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Original Article

Growth hormone activates hepatic and cerebral cholesterol metabolism in small-for-gestational age children without catch-up growth

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Oxysterols;
7α-hydroxycholesterol;
24S-hydroxycholesterol

BACKGROUND: Growth hormone (GH) replacement therapy improves hypercholesterolemia in patients with GH deficiency, suggesting that GH modulates cholesterol metabolism.

OBJECTIVES: We examined GH effects on lipid profiles and cholesterol-related markers reflecting hepatic and cerebral cholesterol metabolism in small-for-gestational age (SGA) children without catch-up growth.

METHODS: This study examined SGA children without catch-up growth (n = 22) and healthy children (controls, n = 11). Based on parents' choice, 11 SGA children received GH at 0.23 to 0.25 mg/kg/d for 6 months, and at 0.34 to 0.36 mg/kg/d for the subsequent 6 months (GH (+) group). The other SGA children received no GH (GH (−) group, n = 11). We ascertained baseline and posttreatment lipid profiles and cholesterol-related markers reflecting hepatic and cerebral cholesterol metabolism.

RESULTS: Baseline lipid profiles of SGA children and controls were similar. Serum 24S-hydroxycholesterol (marker for cerebral cholesterol metabolism) concentration was 19% lower in SGA children than in controls ($P < .05$). Compared with baseline, the GH (+) group low-density lipoprotein concentration had decreased by 6.6% during 6 months and 8.8% during 12 months ($P < .01$), whereas the high-density lipoprotein concentration had increased by 1.7% ($P = .07$) and 3.3% ($P < .01$). Serum

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7α-hydroxycholesterol (marker for hepatic cholesterol elimination) concentration had increased by 34% at 6 months and 35% at 12 months ($P < .01$). In addition, 24S-hydroxycholesterol increased by 25% and 26% ($P < .001$). No marker for cholesterol synthesis or absorption changed. The GH (−) group lipid profiles and oxysterols remained unchanged during the observation period.

CONCLUSION: GH activates hepatic and cerebral cholesterol metabolism in SGA children without catch-up growth.

Introduction

Growth hormone (GH) administration has been widely accepted as a treatment for patients with GH deficiency attributable to insufficient GH secretion.[1,2] In addition, GH replacement therapy is administered as a treatment to small-for-gestational age (SGA) children without catch-up growth.[3–8] Our recent study revealed that the lowering effect of GH on low-density lipoprotein cholesterol (LDL-C) in GH-deficient children is dependent on apolipoprotein (apo) E phenotypes, strongly suggesting that GH affects hepatic cholesterol metabolism.[9] Although the effects of GH on hepatic bile acid synthesis have been examined in animal models and humans,[10–13] other systemic effects of GH treatment on cholesterol metabolism have not been sufficiently elucidated.

Accumulated evidence suggests that GH is involved in cholesterol metabolism not only in the liver but also in the brain. In the central nervous system (CNS), cholesterol catabolism is very slow. Its half-life is about 5 years in adults.[14] After brain cholesterol is oxidized by a specific enzyme, it is eliminated into peripheral blood as 24S-hydroxycholesterol (24S-OHC).[15–17] The 24S-OHC/cholesterol ratio in plasma is 5-fold higher in the first decade of life than in the sixth decade,[18,19] suggesting that cholesterol metabolism in the brain is more active in children than in adults. It is particularly interesting that 24S-OHC is a potent, direct, and selective positive allosteric modulator for the synaptic protein N-methyl-D-aspartate (NMDA) receptor, which is implicated in many fundamental functions, including memory and learning.[20] GH and insulin-like growth factor I (IGF-1) signaling stimulate NMDA receptor expression.[21] Intravenously administered GH can pass through the blood–brain barrier.[22] GH might promote 24S-OHC production in the brain. Therefore, we hypothesized that GH action affects not only hepatic but also brain-specific cholesterol metabolism.

This study examined whether GH activates peripheral and cerebral cholesterol metabolism, or not, in SGA children without catch-up growth. Regarding lipid profiles and physical growth, GH is similarly effective for GH-deficient children and SGA children without catch-up growth. We enrolled only SGA children because it is unethical to follow up GH-deficient children without GH treatment after definitive diagnosis. We measured several cholesterol-related markers in SGA children with and without 12-month GH treatment to evaluate intestinal cholesterol absorption, hepatic cholesterol synthesis, hepatic and extrahepatic bile acid synthesis, hepatic drug metabolism, and brain cholesterol catabolism together with common lipid-related laboratory tests. These parameters were compared with those of children chosen as control subjects.

Materials and methods

Subjects and protocol for GH replacement therapy

We enrolled 3- to 6-year-old SGA children without catch-up growth (n = 22) and age-matched and sex-matched healthy children (n = 11). The standard deviation (SD) scores of birth weight and height of SGA children were found in relation to the respective standard curves representing the mean (SD) values according to the gestational week and day for the Japanese population.[23–25] At birth, the height and/or weight SD scores were less than −2 SDs, which is compatible with SGA.[7,8] At the age of 3 years and older, their height SD scores were less than −2.5 SD, confirming the indication for GH therapy.[7,8] In newborn and infancy periods, these patients never experienced episodes such as asphyxia, respiratory distress, or severe infection. The GH (+) group included children with mild neonatal jaundice (n = 2), transient tachypnea of neonate (n = 1), and transient tube feeding (n = 1). The GH (−) group comprised children with mild neonatal jaundice (n = 2).

At 3 to 6 years of age, they visited hospitals near their homes with their parents, who were concerned about their child's short stature and who were referred to our hospital to receive thorough examinations. From the present study, we excluded cases of GH deficiency, bone disease, malformed syndrome, or chromosomal abnormality. In fact, the SGA children showed normal peak plasma GH concentrations higher than 6 ng/mL for arginine, clonidine, and insulin tests. We also excluded children with a learning disorder, attention deficit hyperactivity disorder, or autism spectrum disorder because of the difficulty of follow-up study.