

Cholesterol Metabolism in Normal and Abnormal Brain Development

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The relatively recent recognition that several genetic syndromes with serious brain involvement are caused by defects in cholesterol biosynthesis has focused attention on a previously unappreciated role of cholesterol metabolism in normal and abnormal brain development (1,2). The first syndrome found to be caused by a defect of post-squalene sterol biosynthesis, Smith-Lemli-Opitz syndrome (SLOS), is a relatively common genetic malformation syndrome with microcephaly and mental retardation. The primary defect in SLOS is in the conversion of 7-dehydrocholesterol (7DHC) to cholesterol, caused by a deficiency of 7-dehydrocholesterol reductase (DHCR7) (3). Early in the study of SLOS, investigators noted that there was a poor correlation of clinical severity with the level of the abnormal metabolite, 7DHC (4). Instead, there was a strong inverse correlation of clinical severity, including brain development, with the patients' blood cholesterol levels at diagnosis, suggesting that the teratogenic factor was not the high level of 7DHC but the deficiency of cholesterol. However certain striking exceptions to this strong correlation—such as one SLOS infant with no malformations, a cholesterol level of 1 mg/dl, and maternal cholesterol level of 350 mg/dl and a second with holoprosencephaly (HPE), a normal blood cholesterol level, but a maternal cholesterol level of 100 mg/dl—suggested that transport of cholesterol from the mother to the developing embryo and fetus may modify the clinical severity of SLOS, perhaps via the transport of LDL from mother mediated by gp330, an embryonic LDL receptor protein (5). Further evidence for an influence of maternal cholesterol metabolism on brain development in SLOS is that mothers whose Apo E genotype was e4/e4 bore SLOS infants who were significantly more mildly affected than mothers whose Apo E genotype was e2/e2 (6). Apo E e4/e4 mothers would be expected to supply more cholesterol to developing embryonic tissues by the LDL-gp330 system. The importance of maternal LDL transport to the developing neuroepithelium also has been supported by the discovery that mice haploinsufficient for gp330 develop HPE (5).

Although detailed studies of cholesterol metabolism and Apo E genotypes in HPE have not yet been completed, we found in a small pilot study that mothers of HPE children had a mean plasma cholesterol level that was 30 mg/dl lower than that of the paired HPE fathers (7). Thus, as in SLOS, maternal factors affecting the delivery of cholesterol from the mother to the embryo may have modifying effects on the severity of HPE or possibly even on the penetrance of HPE-causing genes, which are known to have marked variability in both penetrance and expression. Because the HPE families we studied were unselected with regard to the molecular cause of HPE, the maternal delivery of cholesterol to the embryo may have a role in multiple genetic forms of HPE. Furthermore, the strong association of severe microcephaly (predominantly frontal) and midline defects like agenesis of the corpus callosum with the three sterol disorders in which there are low tissue levels of cholesterol (SLOS, desmosterolosis, and lathosterolosis) may indicate that embryonic cholesterol nutrition may have a causative role in idiopathic microcephaly and agenesis of the corpus callosum.

The most likely link between low embryonic and fetal levels of cholesterol and brain malformations such as HPE, agenesis of the corpus callosum, and microcephaly characteristic of several disorders of cholesterol biosynthesis is impaired function of the signaling cascade that begins with Sonic Hedgehog (SHH), a protein whose function is sensitive to the cellular sterol environment, as shown in a series of elegant studies in the laboratory of P. Beachy (8,9). Although the receptor for SHH, Patched, may be the actual sterol-sensitive element of the SHH signaling pathway, several animal models have established conclusively the important role of impaired SHH function in causing many of the cerebral and extracerebral malformations of SLOS and related sterol disorders (8,9).

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