Supporting information

Impaired oxidoreduction by 11β-hydroxysteroid dehydrogenase 1 results in the accumulation of 7-oxolithocholic acid

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Superimposition of the 3D-protein structures

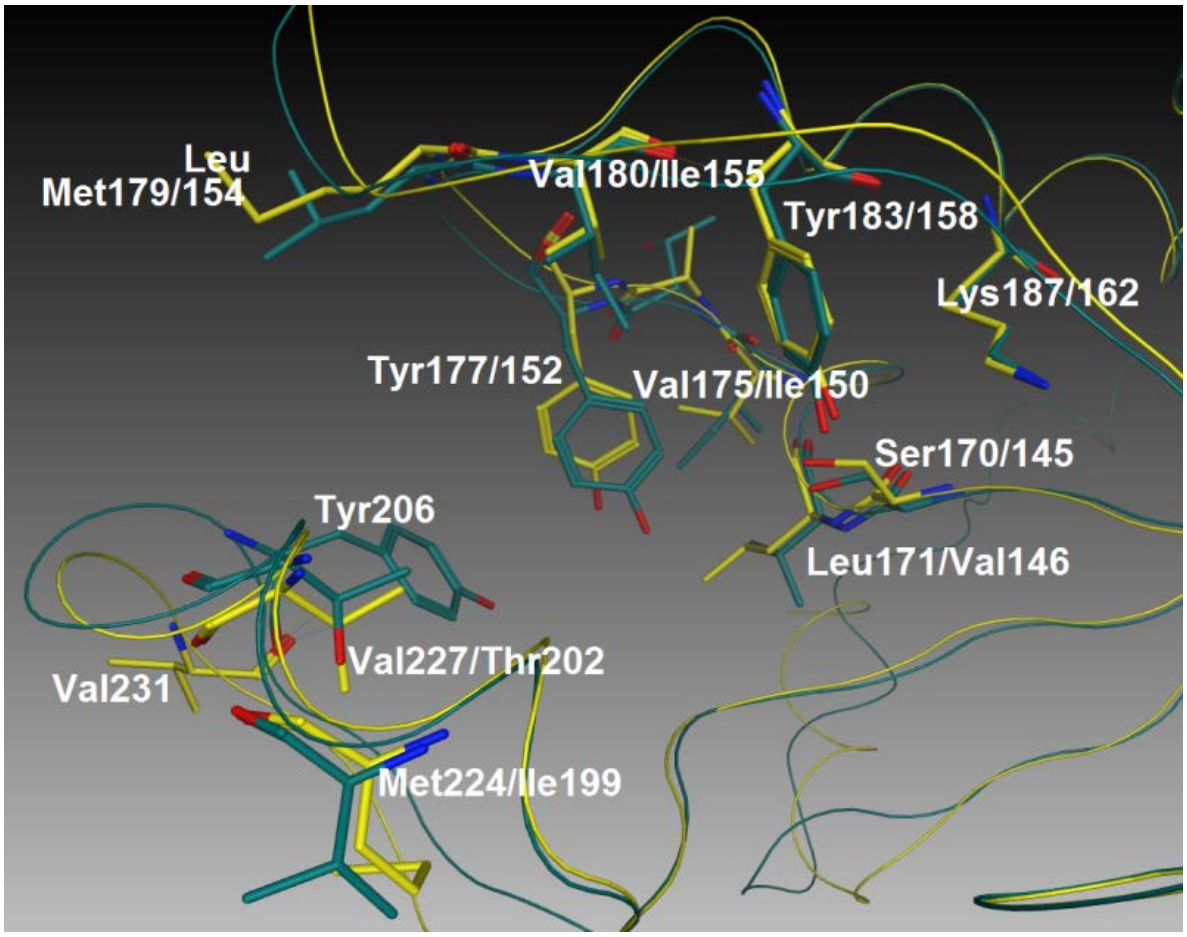
The x-ray crystal structures of the human and guinea-pig 11β-HSD1 were downloaded from the Protein Data Bank (PDB, www.pdb.org (Berman, Westbrook et al. 2000)). PDB-entry 2BEL, chain A (Wu, Kavanagh et al.) was chosen for human protein, and 3LZ6, chain A (Cheng, Hoffman et al. 2010) for guinea-pig protein. The 3D-superimposition was performed using the "protein superpose" tool of MOE 2011.10 (1997-2011 Chemical Computing Group Inc.) This tool superimposes the 3D-protein structures and aligns the primary sequences simultaneously. The default settings of the "protein superpose" tool were kept, with one exception: the program was set to accent secondary structure matches.

The proteins superimposed well, with an RMSD-value of 0.924 Å. In the binding site, most of the amino acids corresponded well to each other. However, some differences were noticed (Table S1 and Figure S1). Most of the differences cause steric limitations (such as Val175 in human corresponds to Ile150 in guinea-pig) or offer different interactions (such as Val227 in human and Thr202 in guinea-pig). These visual inspections alone do not explain why 7-oxoLCA is not reduced by guinea-pig 11β-HSD1. However, the binding site of guinea-pig 11β-HSD1 may be tighter. Especially different folding of the loop where Val231 in human corresponds to Tyr206 in guinea pig causes steric limitations for bulky ligands.

Table S1: Selected amino acids from the 11β-HSD1 binding sites.

Human	**Guinea pig**	**Notice**
Ser170	Ser145	Conserved, catalytic
Leu171	Val146	
Val175	Ile150	
Ala176	Thr151	
Tyr177	Tyr152	conserved
Met179	Leu154	
Val180	Ile155	
Tyr183	Tyr158	Conserved, catalytic
Lys187	Lys162	Conserved, catalytic
Met224	Ile199	
Val227	Thr202	
Val231	Tyr206	

Figure 1: The superimposed binding sites of human 11β-HSD1 (yellow) and guinea-pig 11β-HSD1 (green). The conserved amino acids as well as residues that differ are shown and labelled.



References

Berman, H. M., J. Westbrook, et al. (2000). "The Protein Data Bank." Nucl. Acids. Res. **28**(1): 235-242.

Cheng, H., J. Hoffman, et al. (2010). "The development and SAR of pyrrolidine carboxamide 11β-HSD1 inhibitors." Bioorganic & medicinal chemistry letters **20**(9): 2897-2902.

Wu, X., K. Kavanagh, et al. "The High Resolution Structures of Human, Murine and Guinea Pig 11-Beta-Hydroxysteroid Dehydrogenase Type 1 Reveal Critical Differences in Active Site Architecture."