Gene Targeting of the Acyl-CoA Synthetase Specific to Arachidonate

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The synthesis of acyl-CoA catalyzed by acyl-CoA synthetase (ACS, EC 6.2.1.3) from fatty acid, ATP, and CoA is a crucial reaction in mammalian fatty acid metabolism. In arachidonate metabolism, acyl-CoA synthetase(ACS) plays a key role in the esterification of free arachidonate into membrane phospholipids. Following its release by the action of calcium dependent phospholipase, free arachidonate is believed to be rapidly converted to arachidonoyl-CoA and reesterified into phospholipids in order to prevent excessive synthesis of eicosanoids.

In previous studies, we have characterized five ACSs (designated as ACS1-5) with different tissue distribution. ACS1, ACS2, and ACS5 are similar in structure and fatty acid preference, and completely different from ACS3 and ACS4. The latter are arachidonate-preferring enzymes closely related in structure but expressed in different tissues: ACS3 mRNA is highly expressed in the brain and the mRNA for ACS4 is expressed in steroidogenic tissues including adrenal gland, ovary, and testis.

To learn more about the potential function of ACS4 in arachidonate metabolism, we have produced knock-out mice for ACS4 gene. ACS4+/- females become pregnant less frequently and produce small litters with

extremely low transmission of the disrupted alleles. Striking morphological changes including extremely enlarged uterine filled with numerous proliferative cysts of various size were detected in ACS4+/- females. Furthermore, marked accumulation of prostaglandins were seen in the uterus of heterozygous females. These results indicate that ACS4 is critical for the uterine arachidonate metabolism and heterozygous disruption of its gene lead to impaired pregnancy.