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Microvascularization and angiogenic activity of equine corpora lutea throughout the estrous cycle

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Abstract

Corpus luteum growth and endocrine function are closely dependent on the formation of new capillaries. The objectives of this study were to evaluate (i) tissue growth and microvascular development in the equine cyclic luteal structures; (ii) in vitro angiogenic activity of luteal tissues in response to luteotrophic (LH, PGE_2) and luteolytic ($PGF_{2\alpha}$) hormones and (iii) to relate data to luteal endocrinological function. Our results show that microvascular density was increased in the early and mid luteal phase, followed by a fall in the late luteal phase and a further decrease in the corpus albicans. Hyperplasia of luteal tissue increased until the mid luteal phase and it was followed by tissue regression. Luteal explants were cultured with no hormone added, or with $PGF_{2\alpha}$, LH, PGE_2, LH + PGE_2 or LH + $PGF_{2\alpha}$. Media conditioned by equine luteal tissue from different stages of the luteal phase were able to stimulate mitogenesis of bovine aortic endothelial cells (BAEC), suggesting the presence of angiogenic activity. No difference was observed among luteal structures on their mitogenic capacity, for any treatment used. Nevertheless, Late-CL conditioned-media with $PGF_{2\alpha}$ showed a significant decrease in BAEC proliferation ($p < 0.05$) and LH + $PGF_{2\alpha}$ a tendency to reduce mitogenesis. Thus, prostaglandin $F_{2\alpha}$ may play a role on vascular regression of the CL during the late luteal phase in the

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mare. These data suggest that luteal angiogenesis and vascular regression in the mare are coordinated with the development of non-vascular tissue and might be regulated by many different factors.

Keywords: Corpus luteum; Mare; Angiogenesis; Vascularization; Mitogenic factors

1. Introduction

The formation of luteal structures is characterized by repeating patterns of cellular proliferation [1], remodeling of extracellular matrix [2,3] and changes in luteal vascularity in each ovarian cycle [4]. Many aspects of cyclic changes in the reproductive tract during ovarian cyclicity, implantation, as well as placental function are dependent on physiologic angiogenesis [5–8], which consists of new vascular growth from pre-existing vasculature [9]. This neovasculature is essential for the blood-borne delivery of substrates for steroidogenic cells within the ovary, and enables progesterone (P_4) to be released into the blood stream [10–12]. Tissue growth and regression that occurs in the female reproductive tract appears to be controlled by stimulating or angiogenic/mitogenic substances and by inhibitory or anti-angiogenic/anti-mitogenic growth factors [13–17].

The understanding of the vital, angiogenic processes that occur in the mare's reproductive tract is lacking. Only in the recent past, studies on microvascularization of the mare's reproductive tract, such as the endometrium, follicles and corpus luteum have been carried out [18–21]. As the corpus luteum (CL) growth and its endocrine function are closely dependent on the formation of new capillaries, their dysfunction might be related to a deficient vascularization. In the future, knowledge of this process might help understanding infertility in the mare due to primary luteal function impairment.

Hormonal regulation of the production of angiogenic factors by the CL has been evaluated in vitro [22,23]. It is well documented that luteininzing hormone (LH) and prostaglandin (PG) E_2 are the main luteotrophic hormones, while prostaglandin $F_{2\alpha}$, is luteolytic in nature [24]. Lately, there is growing evidence that besides the main endocrine hormone LH, a number of locally produced regulators, such as growth factors, peptides, steroids and prostaglandins, modulate the response of the CL to these endocrine signals [25].

The objectives of this study were to evaluate (i) luteal tissue growth and microvascular development in the equine cyclic luteal structures; (ii) in vitro angiogenic activity of luteal tissues in response to luteotrophic (LH, PGE_2) and luteolytic ($PGF_{2\alpha}$) hormones and (iii) to relate data to luteal endocrinological function.

2. Materials and methods

2.1. Animals

During the equine breeding season, from the Spring equinox until the end of August, luteal tissue and blood were collected post-mortem at a slaughter facility from randomly designated cycling mares. Mares' reproductive and clinical histories were unknown, but