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Exogenous and endogenous factors in seasonality of reproduction in buffalo: A review

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ABSTRACT

Seasonal breeding in buffalo is influenced by exogenous (photoperiod, climate, nutrition, management) and endogenous (hormones, genotype) factors. Buffalo are negatively photoperiodic and show a natural increase in fertility during decreasing day length. The hormone melatonin is produced by the pineal gland and has a fundamental role in photoperiodic time measurement within the brain. This drives annual cycles of gonadotropin secretion and gonadal function in buffaloes. Some melatonin is released into the systemic circulation and, together with peripherally produced melatonin, acts at somatic tissues. In the ovaries and testes of buffalo, melatonin acts as an antioxidant and scavenges oxygen free radicals to reduce both oxidative stress and apoptosis. This has beneficial effects on gametogenesis and steroidogenesis. Female buffalo treated with melatonin show an improved response to estrus synchronization protocols in out-of-season breeding. Melatonin acts through melatonin receptors MT_1 and MT_2 and the gene for MT_1 (*MTNR1A*) is polymorphic in buffaloes. Single nucleotide polymorphisms (SNPs) in gene *MTNR1A* have been associated with fertility in female buffalo. The knowledge and tools are available to lift the reproductive performance of buffalo. This is highly important as the global demand for nutritious buffalo food products has undergone a sharp rise, and continues to grow. Buffalo can make an important contribution to affordable, nutritious animal protein. This will help address global nutritional security.

1. Introduction

Buffalo have been an important farm animal for more than 5000 years and their significance in global food systems continues to grow [1–6]. Today, buffalo-derived products are found at the very expensive and less expensive extremes of food markets. Buffalo contribute premium, niche food such as mozzarella cheese [7–9] and they are also a source of affordable, highly nutritious meat protein [10,11]. The latter is particularly important in nutritional security in Asia and The Middle East [10–14]. The growth in demand for affordable buffalo 'beef' allows smallholder and landless farmers to participate in global food markets. This creates the opportunity for poverty alleviation and improvement in rural livelihoods in developing countries, and is highly relevant to the 2017 Sustainable Development Goals [15]. In a global food system, vulnerable farmers need to be protected by ethical supply-chains and governance structures.

Growth in buffalo production is constrained by their reproductive biology. Buffalo are generally considered to be late sexually maturing [16–19] and to have an extended postpartum anestrus [16,20,21] compared with cattle. Selection over 30 years in the Italian Mediterranean buffalo reduced age at first calving from 42 to 36 months and, with management, age at first calving was further reduced to 28 months [22]. Buffalo also have a longer gestation period (typically 300–320 days) compared with beef cattle (*Bos taurus* 279–283 day; *Bos indicus*, 290–293 days) [23]. The

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reproductive characteristics of female buffalo make it very difficult for buffalo to produce an offspring yearly. Added to these features is the fact buffalo are negatively photoperiodic seasonal breeders and show natural annual fluctuations in fertility [24–31]. In addition, the vast majority of buffalo are in tropical and subtropical areas where high temperatures and humidity in summer, together with relatively poor nutrition, cause seasonal anestrus [32–35]. Environmental factors can, however, be relative as Italian Mediterranean buffalo are bred out-of-season during summer-spring when the temperature-humidity index is at its highest [29,36–38]. Notwithstanding the reproductive challenges in buffalo, the recent sharp rise in demand for affordable and nutritious buffalo food products has made it necessary to develop new strategies that optimize the reproductive performance of buffalo. This needs to occur in both endowed and non-endowed production systems. Genetic selection for seasonality of breeding and fertility is one strategy that is mentioned below.

This review seeks to bring together information on exogenous and endogenous factors that contribute to seasonality of reproduction in buffalo. Exogenous factors include photoperiod, nutrition, temperature, humidity and management. Endogenous factors include IGF1, insulin, prolactin, thyroid hormones, melatonin, progesterone, and genotype. Melatonin is given particular attention as recent studies have demonstrated a direct beneficial effect on male and female gametes in buffalo, and treatment with melatonin has shown promise in improving fertility in anestrous buffalo.

2. Exogenous factors in buffalo reproduction

Exogenous factors that influence reproductive function in buffalo have been extensively reviewed [5,6,24,25] and this section provides only a general overview. Photoperiod is arguably the main exogenous regulator of reproduction in buffalo. Buffalo are negatively photoperiodic and show a natural increase in fertility in response to decreasing day length [24,26–29]. This is particularly evident at higher latitudes [27] but also occurs in the sub-tropics [39,40]. Buffalo show a decline in fertility in response to increasing day length [26]. The decline in fertility induced by long day length can be partly overcome with assisted reproductive technology (ART), including treatments for ovulation induction coupled with AI [31,39–41]. The potential for melatonin to enhance the response to ovulation induction protocols in anestrous buffalo is discussed below. Assisted reproductive technology is necessary to maintain continuity of reproduction in female buffalo because the 300–320 day gestation, and postpartum anestrous period, causes a decoupling of reproductive function from annual cycles of decreasing day length. There are also market drivers such as the yearly cycle in peak demand for mozzarella cheese which requires Italian Mediterranean buffalo to be bred outside the stimulatory window of decreasing day length [36].

In the tropics and sub-tropics, high temperatures and humidity in summer combine to induce anestrus in buffalo [5,25,42,43]. Management strategies to mitigate these stressors, such as active cooling, are necessary to maintain a degree of productivity. Also during summer, both the quantity and quality of feed are typically reduced, which adds a further nutritional stressor to reproductive function [5,25]. However, as noted above, market demand for mozzarella cheese requires breeding during summer-spring in intensively managed Italian Mediterranean buffalo.

Other than photoperiod, external factors that have a negative impact on reproduction must be managed in order to realize the opportunity presented by the global demand for buffalo food products. Approaches include strategic nutritional supplementation, the use of ART, and the implementation of management strategies (e.g. cooling, loafing space) that optimize the wellbeing of buffalo across endowed and non-endowed production systems.

3. Endogenous factors in buffalo reproduction

3.1. Prolactin, TRH, insulin, IGF1, P_4

Endogenous factors that regulate reproduction in buffalo are generally influenced by exogenous stimuli. An example is prolactin which is elevated during long day length [44]. Female buffalo that enter the condition of 'hyperprolactinemia' in summer due to day length, and heat stress, have reduced gonadotropin secretion and become anestrus [45,46]. A cause-and-effect of elevated prolactin under these conditions was suggested by the improved response to estrus synchronization in buffalo treated with norprolac, which lowered prolactin [45]. Notwithstanding the latter study, it was suggested that hypothyroidism, with elevated thyrotropin releasing hormone (TRH), may combine with elevated prolactin to suppress reproduction in female buffalo [20,47]. The interrelationship of endocrine disruption (prolactin, TRH, thyroid hormones) with stress and reproduction requires further study in seasonal buffalo. Factors associated with metabolism, and which impact gonadal function, such as insulin and IGF1, are typically influenced by nutrition [43,48,49]. IGF1 is particularly important in ovarian folliculogenesis and, in one study, Italian Mediterranean buffalo heifers maintained on a constant nutritional regimen had greater follicular IGF1 during short days compared to long days [50]. This finding suggested that photoperiod can directly affect follicular IGF1 in buffalo, although the mechanism is unknown.

The influence of day length on development of the corpus luteum and secretion of P_4, essential for the maintenance of a pregnancy, is well established in buffalo [27–29,31]. During long days, the corpus luteum is less vascularized and secretes less P_4 [29]. This is associated with greater embryonic mortality in buffalo during long days [27]. These studies were undertaken in Italian Mediterranean buffalo under a relatively constant nutritional regimen and further illustrated the important role of day length in seasonal breeding in buffalo. Nili-Ravi buffalo in Pakistan bred at spontaneous [51] or synchronized [52] estrus had a lower pregnancy rate [51,52] and greater pregnancy failure [52] during summer compared with winter.

3.2. Melatonin

Melatonin, produced by the pineal gland in the brain, has an important role centrally in photoperiodic time measurement which drives seasonal breeding in ruminants, including buffalo [53–56]. Seasonal changes in the circadian pattern of brain melatonin impact on the function of GnRH neurons in the hypothalamus that, in turn, influence pituitary gonadotropin secretion and reproductive function in ruminants [57,58].

Some brain melatonin is released into the general circulation and acts peripherally [59,60]. Melatonin is also produced by somatic tissues [54,55,61] and melatonin receptors (MT_1, MT_2) are expressed peripherally [62–66]. It is now recognized that locally-produced melatonin can have autocrine and paracrine actions at somatic tissues including the ovaries and testes [67–73]. An important property of melatonin, and its metabolites, is a powerful antioxidant action [74–79]. Indeed, melatonin is a more powerful scavenger of oxygen and nitrogen free radicals than vitamin E [76]. The antioxidant property of melatonin protects cells from free radical damage and apoptotic mechanisms. The beneficial effects of melatonin on sperm, oocytes and embryos are conferred, at least in part, by its antioxidant action [80] (Fig. 1). Acyclic buffalo had greater amounts of follicular reactive oxygen species [81] and treatment with melatonin reduced oxidative stress in summer

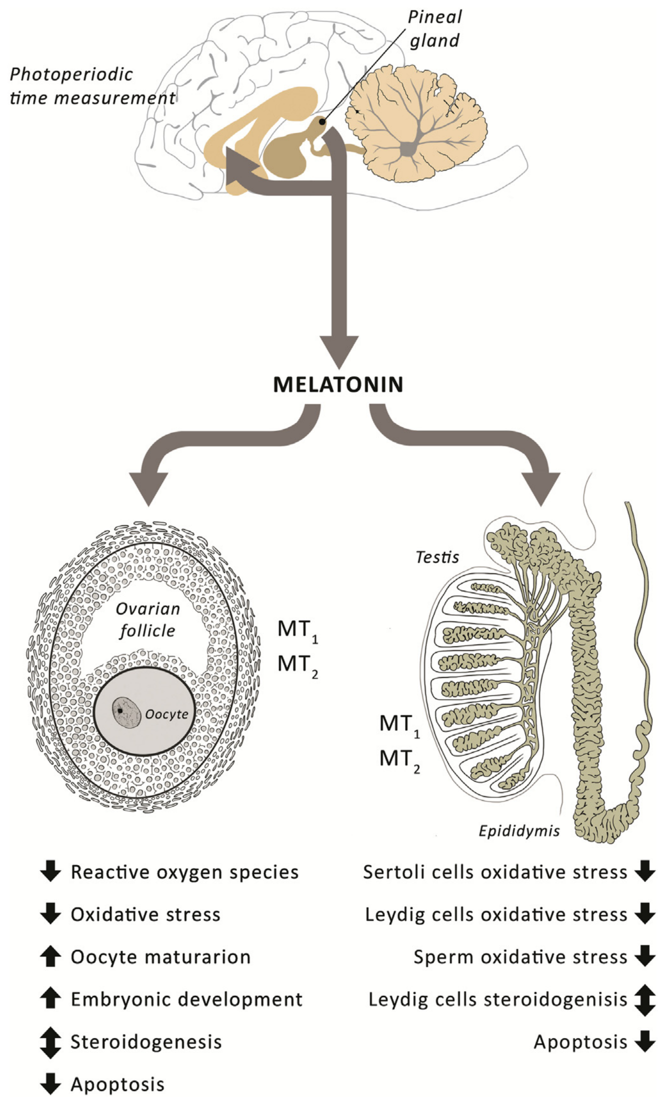

Fig. 1. Actions of melatonin at the brain, ovaries and testes. Within the brain melatonin is involved in photoperiodic time measurement which drives seasonal changes in the activity of GnRH neurons and gonadotrophin secretion. Some melatonin is released into the systemic circulation and, together with locally produced melatonin, influences the function of follicles and oocytes, Sertoli cells, Leydig cells, and sperm. Melatonin is a strong antioxidant and scavenges reactive free radicals to reduce oxidative stress and apoptosis. Melatonin acts through melatonin receptors MT_1 and MT_2 which have been demonstrated on follicles, Sertoli cells, Leydig cells and sperm.

anestrous buffalo [82].

Melatonin is present in seminal plasma and the inclusion of melatonin had a protective effect during cryopreservation of buffalo semen [83,84]. Melatonin also facilitated *in vitro* sperm capacitation in buffalo [85]. Murrah buffalo bulls implanted with melatonin showed an improvement in semen quality during the nonbreeding season [86]. Melatonin treatment also improved semen quality in seasonal Mithun bulls [87]. It can be concluded from these findings that peripherally-derived and testicular melatonin has a role in sperm survival and function in buffalo and other ruminants. The European bison, a seasonal breeder, shows annual changes in testicular melatonin and melatonin receptors MT_1 and MT_2 [88]. Melatonin receptors MT_1 and MT_2 are expressed in sperm of seasonal and non-seasonal breeders [89].

In sheep, melatonin and its receptors MT_1 and MT_2 are expressed by cumulus-oocyte complexes [90] and the corpus luteum [91]. Receptor MT_1 is also expressed by luteal cells in mares [92]. In cattle, the addition of melatonin increased the expression of LH receptors in cultured granulosa cells [93], increased steroidogenic enzymes and P_4 production by cultured thecal cells [94], and decreased apoptosis in cultured granulosa cells [93]. Melatonin also increased steroidogenesis and P_4 production by luteal cells in mares [92] and sows [95]. In buffalo, melatonin increased steroidogenesis and reduced apoptosis in cultured granulosa cells [96]. The supplementation of maturation media with melatonin improved maturation and *in vitro* fertilization of buffalo oocytes [97,98]. Melatonin also improved oocyte maturation and IVF outcome in pigs [99] and sheep [100–102]. Improved oocyte maturation in pigs was associated with lesser reactive oxygen species [99]. In contrast, the presence of melatonin did not improve *in vitro* oocyte maturation or embryo development in cattle [103,104]. Returning to the antioxidant properties of melatonin, follicular fluid of acyclic buffalo had greater amounts of oxygen free radicals and lesser antioxidant capacity compared with follicular fluid of cyclic buffalo [81]. It can be hypothesized that an additional beneficial effect of melatonin is to neutralize free radicals in follicular fluid (Fig. 1). Cryopreservation was associated with greater amounts of reactive oxygen species in *Bos indicus* embryos compared with *Bos taurus* embryos [105], suggesting that the inclusion of melatonin could potentially be beneficial in embryo technologies in *Bos indicus* cattle.

Melatonin is secreted during darkness in 24 h light-dark cycles [106,107]. This means that the duration of melatonin secretion is greater in short days than in long days [108]. An increased period of melatonin secretion in short days has a positive effect on reproductive function in short day breeders (e.g. buffalo, deer, sheep). A decreased period of melatonin secretion in long days has a positive effect on reproductive function in long day breeders (e.g. hamster, horse). The positive relationship between increased duration of exposure to melatonin and stimulation of reproductive function in buffalo [109–111] led to a series of studies that examined the ability of melatonin treatment to overcome seasonal anestrus. A typical design of these studies involved the administration of melatonin (18 mg/50 kg LW) around 40–45 days before the implementation of either a P_4-based [112–114] or GnRH-based [115] estrus synchronization protocol. The general finding from these studies was that prior exposure to melatonin is associated with increased functionality of the corpus luteum and greater capacity to maintain a pregnancy in summer anestrous buffalo heifers [112,113,115] and lactating buffalo cows [114]. The majority of these studies were undertaken in Indian Murrah buffalo in a tropical environment and further studies should be carried out in different environments, including higher latitudes. Seasonally anestrous Anglo-Nubian does, pre-treated with 18 mg melatonin for 42 days before a P_4-based estrus synchronization protocol, had a greater conception rate and greater fecundity compared with does that did not receive melatonin [116]. A similar improvement in fertility was observed in seasonally anestrous New Zealand Romney composite ewes pre-treated with melatonin for 35 days before a P_4-based estrus synchronization protocol [117]. The broad conclusion from these studies in short day breeders is that melatonin has a beneficial effect on fertility in seasonally anestrous females subjected to an estrus synchronization protocol.

The gene for melatonin receptor MT_1 (*MTRN1A*) is polymorphic and has been associated with productive and reproductive traits in buffalo [118,119]. Single nucleotide polymorphisms (SNPs) in gene *MTRN1A* were associated with conception rates in Indian Murrah buffalo heifers treated with melatonin during summer [120]. The gene *MTRN1A* also has a polymorphic site in Italian Mediterranean buffalo [121–123]. The latter was associated with differences in seasonal patterns of mating [121] and the capacity for out-of-season breeding in females [122]. The polymorphism was not associated with puberty in Italian Mediterranean buffalo heifers [123]. A polymorphism in exon II of gene *MTRN1A* was associated with seasonality of breeding in Indian Murrah buffalo cows [124]. However, a polymorphism in exon 1 of gene *MTRN1A* was not associated with reproductive traits in Brazilian Amazon buffalo cows [125,126]. Polymorphism in gene *MTRN1A* was also reported for Indian Chokla sheep [127], Italian Sarda sheep [128], French Mérino d'Arles sheep [129], Greek local breed sheep [130], and Dorset crossbred sheep [131]. In most sheep breeds there was an association between *MTRN1A* polymorphism and out-of-season breeding. The studies on polymorphism in gene *MTRN1A* present the interesting possibility of selecting female buffalo that can be mated at different times of the year in order to meet production and market requirements. Recent genome wide association studies [132–134] and RNA-seq analyses [134] have uncovered polymorphism in other genes associated with reproductive function in female buffalo.

Two features of melatonin in buffalo are worth noting. First, the rise in melatonin during darkness was less pronounced in Italian Mediterranean buffalo heifers compared with older cows [135]. It was suggested that this might explain, at least in part, why seasonal effects on reproduction are less apparent in heifers [22,24,135]. Second, multiparous Italian Mediterranean buffalo that showed clear seasonal changes in reproductive function had a greater increase in melatonin during darkness compared to buffalo that showed less pronounced seasonal changes in reproduction [136]. The difference in nighttime melatonin between seasonal and less seasonal buffalo was observed throughout the year [136]. Buffalo with relatively high nighttime melatonin and seasonal breeding retained these features when relocated to a buffalo farm where local animals had relatively low nighttime melatonin and less pronounced seasonal breeding [137]. It would appear from these studies that both the magnitude (above a threshold) and duration of melatonin secretion during darkness are involved in photoperiodic time measurement which cues reproduction to day length in buffalo. The magnitude of the rise in melatonin in darkness most likely has a genetic component and could potentially be used to select for seasonality, similar to polymorphism in gene *MTRN1A* which codes for melatonin receptor MT_1, as discussed above.

4. Conclusions

The action of melatonin in the brain to regulate photoperiodic time measurement and seasonal breeding is well established in ruminants. More recent evidence indicates that melatonin also acts peripherally at somatic tissues. A direct action of melatonin on ovarian function is strongly supported by the expression of its receptors in follicles and corpus luteum. The benefits conferred by melatonin in out-of-season mating, and the response to estrus synchronization and AI in summer, could result from a combination of (i) systemic and/or local antioxidant effects, (ii) stimulation of steroidogenesis, and/or (iii) suppression of apoptotic mechanisms. The potential to use polymorphism in the melatonin receptor gene *MTRN1A* to select for female buffalo that show optimal reproduction at different times of the year presents an interesting possibility. Efforts to improve fertility in buffalo are a worthy pursuit given the sharp rise in demand for affordable, nutritious buffalo food products. Those to benefit must include smallholder and landless farmers who are increasingly participating in the global food system.

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