Reexamination of Lead(II) Coordination Preferences in Sulfur-Rich Sites: Implications for a Critical Mechanism of Lead Poisoning

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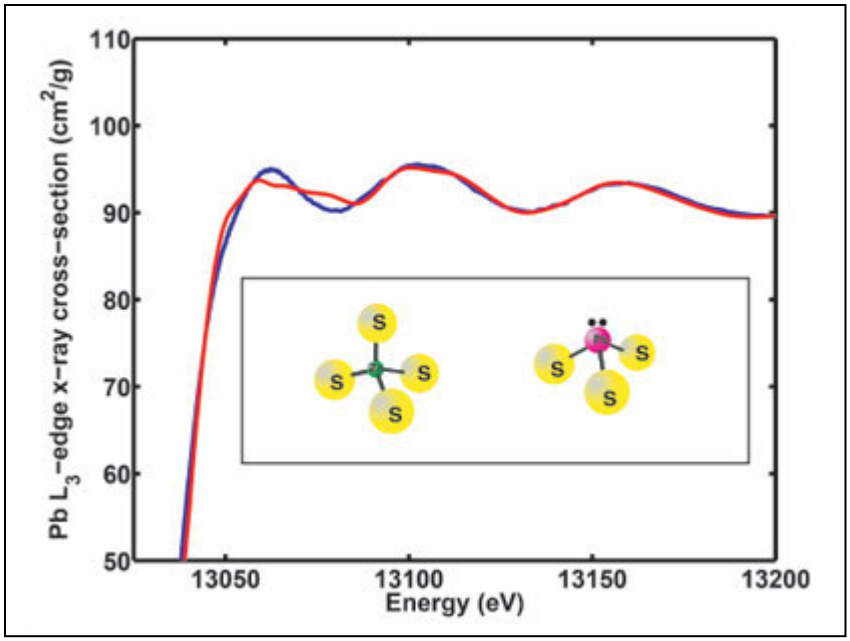

Lead poisoning can damage the brain and nervous system and is particularly dangerous for young children who are still developing. It is estimated that ~2.2% of all U.S. children aged 1-5 years (434,000 children) have elevated blood lead levels (BLLs) (i.e., ≥10 µg/dL), and in certain communities this number is as great as 15%. The developmental toxicity associated with childhood lead poisoning has been attributed to interactions of Pb(II) with proteins containing thiol-rich structural zinc-binding sites. Recently, Penner-Hahn, Godwin and co-workers have used x-ray absorption spectroscopy to define the local structure of the Pb(II) ion in such sites, providing critical insights into how lead alters the structure of these proteins [J. S. Magyar *et al.*, *J. Am. Chem. Soc.* **127**, 9495-9505].

The results of this study show that when Pb(II) is bound to structural zinc-binding peptides it binds in a three-coordinate Pb(II)-S_3 mode, in contrast with Zn(II), which is known to bind in a four-coordinate mode in these proteins. This Pb(II)-S_3 coordination in peptides is consistent with a trigonal pyramidal Pb(II)-S_3 model compound previously reported by Bridgewater and Parkin, but it differs from many other reports in the small molecule literature which have suggested Pb(II)-S_4 as a preferred coordination mode for lead. Reexamination of the published structures of these "Pb(II)-S_4" compounds reveals that, in almost all cases, the complexes are actually oligomers with effective Pb coordination numbers of 5, 6, or 8. The results reported herein combined with this new review of published structures suggest that lead prefers to avoid four coordination in sulfur-rich sites, binding instead as trigonal pyramidal Pb(II)-S_3 or as Pb(II)-S_{5-8}.

These data demonstrate that the Pb(II) coordination sphere is significantly different from that of Zn(II) bound to the same peptides. Zinc binding to CP-CCCC is tetrahedral, with Zn-S_4 coordination; Zn(II) binding in CP-CCCH, CP-CCHC, and HIV-CCHC is also tetrahedral but with Zn-S_3N coordination. By contrast, Pb(II) in both CP-CCCC and CP-CCCH is three-coordinate, Pb-S_3. Because tetrahedral zinc coordination is essential for proper folding of these peptides, these results provide a simple explanation for the observation that Pb(II) does not induce proper folding of the peptides, even when it binds *more tightly* than zinc. Structural zinc-binding domains are commonly found in transcription factors and proteins

involved in gene expression. In these proteins, the zinc-binding domain is the part of the protein that directly binds to DNA; improper folding of these domains will reduce or prevent protein-DNA binding. The studies reported here provide the first detailed, molecular insights into how lead binding to these proteins could directly account for some of the severe developmental problems known to result from lead poisoning.

Primary Citation

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