animal

Review: Control of feed intake by hepatic oxidation in ruminant animals: integration of homeostasis and homeorhesis

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Feed intake is controlled through a combination of long- and short-term mechanisms. Homeorhetic mechanisms allow adaptation to changes in physiological states in the long term, whereas homeostatic mechanisms are important to maintain physiological equilibrium in the short term. Feed intake is a function of meal size and meal frequency that are controlled by short-term mechanisms over the timeframe of minutes that are modulated by homeorhetic signals to adapt to changes in the physiological state. Control of feed intake by hepatic oxidation likely integrates these mechanisms. Signals from the liver are transmitted to brain feeding centers via vagal afferents and are affected by the hepatic oxidation of fuels. Because fuels oxidized in the liver are derived from both the diet and tissues, the liver is able to integrate long- and short-term controls. Whereas multiple signals are integrated in brain feeding centers to ultimately determine feeding behavior, the liver is likely a primary sensor of energy status.

Implications

The uncoupling of energy intake and energy requirements can affect the productive performance of animals. Limitations to feed intake by metabolic mechanisms or by distention of undigested feed residues in the gastrointestinal tract can result in negative energy balance, potentially compromising health, production and reproduction. Excessive energy partitioning to body reserves can result in similar consequences. The disparity between energy intake and requirement is affected by the interaction of diet and physiological state. Understanding the interaction of long- and short-term controls of feed intake will help optimize ration formulation to improve animal health, production and efficiency of nutrient utilization.

Introduction

Mechanisms controlling feed intake must ensure an adequate supply of energy for maintenance, pregnancy, growth and lactation, as well as prevent overconsumption of energy. Homeostatic mechanisms maintain physiological equilibrium, and homeorhetic mechanisms coordinate changes in energy intake necessary to support alterations in the physiological state (Bauman and Currie, 1980). Because most ruminants consume forage-based diets that

are fibrous with relatively low nutrient density, feed intake is often limited by distension from undigested feed residues in the gastrointestinal tract. Conrad *et al.* (1964) proposed that ruminants eat to meet their energy requirements unless limited by the physical bulk of the diet. However, the idea that animals eat to meet their energy requirements fails to explain the insufficient stimulation of feed intake of ruminants in the postpartum period when feed intake is not limited by distention, but negative energy balance persists (Allen, 2014).

Feed is consumed in discrete meals with meal frequency varying from four to five meals per day for grazing cattle (Roche *et al.*, 2008) to 9 to 14 meals per day for lactating cows fed total mixed rations (Grant and Albright, 2000). Meals are initiated when stimulatory (orexigenic) signals intensify and inhibitory (anorexigenic) signals subside, and meals cease when inhibitory signals intensify and stimulatory signals subside. Stimulatory signals include those that are sensory, social, circadian and habitual, as well as a reduction in hepatic energy status, whereas inhibitory signals include distention within the gastrointestinal tract, rumen osmolality, endocrine effects, nutrient sensing by the central nervous system, and elevated hepatic energy status (Allen, 2014). Feed intake is a function of meal size and meal frequency, which are controlled by short-term (homeostatic) mechanisms affecting satiety and hunger over a timescale of minutes. Certain elements of the short-term mechanism

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are likely modulated by homeorhetic signals. Whereas multiple signals are integrated in brain feeding centers to ultimately determine feeding behavior, the liver is likely a key sensor of energy status integrating long- and short-term controls. Research has shown that signals from the liver are transmitted to brain feeding centers via vagal afferents affected by the oxidation of fuels (Langhans *et al.*, 1985; Friedman, 1998). The liver offers the unique advantage of sensing not just energy availability but energy balance relative to nutrient demands (Allen and Bradford, 2012).

The objective of this article is to discuss the liver as a sensor of energy status, integrating short- and long-term controls. The following sections provide background regarding the relationship between fuel oxidation and feed intake, control of feed intake by hepatic oxidation, the type and temporal supply of fuels oxidized in the liver of ruminants, and the control of hepatic oxidation and its modulation over the long and short terms. This will be followed by a discussion of the interactions of diet and physiological state on the control of feed intake through the lactation cycle.

Whole-body oxidation of fuels and feeding

The effect of fuel oxidation on food intake in laboratory species has been reviewed in detail previously (Langhans, 1996; Friedman, 1998). Various metabolic inhibitors have been reported to stimulate feeding by inhibiting the oxidation of glucose or fatty acids (**FA**). Food intake by laboratory species has been stimulated by the inhibition of glycolysis by 2-deoxy-D-glucose (Novin *et al.*, 1973), pyruvate transport across the mitochondrial membrane by α-cyano-4-hydroxycinnamic acid (Del Prete *et al.*, 2004), long-chain FA transport across the mitochondrial membrane by methyl palmoxirate (Friedman and Tordoff, 1986) and etomoxir (Horn *et al.*, 2004), and β-oxidation by mercaptoacetate (Scharrer and Langhans, 1986). In addition, food intake was decreased by the stimulation of fuel oxidation by PPARγ agonists in rats (Fu *et al.*, 2003, 2005) and by knockdown of 11β-hydroxysteroid dehydrogenase type 1 in mice (Li *et al.*, 2011). Synergistic effects of inhibiting glucose and FA oxidation on food intake have been reported; inhibition of glycolysis by 2-deoxyglucose and FA oxidation by methyl palmoxirate synergistically increased feeding in rats (Friedman and Tordoff, 1986), as did inhibition of glycolysis by 2-deoxyglucose and lipolysis by nicotinic acid (Friedman *et al.*, 1986). Furthermore, feeding events were related to periprandial patterns of fat and carbohydrate oxidation measured by respiration calorimetry in lactating cows (Derno *et al.*, 2013).

Control of feed intake by hepatic oxidation

Extensive evidence with laboratory species suggests that the liver provides a common integrated mechanism for the control of feeding behavior by the oxidation of a variety of fuels (Forbes, 1988; Langhans, 1996; Friedman, 1998; Scharrer, 1999). The hepatic oxidation theory (**HOT**) of the control of feed intake has been applied to ruminant animals (Allen *et al.*, 2009; Allen and Bradford, 2012; Allen, 2014) and will be briefly summarized here. Signals from the liver are transmitted to brain feeding centers via vagal afferents (Anil and Forbes, 1988). The signal from the liver may be both inhibitory (affecting satiety) and stimulatory (affecting hunger) and is related to hepatic oxidation of fuels (Friedman, 1997). Feeding behavior is affected by the firing rate of the nerve; increased oxidation decreases the firing rate, inhibiting feeding, whereas decreased oxidation increases the firing rate, stimulating feeding (Friedman, 1997). Fuels extracted from the blood by the liver can be converted to acetyl CoA (**AcCoA**) and oxidized in the tricarboxylic acid (**TCA**) cycle. Hepatic oxidation varies over minutes affecting feeding behavior and is dependent upon the supply of AcCoA and the capacity of the TCA cycle.

Fuels oxidized by the ruminant liver

Fuel supply to the liver is dependent upon the absorption of fuels derived from the diet as well as those supplied by or extracted from the blood by extrahepatic tissues (Figure 1). Fuels extracted from the blood and oxidized in ruminant liver include non-esterified fatty acids (**NEFA**), amino acids (**AA**), lactate, glycerol, short-chain FA (except acetate)
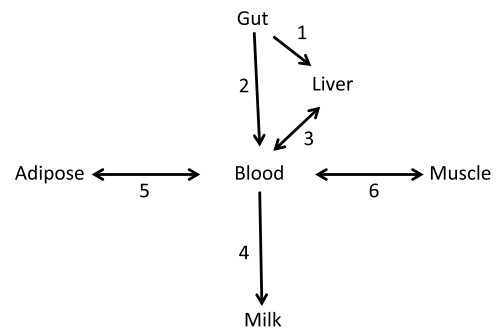

Figure 1 Flow of potential metabolic fuels in ruminant animals. (1) Short-chain fatty acids (FA) produced by ruminal fermentation (e.g. acetate, propionate, butyrate, etc.) as well as glucose, lactate, amino acids, and medium-chain FA flow to the liver from the portal-drained viscera. The type and temporal absorption of potential fuels is dependent upon diet composition and digestion kinetics affecting the site of digestion. Extraction by the liver varies by fuel and over time depending upon enzyme activities and redox state of the liver. Little glucose and acetate are extracted by ruminant liver, sparing them for use by extrahepatic tissues. Propionate extraction from portal blood is high, but extraction of other fuels is lower and variable. (2) Long-chain FA are absorbed in the lymphatic system. (3) Fuels released from the liver include glucose, β-hydroxybutyrate (BHB), acetate, amino acids (AA) and very-low-density lipoproteins. Fuels extracted by the liver from circulating blood include non-esterified FA (NEFA), glycerol, lactate and AA. When AA are supplied in excess, and when AA profile diverges from optimal, their oxidation and use for anaplerosis increases. Glucose output by the liver into the blood is affected by its demand by tissues and controlled primarily by insulin and glucagon. (4) Milk synthesis by the mammary gland is a sink for potential fuels, including glucose, NEFA, acetate, butyrate and AA. Removal of these fuels from the blood likely promotes intake by reducing their availability for oxidation in the liver. (5) Adipose tissue extracts acetate, glucose and NEFA from the blood during lipogenesis and mobilizes triacylglycerol, increasing the availability of NEFA and glycerol for hepatic oxidation. (6) Muscle tissue utilizes glucose, acetate, glycerol, BHB and NEFA as fuels, and AA for protein synthesis. Amino acids are mobilized during negative energy balance, increasing their availability as fuels following deamination, although anaplerosis of glucogenic AA decreases their oxidation compared with ketogenic AA. Lactate from partial metabolism of glucose by the muscle is available for gluconeogenesis or oxidation in the liver (adapted from Allen, 2014 with permission).

and medium-chain FA. Little acetate, if any, is extracted from the blood because of low activity of AcCoA synthetase (Ricks and Cook, 1981) necessary for its conversion to AcCoA and subsequent metabolism. In addition, little glucose is extracted from the blood of mature ruminants that lack glucokinase (Ballard, 1965), ensuring low hepatic glycolysis (Aschenbach *et al.*, 2010). All fuels must be converted to AcCoA in the mitochondria for complete oxidation to CO_2 in the TCA cycle. Fatty acids are converted to AcCoA by β-oxidation, whereas glucogenic fuels are converted to AcCoA through pyruvate by the pyruvate dehydrogenase complex, and ketogenic AA are converted directly to AcCoA after deamination. Although propionate and other glucose precursors can be converted to pyruvate when their supply exceeds the glucogenic flux, conversion of pyruvate to AcCoA is likely inhibited in the postpartum period. Elevated concentrations of AcCoA activate pyruvate carboxylase if energy charge is high (Petersen *et al.*, 1994) and inhibits conversion of pyruvate to AcCoA by the pyruvate dehydrogenase complex (Begum *et al.*, 1983), providing negative feedback and conserving TCA intermediates.

Control of hepatic oxidation

Hepatic oxidation of fuels fluctuates with the energy needs of the liver, which varies over weeks and months (e.g. to support growth and lactation; Reynolds *et al.*, 2004). However, the periprandial pattern of fuel oxidation affects hepatic energy status and is involved in the control of feeding behavior (Friedman, 1997). Energy status of the liver is dependent upon the balance between energy-consuming and energy-producing reactions. Acetyl CoA enters the TCA cycle for oxidation but can also be used for anabolic pathways or exported from the liver as ketone bodies or hydrolyzed and released as acetate (Allen *et al.*, 2009). The entry of AcCoA into the TCA cycle requires oxaloacetate (**OAA**) for the citrate synthase reaction. The availability of OAA is dependent upon the concentration of TCA intermediates and the rate of reactions within the TCA cycle (Allen, 2014). The concentration of TCA intermediates in the mitochondria of hepatocytes is determined by the balance between anaplerosis (entry into the cycle) and cataplerosis (exit from the cycle). Intermediates exit the TCA cycle as they are used in biosynthetic pathways. Pre-gastric fermentation limits glucose available for absorption, so glucose needs are met by gluconeogenesis, which is the primary factor affecting cataplerosis in ruminants (Aschenbach *et al.*, 2010). Anaplerotic metabolites include propionate, glucogenic AA, lactate and glycerol (Aschenbach *et al.*, 2010). Propionate carbon enters the TCA cycle as succinyl CoA, and other metabolites enter the TCA cycle at other sites (i.e. OAA and α-ketoglutarate). The speed at which they are able to stimulate the oxidation of AcCoA is dependent upon the concentrations of enzymes and cofactors, enzyme activity and end-product accumulation of individual reactions (Allen, 2014). Elevated [NADH]/[NAD] and [ATP] indicate energy sufficiency, decreasing the rate of certain reactions and the availability of OAA for the citrate synthase reaction (Allen *et al.*, 2009).

Modulation of hepatic oxidation

Hormones and cytokines modulate hepatic oxidation over both the long and short terms by affecting the availability of AcCoA for oxidation, as well as anaplerosis and cataplerosis of TCA cycle intermediates. This section reviews the major factors modulating hepatic oxidation, including insulin, glucagon, somatotropin and leptin.

Plasma concentration of insulin varies over the long term with elevated concentrations indicating energy adequacy. Insulin is secreted by the pancreas in response to glucose as well as propionate and butyrate (Manns and Boda, 1967). Other nutrients such as NEFA and certain AA can augment glucose-induced insulin secretion (Fu *et al.*, 2013). In addition, insulin secretion is regulated by various hormones, including melatonin, estrogen, leptin, somatotropin and glucagon like peptide-1 (Fu *et al.*, 2013). Insulin suppresses gluconeogenesis and ketogenesis in the liver (Brockman and Laarveld, 1986), modulating hepatic oxidation by reducing cataplerosis of the TCA cycle and increasing the availability of AcCoA for oxidation by decreasing its export from the liver as ketone bodies. Insulin also stimulates lipogenesis and suppresses lipolysis (Brockman and Laarveld, 1986), reducing the concentration of NEFA in the blood. Non-esterified fatty acids are the primary source of AcCoA and are extracted from the blood in proportion to their concentrations (Bell, 1980). Plasma concentrations of insulin and NEFA are inversely related over the long term as well as within the timeframe of meals with pulsatile insulin release in response to absorbed fuels (Allen, 2014). Insulin also stimulates the uptake of AA by muscle tissue and inhibits protein degradation (Brockman and Laarveld, 1986; Lobley, 1992). The mobilization of AA from the muscle occurs during negative energy balance when plasma insulin concentration is low (Heitmann and Bergman, 1980). Amino acids can be oxidized in the TCA cycle after conversion to AcCoA, and glucogenic AA are anaplerotic and can stimulate the oxidation of AcCoA.

Glucagon has both direct and indirect effects on plasma NEFA concentrations (Bobe *et al.*, 2003) by directly increasing lipolysis (Brockman, 1976) but indirectly decreasing lipolysis by increasing the concentrations of glucose and insulin (Brockman, 1978). Therefore, the net effect on lipolysis and NEFA supply to the liver is dependent upon responses of glucose and insulin (Bobe *et al.*, 2003). Glucagon stimulates gluconeogenesis in bovine hepatocytes *in vitro*, but the response is counteracted by insulin (Donkin and Armentano, 1995). Chronic elevation of plasma insulin concentrations inhibits gluconeogenesis, decreasing cataplerosis of TCA intermediates and likely stimulating hepatic oxidation within meals sooner (Allen, 2014).

Somatotropin has a range of biological effects, including stimulation of milk synthesis, increased AA and glucose uptake by the muscle and mammary gland, increased protein synthesis and accretion by skeletal muscle, increased glucose output by the liver and decreased ability of insulin to inhibit gluconeogenesis, increased basal lipolysis during negative energy balance and decreased lipid synthesis during positive energy balance (Etherton and Bauman, 1998). Although somatotropin

secretion is pulsatile with irregular pulses in cattle (Kayusa, 2016), its effects on lipolysis are chronic with no acute effects in ruminants (Houseknecht et al., 1996). Somatotropin likely stimulates feed intake by hepatic oxidation by reducing TCA intermediates; cataplerosis is increased by increasing gluco-neogenesis, and anaplerosis is decreased by reducing AA supply to the liver.

Leptin has been implicated in the control of feed intake, and plasma leptin concentration is correlated with body fat percent and body condition score in lactating cows (Ehrhardt et al., 2000). Leptin treatment of animals causes a dose-dependent decrease in feed intake, and a loss of body weight and fat depots (Pelleymounter et al., 1995). The role of leptin on the regulation of body weight balance is consistent with a fat-related lipostatic signal to the brain, proposed by Kennedy (1953). Leptin increases lipolysis and plasma NEFA concentrations by inhibiting insulin release by the pancreas (Emilsson et al., 1997; Kieffer et al., 1997) and sup-pressing lipogenesis and increasing triglyceride hydrolysis (Houseknecht et al., 1998; Harris, 2014). Whereas leptin's effects on food intake are thought to be mediated centrally via neurotransmitters (Houseknecht et al., 1998), its effects on feed intake might also be from increasing the supply of AcCoA for hepatic oxidation by elevating plasma NEFA con-centrations (Allen, 2014).

Insulin resistance is attributed to decreased maximal effect of insulin (insulin responsiveness) and decreased insu-lin sensitivity (the concentration of insulin to elicit a half-maximal response; Kahn, 1978). The effects of insulin on stimulating lipogenesis and inhibiting lipolysis in adipose tis-sue are affected by various factors (Vernon, 1980). Insulin resistance varies among animals and physiological states, modulating the effects of insulin on plasma NEFA concentra-tions and its supply to the liver. Hyperinsulinemia can cause insulin resistance by downregulating insulin receptors and desensitizing post-receptor pathways (Kahn and Flier, 2000). Insulin resistance of adipose tissue has been positively related to somatotropin in dairy cows (Boisclair et al., 1994; Bell and Bauman, 1997), and a long-term administra-tion of the pro-inflammatory adipokine TNF-α induced insulin resistance in steers (Kushibiki et al., 2001). In contrast, the anti-inflammatory adipokine adiponectin was negatively related to insulin resistance in cows (Giesy et al., 2012).

Metabolites affect insulin sensitivity directly by modu-lating the insulin-signaling pathway, and alter the protein function by post-translational modification by metabolites (e.g. acetylation and palmitoylation; Yang et al., 2018). Sustained elevation of plasma NEFA can interfere with insulin signaling, increasing insulin resistance (Le Marchand-Brustel et al., 2003). Hyperlipidemia impairs the ability of insulin to suppress gluconeogenesis, stimulates glucose uptake into skeletal muscle and inhibits insulin secretion from the pan-creas (Kahn and Flier, 2000). However, NEFA differ in their effects on insulin sensitivity. Saturated FA impair insulin sig-naling and decrease insulin sensitivity, whereas some unsaturated FA, including the polyunsaturated eicosapentae-noic and docosahexaenoic acids and monounsaturated oleic

and palmitoleic acids, are associated with improved insulin sensitivity (Yang et al., 2018). β-hydroxybutyrate inhibits lipolysis in adipose tissue (Taggart et al., 2005), providing negative feedback when AcCoA is in excess.

Interactions of diet and physiological state
The physiological state varies greatly across the lactation cycle, including the prepartum period when preparing for the transition from pregnancy to lactation; the immediate postpartum period characterized by a lipolytic state; peak lac-tation when cows are in negative energy balance and feed intake is increasingly limited by distention; and mid- to late lactation when milk yield decreases and body energy stores replete (Table 1). The effects of diet composition on feed intake are affected by the physiological state of animals (Allen and Piantoni, 2014), and the interactions of diet and physiological state are related to the supply of AcCoA, and the balance between anaplerosis and cataplerosis of the TCA cycle (Figure 2).

Acetyl CoA availability for the citrate synthase reaction. The peripartum period is characterized by a lipolytic state to help meet the challenges of transitioning from pregnancy to lac-tation. The increase in plasma NEFA concentration helps to achieve a successful transition by sparing glucose for the *gravid uterus* prepartum and the lactating mammary gland postpartum, increasing the fat content of colostrum and early milk to improve energy intake by the newborn calf and pro-viding alternative fuels to extrahepatic tissues when lactation is initiated and plasma glucose and insulin concentrations are low. Homeorhetic signals effecting this change include a decline in plasma insulin concentrations beginning several weeks prepartum (Doepel et al., 2002) and an increase in insulin resistance of adipose tissue during the peripartum period (Vernon, 1980).

The depression of feed intake that begins in the days prior to parturition (Ingvartsen and Andersen, 2000) is likely from a steady supply of AcCoA for oxidation in the liver during the

Table 1 *Relative status of characteristics related to the control of feed intake at different stages of lactation in cattle*

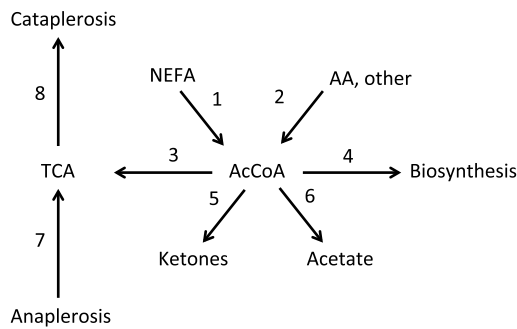| Factor	Stage of lactation			
	Prepartum period	Immediate postpartum	Peak lactation	Mid–late lactation, pregnant
Gut distension	L	L	H	M
Acetyl CoA	M	H	L	M
Anaplerosis	L to H	L to H	L to H	L to H
Cataplerosis	L	H	H	M
Insulin	L	L	M	H
Glucagon	M	H	M	M
Somatotropin	M	H	M	L
Leptin	H	L	M	H
Insulin resistance	M	H	M	L

L = low level; M = medium level; H = high level.

Figure 2 Effects of diet and physiological state on hepatic concentrations of acetyl CoA (AcCoA) and the tricarboxylic acid (TCA) cycle intermediates in ruminant animals. (1) The primary source of AcCoA is β-oxidation of non-esterified fatty acids (NEFA) extracted from the blood. (2) Other sources of AcCoA include amino acids (AA), lactate, glycerol, butyrate and medium-chain FA. (3) AcCoA enters the TCA cycle for oxidation combining with oxaloacetate (OAA) to form citrate. Acetyl CoA is also (4) used in biosynthetic reactions, (5) exported as ketone bodies and (6) hydrolyzed to acetate and released into the bloodstream. The oxidation of AcCoA in the TCA cycle is dependent upon the supply of OAA produced from TCA intermediates. The concentration of TCA intermediates is determined by the balance between anaplerosis and cataplerosis. (7) Anaplerotic metabolites include those of dietary origin, including propionate, glucogenic AA, lactate and glycerol, as well as endogenous sources including lactate, glucogenic AA and glycerol. The rate of anaplerosis by metabolites of dietary origin is highly variable depending upon the diet and the kinetics of digestion and passage. Propionate entry is pulsatile post-prandially as it can be produced, absorbed and extracted from the blood very quickly within the time-course of meals. Other anaplerotic metabolites derived from the diet (e.g. glucogenic AA, lactate) are absorbed post-ruminally with a greater latency for absorption and likely contribute to anaplerosis between meals. (8) Cataplerosis decreases the concentration of TCA intermediates, which are used for gluconeogenesis and other biosynthetic reactions.

lipolytic state (Allen *et al*., 2005). The plasma concentration of NEFA is determined by the balance between supply and removal; supply is from net lipolysis (the balance between lipolysis and lipogenesis) and absorbed dietary lipids, and removal is by oxidation in the liver, muscle and uterus and export as FA in milk. Endogenous and dietary lipids likely decrease feed intake by hepatic oxidation, signaling the brain depending upon the energy charge of the liver, rather than having direct central nervous system (**CNS**) effects (Kuhla *et al*., 2016). Plasma NEFA concentrations increase beginning 2 to 3 weeks prepartum, coinciding with a decrease in plasma insulin concentration, and peak at parturition when plasma insulin concentration reaches its nadir (Doepel *et al*., 2002). Over the first several weeks postpartum, NEFA is exported as milk fat, and net lipolysis decreases as plasma insulin concentrations gradually increase (Doepel *et al*., 2002). Hepatic uptake of NEFA during the postpartum period in excess of FA transport into the mitochondria for β-oxidation results in storage as triglycerides. The production of AcCoA by β-oxidation that exceeds the capacity for oxidation in the TCA cycle and biosynthesis increases export as ketone bodies and hydrolysis and release as acetate. Ketone bodies and acetate are used by extrahepatic tissues to spare glucose, and their export decreases the pool of AcCoA available for hepatic oxidation, helping to alleviate the depression of DMI in the postpartum period.

Dairy cows with higher body condition scores at calving lost more body weight and body condition, over a longer period, than cows with lower condition scores (Garnsworthy and Topps, 1982). In addition, more extensive mobilization of body fat for over-conditioned cows began before calving and continued during the first weeks of lactation (Kokkonen *et al*., 2005). Extensive mobilization of fat by over-conditioned cows during the peripartum period likely increases the supply of AcCoA for oxidation in the liver, suppressing DMI consistent with the HOT.

Insulin resistance of adipose tissue in the peripartum period is related to increased somatotropin and pro-inflammatory cytokines and decreased concentrations of anti-inflammatory cytokines. Plasma concentrations of somatotropin begin to increase several weeks before calving, with peak concentrations reached during the postpartum period (Koprowski and Tucker, 1973), whereas plasma concentrations of IGF-1 have an opposite pattern (Doepel *et al*., 2002). Leptin decreases with the onset of lactation (Kadokawa *et al*., 2000). However, constant intravenous infusion of leptin for 96 h did not affect feed intake of cows in the postpartum period (Ehrhardt *et al*., 2016). A lack of effect of leptin on feed intake of cows in negative energy balance is consistent with its effects attributable to hepatic oxidation because leptin treatment is unlikely to reduce insulin concentrations, when it is already low, or increase insulin resistance of adipose tissue, when it is already elevated, during this period. The elevation of TNF-α during this period was correlated positively with insulin resistance in cows with fatty liver (Ohtsuka *et al*., 2001), and decreased adiponectin concentration in the peripartum period in the dairy cow likely contributes to insulin resistance (Giesy *et al*., 2012). A retrospective study of cows with high *v.* low fat concentrations in the liver during the postpartum period reported that cows with higher liver fat concentrations had lower feed intake, higher plasma NEFA concentrations, increased degradation of AA and anaplerotic reactions, increasing TCA cycling, mitochondrial oxidation of AcCoA and oxidative phosphorylation consistent with the HOT (Schäff *et al*., 2012).

As lactation proceeds, elevated somatotropin continues to direct nutrients to milk production (Etherton and Bauman, 1998), and plasma NEFA concentrations decrease as greater quantities of NEFA are exported as milk fat and increasing plasma insulin concentrations decrease net lipolysis. Hepatic AcCoA concentrations decrease as plasma NEFA concentrations decline, decreasing their export as ketone bodies. The signal from hepatic oxidation gradually diminishes as hepatic AcCoA concentrations decrease and feed intake is increasingly limited by distention by undigested feed residues (Allen, 2014). Whereas the dominant mechanisms controlling feed intake change with diet and physiological state, different mechanisms likely have additive effects on feed intake both within and across days. Synergistic effects on satiety were demonstrated by the additive effects of intraruminal infusion of short-chain FA on feeding behavior of lactating cows when rumens were distended by balloons (Mbanya *et al*., 1993) or forage NDF concentrations of diets (Choi and Allen, 1999).

Priorities in mid- to late lactation include directing nutrients to the fetus and replenishing body reserves. Somatotropin concentrations gradually decline, decreasing milk yield and insulin resistance. Decreased milk production results in elevated plasma glucose and insulin concentrations, increasing the balance between lipogenesis and lipolysis, and decreasing plasma NEFA and hepatic AcCoA concentrations (Piantoni et al., 2015). Although NEFA is likely the dominant source of AcCoA for cows in the postpartum period when cows are in a lipolytic state, other fuels likely contribute to a greater extent when cows are in late lactation (Piantoni et al., 2015). Plasma leptin concentrations increase with body condition (Bradford et al., 2006), limiting adiposity by direct effects on the CNS as well as by increasing plasma NEFA concentrations and the supply of AcCoA for hepatic oxidation (Allen, 2014). Sensitivity to exogenous leptin varies among animals, and obese animals may have reduced sensitivity to leptin, reducing its hypophagic effect (Myers et al., 2012).

Anaplerosis v. *cataplerosis: stimulation of acetyl CoA oxidation.* Intermediates of the TCA cycle that provide OAA for the citrate synthase reaction and used for gluconeogenesis and other biosynthetic reactions are replenished by anaplerotic metabolites derived from the diet and tissues. Propionate is the primary anaplerotic metabolite stimulating hepatic oxidation within the timeframe of meals (Allen, 2000). Propionic acid is produced primarily by the fermentation of starch by rumen microbes and can be produced and absorbed as propionate at very high rates and efficiently extracted by the liver within the timeframe of meals (Allen, 2000). Other anaplerotic metabolites derived from the diet (e.g. glucogenic AA, lactate) are absorbed post-ruminally with a greater latency for absorption and likely contribute to hepatic oxidation extending satiety post-prandially (Allen et al., 2009). Although glycerol and propionate are both 3-carbon glucose precursors with similar energy concentrations, they have different hypophagic effects because propionate is an obligate anaplerotic metabolite, whereas glycerol can enter the gluconeogenic pathway as glyceraldehyde-3-phosphate in the cytosol without stimulating hepatic oxidation. Consistent with this, propionic acid decreased DMI 17% relative to glycerol by decreasing meal size when isoenergetic solutions were infused abomasally in cows in the postpartum period (Gualdrón-Duarte and Allen, 2017).

The production rate of propionic acid by rumen microbes is highly variable depending upon source (Allen, 2000). The starch concentration of diets consumed by ruminants is highly variable ranging from <5% for some grazing ruminants to >30% for some lactating dairy cows and fattening steers. Starch degradation by rumen microbes varies from <50% to >90% (Nocek and Tamminga, 1991). Starch that passes from the rumen can be digested to glucose in the intestine, which is absorbed and enters the circulation or is metabolized to lactate by intestinal tissues. Although increasing dietary starch can increase feed intake when cereal grains are substituted for forages by decreasing ruminal distention (Allen, 1996), increased ruminal starch fermentability decreased feed intake by up to 3 kg/day in several experiments reported in the literature (Allen, 2000). High-moisture corn decreased energy intake of cows in the postpartum period to a greater extent when fed in rations at higher starch concentrations (28% v. 22%) compared with less fermentable dry ground corn (Albornoz and Allen, 2018). Hypophagic effects of a more fermentable starch source in lactating cows were from decreased meal size despite a decreased inter-meal interval, so satiety was likely caused by the absorption of propionate within the timeframe of meals (Oba and Allen, 2003b).

Of the fuels available from the fermentation and digestion of starch, propionate is the most hypophagic. Intraruminal infusion of propionate decreased metabolizable energy intake compared with acetate (Oba and Allen, 2003c), and propionic acid decreased metabolizable energy intake compared with isoenergetic infusion of glucose and reduced DMI compared with isoenergetic infusions of lactic acid when infused into the abomasum (Gualdrón-Duarte and Allen, 2018). Intraruminal infusion of propionic acid reduced metabolizable energy intake by cows in the postpartum period compared with cows in mid-lactation (Oba and Allen, 2003a). Although gluconeogenesis is upregulated for cows in the postpartum period, they were in a lipolytic state with elevated plasma BHB concentrations, whereas cows in mid-lactation were in positive energy balance with low plasma concentrations of BHB. Differences in plasma BHB concentrations likely reflect differences in the supply of AcCoA for hepatic oxidation, consistent with the greater hypophagic effects of propionic acid for cows in the postpartum period. In addition, the hypophagic effects of intraruminal infusions of propionic acid were related linearly with hepatic AcCoA concentrations for cows in the postpartum period (Stocks and Allen, 2012), and the effects were not attenuated over a 3-day intraruminal infusion (Stocks and Allen, 2013). It is noteworthy that propionate interacted with AcCoA in the liver to affect feed intake only during the first 4 h after feeding each day; daily DMI was reduced despite no effect of treatment on feed intake over the remaining 20 h (Stocks and Allen, 2013). This is likely because plasma NEFA concentrations are greatest prior to feeding and lowest several hours after feeding corresponding to the daily peak in plasma insulin concentrations for cows fed ad libitum once per day in the morning (Allen et al., 2005).

Chronic elevation of plasma insulin concentrations likely suppresses feed intake by decreasing cataplerosis, but pulsatile insulin secretion in response to feeding likely clears fuels from the blood more quickly, potentially increasing meal size or decreasing the interval between meals (Oba and Allen, 2000). Concentrations of insulin and NEFA in plasma vary within days and are negatively related on a minute timescale (Figure 3). The depression in feed intake of lactating cows to a more fermentable diet was correlated positively to the insulin response to a glucose challenge; cows with a greater insulin response were better able to maintain feed intake on the
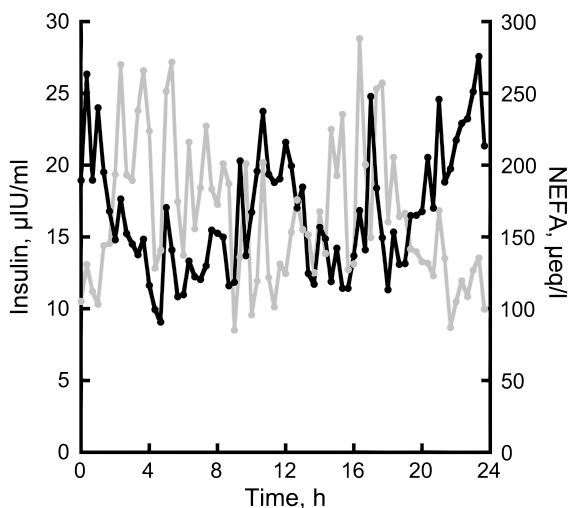
Figure 3 Inverse relationship between plasma insulin (grey line) and non-esterified fatty acid (NEFA; black line) concentrations for an individual cow within a day. Cow was fed *ad libitum*, once per day with blood samples taken every 20 min for 24 h. Increased insulin during and following meals decreases the supply of NEFA for hepatic oxidation, while decreased insulin gradually increases NEFA supply following meals (Allen, 2014 with permission).

more fermentable diet (Bradford and Allen, 2007). Postprandial pulses of insulin interrupt the supply of fuels to the liver by stimulating the uptake of fuels by insulin-sensitive tissues and inhibiting lipolysis in adipose issue. Consistent with this, feed intake over the first 4 h following feeding was highly variable among cows in the immediate postpartum period ranging from 3.7 to 9.6 kg and was positively related to the postprandial reduction of plasma NEFA concentrations which varied from 244 to 1158 µEq/l (Piantoni *et al.*, 2015). Because the change in hepatic AcCoA concentrations was positively correlated with the change in plasma NEFA concentrations, the difference in DMI among cows was likely related to differences in the supply of AcCoA derived from β-oxidation of NEFA, consistent with the HOT. Furthermore, because DMI was not related with plasma concentrations of glucose, insulin, NEFA and BHB, or hepatic concentrations of AcCoA before feeding, or to the change in plasma glucose, insulin or BHB over the 4-h period, the variation in DMI was likely because of differences in insulin resistance among cows.

The mobilization of tissue AA begins prepartum (Doepel *et al.*, 2002; Kokkonen *et al.*, 2005), and high-yielding dairy cows might mobilize up to 1 kg of tissue protein per day in the early postpartum period (Bell *et al.*, 2000). Although AA are used for milk protein synthesis in the postpartum period (Aschenbach *et al.*, 2010), excess AA and AA imbalances will result in deamination of AA, increasing anaplerosis and stimulating the oxidation of AcCoA, potentially suppressing feed intake (Allen, 2014). A meta-analysis by Martineau *et al.* (2016) showed that DMI of cows ranging from early to late lactation was reduced by abomasal infusion of casein when supply of metabolizable protein (**MP**) was positive but increased DMI of cows when MP balance was negative. When MP supply was positive, excess AA were

likely deaminated, increasing anaplerosis and stimulating hepatic oxidation and satiety, whereas increased DMI by casein infusion when MP supply was negative might have been because of increased metabolic pull. Supplementation of rumen-protected methionine has had variable effects on DMI (Patton, 2010; Zanton *et al.*, 2014), and Allen (2014) suggested that supplying limiting AA will likely decrease deamination of other AA and anaplerosis, potentially increasing DMI.

Gluconeogenesis is likely an important determinant of the temporal oxidation of fuels in the liver by increasing cataplerosis of the TCA cycle. The contribution of substrates to gluconeogenesis has been estimated to be propionate (60% to 75%), lactate (16% to 26%), alanine (5%) and other AA (8% to 11%), valerate and isobutyrate (5% to 6%) and glycerol (0.5% to 3%; Aschenbach *et al.*, 2010). In the immediate postpartum period, the contribution of propionate to gluconeogenesis (~60%) is less, and mostly endogenous lactate (~26%) is greater than several weeks later in lactation; together, they account for over 85% of gluconeogenic substrates extracted from the blood by the liver (Aschenbach *et al.*, 2010). Gluconeogenesis is upregulated in early lactation when plasma insulin concentration is low and gradually downregulated by elevated insulin concentrations (Barthel and Schmoll, 2003) as lactation advances and glucose demand decreases. However, excessive lipolysis in the peripartum period can result in hepatic steatosis, reducing gluconeogenesis (Zhu *et al.*, 2000). The depression of DMI by a diet containing a more rapidly fermentable starch source was correlated positively ($r = 0.53$, $P < 0.01$) with plasma insulin concentrations among cows past peak lactation, likely because gluconeogenesis was suppressed by insulin (Bradford and Allen, 2007). The downregulation of gluconeogenesis decreases cataplerosis, increasing the concentrations of TCA intermediates and TCA cycle capacity for oxidation.

More questions
Questions remain regarding the mechanism(s) by which oxidation of fuels by hepatocytes is conveyed to hepatic vagal afferent nerves as well as how hepatic oxidation can be manipulated to alter (increase or decrease) feed intake. Feeding behavior is controlled on a minute-to-minute basis, but little research has evaluated hepatic metabolism over the timeframe of meals. Comprehensive evaluation of metabolite concentrations and isotopic tracer studies are needed to better understand hepatic metabolism over the short term related to feeding behavior. Genetic differences in feed intake among animals have yet to be investigated for factors related to hepatic oxidation of fuels. Differences in the rate of uptake of NEFA from the blood by the liver, peroxisomal oxidation of FA, transport of FA into the mitochondria, rate of production and export of ketone bodies, and rate of hydrolysis of AcCoA and export of acetate from the liver might affect feed intake by their effects on hepatic oxidation. In addition, differences among animals or physiological states for insulin release or insulin sensitivity of adipose tissue might decrease lipolysis within meals, decreasing the supply of AcCoA for oxidation, increasing meal length and size.

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Conclusion

Fuel supply to the liver is dependent upon the absorption of fuels derived from the diet as well as those supplied to or extracted from the blood by extrahepatic tissues. Hepatic oxidation of fuels varies with the needs of the liver over the long term as well as periprandially, affecting feeding behavior. Homeorhetic mechanisms affect the concentrations of insulin, glucagon, somatotropin and leptin, as well as insulin sensitivity of tissues, which interact with diet to affect hepatic oxidation by their effects on the supply of AcCoA, anaplerosis and cataplerosis. Therefore, mechanisms controlling energy intake and partitioning are multiple, entwined and inseparable and are affected by both diet and physiological state. The liver is likely a key sensor of energy status integrating homeostatic and homeorhetic mechanisms, offering the unique advantage of sensing not just energy availability but energy balance relative to nutrient demands.

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Declaration of interest

The author has no conflicts of interest.

Ethics statement

Not applicable.

Software and data repository resources

None.

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