Autoimmune activation of the GnRH receptor induces insulin resistance in a rat model of polycystic ovary syndrome Short Title: GnRHR autoantibody-induced insulin resistance in rats

Hongliang Li[1], Gege Zhang[2], YANKAI GUO[1], Jielin Deng[1], Hayley Fischer[1], LaTasha Craig[1], David Kem[3], and Xichun Yu[1]

[1]The University of Oklahoma Health Sciences Center
[2]Xinjiang Medical University Affiliated First Hospital
[3]Oklahoma State University Center for Health Sciences

April 28, 2020

Abstract

Polycystic ovary syndrome (PCOS), a metabolic and reproductive disease, is frequently associated with type 2 diabetes. We previously demonstrated that autoantibodies (AAb) directed toward the second extracellular loop (ECL2) of the gonadotropin-releasing hormone receptor (GnRHR) are present in a high percentage of PCOS patients. It is unclear whether GnRHR-AAb can induce peripheral tissue insulin resistance (IR) in animal models. In the present study, we examined the impact of GnRHR-AAb on glucose metabolism, inflammation, and insulin signaling in a recently established autoimmune rat model of PCOS. Sixteen rats were divided into two groups: a GnRHR ECL2 peptide-immunized group, and a control group. Sera GnRHR-AAb, luteinizing hormone (LH), and testosterone were measured by ELISA. All immunized rats produced elevated anti-GnRHR ECL2 antibody titers and higher concentration of testosterone and LH. Intraperitoneal glucose tolerance tests demonstrated higher blood glucose levels in immunized rats at 30 minutes and 60 minutes. A homeostatic model assessment of insulin resistance index was also higher. Furthermore, the mRNA expression levels of insulin signaling genes in peripheral tissue were decreased. The concentration of sera TNF-α, IL-1α, and IL-18 were increased, while IL-4 and IL-10 were inhibited in the immunized group. These data support the likelihood of GnRHR-ECL2 AAbs inducing IR in peripheral tissue. GnRHR-ECL2 AAb may alter the synthesis and pulsatile secretion of LH thus leading to hyperandrogenemia, inflammation, and IR. Our studies provide the realistic expectation of new knowledge regarding the etiology of IR in PCOS as well as a pathway for development of novel effective treatment.

Hosted file

Autoimmune activation of the GnRH receptor induces insulin resistance in a rat model of polycystic ovary
available at https://authorea.com/users/304139/articles/434489-autoimmune-activation-of-the-gnrh-receptor-induces-insulin-resistance-in-a-rat-model-of-polycystic-ovary-syndrome-short-title-gnrhr-autoantibody-induced-insulin-resistance-in-rats