Knockout of the FSH Receptor in Adipocytes Does Not Impact Body Composition in a Mouse Model of Post-Menopause

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Post-menopausal women are at higher risk of developing obesity and associated comorbidities, such as diabetes and metabolic disorder, than premenopausal women. Hormonal changes, such as reduced estrogens, are likely to be contributing factors. Menopause is also characterized by increases in pituitary-derived follicle-stimulating hormone (FSH). Recent data suggested that FSH might directly stimulate adipogenesis and block thermogenesis (energy expenditure) in adipocytes. FSH reportedly decreased thermogenic gene expression (*Cox8b* and *Ucp1*) in murine 3T3-L1 cells differentiated into adipocytes. These effects were not observed in cells co-treated with an FSH-neutralizing antibody. The same antibody reduced fat mass and increased lean mass in ovariectomized female mice (OVX), a rodent model of post-menopause, on a standard chow diet or in intact male and female mice on a high-fat diet. In these studies, it was not established whether FSH acted directly through its canonical receptor (FSHR) in adipocytes to mediate its effects. To address this gap, we first differentiated 3T3-L1 cells to adipocytes and followed by treatment with FSH. In contrast to the earlier report, FSH did not alter the expression of markers of lipogenesis (*Cebpa* and *Pparg2*) or thermogenesis (*Ucp1* and *Cox8b*) nor did it impact mitochondrial respiration or lipid accumulation. We also did not detect *Fshr* mRNA in these cells. We next differentiated primary pre-adipocytes from inguinal adipose tissue of adult female mice into white adipocytes. FSH treatment did not alter expression of several markers of adipogenesis or thermogenesis, and did not affect lipid accumulation in these cells. To assess FSH actions in fat in vivo, we generated adipocyte-specific *Fshr* knockout mice ($Fshr^{fx/fx}$;*Adipoq*-Cre, hereafter cKO). Adult cKO and control female mice were OVX at 10 weeks and maintained on standard chow. Eight to 10 weeks later, we performed glucose tolerance and insulin tolerance tests, and determined body composition by EchoMRI. Cre-mediated recombination of the floxed *Fshr* locus in adipocytes was successful, but did not alter body weight, fat or lean mass, or glucose metabolism in OVX cKO relative to control mice. We next performed OVX on control and cKO females at 10 weeks of age, followed by pair-feeding on a high-fat diet for 8 weeks. Again, there were no genotype differences in glucose or insulin tolerance, body weight, lean mass or fat mass. Finally, using a newly developed FSHR-3xHA knockin mouse model, we detected FSHR protein expression in ovarian granulosa cells, but not in inguinal and perigonadal white adipose depots or in intrascapular brown adipose tissue of adult female mice. We similarly failed to detect *Fshr* mRNA in various fat depots. Collectively, our results fail to show FSH effects on adipogenesis in vitro and challenge the hypothesis that FSH acts through the canonical FSHR in adipocytes in vivo. FSH may therefore not represent a relevant therapeutic target for post-menopausal weight gain.