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Beta-3 adrenergic receptor activation induces adipose tissue browning in a sex and depot-dependent manner

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Female cardiometabolic health (e.g., glucose tolerance, body composition) is protected compared to males when fed high-fat-diet (HFD). Activation of the beta-3 adrenergic receptor (β3AR) via the chemical ligand CL316,243 (CL) induces browning in white adipose tissue (WAT), a process sufficient to improve glucose tolerance and reduce visceral adiposity. Our aim was to determine (a) if sex differences exist in CL-induced WAT browning; and (b) if two WAT depots, perigonadal (PGAT) and subcutaneous (SQAT), differ in CL responsiveness, in a sex-specific manner. To this end, 8-week-old male and female mice, bred on a C57BL/6J background were fed HFD for a total of 16 weeks, and given daily CL injections (1ug/g body weight) for the final 2 weeks. We compared those groups using 2x2 ANOVA to determine main and interaction effects (S=sex; T=treatment; SxT=interaction) for browning and adipocyte health markers in PGAT and SQAT (gene expression via qrtPCR; protein expression via Western blot). We report here that the effects of CL are both depot-dependent and sex-specific. As expected, females had greater uncoupling protein 1 (UCP1); however, this was only observed in PGAT (S, $p<0.001$), not SQAT. UCP1 was more responsive in female PGAT (SxT, $p=0.011$); however, sexes were equally responsive in SQAT. Interestingly, in male SQAT, PGC1a (i.e., mitochondrial biogenesis marker) responded significantly better to CL (SxT, $p=0.046$); whereas in PGAT, females were more responsive (SxT, $p=0.026$). We also show for the first time that CL increases glucose-related protein 75 (GRP75), a recently discovered browning marker, in both depots, in both sexes (T, $p<0.05$, both). Lastly, while female PGAT had greater adiponectin, males had higher adiponectin in SQAT (S, $p<0.05$, both). In conclusion, it appears SQAT is more responsive to CL in males, whereas PGAT is more responsive in females, which we hypothesize is partially explained by differences in local estrogen exposure.