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Original article

Relationship of adiponectin, leptin, visfatin and IGF-1 in cow's venous blood and venous cord blood with calf birth weight

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Abstract

The Intrauterine fetal development process is complicated and affected by many regulating factors such as maternal nutritional status, transcription factors and adipokines. Adipokines are kinds of active substances secreted by adipose tissue, including more than 50 kinds of molecules. To explore the correlation between calf birth weights and adipokines including adiponectin, leptin, visfatin, and IGF-1 in cows venous and venous cord blood. Fifty-four healthy multiparous Chinese Holstein cows were used; in which, cows with a calf weight less than 40 kg were included in group A (n=9); those with a calf weight between 40 kg~45 kg were included in group B (n=25) and ≥45 kg were included in group C (n=20), venous blood and cord venous blood was collected. An ELISA kit was used to evaluate the concentration of adiponectin, leptin, visfatin, and IGF-1, correlations between index-index and index-calf birth weight were analysed. In both cows venous and cord venous blood, adiponectin, leptin, visfatin, and IGF-1 levels were significantly correlated with each other ($p<0.01$), and levels of these adipokines in venous blood were significantly higher than cord venous blood ($p<0.01$). Adiponectin, leptin, visfatin, and IGF-1 in venous cord blood were positively correlated with calf birth weights, and significantly correlated with calf birth weights respectively ($p<0.01$). Our study showed that adiponectin, leptin, and IGF-1 were found in venous blood and cord venous blood, and adiponectin, leptin, and IGF-1 in venous and cord venous blood potentially inter-regulated each other; adiponectin, leptin, and IGF-1 in venous blood were not significantly correlated with calf birth weights, while adiponectin, leptin, visfatin, and IGF-1 in venous cord blood were significantly correlated with calf birth weights, respectively.

Key words: adiponectin, leptin, IGF-1, birth weights, cow

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Introduction

Calf birth weight is one of the important genetic parameters of calf breeding and Intrauterine development the process of intrauterine fetal development is complicated and affected by many regulating factors such as maternal nutritional status, transcription factors and adipokines (Herrera and Ortega-Senovilla 2014). Adipokines are kinds of active substances secreted by adipose tissue, including more than 50 kinds such as adiponectin, leptin, visfatin, resistin, omentin and TNF-α. Adiponectin, which plays an important role in the glucose and lipid metabolism regulation and has positive correlations with body fat mass, BMI and waist-to-hip ratio, exists in the body in 3 forms: low molecular weight (LMW), middle molecular weight (MMW) and high molecular weight (HMW); leptin mainly secreted by adipose tissue, has activity of inhibits the synthesis and release of Neuropeptide Y (NPY), reducing feed intake and increasing energy consumption by stimulating the sympathetic nerve; visfatin mainly synthesized by adipose tissue, shows an insulin-like function, promotes glucose transportation and triglyceride synthesis, and down regulates blood sugar level (Xie et al. 2007,Vijayalakshmi et al. 2013); IGF-1, the intermediate protein of multiple signal pathways such as P123K, GSK23, PTP21B, PKC etc. , can promote cell proliferation and differentiation and protein synthesis, and effects fetal growth indirectly. Data indicate that pregnant human and rat adiponectin, leptin, and IGF-1 in venous blood and cord venous blood have a correlation with fetal birth weight (Takaya et al. 2007, Cekmez et al. 2009, Ahlsson et al. 2013, Yanni et al. 2013, Terrazzan et al. 2014, Walsh et al. 2014). Researches on cow adipokines mainly concentrated in serum, amniotic fluid, milk and fat, which had shown that the adipokines participated in pregnancy, estrus and calf growth (Singh et al. 2014, 2014, Kafi et al. 2015). There is still little research on the correlation between adipokines and birth weight, and no study on this correlations in the dairy cows. Our study explores the correlation between calf birth weights and adiponectin, leptin, visfatin, and IGF-1 in cow venous and cord venous blood and provides the basis for research on the influence of adipokines on calf intrauterine development.

Materials and Methods

Animals and management

Fifty-four full-term pregnancy, normally delivered healthy cows with normal fetal development were chosen from 95 Chinese Holstein cows that weigh about 500 kg, parity 2-4, fed in a large-scale dairy farm in Sichuan Province.

Ethics approval

All animal experiments were conducted in strict accordance with the regulations of the animal protection laws of the People's Republic of China (a draft of animal protection laws in China was released on September 18, 2009) and in compliance with the Sichuan Agricultural University for Laboratory Animal Care recommendations for the care and use of laboratory animals (Ya'an, China; Approval No. 2013-028).

Blood collection

Vulvas of cows were disinfected immediately after delivery. The umbilical vein stump was pulled out of the vulva, and 10 ml of umbilical cord blood was collected and placed in a centrifuge tube without anticoagulant at room temperature for 1h, centrifuged at 1500 rpm for 10 min, and the upper serum was then transferred to an EP tube for storage at -20°C.

Tail venous blood was collected on the day of delivery and placed in centrifuge tube without anticoagulant, centrifuged at 1500 rpm for 10 min after 1 h rest at room temperature, the upper serum was transferred to the EP tube, stored at -20°C.

Indicator detection

ELISA was used for evaluation of adiponectin, leptin, visfatin, and IGF-1 in venous blood and cord venous blood. ELISA kits (adiponectin, leptin and IGF-1) were purchased from Nanjing Jiancheng Bioengineering Institute, sensitivity 0.5ng/ml (Batch number: RPF80481RT), all measurement operation steps were strictly followed.

Weights and groups

The newborn calves were weighed immediately after cleaning of amniotic fluid and blood. According to the average CBW on this farm (40- 45 kg), newborn calves less than 40kg were included in the low weight group (group A, 9 cows); between 40 kg ~45 kg were included in the average group (group B, 25 cows); more than 45 kg were included in the high weight group (group C, 20 cows).

Statistical analysis

SPSS 24.0 was used for statistics processing. Distribution of measurement data was tested using the K-S test and expressed by X±S. Single factor analysis of variance was used to compare among groups, and correlation analysis was carried out using bivariate Pearson correlation analysis; the difference is statistically significant if $p<0.05$.

Table 1. Expression level of adiponectin, leptin, visfatin and IGF-1 in cow's venous blood.

Group	Sample size	Birth weight/kg	Adiponectin (mg L^{-1})	Leptin (ng mL^{-1})	Visfatin (ng mL^{-1})	IGF-1 (ng mL^{-1})
A	9	36.68 ± 2.12a	31.41 ± 4.23a	21.07 ± 1.71a	232.29 ± 35.56a	870.07 ± 123.13a
B	25	42.42 ± 1.58b	28.74 ± 3.34a	20.40 ± 2.48a	244.78 ± 38.23a	874.96 ± 123.46a
C	20	48.56 ± 3.59c	28.64 ± 4.55a	21.44 ± 3.05a	248.79 ± 38.01a	843.74 ± 74.76a
F		71.327	1.751	0.896	0.599	0.492
P		<0.001	0.184	0.415	0.553	0.615

Note: Means in the same list with no same lower case letters indicate statistically significant difference at 0.05 probability level. F value means the same as in Table 2.

Table 2. Expression level of adiponectin, leptin, visfatin and IGF-1 in cord venous blood.

Group	Sample size	Birth Weight/kg	Adiponectin (mg L^{-1})	Leptin (ng mL^{-1})	visfatin (ng mL^{-1})	IGF-1 (ng mL^{-1})
A	9	36.68 ± 2.12a	13.16 ± 1.23a	12.09 ± 0.95a	181.95 ± 11.42a	545.62 ± 22.11a
B	25	42.42 ± 1.58b	13.57 ± 0.90ab	12.58 ± 0.93ab	186.47 ± 10.07ab	554.47 ± 28.88a
C	20	48.56 ± 3.59c	14.36 ± 1.16b	12.87 ± 0.60b	192.12 ± 6.66b	582.29 ± 16.34b
F		71.327	4.973	0.280	4.275	10.526
P		<0.001	0.011	0.070	0.019	<0.001

Table 3. Correlation between the expression level of adiponectin, leptin, visfatin, and IGF-1 in cow's venous blood and calf birth weights

Index	Adiponectin		Leptin		Visfatin		IGF-1	
	r	*P*	r	*P*	r	*p*	r	*P*
Birth weight	–0.086	0.538	0.245	0.074	0.003	0.986	–0.060	0.668
Aadiponectin			0.506**	<0.001	0.270*	0.049	0.525**	<0.001
Leptin					0.416**	0.002	0.384**	0.004
visfatin							0.525**	<0.001

Note: Single and double asterisks (*, **) indicate statistically significant difference at 0.05 and 0.01 probability level, respectively. The same as in Table 4.

Results

Concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow venous blood

As shown in Table 1, adiponectin, leptin and IGF-1 were all expressed in cow's venous blood in groups A, B and C. The concentrations of adiponectin were declined with increased CBW, whereas the, visfatin level rose with increased CBW.

Concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow cord venous blood

Adiponectin, leptin, visfatin, and IGF-1 were all expressed in cow cord venous blood in groups A, B and C. Levels of all these adipokines rose with increased calf calves' birth weight. The levels of adiponectin, leptin, and visfatin in group A are significantly lower than those in group C ($p<0.05$), while no significant difference exists between group A and B, group B and C ($p>0.05$). The concentration of IGF-1 in group A was significantly lower than that of group C ($p<0.05$), but not significantly correlated with that of group B ($p>0.05$). (See Table 2)

Correlation between the concentration of adiponectin, leptin, visfatin and IGF-1 in cow venous blood and calf birth weights

As shown in Table 3, the concentrations of adiponectin, leptin, visfatin, and IGF-1 were not significantly correlated with calf birth weight ($p>0.05$). The concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow venous blood had a significant positive correlation with each other ($p<0.05$).

Correlation between the concentration of adiponectin, leptin, visfatin, and IGF-1 in cord venous blood and calf birth weights

As shown in Table 4, the concentrations of adiponectin, leptin, and visfatin had a very significant positive correlation with calf birth weights ($p<0.01$),

Table 4. Correlation between the expression level of adiponectin, leptin, visfatin and IGF-1 in cord venous blood and calf birth weights.

Index	Adiponectin		Leptin		Visfatin		IGF-1	
	r	*P*	r	*P*	r	*P*	r	*P*
Birth weight	0.417**	0.002	0.282*	0.039	0.366**	0.006	0.535**	<0.001
Aadiponectin			0.352**	0.009	0.288*	0.034	0.568**	<0.001
Leptin					0.309*	0.023	0.532**	<0.001
Visfatin							0.480**	<0.001

Table 5. Expression level of adiponectin, leptin, visfatin and IGF-1 in cow venous blood and cord venous blood.

Group	Sample size	Adiponectin (mg L^{-1})	Leptin (ng mL^{-1})	Visfatin (ng mL^{-1})	IGF-1 (ng mL^{-1})
Cow venous blood	54	29.15±4.02a	20.90±2.61a	244.18±37.45a	862.58±106.82a
Cord blood	54	13.79±1.14b	12.61±0.85b	187.81±9.76b	563.30±27.81b
t		26.942	22.148	10.702	19.924
P		<0.001	<0.001	<0.001	<0.001

and the concentration of IGF-1 had a positive correlation with calf birth weight ($p<0.05$). The concentrations of adiponectin, leptin, and IGF-1 in cow's cord venous blood had a significant positive correlation with each other ($p<0.05$).

Concentration and correlation of adiponectin, leptin, visfatin and IGF-1 in cow's venous blood and venous cord blood

As shown in Table 5, the concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow venous blood were very significantly higher than those in cow's cord venous blood ($p<0.01$).

The concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow venous blood had no significant correlation with those in cow's cord venous blood ($p>0.05$).

Discussion

Correlation between calf birth weights and concentrations of adiponectin, leptin, visfatin, and IGF-1 in cow venous blood and venous cord blood

The correlation between adiponectin and fetal development is still under debate. Rosario et al (2015) reported that a low maternal adiponectin level would increase fetal weight in rats. Aye et al. (2015) found that injection of exogenous adiponectin into pregnant rats could increase the maternal insulin sensitivity and prevent an oversized fetus, maternal adiponectin level could influence fetal growth and development, and decreased maternal adiponectin level resulted in low maternal insulin sensitivity and high blood glucose concentration, facilitating the transportation of glucose through the placental barrier, thus affecting the birth weight of the fetus. However, the results in human studies are not consistent. For example, it was reported that low serum adiponectin concentration in obese pregnant women was associated with an oversized fetus (Kadowaki et al. 2007), while Zhang and Xia (2013) reported a non-significant correlation between maternal adiponectin level and fetus birth weight.

In our study, the concentration of adiponectin in cow venous blood had no significant correlation with calf birth weight ($p>0.05$), the concentration of adiponectin had a downward trend with increasing of calf birth weight, suggesting that the adiponectin in cows' venous blood might partly play a regulatory role in calf birth weight.

Kajantie et al. (2004) found that the serum adiponectin level in the umbilical vein increased with fetus development. Cekmez (2009), Tsai et al. (2004) and Zhang *et al.* (2008) also reported a positive correlation between the serum adiponectin level in the umbilical vein and newborn birth weight. However, Lindsay et al. (2003) indicated a non-significant correlation between the serum adiponectin level in the umbilical vein and the fetal birth weight. Corbetta et al. (2005) also found that there was no significant correlation between the serum adiponectin level in the umbilical vein and the birth weight of premature infants, and that adiponectin concentration elevated with fetal development. Cekmez et al. (2011) indicated that the serum adiponectin level in the umbilical vein was negatively correlated with birth weight. So far, there has been no reported study on the serum adiponectin level in the umbilical vein in dairy cattle. In our study, as the calves' birth weight increased, the concentration of adiponectin in cows' cord venous blood saw an upward trend and there was a significant positive correlation with calf

birth weight (p<0.01). These results were consistent with Cekmez et al. (2009), Zhang et al. (2008) and Sohn et al. (2011) who provide results of the research into adiponectin in the human umbilical cord blood and fetal birth weight. Our study indicates that adiponectin in cow cord venous blood could promote the development of calves, might activate the specific receptors in skeletal muscle and liver, increase glucose intake and inhibit gluconeogenesis by increasing the sensitivity of fetal tissues to insulin and IGF-1, thus promoting fetal weight gain.

Gestation accelerates leptin secretion and promotes lipid mobilisation, plays an essential role in fetal growth and development (D'Ippolito et al. 2012). However, the correlation between maternal leptin level and fetus birth weight is still under debate. For example, Walsh et al. (2014) and Perlirz et al.(2009) reported a positive correlation between the serum leptin level in pregnant women and the birth weight of the fetus, but a study indicated a non-significant correlation between the serum leptin level in pregnant women and the birth weight of the fetus(Yu-Jie and Chen 2008). According to this study, the leptin concentration in umbilical veins did not vary significantly with different calf birth weights (p>0.05) and was not significantly correlated with calf birth weight (p >0.05). Tsai et al. (2015) and Zhang et al. (2008) indicated that the serum leptin level in venous cord blood is positively correlated with fetus birth weight. Leptin bound with leptin receptor after entering the fetus and regulated the fetal growth and development after embryo implantation via the Janus kinase/signal transducer and activator of tranions (JAK/STAT) pathway (Lepercq et al. 2001, Karakosta et al. 2013), and promoted angiogenesis in bones, lungs and adipose tissues (Ogueh et al. 2000, Kirwin et al. 2006, Yonekura et al. 2013) to influence the fetus birth weight. Currently, there has been no reported study on the correlation between serum leptin level in dairy cattle and calf birth weight. The results of this study are as follows: as the calf birth weight increased, the concentration of leptin in cow cord venous blood rose and the concentration of leptin in group A was significantly lower than that in group C (p<0.05), while the concentration of leptin in group A and B was not significant difference (p>0.05). Our results were similar to the results of Tsai et al. (2015) and Zhang et al. (2008). Leptin in cows' cord venous blood is significantly positively correlated with calf birth weight, which indicates that leptin in cow cord venous blood played a promoting effect on the growth of calves.

Visfatin is a secreted protein, and has an insulin-like function and promotes blood sugar regulation, lipid storage and preadipocyte differentiation. Mou et al. (2012) found that calves with visfatin Novel 6-bpde gene mutation have a significant difference in CBW and weight to normal calves, and showed that visfatin played an important role in calf growth. Cekmez et al. (2009) found that concentrations of visfatin, adiponectin and insulin in cord blood showed positive correlations to CBW and body length, and that cord blood visfatin, insulin, and adiponectin have positive correlations to each other. The research above indicates that visfatin can regulate fetal growth by co-activities with insulin. In our study, visfatin concentrations in cord blood showed a significant positive correlation with CBW (p< 0.05), and the visfatin level group in group A was significantly lower than in group C (p< 0.05), which is consistent with previous research, suggesting that visfatin in dairy cow cord blood has a similar function to that in humans and can promote energy assimilation and regulate fetal growth.

IGF-1 can inhibit cell apoptosis, promote cell division and differentiation, influence placental transport and metabolism, and accelerate bone mineralisation. It can be synthesized in placental tissues. By influencing the placental transport of glucose and amino acids (Cianfarani et al. 1998, Yuki et al. 2005, Tennekoon et al. 2014), IGF-1 can regulate the insulin release in the fetus, stimulate neural development and growth, increase the synthesis of proteins and lipids, and stimulate the development of the liver, heart and other viscera. The insulin and growth factors produced in the placenta are also involved in the regulation of IGF-1 release, suggesting that IGF-1 is closely related to fetal growth and development. It has been reported that the blood IGF-1 level in pregnant women is positively correlated with the weight of the placenta, but not significantly correlated with the birth weight of the fetus (Terrazzan et al. 2014b). As the results of our study show the IGF-1 in cow venous blood did not fluctuate as the calf birth weight increased (p>0.05) and had no significant correlation with calf birth weight (p>0.05). On the other hand, the concentration of IGF-1 in cow cord venous blood rose with the increase in calf birth weight. The concentrations of IGF-1 in group A and B were significantly lower than in group C (p<0.05). The concentration of IGF-1 in cow cord venous blood in group A, B and C had a significant positive correlation with each other (p<0.01). Our results were similar to the results of Akcakus et al. (2006) in IGF-1 of pregnant women, which indicated that the IGF-1 in cow venous blood had less effect on calf birth weight, while the IGF-1 in cow cord venous blood participated in the intrauterine growth of calves and increased calf birth weight.

Correlation between the concentration of adiponectin, leptin and IGF-1 in cows' venous blood and venous cord blood

Adiponectin, leptin, visfatin, and IGF-1 all belong to macromolecular substance, so it is difficult for them to pass the placental barrier. The placenta has the function of making maternal and fetal processes relatively independent, and mutually connected state. Jin et al. (2011) found that the concentration of adiponectin in human cord venous blood and maternal blood had no correlation, adiponectin in maternal blood had no significant correlation with fetal birth weight but adiponectin in cord venous blood had a positive correlation with fetal birth weight, indicating that the concentration of adiponectin in maternal blood had little effect on fetal adiponectin, while fetal adiponectin mainly regulated fetus growth. This study found that the correlation between the concentration of adiponectin in cow venous blood and venous cord blood was not significant ($p>0.05$). The results of our study are similar to others which indicated that cow venous adiponectin and fetal adiponectin were relatively independent and played a role in the circulation of cows and calves separately.

Some studies showed that as the subcutaneous fat in pregnancy increased, maternal leptin levels were rose and most of the leptin produced by the placenta was transferred to the mother (Lepercq et al. 1998), making maternal serum leptin levels significantly rose. Leptin resistance was prone to occur at this time (Jiang et al. 2009), influencing insulin and IGF-1 sensitivity and causing maternal leptin to change a little; this can ensure that the maternal-fetal nutrition supply has a normal regulation and maintains the development of the fetus. Fetal fat distribution (mainly subcutaneous fat) is different from that of adults and lacks the feedback regulation of adipose tissue, so fetal leptin changes relative to fetal development. Christou et al. (2001) found that maternal serum leptin had a positive correlation with the leptin in cord venous blood. In our study, the concentration of leptin in cow venous blood was significantly higher than that in cow's cord venous blood ($p<0.01$) and there was no significant correlation between them ($p>0.05$). The results were consistent with the studies of humans (Chen et al. 2005). It suggests that there is less effect of leptin in cow venous blood on fetal leptin, and the leptin in cow cord venous blood regulates the intrauterine growth of calves rather than the leptin in cow venous blood.

In our study, the concentration of IGF-1 in cow venous blood was significantly higher than that in cow cord venous blood ($p<0.01$) and there was no significant correlation between them ($p>0.05$). The main reason was due to the placental barrier; maternal IGF-1 cannot be delivered directly to the fetus. However, it has been reported that maternal IGF-1and IGF-1 in venous cord blood are positively correlated (Akcakus et al. 2006). The difference between the two results may be due to species differences in the metabolic patterns of maternal and fetal circulation between the IGF-1 of cow and human. Visfatin concentration in cow venous blood was very significantly higher than cord venous blood ($p<0.01$) but there was no significant correlation between them; cord blood but not venous had a very significant positive correlation with CBW ($p<0.01$). These results indicate that visfatin in venous and cord blood are relatively independent, and maternal and fetal body condition. Visfatin in cord blood can affect calf metabolism, and has an obvious influence on fetal growth.

Adiponectin, leptin, visfatin, and IGF-1 were all expressed in cow venous blood and cord venous blood and played an inter-regulated role; the concentrations of adiponectin, leptin and IGF-1 in cow's venous blood had no significant correlation with calf birth weight while the concentrations of adiponectin and leptin in cow cord venous blood had significant positive correlation with calf birth weight. These results can provide the basis for research on the influence of adiponectin, leptin, and IGF-1 on calf birth weight.

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