Short Communication

Age-Dependent Changes in the Levels of Dolichol and Dolichyl Phosphates in Human Brain*

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Human organs are rich in dolichol, and particularly high concentrations are found in endocrine tissues.[1] The biological role of this lipid has not yet been established, but investigations on model membranes have demonstrated that membrane stability, fluidity and permeability is influenced by dolichol. On the other hand, the phosphorylated derivative is an obligatory intermediate in glycoprotein synthesis and has thus been studied intensively in recent years.

It may be expected that highly specialized nerve cells, like other cells with well-developed membrane systems, require dolichol and its derivatives for normal function. It is known that the dolichol content of the brain in newborn infants is low and increases with age.[2] Furthermore, increased dolichol content in the brain has also been reported in association with certain pathological conditions.[3]

In the present investigation we have determined dolichol, dolichyl-P, cholesterol and phospholipid content in autopsy material from human brain in order to study age-dependent changes and possible specialization in different regions of the brain. Comparison of autopsy material with material from fresh biopsies of various tissues has demonstrated that both dolichol and dolichyl-P are very stable and that their levels in fresh autopsy material are the same as before death.

Experimental

Tissue samples from selected brain regions were homogenized, extracted, subjected to acid and alkaline hydrolysis and applied to a C18 Sep-Pak column, followed by separation on a silica Sep-Pak column, as described earlier.[4] Cholesterol, dolichol and dolichyl-P were quantitated by high performance liquid chromatography using a Hewlett-Packard Hypersil ODS 3 μm reversed-phase column. Total phospholipid was determined in the lipid extract of the homogenate.[5]

Results and discussion

The amount of dolichol in different regions of human brain increased with age (Table 1). The extent of the increase varied greatly between different regions. The increase was highest in the various gray matter regions and in the hippocampus, where there was a 20-fold elevation of the dolichol level between the ages of 2 and 90. On the other hand, during the same period the dolichol content in white matter increased only 2.5-fold, while in the cerebellum, spinal cord and various nerves the corresponding increase varied from 4–11 fold. The isoprenoid pattern was also analyzed, but no differences in the dolichol patterns in the brains of a 2 year-old and of older individuals were observed.

The ratio of dolichol to total lipid in various regions of human brain changed continuously with increasing age (Fig. 1A). The extensive increase in this ratio in the temporal gray matter con-

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Table 1. Distribution of dolichol in brain. All groups (ages 2–5, 33–38, 62–68, 85–91) represent 6–9 individuals and the values given are means.

Region	Content (μg/g wet weight) at age (years)			
	2–5	33–38	62–68	85–91
Gray matter				
frontal	17.1	174	203	249
occipital	26.0	215	306	543
White matter	26.2	36	61	64
Basal ganglia				
putamen	25.4	103	234	340
pallidum	27.1	128	293	318
Hippocampus	25.7	250	343	490
Pons	13.5	74	149	250
Cerebellum	25.4	120	163	190
Spinal cord				
cervical	12.7	61	81	98
lumbal	17.3	81	128	142
Cauda equina	6.3	37	53	73
Femoral nerve	9.4	23	36	40
Optic nerve	34.2	86	114	183

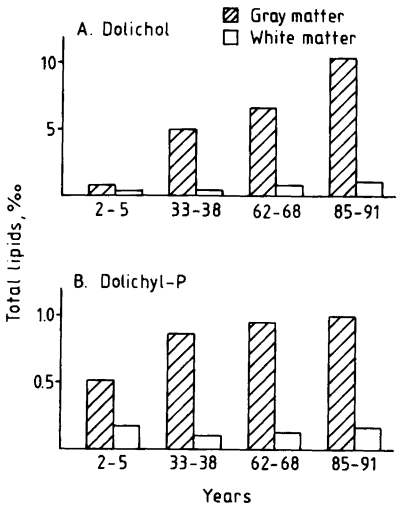

Fig. 1. Changes in the distributions of dolichol and dolichyl-P with age. Dolichol (A) and dolichyl-P (B) content as a percentage of total lipid (dolichol, dolichyl-P, cholesterol and phospholipid) in the gray (shaded columns) and white (open columns) matter at various ages.

trasted with the limited increase occurring in the white matter during the life-span. It appears that dolichol plays different roles in different structures of the central nervous system. In contrast to the findings for the free alcohol, the level of dolichyl-P was already high in the postnatal period in all samples examined (Fig. 1B). Establishment of high levels of the phosphorylated derivative thus occurred in the early stages of life, and accumulation such as seen for the free alcohol did not occur later in life. In some brain regions, such as white matter, the level of dolichyl-P was unchanged throughout the entire life-span. It is clear from these results that the ratio of the two forms of polyprenes in human brain changes greatly with increasing age. In the newborn, about half of the total brain dolichol is phosphorylated, while at ages above 80 only 10–15 % of the total is phosphorylated.

The large variations in regional levels of dolichol suggest the possibility that these findings do not correspond to real changes in cellular chemical composition. Two other major lipids of the brain, phospholipid and cholesterol, were there-

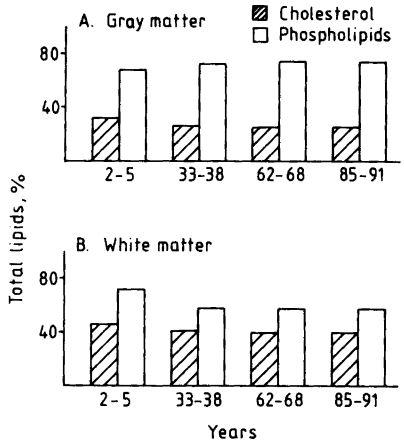

Fig. 2. Changes in the distributions of cholesterol and total phospholipid with age. Cholesterol (shaded columns) and phospholipid (open columns) content as a percentage of total lipids in the gray (A) and white (B) matter at various ages.

fore also determined. As illustrated in Fig. 2A, the relative proportion of cholesterol in gray matter decreased somewhat with age, whereas this was not the case for phospholipid. In white matter, the relative proportions of both phospholipid and cholesterol decreased to a moderate extent (Fig. 2B).

Glycoproteins participate in a number of important cellular functions and it is reasonable that in the postnatal stage substantial amounts of dolichyl-P are required to maintain an acceptable level of oligosaccharide synthesis. Since glycoprotein synthesis in adult animals is at a steady state level, the level of dolichyl-P is also constant, since its main or exclusive function is participation in the synthesis of *N*-linked oligosaccharide chains. As regards increases in dolichol with age, particularly in specific regions of the brain, there is no clear explanation available at present. There are several pieces of evidence indicating that the free alcohol is not a precursor for dolichyl-P, which is formed by a separate biosynthetic pathway.[6] Dolichol accumulation may occur for functional reasons, such as an increase in membrane fluidity to allow more rapid lateral movement of membrane proteins. Other possible effects include modulation of membrane permeability and an increase in the effectiveness of fusion processes.

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