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THE COW AS A MODEL TO STUDY FOOD INTAKE REGULATION

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■ **Abstract** Animal models have been invaluable for studying aspects of food intake regulation that for various reasons cannot be observed in humans. The dairy cow is a unique animal model because of an unrivaled energy requirement; its great drive to eat results in feeding behavior responses to treatments within the physiological range. Cows' docile nature and large size make them ideal for measuring temporal treatment effects because digestion and absorption kinetics and responses in endocrine systems, gene expression, metabolite pools and fluxes, and feeding behavior can be measured simultaneously. Thus, cows are important models to investigate interactions of short-term signals regulating food intake. Furthermore, different physiological states throughout the lactation cycle provide powerful models to study how short- and long-term signals interact to affect long-term energy status. The use of the cow as a model can lead to breakthroughs in understanding the complex interactions of signals regulating food intake.

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INTRODUCTION

The obesity epidemic in the United States and other developed countries has accentuated the importance of studying food intake regulation. Overweight and obese individuals are at increased risk of diseases such as diabetes, high blood pressure, high cholesterol, asthma, and arthritis (83). The proportion of overweight and obese adults in the United States is rising rapidly (35) and has a significant economic impact on the U.S. health care system (110). Although identification of individual satiety factors is progressing rapidly, food intake regulation is extremely complex, and immediate application of research results has been limited. Animal models are utilized to understand physiological and metabolic mechanisms that cannot be observed in human subjects owing to social influence, procedural invasiveness, or ethical limitations. Valuable animal models must provide one or more of the following advantages over human studies: (*a*) the possibility of invasive or repeated sampling with minimal interruption of feeding behavior; (*b*) accessibility of specific organs, portions of the brain, or sections of the gastrointestinal tract for infusion or biopsy; (*c*) existence of genetic polymorphisms or mutations in genes of interest for intake regulation. The use of any of the animal models to study human intake regulation requires the assumption that basic mechanisms controlling feeding behavior are conserved across species.

Rodent models are by far the most commonly used animal models for nutrition and metabolism experiments (42). Rodents require minimal housing facilities and are cost-effective because of their small size. Their extensive use in research provides a rich description of their physiological processes, and variation among strains is well documented and utilized experimentally. Rodent models are also amenable to transgenic manipulation and allow in vivo observation of the effects of gene deletion and overexpression. However, like all animal models, the rodent model has limitations in the study of food intake regulation. Regulatory mechanisms for food intake might be more closely conserved among humans and larger animals; divergence in mechanisms regulating energy intake likely occurred between small and large animals because of different evolutionary pressures (102). Speakman et al. (102) suggested that a system to regulate body mass within strict limits is more advantageous for small animals because they are less starvation-tolerant and have greater mass-dependent predation risk than large animals. Predation also caused rodents to evolve primarily nocturnal feeding behaviors, which may have resulted in further divergence in mechanisms regulating food intake compared with humans.

Rodent models have been invaluable in identifying mechanisms of intake and energy regulation such as the pathways involving leptin and agouti. However, human obesity is not caused by a malfunction of a single mechanism but is

polygenic in nature (19). Research in bovine physiology has focused primarily on polygenic traits, making the cow a valuable biological model for studying complex human health issues such as obesity (43). In addition, the physiological states during the lactation cycle of the dairy cow may provide models that are relevant to conditions observed in humans, including hypophagia associated with stress, short-term regulation of hunger and satiety, and long-term regulation of energy homeostasis.

The use of animal models representing evolutionary clades distinct from rodents increases our ability to dissect the complex processes of food intake regulation that are conserved across many species. The objective of this chapter is to discuss the cow as such an alternate model. In the following sections, we provide background on the nutrition and physiology of the cow as it relates to strengths and limitations as a model for studying food intake regulation. We follow this with specific examples in which the cow has been used to study the effects of temporal pattern of fuel absorption on feeding behavior. We conclude by discussing the value of the different physiological states experienced within lactation cycles for studying the effects of interacting regulators of food intake.

STRENGTHS AND LIMITATIONS OF THE COW AS A MODEL

Lactating dairy cows are unique among animal models used to study food intake regulation for several reasons. They have extremely high energy requirements and marginal nutrient status, which makes them responsive to nutritional changes (Table 1); most energy is partitioned to milk, which is easily measured; they are docile and ideal for intensive measurements of digestion, metabolism, and behavior; and they cycle through different physiological states, greatly affecting energy balance on an annual basis (Figure 1). Few mammals have energy requirements that approach those of high-yielding dairy cows on a metabolic body-weight basis, and none that do have such requirements have been studied as extensively. Although there are very significant differences between fuels available to ruminants and humans because of pregastric fermentation, the basic mechanisms regulating food intake appear to be highly conserved across the species. In some respects, the cow is more similar to humans than is the rat. For instance, cows and humans are similar in respect to circadian eating patterns, ovulation cycles, gestation lengths, and the number of offspring per pregnancy. In addition, the bovine and human genomes seem to exhibit greater collinearity and sequence homology than do the mouse and human genomes (43).

Digestion and Metabolism

Ruminants, like other herbivores, consume diets that are higher in fiber and lower in fat than are diets of nonherbivores. In addition, nutrients absorbed differ markedly from those consumed because of fermentation by microbes in the rumen: organic

TABLE 1 Comparison of energy requirements and metabolic parameters of the cow, human, and rat

Parameter	Cow[a]	Human[b]	Rat[c]
Energy required, kcal d^{-1}	41,800	3081	170
Energy required, kcal $BW_{kg}^{-0.75}$	325	127	86
Maintenance energy, kcal d^{-1}	9270	1769	136
Maintenance energy, % of total	22	57	80
Activity, kcal d^{-1}	1030	1312	34
Milk production, kcal d^{-1}	31,500	—	—
Plasma glucose[d], mg dl^{-1}	55–64	90–130	110–130
Plasma insulin[d], μIU ml^{-1}	8–16	10–80	10–90
Hepatic gluconeogenesis, g glucose d^{-1}	3402	160[e]	2.15[e]

[a]Mature lactating cow: 100 days in lactation, 650 kg, producing 45 kg milk d^{-1} (3.5% fat), housed in individual stall. Energy requirements calculated from (87).

[b]70 kg man with moderate physical activity level, 30 years of age. Energy requirements calculated from (36).

[c]0.4 kg male rat in laboratory housing. Energy requirements calculated from (60).

[d]Typical daily range for fed subjects. Human and rat data from (114).

[e]Maximum rate in fasted subjects (63, 70).

matter (OM) is partially fermented to volatile fatty acids (VFAs; primarily acetic, propionic, and butyric); feed protein is partially degraded to amino acids and ammonia, which are incorporated into microbial protein of high biological value; and unsaturated fatty acids (FAs) are biohydrogenated and isomerized to varying degrees. The major fuels for cows are VFAs from ruminal and intestinal fermentation of OM, glucose from starch digestion in the small intestine (metabolized primarily to lactate by intestinal tissue), and nonesterified FAs (NEFAs) and amino acids absorbed from the gastrointestinal tract and mobilized from body reserves. More than 60% of absorbed amino acids are from microbial protein flowing from the rumen, with the remainder from feed protein escaping ruminal degradation. The large size of the digesta pool and its relatively slow passage from the rumen result in a more consistent absorption of nutrients in ruminants than in nonruminants. Rumen contents of high-producing dairy cows often exceed 100 kg (~15% dry matter), and passage rates of digesta are approximately 2%–4% h^{-1} for fiber, 10%–20% h^{-1} for starch, and 15%–20% h^{-1} for liquid.

Although differences in fuels between humans and cows might be considered a limitation of using cows as models to study food intake regulation, they are also a strength, providing us the opportunity to evaluate basic mechanisms regulating food intake that are conserved across species using very different fuels. This requires an understanding of comparative physiology and metabolism between the species. The physiology and metabolism of dairy cows has been extensively studied and is well documented (Table 1). One difference between cows and

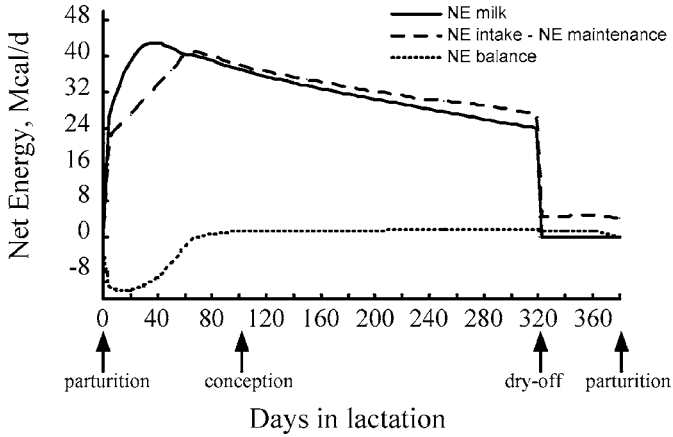

Figure 1 Graphical representation of energy balance through lactation for a mature 650 kg Holstein cow producing approximately 12,700 kg of milk in a 320-day lactation. Milk energy output exceeds net energy intake above the maintenance requirement of 10.3 Mcal day^{-1}, resulting in a large negative energy balance and mobilization of body energy reserves until ~60 days in lactation. The length of the lactation cycle (380 days in this example) is determined by time to conception, which is highly variable (100 days in this example) and gestation length (~280 days). Cessation of milking (dry-off) generally occurs approximately 60 days prior to the following parturition, but is also variable. Energy required for fetal growth increases throughout gestation, peaking at ~4 Mcal day^{-1} of net energy prior to parturition.

humans is that almost no glucose enters from the portal drained viscera in cows (95). Although many ruminant tissues preferentially utilize acetate rather than glucose (45), certain tissues require glucose, and large quantities are required for milk lactose production. As might be expected, the bovine liver functions primarily as a glucose factory. Hexokinase activity is very low in bovine liver (9) and gluconeogenic capacity is extremely high; net hepatic glucose release exceeded 3.5 kg d^{-1} for cows producing ~41 kg d^{-1} of milk (96). Propionate is the primary gluconeogenic substrate in ruminants, accounting for as much as 80% of glucose produced in lactating cows (104). Long-chain FAs (LCFAs) are a major source of energy in bovine liver, which has limited capacity for FA synthesis (45) or triglyceride export (31). As in rodent models, research in the physiology and metabolism of cows is progressing quickly with the use of genomics and this will likely lead to new approaches to study regulation of food intake. For example, the discovery of polymorphisms in the coding region of the leptin gene associated with differences in feed intake in cows (72) could provide a model to study leptin regulation of food intake. Recent sequencing of the bovine genome (86), coupled with the use of proteomics and metabolomics, is expected to further increase the pace of research in ruminant physiology and metabolism.

Energy Requirements and Physiological States

The mean milk yield of cows in the United States was more than 8500 kg year^{-1} in 2003, and it has increased by 16% over the past 10 years (111). Milk yield varies greatly among cows and across stage of lactation; individual cows have produced more than 30,000 kg of milk in a 365-day lactation, with a peak milk yield of over 90 kg d^{-1}. It is not uncommon for milk yield to exceed 60 kg d^{-1} for high-producing cows in early lactation, which requires synthesis of ~4.5 kg d^{-1} glucose [calculated using the formula of (29)] and 50 Mcal of net energy d^{-1} including ~10 Mcal d^{-1} for maintenance requirements of a 650-kg cow.

The dairy cow experiences multiple physiological states throughout a lactation cycle, including extended periods of negative and positive energy balance (Figure 1). Immediately before initiation of lactation, a short nonlactating period (~60 days) allows for mammary involution and ensures adequate nutrient availability for fetal growth and regeneration of mammary epithelial tissue. Around parturition, the cow experiences hypophagia, likely because of physiological stress and immune challenges at parturition. Peak milk synthesis often occurs within 40 days of parturition and imposes a large energy demand on the cow. This rapid increase in energy requirements cannot be matched by increased intake, so body reserves are mobilized. Maximum intake is reached 2–3 weeks following maximum milk yield, allowing a less negative energy balance. As milk production decreases later in lactation, the cow resumes a positive energy balance and begins to replenish body reserves. During the lactation cycle, the energy requirement varies severalfold, and nearly half of the cow's fat reserve may be lost and regained during a lactation (15).

Adaptation to Intensive Measurements

To study interactions between satiety mechanisms in vivo, measurements must be taken over time, often from different organs, with minimal interruption of feeding behavior. Cows thrive in individual stalls and their docile nature allows measurement of feeding behavior along with intensive measurements of site of digestion, fuel supply, and endocrine response. The extremely high energy requirement of lactating cows results in a strong drive to eat, which is maintained even during experimental interventions. We have developed a system to automatically record feed and water consumption, chewing behavior, and ruminal motility for 12 cows simultaneously (23) and to automatically collect blood and rumen fluid samples with minimal disturbance to the cow (2). This system allows continuous (integrated) sampling, pulse sampling as frequently as every 8 minutes, or pulse sampling triggered by behavioral events, without affecting feeding behavior. Behavioral events such as meal initiation have been used to automatically trigger infusion pumps to evaluate factors affecting satiety and hunger (20). In addition, we have demonstrated that needle biopsies of the liver can be collected over the course of a meal without significantly altering meal size ($P > 0.15$; M.S. Allen, unpublished results). These tissue samples as well as those from biopsy of adipose tissue and

muscle can be used to measure temporal patterns of gene expression. Much larger biopsy samples can be taken for measurement of enzyme activity or for proteomic or metabolomic analysis.

Other groups have demonstrated proficiency in measuring portal flux and net liver flux of nutrients during voluntary meals in cattle (17), and in measuring gastric motility and digesta passage (67). Although cattle are not generally used for direct hypothalamic studies, sheep have been used for brain infusion work for years (51, 81), and the cow provides an equally good, albeit more expensive, model (3). In addition, nutrients may be supplied through intestinal or intravenous infusion to modify energy balance. Nutrients may be infused into the rumen, although abomasal or duodenal infusions allow more certain absorption of nutrients by avoiding metabolism by ruminal bacteria. Ruminal and duodenal cannulas may be maintained over multiple lactations without detrimental effects on the health of the animals; we have used groups of cows with both cannulas that averaged as much as 45 kg d^{-1} of milk (46). Abomasal infusion lines are easily placed by reaching through the rumen of a fistulated cow and feeding a catheter line through the reticular-omasal orifice. Although it is true that none of these methods is unique to the cow, the importance of using a large, docile animal with a strong drive to eat cannot be overemphasized. By combining several of these techniques, biologists have the opportunity to use the dairy cow to uncover many of the complex interactions between hormonal, metabolic, and sensory modulators of feeding behavior.

Measurement of Energy Status

In the lactating dairy cow, the large energy demand for lactation overwhelms the energy expended in physical activity. In contrast, physical activity greatly contributes to the energy expenditure of humans and other animals and thus has a large effect on their requirement for energy intake. Furthermore, exogenous infusions of the intake-regulating peptides ghrelin and agouti-related peptide decreased locomotor activity by 20% in rats (107). The large contribution of physical activity to total nonmaintenance energy expenditure and its modification by intake-regulating compounds demands that activity is measured and accounted for in understanding energy balance in humans and rodents at maintenance. Unfortunately, observation of physical activity and calculation of energy expended during physical activity is challenging and may lack accuracy (108). In comparison, observation of milk yield and composition allows convenient and accurate determination of the major portion of energy expenditure of cows. Milk yield is observed at least twice per day and the net energy required to produce milk can be calculated based on the yield of components. The maintenance energy requirement can be estimated from metabolic body size and is ~25% of the total energy requirement of a 650-kg cow producing 45 kg of milk d^{-1} (Table 1). Thus, the ability to more accurately account for the majority of the energy expended in the lactating cow provides an advantage for investigating maintenance of energy balance.

Retained energy is more difficult to measure for ruminants. Differences in body weight gain are difficult to detect because of a large variation in digesta weight relative to meals, and treatment bias can occur if treatments affect the weight of digesta. Ruminal empty body weight is a much more sensitive measure of body weight change and is observed as body weight after removal of ruminal contents through a fistula. Although change in body composition is difficult to assess without sacrificing animals, tissue energy gain can be estimated from change in body weight by assuming that changes occur primarily in adipose tissue.

TEMPORAL EFFECTS OF ABSORBED FUELS

Temporal patterns of fuel absorption and utilization affect food intake by altering meal size and frequency. Satiety factors that affect the length and size of meals include gut distension from the filling effect of foods and various physiological responses to absorbed fuels. Hunger, determined by sensory cues and clearance of fuels from the blood, affects the interval between meals and rate of food consumption. Pregastric fermentation affects the type and temporal pattern of absorption of fuels in ruminants, complicating the evaluation of their effects on feeding behavior. However, cannulation of the gastrointestinal tract allows determination of fuels available for absorption as well as the kinetics of digestion and absorption. Combined measurement of digestion kinetics and feeding behavior allows evaluation of responses to temporal absorption of fuels for different dietary treatments. Modification of feeding behavior by changes in kinetics of ruminal starch digestion and absorption of unsaturated FA are discussed in this section to demonstrate the potential contribution of temporal observations to our understanding of food intake regulation.

Regulation of Food Intake by Hepatic Oxidation of Fuels: Evidence in Ruminants

STARCH DIGESTION KINETICS AND FEEDING BEHAVIOR The rates of ruminal starch digestion and passage vary greatly across grains fed to ruminants and depend upon the type of cereal grain, conservation method, and processing (87). Ruminal digestion kinetics determine the site and extent of nutrient digestion, which can greatly affect the type and temporal pattern of fuels absorbed. Cereal grains that are highly digestible in the rumen can depress food intake of lactating cows; food intake was depressed nearly 3 kg DM d^{-1} ($\sim$13%) when more fermentable grains were substituted in diets of lactating cows in several studies reported in the literature (1). A recent experiment from our laboratory demonstrated that a more rapidly fermented starch source reduced meal size 17%, causing an 8% reduction in food intake despite a 10% decrease in intermeal interval (89). The more fermentable treatment nearly doubled the fractional rate of starch digestion in the rumen, increasing the contribution of VFA as a fuel at the expense of glucose from starch digestion in the small intestine.

Dynamic measures of fuel absorption and feeding behavior provide essential clues regarding the mechanism of diet-induced hypophagia. One possibility is that increased VFA production causes satiety by increasing the osmolality of rumen fluid during meals. Osmolality may stimulate satiety through osmoreceptors in the rumen wall (77) or the release of vasopressin, a hormone that can affect satiety (73), in response to water efflux from the blood to the rumen. Although mechanisms associated with osmolality likely contribute to satiety, changes in osmolality per se do not affect food intake. We reported that sodium chloride (NaCl) infused intraruminally at the onset of spontaneous meals decreased meal size 27% but did not affect daily food intake because intermeal interval decreased 31% compared with sham infusion (20). In that experiment, Na acetate and Na propionate decreased food intake compared with equimolar amounts of NaCl, primarily because of a greater intermeal interval, which indicates delayed hunger.

HYPOPHAGIC EFFECTS OF PROPIONATE Increasing ruminal starch fermentation increases propionate as a proportion of VFA absorbed in addition to increasing the amount of VFA produced (25). Hypophagic effects of propionate infusions have been documented extensively for ruminants (5, 30, 34, 58, 79, 82, 100). Propionate is more hypophagic than acetate or butyrate when infused into the portal vein of sheep (5), and infusion of propionate into the mesenteric veins of steers reduced feed intake, whereas acetate infused at similar rates did not (30). In the infusion study by Choi & Allen (20), propionate decreased dry matter intake compared with acetate by decreasing meal size, a finding that indicates increased satiety. Therefore, propionate likely causes satiety via mechanisms beyond those related to osmolality. Although propionate might be expected to decrease food 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 (91). As the proportion of propionate increased, the reduction in metabolizable energy intake from the diet exceeded that supplied from the infusate. Food 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. Meal frequency also tended to decrease linearly ($P = 0.08$), from 7.4 to 6.1 meals during the 12-h monitoring period, as propionate was increased. Therefore, propionate decreased energy intake compared with acetate by increasing satiety and possibly by decreasing hunger. Propionate also decreased food intake of dairy cows compared to iso-energetic infusions of VFA mixtures (58) or acetate (100). These studies suggest that hypophagic effects of 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 satiety and hunger.

MECHANISM FOR REGULATION OF INTAKE BY PROPIONATE The mechanism by which propionate regulates satiety is not fully understood. More than three decades ago, Baile (7) proposed that propionate receptors in the ruminal region of sheep

might regulate food intake because propionate injections into the ruminal vein during spontaneous meals decreased food intake, but injections of larger amounts into the jugular vein did not. Subsequent research with nonruminants suggests that meals can be terminated by a signal carried from the liver to the brain via afferents in the vagus nerve that are affected by hepatic oxidation of fuels and generation of ATP (38, 75). The mechanism by which intracellular ATP concentrations affect the firing rate of the hepatic vagus has not been determined. Although it is possible that ATP-sensitive potassium channels are involved in signal initiation (39), adenosine-5′-monophosphate (AMP)-activated protein kinase (AMPK) is an emerging candidate. AMPK is activated in response to high AMP concentration (typically corresponding to low ATP concentration), and direct activation of AMPK in the hypothalamus increased food intake of rats (4). The ability of AMPK to phosphorylate ion channels and other proteins involved in signal transduction pathways provides a much broader range of possible mechanisms than does the ATP-sensitive potassium channel.

Regulation of food intake by propionate in ruminants is consistent with this proposed mechanism; propionate might decrease food intake of ruminants by stimulating oxidative metabolism in the liver (1). The liver is involved in regulation of intake by propionate because hypophagic effects of portal infusion of propionate were eliminated by splanchnic blockade with anesthetic, bilateral splanchnotomy, and hepatic vagotomy, as well as with total liver denervation in sheep (6). Of fuels metabolized by the ruminant liver, propionate is likely a primary satiety signal because its flux to the liver increases greatly during meals (18). While propionate is extensively metabolized by the ruminant liver, there is little net metabolism of acetate (95) because ruminant liver has high activity of propionyl CoA synthetase but not acetyl CoA synthetase (26, 97), thus explaining differences in hypophagic effects of infusions of propionate and acetate in ruminants.

Glucose is hypophagic in a variety of nonruminants (37), but intestinal and intravenous glucose infusions have not decreased energy intake of ruminants (1). The absence of effects of portal glucose infusion on food intake by sheep (8) casts doubt on the hypothesis that nutrient receptors in the portal vein mediate the hypophagic effects of glucose (54). Given that mechanisms regulating food intake are well conserved among mammals, it seems unlikely that highly specific receptors for glucose exist in rodents but not in cows. Rather, differences in hypophagic effects of glucose infusion observed between ruminants and nonruminants are likely because of differences in hepatic oxidation of glucose; liver hexokinase activity is low in ruminants compared with nonruminants (9), and in mature ruminants, hepatic removal of glucose appears to be negligible (103). Although the notion of fuel-specific receptors persists (54, 79) and the exact coding mechanisms of peripheral metabolic sensors that control food intake are not definitely known (98), this example is consistent with the hypothesis that feeding behavior is regulated by the hepatic oxidation of fuels. Further research with this animal model holds promise to test this hypothesis further.

HYPOPHAGIC EFFECTS OF PROPIONATE ARE VARIABLE Inconsistent effects of propionate infusion on food intake have led to doubts that VFAs per se are signals of satiety for ruminants (44). However, the partitioning of fuels among different tissues and between metabolic pathways affects food intake substantially (39). Propionate can be used for gluconeogenesis, which consumes ATP, or oxidized in the tricarboxylic acid (TCA) cycle as acetyl CoA, generating ATP. Therefore, the temporal pattern of oxidative metabolism in the liver is greatly altered by both propionate flux to the liver and fate of propionate within the liver (Figure 2). Insulin and glucagon are important for directing fuel partitioning, especially during meals. Decreased rate of gluconeogenesis when plasma glucose and insulin are high is expected to speed oxidation of propionate in the liver and cause satiety sooner. In support of this, the extent of hypophagia caused by propionate infusion increased linearly with plasma glucose concentration in dairy cows (90). Ruminants absorb little glucose during meals, and insulin responses to meals are less extreme than those of nonruminants. However, cephalic stimulation prompts insulin secretion in ruminants (52), and propionate (79) and butyrate (61) are insulin secretagogues. As a result, peripheral insulin concentrations increase substantially within and following major meals in lactating cows (Figure 3). Grovum (44) suggested that hypophagic effects of propionate are through insulin because propionate is an insulin secretagogue and insulin is a putative satiety hormone. However, hypophagic effects of propionate infusions have been observed without an increase in insulin (34, 41), and mechanisms exclusively involving insulin do not explain the elimination of hypophagic effects of portal infusions of propionate by hepatic denervation as discussed above.

In the previously mentioned study from our laboratory (89), more rapidly fermented starch decreased meal size, likely because propionate flux to, and oxidation in, the liver was higher during meals. More rapid increases in plasma insulin concentration during meals for the more fermentable starch treatment (89) likely increased fuel oxidation by inhibiting gluconeogenesis (88). Increased plasma insulin concentrations may have also contributed to increased hunger for this treatment by speeding clearance of fuels from the blood, especially following relatively smaller meals. This might explain inconsistent intake effects of peripheral insulin administration reported in the literature (50); although increased hepatic oxidation of fuels likely causes satiety, increased clearance of fuels from the blood is expected to cause hunger. The less fermentable starch source increased starch flux to the small intestine and likely increased lactate absorption because of glucose metabolism by intestinal tissues. Lactate stimulates hepatic oxidation to a lesser degree than propionate during meals because of the greater lag before lactate absorption and because hepatic extraction of lactate is much less than propionate (96). Hepatic extraction of lactate is probably lower because metabolism of lactate to pyruvate is thermodynamically unfavorable when cytosolic nicotinamide adenine dinucleotide redox potential is high.

These observations of the hypophagic effects of various fuels in ruminants strongly support the theory that hepatic oxidation of fuels contributes to the

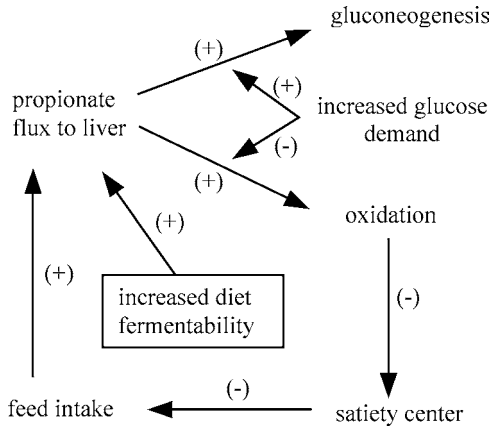

Figure 2 Model to demonstrate how propionate might affect satiety in ruminants. Propionate flux to the liver is affected by feed intake and diet fermentability and increases greatly during meals. Propionate can be used for gluconeogenesis, which consumes ATP, or oxidized in the tricarboxylic acid cycle as acetyl CoA, generating ATP. Supply of propionate to the liver relative to glucose demand should affect the temporal pattern of ATP (and AMP) concentration in the liver and is expected to affect satiety. When glucose demand is high, gluconeogenesis increases and less propionate is oxidized, resulting in greater meal size. When glucose demand is low, a greater fraction of propionate is oxidized, resulting in satiety and smaller meal size.

short-term regulation of food intake. The relative importance of hepatic oxidation of fuels likely varies with other factors such as physiological state, as discussed below.

Satiety from Dietary Unsaturated Fatty Acids

Fat sources are often added to diets of dairy cows with the goal of increasing energy intake to increase milk yield or energy balance. However, fat addition has had inconsistent effects on food intake of dairy cows, partly because of differences in fat sources. A meta-analysis of treatment means from the literature indicated diverse hypophagic effects of different fat supplements; within commonly fed rumen-protected fat sources, calcium salts of palm oil linearly decreased dry matter intake with increasing dietary concentration, whereas hydrogenated FA did not affect dry matter intake (1). Fat sources infused abomasally have different hypophagic effects depending upon source (28), and abomasal infusions have consistently demonstrated the hypophagic effect of unsaturated FA (17). Increasing the proportion of unsaturated LCFAs in rumen-protected fat sources linearly decreased food intake and tended to decrease digestible energy intake of lactating cows (47). Similar effects were reported in a study using human subjects, which indicated that polyunsaturated FAs were more hypophagic than monounsaturated or saturated FAs (76).

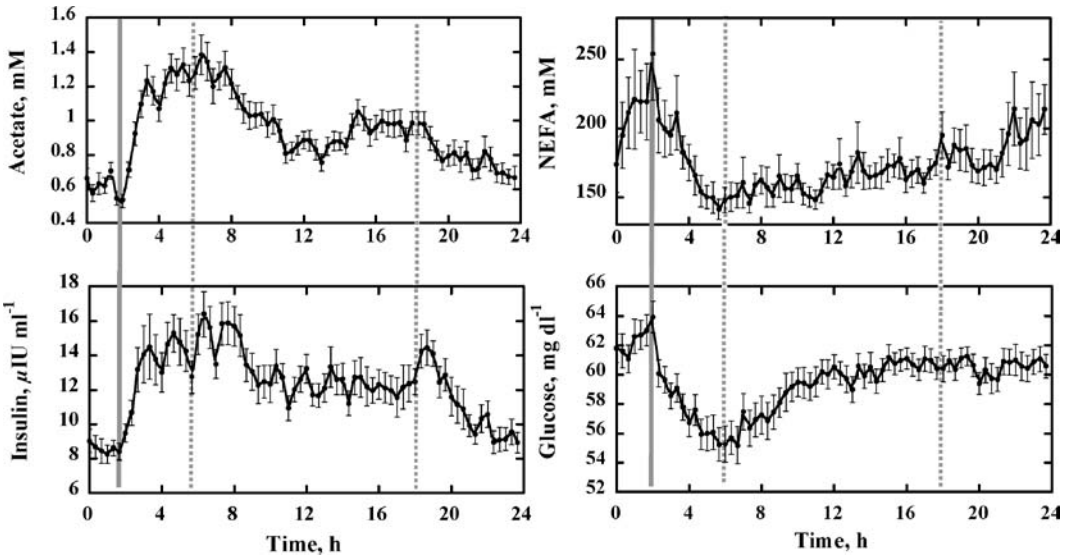

Figure 3 Diurnal variation in plasma insulin, glucose, nonesterified fatty acid (NEFA), and acetate concentration for cows in early to mid lactation offered feed ad libitum. Each data point represents means and standard errors of 32 observations (8 cows × 4 diets) and samples were taken every 20 minutes for 24 hours. Time 0 in the graph is when sampling began at noon; cows were fed once per day at 2 PM (*solid gray line*) and milked at 6 PM and 6 AM (*dashed gray lines*). The conditioned meal is typically the largest meal of the day for dairy cows fed ad libitum followed by 10 or more spontaneous meals (24). Plasma glucose and NEFA concentrations are affected by insulin and mirror its concentration in an opposite manner, whereas plasma acetate concentration is more dependent on absorption following meals and its temporal pattern is similar to that of insulin. (M. Oba & M.S. Allen, unpublished data)

FEEDING BEHAVIOR AND DIGESTION KINETICS Combined measurement of physiological responses with feeding behavior can provide important clues to unravel the mechanism by which unsaturated FAs depress food intake. Feeding supplemental fat can increase plasma NEFA concentration in lactating cows (21), and NEFAs are the primary source of FA oxidized in the liver of ruminants (31). The degree of FA oxidation in the liver is likely involved in the regulation of food intake (40, 74), and Friedman (39) suggested that fat that is oxidized is satiating, whereas fat that is stored is not satiating. Saturated FAs are not oxidized as fuels as rapidly as polyunsaturated FAs in humans (64) and might favor fat deposition over oxidation in rats (101). The depression of food intake with increasing unsaturated FA is consistent with expected differences in FA partitioning and hepatic oxidation. However, differences in hepatic metabolism do not explain the observed effects on feeding behavior and kinetics of digestion and passage as discussed below.

The reduction in food intake in lactating cows fed less saturated FA was through decreased meal size without a compensatory increase in meal frequency (47). Different effects of FA on meal size, and not intermeal interval, suggest that mechanisms other than hepatic oxidation are involved. The contribution of dietary FA to plasma NEFA within the course of a meal is likely small because passage of FA from the rumen of lactating cows is less than 10% h^{-1} (48), causing a lag prior to absorption. In addition, hepatic oxidation of NEFA is limited because insulin increases during meals (112), and propionate, which is rapidly absorbed during meals, inhibits ß-oxidation of FA by decreasing FA transport into mitochondria (62) and by decreasing activity of fatty acyl CoA dehydrogenase (31).

GUT PEPTIDE RELEASE DURING MEALS Gut-derived peptides have received increased attention in recent years for their potential role in meal-induced satiety. Although the contribution of dietary FA to plasma NEFA during a meal is small, flow of FA to the small intestine during a meal is adequate to stimulate release of gut peptides. Both fat and protein enhance expression and secretion of cholecystokinin (CCK), with serum concentrations peaking approximately 30 minutes after meal initiation in cows (22). Fasting quickly decreased plasma CCK concentration and refeeding gradually increased it in cows, with corresponding changes in duodenal CCK mRNA abundance (106). Blockade of CCK receptors by devazepide (MK-329) reduced the depression in food intake caused by a high-fat diet (22). CCK might affect satiety both by slowing gut motility (increasing gut distention and ruminal propionate production) and by acting directly on the nervous system.

INTERACTION OF GUT PEPTIDES AND PROPIONATE Gastrointestinal hormone signals may be integrated with metabolic signals at the level of peripheral nerves or the hypothalamus. Farningham and colleagues (33) investigated the interactions between CCK and propionate infusions in sheep during two-hour portal infusions. Simultaneous infusion of CCK and propionate decreased food intake 40%, but individual infusions at the same concentrations had no effect. The authors

demonstrated that CCK receptors were present in vagal afferent nerves, which suggests that vagal signals initiated by hepatic oxidation of propionate may have been integrated with signals initiated by CCK receptors. Greater stimulation of CCK release for unsaturated fats (in the form of free FA and triglycerides) than for saturated fats (14) might explain the differences in their effects on satiety in the example above.

Hypophagic responses to propionate could also be amplified by other gut-derived hormones. Glucagon-like peptide 1 (GLP-1) is produced in the distal small intestine and is released in response to duodenal infusions of LCFAs and triglycerides in dairy cattle (17, 80). Dietary fat likely stimulates release of GLP-1, enhancing insulin secretion (56). Increased insulin concentrations alter hepatic metabolism, downregulating gluconeogenic pathways and likely directing a greater proportion of propionate toward oxidation. This effect, coupled with rapid liver uptake of propionate during a meal, likely promotes meal termination.

Determining the mechanisms behind diet-induced differences in food intake is complicated and difficult. These examples demonstrate that a change in concentration of any compound in response to a meal is not meaningful unless the timing of the change, the utilization of nutrients, and the organs affected are taken into account. Measurements to assess these factors are relatively easier to achieve in cows than in most other animal models.

INTERACTION OF IMMUNE RESPONSE, STRESS, AND NUTRITION

Hypophagia in the periparturient period is a significant problem in dairy cows, increasing the risk of metabolic diseases such as hepatic lipidosis and metabolic ketosis. Decreased food intake and negative energy balance can be observed as early as 10 days prior to parturition in cows, and intake declines precipitously at parturition and remains suppressed for at least 3–4 days postpartum (59). 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. The etiology of this periparturient hypophagia is not completely understood, and it provides an excellent case study for dissecting possible mediators of intake responses to physiological stress.

Hyperlipidemia in the Periparturient Period

Increased lipolysis in late gestation is likely an evolutionary adaptation to eliminate the mother's dependence on available food and to increase the FA concentration of milk for the first critical days of the neonate's life. However, because NEFAs are taken up by the ruminant liver in proportion to their concentration in plasma (31), lipid mobilization leads to extensive oxidation of FA in the liver. As discussed above, hepatic oxidation of FA may promote satiety and/or suppress hunger.

Therefore, lipid mobilization and hepatic oxidation of FA may inhibit feeding behaviors, widening the energy imbalance and promoting even more lipid mobilization.

Hyperlipidemia in the periparturient period is caused by a reduction in insulin sensitivity of adipose tissues combined with a reduction in plasma insulin concentration; plasma insulin concentrations decline prior to parturition with a nadir below 6 μIU ml^{-1} at four days postpartum (27). It is likely that lipolysis contributes to hypophagia rather than the reverse because plasma NEFA concentrations increase preceding periparturient hypophagia (113). Cytokines as well as growth hormone and other homeorhetic signals reduce insulin sensitivity and responsiveness and increase catecholamine responsiveness (16). These multiple metabolic changes result in plasma NEFA concentrations as much as tenfold higher in early lactation than during gestation (59).

Tissue sensitivity to insulin is decreased both at the onset of lactation (10) and during immune challenges (99), and evidence has emerged that implicates TNF-α in both situations. TNF-α concentrations were highly correlated with the degree of insulin resistance in both pregnant women (68) and postpartum dairy cows (92). Furthermore, blocking TNF-α activity by various means improves insulin sensitivity (57), whereas exogenous TNF-α infusion in cows induced a metabolic state similar to that observed during early lactation and bacterial infection (71). TNF-α and (or) other inflammatory response signals may be responsible for initiating insulin resistance in periparturient cows. However, adipose tissue is not completely unresponsive to insulin; administration of a low dose of insulin three days postpartum decreased plasma NEFA and hepatic triglyceride concentrations and increased food intake of dairy cows (50).

The implications of increased TNF-α production for food intake are not limited to altered insulin sensitivity in adipose tissue. Decreased gastric motility following TNF-α induction as reported in rats (53) would likely decrease food intake in high-producing cows, when physical fill is often the most limiting factor. Furthermore, TNF-α may decrease transcription and activity of PEPCK (55), which would likely dramatically impair gluconeogenic capacity in lactating cows. As discussed above, limiting the utilization of propionate for gluconeogenesis may increase its oxidation and limit meal size.

Hepatic Fatty Acid Oxidation Enhances Hypophagic Effects of Propionate

In early-lactation cows, a shortage of glucose precursors and increased FA oxidation in the liver leads to an abundance of NADH and a lack of TCA-cycle intermediates. This environment results in a buildup of the intracellular acetyl-CoA pool and export of ketone bodies. In this situation, hypophagic effects of propionate may be 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 dramatically increases ATP production and causes satiety,

despite the use of propionate for glucose synthesis (90). Propionate infusion was less hypophagic when it increased plasma glucose concentration in mid-lactation cows, but that was not the case for early-lactation cows with higher plasma ketone concentrations (90).

Excessive mobilization of FA in late gestation or early lactation results in hepatic lipidosis and ketosis, and various treatments have been developed to decrease lipolysis, increase hepatic FA oxidation, or enhance FA export as VLDL. Among the most popular treatments for ketosis are oral drenches of glucogenic 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 (93). Propylene glycol is less hypophagic than propionate because it is converted to lactate and metabolized more slowly (69), and it is less likely to stimulate oxidation in the liver and cause satiety. Thus, calcium propionate may be a less-effective treatment for ketosis because it causes hypophagia by stimulating hepatic oxidation of fuels.

The interactions of stress response, metabolism, and intake regulation have profound human health impacts. Anorexia is experienced during trauma and disease and may prevent adequate nutrient intake (94), while insulin resistance is a prerequisite for metabolic syndrome (84). The periparturient dairy cow provides an excellent model for delineating the central versus metabolic effects of inflammatory response factors such as TNF-α. The condition known as fat cow syndrome (85) is an obvious choice to study the emerging links between obesity, stress, and insulin resistance. In addition, if the satiating effects of hepatic lipid oxidation can be demonstrated in bovines, the early-lactation cow will provide an interesting comparison for intake regulation in humans with hyperlipidemia.

ALTERATION OF MILK YIELD

Milk yield can be greatly altered by management practices such as frequency of milking (105) and length of photoperiod (109), endocrine factors such as growth hormone, thyroxin, and insulin (109), and specific nutrients, allowing the manipulation of fuel partitioning among tissues and evaluation of food intake responses. Homeorhetic signals such as growth hormone are associated with increased intake, yet there are apparently no direct mechanisms for these signals to increase intake (11, 49). However, these lactogenic agents do have a profound influence on metabolism during lactation, significantly increasing energy demand and altering nutrient partitioning. Direction of fuels to peripheral tissues during the postprandial period likely limits hepatic oxidation and delays satiety. This "nutrient pull" may also speed clearance of nutrients from the blood and promote hunger. Thus, homeorhetic signals may interact with dietary fuels to influence food intake.

Nutrient sparing may also provide insight into intake regulation. Intermediates of rumen FA biohydrogenation, including *trans*-10, *cis*-12 conjugated linoleic

acid, decrease milk lipid synthesis in the dairy cow by up to 40% (12) via a coordinated downregulation of genes involved in milk fat synthesis (13). A significant decrease in milk fat synthesis representing a large decrease in energy requirement did not decrease energy intake commensurately, and increased body weight gain was observed (47). The ability to partition fuels in lactating cows provides an experimental model to observe the relationships between energy requirements and food intake.

INTERACTIONS OF SATIETY SIGNALS

It is broadly recognized that the various signals contributing to regulation of intake must be integrated and that this integration likely occurs in the central nervous system. However, the number of systems that are thought to act on hypothalamic control centers makes investigation of interactions a daunting task. The lactating dairy cow is an intriguing model for investigating the integration of signals regulating intake because it is possible to monitor pre- and postprandial changes in the gastrointestinal tract, blood, and liver. Most importantly, many of these observations can be made simultaneously and without interrupting normal feeding behaviors.

During mid-lactation, the large nutrient requirements for peak milk synthesis result in increased stimulation of feeding behavior. However, the high-fiber diets of ruminants require a long retention time in the rumen and increased ruminal fill may signal satiety through stimulation of tension receptors in the rumen wall, thereby limiting maximal energy intake (1). Given the existence of independent physical fill and fuel-responsive satiating mechanisms, rumen fill and nutrient metabolism may interact to alter food intake. Mbanya et al. (82) investigated the effects of rumen distention and ruminal infusions of acetate and propionate during three-hour treatments. Rumen distention, produced by inserting a balloon into the rumen of fistulated cows and inflating the balloon to a volume of 10 liters, did not independently alter food intake, nor did infusions of VFA. However, when balloon distention was combined with infusion of acetate, propionate, or both, feed intake was significantly depressed. This example indicates that peripheral satiety signals are additive and that the integrated signal must reach a threshold to cause satiety.

Although food intake decreases in late lactation, energy intake exceeds the diminishing energy requirements for milk production, allowing replenishment of body reserves (Figure 1). Regulation of food intake is accomplished through a variety of mechanisms, but signals derived from absorbed fuels, sensory stimulation, and gut peptides cannot regulate long-term energy balance. The continued drive to eat in late-lactation cows is likely mediated, in part, by low plasma leptin concentrations. Long-term energy balance is highly controlled (102), and the lipostatic theory proposed by Kennedy (66) describes an adiposity set point that drives regulation of energy intake, which is consistent with these observations. However, long-term signals coordinating energy balance clearly must function through

modification of meal size and frequency. The integration of short- and long-term intake regulation is therefore an area of intense interest (49, 102, 115).

Short- and long-term regulatory mechanisms may interact in several ways. The primary mechanism may be that long-term signals alter the thresholds for response to short-term signals (1, 116). Hypophagia induced by intraperitoneal administration of CCK in rats was greatly increased by concomitant leptin administration, even though rats given only leptin showed no decrease in food intake (32). Similar interactions have been observed in rats treated with leptin and urocortin (65). Both studies provided evidence that integration of these signals occurred centrally. Hormones affecting food intake may also interact by altering the expression or secretion of other hormones. For example, insulin stimulates leptin secretion (78), whereas central leptin administration increases insulin secretion in fasted cows (3).

Clinical applications of findings involving the regulation of food intake have been elusive. One reason is that intake research has focused on individual mechanisms that can be demonstrated conclusively; however, physiological systems are inherently complex, with multiple layers of regulation. Interactions between hormonal, metabolic, and sensory regulators of food intake represent the next frontier of intake research. Use of the lactating cow model in various physiological states could provide valuable insights into these interactions.

CONCLUDING REMARKS

Nonconventional animal models such as the cow provide opportunities to study certain aspects of food intake regulation not possible with rodent models. Cows are unique among animal models to study food intake regulation because their extremely high energy requirements increase their drive to eat, because their docile nature and large size make them ideal for intensive measurements, and because they cycle through various physiological states throughout lactation. They are ideally suited to study interactions among short-term satiety signals affected by the temporal absorption of fuels because digesta flow, nutrient absorption, endocrine response, and feeding behavior can be measured simultaneously. Comparative ease of tissue sampling maximizes the potential for utilization of recent technological innovations for rapid and inexpensive measurement of gene expression and metabolite pools, which promises integrated information to unlock mechanisms regulating food intake. Wide-ranging physiological states throughout lactation and the ability to alter partitioning of fuels to tissues provides us the opportunity to study the interaction of long- and short-term signals, while natural or experimentally induced stimulation of stress and immune function in the cow may provide a valuable model to understand the interaction of stress, immune function, and intake. Future breakthroughs in understanding the multifactorial nature of food intake regulation may depend on alternative animal models such as the cow because of these unique advantages.

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