

JOURNAL OF ANIMAL SCIENCE

The Premier Journal and Leading Source of New Knowledge and Perspective in Animal Science

BOARD-INVITED REVIEW: The hepatic oxidation theory of the control of feed intake and its application to ruminants

M. S. Allen, B. J. Bradford and M. Oba

J Anim Sci 2009.87:3317-3334.

doi: 10.2527/jas.2009-1779 originally published online Jul 31, 2009;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jas.fass.org/cgi/content/full/87/10/3317>



American Society of Animal Science

www.asas.org

BOARD-INVITED REVIEW: The hepatic oxidation theory of the control of feed intake and its application to ruminants¹

M. S. Allen,*² B. J. Bradford,† and M. Oba‡

*Michigan State University, East Lansing 48824-1225; †Kansas State University, Manhattan, 66506; and ‡University of Alberta, Edmonton, Alberta T6G 2P5, Canada

ABSTRACT: Feed and energy intake of ruminant animals can change dramatically in response to changes in diet composition or metabolic state, and such changes are poorly predicted by traditional models of feed intake regulation. Recent work suggests that temporal patterns of fuel absorption, mobilization, and metabolism affect feed intake in ruminants by altering meal size and frequency. Research with nonruminants suggests that meals can be terminated by signals carried from the liver to the brain via afferents in the vagus nerve and that these signals are affected by hepatic oxidation of fuels and generation of ATP. We find these results consistent with the effects of diet on feed intake of ruminants. Of fuels metabolized by the ruminant liver, propionate is likely a primary satiety signal because its flux to the liver increases greatly during meals. Propionate is utilized for gluconeogenesis or oxidized in the liver and stimulates oxidation of acetyl CoA. Although propionate is extensively metabolized by the ruminant liver, there is little net metabolism of acetate or glucose, which may explain why these fuels do not consistently induce hypophagia in ruminants.

Lactate is metabolized in the liver but has less effect on satiety, probably because of greater latency for reaching the liver within meals and because of less hepatic extraction compared with propionate. Hypophagic effects of fatty acid oxidation in the liver are likely from delaying hunger rather than promoting satiety because β -oxidation is inhibited during meals by propionate. A shortage of glucose precursors and increased fatty acid oxidation in the liver for early lactation cows lead to a lack of tricarboxylic acid (TCA) cycle intermediates, resulting in a buildup of the intracellular acetyl-CoA pool and export of ketone bodies. In this situation, hypophagic effects of propionate are likely enhanced because propionate entry into the liver provides TCA cycle intermediates that allow oxidation of acetyl-CoA. Oxidizing the pool of acetyl-CoA rather than exporting it increases ATP production and likely causes satiety despite the use of propionate for glucose synthesis. A better understanding of metabolic regulation of feed intake will allow diets to be formulated to increase the health and productivity of ruminants.

Key words: hepatic vagus, hypophagia, lipolytic state, propionate

©2009 American Society of Animal Science. All rights reserved.

J. Anim. Sci. 2009. 87:3317–3334
doi:10.2527/jas.2009-1779

INTRODUCTION

The idea that the liver is involved in the control of food intake was introduced by Russek (1963), who proposed that feeding behavior of dogs was influenced by glucoreceptors in the liver following Mayer's suggestion that food intake is regulated by changes in blood glucose concentration (Mayer, 1953). As several research

groups contributed to our understanding over time, the idea of hepatic glucoreceptors has evolved into the theory that food intake is controlled by a signal from the liver to the brain that is stimulated by oxidation of a variety of fuels. We call this the hepatic oxidation theory (**HOT**) of the control of food intake, which is supported by a large body of work with rats and other nonruminant laboratory species (see reviews by Forbes, 1988; Langhans, 1996; Friedman, 1998; Sharrer, 1999). Application of this theory to ruminants presents some challenges because ruminal fermentation alters the type and pattern of absorbed fuels, fuels oxidized in the liver of ruminants differ from nonruminants, and feed intake of ruminants consuming roughage is sometimes limited by gut distension. However, the complication of understanding metabolic control of feed intake with ruminal fermentation has been addressed by experiments that

¹Supported by USDA National Research Initiative Competitive Grants No. 2004-35206-14167 (M. S. Allen) and 2008-2007-04229 (M. S. Allen), National Science Foundation Graduate Research Fellowship Program (B. J. Bradford), and Michigan State University Distinguished Fellowship Program (B. J. Bradford).

²Corresponding author: allenm@msu.edu

Received January 8, 2009.

Accepted June 12, 2009.

infused various fuels directly into the abomasum or the bloodstream (Allen et al., 2005).

It is important to note that the pattern of oxidation of fuels (minute to minute) is what affects feeding behavior because the amount of oxidation over longer periods of time (hours or days) is relatively constant and determined by the energy requirements of the liver. According to HOT, energy intake of ruminants will be increased when energy consumed per unit of ATP generated in the liver over time is maximized. Our objective is to review and give evidence for the basic concepts of HOT and discuss its application to ruminant animals, including the extent to which control of feed intake by hepatic oxidation might vary with diet and physiological state of animals.

CONTROL OF FOOD INTAKE BY HEPATIC OXIDATION

Infusion of glucose decreases food intake in a variety of nonruminant species (Forbes, 1995). Nijjima (1969) observed that the firing rate of hepatic vagal afferent nerves in guinea pigs was inversely related to the concentration of glucose in the blood and the firing rate decreased when glucose was infused into the hepatic portal vein (Nijjima, 1981b). The firing rate of these nerves as well as food intake in rabbits increased when glucose metabolism was blocked with 2-deoxyglucose (Novin et al., 1973). More recently, α -cyano-4-hydroxycinnamic acid, which inhibits pyruvate transport across the mitochondrial membrane, decreased glucose oxidation and stimulated feeding in rats (Del Prete et al., 2004). Blocking fat oxidation has also been shown to stimulate feeding in rats. Mercaptoacetate, which inhibits the acyl CoA dehydrogenases, enzymes that catalyze the initial step in each cycle of fatty acid (FA) β -oxidation, stimulated feeding in rats fed a high fat diet (Scharrer and Langhans, 1986). In addition, methyl palmoxirate, an inhibitor of carnitine palmitoyltransferase (CPT) that transports FA into mitochondria, stimulated feeding in rats fed a diet rich in long-chain triglycerides (TG; Friedman et al., 1986) but not in those fed a diet rich in medium-chain TG (Friedman et al., 1990), likely because medium-chain FA do not require CPT for transport into the mitochondria. Medium-chain TG also reduced food intake of rats with a shorter latency than long-chain TG (Satabin et al., 1991); this might be because of their ability to bypass CPT for transport, a faster and more complete hydrolysis and rapid portal delivery to the liver compared with lymphatic system for long-chain TG (Langhans, 1996).

Integrated Mechanism

Inhibition of glycolysis and FA oxidation by combined treatment with 2-deoxyglucose and methyl palmoxirate (Friedman and Tordoff, 1986), or inhibition of glycolysis and lipolysis by combined treatment with 2-deoxyglucose and nicotinic acid (Friedman et

al., 1986), synergistically increased food intake in rats. Langhans et al. (1985b) reported that a variety of other fuels metabolized in the liver including lactate, pyruvate, and glycerol caused hypophagia in rats, which was eliminated by hepatic vagotomy. When rats were fed a high-fat diet, lactate and pyruvate failed to cause hypophagia, likely because high-fat diets are known to decrease pyruvate dehydrogenase activity and therefore oxidation of these fuels (Langhans et al., 1985a). Thus, oxidation of all fuels in the liver might provide a common integrated mechanism for the control of feeding behavior (Friedman and Tordoff, 1986).

Hepatic Energy Status

Evidence that hepatic energy status is related to feeding behavior of rats was provided by a series of experiments by Friedman and coworkers. Ji and Friedman (1999) reported that the time course of compensatory hyperphagia upon refeeding after fasting paralleled restoration of hepatic energy status. Research involving metabolic inhibitors demonstrated a cause-and-effect relationship between hepatic energy status and feeding behavior. Administration of the fructose analog 2,5-anhydro-D-mannitol (2,5-AM) to rats caused a dose-related increase in food intake by creating a metabolic state that resembled fasting (Tordoff et al., 1988). Subsequent research showed that the effect is likely in the liver because the latency for the eating response was less for portal compared with jugular infusion, hepatic vagotomy blocked the eating response, and significant radioactivity was found in the liver but not the brain after administration of radioactive 2,5-AM (Tordoff et al., 1991). Rawson et al. (1994) used ^{31}P nuclear magnetic resonance to show that 2,5-AM is rapidly phosphorylated in the liver, but is not metabolized beyond the 1,6 bisphosphate stage, thereby trapping inorganic phosphate and reducing ATP concentration. Phosphate loading prevented the decrease in hepatic ATP and eliminated the stimulatory effects of 2,5-AM on feeding (Rawson and Friedman, 1994).

Stimulation of eating by inhibiting FA oxidation with methylpalmoxirate (Friedman et al., 1999) or etomoxir (Horn et al., 2004) was also associated with reduced hepatic energy status as measured by liver ATP concentration, ATP-to-ADP ratio, and phosphorylation potential ($[\text{ATP}]/[\text{ADP}][\text{Pi}]$). The synergistic stimulation of feeding from the combined treatment of 2,5-AM and methylpalmoxirate was also related to decreased hepatic ATP/ADP ratio and phosphorylation potential when rats were fed a diet with equal energy (38%) from carbohydrate and fat (Ji et al., 2000). Feeding response to metabolic inhibitors depends upon the basal diet; administration of 2,5-AM stimulated eating in rats fed a low-fat high-carbohydrate diet, but not a high-fat low-carbohydrate diet; however, methylpalmoxirate stimulated eating in rats fed a high-fat low-carbohydrate diet, but not a low-fat high-carbohydrate diet (Horn and Friedman, 1998). Subsequent research

indicated that the interactions among the metabolic inhibitors and diets were consistent with their effects on hepatic energy status (Friedman et al., 2002; Ji et al., 2002). In addition, the AA analog ethionine stimulated eating and decreased hepatic ATP concentration by trapping adenosine as S-adenosyl-L-ethionine (Rawson et al., 1994). This body of work shows that feeding behavior of rats is related to hepatic energy status from oxidation of fuels.

Signal to Brain Feeding Centers

The splanchnic bed is highly innervated by the autonomic nervous system, primarily through the vagus nerve. The liver itself is associated with afferent and efferent hepatic vagal fibers, allowing for substantial crosstalk with the central nervous system (Berthoud, 2004), and the hepatic vagus is the most likely mode of communication allowing for hepatic energy status to be transmitted to CNS loci controlling feeding behavior. Hepatic vagotomy has blocked the stimulation of satiety by a variety of fuels (Langhans et al., 1985b) and stimulation of eating by the metabolic inhibitors 2,5-AM (Tordoff et al., 1991) and mercaptoacetate (Langhans and Scharrer, 1987b). Intraportal infusion of 2,5-AM in anaesthetized rats dose-dependently increased the firing rate of the hepatic vagal afferents at doses previously shown to stimulate food intake (Lutz et al., 1996). Additionally, stimulation of eating by metabolic inhibitors resulted in activation of neuronal activity in rat brain stem, hypothalamus, and forebrain when measured by Fos-like immunoreactivity (Horn and Friedman, 1998).

Although evidence suggests that information regarding hepatic energy status is transmitted via the vagus nerve, the exact mechanism by which energy status of hepatocytes affects the firing rate of the hepatic vagal afferents has not been determined. One possibility is that hepatocyte depolarization leads to the release of compounds that activate nearby vagal afferents (Figure 1). Ouabain, which inhibits the plasma membrane sodium/potassium pump, blocked the reduction in firing rate of hepatic vagal afferents by glucose (Nijima, 1981a), leading Nijima (1983) to propose that glucose metabolism inside receptor cells in the liver reduces activity of hepatic vagal afferents by activation of the energy-dependent sodium/potassium pump. Intraportal infusion of ouabain stimulated eating, but intrajugular infusion did not (Langhans, 1996); and ouabain stimulated feeding in intact rats but not in rats with hepatic vagotomy (Langhans and Scharrer, 1987a), relating the activity of the sodium/potassium pump of liver cells to control of feeding behavior. Administration of 2,5-AM, which stimulated eating in rats, decreased ATP concentration in isolated hepatocytes and increased intracellular sodium concentration measured using ^{23}Na nuclear magnetic resonance spectroscopy (Friedman et al., 2003), providing further evidence that changes in

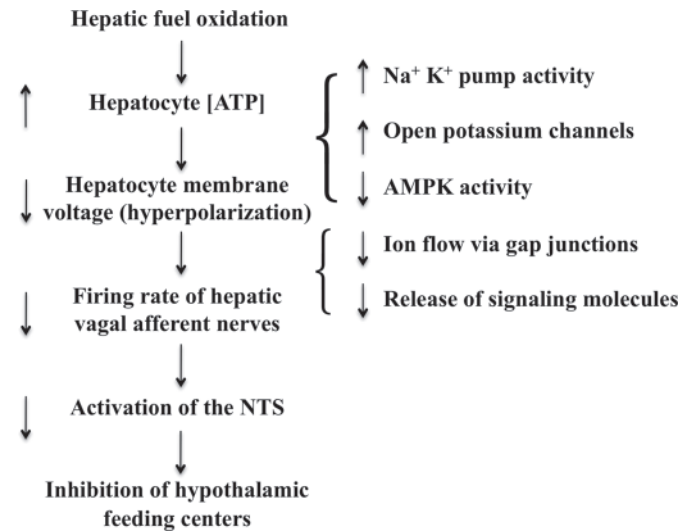


Figure 1. Proposed mechanism for control of feed intake by hepatic oxidation. Pathways that are involved in signal transduction from the liver to the forebrain are shown. Potential mediators are listed to the right for components of the mechanism that remain unresolved. AMPK = adenosine-5'-monophosphate-activated protein kinase; NTS = nucleus tractus solitarius.

sodium/potassium pump activity might be involved in the transduction of a hunger signal associated with energy status of hepatocytes.

Scharrer and colleagues (Rossi et al., 1995; Rossi and Scharrer, 1995; Lutz et al., 1998) provided evidence that potassium channels are involved in the hyperpolarization of the hepatocyte plasma membrane from oxidation of fuels. Rossi et al. (1995) reported that palmitate hyperpolarized mouse liver plasma membrane in a concentration-dependent manner and that the hyperpolarization was greater when mice were fed a high-fat diet compared with a low-fat diet. Hyperpolarization was reversed by inhibiting FA oxidation and blocking the sodium/potassium pump and potassium channels, indicating that hyperpolarization was because of FA oxidation, activation of the sodium/potassium pump, and opening of potassium channels. In addition, hyperpolarization of the mouse liver plasma membrane by lactate (Rossi and Scharrer, 1995) or by lactate, pyruvate, and fructose (Lutz et al., 1998) was prevented by the potassium channel blocker tetra-ethylammonium. Another potential candidate is adenosine-5'-monophosphate-activated protein kinase (AMPK) because AMPK may phosphorylate ion channels and other proteins involved in signal transduction pathways. The AMPK is activated in response to increased adenosine-5'-monophosphate concentration and is inhibited by ATP, and direct activation of AMPK in the hypothalamus increased food intake of rats (Andersson et al., 2004).

Energy status of hepatocytes might be conveyed to the nervous system through close coupling or neuro-modulators (Langhans, 1996). Alternatively, communication might be through a calcium-mediated secre-

tion event because intracellular calcium concentration of isolated hepatocytes increased quickly and markedly after exposure to 2,5-AM (Rawson et al., 2003). Hepatocytes secrete numerous compounds that serve as signaling molecule, including glutamate (Häussinger et al., 1989; Remesy et al., 1997), which is known to activate some vagal afferents (Nijima, 2000).

In toto, this body of work with rats and other nonruminant species suggests that 1) hepatic vagal afferent nerves are connected to brain feeding centers, 2) satiety is associated with a decreased firing rate of these nerves, 3) the signal is stimulated by a variety of fuels, 4) oxidation of fuels is required to generate this signal, and 5) the mechanism involves high energy phosphate bonds of adenosine.

HEPATIC OXIDATION IN RUMINANTS

Long-chain FA, lactate, AA, and glycerol are fuels oxidized in the ruminant and nonruminant liver. However, unlike the liver of nonruminants, plasma glucose is not used by the adult ruminant liver as an energy source. Hepatic uptake of glucose from the blood is negligible in mature ruminants (Stangassinger and Giesecke, 1986) because glucokinase activity is very low (Ballard, 1965). Although glucose infusion has been shown to be hypophagic in a variety of nonruminants (Forbes, 1995), glucose infusion did not reduce food intake when infused intravenously in cows (Dowden and Jacobson, 1960), intraperitoneally in heifers (Simkins et al., 1965), intracerebroventricularly in calves (Peterson et al., 1972), abomasally in lactating cows (Clark et al., 1977; Frobish and Davis, 1977), or intraportally or various other locations in sheep (Baile and Forbes, 1974). Thus, differences in hepatic glucose metabolism and hypophagic responses to infused glucose between ruminants and nonruminants are consistent with HOT. Because glucose infused abomasally is partially oxidized by enterocytes (Huntington et al., 2006), a satiety signal from gut oxidation is unlikely.

Propionate is the primary glucose precursor for ruminants, accounting for as much as 80% of glucose produced in lactating cows (Steinhour and Bauman, 1988). Although propionate can be converted to glucose, it can also be oxidized in the tricarboxylic acid (TCA) cycle (Aiello and Armentano, 1987; Steinhour and Bauman, 1988; Knapp et al., 1992) as well as stimulate oxidation of acetyl CoA derived from other fuels (Allen, 2000). This is another major difference from nonruminants; although propionate can also be metabolized in nonruminant liver, its supply to the liver is at least 10-fold less than in ruminants, minimizing its importance as an oxidative fuel. Ruminant liver has high activity of propionyl CoA synthetase but not acetyl CoA synthetase (Ricks and Cook, 1981) necessary for activation and subsequent metabolism of the respective VFA. As a result, propionate is extensively metabolized by the ruminant liver, but there is little net metabolism of acetate (Reynolds, 1995). Butyrate is almost completely

removed from portal blood and oxidized in the liver (Reynolds, 1995).

METABOLIC CONTROL OF FEED INTAKE IN RUMINANTS

Ruminal digestion kinetics determine the site and extent of nutrient digestion, which can greatly affect the type and pattern of fuels absorbed over time, thereby affecting the temporal pattern of fuel oxidation in the liver and feeding behavior. Retention of digesta in the rumen functions to supply a more consistent flow of starch, long-chain FA (LCFA), and protein to the small intestine, delaying absorption relative to meals, but VFA are rapidly produced and absorbed during meals and are likely responsible for stimulating satiety.

Ruminally Degraded Starch

Rates of ruminal starch digestion and passage vary greatly among grains fed to ruminants and depend upon the type of cereal grain, conservation method, and processing (NRC, 2001). Cereal grains that are highly digestible in the rumen can depress DMI of lactating cows; intake was depressed nearly 3 kg of DM/d (~13%) when more fermentable grains were substituted in diets of lactating cows in several studies reported in the literature (Allen, 2000). Oba and Allen (2003b) demonstrated that a more rapidly fermented starch source reduced meal size 17%, causing an 8% reduction in feed intake despite a 10% decrease in intermeal interval. The more fermentable treatment nearly doubled the fractional rate of starch digestion in the rumen, increasing the contribution of VFA as fuels, especially propionate, and decreasing glucose from starch digested in the small intestine and lactate from glucose metabolism in intestinal tissues.

Diets utilized in the feedlot industry result in regulation of feed intake primarily by metabolic signals rather than ruminal distention, and diet fermentability can clearly influence DMI of feedlot cattle. In a meta-analysis, Galyean and Defoor (2003) found that decreasing dietary starch concentration by increasing dietary roughage (range: 0 to 30% of DM) in feedlot diets consistently increased DMI across 11 studies. Effects of additional roughage on DMI were not explained by relative changes in dietary NE_g; therefore, effects of roughage concentration could not be attributed exclusively to an energy dilution effect (Galyean and Defoor, 2003). Similarly, decreasing diet starch concentration by substituting up to 40% of steam-flaked corn in a feedlot diet with wet corn gluten feed increased DMI by as much as 9%, resulting in greater ADG despite decreased feed efficiency (Parsons et al., 2007). Changes in starch fermentability have consistent effects on DMI as well. Wheat (Fulton et al., 1979) and barley (Bengochea et al., 2005) depress DMI compared with corn, and corn decreases DMI compared with sorghum (Gaebe et al., 1998); these DMI responses are inversely

related to the relative availability of starch across grain types (Huntington, 1997). Increases in starch digestibility due to more extensive grain processing (Brown et al., 2000; Bengochea et al., 2005) or increased grain moisture (Owens et al., 1997; Sindt et al., 2006) also decrease DMI. Besides increasing the amount of VFA produced per kilogram of OM consumed, increasing ruminal starch fermentation also increases propionate as a proportion of VFA absorbed. A signal to terminate meals is most likely caused by propionate for ruminants consuming high-starch diets (Allen, 2000) because its flux to the liver increases greatly during meals (Benson et al., 2002), it is rapidly metabolized in the liver (Reynolds, 1995), and it can stimulate hepatic oxidation.

Propionate. Hypophagic effects of propionate infusions have been documented extensively for ruminants (Allen, 2000). The liver is likely involved in regulation of feed intake by propionate because hypophagic effects of portal infusions of propionate were eliminated by splanchnic blockade with anesthetic, bilateral splanchnotomy, and hepatic vagotomy, as well as with total liver denervation in sheep (Anil and Forbes, 1988). Propionate was more hypophagic than acetate and butyrate when infused into the portal vein of sheep (Anil and Forbes, 1980), and infusion of propionate into the mesenteric vein of steers reduced feed intake, whereas acetate infused at similar rates did not (Elliot et al., 1985). This is consistent with HOT because propionate can be oxidized (Knapp et al., 1992) and stimulate oxidation in the liver, whereas hepatic acetate oxidation is negligible (Knapp et al., 1992).

Although propionate might be expected to decrease DMI compared with acetate because it has greater energy concentration, propionate linearly decreased ME intake compared with acetate in lactating cows when infused intraruminally as iso-osmotic mixtures (Oba and Allen, 2003f). As the proportion of propionate increased, the reduction in ME intake from the diet exceeded that supplied from the infusate. Feed intake was reduced primarily through a linear reduction in meal size from 2.5 to 1.5 kg of DM as propionate increased from 0 to 100% of infusate, which indicates increased satiety. These studies suggest that the depression of feed intake by propionate cannot be explained simply by the additional energy supplied as propionate. It is unlikely that animals consume feed to meet their energy requirements per se but rather have fuel-specific mechanisms regulating feeding behavior.

Lactate. Formulation of diets to shift starch digestion to the small intestine not only decreases propionate production, but also increases lactate absorption from glucose metabolism in the gut (Reynolds et al., 2003). This shift often results in greater feed intake, which is inconsistent with the hypothesis that feed intake is regulated to meet energy requirements (NRC, 2001). In contrast, HOT predicts increased feed intake in response to shifting the site of starch digestion postruminally. Starch digested in the small intestine likely stim-

ulates hepatic oxidation less than ruminally fermented starch, especially within the timeframe of meals, because of the greater lag for starch passing the rumen, and because extraction of lactate from the blood by the liver is much less than propionate (Reynolds et al., 2003). Extraction of lactate by the liver is probably less because metabolism of lactate to pyruvate is thermodynamically unfavorable when cellular NAD/NADH is reduced. Therefore, because of differences in metabolism, HOT predicts that more energy can be absorbed in the form of lactate than propionate.

FA Oxidation

Dietary FA can reduce DMI and energy intake of dairy cows (Allen, 2000), but a role for hepatic oxidation in the hypophagic effects of FA has not been demonstrated for ruminants. We know of only 2 experiments with ruminants using metabolic inhibitors, likely because of the limited supply, cost, and quantities of agents required. In those experiments, mercaptoacetate (which blocks β -oxidation) failed to elicit an eating response in goats (Scherrer, 1986) or in heifers fed a high-fat diet (Choi et al., 1997). Differences in the ability of mercaptoacetate to elicit an eating response between ruminants and nonruminants is likely because activity of acetyl CoA synthetase is less in the ruminant liver (Ash and Baird, 1973) compared with nonruminants (Hanson and Ballard, 1967). Activation of mercaptoacetate to mercaptoacetyl CoA by acetyl CoA synthetase is likely required for competitive inhibition of acyl CoA dehydrogenases blocking β -oxidation (Bauché et al., 1983).

Greater hypophagic effects of unsaturated C18 FA compared with saturated C18 FA, infused abomasally (Drackley et al., 1992) or fed in diets (Harvatine and Allen, 2006), is consistent with HOT because unsaturated FA are more rapidly oxidized than SFA in rats (Leyton et al., 1987) and unsaturated FA were oxidized to a greater extent than stearic acid in bovine hepatocytes (Mashek et al., 2002; Mashek and Grummer, 2003). In addition, greater hypophagic effects of medium-chain FA compared with LCFA (Dohme et al., 2004; Hollmann and Beede, 2008) are consistent with HOT because of faster absorption and transport of medium-chain FA into the mitochondria for oxidation as previously mentioned (Langhans, 1996). However, there are several other mechanisms likely contributing to hypophagic responses to dietary FA, including decreased palatability of diets and release of satiety-inducing gut peptides. The most compelling indirect evidence to link the hypophagic effects of FA in ruminants to hepatic oxidation is the persistent depression of intake for ruminants in a lipolytic state, such as transition cows and stressed receiving calves. In these situations, hunger is likely suppressed from elevated liver energy status driven by oxidation of NEFA mobilized from fat depots.

Transition Cows. Hyperlipidemia in the periparturient period is caused by a reduction in insulin sensi-

tivity of adipose tissues combined with a reduction in plasma insulin concentration; plasma insulin concentrations decline several weeks before parturition with a nadir below 6 μ IU/mL at 4 d postpartum (Doepel et al., 2002). Cytokines, as well as GH and other homeostatic signals, reduce insulin sensitivity and responsiveness of extrahepatic tissues and increase catecholamine responsiveness (Bell and Bauman, 1997). It is likely that lipolysis contributes to hypophagia rather than the reverse because plasma NEFA concentrations increase preceding periparturient hypophagia (Vasquez-Anon et al., 1994). These multiple metabolic changes result in plasma NEFA concentrations up to 10-fold greater in early lactation than during gestation (Ingvarthsen and Andersen, 2000). Uptake of NEFA by the liver increases greatly (Reynolds et al., 2003), resulting in increased FA oxidation and triglyceride storage (Drackley and Andersen, 2006). Gluconeogenic capacity is compromised by the increasing triglyceride concentration in the liver (Piepenbrink and Overton, 2003; Murondoti et al., 2004), increasing the time required to restore plasma glucose concentration.

Support for the role of FA oxidation in hypophagia of periparturient cows is provided by research that has focused on increasing hepatic FA oxidation, with the intent of preventing esterification and hepatic accumulation of TG. Carnitine palmitoyltransferase transports FA into mitochondria, the step that is considered to be rate-limiting for β -oxidation, and carnitine supplementation has been tested for its ability to increase the rate of mitochondrial transport. Feeding 100 g/d of carnitine to transition cows increased *in vitro* palmitate oxidation (Carlson et al., 2006) and decreased feed intake during the first 2 wk of lactation (Carlson et al., 2007). Others have demonstrated that dietary inclusion of *trans* octadecenoic acids increases mRNA abundance of PPAR- α that serves as a master switch for hepatic oxidation of FA (Selberg et al., 2005); *trans* octadecenoic acids also depressed feed intake during wk 4 to 6 of lactation (Selberg et al., 2004). Consistent with HOT, these methods of increasing hepatic FA oxidation depress feed intake of early lactation cows. Additional support is provided by responses of prepartum cows to 2,4 thiazolidinedione, a potent ligand for PPAR- γ that potentiates the action of insulin in peripheral tissues (Smith et al., 2007). Administration of the agent for the final 25 d of gestation decreased plasma NEFA prepartum, decreased β -hydroxybutyric acid (BHBA) as parturition approached, and tended to increase DMI in the peripartum period (Smith et al., 2007).

Hypophagia during the periparturient period is likely caused or exacerbated by stimulation of acetyl CoA oxidation and generation of ATP during meals. We showed that propionate was more hypophagic for cows in a lipolytic state in a dose-response experiment; low rates of propionate infusion decreased feed intake in early lactation cows, but not in mid-lactation cows (Oba and Allen, 2003a). Infusion of propionate at smaller doses increased plasma glucose concentration in both stages

of lactation, suggesting that this rate of infusion did not overwhelm gluconeogenic capacity and likely did not greatly increase propionate oxidation. However, propionate likely stimulated oxidation of acetyl CoA, increasing ATP production in early lactation cows despite the use of propionate for glucose production. This is supported by the observed decrease in plasma BHBA concentration in early lactation cows at lesser infusion rates, whereas NEFA remained elevated.

Stressed Receiving Calves. It is common for calves to exhibit depressed DMI for up to 3 wk after entering the feedlot (Hutcheson and Cole, 1986), which decreases performance and may have negative effects on the marbling potential of cattle (Gardner et al., 1999). Even under the best management conditions, newly received calves undergo substantial stress. Loading and transport, even for only 30 min, results in elevated plasma concentrations of cortisol and epinephrine (Locatelli et al., 1989; Agnes et al., 1990), and simply regrouping acclimated feedlot cattle increases plasma cortisol concentrations (Gupta et al., 2005). Additional stressors such as weaning (Hickey et al., 2003) and castration (Fisher et al., 1997) further stimulate release of stress hormones. Cortisol, epinephrine, and norepinephrine are pleiotropic hormones, but each acts as a lipolytic agent. Therefore, the stress responses observed in receiving cattle typically result in lipolysis and elevated plasma NEFA concentrations (Reynaert et al., 1976; Locatelli et al., 1989; Gupta et al., 2005). Although DMI can be depressed by an adrenergic mechanism independent of hepatic oxidation of FA (Brandt et al., 2007), this stress-induced increase in NEFA release might contribute to DMI depression in newly received cattle. Similar to the situation in the early lactation cow, elevated plasma NEFA provides a new oxidative substrate for the liver, generating additional ATP and suppressing feeding behavior.

Glycerol

Glycerol released from TG during lipolysis or absorbed from the gastrointestinal tract is metabolized in the liver to glycerol 3-phosphate and used in the gluconeogenic or glycolytic pathways. Like propionate, it can be converted to acetyl CoA and oxidized in the TCA cycle. However, unlike propionate, it can enter the gluconeogenic pathway without entering the TCA cycle, thereby increasing plasma glucose without stimulating oxidation of acetyl CoA. Increased availability of glycerol from the biofuel industry has increased interest in feeding glycerol in diets. Experiments reported in the literature generally substituted glycerol for corn at feeding rates of less than 5% of DM and reported no effect on feed intake. Failure of dietary glycerol to stimulate feed intake according to HOT is likely because of the low feeding rate and because glycerol is metabolized by ruminal microbes primarily to propionate (Bergner et al., 1995), resulting in little glycerol absorption.

Efficacy of Ketosis Treatments

Among the most popular treatments for ketosis are oral drenches of gluconeogenic precursors, including propylene glycol and calcium propionate. Although both can theoretically increase plasma glucose and decrease plasma ketones by stimulating oxidation of acetyl CoA in the liver, their efficacy at doing so varies. Propylene glycol consistently decreases plasma NEFA concentrations and usually decreases plasma ketones, whereas calcium propionate does not (Overton and Waldron, 2004). Propylene glycol likely depresses feed intake to a lesser extent than propionate because it is converted to lactate in the liver and metabolized more slowly (Kristensen and Raun, 2007), and it is less likely to stimulate oxidation in the liver and cause satiety. Thus, calcium propionate may be a less effective treatment because it depresses feed intake by stimulating hepatic oxidation of fuels.

Nitrogen Metabolism

Propionate and NEFA are primary fuels that cause hypophagia in ruminant animals (Allen, 2000), but AA are also extensively metabolized in the ruminant liver, especially with excess dietary protein intake and subsequent greater ammonia absorption. Lobley et al. (1995) reported that infusion of NH_4Cl into the mesenteric vein increases leucine oxidation by splanchnic tissues. Ammonia detoxification via urea synthesis requires α -amino nitrogen removal (Reynolds, 1992; Parker et al., 1995), and carbon from AA catabolism is available for oxidative metabolism in the liver.

Hypophagic effects of urea and ammonium are documented in the literature. Wilson et al. (1975) supplied urea to dairy cows from diets or by dosing directly into the rumen and showed that feeding urea depresses DMI regardless of administration method. However, they did not detect treatment effects on blood ammonia concentration. These observations indicate that hypophagia caused by ammonia or urea cannot be fully attributed to undesirable taste or ammonia toxicity. Ammonia metabolism is likely responsible for the hypophagia. Oba and Allen (2003d) showed that intraruminal infusion of ammonium salt of VFA decreased feed intake of lactating dairy cows compared with that of sodium or potassium salts of VFA by decreasing meal frequency without affecting meal size, indicating that ammonium delays the sense of hunger.

It is noteworthy that hypophagic effects of ammonium were exacerbated when infused with propionate compared with acetate (Oba and Allen, 2003e). Ammonia decreases the utilization of propionate carbon for gluconeogenesis (Aiello and Armentano, 1987; Demigné et al., 1991; Overton et al., 1999) and increases propionate oxidation (Aiello and Armentano, 1987; Overton et al., 1999). Therefore, oxidative metabolism in the liver may have been increased to a greater extent when ammonium was infused with propionate. Alternatively,

propionate may have negative effects on urea synthesis in the liver (Choung and Chamberlain, 1995), which allows temporary capture of excess ammonia-N as glutamine in perivenous hepatocytes (Häussinger et al., 1992) and generation of ammonium from glutamine in periportal hepatocytes over time after meals. This extends urea synthesis and generation of oxidizable carbon from AA catabolism in the liver over a longer period of time, which may explain delayed hunger caused by ammonium. Although several explanations are possible, the exacerbated hypophagia from propionate and ammonium is consistent with HOT.

ALTERNATIVE MECHANISMS

Control of feed intake is very complex, and alternative mechanisms have been proposed for control of intake by propionate and LCFA. Several of these alternatives to HOT are discussed in this section.

Specific Receptors

Receptors in the veins draining the splanchnic bed have been proposed for propionate in ruminants (Baile, 1971), and G protein-coupled receptors (**GPR41** and **GPR43**) that are activated by propionate have been identified recently (Brown et al., 2003). These receptors are also activated by acetate, and activation of GPR43 was similar for acetate and propionate, but activation of GPR41 was ~10 to 35% greater for propionate than acetate depending upon concentration (Brown et al., 2003). However, this is an unlikely mechanism for hypophagia from propionate relative to acetate because ruminal production and flux of propionate from the portal-drained viscera are unlikely to approach those for acetate, and peripheral concentrations of propionate are much less than acetate.

The existence of glucose receptors has been proposed (Novin et al., 1973) to explain hypophagia from glucose in a variety of nonruminants (Forbes, 1995). However, intestinal and intravenous glucose infusions have not decreased energy intake of ruminants (Allen, 2000). The absence of effects of portal glucose infusion on feed intake by sheep (Baile and Forbes, 1974) casts doubt on the hypothesis that sensory neurons in the portal vein mediate the hypophagic effects of glucose, given that mechanisms regulating feed intake are well conserved across divergent species (Chiang and MacDougald, 2003). There is broad consensus now that portal glucose infusions modulate feed intake of nonruminants through oxidation of glucose (Mobbs et al., 2005), but there is disagreement as to whether this occurs in sensory neurons or hepatocytes. Because ruminant neural tissue metabolizes glucose (Lindsay and Setchell, 1976) and glucose does not cause hypophagia in ruminants, it seems unlikely that glucose oxidation in sensory receptors induces hypophagia. Rather, differences in hypophagic effects of glucose infusion observed between

ruminants and nonruminants are likely because of differences in hepatic oxidation of glucose as previously discussed. Likewise, the responses attributed to the proposed propionate receptor can be explained equally well by HOT.

Insulin

Although propionate is an insulin secretagogue and insulin is a putative satiety hormone, hypophagic effects of propionate infusions have been observed without an increase in insulin (Frobish and Davis, 1977; Farningham and Whyte, 1993), and mechanisms exclusively involving insulin do not explain the elimination of hypophagic effects of portal infusions of propionate by hepatic denervation. Insulin might have indirect effects on feed intake by increasing oxidation of gluconeogenic precursors in the liver by speeding clearance of fuels from the blood (Allen et al., 2005), and by decreasing lipolysis and NEFA supply to the liver. This might explain inconsistent intake effects of peripheral insulin administration reported in the literature (Hayirli et al., 2002); although increased hepatic oxidation of fuels likely causes satiety, increased clearance of fuels from the blood is expected to cause hunger.

Leptin

Leptin, a peptide hormone produced primarily by adipocytes, plays a central role in the regulation of feed intake. Propionate was recently shown to increase leptin synthesis in rodents (Xiong et al., 2004). However, we reported that neither pulse-dose nor intermediate-term propionate infusions increased plasma leptin concentration in cows (Bradford et al., 2006).

Central Nervous System

Fuels that cross the blood brain barrier might affect feeding behavior by mechanisms independent of hepatic oxidation. Hypophagia from propionate by direct effects on the central nervous system (CNS) rather than (or in addition to) peripheral effects are possible because propionate (and acetate) crosses the blood-brain barrier by carrier-mediated transport (Oldendorf, 1973). Although hypophagic effects of central administration of propionate have not been reported to our knowledge, central lactate metabolism decreased food intake in rats (Lam et al., 2008), and GPR41 and GPR43 (discussed above) are expressed in the bovine CNS (Wang et al., 2009). However, hypophagic effects of propionate from its direct effects on the CNS are much less likely than peripheral effects because 1) various methods of eliminating vagal communication between the liver and the CNS have eliminated the hypophagic effects of infused propionate (Allen, 2000); 2) propionate infusions into the ruminal vein during spontaneous meals decreased feed intake of sheep, but infusions of larger amounts into a jugular vein did not (Baile, 1971); and 3) propi-

onate is more hypophagic for early lactation cows with much greater plasma ketone concentrations than mid-lactation cows (Oba and Allen, 2003a), even though propionate transport across the blood-brain barrier can be inhibited by ketone bodies (Conn et al., 1983). Long-chain free FA cross the blood brain barrier in proportion to their concentration in the blood and might control feeding behavior (Lam et al., 2005). However, stimulation of feeding by inhibition of FA oxidation by mercaptoacetate was eliminated by hepatic vagotomy (Langhans and Scharrer, 1987b), suggesting that FA oxidation in tissues innervated by the hepatic vagus controls feeding behavior.

Small Intestine

The hepatic vagus innervates the small intestine as well as the liver, and results from experiments with hepatic vagotomy must be interpreted with caution (Berthoud and Neuhuber, 2000). Langhans (2008) suggested that oxidation of FA in enterocytes might provide a signal to brain feeding centers because mercaptoacetate infused into the pancreatico-duodenal artery (targeting the proximal duodenum) increased the firing rate of single units from the hepatic vagus, and this response was blocked by infusion of lidocaine into the intestinal lumen. Langhans (2008) further suggested that the liver might not be involved in the control of eating by FA oxidation because inhibition of β -oxidation by mercaptoacetate failed to stimulate eating when FA oxidation was elevated by fasting or adrenoreceptor agonists. However, this evidence is insufficient to refute the role of the liver in control of eating by FA oxidation because the agent used to inhibit β -oxidation stimulates satiety through adrenergic mechanisms as discussed by Allen and Bradford (2009). Although FA oxidation in enterocytes might contribute to the control of feed intake, it does not preclude control of feed intake by hepatic oxidation.

MODEL OF CONTROL OF FEED INTAKE BY HOT IN RUMINANTS

By integrating the effects of various metabolic fuels on feeding behavior, we developed a conceptual model by which feed intake may be controlled in ruminants according to HOT (Figure 2). Hepatic oxidation increases throughout meals, increasing the energy status of hepatocytes and decreasing the discharge rate of hepatic vagal afferents, causing satiety. Hepatic oxidation then declines after meals, decreasing the energy status of hepatocytes, increasing the discharge rate of the hepatic vagus, and causing hunger. Signals from the hepatic vagal afferents are integrated in the nucleus tractus solitarius of the hind-brain before being relayed to the hypothalamus (Forbes, 1992).

Propionate is rapidly taken up by the liver within meals and is converted to TCA cycle intermediates in the mitochondria. Although propionate is used for

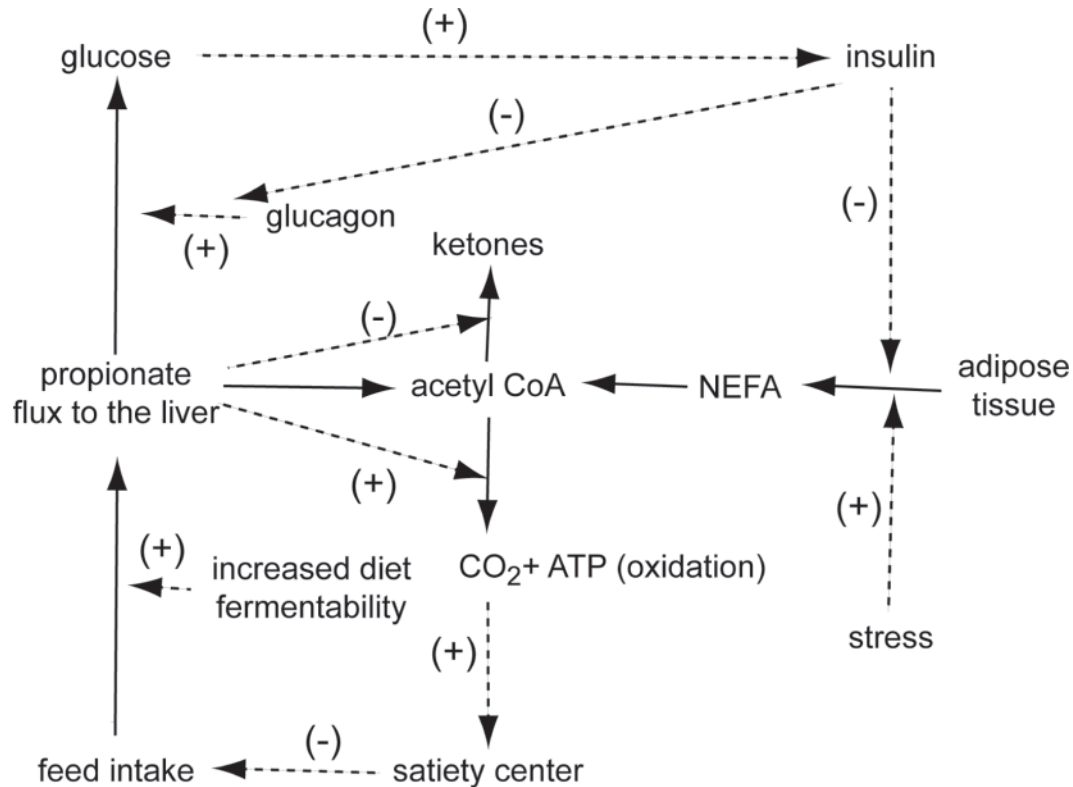


Figure 2. Model by which feed intake might be regulated according to the hepatic oxidation theory. Solid lines show the flow of carbon, whereas dashed lines show stimulation/inhibition of flow. Propionate uptake by the liver can be used for gluconeogenesis, utilizing ATP, or oxidized in the tricarboxylic acid (TCA) cycle through acetyl CoA, producing ATP and stimulating satiety. Acetyl CoA produced from β -oxidation of fatty acids and other ketogenic fuels is oxidized 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 , rapidly generating ATP and stimulating satiety.

gluconeogenesis, there is increased flux of carbon from propionate through pyruvate kinase (Steinhour and Bauman, 1988), allowing oxidation depending upon the fate of pyruvate. If energy charge is low, pyruvate is oxidized in the TCA cycle as acetyl CoA, and if energy charge is high, acetyl CoA allosterically activates pyruvate carboxylase, converting pyruvate to oxaloacetate in a futile cycle that has been shown to occur in 24-h fasted rats (Petersen et al., 1994). Oxidation of propionate within a meal increases the energy state of hepatocytes, generating a satiety signal to terminate the meal. Hepatic oxidation of NEFA is limited during meals because increased insulin release inhibits lipolysis in adipose tissue and uptake of NEFA by the liver (Vasilatos and Wangsness, 1980) and because propionate inhibits β -oxidation of FA by decreasing FA transport into mitochondria (Jesse et al., 1986) and by decreasing activity of fatty acyl CoA dehydrogenase (Emery et al., 1992). Hunger is stimulated as gluconeogenesis depletes the hepatic ATP pool over time.

Fatty acids are oxidized in the mitochondria by β -oxidation to acetyl CoA, which can be further oxidized to CO_2 in the TCA cycle or exported as ketones. The shortage of glucose precursors from increased glucose demand and increased FA oxidation in the liver of transition cows leads to a lack of TCA-cycle intermediates (Zammit, 1990). This environment results in

a buildup of the intracellular acetyl CoA pool and export of ketone bodies (Drackley and Andersen, 2006). One possible mechanism inhibiting oxidation of acetyl CoA is the buildup of NADH from β -oxidation of NEFA (Lopes-Cardozo et al., 1975). However, reducing equivalents are consumed by ketogenesis as well as ATP production for basal metabolism and gluconeogenesis. Hepatic mitochondrial NADH concentration might not be elevated immediately postpartum because the ratio of the concentrations of β -hydroxybutyrate to acetoacetate in the liver and blood decreases during ketosis in ruminants (Bergman, 1971), but conversion of acetoacetate to β -hydroxybutyrate would be stimulated by greater concentrations of NADH. Other evidence suggests that cytosolic NADH concentration also might not be elevated immediately postpartum because extraction of lactate (absolute amount and as a proportion of supply) by the liver was greatest at 11 d in milk (DIM; 45.9%) declining to 15.9% by 83 DIM (Reynolds et al., 2003). This would not occur if NADH concentration is elevated postpartum because conversion of lactate to pyruvate is inhibited by greater concentrations of NADH. Conversion of lactate to pyruvate may also be limited by lactate dehydrogenase concentration, but gene expression changes were not detected for this enzyme through the transition period up to 49 DIM (Loor et al., 2006).

Even if NADH concentration is elevated from β -oxidation of FA in the postpartum period, energy charge is likely variable throughout the day because oxidative phosphorylation (and ATP generation) might be limited if concentrations of CO_2 are decreased; oxidative phosphorylation is modulated by CO_2 through a feed-forward mechanism via the mitochondrial soluble adenylate cyclase signaling cascade (Acin-Perez et al., 2009) and CO_2 is not produced by β -oxidation of FA. However, propionate flux to the liver during meals stimulates oxidation of acetyl CoA in the TCA cycle, providing CO_2 to stimulate oxidative phosphorylation (and ATP generation).

Oxidation of acetyl CoA is further enhanced by decreasing export as ketones because propionate inhibits ketogenesis in the ruminant liver (Faulkner and Pollock, 1986) by decreasing the activity of HMG-CoA synthase (Lowe and Tubbs, 1985). Oxidizing the pool of acetyl CoA rather than exporting it dramatically increases ATP production; for each cycle of β -oxidation of FA, one molecule each of acetyl CoA, FADH_2 , and NADH are produced, potentially yielding ~ 14 ATP if the acetyl CoA is oxidized in the TCA cycle but only ~ 3 ATP if the acetyl CoA is converted to β -hydroxybutyrate. Therefore, hepatic FA oxidation likely contributes to satiety by generating ATP when propionate is absorbed, and negative energy balance is further exacerbated because intake depression limits insulin secretion and promotes continued lipolysis.

APPLICATION TO RUMINANTS

Control of feed intake by hepatic oxidation likely becomes more dominant as nutrient requirements and the filling effect of diets decrease, diminishing the signal from gut distension (Allen, 1996). However, additive effects of ruminal distension by inflation of a balloon and intraruminal infusion of VFA were reported for lactating cows (Mbanya et al., 1993), suggesting that control of feed intake by distension and hepatic oxidation are not mutually exclusive. Hepatic oxidation likely controls feed intake to a greater extent for ruminants in a feedlot setting consuming high-starch diets, for cows with low nutrient requirements, and for animals in a lipolytic state (e.g., periparturient and stressed animals) than for ruminants fed high-forage diets or with very high nutrient requirements such as cows at peak lactation.

Prepartum Cows

The control of feed intake may be dominated by signals from gut distension for dry cows greater than several weeks before parturition, but the contribution from hepatic oxidation likely increases as lipolysis increases and they are switched to a more energy-dense diet closer to parturition. However, composition of diets fed during this period varies greatly and the relative contribution of gut distension to the control of feed

intake increases as the forage fiber concentration increases. Increasing feeding of grain prepartum has not provided consistent benefits for DMI, milk yield, or liver triglyceride concentration postpartum (Grummer, 2008). Although feeding high grain diets might stimulate insulin to limit lipolysis, they also decrease the filling effect of the diet. Increased rumen fill from high forage diets fed prepartum has several potential benefits. Limitation of energy intake prevents excessive lipid accumulation during late gestation and may improve postpartum feed intake (Agenäs et al., 2003; Murondoti et al., 2004; Douglas et al., 2006) by decreasing the pool of FA available for lipolysis and subsequent hepatic oxidation, consistent with H₂O₂. In addition, the greater pool of ruminal digesta and longer ruminal retention time provides energy to sustain animals through calving and buffering capacity when cows consume the more fermentable lactating diet. Although limiting energy intake by increasing the forage fiber concentration of diets may provide benefits, the optimum fermentability of starch in the diet is not clear and requires more research. Limited research suggests benefits of increased starch fermentability before calving. Increasing dietary starch fermentability during the dry period numerically increased plasma insulin concentration and decreased plasma NEFA concentration by 42% in the final 10 d before calving; this increase in prepartum diet fermentability tended to increase feed intake during the first 63 d of lactation (Dann et al., 1999).

Lactating Cows

Further increases in lipolysis after parturition, combined with greater starch diets, likely suppress feed intake because rapid production and absorption of propionate stimulates oxidation of acetyl CoA. If feed intake of fresh cows is controlled primarily by hepatic oxidation, diets with moderate forage fiber concentrations might benefit cows. Forage fiber increases rumen fill, decreasing the risk of abomasal displacement, and increases acetate production, sparing glucose utilization by extrahepatic tissues (Head et al., 1964), although acetate might spare glucose to a lesser extent in early lactation compared with mid lactation (Oba and Allen, 2003a). Although research is needed to evaluate effects of concentration and fermentability of starch on feed intake response, starch sources with moderate ruminal fermentability and high digestibility in the small intestine such as dry ground corn will likely provide more glucose precursors primarily by increasing feed intake.

Milk yield increases rapidly after parturition, and over the next several weeks, increasing plasma glucose stimulates insulin secretion, thereby decreasing lipolysis and plasma NEFA concentration. Because less NEFA is available for oxidation, the acetyl CoA concentration in the liver decreases, decreasing ketone output by the liver. Lack of acetyl CoA and increased glucose demand limit oxidation of fuels in the liver, and satiety signals to the brain decrease. As milk yield increases further

and feed intake control by hepatic oxidation diminishes, control is dominated by distension from gut fill, and cows should be offered a diet that is less filling and more fermentable. This change in the dominant mechanism of intake regulation might occur only 7 to 10 d after calving for some cows in the herd or more than 3 wk for others; the best signs that hepatic oxidation is less limiting are less plasma NEFA and ketone concentrations and steadily increasing feed intake.

As energy requirements decrease after peak milk yield, control of feed intake by gut distension gradually diminishes and control by hepatic oxidation increases. Increased insulin concentration and insulin sensitivity of tissues affect the feed intake response to highly fermentable diets (Bradford and Allen, 2007). Extent of depression in feed intake by a more fermentable diet was positively related to plasma insulin concentration; chronic high plasma insulin concentrations may be indicative of adequate nutritional status and may provide negative feedback on hepatic gluconeogenesis. This relationship is consistent with HOT because decreased use of propionate for glucose production leads to greater propionate oxidation and decreased feed intake. Individual cows with an adequate supply of gluconeogenic precursors may respond to a further increase in supply by decreasing DMI. In addition, insulin response to glucose infusion was negatively related to the extent of depression in feed intake by the more fermentable diet, which might be because cows with strong responses to increased plasma glucose concentration are able to clear nutrients from the bloodstream more quickly after meals, potentially decreasing intermeal interval. Although insulin concentration and sensitivity of tissues to insulin increase as lactation progresses, depression in feed intake from the more fermentable diet was not related to days in lactation or milk yield. Thus, hypophagic effects of propionate vary greatly and optimal diet formulation depends upon the physiological state of animals.

Limiting Lipolysis. A wide variety of approaches have been used in the attempt to manipulate lipid metabolism of dairy cows in the periparturient period. Among the most successful and widely adopted practices is the careful management of body condition during the dry period (NRC, 2001). Excessive body condition at parturition results in dramatically increased plasma NEFA concentrations when periparturient lipolysis occurs. Several studies have demonstrated that feed intake decreases to a greater extent in overweight cows compared with cows managed for moderate BCS at calving (Garnsworthy and Topps, 1982; Holter et al., 1990). The most important hormonal regulators of lipid and carbohydrate metabolism are insulin and glucagon, and several groups have studied the potential use of exogenous hormone treatment to prevent periparturient disorders. Despite the fact that adipose tissue in early lactation cows is relatively insensitive to insulin, a small dose of insulin 3 d postpartum decreased plasma NEFA and BHBA and hepatic TG concentrations and

increased feed intake of dairy cows (Hayirli et al., 2002). However, greater doses of insulin caused hypoglycemia, failed to decrease plasma NEFA concentration, and did not increase feed intake. Administration of exogenous glucagon stimulates insulin secretion and offers the advantage of preventing hypoglycemia because glucagon directly stimulates gluconeogenic flux. Subcutaneous administration of glucagon decreased plasma NEFA concentration and tended to increase feed intake over control after 7 d of treatment (Nafikov et al., 2006). Potential stressors should be reduced as much as possible during the periparturient period because cortisol and catecholamines act as lipolytic agents as previously mentioned.

Feed additives might be options to reduce lipolysis. Although niacin has antilipolytic properties and is commonly included in diets to reduce lipolysis in the periparturient period, there has been little benefit of supplemental niacin for reducing plasma NEFA concentrations (NRC, 2001). This is likely because the amount supplemented (≤ 12 g/d) was inadequate to elicit a response. Most niacin is degraded in the rumen (Santschi et al., 2005) and plasma NEFA concentration of cows was decreased by a much larger dose (45 g/d; French, 2004) or abomasal administration (Pires and Grummer, 2007). Large doses of niacin or ruminally protected niacin may have promise for reducing lipolysis in the periparturient period (Grummer, 2008). Chromium is a component of the glucose tolerance factor and potentiates the action of insulin, and supplementing chromium may also be an effective method of preventing lipolysis (Grummer, 2008).

Feedlot Animals

The effects of diet fermentability on feed intake may not be the primary concern in a feedlot setting. Grain processing has relatively large effects on total-tract starch digestibility, and processing can often improve feed efficiency. However, in some cases, greater diet fermentability depresses DMI enough to decrease animal performance despite improvements in feed efficiency (Zinn, 1993; Owens et al., 1997; Swingle et al., 1999; Parsons et al., 2007). The relative economic importance of feed efficiency vs. ADG varies with feed and yardage costs as well as interest rates, and in some cases, maximizing ADG may be worthwhile even in the face of reduced feed efficiency. In addition, excessive diet fermentability can cause volatile DMI in feedlot cattle (Owens et al., 1998), and this fluctuation in DMI is associated with decreased performance, feed efficiency, and health. Clearly, understanding and predicting intake responses to diets are important in the feedlot industry, whether or not maximizing intake is the goal.

Similar to the situation with periparturient cows, the proper dietary approach to promote DMI in receiving calves is not simple. Long periods without feed from shipping long distances and the stress of shipping increase fat mobilization. Although excessively ferment-

able diets might further suppress feed intake because of propionate stimulating complete oxidation of FA, a low-concentrate diet may allow for continued lipolysis and the resulting hypophagia because it would not adequately stimulate insulin release. This may explain responses to monensin inclusion in a receiving ration as reported by Burrin et al. (1988). Monensin was fed at 0, 11, or 33 mg/kg in a diet containing 75% concentrate for the first 6 d, followed by a 95% concentrate ration with the same monensin treatments. Including monensin at 11 mg/kg numerically increased DMI over the first 28 d on feed, but the 33 mg/kg inclusion rate significantly decreased DMI by 10% (Burrin et al., 1988). Enhanced propionate production by monensin may have benefited DMI at the smaller inclusion rate by promoting insulin secretion and suppressing lipolysis but may have provided enough oxidative substrate to directly increase hepatic ATP concentration and suppress feeding behavior with the greater inclusion rate.

Although it has been clearly demonstrated that feeding 80 to 100% forage to receiving calves decreases DMI (Lofgreen et al., 1975; Lofgreen and Kiesling, 1985), the optimal energy density for receiving rations is not as clear. Berry et al. (2004) found that low-energy diets (55% concentrate) increased DMI compared with greater-energy diets (65% concentrate) during the first 42 d on feed, independent of dietary starch concentration. In contrast, Fluharty and Loerch (1996) reported increased DMI in the first week on feed when calves were fed a ration containing 85% concentrate compared with a 70% concentrate ration. The reason for these conflicting results may be that the metabolic states of the calves were different in each study. Of the studies in which energy density altered DMI in the receiving phase (range of 50 to 85% concentrate), those with the greatest morbidity rates ($\geq 50\%$) found that reduced energy density improved DMI (Lofgreen et al., 1981; Fluharty et al., 1994; Berry et al., 2004), but those groups with lesser morbidity rates ($\leq 43\%$) responded to greater energy density with greater DMI (trials 2 and 3 in Fluharty and Loerch, 1996). If morbidity is a useful indicator of overall stress, these results hint at the conclusion that more stressed calves are better able to maintain DMI when fed diets with moderate energy densities.

The proposed role of NEFA as an intake suppressant in stressed receiving calves may also explain the beneficial effects of supplemental chromium in these situations. High dietary chromium increases insulin sensitivity in cattle (Sumner et al., 2007), which would be expected to promote lipogenesis and suppress lipolysis, resulting in reduced plasma NEFA concentration. Inclusion of high-chromium yeast in a receiving diet tended to increase DMI by 10% relative to controls in one study (Moonsie-Shageer and Mowat, 1993), although plasma NEFA response to treatment was not reported.

Considering responses to monensin and chromium inclusion as well as energy density, it seems clear that stressed receiving calves are more susceptible to diet-

induced DMI depression than acclimated feedlot cattle. The negative energy balance experienced by many of these newly received animals results in greater delivery of FA to the liver, and if this is combined with an excess of propionate or diet-derived FA, hepatic oxidation of these fuels may induce a suppression of feeding behavior.

Altering Propionate Flux to the Liver

Dietary Starch Concentration. Decreasing propionate production and absorption will likely increase meal size and possibly feed intake because propionate is likely the primary fuel stimulating hepatic oxidation within meals. Propionate is a primary end product of starch fermentation, and production rates vary greatly among diets fed to ruminants because of large differences in starch concentration and fermentability (Allen, 2000). Therefore, the rate of propionate production and absorption within meals can be manipulated by diet formulation to alter feed intake of ruminants. Rate of propionate production can be decreased by reducing starch concentration and fermentability and by increasing efficiency of microbial protein production from OM, and absorption rate is likely to be reduced by inhibiting ruminal motility (Allen et al., 2006).

Starch concentration of diets is often reduced by substituting forage or nonforage fiber sources (**NFFS**) such as beet pulp or soyhulls for cereal grains. Dilution of starch in the diet has the added benefit of reducing the fermentation rate of the starch remaining when starch concentration is decreased by adding forage (Oba and Allen, 2003c) or NFFS (Voelker and Allen, 2003), reducing the rate of propionate production. The optimal strategy depends upon the relative cost of ingredients, efficiency of feed utilization, and animal production response. Longer fiber particles from forage compared with NFFS might increase dietary fiber digestibility by increasing ruminal pH through stimulation of rumination and by increasing ruminal retention of fiber (Allen, 1997); however, forage fiber is very filling and forages might limit feed intake compared with NFFS (Allen, 2000). Therefore, when ruminal distension contributes to the control of feed intake, substitution of NFFS for grain might be a better choice than substitution of forage.

Site of Starch Digestion. Substitution of a less fermentable starch source is an option when feed intake is depressed by a rapidly fermented starch source. Although ME concentration can be greater when starch is ruminally fermented (Huntington, 1997), DMI can be depressed, decreasing energy intake. Barley increased ruminal starch digestibility with no effect on total tract digestibility of organic matter, but feed intake of lactating cows was decreased 13% compared with ground corn (McCarthy et al., 1989). Altering dietary starch fermentability will likely be more desirable than replacing starch with fiber for ruminants with high glucose demand, such as early lactation cows, because small

intestinal starch digestion yields more glucose precursors than ruminal fermentation of fiber. It is important to note that the fraction of glucose precursors provided by starch fermentation in the large intestine is much less than in the rumen or small intestine because carbon used to produce microbial cells is lost in the feces. Therefore, careful consideration of site of starch digestion is very important to maximize the yield of glucose precursors over time. Starch sources with less ruminal digestibility should be very digestible in the small intestine to provide the greatest yield of glucose precursors. For instance, dry ground and cracked corn slow the rate of propionate production in the rumen compared with high-moisture corn, but the ground corn will provide more glucose precursors because of greater digestibility in the small intestine and total tract.

Rate of Propionate Absorption. Ruminal motility affects the rate of propionate absorption because mixing of ruminal contents is required to replenish its supply at the ruminal epithelium where it is absorbed (Allen, 1996). Therefore, ruminal motility likely affects the rate at which propionate stimulates oxidation within meals. Ruminal motility is affected by diet and is likely increased by physically effective fiber and decreased by LCFA, butyrate, and bioactive peptides. Long fiber particles increase distension and likely increase ruminal motility by stimulation of mechanoreceptors in the reticulum and cranial sac (Leek, 1969). Infusion of unsaturated LCFA inhibited motility in sheep (Nicholson and Omer, 1983), possibly via release of cholecystokinin (CCK), because CCK inhibits gastric emptying (Reidelberger, 1994) and LCFA increased plasma CCK in lactating cows (Choi et al., 2000). Although decreased motility might increase meal size by slowing the rate of propionate absorption, fat can depress feed intake by other mechanisms including increasing gut distension (Moran and McHugh, 1982). Ruminal contractions are inhibited by undissociated VFA (Crichlow, 1988) and butyrate has greater effects than propionate or acetate (Shinozaki, 1959; Crichlow, 1988). Effects of butyrate on rate of propionate flux to the liver are difficult to predict because butyrate is preferentially oxidized by ruminal epithelium, sparing propionate (Ash and Baird, 1973) and counteracting the effect of butyrate on rate of propionate absorption. Finally, bioactive peptides called exorphins, released from digestion of feed proteins and absorbed intact, modulate gastrointestinal motility (Froetschel, 1996) and abomasal infusion of casein decreased ruminal motility in steers (Kil and Froetschel, 1994).

Nitrogen Metabolism. The role of N metabolism in feed intake regulation has important practical implications. In early lactation, when glucose demand increases substantially, AA from body protein catabolism contribute to gluconeogenesis to a greater extent (Overton et al., 1999). Although the majority of AA carbon is utilized for gluconeogenesis, carbon from ketogenic AA needs to be oxidized, which may decrease the threshold for metabolic fuels from diets to cause

hypophagia. Although greater dietary protein intake is associated with enhanced ammonia-N flux, it is difficult to evaluate specific hypophagic effects of ammonia as greater dietary protein intake can delay satiety indirectly. For example, increasing protein concentration of diets is achieved by decreasing the dietary concentration of readily fermentable carbohydrates or forage fiber, which reduces propionate flux from the rumen and rumen fill, respectively. Greater distension can also be caused if rumen undegraded protein reduces ruminal motility as discussed above. Conversely, greater dietary protein intake may promote DMI in some cases via decreased energy spilling by ruminal microbes, increasing efficiency of microbial protein production (Van Kessel and Russell, 1996) and decreasing yield of propionate and other VFA from fermented organic matter (Allen, 1997).

SUMMARY AND CONCLUSIONS

Control of food intake is multifaceted with alternate and redundant mechanisms that are integrated in brain feeding centers. Contribution of signals from hepatic oxidation of fuels to the control of feed intake has been demonstrated in nonruminants, and this HOT is appealing because of its simplicity and broad explanatory power (Friedman, 1995). The HOT model is consistent with 1) differences in hypophagic effects of glucose infusions between ruminants and nonruminants, 2) greater hypophagia from propionate compared with acetate infusion, 3) elimination of hypophagic effects of propionate by hepatic vagotomy, 4) depression of feed intake by increased ruminal starch fermentation, 5) efficacy of ketosis treatments, 6) hypophagia during the periparturient period (especially for overconditioned cows), 7) effects of insulin and glucagon on feed intake, 8) hypophagic effects of stimulating hepatic FA oxidation in transition cows, and 9) stimulation of feed intake by inhibiting hepatic FA oxidation in transition cows. Therefore, HOT provides a unifying mechanism for explaining behavioral responses to changes in nutrient digestion and metabolism. Although more research is needed to better understand animal response to diets, we believe that HOT can help to formulate diets to improve animal health and farm profitability.

LITERATURE CITED

- Acin-Perez, R., E. Salazar, M. Kamenetsky, J. Buck, L. R. Levin, and G. Manfredi. 2009. Cyclic AMP produced inside mitochondria regulates oxidative phosphorylation. *Cell Metab.* 9:265-276.
- Agenäs, S., E. Burstedt, and K. Holtenius. 2003. Effects of feeding intensity during the dry period. 1. Feed intake, body weight, and milk production. *J. Dairy Sci.* 86:870-882.
- Agnes, F., P. Sartorelli, B. H. Abdi, and A. Locatelli. 1990. Effect of transport loading or noise on blood biochemical variables in calves. *Am. J. Vet. Res.* 51:1679-1681.
- Aiello, R. J., and L. E. Armentano. 1987. Gluconeogenesis in goat hepatocytes is affected by calcium, ammonia and other key me-

- tabolites but not primarily through cytosolic redox state. *J. Comp. Biochem. Physiol.* 88B:193–201.
- Allen, M. S. 1996. Physical constraints on voluntary intake of forages by ruminants. *J. Anim. Sci.* 74:3063–3075.
- Allen, M. S. 1997. Relationship between fermentation acid production in the rumen and the requirement for physical effective fiber. *J. Dairy Sci.* 80:1447–1462.
- Allen, M. S. 2000. Effects of diet on short-term regulation of feed intake by lactating dairy cattle. *J. Dairy Sci.* 83:1598–1624.
- Allen, M. S., and B. J. Bradford. 2009. Comment on control of eating by hepatic oxidation of fatty acids. *Appetite* doi:10.1016/j.appet.2009.06.005
- Allen, M. S., B. J. Bradford, and K. J. Harvatine. 2005. The cow as a model to study food intake regulation. *Annu. Rev. Nutr.* 25:523–547.
- Allen, M. S., J. A. Voelker, and M. Oba. 2006. Effective fiber and regulation of ruminal pH: Its more than just chewing. Pages 270–278 in *Production Diseases in Farm Animals*. N. P. Joshi and T. H. Herdt, ed. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Andersson, U., K. Filipsson, C. R. Abbott, A. Woods, K. Smith, S. R. Bloom, D. Carling, and C. J. Small. 2004. AMP-activated protein kinase plays a role in the control of food intake. *J. Biol. Chem.* 279:12005–12008.
- Anil, M. H., and J. M. Forbes. 1980. Feeding in sheep during intraportal infusions of short-chain fatty acids and the effect of liver denervation. *J. Physiol.* 298:407–414.
- Anil, M. H., and J. M. Forbes. 1988. The roles of hepatic nerves in the reduction of food intake as a consequence of intraportal sodium propionate administration in sheep. *Q. J. Exp. Physiol.* 73:539–546.
- Ash, R., and G. D. Baird. 1973. Activation of volatile fatty acids in bovine liver and rumen epithelium. Evidence for control by autoregulation. *Biochem. J.* 136:311–319.
- Baile, C. A. 1971. Metabolites as feedbacks for control of feed intake and receptor sites in goats and sheep. *Physiol. Behav.* 7:819–826.
- Baile, C. A., and J. M. Forbes. 1974. Control of feed intake and regulation of energy balance in ruminants. *Physiol. Rev.* 54:160–214.
- Ballard, F. J. 1965. Glucose utilization in mammalian liver. *Comp. Biochem. Physiol.* 14:437–443.
- Bauché, F., D. Sabourault, Y. Giudicelli, J. Nordmann, and R. Nordmann. 1983. Inhibition in vitro of acyl-CoA dehydrogenases by 2-mercaptoacetate in rat liver mitochondria. *Biochem. J.* 215:457–464.
- Bell, A. W., and D. E. Bauman. 1997. Adaptations of glucose metabolism during pregnancy and lactation. *J. Mammary Gland Biol. Neoplasia* 2:265–278.
- Bengochea, W. L., G. P. Lardy, M. L. Bauer, and S. A. Soto-Navarro. 2005. Effect of grain processing degree on intake, digestion, ruminal fermentation, and performance characteristics of steers fed medium-concentrate growing diets. *J. Anim. Sci.* 83:2815–2825.
- Benson, J. A., C. K. Reynolds, P. C. Aikman, B. Lupoli, and D. E. Beaver. 2002. Effects of abomasal vegetable oil infusion on splanchnic nutrient metabolism in lactating dairy cows. *J. Dairy Sci.* 85:1804–1814.
- Bergman, E. N. 1971. Hyperketonemia-ketogenesis and ketone body metabolism. *J. Dairy Sci.* 54:936–948.
- Bergner, H., C. Kijora, Z. Ceresnakova, and J. Szakacs. 1995. In vitro studies on glycerol transformation by rumen microorganisms. *Arch. Tierernahr.* 48:245–256.
- Berry, B. A., C. R. Krehbiel, A. W. Confer, D. R. Gill, R. A. Smith, and M. Montelongo. 2004. Effects of dietary energy and starch concentrations for newly received feedlot calves: I. Growth performance and health. *J. Anim. Sci.* 82:837–844.
- Berthoud, H. R. 2004. Anatomy and function of sensory hepatic nerves. *Anat. Rec.* 280A:827–835.
- Berthoud, H. R., and W. L. Neuhuber. 2000. Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.* 85:1–17.
- Bradford, B. J., and M. S. Allen. 2007. Depression in feed intake by a highly fermentable diet is related to plasma insulin concentration and insulin response to glucose infusion. *J. Dairy Sci.* 90:3838–3845.
- Bradford, B. J., M. Oba, R. A. Ehrhardt, Y. R. Boisclair, and M. S. Allen. 2006. Propionate is not an important regulator of plasma leptin concentration in dairy cattle. *Domest. Anim. Endocrinol.* 30:65–75.
- Brandt, K., M. Arnold, N. Geary, W. Langhans, and M. Leonhardt. 2007. Vagal afferents mediate the feeding response to mercaptoacetate but not to the beta (3) adrenergic receptor agonist CL 316,243. *Neurosci. Lett.* 411:104–107.
- Brown, A. J., S. M. Goldsworthy, A. A. Barnes, M. M. Eilert, L. Tcheang, D. Daniels, A. I. Muir, M. J. Wigglesworth, I. Kinghorn, N. J. Fraser, N. B. Pike, J. C. Strum, K. M. Steplewski, P. R. Murdock, J. C. Holder, F. H. Marshall, P. G. Szekeres, S. Wilson, D. M. Ignar, S. M. Foord, A. Wise, and S. J. Dowell. 2003. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J. Biol. Chem.* 278:11312–11319.
- Brown, M. S., C. R. Krehbiel, G. C. Duff, M. L. Galyean, D. M. Hallford, and D. A. Walker. 2000. Effect of degree of corn processing on urinary nitrogen composition, serum metabolite and insulin profiles, and performance by finishing steers. *J. Anim. Sci.* 78:2464–2474.
- Burrin, D. G., R. A. Stock, and R. A. Britton. 1988. Monensin level during grain adaption and finishing performance in cattle. *J. Anim. Sci.* 66:513–521.
- Carlson, D. B., N. B. Litherland, H. M. Dann, J. C. Woodworth, and J. K. Drackley. 2006. Metabolic effects of L-carnitine infusion and feed restriction in lactating Holstein cows. *J. Dairy Sci.* 89:4819–4834.
- Carlson, D. B., J. W. McFadden, A. D'Angelo, J. C. Woodworth, and J. K. Drackley. 2007. Dietary L-carnitine alters periparturient nutrient metabolism and lactation in multiparous cows. *J. Dairy Sci.* 90:3421–3441.
- Chiang, S.-H., and O. A. MacDougald. 2003. Will fatty worms help cure human obesity? *Trends Genet.* 19:523–525.
- Choi, B.-R., D. L. Palmquist, and M. S. Allen. 1997. Sodium mercaptoacetate is not a useful probe to study the role of fat in regulation of feed intake in dairy cattle. *J. Nutr.* 27:171–176.
- Choi, B.-R., D. L. Palmquist, and M. S. Allen. 2000. Cholecystokinin mediates depression of feed intake in dairy cattle fed high fat diets. *Domest. Anim. Endocrinol.* 19:159–175.
- Choung, J. J., and D. G. Chamberlain. 1995. Effects of intraruminal infusion of propionate on the concentrations of ammonia and insulin in peripheral blood of cows receiving an intraruminal infusion of urea. *J. Dairy Res.* 62:549–557.
- Clark, J. H., H. R. Spires, R. G. Derrig, and M. R. Bennink. 1977. Milk production, nitrogen utilization and glucose synthesis in lactating cows infused postpartum with sodium caseinate and glucose. *J. Nutr.* 107:631–644.
- Conn, A. R., D. I. Fell, and R. D. Steel. 1983. Characterization of alpha-keto acid transport across blood-brain barrier in rats. *Am. J. Physiol. Endocrinol. Metab.* 245:E253–E260.
- Crichlow, E. C. 1988. Ruminal lactic acidosis: Forestomach epithelial receptor activation by undissociated volatile fatty acids and rumen fluids collected during loss of reticulorumen motility. *Res. Vet. Sci.* 45:364–368.
- Dann, H. M., G. A. Varga, and D. E. Putnam. 1999. Improving energy supply to late gestation and early postpartum dairy cows. *J. Dairy Sci.* 82:1765–1778.
- Del Prete, E., T. A. Lutz, and E. Scharrer. 2004. Inhibition of glucose oxidation by alpha-cyano-4-hydroxycinnamic acid stimulates feeding in rats. *Physiol. Behav.* 80:489–498.

- Demigné, C., C. Yacoub, C. Morand, and C. Rémésy. 1991. Interactions between propionate and amino acid metabolism in isolated sheep hepatocytes. *Br. J. Nutr.* 65:301–317.
- Doepel, L., H. Lapiere, and J. J. Kennelly. 2002. Peripartum performance and metabolism of dairy cows in response to prepartum energy and protein intake. *J. Dairy Sci.* 85:2315–2334.
- Dohme, F., A. Machmüller, F. Sutter, and M. Kreuzer. 2004. Digestive and metabolic utilization of lauric, myristic and stearic acid in cows, and associated effects on milk fat quality. *Arch. Anim. Nutr.* 58:99–116.
- Douglas, G. N., T. R. Overton, H. G. Bateman II, H. M. Dann, and J. K. Drackley. 2006. Prepartal plane of nutrition, regardless of dietary energy source, affects periparturient metabolism and dry matter intake in Holstein cows. *J. Dairy Sci.* 89:2141–2157.
- Dowden, D. R., and D. R. Jacobson. 1960. Inhibition of appetite in dairy cattle by certain intermediate metabolites. *Nature* 188:148–149.
- Drackley, J. K., and J. B. Andersen. 2006. Splanchnic metabolism of long-chain fatty acids in ruminants. Pages 199–224 in *Ruminant Physiology: Digestion, Metabolism and Impact of Nutrition on Gene Expression, Immunology and Stress*. K. Serjensen, T. Hvelplund, and M. O. Nielsen, ed. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Drackley, J. K., T. H. Klusmeyer, A. M. Trusk, and J. H. Clark. 1992. Infusion of long-chain fatty acids varying in saturation and chain length into abomasum of lactating dairy cows. *J. Dairy Sci.* 75:1517–1526.
- Elliot, J. M., H. W. Symonds, and B. Pike. 1985. Effect on feed intake of infusing sodium propionate or sodium acetate into a mesenteric vein of cattle. *J. Dairy Sci.* 68:1165–1170.
- Emery, R. S., J. S. Liesman, and T. H. Herdt. 1992. Metabolism of long chain fatty acids by ruminant liver. *J. Nutr.* 122:832–837.
- Farningham, D. A., and C. C. Whyte. 1993. The role of propionate and acetate in the control of food intake in sheep. *Br. J. Nutr.* 70:37–46.
- Faulkner, A., and H. T. Pollock. 1986. Propionate metabolism and its regulation by fatty acids in ovine hepatocytes. *Comp. Biochem. Physiol. B* 84:559–563.
- Fisher, A. D., M. A. Crowe, E. M. O'Nualláin, M. L. Monaghan, D. J. Prendiville, P. O'Kiely, and W. J. Enright. 1997. Effects of suppressing cortisol following castration of bull calves on adrenocorticotropic hormone, in vitro interferon-gamma production, leukocytes, acute-phase proteins, growth, and feed intake. *J. Anim. Sci.* 75:1899–1908.
- Fluharty, F. L., and S. C. Loerch. 1996. Effects of dietary energy source and level on performance of newly arrived feedlot calves. *J. Anim. Sci.* 74:504–513.
- Fluharty, F. L., S. C. Loerch, and F. E. Smith. 1994. Effects of energy density and protein source on diet digestibility and performance of calves after arrival at the feedlot. *J. Anim. Sci.* 72:1616–1622.
- Forbes, J. M. 1988. Metabolic aspects of the regulation of voluntary food intake and appetite. *Nutr. Res. Rev.* 1:145–168.
- Forbes, J. M. 1992. Metabolic aspects of satiety. *Proc. Nutr. Soc.* 5:13–19.
- Forbes, J. M. 1995. *Voluntary Food Intake and Diet Selection in Farm Animals*. CAB Int., Oxon, UK.
- French, P. D. 2004. Nicotinic acid supplemented at a therapeutic level minimizes prepartum feed intake depression in dairy cows. *J. Dairy Sci.* 87(Suppl. 1):345.
- Friedman, M. I. 1995. Control of energy intake by energy metabolism. *Am. J. Clin. Nutr.* 62:1096S–1100S.
- Friedman, M. I. 1998. Fuel partitioning and food intake. *Am. J. Clin. Nutr.* 67:513S–518S.
- Friedman, M. I., G. Graczyk-Milbrandt, H. Ji, N. E. Rawson, and M. D. Osbakken. 2003. 2,5-Anhydro-D-mannitol increases hepatocyte sodium: Transduction of a hepatic hunger stimulus? *Biochim. Biophys. Acta* 1642:53–58.
- Friedman, M. I., R. B. Harris, H. Ji, I. Ramirez, and M. G. Tordoff. 1999. Fatty acid oxidation affects food intake by altering hepatic energy status. *Am. J. Physiol.* 276:R1046–R1053.
- Friedman, M. I., J. E. Koch, G. Graczyk-Milbrandt, P. M. Ulrich, and M. D. Osbakken. 2002. High-fat diet prevents eating response and attenuates liver ATP decline in rats given 2,5-anhydro-D-mannitol. *Am. J. Physiol.* 282:R710–R714.
- Friedman, M. I., I. Ramirez, C. R. Bowden, and M. G. Tordoff. 1990. Fuel partitioning and food intake: Role for mitochondrial fatty acid transport. *Am. J. Physiol.* 258:R216–R221.
- Friedman, M. I., and M. G. Tordoff. 1986. Fatty acid oxidation and glucose utilization interact to control food intake in rats. *Am. J. Physiol.* 51:R840–R845.
- Friedman, M. I., M. G. Tordoff, and I. Ramirez. 1986. Integrated metabolic control of food intake. *Brain Res. Bull.* 17:855–859.
- Frobish, R. A., and C. L. Davis. 1977. Effects of abomasal infusions of glucose and propionate on milk yield and composition. *J. Dairy Sci.* 60:204–209.
- Froetschel, M. A. 1996. Bioactive peptides in digesta that regulate gastrointestinal function and intake. *J. Anim. Sci.* 74:2500–2508.
- Fulton, W. R., T. J. Klopfenstein, and R. A. Britton. 1979. Adaptation to high concentrate diets by beef cattle. I. Adaptation to corn and wheat diets. *J. Anim. Sci.* 49:775–784.
- Gaebel, R. J., D. W. Sanson, I. G. Rush, M. L. Riley, D. L. Hixon, and S. I. Paisley. 1998. Effects of extruded corn or grain sorghum on intake, digestibility, weight gain, and carcasses of finishing steers. *J. Anim. Sci.* 76:2001–2007.
- Galyean, M. L., and P. J. Defoor. 2003. Effects of roughage source and level on intake by feedlot cattle. *J. Anim. Sci.* 81:E8–E16.
- Gardner, B. A., H. G. Dolezal, L. K. Bryant, F. N. Owens, and R. A. Smith. 1999. Health of finishing steers: Effects on performance, carcass traits, and meat tenderness. *J. Anim. Sci.* 77:3168–3175.
- Garnsworthy, P. C., and J. H. Topps. 1982. The effect of body condition of dairy cows at calving on their food intake and performance when given complete diets. *Anim. Prod.* 35:113–119.
- Grummer, R. R. 2008. Nutritional and management strategies for the prevention of fatty liver in dairy cattle. *Vet. J.* 176:10–20.
- Gupta, S., B. Earley, S. T. L. Ting, and M. A. Crowe. 2005. Effect of repeated regrouping and relocation on the physiological, immunological, and hematological variables and performance of steers. *J. Anim. Sci.* 83:1948–1958.
- Hanson, R. W., and F. J. Ballard. 1967. The relative significance of acetate and glucose as precursors for lipid synthesis in liver and adipose tissue from ruminants. *Biochem. J.* 105:529–536.
- Harvatine, K. J., and M. S. Allen. 2006. Effects of fatty acid supplements on feed intake, and feeding and chewing behavior of lactating dairy cows. *J. Dairy Sci.* 89:1104–1112.
- Häussinger, D., W. H. Lamers, and A. F. Moorman. 1992. Hepatocyte heterogeneity in the metabolism of amino acids and ammonia. *Enzyme* 46:72–93.
- Häussinger, D., T. Stehle, and J. P. Colombo. 1989. Benzoate stimulates glutamate release from perfused rat liver. *Biochem. J.* 264:837–843.
- Hayirli, A., S. J. Bertics, and R. R. Grummer. 2002. Effects of slow-release insulin on production, liver triglyceride, and metabolic profiles of Holsteins in early lactation. *J. Dairy Sci.* 85:2180–2191.
- Head, H. H., J. D. Connolly, and W. F. Williams. 1964. Glucose metabolism in dairy cattle and the effect of acetate infusion. *J. Dairy Sci.* 47:1371–1377.
- Hickey, M. C., M. Drennan, and B. Earley. 2003. The effect of abrupt weaning of suckler calves on the plasma concentrations of cortisol, catecholamines, leukocytes, acute-phase proteins and in vitro interferon-gamma production. *J. Anim. Sci.* 81:2847–2855.
- Hollmann, M., and D. K. Beede. 2008. Dietary coconut oil and animal fat blend decreases lactational performance of Holstein cows fed a high starch diet. *J. Dairy Sci.* 91(E-Suppl. 1):331.

- Holter, J. B., M. J. Slotnick, H. H. Hayes, C. K. Bozak, W. E. Urban Jr., and M. L. McGilliard. 1990. Effect of prepartum dietary energy on condition score, postpartum energy, nitrogen partitions, and lactation production responses. *J. Dairy Sci.* 73:3502–3511.
- Horn, C. C., and M. I. Friedman. 1998. Metabolic inhibition increases feeding and brain Fos-like immunoreactivity as a function of diet. *Am. J. Physiol.* 275:R448–R459.
- Horn, C. C., H. Ji, and M. I. Friedman. 2004. Etomoxir, a fatty acid oxidation inhibitor, increases food intake and reduces hepatic energy status in rats. *Physiol. Behav.* 81:157–162.
- Huntington, G. B. 1997. Starch utilization by ruminants: From basics to the bunk. *J. Anim. Sci.* 75:852–867.
- Huntington, G. B., D. L. Harmon, and C. J. Richards. 2006. Sites, rates, and limits of starch digestion and glucose metabolism in growing cattle. *J. Anim. Sci.* 84:E14–E24.
- Hutcheson, D. P., and N. A. Cole. 1986. Management of transit-stress syndrome in cattle: Nutritional and environmental effects. *J. Anim. Sci.* 62:555–560.
- Ingvartsen, K. L., and J. B. Andersen. 2000. Integration of metabolism and intake regulation: A review focusing on periparturient animals. *J. Dairy Sci.* 83:1573–1597.
- Jesse, B. W., R. S. Emery, and J. W. Thomas. 1986. Control of bovine hepatic fatty acid oxidation. *J. Dairy Sci.* 69:2290–2297.
- Ji, H., and M. I. Friedman. 1999. Compensatory hyperphagia after fasting tracks recovery of liver energy status. *Physiol. Behav.* 68:181–186.
- Ji, H., G. Graczyk-Milbrandt, and M. I. Friedman. 2000. Metabolic inhibitors synergistically decrease hepatic energy status and increase food intake. *Am. J. Physiol.* 278:R1579–R1582.
- Ji, H., G. Graczyk-Milbrandt, M. D. Osbakken, and M. I. Friedman. 2002. Interactions of dietary fat and 2,5-anhydro-D-mannitol on energy metabolism in isolated rat hepatocytes. *Am. J. Physiol.* 282:R715–R720.
- Kil, S. J., and M. A. Froetschel. 1994. Involvement of opioid peptides from casein on reticular motility and digesta passage in steers. *J. Dairy Sci.* 77:111–123.
- Knapp, J. R., H. C. Freely, B. L. Reis, C. C. Calvert, and R. L. Baldwin. 1992. Effects of somatotropin and substrates on patterns of liver metabolism in lactating dairy cattle. *J. Dairy Sci.* 75:1025–1035.
- Kristensen, N. B., and B. M. L. Raun. 2007. Ruminal and intermediary metabolism of propylene glycol in lactating Holstein cows. *J. Dairy Sci.* 90:4707–4717.
- Lam, C. K., M. Chari, P. Y. T. Wang, and T. K. T. Lam. 2008. Central lactate metabolism regulates food intake. *Am. J. Physiol. Endocrinol. Metab.* 295:E491–E496.
- Lam, T. K. T., G. J. Schwartz, and L. Rossetti. 2005. Hypothalamic sensing of fatty acids. *Nat. Neurosci.* 8:579–584.
- Langhans, W. 1996. Role of the liver in the metabolic control of eating: What we know—and what we do not know. *Neurosci. Biobehav. Rev.* 20:145–153.
- Langhans, W. 2008. Fatty acid oxidation in the energostatic control of eating—A new idea. *Appetite* 51:446–451.
- Langhans, W., G. Egli, and E. Scharrer. 1985a. Regulation of food intake by hepatic oxidative metabolism. *Brain Res. Bull.* 15:425–428.
- Langhans, W., G. Egli, and E. Scharrer. 1985b. Selective hepatic vagotomy eliminates the hypophagic effect of different metabolites. *J. Auton. Nerv. Syst.* 13:255–262.
- Langhans, W., and E. Scharrer. 1987a. Evidence for a role of the sodium pump of hepatocytes in the control of food intake. *J. Auton. Nerv. Syst.* 20:199–205.
- Langhans, W., and E. Scharrer. 1987b. Role of fatty acid oxidation in control of meal pattern. *Behav. Neural Biol.* 47:7–16.
- Leek, B. 1969. Reticulo-ruminal mechanoreceptors in sheep. *J. Physiol.* 202:585–609.
- Leyton, J., P. J. Drury, and M. A. Crawford. 1987. Differential oxidation of saturated and unsaturated fatty acids in vivo in the rat. *Br. J. Nutr.* 57:383–393.
- Lindsay, D. B., and B. P. Setchell. 1976. The oxidation of glucose, ketone bodies and acetate by the brain of normal and ketonaemic sheep. *J. Physiol.* 259:801–823.
- Lobley, G. E., A. Connell, M. A. Lomax, D. S. Brown, E. Milne, A. G. Calder, and D. A. Farningham. 1995. Hepatic detoxification of ammonia in the ovine liver: Possible consequences for amino acid catabolism. *Br. J. Nutr.* 73:667–685.
- Locatelli, A., P. Sartorelli, F. Agnes, G. P. Bondiolotti, and G. B. Piccotti. 1989. Adrenal response in the calf to repeated simulated transport. *Br. Vet. J.* 145:517–522.
- Lofgreen, G. P., J. R. Dunbar, D. G. Addis, and J. G. Clark. 1975. Energy level in starting rations for calves subjected to marketing and shipping stress. *J. Anim. Sci.* 41:1256–1265.
- Lofgreen, G. P., A. E. El Tayeb, and H. E. Kiesling. 1981. Millet and alfalfa hays alone and in combination with high-energy diet for receiving stressed calves. *J. Anim. Sci.* 52:959–968.
- Lofgreen, G. P., and H. E. Kiesling. 1985. Effects of receiving and growing diets on compensatory gains of stressed calves. *J. Anim. Sci.* 61:320–328.
- Loor, J. J., H. M. Dann, N. A. Janovick Guretzky, R. E. Everts, R. Oliveira, C. A. Green, N. B. Litherland, S. L. Rodriguez-Zas, H. A. Lewin, and J. K. Drackley. 2006. Plane of nutrition prepartum alters hepatic gene expression and function in dairy cows as assessed by longitudinal transcript and metabolic profiling. *Physiol. Genomics* 27:29–41.
- Lopes-Cardozo, M., I. Mulder, F. van Vugt, P. G. Hermans, S. G. van den Bergh, W. Klazinga, and E. de Vries-Akkerman. 1975. Aspects of ketogenesis: Control and mechanism of ketone-body formation in isolated rat-liver mitochondria. *Mol. Cell. Biochem.* 9:155–173.
- Lowe, D. M., and P. K. Tubbs. 1985. Succinylation and inactivation of 3-hydroxy-3-methylglutaryl-CoA synthase by succinyl-CoA and its possible relevance to the control of ketogenesis. *Biochem. J.* 232:37–42.
- Lutz, T. A., A. Nijima, and E. Scharrer. 1996. Intraportal infusion of 2,5-anhydro-D mannitol increases afferent activity in the common hepatic vagus branch. *J. Auton. Nerv. Syst.* 61:204–208.
- Lutz, T. A., S. Wild, S. Boutellier, D. Sutter, M. Volkert, and E. Scharrer. 1998. Hyperpolarization of the cell membrane of mouse hepatocytes by lactate, pyruvate, and fructose is due to Ca²⁺-dependent activation of K⁺ channels and of the Na⁺/K⁺-ATPase. *Biochim. Biophys. Acta* 1372:359–369.
- Mashek, D. G., S. J. Bertics, and R. R. Grummer. 2002. Metabolic fate of long-chain unsaturated fatty acids and their effects on palmitic acid metabolism and gluconeogenesis in bovine hepatocytes. *J. Dairy Sci.* 85:2283–2289.
- Mashek, D. G., and R. R. Grummer. 2003. Effects of long chain fatty acids on lipid and glucose metabolism in monolayer cultures of bovine hepatocytes. *J. Dairy Sci.* 86:2390–2396.
- Mayer, J. 1953. Glucostatic mechanism of regulation of food intake. *N. Engl. J. Med.* 249:13–16.
- Mbanya, J. N., M. H. Anil, and J. M. Forbes. 1993. The voluntary intake of hay and silage by lactating cows in response to ruminal infusion of acetate or propionate, or both, with or without distension of the rumen by a balloon. *Br. J. Nutr.* 69:713–720.
- McCarthy, R. D. Jr., T. H. Klusmeyer, J. L. Vicini, and J. H. Clark. 1989. Effects of source of protein and carbohydrate on ruminal fermentation and passage of nutrients to the small intestine of lactating cows. *J. Dairy Sci.* 72:2002–2016.
- Mobbs, C. V., F. Isoda, H. Makimura, J. Mastaitis, T. Mizuno, I. W. Shu, K. Yen, and X. J. Yang. 2005. Impaired glucose signaling as a cause of obesity and the metabolic syndrome: The glucoadipostatic hypothesis. *Physiol. Behav.* 85:3–23.
- Moonsie-Shageer, S., and D. N. Mowat. 1993. Effect of level of supplemental chromium on performance, serum constituents, and immune status of stressed feeder calves. *J. Anim. Sci.* 71:232–238.
- Moran, T. H., and P. R. McHugh. 1982. Cholecystokinin suppresses food intake by inhibiting gastric emptying. *Am. J. Physiol.* 242:R491–R497.

- Murondoti, A., R. Jorritsma, A. C. Beynen, T. Wensing, and M. J. Geelen. 2004. Activities of the enzymes of hepatic gluconeogenesis in periparturient dairy cows with induced fatty liver. *J. Dairy Res.* 71:129–134.
- Nafikov, R. A., B. N. Ametaj, G. Bobe, K. J. Koehler, J. W. Young, and D. C. Beitz. 2006. Prevention of fatty liver in transition dairy cows by subcutaneous injections of glucagon. *J. Dairy Sci.* 89:1533–1545.
- Nicholson, T., and S. A. Omer. 1983. The inhibitory effect of intestinal infusions of unsaturated long-chain fatty acids on forestomach motility of sheep. *Br. J. Nutr.* 50:141–149.
- Nijijima, A. 1969. Afferent impulse discharges from glucoreceptors in the liver of the guinea pig. *Ann. N. Y. Acad. Sci.* 157:690–700.
- Nijijima, A. 1981a. Neurophysiological evidence for hepatic glucose-sensitive afferents. Commentary on “The current status of hepatic theory of food intake control”. *Appetite* 2:151–152.
- Nijijima, A. 1981b. Visceral afferents and metabolic function. *Diabetologia* 20(Suppl.):325–330.
- Nijijima, A. 1983. Glucose-sensitive afferent nerve fibers in the liver and their role in food intake and blood glucose regulation. *J. Auton. Nerv. Syst.* 9:207–220.
- Nijijima, A. 2000. Reflex effects of oral, gastrointestinal and hepatoportal glutamate sensors on vagal nerve activity. *J. Nutr.* 130:971S–973S.
- Novin, D., D. A. VanderWeele, and M. Rezek. 1973. Infusion of 2-deoxy-D-glucose into the hepatic-portal system causes eating: Evidence for peripheral glucoreceptors. *Science* 181:858–860.
- NRC. 2001. Nutritional Requirements of Dairy Cattle. 7th rev. ed. Natl. Acad. Sci., Washington, DC.
- Oba, M., and M. S. Allen. 2003a. Dose-response effects of intraruminal infusion of propionate on feeding behavior of lactating cows in early or midlactation. *J. Dairy Sci.* 86:2922–2931.
- Oba, M., and M. S. Allen. 2003b. Effects of corn grain conservation method on feeding behavior and productivity of lactating dairy cows at two dietary starch concentrations. *J. Dairy Sci.* 86:174–183.
- Oba, M., and M. S. Allen. 2003c. Effects of corn grain conservation method on ruminal digestion kinetics for lactating dairy cows at two dietary starch concentrations. *J. Dairy Sci.* 86:184–194.
- Oba, M., and M. S. Allen. 2003d. Effects of intra-ruminal infusion of sodium, potassium, and ammonium on hypophagic effect of propionate in lactating dairy cows. *J. Dairy Sci.* 86:1398–1404.
- Oba, M., and M. S. Allen. 2003e. Hypophagic effects of ammonium are greater when infused with propionate compared with acetate in lactating dairy cows. *J. Nutr.* 133:1100–1104.
- Oba, M., and M. S. Allen. 2003f. Intraruminal infusion of propionate alters feeding behavior and decreases energy intake of lactating dairy cows. *J. Nutr.* 133:1094–1099.
- Oldendorf, W. H. 1973. Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. *Am. J. Physiol.* 224:1450–1453.
- Overton, T. R., J. K. Drackley, C. J. Ottemann-Abbamonte, A. D. Beaulieu, L. S. Emmert, and J. H. Clark. 1999. Substrate utilization for hepatic gluconeogenesis is altered by increased glucose demand in ruminants. *J. Anim. Sci.* 77:1940–1951.
- Overton, T. R., and M. R. Waldron. 2004. Nutritional management of transition dairy cows: Strategies to optimize metabolic health. *J. Dairy Sci.* 87(Suppl. 13):E105–E119.
- Owens, F. N., D. S. Secrist, W. J. Hill, and D. R. Gill. 1997. The effect of grain source and grain processing on performance of feedlot cattle: A review. *J. Anim. Sci.* 75:868–879.
- Owens, F. N., D. S. Secrist, W. J. Hill, and D. R. Gill. 1998. Acidosis in cattle: A review. *J. Anim. Sci.* 76:275–286.
- Parker, D. S., M. A. Lomax, C. J. Seal, and J. C. Wilton. 1995. Metabolic implications of ammonia production in the ruminant. *Proc. Nutr. Soc.* 54:549–563.
- Parsons, C. H., J. T. Vasconcelos, R. S. Swingle, P. J. Defoor, G. A. Nunnery, G. B. Salyer, and M. L. Galyean. 2007. Effects of wet corn gluten feed and roughage levels on performance, carcass characteristics, and feeding behavior of feedlot cattle. *J. Anim. Sci.* 85:3079–3089.
- Petersen, K. F., G. W. Cline, J. B. Blair, and G. I. Shulman. 1994. Substrate cycling between pyruvate and oxaloacetate in awake normal and 3,3',5-triiodo-L-thyronine-treated rats. *Am. J. Physiol. Endocrinol. Metab.* 267:E273–E277.
- Peterson, A. D., C. A. Baile, and B. R. Baumgardt. 1972. Cerebral ventricle injections of pentobarbital, glucose, and sodium chloride into sheep and calves, and feeding. *J. Dairy Sci.* 55:822–828.
- Piepenbrink, M. S., and T. R. Overton. 2003. Liver metabolism and production of cows fed increasing amounts of rumen-protected choline during the periparturient period. *J. Dairy Sci.* 86:1722–1733.
- Pires, J. A. A., and R. R. Grummer. 2007. The use of nicotinic acid to induce sustained low plasma nonesterified fatty acids in feed-restricted Holstein cows. *J. Dairy Sci.* 90:3725–3732.
- Rawson, N. E., H. Blum, M. D. Osbakken, and M. I. Friedman. 1994. Hepatic phosphate trapping, decreased ATP, and increased feeding after 2,5-anhydro-D-mannitol. *Am. J. Physiol.* 266:R112–R117.
- Rawson, N. E., and M. I. Friedman. 1994. Phosphate loading prevents the decrease in ATP and increase in food intake produced by 2,5-anhydro-D-mannitol. *Am. J. Physiol.* 266:R1792–R1796.
- Rawson, N. E., H. Ji, and M. I. Friedman. 2003. 2,5-Anhydro-D-mannitol increases hepatocyte calcium: Implications for a hepatic hunger stimulus. *Biochim. Biophys. Acta* 1642:59–66.
- Reidelberger, R. D. 1994. Cholecystokinin and control of food intake. *J. Nutr.* 124(Suppl.):1327S–1333S.
- Remesy, C., C. Moundras, C. Morand, and C. Demigne. 1997. Glutamine or glutamate release by the liver constitutes a major mechanism for nitrogen salvage. *Am. J. Physiol.* 272:G257–G264.
- Reynaert, R., S. Marcus, M. De Paepe, and G. Peeters. 1976. Influences of stress, age and sex on serum growth hormone and free fatty acid levels in cattle. *Horm. Metab. Res.* 8:109–114.
- Reynolds, C. K. 1992. Metabolism of nitrogenous compounds by ruminant liver. *J. Nutr.* 122:850–854.
- Reynolds, C. K. 1995. Quantitative aspects of liver metabolism in ruminants. Pages 351–372 in *Ruminant Physiology: Digestion, Metabolism, Growth and Reproduction*. W. V. Englehardt, S. Leonhard-Marek, G. Breves, and D. Geisecke, ed. Ferdinand Enke Verlag, Stuttgart, Germany.
- Reynolds, C. K., P. C. Aikman, B. Lupoli, D. J. Humphries, and D. E. Beever. 2003. Splanchnic metabolism of dairy cows during the transition from late gestation through early lactation. *J. Dairy Sci.* 86:1201–1217.
- Ricks, C. A., and R. M. Cook. 1981. Regulation of volatile fatty acid uptake by mitochondrial acyl CoA synthetases of bovine liver. *J. Dairy Sci.* 64:2324–2335.
- Rossi, R., M. Geronimi, P. Gloor, M. C. Seebacher, and E. Scharrer. 1995. Hyperpolarization of the cell membrane of mouse hepatocytes by fatty acid oxidation. *Physiol. Behav.* 57:509–514.
- Rossi, R., and E. Scharrer. 1995. Hyperpolarization of the liver cell membrane by palmitate as affected by glucose and lactate: Implications for control of feeding. *J. Auton. Nerv. Syst.* 56:45–49.
- Russek, M. 1963. Participation of hepatic glucoreceptors in the control of intake of food. *Nature* 197:79–80.
- Santschi, D. E., R. Berthiaume, J. J. Matte, A. F. Mustafa, and C. L. Girard. 2005. Fate of supplementary B-vitamins in the gastrointestinal tract of dairy cows. *J. Dairy Sci.* 88:2043–2054.
- Satabin, P., E. Auclair, E. Servan, C. Larue Achagiotis, and C. Y. Guezennec. 1991. Influence of glucose, medium- and long-chain triglyceride gastric loads and forced exercise on food intake and body weight in rats. *Physiol. Behav.* 50:147–150.
- Scharrer, E. 1999. Control of food intake by fatty acid oxidation and ketogenesis. *Nutrition* 15:704–714.
- Scharrer, E., and W. Langhans. 1986. Control of food intake by fatty acid oxidation. *Am. J. Physiol.* 250:R1003–R1006.

- Scherrer, W. 1986. Zur Bedeutung von Metaboliten des Fettstoffwechsels für die Regulation der Futteraufnahme beim Wiederkäuer. *Med. vet. Diss. Univ. Zurich, Switzerland.*
- Selberg, K. T., A. C. Lowe, C. R. Staples, N. D. Luchini, and L. Badinga. 2004. Production and metabolic responses of periparturient Holstein cows to dietary conjugated linoleic acid and trans-octadecenoic acids. *J. Dairy Sci.* 87:158–168.
- Selberg, K. T., C. R. Staples, N. D. Luchini, and L. Badinga. 2005. Dietary trans octadecenoic acids upregulate the liver gene encoding peroxisome proliferator-activated receptor- α in transition dairy cows. *J. Dairy Res.* 72:107–114.
- Shinozaki, K. 1959. Studies on experimental bloat in ruminants. 5. Effects of various volatile fatty acids introduced into the rumen on the rumen motility. *Tohoku J. Agric. Res.* 9:237–250.
- Simkins, K. L. Jr., J. W. Suttie, and B. R. Baumgardt. 1965. Regulation of food intake in ruminants. 4. Effect of acetate, propionate, butyrate, and glucose on voluntary food intake in dairy cattle. *J. Dairy Sci.* 48:1635–1642.
- Sindt, J. J., J. S. Drouillard, S. P. Montgomery, and E. R. Loe. 2006. Factors influencing characteristics of steam-flaked corn and utilization by finishing cattle. *J. Anim. Sci.* 84:154–161.
- Smith, K. L., S. E. Stebulis, M. R. Waldron, and T. R. Overton. 2007. Prepartum 2,4-thiazolidinedione alters metabolic dynamics and dry matter intake of dairy cows. *J. Dairy Sci.* 90:3660–3670.
- Stangassinger, M., and D. Giesecke. 1986. Splanchnic metabolism of glucose and related energy substrates. Pages 347–366 in *Control of Digestion and Metabolism in Ruminants*. Proc. 6th Int. Symp. Rumin. Physiol. L. P. Milligan, W. L. Grovum, and A. Dobson, ed. Prentice Hall, Englewood Cliffs, NJ.
- Steinhour, W. D., and D. E. Bauman. 1988. Propionate metabolism: A new interpretation. Pages 238–56 in *Aspects of Digestive Physiology in Ruminants*. A. Dobson and M. J. Dobson, ed. Comstock Publ., Ithaca, NY.
- Sumner, J. M., F. Valdez, and J. P. McNamara. 2007. Effects of chromium propionate on response to an intravenous glucose tolerance test in growing Holstein heifers. *J. Dairy Sci.* 90:3467–3474.
- Swingle, R. S., T. P. Eck, C. B. Theurer, M. De la Llata, M. H. Poore, and J. A. Moore. 1999. Flake density of steam-processed sorghum grain alters performance and sites of digestibility by growing-finishing steers. *J. Anim. Sci.* 77:1055–1065.
- Tordoff, M. G., R. Rafka, M. J. DiNovi, and M. I. Friedman. 1988. 2,5-anhydro-D-mannitol: A fructose analogue that increases food intake in rats. *Am. J. Physiol.* 254:R150–R153.
- Tordoff, M. G., N. Rawson, and M. I. Friedman. 1991. 2,5-anhydro-D-mannitol acts in liver to initiate feeding. *Am. J. Physiol.* 261:R283–R288.
- Van Kessel, J. S., and J. B. Russell. 1996. The effect of amino nitrogen on the energetics of ruminal bacteria and its impact on energy spilling. *J. Dairy Sci.* 79:1237–1243.
- Vasilatos, R., and P. J. Wangsness. 1980. Changes in concentrations of insulin, growth hormone and metabolites in plasma with spontaneous feeding in lactating dairy cows. *J. Nutr.* 110:1479–1487.
- Vazquez-Anon, M., S. Bertics, M. Luck, R. R. Grummer, and J. Pinheiro. 1994. Peripartum liver triglyceride and plasma metabolites in dairy cows. *J. Dairy Sci.* 77:1521–1528.
- Voelker, J. A., and M. S. Allen. 2003. Pelleted beet pulp substituted for high-moisture corn: 2. Effects on digestion and ruminal digestion kinetics in lactating dairy cows. *J. Dairy Sci.* 86:3553–3561.
- Wang, A., Z. Gu, B. Heid, R. M. Akers, and H. Jiang. 2009. Identification and characterization of the bovine G protein-coupled receptor GPR41 and GPR43 genes. *J. Dairy Sci.* 92:2696–2705.
- Wilson, G., F. A. Martz, J. R. Campbell, and B. A. Becker. 1975. Evaluation of factors responsible for reduced voluntary intake of urea diets for ruminants. *J. Anim. Sci.* 41:1431–1437.
- Xiong, Y., N. Miyamoto, K. Shibata, M. A. Valasek, T. Motoike, R. M. Kedzierski, and M. Yanagisawa. 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc. Natl. Acad. Sci. USA* 101:1045–1050.
- Zammit, V. A. 1990. Ketogenesis in the liver of ruminants—Adaptations to a challenge. *J. Agric. Sci.* 115:155–162.
- Zinn, R. A. 1993. Influence of processing on the comparative feeding value of barley for feedlot cattle. *J. Anim. Sci.* 71:3–10.

References

This article cites 187 articles, 96 of which you can access for free at:
<http://jas.fass.org/cgi/content/full/87/10/3317#BIBL>