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Research Paper

Elucidation of specific binding sites and extraction of toxic Gen X from HSA employing cyclodextrin

N.L. Dilani Perera, Jaroslava Miksovska, Kevin E. O'Shea *

Department of Chemistry and Biochemistry, Florida International University, 11200 SW 8th street, Miami, FL 33199, United States

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ABSTRACT

The presence of per and poly-fluoroalkyl substances (PFAS), commonly referred to as *forever chemicals*, in aquatic systems is a serious global health problem. While the remediation of PFAS from aqueous media has been extensively investigated, their interactions with and removal from biological systems have received far less attention. We report herein structural alterations to human serum albumin (HSA) upon addition of perfluoro(2-methyl-3-oxahexanoic) acid (Gen X) monitored by changes to the fluorescence and circular dichroism (CD) spectra of HSA. The equilibrium association constant for Gen X binding to HSA is $7(\pm 1) \times 10^3$ M^{-1} determined from changes in HSA fluorescence emission data during titration. Site-specific HSA binding fluorophores, 8-anilinonaphthalene-1-sulfonic acid (1,8-ANS), warfarin and dansyl-L-proline were used to investigate the specific binding sites of Gen X on HSA. A competitive displacement study yields association constants for Gen X to HSA at the 1,8-ANS, warfarin, and dansyl-L-proline binding sites to be $6.25(\pm 0.5) \times 10^4$ M^{-1}, 1.1×10^6 M^{-1}, and $2.5(\pm 0.2) \times 10^9$ M^{-1} respectively. Addition of β-cyclodextrin (β-CD) and heptakis(6-deoxy-6-amino)-β-cyclodextrin heptahydrochloride to the HSA:Gen X complex leads to the effective extraction of Gen X from the complex with the return of HSA in its native form. Gen X also leads to displacement of site-specific binding fluorophores bound to HSA, while subsequent addition of β-CD extracts Gen X from HSA with the return of the characteristic fluorescence of the HSA bound site-specific agent. These results illustrate the strong and specific binding sites of Gen X on HSA and demonstrate the principles for the potential application of β-CD for the remediation of PFAS from biological systems.

1. Introduction

Perfluoroalkyl substances (PFAS) are used extensively for a wide variety of industrial and domestic applications (Boronow et al., 2019). PFAS contamination of aqueous media is a global problem with serious negative human health consequences (Szilagyi et al., 2020). Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), legacy PFAS, have been extensively used in food packaging, paints, non-stick coatings, and firefighting foams (Weiss-Errico et al., 2018). PFAS are highly persistent due to their incredible stability and can accumulate in different biological and environmental compartments due to their unique chemical properties (Szilagyi et al., 2020; Weiss-Errico et al., 2018; Xin et al., 2019). PFAS are linked to cancers, infertility, kidney, liver, and bladder diseases in humans (Jensen and Leffers, 2008). Studies estimate nearly all the people of the United States have PFOA in their bloodstreams with an average concentration of ≥2 ppb (Weiss-Errico et al., 2018). The bloodstream concentrations of PFAS are significantly higher in people employed in industries that employ PFAS (Zhang et al., 2019).

The production of several legacy PFAS including PFOA was discontinued or eliminated in the USA by 2014 due to their incredible persistence and human health risks (Berg et al., 2014). In response to the phase-out of legacy PFAS, industries moved to the production and applications of alternative PFAS (no PFOA or PFOS) often referred to as emerging PFAS. Among the most problematic emerging PFAS, is the class of per-fluorinated ether carboxylic acids (PFECA) similar to legacy PFAS except with ether functionality inserted into the carbon backbone. Most notorious among the emerging PFAS is Gen X (perfluoro(2-methyl-3-oxahexanoic) acid) (Zareitalabad et al., 2013). While replacement of PFOA and PFOS with PFECA was intended to reduce health risk

Abbreviations: PFAS, perfluoroalkyl substances; Gen X, perfluoro(2-methyl-3-oxahexanoic) acid; HSA, human serum albumin; Trp, Tryptophan; CD, circular