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

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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_{cat}/K_m = ~150-220 M^{-1} s^{-1}), except for ketoprofenoyl-CoA (k_{cat}/K_m = 44 M^{-1} s^{-1}). Conversion of substrates by ACOT2 was slightly more efficient (k_{cat}/K_m = 250-330 M^{-1} s^{-1}), except for ibuprofenoyl-CoA (k_{cat}/K_m = 70 M^{-1} 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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