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Competition between divalent metal ions for HDAC8 enzyme active site: insights from theoretical studies

HDAC8 is a histone deacetylase enzyme that plays a key role in the development of various diseases in humans, including cancers, neurodegenerative diseases, and alcohol use disorder1. Although HDAC8 is classified as a Zn-dependent metalloenzyme, the available information regarding the affinity of different divalent metal ions, such as Fe^{2+}, Ni^{2+}, Co^{2+}, and Mg^{2+}, toward the HDAC8 active site remains inconsistent and unclear, and the mechanism by which these ions compete for the HDAC8 enzyme's active site is still not well understood 2, 3. This raises the question of whether other divalent metal ions, such as Fe^{2+}, Ni^{2+}, Co^{2+}, and Mg^{2+}, can compete for the HDAC8 enzyme-active site 4. In this study, we aim to address the following questions: (1) Can other divalent metal cations (Fe^{2+}, Ni^{2+}, Co^{2+}, Mg^{2+}) found in the intracellular space compete with Zn^{2+} for the metal binding site in the HDAC8 enzyme? , (2) What is the order of increasing affinity of these metal ions (Fe^{2+}, Ni^{2+}, Co^{2+}, Mg^{2+}) towards HDAC8 in different dielectric media? Additionally, these questions become even more intriguing when the HDAC8 enzyme active site is bound with a histone deacetylase inhibitor (HDACi), forming an enzyme-inhibitor complex (HDACi-HDAC8), thus interfering with the HDAC8 enzyme function. To address these questions, we performed density functional theory calculations (DFT) combined with polarizable continuum model computations (PCM). The results obtained helped us understand how the metals interact with the HDAC8 enzyme's active site and compete with the native metal, both when an inhibitor is bound and when it isn't, in both low-polar and polar solvents. The results will help designing more selective and isoform-specific HDACi with improved binding properties.

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