

Regulation of Feed Intake in Transition Cows: Application of the Hepatic Oxidation Hypothesis¹

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Summary

- Prolonged depression of feed intake in the periparturient period can greatly reduce health, reproductive performance, and milk yield.
- Lipolysis in the periparturient period results in increased uptake, storage, and oxidation of fatty acids in the liver.
- Hepatic oxidation of fuels results in a signal from the liver to the brain, known to terminate meals in nonruminants.
- Increased hepatic oxidation of fatty acids in the periparturient period increases acetyl CoA available for oxidation in the TCA cycle.
- Rapid absorption of propionate during meals stimulates oxidation of acetyl CoA and induces satiety.
- Diets should be formulated to minimize fuels that stimulate hepatic oxidation as a percent of total fuels consumed, while increasing plasma glucose concentration and decreasing lipolysis.

Introduction

Decreased feed intake and negative energy balance can be observed as early as 10 days prior to parturition in cows, and feed intake declines precipitously at parturition and remains suppressed for at least 3-4 days postpartum. After more than a week of depressed intake, high-producing dairy cows are faced with a severe energy deficit, even as milk production continues to increase. Prolonged intake depression increases risk of displaced abomasum and can greatly reduce reproductive performance and milk yield. There has been intense interest in reducing the incidence of this condition, but the mechanism for depressed feed intake in the periparturient period has remained elusive (Ingvartsen and Andersen, 2000). However, in the last decade or so the biology of transition cows has been adequately described to give us important clues for likely mechanisms. Concurrently, work with nonruminant species has progressed on metabolic regulation of food intake in which oxidation of fuels in the liver results in a signal from the liver to the brain to terminate meals. This hepatic oxidation hypothesis is consistent with many of the interacting factors affecting feed intake, and although much more research is needed to understand it fully, we believe that it can be applied to increase health and productivity of transition cows. The objective of this paper is to discuss how this hypothesis applies to the regulation of feed intake by transition cows so that strategies can be developed to reduce the severity of the peripartum depression in feed intake.

The “Hepatic Oxidation” Hypothesis

The hypothesis that food intake is regulated by oxidation of fuels in the liver has evolved as advances have been made by several groups over time; some of the most

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pertinent findings are mentioned here (for greater detail see Allen et al., 2005). The idea that the liver is involved in the regulation 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 feed intake is regulated by changes in blood glucose concentration (Mayer, 1953). Nijima (1969) observed that the firing rate of nerves from the liver to the brain in guinea pigs was related to the concentration of glucose in the blood. The firing rate of these nerves as well as food intake increased when glucose metabolism was blocked in rabbits (Novin et al., 1973). Langhans et al. (1985) reported that a variety of fuels metabolized in the liver depressed food intake of rats, which was restored by severing the nerves connecting the liver to the brain. Additionally, inhibition of fatty acid oxidation by an agent that blocks their transport into the mitochondria stimulated feeding in rats fed a high fat diet (Scharrer and Langhans, 1986). Evidence that energy charge² is related to feeding behavior was provided by a series of experiments with rats by Friedman and coworkers. They showed that trapping inorganic phosphate³ to reduce its availability stimulated eating (Rawson et al., 1994) and that adding excess inorganic phosphate prevented this effect (Rawson and Friedman, 1994). Furthermore, liver ATP concentration is inversely related to food intake in rats (Ji and Friedman, 1999). Although the concentration of ATP in the liver is clearly related to the reduction in food intake in response to oxidizable fuels in rats, the exact mechanism by which intracellular ATP concentrations affect the firing rate of the nerves connecting the liver to the brain has yet to be determined. *In toto*, this body of work with nonruminant species suggests that 1) food intake is regulated by a signal via nerves connecting the liver to the brain, 2) satiety⁴ is associated with a decreased firing rate of these nerves, 3) the signal is stimulated by a variety of fuels, 4) metabolism of fuels in the liver is required to generate this signal, and 5) the mechanism involves high-energy phosphate bonds of adenosine.

Ruminants vs. Nonruminants

Fatty acids, lactate, amino acids, and glycerol are fuels oxidized in both ruminant and nonruminant liver. However, while there is net glucose uptake from the blood by the liver in nonruminants, uptake of glucose is negligible in mature ruminants (Stangassinger and Giesecke, 1986). Hexokinase is needed to activate glucose for metabolism and while activity is high in nonruminant liver, it is very low in ruminant liver. This isn't surprising because ruminant liver functions primarily as a glucose factory, producing glucose from precursors including propionate, lactate, amino acids, and glycerol. Propionate is the primary glucose precursor for ruminants but can also be oxidized and stimulate oxidation of other fuels (Allen et al., 2005). Although propionate can also be metabolized in nonruminant liver, supply to the liver is at least 10-fold lower than in ruminants, minimizing its importance as an oxidative fuel. On the other hand, glucose metabolism can increase energy charge in nonruminant liver when it is metabolized to acetyl CoA, because although some acetyl-CoA is used by nonruminant liver for fatty acid synthesis, it is also oxidized. This difference in liver metabolism can explain differences in effects of intravenous glucose infusion on feed intake between

² Energy charge is the degree of phosphorylation of adenosine: $ATP > ADP > AMP$

³ Inorganic phosphate is needed to increase energy charge, e.g. from ADP to ATP

⁴ The psychological feeling of satisfaction during eating resulting in termination of meals and the disappearance of appetite following meals.

ruminants and nonruminants; while intravenous infusion of glucose decreases food intake in a variety of nonruminant species (Forbes, 1995), it does not decrease energy intake in ruminants (Allen, 2000).

Site of Starch Digestion and Feeding Behavior

The 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). Ruminal digestion kinetics determine site and extent of nutrient digestion, which can greatly affect the type and pattern of fuels absorbed over time. While ruminal starch digestion results in the production of volatile fatty acids (VFAs), starch that escapes ruminal digestion can be degraded by enzymes in the duodenum. Although little glucose appears in the portal vein⁵ in ruminants, glucose is efficiently absorbed in the small intestine. Most glucose is metabolized to lactate by intestinal tissue (Reynolds et al., 2003). Therefore, diets with similar concentrations of starch can provide the animal with VFAs and lactate in different proportions depending on the physical characteristics of the starch source.

Cereal grains that are highly digestible in the rumen can depress feed intake of lactating cows; feed intake was depressed nearly 3 kg 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 VFAs, especially propionate, as fuels at the expense of lactate.

Propionate Regulation of Feed Intake

Besides increasing the amount of VFA produced, increasing ruminal starch fermentation also increases propionate as a proportion of VFA absorbed. Depression of feed intake by propionate infusions has been documented extensively for ruminants (Allen, 2000). Intake depression by propionate is greater than the other major fermentation acids (acetate and butyrate) when infused into the portal vein of sheep (Anil and Forbes, 1980), and infusion of propionate into the mesenteric vein⁶ of steers reduced feed intake, whereas acetate infused at similar rates did not (Elliot et al., 1985). Although propionate might be expected to decrease feed intake compared with acetate because it has higher energy content, propionate linearly decreased metabolizable energy intake compared with acetate in lactating cows when infused intraruminally as iso-osmotic mixtures (Oba and Allen, 2003c). As the proportion of propionate increased, the reduction in metabolizable energy 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 DM as propionate increased from 0% to 100% of infusate, a finding that 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.

⁵ Vein that transfers blood from veins draining the gut to the liver.

⁶ Vein carrying blood and nutrients from the gut to the portal vein.

The liver is involved in regulation of feed intake by propionate because depression of feed intake by propionate infusion in sheep was eliminated by severing the nerves connecting the liver to the brain (Anil and Forbes, 1988). Of fuels metabolized by the ruminant liver, propionate is likely a primary signal to terminate meals because its flux to the liver increases greatly during meals (Benson et al., 2002). 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), thus explaining differences in feed intake depression by infusion of propionate compared to acetate. These observations are consistent with the hepatic oxidation hypothesis.

Formulation of diets to shift starch digestion to the small intestine not only decreases propionate production, but also increases lactate absorption. 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, the hepatic oxidation hypothesis predicts increased feed intake in response to shifting the site of starch digestion postruminally. Stimulation of hepatic oxidation by lactate is much less than propionate, especially during meals, because of the greater lag before lactate absorption, 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 lower because metabolism of lactate to pyruvate is thermodynamically unfavorable when cellular NAD/NADH is low (eg. during meals). Therefore, because of differences in metabolism, the hepatic oxidation hypothesis predicts that more energy can be absorbed in the form of lactate than propionate before stimulating satiety.

Propionate Stimulated Oxidation of Acetyl CoA

Although rapid uptake during meals might cause satiety by oxidation of propionate *per se*, propionate might also cause satiety by stimulating oxidation of acetyl CoA (Figure 1). Incomplete oxidation of fatty acids in the liver results in accumulation of acetyl CoA, requiring export of excess acetyl CoA as ketones. Propionate provides

tricarboxylic acid (TCA) cycle intermediates and utilizes reducing equivalents through its conversion to glucose, relieving the primary limitations to complete oxidation of acetyl CoA. In support of this, we showed in a dose-response experiment that low rates of propionate infusion decreased feed

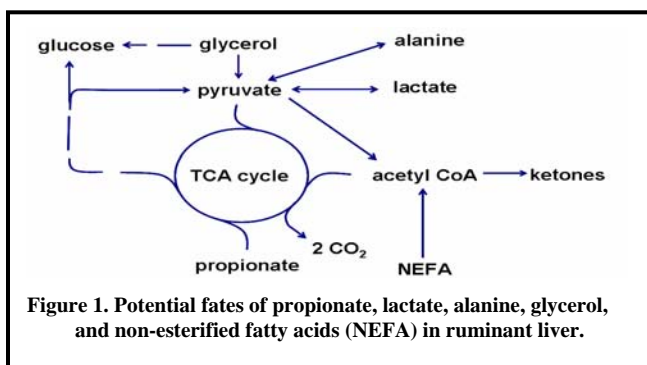


Figure 1. Potential fates of propionate, lactate, alanine, glycerol, and non-esterified fatty acids (NEFA) in ruminant liver.

intake in early lactation cows, but not in mid lactation cows (Oba and Allen, 2003a). Propionate likely stimulated oxidation of excess acetyl CoA in early lactation cows, increasing ATP production despite the use of propionate for glucose production. This is supported by the observed decrease in plasma ketone concentrations in early lactation cows at lower infusion rates while non-esterified fatty acids (NEFA) remained elevated.

Model of Intake Regulation in Transition Cows

We developed a model by which feed intake is regulated in ruminants according to the hepatic oxidation hypothesis and applied it to transition cows (**Figure 2**). Plasma NEFA concentration is elevated as much as tenfold in the periparturient period (Ingvartsen and Andersen, 2000) because of a reduction in insulin sensitivity of adipose tissues combined with a reduction in plasma insulin concentration. Plasma insulin concentrations begin to decline several weeks prior to parturition with a nadir below 6 μ IU/ml at four days postpartum (Doepel et al., 2002). As plasma NEFA concentration rises, uptake of NEFA by the liver increases greatly (Reynolds, et al., 2003), resulting in increased fatty acid oxidation and storage as triglycerides; additionally, buildup of acetyl CoA and reducing equivalents results in export of ketones. *It is likely that this increase in lipolysis contributes to the decrease in feed intake around parturition*, rather than the reverse, because plasma NEFA concentrations increase before the decline in feed intake prepartum (Vazquez-Anon et al., 1994). Hepatic fatty acid oxidation likely contributes to satiety by generating ATP, and negative energy balance is further exacerbated because intake depression limits insulin secretion and promotes continued lipolysis. Furthermore, gluconeogenic capacity is compromised by the increasing triglyceride concentration in the liver (Murondoti et al., 2004; Piepenbrink and Overton, 2003), increasing the time required to restore plasma glucose concentrations.

Minimizing Depression of Feed Intake in Transition Cows

A wide variety of approaches have been used in the attempt to manipulate hepatic fat metabolism in early lactation cows. 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 to cows managed for moderate body condition scores at calving (Garnsworthy and Topps, 1982; Holter et al., 1990). Preventing excessive lipid accumulation in cows during late gestation may improve postpartum feed intake by decreasing the pool of fatty acids available for lipolysis (Douglas et al., 2006) and subsequent hepatic oxidation, consistent with our hypothesis.

Despite the widespread management of late-gestation cows to limit body fat accumulation, postpartum ketosis remains a significant problem. 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 less than propionate because it is converted to lactate and metabolized more slowly, 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 likely depresses feed intake by stimulating hepatic oxidation of fuels.

The most important hormonal regulators of both 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 low dose of

insulin three days postpartum decreased plasma NEFA and hepatic triglyceride concentrations and increased feed intake of dairy cows (Hayirli et al., 2002). However, higher 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 gluconeogenesis. 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). Diets may also be formulated with the goal of limiting lipolysis. Both propionate and glucose stimulate insulin secretion, and increasing diet fermentability can increase plasma insulin concentration. Dann and coworkers (1999) showed that increasing dietary starch fermentability during the dry period numerically increased plasma insulin concentration and decreased plasma NEFA concentration by 42% in the final 10 days prior to calving; this increase in prepartum diet fermentability tended to increase feed intake during the first 63 d of lactation.

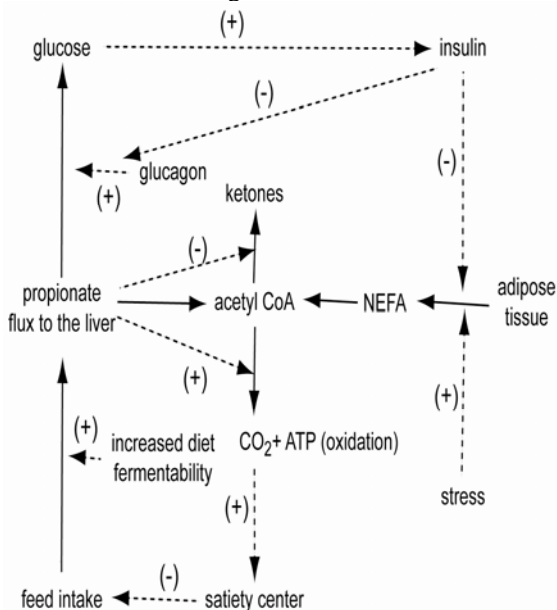


Figure 2. Model by which feed intake might be regulated according to the hepatic oxidation hypothesis. Solid lines show the flow of carbon while dashed lines show stimulation/inhibition of flow. Depression of feed intake in the periparturient period is likely caused or exacerbated by stimulation of acetyl CoA oxidation and generation of ATP during meals. Decreased plasma insulin prepartum results in lipolysis, elevating plasma NEFA. Stress triggers release of catecholamines, increasing lipolysis further. Increased β -oxidation of NEFA increases liver production of acetyl CoA, which can either be oxidized to CO_2 , generating ATP, or exported as ketones. Complete oxidation of acetyl CoA can be limited by allosteric effects of excess reducing equivalents or by lack of oxaloacetate for the citrate synthase reaction of the tricarboxylic acid (TCA) cycle. Rapid uptake of propionate by the liver during meals will increase TCA cycle intermediates, utilize reducing equivalents through its conversion to glucose, and inhibit ketogenesis. This results in increased oxidation of acetyl CoA, generating ATP and stimulating satiety. Plasma glucose concentration is eventually restored, elevating plasma insulin concentration and decreasing lipolysis. However, increased plasma insulin also decreases stimulation of gluconeogenesis by glucagon, increasing oxidation of propionate within meals and terminating meals sooner. Therefore, as plasma glucose concentration increases over time, regulation of feed intake by propionate likely shifts from stimulation of oxidation of acetyl CoA derived from NEFA to oxidation of acetyl CoA derived from propionate.

Other work has focused on increasing hepatic fatty acid oxidation, with the intent of preventing esterification and hepatic accumulation of triglycerides. Carnitine palmitoyltransferase transports fatty acids 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., 2005a) and decreased feed intake during the first 2 weeks of lactation (Carlson et al., 2005b). Others have demonstrated that dietary inclusion of *trans* octadecenoic acids increases mRNA abundance of a transcription factor (PPAR α) that serves as a master switch for hepatic oxidation of fatty acids (Selberg et al., 2005); *trans* octadecenoic acids also depressed feed intake during weeks 4 to 6 of lactation (Selberg et al., 2004). Consistent with the hepatic oxidation hypothesis, these methods of increasing hepatic fatty acid oxidation depress feed intake of early lactation cows.

Conclusion

Although most studies conducted have been focused on other outcomes, such as hepatic fat accumulation or ketone production, the majority of the data from early lactation studies fit the hypothesis that hepatic oxidation of fatty acids contributes to the periparturient depression in feed intake. The hepatic oxidation hypothesis is consistent with: 1) differences between ruminants and nonruminants for feed intake response to glucose infusions, 2) greater depression of energy intake for propionate compared to acetate infusion, 3) elimination of propionate-induced feed intake depression by severing the nerves connecting the liver to the brain, 4) depression of feed intake by increased ruminal starch fermentation, 5) efficacy of ketosis treatments, 6) depressed feed intake during the periparturient period (especially for over-conditioned cows), 7) effects of insulin and glucagon on feed intake, and 8) intake depression by enhancing liver fatty acid oxidation. Therefore, the hepatic oxidation hypothesis provides a unifying mechanism for explaining behavioral responses to changes in both nutrient digestion and metabolism. It provides a new framework for interpreting the results of transition cow experiments and will help us devise strategies to increase feed intake, health and production of periparturient dairy cows.

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