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Research Article

Detection of ghrelin, obestatin and nesfatin-1 in sheep milk: Three-way evaluation in ewe plasma, milk and lamb plasma

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ABSTRACT

Ghrelin, obestatin, and nesfatin-1 peptides are regarded as the primary regulators of the body's appetite and energy balance. However, few studies have explored the roles of these peptides in milk and in metabolic adaptation in sheep. The presence of these peptides was investigated in blood samples from sheep and lambs and in milk samples from sheep during the early lactation phase in the current study. Thirty healthy ewes along with their single lambs were followed through their 3rd to 5th week after giving birth. Blood samples from ewes and lambs, and matched milk samples, were collected and analyzed by using enzyme-linked immunosorbent assay (ELISA) kits. Sampling was conducted over three weeks, and differences among time periods were compared. A significant increase was recorded for ghrelin and obestatin levels in plasma, whereas nesfatin-1 levels were decreased to a considerable extent. The milk samples followed a similar pattern with ghrelin and obestatin levels increased, whereas nesfatin-1 levels decreased. Nevertheless, a similar pattern was recorded for plasma samples. This study detected obestatin and nesfatin-1 peptides from the sheep milk for the first time. It is thought that coordinated action of these peptides affects the body, milking and offspring of sheep during early lactation phase. The increased ghrelin and obestatin levels along with decreased level of nesfatin-1 decreases work in coordination to fulfill energy needs of sheep. The detection of these peptides in milk samples warrants that energy balance of offsprings can be altered by maternal metabolism. This study provides first evidence for the presence of these peptides in the milk samples and confirms that these peptides can alter feeding behavior and energy regulation in lambs.

1. Introduction

Pregnancy and lactation involve neuroendocrine and hormonal alterations as mothers naturally adapt to these metabolically challenging conditions. Lactation not only modifies the serum hormone profile but also alters the ability of specific tissues to respond to hormones (Vernon, 1989). Energy intake and consumption management during the lactation phase are crucial for neonatal metabolism in ruminants. The initiation and maintenance of lactation in sheep, particularly with increasing day length, require the presence of many hormones (Toner *et al.*, 2008). The balance between energy and food intake is regulated by the ghrelin, obestatin, and nesfatin-1 hormones (Stengel *et al.*, 2010). Ghrelin is a gastric hormone that controls food consumption and energy balance (Date *et al.*, 2002). Ghrelin has been identified in the stomachs of humans, rats, cows, pigs, dogs, and horses (Hayashida *et al.*, 2001; Tomasetto *et al.*, 2001). Obestatin is produced by the epsilon cells of the pancreas and plays a critical role in metabolic control. It has been proposed to function as a ghrelin antagonist (Lacquaniti *et al.*, 2011). Obestatin levels are negatively correlated with the homeostasis model evaluation of body mass index (BMI), glucose, insulin, leptin, and insulin resistance, while exhibits a positive relationship with the insulin-sensitive index. These findings suggest a specific role for obestatin in regulating energy homeostasis. The significant correlation between plasma obestatin and ghrelin levels suggests a simultaneous release of these two hormones from a common origin (proghrelin/C-ghrelin) (Zhang *et al.*, 2005). Nesfatin-1 has been proven to reduce food consumption in the rat hypothalamus and third ventricle following injection. Nesfatin is named after the NUCB2 (Nucleobindin-2) protein, which regulates satiety and adiposity (Shimizu *et al.*, 2009). Multiple studies indicate that nesfatin-1 is secreted by peripheral tissues, including adipose tissue, gastric mucosa, endocrine pancreatic β-cells, testes, and the central nervous system (García-Galiano *et al.*, 2010a; Price *et al.*, 2007; Stengel *et al.*, 2010). Nesfatin-1 has been associated with the regulation of body weight, glucose homeostasis, gastrointestinal processes, and the onset of puberty in animals (Atsuchi *et al.*, 2010; Garcia-Galiano *et al.*, 2010b; Su *et al.*, 2010). Recent investigations have demonstrated the presence of ghrelin in humans, notably in colostrum (Aydin *et al.*, 2006) and in regular milk (Aydin *et al.*, 2007). Another study (Aydin, 2013) reported the presence of ghrelin and nesfatin-1

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in the milk of dairy cattle. The statistics on dairy cattle may also be relevant to sheep's milk.

This study was aimed at identifying the presence of the peptide hormones ghrelin, obestatin, and nesfatin-1 in sheep's milk. Serum levels were analyzed to evaluate the compatibility of these peptide hormones in nursing ewes. Finally, a three-way hormone analysis was conducted in sheep, sheep's milk, and lambs by monitoring the plasma levels of ghrelin, obestatin, and nesfatin-1 peptides in the lambs of the studied ewe. The presence of ghrelin, obestatin, and nesfatin-1 in sheep's milk has not yet been reported. If the presence of these hormones in sheep's milk is confirmed, it would indicate that the consumption of this milk by lambs post-birth may support appetite regulation and energy metabolism.

2. Materials and Methods

2.1 Animals

The study utilized 30 mature, clinically normal curly breed sheep under acceptable nutritional conditions, including all lambing. The study was conducted inside the flock of a commercial sheep producer in Bursa province, Türkiye. The sheep gave birth throughout February and April, and samples were taken during this period. The sheep included in the current study were selected based on the date of lambing, and those giving birth on the same date were included. The sheep were aged 24 months and were provided with water and oat hay ad libitum with 500 g of concentrated feed (sheep's milk feed) per animal daily throughout the study. The nutrient contents of the milk feed given to the sheep are shown in Table 1.

The sheep were taken to the pasture in the morning, one week after birth, where they spent an average of 6 h daily. Subsequently, they were housed with their offspring until returning to the pasture the following day. We also included lambs born from these sheep in the research to measure their serum levels of ghrelin, obestatin, and nesfatin-1. The study included 30 healthy, non-twin lambs with birth weights ranging from 3.0 to 5.0 kg. The trial included the lambs at three weeks of age.

2.2 Collection of blood and milk samples

Blood samples were collected from the vena jugularis into heparinized tubes once during weeks 3, 4, and 5 after birth to determine the sheep's hormone levels. Alongside, blood was extracted from the lambs of these sheep using the identical approach. Furthermore, milk samples were obtained by milking. Collected samples were analyzed at the Laboratory of the Department of Biochemistry, Faculty of Veterinary Medicine, Uludag University. Blood and milk samples were instantly transported to the laboratory under cold chain conditions. The whole samples were collected in microcentrifuge tubes containing aprotinin (100µl with 0.6 trypsin inhibitor unit per milliliter of blood; Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) to prevent peptide degradation until the time of analysis, then centrifuged at 3500 g for 7 min at 4°C and stored at -80°C until assayed.

Table 1.
Nutrient content of sheep's milk diet[1].

Nutrient	Sheep's milk feed (in pellet form)[2, 3]
Dry matter (%)	90.25
Crude protein (100% KM[4])	18.22
Raw oil (100% KM[4])	4.08
Raw cellulose (100% KM[4])	9.82
Ash (100% KM[4])	9.49

[1] Feed nutrient analyzes were performed according to the methods specified in AOAC (1990).
[2] ProYem, Sheep Dairy Feed, Matlı Feed Factory, Karacabey, Türkiye.
[3] Raw materials used in sheep's milk feed mix: corn, wheat bran, barley, corn gluten feed, sunflower seed meal, soybean meal, molasses, soybean oil, mineral-vitamin premix, limestone, and salt.
[4] Dry matter

2.3 Plasma hormone analyses

Sheep-specific commercial ELISA kits were used to determine ghrelin, obestatin, and nesfatin-1 concentrations (Sheep Ghrelin [GHRL] ELISA Kit [Mybiosource, Cat.no. MBS2023268, USA], Sheep Obestatin ELISA Kit [Mybiosource, Cat.no. MBS097411, USA], Sheep Nesfatin-1 ELISA Kit [Mybiosource, Cat.no. MBS033040, USA]. Plasma and milk samples were analyzed using a Biotek Epoch plate reader according to the kit protocols.

2.4 Statistical analysis

The Shapiro-Wilk test was employed to test the normality assumption in the dataset. The data were normally distributed; therefore, analyses were performed with the original data. Repeated-measures analysis of variance (ANOVA) was employed to compare ghrelin, obestatin, and nesfatin-1 levels across measurement times within each sheep group. All statistical analyses were conducted using SPSS software (version 28.0, SPSS Inc, USA), and differences were considered significant at a probability threshold of $p<0.05$.

3. Results

3.1 Changes of hormone levels in postpartum sheep over 5 weeks

Plasma ghrelin levels in postpartum lambs significantly increased from the 3rd to the 5th week ($p < 0.001$; Table 2, Fig. 1). Plasma obestatin concentrations exhibited a significant increase from 3rd to 5th week in postpartum ewes, as did ghrelin levels ($p < 0.001$, Table 2, Fig. 2). At weeks three, four, and five, plasma nesfatin-1 levels steadily decreased in contrast to ghrelin and obestatin levels ($p < 0.001$; Table 2, Fig. 3).

3.2 Changes in ghrelin, obestatin, and nesfatin-1 levels in sheep's milk at weeks 3, 4, and 5 of lactation

Sheep's milk demonstrated weekly rises in ghrelin and obestatin levels ($p<0.001$; Table 3, Figs. 1 and 3) during weeks 3, 4, and 5 of the early lactation phases. Moreover, the detection of obestatin and nesfatin-1 hormones in sheep's milk has been documented for the first time in this study. The results indicated that obestatin and ghrelin concentrations in milk were higher in week 5 compared to weeks 3 and 4 ($p < 0.001$; Table 3, Fig. 2). Nonetheless, the concentrations of nesfatin-1 in the milk exhibited a statistically significant weekly reduction, in contrast to the levels of ghrelin and obestatin ($p < 0.001$; Table 3, Fig. 4).

3.3 Changes in plasma ghrelin, obestatin, and nesfatin-1 levels in postpartum lambs at weeks 3, 4, and 5

The levels of ghrelin and obestatin in the blood of lambs exhibited a statistically significant rise over time ($p < 0.001$; Figs. 1-3). We noted a statistically significant decrease in nesfatin-1 levels compared to previous weeks ($p<0.001$; Table 3, Fig. 3).

4. Discussion

We measured the plasma concentrations of ghrelin, obestatin, and nesfatin-1 hormones involved in energy metabolism to examine these

Table 2.
Mean plasma levels of hormones analyzed during the weekly early lactation period in sheep.

Plasma hormone concentrations in postpartum sheep by week					
Analyzed hormones (n = 30)	Week 3 postpartum (mean ± SEM)	Week 4 postpartum (mean ± SEM)	Week 5 postpartum (mean ± SEM)	p value	CV % (intra-assay)
Ghrelin (pg/ml)	50.94 ± 5.37	64.98 ± 6.94	103.08 ± 9.69	<0.001	3.4
Obestatin (pg/ml)	41.03 ± 4.37	59.15 ± 6.16	89.51 ± 7.72	<0.001	3.2
Nesfatin-1 (ng/ml)	4.73 ± 0.31	3.54 ± 0.30	2.56 ± 0.26	<0.001	2.5

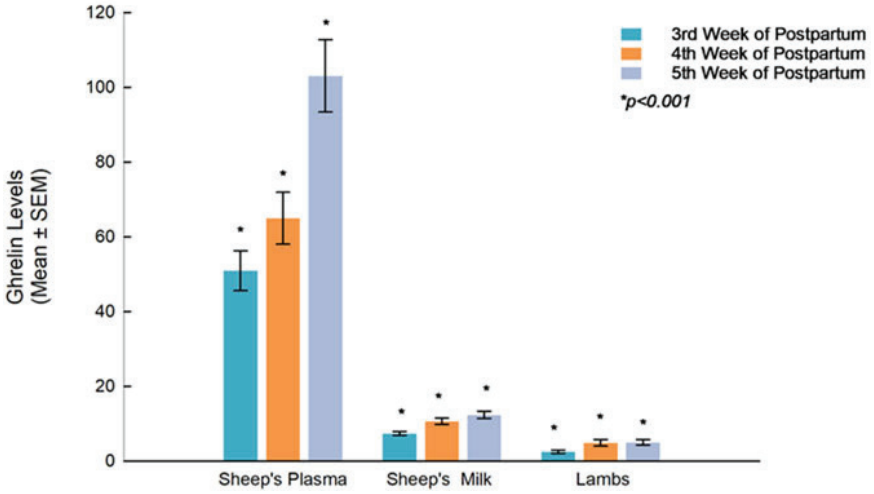

Fig. 1. Mean plasma levels of Ghrelin analyzed during the weekly early lactation period in sheep's plasma, milk and lambs. *denotes significant differences among treatments.

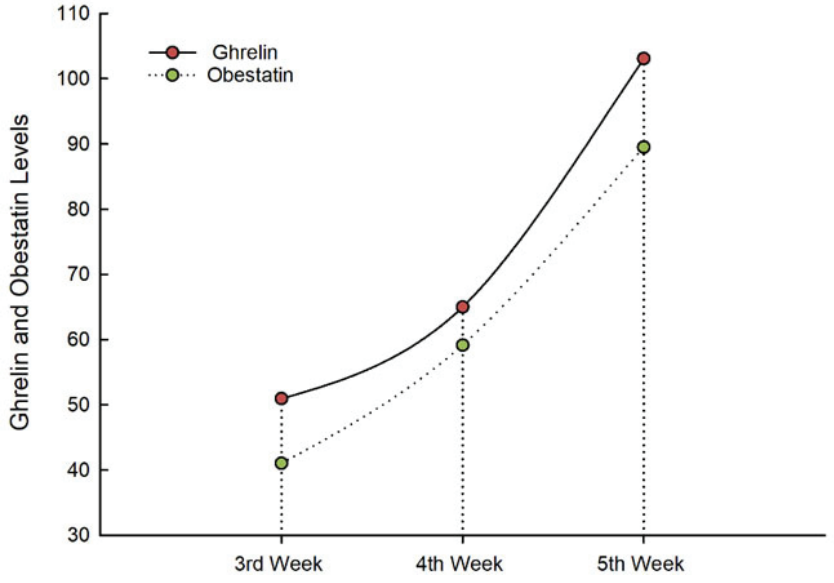

Fig. 2. Mean plasma levels Ghrelin and Obestatin analyzed during the weekly early lactation period in sheep.

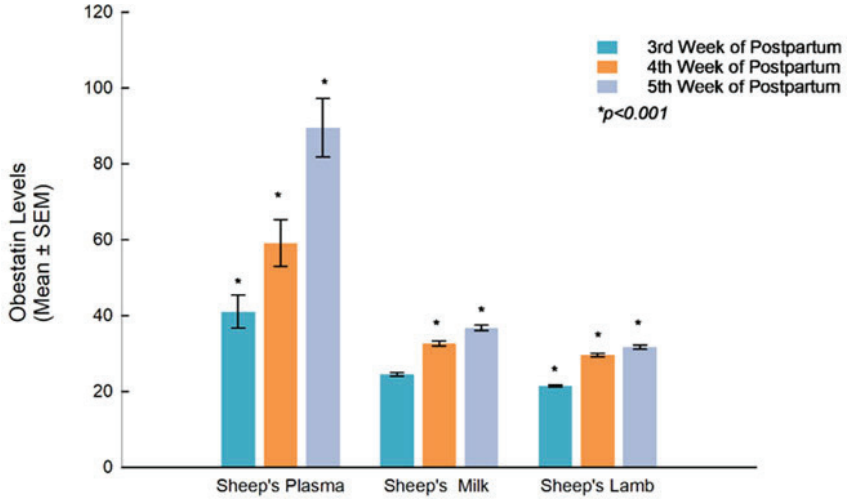

Fig. 3. Mean plasma levels of Obestatin analyzed during the weekly early lactation period in sheep's plasma, milk and lambs. *denotes significant differences among treatments.

Table 3.
Mean plasma levels of hormones analyzed during the weekly early lactation period in lambs.

Plasma hormone concentrations in lambs by week					
Analyzed hormones (n=30)	**Week 3 postpartum (mean ± SEM)**	**Week 4 postpartum (mean ± SEM)**	**Week 5 postpartum (mean ± SEM)**	**p value**	**CV % (intra-assay)**
Ghrelin (ng/ml)	2.51 ± 0.45	4.89 ± 0.89	5.01 ± 0.72	<0.001	1.7
Obestatin (pg/ml)	21.44 ± 0.26	29.58 ± 0.47	31.68 ± 0.56	<0.001	3.6
Nesfatin-1 (ng/ml)	1.25 ± 0.22	1.03 ± 0.18	0.89 ± 0.11	<0.001	1.2

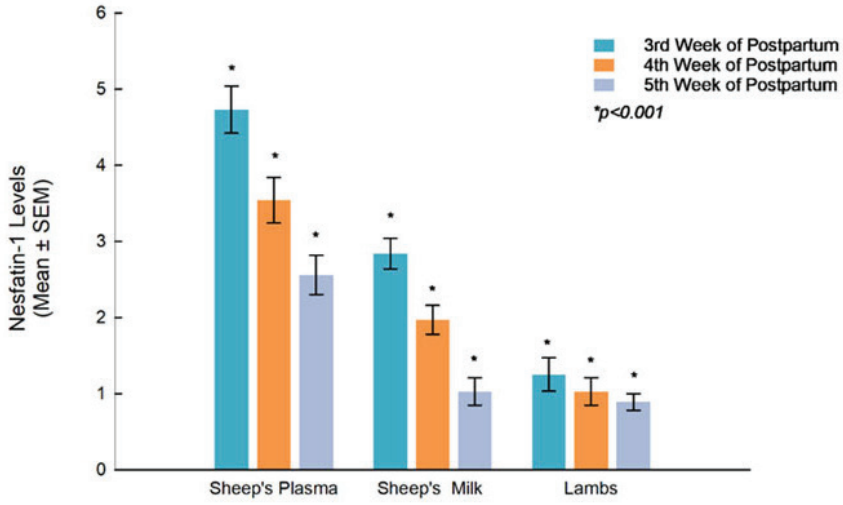

Fig. 4. Mean plasma levels of Nesfatin-1 analyzed during the weekly early lactation period in sheep's plasma, milk and lambs. *denotes significant differences among treatments.

physiological changes during weeks 3, 4, and 5 after parturition. Our results showed a statistically significant increase in plasma ghrelin and obestatin levels from week 3 onwards ($p<0.001$). Contrastingly, nesfatin-1, leptin, and insulin levels decreased statistically over the same period ($p<0.001$) in sheep. Ghrelin has two primary functions: it secretes growth hormone and stimulates the neuropeptide Y/Agouti-related peptide (NPY/AgRP) system to stimulate appetite (Kojima *et al.*, 1999). Results indicated that the increase of ghrelin during lactation in sheep could be a stimulation of the negative energy balance caused by the excess energy expended by the mother due to increased milk yield.

Energy expenditure in terms of breastfeeding and milk production supports nutrient intake during lactation (Woodside, 2007). Moreover, NPY: Neuropeptide Y AgRP: Agouti-related peptide mRNA: Messenger ribonucleic acid expression increases, leading to hunger (Pickavance *et al.*, 1996). Ghrelin is reported to stimulate negative energy balance in dairy cows (Bradford and Allen, 2008) and mice (Sun *et al.*, 2008). It has been demonstrated that increased ghrelin peptide promotes negative energy balance by facilitating stomach emptying (Asakawa, 2005). It is essential to acknowledge that metabolic effects of ghrelin are influenced by age and genetic predisposition. It has been demonstrated that the ghrelin/GHS-R signaling pathway serves as a modulator of energy balance rather than a primary regulator (Sun *et al.*, 2008). The rise of plasma ghrelin in nursing sheep observed in the present study is likely related to ghrelin's function as a modulator in response to the energy deficit.

Obestatin was identified as an anorexigenic peptide, unlike ghrelin (Lagaud *et al.*, 2007), although further research does not corroborate these results (Gourcerol *et al.*, 2006; Green *et al.*, 2007). In our previous study on exogenous acute and chronic administration (by intraperitoneal administration) of ghrelin and obestatin to mice, we found that ghrelin and obestatin worked together, and in the food-restricted mice group, ghrelin and obestatin concentrations increased in parallel (Udum *et al.*, 2016). In this study, it was investigated whether plasma obestatin in lactating sheep is in harmony with ghrelin, and consistent results with our previous study were observed. Plasma obestatin levels of lactating ewes increased statistically significantly in parallel with ghrelin, again supporting the theory that ghrelin and obestatin work together to regulate metabolism and energy balance.

The function of nesfatin-1 in ruminant metabolism is still unclear. A recent study indicated that nesfatin-1 levels decreased in lambs who received dietary supplements and had superior body condition ratings. Nesfatin-1 concentrations were decreased in this group of animals due to heightened hunger and increased energy requirements (Barbato *et al.*, 2021). Therefore, low levels of nesfatin-1 promote the body's recovery of reserves, underscoring its significance as a peptide in energy metabolism. In our study, nesfatin-1 concentrations in both plasma and milk of sheep were inversely related to ghrelin and obestatin levels. As the weeks progressed, ghrelin and obestatin levels increased, while nesfatin-1 values decreased. In this case, nesfatin-1 levels decreased because the ewes needed more energy as their milk yield increased, and ghrelin and obestatin levels increased in response to the increased energy needs. We support the earlier study (Barbato *et al.*, 2021) with our blood and milk data and showed a statistically significant decrease in nesfatin-1 values in sheep's plasma with increasing numbers of weeks.

This is the first study to our knowledge showing the presence and levels of ghrelin, obestatin, and nesfatin-1 in sheep's milk. Previous studies (Aydin *et al.*, 2008, 2006) have reported the presence of obestatin and ghrelin in human milk and noted the presence of nesfatin-1 in dairy cattle (Aydin, 2013). In our investigation, concentrations of ghrelin and obestatin in sheep's milk were consistently increased in accordance with plasma levels in sheep. Aydın *et al.* (2008) reported that ghrelin and obestatin levels in human milk were higher than those in plasma. However, ghrelin and obestatin concentrations in milk were lower than sheep's plasma levels in our study. Nesfatin-1 values in sheep's milk decreased over the weeks, like levels in sheep's plasma, but remained lower than plasma nesfatin-1 levels. We hypothesize that ghrelin, obestatin, and nesfatin-1 peptides in sheep's milk transfer from plasma into milk; however, we need evidence of mammary gland production of these hormones.

Aydin *et al.* (2008) suggest that the mammary gland might secrete these hormones, as they found higher ghrelin and obestatin levels in milk. However, in our investigation, we are unable to substantiate this assertion, as the hormone concentrations in milk were lower than those in plasma. Another study (Ilcol and Hizli, 2007)found that ghrelin levels in human milk were lower than those in maternal plasma, which is consistent with our data. Furthermore, our study focused exclusively on weeks 3, 4, and 5, during which the ewes exhibited elevated milk supply. Determining the levels of these peptides involved in energy metabolism during periods of high milk production may be significant.

Nevertheless, further studies are required to determine whether cells in the mammary gland can produce these peptide hormones. Ghrelin, obestatin, and nesfatin-1 levels were measured in blood samples taken from lambs at weeks 3, 4, and 5 after birth, and we observed increased ghrelin and obestatin plasma levels in lambs while nesfatin-1 levels decreased ($p<0.001$). Although these results were consistent with the hormone and milk values of ewes at weeks 3, 4, and 5, the levels were lower. The plasma levels of ghrelin, obestatin, and nesfatin-1 in lambs might be transmitted from the mother's milk to the offspring or could vary based on the energy needs of the lambs. Given the growing energy requirements of lambs, it is more logical that ghrelin and obestatin levels increase and that nesfatin-1 levels decrease. This is supported by its ability to stimulate growth hormone, considering the function that gave ghrelin its name (growth hormone releasing), and the increase in ghrelin levels by weeks is directly proportional to the growth of lambs. The discovery of ghrelin and obestatin in maternal milk confirms studies suggesting that these compounds may have a lasting impact on the control of eating behavior, metabolism, and energy balance (Savino *et al.*, 2012).

5. Conclusions

We detected the presence of ghrelin, obestatin, and nesfatin-1 in sheep's milk during early lactation. Concentrations of these hormones in milk were lower than those in sheep's plasma. Nonetheless, we demonstrated that plasma ghrelin and obestatin levels in sheep rose at a rate comparable to that observed in milk. In contrast, nesfatin-1 levels decreased in parallel in both sheep's plasma and milk. Although nesfatin-1 levels diminished concurrently in both sheep plasma and milk. Additionally, we noted that plasma levels of ghrelin, obestatin, and nesfatin-1 in lambs had similar rises and declines relative to the plasma and milk levels of their maternal sheep. Our triadic analysis study on the hormone levels of sheep's plasma, sheep's milk, and lamb's plasma showed that these peptide hormones were detectable in all samples. We report that these peptides that regulate energy metabolism in ruminants collaborate, and the presence of these peptides in the mother's milk could be transmitted to their offspring. Alternatively, the production of these peptide hormones in the offspring might be crucial for energy metabolism and growth. In our sheep study and as in our previous research in mice, we have shown that ghrelin and obestatin peptides do not work in opposition but complement each other according to energy metabolism.

CRediT authorship contribution statement

All authors were actively involved in conceptualization, data curation, methods, fundng acquisition and writing review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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