Influence of Protonation on Substrate and Inhibitor Interactions at the Active Site of Human Monoamine Oxidase-A

Zapata-Torres, G., Fierro, A., Miranda-Rojas, S., Guajardo, C., Saez-Briones, P., Salgado, J. C., & Celis-Barros, C. (2012). Influence of protonation on substrate and inhibitor interactions at the active site of human monoamine oxidase-a. Journal of chemical information and modeling, 52(5), 1213-1221. <10.1021/ci300081w> Accessed 20 Jul 2021.

Abstract

Although substrate conversion mediated by human monoaminooxidase (hMAO) has been associated with the deprotonated state of their amine moiety, data regarding the influence of protonation on substrate binding at the active site are scarce. Thus, in order to assess protonation influence, steered molecular dynamics (SMD) runs were carried out. These simulations revealed that the protonated form of the substrate serotonin (5-HT) exhibited stronger interactions at the protein surface compared to the neutral form. The latter displayed stronger interactions in the active site cavity. These observations support the possible role of the deprotonated form in substrate conversion. Multigrid docking studies carried out to rationalize the role of 5-HT protonation in other sites besides the active site indicated two energetically favored docking sites for the protonated form of 5-HT on the enzyme surface. These sites seem to be interconnected with the substrate/inhibitor cavity, as revealed by the tunnels observed by means of CAVER program. pKa calculations in the surface loci pointed to Glu327, Asp328, His488, and Asp132 as candidates for a possible in situ deprotonation step. Docking analysis of a group of inhibitors (structurally related to substrates) showed further interactions with the same two docking access sites. Interestingly, the protonated/deprotonated amine moiety of almost all compounds attained different docking poses in the active site, none of them oriented to the flavin moiety, thus producing a more variable and less productive orientations to act as substrates. Our results highlight the role of deprotonation in facilitating substrate conversion and also might reflect the necessity of inhibitor molecules to adopt specific orientations to achieve enzyme inhibition.

Keywords

Peptides and proteins, Reaction mechanisms, Monomers, Inhibitors, Cavities.