antagonist exendin 9–39 (1nM, P=0.93, 10nM, P=0.64). However, in OB monocultures GLP-1 had no effects on ALP (1nM P=0.93, 10nM P=0.64) indicating a GLP-1-driven increase in osteoblast activity through osteoclast-osteoblast coupling. We then assessed the effect of GLP-1 on OC differentiation by assessing TRAcP activity. Although there was a trend towards increased TRAcP activity upon stimulation with GLP-1 on day 10 of osteoclastogenesis, this was not statistically significant (1nM P=0.12; n=8 donors; 10nM P=0.29, n=4 donors). Our studies indicated GLP-1 may have a direct effect on osteoclasts, and we therefore sought to characterise GLP-1-mediated signalling in these cells. We assessed the effect of GLP-1 on cAMP signalling using LANCE assays and assessed phosphorylation of ERK proteins by Western blot analysis in human OC cultures. OCs treated with 10nM GLP-1 for 30 minutes had increased cAMP signaling (P=0.004, n=12 bone slices from 2 donors) when compared to vehicle. Furthermore, 10nM GLP-1 induced rapid increases in phosphorylated ERK (P=0.03 following 2 minutes exposure, n=4 blots). In conclusion, our studies reveal that GLP-1 increases activity in primary mature human OCs, and OBs, via OCs. Our signaling studies in OCs indicate this is mediated by direct action of GLP-1 on human bone cells.

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Low-Dose Testosterone Augmentation for Treatment-Resistant Depression in Women: An 8-Week, Two-Site, Randomized, Placebo-Controlled Study

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SAT-737

Objective: Nonresponse to selective serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor treatment is common in patients with major depressive disorder (MDD), particularly in women, occurring in about 70% of patients despite adequate dosing. Well-tolerated augmentation strategies are needed, particularly ones that do not cause or exacerbate symptoms such as fatigue and sexual dysfunction. Low-dose testosterone has been shown to improve depression symptom severity, fatigue and sexual function in small studies of women not formally diagnosed with MDD. We sought to determine whether adjunctive low-dose transdermal testosterone improves depression symptom severity, fatigue, and sexual function in women with treatment-resistant MDD. A functional MRI (fMRI) substudy examined effects of testosterone on activity in the anterior cingulate cortex (ACC), a brain region important in mood regulation.

Methods: Randomized, double-blind, placebo-controlled, 8-week trial of adjunctive testosterone cream (AndroFeme® 1, Lawley Pharmaceuticals, Australia) in 101 women, ages 21–70, with treatment-resistant MDD. Testosterone was titrated to achieve blood levels near the upper normal reference limit. Primary outcome measure was depression severity by Montgomery-Asberg Depression Rating Scale (MADRS). Secondary endpoints included fatigue, sexual function, and safety measures. fMRI substudy (n=20) primary outcome was change in ACC activity.

Results: Mean age was 47±14 (SD) years and mean baseline MADRS score was 26.6±5.9. Eighty-seven (86%) participants completed 8 weeks of treatment. MADRS depression scores decreased in both arms [testosterone: 26.8±6.3 to 15.3±9.6; placebo: 26.3±5.4 to 14.4±9.3 (baseline to 8 weeks, respectively)], with no difference between groups (p=0.91). Fatigue and sexual function improved without differences between groups. There were no group differences in side effects. fMRI results demonstrated a relationship between ACC activation and androgen levels pretreatment but no difference in ACC activation with treatment.

Conclusions: This rigorously designed, double-blinded clinical trial did not find significant group differences between adjunctive low dose transdermal testosterone and placebo for antidepressant augmentation in women with treatment-resistant MDD and had a high placebo response rate. Low-dose testosterone was well tolerated but failed to differentially impact overall depressive symptom severity, fatigue, or sexual dysfunction. Testosterone did not result in greater activity in a brain region (ACC) implicated in MDD etiopathology compared to placebo. Thus, the addition of low-dose testosterone to ineffective antidepressant treatment should not be recommended for women with MDD. Further studies using strategies designed to reduce placebo effects may be warranted.

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Effects of Open-Label, Adjunctive Ganaxalone Treatment on Resistant Depression in Postmenopausal Women: A Pilot Study

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