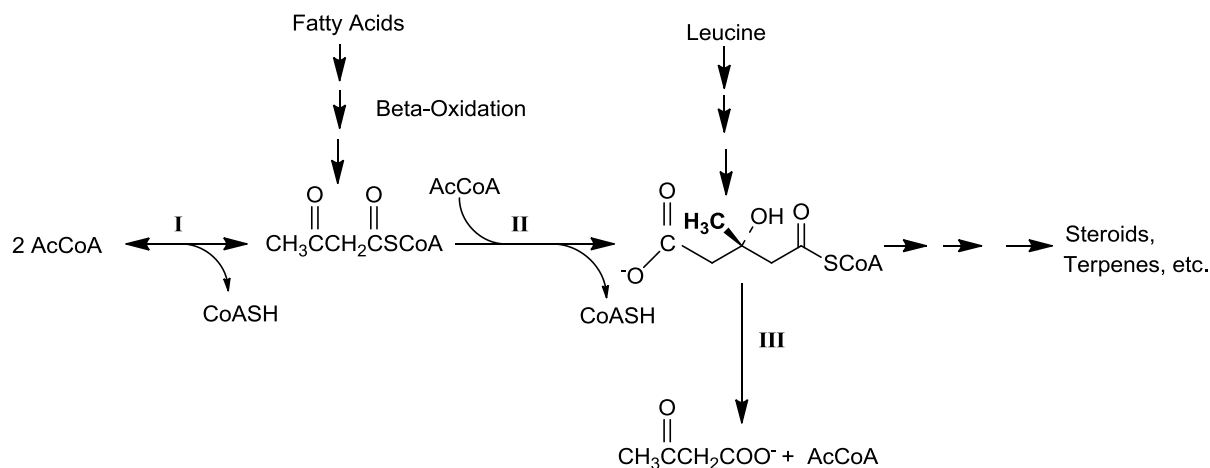


CHEM – 527 Introductory Biochemistry

Reactions Involving HMG CoA

3-Hydroxy-3-methyl glutaryl CoA (HMG CoA) is an intermediate in leucine degradation, steroid biosynthesis, and ketogenesis as is diagrammed below.



1. Citrate cleavage enzyme (ATP: citrate lyase) catalyzes the ATP dependent cleavage of citrate to oxaloacetate and acetyl CoA in the cytosol. It is very strongly inhibited by (-) hydroxycitrate [(2S, 3S)-2,3 dihydroxy-3-carboxyl-glutarate] (*Arch. Biochem. Biophys.* (1969) **135**, 209-217). Both fatty acid synthesis and steroid biosynthesis are inhibited by (-) hydroxycitrate (*Arch. Biochem. Biophys.* (1972) **150**, 183). What does this imply about the intracellular location and precursors of steroid synthesis? Explain.
2. Ketogenesis (reactions I, II & III) is not likely to be inhibited by (-) hydroxycitrate. Taken with the fact that there are isoenzymes for reactions 1 and II, (*J. Biol. Chem.* (1973) **248**, 2275-2284) where in the cell does ketogenesis take place? How many intracellular pools of HMG CoA are there in a liver cell?
3. Compare the reactions catalyzed by HMG CoA synthetase (II), HMG CoA lyase (III); citrate synthetase (TCA cycle enzyme), and citrate cleavage enzyme in terms of their similarities. Can you predict where the equilibrium of each reaction would lie based on the differences in the reactions. (Remember that equilibrium is a thermodynamic state and has nothing to do with mechanism.)