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Chiral inversion of NSAID-CoA esters by human α -methylacyl-CoA racemase 1A

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Ibuprofen and other 2-arylpropanoic acids (2-APAs) are non-steroidal anti-inflammatory drugs (NSAIDs) and the 2S- enantiomers act by inhibition of cyclo-oxygenase 1 and 2 (COX-1 and -2). 2-APA drugs are given as racemic mixtures and chiral inversion is essential for pharmacological activity. This pathway for 2R-ibuprofen consists of conversion to the 2R-acyl-CoA ester, chiral inversion to the 2S-epimer, and hydrolysis to 2S-ibuprofen. The chiral inversion reaction is catalysed by α -methylacyl-CoA racemase (AMACR; P504S). AMACR is increased ~10-fold in prostate and other cancers, and is a novel cancer drug target. Other 2-APAs undergo chiral inversion *in vivo*, but it is unclear if AMACR is involved.

The present study investigates whether AMACR catalyses chiral inversion of other 2-APA-CoA esters. Substrates were incubated with human AMACR 1A in $^2\text{H}_2\text{O}$ -containing buffer and all exchanged the 2-proton, an obligatory step for chiral inversion. Derivatization of products from chiral substrates showed a *ca.* 1:1 epimeric mixture of products, consistent with the proposed deprotonation/reprotonation mechanism. Steady state kinetic analysis showed that most substrates were converted with similar efficiency ($k_{\text{cat}}/K_m = 100\text{-}150 \text{ M}^{-1} \text{ s}^{-1}$). Fenoprofenoyl-CoA was converted much more efficiently ($k_{\text{cat}}/K_m = \sim 1426 \text{ M}^{-1} \text{ s}^{-1}$), due to its low K_m value ($\sim 2.3 \mu\text{M}$ *cf.* 26-74 μM).

The results suggest that all 2-APA drugs undergo the same chiral inversion pathway. 2-APAs may be useful for treatment of cancers with increased AMACR levels.

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