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Review Article

Influence of maternal nutrition and heat stress on bovine oocyte and embryo development

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ABSTRACT

The global population is expected to increase from 7.6 to 9.6 billion people from 2017 to 2050. Increased demand for livestock production and rising global temperatures have made heat stress (HS) a major challenge for the dairy industry. HS been shown to have negative effects on production parameters such as dry matter intake, milk yield, and feed efficiency. In addition to affecting production parameters, HS has also been shown to have negative effects on the reproductive functions of dairy cows. Mitigation of HS effects on dairy cow productivity and fertility necessitate the strategic planning of nutrition, and environmental conditions. The current review will discuss the potential nutriepigenomic strategies to mitigate the effect of HS on bovine embryo.

1. Introduction

The global human population is expected to increase from 7.6 to 9.6 billion people from 2017 to 2050 [1]. In order to meet the nutritional needs of the growing population, there is a critical demand for more efficient livestock production, especially in developing countries [1]. Heat stress (HS) is a major challenge to livestock producers in many countries across the world, especially to those located in desert and tropical climates. As reported by the United States' Environmental Protection Agency (US EPA) [2], the average global temperature is expected to increase by 0.3 °C to 4.8 °C by the year 2100 which may have a negative impact on animal production efficiency if effective heat abatement strategies are not implemented. Together, harsh geographical climates and rising global temperatures make heat stress a critical concern for animal production.

The upper critical limit of the thermo-neutral zone for dairy cattle is approximately 25 °C; thus, dairy cows are at risk of HS when exposed to temperatures above 25 °C [3]. In addition to ambient temperature alone as an indicator of HS, the temperature humidity index (THI), which combines temperature and humidity to create an index score, can also be used to estimate the effect of environmental conditions on dairy cattle [4]. As described by Armstrong [5], THI values can be divided into four categories according to the degree of HS experienced by dairy cows: no HS ($\leq$71), mild HS (72–79), moderate HS (80–90), and severe HS ($>$ 90).

2. Heat stress negatively impact animal production

HS has many negative effects on dairy cow welfare and productivity such as increased rate of respiration, sweating, and peripheral blood flow. HS has also been shown to cause decreased dry matter intake which limits nutrient supply to the mammary gland and results in decreased milk yield and overall feed efficiency [6–8]. Additionally, increased THI results in imbalanced cooling ability of the cow, resulting in heat load that negatively affect DMI and milk production [9,10].

In addition to altering production, HS also alters metabolic pathways including those involved in acid-base homeostasis. Elevated respiration rate decreases the level of circulating carbon dioxide (CO_2), which disrupts the blood carbonic acid to bicarbonate equilibrium. As a result, urinary bicarbonate excretion increases and blood pH becomes unstable which can lead to a number of metabolic issues for the dairy cow [11].

3. Heat stress and altered maternal nutrition impair reproduction capacity

In addition to its negative effects on production, HS impairs the reproductive functions of dairy cows [12]. Elevation of maternal body temperature negatively affects several aspects related to reproduction capacity either directly through effects on oocyte quality, success of fertilization, and/or embryo development [13,14] or indirectly by

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limiting nutrient supply to support reproductive function and/or effects on reproductive hormones secretion and level [15–17].

3.1. Impairment of reproductive hormones

The gonadotropin releasing hormone (GnRH) released from hypothalamus that stimulates the release of Gonadotropins; Luteinizing hormone (LH) and Follicle stimulating hormone (FSH); from anterior pituitary gland are main regulators of ovarian functions [12]. Research on the effect of HS on peripheral blood LH is not giving a consistent picture yet, since some studies recorded increase [18], decrease [19,20] and even no effect [21,22] of HS on LH. However, the decreased LH level could be more reasonable, since low LH level could result in decrease estradiol secreted from the dominant follicle, and thus, decrease fertility by poor expression of estrus, poor follicle maturation, and ovarian inactivity [23]. Moreover, steroid production by cultured granulosa and thecal cells was low when cells were obtained from cows exposed to heat stress 20–26 days previously [24]. Implantation failure and early embryonic death resulted from decreased blood progesterone level during HS condition has been reported in dairy cow [25].Yet, more research is needed to unravel the mechanism by which heat stress alters the levels of circulating reproductive hormones.

3.2. Altering oocyte quality and embryonic development

During hot seasons, cows showed a high incidence of early embryonic mortality due to several reasons. One of these reasons is the direct effect of elevated temperature on follicular development and oocyte competence [26]. In addition, HS negatively affects the superovulation response of cows and subsequently recovered embryos number, and quality [27]. A recent study on pigs reported that gilts exposed to HS during the follicular phase showed a clear induction of ovarian autophagy, and that HS increases anti-apoptotic signaling in oocytes and early follicles [28]. Ultrasonography studies revealed that, the size of the first- and second-wave dominant follicles were reduced under HS conditions [29,30]. This affects the development of other follicles and leads to ovulation problems [31]. HS was also correlated with lower steroid concentrations in the follicular fluid obtained from large follicles and reduced granulosa cell viability [32]. Deleterious effect on follicular development and follicular fluid contents directly reflects on the oocyte quality and affects its developmental competence [26,33,34]. On the molecular level, HS seems to alter the maternal RNA stored at the oocyte. This was observed at subsequent developmental stages before embryonic genome activation which can explain the lower quality blastocysts obtained from oocytes collected in hot season than those from oocytes collected in cold season [35]. However, more researches are still needed to elucidate this point. Embryos are highly susceptible to maternal HS during the first early stages of development and this susceptibility reduced as the development proceeds. Exposer of lactating cows to heat stress at day 1 after oestrus (1–2 cell stage embryos), reduced the proportion of embryos that developed to the blastocyst stage at day 8 after oestrus. However, heat stress in later stages had no effect on the proportion of embryos that were blastocysts at day 8 [36].

In vitro studies indicated that exposure of cultured oocytes to physiologically relevant heat shock (41 °C) during the first 12 h of maturation decreases their cleavage rate and blastocyst rate by 30 to 65% [37–39]. Recently, it has been reported that HS during oocyte maturation is associated with reduced cytoplasmic events and apoptosis of the cumulus cells and therefore compromise the survival of the oocyte itself [40]. The mechanisms by which elevated temperature affects oocyte and embryo physiology are not completely understood. However, several studies elucidated this effect from different prospective. Based on the gene expression patterns, it has been reported that HS stimulates the apoptosis signaling pathway in oocyte by upregulation of *BAX* and *ITM2B* (apoptotic genes) [27] and in early stage embryo by down-regulate genes associated with embryonic survival, such as CDX2, a transcription factor involved in the regulation of embryo implantation and placental development [41]. In another studies, expression of growth/differentiation factor-9 (GDF9) associated with oocyte maturation was downregulated when oocyte was exposed to HS both *in vivo* [42] and in vitro [43]. Furthermore, the apoptotic pathway of Caspases 2, 3, and 7 were upregulated when bovine oocytes were exposed to HS in in-vitro model leading to mitochondrial damage and nuclear fragmentation [44]. On the other hand, impaired micro-tubulin and microfilaments, which are involved in nuclear and organelles transport have been reported as consequences of oocyte exposure to HS [45,46]. The sensitivity of these cytoskeletal elements to HS affects other cytoplasmic organelles including mitochondria, essential element for oocyte developmental competence. Differences in mitochondrial distribution and shape have been recorded in oocytes isolated in hot season compared to cold season [47]. Mitochondrial functions are also influenced by HS with low membrane potential in association with apoptotic pathway activation [48].

It is also possible that HS directly affects embryonic development via epigenetic regulation, or indirectly through decrease DMI and alter the metabolic status of the animal [49,50]. Dobbs et al. [51] showed that DNA methylation was low during the early stages of embryonic development but increased between the six-to-eight-cell-stage to the blastocyst stage. Additionally, in rat model, low protein diet altered the de novo methylation process in early stage embryo [50]. However, the direct effect of HS on bovine embryo DNA methylation- de-methylation mechanistic is not well established.

3.3. Altering maternal DMI and energy balance

Short term HS has been shown to induce negative energy balance (NEB) [52,53], and even exacerbate the existing NEB by prolonging the period of decreased DMI in highly producing dairy cow [12]. Highly producing dairy cows suffer from NEB which usually occurs after calving due to the disparity between dry matter intake (DMI) and an increase demand for milk production [54]. During HS, cows mobilize adipose reserves which results in elevated non-esterified fatty acids (NEFA) [52,53] that have been shown to decrease oocyte and embryo quality in in vitro studies [54–57] .

Blood glucose level was reduced during short term (7 days) [52] and long term (during the hot season) exposure to HS [35]. However, in another *in vivo* short term (4 days) study [53] blood glucose was not affected by HS. This could be due to the short term exposure to HS which could not predict well the impact of HS on blood glucose level. Even more, elevated blood NEFA concentration is also associated with decreased glucose concentration in ovarian follicular fluid [43,54,58]. This reduction of glucose level can significantly impact oocyte development because glucose serves as the main energy source and provides the necessary elements for oocyte maturation including pyruvate, ATP, and reducing agents such as NADPH and glutathione that neutralize the reactive oxygen species (ROS) [59]. Therefore, HS can have indirect negative effects on oocyte and subsequent embryonic development via this reduction in available glucose [54]. In addition, increased NEFA concentrations affect the expression of genes involved in lipid metabolism in various tissues, such as the mammary gland [60], oocytes [54], and the embryo itself [61]. The mRNA abundance of DNMT3A (regulating embryonic DNA methylation), IGF2R (growth factor), and SLC2A1 (glucose transporter) were up-regulated in blastocysts resulting from NEFA exposed oocytes [61,62] resulting in an imbalance embryonic DNA methylation [41].

3.4. Altering anti-oxidant capacity

During HS, maternal total plasma anti-oxidant capacity decreased [42]. Additionally, ROS such as hydrogen peroxide, superoxide anion, and hydroxyl radical are elevated when both the bovine oocyte [43]