Effect of increased intake of milk replacer in young calves on growth and the neonatal mode of action of IGF-I.

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Research

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Abstract

Background Optimizing growth and rumen development of calves in the preweaning period can lead to reduced costs of raising replacement heifers, bulls and fattening beef cattle. In the neonatal period, the quantity and quality of milk replacer consumed by calves directly impacts their growth, development and maturational changes in the somatotropic axis. This study evaluated the effects of plane of nutrition in neonatal calves on growth, development of the somatotropic axis and mode of action of IGF-I. Eight Holstein bull calves (3–4 days old) were fed either a low (LM, average 0.63 kg DM/d) or high (HM, average 1.15 kg DM/d) level of a 28% crude protein milk replacer until slaughtered at 41–42 days old.

Results Compared to LM calves, calves on the HM diet had heavier ($P < 0.01$) body, carcass and semitendinosus muscle weights at slaughter. At three weeks of age, plasma insulin-like growth factor I (IGF-I) concentrations rose more rapidly in HM calves and were significantly higher at three, four and six weeks of age compared to LM calves. IGF-I mRNA levels were higher ($P < 0.01$) in liver, and lower ($P < 0.01$) in longissimus dorsi muscle in HM calves compared to LM calves. Growth hormone and IGF-I receptor mRNA levels in liver and muscle were not affected by plane of nutrition.

Conclusions Increasing intake of a high-protein milk replacer in suckling calves improved growth rate in the preweaning period. The higher plane of nutrition promoted a shift towards an endocrine mode of IGF-I action and a decline in the autocrine/paracrine IGF-I control of muscle growth.

Background

Optimizing growth and rumen development of calves in the preweaning period can lead to reduced costs of raising replacement heifers, bulls and fattening beef cattle. An increased plane of nutrition in the preweaning period can promote growth in replacement heifers so that they reach puberty and calve at an earlier age; and produce more milk at first lactation [1]. Bull calves on a high plane of nutrition in their first six months of life reached puberty at an earlier age than bull calves on a low plane of nutrition [2] and this hastened the availability of salable semen. Beef cattle on a higher plane of nutrition in the preweaning period enter the feedlot at an earlier age and gain weight more efficiently than older aged cattle. In the neonatal period, the quantity and quality of milk replacer consumed by calves directly impacts their growth and development. Jersey calves in their first week of life given more of a high protein milk replacer had increased body weight, higher ADG, and retained more dietary nitrogen than calves on a lower plane of nutrition [3] and Ballou et al. [4] reported that Holstein and Jersey calves on a high plane of nutrition in the preweaning period were more efficient in the utilization of dietary protein for body weight gain. In four earlier studies, adoption of an intensified milk replacer feeding program in preweaning calves; which included feeding more of a high-protein milk replacer led to greater body weight gain, skeletal growth, and lean muscle mass [5, 6, 7, 8]. Kamiya et al. [9] in a companion trial found that an increased intake of a high protein milk replacer in the suckling period increased body growth and improved feed efficiency in Holstein bull calves. Growth was associated with increased carcass weights and enlargement of specific organs that included: liver, spleen, kidneys and abdominal fat. Increased

growth rates in this trial were positively correlated to increased plasma glucose and insulin levels. To investigate the effects of plane of nutrition on blood metabolites and hormones, Daniels et al. [10] fed Holstein heifers different milk replacers and concluded that the somatotropic axis requires further study to understand the effects of nutrition on hypothalamic regulation of metabolism. Circulating levels of insulin-like growth factor I (IGF-I) were higher in studies in which newborn calves received more energy and protein through colostrum or milk replacer [11, 12, 13]. In the perinatal period, maturational changes in the somatotropic axis lead to a growth hormone (GH) dependent endocrine control of IGF-I action and subsequent growth in calves [14, 15]. This change has been attributed to GH receptor (GHR) gene expression following a late gestational cortisol surge [16]. Nutrient levels in late gestation, at parturition and in early lactation can influence these maturational changes in the somatotropic axis. Maternal nutrient restriction in ewes limited fetal nutrient supply and diminished the late-gestational rise in lamb liver GHR gene expression [15]. The influence of early postnatal nutrition on the developmental changes in the somatotropic axis remains largely unknown. Smith et al. [13] reported increased hepatic gene expression for GHR and IGF-I with increasing milk replacer intake of young calves; but failed to observe a consistent nutritional effect on gene expression for GHR or IGF-I in muscle and adipose tissue. We hypothesize that growth and tissue specific responses to early postnatal nutritional manipulation could be due to coordinated maturational changes in components of the somatotropic axis. The objective of this study was to determine if increased nutrient intake in suckling calves affects the neonatal maturation of the somatotropic axis and mode of action of IGF-I on growth in suckling calves.

Methods

Animals and experimental procedures

This study and a companion trial by Kamiya et al. [9] were conducted at the National Agricultural Research Center for Kyushu Okinawa Region (KONARC), and all procedures involving live animals conformed to the KONARC guide for care and use of laboratory animals and were approved by the institutional ethical review committee. Eight neonatal Holstein bull calves, acquired from a commercial dairy farm at 3 to 4 day-old, were housed individually in saw dust bedded pens and offered a low (LM, n = 4) or high (HM, n = 4) quantity of a 30% crude protein, 15% crude fat commercial milk replacer until slaughtered at 41–42 days of age. Amount of milk replacer fed was increased gradually from 0.38 to 0.86 and from 0.57 to 1.71 kg dry matter (DM)/d, and intake averaged 0.63 and 1.15 kg DM/d for the LM and HM groups, respectively. Milk replacer was prepared each day and offered to calves twice daily at 8:30 and 16:00 h. In addition to milk replacer, fresh water and trace-mineralized salt were available to all calves. Details of calf management and feeding practices over the 42-day study are described in the companion paper [9].

Blood sampling and tissue collection for hormone and RNA analyses

Weekly blood samples from one until six weeks of age were collected by jugular venipuncture into evacuated heparinized tubes after recording calf live bodyweight and before the morning feed. Plasma

was separated by centrifugation (1500 g for 15 min at 4 °C) and stored at -30ºC until analyzed. At 41–42 days of age, calves were euthanized by intravenous administration of a lethal dose of sodium pentobarbital (Somnopenthyl, Kyoritsu Seiyaku, Tokyo, Japan) and exsanguinated by severing the main vessels of the neck. To allow for RNA extraction and quantitation in this study, 5–10 g samples of liver, longissimus dorsi (LD) and semitendinosus (ST) muscles were collected immediately after exsanguination, snap frozen in liquid nitrogen and stored at -80ºC until analyzed. Kamiya et al. [9] weighed additional visceral organs and carcass components to assess effects of milk replacer on calf growth and plasma metabolites.

IGF-I determination

Plasma IGF-I concentrations were measured in duplicate by double antibody radioimmunoassay after extraction using an acid-ethanol cryoprecipitation method to remove IGF-I from binding proteins [17]. Recombinant human IGF-I (PeproTech, Rocky Hill, NJ, USA), rabbit anti-human IGF-I (Biogenesis, Poole, UK) and goat anti-rabbit gamma globulin (ICN Pharmaceuticals, Aurora, OH, USA) were used as the radioligand and standard, primary antibody and precipitating second antibody, respectively. Average recovery of spiked IGF-I was 79.1% and the diluted plasma obtained from calves paralleled the standard curve. All samples were assayed in a single run and the intra-assay coefficient of variation was 6.6%.

RNA isolation and reverse transcription (RT) PCR

Messenger RNA levels for GHR, IGF-I and type-1 IGF receptor (IGF-IR) in liver and muscle tissue were determined using quantitative real-time RT-PCR. Total RNA was extracted from 0.1 g samples of frozen tissues using ISOGEN (Nippon Gene Co. Ltd., Tokyo, Japan) according to the manufacturer's instructions, and quantified spectrophotometrically at 260 nm. Total RNA (approximately 5, 2.5 and 1 μg for liver, LD and ST muscles, respectively) was reverse transcribed into first-strand cDNA using a commercially available kit (Amersham Pharmacia Biotech, Little Chalfont, UK). Primers used for amplification of cDNA of GHR, IGF-I and IGF-IR are listed in Table 1.

Table 1
Sequence of bovine cDNA primers used in RT-PCR to measure mRNAa from liver and muscle.

Primer	Primer Sequence	Orientation	Reference
GHR_f	5'-CCAGTTTCCATGGTTCTTAATTAT-3'	sense	18
GHR_r	5'-TTCCTTTAATCTTTGGAACTGG-3'	antisense	
$IGFI_f$	5'-TGCGGGGCTGAGTTGGT-3'	sense	19
$IGFI_r$	5'-CCGTGGGCTTGTTGA AATAAA-3'	antisense	
$IGFIR_f$	5'-CCAAGCTAAACCGGCTCAAC-3'	sense	20
$IGFIR_r$	5'-TTATTACCAAGCCTCCCAC-3'	antisense	
$\beta\text{-actin}_f$	5'-GAGACGTTCAACACTCCTGC-3'	sense	21
$\beta\text{-actin}_r$	5'-GAGCTTCTCCTTGATGTCAC-3'	antisense	

[a] mRNA of growth hormone receptor (GHR), insulin-like growth factor I (IGFI), type-1 IGF receptor (IGF-IR) and β-actin control.

cDNA was amplified in a LightCycler® Quick System 330 RT-PCR System (Roche Diagnostics, Tokyo, Japan) and quantitated fluoroscopically using a FastStart DNA Master SYBR Green I reagent kit. The amplification program consisted of 10 min for activation at 95 °C followed by 45 cycles of PCR (95 °C for 10 s, primer dependent annealing temperature for 5 s and 72 °C for 10 s). From a pooled sample of each tissue (n = 8), standard curves were established for each gene from a 10x serial dilution of mRNA collected. β-actin mRNA was used as a reference gene to normalize tissue mRNA values. The measured mRNA abundance represented the ratio of mRNA for GHR, IGF-I and IGF-IR to β-actin. Average mRNA abundance values for LM calves were standardized to 100, and HM calf values are relative to LM values.

Data analysis

This six-week trial was set up as a completely randomized design with two treatments (LM and HM) and four calves allotted to each treatment. The general linear model (GLM) procedure of SAS (release 8.1; SAS Institute. Inc., Cary, NC) was used to analyze treatment effects on final body, carcass and muscle weights, and mRNA abundance levels for GHR, IGF-I and IGF-IR from liver and muscle tissues. Weekly plasma IGF-I levels were analyzed by repeated-measures ANOVA using PROC GLM in SAS. Calf represented the subject, and week was the class variable in the repeated-measures model. All data are presented as means ± SEM. Differences in means with P-values < 0.05 were considered significant, and P-values < 0.1 were considered as trends.

Results

Body, carcass and muscle weights

The influences of increased milk replacer intake in newborn calves on growth performance, plasma metabolites and insulin concentrations, organ allometry and growth of carcass components have been presented in detail in the companion paper [9]. For this study, calf body, carcass and ST muscle weights at slaughter are reported in Table 2 to allow for the interpretation of the effects of changes in plasma IGF concentrations, and mRNA abundance levels for IGF-I, GHR and IGF-IR in liver and muscle.

Table 2
Body, carcassa and semitendinosus muscle weights of Holstein calvesb fed two levelsc of milk replacer.

Variable	LM	HM	P-value[d]
Live body weight (kg)	60.7 ± 2.0[e]	83.9 ± 1.4	< 0.001
Empty body weight (kg)	56.8 ± 1.9	77.6 ± 1.1	< 0.001
Carcass weight (kg)	41.6 ± 1.6	56.4 ± 1.1	< 0.001
Semitendinosus muscle (g)	250 ± 3	339 ± 15	0.001

[a]Viscera-free carcass including hide, feet and tail.

[b]41-42 days old bull calves.

[c]Low (LM, n = 4) and high (HM, n = 4) levels of milk replacer

[d]Significant at P < 0.05

[e]Standard error of the mean

Increased nutrient intake in HM calves resulted in greater (P < 0.001) live and empty body weights at slaughter compared to LM calves. HM calves also had significantly heavier carcasses and ST muscle weights (Table 2).

Plasma IGF-I and mRNA abundance in liver and muscle

Plasma IGF-I concentrations followed a similar pattern in all calves increasing after day 14 until the end of the trial, but HM calves had significantly higher levels of IGF-I from day 21 compared to LM calves (Fig. 1).

Fig.1 Blood plasma IGF-I concentrations of Holstein calves[a] fed low or high level[b] of milk replacer. **a** bull calves. **b** LM: low level of milk replacer (n=4); HM: high level of milk replacer (n=4). Means ± SEM with different letters differ (P<0.01).

Higher plasma IGF-I levels (P < 0.01) in HM calves at the end of the trial were positively correlated to increased muscle, carcass and body weights. An increased intake of milk replacer in HM calves altered the level of mRNA in organs and tissues when compared to LM calves (Fig. 2). mRNA abundance levels in liver and muscle for GHR and IGF-IR were not affected (P > 0.1) by plane of nutrition. In HM calves, liver

mRNA abundance levels for IGF-I were significantly higher than levels measured in LM calves (Fig. 2, B). In muscle, HM calves had less mRNA for IGF-I compared to LM calves. The amount of mRNA was significantly less in LD muscle, and tended to be less in ST muscle in HM calves.

Discussion

Increasing the plane of nutrition in newborn calves improves growth and nutrient utilization. We have reported that increasing consumption of commercial milk replacer in suckling Holstein bull calves leads to an overall increase in body growth with improved feed efficiency, and specific changes in growth rates of abdominal organs and tissues [9]. Improved body, carcass and ST muscle weights at 42 days of age in calves on a higher plane of nutrition in this study (Table 2) supports the work of Byrne et al. [2] and others [11, 1]. While the increased body weight gain is not always sustained into adulthood, suckling bull and heifer calves on a higher plane of nutrition reach puberty at an earlier age and producers see an economic advantage over later maturing livestock. The improvements in growth rate in our study are associated with improved nutrient availability, an increase in size of metabolically active organs that include the liver and kidneys, and higher circulating levels of insulin [9] and IGF-I (Fig. 1). Others have reported increased circulating IGF-I concentrations in response to an increased plane of nutrition; and noted a positive correlation between plasma IGF-I levels and growth rates in young suckling calves [11, 13]. The elevated plasma IGF-I levels in this study were associated with increased liver synthesis of the hormone. HM calves had significantly higher liver IGF-I mRNA levels compared to LM calves (Fig. 2), and the results support those of Radcliff et al. [22] and Smith et al. [13]. Cordano et al. [23] found that hepatic IGF-I mRNA levels were closely correlated with plasma IFG-I concentrations and that protein and energy intake largely determines endocrine IGF-I production in the liver. In this study, there were no significant differences in liver GHR, or IGF-IR concentrations based on mRNA abundance (Fig. 2); whereas, Frieten et al. [24] noted an increase in hepatic GHR levels in 50-day old calves fed ad libitum milk replacer. The somatotropic axis is functional in neonatal calves [23] and is known to mature with age. Liver samples were obtained earlier in this study at 42 days of age. In addition, the number of GH receptors in the liver is low [25] and they represent only one of several somatotropic factors influencing hepatic IGF-I synthesis. Coupled with the small number of calves and mRNA abundance methodology used this study compared to Frieten et al. [24], it may have been difficult to detect significance in hepatic GHR mRNA even though HM calves had a numerically larger relative GHR mRNA abundance value compared to LM calves (Fig. 2).

Increased plasma IGF concentration in the HM calves was associated with an increase in liver IGF synthesis as suggested by greater hepatic mRNA abundance for the IGF gene and a significantly larger liver [9] compared to LM calves at 42 days of age. Since the increased liver production of IGF-I does not appear to be associated with a GH mediated response, we suggest that the increased plane of nutrition leads to a modulation of hepatic GHR that in turn stimulates transcription of IGF-I through some post receptor mechanism. Daniels et al. [10] in a similar study found no effect of diet on concentrations of circulating GH but did report significant effects on circulating IGF-I, IGF binding proteins and glucose.

In LD and ST muscle compared to liver, we observed an inverse response for IGF-I gene expression in calves on a higher plane of nutrition. HM calves had lower LD ($P < 0.01$) and ST ($P = 0.06$) mRNA abundance levels for IGF-I (Fig. 2) which suggests upregulation in the liver and downregulation in target tissues that contribute to circulating IGF-I levels. The coordinated tissue-specific changes in IGF-I mRNA expression clearly demonstrate that increased nutrient intake in neonatal calves accelerates the perinatal shift in the functionality of the somatotropic axis toward an endocrine mode of IGF-I action as described by Fowden et al. [14] and Hyatt et al. [15]. Smith et al. [13] failed to detect a consistent nutritional effect on gene expression of GHR or IGF-I in tissues apart from liver presumably because they employed a less sensitive RNase protection assay for mRNA determination. Vestergaard et al. [26] found that increased feeding level but not GH treatment increased IGF-IR density in LD muscle of prepubertal heifers. We did not detect any significant changes in the mRNA abundance for IGF-IR in LD or ST muscles (Fig. 2) despite a significant increase in ST muscle mass in HM calves (Table 1). IGF-IR intercellular signaling and subsequent protein synthesis in muscle may be modified by the plane of nutrition. In our companion study [9], circulating levels of glucose and insulin were higher in HM calves and may modulate the intercellular response to IGF-I in addition to having direct impacts on muscle growth. MacPherson et al. [27] have demonstrated that the rise in insulin in calves fed more milk replacer is not associated with a decrease in insulin sensitivity. Insulin receptors and IGF-IR share a similar structure and are both members of the tyrosine kinase family, so it is possible that elevated insulin levels may alter IGF-IR activity in addition to promoting uptake of glucose and amino acids into tissues to support growth.

Conclusions

An increased plane of nutrition in suckling calves enhances preweaning growth. Within the somatotropic axis controlling growth, enhanced nutrition promotes a shift towards an endocrine mode of IGF-I action and a decline in the autocrine/paracrine IGF-I control of muscle growth. In addition to providing more nutrients and energy, the intake of a high-quality milk replacer may alter the signaling of IGF-IR and GHR in metabolically active tissues by altering levels of other anabolic hormones like insulin.

List Of Abbreviations

ADG: Average daily gain

ANOVA: Analysis of Variance

cDNA: Copied deoxyribonucleic acid

d: Day

DM: Dry matter

DNA: Deoxyribonucleic acid

GH: growth hormone

GHR: Growth hormone receptor

GLM: General linear model

HM: High level of milk replacer

IGF: Insulin-like growth factor

IGF-1: Insulin-like growth factor 1

IGF-1R: Insulin-like growth factor type 1 receptor

LD: Longissimus dorsi muscle

LM: Low level of milk replacer

mRNA: Messenger ribonucleic acid

P: Probability

PCR: Polymerase chain reaction

PROC: Procedure

RNA: Ribonucleic acid

RNase: Ribonuclease

RT-PCR: Reverse transcription polymerase chain reaction

SAS: Statistical Analysis System

SEM: Standard error of the mean

ST: Semitendinosus muscle

Declarations

Ethics approval and consent to participate

This study was conducted at the National Agricultural Research Center for Kyushu Okinawa Region (KONARC), and all procedures involving live animals conformed to the KONARC guide for care and use of laboratory animals and were approved by the institutional ethical review committee.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Figures

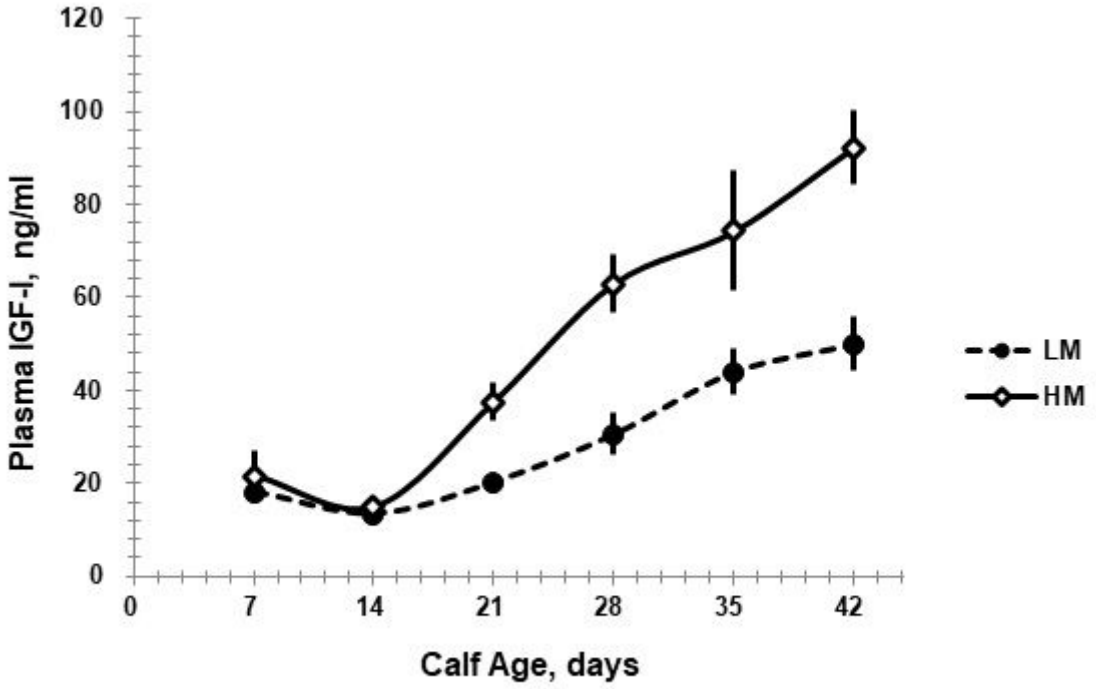

Figure 1

Blood plasma IGF-I concentrations of Holstein calvesa fed low or high levelb of milk replacer. a bull calves. b LM: low level of milk replacer (n=4); HM: high level of milk replacer (n=4). Means ± SEM with different letters differ (P<0.01).

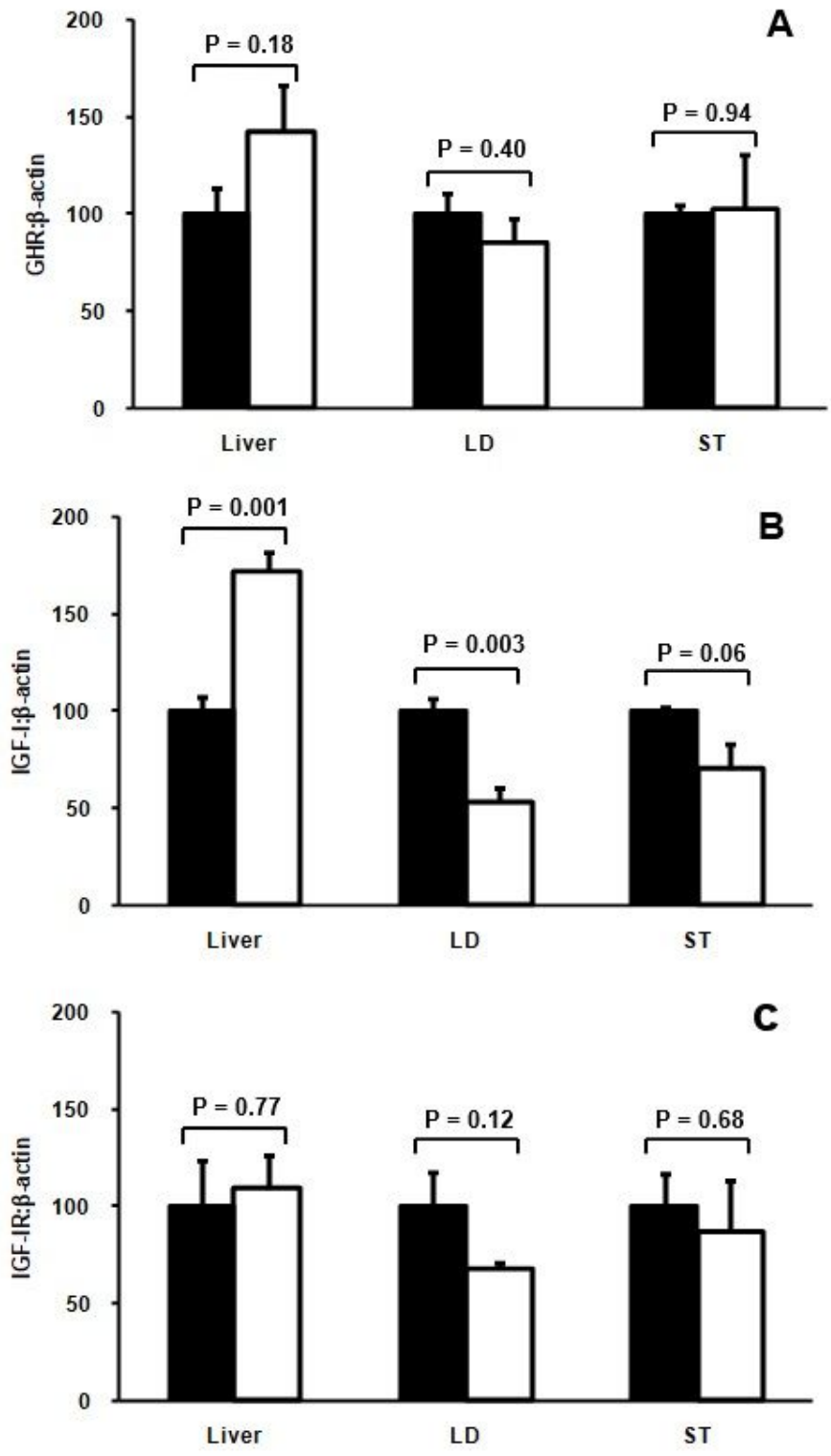

Figure 2

mRNA abundance levels in liver and muscle tissues. a growth hormone receptor (GHR); b insulin-like growth factor-I (IGF-I) and c type-1 IGF receptor (IGF-IR) in the liver, longissimus dorsi (LD) and semitendinosus (ST) muscles of 41-42 day old Holstein bull calves fed a low level (LM, n=4, ■) or high level (HM, n=4, □) of commercial milk replacer. Values represent ratio of mRNA of target gene to β-actin.

HM ratios are relative to LM ratios which were standardized to 100. Mean ratios ± SEM are displayed with P values. $P<0.05$ differ significantly.