DISTRIBUTION AND PROPERTIES OF NADPH-LINKED ALDEHYDE REDUCTASES FROM RAT BRAIN SYNAPTOSOMES

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Studies on the subcellular distribution of NADPH-linked aldehyde reductase from rat brain showed that 10% of the total reductase activity is located in the mitochondrial-synaptosomal fraction. There are differences in the percentages of reductase activity found in the synaptosomes compared to cytosol in various regions of the brain. The NADPH-linked aldehyde reductase from the synaptosomal fraction exhibited a nonlinear Lineweaver-Burk plot. This nonlinearity is due to the presence of two distinct aldehyde reductases, which can be distinguished by Michealis constants for p-nitrobenzaldehyde of $4.1 \times 10^{-5}$ M and $2.6 \times 10^{-6}$ M. The two NADPH-linked aldehyde reductases isolated from synaptosomes were further characterized according to pH optima, and $K_i$ values for inhibition by barbiturates. In addition regional distributions for the two enzymes were determined. The $K_i$ values for pentobarbital for the "high $K_m$" enzyme and the "low $K_m$" enzyme were estimated to be $2 \times 10^{-5}$ M and $6 \times 10^{-5}$ M.

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respectively. It was concluded from the above studies that the low $K_m$ reductase is probably responsible for 3,4-dihydroxyphenylglycoaldehyde (derived from norepinephrine) reduction in brain and a role of the high $K_m$ enzyme for protection of neurons from high concentrations of chemically reactive aldehydes was proposed.

INTRODUCTION

It is well known that the biogenic monoamines are involved in central nervous system (CNS) function. In the brain the amines norepinephrine, dopamine, and serotonin may be deaminated by the enzyme monoamine oxidase (MAO) to their corresponding biogenic aldehyde derivatives (1,2). In brain and other tissues these biogenic aldehydes can be oxidized to their corresponding acid metabolites or reduced to the alcohol derivatives (3,4). Breese et al. and Rutledge and Jonason observed that formation of predominantly acid or alcohol metabolites of phenylethylamines in brain preparations depended on the specific biogenic amine precursor employed (5–7). These metabolites are formed from the corresponding biogenic aldehyde intermediates either by an oxidative or reductive pathway.

The isolation, purification, and partial characterization of two NADPH-linked aldehyde reductases from bovine and porcine brain has been reported by Erwin and coworkers and by Turner and Tipton (8–10). In addition, it was observed that brain tissues contain an NADPH-dependent aldehyde reductase (8). The NADPH-linked aldehyde reductase was found to catalyze the reduction of a number of aldehydes, including substituted benzaldehydes, substituted phenylacetaldehydes, and some long-chain aliphatic aldehydes. However, short-chain aliphatic aldehydes were not reduced by the enzyme. It was found that the enzyme was localized primarily in the soluble supernatant fraction of rat brain homogenates while the crude mitochondrial fraction represented from 1.3% to 15% of the total aldehyde reducing capacity of the brain depending on the isolation media used. Upon isolation of the synaptosomes by a sucrose density gradient, Turner and Tipton reported 70% of the enzyme activity found in the crude mitochondrial fraction was subsequently associated with the synaptosomal fraction (10).

It recently has been shown that rat, bovine, monkey, and human brains contain at least two NADPH-linked aldehyde reductases (11–15). These enzymes have been shown to differ in kinetic parameters as well as pH optima and molecular weight. Ris and von Wartburg have suggested that different subcellular localization could represent a reason