Testosterone undecanoate is a novel oral testosterone therapy under development for the treatment of male hypogonadism. We studied the effects of testosterone undecanoate (225 mg twice daily) on ambulatory blood pressure (ABP) and heart rate, in 138 men with hypogonadism (mean age, 54 years, 79% white, 48% with a history of hypertension). Ambulatory BP and heart rate and hematologic parameters were obtained at baseline and following 4 months of daily therapy. Changes from baseline in ambulatory 24-hour, awake, and sleep systolic BP of 3.8 (p=0.06), 5.2 (p=0.01), and 4.3 mmHg (p=0.07) were observed post-treatment, respectively. Smaller changes in the diastolic BP were observed (1.2 (p=0.13), 1.7 (p=0.04), and 1.7 mmHg (p=0.11) for 24-hour, awake, and sleep, respectively). Changes in the 24-hour, awake and sleep heart rates were 1.9 (p=0.07), 2.6 (p=0.02), and 0.4 (p=0.68) beats/minute respectively. There were no significant differences in changes from baseline in the 24-hour ambulatory BP for the 57 subjects who had a medical history of hypertension versus the 61 subjects who did not have hypertension: 4.5/1.5 mmHg in the hypertension subgroup versus 3.2/0.9 mmHg in the non-hypertensive subgroup (p = 0.53/0.46 between groups). Hematocrit and hemoglobin increased by 3.2% and 0.9 g/dl in all subjects after 4 months of therapy. In those men in the top quartile of changes in hematocrit (corresponding to upper / lower boundary increases of 6 and 14% with 9.3% achieving levels > 52%), the largest increases in ambulatory systolic BP (8.3 mmHg) were observed, whereas the changes in ambulatory systolic BP in the lower 3 quartiles were substantially smaller (1.6, 3.2, and 2.7 mmHg in quartiles 1, 2 and 3 of hematocrit change, respectively). In conclusion, these data demonstrate increases in ambulatory BP occurred following 4 months of oral testosterone undecanoate, particularly in those men whose hematocrit rose by > 6% or whose resultant hematocrit was 52% or higher. Hence, hematocrit maybe a useful clinical parameter that could effectively predict the risk of developing increases in BP on oral testosterone undecanoate.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Regulation of Low-Density Lipoprotein Receptor Expression in Triple Negative Breast Cancer

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Preclinical models and clinical studies suggest that hypercholesterolemia promotes breast cancer progression [1,2]. The expression of the low-density lipoprotein receptor (LDLR) has been positively associated with poorer recurrence-free survival in human breast cancer studies [3]. Mechanistically, LDLR has been demonstrated to play a role in the increased tumor growth associated with hypercholesterolemia, as knock-down of LDLR led to decreased tumor growth in setting of elevated circulating LDL cholesterol. The aim of this study was to identify factors which up-regulate expression of LDLR in triple negative breast cancer (TNBC). In glioblastoma, hyper-activation of the epidermal growth factor receptor (EGFR) signaling pathway has been associated with greater LDLR expression and susceptibility to targeting of cholesterol metabolism[4]. As EGFR is frequently expressed in TNBC[5], we examined if increased LDLR expression is associated with activation of the EGFR signaling pathway in TNBC. The expression of LDLR in the TNBC cell lines, MDA-MB-231 (231) and MDA-MB-468 (468) was examined pre- and post-EGF stimulation of the EGFR and in the presence of chemical inhibitors. Cells were grown in DMEM/10% FBS/1% Pen/strep (P/S), and experiments were performed under reduced serum conditions at 1.25%FBS/DMEM/1%P/S. In the absence of stimulation, LDLR protein expression was 3-fold higher in 231 vs 468 cell lines. This was despite mRNA expression being comparable at baseline, suggesting that the difference in protein expression was post-transcriptionally mediated. Treatment with 10 ng/mL EGF for 2 hours led to an increased activation of the EGFR, phosphorylation of Akt and extracellular signal regulated kinase (ERK) in both cell lines but induced an increase in LDLR protein and mRNA expression only in 468 cells. Treatment of 468 cells with EGF after exposure to actinomycin, a transcription inhibitor, revealed that EGF treatment resulted in reduced degradation of LDLR mRNA (p = 0.002) over 3 hours, suggesting that the EGF-induced increase in LDLR expression was by protection of LDLR mRNA from degradation. Chemical inhibition of the ERK pathway with 20 μM UO126 reduced both the EGF-induced increase in LDLR expression in 468 cells (p = 0.015) as well as the high baseline expression of LDLR by half in 231 cells (p = 0.001). Overall our results suggest that the EGFR/ERK signaling pathway regulates LDLR expression in TNBC, supporting the increased anabolic needs of this aggressive, swiftly expanding form of breast cancer.

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Reproductive Endocrinology

FEMALE REPRODUCTION: BASIC MECHANISMS

Maternal Behaviour in Mice Is Modified by a High Fat Diet in Pregnancy

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Background: About a third of pregnant women of age 20-39 are obese, which carries significant risks for the mother and fetus, and adversely impacts pregnancy outcome. Specifically, women with obesity are at increased risk for peripartum depression. Maternal behaviour in mice is influenced by changes in hormone signaling in pregnancy, which is associated with effects on adult neurogenesis in the brain. Thus, we used mouse as a model system to gain further insight into the possible relationship between overeating/obesity and brain physiology and maternal