[S4-1] [10/10/2003(Fri) 09:30-10:10/ Grand Ballroom 105]

Acetoacetyl-CoA Synthetase, a Novel Cytosolic Ketone Body-Utilizing Enzyme that Specifically Activates Acetoacetate to its Coenzyme A Ester

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In mammalians, ketone bodies (acetoacetate, D(-)-3-hydroxybutyrate and acetone) are generated mainly in the liver via the 3-hydroxy-3-methylglutaryl-CoA pathway, carried to and utilized in extrahepatic tissues as an energy source during starvation and diabetes in particular due to their overproduction as the consequence of elevated fatty acid oxidation and lowered glucose metabolism. Mitochondrial succinyl-CoA:3-oxoacid CoA-transferase (SCOT) has long been regarded as the only enzyme catalyzing conversion of acetoacetate to its CoA ester for the utilization thereof. However, accumulated evidences indicated the presence of a second acetoacetate-activating enzyme, acetoacetyl-CoA synthetase (AACS), in the cytosolic fraction of the cells. We purified this enzyme for the first time as a discrete acetoacetate-specific ligase from a sludgy bacterium, *Zoogloea ramigera* I 16-M, which produces poly(3-hydroxybutyrate), a biodegradable plastic, as its intracellular energy reserve. Then we purified AACS also from rat liver and isolated its cDNA to investigate the expression level thereof. This enzyme was negatively regulated in rats by fatty acyl-CoAs similarly as acetyl-CoA carboxylase, a rate-limiting enzyme for fatty acid synthesis. The AACS specific activity in the liver remarkably increased and then decreased during the development, and increased upon administration of hypocholesterolemic compounds, cholestyramine and/or pravastatin. The hepatic AACS specific activity markedly decreased in streptozotocin-induced diabetic rats as in the case of 3-hydroxy-3-methylglutaryl-CoA reductase or acetyl-CoA carboxylase. Furthermore, the expression level of AACS mRNA was high in brain, especially in the midbrain, pons/medulla, cerebral cortex, hippocampus and cerebellum according to the in situ hybridization using a labeled probe, significantly different from SCOT mRNA in the localization profile. These results suggest that cytosolic AACS plays significant roles different from those of mitochondrial SCOT by supplying acetoacetyl-CoA directly from acetoacetate for the synthesis of physiologically important lipidic substances in the lipogenic tissues.