IMPACT OF SUPRA-PHYSIOLOGIC RETINOIDS ON OVALBUMIN-SENSITIZED F344 LUNG TISSUE AND REVERSAL OF RELATED PATHOLOGY BY CITRAL

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Abstract: The role of retinoids (All Trans Retinoic Acid; ATRA, and Retinyl Palmitate; RP) in the development of lung hypervitaminosis A pathology is not well understood or established in the literature. As well, the role of Citral (inhibitor of retinoid function) in the reversal of lung pathology is also not ascertained under an in vivo setting. Therefore, it is hypothesized that ovalbumin exposure will sensitize lung tissues to supra-physiologic levels of retinoids leading to tissue pathology and that Citral 1 and 2 will reverse or ameliorate the related pathological damage to lung tissues. Even though ovalbumin and retinoids have been previously applied through intra-tracheal route in cancer prevention and immunological research, the objective of this pilot study was to evaluate techniques, establish functional dosing and generate preliminary data before further experimentation. This IACUC approved in vivo study consist of twenty one (n = 21) Fischer 344 rats (200 to 400g) which were randomly assigned to controls and two ovalbumin-sensitized treatment groups (low; 0.15 mg/kg and high; 0.30 mg/kg, all sensitized by intra-peritoneal injection at day 1) and were also dosed at day 7 with 40 and 80 mg/kg each of ATRA or RP as well as 20 and 50 mg/kg each of Citrals 1 or 2 individually or in combination to represent low and high for all four chemicals, which were administered by intra-peritoneal injection. Citral is a non-toxic chemical that exists in two forms (diethyl; C1 or cis-trans dimethyl; C2). Positive and negative controls for each treatment were also included in the study. Animals were housed in rat cages at the JSU Research Animal Core Facilities and were placed on a 12:12 light–dark cycle. A standard rodent diet and water access were provided ad libidum. Rat weights were recorded on Day 1 and 21, all animals were sacrificed on day 21 and lung tissues were processed for histopathology. Slides were prepared and were digitized for comparison of tissues pathology. Results showed that even though C1 and C2 were not toxic individually, their combination at high dosing was lethal. As well, the combination of high dosing of RP and C1 was also lethal. Exposure of ovalbumin-sensitized rats to ATRA showed various levels of lung tissue damage that was not ameliorated by Citrals. RP exposure caused various levels of tissue damage that was not reversed by either C1 or C2. Taken together, the study showed that there are variable pathologic responses from the interaction of ovalbumin, Citrals and retinoids and those Citrals failed in reversing tissue pathologies. These findings warrants further investigation as to the actual role of these interactions in relation to chronic lung disease and the possibility of reversing retinoid-mediated pathologies in the Fisher rat model.

Key words: ATRA, RP, Citral, F344, Ovalbumin, Chronic Lung Pathology, Hpervitaminosis A

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