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Article *in* Animal Production Science · August 2014

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http://dx.doi.org/10.1071/AN14478

Review

Drives and limits to feed intake in ruminants

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Abstract. The control of energy intake is complex, including mechanisms that act independently (e.g. distention, osmotic effects, fuel-sensing) as well as interacting factors that are likely to affect feeding via their effects on hepatic oxidation. Effects of ruminant diets on feed intake vary greatly because of variation in their filling effects, as well as the type and temporal absorption of fuels. Effects of nutrients on endocrine response and gene expression affect energy partitioning, which in turn affects feeding behaviour by altering clearance of fuels from the blood. Dominant mechanisms controlling feed intake change with physiological state, which is highly variable among ruminants, especially through the lactation cycle. Ruminal distention might dominate control of feed intake when ruminants consume low-energy diets or when energy requirements are high, but fuel-sensing by tissues is likely to dominate control of feed intake when fuel supply is in excess of that required. The liver is likely to be a primary sensor of energy status because it is supplied by fuels from the portal drained viscera as well as the general circulation, it metabolises a variety of fuels derived from both the diet and tissues, and a signal related to hepatic oxidation of fuels is conveyed to feeding centres in the brain by hepatic vagal afferents stimulating or inhibiting feeding, depending on its energy status. The effects of somatotropin on export of fuels by milk secretion, effects of insulin on gluconeogenesis, and both on mobilisation and repletion of tissues, determine fuel availability and feed intake over the lactation cycle. Control of feed intake by hepatic energy status, affected by oxidation of fuels, is an appealing conceptual model because it integrates effects of various fuels and physiological states on feeding behaviour.

Additional keywords: fuel sensing, hepatic oxidation theory, hunger, metabolic control, satiety.

Received 4 April 2014, accepted 16 June 2014, published online 19 August 2014

Introduction

The control of feed intake is complex, with redundant mechanisms to prevent overconsumption of nutrients. The obesity epidemic in developed countries has heightened the importance of studying food-intake regulation, and a variety of anorexigenic signals have been identified by research with laboratory species that affect food intake over the short and long terms. Much less research has been conducted related to control of feed intake in ruminants. While many putative mechanisms controlling feeding behaviour that have been identified in laboratory species are relevant to ruminant species, there are some basic differences among species that must be considered. For instance, ruminant diets contain lower fat and higher fibre contents than do diets consumed by non-ruminant species. In addition, pre-gastric fermentation in the rumen greatly affects the type and temporal supply of absorbed fuels; rapid fermentation of organic matter can greatly increase supply of absorbed fuels within meals while the reservoir of fermenting digesta in the reticulorumen, and the semi-continuous outflow of nutrients from the reticulorumen, results in a more consistent supply of absorbed fuels between meals. Furthermore, little glucose is absorbed once animals develop into functioning ruminants (Stangassinger and Giesecke 1986), so the liver becomes a glucose 'factory' with little need for, or capacity to absorb, glucose from the blood. In addition, the ruminant liver has little capacity for lipogenesis or export of triacylglycerol (TAG; Kleppe *et al*. 1988). While these differences, among others, must be considered when applying the results from laboratory species to ruminant animals, the basic mechanisms controlling feeding behaviour are likely to be conserved across species (Allen *et al*. 2005).

Some satiety factors have independent effects on feeding behaviour, while others are likely to be integrated through their effects on metabolism. There is a growing consensus of the importance of fuel-based sensing among tissues. The liver is likely to be the primary sensor of energy status that integrates short- and long-term mechanisms to affect satiety and hunger. Independent mechanisms might have additive effects but individual mechanisms are likely to dominate control of feed intake at times, depending on diet and physiological state of animals (Allen *et al*. 2009). Increased understanding of the control of feed intake is critical to formulate diets to increase health, productivity, and efficiency of nutrient utilisation in ruminants. This article presents a conceptual model of the control of feeding behaviour of ruminants that integrates effects of diet and physiological state.

Temporal control of feed intake

Mechanisms affecting feed intake have temporal effects that vary from minutes and hours to weeks and months. Long-term

mechanisms include those that affect maintenance of bodyweight (e.g. increases in blood leptin concentration with increasing adiposity) as well as homeorhetic adaptations to pregnancy and lactation (e.g. changes in blood concentrations of hormones and cytokines over the lactation cycle). Mechanisms in effect over the short term are related to diet characteristics affecting gut distention, gut peptides, and oxidation of fuels, with variable response depending on physiological state (Allen *et al*. 2009). Therefore, feed intake, which is a function of meal size and frequency, is determined by the interaction of mechanisms with diverse temporal effects. Response in feeding behaviour to diet is influenced by the supply of fuels in the blood (Fig. 1), which is affected by physiological state. Physiological state is characterised by differences in gluconeogenesis in the liver, mobilisation and uptake of fuels (e.g. non-esterified fatty acids, glycerol and amino acids) by extrahepatic tissues, and secretory capacity of mammary tissue, and is determined by secretion and sensitivity of tissues to hormones (e.g. insulin, leptin, somatotropin, catecholamines) and cytokines (e.g. leptin, TNFα). Diet characteristics that interact with physiological state to affect satiety and hunger over the span of minutes and hours can have long-term effects on feed intake and energy balance.

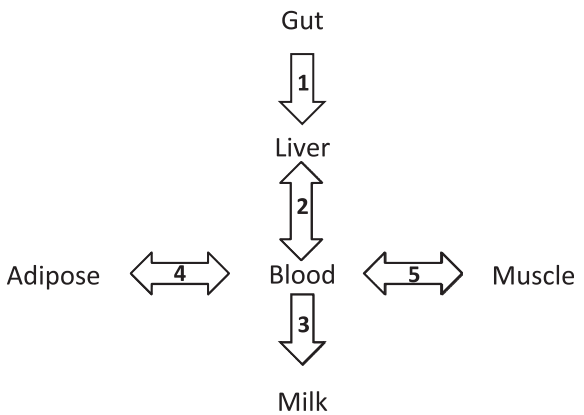

Fig. 1. Flow of fuels in ruminant animals. Short-chain fatty acids (FA) produced by ruminal fermentation (e.g. acetate, propionate, butyrate, etc.) as well as glucose, lactate, amino acids, and medium-chain FA flow to the liver from the portal-drained viscera (1), while long-chain FA are absorbed in the lymphatic system. The type and temporal absorption of fuels is dependent on diet composition, and digestion kinetics affecting the site of digestion. Extraction by the liver varies by fuel and over time, depending on enzyme activities and redox state of the liver (2). Little glucose and acetate is extracted by ruminant liver, sparing them for use by extrahepatic tissues. Propionate extraction from portal blood is consistently high but extraction of other fuels is lower and variable. Fuels extracted by the liver from circulating blood include non-esterified FA (NEFA), glycerol, lactate, and amino acids. Utilisation of amino acids as fuels increase when they are supplied in excess, and when amino acid profile diverges from optimal. Glucose output by the liver into the blood is affected by its demand by tissues and controlled by insulin and glucagon. Milk synthesis by the mammary gland is a sink for fuels including glucose, NEFA, acetate, and amino acids (3). Removal of these fuels from the blood is likely to stimulate intake by reducing their availability for oxidation in the liver. Adipose tissue extracts acetate, glucose, and NEFA from the blood during lipogenesis and mobilises triacylglycerol, increasing availability of NEFA and glycerol for hepatic oxidation during lipolysis (4). Muscle tissue utilises glucose, acetate, glycerol, BHBA, and NEFA as fuels, and amino acids during protein synthesis (5). Amino acids are mobilised during negative energy balance, increasing their availability as fuels following deamination. Lactate from partial metabolism of glucose by muscle is also available for gluconeogenesis or oxidation in the liver.

Signals affecting feeding behaviour

Feeding behaviour is determined by the integration of central and peripheral signals in brain feeding centres. These include stimulatory (orexigenic) signals that increase hunger as well as inhibitory (anorexigenic) signals that increase satiety. Initiation of meals is likely to be determined when inhibitory signals from the previous meal subside and stimulatory signals increase (Fig. 2*a*). Conversely, feeding is likely to continue until inhibitory signals intensify and stimulatory signals diminish (Fig. 2*b*).

Stimulatory signals

Various sensory, social, circadian and habitual factors contribute to stimulate feeding. However, meal initiation is likely to be dependent on energy status of the animal at any specific time; the probability of meal initiation is likely to be negatively related to energy status (Friedman 1997). Conrad *et al*. (1964) proposed that ruminants eat to meet their energy requirements unless prevented by the physical bulk of the diet. Further, Booth (1972) proposed the 'energostatic' control of food intake, suggesting that animals eat to balance energy consumed with energy required, and

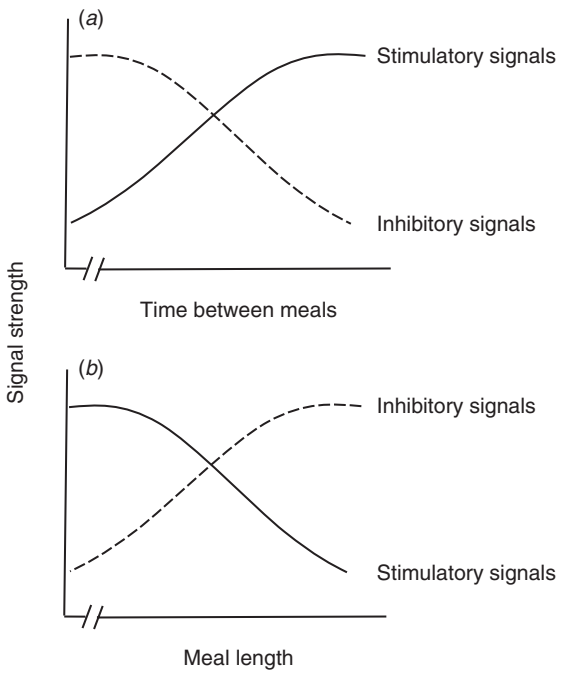

Fig. 2. Expected temporal pattern of stimulatory (orexigenic) and inhibitory (anorexigenic) signals in the interval (*a*) between meals and (*b*) during meals. Inhibitory signals from ruminal distention, osmolality and oxidation of fuels gradually decline following meals, and increase during meals, while stimulatory signals related to low-energy status increase preprandially and decline during meals.

Weston (1996) suggested that the strength of hunger signals is linearly related to the magnitude of the energy deficit. However, these theories fail to explain the suppression of appetite and extended negative energy balance in the peripartum period that begins a week or more before parturition. In addition, the physiological mechanisms by which animals eat to their requirements are uncertain; is hunger primarily the absence of satiety or does it depend on mechanisms that specifically stimulate feeding?

Research with rodents and other laboratory species has indicated that feeding behaviour is affected by oxidation of fuels and the signal to brain feeding centres is via hepatic vagal afferents. The signal from the liver might be both stimulatory and inhibitory, depending on the firing rate of vagal afferents; firing rate is increased as energy status decreases, stimulating feeding, and is decreased when energy status increases, inhibiting feeding (Friedman 1997). The common hepatic vagus innervates the liver as well as other tissues including the duodenum (Berthoud 2004). The liver is likely to be the primary sensor across mammalian species because it is a key anabolic organ with the unique advantage of sensing energy supply relative to energy demand (Allen and Bradford 2012). Enterocytes are also innervated by the common hepatic vagus and have been proposed to sense fat oxidation (Langhans 2008), however, they are less likely to sense oxidation of other fuels or provide an integrated signal related to energy needs (Allen and Bradford 2012).

Feeding is likely to be related to hepatic energy status as discussed by Friedman (1997) with the following evidence using rats as a model: (1) hepatic ATP content is decreased by fasting and increased by re-feeding, (2) prevention of ATP production by trapping inorganic phosphate stimulates feeding, while phosphate loading reverses the effects on ATP and feeding, (3) trapping the adenine moiety of ATP by ethionine also stimulates feeding, indicating that the mechanism affecting feeding is related to ATP *per se* and not inorganic phosphate, (4) the decline in liver ATP by trapping inorganic phosphate coincided temporally with the feeding response, and (5) the probability of meal initiation was negatively related to liver ATP content. While energy utilisation by the liver is likely to be consistent over the short term of days, oxidation of fuels and production of ATP over minutes can vary greatly, affecting feeding behaviour and feed intake. Therefore, normal fluctuations in liver ATP content within days might be both stimulatory and inhibitory.

In contrast to the many molecules discovered or proposed to inhibit feeding, ghrelin, a circulating peptide secreted primarily by cells in the abomasum in ruminants (Hayashida *et al*. 2001), is the only hormone discovered to stimulate initiation of meals. Ghrelin has been reported to stimulate feeding when infused peripherally in cattle (Wertz-Lutz *et al*. 2006) and when infused centrally in sheep exposed to long, but not short, photoperiod (Harrison *et al*. 2008). Ghrelin concentration increases in ruminants before scheduled (conditioned) meals and periprandial concentrations decrease as frequency of feeding increases (Sugino *et al*. 2002). Ghrelin is a putative signal of energy insufficiency and dependent on energy balance; its concentration increases with fasting and decreases with feeding (Wertz-Lutz *et al*. 2006). Further, the pre-prandial ghrelin surge associated with the conditioned meal was observed only for cows in negative, but not positive, energy balance (Bradford and Allen 2008). Although ghrelin has been shown to stimulate feeding, its effects on feed intake over days are questionable for ruminants fed *ad libitum*. Long-term ghrelin infusion did not affect dry matter intake (DMI) of cows in early lactation (Roche *et al*. 2008*b*) and plasma ghrelin concentration was not related to feed intake of dairy cows in early lactation (Borner *et al*. 2013). Meal size is generally greater for conditioned meals compared with spontaneous meals (Dado and Allen 1994), which might be from stimulatory effects of ghrelin. However, the ghrelin surge is only observed at conditioned meals and it likely has no effect on the size of spontaneous meals. Furthermore, sustained effects of a larger conditioned meal on satiety might delay initiation of the subsequent spontaneous meal, diminishing the effects of the larger conditioned meal on daily feed intake. Although direct effects of ghrelin on feed intake of ruminants fed *ad libitum* is uncertain, it might have long-term effects on feed intake through its effects as a secretagogue for somatotropin (Bradford and Allen 2008), which increases growth and lactational performance, thus increasing clearance of fuels from the blood and feed intake over the long term, as discussed below.

Inhibitory signals

Many inhibitory signals have been identified or proposed and have been discussed in recent comprehensive reviews by Forbes (2007*b*) and Roche *et al*. (2008*a*). Inhibitory signals include those related to rumen distention, rumen osmolality, gut peptides (e.g. cholecystokinin and glucagon-like peptide 1), pancreatic hormones (e.g. insulin, glucagon, amylin) and adipokines (e.g. leptin), as well as specific nutrient sensing by the central nervous system. Physical distention of the rumen often limits feed intake in ruminants and is supported by diverse evidence (Allen 1996; Forbes 2007*b*). Tension receptors located primarily in the reticulum and cranial sac respond to distention (Leek 1986), signalling brain feeding centres via vagal afferents. Ruminant diets vary widely in their filling effects, primarily because of variation in diet content and digestion characteristics of forage fibre. Ruminal distention is caused by both mass and volume of digesta (Allen 1996) and the initial moisture concentration as well as water holding capacity of digesta over time are likely to affect ruminal distention, especially for ruminants consuming feeds with high moisture content such as grazed pasture.

Increased ruminal osmolality inhibits feeding (Ternouth and Beattie 1971) and osmolality of rumen fluid increases during meals from ingestion of salts and rapid production of fermentation acids. The mechanism might be related to stimulation of osmoreceptors in the rumen wall (Leek and Harding 1975) or the release of vasopressin, a hormone with anorectic effects (Langhans *et al*. 1991), in response to systemic dehydration from water flux from the blood to the rumen (Allen 2000). Although the inhibitory signal from increased osmolality is likely to increase in intensity throughout meals contributing to satiety, it is likely to be transitory, with little effect on feed intake. In support of this, NaCl infused intraruminally at the onset of spontaneous meals decreased meal size 27% but did

not affect daily DMI because intermeal interval decreased 31% compared with sham control (Choi and Allen 1999).

The gut peptides cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) have been implicated in short-term control of feed intake in ruminants (Bradford *et al*. 2008; Relling and Reynolds 2008), and a CCK receptor antagonist prevented the depression in feed intake by a diet high in unsaturated FA fed to dairy cattle (Choi *et al*. 2000). These peptides are secreted in the small intestine in response to different nutrients in the chyme and have been related to decreased gastric emptying, increased retention time in the rumen and increased digestive enzyme release (CCK), potentially improving digestibility. However, increased retention of digesta will increase distention, potentially decreasing feed intake. In addition, CCK might have neural effects through activation of vagal or splanchnic afferent neurons conveying an inhibitory signal to brain feeding centres (Reidelberger 1994). Lack of meal-associated increases in their plasma concentrations, despite the reduction in feed intake by unsaturated fatty acids that was associated with elevated plasma concentrations of CCK and GLP-1, was likely because of a consistent flow of nutrients to the small intestine of ruminants (Bradford *et al*. 2008). Therefore, these gut peptides are more likely to provide a more consistent signal altering the sensitivity to more transient signals derived from the diet to affect feeding behaviour rather than their pulsatile secretion during meals.

The pancreatic hormones insulin and glucagon are the most important hormonal regulators of lipid and carbohydrate metabolism and are putative satiety hormones (Woods *et al*. 2006). However, they have had inconsistent effects on feed intake in ruminants that might be explained by their effects on metabolism (Allen *et al*. 2009), as discussed below. Leptin induces satiety and might help maintain bodyweight over the long term as its secretion by adipocytes is correlated with the size of the body fat deposits (Houseknecht *et al*. 1998). Leptin concentration in blood was related to body condition score (BCS) of lactating cows ($r = 0.61$, $P < 0.001$; Bradford *et al*. 2006) while insulin, another putative adiposity signal, was only weakly related in a different experiment ($r = 0.33$, $P < 0.10$, Bradford and Allen 2007).

Specific nutrient sensors might act centrally to contribute to satiety. Various metabolites have been suggested to elicit a central anorexigenic signal including non-esterified fatty acids (NEFA), betahydroxybutyric acid (BHBA), glucose, glutamine, and other amino acids. While plasma concentrations of NEFA and BHBA increased dramatically (>4×), beginning ~10 days prepartum until ~10 days postpartum, their concentrations in cerebrospinal fluid (CSF) were unchanged (Laeger *et al*. 2013), suggesting that they do not have central anorectic effects during the peripartum period. Glutamine was identified as a potential central anorexigenic signal because its concentration in CSF increased despite a reduction in its concentration in plasma during this period (Laeger *et al*. 2013). Feed restriction of cows in mid-lactation decreased CSF concentrations of serine, threonine and tyrosine, suggesting that these amino acids might also act centrally as anorexigenic signals in cows (Laeger *et al*. 2012). While plasma concentrations of NEFA and BHBA increased with feed restriction, their concentrations in CSF did not (Laeger *et al*. 2013). Anorectic effects of BHBA have been demonstrated in ruminants but results have been inconsistent; elevation of plasma BHBA concentration from 0.59 to 1.74 mmol/L by intravenous infusion had no effect on feed intake of lactating cows (Zarrin *et al*. 2013); the anorectic effects of BHBA might be more related to its perturbation of acid–base balance. Elevation of plasma NEFA and BHBA concentrations in the peripartum period and during feed restriction in mid-lactation cows without an increase of these molecules in CFS suggests that their anorectic effects, if any, are more likely from peripheral signals. While central sensing of certain specific metabolites might stimulate anorexigenic signals, other metabolites are likely to elicit a peripheral signal and affect feeding by their hepatic metabolism.

Metabolic control of feeding

Broad evidence with laboratory species suggests that the liver provides a common integrated mechanism for the control of feeding behaviour by oxidation of a variety of fuels (Friedman and Tordoff 1986) as previously discussed. We call this the hepatic oxidation theory (HOT) of the control of feed intake and have applied it to ruminant animals (Allen *et al*. 2009). Temporal patterns of fuel absorption, mobilisation and metabolism affect feed intake by altering meal size and frequency in ruminants consistent with HOT (Allen *et al*. 2009). The link between hypophagic effects of fuels and their oxidation in the liver, as well as differences among species, provides strong support for metabolic control of feeding (Allen *et al*. 2009; Allen and Bradford 2012).

Fuel oxidation in the ruminant liver

Fuels that are oxidised, or stimulate oxidation of acetyl CoA in the ruminant liver, include NEFA, amino acids, lactate, glycerol, and propionate. Unlike non-ruminant species and pre-ruminant calves, hepatic removal of glucose is negligible in mature ruminants (Stangassinger and Giesecke 1986), likely because activity of hexokinase decreases dramatically as ruminant species develop into functioning ruminants (Ballard 1965). Glucose is hypophagic in non-ruminants, but not in ruminants, which is likely related to differences in their liver's ability to oxidise glucose extracted from the blood (Allen 2000).

Non-esterified FA are the primary fuels oxidised in the liver. They are extracted from the blood in proportion to their concentration (Bell 1980) and oxidised by β-oxidation in mitochondria (or oxidised in peroxisomes or microsomes) or esterified and stored as TAG and later oxidised or exported as very low-density lipoproteins (VLDL). Ruminants have limited capacity to export stored TAG as VLDL compared with non-ruminants (Kleppe *et al*. 1988) and excessive lipolysis, especially during the transition from pregnancy to lactation, can result in hepatic steatosis, reducing gluconeogenesis and the ability of the liver to detoxify ammonia (Zhu *et al*. 2000). Long-chain FA (LCFA) that are too long for transport into the mitochondria can be oxidised in peroxisomes to medium chain FA (MCFA) that can readily enter the mitochondria. Long-chain FA are transported into mitochondria by carnitine acyltransferase (CAT1) by binding them to carnitine. The balance between transport of NEFA into mitochondria and their esterification and storage as TAG is affected by several factors, including

enzyme activities and availability of carnitine. Propionate inhibits FA transport into mitochondria (Jesse *et al*. 1986) and decreases activity of fatty acyl CoA dehydrogenase (Emery *et al*. 1992) likely interrupting production of acetyl CoA during meals. Inhibition of CAT1 by methyl palmoxirate stimulated feeding in rats fed a diet containing LCFA but not a diet containing MCFA (Friedman *et al*. 1990). This is consistent with HOT because MCFA are transported in the portal blood directly to the liver and do not require protein-mediated transport to cross the mitochondrial membrane (Papamandjaris *et al*. 1998). In addition, carnitine supplemented to transition cows increased *in vitro* oxidation of palmitate (Carlson *et al*. 2006) and depressed feed intake (Carlson *et al*. 2007), consistent with HOT.

Each cycle of β-oxidation yields one molecule each of acetyl CoA, $FADH_2$, and NADH. The process continues, shortening the FA by 2 carbons during each cycle, until the entire chain is cleaved into acetyl CoA units (or until there is a propionyl CoA terminal in the case of odd-chain FA). Acetyl CoA, in turn, can be oxidised in the tricarboxylic acid (TCA) cycle or exported as ketone bodies or acetate. Each cycle of mitochondrial β-oxidation yields at least 14 ATP if acetyl CoA is oxidised in the TCA cycle, but much less if it is exported from the liver without further oxidation. In contrast to mitochondrial β-oxidation, peroxisomal β-oxidation results in a loss of energy as heat because less energy is conserved as reducing equivalents (Reddy and Mannaerts 1994). Partial oxidation of LCFA in peroxisomes might help alleviate hypophagia associated with the lipolytic state unless thermogenesis from energy spilling inhibits feeding. Although reducing equivalents produced by mitochondrial β-oxidation undergo oxidative phosphorylation (OXPHOS) to generate ATP, there may be a lag phase during which reducing equivalents may accumulate before ATP generation by OXPHOS. This temporal disconnect between production of reducing equivalents and the increase in ATP might be linked to feeding because OXPHOS is stimulated by bicarbonate ions (Acin-Perez *et al*. 2009); increased anapleurosis during meals stimulates oxidation of acetyl CoA in the TCA cycle, producing carbon dioxide, increasing bicarbonate, and stimulating ATP production by OXPHOS (Allen and Piantoni 2013).

Acetyl CoA is the metabolic crossroad that all fuels must be converted to for oxidation but some fuels are anapleurotic and can also stimulate oxidation of acetyl CoA in the TCA cycle. Anapleurotic fuels include glucogenic amino acids, glycerol, lactate and propionate. Of all fuels derived from the diet, propionate is most likely to stimulate oxidation within meals, especially when high starch diets are fed, because it can be produced rapidly, is readily extracted from the blood by the liver, and is anapleurotic, providing oxaloacetate for the citrate synthase reaction, stimulating oxidation of acetyl CoA in the TCA cycle (Allen *et al*. 2009). Propionic acid is produced primarily from fermentation of starch in the rumen and its production rate is highly variable depending on its source. An experiment from our laboratory demonstrated that a more-fermentable starch source reduced DMI by decreasing meal size, despite a decrease in intermeal interval compared with a less-fermentable starch source (Oba and Allen 2003*b*). The more fermentable diet nearly doubled the fractional rate of starch fermentation, increasing the contribution of short-chain fatty acids (SCFA) as fuels at the expense of glucose from starch digestion in the small intestine. Because the more fermentable starch decreased meal size, it is likely that satiety was caused by absorption of fuels within the timeframe of meals. In contrast, other anapleurotic fuels derived from the diet (e.g. glycerol, lactate, and glucogenic amino acids) are absorbed post-ruminally, with a greater latency for absorption. While they can stimulate hepatic oxidation of acetyl CoA, contributing to satiety, they are likely to have a greater effect by extending satiety between meals.

Propionate is hypophagic compared with acetate, consistent with their ability to stimulate hepatic oxidation (Allen 2000). Acetic acid, produced primarily by ruminal fermentation of fibre, is generally more abundant but, unlike propionate, hepatic extraction of acetate from the blood is low. Extraction is dependent on activation by their respective acyl CoA synthetases; activity of propionyl CoA synthetase is high while activity of acetyl CoA synthetase is low (Ricks and Cook 1981). In addition, propionate is anapleurotic and stimulates oxidation of acetyl CoA in the TCA cycle while acetate is not (Allen and Piantoni 2013). Glycerol, like propionate, is a glucose precursor but enters the gluconeogenic pathway at glyceraldehyde-3-phosphate and is less likely to enter the TCA cycle, stimulating oxidation. Propionic acid decreased feed intake 17% relative to glycerol by decreasing meal size when isoenergetic solutions were infused abomasally in cows in the postpartum period, consistent with HOT (Gualdron-Duarte and Allen 2014). While the ability of fuels to stimulate hepatic oxidation is consistent with their hypophagic effects, feeding behaviour response to diet is also affected by physiological state.

Interaction of diet with physiological state

Physiological state is characterised by differences in blood concentrations and sensitivity of tissues to hormones and cytokines that affect many metabolic processes including gluconeogenesis and mobilisation and uptake of fuels by tissues. Whereas insulin and glucagon are putative satiety hormones (Woods *et al*. 2006), their effects on feed intake for ruminants are likely dependent on their effects on metabolism of fuels (Allen *et al*. 2009). Similarly, effects of somatotropin and leptin affect availability of fuels and their indirect effects on hepatic oxidation might contribute to their long-term effects on feed intake.

Gluconeogenenic flux

Gluconeogenesis is affected by insulin and glucagon and gluconeogenic flux is an important determinant of the temporal oxidation of fuels in the liver (Allen *et al*. 2009). The extent of feed intake depression by a diet containing a more rapidly fermentable starch source was related positively to plasma insulin concentration ($r^2 = 0.28$, $P < 0.01$; Bradford and Allen 2007), and the hypophagic effects of propionate were linearly related ($r^2 = 0.45$, $P < 0.01$) to plasma glucose concentration in experiments using cows in mid- to late lactation (Oba and Allen 2003*c*). Plasma glucose concentration increases as glucose demand by body tissues is more nearly satisfied,

stimulating release of insulin by the pancreas. Gluconeogenesis is upregulated in early lactation when plasma insulin concentration is low and gradually downregulated by elevated insulin concentration (Barthel and Schmoll 2003) as lactation advances and glucose demand decreases. Downregulation of gluconeogenesis limits propionate flux to glucose so absorbed propionate is increasingly oxidised in the liver, causing satiety sooner within meals.

Tissue supply and uptake of fuels

Plasma insulin concentration decreases, beginning several weeks prepartum and remains low for several weeks postpartum, resulting in a lipolytic state and elevated plasma NEFA concentration. The depression in feed intake during the transition from gestation to lactation is likely because of the constant supply of NEFA to the liver; plasma NEFA concentration and DMI are inversely related during the peripartum period and hepatic oxidation of NEFA is likely to result in a more consistent inhibitory signal from the liver stimulating satiety (Allen *et al*. 2009). In support of this, a low-dose of slow-release insulin administered to cows in the postpartum period interrupted the flux of NEFA to the liver and increased feed intake (Hayirli *et al*. 2002). Feed intake gradually increases as plasma NEFA is exported in milk and glucose demand is satisfied as lactation progresses.

Insulin concentration over the long-term (days, weeks) indicates energy adequacy, affecting tissue uptake or mobilisation of fuels and regulating their oxidation in the TCA cycle through its effects on gluconeogenesis. However, release of insulin at meals might have opposite effects on feed intake. Pulsatile insulin secretion in response to feeding might clear fuels from the blood more quickly, potentially decreasing the interval between meals (Oba and Allen 2000). While the extent of feed-intake depression by a more fermentable diet was related positively to plasma insulin concentration, consistent with effects of insulin on gluconeogenesis, it was related negatively to insulin response to an intravenous glucose challenge (r^2 = 0.40, $P < 0.01$ quadratic); cows with greater insulin secretion from the glucose infusion were better able to maintain feed intake on the more fermentable diet (Bradford and Allen 2007). Plasma insulin concentration and insulin response to a glucose challenge were not related in that experiment and together they explained over two-thirds of the variation in feed intake response among cows to increased ruminal starch fermentability of diets. Insulin concentration within a day is negatively related to plasma NEFA concentration (Fig. 3) and postprandial insulin pulses interrupt fuel supply to the liver by stimulating uptake of fuels by insulin-sensitive tissues and inhibiting lipolysis in adipose tissue. Insulin sensitivity of tissues varies among animals and across physiological states and this is likely to be an important determinant of feed-intake response to postprandial insulin secretion. Consistent with this, feed intake over the first 4 h following the conditioned meal was positively related to the extent to which plasma NEFA concentration decreased for cows in the postpartum period (Piantoni *et al*. 2014).

Temporal variation in the concentration of amino acids in blood likely contributes to control of feeding behaviour by their

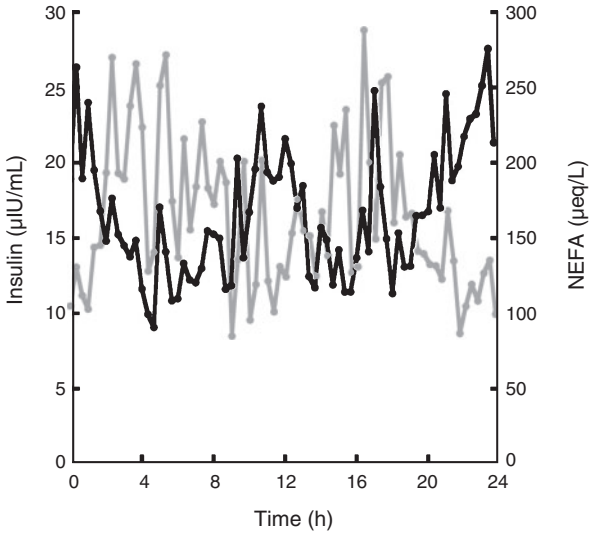

Fig. 3. Inverse relationship between plasma insulin (grey line) and non-esterified fatty acid (NEFA; black line) concentration for an individual cow within a day. Cow was fed *ad libitum*, once per day with blood samples taken every 20 min for 24 h. Increased insulin during and following meals decreases supply of NEFA for hepatic oxidation while decreased insulin gradually increases NEFA supply following meals (unpubl. data from Oba and Allen 2003*b*).

metabolism in the liver. Insulin stimulates uptake of amino acids by muscle tissue and inhibits protein degradation (Lobley 1992) thus affecting supply of amino acids to the liver. Mobilisation of amino acids from muscle occurs during negative energy balance when plasma insulin concentration is low (Heitmann and Bergman 1980). Amino acids can be oxidised in the TCA cycle through acetyl CoA and some (anapleurotic) amino acids can stimulate oxidation of acetyl CoA. Amino acid imbalances increase their potential for deamination and oxidation, contributing to satiety.

Growth and lactation, stimulated by somatotropin and growth factors, increase energy requirements and the response in feed intake by bovine somatotropin follows the response in milk yield (Bauman 1999). Increased flux of fuels to extrahepatic tissues decreases their availability for oxidation in the liver, potentially stimulating feed intake. While leptin acts centrally to affect satiety (Houseknecht *et al.* 1998), effects of leptin on availability of fuels oxidised in the liver might be involved in its effect on long-term energy balance. Leptin decreases insulin secretion by the pancreas and reduces insulin inhibition of lipolysis (Houseknecht *et al*. 1998), increasing plasma NEFA concentration. Therefore, greater leptin secretion in response to increased adiposity, might increase the supply of NEFA for potential oxidation in the liver, contributing to satiety.

Hepatic acetyl CoA

Content of acetyl CoA in hepatocytes varies by physiological state (Stocks and Allen 2012) as well as diurnally (Piantoni *et al*. 2014). The primary source of acetyl CoA is from mitochondrial β-oxidation of NEFA but all fuels (e.g. lactate, glycerol, AA) that are completely oxidised in the mitochondria enter the TCA cycle via metabolism to acetyl CoA. Hypophagic

effects of anapleurotic metabolites appear to be dependent on the availability of acetyl CoA to be oxidised. We reported that hypophagic effects of intraruminal infusions of propionic acid were linearly related to hepatic acetyl CoA content for cows in the postpartum period (Stocks and Allen 2012) and that the hypophagic effects were not attenuated over a 3-day infusion (Stocks and Allen 2013). This is consistent with previous results from our laboratory, in which propionic acid was more hypophagic for cows in the postpartum period compared with cows in mid-lactation (Oba and Allen 2003*a*); cows in the postpartum period were in a lipolytic state with elevated plasma BHBA, indicating elevated hepatic acetyl CoA content, while cows in mid-lactation were in positive energy balance with low plasma concentration of BHBA.

Circadian feeding patterns might be affected by hepatic acetyl CoA content. Intraruminal infusion of propionic acid interacted with acetyl CoA in the liver to affect feed intake only for the first 4 h following feeding for cows in the postpartum period fed *ad libitum*; daily DMI was reduced despite no effects of infused propionic acid on feed intake over the remaining 20 h (Stocks and Allen 2013). Propionate and other anapleurotic metabolites derived from the diet are likely to stimulate oxidation of acetyl CoA following feeding, reducing its content in the liver over the first several hours after feeding. While oxidation of acetyl CoA is likely to contribute to the total satiety signal, its content in the liver is affected by its rate of production as well as its rate of oxidation and export as ketone bodies and acetate. Production of acetyl CoA by β-oxidation is dependent on supply of NEFA to the liver, which is reduced postprandially by effects of absorbed fuels on insulin secretion (Fig. 3). Plasma NEFA concentration was greatest before feeding for lactating cows fed *ad libitum* once per day in the morning, corresponding to the daily nadir in plasma insulin concentration, while the daily nadir in plasma NEFA concentration was 4–8 h after feeding corresponding to the daily peak in plasma insulin concentration (Fig. 4). The reduction in NEFA supply to the liver during meals, affected by insulin secretion and sensitivity of adipose tissue, might affect feeding behaviour response to absorbed fuels by reducing acetyl CoA available for oxidation. Hepatic acetyl CoA concentration decreased over the first 4 h following feeding corresponding to a decrease in plasma NEFA concentration and cows with greatest DMI over the first 4 h after feeding had greatest decrease in both plasma NEFA and hepatic acetyl CoA concentration (Piantoni *et al*. 2014).

Integration of signals controlling feeding behaviour

The liver is an ideal candidate to sense energy status because it is supplied by fuels absorbed from the portal-drained viscera as well as those from the general circulation. Both supply of fuels from tissues and their hepatic oxidation are affected by physiological state, consistent with short- and long-term control of feed intake. The signal from the liver and other peripheral signals are relayed to brain feeding centres by sensory nerves and integrated with those having direct central effects. Synergistic effects of signals have been demonstrated for

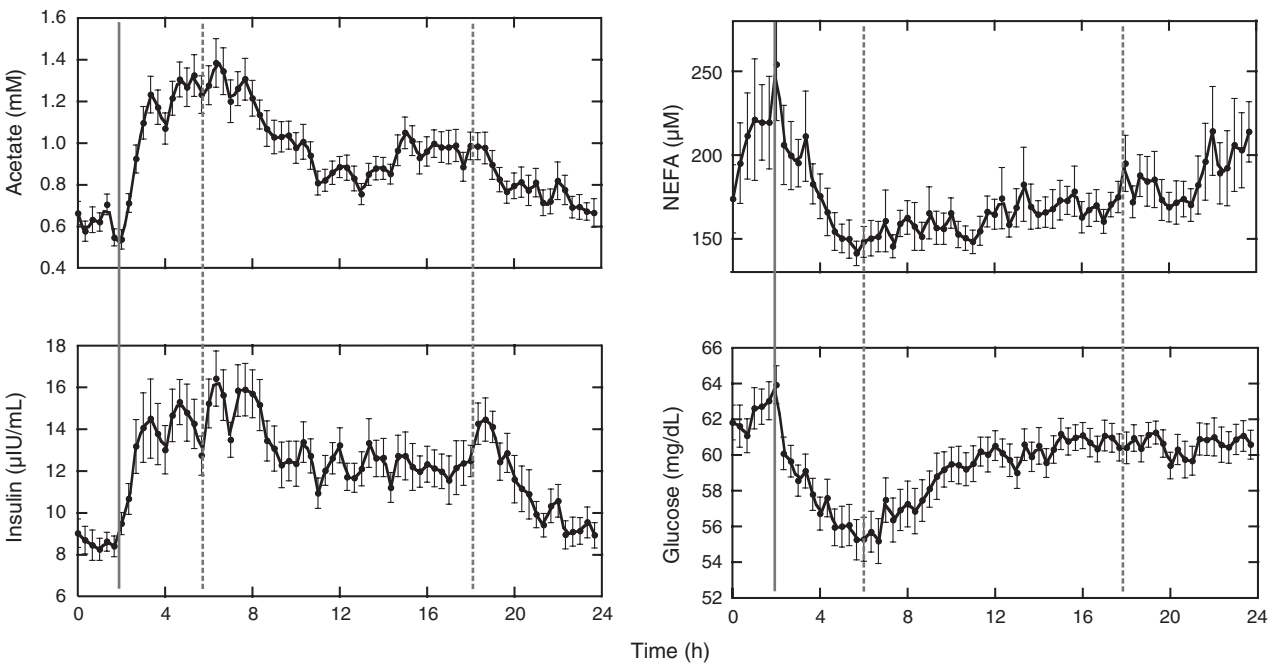

Fig. 4. Diurnal variation in plasma insulin, glucose, non-esterified fatty acid (NEFA), and acetate concentrations for cows in early to mid-lactation offered feed *ad libitum*. Each data point represents means and standard errors of 32 observations (8 cows by 4 diets), and samples were taken every 20 min for 24 h. Time 0 in the graph is when sampling began at 1200 hours; cows were fed once per day at 1400 hours (solid grey line) and milked at 0600 hours and 1800 hours (dashed grey lines). The conditioned meal is typically the largest meal of the day for dairy cows fed *ad libitum*, followed by 10 or more spontaneous meals. Plasma glucose and NEFA concentrations are affected by insulin and mirror its concentration in an opposite manner, whereas plasma acetate concentration is more dependent on absorption following meals and its temporal pattern is similar to that of insulin. Adapted from Allen *et al.* (2005), with permission.

ruminants with additive effects of intraruminal infusion of SCFA on feed intake of lactating cows when rumens were distended by balloons (Mbanya *et al.* 1993) and forage NDF content of the diet (Choi and Allen 1999). The relative contribution of different signals likely varies temporally, within and across days. For instance, osmotic effects on satiety are likely short-lived compared with the more sustained effect of absorbed fuels on hepatic oxidation. Further, hepatic oxidation of fuels likely dominates control of feed intake for ruminants in a lipolytic state such as in the postpartum period or when diets with high-energy content are fed to animals with low energy requirements. Alternatively, ruminal distention likely dominates control of feed intake when ruminants with high-energy requirements are fed diets with low energy density. Feed intake response to a reduction in the filling effect of diets was positively related to milk yield of cows when feeding a forage with greater fragility (Oba and Allen 1999) or a diet containing less forage NDF (Voelker *et al.* 2002), indicating that ruminal distention is likely to become a more dominant signal affecting feed intake as energy requirements increase.

Feed intake is a function of meal size and frequency; meal size is determined by rate of eating and meal length and meal frequency is determined by the length of time between meals (intermeal interval) and meal length. Multiple signals with varied temporal effects are integrated in the brain to determine meal length and time between meals. Forbes (1999, 2007*a*) suggested that all signals related to hunger and satiety might be sensed as discomfort and animals might eat to minimise total discomfort. Discomfort is caused by gut distention, consumption of toxic substances, and heat stress but might also be caused by sensing excessive or insufficient fuels.

Meal length

Meals are likely terminated by anorexigenic signals related to distension, osmolality and hepatic oxidation of fuels for ruminant animals (as previously discussed). It is likely that the signals are additive to some extent and dominance of individual signals vary temporally. Mass and volume of ruminal digesta, osmolality of rumen fluid and hepatic energy status increase within meals at rates dependent on diet characteristics and consumption rate by the animal. Rate of eating is affected by dietary factors related to physical form, sward density when grazing, sensory signals related to taste and olfaction, absorbed fuels, as well as social interactions among animals. The signal intensity related to ruminal distention varies at the initiation of meals depending on the mass and volume of digesta remaining from the previous meal. As eating continues and distention increases, tension receptors in the reticulorumen increase the firing rate of vagal afferents. The rate at which distention increases is dependent on the rate of eating and the initial filling effect of the diet, affected by the content of forage fibre and moisture content (Allen 1996). The rate of increase in ruminal osmolality is dependent on the concentration of mineral salts in the diet and the rate of production of SCFA, which is highly variable among ruminant diets and depends primarily on the diet content and fermentability of starch and other rapidly fermentable carbohydrates.

The extent to which hepatic oxidation contributes to meal termination is likely dependent on the balance between ATP production and utilisation in the liver. Utilisation of ATP is determined by energy needs of the liver and is likely to be consistent across days. However, energy needs of the liver vary over the long term such as when the liver mass is changing with growth and over the lactation cycle. The production of ATP within meals is affected by the rate of production of anapleurotic fuels (e.g. propionate), and contents of acetyl CoA and reducing equivalents in the liver, as well as enzyme activities, and it is highly variable by diet and physiological state (Allen and Piantoni 2013). Carbon flux through acetyl CoA is affected by diet by interrupting lipolysis through stimulation of insulin secretion and by reducing NEFA transport and β-oxidation in the mitochondria. However, the extent to which absorbed fuels affect the flux of carbon through acetyl CoA within the timeframe of meals has not been investigated. Propionic acid, produced by starch fermentation, is rapidly absorbed and extracted by the liver, stimulating oxidation of acetyl CoA and OXPHOS, likely decreasing the firing rate of the hepatic vagus and contributing to satiety (Fig. 5). Increased ruminal starch fermentability decreased DMI by reducing meal size, likely by stimulating oxidation in the liver (Oba and Allen 2003*b*) and the anorectic effects of propionate are linearly related to the content of acetyl CoA in the liver (Stocks and Allen 2012). Hepatic acetyl CoA is abundant for cows in negative energy balance that are in

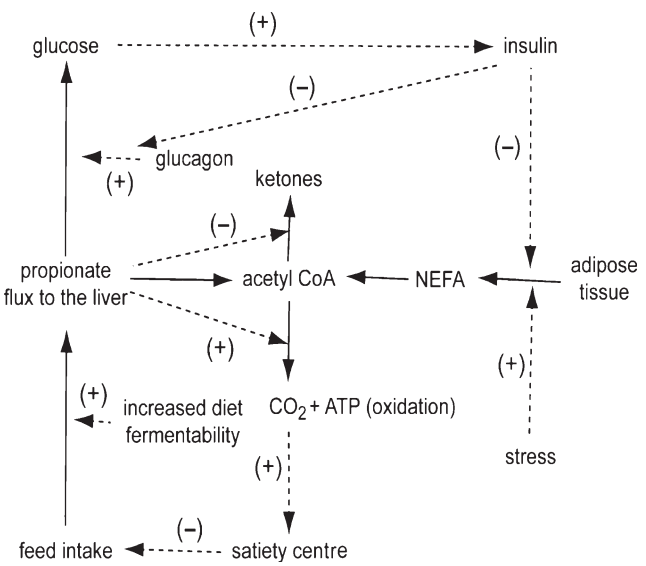

Fig. 5. Model by which feed intake might be controlled according to the hepatic oxidation theory. Solid lines show the flow of carbon while dashed lines show stimulation or inhibition of flow. Propionate can be used by the liver for gluconeogenesis, utilising ATP, or oxidised in the tricarboxylic acid (TCA) cycle through acetyl CoA, producing ATP. Acetyl CoA produced from β-oxidation of fatty acids and other ketogenic fuels is oxidised in the TCA cycle or exported as ketones. Decreased insulin concentration, increased insulin resistance, and stress increase lipolysis, thereby increasing the pool of acetyl CoA through β-oxidation of NEFA. Propionate uptake during meals stimulates oxidation of acetyl CoA to CO_2, generating ATP, increasing energy charge, and stimulating satiety. Adapted from Allen *et al.* (2009), with permission.

a lipolytic state but its content in the liver is much lower for cows in positive energy balance (Piantoni *et al.* 2014). When hepatic acetyl CoA content is low, propionate uptake by the liver in excess of its flux to glucose is likely to be increasingly metabolised to acetyl CoA during meals, and oxidised in the TCA cycle, stimulating satiety (Allen *et al*. 2009). Therefore, the extent to which a signal from the liver is involved in meal termination likely depends on the flux of propionate and other anapleurotic fuels to the liver, rate of gluconeogenesis, availability of acetyl CoA, and the speed at which the TCA cycle spins, affected by enzyme concentration and activity (Allen and Piantoni 2013).

Ghrelin might increase the length and size of the conditioned meal and its release is affected by diet. The reduction in feed intake by fat supplements might have been from their tendency to suppress the ghrelin surge at the conditioned meal (Bradford *et al*. 2008). Digested nutrients stimulate release of various anorectic hormones as they pass sequentially through the small intestine. These hormones have diverse functions including reducing rumen motility, increasing retention time and therefore distention, stimulating secretion of digestive enzymes and anabolic hormones by the pancreas, and stimulating satiety centrally. Anorectic effects of gut hormones likely affect thresholds by which more transient signals affect satiety and meal termination as discussed previously.

Interval between meals

Meals are initiated at a time when inhibitory signals from the previous meal are diminishing and stimulatory signals are increasing (Fig. 2*a*). The rate at which inhibitory signals decrease following meals is dependent on the size of the meal, the type and temporal absorption of fuels, and the physiological state of the animal. Effects of ruminal osmolality are likely to be transient if water is available for animals to quench their thirst following meals. While the initial filling effect of the diet is affected by the forage NDF content, its effect on distention over time depends on its clearance from the rumen, affected by chewing activity, rumen motility, forage fragility, and ease of enzymatic hydrolysis as well as its water holding capacity (Allen 2000). These factors are highly variable across forages and can have a large effect on feed intake by extending the signal related to distention over time.

Hepatic oxidation of fuels continues following meal termination as fuels from ruminal fermentation and intestinal digestion continue to be absorbed. The temporal supply of SCFA from ruminal fermentation varies greatly relative to meals but retention of digesta in the rumen ensures an uninterrupted supply from continuous fermentation. Starch generally ferments and passes from the rumen more rapidly than fibre and its pool size in the rumen is rapidly depleted following meals. As such, absorption of propionic acid from the rumen is more pulsatile than absorption of acetic acid. Starch passing from the rumen to the small intestine is digested to glucose, which is absorbed and either enters the circulation or is metabolised to lactate by intestinal tissues. The extent to which hepatic energy status is elevated over time following meals is likely dependent on the supply of anapleurotic fuels from the diet. Amino acid imbalances, either from an oversupply of all, or a deficiency of limiting amino acids, increases their utilisation as fuels, potentially decreasing DMI by extending the interval between meals. Ammonium, compared with sodium, exacerbated the hypophagic effects of propionate when infused intraruminally in lactating cows by extending the interval between meals, possibly by stimulating hepatic oxidation between meals (Oba and Allen 2003*d*). This might be because ammonia detoxification by urea synthesis requires α-amino nitrogen removal (Reynolds 1992), increasing availability of carbon from amino acid catabolism for oxidative metabolism in the liver. Once supply of absorbed fuels is diminished, hepatic oxidation is likely to slow down, decreasing hepatic energy status and increasing the firing of hepatic vagal afferents, stimulating hunger.

Supply of circulating fuels to the liver likely affects the intermeal interval and is affected by the uptake and mobilisation of fuels by tissues. Clearance of fuels from the blood varies with insulin response to absorbed fuels, sensitivity of tissues to insulin, and their secretion in milk. Intraruminal infusion of propionate decreased DMI by decreasing meal size by cows in the postpartum period and in late lactation but increased intermeal interval for cows in late lactation only, likely because of differences in fuel clearance from blood (Oba and Allen 2003*a*). We observed similar effects for sodium acetate and sodium chloride on meal size, but intermeal interval was increased by sodium acetate only, decreasing DMI when infused intraruminally at spontaneous meals in lactating cows (Choi and Allen 1999). Although little, if any, absorbed acetic acid is oxidised in the liver, continuous production and absorption from the rumen and use by extrahepatic tissues, spares fuels that are oxidised, extending satiety between meals. Lipolysis increases as the insulin surge following meals subsides, increasing the supply of NEFA to the liver (Fig. 4) and oxidation of NEFA likely increases before the initiation of meals and declines postprandially as oxidation of carbohydrates increase. Analysis of respiratory gas emissions by cows in late lactation indicated that fat oxidation accelerates preprandially and declines with feeding as carbohydrate oxidation increases (Derno *et al*. 2013) consistent with the expected pattern of fuel oxidation relative to meals.

Concluding remarks

Mechanisms controlling energy intake and partitioning are entwined and inseparable and are affected by diet and physiological state. The liver is likely to be an important sensor of energy status, conveying a signal to feeding centres in the brain to both stimulate and inhibit feeding. The conceptual model presented in this article might help improve our understanding of control of feeding in ruminant animals. Advancements in improving accuracy of prediction of feed intake are questionable because of the complexity of interactions and the difficulty of predicting the type and temporal supply of absorbed fuels in ruminants, clearance of fuels from the blood, and fate of fuels in the liver over the short term. However, a more mechanistic understanding of how metabolism of fuels affects feeding behaviour will allow improvements in diet formulation to manage energy intake and

partitioning in ruminants. Increased understanding of the control of feeding behaviour can help focus research efforts to increase energy balance in the postpartum period, devise feeding strategies considering circadian control of feed intake, and might lead to other nutritional or pharmaceutical interventions to control feed intake to improve health, production and nutrient utilisation of ruminant animals.

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