EXPERIMENTAL HYPERHOMOCYSTEINEMIA IN RATS: A MODEL TO EXPLORE MOLECULAR CUES TO POLYCYSTIC OVARY SYNDROME

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OBJECTIVE: To elucidate the cause and effect links between different metabolic associates of polycystic ovary syndrome (PCOS) induced by experimental hyperhomocysteinemia (HHcy).
DESIGN: Post-pubertal Sprague-Dawley rats of 50-55 day of age were gavaged with homocysteine through drinking water at a dose of ~100 mg/kg/day for a period of one month.
MATERIALS AND METHODS: They were evaluated for magnitude of HHcy and basic tenets of PCOS including i) development of polycystic ovaries ii) altered gonadotropin status, iii) hyperandrogenemia, iv) glucose intolerance, insulin resistance (IR), and v) dyslipidemia. The effect of homocysteine on insulin-mediated cellular uptake of 2-deoxy-D-[1-3H] glucose was evaluated in L6 rat skeletal muscle cell line *in vitro*. Expression of certain regulatory factors concerned with ovarian steroidogenesis (Wnt4, steroidogenic acute regulatory protein (StAR), aromatase), follicular recruitment (anti-Mullerian hormone (AMH)), homocysteine metabolism (methylenetetrahydrofolate reductase (MTHFR)) and IR (calpain 10 (CALP10)) were analyzed by qRT-PCR. All comparisons were made with age-matched control.
RESULTS: The treated rats developed moderate degree of HHcy and replicated morphologic as well as many metabolic spectra of PCOS. Homocysteine attenuated insulin-mediated cellular uptake of 2-deoxy-D-[1-3H] glucose in dose-dependent manner. The treated rats had higher expression of liver CALP10 and exhibited significant glucose intolerance, IR and dyslipidemia. Expressions of Wnt4, aromatase and MTHFR were down-regulated, while there was overt expression of StAR and increased serum levels of testosterone. Hence, HHcy at one end induces IR and glucose intolerance, while on the other hand attenuates Wnt4 signaling cascade that inducts stimulation of StAR and inhibition of aromatase to overpower ovarian androgen synthesis. HHcy and hyperandrogenemia, individually or collectively, down-regulates ovarian AMH with simultaneous down-regulation of MTHFR prohibiting the homocysteine transmethylation pathway.
CONCLUSION: Experimental HHcy in rats develops an array of biochemical and ovarian phenotypes that characterize major morphologic and metabolic tenets of PCOS, and may serve as a useful tool to explore the pathogenesis of the syndrome.