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Impact of High Temperature on Oocytes and Embryos: A Review

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ABSTRACT

High temperature is one of the leading factors for declining reproductive performance in livestock and other species as a result of heat stress causing severe economic losses. The embryonic death caused due to heat stress is having a multifactorial mechanism in the live animal. Heat stress could influence reproductive physiology through modulating the flow of blood to the reproductive tract, ovarian steroid concentrations, and patterns of follicular development. The elevated oviductal and uterine temperature associated with heat stress makes the survival of embryos difficult. High-temperature in *in vitro* culture of embryos has been reported to impact embryonic development. Similarly, increased *in vitro* culture temperatures can compromise oocyte activity and reduce the fertilization rate. Studies have demonstrated that there were lethal effects of heat shock on *in vitro* cultured embryos of cattle at 41.0 - 43.0°C. These experimental temperatures, however, are higher than those encountered by heat-stressed cows which ultimately reduced their fertility. Furthermore, a lot of research has been conducted in livestock species all indicating that exposure to high temperature is detrimental to oocytes and embryonic developmental processes as it leads to cell damage and may interfere with oocyte maturation, and fertilization process. It concludes that the longer exposure of oocytes and embryos to high temperatures causes more damage to oocytes and embryos.

Introduction

Among various stresses that affect livestock performance, heat stress is considered one of the major concerns for the reproductive performance of cattle and other livestock species resulting in severe economic losses (Rivera and Hansen, 2001). Several aspects of reproductive physiology are affected by heat stress, such as blood flow to the

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reproductive system, ovarian steroid concentrations, and follicular development (Trout et al., 1998; Wolfenson et al., 1995; Badinga et al., 1993). Several studies have shown that embryonic development was found reduced upon the culture of embryos at high temperatures (Rivera and Hansen, 2001; Edwards and Hansen, 1996; 1997). Similarly, oocyte function and fertilization rate were found compromised after increasing culture temperatures (Edwards and Hansen, 1996; Baumgartner and Chrisman, 1987). In cattle embryos cultured at high temperatures of 41.0-43.0°C showed harmful effects on their development (Edwards and Hansen, 1996; 1997; Ealy and Hansen, 1994). Usually, bovine embryos are grown at 38.0-39.0 °C but these experimental temperatures are higher which ultimately showed reduced fertility (Edwards et al., 2005).

Several studies observed that the fertility of many farm animals such as cattle (Cavestany et al., 1985; Badinga et al., 1985; Wang et al., 2009), pigs (Omtvedt et al., 1971), sheep (Dutt, 1963), and buffalo (Vijayalakshmy et al., 2020) found to be lower in summer than in any other season. It was also reported that heat stress causes damage to oocytes which ultimately affected the embryonic development (Rivera and Hansen, 2001; Edwards and Hansen, 1997) and induces infertility by affecting hormonal secretion (Wolfenson et al., 2000). Oocytes taken from cows during the summer season had a reduced ability to grow into blastocysts after in vitro fertilization (Al-Katanani et al., 2002; Rutledge et al., 1999). Heat stress increased the proportion of arrested and abnormal embryos produced in heifers when exposed to high heat between the onset of estrus and insemination (Putney et al., 1989), implying that oocyte maturation is susceptible to high temperatures. Similarly, in vitro maturation of bovine oocytes at high temperatures reduced cleavage and blastocyst formation rates (Abdelnour et al., 2020; Roth and Hansen, 2004).

The resumption of the first meiotic division, followed by the progression of meiosis to the metaphase II stage, constitutes nuclear maturation, whereas cytoplasmic maturation encompasses a variety of steps required for the oocyte to achieve the capacity to meet the formation of male pronuclei, monospermic fertilization, and early embryonic development. (Eppig et al., 1996) as summarized in Fig 1 and 2. The oocytes and embryos are sensitive to heat stress due to insufficient production of heat shock protein (HSP) (Edwards and Hansen, 1996). For bovine embryos, the most sensitive period for heat shock is the 8-16 cells stage of embryo (second day's post-fertilization) and thereafter the embryo begins to acquire resistance against high temperatures (Ealy et al., 1993). The notion has also recently been supported by Pöhland and observed that the 2 cells embryos are not able to synthesize HSP70 in response to heat stress (Pöhland et al., 2020). However, 2 - 4 cells stage mouse embryos able to support the induced thermo-tolerance. A study conducted on mice showed that in 8 cell stages embryos were able to synthesize HSP prematurely due to embryonic genome activation at this stage (Ealy et al., 1993). Contrary, Saeki et al. (1999) reported that the 1 cell stage is also able to syntheses HSP due to the existence of maternal transcription of messenger RNA (mRNA).

A study conducted by Alves et al. (2013), in which in vitro maturation of oocytes occurs at 40°C and they found significant reduction in cleavage rate (31.46% ± 2%), morula formation rate (35.64% ± 2%), and blastocysts formation rate (0.0%) than the cleavage rate (68.23% ± 2%), morula formation rate (50.16% ± 2%) and blastocysts formation rate (43.28% ± 1%) in the control group. Similarly, when oocytes were exposed at the higher temperature of 40°C and 41°C for 12 hours then reduction was observed in development to 35% and 18% blastocysts stage at respective temperatures (Edwards and Hansen, 1996; Edwards and Henson, 1997). In addition, exposure of high temperature to bovine oocytes to thermal stress during the first 12 hours of maturation reduced cleavage rate as well as blastocyst formation rate (Fig 1 and 2; Roth and Hansen, 2004). Tseng et al. (2006) also reported a similar result in which the rates of blastocyst formation in pig were reduced after post-maturation heat shock to oocytes.

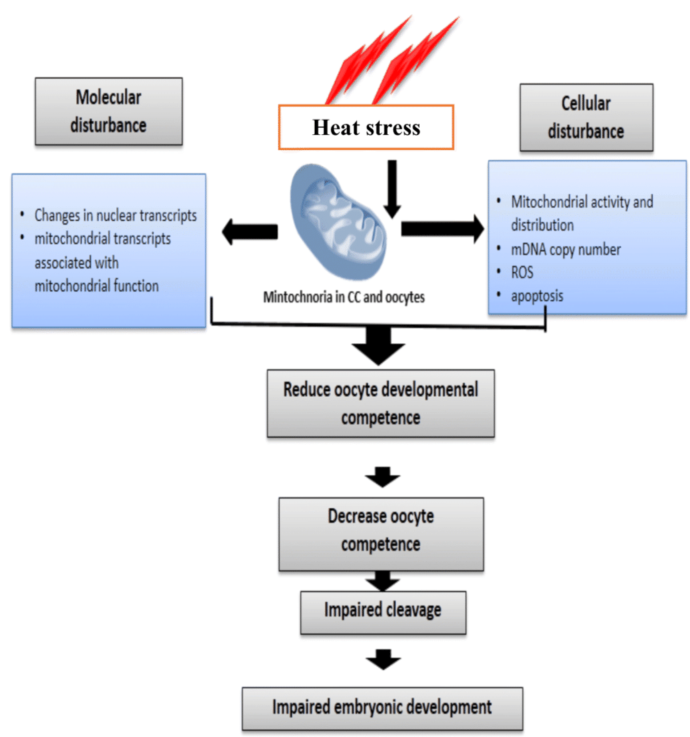

Fig 1. Impact of heat stress on mitochondria function of oocyte and cumulus cells (Abdelnour et al., 2020).

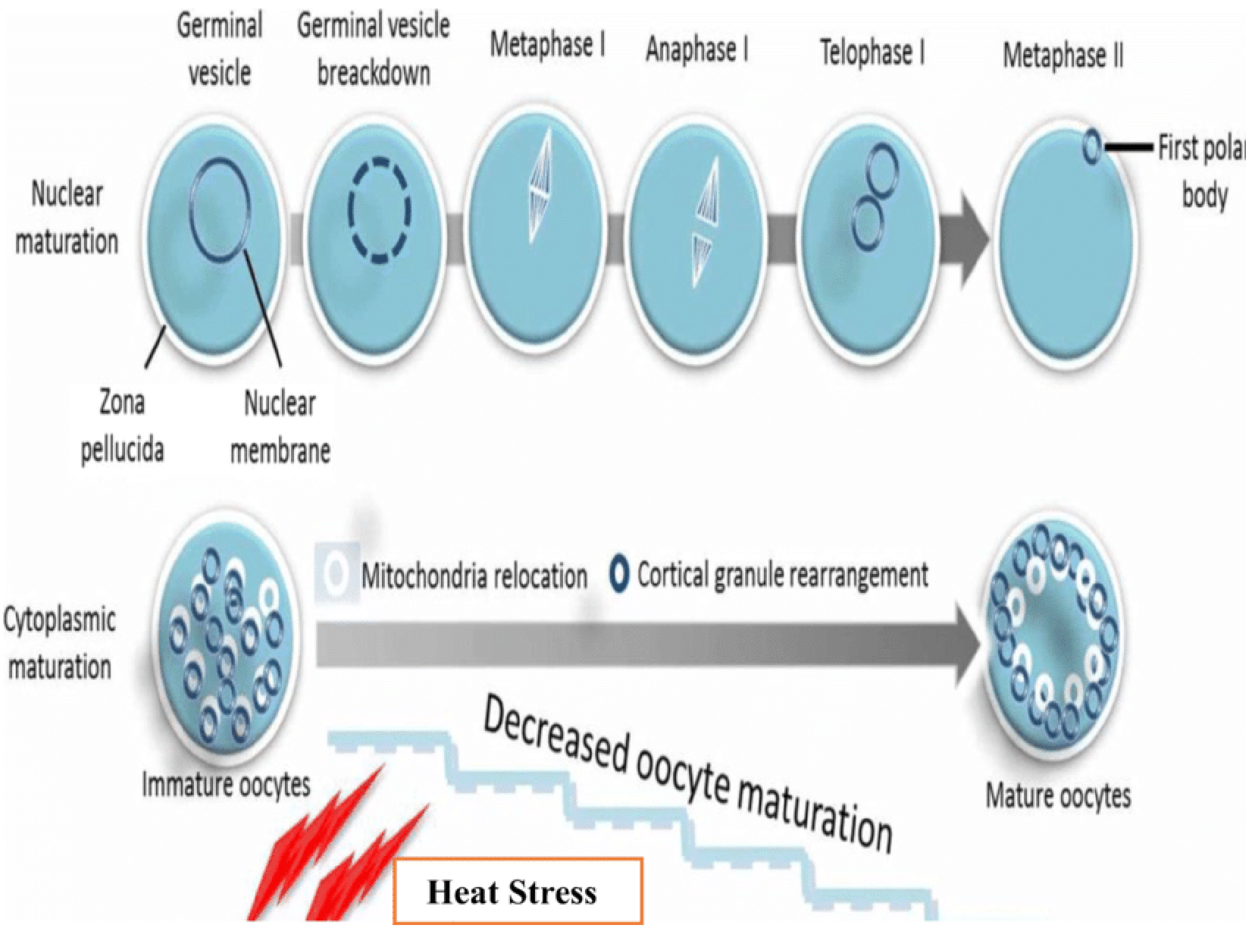

Fig 2. Events show how nuclear and cytoplasmic maturation is affected by extreme heat (Abdelnour et al., 2020).

Another study showed that when oocytes were exposed at 40°C or 42°C for one hour had no harmful effects on blastocysts formation after the IVF (Ju et al., 1999). Subsequently increased in the temperature to 43°C and exposed oocytes for 45 minutes the developmental competencies of treated oocytes were rigorously found reduced (Ju et al., 1999). These studies suggest that *in vitro* embryo production is limited by temperature and exposure duration (Ealy et al., 1995; Ju et al., 1999). Krininger III et al. (2003) suggested that the exposure of heat shock or the intensity of temperature and duration of exposure to oocytes leads to reduced cleavage rate and blastocysts formation rate. There is variation in the observation; some reports showed that when 2-cells stage bovine embryos cultured at 40°C for 3 hours which not affect the developmental potential to blastocysts, whereas, oocytes subjected to the culture at 41°C and 42°C for 12 hours (a long period) then embryonic development was found significantly compromised (Ealy et al., 1995; Tseng et al., 2004). A similar observation was noticed in porcine embryos cultured at high temperatures in which viability and developmental competence of oocytes and embryos were proportionate to the temperature intensity and exposure duration (Ju and Tseng, 2004).

Consequences of extreme heat on estrus and endocrine activity in female reproduction

The length and passion of estrus in dairy cows are shortened by heat stress (Trout et al., 1998) and increased anestrus and silent ovulation (Gwazdauskas et al., 1981). It is difficult to detect estrus as a result of these changes; thereby the number of pregnancies is reduced due to the low success rate in artificial inseminations. Reproductive performance in beef cows is affected by heat stress. Reproductive functions are greatly affected by heat stress as well as endocrine activities in females. Increased temperature disrupts hormonal secretion by reducing luteinizing hormone (LH), follicle-stimulating hormone (FSH, Gilad et al., 1993), and progesterone (Burke et al., 2001) in cows and estradiol (E2) in goats (Ozawa et al., 2005). Due to decreases the secretion of progesterone by heat stress results in diminished LH surge in sheep (Hill and Alliston, 1981), which also changes the luteal phase and ovulation in humans (Carpenter and Nunneley, 1988), reduces estradiol levels and concentration of estradiol within follicles, aromatase activity and in goats the level of LH receptor associated with late ovulation (Ozawa et al., 2005). Gonadotropin receptors and the amount of aromatase activity in granulosa cells as well as the concentration of estradiol in follicular fluid collected from rat follicle are all lessened (Shimizu et al., 2005). An *in vitro* study conducted at high temperatures revealed that there was a reduction in androstenedione, follicular steroidogenesis, and estradiol concentration (Bridges et al., 2005). However, less effect was observed on levels of estradiol, progesterone, and insulin-like growth factor-binding protein in dominant follicles upon exposure of dairy cows to extreme heat despite the rise in rectal temperature (Guzeloglu et al., 2001). These differences in responses to extreme heat depend on the duration of exposure, nutritional status, stage of the estrous cycle, and other environmental factors especially humidity and wind (De Rensis and Scaramuzzi, 2003). There is a difference in ovarian functions of lactating cows and dry cows as well as in heifers since milking activity in lactating cows leads to the production of more heat (Sartori et al., 2002). Lactating animals are more prone to hyperthermia as the high milk yield in dairy cows compromises the thermoregulatory capabilities of the lactating dairy cow. As a result, heat stress has a greater negative impact on fertility in high-producing dairy cows than low-producing dairy cows (Moura and Paula-Lopes, 2020).

High temperatures influence the development of follicles and the quality of the oocyte

Heat stress undesirably has damaging effects on ovaries by preventing follicular growth and altering oocyte number and quality. It decreases the level of inhibin which rapidly decreases the size of the dominant follicle of the first wave and hampers the emergence of the second dominant follicle (Roth et al., 2000). For oocyte growth and quality, the condition inside the follicle is very important. In dairy cows, the developmental competence and number of oocytes after *in vitro* fertilization are greatly affected by high ambient temperatures but have less effect on beef cows (Hansen et al., 2001). It was reported that exposure of cows to high temperature decreases estradiol production and viability of granulosa cells as well as declined androstenedione production by theca cells (Roth et al., 2001). Blood glucose levels and non-esterified fatty acid (NEFA) affect follicles under heat stress conditions. Reports have shown that bovine follicular fluid has ~85% glucose of the plasma glucose level in the winter season which found significantly decreases in summer in follicular fluid (Shehab-El-Deen et al., 2010). In contrast, heat stress did not affect the level of NEFA in follicular fluid although its level was found significantly significant increase in plasma level (Shehab-El-Deen et al., 2010). These results indicate that the summer season affects the condition of the follicles by the change in nutrition or biochemical components. Whereas, the oxygen concentration in the follicular fluid was not changed in heat and non-heat stressed conditions (de Castro et al., 2008). However, the blood oxygen pressure of the ovarian vein of porcine did not affect by maternal heat stress (Wettemann et al., 1988). Heat stress is characterized by an increase in core body temperature (hyperthermia) which is represented by the measurement of rectal temperatures. The ovarian temperatures are found lesser (around 1-1.5°C) than rectal temperatures in several species such as bovine, porcine, caprine, rabbit, and human (Grinsted et al., 1985; Grøndahl et al., 1996). On the contrary, in rabbits heat stress decreased the ovarian, cervical, and oviductal blood flows by 20–30% and increased vulval blood flow by 40% irrespective of pregnancy or lactation status (Lublin and Wolfenson, 1996). Taken together, it is needed to know the effects of elevated body temperature on oocyte functions, understanding the molecular and cellular mechanisms triggered by elevated temperature is vital to establish effective thermal protective approaches. To clarify follicular and oocyte growth, more research is needed to see how heat stress impacts local reproductive organs. The impact of high temperatures on female reproductive functions is summarized in Fig. 3.

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

Several *in vivo* and *in vitro* studies have documented that heat stress affects the maturation and developmental competence of oocytes. A female exposed to heat stress post-fertilization caused decreases in the quantity and quality of embryos after super-ovulation in cattle (Ealy and Drost, 1993) and mice (Ozawa et al., 2002; Ozawa et al., 2004; Roth et al., 2008). Heat stress also caused decreases in fetal growth in pigs (Wettemann et al., 1988), mice (Roth et al., 2008), and beef cows (Biggers et al., 1987). Exposing oocytes at the GV stage with high temperature inhibits the formation of the MII stage in mice (Wang et al., 2009) and cow (Payton et al., 2004; Sugiyama et al., 2007; Zhandi et al., 2009). Other studies also favor that high heat stress occurs during ovulation and/or oocyte maturation affect the capacity of the oocyte to be fertilized and consequently retarded the embryonic development or cause abnormalities such as nuclear and cytoskeletal alterations (Wang et al., 2009; Roth and Hansen, 2005; Ju and Tseng, 2004; Payton et al., 2004) and apoptosis in cumulus-oocyte complexes (COCs) which increase the secretion of phosphatidylserine, an apoptosis indicator (Soto and Smith, 2009; Zhandi et al., 2009; Tseng et al., 2006; Roth and Hansen, 2004). Fig 4 shows that when bovine oocytes are exposed to heat stress during in vitro maturation, the number of TUNEL-positive COCs cells around them increases. On the other hand, oocytes exposed to heat stress for a short period showed less impact on *in vitro* maturation of oocytes (Edwards et al., 2009; Schrock et al., 2007;). Contrary results of heat stress on *in vitro* or *in vivo* oocyte maturation need to be careful analysis. At the time of fertilization spermatozoa exposed to high heat stress which subsequently decreased embryonic development, suggests that heat stress is also detrimental for sperms (Sugiyama et al., 2007). Apart from females, heat stress also affects males to reduce the number of sperm count with intact acrosomes at the time of ejaculation (Murase et al., 2007). After fertilization embryos undergo several changes such as cell proliferation, cell differentiation, initiation of expression of many genes and signaling pathways which are pre-requisite for implantation. If the maternal body is exposed to heat stress during this time, the pre-implantation development is likely to be seriously harmed, either directly by the heat stress or indirectly by the detrimental changes in the reproductive tracts. It was observed in mice when maternal reproductive organs exposed to heat stress in vivo inhibited embryonic development at an early stage (Ozawa et al., 2004; 2002) and cows (Ealy et al., 1993). Detail studies are required to address the stages at which embryos become vulnerable to heat stress.

In vitro and *in vivo* studies have clearly shown that the sensitivity of bovine embryos to heat stress is stage-specific (Ealy et al., 1993; Krininger et al., 2003; Sakatani et al., 2004). Experimentally shown in bovine, heat stress inhibited embryonic development at 8-16 cell stages which correspond to 48-72 h post-fertilization (Sakatani et al., 2004). This stage is known as the maternal to zygote transition stage where the zygote genome becomes activated. In mouse and cow embryos, the zygotic genome activation (ZGA) stage is most sensitive to heat stress, which occurs at the 2-cell stage in mice (Schultz, 1993) and the 8- to 16-cell stage in bovine (De Sousa et al., 1998). Both during and after ZGA, the chromatin structure of embryonic cells may

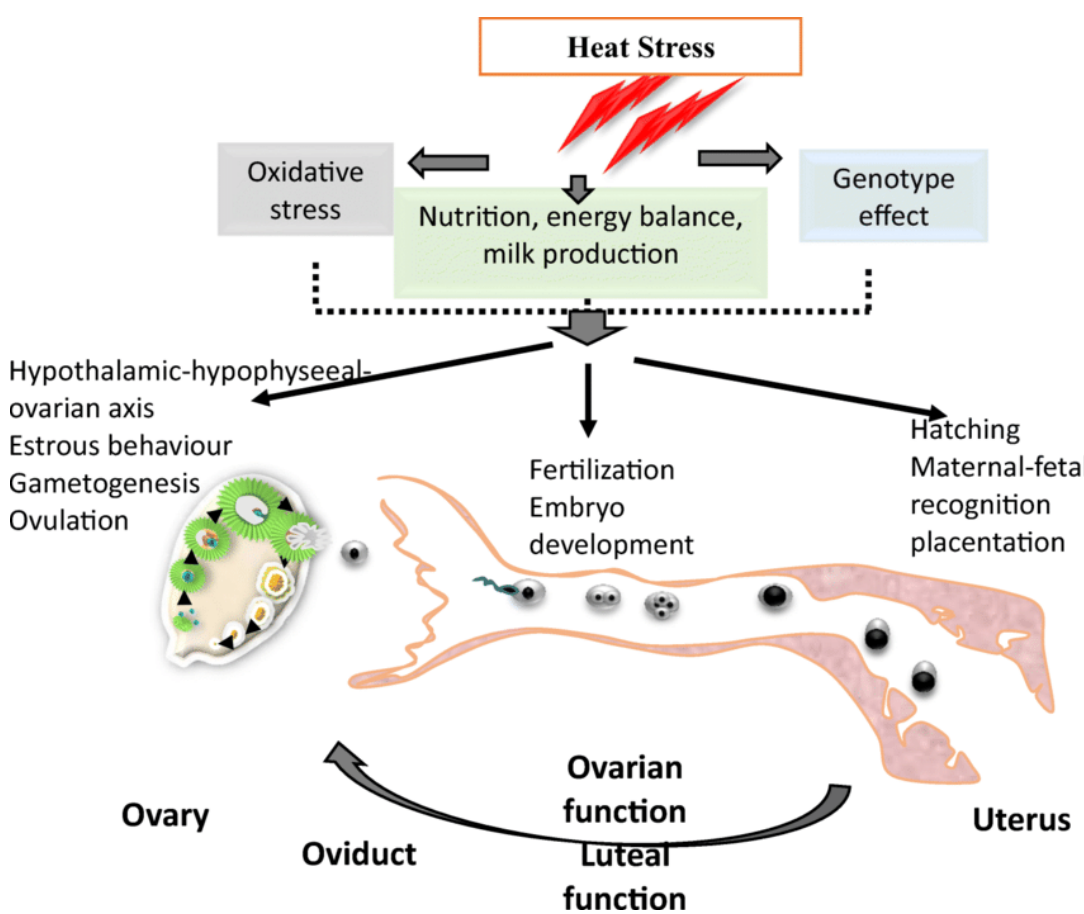

Fig 3. Summary of the impact of heat stress on female reproductive functions (Abdelnour et al., 2020).

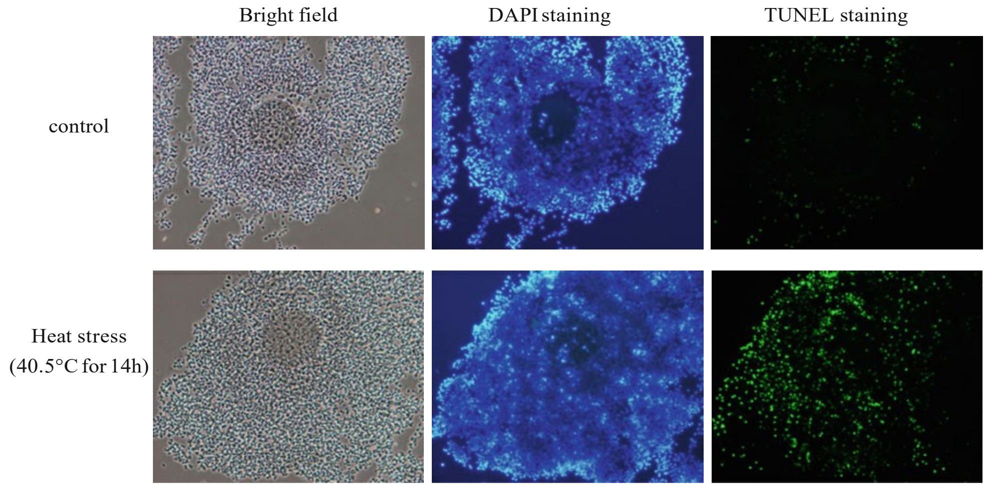

Fig. 4. Apoptosis induced by heat stress in matured cumulus-oocyte complexes (COCs) of cattle. After COCs were collected from follicles, they were matured for 20 h in maturation medium and were exposed to 40.5˚C for 14 h followed by fixation and TUNEL staining (Takahashi, 2011).

change in response to heat stress (Edwards, 1998), which might interrupt gene expression and induces apoptosis in embryonic cells (Soto and Smith, 2009; Paula-Lopes and Hansen, 2002a; 2002b), pigs (Isom et al., 2007; Jin et al., 2007) and rabbits (Makarevich et al., 2007). Hence, after this stage, exposure to heat stress becomes less detrimental for embryonic development and cell proliferation (Sakatani et al., 2004). Taken together with this knowledge on the most sensitive time of heat stress on embryos, we could use it to determine the ideal timing for embryo transfer in animals to avoid early embryonic loss after artificial insemination (Drost et al., 1999; Putney et al., 1989;).

In conclusion, heat stress has detrimental effects on germ cells (oocytes and sperm), preimplantation embryos, and the reproductive function of livestock in general. Several pieces of evidence indicate that high temperature hampers the oocyte developmental competence via a series of molecular and cellular changes such as heat shock response, unfolded protein response, and autophagy. Therefore, identification and characterization of cellular thermo-protective molecules could be considered as an alternative to reduce the effects of high temperature in reproductive function. Hence, further studies need to be carried out to elucidate the genes and pathways that are involved in both cellular and physiological responses to heat stress which would help to the regulator and improve livestock reproduction.

Competing Interest

There is no conflict of interest among the authors.

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