Chapter 2
Biosynthesis of Plasmalogens in Brain

2.1 General Considerations and Distribution of Plasmalogens in Brain

Plasmalogens account for the major portion of the ethanolamine glycerophospholipids in the adult human brain (50%), but the brain of newborn babies has low levels (7% of total phospholipids mass) (Horrocks and Sharma, 1982). Levels of ethanolamine plasmalogen (PlsEtn) increase rapidly during the intense period of myelination and ethanolamine glycerophospholipids of myelin sheath contain up to 70% PlsEtn. An eight-fold increase in PlsEtn levels per gram of brain tissue occurs in white matter during first year of life so that PlsEtn accounts for 20% of the glycerophospholipid mass and 70% of the ethanolamine glycerophospholipids (Balakrishnan et al., 1961). At that time, myelination is rapid. The highest level of myelin is between 30 and 40 years of age (Toews and Horrocks, 1976). In human brain, there is a steep rise in PlsEtn content, followed by a further rise up to 30–40 years of age. This is followed by a decline of PlsEtn levels during normal aging. At 70 years of age, the levels of PlsEtn are 18% less than at 40 years of age (Rouser and Yamamoto, 1968; Horrocks et al., 1981). In chicks, there is a marked increase in plasmalogen levels in synaptosomes during the first 3 days after hatching (Getz et al., 1968). Collectively, these studies suggest that plasmalogens are major glycerophospholipids in brain tissue. Their metabolism may be involved in signal transduction processes associated with neural cell functions such as synaptogenesis, myelination, and ion transport (Farooqui and Horrocks, 2001).

Plasmalogens impart membranes with different biophysical properties such as phase transition temperature, bilayer thickness, acyl chain packing free volume, and lateral domain. The perpendicular orientation of the sn-2 acyl chain at the membrane surface and the lack of a carbonyl group at the sn-1 position in plasmalogens affect the hydrophilicity of the head group, resulting in stronger intermolecular hydrogen bonding between the head groups (Lohner, 1996). These properties allow PlsEtns to adopt the inverse hexagonal phase and may be responsible for a different membrane potential compared with other glycerophospholipids (Lohner, 1996). This property affects lipid packing, fluidity, and interaction with neural membrane receptors and ion channels. In cellular membranes and lipoproteins,
plasmalogens account for 15–20% and 5% of all phospholipids, respectively (Nagan and Zoeller, 2001; Engelmann et al., 1994). PlsEtn and PlsCho are the two major plasmalogen species found in mammalian cell membranes. In most cells, PlsEtns exceed the choline plasmalogens by 10-fold, with the exception of cardiac and skeletal muscle where choline plasmalogen dominates. The level of plasmalogens in brain tissue depends on the degree of myelination and increases rapidly during myelinogenesis (Horrocks, 1972; Horrocks and Sharma, 1982). Factors that modulate the levels of plasmalogens in neurons, astrocytes, and oligodendrocytes during myelination and aging remain unknown.

2.2 Biosynthesis of Plasmalogens

The enzymes for plasmalogen biosynthesis have not been purified and characterized from brain tissue. The reasons for this lack of information on the purification and characterization of plasmalogen biosynthesizing enzymes from brain are not known. However, the low activity of plasmalogen synthesizing enzymes, complex, laborious, and time consuming assays for determining activities, and the heterogeneity and complex organization of brain tissue may be responsible for the lack of information. Several investigators have reviewed the biosynthesis of plasmalogens in nonneural tissues (Fig. 2.1) (Horrocks and Sharma, 1982; Lee, 1998; Nagan and Zoeller, 2001; Murphy, 2001; Brites et al., 2004). The starting metabolite for plasmalogen biosynthesis is dihydroxyacetone phosphate from glycolysis, which is used to form the glycerol backbone of the plasmalogen. The biosynthesis of plasmalogens is initiated in peroxisomes and completed in the endoplasmic reticulum. Thus, the first three enzymes of plasmalogen biosynthesis, dihydroxyacetone phosphate acyltransferase, alkyl dihydroxyacetone phosphate synthase, and acyl/alkyl dihydroxyacetone reductase, are located in peroxisomes. The endoplasmic reticulum contains the other enzymes, namely 1-alkyl-sn-GroP acyltransferase, 1-alkyl-2-acyl-sn-GroP phosphohydrolase, and 1-alkyl-2-acyl-sn-Gro: CDP-choline (CDP-ethanolamine) choline (ethanolamine) phosphotransferase.

The rate-limiting step for plasmalogen biosynthesis has not been identified. However, it is proposed that regulation point lies downstream from first three steps (Nagan and Zoeller, 2001). This suggestion is based on the incorporation of 1-O-[9′-(1″-pyrenyl)]nonyl-sn-glycerol (pAG), a fluorescent ether lipid with a pyrene moiety covalently attached at the alkyl chain terminus (Zheng et al., 2006) (Fig. 2.2). CHO-K1 and NRel-4 cells take up this ω-pyrene-labeled 1-O-alkyl-sn-glycerol. NRel-4 cells are a variant defective in dihydroxyacetone phosphate acyltransferase. Treatment of CHO-K1 and NRel-4 cells results in the incorporation of pAG into ethanolamine and choline phospholipids as well as into a neutral lipid fraction tentatively identified as alkylacylglycerols. NRel-4 cells incorporate more fluorescence in the phospholipid fraction than CHO-K1, specifically in the ethanolamine phospholipids. Analysis of the fluorescent lipids demonstrates that 93% of the pAG is taken up by glycerolipids with the intact ether bond. Although