen by the polarization microscopy; thick arrows, AR-positive cells. Scale bars: **A** and **F** 250 µm; **B** 20 µm; **C** 25 µm; **D**, **H**, **I**, and **J** 50 µm; **E** 10 µm; **G** 40 µm

physiological aspects of this gland, suppressing the historically constructed vestigial concept of this organ in females [63].

Particularly in the rodent group, this gland was reported in female rats [60], plains viscacha [64], and gerbils [11, 65]. In gerbils, it is located at the bladder neck and distributed in a ventrolateral position in relation to the urethra, being homologous to the male ventral prostate lobe and sharing several morphological similarities [65] (Fig. 3). Similarly to males, in females this gland is composed of alveoli inserted in a fibromuscular stroma (Fig. 3B). In both epithelial and stromal compartments, cells express steroid receptors, such as AR (Fig. 3E) and estrogen receptor (ER) [11, 65], being the morphology of these glands responsive to physiological variations in the estrous cycles [66]. Although not all the biological functions of this gland are clear, relevant aspects related to its morphophysiology in Mongolian gerbils have been reported in the scientific literature, contributing to better understanding of this organ [46, 67, 68].

The early events of female gerbil prostate development were recently reported [67]. The study filled an important gap in the literature, showing the dynamic of the female prostatic budding during the prenatal period. Surprisingly, it was demonstrated that the buds arise in a caudal region of the urogenital epithelium, distant from the paraurethral mesenchyme located at the bladder neck [67]. This is interesting evidence when comparing the budding dynamic between males and females: the male ventral prostate of rodents is characterized by the budding events occurring at the bladder neck, near the ventral mesenchymal pad [32] which is the counterpart of the paraurethral mesenchyme in females [67]. Together, these pieces of evidence allowed more detailed understanding of the prostate organogenesis in both sexes.

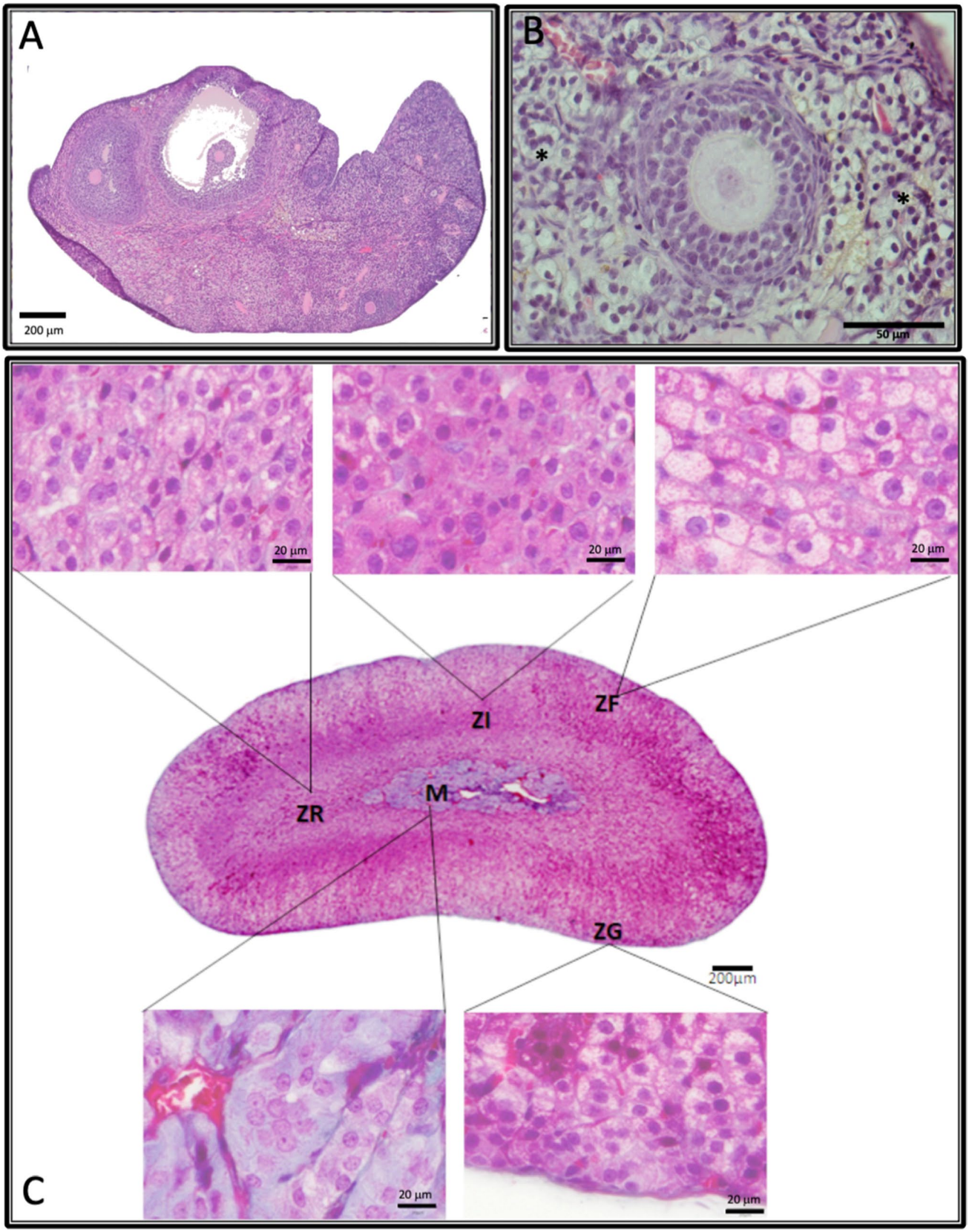
Gerbils have also been employed in studies focusing on the impact of EDCs on the female prostate [54, 57, 69]. Rodríguez et al. (2016) reported that intrauterine exposure to BPA impacts the gerbil prostate in both the neonatal period and adulthood, especially affecting female animals that showed higher prostatic proliferative rates. Other studies showed that aluminum, an EDC with estrogenic potential [54, 58], and methylparaben [70] induce hyperplastic growth and impair steroid hormonal signaling in the female prostate. Some reports have shown the impacts of testosterone cypionate during prenatal periods [45, 46, 68]. Biancardi et al. [45, 71, 72] reported that male and female gerbils prenatally exposed to testosterone cypionate show increased susceptibility to the development of prostatic diseases in adulthood and senile life. Although the underlying mechanisms are not clear, Manso et al. (2021) showed that the 15-day-old female gerbils exposed to T during prenatal life develop smooth muscle hyperplasia in ectopic prostate alveoli. Interestingly, this muscle hyperplasia is also observed in 1-year-old females [71], suggesting that these changes, once installed, are carried throughout life.

New approaches are necessary to elucidate, in terms of physiology, the role of the female prostate. With Mongolian gerbils, the possibility of applying both male and female animals enable new advances in studies with EDCs in both sexes, uncovering the effects of these compounds in a gender-specific manner. Finally, gerbils provide additional information about the genetic basis that contributes to prostatic diseases such as hyperplasia and cancer, with the potential to provide new and important information for the reproductive biology field.

Mammary Gland

Although investigations applying Mongolian gerbils as experimental models for mammary studies have recently increased, they are still scarce. The fact that gerbils tend to spontaneously develop proliferative lesions in the male and female prostate led to the idea of expanding the studies to the mammary gland. The potential of these rodents as a model for mammary pathologies was confirmed by recent publications, to be discussed below.

Gerbils show four pairs of mammary glands: two thoracic and two inguinal or abdominal, which do not communicate with each other. The histological features of this gland (Fig. 3) were described in 2017, when Leonel and collaborators discussed the remodeling process during physiological windows of development [15]. The mammary morphology of gerbils is very similar to that of other rodents, such as rats [73] and mice [74], but a shorter involution period after weaning and higher rates of proliferating cells are distinctive of this species [15]. These findings led to further investigations about the morphological aspects of the postlactational involution of the mammary gland in gerbils. In 2020 a study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◂**Fig. 4** The morphological aspects of the Mongolian gerbil (*Meriones unguiculatus*) ovary and adrenal gland. **A** An overview picture from the ovary, showing the presence of antral follicles and large areas of interstitial glands. **B** Interstitial glands (asterisk) are present throughout the ovarian stroma and are more extensive in older individuals. **C** A schematic illustration provides pictures from all layers of the adrenal gland. ZR, zona reticularis; M, medulla; ZI, zona intermedia; ZF, zona fasciculata; ZG, zona glomerulosa. **A** and **B** Hematoxylin and eosin; **C** Gomori's trichrome. Scale bars: **A** and **C** (central picture): 200 µm; **B** and **C** 20 µm

revealed that telocytes are supposed to influence the mammary regression process in gerbils, specifically affecting extracellular matrix lysis and angiogenesis [75].

As a gland responsive to reproductive hormones, the mammary gland is susceptible to the physiological variations in the estrous cycles. Such changes are mainly variations in the tissue proliferation rates in response to estrogenic and progestogenic phases in the epithelial compartment. However, during gestation, the proliferative stimulus in the mammary gland occurs later in Mongolian gerbils [15]. This profile remains throughout lactation, with a wider luminal compartment and absence of a continuous apical limit in the epithelium. During post-weaning involution, the epithelial cells are detached by shedding of the basement membrane towards the lumen. In the first phase of involution, apoptosis is mediated by caspase-3 [76]; there is also a significant increase in collagen and elastic fibers in the stroma, characterized by remodeling and differentiation of cellular elements [75].

The effects of BPA have also been studied in the mammary gland in this model. This xenoestrogen has already shown a pro-tumoral potential in the gerbil mammary gland after perinatal exposure [77, 78]. In addition, the gestational and lactational windows of susceptibility provide a substantial BPA exposure risk for the development of carcinogenesis in mothers due to aging [79].

To the best of our knowledge, gerbil mammary tumors were first described in 2021. The authors described the presence of mammary carcinomas in aged females after their exposure to BPA during the gestational and lactational windows of susceptibility [79]. However, exposure to the carcinogen N-nitroso-N-methylurea showed no impacts on the morphology of the young adult gland after 3 months of administration [78], suggesting that in gerbils, differently from mice, a longer period is necessary for the development of hyperplastic lesions.

Among the relevant aspects linked to endocrine disruption, the modulation of hormone receptors has been raised as a key factor of the mammary tissue tumorigenesis. In particular, regulation of ER-β expression and the increase in ER-α are important aspects that induce the neoplastic process [77]. Furthermore, the nuclear translocation dynamics of AR and HER2/ErbB2 in mammary epithelium were highlighted [80]. Other aspects, such as inflammation [81] and stromal remodeling [76, 79], have been reported as disrupting mechanisms of BPA.

Despite the advances in the study of mammary gland in this species, several aspects are yet to be uncovered. Studies concerning embryological development of mammary gland in both female and male gerbils are necessary to highlight important aspects that define specific morphophysiological alterations. Finally, further research with different endocrine disruptors, such as phthalates and parabens, would be interesting to demonstrate the potential disrupting impacts in the gerbil, which has already been shown to be an adequate model for neoplastic development.

Ovaries

The morphological description of Mongolian gerbil ovary (Fig. 4A and B) has been described in a limited number of studies. Anatomically the adult gerbil ovary is irregular, being externally shaped by the cyclic presence of antral follicles and the corpus luteum [17]. In young animals, a clear limit between the cortex and medulla may be present; however, in aged individuals, most of the stroma is replaced by interstitial steroidogenic glands [82], as described in other rodent species [83]. These comprise a group of cells that replace the typical stromal areas, previously composed of fibroblasts, extracellular matrix fibers, and blood vessels. Such steroidogenic cells show eosinophilic granules and numerous cytoplasmic lipid droplets, organized as strings or nests [82].

Spontaneous pathologies, such as cystic ovaries, appear to be particularly common in these rodents, being unilateral or bilateral [84, 85] [80]. One study described a 50% incidence of cysts in ovaries from gerbils older than 1 year [86]. In gerbils older than 2 years of age, the incidence of ovarian neoplasia is high and includes granulosa, thecal, and luteal cell tumors, dysgerminomas, and teratomas [84, 87]. With such a high occurrence of spontaneous alterations, gerbils are potentially useful as a laboratory model for further elucidation of these ovarian pathological conditions [8].

The study of ovarian alterations as outcomes of endocrine-disrupting chemicals were described in Mongolian gerbils. Animals exposed to EDCs during developmental phases [88] or in adulthood [11, 89] presented alterations in the ovarian morphology and in folliculogenesis. The endocrine disrupting impact of 17α-ethinylestradiol, an estrogenic compound of many contraceptive pills, was described in the ovary of Mongolian gerbils [88]. The authors described changes in the rates of follicle activation when exposure to this compound occurred during the pubertal window of susceptibility; deposits of lipofuscin in the tissue were increased as an outcome of exposure, as well as

hyperplasia of stromal interstitial glands, increased height of superficial ovarian epithelium, and increased thickness of the tunica albuginea in old gerbils.

The combination between levonorgestrel, a synthetic progestogen, and quinestrol, a synthetic estrogen, showed an efficient contraceptive effect in gerbils [89]. The mechanism of this effect was characterized by changes in the expression of estrogen, progesterone, and luteinizing hormone receptors and was both time- and dose-dependent [89]. The reversibility of these effects was also evaluated [90] and showed that steroidogenic enzymes levels were restored 15 days after discontinuing the treatment.

Finally, the effects of androgenic compounds in the gerbil ovarian tissue were reported by Santos et al.. A hyperandrogenic treatment was promoted with testosterone cypionate during 21 days in adult female gerbils. The authors concluded that testosterone resulted in a polycystic condition and stromal hyperplasia in this gonad [11]. Indeed, a case report described the presence of an interstitial cell tumor in an individual, characterized by the presence of packets and cords of polygonal to rounded tumor cells with a fibrous stroma and numerous empty cavities among the tissue [91]. These tumors are known to increase steroid synthesis, causing endocrine dysfunction, but no relation to a previous androgenic environment was raised by the authors.

The normal morphological features of Mongolian gerbils' ovaries, especially at aging, may be linked to the well-known pathological features of the polycystic ovarian syndrome in humans, in which thickening of the tunica albuginea, ovarian stromal hyperplasia, stromal cell luteinization, and large cystic antral follicles are present [92]. These aspects are in accordance with typical alterations caused by hyperandrogenism, a regular characteristic of female Mongolian gerbils in comparison to other rodents, and luteinization of the stromal cells. Our unpublished data confirmed such an androgenic role in the ovarian stromal glands, by the expression of aromatase, 5-α reductase, and 17-β HSD in steroidogenic cells.

Uterus

Mongolian gerbils present a bicornuate uterus, which consists of two separate horns connected by a short uterine body. In the adult, it is possible to observe histologically well-defined endometrial and myometrial layers. The cells of the luminal epithelium have a well-characterized polarity with long microvilli on its apical surface; moreover, it is possible to identify vesicles in the apical region of the epithelial cells, related to the secretion of the uterine epithelium [93]. In the endometrium, uterine glands are responsible for secreting the uterine fluid; unlike in mice, these glands are arranged throughout the uterine lumen and are composed of columnar cells with many granules that vary according to the phase of the estrous cycle [94]. Also, as in humans, the gerbil uterus responds to hormonal changes. Studies have shown that the gerbil uterus tends to decrease in size after ovariectomy in response to the hormonal decline, becoming responsive to the replacement of hormones such as estrogens [95].

Previously published data revealed that the chemosterilants levonorgestrel and quinestrol, applied in association as a method to control Mongolian gerbils' population in the 2000s in China and Mongolia, were able to increase the expression of ERα in the uterine tissue [89]. Quinestrol alone impacts the uterine weight [90]. Differently from the ovary, the expression of ERα in the uterus shows a primary mediation, instead of ERβ. This confirms that in gerbils, the tissue specificity of hormone receptors is an aspect that must be better elucidated and understood, in order to improve knowledge about the reproductive physiology of this species.

Another aspect reported in the hormonally induced gerbil's uterus was the mechanism of decidualization in the uterine horns [96]. The work led the conclusion that decidualization can be artificially induced in gerbils when estradiol, progesterone, and relaxin are administered to ovariectomized animals. The authors reinforce that, according to morphological analysis, the aspects of decidua cells are similar to that observed in rat tissue. Such similarity to another widely applied species reinforces the ability of gerbils to be established as a model for studies in reproductive biology.

Adrenal Gland

When compared to other species, the Mongolian gerbil has a large adrenal gland in relation to its body size, with a morphology very similar to that of humans; its shape typically resembles an elongated triangle, which is often covered by adipose tissue [91]. Like in other rodents, it is histologically divided into three cortical regions: zona glomerulosa (ZG), zona fasciculata (ZF), and zona reticularis (ZR); these layers enclose the medulla (M) [97] (Fig. 4C). The ultrastructure of cells in the transitional region between ZF and ZR, called the zona intermedia or intermediary zone (ZI), varies according to the hormonal status of the individual: physiologically, animals show cells with whorls of rough endoplasmic reticulum and few lipid droplets; after ovariectomy, this region is enlarged, showing hypertrophic cells with a greater number of lysosomes, larger mitochondria, and the presence of some deposits of glycogen [98].

According to unpublished data from our group, in Mongolian gerbils, the ZR occupies most of the adrenal cortex and is rich in collagen fibers (Fig. 4C). Its cells are smaller than those from the other zones, with a slightly acidophilic cytoplasm, spherical nucleus, and a clearly visible nucleolus.

These cells are organized in anastomosed cords interspersed with blood capillaries. ZR comprises the ZI [97], whose cells show a more eosinophilic feature in the cytoplasm. In this region, cells with concentric whorls of rough endoplasmic reticulum were also found [99]. ZF is organized in cords of larger cells, with a lighter cytoplasm showing lots of lipid droplets, a spherical nucleus, and visible nucleolus (Fig. 4C). Finally, ZG is the thinnest of the cortical zones, and its cells are slightly flattened and grouped (Fig. 4C).

In the rat and mouse, the ZR is not as evident as in humans; in addition, the DHEA concentration is low and does not increase after adrenarche [100] and CYP17A1, an enzyme which plays a key role in the synthesis of adrenal androgens and was not consistently detected in the adrenal gland of these animals [101]. In gerbils, however, the three zones of the cortex are evidenced, being like the primate adrenal morphology [102]. Furthermore, the main adrenocortical hormones identified in gerbils are DHEA, testosterone, progesterone, and androstenedione [103], and unpublished data from our research group show the significant presence of the enzyme CYP17A1 and cortisol in the adrenal gland of these animals as well.

The gerbil adrenal gland is closely related to other organs of the reproductive system. Studies have shown that the steroid precursors produced in the adrenal gland of these animals, such as pregnenolone, 17-OH-progesterone, progesterone, and DHEA, influence the steroidogenesis of the interstitial cells of the testicles [104, 105]. It has also been observed that ovariectomy stimulates adrenal function, indicating an endocrine correlation between these two organs [98].

The available information on gerbil adrenal morphology suggests that this is an animal model suitable for studies of this gland, since its structure and, therefore, physiology, mainly in terms of the cortical region, demonstrate many similarities to the human suprarenal gland [99]. However, many questions remain unanswered, such as which enzymes are expressed by adrenocortical cells, what the similarities are in the development of the gland (the existence of a fetal zone, for example) to expand understanding of androgen secretion by the adrenal gland, and what its contribution is to the regulation exerted by steroid hormones.

Final Remarks and Conclusion

The studies assembled in this review shed light on the Mongolian gerbil as an important alternative to the use of inbred rats and mice in scientific research. Publications referring to the reproductive tract of these rodents showed that they have great potential and applicability due to morphophysiological and pathological aspects. Still, proximity to organs of other well-established rodent experimental models, such as rats and mice as described here, is a fundamental element that contributes to gerbil's use in reproductive biology research. Furthermore, the studies performed in the prostate gland of both male and female individuals are substantial and provide a consistent basis for discoveries in embryology, mechanisms for disrupting compounds, and therapies. Despite other fields, such as female reproductive organs and male gonads are yet to be further explored, we have seen an expansion of knowledge with few published data in the last years, especially regarding the mammary gland and ovaries. Studies performed by research groups from China, cited throughout the review, have contributed to such knowledge while developing methods for gerbils' population control in Asian countries, due to damages caused by this species in grasslands and to livestock.

As reported above, gerbils have contributed to the expansion of the knowledge about different subjects in the reproductive field, especially regarding prostate biology. Some positive aspects that characterize them as an adequate animal model are (1) the high incidence of spontaneous proliferative lesions and neoplasia, (2) a good tolerance to the vivarium environment and to long-term treatments, (3) a long lifetime in comparison to other rodents, (4) they are docile, and, last but not least, (5) they show useful particularities in their reproductive tract (well-developed prostate gland in both male and female individuals and deep morphophysiological changes in the ovarian tissue in response to the natural androgenic environment). In contrast, some unfavorable aspects might be related to the lack of official breeding centers and development of reproductive technologies, which has impaired the development of specific genetically modified strains. The growing interest in this model might, however, encourage these advances and contribute to the use of Mongolian gerbils as experimental models in research.

In a nutshell, for reproductive biology, advantages were exceeded in Mongolian gerbil. Short-term pregnancy and lactation, completely described in literature, enhance and accelerate the long-term analyses as observed in other species. Male and female present a functional prostate gland, only possible due to the natural androgen modulation in the perinatal period. Due to that feature, female prostate gland, and other hormone-dependent organs, could be analyzed in the same specimen, providing a systemic and integrated study. For adrenal, and prostate, the similarities in function and structure with human suprarenal gland are impressive features, as explained above. The main disadvantages that could be cited are linked to laboratory routines and technical limitations. As it is a small animal, some organs, such as the male and female prostate, present certain limitations of techniques, such as for molecular analysis. Still, for the mammary gland, primary cell culture techniques and primary formation of organoids need to be improved, since this organ has a large amount of adipose tissue, which makes it

difficult to separate the compartments by conventional techniques. These adversities are limited to the development of techniques that need to be improved from new studies with this experimental model.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval This is a Review of Literature and has not involved the use of any unpublished data. Ethical approval is dismissed in this case.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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