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| **Female sex hormones modulate asthma severity by altering cellular metabolism** |
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| **Introduction/Aim:** Adult females are disproportionately affected by asthma. Many pre-menopausal females experience worsened asthma during the late-luteal and early-follicular phases of the menstrual cycle. Females using an oral contraceptive pill (OCP), which controls fluctuations in female sex hormones, have improved asthma, whilst females using estrogen-based menopausal hormone therapy have more severe disease. In this study we sought to investigate the relationship between female sex hormones, cellular metabolism and asthma severity, and determine whether hormone-mediated effects on metabolism can be harnessed therapeutically. **Methods:** We assessed the effects of estradiol, depot-medroxyprogesterone acetate (DMPA), oral ethinylestradiol/levonorgestrel (representing combined OCP), NLRP3 inflammasome and glucose targeting treatments on key features of disease and expression of metabolism-associated genes in experimental asthma. The effects of the OCP on asthma outcomes, and relationships between female sex hormone receptor and type 2 (T2) and non-T2 cytokine and metabolism-associated gene expression, were also assessed in subjects with asthma.**Results:** Estradiol treatment promotes severe disease associated with NLRP3 inflammasome and neutrophilic inflammatory responses, whilst DMPA and OCP interventions reduce T2 responses and disease, in experimental asthma. Importantly, 17β-estradiol increases, whilst DMPA and OCP decrease, lung expression of the glucose transporter GLUT1. Targeting GLUT1 (via BAY876), or NLRP3 responses (via MCC950) protects against features of estradiol-induced severe experimental asthma. Importantly, OCP use is associated with lower T2 cytokine and GLUT1 expression, and GLUT1 expression positively correlates with estradiol receptor expression and T2 as well as non-T2 responses, in the sputum of asthmatics. **Conclusions:** Female sex hormones affect the immunopathogenesis of asthma by modifying metabolism. These data highlight the potential for harnessing sex hormone-mediated effects on metabolism and NLRP3-mediated responses for the improved control of asthma, particularly in severe asthma.**Grant Support:** PRC Healthy Lungs, Edith Ethel Ward Perpetual PhD top up scholarship |