Ceramide ratios are affected by cigarette smoke but not heat-not-burn or e-vapor products aerosols across four independent mouse studies

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Abstract

Ceramides are among the emerging lipid markers for diverse conditions, including cardiovascular disease (CVD), obstructive pulmonary disease (COPD), and aging. Smoking is an important risk factor for the development of COPD and CVD. This study aimed to further elucidate the role of ceramides as a key lipid class dysregulated in disease states. We developed and validated an LC–MS/MS method for absolute quantification of ceramides (Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/24:0), and Cer(d18:1/24:1(15Z)). We deployed it together with proteomics and transcriptomic analyses to assess the effects of cigarette smoke (CS) from a reference cigarette as well as aerosols from heat-not-burn (HnB) tobacco and e-vapor products in apolipoprotein E-deficient (Apoe-/-) mice. In the lungs, CS exposure substantially elevated the ratios of Cer(d18:1/24:0) and Cer(d18:1/24:1) to Cer(d18:1/18:0) in two independent Apoe-/- mouse inhalation studies. Data from previous studies, in both Apoe-/- and wild-type mice, further confirmed the reproducibility of this finding. Elevation of these ceramide ratios was also observed in plasma/serum, the liver, and—for the Cer(d18:1/24:1(15Z)) to Cer(d18:1/18:0) ratio—the abdominal aorta. Moreover, the levels of acid ceramidase (Asah1) and glucocerebrosidase (Gba)—lysosomal enzymes involved in the hydrolysis of glucosylceramides—were consistently elevated in the lungs after CS exposure. In contrast, exposure to HnB tobacco product and e-vapor products aerosols did not induce significant changes in the ceramide profiles or associated enzymes. Our work in mice contributes to the accumulating evidence on the importance of ceramide ratios as biologically relevant markers for respiratory disorders, adding to their already demonstrated role in cardiovascular disease risk assessment in humans.