ABSTRACT OF DISSERTATION

CHARACTERIZATION OF THE E3 ISOZYME OF ALDEHYDE DEHYDROGENASE FROM HUMAN AND RAT LIVER: METABOLISM OF BETAINE ALDEHYDE

by MING-KAI CHERN

Dissertation Director:

Professor Regina Pietruszko

This work describes the identification and characterization of human betaine aldehyde dehydrogenase, an essential enzyme of the metabolic pathway from choline to betaine. Purification of the enzyme has demonstrated that betaine aldehyde dehydrogenation is catalyzed by the human E3 isozyme which was previously characterized as γ-aminobutyraldehyde dehydrogenase with broad substrate specificity. Based on Vmax value comparison betaine aldehyde is the best known substrate of the E3 isozyme, the only enzyme in the human liver metabolizing this aldehyde. It also describes animal experiments using alcohol-fed rats and controls to find out whether alcohol (acetaldehyde) metabolism affects steady state levels of betaine aldehyde. The inhibitory effect of acetaldehyde on betaine aldehyde dehydrogenation during ethanol metabolism is predicted from the Km values of both E3 isozyme and the rat liver betaine aldehyde dehydrogenase for betaine aldehyde and acetaldehyde. The results show no significant change of

betaine aldehyde concentration, arguing against this prediction. One of the reasons may be that betaine aldehyde could be metabolized in mitochondria by an enzyme with properties different from those of E3 isozyme. The mitochondrial metabolism of betaine aldehyde is indicated by the fact that incubation of choline, the precursor of betaine aldehyde, with rat liver mitochondria, produces not only betaine aldehyde but also betaine. However, the rat liver mitochondrial betaine aldehyde dehydrogenase, first purified to homogeneity during this investigation, is similar to E3 isozyme. The rat enzyme is a tetramer, able to metabolize γ-aminobutyraldehyde, acetaldehyde, glycolaldehyde, with the highest Vmax/Km ratio for γ-aminobutyraldehyde, and also catalyze ester hydrolysis. Its properties with activators or inhibitors also resemble E3 isozyme, except for the Ki value of cimetidine which is 30 fold higher for the rat mitochondrial enzyme than for E3 isozyme. The isolated peptides can be easily located within the human E3 isozyme sequence, demonstrating structural similarity. Betaine can function in the cell as an osmotic regulator or a methyl group donor for the formation of methionine.