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Hypothalamic Integration of Nutrient Status and Reproduction in the Sheep

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Contents
Nutrient availability is a determinant of reproductive success. It is well known that inadequate nutrition results in reproductive failure due to a number of factors including delay of puberty or anoestrous in post-pubertal animals. The lack of nutrients is detected primarily by changes in circulating nutrient molecules and hormones and communicated directly or indirectly to the hypothalamus and brain stem for integration. The general effect is that low nutrition leads to increased appetite stimulation and reduced reproductive performance. When nutrition is adequate, the reverse is true. Both aspects will be the focus of this review. One result of the lack of nutrients is a reduction in luteinizing hormone (LH) concentrations and pulse frequency. Nutrient signals, such as glucose availability, hormonal signals, such as insulin and leptin, and neuroendocrine signals, such as neuropeptide Y and corticotropin-releasing hormone, have been clearly demonstrated to interact to produce changes in LH and reproductive success. Other signals, such as fatty acids, ghrelin, agouti-related peptide, melanin-concentrating hormone, orexin, melanocyte-stimulating hormone, kisspeptin, neurokinin, dynorphin and gonadotropin inhibitory hormone may also play a role in integrating nutrition and reproduction. This review will focus on the major features of the reciprocal control of appetite and reproduction in sheep.

Introduction

Inadequate nutrition results in delayed puberty or prolonged anoestrus primarily due to altered luteinizing hormone (LH) secretion resulting from altered secretion of gonadotropin-releasing hormone (GnRH; reviewed by Schillo 1992). The subsequent secretion of LH from the pituitary is governed by release of GnRH from the hypothalamus; each LH pulse is a direct reflection of a GnRH pulse released into the hypophyseal portal system (Clarke and Cummins 1985). Fasting and chronic food restriction in sheep decreases the secretion of LH, resulting in reproductive quiescence (Foster and Olster 1985; Kile et al. 1991). Reduced nutrition results in the suppression of pulsatile LH release and the cessation of gonadal activity in mammals (Foster and Olster 1985; Landefeld et al. 1989; Ebling et al. 1990; Kile et al. 1991). The reduced LH pulse frequency reflects the slower frequency of GnRH release that occurs with reduced nutrition (I'Anson et al. 2000). Subsequent refeeding restores pulsatile secretion of LH (Foster and Olster 1985). The question remains as to how these neuroendocrine changes are brought about, and to what degree appetite sensing and regulating systems might be involved in control of reproduction. Evidence garnered over the past forty years strongly suggests the neural circuitry residing in the hypothalamus possesses a functional duality when it comes to neuroendocrine control of reproduction and appetite, resulting in the same neural populations being privy to the reproductive status and metabolite milieu and in turn eliciting changes to maintain homeostasis.

A number of factors have been examined to determine how the brain perceives reduced nutrient intake, including metabolic fuels such as glucose and fatty acids or hormonal signals such as insulin and leptin. For example, fasted ewes displayed decreased plasma concentrations of insulin-like growth factor-I (IGF-I), insulin, leptin and LH (Kosior-Korzecka et al. 2006). By contrast, nutritional stimulation of LH in male sheep occurs in concert with increased cerebrospinal fluid (CSF) concentrations of insulin, glucose and some amino acids (Miller et al. 1998), and increased circulating concentrations of insulin and leptin (Zhang et al. 2004). LH pulse frequency correlated with CSF insulin concentrations in thin sheep fed *ad libitum* and CSF insulin and leptin concentrations in fat sheep fed 50% of maintenance requirements, suggesting regulation of LH by metabolic factors may be dependent upon nutritional history of the animal (Miller et al. 2007) and suggesting a strong link between nutritional status and reproductive success. Thus, this review will focus on the impact of peripheral metabolic signals fatty acids, glucose, insulin and leptin on the secretion of LH as well as the integration with hypothalamic factors driving a change in GnRH synthesis and release in sheep.

Fatty acids

Nutrient restriction sufficient to reduce reproductive performance is associated with elevated circulating concentrations of non-esterified free fatty acids (NEFA; Shevah et al. 1975). Refeeding of ovariectomized (OVX), hypogonadotropic, chronically feed-restricted ewes resulted in normalization of circulating concentrations of ketone bodies preceding restoration of LH (Szymanski et al. 2007). However, administration of NEFA to OVX ewes and ewe lambs did not alter circulating concentrations of LH although concentrations of GH were increased indicating a central response to NEFA (Sartin et al. 1988; Estienne et al. 1989, 1990).

Rams fed sodium acetate, sodium propionate and vegetable oil showed increased circulating concentrations of LH (Boukhliq and Martin 1997). Additionally, infusion of propionate into the mesenteric vein of feed-restricted ewes reduced feed intake (reviewed by Sartin et al. 2011) and increased the LH pulse frequency (Szymanski et al. 2011), although the effect was

transient and may have been the result of propionate meeting a portion of the energy needs of the ewes.

Insulin and glucose

Given the role of insulin in regulating glucose, studies examining the role of glucose in the regulation of LH have also examined the role of insulin. Administration of insulin-reduced plasma concentrations of LH in OVX ewes (Clarke et al. 1990) and intact and castrated rams (Adam et al. 1998; Kittok 1999), but administration of i.v. glucose prevented the effect of insulin treatment on LH, suggesting neuroglycopenia and not a direct action of insulin was responsible for the decreased LH (Clarke et al. 1990). Furthermore, peripheral and intracerebroventricular (ICV) administration of 2-deoxyglucose, a glucose antagonist, decreased LH pulse frequency in castrated males (Bucholtz et al. 1996) and peripheral administration of 2-deoxyglucose decreased concentrations of LH in OVX ewes (Funston et al. 1995). Additionally, administration of 2-deoxyglucose into both the lateral and 4th ventricle of OVX ewes suppressed LH pulse frequency (Ohkura et al. 2000). Thus, central glucose availability appears to be critical for LH secretion.

Acute, high-dose insulin reduces glucose availability and LH secretion, however chronic, lower dose insulin may also play a direct signalling role in the regulation of LH. Acute administration of insulin to feed-restricted, OVX ewes did not affect concentrations of LH (Hileman et al. 1993). However, feed-restricted, OVX ewes given ICV infusions of insulin or insulin and glucose, but not glucose alone for 2 days had increased concentrations of LH (Daniel et al. 2000). In castrated sheep with streptozotocin-induced diabetes, insulin supplementation increased LH pulse frequency (Bucholtz et al. 2000). Supporting a role of insulin stimulating LH via action in the central nervous system, peripheral administration of insulin to castrated sheep with streptozotocin-induced diabetes increased CSF concentrations of insulin, and ICV infusion of insulin for 5 days resulted in increased LH pulse frequency (Tanaka et al. 2000). In thin sheep, ICV infusion of insulin increased LH but not after the increased feed intake caused the sheep to become fat, and, alternatively, after fat sheep were feed-restricted to become thin, insulin increased LH (Miller et al. 2011). Thus, insulin appears to be important for hypothalamic stimulation of LH secretion, at least in thin sheep.

Leptin

Leptin mRNA, plasma concentrations and CSF concentrations increase with increased adiposity in sheep (Kumar et al. 1998; Blache et al. 2000; Delavaud et al. 2000; Ehrhardt et al. 2000). This relationship has led many to examine the effect of leptin on LH concentrations with varying, and conflicting, results. Leptin infused ICV, decreased LH pulse frequency in rams, possibly due to decreased feed intake (Blache et al. 2000). However, ICV infusion of leptin to well-fed or undernourished OVX ewes had no effect on LH (Henry et al. 1999; Morrison et al. 2001), and intravenous infusion of leptin did not affect circulating concentrations of LH in well-fed ewe lambs (Morrison et al. 2002).Yet, repeated subcutaneous administration of leptin prevented fasting-induced decreases in LH pulse frequency in castrated male sheep (Nagatani et al. 2000), and ICV infusion of leptin using a constant lower dose as opposed to an increasing dose used by Morrison et al. (2001) increased circulating concentrations of LH in feed-restricted, OVX ewes (Henry et al. 2001a). Additionally, ICV infusion of leptin attenuated the effect of a 72-hour fast on circulating concentrations of LH in OVX ewes and fasted lambs (Henry et al. 2004; Wojcik-Gladysz et al. 2009). Administration of leptin ICV also increased circulating concentrations of LH in oestradiol-implanted castrated sheep, but the response differed in a seasonally dependent manner (Miller et al. 2002). Thus, although it is unclear whether the cause of the differences in reported response is due to differences between sexes, dose/source of leptin or duration of administration, leptin appears to stimulate LH in nutritionally restricted sheep.

Although leptin has been shown to reduce the age of puberty onset in other mammals (Farooqi 2002; Apter 2003), it is unknown whether similar effects would be found in sheep. However, Rosales Nieto et al. (2013) report that leptin levels positively correlated with earlier puberty onset in ewe lambs. Yet, moderate food restriction did not delay puberty onset in lambs (Recabarren et al. 2004), suggesting that sheep may possess a relatively lower permissive threshold of circulating leptin levels than other animals. Indeed, more work is needed in this area.

Leptin receptors belong to the Class I cytokine family and occur in five different isoforms in the rodent that originated from alternative splicing (Lee et al. 1996). The long form of leptin receptor, which predominates in target tissues of the brain and hypothalamus, functions through two pathways: JAK2-STAT and MAPK (Baumann et al. 1996; Ghilardi et al. 1996; Bjøbaek et al. 1997; Ghilardi and Skoda 1997). To date, the only information regarding leptin receptor expression in the ewe hypothalamus is that of the long form, which is thought to be primarily involved in signal transduction. In the ewe, long form leptin receptors are expressed in the hypothalamus within the periventricular (Pe), paraventricular (PVN), supraoptic, dorsomedial hypothalamic (DMH), ventromedial hypothalamic (VMN) and arcuate (ARC) nuclei of sheep (Iqbal et al. 2001a). Specifically, leptin receptors are expressed in the same cell bodies that also contain neuropeptide Y (NPY), galanin, proopiomelanocortin (POMC), tyrosine hydroxylase, corticotropin-releasing hormone (CRH), melanin-concentrating hormone (MCH) and orexin, suggesting leptin has the ability in the sheep to control appetite, autonomic function, growth and reproduction. Interestingly, leptin receptors are not expressed on GnRH neurons, suggesting a second neural target by which leptin influences GnRH neurons. The evidence suggests that leptin creates a permissive signal to the brain allowing 'normal' reproductive output to commence or resume.

It is tempting to oversimplify and summarize that with adequate glucose availability, chronic, low doses of insulin and leptin stimulate LH secretion in sheep. However, the reality is much more complicated. Other peripheral factors may also play a role. Low doses of IGF-I stimulate LH in wethers with or without oestrogen treatment (Adam et al. 1998). Ghrelin-administered ICV decreased plasma concentrations of LH in OVX ewes (Iqbal et al. 2006), and in oestradiol-implanted castrated male sheep exposed to short days (Harrison et al. 2008). Photoperiod also altered the response of oestradiol-implanted, feed-restricted, castrated male sheep to glucose infusion such that LH pulse frequency and amplitude increased during long days but not short days (Archer et al. 2005). Additionally, sex and steroid environment is important in mediating the response as insulin-induced hypoglycaemia delayed an oestrogen-induced LH surge in OVX ewes (Medina et al. 1998), and peripheral insulin administration delayed the LH surge (Saifullizam et al. 2010). In summary, multiple factors are involved in the regulation of LH, with input of nutritional status primarily coming from glucose availability and insulin and leptin signalling. The role of glucose, insulin and leptin in the regulation of LH suggests factors controlling feeding act via the hypothalamus to play a role in regulating GnRH.

Interaction Between Feeding and Reproduction Control by the CNS

Nutrient molecules such as glucose, propionate and fatty acids combined with endocrine signals such as leptin, insulin and ghrelin communicate either directly to the central nervous system or indirectly via peripheral afferent nerves and ultimately integrate within the central nervous system (reviewed by Sartin et al. 2010, 2011) to regulate appetite regions of the hypothalamus. Appetite control is largely focused on the ARC, VMN, lateral hypothalamic area (LHA) with reciprocal connections to the brain stem with the nucleus tractus solitarius (NTS). The final output being regulation of feed consumption.

Neurons involved in food intake regulation can broadly be divided into those secreting orexigenic neuropeptides (e.g. NPY, agouti-related protein (AgRP), MCH or orexin) and anorexigenic neuropeptides, (e.g. products of POMC, cocaine- and amphetamine-related transcript or CRH) (Sartin et al. 2010, 2011). The majority of the neuronal systems secreting orexigenic and anorexigenic neuropeptides are produced in the ARC at the base of the mediobasal hypothalamus. Other brain areas involved in control of food intake are located primarily downstream of the ARC: including, the PVN, which produces anorexigenic peptides thyrotropin-releasing hormone (TRH), CRH and oxytocin, the lateral hypothalamus (LHA) and perifornical area (PFA), secreting the orexigenic substances orexin A (OXA) and MCH (reviewed by Sartin et al. 2010, 2011). We will focus on factors that have been shown experimentally to be involved in ovine feeding and reproduction and discuss potential players in need of further study.

Neuropeptide Y

No discussion of neuroendocrine control of reproduction and feeding could logically start anywhere other than NPY. NPY has long been shown to be a potent inducer of feed intake in a number of species, including sheep (reviewed by Sartin et al. 2010). Expressed in the ARC with pathways terminating in the DMH, VMN and Pe in sheep (Chaillou et al. 2002a; Polkowska et al. 2006), NPY is considered the primary orexigenic neuropeptide in most species. Fasting increases NPY gene and protein expression, and feeding has the opposite effects in sheep (McShane et al. 1992; Polkowska and Gladysz 2001), while NPY-injected ICV in sheep can increase feed intake (Miner et al. 1989). Interestingly, leptin and insulin receptors have been found in NPY soma and fibres in the rodent (Li et al. 1999; Williams et al. 1999), suggesting a mechanism for integrating peripheral nutrient signals to control appetite. The ICV administration of NPY increased plasma growth hormone concentrations and decreased plasma LH concentrations (Malven et al. 1992; McMahon et al. 1999; Morrison et al. 2003). NPY-delivered ICV decreased LH and stimulated food intake in normal to high fat animals but not thin or fasted sheep (Miller et al. 2011). Actions of NPY to reduce LH in the sheep act via NPY-Y2 receptors in contrast to feeding, which utilizes the Y1 receptor (Clarke et al. 2005).

In the sheep, a subset of NPY neurons project to the GnRH-rich preoptic area (POA), suggesting a direct connection between inhibitory NPY fibres and GnRH soma (Dufourny et al. 2005). The same NPY cell population express the long form of leptin receptor suggesting a short neural circuit whereby leptin levels communicate lipid energy stores onto NPY neurons of the ARC (Williams et al.1999). Thus, low leptin levels (i.e. low energy stores) increase NPY resulting in inhibition of GnRH and subsequently inhibition of LH release. However, in the sheep, this direct synaptic connection has yet to be demonstrated nor has the expression of the NPY receptor in GnRH neurons.

Agouti-related peptide

In fasting or low body condition sheep, concurrent with increased NPY expression (driving feeding behaviour and inhibiting GnRH release), there is a corresponding increase in AgRP (Henry et al. 2001b; Archer et al. 2004; Wagner et al. 2004). Moreover, ICV infusion of AgRP stimulates feed intake in the sheep (Wagner et al. 2004). A portion of AgRP neurons in the ARC colocalize with NPY, suggesting these neurons play a role in food intake (Sheppard et al. 2011). As a melanocortin receptor antagonist, AgRP may influence melanocortin stimulatory effects on reproduction (see MSH and orexin). However, with the few previously cited exceptions, the role of AgRP in feeding behaviour and reproduction in the sheep has been under researched.

Melanin-concentrating hormone

In the sheep, MCH immunoreactive perikarya have been localized ventromedially to the internal capsule

and in the dorsolateral hypothalamus (Tillet et al. 1996). The MCH neurons project to both the ARC and VMN (Qi et al. 2008). While leptin receptors are expressed on MCH neurons, neither leptin nor fasting altered MCH expression (Chaillou et al. 2003; Whitlock et al. 2005; Qi et al. 2010). However, Whitlock et al. (2005) demonstrated a potent effect of ICV-injected MCH to increase feed intake. MCH has been shown to directly inhibit GnRH neurons in mice (Wu et al. 2009).Yet, there is sparse evidence of MCH's role in reproductive regulation in ruminants. Although gonadotropin inhibitory hormone (GnIH) neurons have been shown to directly project to MCH neurons, inhibitory effects of MCH on LH have not been observed in sheep (Qi et al. 2009; Whitlock et al. unpublished data).

Orexin

Orexin perikarya are localized to the zona incerta (ZI) and LHA in sheep (Iqbal et al. 2001b) with its receptor localized to the ARC, median eminence, LHA and ventral portion of the POA (Zhang et al. 2005). These studies suggest orexin may participate in the integration of appetite, metabolism and endocrine responses. Indeed, leptin receptors are expressed in orexin neurons, and leptin injection will inhibit orexin cells in the arcuate nucleus (Qi et al. 2010). Moreover, ICV injection of orexin B was found to stimulate feed intake in sheep (Sartin et al. 2001). Because orexin neurons were found in close proximity to GnRH neurons, orexin was hypothesized to have an effect on reproductive regulation (Iqbal et al. 2001b). Orexin expression was found to be positively correlated with melanocortin agonist induction of LH during the luteal phase in ewes, suggesting a possible involvement in orexin in LH release (Backholer et al. 2009). However, ICV orexin B injections failed to change plasma LH in sheep (Sartin et al. 2001). It is unclear whether orexin A treatment would elicit a change in LH release in sheep, but it cannot be ruled out at this time.

Melanocyte-stimulating hormone

The primary role of MSH (a melanocortin product of the proopiomelanocortin gene) is to inhibit appetite, and the melanocortins increase LH and resume LH pulsatility in lean sheep. Although melanocortin neurons do not synapse directly to GnRH neurons, melanocortin agonists increase orexin gene expression and Kiss1 gene expression, which suggests a critical role for melanocortin neurons in communicating nutrient status to the GnRH system (Backholer et al. 2009). However, there is scant evidence for direct actions of MSH on reproduction and appetite control in sheep.

Corticotrophin-releasing hormone

Animals face many environmental stressors (e.g. predation, infection, lack of adequate food sources). These stressors vary greatly, therefore determining the mechanisms by which each affects the organisms is a daunting task; however, it is generally accepted that robust stress will lead to a reduction in reproductive output (Smith and Dobson 2002; Smith et al. 2003). Following this logic, several researchers have examined hypothalamic CRH as a point of focus in the stress-induced inhibition of GnRH. CRH expression in the hypothalamus is primarily in the PVN (Matthews and Challis 1995). CRH neurons do not directly contact GnRH soma but do project to the median eminence and ARC suggesting CRH is upstream of the ARC regulation of reproduction or can modulate GnRH release at the point of release (Rivalland et al. 2006; Ghuman et al. 2010). In stressed sheep, CRH expression is increased and this increase is accompanied by a decrease in GnRH secretion (Battaglia et al. 1998). ICV Infusion of CRH in the follicular phase will decrease LH secretion (Ciechanowska et al. 2011).

Dobson et al. (1999a,b) showed that stressed ewes display a reduction in LH release but the inhibitory effects varied depending on the hormonal status of the ewe and the time of year (Dobson et al. 1999a,b). However, there are other reports of a stimulatory role for central CRH on reproduction. Contrary to the hypothesized role of CRH as an inhibitor of reproductive activity, ICV treatment with CRH increased LH secretion in the ram (Caraty et al. 1997; Tilbrook et al. 1999). This action is likely via the CRH type 2 receptor, as urocortin, the endogenous ligand for the CRH type 2 receptor, stimulated LH concentrations and decreased feed intake in OVX ewes (Holmberg et al. 2001).

Chaillou et al. (2002b) reported that underfeeding ewes will increase the number of CRH immunoreactive neurons, without measurable changes to plasma cortisol levels, indicating that the rise of CRH due to food restriction was not released into the portal blood nor linked to the pituitary-adrenal axis activation (Chaillou et al. 2002b). This establishes a possible duality of CRH in (i) inhibition of reproduction when an animal encounters a stressor and (ii) possible stimulation of LH release when CRH levels rise centrally not due to global stress induction, but possibly due to modulation by metabolite status. Leptin has been reported to either increase (Clarke et al. 1993) or decrease (Evans 1999) CRH release from hypothalamic tissue in culture. Studies *in vivo* suggest that leptin increases PVN CRH expression and hypothalamic CRH content, and this increased CRH activation is secondary to POMC neurons in the ARC, which may additionally reduce appetite (Qi et al. 2010). Indeed, the disparate findings regarding CRH requires further investigation but the findings, to date, suggest the sheep may be unique in its integration of stress, reproduction and food intake.

Kisspeptin-neurokinin-dynorphin neurons

Kisspeptin (Kp) is a potent stimulator of reproduction. Some Kp cells in the ARC also coexpress neurokinin B (NKB; also known as tachykinin 2) and dynorphin (DYN) and have been termed 'KNDy' neurons (Foradori et al. 2006; Goodman et al. 2007; Cheng et al. 2010). The establishment of KNDy neurons as a critical mediator of the central control

of reproduction (reviewed by Lehman et al. 2010) in itself implicates this neural population as a possible site of nutritional-dependent regulation of reproduction in the sheep. KNDy neurons make reciprocal connections with NPY and POMC cells (Backholer et al. 2010). Kp treatment has been shown to produce reduced POMC and increased NPY gene expressions (Backholer et al. 2010) and Kp injections ICV increase plasma GH (Whitlock et al. 2010), which suggest a mechanism for regulating metabolism and/or appetite. While Backholer et al. (2010) reported that Kp cells in the preoptic area and ARC express the leptin receptor using single-cell laser capture and RT-PCR, Louis et al. (2011) failed to identify Kp cells immunoreactive for leptin receptor. Further work is needed to understand the interaction between KP, NPY and POMC *in vivo*.

Stimulation of the DYN receptor (Kappa opioid receptor) has been shown to increase food intake in sheep (Baile et al. 1987). Particularly, ICV infusion of dynorphin is highly effective in inducing feeding (Baile et al. 1987; Della-Fera et al. 1990). Della-Fera et al. (1990) demonstrated that ICV injection of DYN was able to block the satiety-inducing effects of rumen distension or increased intraruminal concentration of propionate. ARC DYN neurons are involved in progesterone negative feedback during the luteal phase of the ovarian cycle. Almost all of the DYN neurons of the KDNy cell population express progesterone receptors (Foradori et al. 2002). Progesterone treatment increases DYN expression, and during the luteal phase when progesterone levels are high, the kappa opioid receptor-specific antagonist Nor-Bin has been show to release the ewe from progesterone inhibition on GnRH/LH release (Foradori et al. 2002, 2005; Goodman et al. 2004). In addition, DYN neurons synapse with GnRH cells in the sheep POA (Foradori et al. 2002). These data suggest, in the sheep, DYN neurons are capable of responding to both changes in steroidal hormones and nutritional status and transferring that information directly to GnRH cells.

Neurokinin B is predominantly expressed in the ARC, and NKB signalling has emerged as a key player in the neuroendocrine regulation of reproduction (Goubillon et al. 2000). NKB has been implicated in the steroid feedback control of GnRH release (Rance et al. 2010). It has been recently discovered that human mutations in the gene encoding this peptide or its receptor, the neurokinin-3 receptor (NK3R or TACR3), result in a defect in the control of GnRH with subsequent hypogonadism. Administration of NK3R agonists has shown variable effects on LH secretion depending on the animal model and the steroid milieu. On the contrary, senktide (a NK3R agonist), injected ICV stimulated LH secretion in the ewe (Billings et al. 2010) and produced an increase in LH levels similar to those found in the preovulatory LH surge. Therefore, it seems that the effects of NKB may be species-dependent. There is very little known about NKB involvement in feeding, and no reports in sheep, however in the rat, MCH neurons have been shown to express the NK3R and produced an increase in the MCH mRNA expression in cultured hypothalamic slices (Cvetkovic et al. 2003).

Gonadotropin inhibitory hormone

This RF-amide-related peptide (RFRP) was discovered in birds and has been shown to have inhibitory control over GnRH (see Clarke 2011 for review). The RFRP genes are found in neurons of the DMH and Pe, with neurons terminating at the median eminence and in apposition to GnRH neurons, providing a pathway for release into the sheep portal blood (Smith et al. 2012) and terminate adjacent to GnRH neurons, providing a mechanism for control of reproduction. Intravenous injections of GnIH reduced LH in OVX sheep, and GnIH can inhibit GnRH-stimulated LH release *in vitro* (Sari et al. 2009). ICV infusion of GnIH-3, one of the peptides encoded by the RFRP gene, had no effect on reproduction, but it increased feeding in most species tested, including sheep (Clarke et al. 2012). Thus, increased feeding and decreased reproduction appear to be linked to this peptide. These studies suggest that GnIH may also serve as a component of a switch controlling reproduction and feeding.

Conclusions

Many of the factors discussed have primary roles and others may serve as modifiers of the control of reproduction in sheep (Table 1). And while overly simplistic, in times of decreased feeding, these nutrient and endocrine mechanisms interact at the hypothalamus to reduce reproduction and enhance feeding. Thus, nutrient reprioritization occurs in part at the expense of reproductive function as a survival mechanism. For example, reduced insulin occurs to spare glucose for

Table 1. Summary of reproduction and appetite regulators in sheep 928

Factor	Reproduction	Appetite
Fasting	–	+
Fed	+	–
Glucose	+	–
2-deoxyglucose	–	+
Insulin	+ in thin sheep NE in well-fed sheep	–
Non-esterified free fatty acids (NEFA)	NE	–
Leptin	+ in thin sheep NE in well-fed sheep	–
IGF-I	+	NE
Ghrelin	–	+
Neuropeptide Y (NPY)	–	+
Agouti-related peptide (AgRP)	?	+
Melanin-concentrating hormone (MCH)	NE/?	+
Melanocyte-stimulating hormone (MSH)	?	–
Orexin	NE/?	+
Corticotrophin-releasing hormone (CRH)	?	?
Gonadotropin-releasing hormone (GnRH)	+	NE
Kisspeptin	+	NE
Gonadotropin inhibitory hormone (GnIH)	–	+

NE indicates no effect, + indicates stimulatory, – indicates inhibitory, ? indicates action is unknown.

CNS function, reduced leptin to allow stimulation of NPY to in turn increase appetite as well as changes in anabolic hormones, and ultimately, reduce Kp and GnRH until feed is more readily available. When feed availability is more plentiful, the process is reversed, increasing insulin, IGF-I, leptin and anorexigenic molecules, while reducing orexigenic hypothalamic appetite molecules and favouring reproduction. Concurrent to these changes are increased Kp and GnRH and a resumption of reproduction.

Conflict of Interest

None of the authors have any conflicts of interest to declare.

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