Native and recombinant bovine placental lactogens

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SUMMARY

The bovine placenta produces a wide variety of proteins that are structurally and functionally similar to the pituitary proteins from the GH/PRL gene family. Bovine placental lactogen (bPL) is a 200-amino acid long glycoprotein hormone that exhibits both lactogenic and somatogenic properties. The apparent molecular masses of purified native (n) bPL molecules (31-33 kDa) exceed 23 041 Da, which is the theoretical molecular mass of the protein core. At least six isoelectric variants (pI: 4.85-6.3) of bPL were described in cotyledonary extracts and three different bPL isoforms (pI: 4.85-5.25) were found in fetal sera. The bPL molecules that are detected in higher concentrations in peripheral circulation exhibit a more acidic pI than those present in placental homogenates. This may reflect an important glycosylation process occurring just prior to the bPL secretion. The bPL mRNA is transcribed in trophectoderm binucleate cells starting from Day 30 of pregnancy until the end of gestation. In mothers, bPL is involved in the regulation of ovarian function, mammogenesis, lactogenesis, and pregnancy stage-dependent adaptation of nutrient supplies to the fetus. Due to the higher fetal, compared to maternal concentrations of circula-

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Native and recombinant bPLs

...taining hormone, it has been suggested that bPL primarily targets fetal tissues. Reproductive Biology 2008, 8: 85-106.

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INTRODUCTION

The placenta of primate, rodent, and ruminant species secretes one or more polypeptide hormones belonging to the growth hormone (GH)/prolactin (PRL) gene family. These hormones are structurally related and share several biological features [74]. The GH/PRL gene family includes the placental lactogens (PLs), the prolactin-related proteins (PRP), the prolactin-like proteins (PLP), and the placental growth hormone variant (GH-V; tab. 1).

Table 1. Accession numbers of SwissProt and GenBank databases of different members of the bovine GH/PRL gene family

<table>
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*please note that the bovine PRP family is probably not complete till now
Several radioreceptor and bio-assays (reviewed by Anthony et al. [3]) have proven that placental lactogens exhibit prolactin-like (lactogenic) activity. Since the molecules also display somatogenic activities, they are named chorionic somatomammotropins (CS; [1]).

PRL, GH, and PLs are thought to have arisen from a common ancestral gene by two successive tandem duplications [52]. PLs produced by trophectoderm of ruminant and rodent species derived from a PRL lineage, while human (hPL) and primates PLs are of GH origin [fig. 1; 25, 31, 51, 69, 79]. Bovine PL (bPL) is one of the most extensively investigated placental proteins and this may be attributed to its potential use for increasing cattle productivity (meat and milk productions). The present review summarizes current information on the bovine native (glycosylated) and recombinant (nonglycosylated) placental lactogen forms, with emphasis on their structure and potential biological actions. We especially focus on the significance of glyco-diversity in reproductive hormones.

Figure 1. Evolution of somato-mammotropins from a common ancestral peptide. MA: million years ago. Adapted from Martal ([51]; PhD Thesis, Université Paris-Orsay, 1980).
GLYCOBIOLOGY OF REPRODUCTIVE HORMONES

Overview on the general structure of glycoprotein hormones

A large number of biological characteristics of reproductive protein hormones can be discerned intuitively, even from a very rudimentary consideration of its molecular structure. Small peptides (e.g. thyrotropin-releasing hormone; [8]) have only a limited surface for reaction with a receptor, so the total information content of such a molecule is necessarily limited. A polypeptide may exhibit a high flexibility with regards to its interaction with one or more receptor molecules which enables a modulation of the hormone intracellular signaling. Large polypeptides belonging to the GH/PRL/PL gene family have numerous interactive epitopes capable of independent or concomitant interactions with many binding sites. Thus, the informational content is multifaceted e.g. GH or PRL stimulates a target cell by binding to two receptors simultaneously and by forming a hormone bridge between them [24].

Trophic hormones (e.g. PRL, GH, follicle stimulating hormone or FSH, luteinizing hormone or LH) have a propensity to become globular proteins. Immediately after the synthesis in the endoplasmic reticulum (ER), linear peptide chains (generally longer than 50 amino acids) fold into secondary structures (alpha helix or antiparallel beta-pleated sheet), then association through disulfide bonds leads to the formation of a stable, three-dimensional arrangement. In hormones composed of a single polypeptide chain (e.g. insulin, GH, PRL, PLs), the tertiary structure is the highest level of attained conformation. In hormones constituted of two or more subunits (e.g. FSH, LH), different monomers (a three-dimensional arrangement of a single-chain polypeptide molecule) are assembled in a larger quaternary structure. Both tertiary and quaternary structures are very stable and resistant to many external factors that attempt to disrupt their native conformation.

The nascent protein hormones can undergo a series of different post translational modifications such as glycosylation, phosphorylation, or sulfatation. The modifications may be species-, tissue-, and time-
dependent, and are determined by hormone primary structure (amino acid composition). Glycosylation is the most widespread covalent modification of the nascent protein chains. This post-translational modification is essentially restricted to peptide chains that are sufficiently long to adopt the tertiary structure. The glycans attached to glycoproteins are polysaccharides composed of a large variety of linked sugar (monosaccharide) residues (e.g. neutral sugars, amino sugars, uronic acid, and neuraminic/sialic acid). The numerous hydroxyl groups of the many pentose and hexose sugars allow for both bivalent and trivalent links, thus leading to the formation of linear or branched antenna-like polysaccharide structures [83].

Depending on their anchorage site, the glycan chains of glycoproteins are categorized as \(N\)-linked [on amide nitrogen of asparagine (Asn) side chain] or \(O\)-linked ones [on hydroxyl oxygen of serine (Ser) and threonine (Thr) side chains]. Glucose (Glc), mannose (Man), galactose (Gal), \(N\)-acetylglucosamine (GlcNAc), \(N\)-acyetylglactosamine (GalNAc), fucose (Fuc), and sialic acid (Sia) are the main sugars which participate in both \(N\)-glycoprotein and \(O\)-glycoprotein structures. The \(O\)-glycosylation process takes place in the Golgi apparatus and involves glycosyltransferases, enzymes which add the glycans directly to the tagged amino acids. This kind of glycosylation results generally in forming of nonbranched glycan structures. The \(N\)-glycosylation process is more complex. Both protein synthesis and the synthesis of the glycan chain occur simultaneously in the endoplasmic reticulum (ER; [37]).

**Significance of glycosylation to the function of reproductive hormones**

The molecular mass of biologically active glycoproteins varies markedly. At one extreme, there are molecules such as adenosine (267 Da), an autocrine/paracrine hormone containing a single ribose sugar. At the other extreme, there are larger globular proteins (> 30 kDa) exemplified by human chorionic gonadotropin (hCG) which contains four complex bi-antennary glycan chains attached to Asn residues and four glycans attached to Ser residues.
The ability to accurately determine the oligosaccharide residues in glycoproteins or in other glycoconjugates has revealed a remarkable complexity and diversity of glycan moiety of these molecules. In addition to their purely structural role, glycans are necessary to achieve the correct folding of glycoproteins, to regulate the half-life of the molecules, and to mediate specific recognition by receptors [76]. Alterations in glycan contents induce complex effects especially when regarding hormones, growth factors, and cytokines (e.g. PRL, LH, PLs). Sometimes the loss of glycosylation leads to the transformation of agonist to antagonist. Altered glycosylation pattern may also produce changes in the specificity and affinity of the molecule as well as in its intracellular signaling. Under in vivo conditions, the clearance rate in peripheral circulation may reduce or amplify the biological actions of glycoprotein hormones.

It is noteworthy to mention that in ruminants bPL is the only PL molecule secreted in a glycosylated form. The specific role of glycosylation of bPL has not yet been deeply investigated. There are also other bPL characteristics that distinguish the bovine hormone from those secreted by the placenta of other eutherian species. In pregnant ewes and goats, PLs are secreted mainly into maternal circulations and fetal PL levels are 100 times lower than the maternal level [9, 22], whereas bPL concentrations during pregnancy are higher in fetal than in maternal compartments [6].

**GENERAL STRUCTURE OF PLACENTAL LACTOGENS**

PRL, GH and PL hormones belong to a more extended family of proteins referred to as hematopoietic cytokines [33]. PL molecules, as other members of this family, display the classic long-chain cytokine fold consisting of a four-helix bundle with the alpha-helices arranged in an up-up-down-down topology with two long cross-over loops (fig. 2A; [27, 80]). PL receptors also belong to the cytokine receptor superfamily. The ternary complex resulting from the binding between ovine PL (oPL) and the extracellular domain of the rat prolactin receptors 1 and 2 (rPRLR1 and rPRLR2; fig. 2B) was recently described [27].
Biochemical characteristics of native and recombinant bPL

As early as 1976, Buttle and Forsyth [10] demonstrated the expression of lactogenic activity by co-culture of mouse mammary tissue and cow cotyledonary tissue removed at different stages of gestation. After five days in culture, the in vitro secretion of lactogenic molecules was equivalent to about 300 ng of bovine prolactin (bPRL) per millilitre of medium. Some time later, the purification and characterization of native glycosylated bPL (nbPL) was reported by several groups including ourselves [4, 5, 11, 26, 54].

The molecular mass of nbPL was estimated to be 31-33 kDa in both placental explant cultures and purified extracts [5, 11]. The mature nbPL has 200 residues, with a 36-amino acid signal peptide [65]. Its primary sequence exhibits 50% and 23% homology to bPRL and growth hormone (bGH), respectively (reviewed by Anthony et al. [3]). Compared with
bGH, bPL has 12–13 additional amino acids at the N-terminal domain of the molecule. Similar to mammalian PRL, it has a third disulfide bond located in this N-terminal region [13].

The apparent molecular mass of purified nbPL exceeds 23 041 Da which is the theoretical molecular mass of the protein core (after removal of the signal sequence and the propeptide) of bPL precursors. Although the estimated pI (isoelectric point) of the polypeptide chain of bPL (200 amino acids) is 6.86, a large heterogeneity of pI has been reported in the literature. At least six isoelectric variants (pI: 4.85-6.3) of bPL were described in cotyledonary extracts [11] and three different bPL isoforms (I, II and III; pI: 4.85-5.25) were found in fetal sera [12]. It was demonstrated that bPL molecules that are secreted in higher concentrations in peripheral circulation exhibit more acidic pI, whereas molecules with basic pI are predominant in placental homogenates. Byatt et al. [12] suggested that bPL undergoes an important glycosylation process just before secretion which results in the formation of bPL molecules with a large heterogeneity of the attached O-linked and triantenary N-linked oligosaccharides [13]. Sialic acid is the main charged sugar residue commonly found in placental glycoproteins (reviewed by Stockell-Hartree and Renwick [71]) and is related to isoelectric points of the secreted molecules. Different degree of sialylation may account, at least partially, for differently charged isomers of circulating bPL [67].

Recombinant bPL (rbPL) is produced by Escherichia coli as a nonglycosylated hormone [38]. The biological effects mediated by rbPL are not fully understood, but it has been hypothesized that they may not be different from those mediated by the native bPL hormone [14].

**Binding properties and in vitro activity**

Binding to the PRL receptor is one of the main characteristics of ruminant PL molecules. Therefore, the Nb2 lymphoma cell bioassay was used by several authors as a tool to investigate bPL function both in plasma samples and in explant culture media [63, 73]. The lactogenic activity of bPL is almost equipotent to that of highly purified ovine (o)PRL [63]. Due to the structural
and functional similarities between bPL and bPRL it has been assumed that these molecules have evolved from the ancestral gene of the PRL lineage [69]. It is likely that other members of the PRL family such as PRP and PLP have also been generated by gene duplication from PRL [79].

In primates, hPL shares 85% sequence identity with human GH (hGH). However, its binding capacity to the hGH receptor is 2 300-fold weaker than that of hGH [49]. In contrast, bPL - which exhibits approximately 20% of the amino acid sequence identity with the amino acid sequence of bGH [65] - was found to bind to bGH receptor with high affinity [70, 77].

The effect of enzymatic deglycosylation of nbPL on receptor binding and biological activity was described by Byatt et al. [13]. These authors reported that the removal of N-linked oligosaccharides from nbPL increased the binding of bPL to GH receptor (about 1.2- to 2.3-fold) whereas removal of O-linked sugar chains had no effects on the prolactin-like activity of bPL. Glycosylated and nonglycosylated forms of bPL had slightly different affinities for the bGH receptor and had no effect on the lactogenic binding sites which suggests that glycosylation is not required for the biological functions of bPL.

Ruminant PLs bind to different receptors from the GH/PRL/PL gene family (fig. 3). PLs can bind and activate heterologous (human, rabbit,

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**Figure 3.** Potential ways of placental lactogen (PL) binding to the members of the cytokine receptor family in ruminants; A/ PL binds to a distinct ruminant PL receptor (PL-R); B/ PL activates an hypothetical variant of growth hormone receptor (GH-R) with mutation in its extracellular domain (ECD); C/ PL activates prolactin receptor (PRL-R) homodimers; D/ PL stimulates the formation of PRL-R/GH-R heterodimers. Numbers 1 and 2 represent two sites of the PL.
mouse) GH receptors with equal potency compared with their GH counterparts [39]. Interestingly, PL molecules were considered to be antagonists of biological activities of GH since they occupy the homologous GH receptors without inducing their homodimerization. Thus, it may be hypothesized that different mechanisms or receptors are involved in somatogenic potency of ruminant PLs (reviewed by Goffin et al. [32]). A distinct receptor, specific for PLs, has been reported to be expressed in ovine fetal liver [29] and bovine endometrium [30]. However, attempts to clone such PL receptor have been unsuccessful.

SYNTHESIS AND SECRETION OF BOVINE PLACENTAL LACTOGENS

Expression in trophectoderm cells and in trophoblastic cell lines

The most characteristic element of the ruminant placenta is the presence of binucleate cells (BNC or diplokaryocytes) in the trophectoderm. BNC arise from chorionic mononucleate cells by karyokinesis without subsequent cytokinesis. The youngest cells are located deep in the trophectoderm and maturation takes place progressively as they migrate towards the maternal epithelium [84]. In cattle, after their migration, BNC fuse with uterine cells, resulting in the formation of short-living trinucleate cells, which secrete their products into the maternal circulation [85].

The bPL mRNA is transcribed in trophoblastic cells after Day 30 of pregnancy but not before day 25 during the peri-implantation period [86]. Most of the BNC (>95%) express bPL proteins from Day 60 of gestation onwards, whereas no expression is detected in mononucleate cells [59, 85, 86]. The synthesized PL proteins are stored in membrane-bound secretory granules in BNC, which occupy up to 50% of the cytoplasm of trinucleate trophoblastic cells (fig. 4). The mechanism controlling the synthesis and secretion of PLs in ruminant species has not yet been elucidated. In ewes, the number of BNC expressing oPL decreases during late gestation. Because fetal cortisol regulates the number of BNC, it is possible that this hormone exerts a certain control over PL production in sheep [7, 81].
Figure 4. Electron photomicrography of cow placentome (150 day post coitum); A/ Two granulated binucleate cells (BNC) in fetal trophectodermal epithelium (T). One BNC migrated up to the microvillar junction (indicated by arrows). No granules are visible in the maternal epithelial cells (U; magnification 1 300×); B/ BNC just after fusion with a maternal uterine epithelia cell (asterisk). This fusion interrupts (between arrows) the microvillar junction between trophectoderm and uterine epithelium (3 000×); C/ Trinucleate cells (maternal giant cells) in the maternal uterine epithelium. These cells contain numerous granules equivalent in phosphotungstic acid staining reaction to those of BNC (1 800×). Note that the microvillar junction staining is interrupted above the trinucleate cell (between arrows). Adapted from Wooding and Beckers ([85]; Cell Tissue Research 1987, 247 667-673) with permission from Springer.
A new bovine trophoblast cell line (BT-1) was created in 2001 and used as a model to study trophoblast differentiation [66]. BT-1 cells proliferate without feeder cells in a collagen-coated culture vessel [55, 66]. Under these conditions, the cells express different placental proteins such as interferon tau and pregnancy-associated glycoproteins (PAG), but they express only negligible amounts of bPL. However, once they differentiate into BNC on collagen gel, these BNC cells exhibit characteristic features such as increased nuclear DNA content and an increased expression of bPL. These results strongly suggest that the expression of bPL is closely related to the differentiation of trophoblast cells.

**Concentrations of PLs in maternal and fetal circulations**

Maternal concentrations of placental-secreted molecules are regulated by the biosynthesis rate, the ability to cross the placenta barrier, the binding with the target tissues, and the clearance rate from the circulation. Interestingly, the pattern of maternal PL concentrations during pregnancy is similar in humans [41], sheep [36], goats [22], rats [61], mice [56], and cattle [6, 78]. In general, maternal PL concentrations increase with gestational age, peak during the last trimester, and then decrease at or near parturition. Nevertheless, the magnitude and the relationship between maternal and fetal PL concentrations is highly species dependent. For instance, with the exception of cattle, PL concentrations are higher in maternal than in fetal circulations.

The purification of nbPL as well as the synthesis of rbPL led to the development of specific and highly sensitive radioimmunoassay systems for bPL concentration measurements in cattle [2, 6, 34, 40, 78]. bPL can be detected in maternal plasma of some pregnant cows after Day 60 of gestation [6]. Maternal concentrations of bPL increase gradually until Day 200 of gestation (up to 0.6 ng/ml). Therefore, bPL concentrations increase two-fold between Day 200 and Day 220 (up to 1.3 ng/ml) and remain between 1.3 and 2 ng/ml until parturition. The levels of bPL concentrations in cattle are almost negligible when compared with those measured in other species (up to 1 000 times higher) or with those of other placental glycoproteins such as PAG [87].

The half-life of rbPL in maternal circulation was estimated to be approximately 7.5 minutes [14]. The half-life of nbPL was not determined in
vivo. However, the sharp decrease of maternal bPL concentrations within 24 hours after calving also indicates a rapid clearance rate for the glycosylated form [6]. The relatively short half-life of bPL associated with an hypothetical higher binding of this molecule to the mammary gland tissue are believed to be among the main factors responsible for the moderate concentrations of bPL in maternal circulation of pregnant cows [73].

Beckers et al. [6] for the first time measured fetal bPL concentrations by means of a homologous RIA developed with the use of a highly purified preparation of nbPL glycosylated form. By using sensitive RIA (5-10 pg/ml), they described fetal bPL concentrations which declined from 25-30 ng/ml on Day 90 of gestation to 5-15 ng/ml at the term. A similar fetal bPL profile was reported by Byatt et al. who used a nbPL preparation purified from secretory granules from BNC cells [12]. More recently, Alvarez-Oxiley et al. [2] demonstrated that fetal bPL concentrations appeared to be higher when measured with rbPL as a standard compared to glycosylated standard (fig. 5). Interestingly, the difference decreased toward the end of gestation (from 27.3±2.8 ng/ml to 2.82±0.95 ng/ml and from 15.8±1.5

Figure 5. Fetal bovine placental lactogen (bPL) concentrations (mean±SEM) during gestation as measured by twelve different RIA systems. Most RIA systems using a recombinant bPL as standard (○) gave higher concentrations in fetal sera whereas those based on the use of native glycosylated bPL (●) gave lower concentrations. Asterisks denote significant differences between groups (p < 0.05). Adapted from Alvarez-Oxiley et al. ([2]; Reproduction Fertility and Development 2007, 19 877-885) with permission from CSIRO Publishing.
Native and recombinant bPLs

ng/ml to 1.59±0.5 ng/ml when rbPL and nbPL standards were used, respectively. These results suggest a lower rate of glycosylation of bPL during late pregnancy. Similarly, Klisch et al. [43, 44] reported that the glycosylation pattern of bovine placental hormones such as PAG and PRP-I (produced by the same BNC than bPL) changes before parturition. These authors demonstrated that the apparent molecular mass of PAG and PRP-I decreases before parturition, indicating that asparagine-linked glycans disappear in late gestation. The functional implication of changes in the glycosylation patterns of placental hormones during late pregnancy is still not clear [43, 44, 72] but may be related to a modulation of receptor binding or regulation of serum half-life as it has been demonstrated for PAG [44] and other placental glycoprotein hormones [45]. The higher concentrations of bPL in the fetal than in the maternal plasma might also indicate that bPL primarily targets fetal tissues rather than those of the dam.

Among the main factors influencing the peripheral concentrations of PL in bovine species are gestation stage, placental mass, fetal weight, litter size, breed of fetuses, and nutritional status of the mother. Concentrations of bPL increased in maternal serum as gestation progressed [6, 78]. Concentrations of bPL can also be affected by nutrient intake and body condition scores (BCS). Cows presenting low BCS between Days 200 and 256 of gestation have higher plasma bPL concentrations than cows having moderate BCS [60]. Torto [75] reported that pregnant Holstein heifers fed with low concentrations of crude protein content (10.3%) in their forage diet had increased bPL concentrations in the maternal blood. Differences in maternal bPL concentrations were also demonstrated in dams bearing different breeds of fetuses [34]. Conversely, concentration of bPL in maternal blood was not significantly affected by the number of fetuses being carried [58].

DIFFERENT ASPECTS OF IN VIVO ACTIVITY OF PLACENTAL LACTOGENS

The biological activities of PLs have been observed mainly in rodents (reviewed by Linzer and Fisher [48]). In ruminants, the biological functions are not fully understood yet. In the latter species, PL molecules are sup-
posed to have multiple biological effects related to luteotropic activity, mammogenesis, lactogenesis, and fetal growth [68] although these predictions have not always been supported by empirical observations.

**Luteal function**

Ruminant PLs have been inferred to be potentially luteotropic because oPL acts as a luteotropin when administrated to pseudopregnant rats [18]. Lucy et al. [50] reported that recombinant bPL bind to the luteal microsomal fraction in heifers, increasing both the size of corpus luteum (CL) and the plasma progesterone concentrations. Conversely, oPL has no effect on progesterone secretion in ewes [82]. These findings suggest the presence of a PL-mediated signaling system in CL in cows and rodents, but not in ewes. In rodents, the luteotropic effect of PLs occurs via the PRL receptor [27, 48]. The PRL receptor is expressed in bovine CL [50], however neither GH nor PRL are able to compete with bPL for binding with luteal PRL receptors. These results suggest that bovine CL may express distinct bPL receptors which are different from receptors of GH and PRL [30, 42]. It cannot be excluded that bPL has a particular role associated with CL function during pregnancy [50].

**Pregnancy-maternal adaptation**

It has long been thought that PL is a factor involved in the partitioning of nutrients to maintain nutrient supply for fetal development [35]. Rasby et al. [60] studied the effect of nutrition and body reserves on fetal development and measured the concentration of nutrients and PL in the maternal plasma of pregnant cows exhibiting low or moderate body condition scores (low BCS or moderate BCS). There was no significant difference in fetal growth rate between low and moderate BCS groups. Maternal plasma bPL concentrations were increased in cows with low BCS, whereas total fructose concentration in allantoic fluid was reduced. Interestingly, uterine mass was lower, but both chorio-allantoic and cotyledonary weights were higher in cows with low BCS than in those with moderate BCS. Be-
cause concentrations of fructose (the major energy source in the placenta) were reduced in cows with low BCS, a higher bPL concentration could be related to a mechanism that results in an increase in the availability of nutrients in the fetal unit. The higher allantoic and cotyledonary mass can also represent a compensatory mechanism for an increase in the amount of nutrients reaching the feto-placental compartment in cows with low BCS.

**Fetal growth**

The involvement of PLs in the regulation of fetal growth has been investigated in different species. In humans, the somatogenic effect of hPL was suggested by the presence of specific hPL receptors in fetal tissue and by its stimulatory effect on amino acid uptake and glyconeogenesis in fetal tissues [28]. In ruminants, alteration of PLs concentrations by their direct infusion into the maternal and fetal circulations [23, 57, 64] has also suggested that PLs regulate fetal growth by stimulating uptake of maternal nutrients to the fetus and by stimulating the fetus to use the substrates.

By using another approach, Leibovich et al. [47] reported increased oPL plasma concentrations, higher birth weight of newborns, and increased milk yield in pregnant ewes that were immunized against recombinant oPL. They hypothesized that in immunized ewes, the secreted oPL was immediately neutralized by its own antibodies resulting in the activation of placental oPL synthesis and/or secretion and thereby leading to higher oPL concentration in the feto-placental compartment. However, no further investigations were conducted in order to confirm this hypothesis.

**Mammogenesis and lactogenesis**

Lactogenic hormones are required for full lobulo-alveolar growth in the mammary gland, and ovarian steroids are needed for ductal growth [20, 21, 46, 53]. In dairy heifers, mammogenesis is not inhibited by bromocriptine (an inhibitor of PRL secretion) treatment administrated during the later half of gestation [62]. This result suggests that bPL is a potential substitute for pituitary PRL. Recombinant bPL has been reported to have mitogenic
activity in mammary tissue, although bPRL seems to be more potent than rbPL for the induction of milk synthesis [16]. It is intriguing that exogenous-
ly administrated rbPL may or may not increase milk yield, depending on lactation stage. Byatt et al. [17] examined the effect of exogenous rbPL on milk yield in dairy heifers treated with steroids in order to induce lactation. The milk yield of heifers treated with rbPL was 22% higher than that of controls. In this model, recombinant bGH increased milk yield in both bPL-treated and control heifers and stimulated higher yield increase in heifers treated with rbPL. In another study, Byatt et al. [15] reported that in lactating dairy cows, exogenous administration of rbPL increased milk yield, although bPL was less potent than bGH. Administration of either bPL or bGH decreases blood concentrations of urea nitrogen, and increases serum concentrations of insulin-like growth factor-I. Plasma concentrations of nonesterified fatty acids and glucose were also increased by bGH, but PL had little or no effect on lipolysis. Dry matter intake was increased by bPL but not by bGH. These effects of rbPL in lactating dairy cows indicate that bPL is a potent agonist for increasing milk yield without altering lipolysis and insulin sensitivity. However, it is accepted that the galactopoietic effect of rbPL can be simply exerted via an increase in dry matter intake.

CONCLUSIONS

Whereas the histological architecture of the placenta was quite conserved along the evolution of the ruminants, the molecular structure and plasma profiles of bovine placental lactogen are very distinct from those described in the sheep and goat. Bovine PL is the only glycosylated PL molecule isolated from the ruminant placenta. Higher concentrations of bPL are observed in the fetal than in the maternal plasma, which suggests that bPL primarily targets fetal tissues rather than those of the dam. According to different authors, bPL is involved in the regulation of ovarian function, mammogenesis, lactogenesis, pregnancy-stage dependent adaptation, and fetal growth. However, further investigations are needed to understand any direct implication of bPL on fetal tissue growth.
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