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REVIEW

Roles of antioxidant enzymes in corpus luteum rescue from reactive oxygen species-induced oxidative stress

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Abstract Progesterone produced by the corpus luteum (CL) regulates the synthesis of various endometrial proteins required for embryonic implantation and development. Compromised CL progesterone production is a potential risk factor for prenatal development. Reactive oxygen species (ROS) play diverse roles in mammalian reproductive biology. ROS-induced oxidative damage and subsequent adverse developmental outcomes constitute important issues in reproductive medicine. The CL is considered to be highly exposed to locally produced ROS due to its high blood vasculature and steroidogenic activity. ROS-induced apoptotic cell death is involved in the mechanisms of CL regression that occurs at the end of the non-fertile cycle. Luteal ROS production and propagation depend upon several regulating factors, including luteal antioxidants, steroid hormones and cytokines, and their crosstalk. However, it is unknown which of these factors have the greatest contribution to the maintenance of CL integrity and function during the oestrous/menstrual cycle. There is evidence to suggest that antioxidants play important roles in CL rescue from luteolysis when pregnancy ensues. As luteal phase defect impacts fertility by preventing implantation and early conceptus development in livestock and humans, this review attempts to address the importance of ROS-scavenging antioxidant enzymes in the control of mammalian CL function and integrity.

KEYWORDS: antioxidants, corpus luteum, oxidative stress, progesterone, reactive oxygen species

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Introduction

In mammalian species, the main function of the corpus luteum (CL) is the synthesis of progesterone which is required for the establishment of a uterine environment suitable for the development of peri-implantation conceptus (embryo and associated extra-embryonic membranes) and the successful progression and maintenance of pregnancy (Ryan, 1969). Progesterone acts on the endometrium to regulate the synthesis of growth factors, cytokines, transport and adhesion proteins, protease inhibitors, hormones and enzymes which are primary regulators of conceptus implantation, survival and development (Graham and Clarke, 1997). Thus, compromised CL progesterone production is a potential risk factor for prenatal development and pregnancy outcomes (Arredondo and Noble, 2006; Diskin and Morris, 2008).

The periodic CL regression allows initiation of a new reproductive cycle. The demise of the CL at every non-fertile cycle is characterized by the loss of capacity of the luteal cells to produce and secrete progesterone (functional regression) and death of luteal cells (structural regression) (**Figure 1**). The mammalian CL contains two types of steroidogenic cells, designated large and small luteal cells. Luteal cells are organized between connective tissue and abundant vasculature. The small and large luteal cells are recognizable by light microscopy and have intact and normal appearance in the healthy rescued CL, whereas they are disorganized and exhibit nuclear chromatin condensation and pyknosis in the non-rescued CL (**Figure 1**). Fluorescent DNA fragments are rarely present in the healthy and functional CL (rescued CL of early pregnancy) whereas they are abundant in the regressed CL (non-rescued CL of the late oestrous cycle) (**Figure 1**).

Although the mechanisms of CL rescue from cell death and maintenance of progesterone production are very complex and vary among mammalian species (Niswender et al., 2000), there is substantial evidence that reactive oxygen species (ROS) are key factors in determining the CL lifespan (Behrman et al., 2001) and that antioxidants play significant roles in CL physiology during the oestrous/menstrual cycle (Al-Gubory et al., 2005, 2006; Sugino, 2006; Sugino et al., 2000a). Luteal ROS production and propagation depends upon several regulating factors, including luteal antioxidants, steroid hormones and cytokines, and their crosstalk. However, it is unknown which of these factors have the greatest contribution to CL function. In addition, the sequence of events leading to the functional and structural luteal regression at the end of the oestrous/menstrual cycle is still not clear. The scarce in-vivo reports studying the CL of rats (Sugino et al., 1993a), women (Sugino et al., 2000a) and sheep (Al-Gubory et al., 2004; Arianmanesh et al., 2011) have shown the importance of antioxidant enzymes in the control of CL function during the peri-implantation period. As a luteal phase defect can impact fertility by preventing implantation and early conceptus development in livestock and humans, this review attempts to address the importance of ROS-scavenging antioxidant enzymes in the control of mammalian CL function and integrity.

ROS and ROS-scavenging systems

The production of adenosine triphosphate is derived from the mitochondrial respiratory chain oxidative phosphorylation, which is the main source of oxygen-free radicals and non-radical ROS. The ROS include superoxide anion ($^{\cdot}O_2^-$), hydroxyl radical ($^{\cdot}OH$), nitric oxide ($^{\cdot}NO$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$). ROS are also produced via enzymic pathways, including the activity of membrane-bound NADH and NADPH oxidases, the activity of xanthine oxidase, the metabolism of arachidonic acid by lipoxygenases and cyclo-oxygenases (COX) and the mitochondrial cytochrome P450 (Bedard and Krause, 2007; Cho et al., 2011; Zangar et al., 2004).

Aerobic cells are equipped with antioxidant enzymes that control ROS production and prevent their propagation to toxic ROS (**Figure 2**). The conversion $^{\cdot}O_2^-$ to H_2O_2 by superoxide dismutase (SOD) is the first enzymic antioxidative pathway. Two different SOD were identified: copper–zinc-containing SOD (SOD1) is predominantly localized in the cytosol and also found in mitochondria (Okado-Matsumoto and Fridovich, 2001), and manganese-containing SOD (SOD2) occurs in the mitochondrial matrix (Weisiger and Fridovich, 1973). Glutathione peroxidase (GPX) is a group of selenium-containing enzymes that belong to the first antioxidant mechanism preventing the propagation of highly reactive ROS by catalysing the conversion of H_2O_2 to H_2O and O_2. NADH and NADPH are key elements in the control of ROS production and maintenance of cellular redox state (Kirsch and De Groot, 2001). The mitochondrial $NADP^+$-dependent isocitrate dehydrogenase generates NADPH via oxidative decarboxylation of isocitrate (Jo et al., 2001).

Role of ROS in corpus luteum steroidogenesis

Like any aerobic cells, those of the CL produce ATP through the respiration of O_2 with the consequence of luteal ROS production. The rate-limiting step in steroidogenesis in all steroidogenic organs, including the CL (Christenson and Devoto, 2003), is the transfer of cholesterol from the outer to the inner mitochondrial membrane where it is converted into pregnenolone by the enzyme cytochrome P450 side chain cleavage (P450scc). Luteal ROS are generated via enzymic pathways of the mitochondrial cytochrome P450 (Zangar et al., 2004). In the CL, ROS are produced by macrophages (Sugino et al., 1996) and luteal cells (Kato et al., 1997) where they can affect progesterone production. Indeed, there is substantial evidence to indicate that ROS regulate steroid hormone biosynthesis in the CL. The induction of ovarian SOD by LH, which in turn could lead to the production of H_2O_2, suggests that this action is involved in the mechanism by which LH stimulates progesterone secretion in the rat CL (Laloraya et al., 1988). Carlson et al. (1993) indicated that ROS can function beneficially to control the production of progesterone by luteal cells over the course of the reproductive cycle and inhibit progesterone synthesis at the end of the cycle. The $^{\cdot}O_2^-$ radical is reported to be involved in the mechanism by which LH stimulates progesterone secretion in the rat CL (Sawada and