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Hydrolysis of ibuprofenoyl-CoA and other 2-APA-CoA esters by human Acyl-CoA thioesterases (ACOTS) 1 and 2

X. Qu, A. Leung, A. C. Allan, G. Chui, T. J. Hutchings, P. Jiao, L. Johnson, W. Y. Leung, P. K. Li, G. R. Steel, A. S. Thompson, M. D. Threadgill, T. J. Woodman, and M. D. Lloyd

Medicinal Chemistry, Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom; M.D.Lloyd@bath.ac.uk

Ibuprofen and other 2-arylpropanoic acids (2-APAs) are non-steroidal anti-inflammatory drugs (NSAIDs) and the 2*S*- enantiomers inhibit 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. The pathway for 2*R*-ibuprofen consists of conversion to 2*R*-ibuprofenoyl-CoA, chiral inversion to the 2*S*-epimer, and hydrolysis to 2*S*-ibuprofen. The last step is catalysed by an acyl-CoA thioesterase (ACOT). It is unknown which of the human ACOTs are involved in 2-APA chiral inversion. Chiral inversion is peroxisomal and mitochondrial with COX located in the endoplasmic reticulum, implying export of 2*S*-APA-CoA esters to the cytosol is necessary. Mitochondria toxicity of 2-APAs has also been reported.

The present study investigates the potential roles of ACOT1 (cytosolic) and ACOT2 (mitochondrial) in 2-APA metabolism. Myristoyl-CoA, *S*- and *R*-2-methylmyristoyl-CoA and 2-APA-CoA substrates were assayed with recombinant human enzymes and the CoA product quantified. Most substrates were converted by ACOT1 with similar efficiency ($k_{\text{cat}}/K_m = \sim 150\text{-}220 \text{ M}^{-1} \text{ s}^{-1}$), except for ketoprofenoyl-CoA ($k_{\text{cat}}/K_m = 44 \text{ M}^{-1} \text{ s}^{-1}$). Conversion of substrates by ACOT2 was slightly more efficient ($k_{\text{cat}}/K_m = 250\text{-}330 \text{ M}^{-1} \text{ s}^{-1}$), except for ibuprofenoyl-CoA ($k_{\text{cat}}/K_m = 70 \text{ M}^{-1} \text{ s}^{-1}$). ACOT2 therefore prefers substrates with multiple aromatic rings.

The study shows that all tested 2-APA-CoA esters were substrates for human ACOT1 and ACOT2, consistent with a role in 2-APA metabolism.

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