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Xanthates as Useful Probes for Testing the Active Sites of Cytochromes P450 4A11 and 2E1: Molecular Modeling Study

Iglika Lessigiarska[1], **Tsveta Stoyanova**[2], **Ilza Pajeva**[1], **Stanislav Yanev**[2]

[1]Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Block 105, 1113 Sofia, Bulgaria
[2]Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Block 23, 1113 Sofia, Bulgaria

Abstract. Saturated fatty acids (FA), such as lauric acid (LA), are metabolized by different cytochrome P450 isoforms to ω- and (ω-1)-hydroxy products, in human by CYP4A11 and CYP2E1, respectively. Xanthates (dithiocarbonic acid derivatives) with a long alkyl chain have structure similar to the fatty acids, which are hydroxylated with highest rate from CYP 4A and 2E1 forms. In previous experiments we have shown that LA-ω-hydroxylation by CYP 4A11 is inhibited in a competitive manner by the xanthates with long alkyl chain substitution (C12-xanthater being the most potent inhibitor). On the other hand LA-(ω-1)-hydroxylation reaction by purified CYP2E1 is inactivated by a mechanism-based type.

We hypothesize that 2E1 active site allowed C12-xanthate to coordinate to the heme with its most vulnerable dithiocarbonic head leading to a mechanism-based inactivation. Just in opposite, 4A11 coordinates this head with its polar recognition-binding group in the "entry" of the active site, exposing in this way the xanthate alkyl chain "queue" to the heme. The probable ω-hydroxylated xanthate product inhibits in a competitive manner the hydroxylation of LA.

The suggested differences in the interactions of C12-xanthate with the two cytochrome P450 isoforms were investigated by molecular modeling of its interactions with the enzyme. The structure of C12-xanthate was built, optimized and docked into the active sites of 2E1 and 4A11 isoforms using the Docking tool in MOE software (v. 2014.09). Protein structures were taken from the Protein Data Bank (Cytochrome P450 2E1) and Swiss Model repository (Cytochrome P450 4A11) and prepared for docking by the 3D protonate tool in MOE. The default settings were used in the docking protocol and the best 10 docking poses of C12-xanthate were kept and analyzed.

The results suggest that C12-xanthate may interact in a different way with the active sites of the both enzymes. In the active site of 4A11 mainly the alkyl chain of the xanthate molecule was directed towards the

heme. In 2E1, orientations of similar scores were generated both, with the xanthate alkyl chain and with the dithiocarbonic moiety directed towards the heme. Thus, the molecular modeling results support our hypothesis of interaction of C12-xanthate with the enzymes. Further studies on the interactions of xanthates are ongoing.