Neuregulin-1 signaling in corpus luteum

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Abstract

The corpus luteum (CL) is an absolute requirement for reproductive success to regulate the estrous/menstrual cycle and pregnancy by producing progesterone (P4). CL is a transient ovarian endocrine gland that develops from a dominant ovulated follicle in the ovary by the mid-cycle surge of luteinizing hormone (LH). The lifespan of CL is tightly regulated by survival and cell death signals, including endocrine (LH), intra-ovarian regulators, and cell-cell interactions. Neuregulin 1 (NRG1) is a member of the epidermal growth factor-like factor family that mediates its effect through the erythroblastoma (ErbB) family. However, the detailed mechanisms associated with the interplay of NRG1 in CL function are unknown. In this study, we investigated the potential impact of NRG1 on rat CL and luteal cell (LC) function. Our experimental results suggest that LH has differential effects on the expression of NRG1 and ErbB receptors in CL during pregnancy. On day 12 in pregnant rats, NRG1 and ErbB2/3 receptors are highly expressed in LCs with a positive correlation with StAR expression and serum LH and P4 concentrations. In contrast, on day 22, pregnant rats had significantly decreased serum LH and P4, suggesting luteolysis had occurred with low expression of NRG1 and ErbB receptors. To define the role of NRG1 in LCs, monolayer LCs were cultured and treated with different doses of cytokines in the presence of exogenous recombinant NRG1 or absence of NRG1 (knockdown, siNRG1) since various cytokines are produced within the CL for vascularization. Under these experimental conditions, siNRG1 alone or cytokines-treated LCs showed significantly higher cell death in a time and dose-dependent manner when compared with parallel controls. In contrast, exogenous NRG1 co-treated LCs with cytokines showed delayed apoptosis. These results are further corroborated by pro-survival and anti-inflammatory protein expression. Furthermore, these experimental studies also provided direct evidence that the gain of NRG1 maintains the phosphorylation of ErbB2 and ErbB3, along with PI3K, Akt, and Erk. In contrast, a loss of NRG1 directly inhibited the phosphorylation of ErbB2/3, Akt, and ERK-1/2 in LC. Collectively, these results provide new evidence of the supporting role of NRG1 in maintaining the function of CL.

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