Invited review: Growth-promoting effects of colostrum in calves based on interaction with intestinal cell surface receptors and receptor-like transporters

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ABSTRACT

The postnatal development and maturation of the gastrointestinal (GI) tract of neonatal calves is crucial for their survival. Major morphological and functional changes in the calf's GI tract initiated by colostrum bioactive substances promote the establishment of intestinal digestion and absorption of food. It is generally accepted that colostrum intake provokes the maturation of organs and systems in young calves, illustrating the significance of the cow-to-calf connection at birth. These postnatal adaptive changes of the GI tissues in neonatal calves are especially induced by the action of bioactive substances such as insulin-like growth factors, hormones, or cholesterol carriers abundantly present in colostrum. These substances interact with specific cell-surface receptors or receptor-like transporters expressed in the GI wall of neonatal calves to elicit their biological effects. Therefore, the abundance and activity of cell surface receptors and receptor-like transporters binding colostrum bioactive substances are a key aspect determining the effects of the cow-to-calf connection at birth. The present review compiles the information describing the effects of colostrum feeding on selected serum metabolic and endocrine traits in neonatal calves. In this context, the current paper discusses specifically the consequences of colostrum feeding on the GI expression and activity of cell-receptors and receptor-like transporters binding growth hormone, insulin-like growth factors, insulin, or cholesterol acceptors in neonatal calves.

Key words: cow-to-calf connection, digestive tract, mammary gland, perinatal period, cell surface receptor

INTRODUCTION

The Cow-to-Calf Connection for the Postnatal Development of Calves

After birth, the transfer of nutrients from mother to fetus ceases and the neonate must orally ingest nutrients and digest them. Colostrum is typically the first food ingested by the calf. Thus, colostrum intake exposes the gastrointestinal (GI) tract of neonatal calves to nutrients (e.g., fat, lactose) and various bioactive substances such as immunoglobulins, IGF, insulin, or cholesterol (Table 1; Koldovský, 1989). Bioactive substances found in mammary secretions elicit their biological effects directly on the wall of the calf's GI tract, are first transported across intestine into the calf's circulation, or both. These substances are either locally synthesized in maternal mammary tissues, are transferred from blood circulation by various mechanisms, or both (Baumrucker and Albrecht, 2014; Baumrucker and Bruckmaier, 2014). The transfer of some bioactive substances present in colostrum is mediated by cell surface receptors and receptor-like transporters located within the calf GI tract (Baumrucker and Albrecht, 2014; Ontsouka and Albrecht, 2014). For example, the transport of IgG₁ from maternal blood circulation into colostrum is mediated by neonatal Fc receptor (FcRn), whereas that of cholesterol is thought to involve ATP-binding cassette (ABC) transporters of classes A and G (Mayer et al., 2005; Lu et al., 2007; Mani et al., 2009, 2010). Other additional transporters are also involved in cholesterol transport. They include, for instance, the scavenger receptor (SR)-B1 (Truong et al., 2010; Ji et al., 2011), the Niemann Pick C1-like protein 1 (NPC1L1; Altmann et al., 2004; Davis et al., 2004), and NPC1 (Mani et al., 2009) whose transport mechanisms, however, are not a focus of the current review.

Bioactive substances in colostrum have beneficial effects on morphological growth and functional maturation of the GI tract as well as on the metabolic, en-

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Table 1. Selected constituents of colostrum milked on d 1, 2, and 3 after parturition fed to calves^{1,2}

Trait	Milking 1 (first colostrum)	Milking 3 (transition milk)	Milking 5 (mature milk)
DM, g/kg	240	165	157
Gross energy, MJ/kg of DM	24.9	24.1	22.3
CP, g/kg of DM	555	468	345
Crude fat, g/kg of DM	265	263	197
Nitrogen-free extract, ³ g/kg of DM	104	226	402
Crude ash, g/kg of DM	75	45	55

¹Colostrum fed on d 1 to 4 of life was derived from pooled milkings 1, 3, and 5 (d 1, 2, and 3 of lactation, respectively) from about 70 dairy cows.

²Data shown are from Sauter et al. (2004).

³The nitrogen-free extract was calculated as $100 - \% (\text{moisture} + \text{CP} + \text{lipid} + \text{ash})$.

doctrine, and health status in neonatal calves (Buhler et al., 1998; Blattler et al., 2001; Blum, 2006). An important feature characterizing the maturation of the GI tract in neonatal calves fed with colostrum is the replacement of vacuolated fetal-like intestinal epithelium present at birth by mature intestinal epithelium containing polarized enterocytes (Bittrich et al., 2004). The morphological modification of the calf's intestinal epithelium happens within a few days after birth and corresponds to a so-called gut closure. The vacuolated fetal-like epithelial cells are permeable to colostral macromolecules such as IgG₁, whose transfer into the circulation is determinant for the survival of neonatal calves. The timing of the gut closure for macromolecules is possibly influenced by some colostral factors or mechanisms that prevent excessive macromolecular absorption (Vukavić, 1984; Jochims et al., 1994).

Key characteristics of the maturation of the GI tract in neonatal calves include the establishment of new digestive and absorptive capabilities, which are undeveloped at birth. An example includes the ability to digest milk lactose (Bird et al., 1996; Ontsouka et al., 2004c; Steinhoff-Wagner et al., 2014). The above-mentioned adaptive changes and benefits associated with colostrum feeding demonstrate the relevance of the cow-to-calf connection for the successful extra-uterine life in neonatal calves.

Content of Selected Bioactive Substances in Bovine Blood and Mammary Secretions

Many bioactive substances are transferred from the blood of dairy cows into mammary secretions (in particular colostrum). Concentrations of numerous of these [e.g., IgG₁, cholesterol, growth hormone (GH), IGF-1, or insulin] vary during the perinatal period in mammary secretions and blood.

Considering the importance of blood for milk secretions, it should be noted that the total blood volumes

in dairy cows show wide variations within, and are different between developmental or physiological stages (Turner and Herman, 1931 and Table 2). A positive relationship between blood volume and an increase in BW and age of dairy cattle has been shown. In addition, an average total blood volume of 45 L (corresponding to 77.5 mL/kg of BW) was found in lactating dairy cows, whereas corresponding values for nonlactating dairy cows were 34 and 61 mL/kg of BW (Turner and Herman, 1931).

IgG₁, Cholesterol, and Its Derivatives. Blood serum IgG₁ concentrations of 9.8 to 11.8 mg/mL were observed during the early dry period followed by a decline (5.3 and 9.3 mg/mL) at parturition (Murphy et al., 2005; Table 2). During lactation, serum IgG₁ oscillated between 10 and 12.4 mg/mL in dairy cows (Murphy et al., 2005; Table 2). Concerning the content of IgG₁ in milk secretion, significant amounts are transferred from blood into colostrum. The IgG₁ concentrations in colostrum were reported to vary between 75 and 96 mg/mL (Murphy et al., 2005; Table 2).

Cholesterol requirements by mammary gland tissues, respectively, by mammary epithelial cells or mammary adipocytes, increase with the onset of lactation (Mani et al., 2010). The circulating cholesterol consists of fractions bound to carrier lipoproteins, namely chylomicrons, very low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins, whose major constituent is apolipoprotein (apo) A-1. The content of blood serum total cholesterol is high during the dry period (~2,320 mg/L) and declines to approximately 389 to 1,159 mg/L in early lactation (Table 2). Blood serum cholesterol levels steadily increase during lactation to values ranging from 2,319 to 2,706 mg/L in late lactation (Mohebbi-Fani et al., 2006; Mani et al., 2009; Table 2). Cholesterol is a component of milk and is higher in colostrum than in mature milk (Shope and Gowen, 1928, Table 2). The reported concentrations of cholesterol in colostrum 24 h after parturition are be-

tween 610 and 890 mg/L, whereas levels in mature milk are low (100 to 280 mg/L; Shope and Gowen, 1928; Jensen et al., 1991; Talpur et al., 2006).

GH, IGF-1, and IGF Binding Proteins. Concentrations of hormones and growth factors also vary in serum and mammary secretions during the perinatal period. Growth hormone is released from the anterior pituitary in a pulsatile manner similar to other species (Tannenbaum and Martin, 1976; Plouzek and Trenkle, 1991; Kasuya, 2015). The episodic release of GH for lactating cows was first reported by (Vasilatos and Wangsness, 1981) who observed 8 to 9 GH spikes per day. This mode of repeated release showing a less than 24-h interval is defined as ultradian GH secretion rhythm. In some studies where sequential blood samples were collected for instance at 30-min intervals over 72 h, an irregular pulsatile GH secretion has been documented (Mollett and Malven, 1982; Borromeo et al., 1994). Conversely, some reports also described both a regular pulsatile GH secretion under 12:12 light:dark lighting conditions and a suppression of nocturnally increased GH release by 1 h of light exposure (Kasuya et al., 2008, 2012). In these studies, sequential samplings at 1-h intervals for 24 h or at 15-min intervals for 3 h have been applied (Kasuya et al., 2012). Besides, it is also known that GH secretion is altered by exogenous and endogenous variables such as the blood profile of ghrelin (Khatib et al., 2014) or the feeding regimen applied to animals. With respect to the latter, GH secretion tended to synchronize among animals when they were fed once per day (Wheaton et al., 1986), whereas feeding twice per day or ad libitum was associated with trough or absence of regular GH secretions (Plouzek and Trenkle, 1991; Woolliams et al., 1993).

Considering all aspects discussed above, it can be difficult to compare GH levels across studies if sam-

pling time is unknown or unstandardized. Despite this, it was reported that the concentration of GH is low in cow plasma during the dry period (~ 3.5 $\mu\text{g/L}$) and transiently increases in the first few days of lactation to 6 to 7 $\mu\text{g/L}$ before returning to baseline values 3.2 and 4.4 $\mu\text{g/L}$ (Oda et al., 1989). As compared with levels in blood, mammary secretions exhibit lower GH levels. However, concentrations of GH in colostrum of ~ 2 $\mu\text{g/L}$ are higher than those detected in mature milk (0.1–0.3 $\mu\text{g/L}$; Oda et al., 1989).

Insulin-like growth factors are important bioactive substances that exist in both free and bound forms in serum and mammary secretions. Blood serum IGF-1 levels vary throughout the pregnancy-lactation cycle. Insulin-like growth factor-1 levels of about 100 to 130 $\mu\text{g/L}$ were detected in the dry period followed by a relative decline at the onset of lactation (i.e., 63.6–91 $\mu\text{g/L}$; Vicini et al., 1991; Taylor et al., 2004; Puvogel et al., 2005). However, serum IGF-1 increases during lactation to reach the highest values at late lactation (89.1–169.4 $\mu\text{g/L}$; Vicini et al., 1991; Miller et al., 2006). The circulating IGF-1 levels in dairy cows are influenced by various factors such as, for instance, the parity number. In this regard, serum IGF-1 levels are lower in multiparous than primiparous dairy cows (Taylor et al., 2004). Concerning mammary secretions, high IGF-1 levels are present in colostrum compared with mature milk. Insulin-like growth factor-1 concentrations up to $\sim 3,000$ $\mu\text{g/L}$ were found in colostrum versus only 5 to 50 $\mu\text{g/L}$ in mature milk (Malven et al., 1987; Vega et al., 1991). Most of the IGF-1 present in bovine colostrum is in free form (i.e., not associated with IGF binding proteins, **IGFBP**; Schams and Einspanier, 1991), indicating higher IGF-1 bioavailability. However, the reverse is true in mature milk (Schams and Einspanier, 1991). The low IGF-1 concentrations

Table 2. Content of selected bioactive substances in bovine serum and mammary secretions¹

Trait	Blood		Milk secretions		Source
	Pregnancy	Lactation	Colostrum	Mature milk	
IgG ₁ , mg/mL	9.8 to 11.8	5.3 to 12.4	75 to 96	NM	Murphy et al. (2005) Shope and Gowen (1928); Mani et al. (2009); Viturro et al. (2010)
Cholesterol, mg/mL	2,320	389 to 2,706	610 to 890	102 to 449	
IGF-1, $\mu\text{g/L}$	152 $\pm$ 56	31 $\pm$ 4	$\sim 3,000$	5 to 50	Malven et al. (1987); Vega et al. (1991)
IGF-2, $\mu\text{g/L}$	~ 180	~ 180	1,825 $\pm$ 608	1 $\pm$ 0.1	Vega et al. (1991); Vicini et al. (1991)
IGFBP, $\mu\text{g/L}$	2.2 to 3.2	2.0 to 2.4	~ 3	~ 2	Puvogel et al. (2005)
GH, $\mu\text{g/L}$	3.5	3.2 to 7.1	~ 2	0.1 to 0.3	Oda et al. (1989)
Insulin, $\mu\text{g/L}$	0.71	0.57 to 0.97	6 to 37	4 to 7	Malven et al. (1987); Vicini et al. (1991)
Total blood volume, L (mL/kg of BW)	15.9 to 52.5 (39.4 to 82.3)	29.1 to 58.1 (54.3 to 102.1)	NA	NA	Turner and Herman (1931)

¹IGFBP = IGF binding protein; GH = growth hormone; NM = not measured; NA = not applicable.

measured in mature milk as compared with colostrum are not due to the dilution effect of increasing milk yield. It has been reported that changes of the IGF-1 level versus milk volume do not coincide (Campbell and Baumrucker, 1989).

Unlike IGF-1, serum IGF-2 levels remain stable at ~ 180 $\mu\text{g/L}$ along the dry period, early, and late lactation (Vega et al., 1991; Vicini et al., 1991). Similar to the distribution of IGF-1 in mammary secretions, IGF-2 concentrations are higher in colostrum ($\sim 1,825$ $\mu\text{g/L}$) than in mature milk (~ 1 $\mu\text{g/L}$) (Vega et al., 1991). In general, levels of IGF-2 found in colostrum are much lower than of IGF-1, supporting the predominant role of IGF-1 as a colostral bioactive factor.

Insulin. Insulin is another important bioactive substance present in biological fluids. The circulating concentrations of insulin in dairy cow during dry period are close to 0.71 $\mu\text{g/L}$, and decline in early lactation to ~ 0.57 $\mu\text{g/L}$ (Vicini et al., 1991). However, blood insulin levels increase during the course of lactation to ~ 0.97 $\mu\text{g/L}$ (Vicini et al., 1991). Regarding insulin concentrations in mammary secretions, it is reported that colostrum contains 6 to 37 $\mu\text{g/L}$ of insulin (Malven et al., 1987), whereas mature milk has a relatively low insulin content (4 to 7 $\mu\text{g/L}$; Malven et al., 1987).

Several other bioactive substances (whose specific receptors are beyond the focus of the current review) are also variably abundant in mammary secretions. They include for example transforming growth factors, epidermal growth factors, prolactin, or leptin (not shown in Tables 2 and 3; Jin et al., 1991; Iacopetta et al., 1992; Pinotti and Rosi, 2006). Although colostral levels of each of these factors are lower than of IGF-1 (data not shown), potential biological effects should not be neglected.

Consequences of Colostrum Intake on Blood Profiles in Neonatal Calves

IgG₁, Cholesterol, and Its Derivatives. The amounts of ingested colostral bioactive substances are

variably transferred across the calf's intestine into the bloodstream (Hammon and Blum, 1998; Rauprich et al., 2000; Stelwagen et al., 2009). Among them, macromolecules (e.g., IgG₁) are substantially transferred to the calf's circulation in their native forms (Hadorn and Blum, 1997; Rauprich et al., 2000; Stelwagen et al., 2009), underlying the direct benefits of the cow-to-calf connection at calving. It is known that intake of maternal IgG₁ through colostrum feeding is essential to build up the immune protection of newborn calves against microbes and pathogens (Jochims et al., 1994). Amounts of ingested colostral IgG₁ drastically enhance the circulating levels of IgG₁ in neonatal calves above threshold, enabling efficient immune protection (Murphy et al., 2005). In parallel, several other colostral proteins (e.g., apoA-1, apoA-IV, or serum amyloid A) contribute to reinforcement of the neonatal immune system. Together with this immunity-promoting effect, the mentioned colostral proteins also influence the postnatal maturation of the GI tract in neonates (Bendixen et al., 2011; Hernandez-Castellano et al., 2015).

Interestingly, feeding a high cholesterol diet as compared with a low cholesterol diet has stimulatory effects on intestinal digestion and absorption during early postnatal life (Engelhardt et al., 1991). Altogether, the previously mentioned bioactive substances contribute to improve the perinatal adaptation and survival in neonatal calves. Regarding the effects of colostrum feeding on blood metabolic and endocrine traits of neonatal calves, a gradual change in the blood serum profiles of lipids (e.g., cholesterol, triglycerides, apoA-1), hormones, and growth factors (Kühne et al., 2000; Rauprich et al., 2000; Herosimczyk et al., 2013) has been reported. Serum cholesterol levels in neonatal calves changed depending on both the developmental age and feeding regimen (Kühne et al., 2000; Herosimczyk et al., 2013). Cholesterol extracted from the ingested colostrum contributes to fulfill the elevated demands associated with postnatal development when rapid tissue and organ growth occurs (Gofflot et al., 2003; Pfrieder, 2003). Blood serum cholesterol levels in

Table 3. The blood concentration of selected substances in colostrum-fed calves¹

Trait	Day from birth		Source
	d 1	d 3 to 7	
IgG ₁ , mg/mL	~ 0.5	~ 12 to 16	Rauprich et al. (2000)
Cholesterol, mg/L	120 to 190	430 to 890	Kühne et al. (2000); Rauprich et al. (2000)
IGF-1, $\mu\text{g/L}$	134	103 to 138	Kühne et al. (2000)
GH, $\mu\text{g/L}$	6 – 10	10 to 20	Kühne et al. (2000)
Insulin, $\mu\text{g/L}$	~ 0.6	~ 0.6	Rauprich et al. (2000)
Hematocrit, L/L of blood	0.36 to 0.39	0.23 to 0.29	Rauprich et al. (2000)

¹IGFBP = IGF binding protein; GH = growth hormone.

neonatal calves during the first days of life seem to be proportional to the amounts of ingested colostrum. High serum cholesterol levels of ~869 mg/L have been detected in calves fed with high amounts of colostrum compared with ~580 mg/L measured in calves fed with low amounts of colostrum (Kühne et al., 2000). In line with this, blood serum cholesterol levels were lowest (>290 mg/L) in neonatal calves fed with milk replacer containing less cholesterol (Kühne et al., 2000).

GH, IGF-1, and IGFBP. As discussed above, GH is released in a pulsatile manner, and its circulating levels are affected by several variables such as light exposition, circulating hormones, or feeding regimen. Despite this, basal serum GH levels in neonatal calves tend to rise with colostrum feeding (Kühne et al., 2000; Rauprich et al., 2000). The basal serum GH levels of ~11 to 16 µg/L on d 1 of life increased by up to 7 times a few hours after colostrum feeding (Kühne et al., 2000). The basal levels were between 10 and 20 µg/L depending on the developmental age (Kühne et al., 2000). The increase of serum GH levels above those present in colostrum ingested by calves may result at least partly from the effects of colostrum GHRF that possibly stimulates the release of endogenous GH by the pituitary gland of neonatal calves.

For IGF-1, serum concentrations of approximately 121 to 175 µg/L were found on d 1 in neonatal calves fed with colostrum or milk replacer containing trace amounts of IGF-1 (Hammon and Blum, 1997b; Kühne et al., 2000). The IGF-1 levels from d 4 to 7 of life varied from 97 to 138 µg/L (Kühne et al., 2000; Rauprich et al., 2000). In contrast, corresponding levels in calves fed with milk replacer were lower than the concentration of 75 µg/L (Kühne et al., 2000). The lack of drastic differences in the levels of circulating IGF-1 between neonatal calves fed colostrum and milk replacer (barely containing IGF-1) underlines that only marginal amounts of colostrum IGF-I are transferred into the bloodstream in neonatal calves (Baumrucker and Blum, 1994; Vacher et al., 1995; Blum and Hammon, 2000). A correlation of serum IGF-1 levels and hepatic IGF-1 mRNA has also been described in calves (Cordano et al., 2000). These different findings may indicate that serum IGF-1 is regulated mainly through endogenous production or by changing its clearance. Blood IGF-1 levels are positively correlated with concentrations of IGFBP-3 (i.e., the main carrier determining its bioavailability), but negatively associated with IGFBP-2 serum concentrations (Hammon et al., 2000). The optical densities (proportionally related to serum content) of serum IGFBP-3 in the first week varied between 0.88 to 0.98 arbitrary units on d 1 of life, whereas values fluctuated between 0.27 to 0.93 arbitrary units on d 7 of life (i.e., after a longer explosion to colostrum;

Hammon and Blum, 1997b). The delay or omission of colostrum intake has been shown to negatively affect blood IGF-1 levels in neonatal calves (Hadorn et al., 1997; Hammon and Blum, 1997b; Hammon et al., 2000). The IGF-1 contained in colostrum elicits its biological effects on the GI tract primary from the luminal side. Some studies report that colostrum feeding stimulates the IGF-1 gene expression in GI and hepatic tissues (Pfaffl et al., 2002; Sauter et al., 2003; Ontsouka et al., 2004b). On the other hand, one report demonstrated low abundance of IGF-1 mRNA transcripts in hepatic tissues as compared with small intestinal tissues in 5- and 26-d-old calves (Flaga et al., 2011). Altogether, these findings support the concept that IGF-1 elicits its actions on the calf's GI tract through endocrine and paracrine or autocrine ways.

Insulin

Serum insulin profiles of neonatal calves are different after feeding high or low amounts of colostrum, or with milk replacer (Hammon and Blum, 1998; Kühne et al., 2000; Rauprich et al., 2000). Baseline serum insulin levels (~0.25 to 0.75 µg/L) transiently increase in both calves fed with high or low intensities of colostrum and peak to values of ~1.25 and 1.75 µg/L on d 1 and 2 of life, respectively (Rauprich et al., 2000). In contrast, on d 7 of life serum insulin markedly differed between a high-intensity colostrum diet (reaching 2.25 µg/L) and low-intensity colostrum diet (values <0.75 µg/L; Kühne et al., 2000; Rauprich et al., 2000). There are controversial data regarding a potential absorption of ingested insulin across the calf intestines. A stronger insulin response observed in neonatal calves consecutive to colostrum feeding might be due to stimulation of intestinal lactase activity, which allows lactose digestion and hence the intestinal absorption of glucose and galactose (Tivey et al., 1994). In addition to intestinal absorption, the blood glucose concentration is affected by endogenous production via gluconeogenesis.

Requirements for the Effectiveness of the Cow-to-Calf Connection

The stimulation of the postnatal growth and development in neonatal calves relies on the interaction between endogenous/exogenous ligands and their corresponding receptors or receptor-like transporters expressed in the wall of the calf's organs and system organs. The reminder of this review provides information on expression and activity of cell surface receptors that bind exogenous and endogenous cholesterol carriers, GH, IGF, and insulin in neonatal calves fed with colostrum.

SELECTED GROWTH-PROMOTING SYSTEMS INDUCING GROWTH AND MATURATION OF DIGESTIVE FUNCTIONS IN NEONATAL CALVES

How Might Cholesterol and Cholesterol Derivatives Ingested as Part of Colostrum Influence the Development of the Calf?

It is important to note that cholesterol is a structural constituent of biological membranes and is abundantly present in plasma membrane domains called lipid rafts. These domains serve as signaling platforms, where cell surface receptors mediating the effects of hormones or growth factors (e.g., IGF or insulin; Simons and Ikonen, 1997; Simons and Toomre, 2000) are abundantly present. Based on that, it can be assumed that alteration of cellular cholesterol consecutive to cholesterol intake might influence the intestinal signaling via IGF and insulin.

Recent evidence from adult cattle showed that cholesterol homeostasis is regulated by the apoA-I/ABCA1 pathway (Ontsouka et al., 2013), similar to mechanisms known in other cells types (Figure 1 and Tang et al., 2006). Concerning the neonates, activation of intestinal ABC cholesterol transporters by the corresponding endogenous ligands (e.g., apoA-I or serum amyloid A) has been reported to influence the intestinal lipid absorption as well as plasma lipid levels (Thurnhofer and Hauser, 1990; Iqbal et al., 2013; Lou et al., 2014). The mentioned effects are crucial because lipids are among the major energy sources of neonatal calves after birth. On the other hand, it was also observed, for instance, in piglets that feeding a high cholesterol diet promotes intestinal lactase activity (Engelhardt et al., 1991), suggesting the importance of cholesterol in determining the glucose profile in neonate calves. Lactase activity is required to break lactose into glucose and galactose for further absorption across the calf's intestine (Dudley et al., 1998). An insufficient intestinal lactase activity is also described as a major cause of perinatal diarrhea and morbidity in neonatal calves (Kien et al., 1996; Shulman et al., 1998). The activation of ABCA1 has an effect not only on cellular cholesterol levels but also on intestinal functions (Remaley et al., 2001; Stonik et al., 2004). One example of such effects on intestinal functions is the regulation of intestinal innate immune responses, which is important for postnatal adaptation of neonates (Tang et al., 2009; Cheng et al., 2012; Mogilenko et al., 2012). Another feature relating cholesterol and GI development is associated with activation of tissue angiogenesis by apoA-1/ABCG1 interaction (Fang et al., 2013). In this regard, it is suggested that an extended GI vascular system acts as a gateway for endocrine stimulation of GI growth.

Cholesterol is metabolized to bile acids. Released hepatic bile acids into the small intestine facilitate the digestion and absorption of lipids (Insull, 2006). These cholesterol derivatives elicit hormone-like effects through the activation of specific cell surface receptors (Maruyama et al., 2002; Lefebvre et al., 2009). Beside ABC transporters, other transport proteins such as the scavenger receptor (SR)-B1 (Truong et al., 2010; Ji et al., 2011), NPC1L1 (Altmann et al., 2004; Davis et al., 2004), and NPC1 (Mani et al., 2009) play also a role in regulating cellular cholesterol homeostasis. However, the mechanisms involved are beyond the scope of the current review.

How Might GH Ingested as Part of Colostrum Influence the Development of the Calf?

In general, bioactive substances influence the postnatal growth and adaptation of the digestive functions in neonatal calves through endocrine, paracrine, and autocrine actions (Blum, 2006). The stimulatory effects of colostrum GH on the calf's GI tract are exerted directly from the intestinal lumen in autocrine and paracrine ways (Blum, 2006). In addition, circulating GH, whose levels are dependent of the balance between the hypothalamic emissions of GHRF (an enhancer of blood GH levels) and somatostatin (a suppressor of blood GH levels) as well as colostrum intake (Kühne et al., 2000; Rauprich et al., 2000), influences the intestinal growth via endocrine actions (Blum, 2006). As depicted in Figure 1, the action of GH (colostrum and circulating) on the calf's GI development requires its interaction with a single-pass membrane GH receptor (**GHR**). The latter is a glycoprotein consisting of one extracellular domain and one intracellular domain. Activation of GHR leads to the stimulation of cytosolic tyrosine kinase Jak-2 with subsequent initiation of biological responses (Leung et al., 1987; Carter-Su et al., 1996). Except for the liver, adipose tissue is considered to be the only tissue where the effects of GH, mainly lipolysis, are directly mediated via GHR. However, data obtained from molecular biology techniques (described in the chapter below) have identified the mRNA transcripts encoding GHR in the GI tissues of neonatal calves, implying that the effects of GH can indeed be directly mediated through intestinal GHR. In general, the physiological effects of GH include the regulation of organ growth and development as well as modulation of the neonatal calf's energy balance.

How Might IGF and IGFBP Ingested as Part of Colostrum Influence the Development of the Calf?

The IGF-1 and IGF-2 that are abundantly present in biological fluids (especially colostrum; Table 2 and

Figure 1. Selected cellular growth-promoting systems belonging to the somatotrophic axis and cholesterol-regulating system. The figure illustrates the signal transduction pathways for the ligand-induced activations of cell-surface receptors and the receptor-like ATP-binding cassette (ABC) cholesterol transporter A1 (ABCA1). The activation of the type-1 insulin-like growth factor (IGF) receptor by IGF-1 or insulin stimulates insulin receptor substrate (IRS; hexagon shape) 1, which then activates phosphatidylinositol-3 kinase (PI3K). This leads to transcriptional regulation of gene expression (pathway A). Additional postreceptor events involve recruitment of Src homology-collagen (Shc protein; triangle shape) and activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway (pathway B). The biological effects of GH involve the activation of GHR and the associated kinase protein, Janus kinase (Jak-2; round shape). This triggers the recruitment and stimulation of the signaling molecules in pathways A and B. In addition, Jak-2 activates the signal transducer and activator of transcription (STAT) pathway (pathway C). The ABCA1 is activated by the interaction in a receptor/ligand fashion of its endogenous ligand, apolipoprotein-A1, which stimulates pathways A, B, and C. These signaling pathways regulate cell growth, proliferation, and survival, as well as metabolic and immune functions. GRB2, growth hormone receptor-binding protein-2. For simplification, some details and implicated molecules have been omitted. Color version available online.

3) influence the postnatal development of the calf's GI tract (e.g., increase of villus size, crypt cell proliferation) through autocrine, paracrine, and endocrine effects. The IGF-1 and IGF-2 show more than 60% sequence homology and bear strong structural resemblances to insulin. Colostral IGF exert essentially direct

autocrine/paracrine effects on the GI tract by acting from the luminal side on IGF receptor types 1 and 2 (**IGF-1R** and **IGF-2R**) and on the insulin receptor (**InsR**) present on the wall of the calf's GI tract (Ontsouka et al., 2004b,d; Steinhoff-Wagner et al., 2014). The biological availability of colostral IGF and their

interaction with specific receptors mentioned above is modulated by colostral IGFBP isoforms (1 to 6) that bind to IGF with higher affinity.

The cell surface receptors mediating the effects of colostral IGF-1 in the GI tract (IGF-1R and InsR) are composed of 2 extracellular cysteine-rich domains (α -subunits) and 2 intracellular domains (β -subunits) exhibiting an intrinsic tyrosine kinase activity, whose activation ultimately leads to the initiation of cellular responses (Figure 1). Additionally, IGF-1 actions might be mediated through an interaction with a hybrid insulin/IGF receptor (Poiraudau et al., 1997). Unlike IGF-1R or InsR, IGF-2R (not depicted in the figure) lacks tyrosine kinase activity. Instead, IGF-2R seems to signal by interacting with G proteins (Poiraudau et al., 1997; Fernandez and Torres-Aleman, 2012). Apart from colostral IGF, the development of the GI tract is also influenced by blood IGF. The liver is supposed to be the main organ releasing IGF-1 and IGF-2 into blood as a result of the interaction of circulating GH with hepatic GHR (Cordano et al., 2000; Butler and LeRoith, 2001).

How Might Insulin Ingested as Part of Colostrum Influence the Development of the Calf?

The colostral insulin triggers InsR and IGF-1R, which are expressed on the wall of the calf's GI tract (Figure 1). The affinity of insulin for the InsR is hundreds- to thousands-fold higher than that of IGF-1 (Kido et al., 2001). As stated above for IGF-1, it is likely that colostral insulin also mediates an action by interacting with a hybrid insulin/IGF receptor (Poiraudau et al., 1997). Similar to IGF-1R, the InsR consists of 2 extracellular cysteine-rich domains (α -subunits) and 2 intracellular domains (β -subunits) that confer tyrosine kinase activity (Figure 1). The interaction of colostral insulin with the InsR present on the wall of the GI tract induces intracellular cascade events that lead to biological responses beneficial for intestinal growth. Insulin is important for glucose utilization and intestinal cell proliferation. Unlike circulating IGF that mirror the hepatic production, circulating insulin is principally secreted by pancreatic β cells of the islets of Langerhans in response to elevated blood glucose concentrations. Insulin secretion may also be stimulated by other components of colostrum fed to calves such as certain AA, glucagon-like peptide, fatty acids, and sulfonylureas (van Loon et al., 2000; Proks et al., 2002; Poitout et al., 2006).

Messenger RNA of Receptors of the GH-IGF and Insulin Axes in Neonatal Calf Intestinal Tissues

Several studies have been performed to examine the distribution of receptors mediating the effects of ligands

of the somatotrophic axis and the insulin system, namely GHR, IGF-R, and InsR along the GI tract of neonatal calves. In this context, the effects of colostrum intake (containing high amounts of bioactive substances, e.g., IGF-1; Table 2), developmental age, and treatment with glucocorticoids (whose levels drastically increase at birth) on the GI gene expression of these receptors have been investigated.

Several research groups used full-thickness calf GI tissues in their attempts to evaluate mRNA transcript abundance of numerous relevant genes (e.g., GHR, IGF-R, and InsR; Pfaffl et al., 2002; Georgieva et al., 2003; Ontsouka et al., 2004b). Expression of several of these transcripts was found to vary based on the location within the GI, the gestational age of the animal, the diet fed to the animal, or combinations of these factors. For instance, the differential abundance of GHR and IGF-1R mRNA transcripts among intestinal segments had been found in intestinal mucosa of young calves of 64 d of age (Velayudhan et al., 2008). This suggests a site-specific importance of the aforementioned receptors in mediating GI growth-promoting effects exerted by ingested GH, IGF, and insulin after colostrum intake as well as by circulating levels of these bioactive compounds (Tables 2 and 3). A detailed summary on the actions of bioactive substances originating from blood circulation, colostrum intake, and local tissue synthesis is provided in the review by Blum (2006).

The mRNA levels of GHR, IGF-1R, IGF-2R, and InsR in the ilea of fetal calves were lower than those of full-term calves. Notably, however, different trends were observed in other GI compartments, including the duodenum, jejunum, and colon (Georgieva et al., 2003). Interestingly, mRNA levels of the mentioned receptors increased from proximal to distal regions along the GI tract, such that the colon had significantly higher mRNA levels of GHR, IGF-1R, IGF-2R, and InsR than the small intestine (Georgieva et al., 2003). In the above mentioned studies, the mRNA abundance of GHR, IGF-1R, IGF-2R, and InsR was detected by using the same amount of cDNA rendering the comparison among tested GI segments possible. Moreover, it has been reported that the amounts of total RNA extracted per milligram of wet full-thickness tissues (Ontsouka et al., 2004a) or mucosal tissues (Velayudhan et al., 2008) from different calf intestinal locations did not statistically differ. Based on that, it is unlikely that extrapolation of the receptor mRNA levels to the intestinal tissue weight would affect the differences in receptor expression reported between intestinal segments of neonatal calves. Interestingly, the results of functional radioreceptor assays confirmed the differential abundance of intestinal IGF-1R, IGF-2R, and InsR in neonatal calves (Hammon and Blum, 2002). The

feeding of exogenous IGF-1 has been shown to alter the intestinal receptor expression, especially of IGF-1R (Baumrucker et al., 1994b; Hammon and Blum, 2002).

It was also demonstrated that the mRNA abundances of the different receptors belonging to the somatotrophic axis differed within a given intestinal compartment. For example, in the ileum the gene expression level of the InsR was greater than that of GHR and IGF-1R, which again were higher than that of IGF-2R on d 1 or 5 of life (Pfaffl et al., 2002; Ontsouka et al., 2004b).

Studying the effects of developmental age and feeding, it has been reported that significant shifts in receptor gene expression occurred in the esophagus, stomach (rumen, fundus, pylorus), small intestines (duodenum, jejunum, ileum), and colon between d 1 and 5 after birth depending on the considered GI site. Overall, as age increased, and the GI tract was longer exposed to bioactive factors present in mammary secretions (Table 2), the mRNA levels of InsR, GHR, and IGF-1R increased (especially in the small intestine), whereas those of IGF-2R markedly decreased (in almost all tested segments of the GI tract). These findings suggest the importance of InsR, GHR, and IGF-1R in mediating the postnatal development and adaptation of newborn calves. This concept is supported by the fact that dietary IGF-1 increased the protein expression of IGF-1R in intestinal mucosa of neonatal calves (Baumrucker et al., 1994b). The mRNA measurements also indicated that levels of IGF-1R were significantly higher in the fundus and ileum on d 5 than on d 1 of life, and positive correlations between the mRNA transcript abundance of IGF-1R and IGF-1 were found in the small intestine on d 5 of life (Ontsouka et al., 2004b). Regarding the IGF-2R, the mRNA abundances in all GI sites, except the colon, were lower on d 5 than on d 1 (Ontsouka et al., 2004b). It was thus speculated that IGF-2R might play roles in mediating growth inhibition with exposure of the GI wall to colostrum/milk.

It is well known that the colostrum received by neonatal calves contains high amounts of IGF-1 (~3,000 µg/L), which might stimulate postnatal intestinal digestion and absorption by increasing the circumferences, areas, and lengths of the villi (Baumrucker et al., 1994a; Hammon and Blum, 1997a; Buhler et al., 1998). It was observed that colostrum feeding for 4 d had variable effects on the mRNA levels of IGF-1R along the GI segments. The receptor abundance was greater in the fundus than in the esophagus, pylorus, ileum, and colon, whereas these levels were higher than those found in the rumen, duodenum, and jejunum (Ontsouka et al., 2004a). Similarly, the mRNA levels of IGF-2R were higher in the colon than in the rumen and esophagus. The gene expression of GHR was higher in the pylorus, fundus, esophagus, duodenum, jejunum,

and colon as compared with the ileum, where the level was greater than in the rumen. In contrast, the mRNA levels of InsR in the fundus, pylorus, and esophagus were greater than those in the duodenum, colon, and rumen, which were higher than those in the jejunum and ileum after 4 d of colostrum feeding (Ontsouka et al., 2004a). In addition to the transcripts corresponding to receptors, mRNA encoding their specific ligands (IGF) and binding proteins (IGFBP) were detected. This finding further suggests that the receptor-mediated growth-promoting effects of the somatotrophic axis are likely to be exerted in an autocrine manner, a paracrine manner, or both. Our own data and those of other laboratories (Zhao et al., 2001; Knott et al., 2004) collectively show that all components of the GH-IGF system are present in the GI smooth muscle tissues of neonatal calves, supporting the notion that IGF-1R might also contribute to mediating the GI motor functions of newborn calves.

None of the multiple investigations cited hereafter studying the importance of the somatotrophic axis for the perinatal development of the GIT in calves (Pfaffl et al., 2002; Georgieva et al., 2003; Ontsouka et al., 2004b) has specifically examined whether the ontogenetic or feeding effects (or both) were associated with an alteration of the receptor expression across the intestinal layers. Such investigations are important because changes in the densities of GHR, IGF-R, and InsR in the smooth muscle layer do not necessarily influence the proliferation of mucosal enterocytes, which are more directly linked to the absorption of energy sources and nutrients. In one study using neonatal calves, this aspect was addressed (Ontsouka et al., 2004d). It has been reported that mRNA levels of GHR and InsR differed in the villi and crypts of the small intestine depending on the intestinal segments. In the jejunum for instance, the mRNA abundance of InsR in crypts was greater than in the villi, whereas in the ileum, the mRNA levels of GHR and InsR were higher in crypts than in the villi (Ontsouka et al., 2004d). The authors speculated that the growth-promoting effects of age/feeding have greater force in the crypt areas (proliferative regions containing immature enterocytes) than in the villi (absorptive areas containing mature enterocytes). In this regard, an increase of intestinal crypt depths in neonatal calves fed with colostrum has been reported (Bittrich et al., 2004). In parallel, differential expression levels of other components of the GH-IGF system along the villus-crypt axis were found, including IGFBP-2, being higher in crypts than villi; IGFBP-3, being higher in crypts than villi in the jejunum; IGF-2 and IGFBP-3, being higher in villi than crypts; and IGFBP-2, being higher in crypts than villi in the ileum (Ontsouka et al., 2004d). Collectively, the biological effects exerted by the somatotrophic axis might involve the

autocrine/paracrine stimulation of enterocyte maturation along the villus-crypt axis.

Regarding the hormonal regulation of the somatotrophic axis changes in the profile of certain hormones (e.g., glucocorticoids) have been associated with modulation of the postnatal development of the GI tract in newborn calves (Sauter et al., 2004). The administration of synthetic glucocorticoids (e.g., dexamethasone, 30 µg/kg of BW per day for 4 d) had an influence on the GI gene expression levels of GHR, IGF-1R, and InsR in neonatal calves fed with colostrum or milk-based formula for 4 d (Ontsouka et al., 2004a). It was found that dexamethasone altered the mRNA abundances of IGF-1R, GHR, and InsR, and that these effects differed by the sampled GI tract site and (partly) the feeding regimen. In colostrum-fed calves, dexamethasone significantly decreased the mRNA levels of IGF-1R (in the esophagus, ileum, and colon), IGF-2R (in the fundus), GHR (in the fundus), and InsR (in the esophagus and fundus). In formula-fed calves, in contrast, dexamethasone increased the mRNA levels of IGF-2R (in the pylorus) and GHR (in the ileum), but decreased the level of IGF-1R (in the fundus). Other studies reported that dexamethasone increased the plasma concentration of IGF-I, but decreased those of GH, IGFBP-1, and IGFBP-2, and elevated the hepatic mRNA levels of GHR (Sauter et al., 2003). Taken together, these data suggest that glucocorticoids are important regulatory factors for the maturation of the somatotrophic axis. Thus, they support the successful adaptation of neonatal calves to extra-uterine life.

SUMMARY

Several studies outlined in this review show the importance of colostrum feeding on overall growth and development of neonatal calves. In the scope of this paper, the term cow-to-calf connection has been used to characterize the effects of colostrum feeding in neonatal calves. The cow-to-calf connection changes the blood serum levels of metabolites and endocrine factors such as GH, IGF-1, or cholesterol transporters in neonatal calves. The cow-to-calf connection was often associated with an increase of GI receptor expression (e.g., InsR, GHR, and IGF-1R) especially in the small intestine. The benefits of colostrum feeding on GI maturation and function were evidenced by increases in crypt depths or villus height for instance. An increase of GHR and InsR expression in intestinal crypts has been observed, suggesting their role in promoting enterocyte renewal and proliferation. The detection of the mRNA transcripts of all components of the GH-IGF and insulin system in GI tissues combined with the presence of ligands of this system in colostrum and

blood indicate the co-existence of autocrine, paracrine, and endocrine regulations of the postnatal adaptation of neonatal calves. The mRNA abundances of selected components of the somatotrophic axis and the insulin system vary depending on the GI locations and were altered by age/feeding or by dexamethasone treatment. Regarding metabolic profiles, the increase of the serum lipids, in particular of cholesterol and apoA-1, after colostrum feeding supports the importance of cholesterol and cholesterol-related systems in mediating postnatal growth and development in cattle. The information compiled in this review suggests a role of GI cell surface receptors and receptor-like transporters in the management of perinatal mortality and morbidity in calves.

Future studies should investigate in depth the effects of cholesterol and cholesterol-related system on the intestinal cell signaling and activities, with a focus made on the role of ABCA1 and other cholesterol transporters on intestinal angiogenesis. An increase of blood flow toward the GI tissues would provide amounts of nutrients and endocrine factors to accelerate the tissue growth and maturation.

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