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Review: Early and late determinants of puberty in ruminants and the role of nutrition

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ABSTRACT

This article reviews the scientific literature on puberty with a focus on ruminants and draws inference, where appropriate, from recent findings in transgenic mouse models and human pathology. Early genetic determinants of puberty have been discovered in humans suffering from hypogonadotropic hypogonadism or central precocious puberty. Transgenic mouse models selected on the basis of the causative defective genes helped in discovering the cellular and molecular mechanisms involved. Most of the genes found are involved in the development of neuroendocrine networks during embryo development and early postnatal life. Notwithstanding that the development of neuroendocrine networks takes place early in puberty, a delay or acceleration in the development of Gonadotropin Releasing Hormone (**GnRH**) neurons has an impact on puberty onset inducing a delay or an advance, respectively. Among the genes discovered in humans and laboratory models, only a few of them displayed polymorphisms associated with advanced sexual maturity, but also marbling, growth traits and callipygian conformation. This could be related to the fact that rather than puberty onset, most research monitored sexual maturity. Sexual maturity occurs after puberty onset and involves factors regulating the maturation of gonads and in the expression of sexual behaviour. The association with growth and metabolic traits is not surprising since nutrition is the major environmental factor that will act on late genetic determinants of puberty onset. However, a recent hypothesis emerged suggesting that it is the postnatal activation of the GnRH neuronal network that induces the acceleration of growth and weight gain. Hence, nutritional factors need the activation of GnRH neurons first before acting on late genetic determinants. Moreover, nutritional factors can also affect the epigenetic landscape of parental gamete's genome with the consequence of specific methylation of genes involved in GnRH neuron development in the embryo. Season is another important regulator of puberty onset in seasonal small ruminants and appears to involve the same mechanisms that are involved in seasonal transition in adults. The social environment is also an underestimated factor affecting puberty onset in domestic ruminants, most research studies focused on olfactory cues, but the genetic basis has not heretofore been adequately tackled by the scientific community. Additionally, there is some evidence to suggest transgenerational effects exist, in that nutritional and social cues to which parents were exposed, could affect the epigenetic landscape of parental gametes resulting in the epigenetic regulation of early genetic determinants of puberty onset in their offspring.

Implications

This article reviews the scientific literature on puberty with a focus on ruminants. It highlights the role played by early and late genetic determinants involved during embryo development and during infancy and juvenile stages, respectively. Late determinants are mostly influenced by nutrition, season and social cues. The main message is that early determinants programme the timing of puberty by shaping the neuroendocrine networks controlling the reproductive axis and late determinants modulate this timing according to more or less favourable environmental cues.

Introduction

Puberty is an important physiological milestone in mammals. It involves the onset of reproductive function but also changes in metabolism, behaviour and cognition. While puberty is defined as the time of the first emission of gametes, the pubertal or sexual maturation process also concerns the gradual physiological

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modifications affecting the individual until first emission of gametes. For the sake of precision, we will refer to "puberty onset" as the time of the first emission of gametes, the "prepubertal period" as the period during which all of these physiological changes gradually occur, and the "timing of puberty" will refer to the mechanisms involved during the prepubertal period up to puberty onset.

Puberty onset is often expressed as an age. While the time of the first ovulation can be detected easily when females are carefully monitored, it is more difficult in males since spermatogenesis is a continuous process and it is necessary to continuously collect and assess semen in order to precisely establish the presence of an appreciable quantity of sperm. This involves the normal expression of mounting behaviour, intromission and ejaculation. It is impractical at farm level to follow each individual to determine the exact timing of puberty onset; typically, females are monitored for sexual receptivity, the primary sign of oestrus. However, oestrus behaviour can be observed in the absence of ovulation and, conversely, ovulation can occur without behavioural signs of oestrus. Moreover, the careful monitoring of puberty does not imply that the animals are fertile. Reproductive maturity is the age at which the animals exhibit good fertility *i.e.,* in males, sperm count in ejaculates is normal (see Brito et al., 2004), and in females, the odds for a successful pregnancy are optimal. Thus, "reproductive maturity" defines the period at which the animals display acceptable fertility according to their species and breed. Physiological mechanisms involved in puberty timing and reproductive maturity depend on different determinants.

In this review, after briefly presenting the main physiological changes occurring during the prepubertal period, we will discuss the role of early determinants and late environmental determinants of puberty onset.

Physiological changes – an endocrine revolution

In all mammals studied, the prepubertal changes affect different physiological functions. In primates, and especially in humans, the prepubertal period is associated with a sharp increase in the growth curve (see for a review Rogol et al., 2003). An acceleration of growth is also observed in non-primate mammals but to a lesser extent. Fat deposition also occurs and leads to a change in body mass index. In fact, in ruminants, it is rather common to use weight as an indicator of puberty onset rather than age (Kenny et al., 2018). These observations led to the theory of "the critical mass hypothesis ", stating that puberty onset will occur only at a given percentage of body fat composition, depending on the species, breed and environmental cues. A general rule can be drawn for all species studied; puberty onset occurs at approximately 60% of final BW. In cattle breeds characterised by a heavy mature weight, puberty onset is attained later than in breeds characterised by a shorter stature (Diskin & Kenny, 2014). It is a common practice to offer cattle a higher-energy diet during the prepubertal period to accelerate puberty onset and physical maturation (Kenny et al., 2018).

For normal reproductive function, the key endocrine event during the prepubertal period is the gradual increase in the secretion of gonadotropins: LH and FSH (Schally, 1970; Clarke et al., 1983; Alexander & Irvine, 1987). In primates, including humans, the rise in LH occurs in pulses of secretion the frequency of which increases firstly during the night, gradually extending to the diurnal period (Watanabe and Terasawa, 1989). LH and FSH are under the control of the neurohormone Gonadotropin Releasing Hormone (**GnRH**) which is released in capillaries located in the median eminence of the hypothalamus (Harris & Ruf, 1970). GnRH is then transported in the portal veins to a second capillary network located in the anterior pituitary (Szabó & Csányi, 1982) where gonadotroph cells release LH and FSH. GnRH is released in an episodic manner giving rise to pulses of secretion of LH. This pulsatile profile is due to the short duration of secretion associated with the rapid degradation of GnRH in the blood (half-life 2 minutes). Both LH and FSH are released in an episodic manner which is very clear from peripheral plasma LH but less evident for FSH. The peripheral plasma profile of FSH secretion does not appear to be pulsatile due to the elevated plasma half-life of the hormone that equilibrates plasma concentrations.

In ewes and heifers, the mid-pubertal period is characterised by an increase in LH pulse frequency (1–4 pulses/24 h to 15–20 pulses/24 h) associated with a decrease in LH pulse amplitude (8 ng/mL to <2 ng/mL) (Day et al., 1984; Claypool and Foster, 1990) (see Fig. 1).

It is commonly accepted that the timing of puberty is dependent on the activation of GnRH neurons and GnRH release. In species where GnRH can be monitored by canulating portal veins such as sheep: Clarke and Cummins, 1982, Levine et al., 1982: cattle: Yoshioka et al., 2001) or pituitary venous effluent in horse (Irvine and Alexander, 1994), GnRH secretion is always pulsatile in adult males and its frequency is rather stable (one pulse/hour approximately). In adult females, GnRH secretion is pulsatile during the follicular phase with an increasing frequency reaching its maximum at the end of the follicular phase. When oestradiol plasma concentration reaches a high level (preovulatory level), the oestradiol feedback becomes positive and drives the rise of GnRH basal secretion leading to the GnRH surge that will last several hours. The GnRH surge induces a similar increase in LH: the preovulatory surge that precedes ovulation (cow, ewes). During the luteal phase, GnRH is at its lowest concentration and pulse frequency: 1 pulse/6 hours. Thus, GnRH neuron activation appears to be the first step towards puberty onset. In fact, it is more accurate to say "the reactivation of GnRH neurons" since GnRH neurons are functional during the late foetal period and early postnatal life in altricial species such as humans, for which plasma gonadotropins are elevated up to six months after birth (Renault et al., 2020). Such activation of the gonadotropic axis has also been reported in other altricial species such as mice and rats and has been referred to as "minipuberty". In precocial species, such as the sheep, the hypothalamo-pituitary gonadotropic axis is activated at mid-pregnancy and inhibited before the end of pregnancy; therefore, LH and FSH concentrations are very low at birth in these species (Savoie et al., 1981).

Early determinants of puberty onset

One of the most important early determinants of puberty in mammals is the timing of GnRH neuron development during embryogenesis (Fig. 2). Since the discovery of the extracerebral origin of GnRH neurons (see Duittoz et al., 2022 for a review), there has been extensive work on the factors involved in GnRH neuron migration from the olfactory placode towards the hypothalamus. In sheep foetuses, GnRH expression is detected around day 26 of gestation; GnRH neurons start their nasal migration at day 30 of gestation along vomeronasal and terminal nerves towards the cribriform plate that they cross at day 35 of gestation. Then, the GnRH neurons follow terminal nerve fibres that terminate in the preoptic area and anterior hypothalamus, the final location of GnRH neurons around day 60 of gestation. GnRH neurons subsequently extend their axons towards the median eminence, where the neurohormone is released and carried to the pituitary by the hypothalamo-pituitary portal system. *In utero* serial blood sampling of sheep fœtuses at day 80 of gestation demonstrated a pulsatile LH profile with a frequency of one pulse per hour (Clark et al.,

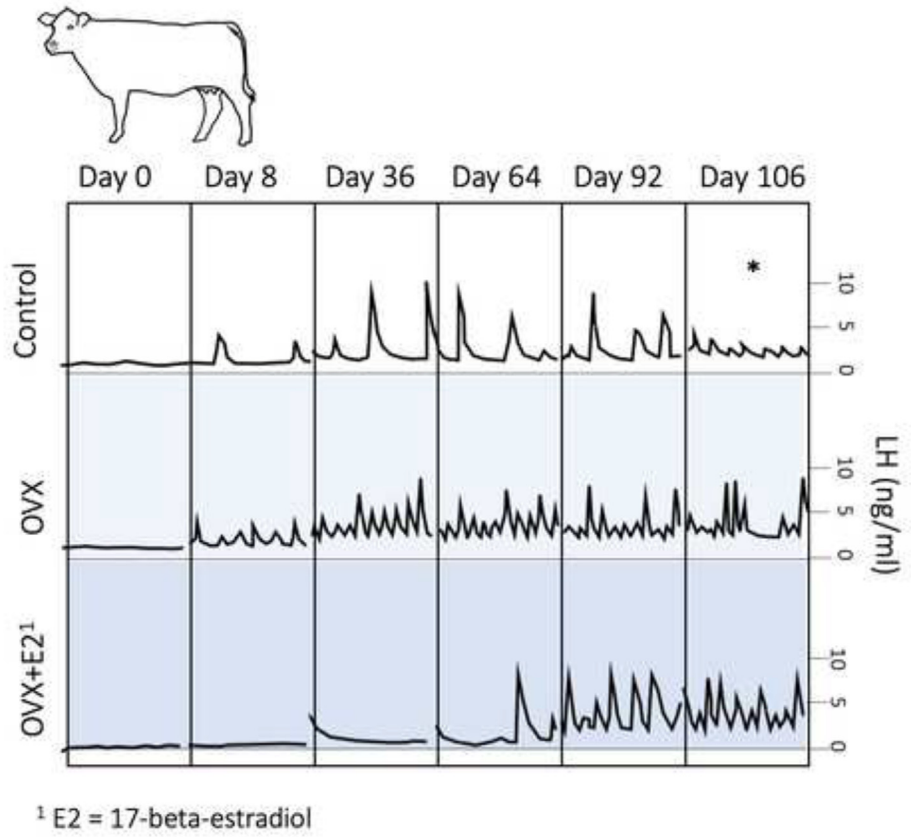

Fig. 1. LH pulsatility profiles in prepubertal heifers (source: Day et al., 1984). In the Control group, heifers reached puberty onset within 106 days. LH pulsatility started at day 8 with two pulses detected during the eight-hour period, and gradually increased in frequency and amplitude. At day 106, LH pulses were of low amplitude but high frequency, the signature of the proestrus stage of the first estrous cycle (*). In ovariectomised (OVX) heifers, there is no E2[1] negative feedback, an LH pulse was detected at day 36 and high amplitude high-frequency pulses were detected on day 92. Overall, LH secretion was higher in OVX heifers than in control heifers, confirming the gonadostat hypothesis is due to a high sensitivity to negative E2 feedback. In OVX heifers supplemented with estradiol implants (OVX + E2), LH pulsatility was detected at day 8 and gradually increased in frequency and amplitude with time. [1]E2 = 17-beta-estradiol.

1984). In contrast, at day 120 of gestation, LH concentrations were below the assay detection level. Taken together, these results demonstrated that the hypothalamic GnRH control of LH pulsatile secretion is functional early in development and that an inhibitory mechanism blocked GnRH secretion during the infancy period: the "gonadostat" hypothesis.

Work on human patients suffering from idiopathic hypogonadotropic hypogonadism (**IHH**) highlighted several genetic determinants involved in GnRH neurogenesis, GnRH neuronal migration and *GNRH* expression itself (see Table 1).

The high frequency of mutations in genes involved in GnRH neuron development found associated with early or delayed puberty in humans suggests that these early events play an important role (see Duittoz et al., 2022 for a review).

Could this be the case in ruminants? In human studies, the main bias is that only pathological phenotypes such as precocious puberty *i.e.* before 8 yo, or absence of puberty such in the case of IHH, are typically investigated. Therefore, determinants of GnRH neuron development may have been enriched since a defect in their expression will lead to a drastic phenotype. In ruminants, animals not exhibiting puberty onset are rapidly eliminated without any genetic enquiry and those with early puberty onset may be not detected. Nevertheless, several genes involved in GnRH neuron development have been found to be associated with puberty onset in ruminants. In mouse, the major gene *Cdh7,* which encodes a calcium-dependent cell–cell adhesion molecule, is involved in the neurogenesis of GnRH neurons. *CDH7* mutations are found in isolated/idiopathic hypogonadotropic hypogonadism (IHH) in humans (Kim and Layman, 2011) and have been reported to be hypermethylated in sheep with advanced puberty onset (Gross et al., 2020). In that study, the authors investigated the effect of a supplementation of paternal feed with the methyl donor methionine on sperm epigenetic marks and puberty in the F1 generation, interestingly highlighting the epigenetic control of early genetic determinants by parental nutrition. Another major gene, *Otx2*, a homeobox transcription factor, is involved in GnRH neuron neurogenesis in mice. In small ruminants, a binding site for Otx2 was found in the promotor region of *Kiss1* gene (Li et al., 2019). Indeed, Kiss1 and its receptor Kiss1R or GPR54 are major regulators of GnRH expression. They play a role early during the onset of GnRH expression in embryonic neurons but also during the prepubertal period by increasing GnRH expression at puberty. In addition, a recent RNA sequencing (**RNASeq**)-based analysis conducted on hypothalamic tissue of heifer calves offered either a high or moderate plane of nutrition during the first five months of life suggesting that the immune system, and interleukin 1 beta in particular, could play an important role in diet-dependent maturation process of the hypothalamus during the prepubertal period in cattle by regulating GnRH release (Sánchez et al., 2014).

Other early genetic determinants of GnRH neuron development in mice and humans have been associated with growth traits and muscle marbling in cattle, suggesting their involvement in metabolic pathways (*Nhlh2*: Brennan et al., 2006; *Gli3*: Huang et al., 2013). Additionally, the recent weighted gene co-expression network analysis conducted by Keogh and Kenny (2022), utilising RNASeq data from hypothalamic, pituitary, adipose and testicular

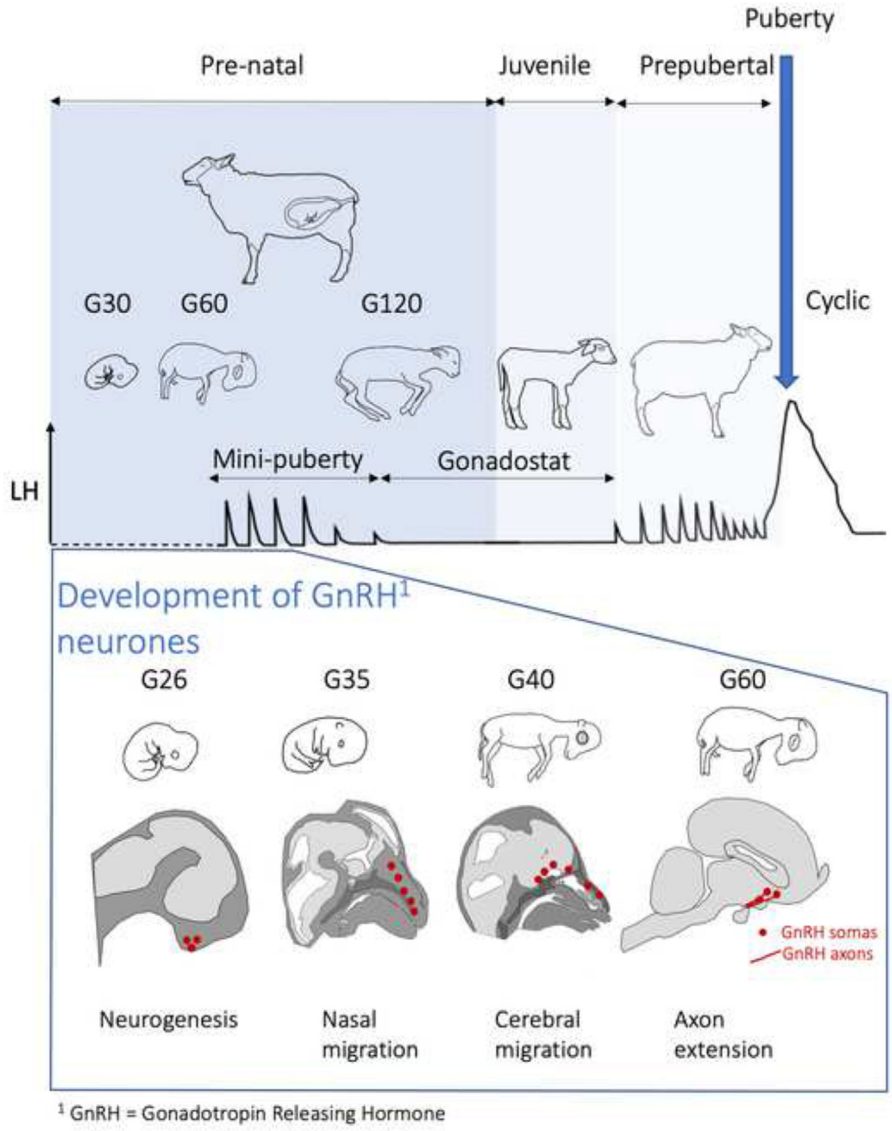

Fig. 2. LH secretion during prenatal, infancy and juvenile periods and the development of GnRH[1] neurons in sheep. In chronically catheterised ovine foetuses, Clark et al., (1984) demonstrated that the pulsatility of LH secretion was present at 79 days of gestation but not at 140, suggesting that the minipuberty phenomenon is a strictly prenatal event in this species. In the sheep, GnRH expression was detected in embryos at 26 days of gestation (G26). GnRH immunoreactive neurons were detected in the medial part of the olfactory anlage at 30 days of gestation (G30), suggesting the end of the neurogenesis of GnRH neurons. Nasal migration occurs between 30 and 35 days of gestation (G30-G35), GnRH neurons are located along the vomeronasal and terminal nerves between the vomeronasal organ and the cribriform plate of the ethmoid bone. At 40 days of gestation (G40), GnRH neurons have crossed the nasal-forebrain junction and entered the brain at 60 days of gestation (G60), most GnRH neurons are located at their final destination in the preoptic area and the anterior part of the hypothalamus and they send axonal projections towards the median eminence where GnRH is released. [1]GnRH = Gonadotropin Releasing Hormone.

tissue clearly provides evidence that GnRH signalling is responsive to prevailing metabolic status and is a key mediator of early sexual development in the bull calf.

In cattle, the heritability of age at puberty is moderate to high depending on breed, and rearing systems which suggests that the timing of puberty is likely to involve the contribution of multiple genes. These genes are located across several chromosomes and form an array or network regulating the timing of puberty. The polymorphisms in some of those genes may cause down- or up-regulation of certain transcripts, or affect the functionality of these transcripts and ultimately the proteins they code for (Vargas et al., 1998; Kenny et al., 2018). For example, IGF1 and IGF1-related genes (*IGF1R*, *IGFBP2*, *IGFBP4*) are associated with puberty onset traits in both male and female cattle (Lirón et al., 2012; Fortes et al., 2013; Kenny et al., 2018).

INSL3 encodes a major secretory product of testicular Leydig cells and is proving to be an excellent marker for Leydig cell differentiation and functional capacity during sexual development of cattle. For example, calves offered a high plane of nutrition, resulting in advanced sexual development in early life, displayed higher testicular expression of *INSL3* at 12 weeks of age compared with their contemporaries offered a more moderate diet (Coen et al., 2021). Furthermore, another recent study showed that a high plane of nutrition in the first 6 mo of life, but not later, increased systemic concentrations of INSL3 in young bulls (Anand-Ivell et al., 2019). Moreover, in that study, INSL3 concentration at 4 months of age correlated well (negatively) with the timing of puberty, as well as with testis size at 18 months of age (Anand-Ivell et al., 2019). In agreement, Sakase et al. (2018) found that blood INSL3 concentrations may be a robust and repeatable biomarker for

Table 1
Early determinants of the timing of puberty involved in Human and mouse and their involvement in puberty or growth traits in ruminants.

Genes	Impact on GnRH[1] neurones development	Reference Mouse model	Reference Human syndrome	Reference Ruminants
CDH7	Neurogenesis	Kim and Layman (2011)	IHH[2] + CHARGE[3] syndrome (Kim and Layman, 2011)	Increase in methylation and advance puberty in sheep (Gross et al., 2020)
NHLH2	Neurogenesis	Cogliati et al. (2007)	IHH and BW control (Topaloglu et al., 2022)	Nhlh2 close to a QTL[4] for marbling in cattle (Brennan et al., 2006)
OTX2	Neurogenesis	Diaczok et al. (2011)	Hypopituitary (Diaczok et al., 2011)	Binding site for Otx2 in the promoter of *Kiss1* gene in sheep (Li et al., 2019)
GLI3	Migration	Taroc et al., (2020)	Precocious puberty (Brauner et al., 2021)	Association with growth traits in cattle (Huang et al., 2013)
KISS/GPR54	GnRH Expression	de Roux et al., (2003)	IHH (de Roux et al., 2003)Precocious puberty (Teles et al., 2008)	Presence of a Kiss1-dependent binding element in the promoter region of GnRH in goat (Li et al., 2019)
DLK1	Not known	None	Precocious puberty (Dauber et al., 2016)	Callypige sheep (Charlier et al., 2001)

[1] GnRH = Gonadotropin Releasing Hormone.
[2] IHH = Idiopathic Gonadotropin Releasing Hormone.
[3] CHARGE = Coloboma, Heart defect, Atresia Choanae, Retarded Growth and development, Genital hypoplasia, Ear abnormalities/deafness.
[4] QTL = Quantitative Trait Loci.

determining total testicular volume and degree of sexual maturity in prepubertal bull calves.

Genome-wide association studies (**GWASs**) using microsatellites or single nucleotide polymorphism (**SNP**) markers have also been conducted to identify quantitative trait loci (**QTL**) regions associated with puberty onset traits. The X chromosome hosts 10 237 QTL related to puberty (see Shao et al., 2021 for a review). Among the genes found to be associated with age at puberty were genes associated with GnRH neuron activity: *KISS1*, *KISS1R*, *GNRHR*, *LEP*, *LEPR* and *NPY*. By studying two populations of Brahman (indicine) and Tropical composite (taurine), candidate genes and pathways common to both breeds were identified; the use of a regulatory impact factor metric allowed the identification of key transcription factors controlling the network expression (Fortes et al., 2011). These authors found an enrichment of genes involved in axon guidance, cell adhesion, ErbB signalling, and glutamate activity, pathways that are known to be involved in prepubertal GnRH neuron maturation and affect the pulsatile release of GnRH.

However, considering the multigenic basis of puberty onset, inference based on GWAS studies must be taken cautiously since these studies typically target specific breeds or crossbreeds with a limited number of animals employed. Moreover, the traits considered to define puberty onset may be related to other physiological regulations, for example age of sexual precocity (*i.e.* oestrous behaviour) or the age at first calving as a proxy for puberty (*i.e.* it encompasses the process of sexual maturity). In cattle, QTL associated with heifer and bull puberty onset contain only a few genes identified in humans. Whether this finding reflects the involvement of different gene networks or a different sampling approach requires clarification.

As mentioned earlier, the prepubertal period is associated with metabolic changes inducing fat deposition, and an acceleration of growth. There is an extensive literature on the role of nutrition, fat deposition and metabolic factors in the timing of puberty. However, a recent study in which neuropilin-1, the receptor of the guidance factor semaphorin 3A, was specifically deleted in GnRH neurons in mice yielded surprising results. As expected, the migration of GnRH neurons was increased and puberty onset was advanced but unexpectedly the females bearing the deletion had also an earlier prepubertal weight gain (Vanacker et al., 2020). These intriguing results suggest that the activity of postnatal GnRH neurons could also play a role in the metabolic control involved in energy metabolism and weight gain. Hence, early genetic determinants of GnRH neuron development and late environmental determinants are not independent and could exert combined effects. In their recent gene co-expression analysis, Keogh and Kenny (2022) reported a clear direct association between higher dietary intake in early life resulting in greater concentrations of insulin and IGF1 and subsequent enrichment of biochemical pathways related to GnRH release and signalling in bull calves.

Late determinants of puberty onset

The timing of puberty is a complex physiological mechanism not yet fully elucidated. It is one of the best examples of the interaction between genotype and environmental cues. From an evolutionary point of view, the reproductive success of a mammalian species relies on the successful renewal of generations. This requires (i) that the mother is sufficiently fit to sustain pregnancy and lactation (ii) that offspring birth occurs within a period of the year that will guarantee the new generation access to high-quality feed that will (iii) favour puberty onset to prepare to the new breeding season and the subsequent generation. Season, nutrition and social interactions are three major environmental factors involved in puberty onset (Fig. 3).

Season

Photoperiod is a strong regulator of the age at puberty in seasonal ruminants. For example, lambs born at the end of winter or early spring will reach puberty onset at the next breeding season in autumn six months later, whereas lambs born in autumn will reach puberty the next autumn twelve months later (Foster et al., 1986) (Fig. 4). An experiment performed on ovariectomised ewes supplemented or not with 17-beta oestradiol (**E2**) clearly demonstrated the existence of an increase in sensitivity to the negative E2 feedback (Legan et al., 1977). During the anoestrus period, LH pulsatility decreases, ovarian cyclicity ceases in females and spermatogenesis is less efficient, testosterone secretion is decreased in males causing the reduction of testicular volume. The neuroendocrine mechanisms involved in the seasonal control of reproduction have been well described in adult sheep. Briefly, in sheep, the neuroendocrine mechanisms of photoperiod action on reproduction are driven by pineal melatonin secretion in the cerebrospinal fluid (Legros et al., 2014) and its action on melatonin receptors located in the premammillary hypothalamus (Chemineau et al., 2010; Shabajee-Alibay et al., 2022) and in the *pars tuberalis* of the hypophysis (Dardente et al., 2014). Melatonin is the key factor that signals photoperiodic changes to the hypothalamus in seasonal mammals (Cipolla-Neto et al., 2018). We know

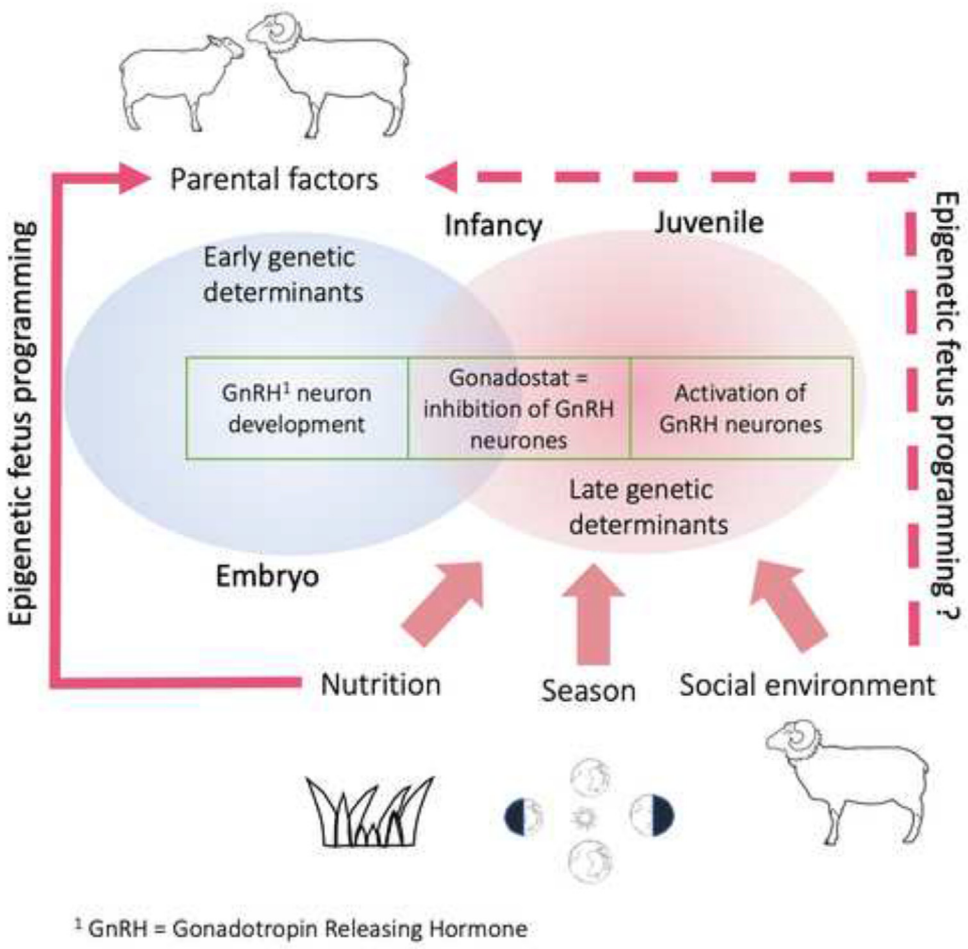

Fig. 3. Schematic representation of the time-dependant involvement of early and late determinants of the timing of puberty in sheep. Early genetic determinants shape the development of the neuroendocrine networks controlling the reproductive axis, late genetic determinants are involved in the reactivation of these neuroendocrine networks, either by inhibiting inhibitory inputs or by activating excitatory inputs.

that kisspeptin is a major controller of the transition, and during the anoestrus stage, *Kiss1* gene expression is decreased compared to the reproductive stage (see Smith and Clarke, 2010 for a review). However, the molecular and cellular mechanisms involved between melatonin action on its receptors and the activation of kisspeptin neurons are not known yet. In addition to Kisspeptin, the neurotransmitter dopamine plays a role in the transition and in maintaining the anoestrus stage (Goodman et al., 2012). The inhibitory peptide gonadotrophin-inhibiting hormone (**GnIH**) also known as RFRP3 has been shown to be involved in inhibiting GnRH neurons during anoestrus (Clarke et al., 2009); however, these results have not been confirmed in similar studies in sheep (Decourt et al., 2016). In lambs born in autumn, the delay in puberty onset is caused by a prolonged hypersensitivity to E2 negative feedback and probably involves the same neuroendocrine pathways as for anoestrus to reproductive season in adult animals (Smith and Clarke, 2010). Melatonin implants are employed in sheep breeding to overcome seasonal anoestrus but remained rarely used to advance puberty in lambs despite their efficacy (Pool et al., 2020).

Nutrition

Nutritional factors have been long known to play a major role in puberty onset. In humans, the age at menarche (first menstruation) displayed a gradual advance in industrialised populations and it is commonly accepted that this trend was linked with improvements in nutrition and health (Sørensen et al., 2012). However, since the 1960s, the trend has levelled off, suggesting that nutritional factors are efficient to advance puberty only when teenagers suffer from undernutrition. The critical fat mass hypothesis was laid in the late seventies by comparing historical data of age at puberty and weight from various industrialised countries (Baker 1985; Kiess et al., 2000). With the discovery of the fat-signalling hormone leptin (Zhang et al., 1994), there was a great expectancy to demonstrate that Leptin (encoded by *LEP*) was the messenger produced by the adipocytes that signals the metabolic state to the hypothalamus and allows or not the onset of puberty. Animals and humans deficient for *LEP* or its receptor *LEPR* do not undergo puberty are infertile (Chehab et al, 1996). In subjects with leptin signalling deficiency, chronic leptin administration triggered puberty onset and restored fertility (Farooqi et al., 2002). However, leptin administration to healthy rats did not advance puberty onset and in healthy humans did not rise LH concentrations (Cheung et al., 1997). In healthy ewes (Morrison et al., 2001) and cows (Amstalden et al., 2002), leptin did not affect LH secretion nor advance sexual maturity either. In fact, central administration of leptin increased LH secretion only in fasted cow and ewe, but not in control animals, suggesting that the metabolic state is crucial to regulate the hypothalamic response to leptin (see Barb and Kraeling, 2004 for a review). Other hormones or nutrients such as glucose, fatty acids, and aminoacids can regulate the activity of GnRH neurons in a direct or indirect manner. The neuroendocrine integrating centre is located in the arcuate nucleus of the

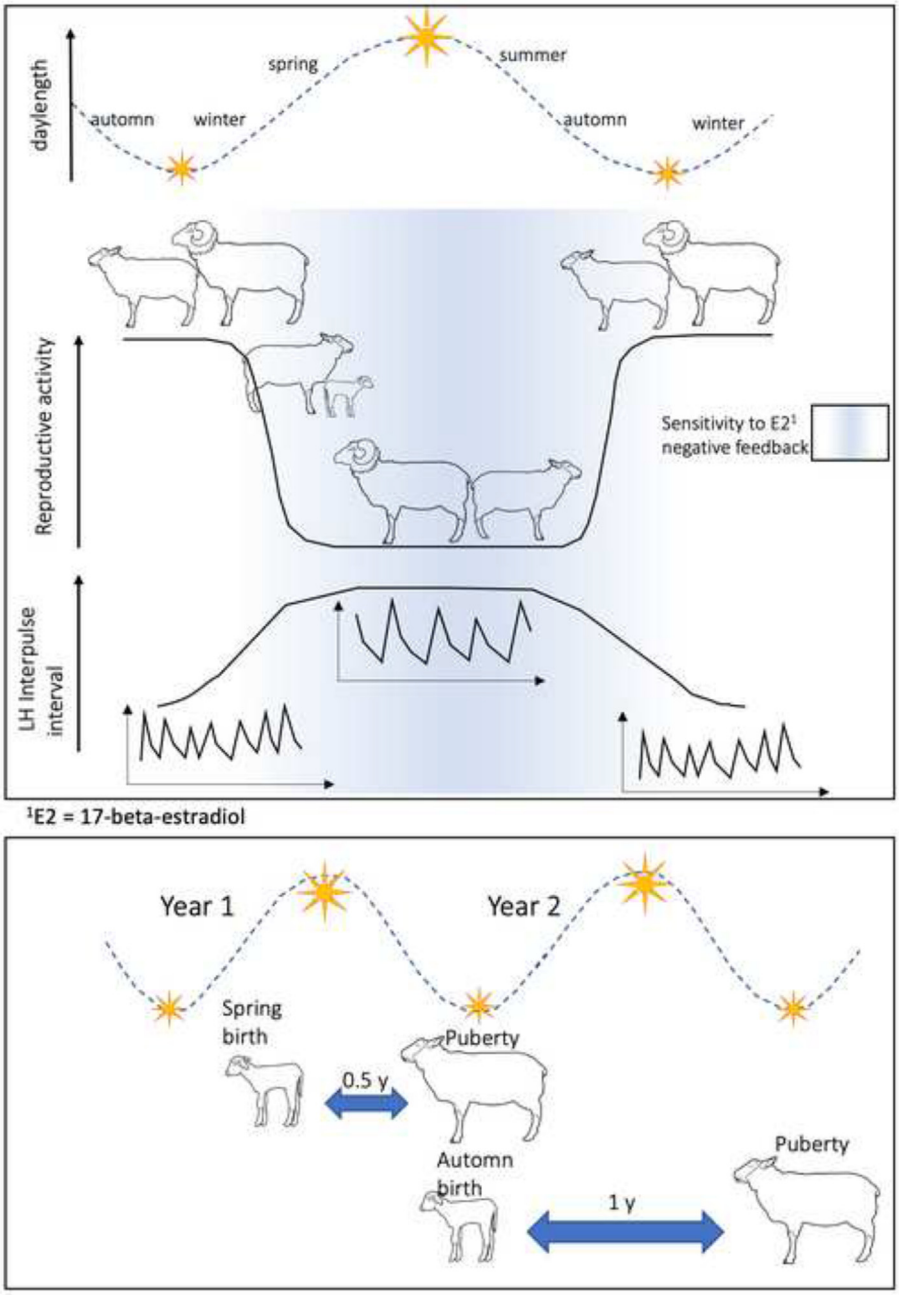

Fig. 4. Seasonal regulation of puberty onset in sheep. A. This schematic representation shows the link between day length across seasons, the reproductive activity, LH secretion in adult ram and ewe. B. This panel shows the one-year delay in puberty onset for lambs being born in autumn compared to lambs born in spring who will reach puberty the next autumn.

hypothalamus and involves neuropeptide Y, agouti-related protein, proopiomelanocortin and kisspeptin neurons and expresses *LEPR*. However, *LEPR* deletion in kisspeptin-expressing neurons did not disturb puberty onset or fertility in mice (Donato et al., 2011). Hence, leptin is not the metabolic gatekeeper of puberty but plays a permissive role in the metabolic gating of puberty onset. Besides the role of the fat mass, studies from Merino ewe lambs selected for muscle development showed a greater weight at puberty and an advance of puberty onset (Rosales Nieto et al., 2015) suggesting that muscle mass can also signal to the hypothalamus to allow puberty onset. Which mediator produced by myocytes is involved, remains unknown. The bone mass may also be a putative regulator of puberty onset. The role of uncarboxylated osteocalcin in male reproduction has been demonstrated in mice and suggests that uncarboxylated osteocalcin is indispensable for adequate testosterone production and spermatogenesis (Oury et al., 2011). The presence of uncarboxylated osteocalcin receptors GPRC6A and GPR158 within the brain including the hypothalamus, and in the pituitary suggests a possible role in the regulation of the activity of GnRH neurons (Shan et al., 2020).

The influence of pre- and postnatal nutrition on the ontogeny of sexual development in cattle has been reviewed by Kenny et al. (2018). In particular, there is now overwhelming evidence to support the importance of early-life nutrition in regulating the timing of puberty in both bulls and heifers. For both genders, there are significant indications that an improved metabolic status, early in calfhood, advances maturation of the hypothalamic–pituitary–gonadal axis, therefore facilitating earlier sexual development.

Although advancing sexual maturation is a desirable goal, it is important that any strategy used does not impinge upon normal gametogenesis or postpubertal fertility potential. Studies conducted to-date in both male (Byrne et al., 2018) and female cattle (Kelly et al., 2020) indicate that there is no evidence of a latent detrimental effect of early-life dietary enhancement on subsequent gamete quality or fertility (Kenny et al., 2018). Indeed, the findings of Perrier et al. (2020) demonstrate that while a high plane of nutrition during the first 6 months of life in bull calves induced modest latent modifications of the sperm methylome after puberty, this was likely more reflective of advanced puberty onset rather than the plane of nutrition *per se* and was not related to any measure of sperm viability or IVF-based embryo development.

Social cues

In seasonal mammals, the photoperiodic control of reproduction can be overcome by social interactions. Early work with mice and rats demonstrated that social interactions and female-female interactions could modify female reproduction: (a) oestrous synchronisation between females in the presence of a male, the 'Whitten effect (b) the inhibition of embryo implantation in the presence of a new male, the 'Bruce effect' and (c) the advance of puberty onset in the presence of a male, the 'Vandenbergh effect'. These effects have been described in various mammalian species; for example, in goats, prepubertal (3-month-old) alpine does exposed to sexually active males attained puberty 6 weeks earlier that prepubertal females that were not exposed (Chasles et al., 2018). In a seasonal species such as the sheep and goats, in the presence of sexually active males, anoestrus ewes recovered full cyclicity (Delgadillo et al., 2020). All these "male effects" on female reproductive status involve the transmission of olfactory signals to the medial amygdala via the main and accessory olfactory systems (Bergan et al., 2014). In addition to the biostimulatory effect of the male in inducing more precocious puberty in females, there is also evidence of an interactive effect with the prevailing metabolic status of the female (Diskin and Kenny, 2014). For example, the study of Roberson et al. (1991) showed that while exposure to a bull-induced puberty in heifers, the effect was accentuated in heifers achieving high compared with moderate rates of gain during the prepubertal period.

Conclusion

Early genetic determinants of puberty onset are well studied in humans for evident reasons. Most genes involved in pathology are related to the development of neuroendocrine networks such as GnRH neuronal network. In ruminants only, a few genes identified as major regulators of puberty onset in human and transgenic mouse models have been associated with sexual maturity in GWAS studies. Strikingly, some were found associated with growth and metabolic traits. It is not so surprising since major genes involved in pathological conditions in humans are associated with an absence or delayed puberty. If this condition occurred in domestic ruminants, they were generally eliminated. The link between early genetic determinant and growth and metabolic trait is not so surprising. Although late genetic determinant that respond to nutritional status are different genes, a recent study in the mouse suggested that the development of GnRH neuron itself could regulate peripheral adiposity, acting as a bridge between both reproductive and metabolic axes. Certainly, there is clear evidence that in ruminants, as with other mammals, prevailing nutrition and metabolic status during early development have both concurrent and latent effects on the ontogeny of sexual development of both males and females. Furthermore, research within sheep demonstrates the potential for modification to the epigenetic landscape of the parental gamete's genome leading to the epigenetic regulation of early genetic determinants of puberty onset in the offspring. In conclusion, there is a need for a better knowledge on the genetic architecture of sexual development in ruminants as well as the interaction of inherent and environmental influences such as nutrition and social cues on the epigenetic regulation of the parental genome and any latent consequences for the sexual maturation of their offspring.

Ethics approval

None.

Data and model availability statement

No data or models were produced in this article and thus not deposited in an official repository.

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Declaration of interest

None.

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Transparency Declaration

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