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Why Dry Matter Intake (DMI) in Early Lactation Does Not Fullfill the Entire Energy Requirement of the Lactating Cow? : A Review

(Mengapa Intake Bahan Kering Selama Awal Laktasi Tidak Dapat Memenuhi Seluruh Kebutuhan Energi pada Sapi Perah Laktasi? : Suatu Kajian Pustaka)

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ABSTRAK: Regulasi intake merupakan fenomena biologis yang kompleks. Berbagai macam signal seperti hormon dan metabolit dapat berperan secara potensial dalam penurunan nafsu makan sapi perah setelah kelahiran. Meskipun leptin telah diusulkan sebagai salah satu faktor yang berpengaruh dalam regulasi intake, kemungkinan leptin tidak berperan besar dalam penurunan intake sapi perah selama awal laktasi. Berdasarkan asumsi strategi sapi perah untuk memobilisasi simpanan lemak tubuh selama awal laktasi, umpan balik signal yang berperan besar dalam regulasi intake selama laktasi adalah produk-produk metabolis dari pemecahan simpanan lemak tubuh. Signal yang berperan dalam penurunan nafsu makan setelah kelahiran kemungkinan berhubungan dengan peningkatan uptake metabolit dalam liver dan oksidasi asam-asam lemak dari produk pemecahan lemak tubuh. Pemahan tentang kemungkinan alasan-alasan mengapa sapi perah tidak dapat meningkatkan regulasi intake pakan secara maksimum segera setelah kelahiran, dapat memberi gambaran dan arah dalam memformulasikan hipotesis-hipotesis riset tentang mekanisme penekanan intake bahan kering sapi perah selama awal laktasi.

Kata Kunci: Leptin, bahan kering, energi, sapi perah

Introduction

Post partum transition period (3-4 week post partum) has been recognized as the most critical phase of the lactation cycle for the dairy cow. At this period the nutrients demands are increasing dramatically for milk production, but typically, the cows experience slow recovery of feed intake after calving until they reach their peak feed intake approximately 8-4 weeks post partum. Hence, the dry matter intake (DMI) does not fulfill the entire energy demand of the early lactating cow, which results in the cow's state of negative energy balance (NEB). When the cow enters the energy-deprived state, body fat storage is mobilized. This mobilized body fat provides extra energy for the increased energy demand during early lactation. However, over mobilization of body fat can contribute to the health problems in transition dairy cow (Drackley, 1999). The objectives of the present paper are to evaluate why dairy cow does not up regulate maximum feed intake shortly post-partum partum, and how is the possible mechanism involved in the slow increase of DMI during post-partum early lactating period.

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Why Does Cow Mobilize Body Fat Reserves Post Partum?

It is usually assumed that the body fat mobilization during early lactation is entirely a response to a shortfall in food energy intake relative to milk energy output. This implies that increasing energy content of the food being offered would decrease body fat mobilization in early lactation, or decreasing the nutrient availability would result in an increase in mobilization of body fat (e.g. Friggens *et al.*, 1998). However, there are many studies show that this is not always the case (eg. Grummer *et al.*, 1995). In fact, the use of body reserves to meet their nutrient requirement during lactation is extraordinary in several species such as in seal and whales (Oftedal, 1993), and in rat (Friggens *et al.*, 1993). Even in situations where the environmental pressure to mobilize body lipid in early lactation is removed, for instance by providing abundant levels of nutritional resources, why should the mother still mobilize body reserves?

Mother nature has accorded the ability of the mammals to produce milk for survival of the newborn. The mammary glands have a high metabolic rate during lactation, but its products do not give direct effect to the mother. This indicates that mammals have the ability to give a high priority to lactation in order to ensure the survival of their

young (Bauman, 2000). It is proposed that body reserves mobilization in early lactation and the subsequent gain in body reserves during pregnancy are to a large extent genetically driven (Friggens *et al.*, 2004), and body fat mobilization is not a response but rather a natural component of a safeguarding reproductive success by strategic use of body reserves (Knight, 2001, and Friggens, 2003).

Lactation of the modern dairy cow may also still be viewed as a part of the cows' natural roles to maintain their reproductive function. In this view, the ability of the dam to support demands of future offspring in a constrained environment will depend to a large extent on the size of her body reserves (Friggens, 2003). The vast majority of mammals have evolved the strategy of preparing for forthcoming lactation by accumulating body fat reserves. For example, the proportion of lactational resources derived from body mobilisation can approach 100% in some species of seals, whales and bears (Oftedal, 2000). The ability to provide the young with easily digestible nourishment independently of food availability at that time and location has been proposed to be the main evolutionary advantage of lactation (Vernon and Pond, 1997). At the start of lactation, failure to produce milk will result in the death of the calf, so at this time there is a benefit in having a large body reserves to safe guard milk production.

Also, by using body reserves to produce milk, the dam spends less time foraging and stays closer to protect the young from the predators. As lactation progresses towards weaning the negative consequences of lactational failure and the risk of predator attack diminish, the need for large body reserves reduce. Thus, the body fat mobilisation during early lactation of dairy cow should not only be viewed as a nutritional or energetic support for high milk production, but should also be viewed as a part of the cow's strategy to achieve the goal of maintaining reproductive cycle. In this perspective, the slower feed intake recovery after parturition, may not solely be viewed as the cow's inability to maximize intake, but also be associated with the cow's natural ability to optimize the survival of the young.

Does Leptin Play A Role in Coordinating the Feed Intake in Early Lactation?

Voluntary dry matter intake (VDMI) in ruminants is negatively correlated with body reserves at a given physiological state (Bines and Morant, 1983). Increased fatness or body reserves also have been indicated to down regulate VDMI in sheep (Foot, 1972). This supports the lipostatic theory (Kennedy, 1953) that the regulation of body reserves and food intake is coordinated. Parabiosis studies in rat gave further proof that humoral signals are involved in the coordination of body fat and feed intake (e.g. Hervey, 1959, and Parasmewaran *et al.*, 1977). An adipose-derived signal, which is now known as leptin, has been implicated to be the factor that may involve in maintaining energy reserves at a presumed set point by regulating feed intake, energy expenditure and whole body energy homeostasis in rodents and human (Houseknecht *et al.*, 1998). However, in periparturient ruminants, plasma leptin declined progressively before parturition and remained low during early lactation (Ingvarsten and Boisclair, 2001). Thus, in early lactating cows plasma leptin may not reflect changes in adiposity, and hence may not regulate feed intake.

In contrast to most other metabolic hormones, leptin acts predominantly on regions of the brain involved in the regulation of energy metabolism, such as the arcuate, ventromedial anddorsomedial nuclei of the hypothalamus (Houseknecht *et al.*, 1998). Leptin is unlikely to contribute to reduce appetite at early lactation because maternal plasma leptin was progressively declined (by 50%) after parturition, and remained depressed during early lactation of sheep (Endhart *et al.*, 2001, and Ingvarsten and Boisclair, 2001), and dairy cow (Leury *et al.*, 2003). The decline in plasma leptin post partum has been attributed to inhibition of adipose tissue leptin synthesis associated with the negative energy balance of early lactation (Block *et al.*, 2001). The decline in plasma leptin mirrors that of plasma insulin and glucose but is reciprocal to plasma GH and NEFA (Leury *et al.*, 2003, and Ingvarsten and Boiscliar, 2001). Leury *et al.*, (2003) and Block *et al.*, 2003) found that insulin infusion is capable of increasing plasma leptin in dairy cows but this effect is attenuated considerably during early lactation. Exogenous growth hormone did not have independent effect on plasma leptin in early lactation, but it inhibits insulin mediated leptin synthesis. Therefore, in early-lactating-undernourished dairy cows, reduced plasma insulin could account for a portion of the decline in plasma leptin, but the increase in plasma GH is unlikely contribute to the post partum reduction of plasma leptin.

The low plasma leptin post parturition in dairy cows may signal to the brain that a state of energy insufficient prevails in the periphery, because plasma leptin remained high in cows not milk after parturition (Block *et al.*, 2001). Low plasma leptin during early lactation could have benefits to promote an increase in feed intake (Leury *et al.*, 2003). In fasting sheep, low plasma leptin is correlated with up regulation of NPY and AgRP, and a tendency to lower expression of POMC and CART (Adam *et al.*, 2002). Thus, low plasma leptin in the early lactation dairy cow may be related to the similar changes in neuropeptide expression.

Therefore, during the early stage of lactation, regulation of feed intake may not be the most important function of leptin, and the main role of leptin post-partum may be to coordinate adaptation that promote energy conservation required to survive periods of nutritional deprivation. This is supported by the study that leptin therapy attenuates the neuroendocrines response to fasting in mice (Ahima *et al.*, 1996). As well, reduction in plasma leptin could benefit early lactating cows by decreasing the peripheral tissue to insulin, and partition of glucose to mammary gland (Bell, 1995). In rodents, total absence of leptin is associated with insulin resistance, whereas leptin therapy stimulate peripheral glucose utilisation under basal and hyperinsulinemic condition (Barzilai *et al.*, 1999). Additionally, low plasma leptin associated with nutritional insufficiency in early lactation is suggested to share many adaptations such as depressed reproductive and higher metabolic efficiency (Ingvarsten and Boisclair, 2001). Low plasma leptin during early lactation may signal that energy supply is not adequate for reproduction.

How Does Lipid Mobilization Down Regulate Feed Intake in Early Lactation

Voluntary dry matter intake (VDMI) in ruminants is negatively correlated with body reserves at a given physiological state (Bines and Morant, 1983). Increased fatness or body reserves also have been indicated to down regulate VDMI in sheep (Foot, 1972). This supports the lipostatic theory (Kennedy, 1953) that the regulation of body reserves and food intake is coordinated. Parabiosis studies in rat gave further proof that humoral signals are involved in the coordination of body fat and feed intake (e.g. Hervey, 1959, and Parasmewaran *et al.*, 1977). Elevated blood concentration of growth hormone (GH) during early lactation is believed to be the hormone responsible to increase lipolysis (Bauman, 2000). As large amount of adipose tissue are mobilized during early lactation, the plasma NEFA, glycerol and ketone bodies are increased (Drackely, 1999). Although a negative correlation were observed between feed intake and plasma levels of NEFA, glycerol and ketone bodies (Carpenter and Grassman, 1983), the mechanism is not clear.

Glycerol may be one of the candidate signals for the effect of body fat and mobilization on food intake regulation during early lactation. Bray (1973) suggested glycerol as an indicator of total body fat mass. Adipose cells contain sufficient glycerol kynase to reutilize most of the free glycerol, and during hydrolysis of triglecrydes, glycerol is released from adypocytes into the plasma. Basal lipolysis and therefore glycerol release increase with fat cell size. It was hypothesized that glycerol could act as a satiety signal if the hypothalamus could sense the amount of glycerol being converted to glucose in the liver (Bray, 1973). However, Langhans *et al.* (1983) concluded that hypophagic effect of glycerol was not caused by glycerol or by the conversion of glycerol to glucose. Subcutaneous administration showed a variable results, and only non-physiological levels reliably reduced food intake in rats (Carpenter and Grosman, 1983). Glycerol may influence feeding through central nervous system (CNS) mechanism since intracerebroventricular (ICV) infusion of glycerol in rats has been shown to suppress feeding (Davis *et al.*, 1981). Scharrer and Langhas (1990) stated that metabolism of glycerol appears to be essential its hypophagic effect in rats. However, elevated plasma glycerol level by infusion and feeding glycerol did not influence on feed intake (Carpenter and Grossman, 1983), and the authors concluded that plasma glycerol levels are relatively minor lipostatic influence on hunger. As well, Ingvartsen *et al.* (1999) reported that in early lactation higher glycerol only found in heifers but not found in cows that were on high feeding level pre-partum. Thus, glycerol does not seem to be a strong candidate for a signal mediating lower intake in periparturient cattle.

An increased rate of lipolysis and oxidation of fatty acids, in the early lactation cows, is usually associated with an increased production of ketones bodies (Drackely, 1999). Hence, ketone bodies may be one of the satiety factors depressing food intake.

Subcutaneous injection of beta hydroxyl butyrate (BHBA) has shown to cause hypophagia in rats (Fisler *et al.*, 1995), and it seemed likely that the liver is involved in depression of intake by during injection of BHBA (Sharrer and Langhans, 1990). However, Stricker *et al.* (1977) argued that the liver does not involved in the satiety effect of BHBA because liver can not synthesize BHBA beyond acetoacetate. Sun *et al.* (1997) found that ICV infusion of BHBA reduced body weight but not food intake. The effect of BHBA on intake regulation during the early lactation may not be strong.

NEFA is another possible candidate for feedback signals for feed intake regulation during the early lactation. Plasma NEFA concentration is elevated during early lactation, and there is a negative relationship between the plasma NEFA and VDMI in cattle (Grummer, 1993). Continuous long term intravenous infusion of long chain free fatty acids has been shown to reduce DMI in rats (Carpenter and Grossmann, 1983).

Ingvarsten and Andersen (2000) suggested that fatty acids oxidation in the brain and liver may provide possible signal in intake regulation during early lactation. Kasser *et al.* (1985) reported that rates of fatty acids oxidation in the ventrolateral hypothalamus (VLH) and fatty acids synthesis in ventromedial hypothalamus (VMH) were linearly related to the peripheral energy status. The VLH of underfed rats had 40% increased in fatty acid oxidation and 9% decrease of glucose oxidation, and the overfed rats had a 36% decrease in fatty acid oxidation and 20% increase in glucose oxidation, compared to the control. They proposed that if an increase in free fatty acids oxidation for undernourished rats inhibits activity of VLH cells that are normally activated by glucose, then it may be that the elevated plasma free fatty acids concentration may lead to a decrease in feed intake. This is because activity of VLH increases feed intake and activity of VMH decreases feed intake (Harris and Martin, 1984). However, Beverly and Martin (1991) has failed to test this hypothesis that inducing chronic changes (14d) in VLH fatty acids oxidations did not affect feed intake. Thus, it is unlikely that fatty acids oxidation in the VLH plays an important role in regulating feed intake.

Liver of dairy cows after parturition is faced with markedly increased uptake of NEFA mobilized from adipose tissue. Carnitine palmitoyl-transferase-1 (CPT-1) an enzyme involved in the uptake of NEFA into the hepatic mitrochondria has been suggested to have a significant effect on determining the relationship between fatty acids oxidation and feed intake (Drackley, 1999). Studies have shown that CPT-1 activity is greater in 1 –21 days post partum than at 65 d postpartum (Dann *et al.*, 2000). CPT-1 is inhibited by malonyl CoA, which is formed from acetyl-CoA, by acetyl-CoA carboxylase. Acetyl-CoA carboxylase is active during the well-fed state, when insulin is high, and conversely it is inactive during undernourished state, when insulin is low (Drackley *et al.*, 2001). Malonyl-CoA concentration is responsive to changes in insulin and glucagons in ruminants (Knapp and Baldwin, 1990), increasing when insulin increase and vice versa. In rodents models, decrease in the sensitivity of CPT-1 to inhibition by malonyl-CoA follow decrease in insulin, which serve to amplify the signal and increase transport of NEFA into mitochondria (Zammit, 1996). Thus, during early lactation, when plasma insulin is relatively low, the increased CPT-i concentration (Dann, 2000) may be due to a decrease in malonyl-CoA concentration or due to decrease sensitivity of CPT-1 to malonyl-CoA inhibition. When the activity of CPT-1 is increased, uptake and oxidation of NEFA by the hepatic mitochondria is increased. Total oxidation of palmitate by liver homogenates was about 12% greater at day1 postpartum than at 21day prepartum (Drackley *et al.*, 2001).

Studies on the effects of free fatty acids oxidation on feed intake have been done by using mercaptoacetate, which depress Acyl-CoA dehydrogenase activity (Sharer and Langhans, 1986) or using methyl palmoxirate, which depresses the mitrochondrial CPT-1 concentration (Friedman *et al.*, 1990). Inhibiting fatty acids oxidation with administration of methyl palmoxirate increased feed intake in rats, particularly when the rate of fatty acids oxidation is relatively high (Friedman *et al.*, 1999). Langhans and Scharrer (1987) concluded that the hypophagia is most likely mediated by hepatic receptors, because inhibition of fatty acid oxidation by mercaptoacetate diet was partially blocked by hepatic branch vagotomy. Scharrer and Langhans (1988) proposed that the hypophagia is most likely linked to mitochondrial oxidation of NEFA, which give satiety signals to the brain mediated by vagal afferents. Thus, the satiety signals may be initiated, at least in part, by hepatic receptors, which then stimulate the vagal afferents in order to communicate signals of metabolic status to the brain (Ingvarsten *et al.*, 1999). Additionally, Langhans

(1996) proposed that satiety could be resulted from fatty acids oxidation in mitochondria that may affect the hepatocyte membrane potential through cytosolic ATP and Na-pump activity. This is supported by study of Friedman, *et al.* (1999) showing that methyl palmoxirate-induced increase in feed intake were negatively correlated with liver ATP content, and ATP to ADP ratio, indicating that a decrease in fatty acid oxidation can stimulate feed intake by reducing hepatic energy production.

Conclusion

Based on the cows' strategy to mobilize body fat during the early lactation, the metabolic products from lipolysis are likely the possible candidates for signalling the regulation of feed intake. Feedback signals from the elevated oxidation of NEFA in the liver possibly contribute to the down regulation of feed intake during the early lactation when mobilisation of body fat is high. The low plasma insulin concentration during early lactation may result in elevating CPT-1 activity due to a decrease in malonyl-CoA concentration and due to a decrease in sensitivity of CPT-1 to malonyl-CoA inhibition. When the activity of CPT-1 is increased, uptake and oxidation of NEFA by the hepatic mitochondria is increased. This may initiate satiety signals to hepatic membrane potential, and then it stimulates the vagal afferents in order to communicate signals to the satiety center of the hypothalamus. These mechanisms may result in slow recovery of feed intake after calving, and hence DMI in early lactation does not fulfil the entire energy requirement of the lactating cow.

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