ผลของการให้ Recombinant bovine somatotropin (rbST)
ต่อการทำงานของต่อมน้ำนมในแพะนม
ลูกผสมซาเนนระยะท้ายของการให้นม

นางสาวกุลภา พลรัตน์



วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาสรีรวิทยาการสัตว์ ภาควิชาสรีรวิทยา
คณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2547
ISBN 974-17-6159-7

# EFFECTS OF EXOGENOUS RECOMBINANT BOVINE SOMATOTROPIN (rbST) ON MAMMARY FUNCTION IN LATE LACTATING CROSSBRED SAANEN GOATS

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Animal Physiology
Department of Physiology
Faculty of Veterinary Science
Chulalongkorn University
Academic Year 2004

ISBN 974-17-6159-7

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|---|---|
| Thesis title | Effects of exogenous recombinant bovine somatotropin (rbST) on mammary function in late lactating crossbred Saanen goats |
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กุลภา พลรัตน์ : ผลของการให้ recombinant bovine somatotropin (rbST) ต่อการทำงานของต่อมน้ำนมในแพะนมลูกผสมซาเนนระยะท้ายของการให้นม. (EFFECTS OF EXOGENOUS RECOMBINANT BOVINE SOMATOTROPIN (rbST) ON MAMMARY FUNCTION IN LATE LACTATING CROSSBRED SAANEN GOATS) อ. ที่ปรึกษา: ศ.น.สพ.ดร. ณรงค์ศักดิ์ ชัยบุตร, อ.ที่ปรึกษาร่วม : รศ.น.สพ. สมชาย จันทร์ผ่องแสง 50 หน้า. ISBN 974-17-6159-7

การทดลองครั้งนี้มีวัตถุประสงค์ เพื่อศึกษาผลของ recombinant bovine somatotropin (rbST) ต่อแพะนมลูกผสมซาเนนในระยะท้ายของการให้นม และกลไกที่ทำให้เกิดการเปลี่ยนแปลงจากปัจจัยภายในและภายนอกต่อมน้ำนม ที่มีผลต่อการทำงานของต่อมน้ำนม ในการทดลองใช้แพะนมลูกผสมซาเนนที่อยู่ในช่วง 24 สัปดาห์หลังคลอด จำนวน 10 ตัว แบ่งเป็น 2 กลุ่มๆ ละ 5 ตัว โดยทั้ง 2 กลุ่มมีปริมาณน้ำนมใกล้เคียงกัน แพะนมในกลุ่มควบคุม ถูกฉีดด้วย sesame oil ที่ปราศจากฮอร์โมน ส่วนแพะนมในกลุ่มทดลอง ถูกฉีดด้วยฮอร์โมน rbST ในรูป prolong-released ปริมาณ 250 มิลลิกรัม เข้าใต้ผิวหนังบริเวณหัวไหล่ จำนวน 2 ครั้ง ห่างกัน 14 วัน และทำการตรวจสอบผลการทดลอง ในวันที่คาดว่าฮอร์โมนมีผลสูงสุด คือหลังจากฉีดฮอร์โมนไปแล้ว 7 วัน

ผลการทดลองพบว่า หลังจากฉีดฮอร์โมน rbST ผลผลิตน้ำนมตลอด 4 สัปดาห์ของการทดลองเพิ่มขึ้น 37% โดยมีผลผลิตน้ำนม หลังจากฉีดฮอร์โมนครั้งที่สอง สูงกว่าในครั้งแรก (+19%) องค์ประกอบหลักในน้ำนม ได้แก่ ไขมัน โปรตีน และน้ำตาลแลคโตส ไม่เปลี่ยนแปลง เมื่อการให้นมดำเนินต่อไป ปริมาณโซเดียมในน้ำนมของแพะนมในกลุ่มควบคุมสูงขึ้น ในขณะที่กลุ่มทดลอง มีค่าลดลงอย่างมีนัยสำคัญหลังจากฉีดฮอร์โมน rbST ครั้งที่ 2 ทำให้อัตราส่วนของโซเดียม และโปตัสเซียมในน้ำนมลดลงอย่างมีนัยสำคัญ ในการทดลองครั้งนี้ไม่มีความแตกต่างอย่างมีนัยสำคัญ ในการนำสารอาหารต่างๆ เข้าสู่เต้านม ในแง่ของความเข้มข้นในพลาสมา ค่าผลต่างของความเข้มข้น และเปอร์เซ็นต์ของการนำไปใช้ ความเข้มข้นของ IGF-1 ในพลาสมาสูงขึ้นอย่างมีนัยสำคัญ ($P<0.05$) หลังจากการฉีดฮอร์โมน rbST ครั้งที่ 2 และทั้ง 2 กลุ่มแตกต่างกันอย่างมีนัยสำคัญ ($P<0.05$) ฮอร์โมน rbST ส่งผลให้ปริมาณน้ำทั้งหมดภายในร่างกาย และปริมาณน้ำนอกเซล เพิ่มขึ้นอย่างมีนัยสำคัญยิ่ง ($P<0.01$) ตลอดช่วงระยะเวลาทั้งหมดในการทดลอง และมีผลแตกต่างอย่างมีนัยสำคัญยิ่งระหว่างทั้ง 2 กลุ่ม

จากการทดลองสรุปได้ว่า ฮอร์โมน rbST สามารถเพิ่มผลผลิตน้ำนมในแพะนมลูกผสมซาเนนระยะท้ายของการให้นม โดยส่งผลต่อการเปลี่ยนแปลงปัจจัยภายในต่อมน้ำนม ในด้านการป้องกันการรั่วของเยื่อกั้น ในการแลกเปลี่ยนเพื่อนำสารอาหาร และอิออนต่างๆ ซึ่งส่งผลให้อัตราการสังเคราะห์น้ำนม และการสร้างน้ำตาลแลคโตสเพิ่มขึ้น นอกจากนี้ ฮอร์โมน rbST ยังส่งผลต่อปัจจัยภายนอกต่อมน้ำนม ในการควบคุมของเหลวภายในร่างกาย โดยการเพิ่มปริมาณน้ำทั้งหมดในร่างกาย และปริมาณน้ำนอกเซล กลไกการทำงานของ rbST อาจเกี่ยวข้องกับการเพิ่มขึ้นของ IGF-1 ในพลาสมา ซึ่งอาจทำให้เกิดการเพิ่มของอัตราการไหลของเลือด และการนำสารอาหารไปยังต่อมน้ำนม

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| ภาควิชา | สรีรวิทยา | ลายมือชื่อนิสิต..... |
| สาขาวิชา | สรีรวิทยาการสัตว์ | ลายมือชื่ออาจารย์ที่ปรึกษา..... |
| ปีการศึกษา | 2547 | ลายมือชื่ออาจารย์ที่ปรึกษาร่วม..... |

## 4375575331 : MAJOR ANIMAL PHYSIOLOGY

KEY WORD: RECOMBINANT BOVINE SOMATOTROPIN / MAMMARY FUNCTION / CROSSBRED SAANEN GOATS / LATE LACTATION

KULAPA POLRATANA: EFFECTS OF EXOGENOUS RECOMBINANT BOVINE SOMATOTROPIN (rbST) ON MAMMARY FUNCTION IN LATE LACTATING CROSSBRED SAANEN GOATS.

THESIS ADVISOR : PROF. NARONGSAK CHAIYABUTR, D.V.M., Ph.D.

THESIS COADVISOR : ASSOC. PROF. SOMCHAI CHANPONGSANG, D.V.M., M.S., 50 pp.

ISBN 974-17-6159-7.

The aim of this experiment was to evaluate the effects of rbST on milk production in late lactating crossbred Saanen goats. The mechanism by which rbST acts on mammary function including direct or indirect effects, an intra or extra mammary factors were carried out. Ten, multiparous, non-pregnant crossbred Saanen goats in late lactation, approximately 24 weeks postpartum were used in this study. The experimental goats were divided equally into control group injected with sesame oil as placebo and experimental group treated with rbST. The experimental goats received 250 mg of slow-released-formulation rbST by subcutaneous injection at the subscapular region. Seven days later, corresponding to the expected maximum response to each rbST were determined the mechanisms.

The present study found that milk yield over the 4 weeks of this experiment increased 37% and the response to the second injection was greater than the first injection (+19%). Major milk constituent was no significant change. In contrast to the rbST treated goats, concentration of milk Na in the control goats were increased by the progress of lactation. After the 2$^{nd}$ rbST administration, treated goats were decreased significantly of milk Na concentration and the ratio of milk Na/K also decreased significantly ($P<0.05$).The arterial plasma concentrations, A-V differences and mammary extraction ratio of precursors for milk synthesis were not statistical different. The plasma IGF-1 concentration was increased significantly after 2$^{nd}$ rbST injection. Body fluid compartments for PV, ECW and TBW were significantly increased coincided with an increase in milk yield.

The present results indicated that rbST affected the mammary function to increase milk yield in late lactating crossbred Saanen goats by involving the intra-mammary factors to maintenance of tissue integrity. Moreover, the rbST may mediate via IGF-1, mainly acts on extra-mammary factors involving body fluid regulations. The mechanism by which rbST could increase TBW and ECW to make up the largest portion of milk during milk synthesis.

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| Department | Physiology | Student's signature..... |
| Field of study | Animal Physiology. | Advisor's signature..... |
| Academic year | 2004 | Co-advisor's signature…….. |

# ACKNOWLEDGEMENTS

I would like to express my deep gratitude to my advisor, Professor Dr. Narongsak Chaiyabutr and my co-advisor, Associate Professor Somchai Chanpongsang for their helpful consultation and guidance. My thanks also expressed to the thesis committee for their valuable suggestions.

My sincere and warm appreciation is expressed to Miss Siripen Komolvanich, Assistant Professor Sumphan Thamachareon for their help and technical suggestion and Miss Hathaithip Park-insee for their valuable assistance in this work. My thanks would also express to the Department of Veterinary Public Health and the Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University for provision the facilities used in the experimental works.

I am also indebted to experimental goats from Virat Farm, Petchburi and Lamar's family, and works was supported in part by the Department of Livestock Development, Western Veterinary Research and Development, which bring me to succeed in my experimental works.

Finally, I am deeply grateful to my family for their kind encouragement throughout my study period.

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# ABBREVIATIONS

| | |
|---|---|
| rbST | Recombinant bovine somatotropin |
| pST | Porcine somatotropin |
| hST | Human somatotropin |
| IGF-1 | Insulin-like growth factor-1 |
| GRF | Growth hormone-releasing factor |
| MBF | Mammary blood flow |
| MPF | Mammary plasma flow |
| NEFA | Non-esterified fatty acids |
| hPRL | Human prolactin |
| BP | Binding protein |
| IGFBP | Insulin-like growth factor binding protein |
| A-V | The arterio-venous difference |
| A | The plasma metabolites concentration from artery |
| V | The plasma metabolites concentration from milk vein |
| BHBA | β-hydroxybutyrate |
| TG | Triglyceride |
| ng | nanogram |
| ml | milliliter |

| | |
|---|---|
| μmole | micromole |
| mmole | millimole |
| gm% | gram/100 milliliter |
| $[Glu]_a$ | The plasma concentration of glucose in arterial blood |
| $[TG]_a$ | The plasma concentration of triglyceride in arterial blood |
| $[BHBA]_a$ | The plasma concentration of β–hydroxybutyrate in arterial blood |
| $[Acetate]_a$ | The plasma concentration of acetate in arterial blood |

# CHAPTER I

# INTRODUCTION AND AIMS

It is well documented that exogenous bovine somatotropin (bST) or bovine growth hormone (bGH) increases milk production (10-40%) in lactating ruminants (Bauman and Vernon, 1993). Bovine growth hormone can be used in either goats or sheep, apparently because the hormones of both species have almost identical amino acid sequences (Miller and Ebernardt, 1983). Therefore, bST administration may be considerable benefit in small dairy ruminants, particularly goats, for which stage of lactation is synchronized as a result of the seasonal breeding cycle (Chiofalo et al., 1999). However, it still affects differently in each species including stage of lactation, therefore the mechanism of action of ST remains to be elucidated.

The lactating mammary gland depends upon an adequate supply of nutrients and hormonal stimuli from blood to sustain milk synthesis; however, it has been established that ST does not achieve through a direct action on the mammary gland because they possess no receptor (McDowell et al., 1987). Therefore, the augmented production associated with exogenous bST may increase in the requirement of animals for milk precursor and energy substrate. It may result from an influence the supplies of key nutrients to the mammary gland, thereby influencing the capacity of the mammary gland to synthesize milk or the result of a homeorhetic in body fluid distribution. It is found that GH deficiency is associated with decreased plasma volume (PV), extra-cellular volume (ECV) and total body water (TBW) in both human and animals (Moller et al., 1996).

It is known that during lactation, the animals consume more water to make up the largest portion of milk and waste products. This also affects other body functions; for example blood volume and cardiac output were increased in lactating dairy goats (Chaiyabutr et al. 1980). The changes in blood volume, osmolality and other vascular adjustments are delicate and continuous process under the control of hormones. An increase in water intake during lactation closely associates with an increase in water

secretion in milk composition, which composes of 87% of water (Woodford et al., 1984; Murphy, 1992). A study on the reverse process at the end of lactation found that after the cessation of milking in lactating goats, water consumption decreased markedly but no significant changes in plasma volume, osmolality and packed cell volume in the short period (Chaiyabutr, 1981). During dehydration, milk yield of lactating goats fell to 35% and total yield of milk solid and milk water were 70 and 67% of normal group, respectively (Maltz and Sbkolnik, 1984). Furthermore, it was found that milk and plasma osmolality increased and plasma Na+ concentration decreased (Dahlborn, 1987)

A study on the regulation on the body fluids and mammary circulation has been shown that milk yield of the late lactation was significant lower than early lactation corresponding markedly declined in mammary blood flow and also markedly reduced in the levels of plasma growth hormone (Chaiyabutr et al., 1999). The late lactating cattle administration with rbST increased in both milk yield and mammary blood flow (Tanwattana, 2003). However, Lacasse and Prosser (2003) reported that mammary blood flow does not limit milk yield in lactating goats. The rbST treated cows in early lactation were significantly increased in plasma volume and blood volume. An empty body water was significantly increased which associated with an increase the extra-cellular water. (Maksiri, 2003). Thus, a research in the control mechanism for body water regulation in late lactating crossbred dairy goats in the rbST treatment is still inadequate and to be elucidated.

It is important to understand the mechanism of physiological adjustments of body water and mammary function during declining of milk yield. Therefore, the aim of the present study is to evaluate the effects of exogenous bST on mammary function and other physiological parameters in late lactating crossbred Saanen goats.

# CHAPTER II

# BACKGROUND INFORMATION

Recombinant bovine somatotropin (rBST) is a synthetically derived hormone that may be identical to naturally occurring bovine growth hormone, or slightly modified by the addition of extra amino acids. In 1993, sometribove (Posilac; Monsanto Corporation, St. Louis, Missouri, USA) was approved for use in the United States. It is currently undergoing FDA review for use in lactating dairy cows to increase milk production. It is a major participant in controlling several complex physiologic processes, including growth, metabolism and lactation. Physiologic effects of growth hormone can be seen below.

## The structure of growth hormone

Growth hormone or somatotropin is a protein hormone synthesized by the anterior pituitary gland. The secretion of growth hormone from the pituitary gland is regulated by two peptides: the growth hormone-releasing factor (GRF), which stimulates the release and the somatostatin, which inhibits the release. In addition to these two peptides, a third as yet unidentified hormone, binds to the growth secretagogue receptor to stimulate growth hormone release using a signal transduction pathway distinct from that of GRF is reported (Etherton and Bauman, 1998).

Growth hormone contains 191 amino acids, and bovine somatotropin (bST) and porcine somatotropin (pST) share a high degree of amino acid sequence similarity (~ 90%) (Bauman and Vernon, 1993). In contrast, the amino acid sequence of both bST and pST is appreciably different from that of human somatotropin (hST) (~35% of the amino acids in hST differ from these of bST and pST). Because of this difference, bST and pST have no effect on human growth, which is consistent with their binding affinity to the hST receptor being several orders of magnitude lower than that of hST.

It is noted that there are variant forms of growth hormone. For example, bST is released from the pituitary as four variants. These variants have either a leucine or valine substitution at position 127 and an alanine (191 amino acid sequence) or a phenylalanine (190 amino acid sequence) at the $NH_2$ terminus. The variation in the $NH_2$ terminus is due to differences in the cleavage of the signal peptide. The frequency of these gene alleles differs among dairy breeds (Bauman and Vernon, 1993).

Recombinantly derived forms of bST (bST) that have been used experimentally can differ slightly from the bST produced by the pituitary gland. Depending on the manufacturing process, from 0 to 8 extra amino acids are attached to the N-terminus of the bST molecule. However, when the same purification techniques are used, recombinantly derived and pituitary-derived bST have similar potency in various biological test systems (Bauman and Vernon, 1993; Etherton and Bauman, 1998).

Exogenous growth hormone must be injected to be biologically active. The digestive tract secretes enzymes that break proteins down to amino acids to be absorbed. If exogenous growth hormone is given orally, it is broken down to amino acids in the digestive process just like other dietary proteins. This reason is that bST is cleared rapidly from the blood stream and is not stored in the body. Clearance of bST occures by normal body mechanisms and involves breaking the protein down to amino acids. Thus, to achieve a sustained increase in milk yield, one needs to give daily injections or use a prolonged-release formulation of bST. Several prolonged-release formulations have been developed that are small volumes to be administered by subcutaneous injection at time intervals ranging from 2 to 4 weeks (Bauman, 1992; Muller, 1992).

**Mechanisms of action of growth hormone**

Growth hormone is a homeorhetic control that affects numerous target tissues in ways that is highly coordinated to affect marked changes in nutrient partitioning

among these tissues. Two cell types that are well established as major direct targets of growth hormone are the adipocyte and the hepatocyte. In contrast, effects on mammary tissue are thought to be indirect.

**Milk production response to bST**

For all species, milk yield follows the lactation curve, increasing to peak yield and then declining at weaning or the cessation of milking. For dairy cows, genetic selection has greatly increased two interrelated factor, peak yield and lactation persistency, defined as the change of yield with time in mid-lactation. Broster and Broster (1984) calculated that peak yield of dairy cow's accounts for 66 to 80% of the variance in total yield compared with 8 to 12% for persistency. Peak yield is in turn determined by secretory cell number and by secretory activity per cell. Studies in goats by Knight and Wilde (1993), show that parenchyma cells increase in number during pregnancy and early lactation. Between parturition and peak lactation secretory cells increase in size and become more fully differentiated. After peak, cell loss is largely responsible for decline in milk yield, but the activity per cell is maintained.

Milk yield increase after bST treatment is observed in cows of all parities, but the magnitude of the increase in milk yield varies according to stage of lactation (Peel and Bauman, 1987). In general, the response has been small or negligible when bST is administered in early lactation prior to peak yield. Therefore, the possible commercial use would probably be over the last two- third or three-fourth of the lactation cycle (Bauman and Vernon, 1993). Lactation response to bST is a function of the daily dose represented by a hyperbolic dose-response curve with a pattern of diminishing marginal returns to increasing doses (McGuffey and Wilkinson, 1991).

Exogenous growth hormone enhances milk production in dairy cows by coordinating a complex series of adaptations within the body. Treatment with bST increases the rate of milk production within the mammary gland and provides the necessary nutrients in support of this enhanced rate of milk synthesis. Voluntary feed intake does not increase until several weeks after increases in milk yield in bST-treated

cows (Burton et al., 1994). The magnitude of the increase in feed intake is dependent upon the increase in milk yield, the degree of body condition change, and the nutrient density of the diets. The nutrient partitioning response to bST treatment that supports increased milk yield particularly concerns the preferential oxidation of fatty acids and the sparing of glucose by peripheral tissues. The increased substrate utilization by the mammary gland may in turn provide a stimulus for increasing feed intake (Bauman and Vernon, 1993).

The major blood precursors for the formation of milk are glucose, acetate, fatty acids, β-hydroxybutyrate, triglyceride and amino acid. Treatment of lactating cows with bST has been shown to augment insulin resistance in peripheral tissues (Sechen et al., 1990). bST had no effect on plasma glucose concentrations but increased the irreversible loss rate of glucose by 12% (Bauman et al., 1988). Milk lactose production represented a major use of lost glucose. McDowell et al. (1987) demonstrated that bST treatments reduced glucose uptake by the hind limb muscle and increased glucose uptake by the mammary gland. Peel et al. (1983) reported that bST treatments did not affect plasma concentrations of glucose, insulin, glucagon, prolactin, tri-iodothyronine, thyroxine or cortisol in either early or late lactation. In many mammalian cells, a major point of metabolic regulation of glucose utilization is the transport of glucose across cell membranes, which is mediated by a family of tissue-specific facilitative glucose transporter (Kahn, 1992). Mammary gland mainly expresses GLUT1 glucose transporter protein (Zhao et al., 1999 and Zhao et al., 1996) whereas muscle and fat primarily express GLUT 4 (Zhao et al., 1996).

Analysis of milk for intra-cellular constituents, such as glucose, has proved useful, changes in the concentration of glucose in milk have been found to correlate significantly with changes in milk production under a variety of situations such as feed restriction (Chaiyabutr et al., 1981) and suppression of secretion (Faulkner et al., 1981). These, together with direct data on mammary glucose concentrations, indicate that milk glucose concentrations reflect intra-cellular concentrations (Faulkner et al., 1981).

Faulkner (1999) reported that there were increased in the availability of glucose within the mammary epithelial cell in response to growth hormone treatment.

Increased milk yield should reflect increased flow of blood carrying milk precursors to the mammary gland. Control of mammary blood flow (MBF) may be a way to control nutrient partitioning. Cardiac output was reported to be 10% higher and MBF increased by 35% in bST-treated cows studies by Davis et al. (1988). Tannaer and Hauser (1989) also reported higher cardiac output in a study. Heart rates were monitored regularly in several studies. Heart rate was slighter higher in bST-treated cows at high dose rate but was still within normal range (Soderholm et al., 1988 and Eppard et al., 1987).

The daily outputs of major milk constituents (lactose, fat, protein, minerals and vitamins) are elevated by an amount comparable to milk volume in bST-treated cows (Bauman and Vernon, 1993 and Burton et al., 1994). The concentrations of fat and protein in milk normally vary as a result of factors such as genetics, breed, stage of lactation, season, diet and nutritional status. These similar factors also affect the composition of milk from bST-treated cows (Etherton and Bauman, 1998).

**Effects of bST on lipogenesis and lipolysis**

Propionate and acetate are the main energy sources in ruminant animals because of their availability and high rate of uptake by the lactating mammary gland, acetate and to a lesser extent, β-hydroxybutyric acid are considered the most important energy metabolites in mammary gland metabolism of ruminants. Two of the most significant functions of acetate are to supply carbon atom for *de novo* synthesis of fatty acids and to generate adenosine triphosphate through the tricarboxylic acid acid cycle and the electron transport system. Growth hormone has dramatic effects on adipose tissue and lipid metabolism. Both lipogenesis and lipolysis are altered by growth hormone treatment, with effects on lipid synthesis being of major importance if

animals are in positive energy balance, whereas effects on lipolysis predominate when animals are at an energy balance near zero or negative (Bauman and Vernon, 1993).

When cows are near zero or in negative energy balance, bST treatment increases mobilization of body fat reserves as evidenced by chronic elevation in circulating concentrations of nonesterified fatty acids (NEFA). A decreased body fat content and an increased milk fat content with the pattern of these extra fatty acids reflecting body fat stores (Bitman et al., 1984; Eppard and Bauman, 1985 and Sechen et al., 1990). This situation is most likely occurring when bST treatment is initiated in early to mid-lactation and the increased reliance on NEFA as metabolic fuel facilitates the previously discussed reduction in glucose oxidation.

In contrast, when animals are in positive energy balance at the time bST treatment is initiated (i.e. when some lipid synthesis and storage is occurring in adipose tissues), the major effect of growth hormone is to inhibit lipid synthesis with little or no change in lipolysis or milk fat percent and fatty acid composition (Eppard and Bauman, 1985; Peel and Bauman, 1987 and Sechen et al., 1989). This situation is most likely to occur when bST is initiated in mid or late lactation and the decrease in nutrient utilization for body fat stores enables nutrients to be redirected to other tissues to support the increased milk synthesis.

The regulation of lipolysis involves cAMP and a signal transduction system that includes stimulatory G proteins (GS) and inhibitory G protein (Gi). Catecholamines affect lipolysis through the GS system, and growth hormone treatment dramatically increases the lipolytic response to catecholamines in lactating cows (McGuffey and Wilkinson, 1991 and Sechen et al.1990). This change in response to catecholamines is evident within 15 h after the initiation of growth hormone treatment and is observed regardless of whether animals are in a positive or negative net energy balance (Etherton and Bauman, 1998).

Growth hormone treatment *in vivo* or *in vitro,* Result in only modest changes in $\beta$ and $\alpha_2$-adrenergic receptor numbers. Furthermore, examination of the $G_S$ proteins and other downstream components of the lipolytic signal transduction cascade demonstrated no differences in adipose tissue from bST-treated and control animals. These results raised the possibility that the major mechanism by which growth hormone altered lipolysis might involve the antilipolytic system of adipocytes. Adenosine was a likely candidate because it is an autocrine/paracrine factor that exerts an acute antilipolytic effect via the $G_i$ system. Indeed, chronic treatment with growth hormone decreases the antilipolytic effects of adenosine in adipose tissue (Lanna et al., 1995 and Houseknecht and Bauman, 1997).

**Effects of bST on carbohydrate metabolism**

Hepatic rates of gluconeogenesis are increased with growth hormone treatment of dairy cows as demonstrated by *in vivo* and *in vitro* studies (Knapp et al., 1992 and Pocius and Herbein, 1986). Mechanisms include a decreased ability of insulin to inhibit gluconeogenesis. Thus the reduction in hepatic response to insulin in bST-treated cows allows the liver to sustain an increased rate of gluconeogenesis that is critical to support the increase in the synthesis of milk components. When bST treatment is initiated, glucose turnover increases and glucose oxidation decreases (Bauman et al., 1988). In contrast, growth hormone treatment had no effect on liver glycogen concentration in lactating cattle in positive energy balance (Pocius and Herbein, 1986) although growth hormone treatment did induce a small decrease in cows in negative energy balance (Knapp et al., 1992). Liver glycogen reserves are to limit to sustain increased glucose output by the liver in lactating cows.

**Effects of bST on protein metabolism**

The effects of growth hormone on growth and protein metabolism depend on an interaction between growth hormone and somatomedins, which are polypeptide

growth factors (70 amino acids) secreted by the liver and other tissues in response to stimulation by growth hormone. Little is known about the effects of growth hormone on protein metabolism of domestic animals compared to lipid or carbohydrate metabolism. It is clear that growth hormone treatment increases muscle protein accretion in growing animals and milk protein synthesis in lactating cows. However, the precise mechanisms are not clear, and the extents to which the effects of growth hormone on protein metabolism are direct or mediated by insulin-like growth factor -1 (IGF-1) remain unclear.

**Effects of bST on mammary function**

Treatment with bST causes a dramatic increase in the uptake and utilization of nutrients for the synthesis of milk. However, it has proven to be difficult to document specific mechanisms. At the cellular level, the magnitude of the biochemical changes would likely be small, and mammary epithelial cells, which are actively secreting milk components, are difficult to maintain *in vitro* because of their high rates of metabolic activity (Etherton and Bauman, 1998). Nevertheless, the pattern of response to bST and the change in the shape of the lactation curve indicate that the bST effects involve both an increase in the rates of milk component synthesis per cell and improved maintenance of secretory cells.

Baldwin and Knapp (1993) demonstrated that bST-treated cows had increased protein synthetic capacity as indicated by an increase RNA per gland. Knight et al (1990) observed that the decline in mammary cell numbers that normally occurs during lactation was prevented in goat that received growth hormone for 22 wk. Kleinberg et al. (1990) reported that rat growth hormone was more potent than human prolactin (hPRL) in stimulating mammary development in hypophysectomized castrated male rats supplemented with17$\beta$-estradiol. In addition, local implantation of bovine or mouse growth hormone in the mammary gland stimulated end bud formation in female mice. The bST is also mammogenic in dairy cows. Sejrsen et al. (1986) found that

systemic administration of bST to growing heifers increased the proliferation of mammary growing tissues.

The mechanism by which growth hormone affects mammary gland function is still uncertain but appears to be indirect, involving the IGF system. Several lines of evidence indicate that exogenous somatotropin does not act directly on the mammary gland (Peel and Bauman, 1987). Bovine research has been focused on the association between bST and IGF-1 primarily. Implicating IGF-1 in bovine galactopoiesis includes observations of chronically elevated IGF-1 concentrations in blood and lactating mammary tissue during periods of bST administration (Glimm et al., 1988 and Prosser et al., 1989). Administration of bST to lactating cows causes an increase in concentration of IGF-1 in blood (Davis et al., 1987). Sharma et al. (1994) found that bST increased serum growth hormone of late lactation cows by more than two folds and increased serum IGF-1 concentration two folds above those of late lactation controls. $IGF_s$ have both acute metabolic and long-term growth promoting effects. $IGF_s$ probably act as local tissue growth factors rather than as circulating hormone.

The concept of local regulation of blood flow is well accepted for other tissues, but has received only minimal investigation in the mammary gland. The IGF might also be locally produced factors that could regulate MBF; IGF-1 mRNA has been detected in mammary tissue of lactating cows (Glimm et al., 1992) and IGF-1 immunoreactivity has been detected by indirect immunofluorescence in blood vessels within lactating bovine mammary tissue (Glimm et al., 1988). Its origin appears to be in the systemic circulation but increased concentrations of radiolabelled IGF-1 in the local environment of individual mammary glands have been show to be reflected in an increased concentration in milk from that gland (Prosser et al., 1991a). In addition, increased concentrations of IGF-1 in milk appear to correlate with increased levels in mammary secretory tissue (Prosser et al., 1991b).

Most IGF-1 circulates bound to binding protein (BP; 95%), which exist in numerous molecular forms and are produced from a variety of tissues (McGuire et al., 1992 and Prosser et al., 1989). Two dominant forms of IGFBP exist in most species.

One form is dependent on growth hormone for its secretion from the liver (Mr of 150000 when complexes with IGF-1) whereas the other form is growth hormone-independent (Mr of 50000 when complexes with IGF-1). The growth hormone-dependent BP at binds most liver-produced IGF-1 or near the time of secretion but the BP status of IGF-1 acting in an autocrine or paracrine fashion is not well defined and may be tissue-specific. Considering the complexity of normal regulation of mammary cell physiology, it is probable that the growth hormone does not act alone during galactopoiesis. Rather, growth hormone may also induce regulatory molecules, which direct and maintain lactation (Burton et al., 1994).

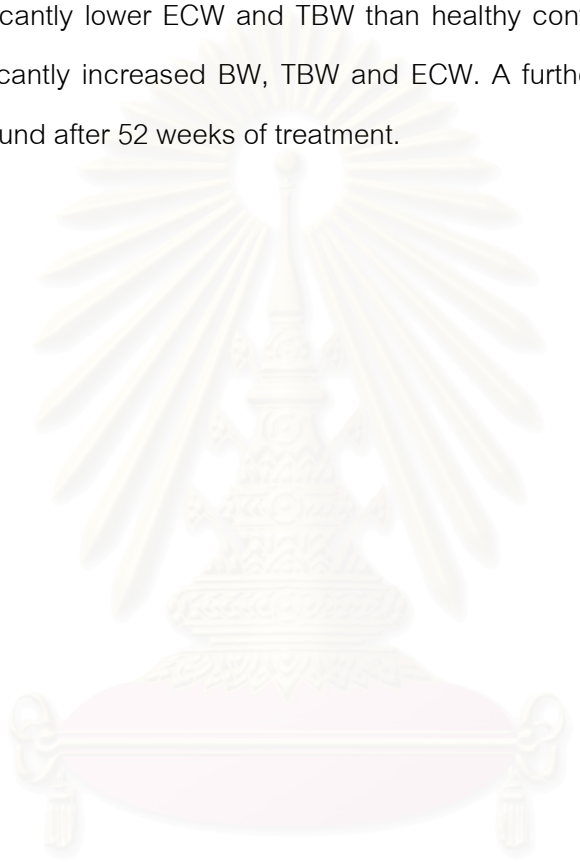
**Growth hormone and body fluids regulation**

Body fluids are divided into intra-cellular fluid and extra-cellular fluid compartments. Intra-cellular fluid is the largest compartment, accounting for about two-thirds of the water in the body. The extra-cellular fluid comprises water around cells and connective tissue, water in plasma and trans-cellular water or water in the gastrointestinal (GI) tract. GI water accounts for 15-35% of body weight. The late lactating cows had GI water about 10-11% lower than early lactation (15% of BW) (Woodford et al., 1984).

Loss of water from the body occurs through milk production, urine excretion, fecal excretion, sweat and vapor loss from the lung. Holter and Urban (1992) found that water losses through milk of cows producing 33 kg/d were about 26-34% of total water intake (feed plus free water consumed).

It has been reported that injection with bST significantly increased body water of animals due to lower body lipids (Chiliard et al., 1991). The study in human, several studies have recently shown that growth hormone deficiency (GHD) in adults is associated with reduction in total body water (TBW) and extra-cellular water (ECW). Suggestion a low TBW could be explained by a lower ECW compartment

(Binnerts et al., 1992). Several other studies directly measured ECW, but not TBW, with variable reports of low ECW, a proportional decrease in ECW corresponding to a decrease in fat-free soft tissue mass (FFSTM). In GHD adults, GH therapy appears to increase fat-free mass (FFM) and decrease fat mass (FM), thereby improving body composition. A study on the effects of GH replacement therapy for 4 and 52 weeks on body water distribution by Janssen and co-worker (1997) showed that patients with GHD had significantly lower ECW and TBW than healthy controls. Four weeks of GH treatment significantly increased BW, TBW and ECW. A further increase in TBW, but not ECW, was found after 52 weeks of treatment.



# CHAPTER III

# MATERIALS AND METHODS

## Experimental animals

Ten, multiparous, non-pregnant crossbred Saanen goats (49.21± 10.70 kg) in late lactation (24 weeks postpartum) were free from obvious abnormalities of the mammary gland, brucellosis, paratuberculosis and tuberculosis. All animals were housed in individual small pens type sheds. Mangers were separated to allow feed and water intake measurement. They were fed with chopped grass *ad libitum* and concentrate mixture (lactating goat formula), related to milk production and water was available at all times. The minimum and maximum temperature in the shed was 25 ± 1ºC and 30 ± 2 ºC respectively, and the relative humidity was 52 ± 11 %.

## Feeding and milking

Animals were fed twice daily at 0700 and 1600 h. Daily feed refusals were weighed and feeding was adjusted to allow 5% refusals and weekly samples of diet were taken and kept frozen at -20 ºC for later chemical analysis. Samples were dried to a constant weight in a forced - air oven at 50 ºC, and analyzed for N by the Kjeldahl method. The ADF, NDF, and lignin were also determined. Absolute DM was obtained by drying in a vacuum oven at 100 ºC. The chemical composition of feeds is presented in **Table 1**. Regarding milking process, animals were milked in their pens once daily at 0700 h by hand milking and recorded milk weights.

**Table 1 Chemical composition of feed components (% on dry matter basis).**

| Particulars | Chopped grass | Concentrate |
|---|---|---|
| Dry matter | 68.0 | 90.0 |
| Crude protein | 14.8 | 19.2 |
| Acid detergent fibre | 17.8 | 22.5 |
| Neutral detergent fibre | 33.0 | 29.3 |

## Experimental procedures

Animals were divided equally into control and experimental groups. Three consecutive periods of experiments were carried out in each group, consisting of the pretreatment period (24 weeks postpartum), 1st (25-26 weeks postpartum) and 2nd (27-28 weeks postpartum) treatment periods. In the treatment periods, animals in the experimental group were injected subcutaneously at post-scapular region with 250 mg recombinant bovine somatotropin (rbST), suspended in 396 mg sesame oil for prolonged-release action (POSILAC, Monsanto, USA), two times at 25 and 27 weeks postpartum while animals in the control group were injected subcutaneously at post-scapular region with 396 mg sterile sesame oil without rbST as placebo. In each period, measurements of plasma volume, extra-cellular fluid, and total body water were carried out and milk samples were collected to determine milk composition. After that, the body weight of animals was measured.

## Experimental protocol

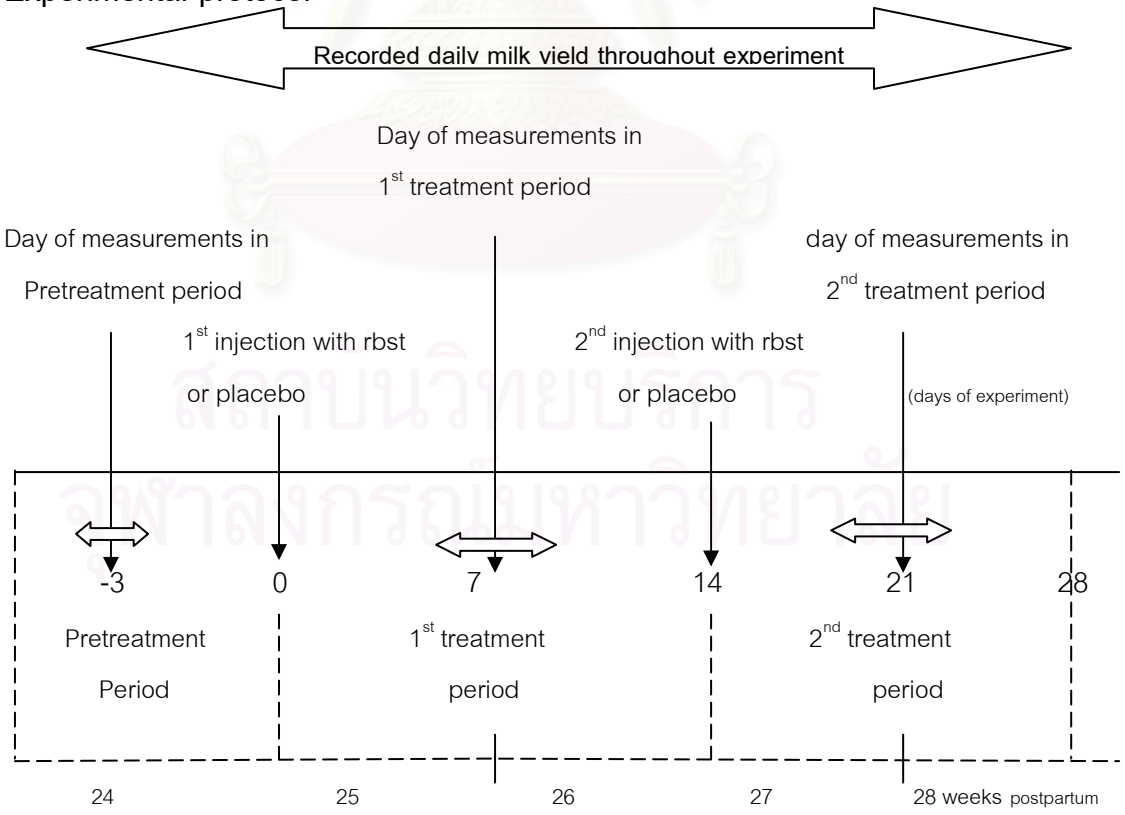



**Figure1: The experimental protocol of this experiment**

**Figure 1** shows the experimental protocol, which was performed in 28 days, and milk weights were recorded at each milking throughout the experiment. During the pretreatment period, feed and water intake were measured for 7 days before treatment. At the days of measurement in this period, milk sample about 30 ml were preserved with 0.1 ml of formaldehyde (40% v/v) and stored at 4 ºC until analysis and heparinized blood samples from both arterial blood and milk vein were kept in crushed ice. Blood samples were centrifuged at 3,000 rpm for 10 min, divided into 10 aliquots and stored at -20 ºC until analysis. At day 0, all animals were 1$^{st}$ injected with either rbST or placebo in experimental animals or control animals, respectively. Seven days later at day 7, the measurement of 1$^{st}$ treatment period was performed like the pretreatment period. For 14 days after 1$^{st}$ injection, the 2$^{nd}$ injection with rbST or placebo was done and day 21, the measurement for mammary function and body fluid were done.

## Determinations of plasma volume (PV), extra-cellular fluid (ECF) and total body water (TBW)

In each period of an experiment; PV, ECF and TBW were measured by dye dilution technique using of Evans blue dye (T-1824) (Merck, Darmstadt, Germany), sodium thiocyanate (NaSCN) and antipyrine, respectively. A preinjected venous blood sample approximately 5 ml was drawn into a heparinized tube, and then, 3 ml sterile 0.5% T-1824 in normal saline, 5 ml sterile 10% NaSCN solution and 5 ml sterile 10% antipyrine solution were given into jugular vein catheter. Serial heparinized venous blood samples were obtained at 15, 25, 35 and 45 min after dye injection. The dilution of dye at time 0 was determined by using semilogarithmic concentration on time extrapolation. Blood volume (BV) was calculated from the PV and packed cell volume (PCV) from the equation, shown below

$$BV\ (l) = \frac{PV}{1\text{-}PCV}$$

**Intra-cellular fluid (ICF) was calculated by subtracting ECF from TBW.**

## Determinations of plasma osmolality and Na+, K+, $Cl^-$ in plasma

Plasma samples in each period of an experiment were collected to measure plasma osmolality determined with the freezing point depression method by using osmometer (model 3D3, Advanced Instrument, Massachusetts, USA). The concentration of Na+, K+ and $Cl^-$ in plasma were determined by flame photometer (410C, Corning, England) and chloride analyzer (925, Corning, England), respectively.

### Determinations of plasma metabolites

Plasma samples from milk vein and ear artery in each period of experiment were used to determine plasma metabolites (acetate, ß-hydroxybutyrate, glucose and triglycerides). Both arterial and venous plasma acetate concentrations were assayed by enzymatic method using principle of converted acetate in the presence of the enzyme acetyl-CoA synthetase (ACS) with adenosine-5-triphosphate (ATP) and coenzyme A (CoA) to acetyl-CoA . The determination is based on the formation of NADH measured by the increase in light absorbance at 340 nm (Boehringger Mannheim).

Plasma ß-hydroxybutyrate concentrations were assayed by colorimetric method using enzymatic reaction in the presence of the enzyme ß-hydroxybutyrate dehydrogenase is oxidized by nicotinamide-adenine dinucleotide (NAD) to acetoacetate and measured at its maximum in the visible range at 492 nm (Boehringger Mannheim).

The enzymatic colorimetric test for glucose method without deproteinisation (GLUCOSE liquicolor, Wiesbaden, Germany) was used to determine arterial and venous plasma glucose concentrations. The glucose was determined after enzymatic oxidation in the presence of glucose oxidase. The formed hydrogen peroxide reacts under catalysis of peroxidase with phenol and 4-aminophenazone to a red-violet quinoneimine dye as indicator and measured at wavelength 500 nm.

The enzymatic colorimetric test for triglycerides (TRIGLYCERIDES liquicolor mono, Wiesbaden, Germany), which is enzymatic colorimetric test were used in this study. Plasma triglycerides were determined after enzymatic hydrolysis with lipases. Indicator was quinoneimine formed from hydrogen peroxide 4-aminoantipyrine and 4-chlorophenol under the catalytic influence of peroxidase and measured at wavelength 500 nm.

## Determinations of the mammary extraction ratio

The mammary extraction ratio was calculated from the mammary Arterio-Venous concentration difference as "A-V"(mmol/l) divided by arterial concentration and using the equation as following:

$$\text{Mammary extraction ratio} = [(A-V)/A] \times 100$$

A = arterial plasma metabolites concentration

V = venous plasma metabolites concentration

## Analysis of milk samples

Milk samples in each period were warmed in water bath at 37 ºC for 15 min and mixed to be homogenous milk.

## Determinations of milk composition and milk osmolality

Milk fat, protein and lactose were determined by Milkoscan ( 310M, Denmark). The milk osmolality was determined by osmometer using the freezing point depression technique (model 3D3, advanced instrument, Massachusetts, USA)

## Determinations of milk Na+, K+ and $Cl^-$ concentration

Pipet the 1 ml. of milk sample in each period and add 0.5 ml of 3% TCA into the separately reacting tube mixed together and centrifuged at 10,000 rpm for 10 minutes. Transferred the 50 µl of aqueous milk into the test tube mixed well with 10 ml of the diluents and determined the Na+ and K+ content by the flame photometer (410C, Corning, England). Milk $Cl^-$ concentration was determined by chloride analyzer (925, Corning, England),

## Statistical analysis

All data were calculated as the mean $\pm$ SD, the statistical significant differences was evaluated using the paired t-test for the difference between periods in the same group and using the unpaired t-test for the difference between groups.

# CHAPTER IV

# RESULTS

## Milk yield and its composition (Figure2, Table 2)

Milk yield of the control animals and rbST treated animals for the entire experimental period is shown in **Figure 2**. Milk yield in the control animals injected with sesame oil 396 mg without rbST as a placebo started to decline at day 3 and decreased significantly ($P<0.05$) at week 2 and 3 of experimental periods. Milk yield in the rbST treated group increased stepwise throughout periods of study. It increased to the maximum value in each period on day 7 and day 21 after rbST injection. It increased significantly ($P<0.05$) on day 6 to day 9 and day 17 after treatment.

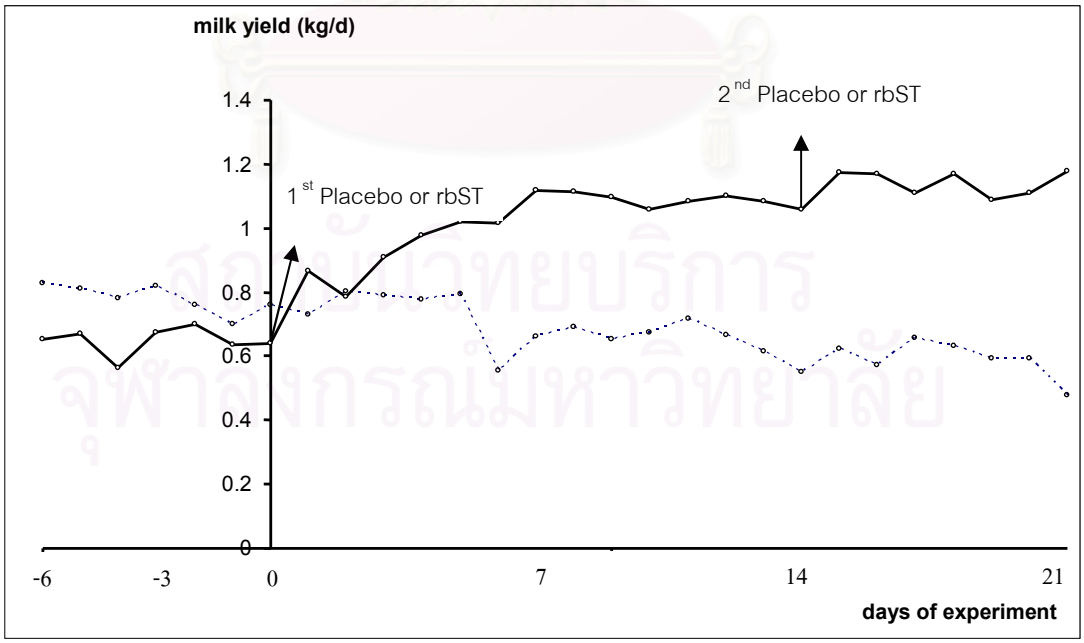



Figure 2 Milk yield in the control animals (----○----) and rbST treated animals (—○—)

Milk yield in the control animals decreased significantly ($P<0.01$) both at day 7 after 1st injection from 0.47 ± 0.16 kg/d to 0.30 ± 0.18 kg/d and at day 21 after 2nd injection as compared with the pretreatment period (0.71 ± 0.17 kg/d). In contrast to the control animals, milk yield of the animals given rbST increased significantly ($P<0.05$) from 0.68 ± 0.34 kg/d (pretreatment period) to 1.28 ± 0.68 kg/d at day 7 after 1st rbST injection and 1.32 ± 0.63 kg/d at day 21 after 2nd rbST injection.

There were no significant ($P>0.05$) effects of both 1st and 2nd injection on milk composition (milk fat, protein and lactose percentage) of two groups. Milk lactose percentage increased from 4.11 ± 0.66 gm% in the pretreatment period to 4.33± 0.69 gm% after 2nd rbST injection.

Milk $K^+$ and $Cl^-$ content were no significantly different between either periods or between groups. The contents of $Na^+$ in milk and the $Na^+/K^+$ ratio of rbST treated animals were decreased significantly ($P<0.05$) in the 2nd study period with respect to the pretreated period.

Milk osmolality were no significantly different between the control animals and the rbST treated animals in either the similar period or between pretreatment and the 1st, 2nd treatment periods in the same group.

Table 2: Milk yield and its compositions in the control and the rbST treated animals

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| **Milk yield (kg/d)** | | | |
| control group | 0.71 ± 0.17 | 0.47 ± 0.16 ** | 0.39 ± 0.18 ** |
| experimental group | 0.68 ± 0.34 | 1.28 ± 0.68 * | 1.32 ± 0.63 * |
| Control vs. experimental group | NS | P<0.05 | P<0.05 |
| **Milk composition** | | | |
| ■ Fat (gm %) | | | |
| control group | 3.94 ± 1.25 | 4.04 ± 1.61 | 4.88 ± 1.55 |
| experimental group | 4.92 ± 1.22 | 4.48 ± 0.84 | 4.55 ± 1.34 |
| Control vs. experimental group | NS | NS | NS |
| ■ Lactose (gm %) | | | |
| control group | 4.45 ± 0.20 | 4.35 ± 0.19 | 4.03 ± 0.56 |
| experimental group | 4.11 ± 0.66 | 4.11 ± 0.86 | 4.33 ± 0.69 |
| Control vs. experimental group | NS | NS | NS |
| ■ Protein (gm %) | | | |
| control group | 3.76 ± 0.40 | 3.81 ± 0.32 | 3.97 ± 0.42 |
| experimental group | 4.24 ± 1.49 | 4.43 ± 1.91 | 4.19 ± 1.20 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

Table 2 (cont.): Milk yield and its compositions in the control and the rbST treated animals

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| **Milk composition** | | | |
| ■ Na+ (mmol/l) | | | |
| control group | 29.46 ± 6.77 | 29.66 ± 8.03 | 29.92 ± 7.03 |
| experimental group | 31.10 ± 8.33 | 26.70 ± 10.22 | 26.48 ± 6.54 * |
| Control vs. experimental group | NS | NS | NS |
| ■ K+ (mmol/l) | | | |
| control group | 76.60 ± 8.32 | 82.00 ± 8.15 | 78.20 ± 11.10 |
| experimental group | 77.00 ± 9.62 | 80.40 ± 6.58 | 75.20 ± 18.94 |
| Control vs. experimental group | NS | NS | NS |
| ■ $Cl^-$ (mmol/l) | | | |
| control group | 36.20 ± 5.31 | 40.40 ± 4.83 | 34.40 ± 2.70 |
| experimental group | 33.40 ± 4.56 | 34.00 ± 5.57 | 34.80 ± 7.46 |
| Control vs. experimental group | NS | NS | NS |
| ■ Na+/K+ ratio | | | |
| control group | 0.38 ± 0.10 | 0.36 ±0.14 | 0.38 ± 0.12 |
| experimental group | 0.40 ± 0.15 | 0.33 ± 0.16 | 0.36 ± 0.04* |
| Control vs. experimental group | NS | NS | NS |
| **Milk osmolality (mOsm/kg $H_2O$)** | | | |
| control group | 443.80 ± 89.31 | 382.00 ± 61.27 | 365.60 ± 50.45 |
| experimental group | 420.20 ± 80.80 | 401.41 ± 116.38 | 401.00 ± 67.35 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

**Dry matter intake, water intake and total dry matter intake / milk yield (Table 3)**

In this experiment, commercial concentrate (milking goat feed, C.P. 991-16) were fed related to individual milk yield. Dry matter intake (DMI) of concentrate were decreased significantly ($P<0.05$) in the control group. Total DMI as a percent BW were not significantly different between control and experimental group in all periods of experiment and between periods in the same group. No significant differences in water intake between periods and between groups were apparent but in the control animals tended to decrease of water intake (5.92 ± 2.37 to 5.47 ± 2.4 and 4.17 ± 2.4 kg/d) and the rbsT treated animals tended to increase (5.84 ± 3.12 up to 7.01± 2.97 and 7.16 ± 5.30 kg/d) from pretreatment period.

An evaluation of the dry matter intake and milk yield revealed that the mean ratios of total DMI to milk yield of goats given rbST (4.0 ± 1.0) were lower than those of control animals given placebo (11.2 ± 1.4) and significant ($P<0.05$). The mean ratios of total DMI to milk yield decreased significantly ($P<0.05$) in the second period of treatment when compared with pretreatment period in goats given rbST.

## Effects of rbST administration on mammary function:

**Concentration of arterial plasma acetate, arterio-venous concentration difference (A-V) and mammary extraction ratio (Table 4)**

The mean arterial plasma acetate concentration, A-V differences and mammary extraction ratio were not significantly different between control animals and rbST treated animals in all periods of experiment. There were no significant changes in all parameters of acetate in each group throughout period of study.

Table 3: Dry matter in take, water intake and total dry matter intake/milk yield in the placebo and rbST treated animals.

| | | Treatment | |
|---|---|---|---|
| | Pre-treatment | 1st injection | 2nd injection |
| **Dry matter intake (kg/d)** | | | |
| ■ Concentrate | | | |
| control group | 0.68 ± 0.16 | 0.45 ± 0.15 * | 0.28 ± 0.18 ** |
| experimental group | 0.64 ± 0.33 | 1.21 ± 0.65 * | 1.25 ± 0.60 * |
| Control vs. experimental group | NS | P<0.05 | P<0.05 |
| ■ Roughage | | | |
| control group | 3.77 ± 1.57 | 3.15 ± 1.24 | 3.65 ± 1.05 |
| experimental group | 3.49 ± 1.42 | 3.16 ± 1.56 | 3.53 ± 1.02 |
| Control vs. experimental group | NS | NS | NS |
| ■ Total DMI intake | | | |
| control group | 4.41 ± 1.80 | 3.59 ± 1.24 | 3.92 ± 1.16 |
| experimental group | 4.17 ± 1.37 | 4.37 ± 1.02 | 4.78 ± 1.60 |
| Control vs. experimental group | NS | NS | NS |
| ■ Total DMI intake (%BW) | | | |
| control group | 8.26 ± 2.64 | 6.87 ± 1.86 | 8.26 ± 5.06 |
| experimental group | 8.91 ± 5.23 | 9.30 ± 2.61 | 10.60 ± 4.99 |
| Control vs. experimental group | NS | NS | NS |
| **Water intake (kg/d)** | | | |
| control group | 5.92 ± 2.37 | 5.47 ± 2.4 | 4.17 ± 2.41 |
| experimental group | 5.84 ± 3.12 | 7.01 ± 2.97 | 7.16 ± 5.32 |
| Control vs. experimental group | NS | NS | NS |
| **DMI/Milk yield** | | | |
| control group | 6.17 ± 2.65 | 8.21 ± 3.35 | 11.23 ± 12.98 |
| experimental group | 6.07 ± 2.10 | 5.59 ± 5.38 | 3.99 ± 1.03 * |
| Control vs. experimental group | NS | NS | P<0.05 |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

Table 4: The concentration of arterial plasma acetate [Acetate (a)], A-V concentration difference, mammary extraction ratio in the control animals and animals treated with rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| **Acetate(a) (mmol/l)** | | | |
| control group | 0.33 ± 0.12 | 0.42 ± 0.25 | 0.44 ± 0.17 |
| experimental group | 0.32 ± 0.29 | 0.16 ± 0.06 | 0.21 ± 0.18 |
| Control vs. experimental group | NS | NS | NS |
| **A-V dif. (mmol/l)** | | | |
| control group | 0.24 ± 0.12 | 0.18 ± 0.12 | 0.21 ± 0.15 |
| experimental group | 0.28 ± 0.26 | 0.10 ± 0.07 | 0.16 ± 0.17 |
| Control vs. experimental group | NS | NS | NS |
| **Extraction ratio (%)** | | | |
| control group | 72 ± 23 | 57 ± 26 | 57 ± 39 |
| experimental group | 83 ± 13 | 63 ± 33 | 64 ± 25 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

**Concentration of arterial plasma ß-hydroxybutyrate (BHBA), arterio-venous concentration difference (A-V) and mammary extraction ratio (Table 5)**

There were no significantly difference in the mean arterial plasma BHBA, A-V difference and mammary extraction ratio between control and rbST treated animals during experiment when compared with pretreatment period in the same group. The 2nd rbST injection, arterial plasma BHBA (1.74 ± 0.49 mmol/l) and A-V difference (0.72± 0.53 mmol/l) of experimental group were higher than those of pretreatment period (1.37± 0.70 and 0.56 ± 0.49 mmol/l, respectively), and placebo group at the same time.

Table 5: The concentration of arterial plasma ß-hydroxybutyrate (BHBA a), A-V difference, mammary extraction ratio in the control animals and animals treated with rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| **BHBAa (mmol/l)** | | | |
| control group | 1.23 ± 0.33 | 1.05 ± 0.37 | 1.21 ± 0.41 |
| experimental group | 1.37 ± 0.70 | 1.34 ± 0.39 | 1.74 ± 0.49 |
| Control vs. experimental group | NS | NS | NS |
| **A-V dif. (mmol/l)** | | | |
| control group | 0.46 ± 0.21 | 0.23 ± 0.10 * | 0.47 ± 0.31 |
| experimental group | 0.56 ± 0.49 | 0.27 ± 0.17 | 0.72 ± 0.63 |
| Control vs. experimental group | NS | NS | NS |
| **Extraction ratio (%)** | | | |
| control group | 37 ± 15 | 21 ± 4 | 37 ± 21 |
| experimental group | 38 ± 27 | 19 ± 8 | 36 ± 25 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

**Concentration of arterial plasma triglyceride (TGa), arterio-venous concentration difference (A-V) and mammary extraction ratio (Table 6)**

There were no significantly difference in the concentration of arterial plasma triglyceride, A-V concentration differences and the mammary extraction ratio for either goats given rbST or the control animals throughout periods of studies. The percent changes for the declining of A-V difference and mammary extraction ratio of TG in the control animals were higher than rbST treated animals.

Table 6: The concentration of arterial plasma triglyceride [TG (a)], A-V concentration difference, mammary extraction ratio in the control animals and animals treated with rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| TG(a) (mmol/l) | | | |
| control group | 0.59 ± 0.04 | 0.55 ± 0.05 | 0.61 ± 0.07 |
| experimental group | 0.58 ± 0.06 | 0.54 ± 0.06 | 0.51 ± 0.08 |
| Control vs. experimental group | NS | NS | NS |
| A-V dif. (mmol/l) | | | |
| control group | 0.1 ± 0.05 | 0.04 ± 0.03 | 0.06 ± 0.06 |
| experimental group | 0.13 ± 0.1 | 0.09 ± 0.09 | 0.06±0.03 |
| Control vs. experimental group | NS | NS | NS |
| Extraction ratio (%) | | | |
| control group | 17 ± 9 | 8 ± 5 | 10 ± 11 |
| experimental group | 22 ± 15 | 16 ± 13 | 12 ± 4 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

**Concentrations of arterial plasma glucose (GLUa), arterio-venous concentration difference (A-V) and mammary extraction ratio (Table 7)**

The arterial plasma glucose concentrations, A-V difference and mammary extraction ratio showed no differences between the control and rbST treated animals. In comparison between periods of experiment, the concentration of arterial plasma glucose, plasma A-V difference and the mammary extraction ratio were not significantly different in both groups. The rbST treated animals showed tendency to increase in arterial plasma glucose level after injected 2$^{nd}$ rbST by average 11% while GLUa of the control animals given sesame oil slightly decreased by approximately 1.7%.

Table 7: The concentration of arterial plasma glucose [GLU (a)], A-V concentration difference, mammary extraction ratioin in the control animals and animals treated with rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| GLU(a) (mmol/l) | | | |
| control group | 3.90 ± 0.86 | 4.06 ± 0.83 | 3.83 ± 0.43 |
| experimental group | 4.58 ± 1.43 | 4.83 ± 1.3 | 5.1 ± 3.34 |
| Control vs. experimental group | NS | NS | NS |
| A-V dif. (mmol/l) | | | |
| control group | 1.01 ± 0.60 | 0.49 ± 0.35 | 0.74 ± 0.48 |
| experimental group | 1.47 ± 1.17 | 0.85 ± 0.33 | 1.23 ± 0.63 |
| Control vs. experimental group | NS | NS | NS |
| Extraction ratio (%) | | | |
| control group | 24 ± 11 | 11 ± 7 | 26 ± 18 |
| experimental group | 31 ± 20 | 18 ± 6 | 27 ± 11 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

## Plasma volume, blood volume and packed cell volume (Table 8)

Plasma volume (PV) in the rbST treated animals increased significantly (P<0.01) from the pretreatment period, from 2.53 ± 0.31L to 4.05 ± 0.66L in the 2$^{nd}$ study period. In contrast to the rbST treated animals, PV of the control animals decreased stepwise from 2.86 ± 0.68L at pretreatment period to 2.52 ± 0.67L and 2.17 ± 0.63L at 1$^{st}$ and 2$^{nd}$ injections of placebo, respectively. After 2$^{nd}$ of injection for 7 days, there were significantly difference (P<0.01) in the plasma volume of placebo compared to rbST treated animals.

Blood volume (BV) also increased significantly ($P<0.05$) in the rbST treated animals from 3.53± 0.44L before injection to 5.28± 0.76L after 2nd rbST administration for seven days. There were significantly ($P<0.001$) different between control and rbST treated animals in the 2nd study period. Body weight (BW) in two groups of animals did not change. PV and BV as percentage BW in the animals given rbST significantly ($P<0.001$) increased from 5.43± 1.60% to 8.52± 0.86% after 2nd rbST injection. There were significantly different of the blood volume between the control and rbST treated animals. Pack cell volume (PCV) of the rbST treated animals was increased significantly ($P<0.05$) after 1st rbST injection but no significant change in the control animals was apparent. There were no statistically different of PCV between placebo and rbST treated animals.

**Total body water (TBW), extra-cellular water (ECW), intra-cellular water (ICW) and the ratio of ECW/TBW (Table 9)**

Total body water in the rbST treated animals at 2nd study period was highly significant ($P<0.05$) from pretreatment period. In contrast to the rbST treated animals, TBW of the control animals decreased stepwise from 26.5± 8.79L to 20.11± 4.00L. It was statistically different ($P<0.01$) between the animals given placebo and rbST. When TBW was calculated as percentage of BW, the rbST treated animals was significantly increased in the 2nd study period. In contrast to the rbST treated animals, TBW (%BW) in the 2nd study period of control animals was significantly decreased. There were statistically different between control and rbST treated animals in the 1st and 2nd study period.

The animals given rbST increased in ECW and significant changed ($P<0.05$) in the 2nd rbST injection. In contrast to rbST treated animals, the animals without rbST decreased in ECW coincided with milk production. Intra-cellular water was calculated by subtracting ECW from TBW. Both ICW and the ratio of ECW/TBW were not statistically different between treatments and between groups.

Table 8: Plasma volume (PV), blood volume (BV) and packed cell volume (PCV) in the goats given rbST and without rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| **PV (l)** | | | |
| control group | 2.86 ± 0.68 | 2.51 ± 0.67 | 2.17 ± 0.63 |
| experimental group | 2.53 ± 0.31 | 3.27 ± 1.10 | 4.05 ± 0.66 ** |
| Control vs. experimental group | NS | NS | P<0.01 |
| **PV (%BW)** | | | |
| control group | 5.42 ± 0.96 | 5.08 ± 1.82 | 4.74 ± 1.34 |
| experimental group | 5.43 ± 1.60 | 6.19 ± 1.10 | 8.52 ± 0.88 ** |
| Control vs. experimental group | NS | NS | P<0.001 |
| **BV (l)** | | | |
| control group | 3.68 ± 0.85 | 3.18 ± 0.67 | 2.74 ± 0.82 |
| experimental group | 3.53 ± 0.44 | 4.27 ± 1.69 | 5.28 ± 0.76 * |
| Control vs. experimental group | NS | NS | P<0.001 |
| **BV (%BW)** | | | |
| control group | 6.96 ± 0.89 | 6.40 ± 2.05 | 5.97 ± 1.70 |
| experimental group | 7.46 ± 2.04 | 8.05 ± 1.6 | 11.12 ± 1.10* |
| Control vs. experimental group | NS | NS | P<0.001 |
| **PCV (%)** | | | |
| control group | 21.40 ± 4.08 | 22.90 ± 5.25 | 22.20 ± 3.56 |
| experimental group | 21.20 ± 3.49 | 30.30 ± 7.71 * | 23.40 ± 3.91 |
| Control vs. experimental group | NS | NS | NS |
| **Body weight (kg)** | | | |
| control group | 52.10 ± 13.20 | 52.72 ± 11.92 | 53.32 ± 13.23 |
| experimental group | 46.32 ± 8.19 | 48.08 ± 7.22 | 47.96 ± 8.89 |
| Control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

Table 9: Extra-cellular water (ECW), total body water (TBW), intra-cellular water (ICW) and the ratio of ECW/TBW in the goats given placebo and rbST.

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| ECW (l) | | | |
| control group | 9.88 ± 3.00 | 8.74 ± 1.66 | 7.86 ± 1.07 |
| experimental group | 9.09 ± 1.14 | 10.20 ± 2.96 | 11.38 ± 1.54 * |
| Control vs. experimental group | NS | NS | P<0.01 |
| ECW (%BW) | | | |
| control group | 18.84 ± 5.02 | 17.68 ± 5.57 | 16.49 ± 2.61 |
| experimental group | 19.42 ± 4.30 | 19.99 ± 2.04 | 23.95 ± 1.79 |
| Control vs. experimental group | NS | NS | P<0.001 |
| TBW (l) | | | |
| control group | 26.50 ± 8.79 | 21.30 ± 2.80 | 20.11 ± 4.00 |
| experimental group | 24.74 ± 5.70 | 27.13 ± 6.61 | 33.39 ± 6.10 * |
| Control vs. experimental group | NS | NS | P<0.01 |
| TBW (%BW) | | | |
| control group | 50.96 ± 7.19 | 42.50 ± 10.93 | 39.54 ± 6.45 ** |
| experimental group | 53.41 ± 7.11 | 56.48 ± 7.20 | 70.09 ± 8.66 * |
| Control vs. experimental group | NS | NS | P<0.001 |
| ICW (l) | | | |
| control group | 16.45 ± 4.93 | 12.56 ± 4.40 | 12.25 ± 3.43 |
| experimental group | 15.81 ± 8.80 | 17.93 ± 5.15 | 22.01 ± 4.69 |
| Control vs. experimental group | NS | NS | P<0.01 |
| ICW (%BW) | | | |
| control group | 32.74 ± 6.36 | 24.78 ± 9.95 | 19.89 ± 7.78 |
| experimental group | 35.44 ± 13.09 | 34.67 ± 8.29 | 46.17 ± 7.28 |
| Control vs. experimental group | NS | NS | P<0.001 |
| ECW/TBW ratio | | | |
| control group | 0.40 ± 0.10 | 0.40 ± 0.13 | 0.38 ± 0.07 |
| experimental group | 0.37 ± 0.11 | 0.38 ± 0.09 | 0.36 ± 0.03 |
| Control vs. experimental group | NS | NS | P<0.05 |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

## Concentration of plasma Na+, K+, $Cl^-$ and plasma osmolality

The data reported in **Table 10** show that the progress of lactation in late lactating crossbred Saanen goats without rbST administration had significant decrease in plasma osmolality. There were no significantly different of plasma osmolality between control and rbST treated animals. The mean concentration of plasma Na+ in the control animals decreased significantly during lactation from 152.6± 6.02 to 144.80± 9.65 and 140.60± 6.43 mmol/l, but in the rbST treated animals only significant changed in the $1^{st}$ study period compared with initial values of experiment. There were no significantly different of plasma Na+ concentration between control and rbST treated animals. Plasma K+ and $Cl^-$ did not differ significantly between periods of study and between groups of animals.

Table 10: Plasma osmolality, concentration of plasma Na+, K+, $Cl^-$ in the control and the animals treated with rbST

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| Plasma osmolality (mOsm/kg$H_2O$) | | | |
| control group | 304.20 ± 5.07 | 295.40 ± 5.50 ** | 295.20 ± 7.46 * |
| experimental group | 298.40 ± 4.16 | 295.00 ± 7.87 | 296.00 ± 8.66 |
| control vs. experimental group | NS | NS | NS |
| ■ Na+ (mmol/l) | | | |
| control group | 152.60 ± 6.02 | 144.80 ± 9.65 * | 140.60 ± 6.43 ** |
| experimental group | 149.40 ± 5.03 | 146.20 ± 3.77 * | 146.00 ± 6.04 |
| control vs. experimental group | NS | NS | NS |
| ■ K+ (mmol/l) | | | |
| control group | 4.86 ± 0.48 | 4.88 ± 0.44 | 4.84 ± 0.49 |
| experimental group | 4.72 ± 0.43 | 4.96 ± 0.32 | 4.90 ± 0.35 |
| control vs. experimental group | NS | NS | NS |
| ■ $Cl^-$ (mmol/l) | | | |
| control group | 111.80 ± 1.48 | 109.60 ± 1.95 | 110.00 ± 2.65 |
| experimental group | 107.20 ± 2.49 | 109.80 ± 2.86 | 111.00 ± 2.10 |
| control vs. experimental group | NS | NS | NS |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

## Effects of rbST administration on the plasma concentration of IGF-1 [IGF-1(a)]

**Table 11** shows the mean values of the plasma IGF-1 concentration of the late lactating crossbred Saanen goats in both control and rbST treated animals. In the control animals, there were no significant different of plasma IGF-1 concentration during the periods of experiment. In rbST treated animals, the plasma concentration of IGF-1 after rbST injection were higher than pretreatment period and significantly ($P<0.05$) increase after the 2nd rbST administration. The plasma IGF-1 concentration was significantly ($P<0.05$) increased in animals given rbST when compared with those of control animals at the 2nd treatment period.

**Table 11 the concentration of arterial plasma IGF-1 in the control animals and animals treated with rbST**

| | Pre-treatment | Treatment | |
|---|---|---|---|
| | | 1st injection | 2nd injection |
| IGF-1(a) (µg/ml) | | | |
| control group | 225.50 ± 105.04 | 210.00 ± 45.25 | 202.00 ± 8.49 |
| experimental group | 262.50 ± 135.60 | 844.00 ± 444.06 | 774.00 ± 121.62 * |
| Control vs. experimental group | NS | NS | P<0.05 |

Values are means ± SD.

P-value by paired t-test with respect to the pretreated period in the same group (*P<0.05, **P<0.01)

P-value by unpaired t-test with respect to the similar period of experiment between control and the animals treated with rbST (P<0.05) and NS = no significant

# CHAPTER V
# DISCUSSION

In the late lactation (24 weeks postpartum), milk yield was significantly increased (~37%) in crossbred Saanen goats treated with rbST especially day7 after exogenous hormone administration. This is consistent with the findings of previous studies on late lactating goats (Baldi et al., 2002; Gallo et al., 1997) and dairy ewes (Chiofalo et al., 1999), which a galactopoietic effect of bST during the declining phase of lactation was reported. The maximum effect on day 7 also reported in rbST treated cows during late lactation (Fullerton, 1989). As lactation advanced, the reduction in milk yield was smaller in the rbST treated animals than in the control goats. Milk yield response to the second injection was greater (+77% compared with controls) than to the first (+58%) injection; thus rbST affects the shape of the lactation curve. This response was an effect of bST treatment, which improved lactation persistency (Gallo et al., 1997).

Milk compositions in rbST treated goats including fat, protein and lactose concentrations did not significant differ from the control animals or from the pretreatment period. These results are similar to the results of Mepham and co-worker (1984). However, Disenhaus et al. (1995) reported that a reduction in milk protein was apparent in dairy goats treated with bST. Several factors may involve including stage of lactation, energy balance, nutrition management and a dilution effect of increased milk yield (Baldi, 1999).

In the present experiment, rbST treated goats had a significantly lower Na concentration in milk and also significantly lower Na+/K+ ratio than milk in the pre-treated period. During late lactation, the involution of the mammary gland, tissue permeability is markedly increased and breakdown of junctions between adjacent epithelial cells would be a cause of these changes (Baldi et al., 2002; Nguyen and Neville, 1998). The results do not exclude the possibility that rbST is involved in maintenance of the tissue integrity and other intra-cellular processes in the mammary

gland. In other studies, Stelwagen et al. (1999) indicated that an alteration in the Na+ to K+ ratio would involve a reduction in milk secretion. Therefore, the decline in milk secretion with leaky of tight junction, at least in part, can be explained by an increase in the Na+/K+ ratio. In the control animals the slightly lower albeit but not significantly lower of milk lactose percentage following the advanced of lactation. In contrast to the rbST group, the control animals showed an elevation in the Na+ to K+ ratio which also affected lactose synthesis adversely (Stelwagen et al., 1999). Perhaps, as a result of lower protein synthesis following a higher Na+/K+ ratio (Falconer et al., 1978) that enzymes involved in lactose synthesis may be limiting. Because lactose is the major osmol in milk and thus, determines milk volume. A decrease in milk secretion related to tight junction (TJ) may result from a decrease in lactose synthesis brought about by an interaction between TJ and the cytoskeleton (Stelwagen et al., 1997) or be a direct effect of an elevated Na+ to K+ ratio or both.

It is recognized that an increase in milk production is closed correlated to dry matter intake and dry matter intake to water consumption (Murphy, 1992). In the present study, there were no significant change of DMI, water intake and body weight throughout experimental period. Similar responses in milk yield by lactating dairy cows and goats without corresponding increasing in DMI have been reported by Bareille et al. (1997) and Davis et al. (1999). However, the effect of rbST administration significantly influenced the milk production efficiency. The ratio of DMI to milk yield in rbST treated goats was lower than pre-treated period and decreased significantly after 2$^{nd}$ rbST administration. This result was similar to the results of Maksiri's experiment (2003) in early lactating dairy cows treated with rbST. It indicated that the energy output in milk and for maintenance was greater than energy consumed in the food for the rbST treated animals. There was no report about water intake in dairy goat related to milk production combined with bST treatment. Although, daily mean water intake in the lactating black Moroccan goats was greater than non-lactating (Hossaini et al., 1994).

It is known that glucose is utilized primarily for lactose and glycerol synthesis and generation of reducing equivalents. Because little glucose is stored, the increased

requirement is met partly through increased uptake, but primarily through gluconeogenesis from propionate, amino acids, lactate and glycerol in the liver. There was an increase in glucose production independent of feed intake, which must involve gluconeogenesis from body reserves of protein (Collier et al., 1984). In the present study, total dry matter intake (%BW) and body weight tended to increase (no significant) throughout experimental period corresponding with increase of milk lactose percentage in rbST treated goats, which was different from the control animals. Increasing of arterial plasma glucose concentration in rbST treated goats was consistent with previous reports on dairy goats (Faulkner, 1999) and dairy cattle (McDowell et al., 1987). However, glucose uptake in the lactating mammary gland of the goat must therefore be carried out by an insulin-independent carrier, possible GLUT1 and glucose supply is not a limiting factor for uptake under in vivo condition. Thus, mammary synthetic capacity also involves a capacity of mammary glucose uptake, which may be influenced by variations in glucose carrier number, as well as mammary metabolic activity (intra-cellular glucose concentration). In the present results, there were no significant changes in mammary arteriovenous concentration differences of glucose that was similar to the daily injection of growth hormone in lactating goats (Mepham et al., 1984). Mammary extraction of glucose changed markedly during lactation advanced, following the overall changes in milk yield. In contrast to the control animals, bST stimulated milk yield, despite less efficient glucose extraction (Nielsen et al., 2001). Similar responses were found in this experiment that was no significant change in mammary extraction ratio of glucose in rbST goats.

Long-chain fatty acids and two-carbon acetate provide the majority of energy for milk synthesis and mammary gland oxidation. In ruminant, the carbon sources used for fatty acid synthesis are acetate and ß-hydroxybutyrate (BHBA). Acetate seems to be an important carbon source for medium chain length of fatty acid. In this experiment, the arterial plasma concentration, A-V differences and mammary extraction ratio of acetate were lower than pretreatment period and there were no significantly different between control and rbST treated animals which was similar to Fleet et al. (1988) who showed a decrease in the level of plasma acetate. However, it does differ from the previous report

on mid-lactating cows, possibly that growth hormone exerted metabolic effects which differed with stage of lactation (McDowell et al., 1987).

The other volatile fatty acids in the form of ß-hydroxybutyrate (BHBA) arise mainly from butyrate in rumen. Seven days after 2nd rbST administration, arterial plasma concentrations of BHBA and A-V differences tended to increase, but no effects of rbST on mammary extraction ratio of BHBA. These results were similar to the results in short-term effect of exogenous growth hormone in mid lactating ewes (McDowell et al., 1988) and mid lactating dairy cows (McDowell et al., 1987). However, in large ruminant, no change was measured for plasma non-esterified fatty acids (NEFA) at peak lactation in cows. The reduction in plasma BHBA concentration observed as cows progressed from early to mid lactation. The rise in the BHBA plasma arterial concentrations in early lactation would be likely the result of an increase in ketogenesis from NEFA. The correlation between the NEFA and BHBA plasma arterial concentrations have been noted (Miller et al., 1991).

Concentration of arterial plasma triglycerides (TGa) associated with very low-density lipoprotein decreased significantly in mid lactating ewes after daily injected with 0.1 mg/kg.BW of bGH (McDowell et al., 1988). In this experiment, the TGa in goats given rbST was similar to rbST treated ewes but there was no significantly. In the present study, A-V differences and extraction ratio tended to decrease but its values were still higher than the placebo group. McDowell and co-worker (1987) reported that the extraction of TG by the mammary gland varied from 30 to 40%, and Sechen et al. (1989) demonstrated that during lactation, measurement of A-V differences of FFA across the mammary gland together with mammary blood flow did not provide a quantitative estimation of their total uptake by mammary tissue, since there was release of FFA into venous blood due to triglycerides hydrolysis during the uptake of plasma TG.

Several studies have recently shown that growth hormone deficiency (GHD) in human is associated with a reduction in total body water (TBW) and extra-cellular water (ECW) (Janssen et al., 1997; Hoffman et al., 1995). GH therapy in short time increased

extra-cellular volume, whereas substitution for a longer time was required to normalize both extra and plasma volume (PV) (Moller et al., 1996). Few data are available in goats related to milk yield. This research found that the rbST treated goats had significantly increased in PV, ECW and TBW corresponding with increase in milk production. In contrast to rbST treated goats, animals received sesame oil without rbST decrease significantly of TBW, ECW, PV and milk production during lactation advanced. These results can compare to starved lactating goats that cardiac output, stroke volume, mammary blood flow, blood volume decreased markedly and hematocrit increased but plasma osmolality remain unchanged which coincided with a marked reduction of the rate of milk secretion (Chaiyabutr et al., 1980). Janssen and co-worker (1997) found a low ECW/TBW ratio in adults with growth hormone deficiency (GHD), which can be normalized by 0.6 IU/day rhGH treatment and changed mainly in ECW, but also in TBW, appeared to be unsatisfactory. The present study also found a lower ECW/TBW ratio than pretreatment period, but TBW also changed markedly, a high TBW of rbsT treated goats may relate to the adaptation of animals to the tropical environment. Thus, a higher water reserve in animals given rbST would not only provide a higher reservoir of soluble metabolites for biosynthesis of milk but was also useful in slowing down the elevation in body temperature during lactation in hot conditions (Chaiyabutr et al., 1997). A proportional decrease in ECF corresponded to a decrease in fat-free soft tissue mass (FFSTM). GH therapy appears to increase free-fat mass (FFM) and decreased fat mass (Janssen et al., 1997). An increased in both absolute TBW and ECW of rbST treated goats throughout this experiment might be resulted in part from a slightly increase in body weght, mainly might be changed in body composition. A higher proportion increase in body weight of rbST treated goats than those of control goats would consider to be the direct effect of somatotropin on the increased body cell mass and FFM. This may be attributed to an accumulation of body water, which this study presented that the plasma osmolality of rbST treated animals remained constant, but in the control animals was significant decreased during the course of lactation. The retention of water and sodium has been reported in acromegaly and following administration of human GH in adults (Biglieri et al., 1961) and children (Lampit et al., 1998). The effect of GH on the renal tubular reabsorption of sodium would be another

explanation of an induction in expansion of both TBW and ECW. Further evidence has shown that GH (or IGF-1) may act directly on renal function relating to receptors of both GH and IGF-1 on the renal proximal tubular cell (Janssen et al., 1997).

The effect of rbST to mammary circulation is indirect, mediated via insulin like growth factor-1 (Capuco et al., 2001). The present results confirmed the study in the goats that the plasma IGF-1 level increases in response to GH treatment (Davis et al., 1988). An arterial infusion of IGF-1 into the mammary gland has also been shown to stimulate blood flow to the gland and increase milk production (Prosser et al., 1990). It is possible that rbST exerts its effects indirectly by stimulation IGF production. It has been reported that IGF-1 may increase blood flow to the mammary gland and enhance transportation of milk precursors to the gland. It eventually alters the synthetic capacity of secretory cells and promotes persistence of lactation by slowing the rate of mammary involution (Baldi et al., 2002).

In conclusion, the present study has shown that rbST administration to Crossbred Saanen goats in the late stage of lactation can increase milk yield. This response was due to both the short-term response immediately after injection (26%) and the medium–term effect on lactation persistency. The effect of rbST was in large part due to an increase in both ECW and TBW. An increase of ECW compartment correlated to the increase of PV and corresponding with milk production. In other part, rbST also improved the ratio of Na+ to K+ ratio in milk, which indicated the leaky tight junction. The Na+/K+ ratio decreased after rbST treated that mean the effects of rbST could be maintenance of the tissue integrity during progress of lactation. Finally, these experiments confirm the mechanism by which rbST affect mammary function indirectly by the action of IGF-1 but not mediated solely. The action of IGF-1 on mammary gland in rbST treated goats may be due to an elevation of body fluid in distribution of milk precursors to the gland.

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