Leptin Contributes to the Development of the Corpus Luteum
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Abstract
The mechanistic events of female infertility have been investigated for over 50 years and despite progress many causes of infertility remain elusive. However, over half of idiopathic infertility issues have been attributed to a defective ovarian tissue responsible for the maintenance of a conceptus, the corpus luteum (CL). Many CL defects are attributed, in part, to abnormal vasculogenesis (angiogenesis), which occurs primarily during the developmental stage of the luteal lifespan. A few well-established angiogenic growth promotants have been implicated in luteal angiogenic processes but the mechanisms of the process are still under investigation. Recent evidence supports a role for the adipokine hormone leptin as a probable component in the angiogenic and developmental processes of a CL. Leptin expression is present during the developmental and maturation stages of the luteal lifespan and stimulates the expression of angiogenic hormones in the CL. Induced leptin deficient CL have a higher occurrence of abnormal, underdeveloped gross morphology and an increase in the number of large diameter vessels and large luteal cells. Leptin replacement therapy in leptin deficient CL accelerates tissue development, increasing overall tissue mass and forming a structure that resembled a mature CL during the early stages of development. Collectively, the evidence supports the supposition that leptin is involved in the angiogenic and developmental processes of luteal tissue.

Keywords: Leptin; Corpus luteum; Angiogenesis development

Commentary
The corpus luteum (CL) is an important ovarian tissue that secretes progesterone, a steroid hormone essential for the maintenance of pregnancy in mammals. It exhibits tumorigenic growth properties during the developmental process, doubling in size and cell number every 60-70 h [1]. In order to support the exponential tissue growth the CL is highly vascularized, having the highest rate of blood flow per unit of tissue in the female body [2]. Inappropriate vasculogenesis leads to aberrant CL development and reduced circulating concentrations of progesterone [3]. The reduced progesterone is associated with an increased occurrence of miscarriage [4], which is not mitigated with the use of synthetic progestins in subjects suffering recurrent miscarriages [5]. Hence, understanding the underlying mechanisms of luteal development, including the angiogenic process, can potentially lead to therapies that correct luteal deficiencies and ameliorate luteal infertility. Vascularization of the CL occurs through an angiogenic process where vessels form from pre-existing vascular networks of an ovulated follicle. This process is regulated in part by the angiogenic hormones vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and angiopoietin 1 (AngI). Both VEGF and FGF2 promote capillary membrane destabilization, endothelial cell differentiation, proliferation, migration and vascular tube formation in human, bovine, and ovine luteal tissue [6,7]. Angiopoietin 1 then promotes the maturation and stabilization of nascent vessels through the recruitment of stromal support cells, including pericytes and smooth muscle cells [8]. Each of these angiogenic factors is regulated by the adipokine hormone leptin, which has previously been reported to exhibit angiogenic properties in non-ovarian tissues [9,10]. The expression of leptin and its receptor have been identified in luteal tissue, but the function of leptin was believed to be limited steroidogenic regulation. However, its role in luteal steroidogenesis has proven to be moderate without the addition of growth promoting hormones [11,12] which suggests that leptin may serve an alternate function previously overlooked that is supportive of the highly vascular tissue.

In 2014, Wiles et al. [13] reported that leptin upregulates the expression of VEGF, FGF2 and AngI in cultured dispersed lutea, but this stimulatory effect was limited to the early developing lutea despite sustained luteal expression of leptin and its receptor in the mature CL. This implied that leptin might be involved in luteal angiogenic processes as the CL forms. This supposition was explored by creating a leptin deficient CL with the infusion of a leptin antibody throughout the development and maturation stages of the luteal lifespan. The induced luteal leptin deficiency increased the occurrence of CL with an abnormal, persistently underdeveloped gross morphology during the late stage of the luteal lifespan, frequently resembling an early developing CL [14]. Furthermore, leptin deficiency altered the microscopic morphological landscape by increasing the number of large diameter vessels (Table 1) and population of large luteal cells (Table 1) [14]. These changes in luteal morphology may be a compensatory adaptation to the reduction in the contribution of leptin to the angiogenic processes during CL development. The adaptation may have prevented an initial impairment of progesterone production by modifying vasculature to provide ample substrate for hormone synthesis and increased the large luteal cell population to increase progesterone synthesis [15]. The aberrant morphology of leptin deficient lutea can be reversed when leptin replacement therapy is applied during the early stage of

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Avg. large luteal cells per area**</th>
<th>Avg. small luteal cells per area**</th>
<th>Ratio of large/small luteal cells per area*</th>
<th>Avg. large vessel diameter* (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>59.20 ± 1.54**</td>
<td>43.94 ± 2.15**</td>
<td>1.4 ± 0.08*</td>
<td>21.3 ± 0.03*</td>
</tr>
<tr>
<td>Leptin Antibody</td>
<td>76.3 ± 1.79*</td>
<td>33.11 ± 1.16*</td>
<td>2.3 ± 0.32*</td>
<td>33.0 ± 0.33*</td>
</tr>
</tbody>
</table>

*a,b Superscripts indicates means different between treatment groups (P<0.01); *Effect of treatment is significant (P<0.001); #Area of tissue=26.6 x 10^4 μm^2 at 20x magnification

Table 1: Microscopic morphology of mature CL from control and leptin antibody treatment groups.

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3.06 ± 0.08
85.32 ± 3.34
4
16.32 ± 0.65

Microscopic morphology of developing CL from control and leptin

Table 2: Microscopic morphology of developing CL from control and leptin antibody+leptin treatment group.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Avg. # of large luteal cells per area**</th>
<th>Avg. # of small luteal cells per area**</th>
<th>Ratio of large/small luteal cells per area**</th>
<th>Avg. large luteal cell size per area** (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>235.84 ± 6.11a</td>
<td>82.92 ± 3.25a</td>
<td>3.06 ± 0.08a</td>
<td>16.32 ± 0.65a</td>
</tr>
<tr>
<td>Leptin Antibody+Leptin</td>
<td>85.32 ± 3.34a</td>
<td>51.76 ± 2.43a</td>
<td>1.86 ± 0.06a</td>
<td>22.56 ± 0.70b</td>
</tr>
</tbody>
</table>

a,b Superscripts indicates means different between treatment groups (P<0.0001); *Effect of treatment is significant (P<0.0001); #Area of tissue=26.6 × 10^4 μm^2 at 20x magnification

Published data [14] and adapted for commentary

References