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Abnormal Sterol Metabolism in Holoprosencephaly

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Abstract

Holoprosencephaly (HPE) is the most common structural malformation of the developing forebrain in humans. The HPE phenotype is extremely variable and the etiology is heterogeneous. Among a variety of embryological toxins that can induce HPE, inhibitors, and other perturbations of cholesterol biosynthesis have been shown to be important factors, most likely because cholesterol is required in the Sonic hedgehog signaling cascade. Decreased levels of maternal cholesterol during pregnancy increase the risk for preterm delivery, but they are not associated with congenital malformations. However, if the fetus is affected by an inborn error of endogenous cholesterol synthesis, a reduction of maternal cholesterol concentration and cholesterol transport over the placenta aggravates the phenotypic expression. Exposure to lipophilic statins in early pregnancy may be associated with a substantial risk for structural CNS defects.

Keywords

holoprosencephaly; cholesterol biosynthesis; cholesterol precursors; Smith–Lemli–Opitz syndrome; Shh signaling

INTRODUCTION

Holoprosencephaly (HPE) is a common congenital malformation characterized by incomplete cleavage of the embryonic forebrain [Muenke and Beachy, 2001]. HPE occurs in ~1 in 10,000 births and 1 in 250 conceptions [Muenke and Beachy, 2001]. Features in mutation-positive patients range from cyclopia with a proboscis and a single prosencephalic vesicle to obligate mutation carriers with normal neuroimaging by MRI and normal facial appearances. Multiple genetic causes of HPE have been identified, the most common of which are cytogenetic abnormalities [Roessler and Muenke, 1998, 2010]. The most common genetic finding in infants with familial HPE is heterozygous mutations in *Sonic Hedgehog* (*Shh*) [Roessler et al., 1996; Muenke and Beachy, 2001; Roessler and Muenke, 2010]. Other HPE genes identified to date include functional elements of the Shh pathway and members of interacting pathways and other pathways integral to forebrain development (Zinc finger transcription factor 2 (*ZIC2*) [Brown et al., 1998], TG-interacting factor (*TGIF*) [Gripp et al., 2000], Patched1 (*PTCH1*) [Ming et al., 2002], Gli protein 2 (*GLI2*) [Roessler et al., 2005], and Dispatched1 (*DISP1*) [Roessler et al., 2009]). The Hedgehog (Hh) proteins play a major role in embryonic development. Shh is essential for CNS patterning and impairment

of Shh signaling severely affects CNS morphogenesis with greatest effects in the midline [Roessler and Muenke, 2010].

Many studies have shown that the expressed HPE phenotype is extremely variable even in families segregating a heterozygous HPE-causing mutation [Solomon et al., 2010]. Further, some patients with HPE have had mutations identified in more than one HPE gene or in other molecules of the Shh signaling pathway. These findings suggest that the phenotypic variability may reflect a combination of genetic, epigenetic, and environmental influences [Ming and Muenke, 2002].

As cholesterol modification is essential for Shh signaling, the availability of sufficient cholesterol to the embryo is a key component for the proper function of the Shh signal transduction apparatus. In this review we will discuss the pivotal role of cholesterol in normal forebrain development.

CHOLESTEROL AND SONIC HEDGEHOG SIGNALING

Hh proteins are indispensable for embryonic development because they coordinate the growth and patterning of cellular assemblies. Shh, the best characterized of these factors, acts on neuronal cells resulting in the establishment of the left–right axis and definition of the anterior–posterior axis of the limb. It also participates in the development of the pituitary gland, neural crest cells, midbrain, cerebellum, oligodendrocytes, and the eye and face [Roessler and Muenke, 2003, 2010]. Loss of Shh function in *Shh*^{−/−} mouse embryos is associated with a loss of ventral structures throughout the neuraxis and with an absence of ventral forebrain structures resulting in cyclopia and alobar HPE [Chiang et al., 1996]. Loss of function mutations at the human *Shh* locus are associated with an autosomal dominant form of HPE, which is less severe than that seen in the *Shh*^{−/−} mouse, indicative of haploinsufficiency.

A unique feature of all Hh proteins is the dependency of their signaling activity on cholesterol modification. The protein biosynthesis of Shh involves internal cleavage and covalent binding of cholesterol to the N-terminal domain to form the active signaling molecule [Porter et al., 1996]. Additionally, a palmitoyl group is added to the amino-terminal end. The Shh signaling cascade is regulated by two transmembrane proteins, patched (Ptc) and smoothened (Smo). Ptc suppresses the activity of Smo, a process that is released by binding of Shh to Ptc. Through an unknown mechanism, activation of Smo initiates transcription of Shh-responsive genes through the Gli family of transcription factors (Fig. 1).

Initially, it was hypothesized that cholesterol precursors such as 7-DHC or lathosterol would disrupt the autoprocessing reaction of Shh or the interaction of Shh with the receptor Ptc (Fig. 1). However, Cooper et al. [2003] showed that Shh was efficiently processed in SLOS and lathosterolosis cells, which are characterized by an accumulation of 7-DHC and lathosterol, and that Shh signaling was impaired by decreased intracellular cholesterol concentration at the level of Smo. Corcoran and Scott [2006] demonstrated that Smo could be directly stimulated by cholesterol and by certain oxysterols when sterol synthesis was blocked.

INHIBITORS OF CHOLESTEROL BIOSYNTHESIS

Early evidence that cholesterol was essential to forebrain morphogenesis came from the observation that HPE is induced in lambs born to ewes that consumed *Veratrum californicum*. The teratogenic compounds of this plant were identified as the steroidal alkaloids, cyclopamine, and jervine, which resemble cholesterol in structure [Binns et al., 1963; Keeler and Binns, 1968] (Fig. 2). Additionally, jervine acts as a distal inhibitor of cholesterol biosynthesis [reviewed in, Mann and Beachy, 2000]. The HPE phenotype can also be experimentally induced by exposure of rat embryos to inhibitors of the distal steps of cholesterol biosynthesis (AY9944, BM15766, and triparanol, Fig. 1) causing accumulation of cholesterol precursors and decreased cholesterol concentrations [Roux, 1964; Roux and Aubry, 1966].

As HPE and other malformations observed in these animal models occur in structures whose embryonic patterning depends on Shh signaling, and heterozygous mutations in the *Shh* gene are the most common genetic finding in familial HPE in humans [Muenke and Beachy, 2001], the inhibitors were thought to cause HPE by reducing Shh processing or signaling by either accumulation of abnormal sterols or depletion of cholesterol. As the HPE phenotype could be prevented by supplying sufficient dietary cholesterol to the pregnant rats in addition to the inhibitor AY9944, cholesterol depletion seemed the most likely mechanism. However, HPE produced by cyclopamine could not be prevented by exogenous cholesterol [Incardona et al., 1998] and cyclopamine has later been shown to directly inhibit Smo, the transmembrane protein which is obligate for transduction of the Shh signal across the plasma membrane into the cell [Chen et al., 2002].

DEFECTS OF CHOLESTEROL BIOSYNTHESIS

The 27-carbon cholesterol molecule is synthesized from lanosterol, the first sterol in the cholesterol synthesis pathway, via a series of ~30 enzymatic reactions. Defects in seven enzymes of the distal cholesterol biosynthesis pathway resulting in congenital malformation syndromes have been identified so far (Fig. 3). The most common of these conditions is Smith–Lemli–Opitz syndrome (SLOS, OMIM 270400) with an estimated incidence of 1 in 20,000 to 1 in 60,000. SLOS is an autosomal recessive disorder, resulting from a deficiency of microsomal 7-dehydrocholesterol reductase (DHCR7), the enzyme that converts 7-dehydrocholesterol (7-DHC) to cholesterol in the last step of cholesterol biosynthesis. This results in an accumulation of 7-DHC and its isomer 8-dehydrocholesterol (8-DHC) in plasma and all tissues and, in most patients, a marked deficiency of cholesterol. The human *DHCR7* gene is located on chromosome 11q13 [Fitzky et al., 1998; Wassif et al., 1998; Waterham et al., 1998] and more than 100 different mutations have been identified to date.

Patients with SLOS show wide clinical variability, ranging from intrauterine or neonatal death due to multiple congenital anomalies to minimal facial dysmorphisms and behavioral and learning problems [Kelley and Hennekam, 2000]. Typical facial features include microcephaly, a narrow bifrontal diameter, ptosis, anteverted nares, microretrognathia, and low set, posteriorly rotated ears. Midline clefts ranging from a bifid uvula to lip and palatal clefts are common. More than 95% of SLOS patients have unilateral or bilateral syndactyly

of toes 2 and 3, typically Y-shaped. Other limb abnormalities include short and proximally placed thumbs, postaxial polydactyly, and various foot deformities. Male patients show varying degrees of genital anomalies. HPE is found in ~5% of cases. Additionally, other midline malformations of the central nervous system have been described [Weaver et al., 2010].

Examination of cholesterol biosynthesis in lymphoblastoid cell lines of 228 patients with HPE showed impaired cholesterol biosynthesis in 22 patients (9.6%) [Haas et al., 2007]. In one patient, SLOS was diagnosed, whereas others had clearly reduced cholesterol biosynthesis with a sterol pattern different from that seen in patients with known single defects of cholesterol biosynthesis enzymes. Five of these patients had alterations in known HPE genes in addition to their sterol abnormalities, suggesting that defective regulation of cholesterol biosynthesis could further aggravate impaired Shh signaling. In five other patients there was an accumulation of the cholesterol precursors lanosterol, lathosterol, desmosterol, 7- and 8-DHC to nearly the same amount, whereas cholesterol synthesis was variably reduced. This pattern could be explained by a disruption of the previously reported transport of newly synthesized cholesterol precursors from the endoplasmic reticulum (ER) to the plasma membrane. In earlier studies, it was shown that desmosterol, lathosterol, lanosterol, zymosterol, and 7-DHC were transported from their site of synthesis in the ER to the cell membrane [Lange and Muraski, 1987; Echevarria et al., 1990]. The purpose of this transport process is unclear, but a regulatory role seems likely. An impaired intracellular transport of cholesterol precursors and a resulting decrease in cholesterol could alter Shh signaling in these patients.

CHOLESTEROL IN EARLY EMBRYOGENESIS

It has been well documented that the maternal circulation supplies large amounts of LDL cholesterol to the trophoblast for progesterone synthesis early in human pregnancy [Lurie et al., 1966]. It has also been demonstrated that subfractions of HDL cholesterol can function in this capacity [Lafond et al., 1999] and may be incorporated into trophoblastic cells. Most studies of nutrient transfer on early gestation have been performed in rodents, whose yolk sac functions differ substantially from that of humans [Jauniaux and Gulbis, 2000]. Recently it has been shown that the ATP-binding cassette transporter A1 (Abca1) is involved in cholesterol transport from maternal to fetal circulation in mice and that agonists of the liver-X-receptor transcription factors (LXRs) can upregulate the expression of Abca1 and increase cholesterol transfer to the fetus [Lindegaard et al., 2008] but this has not been demonstrated in humans yet.

Low maternal serum cholesterol during pregnancy has been shown to be associated with preterm delivery, but this could only be observed among white mothers [Edison et al., 2007]. Additionally, term infants of mothers with low cholesterol had significantly lower birth weight than those of control mothers. However, low maternal cholesterol was not associated with an increased risk of congenital anomalies in this study [Edison et al., 2007]. In a retrospective study, the risk of gestational exposure to the cholesterol lowering statin drugs was assessed [Edison and Muenke, 2004a,b]. Seventy reports were evaluated, and structural defects were found in a third of exposed pregnancies. In five further cases, fetal

death occurred, and there was intrauterine growth restriction in four cases. The majority of structural defects were consistent with an impairment of the Shh signaling pathway. One patient had HPE and in two others, severe midline CNS malformations were reported. All adverse effects occurred after exposure to lipophilic statins, which equilibrate between maternal and embryonic compartments and achieve embryoplacental concentrations similar to those of maternal plasma, impairing fetal cholesterol biosynthesis in addition to lowering maternal cholesterol. Using a case series approach, Petersen et al. [2008] did not observe an association between maternal statin exposure and congenital defects.

A small study of parents of infants with HPE found that the mothers of these severely affected children had significantly lower serum cholesterol levels (138 ± 6 mg/dl) than did the fathers (178 ± 6 mg/dl), suggesting that low maternal serum cholesterol might have been permissive for expression of the full HPE phenotype (Muenke and Kelley, unpublished work). In a study regarding disease severity in SLOS patients in correlation with the apo E genotype of their mothers, a more severe phenotype was found when mothers had the E2 genotype, which is associated with low cholesterol concentrations [Witsch-Baumgartner et al., 2004]. There were significantly more oral anomalies (cleft lip or palate), malformations which are part of the HPE spectrum, and lower cholesterol concentrations in the group with maternal E2 alleles, suggesting that the maternal apo E genotype affects cholesterol transport from mother to embryo, which may become a critical factor in the context of limited endogenous cholesterol biosynthesis.

DISCUSSION

Although the complex processes of Shh signal transduction have not been completely elucidated, it is now clear that cholesterol is indispensable for the function of this signaling cascade. Inborn errors of cholesterol biosynthesis in SLOS, as well as inhibition of defined enzymes of the pathway by chemicals or drugs, lead to malformation syndromes including HPE [Weaver et al., 2010]. Impaired Shh signaling in these conditions is caused by decreased cellular levels of cholesterol, not the increase of any cholesterol precursor [Cooper et al., 2003].

It has been previously suggested that the phenotypic expression of HPE is most likely influenced by multiple genetic and environmental factors [Ming and Muenke, 2002]. The lack of sufficient cholesterol during embryogenesis either due to reduced placental cholesterol transfer or to fetal defects of cholesterol biosynthesis or transport is certainly a key factor in this scenario.

There is a need for detailed study of cholesterol transport across the placenta. Of particular interest is certainly the involvement of apo E and ABCA1 in HPE pregnancies. Further research should concentrate on the modulation of maternal–fetal cholesterol transport. In addition, controlled epidemiologic studies evaluating the potential teratogenic effects of cholesterol lowering drugs during pregnancy are necessary.

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Biographies

Dorothea Haas is a senior pediatrician and metabolic consultant at the University Children's Hospital of Heidelberg. Her clinical and research interests have focused on inborn errors of cholesterol biosynthesis.

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Figure 1.

Shh biosynthesis and signaling. The Shh protein is modified by covalent binding of cholesterol and palmitate. In the responding cell Ptc1 maintains Smo in an inactive state (Smo_i). Binding of Shh to Ptc1 releases this process. The activation of Smo (Smo_a) initiates transcription of Shh-responsive genes through the Gli family of transcription factors. Smo can also be directly stimulated by cholesterol and by certain oxysterols.

Figure 2.

Chemical structures of cholesterol and of the compounds eliciting HPE. Cyclopamine, a teratogen that inhibits the Shh signaling cascade at the level of Smo, is found in plants of the species *Veratrum californicum*. AY9944, BM15766, and triparanol have been characterized as inhibitors of distal steps of cholesterol biosynthesis. Jervine is an inhibitor of both the Shh signaling cascade and of cholesterol biosynthesis.

Figure 3. Pathway of distal cholesterol biosynthesis. Enzyme defects known for specific human diseases are indicated by a bar. The inhibitors are printed in bold, below the enzymes they inhibit.