Inhibition of the BCRP Transporter by Perfluorooctanesulfonic Acid: Potential Mechanism for Hyperuricemia

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Humans are extensively exposed to per- and polyfluoroalkyl substances (PFAS) or 'forever chemicals' through consumption of contaminated food and water, inhalation of dust/soil, and other direct contact. Epidemiological studies have showed that exposure to a notable PFAS, perfluorooctanesulfonic acid (PFOS) is associated with elevated serum urate levels, which can increase risk of cardiovascular disease. The breast cancer resistant protein (BCRP, ABCG2) regulates the efflux of several drugs, toxins, and endogenous molecules such as uric acid. We sought to determine whether PFOS acts as an in vitro BCRP inhibitor which may be a novel mechanism by which PFAS dysregulate excretion of uric acid. To test our hypothesis, HEK293 cell lines with stable expression of an empty vector (EV), wildtype (WT), and BCRP Q141K variant were cultured. The Q141K variant causes reduced BCRP function and is a susceptibility factor for developing hyperuricemia. MDCK cell lines with stable expression of an empty vector (EV), human BCRP (hBCRP), and mouse BCRP (mBCRP) were also cultured. Transport assays using probe fluorescent substrate of BCRP, Hoescht 33342, in the presence and absence of PFOS (5-10 ?M) was performed to quantify BCRP function. As expected, HEK293-Q141K cells had markedly reduced BCRP function compared to WT cells. PFOS (10 μM) increased BCRP substrate accumulation by 18-fold in WT cells and 26-fold in Q141K cells. Similar inhibition of mouse BCRP transporter function was observed. Here we show a novel mechanism by which PFAS act as an in vitro BCRP inhibitor, which could lead to hyperuricemia in exposed populations. Supported by MARC, R01ES029275, P30ES005022, SOT Intern Program, and ASPET SURF Program.