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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SUN-303

Resistance to selective serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor treatment occurs in about 50% to 70% of patients with major depressive disorder (MDD), a condition associated with significant morbidity that affects women at higher rates than men. Few well-tolerated, effective augmentation therapies are available for such patients, and new therapeutic strategies for resistant depression are needed. The neuroactive steroid metabolite of progesterone, allopregnanolone, is a positive allosteric modulator of $GABA_A$ receptors and a putative treatment for mood disorders. We performed a pilot study to determine whether an oral allopregnanolone analog (ganaxolone) may be effective adjunctive therapy for resistant depression in postmenopausal women. Ten postmenopausal women (age 62.8±6.3 years, range 53–69) with resistant depression [current DSM-IV major depressive episode per the Structured Clinical Interview for DSM-IV, Montgomery-Asberg Depression Rating Scale (MADRS) ≥16 despite treatment with an adequately dosed antidepressant for ≥6 weeks] were studied. Open-label ganaxolone (225 mg BID, increased to 450 mg BID if tolerated) was administered for 8 weeks, followed by a 2-week taper. Mean total MADRS depression score (primary endpoint) decreased by 8 weeks [24.4±1.6 (SEM) to 12.8±2.9, p=0.015] and persisted over the two-week taper (p=0.019); 44% of subjects experienced response (score decrease ≥50%) and remission (final score <10), which persisted in 100% and 50% of subjects at 10 weeks, respectively. Secondary endpoints showed significant improvement, including the Inventory of Depressive Symptomatology-Self-Report (IDS-SR; p=0.003), MADRS Reduced Sleep subscale (p<0.001), Symptoms of Depression Questionnaire (SDQ) total score (p=0.012), and SDQ subscales for disruptions in sleep quality (p=0.003) and changes in appetite and weight (p=0.009) over 8 weeks. No significant effects were observed on quality of life or sexual function. All subjects experienced sleepiness and fatigue; 60% experienced dizziness. In conclusion, adjunctive ganaxolone in this open label pilot study appeared to exert antidepressant effects in postmenopausal women with resistant depression but produces sedation with twice-daily dosing. The observed positive effects on sleep and the potential for sustained treatment effects merit further study, as ganaxolone may be particularly beneficial to patients with depression and insomnia. Randomized, placebo-controlled studies are necessary to rule out placebo effects. Given the sedation experienced by most participants, nighttime dosing only should be considered for future studies. Finally, should rigorous studies confirm an antidepressant effect, it will be important to identify subsets of women who respond (e.g. women with neuroactive steroid dysregulation) and mechanisms of action.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS I

Two Cases of Hypoparathyroidism Due to Activating Calcium Sensing Receptor Mutation

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SAT-077

Introduction

The extracellular calcium-sensing receptor (CaSR) expressed mainly in the parathyroid gland and kidneys regulates calcium (Ca^{+2}) homeostasis through parathyroid hormone (PTH) secretion. Activating mutations of *CaSR* can lead to autosomal dominant hypocalcemia and severe congenital hypoparathyroidism. Constitutively activated CaSR receptors blocks PTH release leading to hypocalcemia, hyperphosphatemia and decreased Ca^{+2} reabsorption from the kidney.

Case 1:

14 year old male presented for an evaluation of hypocalcemia and hyperphosphatemia found on routine blood work. He denied symptoms of hypocalcemia. He had normal vital signs, positive Chovstek sign but rest of exam was unremarkable. His lab results showed low Ca^{+2} 8.1 mg/dl (8.6–10 mg/dl), high phosphorus 6 mg/dl (2.7–4.5 mg/dl) and inappropriately normal PTH 26.8 pg/ml (10–65 pg/ml). FISH was negative for DiGeorge. Genetic testing showed heterozygous *CaSR* gene mutation I822T, variant of uncertain significance. His father with primary hypoparathyroidism has the same *CaSR* gene mutation; mother is healthy and tested negative for this variant. Given the inheritance pattern of the mutation, it is likely a pathologic mutation. He is maintained on Calcium (1500 mg BID) and Calcitriol (0.5 mcg PO BID) and is doing well.

Case 2:

One day old premature 32-week old infant girl was found to have early onset neonatal hypocalcemia 6.1 mg/dl (6.2–11 mg/dl) during NICU admission for respiratory distress, inappropriately normal PTH 18.5 pg/ml and high phosphorus 8.8 mg/dl (4.6–7.9 mg/dl). She had no symptoms of hypocalcemia in the NICU or at home. She did not have any dysmorphic features. FISH was negative for DiGeorge. Genetic testing to sequence genes including *AIRE, AP2S1, CASR, GNAS, HADHA, HADHB, PTH1R, SOX3, STX16, TBCE* was done and revealed a novel heterozygous mutation in the *CaSR* gene for a missense variant c.2495T>C (p.lle832Thr) and *STX16* c.644A>T, possibly benign variant. Unfortunately, the parents have not consented to testing yet. Further familial and functional characterization of this new variant is necessary to confirm its possible pathogenetic role in this hypocalcemic patient. Currently she is maintained on ergocalciferol 800 IU, calcitriol 0.25 mcg and sevelamer 3 packets daily and is doing well.

Conclusion:

In the workup for primary hypoparathyroidism without dysmorphic features and tests negative for DiGeorge, *CaSR* mutations should be investigated as part of the differential as we have identified variants in the *CaSR* gene in 2 children with asymptomatic hypocalcemia, one of which is a novel mutation which has never been reported before.

Neuroendocrinology and Pituitary

CASE REPORTS IN CLASSICAL AND UNUSUAL CAUSES OF HYPOPITUITARISM

Association Between Hypogonadotrophic Hypogonadism and NARP Due to Mitochondrial Disease

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