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Unfolding protein response signaling is involved in development, maintenance, and regression of the corpus luteum during the bovine estrous cycle

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ABSTRACT

The corpus luteum (CL) is a transient endocrine organ. Development, maintenance, and regression of CL are effectively controlled by dynamic changes in gene expression. However, it is unknown what types of gene are affected during the CL life span of the estrous cycle in bovine. Here, we determined whether unfolded protein response (UPR) signaling via eIF2α/ATF4/GADD34, p90ATF6/p50ATF6, and IRE1/XBP1, which is a cellular stress response associated with the endoplasmic reticulum (ER), is involved in the bovine CL life span. Our results indicated that expression of Grp78/Bip, the master UPR regulator, was increased during the maintenance stage and rapidly decreased at the regression stage. Additionally, UPR signaling pathways genes were found to be involved in luteal phase progression during the estrous cycle. Our findings suggested that Grp78/Bip, ATF6, and XBP1 act as ER chaperones for initiating CL development and maintaining the CL. In addition, we investigated whether ER stress-mediated apoptosis is occurred through three UPR signaling pathways in CL regression stage. Interestingly, pIRE1 and CHOP were found to be involved in both the adaptive response and ER stress-mediated apoptosis. During the CL regression stage, increased expression of pJNK and CHOP, two components of ER stress-mediated apoptotic cascades, occurred before increased level of cleaved caspase 3 were observed. The present investigation was performed to identify a functional link between UPR signaling and CL life span during the bovine estrous cycle. Taken together, results from this study demonstrated that UPR protein/gene expression levels were different at various stages of the bovine CL life span. Variations in the expression of these protein/genes may play important roles in luteal stage progression during the estrous cycle.

1. Introduction

The corpus luteum (CL) is a transient endocrine organ. The main function of this organ is to produce progesterone (P4), which is necessary for pregnancy maintenance and estrous cycle regulation [1]. Rapid development of the CL occurs after ovulation [2], and is accompanied by the proliferation and differentiation of granulosa cells into luteal cells [3]. If pregnancy does not occur, the CL regresses within a few days and a new ovulation cycle begins [2].

The functional capacity of the CL to produce progesterone may also be associated with regulation of the CL life span. Luteal cells of the CL are secretory cells. Three steroidogenic enzymes are required for progesterone production by the luteal cells: steroidogenic acute regulatory protein (StAR), the p450 cholesterol

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side-chain cleavage enzyme (P450scc), and 3β-hydroxysteroid dehydrogenase (3β-HSD) [4]. Therefore, these steroidogenic enzymes are consistently needed for progesterone synthesis. Thus, it is likely that the ER of luteal cells is also involved in the synthesis of steroidogenic enzymes that regulate the CL life span.

The endoplasmic reticulum (ER) plays a central role in protein synthesis and folding [5,6]. ER functional overload, including excessive protein synthesis and accumulation of unfolded proteins in the ER lumen, results in ER stress [6]. For survival and adaption, cells have developed the unfolded protein response (UPR), a self-protective mechanism against ER stress [7]. The UPR of mammalian cells is mediated by three ER transmembrane proteins that act as proximal sensors of ER stress [6,8]: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and protein kinase-like ER kinase (PERK). In the presence of ER stress, sequestration of the ER chaperone protein Grp78/Bip by unfolded proteins activates these three sensors by inducing the phosphorylation of IRE1 and PERK/eukaryotic translation initiation factor 2α (eIF2α), and cleavage of ATF6 [9]. The UPR is fundamentally cyto-protective, but an excessive or prolonged UPR expression can result in cell death predominantly through the induction of ER stress-mediated apoptosis [10]. Prolonged ER stress induces the activation of the pro-apoptotic C/EBP homologous protein (CHOP), Jun N-terminal kinase (JNK), and caspases through three UPR pathways, which in turn promotes apoptosis [11]. However, it is not clear whether UPR signals affect the CL life span.

In a previous study, we demonstrated that the UPR plays important roles in steroidogenic enzyme expression by modulating the ATF6 pathway as well as ER stress-mediated apoptosis in human chorionic gonadotropin (hCG)-stimulated Leydig cells [12]. Therefore, we hypothesized that the UPR may significantly influence the CL life span by regulating steroidogenic enzyme expression in bovine CL. The goal of the present study was to investigate differences in the expression of UPR-associated genes at the protein and RNA level in bovine CL tissues according to the CL life span stage.

2. Materials and methods

2.1. Collection of CLs from ovarian tissues

Ovaries were obtained during the estrous cycle from non-pregnant cows at a local abattoir (Kimhae, Kyungnam, Korea) transported to the laboratory [13]. CL tissues were removed from the ovaries in the laboratory (Supplementary Fig. 1). The luteal phase was divided into three main groups according to macroscopic appearance of the CL tissues as previously described [14,15]. As shown Fig. 1A, the early stage of the CL is characterized by the formation of reddish brown soft tissue (development; Early 1 and 2). CL tissues of the mid stage are tan and orange, and large and hard (maintenance; Mid 1–3). CL tissues of the late stage are completely orange to light yellow and small in size (regression; Late 1).

And each group was further subdivided in the following manner: development [Early 1 (2–4 d after ovulation) and 2 (5–7 d after ovulation)], maintenance [Mid 1 (8–11 d post-ovulation), 2 (12–14 d post-ovulation), and 3 (15–17 d post-ovulation)], and regression [Late 1 (18–20 d post-ovulation)]. For one independent experiment, we obtained CL tissue sample from at least seven ovaries in each luteal stage ($n = 7$ ovaries per stage).

2.2. RNA extraction and reverse transcription PCR

Total RNA was isolated from each individual CL tissue sample using TRIzol reagent (Invitrogen, CA) according to the manufacturer's instructions. Each cDNA was synthesized from the aliquots (1 μg/μl) of total RNA with AccuPower® RT-PCR Premix (Bioneer, Korea). PCR was carried out using AccuPower® PCR Premix (Bioneer) containing specific primers for steroidogenic enzymes (Table 1). The PCR products were separated by electrophoresis in 2% gels. Band intensities were quantified with ImageJ software (NIH, Bethesda, MD).

2.3. Detection of XBP1 splicing by RT-PCR

The cDNA was synthesized from 1 μg of each total RNA using oligo(dT) primers and AccuPower® RT-PCR (Bioneer, Korea). PCR was performed using 2× PCR Premix (Enzynomics, Korea) containing specific primers (Table 1) for splicing XBP-1. The PCR products were digested with Pst1 and then separated by electrophoresis in 2% agarose gels.

2.4. Protein extraction and Western blotting

Total proteins were extracted from CL in ice-cold PRO-PREP protein lysis buffer (iNtRON, Korea). CLs lysate were separated by SDS–PAGE in 12% gels. After electrophoresis, the separated proteins were transferred onto nitrocellulose membranes (Pall Life sciences, NY). After blocking, the membranes were incubated with anti-GADD153, anti-GADD34, anti-CREB2/ATF4, anti-p90ATF6, anti-3β-HSD (Santa Cruz Biotechnology, CA), anti-Grp78/Bip, anti-IRE1, anti-eIF2a, anti-phospho-eIF2a, anti-SAPK/JNK, anti-phospho-SAPK/JNK, anti-cleaved caspase 3 (Cell Signaling, MA), anti-phospho-IRE1 (Abcam, MA), and anti-p50ATF6 (obtained from Dr. In Kyu Lee) antibodies. The membranes were then incubated with a secondary HRP-conjugated anti-goat/mouse/rabbit IgG (Thermo, Scientific, MA). Antibody binding was detected using an ECL kit (Advansta, CA).

2.5. Statistical analysis

All data were analyzed using a one-way ANOVA followed by Dunnett's multiple comparison tests. All calculations were performed using the GraphPad Prism 5.0 software package (San Diego, CA). Differences were considered significant at $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

3. Results

3.1. Steroidogenic gene expression in the CL is altered according to the luteal phase of the bovine estrous cycle

Western blotting results showed that the expression of 3β-HSD protein was increased 2.2-fold by Mid 1 ($p < 0.05$) compared to the Early 1 stage (Fig. 1E). Moreover, 3β-HSD protein levels decreased thereafter and almost disappeared during the Late 1 stage ($p < 0.001$ compared to the Mid 1). In addition, expression patterns of StAR, P450ssc and 3β-HSD mRNA as steroidogenic enzymes involved in progesterone synthesis were similar to those of 3β-HSD protein expression (Fig. 1B–D). Based on these results, we determined that the CL tissues could be used for the subsequent experiments.

3.2. UPR signaling is involved in luteal phase progression during the estrous cycle

To confirm whether the three main UPR pathways affect the CL life span from development to regression, we measured the expression levels of eIF2α/ATF4/GADD34, p90ATF6/p50ATF6, and IRE1/XBP1. Initially, we observed that levels of Grp78/Bip protein as a major ER stress marker were significantly increased and maintained until Mid 3 ($p < 0.05$; Fig. 2A), and significantly de-

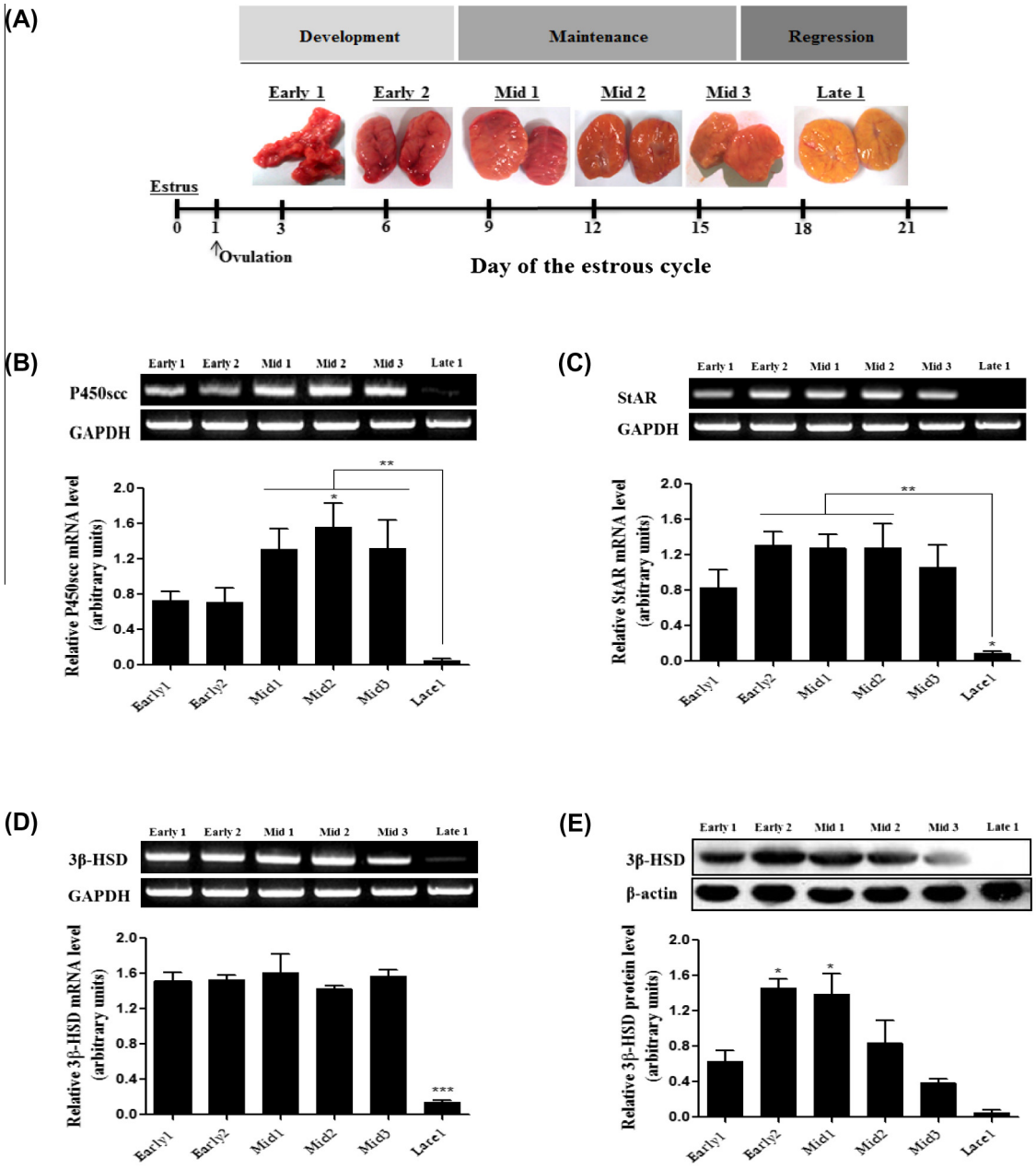

Fig. 1. Changes in steroidogenic gene expression levels according to stage of the luteal phase of the bovine estrous cycle. (A) CL tissues from different days of the estrous cycle were isolated according to morphological characteristics of the bovine ovaries. The CL tissues were carefully separated into Early 1 and 2; Mid 1–3; Late 1 according to the luteal phase. Day 0 was the day of estrous. (B–D) Expression of steroidogenic enzymes involved in progesterone synthesis according to stage of the luteal phase. RT-PCR analysis of P450ssc, StAR, and 3β-HSD as steroidogenic enzymes, and GAPDH mRNA as a control in CL tissues classified according to luteal phase. (E) Western blot analysis of 3β-HSD protein in CL tissues according to luteal phase. Relative 3β-HSD protein levels were normalized to β-actin as a control. Data in the bar graph represents the means ± SEM of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to Early 1.

creased during Late 1 compared to the Mid 3 stage ($p < 0.01$; Fig. 2A).

To evaluate the effect of the first UPR pathway, we measured the phospho-eIF2α, GADD34, and ATF4 protein levels. As shown in Fig. 2B, the levels of phospho-eIF2α were decreased ($p < 0.05$) at Mid 3 and Late 1 compared to Early 1. In contrast, the expression of GADD34 gradually increased 2.0-fold by Mid 3 stage from Early 1 ($p < 0.05$; Fig. 2C). Furthermore, the expression levels of ATF4 as a downstream factor of the PERK pathway were consistently increased 3.9-fold from the Early 1 to Mid 3 stage ($p < 0.05$; Fig. 2D). Interestingly, the expression of GADD34 and ATF4 almost disappeared during the Late 1 stage ($p < 0.05$ compared to Mid 3).

As a second indicator for the UPR activation, we measured the expression levels of both p90ATF6 and p50ATF6. While the protein levels of p90ATF6 were remarkably reduced from the Early 2 stage ($p < 0.01$), p50ATF6 levels were significantly increased ($p < 0.05$) from the Early 2 stage and then steadily decreased ($p < 0.01$ compared to the Early 2 and Mid 1) until the Late 1 stage (Fig. 2E and F).

We confirmed that the third hallmark of the UPR is XBP1 mRNA splicing by activated IRE1. To determine whether progression of the luteal phase is related to IRE1 activation and alternative XBP1 mRNA splicing, we performed Western blotting and RT-PCR to detect phospho-IRE1 and measure spliced XBP1 mRNA levels, respectively. As shown in Fig. 2G, phospho-IRE1 levels were significantly increased ($p < 0.05$) from the Early 1 to 2 stage, and increased 5.5-fold by the Mid 3 stage ($p < 0.01$). IRE1 activity was also measured by monitoring the amount of spliced XBP1 mRNA

Table 1
Primer sequence for reverse transcription PCR.

Target	Primer	Sequence reported 5′–3′	T_m (°C)	Amplicon length (bp)
HSD3B1 (3β-HSD)	Sense	CTAATGGGTGGGCTCTGAAA	55	537
	Antisense	CACGCTGTTGGAAAGAGTCA		
XBP1	Sense	AAACAGAGTAGCAGCTCAGACTGC	61	743
	Antisense	TCCTTCTGGGTCCACTTCTGGGAG		
StAR	Sense	CAGGGAGAGGTGGCTATGCA	56	262
	Antisense	CCGTGTCTTTTCCAATCCTCTG		
P450scc (CYP11A1)	Sense	CACCGATATTATCAGAAACCC	50	249
	Antisense	ATTGGTGATGGACTCAAAGG		
GAPDH	Sense	ACCACAGTCCATGCCATCAC	55	452
	Antisense	TCCACCACCCTGTTGCTGTA		

3β-HSD, 3β-hydroxysteroid dehydrogenase; StAR, steroidogenesis acute regulatory; P450scc, cytochrome P450 side-chain cleavage; XBP1, X-box binding protein 1; T_m, melting temperature; For, forward; Rev, reverse.

produced during the luteal phase. The appearance of spliced XBP1 was increased 1.8-fold from the Early 1 to 2 stage ($p < 0.01$) and rapidly decreased thereafter (Fig. 2H).

3.3. ER stress-mediated apoptosis is induced through the three UPR signaling pathways during the CL regression stage

To confirm whether the ER stress-mediated apoptotic pathway is associated with the CL regression stage. We therefore determined whether the levels of CHOP, phospho-JNK, and cleaved caspase 3 are increased during the regression stage of the luteal phase. As shown in Fig. 3A and B, the levels of CHOP and phospho-JNK proteins were increased at the Early 2 stage, and significantly increased 11.6- and 2.6-fold, respectively, by the Mid 3 stage ($p < 0.01$). In turn, cleaved caspase 3 was only detected during the Late 1 stage ($p < 0.001$; 6.0-fold increase; Fig. 3C).

4. Discussion

Our study is the first to describe changes in the expression of UPR genes at the protein and RNA level according to stage of the bovine CL life span. We showed that all three UPR signaling pathways were involved in luteal phase progression. In addition, expression of phospho-JNK and CHOP, two components of ER stress-mediated apoptotic cascades, was increased prior to increased level of cleaved caspase 3 were observed during the CL regression stage.

The CL plays a central role in regulating the estrous cycle [1,16]. Many studies have demonstrated that CL development enhances the expression of steroidogenic enzymes to promote progesterone production and maintain this capacity during the entire CL life span until regression [17]. In particular, 3β-HSD is a major steroidogeneic enzyme responsible for progesterone synthesis [18]. Therefore, CL obtained from non-pregnant cows at a local abattoir was not only classified in this study according to morphological characteristics but also the levels of 3β-HSD expression (Fig. 1). As expected, 3β-HSD protein expression increased from the Early 1 to Mid 1 stage. During the Mid 2–3 stages, 3β-HSD expression gradually decreased. Subsequently, 3β-HSD protein was barely detected during the Late 1 stage. These results demonstrated that the bovine CL we collected were suitable for our study of gene expression changes according to the luteal phase of the estrous cycle.

The ER of luteal cells may be sensitive to alterations in homeostasis of steroidogenic enzyme synthesis during progesterone production. It is well known that UPR signaling plays an important role in the maturation of secretory cells including antibody-producing plasma cells, osteoblasts that secrete collagen, and insulin-secreting pancreatic β-cells [19]. As such, UPR signaling has been shown to regulate the expression of specific proteins [6,19]. Since the CL need steroidogenic enzymes to produce progesterone, the UPR may also play a significant role in regulating steroidogenic enzyme expression during the estrous cycle. The present study has provided the first evidence of dynamic protein expression patterns associated with three UPR-related signaling pathways in the CL during the natural bovine estrous cycle.

First, Grp78/Bip, the master UPR regulator, dissociates from the three ER stress transducers (PERK/eIF2α, ATF6, and IRE-1) and then functions as an ER chaperone [11,20]. Grp78/Bip retains its anti-apoptotic properties and interferes with caspase activation by directly interacting with apoptotic pathway intermediates [21,22]. As shown in Fig. 2A, Grp78/Bip expression was increased at the Early stage, was maintained until the Mid 1–3 stage, and rapidly decreased during the Late 1 stage. Rapidly decreasing Grp78/Bip expression observed during the regression stage might be induced by ER-stress mediated apoptosis signaling such as caspase 3 cleavage (Figs. 2A and 3C). Results from the present study suggest that Grp78/Bip may both function as an ER chaperone and block caspase activation during the Early and Mid stages.

Under ER stress, PERK phosphorylates eIF2α, resulting in generalized attenuation of translation [21]. During the recovery response, the induction of GADD34 protein expression participates in feedback inhibition of translation [23]. Our results showed that the level of phospho-eIF2α decreased while that of GADD34 increased by the Mid 3 stage. These findings suggest that GADD34 expression may help maintain steroidogenic enzyme expression.

PERK pathway activation also leads to the induction of ATF4 expression [24]. ATF4 initiates a cascade promoting transcription of the pro-apoptotic factor CHOP [5,6]. Our results demonstrated that CHOP expression during the Mid 3 stage may be increased by ATF4 and induce apoptosis (Figs. 2D and 3A). It has been reported that ATF6 constitutively expressed as a 90-kDa protein (p90ATF6) is directly converted into a 50-kDa protein (p50ATF6) in cells experiencing ER stress [11,25]. As shown in Fig. 2E and F, the expression patterns of p90ATF6 and p50ATF6 were completely opposite during the Early stage.

After ovulation, granulosa cells evolve into granulosa lutein cells of the CL that produce progesterone [26]. In our experiments, we found that both p50ATF6 and CHOP expression was increased during the Early 1 and 2 stages (Figs. 2F and 3A). So far, the identified targets of ATF6 include ER chaperone proteins such as CHOP [27]. Although p50ATF6 can induce CHOP mRNA expression, no reports have linked ATF6 to ER stress-induced apoptosis. It seems that ATF6-mediated CHOP expression during the Early 1 and 2 stages counteracts the ability of ER stress to prevent granulosa cells differentiation during CL development. In addition, up-regulation of CHOP expression has been observed during cell differentiation [5]. Our findings therefore suggest the possibility that ATF6 and ATF4-mediated CHOP expression may be involved in granulosa cell differentiation during CL development and apoptosis during the regression stage.

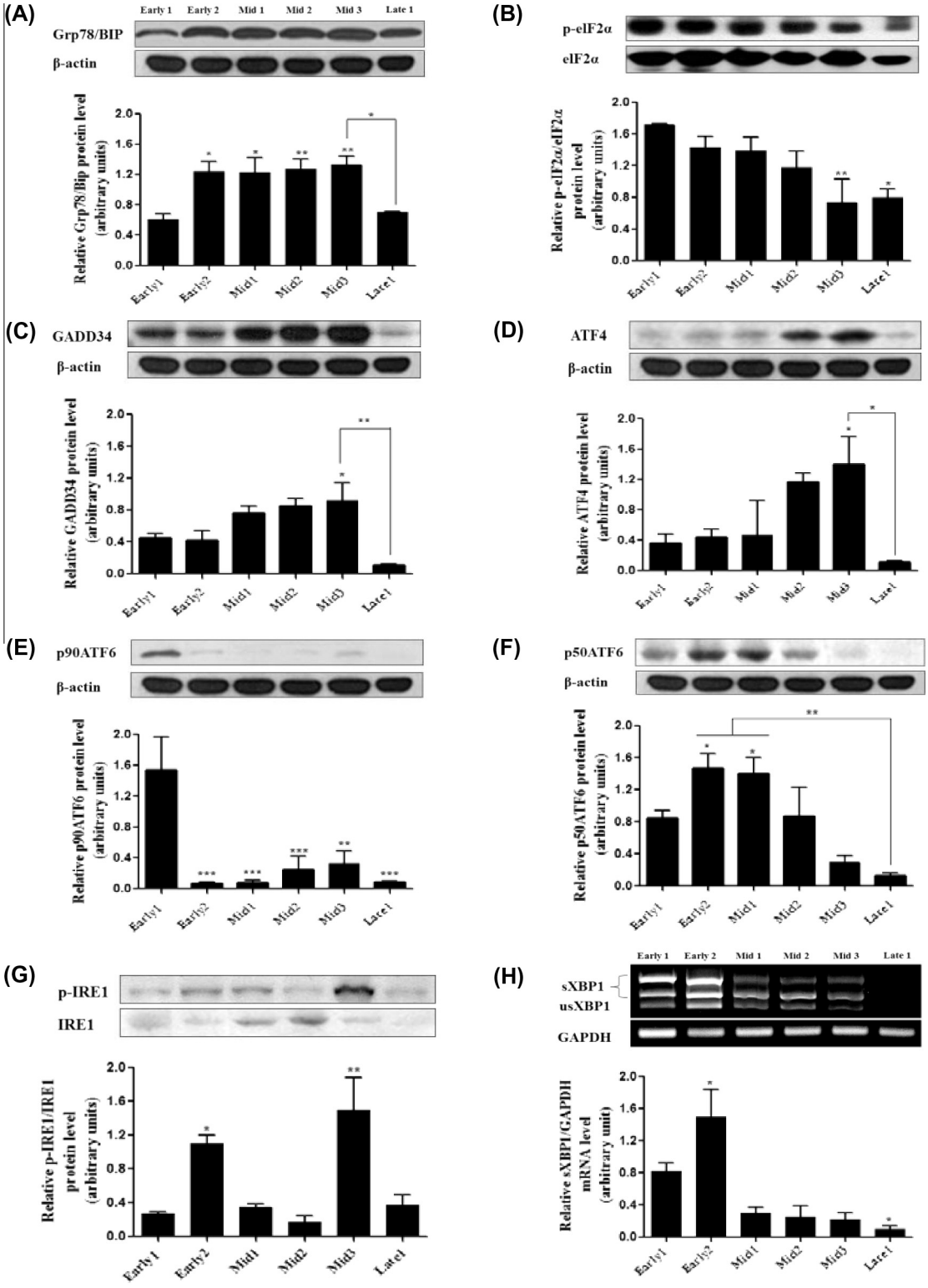

Fig. 2. Changes of UPR signaling protein levels during stage of the luteal phase. (A–G) Western blotting was performed to the protein levels of GRP78/Bip, PERK/eIF2α signaling (ATF4, GADD34 and p-eIF2α), ATF6 signaling (p90ATF6 and p50ATF6), IRE1 signaling (IRE1 and p-IRE1) as a major UPR marker in CL tissues at different stages of the luteal phase and β-actin protein as a control. (H) Representative RT-PCR analysis of spliced XBP1 (sXBP1), and unspliced (usXBP1) XBP1 mRNA levels as ER stress makers in CL tissues and GAPDH mRNA as a control. Data in the bar graph represents the means ± SEM of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to Early 1.

IRE1 is a dual-activity enzyme with an endonuclease domain and serine-threonine kinase domain [11,28]. In the current study, phospho-IRE1 levels were significantly increased during the Early 2 stage and further elevated at Mid 3 (Fig. 2G). XBP1 mRNA splicing by activated IRE1 occurred during the Early 2 stage (Fig. 2H). JNK activation by phospho-IRE1 as a serine–threonine kinase was also significantly increased during the Mid 3 stage (Fig. 3B). Activated IRE1 initially promoted the UPR by splicing XBP1 mRNA during

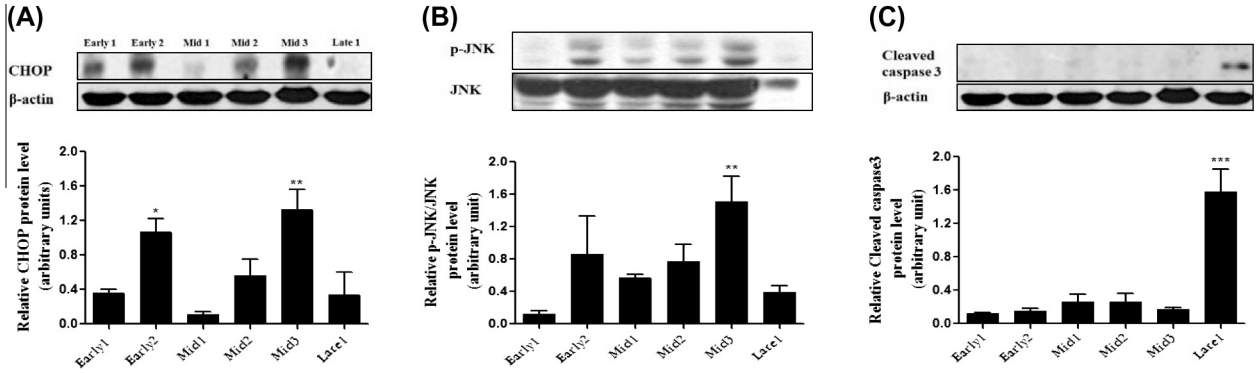

Fig. 3. Expression of ER stress-mediated pro-apoptotic protein levels during luteal phase. (A–C) Western blot analysis of CHOP, JNK signaling (JNK and p-JNK), and cleaved caspase 3 expression protein level as ER stress-mediated apoptosis markers in CL tissues classified according to luteal phase and and β-actin protein as a control. Data in the bar graph represents the means ± SEM of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to Early 1.

the Early 2 stage. However, if progesterone synthesis persists phospho-IRE1 would ultimately trigger luteal cell apoptosis by recruiting phospho-JNK during the Mid 3 stage.

Proteins downstream of all three UPR pathways contribute to the induction of apoptosis in the presence of ER stress. Activation of the PERK/eIF2α and IRE1 pathways leads to the induction of CHOP expression and JNK phosphorylation, respectively [6]. Prolonged ER stress promotes the cleavage and subsequent activation of pro-apoptotic caspase 3, thereby leading to apoptosis [29].

As expected, we detected cleaved caspase 3 during the Late 1 stage (Fig. 3), resulting in decreased 3β-HSD expression (Fig. 1C). JNK activation and CHOP expression via ER stress-mediated pro-apoptotic signaling cascades occurred before caspase 3 activation. These results suggest that increased levels of CHOP, phospho-JNK, and cleaved caspase 3 lead to ER stress-mediated apoptosis and CL regression.

Based on our results, several genes involved in UPR signaling are believed to be activated during different stages of the luteal phase. This may be related to the regulation of luteal phase progression during the bovine estrous cycle. In particular, Grp78/Bip, ATF6, and XBP1 act as ER chaperones during CL development and maintenance. Interestingly, phospho-IRE1 and CHOP are involved in both the adaptive response and ER stress-mediated apoptosis. However, additional studies are needed to elucidate the mechanism through which UPR-associated genes act to regulate steroidogenic enzyme expression and the CL life span. We will attempt to further characterize the relationship between UPR-associated genes and CL life span in further detail using primary luteal cells. We will also evaluate changes of UPR gene expression in CL samples from various species.

In summary, the present study provides the first evidence for dynamic changes in the expression of proteins associated with the three UPR-related signal pathways in the CL during the natural bovine estrous cycle. Our results suggest a functional link between UPR signaling and the CL life span during the estrous cycle. In addition, these data will be helpful for better understanding the basic mechanisms that govern the natural estrous cycle of bovines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.10.056.

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