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Nerve Agent Processing by Human Carboxylesterase I. Christopher D. Fleming¹, Carol C. Edwards³, Douglas M. Cerasoli², Philip M. Potter³, Matthew R. Redinbo¹, ¹Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, ²U.S. Army Medical Research Inst., Bethesda, MD, ³St. Jude Research Hospital, Memphis, TN, USA.

Organophosphate nerve agents (OPs) are a class of neurotoxins that are deadly to a milligram level of exposure. OPs covalently modify the acetylcholinesterase (AcChE) enzyme, causing rapid muscle paralysis. Given the limited treatment options that currently exist, the development of an effective OP hydrolase may provide a prophylactic option for military and civilian first responders. Human carboxylesterase I (hCE1), a promiscuous drug metabolism enzyme, is a candidate for development into an efficient nerve agent hydrolase. Here we present the crystal structures of hCE1 in covalent, proto-aged acyl-enzyme intermediate complexes with the nerve agents Tabun, Soman, and Cyclosarin to 2.7 Å, 2.7 Å, and 2.3 Å resolution, respectively. These results reveal that hCE1 is resistant to permanent covalent “aging” observed with other serine hydrolases, including AcChE. These structures provide a framework to identify mutations that may increase the nerve agent hydrolase activity of hCE1.