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Review article

Analysis of the IGF-system in milk from farm animals – Occurrence, regulation, and biomarker potential

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ABSTRACT

IGFs and IGF-binding proteins (IGFBPs) are abundantly present in milk and in dairy products. Compared to the IGFs, the IGFBP have received less attention in milk, although truncated IGFBPs and IGFBP-glycosylation have been described in milk. Thereby, complex control of local IGF-effects can be assumed on the levels of IGFBPs, proteases, and protease inhibitors. The present review collects the current knowledge both on presence and regulation of IGFs and IGFBPs in milk particularly from dairy animal species. As a rule higher levels of IGF-I, IGF-II, and IGFBPs are measured around parturition if compared to later time-points of lactation. In all farm animal species included in this review, it is found that the relative abundancies of IGFBPs in milk and serum are similar, with IGFBP-3 and -2 characterized by higher concentrations if compared to IGFBP-4 or -5. The concentrations of IGFs and IGFBPs in milk or dairy products can be altered by hormones, dairy processing, or fermentation. Because milk can be used for non-invasive biomarker research, quality management, and health monitoring, we discuss novel directions of IGF-analysis and potential on-site biomarker research in milk.

1. Introduction

IGFs and IGFBPs impact on cell physiology, growth, and metabolism throughout the body and a number of recent reviews has addressed specific functions of the IGF-system [1–8]. IGF-I as the dominant growth factor postnatally, is known to control the cell cycle and to increase cell proliferation or to inhibit apoptosis [9–11]. After birth, IGF-II is not a physiological regulator of somatic growth. However expression of IGF-II is increased in a number of malignant conditions [12] or in the clinical setting of metabolic dysfunction including obesity or diabetes [13]. IGFBP-1 to -6 on one hand are thought to mediate cell type specific effects of the IGFs. On the other hand, IGFBPs have IGF-independent effects inside or outside the cell [14,15]. In addition, IGFBPs may be processed by posttranscriptional modifications [16] or by distinct proteases giving rise to defined IGFBP-fragments [17]. Due to the high complexity of IGF-compounds in milk, the IGF-system has tremendous potential for biomarker research. In farm animals, milk is available noninvasively and in large quantities. Compared to the IGFs [18], IGFBPs have received much less attention in milk. The physiological significance of IGFs and IGFBPs in milk has been discussed by Gauthier et al. in 2006 [19] and a recent update will follow as a separate review soon (manuscript in preparation). The present review will focus both on occurrence and regulation of IGFs and IGFBPs in dairy milk and discuss biomarker potential of milk-borne IGFs and IGFBPs in farm animals.

2. Analysis of the IGF-system in milk

In milk IGF-I and IGF-II as well as all six IGFBPs have been identified so far [20–23]. The concentrations of IGFs and IGFBPs tremendously may vary in this matrix, sometimes with concentrations above blood levels [21,24].

2.1. Ruminants

Worldwide, cow milk amounts to 83% of dairy production, with about 13% from buffalo, 2.4% from goat, 1.4% from sheep and 0.3% from camel [25]. Generally, comparing bovine IGF (Table 1) and IGFBP (Table 2) concentrations in milk and colostrum, it is clear, that there are much higher concentrations in prepartum secretions or colostrum and

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Table 1
Concentrations of IGF-I and IGF-II in mammary secretions of farm animal species. Timepoint of lactation in days (d), weeks (w) or months (m) (TG: transgenic; LOD: limit of detection).

Species	IGF-I (ng/ml)	IGF-II (ng/ml)	Sampling	Method	Reference
Cattle	1000–3000		Colostrum		[29]
	10–50		Milk		
	190–233	207–216	Colostrum	RIA	[30]
	4–10	2–6	w2 and w7		
	248–1850		Colostrum	ELISA	[27]
	27–101		5th milking		
	312	187	Colostrum	RIA	[35]
	≈ 300		Colostrum	TR-IMFA	[36]
	7		d6		
	< 5	32	Milk	RIA	[35]
	< 5	40	MR	RIA	[35]
	4–9 (LOD: 1 pg/ml)			ECLIA	[31]
	Des1-3-IGF-I		Colostrum, milk	RIA	[32,34]
Buffalo	≈ 800		Colostrum	RIA	[38]
	≈ 200		d1–d14		
	2		w12–w19	ELISA	[39]
Goat	626		Colostrum	RIA	[114]
	13		Milk	RIA	[44]
	5		m5	RIA	[42]
Sheep	199		d140		[115]
Horse	259		Colostrum		[55]
	11		d5		
Pig	72	165	Colostrum	RIA	[51]
	10	11	d5		
	67–357		Colostrum	RIA	[53]
	4–14		d4-d14		
	36	56	Colostrum	RIA	[54]
	3–4	16	d14–d24		
	TG: 949		Colostrum		

that mature bovine milk predominantly contains IGF-I and IGFBP-3 [21,26–30]. According to Blum and Baumrucker the ranking of the IGFBP concentrations in bovine mammary secretions are IGFBP-3 > IGFBP-2 ≅ IGFBP-4 > IGFBP-5 [21,24]. In colostrum IGF-I and IGF-II concentrations higher than 1000 ng/ml have been measured whereas in mature milk the concentrations range between 2 and 300 ng/ml. For the assessment of extremely low IGF-I concentrations in bovine milk an electrochemiluminescent assay was developed with a limit of detection < 0.001 ng/ml [31]. The assay was used for the quantitation of IGF-I in two frozen milk samples and revealed values of 4–9 ng/ml in serial dilutions of both samples [31]. In addition to intact IGF-I, N-terminally truncated IGF-I (des1-3-IGF-I) was identified in bovine colostrum [32]. Truncated IGF-I, which amounted to about one third of total IGF-I purified from bovine colostrum, is characterized by increased biological activity [32] due to reduced IGFBP-binding affinity [33]. Des1-3-IGF-I is also present in mature bovine milk, however amounts to only 3% of total IGF-I [34]. Similar to human milk, IGFBP-3 and IGFBP-2 were identified as the most abundant binding proteins in bovine mammary secretions [19]. In bovine colostrum, Lee and colleagues have identified glycosylation of an unidentified 37 kDa IGFBPs by the use of N-glycanase and Western ligand blotting [35]. The concentration of IGFBPs is high in bovine prepartum milk-like secretions (BPMS), colostrum and late lactation milk, and low in milk of mid lactation [36]. IGFBP-2 was analyzed in milk samples derived in 3-week intervals from dairy cows and goats after birth until week 39 and 49, respectively [37]. In milk derived from cows, the concentrations of IGFBP-2 declined after birth from about 600 ng/ml in colostrum to < 20 ng/ml at week 18 [37]. Towards week 49 of lactation IGFBP-2 concentrations in milk slowly increased up to about 40 ng/ml [37]. In goat milk an almost identical pattern was observed [37]. The findings nicely confirm results from the previous study in dairy cows showing highest levels of IGFBP-2 concentrations in colostrum followed by a sharp decrease until week 24 and a slight increase afterwards [36]. Compared to IGFBP-2 concentrations in milk, IGFBP-3, -4, and -5 follow the same pattern during lactation [36]. Notably, before birth the concentrations of IGF-I and IGFBP-3 in milk exceeded those in colostrum, nevertheless, colostrum revealed the highest proliferative activity if compared to other milk before or after birth [36]. About 1 week after birth, IGFBP-2 appears to be the dominant IGFBP present in milk [36].

In colostrum of Egyptian buffalos IGF-I was high around parturition (≈ 800 ng/ml) and decreased to about 300 or 200 ng/ml, within 12 or 24 h [38]. Until day 14 there was no further decline of IGF-I in buffalo milk and the pattern of IGF-I concentrations in milk samples derived from buffalo were almost identical if compared to Holstein cows in the course of lactation [38]. Interestingly between week 12 and week 19 of lactation, IGF-I concentrations in buffalo milk were increased (week 12–13: 1.7 ng/ml; week 17–19: 2.5 ng/ml) [39]. IGFBP-5 was quantified in milk from Murrah buffalos and compared to Sahival cattle [40]. In both groups IGFBP-5 were on high levels (≈ 300.000 ng/ml) around parturition but almost undetectable after 50, 100, and 150 days of lactation [40]. At later time points of lactation (200–300 days), increases of IGFBP-5 concentrations in milk were identified particularly in Sahival cow milk and on significantly lower levels also in buffalo milk. Additional IGFBPs were not described in buffalo milk to our knowledge.

In goat milk IGF-I, IGF-II and IGFBP-2 were identified [41]. About 5 months postpartum, IGF-I concentrations ranged around 5 ng/ml in goats [42]. As demonstrated by the injection of radiolabeled peptide hormones and IGFBPs in goats, IGF-I, IGF-II, IGFBP-2, and IGFBP-3 can pass over from the circulation to mammary secretions, [43–46]. Milk borne IGFs and IGFBPs, at least in goats, can thus origin also from other than mammary cells. In dairy cows characterized by increased concentrations of IGF-I in the circulation, also higher IGF-I concentrations were found in mammary secretions [47]. By comparison with IGF-I levels in both matrices however a passive diffusion between both matrices was not suggested for IGF-I [47]. In sheep milk IGFBP-2 seems

Table 2
Absolute or relative concentrations of IGFBPs in mammary secretions of farm animal species (*ng/ml; timepoint of lactation in days (d), weeks (w) or months (m); relative abundance is indicated as follows: + + + + > + + + > + + > +).

Species	IGFBP-1	IGFBP-2	IGFBP-3	IGFBP-4	IGFBP-5	Sampling	Method	Ref.
Cattle		+ +	+ + +	+ +	+			[21]
		+ + +	+ + +	+ +	+	d1-m5	WLB	[26]
		+ + +	+ + +	+ +	+	d1-w24	WLB	[36]
					+	d50–300	ELISA	[40]
	Total IGFBP activity: 7270*					w2–3	RLA	[30]
		+ +	+ + +	+ +	+	Colostrum	WLB	[35]
Buffalo					+	d50–300	ELISA	[40]
Sheep		+					WLB	[48]
Pig		+ + +	+ + +	+	+	d4	RIA	[51]
			2550*			Colostrum	RIA	[116]
			910*			Milk		

to be the dominant binding protein [48].

In camel milk the IGF-system so far has not been assessed. However, the analysis of IGF-I in camel serum by a radioimmunoassay developed against human IGF-I [49], both in the neonate and in the mother revealed higher IGF-I levels around parturition (> 600 ng/dl) and a significant decline at later time points (day 30: < 205 ng/dl) of lactation [50].

2.2. Other species

After delivery, IGF concentrations in milk also declined in pigs from 72 ng/ml at day 1 to 10 ng/ml for IGF-I at day 28 and from 165 ng/ml at day1 to 11 ng/ml at day 28 for IGF-II [51]. Interestingly, primiparous gilts have lower IGF-I concentrations in milk if compared to multiparous sows and fat supplementation of food increased both milk IGF-I and growth rates in piglets [52]. Total IGF-binding activity in porcine milk increased from day 1 to day 4 after delivery and decreased thereafter [51,53]. IGFBP-2 and IGFBP-3 appear to represent the most abundant IGFBPs in porcine milk followed by IGFBP-4 and an additional at that time unidentified IGFBP characterized by a molecular weight of 28 kDa [51]. A band around 28 kDa was identified by Monaco and colleagues as IGFBP-5 [54]. Interestingly, IGFBP-5 represents the dominant IGFBP around delivery in pigs [54]. Transgenic overexpression of human IGF-I in the mammary gland of pigs increased the concentrations of IGF-I from 36 ng/ml in non-transgenic pigs up to almost 1000 ng/ml around parturition in transgenic pigs [54]. In parallel, also the concentration of IGFBP-2 and IGFBP-5 were significantly increased in that study [54]. Also in horse colostrum higher IGF-I concentrations were measured if compared to milk 5 days after parturition [55]. Finally, IGF-I was also measured in mammary secretions derived from tammar wallabies [56]. The concentrations of IGF-I in wallaby milk increased between day 99 and day 205 from 16.5 ng/ml to > 1000 ng/ml, which is a > 60-fold increase [56]. Towards the end of lactation IGF-I concentrations in milk fell to about 300 ng/ml [56]. The high IGF-I concentrations in milk between days 200 and 220 of lactation coincided with an increased proliferative activity in cultured rat L6 myoblasts [56]. Very recently, IGFBP-5 was identified by mass spectrometry in milk from the tammar wallaby at day 20, 60, and 120 day of lactation and discussed in a context of lung development in the pouch young [57].

3. Control of IGF and IGFBP concentrations in milk

IGF and IGFBP concentrations in milk can be affected by local expression in the mammary gland during growth and differentiation but also during involution of the mammary gland. In addition we know that IGF-compounds also derive from other parts of the body as IGFs and IGFBPs can be transferred from the blood to milk.

3.1. Hormonal control of IGF compounds in milk

It is well accepted that GH represents a galactopoietic hormone increasing IGF-I concentrations both in vertebrate plasma and in milk [45,58,59]. Hormonal control of the mammary gland has been exquisitely revised recently [60]. Considering hormonal control of IGF-compounds in milk, it also just recently was shown that local expression of growth hormone (GH) in mammary glands of transgenic goats increased RNA expression of IGF-I, IGF-II, and IGFBP-3 [61]. In their study Bao et al. discuss a model where IGF-I from stromal cells in a paracrine fashion stimulates proliferation and branching of alveolar epithelial cells [61]. Interestingly, GH-transgenic goats produce more milk between day 1 and day 30 of lactation, however, biochemical milk parameters (e.g. lactose content or protein content) were different only on the first day of lactation [61]. Also in goats, a retrospectively formed group of *responders* after GH-injection had 40% increased concentrations of IGF-I in their milk [62]. Subcutaneous injection of GH in cows also increased milk yield and the concentrations of IGF-I in milk from 3 ng/ml to 12.3 ng/ml after 7 days of treatment [63]. GH injection in cows increased hepatic but not mammary IGF-I mRNA expression [64], which is surprising, because mammary stromal cells respond to external GH application with increased expression of IGF-I mRNA expression [65]. Systemic injection of insulin combined with glucose alone had no significant effect on IGF-I concentrations in milk from Holstein cows [66]. However, insulin increased the positive effect of GH on the concentrations of IGF-I in milk and other milk parameters (milk yield, protein yield, casein yield) [66]. Notably, insulin infusion also restored IGF-I serum concentrations in periparturient cows characterized by negative energy balance by increasing the expression of GH receptor in the liver [67]. Short term treatment with GH and estrogen increased protein levels of IGF-I but decreased those of IGFBP-3 in mammary tissues isolated from Friesian heifers at an age of 18 months [68]. The increased ratio of IGF-I/IGFBP-3 was discussed in a context with mammogenesis [68]. Estrogen had no effect on stromal IGF-I mRNA expression [65] but suppressed expression of IGF-I mRNA in the mammary gland from pregnant pigs [69]. In mouse primary mammary epithelial cells (MEC), IGF-II mRNA and protein expression was induced by prolactin and alveologenesis was impaired in IGF-II deficient MEC [70]. Since expression of IGF-II in prolactin receptor deficient MEC restored alveologenesis, IGF-II was discussed as a mediator of prolactin-related morphogenesis in the mammary epithelium [70]. Sodium butyrate, which increased mRNA expression and secretion of IGFBP-3 in vitro [71], also increased linear growth and serum concentrations of GH and IGF-I in calves, if supplemented to the milk in a dose dependent manner [72].

Compounds from the IGF-system may also derive from non-mammary tissues since radiolabeled IGFs and IGFBPs systemically injected in goats [41] or rats [73] can be transferred from blood to milk, which in particular may explain the high hormone concentrations found in colostrum. As a consequence, exogenous or endogenous factors affecting concentrations of IGF-compounds in the circulation may also have effects on the IGF-system in the milk. Nevertheless, there is also an example of independent regulation of the IGF-system in the circulation if compared to milk, because seasonal changes affected concentrations of IGF-I in the serum but not the milk from lactating cows [74].

For the control of milk proteins also local distribution within the mammary tissue has to be concerned. In the transition period from pregnancy to lactation the closure of mammary epithelial tight junctions is observed. Thereby, secretion of milk proteins via the apical membrane is increased whereas secretion through the basolateral membrane is decreased, which guides secretory proteins to the mammary ducts and to a lower extent to the extracellular space [75]. Accordingly, Tonner and colleagues observed increased secretion of IGFBP-5 versus local distribution in the mammary gland in response to the lactogenic switch [76]. Increased expression of IGFBP-5 observed in rats or pigs during involution, teat sealing, or suckling removal, was suppressed after gland rescue in sows [77] or after 2 days of prolactin injection in rats [78]. By contrast, local production of IGF-I and IGFBP-3 in mammary glands reduced apoptosis during involution in lactating transgenic mice [79]. In pigs, high expression of prolactin receptor and low expression of IGFBP-5 were discussed as permissive conditions for the functional lactating mammary gland [80]. Application of 17-beta-estradiol, after suckling removal, as well as GH, progesterone, corticosterone, and an antiserum to IGF-I had no effect on IGFBP-5 concentrations [78]. Notably, IGFBP-5 expression during mammary gland involution is a (direct or indirect) target of signal transducer and activator of transcription 3 (STAT3), which is regulated by multiple growth factors, cytokines, and hormones including GH [81]. In fact in the mammary gland of transgenic goats GH induced mRNA expression of IGF-I, IGFBP-3, and IGFBP-5 [82]. In mice, the expression of IGFBPs is strongly compartmentalized in the mammary gland and depends on lactational age [83]. Expression of most of the IGFBPs is low during late lactation, whereas expression of IGFPB-2 and IGFBP-5 is increased

during forced gland involution after pup removal [83].

In addition to hormonal control also sampling [84], milking frequency [85,86], and milk processing [26] have an effect on the presence of IGFs and IGFBPs in milk or dairy products. Accordingly, cisternal colostral milk has a higher concentration of IGF-I than alveolar milk [84]. Thus, the time-point of sampling determines the absolute concentration of the analyte [84]. Higher milking frequency in dairy cows suppressed mammary expression of IGFBP-1, IGFBP-3, or -5 and was discussed in a context both of higher proliferative and secretory activity of mammary epithelial cells in response to 4 times per day versus once per day milking [85,86].

3.2. IGFs and IGFBPs in dairy products

IGFBP-2 to -5 are present in bovine milk and skimmed milk but not in cream from the same species and after ultracentrifugation (2 h, 50,000 g) most of the IGFBPs were present in the intermediate aqueous fraction [26]. Heat inactivation of virulent cytomegalovirus in human breast milk for 30 min at 63 °C (Holder-Pasteurisation) resulted in a partial degradation of IGF-I (− 39%), IGF-II (≈ − 10%), IGFBP-2 (≈ − 19%), and IGFBP-3 (− 7%) [87]. By contrast short term inactivation of human breast milk (5 s at 62, 65, or 72 °C) almost completely preserved the IGFs and IGFBPs assessed in that study [87]. Also dairy processes have a fundamental effect on IGF-I concentrations [88]. Accordingly, heat treatment of cows bulk milk for 15 min at 75 °C or 85 °C decreased IGF-I concentrations by almost 50%, whereas autoclaving completely eliminated immunoreactive IGF-I [88]. Similarly, fermentation results in an almost complete loss of IGF-I only if the pH is close to 4.06 [88]. In homogenized milk or in milk reconstituted from dry milk no alteration of IGF-I could be observed [88].

3.3. Proteolysis of IGFBPs in milk

Proteolysis of IGFBPs is an important part of functional regulation, both of IGFs and IGFBPs and as mentioned earlier, IGFBP-2 fragments have been detected in human milk [89,90]. In the mouse mammary gland, pregnancy-associated plasma protein (PAPP)-A was identified [91]. Since PAPP-A is known to cleave IGFBP-2, -4, and -5 [17], also other truncated IGFBPs may be present in milk. In addition to intact, truncated IGFBP-5 characterized by a molecular weight of 21 kDa was present in rat milk after removal of the litter [78]. In breast cancer cell lines estrogen increased the IGFBP-protease cathepsin D [92] and both estrogen and proteases are discussed in context of breast cancer [93].

3.4. Effect of diet

Removal of food for a period of 2 days decreased serum IGF-I but increased serum IGFBP-2 concentration in lactating Holstein cows [94]. Also in humans low protein intake is associated with decreased serum IGF-I concentrations [95] or prolonged fasting increased IGFBP-2 serum concentrations [96]. By contrast, 50% feed restriction over a period of 4 days did not affect the concentration of IGFBP-2 in serum [97]. Notably, after 16–30 weeks of lactation a slight reduction of IGFBP-2 concentrations in milk was observed in cows fed a diet characterized by reduced energy content and increased protein content if compared to controls [37]. By mild nutrient restriction, on a diet providing only 70% of the daily needs for protein and energy neither blood nor colostrum from dairy cows contained altered concentrations of IGF-I [47]. Food restriction over a period of 36 h in dairy cows reduced concentrations of IGF-I in plasma but not in afferent lymph [98]. Concentrations of IGF-II were unaffected by food restriction in both matrices [98]. The effects of food supplementation with essential oils from oregano, considered to improve meat quality, had no effect on IGF-I levels in colostrum or milk from sows [99]. Notably the known effects also of distinct dietary compounds on the IGF-system, such as conjugated linoleic acids [100], secondary plant products [101], or trace elements [102] may impact on the composition of the IGF-system in milk or dairy products as discussed earlier.

4. Biomarker potential of IGF-compounds in milk

From dairy animals milk is available on a basis of routine and can be screened for potential biomarkers including the IGF-system which is thought to have predictive potential for the physiological status in selected animals [26]. Accordingly, a positive correlation was described between IGF-I concentrations in fore-milk from dairy cows and somatic cell count, due to the elevated number of polymorphonuclear leucocytes (PMNL) [103]. The authors speculated that in acute clinical or during chronic subclinical mastitis IGF-I, originating from activated alveolar macrophages is directly secreted as a chemotactic attractant for PMNL into milk [103,104]. In addition, IGFBP-5 was massively increased in milk from cows and buffalos at peak lactation diagnosed at mastitis [40]. The increase was tremendous, comparing < 20 ng/ml in normal milk versus > 700 ng/ml in milk from cows with mastitis [40]. Expression analysis on the level of mRNA confirmed high expression of IGFBP-5 in somatic and epithelial cells from the mammary gland of cows [40]. IGFBP-5 as an effector of cell-death during mammary involution [76] may thus correlate with reduced secretory capacity of the mammary gland. In fact, also short lactating cows or buffalos had almost 10-fold higher levels of IGFBP-5 in their milk compared to normal lactating animals [40]. Other IGFBPs, also may be useful for routine monitoring since those might reflect the condition of the GH-IGF-I axis as suggested by Mesotten and van den Berghe in humans [105]. Accordingly, IGF-I and IGFBP-3 are high during normal GH-secretion, whereas the group of IGFBPs characterized by smaller molecular weights, particularly IGFBP-2, are suppressed by GH [105]. Thus a ratio of IGFBP-3/IGFBP-2 detects alterations of GH secretion with outmost sensitivity. In humans, GH secretion is altered during acute or chronic illness or disease [105], the assessment of complex signatures consisting of IGFs, IGFBPs and IGFBP-ratios may be useful for sensitive health monitoring also in farm animals. Piechotta et al. [106] and Mysegades [107] already provided specific support for this hypothesis in dairy cows since they observed altered expression of IGFBP-2 in conditions of ketosis or elevated body temperature. A current problem of IGFBP-related biomarker research is due to proteolysis of IGFBPs as discussed earlier in this review. Because ELISA assays could measure both intact and fragmented IGFBPs, it is necessary to include structural and functional information on a particular potential IGFBP-related biomarker, which can be achieved e.g. by Western ligand blotting for intact IGFBPs [108] or time-resolved immunofluorometric assays e.g. for the assessment of defined IGFBP-fragments [109]. Already today, it is possible to perform on-site biomarker research, health management, and quality control by means of protein microarrays combined with fluorescence optics coupled to an ordinary smartphone [110]. By this methodology elevated IGF-I concentrations in extracted milk samples from GH-treated dairy cows were confirmed [110]. In a perspective, microarray based technologies developed in hand-held formats definitely will expand the chemical class of proteins since miRNA [111], metabolites [112], or toxic substances [113] also are highly attractive to biomarker research in milk.

5. Summary and conclusion

Based on the achievements of research so far dedicated to the IGF-system in milk and dairy products it is clear that IGF-I, IGF-II, and all IGFBPs can be detected in milk. Compared to IGF-I, IGF-II and particularly the IGFBPs have received much less research in milk and in dairy products. In general, the composition of IGFBPs in milk is similar to the IGFBP-profile in serum, with IGFBP-3 and -2 characterized by higher abundancy if compared to IGFBP-4 and -5. Perinatally, higher concentrations of IGFs and IGFBPs are detected if compared to later time-points of lactation. As a potential reason for the sharp decline

of the IGF and IGFBP concentrations in mammary secretions during transition from pregnancy to lactation, closure of the tight junction has been suggested. In addition, the IGF-system can be regulated by locally produced or systemically injected GH. Interestingly, the effect of GH on IGF-I expression in mammary cells or IGF-I concentration in milk appears to be co-regulated by insulin, estrogen or dietary sodium butyrate. The concentrations of IGFs and IGFBPs further can be altered by dairy processing, such as sterilization or fermentation, whereas homogenization had no effect on IGF-I concentrations in milk. In addition to intact also fragmented variants have been described in milk for IGF-I, IGFBP-2, and IGFBP-5. While the physiology of proteolytic degradation of IGFs and IGFBPs remains to be investigated in milk, there are urgent needs for the application of appropriate analytical approaches. Given the central importance of the IGF-system for health and metabolism and because milk is accessible by noninvasive methods or routinely available, it may represent an ideal matrix for IGF-related health monitoring and herd management.

Conflicts of interest

CH, EW and AH are related to Ligandis GbR. SO is employed by MQD M-V mbH, Institut für Analytik und Hygiene, Güstrow.

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