Domestic Animal Endocrinology xxx (2020) 106434

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.journals.elsevier.com/domestic-animal-endocrinology

Nutritional control of puberty in the bovine female: prenatal and early postnatal regulation of the neuroendocrine system

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ARTICLE INFO

Article history:
Received 14 November 2019
Received in revised form 2 January 2020
Accepted 3 January 2020

Keywords:
Heifers
Hypothalamus
Leptin
Nutrition
Puberty

ABSTRACT

Puberty is a complex biological event that requires maturation of the reproductive neuroendocrine axis and subsequent initiation of high-frequency, episodic release of GnRH and LH. Nutrition is a critical factor affecting the neuroendocrine control of puberty. Although nutrient restriction during juvenile development delays puberty, elevated rates of body weight gain during this period facilitate pubertal maturation by programming hypothalamic centers that underlie the pubertal process. Recent findings suggest that maternal nutrition during gestation can also modulate the development of the fetal neuroendocrine axis, thus influencing puberty and subsequent reproductive function. Among the several metabolic signals, leptin plays a critical role in conveying metabolic information to the brain and, consequently, controlling puberty. The effects of leptin on GnRH secretion are mediated via an upstream neuronal network because GnRH neurons do not express the leptin receptor. Two neuronal populations located in the arcuate nucleus that express the orexigenic peptide neuropeptide Y (NPY), and the anorexigenic peptide alpha melanocyte-stimulating hormone (αMSH), are key components of the neurocircuitry that conveys inhibitory (NPY) and excitatory (αMSH) inputs to GnRH neurons. In addition, neurons in the arcuate nucleus that coexpress kisspeptin, neurokinin B, and dynorphin (termed KNDy neurons) are also involved in the metabolic control of puberty. Our studies in the bovine female demonstrate that increased planes of nutrition during juvenile development lead to organizational and functional changes in hypothalamic pathways comprising NPY, proopiomelanocortin (POMC, the precursor of αMSH), and kisspeptin neurons. Changes include alterations in the abundance of *NPY*, *POMC*, and *Kiss1* mRNA and in plasticity of the neuronal projections to GnRH neurons. Our studies also indicate that epigenetic mechanisms, such as modifications in the DNA methylation pattern, are involved in this process. Finally, our most recent data demonstrate that maternal nutrition during gestation can also induce morphological and functional changes in the hypothalamic NPY system in the heifer offspring that are likely to persist long after birth. These organizational changes occurring during fetal development have the potential to not only impact puberty but also influence reproductive performance throughout adulthood in the bovine female.

1. Introduction

Puberty is a complex maturational and biological event in the female mammal that involves physical and behavioral modifications associated with activation of the

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https://doi.org/10.1016/j.domaniend.2020.106434

hypothalamic-pituitary-ovarian axis and subsequent establishment of reproductive cyclicity [1]. Pubertal maturation is initiated largely at the hypothalamic level by the increased activation of neurons secreting GnRH. The increase in pulsatile release of GnRH and subsequent rise in LH pulse frequency support the final development of ovarian follicles and steroidogenesis required for first ovulation [2]. Pubertal maturation is controlled largely by genetics and environmental factors, among which nutrition plays a pivotal role. Epidemiological data in humans and research findings in several animal models unequivocally demonstrate that increased nutrient intake during early development (infantile and juvenile) advances puberty in females [2,3].

The timing of puberty onset has important implications for livestock production, particularly for the beef cattle industry. Beef production in almost all situations is seasonal in nature to coordinate feed resources with the nutrient requirements of the dam. Regardless of the time of the breeding season, the seasonal nature of beef production exacerbates the resultant loss in efficiency if puberty does not occur at the appropriate age. Lifetime productivity of beef heifers is largely dependent on their ability to reach reproductive maturation, to conceive early during their first breeding season, and to calve for the first time by approximately 24 mo of age [4]. In addition, the incidence of multiple estrous cycles before targeted breeding positively influences yearling fertility [5]. However, a significant proportion of heifers within existing beef production systems fail to reach the developmental end points necessary to facilitate early puberty (puberty before 14 mo of age) [6]. This is particularly true for later-maturing breeds (eg, *Bos indicus*-influenced) in which the skeletal size required to support a healthy and safe pregnancy is often attained well before puberty. Therefore, a better understanding of the neuroendocrine mechanisms underlying puberty can assist in the development of novel managerial strategies that exploit brain plasticity during critical windows of development to successfully program early puberty in heifers.

In addition to generating translational information to the livestock industry, the use of the bovine female as an animal model to study the effects of nutrition on neuroendocrine function also has the potential to generate fundamental knowledge with human biomedical relevance. Large animal models, such as sheep and cattle, have made significant contributions to a better understanding of several reproductive processes in humans [7]. Some benefits of using the bovine for neuroendocrine and reproductive research include the following attributes: 1) The bovine female is a non–litter-bearing species that is amenable to different surgical and experimental procedures. 2) The large body size allows for detailed and repetitive hormonal profiling and measurement of hypothalamic secretion of neuropeptides via cannulation of the third ventricle of the brain. 3) Bovidae are domesticated, can be maintained most of the time in a natural environment, and thus are less likely to be subjected to the stress of extreme confinement. 4) Cattle are a precocial species with a gestation length similar to humans; therefore, the trajectory of development of several organs systems, such as the brain and ovary, follows a similar pattern as that of humans [8].

The objectives of this review are to present an overview of the neuroendocrine mechanisms controlling puberty in heifers, discuss the effects of nutrition on pubertal development, and summarize recent research findings regarding the programming effects of nutrition during gestation and early postnatal life on hypothalamic pathways that control puberty. Although this review focuses primarily on the bovine female, supporting data from other species, including sheep and rodents, are also discussed.

2. Neuroendocrine control of puberty

2.1. Prepubertal pattern of LH secretion

In the heifer, as well as other female mammals, the final developmental process underlying the attainment of sexual maturation lies within the hypothalamus [1,2,9]. Thus, low-frequency release of GnRH into the hypothalamic-pituitary portal system during prepuberty is ultimately transformed into a high-frequency pattern of release as sexual maturation progresses. A corresponding acceleration in the secretion of LH from pituitary gonadotropes follows and permits the final maturation of ovarian follicles and first ovulation [10,11]. The peripubertal increase in frequency of LH pulses is not observed in the heifer until approximately 50 d before pubertal onset; therefore, LH secretion patterns cannot be used to reliably predict the timing of puberty before this period [12]. Importantly, inadequate stores of LH in the anterior pituitary do not contribute to the prepubertal state. In ruminants, a very low frequency pattern of GnRH release is sufficient to stimulate LHβ synthesis by gonadotropes and induce normal pituitary stores of LH during prepuberty [13] as well as other states of infertility (eg, postpartum anestrus). Although the secretion of FSH is also controlled by hypothalamic GnRH release, FSH is not a limiting factor in pubertal attainment [13]. Moreover, its temporal secretion after puberty is modulated to a much greater degree by circulating concentrations of estradiol-17β and the ovarian peptides, inhibin and activin, than by GnRH [14,15].

The role of GnRH as the master controller of reproduction became dogma nearly 50 yr ago when it was identified as the sole neuropeptide controlling both LH and FSH release [16]. However, the observation that LH is released in an episodic or pulsatile manner was first discovered serendipitously in the female monkey by Knobil and colleagues [17]. It was soon determined that this episodic pattern of release was a direct result of the synchronous depolarization of GnRH neurons [18] and characterized by volleys of multiunit electrical activity in the medial basal hypothalamus [19–22]. The phenomenon of synchronous firing of hypothalamic GnRH neurons has been referred to historically as the GnRH pulse generator [23,24] but, until recently, has remained a “black box” mechanistically. This began to change in the early 2000s following the discovery of kisspeptin. Characterization of loss-of-function mutations in a variant of the GPR54 receptor, now termed Kiss1R, in humans and mice [25,26], followed by characterization of its ligand, kisspeptin, brought about a new understanding of how GnRH neurons are controlled [27–29]. Disruption of the kisspeptin signaling network

results in disruption of the GnRH secretory process and failure to attain puberty [25–27]. Correspondingly, intracerebral administration of kisspeptin accelerates the onset of ovulation in prepubertal rats [30] and ewe lambs [31]. Although most of the work characterizing this complex signaling network has not been accomplished in cattle, a significant contribution to our understanding has come from another ruminant, the ewe [31–34]. Systematic descriptions of the location and architecture of kisspeptin neurons have now been reported, including the identification of a subset within the arcuate nucleus (ARC) that colocalizes 3 peptides, kisspeptin, neurokinin B (NKB), and dynorphin (termed KNDy neurons) [35]. These neurons also coexpress receptors for NKB and dynorphin [32]; however, they do not contain kisspeptin receptors [35]. The KNDy neurons secrete kisspeptin in response to their own release of NKB, which results in kisspeptin release at two locations: GnRH cell bodies and their terminals in the median eminence of the hypothalamus [35–38]. This sequence initiates the synchronous release of GnRH. In turn, the activation of KNDy neurons causes the release of dynorphin, which inhibits KNDy neuron activity. The repeating cascade of this locally controlled cycle provides, for the first time, a plausible explanation for the so-called GnRH pulse generator [39]. In the ewe, there are other kisspeptin neurons in the preoptic area (area immediately rostral to the hypothalamus) that do not coexpress NKB or dynorphin [40]. However, similar to KNDy neurons, they do contain estrogen receptor-α (ER-α) [41]. Estradiol suppresses *Kiss1* transcript abundance in the ARC but positively modulates kisspeptin neurons in the preoptic area [41,42]. Knockout of *ESR1* (gene encoding for ER-α) in all kisspeptin-expressing neurons advances the onset of puberty in mice, supporting the contention that estradiol inherently restrains GnRH/LH secretion, ovarian function, and pubertal onset through ER-α [42,43].

2.2. Neuroendocrine escape from estradiol negative feedback

The interrelationship between ER-α and kisspeptin neurons provides a potential basis through which changes in negative feedback sensitivity to estradiol could regulate the timing of puberty. During the juvenile period, a gonad-dependent suppression of LH develops due to an increase in sensitivity to the negative feedback effects of estradiol [10,12,44]. In many species, particularly cattle and sheep, a clear decrease in estradiol-negative feedback sensitivity during the late juvenile period heralds the onset of puberty [11,12]. Experimentally, the efficiency of estradiol in reducing the number of LH pulses decreases with age in ovariectomized heifers [45]. This effect serves as the basis for the transition to a high-frequency pattern of GnRH/LH release at pubertal onset (Fig. 1). However, Bedenbaugh et al [46], using the ewe as a model, found that the increase in LH pulsatility in prepubertal, ovariectomized (OVX)-estradiol-replaced ewe lambs was associated with an increase, rather than a decrease, in *ESR1* mRNA abundance in kisspeptin neurons in the ARC. This occurred despite the observation that the number of kisspeptin neurons was reduced by estradiol. Similarly, the absence of estradiol replacement in OVX ewe lambs resulted in an increase in abundance of *ESR1* mRNA and percentage of kisspeptin

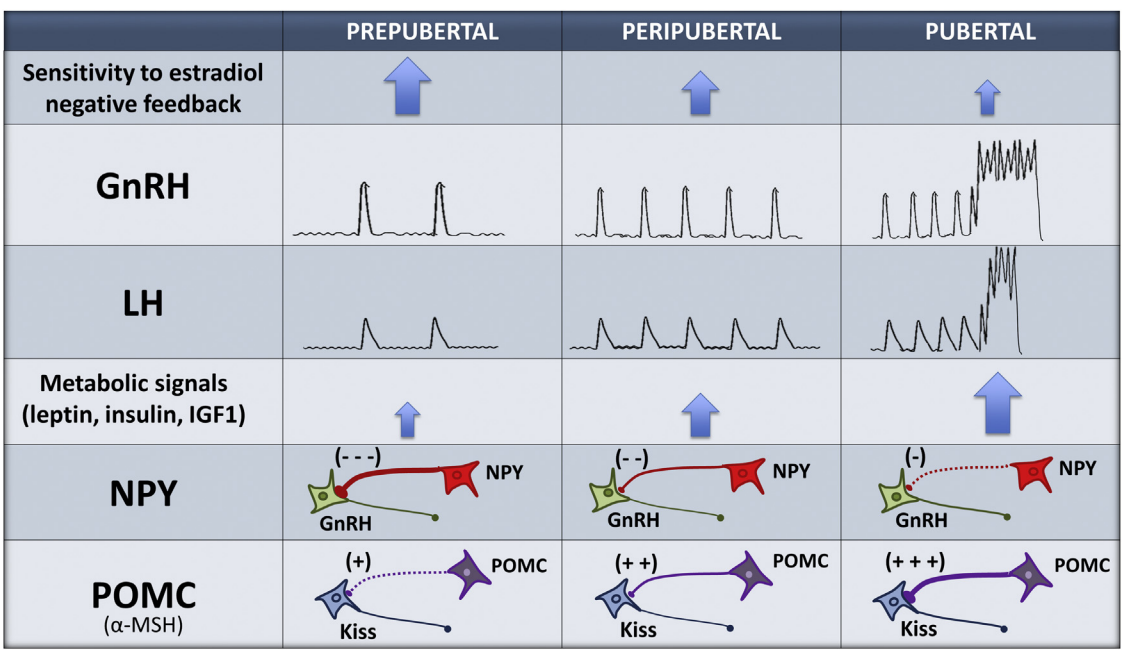

Fig. 1. Hormonal, metabolic, and neuroendocrine changes occurring during pubertal maturation in the bovine female. Increased rates of body weight gain result in elevated concentrations of metabolic signals, such as leptin, insulin, and IGF1, which in turn promote changes within the neuroendocrine system. These changes include a reduction in NPY inhibitory tone and increased POMC excitatory tone. Consequently, the sensitivity to the inhibitory effects of estradiol on GnRH secretion decreases, resulting in increased pulsatile secretion of GnRH and LH. This increased pulsatile secretion of LH is critical to support the final stages of follicular development and first ovulation. NPY, neuropeptide Y; POMC, proopiomelanocortin.

neurons containing ER-α protein in the ARC. These observations are contrary to expectations and thus failed to provide an explanation for the well-characterized pubertal escape from estradiol-negative feedback in ewe lambs and heifers.

The development and maturation of an estrogen-active preovulatory follicle results in increased circulating concentrations of estradiol that ultimately initiate a GnRH-mediated surge of LH. However, this separate positive feedback mechanism is functional well before puberty [44] and thus is not a limiting factor in final establishment of the pubertal state.

2.3. Metabolic signals regulating pubertal onset

The metabolic status of an individual is perceived by the central nervous system (CNS) through a variety of signals, including several that circulate in the bloodstream. These metabolic signals can modulate the secretion of both GnRH and LH, either directly or indirectly [47]. Insulin, insulin-like growth factor-1 (IGF1), leptin, and ghrelin are metabolic hormones that have significant effects on the timing of puberty [47,48]. For example, both insulin and IGF1 respond to increasing planes of nutrition and serve as positive modulators of neuroendocrine signaling pathways in the hypothalamus that promote secretion of GnRH [47,48]. Correspondingly, dietary energy restriction delays onset of puberty [49–51]. Although concentrations of leptin and insulin are positively correlated with nutritional plane, ghrelin (produced primarily in the stomach) is secreted during fasting and chronic dietary energy restriction and may play a role in delaying pubertal onset [52].

Prepubertal females under a positive plane of nutrition generally exhibit increasing concentrations of insulin, IGF1, and leptin as puberty approaches [53,54]. Leptin, first discovered and characterized in the mid-1990s, is synthesized primarily by adipocytes [55]. In general, increased adiposity in developing prepubertal heifers and other female mammals is accompanied by increased concentrations of plasma leptin [53,54], which plays a permissive role in the establishment of puberty [9,56]. Genetic mutations that eliminate leptin production or synthesis of its receptor result in the failure to attain puberty and lifelong sterility [57]. If leptin is replaced in leptin-deficient obese female mice, fertility is restored [58]. Frisch [59] first proposed the idea that a critical amount of fat is necessary for adequate fertility in humans. Significant declines in adipose tissue reserves result in aberrant effects on ovarian cycles in female mammals, and this persists until fat reserves are restored to some minimum level. Because reproduction ceases well before starvation, mechanisms that signal negative energy balance to hypothalamic centers controlling reproduction must be operable. In the ruminant, the stimulatory effects of leptin on secretion of both GnRH and LH are restricted primarily to periods of nutritional stress [60–62]. These effects have been demonstrated to occur through direct actions at both hypothalamic and pituitary levels [62,63]. Effects at the hypothalamic level may influence the secretion of GnRH by changing the sensitivity of the reproductive neuroendocrine axis to estradiol [2,10,12,13]. Because GnRH neurons do not express the leptin receptor [64] or ER-α [65], other hypothalamic signaling pathways mediate the effects of a changing leptin environment in ruminants. These include neuropeptide Y (NPY) [66–68] and proopiomelanocortin (POMC) [69] neurons that project to and modulate GnRH neuronal activity (Fig. 1).

2.4. Neuroendocrine pathways mediating the metabolic control of puberty

Metabolic hormones, such as leptin, insulin, and IGF1, influence the functioning of hypothalamic neurons and other cellular components, controlling the secretion of neuropeptides that regulate feed intake, energy expenditure, and GnRH secretion [70]. The ARC is a hypothalamic area particularly sensitive to metabolic signals and is therefore a main region of integration of hormones and other metabolic cues with adjacent hypothalamic nuclei, as well as with other regions of the CNS [71].

Two neuronal populations in the ARC are key intermediators of leptin and other metabolic cues signaling to GnRH neurons: POMC and agouti-related peptide (AgRP)/NPY neurons [72]. Transcription of *POMC* is positively regulated by leptin [73] and results in production of the anorexigenic peptide alpha-melanocyte-stimulating hormone (α-MSH). Gonadotropin-releasing hormone neurons can be directly excited by α-MSH via activation of the melanocortin receptor MC4R [74], which is antagonized by AgRP [75]. The orexigenic peptides AgRP and NPY are produced under conditions of low leptin signaling, fasting, or undernutrition [76]. Neuropeptide Y has been shown to inhibit GnRH secretion in several female mammals, including the cow [66]. Recent observations showing that the absence of leptin receptors exclusively in AgRP-expressing neurons delays age at first estrus in mice [77] highlight the importance of leptin signaling within the NPY/AgRP population during pubertal maturation. Moreover, modulation of melanocortin signaling via ablation of AgRP or heterozygosity of MC4R completely restored pubertal development and fertility in leptin receptor–deficient mice. This demonstrates the importance of the melanocortin system in mediating leptin's regulation of GnRH secretion and puberty [78].

Kisspeptin, which as discussed earlier directly regulates secretion of GnRH, is also involved in the metabolic control of reproductive function. Transcription of the gene that encodes kisspeptin, *Kiss1*, is regulated by leptin; hypoleptinemia reduces hypothalamic *Kiss1* mRNA in rodents, and administration of leptin prevents the fasting-induced decrease in *Kiss1* mRNA abundance [79,80]. At least a subset of kisspeptin neurons in mice [79] and sheep [81] contains the leptin receptor, indicating that leptin may directly influence kisspeptin production and release. Indeed, leptin was demonstrated to directly depolarize kisspeptin neurons from guinea pigs [82]. However, in mice, it has been proposed that the action of leptin in facilitating the onset of puberty may not require direct actions of leptin on kisspeptin neurons but may involve interneurons located in the ventral premammillary nucleus [83]. Similarly, observations in ewes and female rats indicate that the main effects of leptin on kisspeptin neuronal

activity involve intermediate neuronal groups, which likely include NPY [81] and POMC neurons [84,85].

3. Postnatal nutritional regulation of puberty

3.1. Nutritional acceleration of puberty in heifers

The influence of nutritional status during early postnatal development on reproductive maturation is well known in cattle [5,53,86]. Previous studies conducted by our group [51,54,68] and others [87] have shown that increasing nutrient intake during juvenile development can markedly advance puberty in heifers. In studies carried out by Gasser et al [87], most heifers weaned at approximately 3 mo of age and fed high-concentrate diets to achieve high rates of body weight gain attained puberty before 300 d of age (precocious puberty). Although those studies were performed in *Bos taurus* breeds of cattle (Angus and Hereford), similar findings were observed in our studies using *B indicus*–influenced heifers, which are later maturing (Angus heifers typically reach puberty around 12 mo of age, whereas *B indicus*–influenced heifers reach puberty between 14 and 18 mo of age). In our studies, heifers were weaned between 3.5 and 4 mo of age and fed a high-concentrate diet to promote a rate of body weight gain of approximately 1 kg/d [51,68]. This dietary regimen significantly advanced puberty, with a high percentage (~85%) of heifers reaching puberty before 12 mo of age compared to <20% for heifers gaining only 0.5 kg/d during the same period.

To identify the developmental periods in which heifers are most sensitive to the nutritional programming of early puberty, we used a stair-step nutritional regimen involving alternate periods of feed restriction and re-feeding. Importantly, we found that heifers that gained body weight at high rates between 4 and 6.5 mo of age and were subsequently subjected to a marked feed restriction between 6.5 and 9 mo of age, still attained early puberty (puberty <12 mo of age) at rates comparable to heifers fed a high-concentrate diet continuously [51]. Similarly, *B taurus* heifers that were fed to gain body weight at high rates between 126 and 196 d of age exhibited a high incidence of precocious puberty [87]. However, puberty was not advanced to the same extent when heifers were fed a similar diet later during juvenile development. Collectively, these results indicate that during early development, plausibly between 4 and 9 mo of age, heifers are more sensitive to the programming effects of nutrition in advancing puberty.

3.2. Metabolic and neuroendocrine mechanisms

In the bovine female, nutritional regimens that promote high rates of body weight gain (1 kg/d) are accompanied by greater adiposity and increased circulating concentrations of the metabolic hormones leptin, insulin, and IGF1 when compared to heifers gaining 0.5 kg/d of body weight [51,67,88]. These metabolic changes induced by increased rates of body weight gain promote modifications in the reproductive neuroendocrine axis, which ultimately result in increased pulsatile release of GnRH and LH. Utilizing prepubertal heifers subjected to third cerebral ventricle cannulation, we observed that pulse frequency of GnRH (cerebrospinal fluid) and LH (jugular blood) was indeed higher in heifers gaining 1 kg/d when compared to heifers gaining 0.5 kg/d between 4 and 8 mo of age [68].

The cellular and molecular mechanisms underlying the effects of metabolic signals on GnRH secretion involve multiple hypothalamic pathways and neuropeptides. Increased body weight gain during juvenile development reduced *AgRP* [88] and *NPY* [67,88] mRNA abundance in the ARC, decreased the concentrations of NPY in the cerebrospinal fluid collected from the third ventricle of the brain [68], and reduced the magnitude of NPY neuronal inputs to GnRH neurons [67]. In addition, increased rates of body weight gain increased the abundance of *POMC* mRNA and α-MSH (a product of the *POMC* gene) immunostaining in the ARC [69]. An increased number of α-MSH immunopositive contacts on kisspeptin neurons and a greater percentage of kisspeptin neurons innervated by α-MSH fibers were also observed in heifers gaining body weight at a high rate [69]. Collectively, these observations suggest that increased rates of body weight gain induce metabolic changes in prepubertal heifers, which in turn act in the hypothalamus to decrease NPY inhibitory tone and increase the POMC (via α-MSH) excitatory stimulus on kisspeptin and GnRH neurons, thus promoting the prepubertal increase in GnRH/LH pulsatile secretion.

Epigenetic mechanisms, such as DNA methylation, appear to play an important role in this process. Increased rates of body weight gain during juvenile development altered the DNA methylation pattern in the ARC of prepubertal heifers [89]. Among the genes that carried significant modifications in the methylation status was the gene encoding for growth hormone receptor (*GHR*), whose expression in the ARC is mostly abundant in NPY-containing neurons [90]. Heifers subjected to accelerated juvenile growth exhibited hypermethylation in *GHR*, which was associated with a decrease in *GHR* mRNA abundance in the ARC [89]. Therefore, the potential reduction in growth hormone signaling to NPY/AgRP neurons, through epigenetic-driven alterations of *GHR* transcript abundance, may be involved in programming early puberty in heifers. These observations corroborate the notion that epigenetic modifications are pivotal players in the process of early programming of metabolic and reproductive functions.

4. Prenatal nutritional regulation of puberty

Fetal programming, also known as developmental programming, is the concept that the prenatal period, a period in which organogenesis and tissue differentiation occur through tightly controlled and timed mechanisms, is a critical window of susceptibility for programming the offspring's phenotype [91]. Changes in the in utero environment during this critical developmental period can have lasting implications on postnatal growth and health of the offspring. Fetal programming effects have been demonstrated in multiple species and indicate that the time, length, and nature of the maternal insult/stimulus are important influences in physiological outcomes [92–94]. Specifically, calves that experienced nutritional insult

during the second and third trimesters of gestation are known to be highly susceptible to these adverse physiological outcomes [95].

From a neuroendocrine standpoint, studies in rodents have shown that maternal nutrition during gestation modulates hypothalamic pathways controlling GnRH release, thus programming puberty in the female offspring [96–98]. In cattle, however, the effects of prenatal nutrition on the offspring's neuroendocrine system remain virtually unexplored. Using a bovine model of prenatal undernutrition or overnutrition during the second and third trimesters of gestation, we have recently begun to explore the effects of prenatal nutrition on brain development and neuroendocrine function in female offspring (Fig. 2). Some of our initial findings are summarized in the following sections.

4.1. Leptin transport across the blood-brain barrier

Leptin is a key hormone conveying metabolic information to the CNS, and changes in nutritional status can modulate its transport across the blood-brain barrier [99]. In a study in which obese and lean adult sheep were fed to either gain or lose weight, it was reported that obese animals had impaired transport of leptin across the blood-brain barrier [99]. Moreover, the transport of peripherally administered leptin across the blood-brain barrier was not reversed after significant body weight loss in obese sheep. These findings and data generated in other animal models suggest that exposure of animals to a hyperleptinemic environment, such as that expected to occur in the fetus of a dam on a high nutritional plane, can result in irreversible physiological changes within the blood-brain barrier. Therefore, we postulated that offspring of dams with broadly varying degrees of nutrition during gestation may develop a leptin-resistant state due to structural alterations in the blood-brain barrier.

To test this premise, we investigated the transcript abundance of several leptin receptor isoforms in the choroid plexus of heifers subjected to different prenatal (thin, moderate, and obese) and postnatal (low and high) nutritional treatments. Notably, the transport of leptin across the blood-brain barrier depends on the expression of the different short isoforms of the leptin receptor, which act as leptin transporters in endothelial cells [100]. We found that prenatal nutrient restriction significantly reduced the mRNA abundance of the short form of the leptin receptor ObRc in the choroid plexus of prepubertal heifers, while no changes were observed for the ObRa isoform [101]. Furthermore, the mRNA abundance of total leptin receptor (ObRt) was also reduced in the choroid plexus of heifers subjected to prenatal undernutrition.

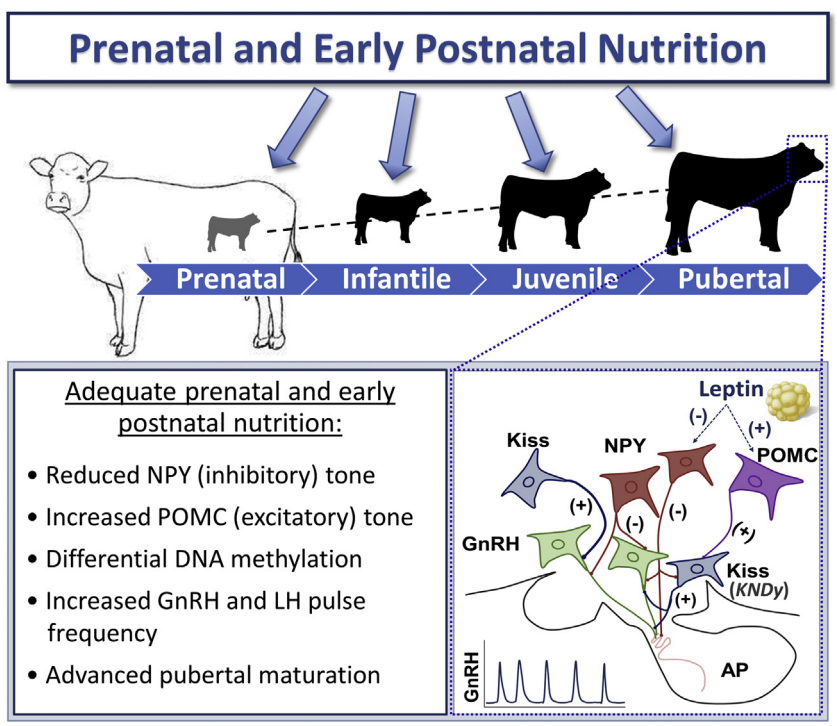

Fig. 2. Schematic diagram summarizing the effects of prenatal and early postnatal nutrition on the development of the neuroendocrine system in heifers. Changes in the nutritional and metabolic status occurring at any developmental period between fetal life and puberty can impact the development of hypothalamic pathways that control GnRH secretion and pubertal maturation. Adequate maternal nutrition during gestation in conjunction with elevated rates of body weight gain during early postnatal development results in several endocrine and neuroendocrine changes that promote early puberty. These include 1) increased circulating concentrations of leptin, insulin, and IGF1; 2) reduced *NPY* mRNA abundance and NPY (inhibitory) inputs to GnRH neurons; 3) increased *POMC* mRNA levels and α-MSH (excitatory) inputs to kisspeptin neurons; and 4) increased pulsatile secretion of GnRH and LH. NPY, neuropeptide Y; POMC, proopiomelanocortin.

Interestingly, postnatal nutrient restriction increased the mRNA levels of ObRb, the long isoform of the leptin receptor involved in leptin signaling, in the choroid plexus of heifers subjected to prenatal undernutrition. These results indicate that prenatal undernutrition modulates the transcript abundance of the different isoforms of the leptin receptor in the choroid plexus, potentially reducing leptin transport across the blood-brain barrier in prepubertal heifers. This premise is currently being investigated using the third ventricle cannulation model.

4.2. Neuropeptide Y pathway

Using the same experimental paradigm mentioned previously, we investigated the interactive effects of prenatal (restricted, moderate, and overnutrition) and postnatal nutrition (low and high) on the numbers of NPY (inhibitory) projections toward GnRH neurons. Although none of the treatment combinations altered the number of GnRH neurons, reduced postnatal nutrition increased the number of GnRH neurons in close apposition to NPY-containing projections [101]. Remarkably, these effects were significantly greater in heifers from nutritionally restricted dams, suggesting that prenatal undernutrition interacts with postnatal nutrition to modulate the extent of NPY neuronal inputs to GnRH neurons. Although the functional relevance of this finding remains to be fully explored, it is likely that the effects of prenatal undernutrition increasing NPY projections to GnRH neurons will inhibit GnRH pulsatile release and hinder the process of pubertal development in heifers. As discussed in the following section, some of our preliminary results support this premise.

4.3. Effects of maternal nutrition on pubertal development

Our preliminary results indicate that maternal nutrition during gestation interacts with early postnatal nutrition to program the age at puberty in heifers. Although the effects of postnatal nutrition were more significant than the maternal effects on age at puberty, heifers born from dams subjected to nutrient restriction were more sensitive to the deleterious effects of limited postnatal growth [102]. Heifers born from nutrient-restricted dams and subjected to limited postnatal growth reached puberty approximately 90 d later than heifers from overnourished cows that gained body weight at high rates postnatally [102]. In conjunction with our neuroanatomical studies, these observations suggest that prenatal undernutrition may result in functional changes within the neuroendocrine system that result in delayed puberty and may potentially impact subsequent reproductive function during adult life. The long-term repercussions of prenatal undernutrition on reproductive neuroendocrine function are currently under investigation.

Contrastingly, a previous study reported that maternal nutrient restriction during the second and third trimesters of gestation did not affect growth rates, age at puberty, or antral follicle counts in offspring heifers [95]. This discrepancy in results could be due to the fact that the level of nutrient restriction in the study by Cushman et al [95] was very moderate compared to our studies. In their study, restricted cows had a body condition score of 5.5 to 6 (scale from 1 to 9; 1: emaciated, 9: obese), whereas in our study, restricted cows had a body condition score of 3 to 3.5. Another possibility is that in their study *B taurus* heifers were used compared to *B indicus*–influenced heifers in our studies. Nevertheless, considering the importance of fetal programming to animal agriculture and the limited data available, additional studies in cattle are needed to determine the long-term effects of gestational undernutrition on the offspring and to elucidate the underlying mechanisms.

5. Summary and future directions

In summary, nutrition during gestation and early postnatal life can regulate the development of the neuroendocrine system and influence puberty in cattle and other mammalian species. Among the several metabolic signals that may be involved in this process, leptin plays a critical role in conveying metabolic information to the CNS and also exerts significant organizational effects modulating brain development. Neurons expressing NPY and POMC in the ARC are important components of the neurocircuitry controlling GnRH release and are targets for the organizational and activational effects of leptin. In addition, KNDy neurons in the ARC are a central component of the GnRH pulse generator and are also influenced by the programming effects of early nutrition. These organizational changes occurring during fetal and early postnatal development are likely to not only impact puberty but also influence reproductive performance throughout adulthood in the bovine female. We are currently investigating this hypothesis in a relatively large group of nutritionally programmed heifers. In the future, it will be important to determine the transgenerational effects of perinatal nutrition in cattle because findings in other animal models suggest that many phenotypic traits expressed in the F1 generation can be transmitted to subsequent generations (F2 and F3). Although these studies are difficult to perform in cattle due to the long generation interval, this information could have important implications for lifetime animal health and productivity.

CRediT authorship contribution statement

R.C. Cardoso: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **S.M. West:** Investigation, Writing - original draft, Writing - review & editing. **T.S. Maia:** Investigation, Writing - original draft, Writing - review & editing. **B.R.C. Alves:** Investigation, Writing - original draft, Writing - review & editing. **G.L. Williams:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Acknowledgments

This work was supported by Agriculture and Food Research Initiative Competitive Grants no. 2013-67015-20960 (GLW) and 2018-67015-27595 (RCC and GLW) from the USDA National Institute of Food and Agriculture.

The authors declare that there is no conflict of interest.

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