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Title: Compound A (CpdA) suppressed production of corticosteroid-resistant chemokines via GR-independent mechanisms in airway smooth muscle (ASM) cells

Ms. Adelina 18874 Gavrila ag354@le.ac.uk [1], Mrs. Latifa 18875 Chachi lc146@le.ac.uk [1], Dr. Omar 18876 Tliba Omar.Tliba@jefferson.edu [2], Prof. Christopher 18877 Brightling ceb17@le.ac.uk MD [1] and Dr. Yassine 19319 Amrani ya26@le.ac.uk [1]. [1] Institute for Lung Health, Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom and [2] Department of Pharmaceutical Sciences, Jefferson School of Pharmacy, Thomas Jefferson University, Philadelphia, United States .

Body: Recent evidence showed the therapeutic value of the natural dissociated steroid receptor ligand Compound A (CpdA) in a murine model of allergic asthma. In addition, the ability of CpdA to dissociate the transrepression function from the transactivation action has been implicated in the beneficial effects of CpdA in numerous in vitro studies. Here we used CpdA in a cellular model of cytokine-induced corticosteroid resistance to determine the anti-inflammatory mechanisms involved. ELISA assays showed that CpdA differentially inhibited production of steroid-resistant chemokines (CCL5, CX3CL1, CXCL10) induced by TNFα/IFNγ. To investigate whether CpdA acts via a GR-dependent pathway, we assessed the ability of CpdA to induce well-known GR-inducible genes and whether the steroid antagonist RU486 could prevent CpdA effects. RT-PCR assays showed that while CpdA did not induce the expression of Glucocorticoid-induced leucine zipper (GILZ) (2-4-6-24hr, n=3), MAPK phosphatase 1 (MKP-1) mRNA expression was significantly increased at 2hr but not at later time points (4-6-24hr, n=4). Furthermore, in contrast to Fluticasone which induced translocation of GRα to the nucleus assessed by Immunofluorescence, CpdA treatment for 2 and 6hr did not induce GRα nuclear translocation. RU486 (1µM) blocked the inhibitory action of Fluticasone on CCL5 production by TNFα (n=4) but in contrast it had no effect on the inhibitory action of CpdA on the induction of Fluticasone-resistant chemokine CCL5 induced by TNFα/IFNγ (n=4). These data suggest that CpdA suppressed the expression of different corticosteroid-resistant chemokines possibly via GR-independent pathways.