Veterinary Integrative Sciences 2025; 23(2): e2025053-1-27. DOI: 10.12982/VIS.2025.053

Veterinary Integrative Sciences
ISSN: 2629-9968 (online)

Review article

A descriptive review of the role of exogenous bovine somatotropin on milk secretion mechanisms at different stages of lactation in crossbred Holstein cattle in the tropics

Narongsak Chaiyabutr [1,3,4,*], Somchai Chanpongsang[2] and Sumpun Thammacharoen[1]

[1]*Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand.*
[2]*Department of Animal Husbandry, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand.*
[3]*Academic of Science, Royal Society of Thailand.*
[4]*Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok 10330, Thailand.*

Abstract

This review aims to better understand the regulation of milk yield in response to the prolonged administration of recombinant bovine somatotropin (rbST) in 87.5% crossbred Holstein cattle in the tropics. Prolonged administration of rbST at different stages of lactation is associated with an increase in milk yield, which correlates with an increase in milk lactose yield and mammary glucose uptake, due to an increase in mammary blood flow. Lactose synthesis is up-regulated in response to the administration of rbST. The glucose taken up by the mammary gland in early lactation increases flux through the lactose synthesis and pentose phosphate pathways, leading to significant increases in NADPH formation for fatty acid synthesis during rbST administration. The incorporation of glucose carbon into milk increases milk citrate and triacylglycerol concentrations but not milk lactose as lactation advances under rbST treatment. The stimulatory effect of rbST on milk yield would be transiently and significantly increased in early lactation and decrease in late lactation, even though there is a high level of udder blood flow. With prolonged administration of rbST, the regulation of biosynthetic capacity within the mammary gland would be influenced more by intra-mammary factors than by systemic factors. As lactation advances, a smaller proportion of glucose would be metabolized for lactose synthesis, with more being metabolized via the Embden-Meyerhof pathway and the tricarboxylic acid cycle.

Keywords: Crossbred Holstein cattle, Milk secretion, Recombinant bovine somatotropin, Stages of lactation.

*Corresponding author: Narongsak Chaiyabutr, Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: narongsak.c@chula.ac.th

Article history; *received manuscript: 17 August 2024,*
revised manuscript: 15 September 2024,
accepted manuscript: 17 September 2024,
published online: 19 September 2024,
Academic editor; *Korakot Nganvongpanit*

INTRODUCTION

The major problem for Thai dairy practices is the low milk yield and short lactation period of both pure exotic and crossbred dairy cattle. The decrease in milk yield after peak lactation in dairy cattle has long been a biological conundrum for mammary biologists and a significant cause of lost income for dairy farmers. Many factors can affect milk production in dairy cattle in the tropics, including high environmental temperatures, the lower genetic potential for milk production in indigenous cattle, and inadequate forage supply during the summer months. Several approaches have been attempted to improve dairy productivity in the tropics, such as selecting suitable crossbreeds of indigenous and exotic cattle for these environments.

It is known that lactating dairy cows metabolize large amounts of water and are rapidly affected by water deprivation. An increase in water intake during lactation closely matches the increase in water secreted in milk, with milk composition consisting of about 87% water. Alterations in bodily function during lactation are apparent; for example, blood volume (Chaiyabutr et al., 1997) and cardiac output (Hanwell and Peaker, 1977) increase. These changes may effectively alter body fluid and circulatory distribution, including the blood supply to the mammary gland. During early lactation, nutrient partitioning related to circulatory distribution is known to contribute resources to the mammary gland for high milk synthesis (Linzell, 1974). High-producing dairy cows generally enter a negative energy balance (NEB) because their level of dry matter intake (DMI) does not meet the demands imposed by the onset of milk production (Bauman and Currie, 1980). Consequently, they mobilize body tissue to overcome this shortage. The lactating mammary gland depends on its blood supply to provide substrates at appropriate rates to sustain milk synthesis. The rate of substrate supply to the mammary gland is determined by substrate concentration in the plasma and mammary blood flow. There is evidence that substrate supply to the mammary gland is often inadequate to maintain the maximum rate of milk synthesis. This raises the question: do changes in bodily function (water balance, general circulation, and mammary circulation) alone affect milk secretion, or is the effect solely due to inadequate utilization of substrates in the mammary gland in crossbred dairy cattle? As glucose is the principal precursor of lactose, the decrease in milk lactose can be explained by a change in the mammary utilization of glucose (Faulkner and Peaker, 1987). Lactose is a highly osmotic component, which facilitates the drainage of water from blood to the alveolar compartment. As such, it is the principal milk component regulating the volume of milk production. Glucose is known to play an important role not only in lactose synthesis but also in providing the reducing equivalents required for the de novo synthesis of fatty acids in the mammary gland (Chaiyabutr et al., 1980). Very few data are available regarding the dynamics and regulation of glucose metabolism in the whole body and the mammary gland of different types of crossbred cattle. Insights into the study of glucose metabolism for the synthesis of milk components in different metabolic pathways in the mammary gland have improved understanding of the factors influencing low milk yield in crossbred dairy cattle in the tropics.

During lactation, coordination between nutrient delivery and biosynthetic capacity is thought to be under endocrine control via a homeorhetic mechanism. The role of endocrine regulation in the initiation and maintenance of lactation is well-established across many species. However, the hormonal requirements differ considerably among mammalian species. For example, in rabbits, prolactin alone can maintain lactation, while in cows, prolactin is not a rate-limiting hormone in established lactation, with growth hormone becoming relatively more important (Hart, 1973; Mepham, 1993). Previous studies have shown that the shorter lactation persistency observed in crossbred Holstein cattle during the transition from early to mid-lactation is due to a reduction in growth hormone levels (Chaiyabutr et al.,

2000a, 2000b). However, the mechanism by which growth hormone influences milk production in crossbred dairy cattle remains unclear. Very few studies have examined circulating hormones during lactation in crossbred dairy cattle. Several lines of evidence suggest that the administration of growth hormone does not act directly on the mammary gland, as growth hormone receptors have not been demonstrated on the epithelial cells of mammary tissue (Akers, 1985). The circulating concentrations of certain hormones are expected to change and be related to the mechanisms responsible for controlling milk secretion in different types of crossbred Holstein cattle.

Milk secretion is a continuous process that requires a consistent supply of substrates for milk production. Glucose is known to be the principal precursor of lactose synthesis. Lactose is the major osmotic factor in milk synthesis and is required in proportion to the amount of milk produced (Linzell and Peaker, 1971). The regulation of milk yield is primarily based on the quantity of glucose extracted by the mammary gland and converted into lactose. The rapid decline in lactose biosynthetic pathways has been shown to contribute to the shorter persistency of lactation as lactation progresses from mid to late stages in 87.5% Holstein-Friesian (87.5% HF) cows. However, few studies have examined the effects of bovine somatotropin on the interaction between body fluids, glucose metabolism, and mammary function in crossbred dairy cattle during early to mid-lactation, despite findings that the application of rbST promotes higher milk production without differences in body condition between the two rbST formulations and the control group (Gomez et al., 2022). This bibliographical review aims to highlight the regulatory mechanisms underlying the markedly low milk yields and shorter lactation persistency in crossbred Holstein cattle in the tropics. It provides an updated summary of the effects of prolonged bovine somatotropin administration on physiological changes in both extra-mammary and intra-mammary factors at different stages of lactation in crossbred Holstein cows. Investigating the temporal changes in mammary epithelial cells and studying the metabolic pathways of glucose utilization by the udder would provide greater insight into the cellular mechanisms that regulate milk production in crossbred Holstein cattle containing 87.5% Holstein genes during bovine somatotropin administration.

MANAGEMENT FACTORS INFLUENCE THE USE OF rbST

It is known that good management is a major factor in determining milk yield response, as is the quantity and quality of feed provided. To ensure a high response in milk yield to rbST administration, several factors must be considered, including maintaining a normal environmental temperature, avoiding overcrowding, and designing facilities to facilitate feeding. Adequate water must be provided to protect against the effects of high environmental temperature, and sufficient shade should be available. Thus, when rbST administration is used, it is essential to prepare for potential risks by controlling management and physiological factors. The purpose of this review is to highlight the bodily changes in crossbred HF cattle during long-term bovine somatotropin administration at different stages of lactation (Figure 1) and to demonstrate that these changes are not due to alterations in their control physiology.

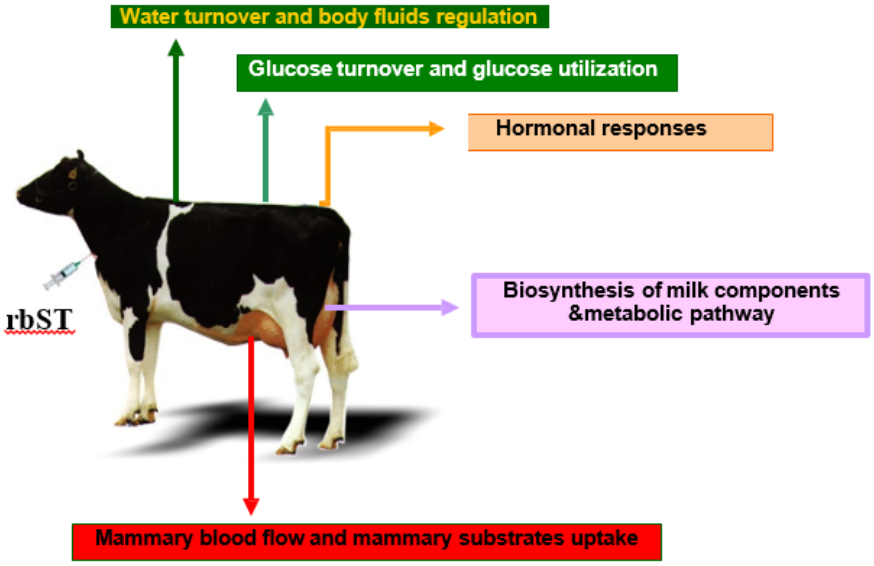

Figure 1. A schematic highlights various physiological changes in both extra-mammary and intra-mammary tissues, studied in relation to mammary function during long-term exogenous rbST administration in different stages of lactation.

The research management has been designed to study the effect of prolonged administration of rbST in two groups of non-pregnant, crossbred, 87.5% HF, with five animals in each group. The animals in each group were fed rice straw treated with 5% urea as the source of roughage. All animals were housed in sheds, tethered in individual stalls, and fed twice daily. The maximum temperature in the shed at noon was 34±1°C, and the minimum temperature at night was 26±1°C. The relative humidity was 68±12%. Each animal was designed to receive an average of 4 kg/day of urea-treated rice straw as roughage (Chaiyabutr et al., 2005) in combination with the same concentrated mixture (7 kg/day) to maintain a moderate body condition score (2.5 on a scale of 1 to 5). Each day, the food was given in equal portions at about 06:00 and 17:00 when the animals were milked. The animals had free access to water and were fed their respective rations throughout the experimental period. These management practices ensured that relevant and specific aspects of the bST effect in crossbred cattle in the tropics were addressed.

STUDY DESIGN METHODOLOGY

Animals were divided into two groups: control (n=5) and experimental (n=5). Each group underwent four consecutive study periods, which included a pretreatment period and three treatment periods. The pretreatment period lasted 65 days postpartum, before the lactation peak. The three treatment periods were: 95 days postpartum (early lactation), 155 days postpartum (mid-lactation), and 215 days postpartum (late lactation) (Figure 2). The pretreatment study began on the first day of each lactating stage. At the end of the pretreatment period, the animals received a subcutaneous injection of 500 mg of rbST (POSILAC, Monsanto, USA). Following this, the animals were injected with two additional doses of rbST every 2 weeks. The treatment study began within 2 days after the third injection. The pretreatment, the three doses of injections, and the treatment periods were completed within the first 30 days, and the same procedures were applied to each lactating stage. During the final 30 days of each lactating stage, no experiments were conducted to allow milk yield to return to control levels, following the effects

of rbST treatment (Kirchgessner et al., 1991). Animals in the control group received subcutaneous injections every 14 days of 800 mg of sterile sesame oil without rbST. Injections for both groups were administered at the tail head depression (ischiorectal fossa). From the pretreatment period through the end of the treatment periods, both groups of animals were fed the same ration, starting before parturition and continuing until the study's completion. Dry matter intake was measured by weighing the concentrate and roughage offered and refused each day. The animals were milked twice daily, at around 0600 and 1700 hours, using a milking machine, and milk production was recorded daily.

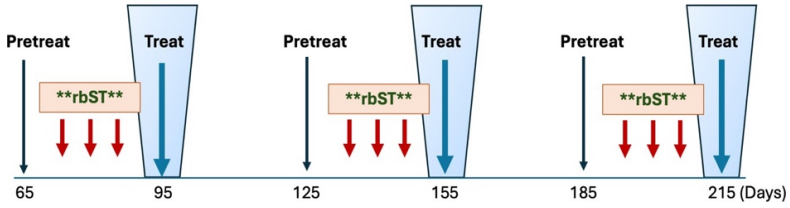

Figure 2. Diagram illustrating the time course of studies in each cow supplemented with rbST at different stages of lactation. "Pretreat" refers to the timed study for pre-treatment, while "Treat" denotes the timed study for treatment.

MILK PRODUCTION AND MAMMARY BLOOD FLOW

MILK PRODUCTION

The rbST has been used to increase milk production; in this case, rbST is administered from 65 days postpartum until the end of lactation. It is evident that milk yield significantly increases following rbST administration. The rbST treatment begins at an earlier stage of lactation, with a peak in milk yield increase observed on day 85 during early lactation and on day 150 during mid-lactation. However, the incremental increase in milk yield with rbST is less pronounced by day 215 in late lactation as compared to the pre-treatment period (Figure 3). These results indicate that the increase in milk yield in dairy crossbred cattle in response to rbST administration is not sustained for long and is influenced by the stage of lactation. The low response in milk yield during rbST treatment across different stages of lactation is consistent with previous reports in dairy crossbred cattle (Phipps et al., 1991). A rapid decline in milk yield in rbST-treated animals seems similar to that observed in higher-yield cows (Chase, 1993). However, the variation in responses may depend on intramammary factors required to achieve maximal response. Extramammary factors, such as management and diet, are variable since animals are fed ad libitum. The ratio of DMI to milk yield in rbST-treated animals is lower during early lactation compared to the pre-treatment period, but animals continue to gain weight throughout the experiment in both groups. It is known that milk secretion support comes through the provision of substrates and stimulation of mammary cell activity. However, the increased milk yield with rbST, relating to mammary cell activity, appears contradictory. While some studies show no mammogenic effect of rbST (Binelli et al., 1995), others suggest a possible mammogenic effect when cattle are administered rbST (Knight et al., 1992). This indicates that the increased milk yield with rbST treatment in the present study is more dependent on adequate nutritional provision than on the mobilization of body stores. During early lactation, the increase in milk yield with rbST treatment without loss of body weight is suggested to be due to adequate feeding, allowing for the

replacement of body reserves (Chaiyabutr et al., 2005). However, milk yield in the first lactation of crossbred animals is generally lower than in multiparous cows (Sullivan et al., 1992). The physiological differences between crossbred animals and exotic breeds are inherited and affect their capacity for milk production.

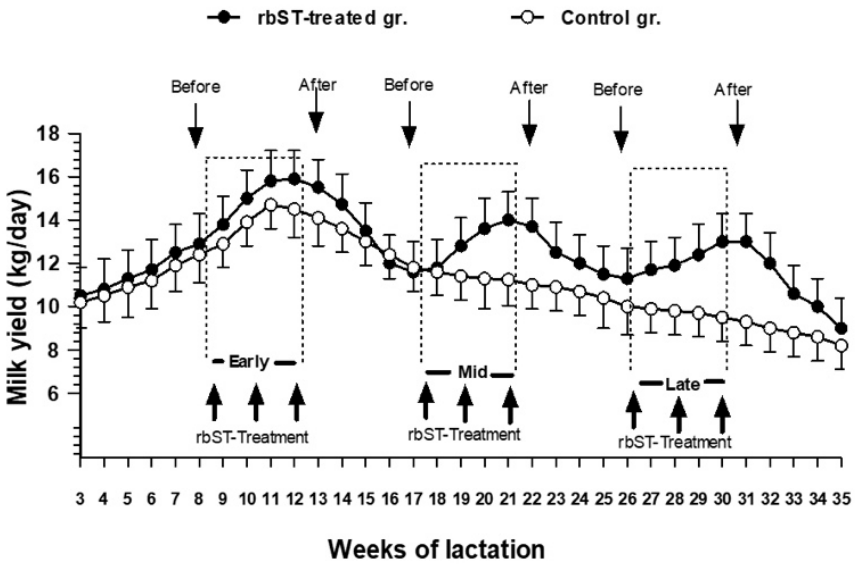

Figure 3. Means and standard deviations (n=5) of milk yield for control animals and rbST- treated animals at different stages of lactation (Adopted and modified from Sitprija et al., 2010).

It is known that the metabolic demands of lactation in dairy cattle are typically met by dietary intake during early lactation. In crossbred HF animals treated with rbST, there has been no indication of body tissue mobilization, as evidenced by stable plasma levels of both triglycerides and glucose (Chaiyabutr et al., 2005). Triglycerides are restored during periods of excess energy availability and mobilized during periods of energy deprivation. The lack of significant change in plasma triglyceride concentration supports the interpretation that the extra energy required to support increased milk yield comes from surplus nutrients of DMI rather than from greater mobilization of body reserves. However, the milk fat content in rbST-treated animals has been shown to increase (Figure 4), while milk protein and lactose concentrations are not affected by rbST treatment (Sitprija et al., 2010). Peel and Bauman (1987) reported that rbST administration does not change the milk protein percentage in cows with a positive nitrogen balance, but the milk protein percentage tends to decline in cows with a negative nitrogen balance. A similar increase in milk fat content due to rbST injection has also been observed previously (West et al., 1990).

Milk fat is synthesized in the mammary epithelial cells from both blood lipids and de novo synthesis within these cells. The milk fat content of cows with a positive energy balance is not influenced by rbST treatment, and milk fat yield follows the trend of milk production (West et al., 1990). However, an increase in milk fat after rbST injection is associated with higher yields of long-chain fatty acids characteristic of plasma-free fatty acids and body fat (Chaiyabutr et al., 2007b; Chaiyabutr et al., 2008a). The effects of rbST on total milk fatty acid concentrations are evident throughout the stages of lactation. Administration of rbST markedly increases the concentrations of long-chain fatty acids (C16:0-C18:2) in the milk of crossbred 87.5% HF cattle at each stage of lactation (Figure 4). Thus, the observed

lipolytic activity appears to be a direct effect of rbST treatment rather than a consequence of changes in energy balance. The concentration of fatty acids in rbST milk, specifically palmitic acid (16:0) and oleic acid (C18:1), which oleic acid was significantly higher ($p < 0.05$) than in control milk. Oleic acid is a predominant preformed fatty acid in adipocytes and is released during lipolysis. It has been suggested that rbST may induce a delay in the natural reduction of preformed fat throughout lactation, which would explain the higher levels of C18:1 in milk from rbST-treated animals (Barreiro et al., 2022).

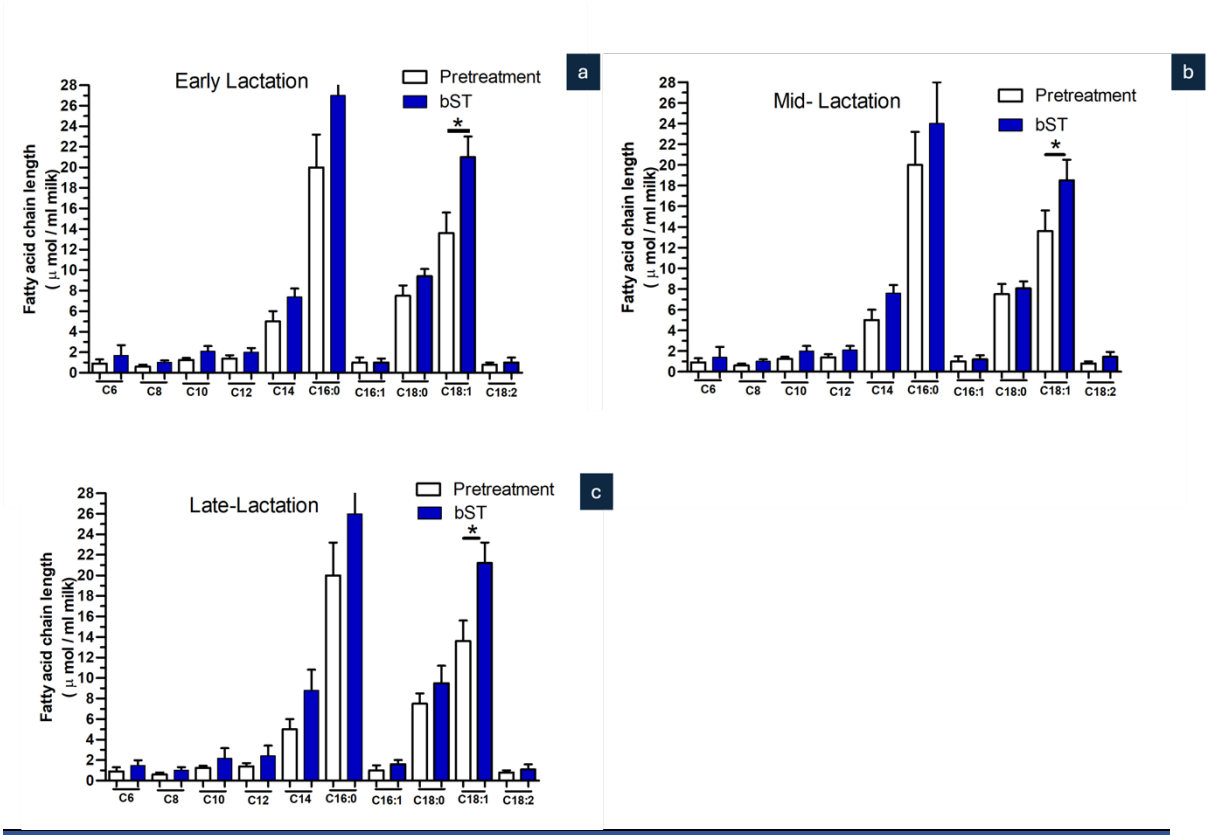

Figure 4. Fatty acid composition of milk fat during rbST administration at different stages of lactation (early=a, mid=b, late=c) in crossbred 87.5% HF cattle. P-values: *P< 0.05, P- values by unpaired t-test between control animals and rbST treated animals, (n=5 in each group). (Adopted and modified from Chaiyabutr et al., 2008b).

MAMMARY BLOOD FLOW

The mammary blood flow measurements in crossbred HF animals were recorded using the continuous dye dilution technique on standing animals, as described by Chaiyabutr et al. (2007a). In brief, a short-term (10 seconds) continuous infusion of the dye dilution marker (dye T-1824, Evans blue in sterile normal saline) was performed via a catheter inserted into either the left or right milk vein by a peristaltic pump under local anesthesia. After starting the infusion of the dilution marker, blood was drawn from another catheter downstream in the milk vein at a constant rate into a heparinized tube. Plasma samples were used to calculate blood flow in half of the udder.

In Figure 5, a long-term study with rbST treatment in crossbred HF cows showed an increase in mammary blood flow to the udder at all stages of lactation, which agrees with several reports in both cows and goats (Mepham et al., 1984; Davis et al., 1988; Gulay et al., 2004). The marked increase in mammary blood flow

in rbST-treated animals could not be attributed to a change in blood volume or plasma volume, as relative values as a percentage of body weight remained nearly constant. In lactating dairy cows, an increase in blood flow to the mammary gland may allow plasma volume to remain nearly constant despite a loss of body weight (Woodford et al., 1984). However, the exact mechanism by which rbST increases milk production is not fully understood, but it is believed that blood flow to the mammary glands is increased. It has been suggested that the marked increase in blood flow through the mammary glands resulting from rbST administration may be partly due to local vasodilation (Linzell, 1974), which facilitates the distribution of milk precursors to the gland. An increase in mammary blood flow (MBF) is also an effect of increased cardiac output to the udder without alterations in heart rate during growth hormone treatment (Davis et al., 1988). An increase in both blood volume and plasma volume in rbST-treated animals would provide greater venous return and stroke volume, leading to increased cardiac output and, consequently, increased blood supply to the mammary gland. Thus, the elevated milk yield after the peak period, compared with controls, could be primarily due to an increased availability of substrates for the mammary gland.

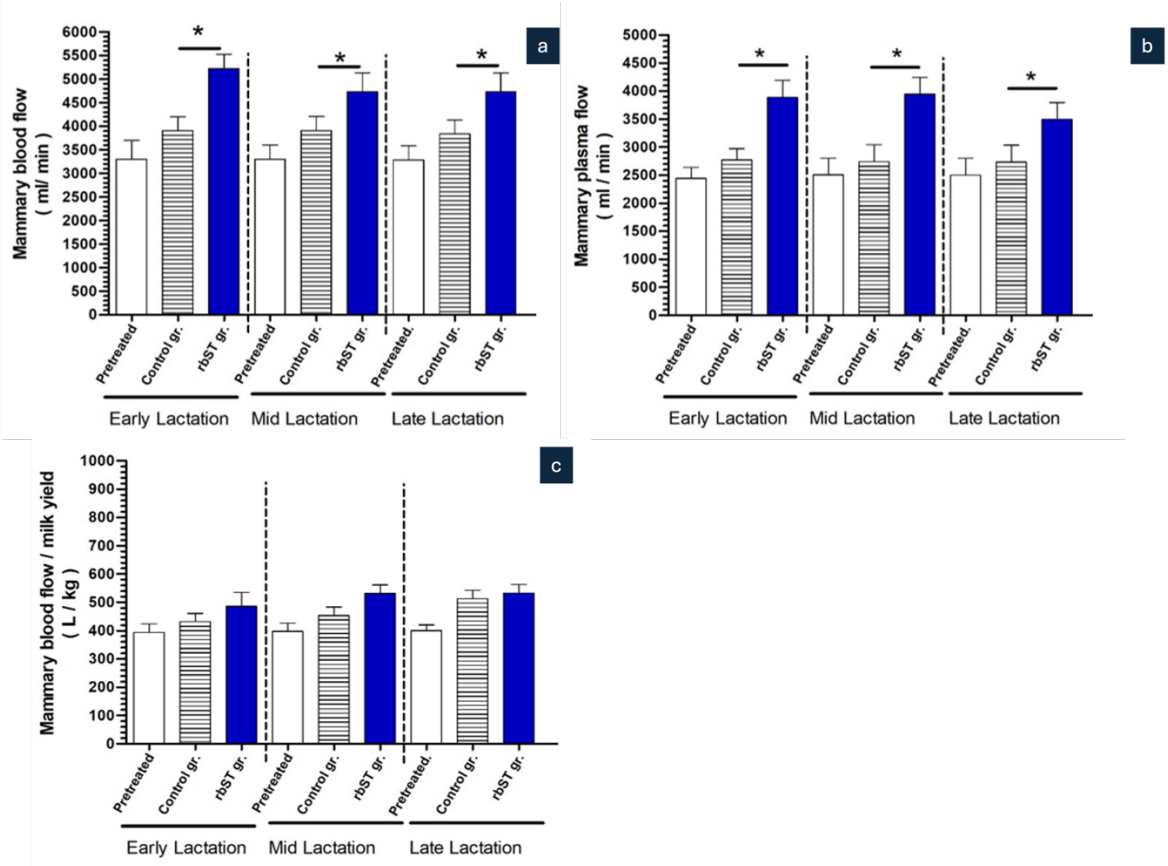

Figure 5. Means and standard deviations (n=5) for mammary blood flow (a), mammary plasma flow (b), and the ratio of mammary blood flow to milk yield (c) in control and rbST-treated animals at different stages of lactation. P-values: *P< 0.05, P- values by unpaired t-test between control animals and rbST treated animals. (Adopted and modified from Chaiyabutr et al.2005).

The progressive decline in milk yield in rbST-treated animals during late lactation, despite a higher level of either MBF or extracellular water (ECW), could be attributed to changes in intra-mammary factors. It has been reported that the effect of somatotropin on MBF does not involve a direct action of somatotropin on

the udder (Collier et al., 1984). Additionally, in vitro studies suggest that bovine somatotropin (bST) does not directly stimulate mammary secretory function (Gertler et al., 1983). The indirect action of rbST on mammary function may be mediated via insulin-like growth factor-1 (IGF-1) (Capuco et al., 2001), whereas other studies have demonstrated the direct effect of IGF-1 on increased mammary blood flow and milk production (Etherton and Bauman, 1998). However, the administration of rbST in late-lactating crossbred HF cows has been shown to elevate milk yield in conjunction with increased plasma IGF-1 concentration and udder blood flow (Tanwattana et al., 2003). These studies confirm that mammary blood flow is a major determinant of nutrient supply for milk synthesis and follows the pattern of changes in milk yield.

BODY FLUID REGULATION MECHANISMS

It is known that lactating dairy cows metabolize large amounts of water and are rapidly affected by water deprivation (Murphy, 1992). During lactation, many bodily functions are altered; for example, blood volume and cardiac output increase (Hanwell & Peaker, 1977). In the tropics, dairy cattle utilize body water to maintain homeostasis through lactation and thermoregulation. Increased water intake during lactation closely matches the increase in water secreted in milk, as milk composition is about 87% water. Alterations in body fluid may affect circulatory distribution, including blood supply to the mammary gland. This review builds on previous reports to clarify the effects of prolonged rbST administration on body fluid regulation and milk production in crossbred 87.5% HF cattle.

TOTAL BODY WATER AND RATE OF WATER TURNOVER

In this section, a brief description of methods for measuring water metabolism during rbST administration at different stages of lactation is provided. According to the study by Chaiyabutr et al. (1997), measurements of water metabolism, including water turnover rate (WTO) and total body water (TBW) in dairy cattle, are performed using tritiated water dilution techniques. Briefly, dairy cattle are injected intravenously with carrier-free tritiated water in normal saline at a single dose of 3,000 µCi per animal. The equilibration time is determined by taking serial venous blood samples collected at time intervals for 3 days following the injection. Samples are prepared for counting using the internal standardization technique. The corrected activity of samples, in disintegrations per minute (d.p.m.), is plotted on semi-logarithmic paper against time. The dilution curve of tritiated water in plasma is described by an exponential equation using a one-compartment model:

$$Yi = Ae\text{-}klt$$

Where Y is the concentration of tritium in plasma at time t (nci/ml); A is plasma concentration intercept 1 in nci/ml; The extrapolated activity at theoretical zero time of complete mixing of radioisotope is used to determine the total body water space (TOH). The TOH space is calculated:

TOH space (ml) = [standard count (dis/min) x dose (ml)] / [radio activity counts at zero time (dis/min)]

The biological half-life of tritium-labelled water (T l/2) is determined from the slope of the linear regression line obtained from a plot on semi-logarithmic paper

of the activity of the samples taken over the period of 3 days against time. The water turnover rate is calculated from the equation:

$$WTO\ (l/day) = 0.693 \times TOH\ space / T\ l/2$$

Total body water (TBW) is calculated by using the corrected factor (1 - fraction of plasma solids) x TOH space.

EXTRACELLULAR WATER AND BLOOD VOLUME

The dye dilution technique using sodium thiocyanate and Evans blue dye (T-1824) is employed to estimate ECW and plasma volume, respectively. Venous blood samples from the jugular vein are collected at 20, 30, 40, and 50 minutes after dye injection, and the zero time is determined by extrapolating the concentration on semi-logarithmic paper. Blood volume is calculated from the plasma volume and packed cell volume. Intracellular water (ICW) is determined by subtracting ECW from TBW

The effect of rbST administration in crossbred HF animals influences bodily functions, particularly extra-mammary functions, throughout all study periods. rbST-treated animals show increased body fluid compartments, such as TBW, ECW, and blood volume (Figures 6 and 7), while control animals exhibit decreased TBW compared to pretreatment values in the early period of lactation (Maksiri et al., 2005). Initiating rbST treatment at an earlier stage of lactation has been noted to increase empty body water (EBW) (Chaiyabutr et al., 2007a). This increase in EBW in rbST-treated animals is attributed to an expansion of the extracellular fluid (ECF) compartment, with no noted changes in the intracellular fluid (ICF) compartment throughout lactation. The increased ECW in rbST-treated animals may partly result from a decrease in fat mass during early lactation. Janssen et al. (1997) reported that administration in growth hormone-deficient patients expands both ECW and TBW.

Several possible explanations for this finding exist. An increase in TBW and ECW may be influenced by increased voluntary intake (MacFarlane et al., 1959), which has been reported to occur a few weeks after rbST administration (Coghlan et al., 1977). The greater percentage increase in live weight of rbST-treated animals can be partially attributed to the direct effect of somatotropin on increased body cell mass and fat-free mass, leading to an accumulation of body water. Another explanation for water retention in the ECW sodium (Wyse et al., 1993). The higher TBW and ECW in rbST-treated animals not only provide a larger reservoir of soluble metabolites for milk biosynthesis but also help mitigate any increase in body temperature during lactation in hot conditions. An increase in both metabolic activity and heat production has been reported in rbST-treated cows (West et al., 1991). Johnson et al. (1991) and West et al. (1994) suggested that although rbST increases heat production, it also enhances heat dissipation. According to Chaiyabutr et al. (2007a), increases in the water turnover rate per fat-free, wet body weight ($kg^{0.82}$) and the biological half-life of tritiated water occur in both control and rbST-treated animals as lactation advances, with more pronounced increases in rbST-treated animals compared to either the pretreatment period or control animals (Figure 7). This indicates that body water loss during increased milk yield in rbST-treated animals may be compensated by a larger body water pool, restoring their body fluids to equilibrium without significant changes in body water turnover rate or water half-life. These changes are attributed to the increased water requirement and loss due to milk secretion, which is generally about 87% water. Control animals, being 87.5% HF, are genetically closer to the exotic Bos taurus

breed and may exhibit poorer adjustment to tropical environments (Nakamura et al., 1993; Chaiyabutr et al., 2000a). The lower TBW and ICW values of control animals without rbST treatment during advanced lactation suggest that these changes could influence lactation persistency. These animals are unable to maintain their body fluids, leading to the rapid end of their normal short lactation period.

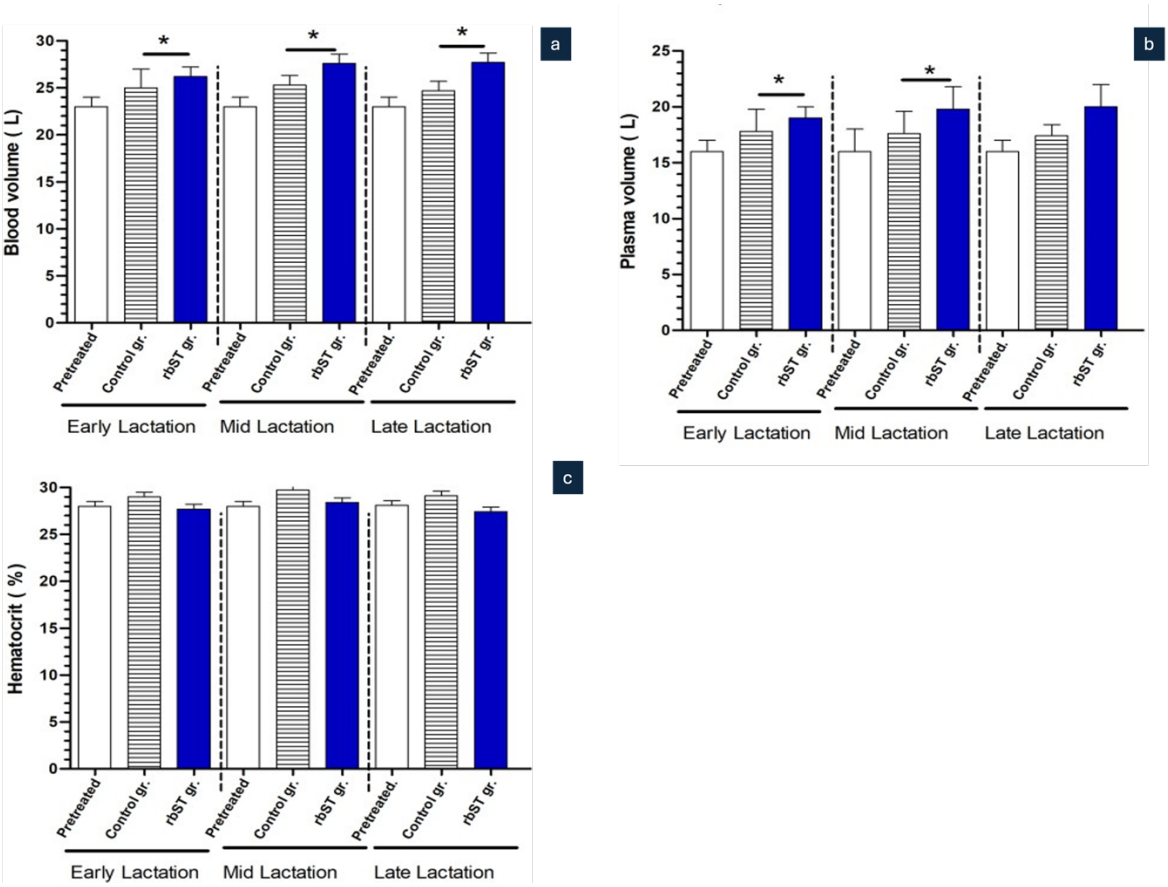

Figure 6. Means and standard deviation (n=5) for plasma volume (a), blood volume (b) and hematocrit (c) of the control animals and rbST treated crossbred HF animals in different stages of lactation. P- values: *P< 0.05, P- values by unpaired t-test between control animals and rbST treated animals. (Adopted and modified from Chaiyabutr et al., 2007a).

ROLE OF HORMONE SUPPLY VARIABILITY

The experiment by Chaiyabutr et al. (2005 and 2015) demonstrated an increase in milk yields and circulating levels of IGF-I throughout lactation in animals treated with rbST (Figure 8). These findings are consistent with previous studies showing that the injection of somatotropin elevates plasma IGF-I concentrations (Davis et al., 1987; Tanwattana et al., 2003). Somatotropin increases milk yield through a mechanism that does not involve direct action on the mammary gland (Collier et al., 1984). The indirect effects of somatotropin on milk production are believed to be mediated either via IGF-I or through nutrient partitioning effects (Bauman, 1992). During long-term rbST administration, milk yield rises to a peak in early lactation and then gradually declines over 32 weeks of the experiment, while plasma concentrations of IGF-I and mammary blood flow remain unchanged in rbST-treated animals. These findings suggest that the stimulatory effect of rbST on milk production is not solely mediated by IGF-I. Changes in milk production during

the progression of lactation in rbST-treated animals may be regulated not only systemically but also locally within the mammary gland.

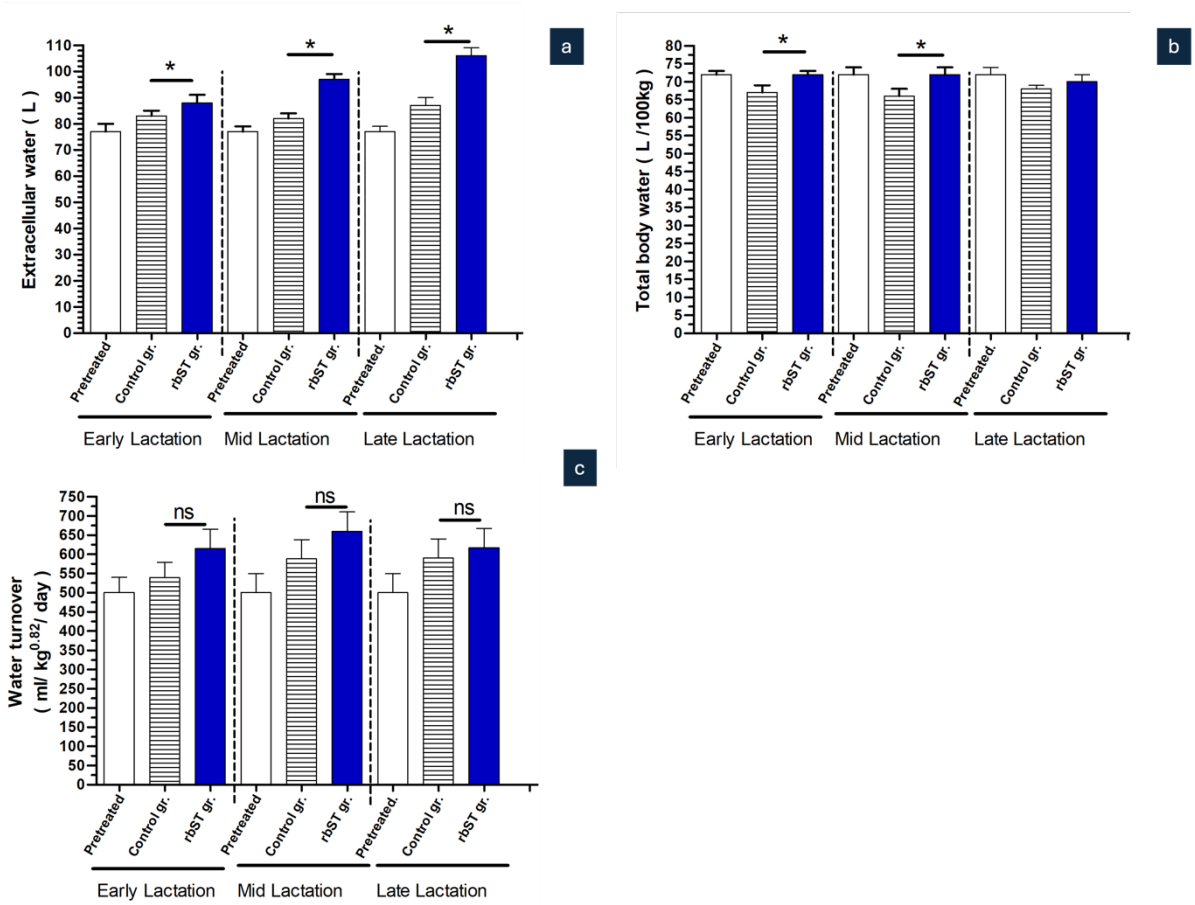

Figure 7. Means and standard deviation(n=5) for extracellular water (a), total body water (b) and water turnover rate (c) of the control animals and rbST- treated crossbred HF animals in different stages of lactation. P- values: *P< 0.05, ns= not significant, P- values by unpaired t-test between control animals and rbST treated animals. (Adopted and modified from Chaiyabutr et al., 2007a).

Several possible explanations for this finding exist. It may involve increased synthesis of plasma IGF-I binding proteins as lactation progresses, which bind to IGF-I in the blood and modulate the level of free IGF-I before it reaches the mammary gland. It has been reported that approximately 95% of infused IGF-I is bound by IGF binding proteins (LeRoith et al., 2021). The mammary tissue itself is capable of synthesizing IGF-binding proteins (e.g., IGFBP-5) during mammary gland involution in late lactation, which could inhibit IGF-mediated cell survival (Tonner et al., 1997; Flint and Knight, 1997) and initiate involution, leading to a decrease in milk yield.

No relationship between growth hormone and insulin is apparent for rbST-treated animals in early lactation. However, elevated plasma insulin concentrations are noted in later lactation during periods of increased plasma concentrations of exogenous growth hormone. This elevation in insulin would spare glucose for peripheral tissues (non-mammary glucose utilization), allowing more glucose to be utilized by the mammary gland in late lactation. Chaiyabutr et al. (2015) reported that plasma IGF-I concentrations are markedly elevated, while plasma leptin levels are significantly decreased during rbST administration (Figure 8). These findings indicate that both IGF-I and leptin responses are key mediators of rbST in

stimulating galactopoiesis in crossbred HF animals, though they are regulated differently. A significant response to rbST, characterized by high plasma IGF-I concentrations, likely plays a direct role in stimulating milk production by enhancing mammary gland function. The observed low plasma leptin levels result from the lipolytic effect of rbST administration, which subsequently increases DMI to supply nutrients to the mammary gland and facilitate milk synthesis.

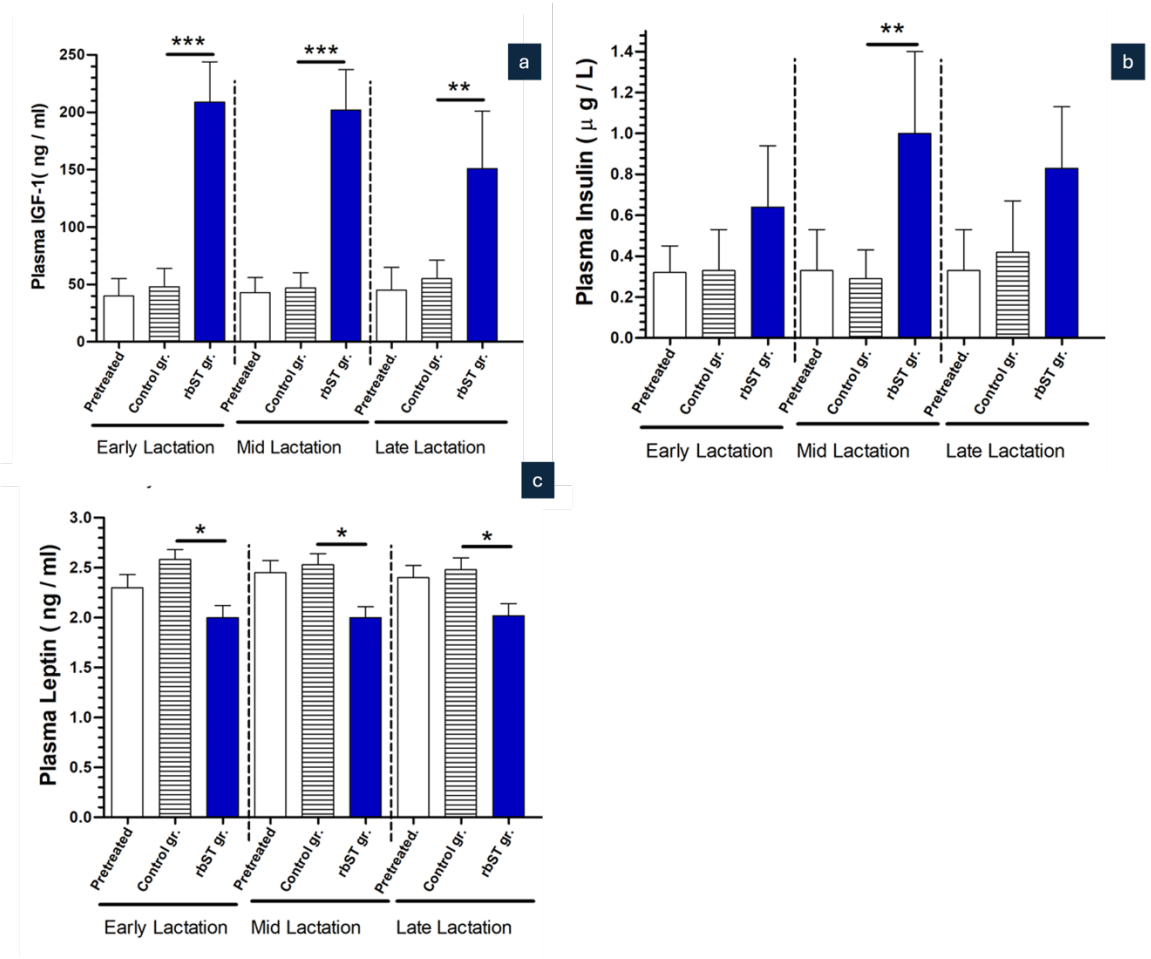

Figure 8. The plasma concentrutions of the insulin like growth factor 1 (IGF-1) (a), insulin (b) and leptin (c) in diferent stages of lactation in the control and rbST-treated animals (n=5 in each group). P- values: *P< 0.05, **P<0.01, ***P,0.001, P- values by unpaired t-test between control animals and rbST treated animals. (Adopted and modified from Chaiyabutr et al., 2005 and 2015).

GLUCOSE METABOLISM AND GLUCOSE UTILIZATION IN THE MAMMARY GLAND

GLUCOSE TURNOVER MEASUREMENT

Glucose kinetic studies in each crossbred HF animal are performed using radioactive glucose, specifically [3-^{3}H]glucose and [U-^{14}C]glucose. According to Chaiyabutr et al. (2008a), both whole-body glucose metabolism and intramammary glucose metabolism have been described. In brief, glucose kinetic studies at different stages of lactation are conducted using continuous infusion of [U-^{14}C]glucose and [3-^{3}H]glucose solutions. A priming dose of radioactive glucose in 20 ml of normal saline, containing 60 µCi of [3-^{3}H]glucose and 40 µCi of [U-

^{14}C]glucose, is administered intravenously via an ear vein catheter, followed by a continuous infusion (using a peristaltic pump) at 1 ml/min of normal saline solution (0.9%) containing 2 µCi/ml of [U-^{14}C]glucose and 3 µCi/ml of [3-^{3}H]glucose for 3 hours. During the last hour of continuous infusion, three sets of blood samples are collected at 20-minute intervals. Venous blood samples are collected from the milk vein via a catheter, while arterial blood samples are collected from the coccygeal artery using a #21 needle. Blood samples in heparinized tubes are kept on crushed ice for chemical analysis.

The glucose turnover rate in the whole animal (T), expressed as µmol/min, is calculated from the equation:

$$T = I/GA$$

Where, I = rate of infusion of [U-^{14}C]glucose or [3-^{3}H]glucose (µCi/min) and GA = specific activity of ^{14}C- or ^{3}H-glucose in arterial plasma at equilibrium (µCi/µmol).

Recycling of glucose carbon in the whole animal, expressed as % glucose turnover, is calculated from the equation:

$$\text{Recycling} = (T3\text{-}T14) \times 100/T3$$

Where, T3 = Reversible turnover of glucose calculated from [3-^{3}H]glucose
T14 = Irreversible turnover of glucose calculated from [U-^{14}C]glucose

In glucose kinetic studies using [3-^{3}H]glucose and [U-^{14}C]glucose infusion, the total glucose entry rate (reversible turnover rate of [3-^{3}H]glucose) and glucose utilization rate (irreversible turnover rate of [U-^{14}C]glucose) increased significantly during rbST administration in crossbred HF cattle in mid-lactation compared to the control animals (Figure 9). The reversible turnover rate of [3-^{3}H]glucose represents the total glucose turnover rate since ^{3}H is not recycled from products of partial glucose degradation (Katz et al., 1965). Thus, recycling of glucose carbon, as estimated by simultaneous injection of [3-^{3}H]glucose and [U-^{14}C]glucose, showed no differences between the controls and rbST-treated animals during advanced lactation. These results suggest that a constant level of tricarbon units, originally derived from glucose, is reincorporated into glucose, unaffected by rbST treatment.

Glucose metabolism and energy balance are known to be influenced by insulin action. An increase in plasma insulin levels during rbST administration at different stages of lactation in crossbred HF animals has been noted (Chaiyabutr et al., 2005), while plasma glucose levels and plasma glucose clearance remain unchanged. This indicates that rbST is antagonistic to insulin in insulin-sensitive tissues (Rose and Obara, 1996), which would prevent the uptake of glucose by peripheral tissues and thus spare glucose for the mammary gland, which is insensitive to insulin (McGuire et al., 1995).

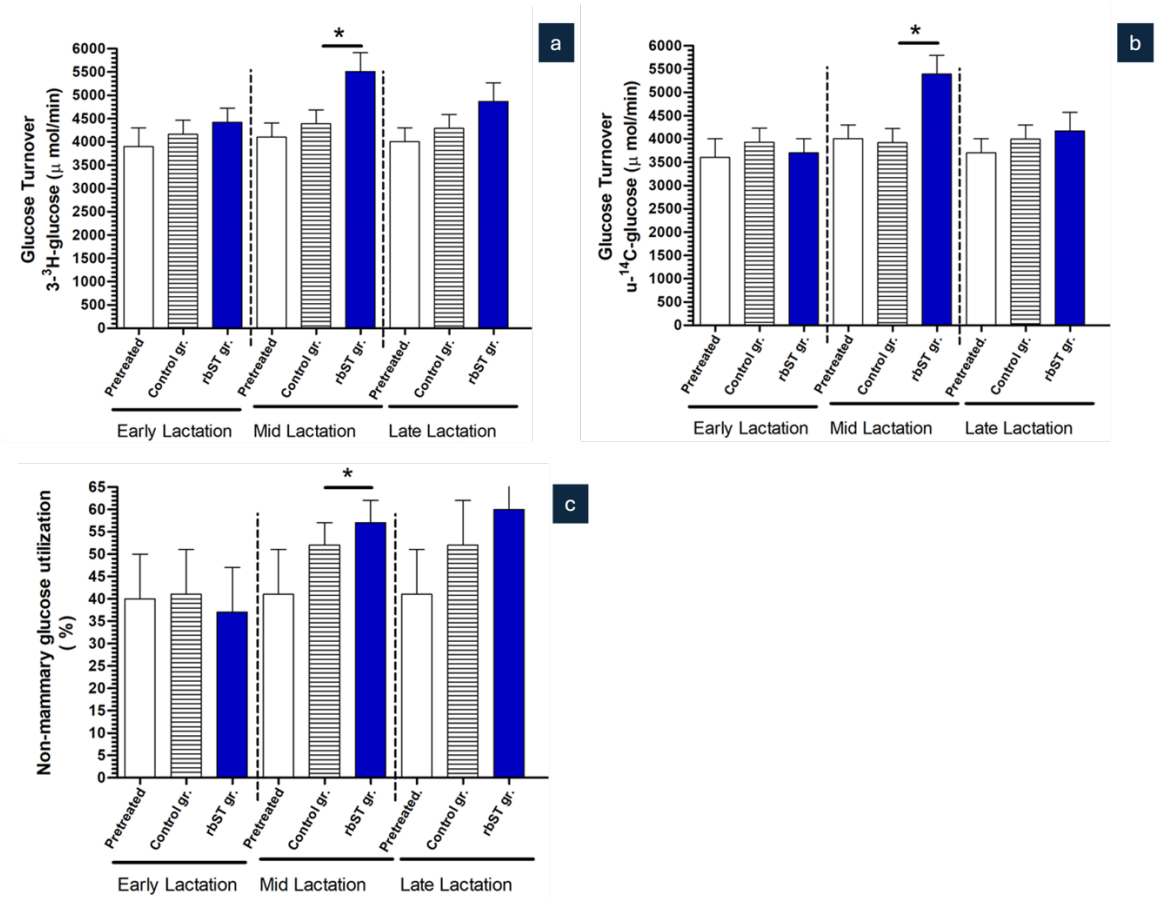

Figure 9. Means and standard deviation (n=5) of glucose turnover rate for reversible turnover of glucose [3-^{3}H]glucose (a), irreversible turnover of glucose [U-^{14}C]glucose (b) and non-mammary glucose utilization (c) during rbST administration at different stages of lactation of crossbred HF. P- values: *P< 0.05, P- values by unpaired t-test between control animals and rbST treated animals. (Adopted and modified from Chaiyabutr et al., 2008b).

MAMMARY GLAND GLUCOSE UTILIZATION AND METABOLIC PATHWAYS

Measurements of glucose utilization in the mammary gland after prolonged rbST administration were performed using glucose kinetic studies with [3-^{3}H]glucose and [U-^{14}C]glucose infusion. Blood samples and milk secretion were collected concurrently during glucose kinetic studies. The uptake of glucose by the udder (UG), expressed as μmol/min, was calculated using the following equation:

$$UG = MPF \times (PA-PV)$$

Where:
MPF = Mammary plasma flow (ml/min);
PA = Concentration of glucose in coccygeal arterial plasma (μmol/ml);
PV = Concentration of glucose of plasma from milk vein (μmol/ml)

The milk component output (MO), expressed as μmol/min and was calculated from the equation:

$$MO = Ms \times Cc/1000$$

Where:
Ms = Milk secretion rate (ml/min);
Cc = Concentration of components in milk (µmol/ L)
Incorporation (A) of radioactivity from glucose into milk components was calculated from the equation:

$$A = MA/GA \times t$$

Where:
A = Incorporation of radioactivity from glucose into milk components (µmol/min)
MA = Total activity of ^{3}H or ^{14}C in the milk components (µCi)
GA = Specific activity of ^{14}C-or ^{3}H-glucose in arterial plasma at equilibrium (µCi/µmol)
t = Time of infusion (min)

The udder cannot synthesize its own glucose due to a lack of glucose-6-phosphatase (Scott et al., 1976); therefore, it must extract glucose from circulating blood. The udder extracts most of the glucose available in the whole body (between 60% and 85%). The mammary uptake of glucose is primarily determined by the quantity of blood irrigating the organ, the arterial glucose concentration, and the udder's ability to extract glucose from blood plasma. Arterial glucose concentrations reflect the balance between glucose input and output in the body.

It is known that an increase in milk yield can be achieved only by increasing the rate of lactose synthesis. The lactating udder utilizes most of the glucose entering the circulation of ruminants, and irreversible glucose loss from plasma is highly correlated with lactose output (Bickerstaffe et al., 1974). The role of glucose in regulating milk secretion has also been demonstrated in the isolated perfused udder (Hardwick et al., 1963). Therefore, the regulation of milk yield in animals is mainly based on the mechanisms governing the quantity of glucose extracted by the udder and converted into lactose. The metabolic fate of glucose metabolism will consider the utilization in the whole body as it relates to the utilization in the mammary gland during lactation.

The effect of prolonged rbST administration on nutrient uptake by the mammary gland of 87.5% HF animals has been noted (Chaiyabutr et al., 2007b). The supply of glucose is a principal determinant of milk yield, as glucose is required for lactose production. A marked increase in milk yield without an alteration in lactose concentration during early lactation in rbST-treated animals indicates a substantial increase in the supply of glucose to the mammary gland (Bauman and McCutcheon, 1986). Glucose is essential for milk secretion, and the glucose moiety of lactose is derived directly from plasma glucose (Ebner and Schanbacher, 1974). In both control and rbST-treated crossbred HF animals, milk secretion is not dependent on blood glucose levels, as plasma glucose concentrations remain constant over a wide range of stages of lactation. The marked increase in udder blood flow in rbST-treated 87.5% HF animals supports the previous conclusion from a study in cows and goats by Linzell (1973) that glucose uptake is primarily determined by mammary blood flow.

The udder cannot synthesize its own glucose due to a lack of glucose-6-phosphatase (Scott et al., 1976), so it must extract glucose from circulating blood. The udder extracts most of the glucose available in the whole body (between 60% and 85%). Mammary uptake of glucose is mainly determined by mammary blood flow, arterial glucose concentration, and the udder's ability to extract glucose from blood plasma. Arterial glucose concentrations reflect the balance between glucose input and output in the body. The quantity of blood irrigating the udder results from complex regulatory mechanisms, depending both on the partitioning of cardiac

flow between different tissues in the body and local regulation that allows a given organ to adjust its arterial nutrient flow to its level of metabolic activity

The metabolic fate of nutrients, particularly glucose metabolism, the biosynthetic pathway for lactose synthesis (Chaiyabutr et al., 2008a), and the utilization of glucose in the whole body in relation to its utilization in the mammary gland in both control and rbST-treated animals have been studied (Chaiyabutr et al., 2008b). It is clear that changes in milk yield during rbST administration which exerts its galactopoietic action, in part, through both intra-mammary and extra-mammary effects (Chaiyabutr et al., 2008b). An increase in milk yield during rbST administration is thought to be primarily determined by lactose secretion (Linzell and Peaker, 1971). Lactose is synthesized in the mammary secretory cells from glucose derived from the blood. The concentration of milk glucose has been shown to increase coinciding with an increase in milk yield during rbST administration in both early and mid-lactation (Chaiyabutr et al., 2021). This reflects the intracellular glucose concentration (Kuhn and White, 1975; Faulkner et al., 1981), as glucose freely permeates across Golgi vesicles and apical membranes of the mammary secretory cells (Faulkner and Peaker, 1987). Mammary cells cannot synthesize free glucose because they lack glucose-6-phosphatase activity (Threadgold and Kuhn, 1979). The high concentrations of milk glucose in rbST-treated animals are likely related to a high rate of glucose uptake by the mammary gland, consistent with the higher mammary blood flow observed during rbST administration (Chaiyabutr et al., 2005). During early lactation, a large portion of the conversion of intracellular glucose to intermediary metabolites in rbST-treated animals is primarily used in the lactose biosynthetic pathway compared to controls.

In general, an increase in milk yield can be attributed to an increase in the rate of lactose synthesis (Linzell and Peaker, 1971). However, an increase in lactose yield during rbST administration is not related to the lactose concentration in milk, which remains largely unchanged. These results can be attributed to differences in the activity of the mammary epithelial cells between control and rbST-treated animals. The synthesis of lactose involves the combination of glucose and UDP-galactose, with the latter originating from glucose-6-phosphate (Ebner and Schanbacher, 1974). In contrast to control animals, rbST administration results in increases in both milk yield and glucose uptake by the mammary gland, which are accompanied by increases in the secretion of both milk glucose and glucose-6-phosphate (Chaiyabutr et al., 2008a). These results coincide with the calculation of glucose-6-phosphate metabolism to the galactose moiety of lactose in rbST-treated animals, which was higher than in control animals during early lactation. The availability of cytosolic glucose-6-phosphate in the mammary epithelial cells of rbST-treated animals in early lactation would be sufficient to account for cytosolic lactose synthesis. Decreases in the metabolism of glucose-6-phosphate to the galactose moiety of lactose in mid- and late lactation in both groups (Chaiyabutr et al., 2008b) would affect lactose synthesis and milk production. Low enzymatic activity for lactose synthesis might be expected as lactation advances in crossbred animals. However, lactose synthesis is a complex process (Kuhn et al., 1980), and more information is needed to elucidate the changes in enzymatic activity in this system.

The glucose taken up by the mammary gland is quantitatively used directly in the synthesis of lactose, while other portions are metabolized via the pentose phosphate pathway, the Embden-Meyerhof pathway, and the tricarboxylic acid cycle. Glucose carbon is used by mammary cells to produce lactose, citrate, and triacylglycerol for milk secretion. The data obtained for the utilization of glucose carbon for the synthesis of lactose, triacylglycerol, and citrate during early, mid, and late lactation are higher in rbST-treated animals compared to control animals (Figures 10, 11, and 12). The differences in these results between control and rbST-treated animals, without a reduction in feed intake, may be explained by differences in nutrient partitioning or utilization in the mammary gland. In addition to the use of

glucose carbon for milk synthesis, hydrogen from glucose has been shown to be incorporated into milk fat. In vitro studies have shown that glucose metabolism via the pentose phosphate pathway may not be as important for NADPH production as it is in rats. Fatty acid synthesis from acetate can occur in the absence of glucose in mammary tissue slices (Balmain et al., 1954) and the perfused goat udder (Hardwick et al., 1963). In the present studies, estimates of the contribution of the pentose phosphate pathway in providing NADPH for fatty acid synthesis in vivo are based on the assumption that all the glucose oxidized to CO_2 was metabolized via the pentose phosphate pathway. The metabolism of glucose-6-phosphate via the Embden-Meyerhof pathway or the pentose phosphate pathway has been estimated in the goat udder in vivo (Chaiyabutr et al., 1980). However, few data are available from in vivo studies of crossbred HF lactating cows. In vivo studies show that glucose-6-phosphate metabolism via the pentose phosphate pathway accounted for 9% to 18% in both control and rbST-treated crossbred HF groups. These estimations contrast with experiments in the isolated perfused cow udder by Wood and co-workers (1965), in which about 23% to 30% of glucose was metabolized via the pentose phosphate pathway. The difference in estimation is likely due to the lack of consideration for the recycling of glucose-6-phosphate, which occurs when glucose is metabolized via the pentose cycle in the udder, leading to the consequent loss of ^3H from glucose-6-phosphate (Davis and Bauman, 1974). However, the net proportion of glucose-6-phosphate metabolism via the pentose cycle pathway during different stages of lactation in rbST-treated animals appears to be higher than in control animals. Metabolism of glucose via the pentose phosphate pathway yields two molecules of NADPH per molecule of glucose, only one of which could be labeled with ^3H in the experimental design. The data presented here provide evidence that 29% to 34% of the NADPH required in different stages of lactation for fatty acid synthesis de novo from glucose metabolism in the udder of rbST-treated animals, while 38% to 41% is required in control animals. If there is a common pool of glucose-6-phosphate available for both lactose synthesis and pentose phosphate metabolism, then the recycling of glucose-6-phosphate within the udder would result in a too-low value for NADPH production from glucose. The net metabolism of glucose in the pentose phosphate pathway can be calculated from the incorporation of ^3H from [3-^3H]glucose into fatty acids, assuming that the NADPH formed is used exclusively for fatty acid biosynthesis (Katz et al., 1974). This technique has been used to study in vitro metabolism of rat mammary and adipose tissue (Katz et al., 1966; Katz and Wals, 1970, 1972) and in vivo metabolism of goat mammary tissue (Chaiyabutr et al., 1980). Based on the techniques and calculations of Katz and co-workers (1974) and assuming that cytosolic NADPH is used only for fatty acid synthesis, it has been shown that glucose phosphorylated by the udder of rbST-treated animals is metabolized via the pentose phosphate pathway at a higher rate than in control animals.

In rbST-treated animals, a high proportion of the glucose taken up by the udder that is oxidized in the tricarboxylic acid cycle would be apparent in mid- and late lactation. High values of both the proportion and absolute amount of glucose carbon incorporated into milk citrate and milk triacylglycerol of rbST-treated animals during mid- and late lactation provide evidence supporting an increased proportion of glucose-6-phosphate metabolized via the Embden-Meyerhof pathway. It has been shown that the metabolism of glucose-6-phosphate by the Embden-Meyerhof pathway can result in ^3H being retained in glycerol if the triose phosphate isomerase reaction is not at equilibrium (Katz and Rognstad, 1976). Metabolism of glucose-6-phosphate by the pentose phosphate pathway usually results in the loss of all ^3H from [3-^3H]glucose in lactating cows. The high metabolism of glucose-6-phosphate in early lactation of rbST-treated animals appears to be due primarily to a high flux through the lactose synthesis and pentose phosphate pathways, likely reflecting the high milk production during rbST

treatment. Tritium and carbon-14 have also been shown to be incorporated into milk citrate, which increased as lactation advanced in rbST-treated animals, whereas it remained at the same levels during the pretreatment period in the control animals.

It has been postulated that milk citrate could be synthesized from 2-oxoglutarate via the NADP-dependent isocitrate dehydrogenase reaction (Hardwick, 1965). In addition, ^{3}H is lost to NADPH or water during metabolism via the pentose phosphate pathway or glycolytic pathway, so it is likely that ^{3}H incorporation into milk citrate occurs via $NADP^{3}H$. The incorporation of ^{3}H into milk citrate may occur in different ways during the exchange reaction of cytosolic NADP-dependent isocitrate dehydrogenase. Both fatty acid synthesis and the NADP-dependent isocitrate dehydrogenase reaction may differ between control animals and rbST-treated animals, despite possibly sharing a common pool of cytosolic NADPH.

CONCLUSIONS

The data presented here provide an in vivo estimation of glucose metabolism in the udder and its distribution among lactose synthesis, the pentose phosphate pathway, and the Embden-Meyerhof pathway during rbST administration in 87.5% HF animals. As shown in Figures 10, 11, and 12, an average of 10% to 18% of the glucose taken up by the udder of rbST-treated animals at different stages of lactation is metabolized via the pentose phosphate pathway, contributing to NADPH production. The increased intracellular glucose concentration during rbST administration leads to an elevated level of glucose-6-phosphate, which enhances flux through both the lactose synthesis and pentose phosphate pathways. Although we have substantial knowledge of the differences in glucose metabolism regulation between control and rbST-treated animals, many questions remain unanswered. In particular, we have limited understanding of the variations in enzymatic activities during rbST administration at different stages of lactation, which affect the rate of these metabolic pathways.

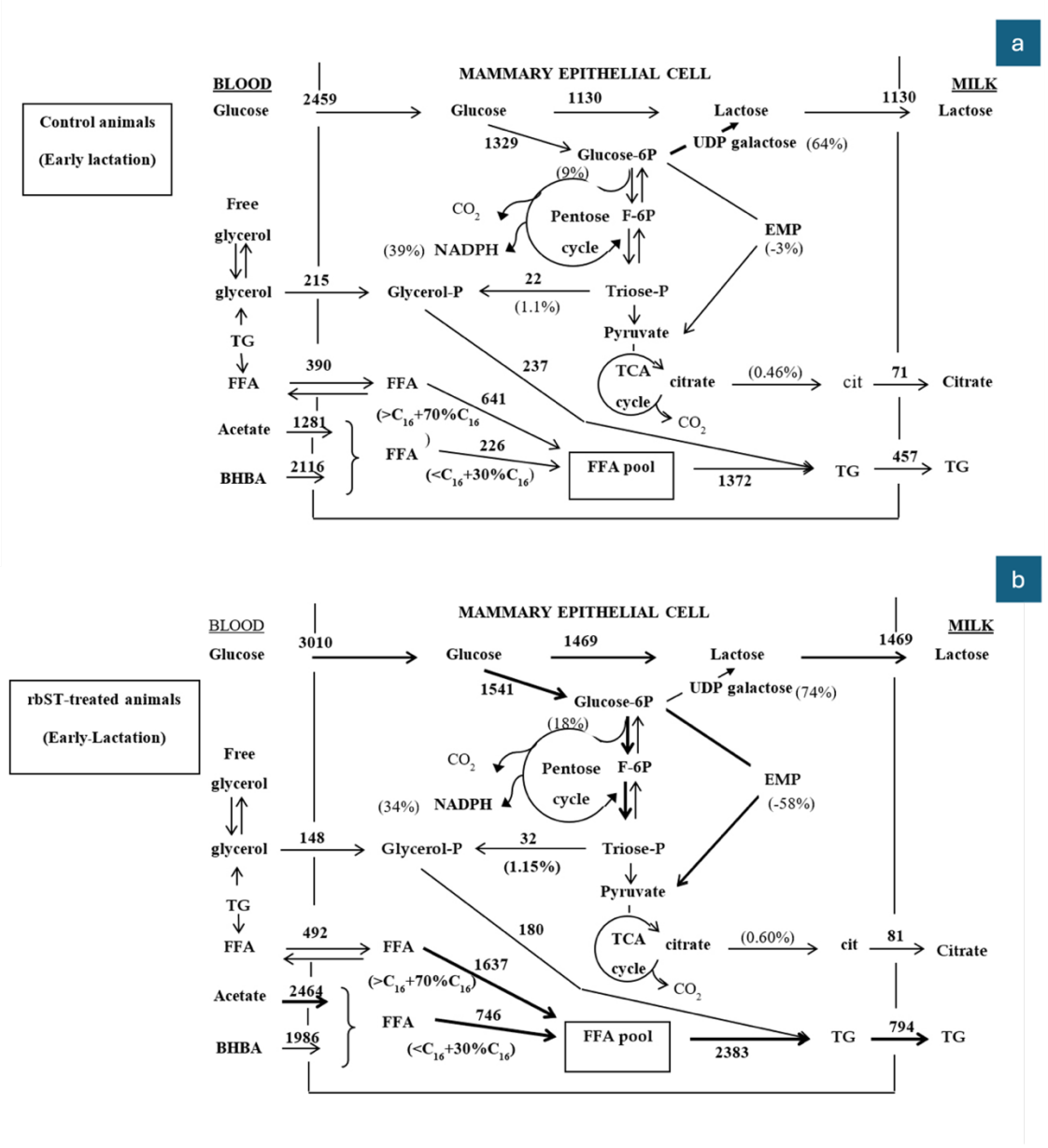

Figure 10. Description of the intracellular partitioning of glucose between differet metabolic pathways involved in the metabolism of the precursor of milk in mammary epithelial cells of control animals and rbST treated animals in the early lactation (The value shown are in micromole/min.) (Adopted data from Chaiyabutr et al., 2007b and 2008b). Abbreviations: Glucose-6P (glucose-6-phosphate), F-6P (fructose-6-phosphate), EMP (Embden-Meyerhof pathway), TG (triglyceride), FFA (free fatty acid), BHBA (beta hydroxybutyric acid).

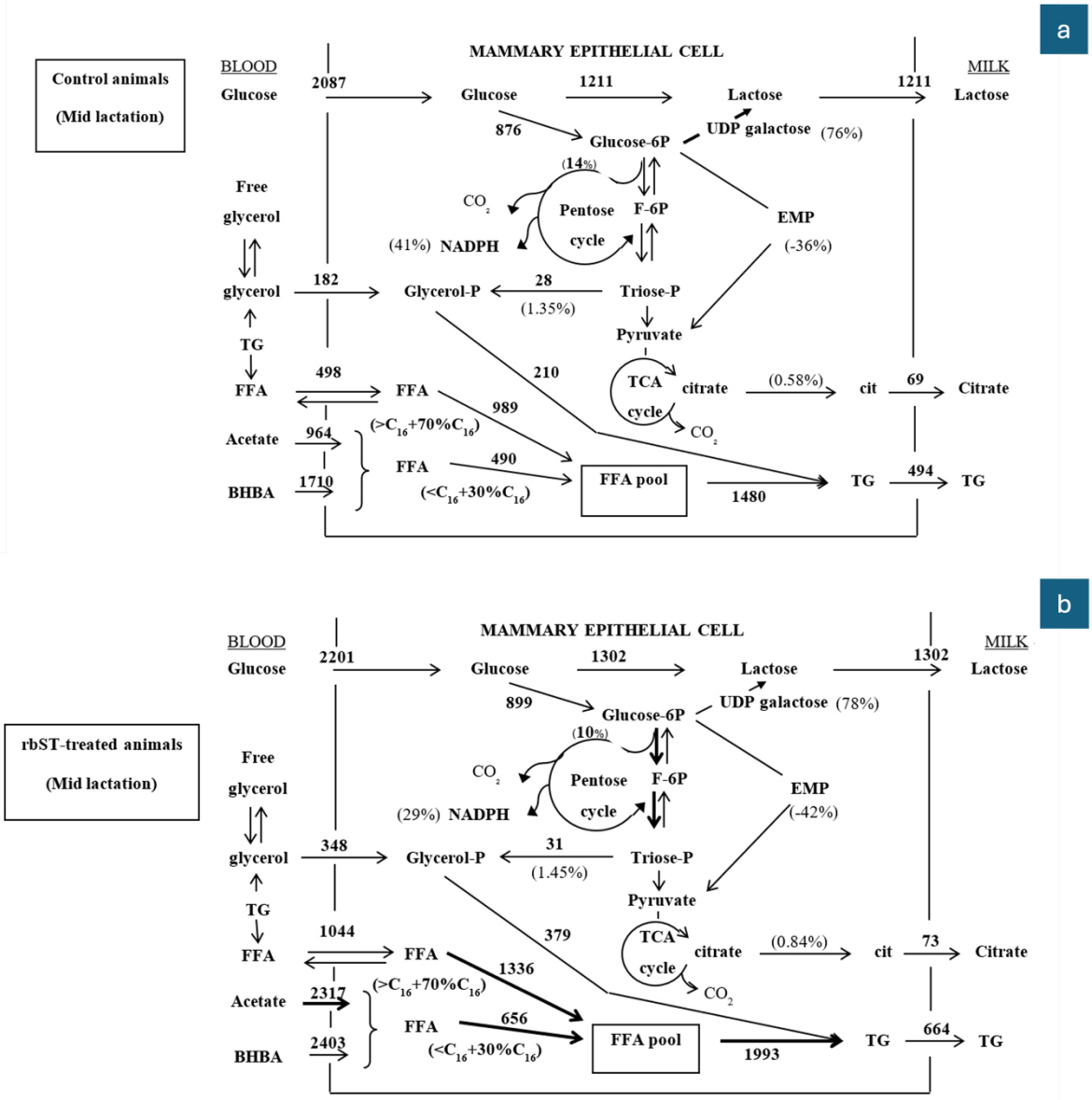

Figure 11. Description of the intracellular partitioning of glucose between differet metabolic pathways involved in the metabolism of the precursor of milk in mammary epithelial cells of control animals and rbST treated animals in the mid-lactation (The value shown are in micromole/min.) (Adopted data from Chaiyabutr et al., 2007b and 2008b). Abbreviations: Glucose-6P (glucose-6-phosphate), F-6P (fructose-6-phosphate), EMP (Embden-Meyerhof pathway), TG (triglyceride), FFA (free fatty acid), BHBA (beta hydroxybutyric acid).

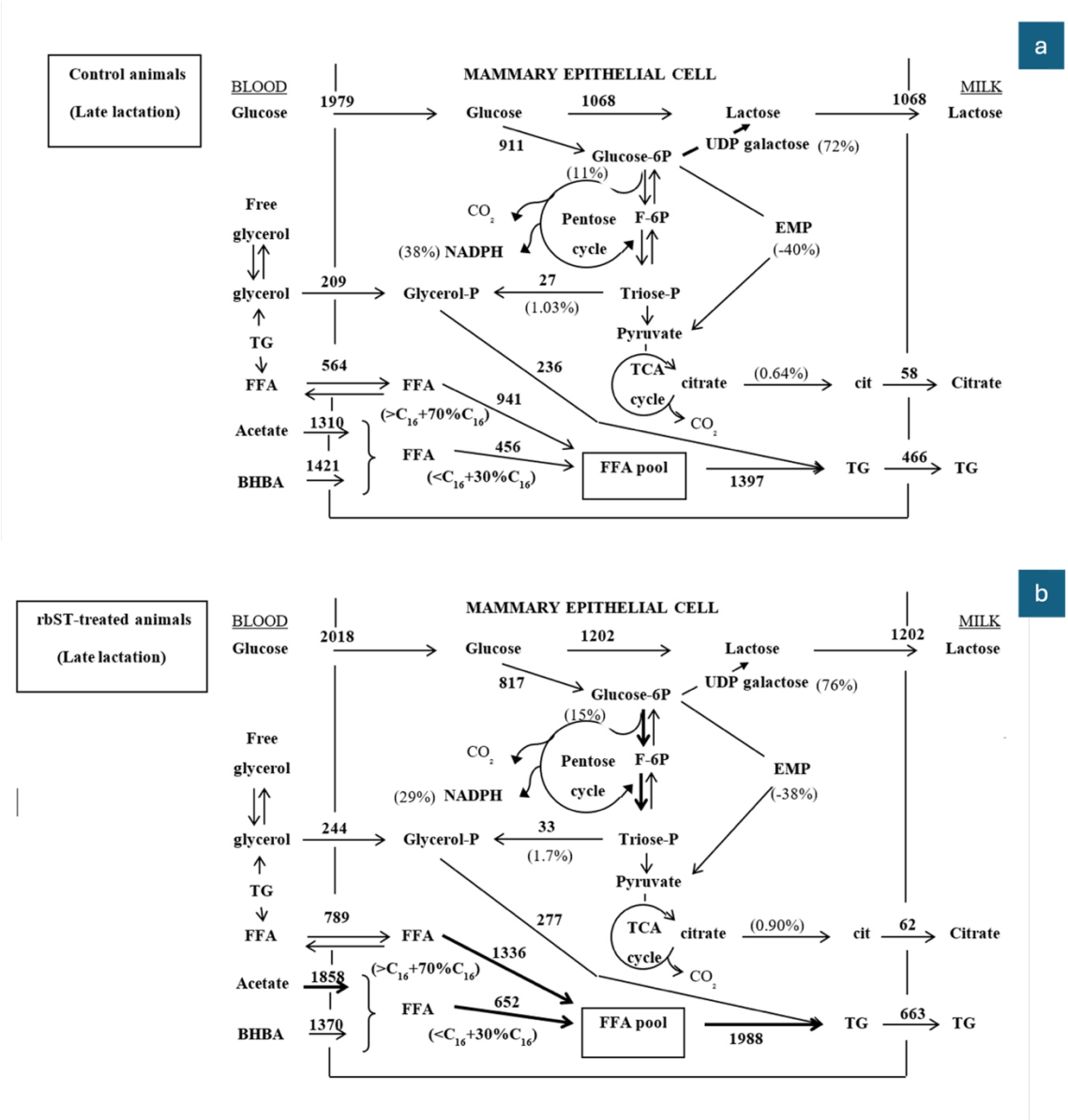

Figure 12. Description of the intracellular partitioning of glucose between differet metabolic pathways involved in the metabolism of the precursor of milk in mammary epithelial cells of control animals and rbST treated animals in the late lactation (The value shown are in micromole/min.) (Adopted data from Chaiyabutr et al., 2007b and 2008b). Abbreviations: Glucose-6P (glucose-6-phosphate), F-6P (fructose-6-phosphate), EMP (Embden-Meyerhof pathway), TG (triglyceride), FFA (free fatty acid), BHBA (beta hydroxybutyric acid).

Further research is needed to determine whether the high enzymatic activity of fructose-1,6-bisphosphatase or the lower activity of pyruvate dehydrogenase in the mammary gland of rbST-treated animals is consistent throughout lactation or specific to early lactation, leading to increased metabolism of glucose-6-phosphate via the Embden-Meyerhof pathway and the tricarboxylic acid cycle. Additionally, the effect of high environmental temperatures, particularly in genetically exotic cattle in the tropics, on changes in enzymatic activity in mammary epithelial cells is not well understood. The changes in extra-mammary parameters do not provide detailed information. It is important to further our understanding of how intra-mammary parameters change in relation to the shorter persistency of milk production. Moreover, it is crucial to determine whether, in addition to systemic

parameters, we need to understand the specific transporters of upstream substrates in mammary epithelial cells under high environmental temperatures in crossbred dairy cattle, as this could reveal alternative metabolic pathways for milk production.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this article and collaboratively determined the scope and structure of the review. NC led the drafting of the manuscript, and all authors participated in revising it and approved the final version.

CONFLICT OF INTEREST

There is no conflict of interest in the final version of the article.

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How to cite this article;
Narongsak Chaiyabutr, Somchai Chanpongsang and Sumpun Thammacharoen. A descriptive review of the role of exogenous bovine somatotropin on milk secretion mechanisms at different stages of lactation in crossbred Holstein cattle in the tropics. Veterinary Integrative Sciences. 2025; 23(2): e2025053-1-27.