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REVIEW ARTICLE

Heat stress on reproductive function and fertility in mammals

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Abstract In most mammalian species including cattle, heat stress has deleterious effects on nutritional, physiological and reproductive functions. Exposure of animals to a hot environment causes an increase in body temperature in mammals, including domestic animals. High ambient temperature also causes a decrease in the length and intensity of estrus by disturbing ovarian function as well as decreasing pregnancy rate after artificial insemination. Therefore, it is important to understand the effects of heat stress on reproductive function in order to improve the production of domestic animals. Heat stress decreases appetite, weight gain, and milk yield in dairy cattle. It also adversely affects the reproductive performance of both sexes. In males, it reduces spermatogenic activity, while in females it adversely impacts oogenesis, oocyte maturation, fertilization development and implantation rate. Detection and evaluation of the deteriorating effects of heat stress on reproductive organs and cells can help to design measures to prevent them and improve reproductive functions. In this review, we discuss the impacts of heat stress on reproductive functions.

Keywords Heat stress · Livestock animal · Mammal · Oxidative stress · Reproductive function

Introduction

There are many different climatic zones around the world which are highly affected by latitude, altitude, water area, oceans, winds or evaporative conditions. Mammals, including humans and livestock animals, are living in such variable environmental conditions. Most mammals have body temperatures of 35–39°C [1]. These temperatures are maintained above environmental temperatures through the generation of metabolic heat. Body temperatures are normally maintained in a narrow range by heat production and loss, although disease, poor nutrition and extreme environmental temperatures can upset the balance.

Heat stress caused by high ambient temperature in summer can result in increased body temperatures and can decrease growth, milk production and fertility in livestock. Many studies have examined the effects of ambient temperature and humidity on the physiology of livestock. Berman et al. [2] suggested that the upper limit of ambient temperatures at which high milk-yielding dairy cows may maintain a stable body temperature (38.5°C) is 25–26°C, and that at environmental temperatures above 25°C, practices should be instituted to minimize the rise in body temperature. High environmental temperature increases the body temperature in lactating cows to near 40°C [3]; however, this drastic elevation of body temperature is not observed in heifers even under high environmental temperature [3]. This may be because of the extra heat produced in association with milk production and less heat loss as a result of the smaller difference of temperature between body and environment. Milk production significantly decreases with increasing body temperature [4, 5]. In addition, heat stress decreases food intake and body weight in pigs [6, 7]. As well as productivity, heat stress widely affects the reproductive functions in mammals with a reduction of pregnancy rate in cattle [8] and pigs [9]. The objective of this review is to describe the effect of heat stress on reproductive functions in male and female mammals including livestock animals.

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Heat stress on male reproduction

In males, the testis is suspended in a scrotum outside the body in order to keep the temperature lower than core body temperature, which is required for normal spermatogenesis. The testis temperature is between 2 and 8°C below core body temperature in mice [10], humans [11] and bulls [12]. In bulls, bovine testicular temperature must not exceed 33–34.5°C for normal spermatogenesis [13, 14]. Hyperthermia has a detrimental effect on testicular functions such as inhibiting spermatogenesis in mice [15], rats [16], pigs [17, 18], sheep [19], cows [20] and horses [21]. For effective production of livestock animals, high fertility of semen is necessary for obtaining fertility after artificial insemination or natural mating; however, high summer temperatures have been shown to decrease semen quality in bulls, rams [19, 22–24] and boars [18, 25]. Heat stress to testis with acute scrotal heating decreases not only semen quality, but also decreases embryo quality after fertilization with normal female mice [15, 26–28] as well as fetal growth [26]. Heat stress has several adverse effects on reproductive tissues in mice and cows, including germ cell loss, poor morphology, low sperm quality, and abnormal DNA and chromatin structure [29–31]. Heat stress to the testis increased the number of apoptotic germ cells in mice [27, 32] and rats [16, 33] and disturbed gene expression in mice [10, 30, 34, 35]. Some evidence showed that X and Y spermatozoa are differentially affected by heat stress. The sex ratio of embryos shifted towards female when female mice were crossed with male mice treated with heat stress on the day of mating [30].

Heat stress also affects the endocrine and biochemical condition of male animals. Summer heat increased the level of thiobarbituric acid reactive substances (TBARs) which is an oxidative marker, and decreased glutathione peroxidase (GPx) level which is an antioxidant enzyme in bovine seminal plasma [36, 37]. Similar changes were observed in rams [38, 39]. Heat stress also has endocrine effects, reducing the plasma luteinizing hormone (LH) level in bulls [40, 41] and increasing the plasma testosterone level in boars [18].

Effects of heat stress on female reproduction

Estrus and endocrine status

Heat stress reduces the duration and intensity of estrus in dairy cows [42–44], increases anestrus and silent ovulation [43], and reduces the number of mounts in hot weather than in cold weather [45]. These changes make it difficult to detect estrus, so that artificial inseminations are less successful and the number of pregnancies is reduced. Heat stress also affects reproductive functions in beef cows. Pedometer measurements showed a decrease in the number of steps, which reflects the intensity of estrous behavior, at the day of estrus with an increase in ambient temperature in summer (Fig. 1). In another case, a clear increase in the number of steps was observed in an individual cow when ambient temperature decreased (Fig. 1).

Heat stress affects many reproductive functions including endocrine activities in females. High temperature disturbs hormone secretion such as decreasing LH, follicle-stimulating hormone (FSH) in cows [46, 47], progesterone in cows [48, 49], and estradiol (E2) in goats [50]. Heat stress also reduces the level of progesterone and causes a loss of LH surge in sheep [51]. Heat stress also changes the luteal phase and ovulation in humans [52], and reduces the levels of estradiol and follicular estradiol concentration, aromatase activity and level of LH receptor associated with delayed ovulation [50] in goats. Heat stress also lowers the levels of gonadotropin receptors and aromatase activity of granulosa cells and the follicular fluid concentrations of estradiol collected from rat follicle [53]. An in vitro study revealed a decrease of follicular steroidogenesis, androstenedione and estradiol of follicle wall exposed to heat stress [54]. On the other hand, less effects on insulin-like growth factor binding protein, E2 and progesterone levels in dominant follicles have also been reported after heat stress exposure to dairy cows despite the elevation of rectal temperature [55]. These different responses need to be considered with regard to exposure time, estrous cycle, nutritional status [56], and other environmental conditions such as wind and humidity. Ovarian function in lactating cows is different from that in dry cows and heifers, because lactating cows generate more heat as a result of milk production [3].

Effect of heat stress on follicular development and oocyte quality

Heat stress negatively affects ovaries by inhibiting follicular growth and oocyte quality. Heat stress reduces inhibin levels by hastening the decrease in size of the first-wave dominant follicle and the emergence of the second dominant follicle [57, 58]. Intrafollicular condition is important for oocyte growth and quality. High ambient temperatures significantly decrease the number of oocytes and developmental competence following in vitro fertilization in dairy cows but have less effect on beef cows [59]. Exposing dairy cows to heat stress decreased estradiol production and viability of granulosa cells and also decreased androstenedione production by thecal cells [60]. Some metabolic markers such as blood level of glucose and non-esterified fatty acid (NEFA) affect the condition of the follicles under heat stress conditions. It is reported that the

Fig. 1 Disturbance of estrus behavior of cows in summer season (June–September, 2010). *Upper* Temperature and humidity at Kumamoto Japan in summer. *Lower* Number of daily steps of individual cow. *Red bars* show the number of daily steps on the day in which the cows showed standing estrus (*arrows*)

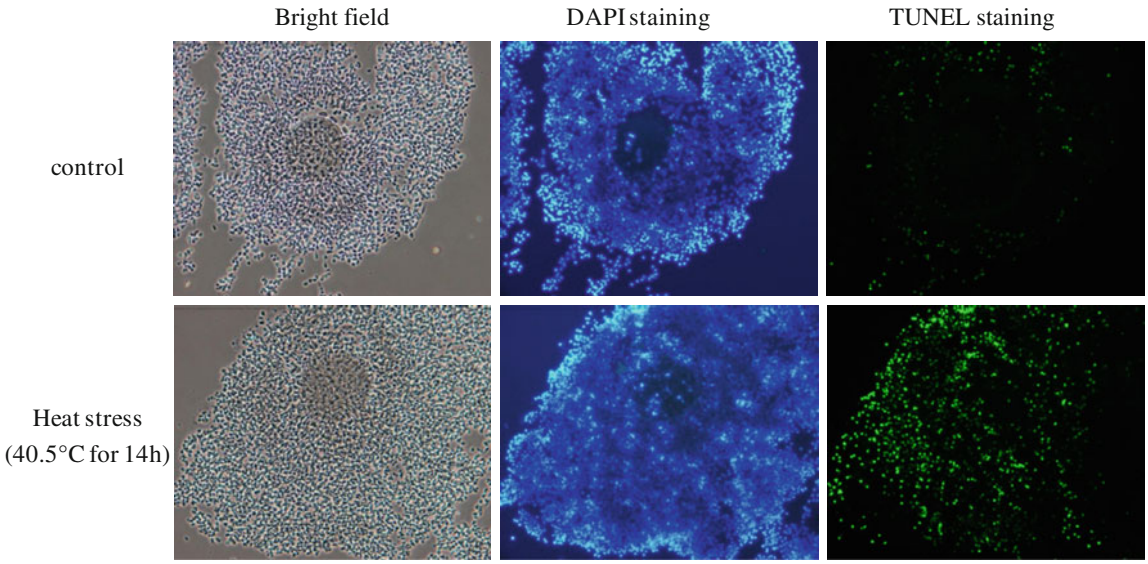

Fig. 2 Heat stress-induced apoptosis in bovine matured cumulus–oocyte complexes (*COCs*). After COCs were collected from follicles, they were matured for 20 h in maturation medium. COCs were exposed to 40.5°C for the latter 14 h followed by fixation and TUNEL staining

glucose level of bovine follicular fluid is about 85% of the plasma glucose level in the cool season and that the follicular glucose level significantly decreases in summer with a similar decrease in blood glucose level [61]. In contrast, heat stress did not affect the level of NEFA in spite of a significant increase in plasma level [61]. Taken together, these results indicate that the condition of follicles is affected by body blood nutrition or biochemical components which vary in the summer season. However, oxygen is probably not a factor because its concentration in the follicular fluid does not vary in heat and non-heat stressed conditions [62].

Although rectal temperatures are often considered representative of core body (and hence tissue) temperatures, ovarian temperatures are kept 1–1.5°C cooler than rectal temperatures in several species, including cattle, pigs, rabbits and humans [63–66]. Maternal heat stress did not affect the blood oxygen pressure in the ovarian vein of swine [67]. On the contrary, ovarian, cervical and oviductal blood flows decreased by 20–30% by heat-stressed rabbit while vulval blood flow rose by 40%, irrespective of pregnancy and/or lactation status [68]. These studies indicate that it is necessary to study the effect of body temperature and local blood flow associated with local temperature and distribution of nutrition to follicles for oocyte growth. However, it is unclear how follicular temperature is affected in heat-stressed ovaries. Further studies are needed to determine how heat stress affects local reproductive organs to clarify the follicular and oocyte growth.

Effects of heat stress on oocyte growth, fertilization and early embryonic development

Many in vitro and in vivo studies have examined the effects of heat stress on maturation and developmental competence of oocytes. Exposing females to heat stress after fertilization caused decreases in the quality and quantity of embryos in cows after superovulation [69, 70] and mice [71–75], and caused decreases in fetal growth in pigs [67], mice [74] and beef cows [76]. In vitro studies also revealed the effect of heat stress on oocyte maturation. Exposing GV stage oocytes to high temperature inhibits the rate of MII stage oocytes in mice [77, 78] and cows [79–82]. Although, experimental heat stress coincident with ovulation and oocyte maturation may or may not have an effect on the capacity of oocytes to be fertilized, the resultant embryos are more likely to develop slowly or abnormally. Exposure of oocytes to heat stress during in vitro maturation caused nuclear and cytoskeletal alterations in mice [77], pigs [83] and cows [79, 84]. Heat stress also induces cumulus–oocyte complexes (COCs) to undergo apoptosis. Figure 2 shows the increase in the number of TUNEL-positive cells in cumulus cells surrounding bovine oocytes when COCs were exposed to heat stress during in vitro maturation. Heat stress also induced apoptosis in bovine oocytes [82, 85, 86] and an increase in phosphatidylserine, an indicator of apoptosis in porcine oocytes [87]. On the other hand, short exposures to heat stress seem to have less effect on oocyte maturation in vitro [88–90]. Careful analysis is necessary to clarify the opposite results of heat stress on oocyte maturation in in vitro or in vivo conditions. Heat stress at the time of fertilization also decreased subsequent embryo development, which suggests that heat stress has detrimental effects on both on oocytes and sperm [81]. In males, heat stress reduces the number of sperm with intact acrosomes at the time of ejaculation [18].

In addition to oocyte maturation, development of preimplantation embryos after fertilization is also affected by the surrounding environment. Exposing preimplantation embryos to heat stress decreased their development in mice [91] and cows [92, 93] and decreased the total cell number of blastocysts [93].

Developing embryos during the short period (4–8 days) between fertilization and implantation undergo dynamic growth, cell proliferation, cell differentiation, and many changes in gene expression. Therefore, if the maternal body is exposed to heat stress during this period, it is likely that the preimplantation development is severely affected directly by heat stress itself or indirectly by the deleterious change of reproductive tracts. The stage at which embryos become susceptible to heat stress has been studied. In vivo maternal heat stress inhibited embryo development at an early stage in mice [71, 75] and cows [70]. In vitro studies have clearly shown that the sensitivity of bovine embryos to heat stress is stage-specific [93–95] as well as in in vivo studies [70]. In cows, in vivo and in vitro experiments showed that embryo development is significantly inhibited by heat stress approximately 48–72 h after fertilization, which corresponds to the 8–16 cell stage [93]. After this stage, heat stress exposure has less effect on the rate of development and cell proliferation [93]. In mouse and cow embryos, the stage that is most sensitive to heat stress is approximately the time of zygotic genome activation (ZGA), which occurs at the 2-cell stage in mice [96] and at the 4- to 8-cell stage in cows [97, 98]. Both during and after ZGA, heat stress can also change the chromatin structure of embryonic cells [99], which might disturb gene expression. In addition to inducing apoptosis in maturing oocytes, heat stress also induces apoptosis in embryonic cells in cows [86, 100, 101], pigs [102, 103] and rabbits [104].

Knowledge of when an embryo is most sensitive to heat stress can be used to select the best time for embryo transfer by preventing the early embryonic loss after artificial insemination in cows [105, 106].

Effects of heat stress on post-hatching development and placentation

Maternal heat exposure after fertilization decreases the pregnancy rate and causes embryonic death before implantation [70, 71]. Such conditions might disturb the intrauterine environment both for embryos and uterine tissue. We recently found that the viability of uterine epithelial cells recovered from uterine flushing at the time of embryo collection in beef cows decreased in summer (Fig. 3). At this time, embryo quality also tended to decline.

A high level of prostaglandin F2α (PGF2α) inhibited implantation, altered embryo development and induced luteal regression [107]. Maternal recognition of pregnancy is an initial step for embryo implantation and placentation. The corpus luteum secretes progesterone, which has roles in follicular growth and the establishment and maintenance of pregnancy. Luteal function is inhibited by summer heat, causing decreases in progesterone levels in luteinized granulosa cells, theca cells and plasma [108] in both dairy cows [48] and beef cows [49]. One of the many factors controlling luteal function is PGF2α which is mainly secreted by the uterus. On the other hand, elevated uterine luminal concentrations of PGF2α have been negatively associated with embryo quality and pregnancy rates [109] and have been shown to have a toxic effect on in vitro development of embryos in rabbits [110], rats [111] and cows [112, 113]. Administration of PGF2α to pregnant mice on day 4 reduced the decidual reaction around the implantation chamber [114]. Secretion of PGF2α is affected by heat stress in endometrial tissues of pregnant and non-pregnant bovine uterus [115]. Also, maternal heat stress increases placental PGF2α and PGFM levels [116].

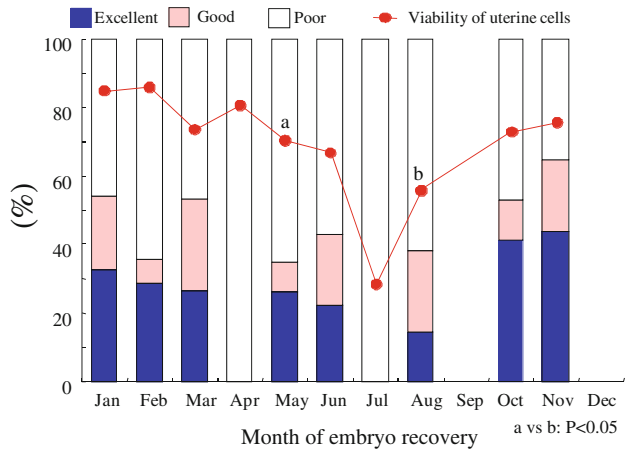

Fig. 3 Seasonal changes of embryo quality and viability of uterine epithelial cells recovered on day 7 from Japanese black cows. Uterine epithelial cell clots were recovered from uterine flushing at the time of embryo collection in beef cows. After enzymatic dispersion, cell viability was determined by trypan blue staining

Heat stress also has detrimental effects on placentation and fetal growth. Maternal heat stress decreases growth retardation [117] and size of placenta in rats [118], and placental weight [119, 120] and placentome size [121] in sheep, but has less effect on humans [122]. Maternal heat stress in cow reduces the levels of placental hormones, which disturbs placental function and slows fetal development [123]. Maternal heat stress and nutritional status during gestation also have strong effects on fetal development [124]. Heating the scrota for extended periods also results in decreased fetal weight [125] which indicates that the impact of heat stress on paternal gamates at the earlier stage highly affects fetal growth.

Oxidative stress in heat stressed reproductive functions

Heat stress not only affects animals by reducing the reproductive functions but it also has physiological and nutritional effects followed by retardation and reduced milk production in cattle. In summer, an increase of body temperature significantly decreased milk production [4, 5]. Increase of body temperature by heat stress also caused decrease of food intake and body weight in pigs [6, 7]. As well as reducing productivity, heat stress widely affects the reproductive functions in mammals with a reduction of pregnancy rate in cattle.

Oxidative stress is one of the many parameters used to indicate the physiological status in cells and tissues of an animals' body. Heat stress affects the oxidative stress-related physiological status in females as well as males. Heat stress caused increases in oxidative markers, such as the levels of TBARS, superoxide dismutase (SOD) and catalase in plasma and erythrocytes in humans [126], cows [127], goats [128] and mice [129], and in the liver in rats [130]. Maternal heat stress changes the redox status in the oviduct in mice [75, 129]. Several antioxidant enzymes that are expressed in the oviduct vary during the estrous cycle in cows [131]. We also found seasonal differences in the redox status of oviductal fluid collected from dairy and beef cows (Fig. 4). Together, these studies referring to [75, 129, 131] and Fig. 4 indicate that decreased redox status and/or increased oxidative stress lead to deterioration of intraoviductal conditions with adverse effects on ovulated oocytes, ejaculated sperm and fertilized embryos.

Early embryonic development is also affected by heat stress-induced oxidative stress. Heat stress increased

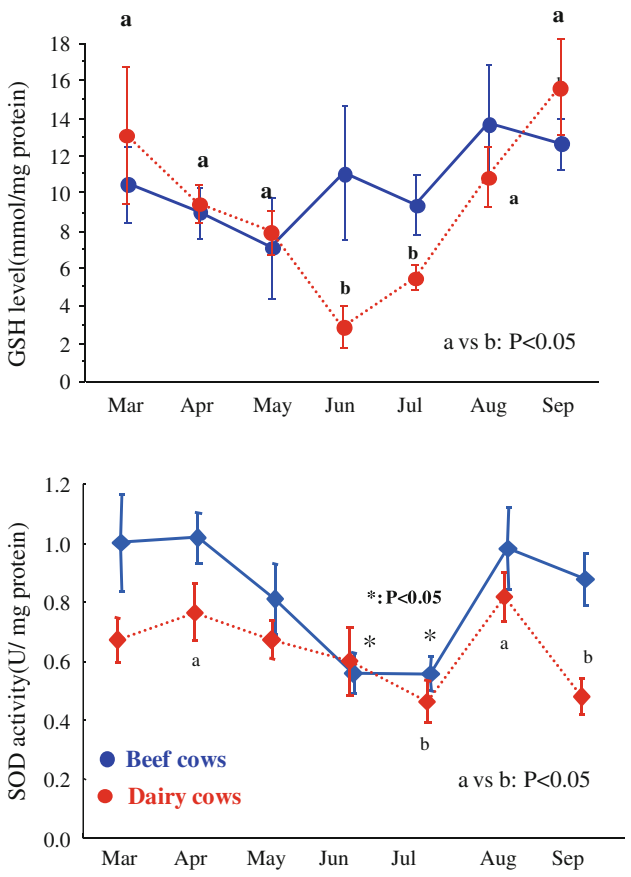

Fig. 4 Seasonal changes of GSH levels and SOD activity in oviductal fluids collected from beef and dairy cows. Oviducts were collected from slaughtered dairy and beef cows from March to September. After trimming, oviducts were flushed with 0.5 ml PBS. Collected flushing was centrifuged to remove the cell clots. GSH levels and SOD activities were then measured. Measured GSH and SOD levels were normalized to total protein concentration in the oviductal flushing

intracellular reactive oxygen species (ROS) in embryos of mice [71] and cows [93]. Interestingly, at the time when bovine embryo development is critically inhibited by heat stress (days 0–2), ROS generation in heat-stressed embryos significantly increases [93]. After day 2, heat stress has less effect on embryo development as well as less effect on ROS generation or accumulation. Administration of antioxidative polyphenol [74], vitamin E [132] or melatonin [133] to heat-stressed female mice improved the development of mouse embryos. β-Carotene had a similar effect on the pregnancy rate of heat-stressed dairy cows [134, 135]. In vitro administration of antioxidants such as anthocyanin [136], astaxanthin [137] or 2-mercaptoethanol [138] improved embryo development of heat-stressed bovine embryos associated with intracellular ROS and glutathione (GSH) synthesis [138]. Furthermore, in vivo heat stress also caused a decrease in GSH of oocytes and embryos, and elevated ROS levels associated with DNA damage in mice [71].

These findings provide both direct and indirect evidence of a close relationship between heat and oxidative stress in embryo development. GSH maintains the intracellular redox status of embryos and is associated with their development and quality in many species including mice [139], rats [140], rabbits [141], pigs [142] and cows [143, 144]. GSH can improve the thermotolerance of mice [145], which suggests that redox status is an important determinant of thermotolerance. Therefore, using antioxidants to control the intracellular or extracellular redox status both in vivo and in vitro may be a way to reduce heat stress-related oxidative stress.

Impact of heat stress on human live food production and reproduction in future

Global temperatures have risen about 0.7°C since the beginning of the industrial revolution in the 18th century, causing climate change all over the world by possible greenhouse gasses. Recent weather reports show that the incidences of summer heat waves, heavy rains or drought have been increasing with rising temperature. It is likely that global warming will have severe impacts on the physiology and reproduction of mammals of both sexes. The impact of elevated temperatures on reproductive functions in males and females is summarized in Fig. 5.

Mammals including livestock animals have adapted to variable environments all over the world which typically include high ambient temperatures. In these environments, mammals have acquired genetic variation and improved mechanisms for controlling body temperature and managing heat stress. On the other hand, genetic selection of livestock by humans has made them more susceptible to heat stress. This is especially the case with dairy cows which generate large amounts of metabolic heat for milk production. In dairy cows selected for high milk production, the conception rate decreases dramatically in summer than in winter [146]. However, the effects of heat stress on milk production and body temperature vary among breeds [147], and are less in beef cows than in dairy cows. This decline of reproductive performance is thought to be due to an imbalance of heat production and loss [148]. Such breed differences in heat stress are attributed not only to biological body but also to cellular response of immune cells [149], embryos [150–152] as well as a combination of semen [124, 153, 154]. Therefore, further studies of genes involved in cellular and physiological responses to heat stress are needed to control and improve mammalian reproduction.

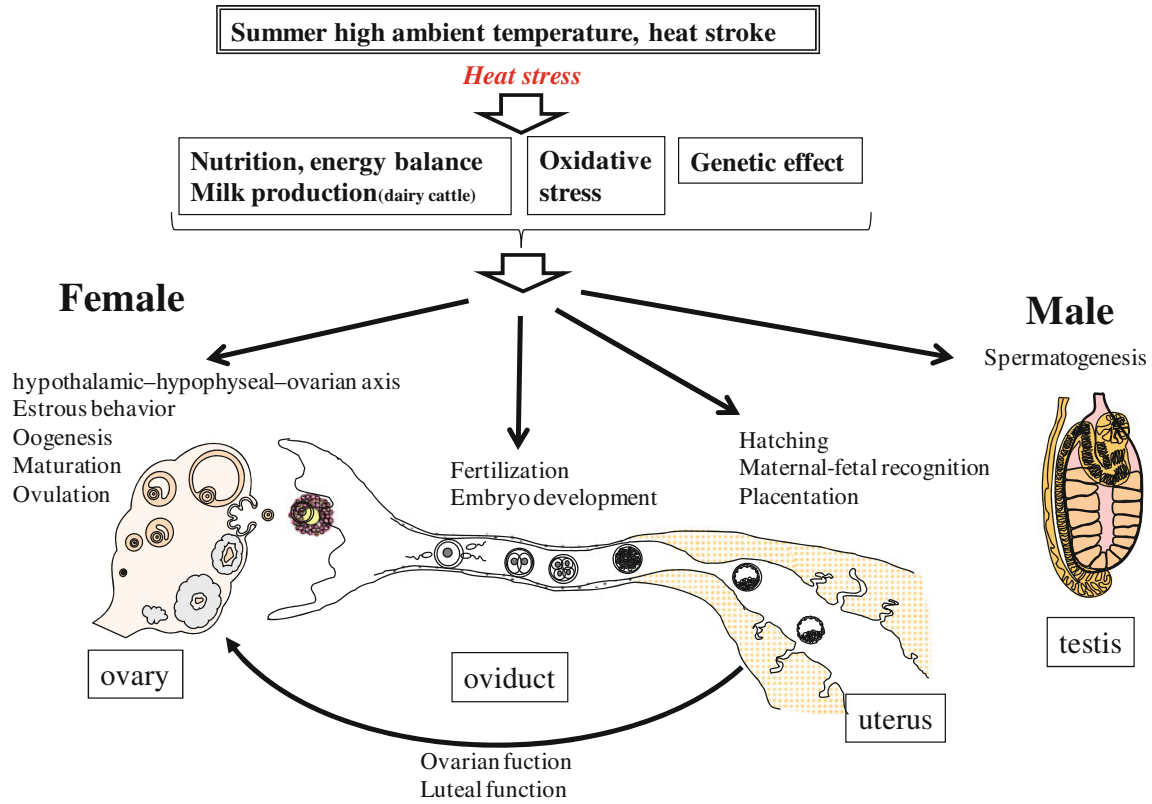

Fig. 5 Schematic diagram of the effects of heat stress on reproductive functions in male and female mammals

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