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Exposure to Benzo[a]pyrene Augments Ultraviolet B radiation-induced Systemic Immunosuppression in a Platelet-activating factor-receptor dependent manner

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Exposure to multiple and often simultaneous environmental stressors such as ultraviolet radiation (UVR) and polycyclic aromatic hydrocarbons (PAH) exerts immunomodulatory, as well as pro-carcinogenic effects. However, a significant knowledge gap exits in the interactions between UVB and a potent PAH compound, benzo[a]pyrene (BaP), as well as their cumulative effects and mechanisms. As UVB-induced systemic immunosuppression is dependent upon the receptor for the lipid mediator, Platelet-activating factor (PAF), and large extracellular vesicles known as microvesicle particles (MVP), the present studies were designed to assess if PAF-receptor (PAFR) and MVP could be involved in augmenting UVB effects by BaP. Our first studies demonstrate that BaP absorption was higher in UVB (~3.5 a.u.) compared to UVA (~1.2 a.u.) range. Since UVA does not induce PAF and MVP generation, we hypothesized that BaP +UVB could generate increased UVB-MVP and PAF agonists. Using PAFR-expressing and deficient cellular models, we demonstrate that BaP+UVB augments MVP and PAF agonists generation only in PAFR-expressing, but not in PAFR-deficient cells. As PAH compounds, in great part, act as aryl hydrocarbon receptor (AHR) agonists, we found that tetrachlorodibenzo dioxin (TCDD), a potent AHR agonist, alone or TCDD+UVB, neither generate MVP nor PAF agonists, indicating the involvement of PAFR in mediating BaP+UVB effects. Next studies demonstrate that Bap+UVB induce systemic immunosuppression only in PAFR-expressing wild type (WT) mice, which was dependent upon the dose of UVB fluences, but not in PAFR-deficient mice, validating the critical role of PAFR in this effect. Notably, this BaP+UVB-induced systemic immunosuppression in WT mice was blocked by imipramine, an inhibitor of an acid sphingomyelinase (aSMase) enzyme involved in MVP release. Importantly, increased plasma MVP release was noticed in WT mice treated with BaP+UVB compared to BaP and UVB alone treatments, which was blocked by imipramine. While studies to determine the involvement of immunosuppressive regulatory T cells (Tregs) and cytokines, as well as validating the role of aSMase enzyme in BaP+UVB-induced systemic immunosuppression are ongoing, these findings provide a novel mechanism by which a PAH pollutant can augment UVB-induced effects. Overall, these findings address an important question and underlying mechanisms in the pharmacology of photobiology as to how skin exposure to environmental stressors can generate systemic effects.

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