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Oxysterol changes along with cholesterol and vitamin D changes in adult phenylketonuric patients diagnosed by newborn mass-screening

Hironori Nagasaka [a,*], Yoshiyuki Okano [b], Akihiko Kimura [c], Tatsuki Mizuochi [c], Yoshitami Sanayama [d], Tomozumi Takatani [e], Saori Nakagawa [f], Eri Hasegawa [f], Ken-ichi Hirano [g], Hiroshi Mochizuki [h], Toshihiro Ohura [i], Mika Ishige-Wada [j], Hiromi Usui [j], Tohru Yorifuji [k], Hirokazu Tsukahara [l], Satoshi Hirayama [m], Akira Ohtake [n], Susumu Yamato [f], Takashi Miida [m]

[a] Department of Pediatrics, Takarazuka City Hospital, Takarazuka, Japan
[b] Department of Genetics, Hyogo College of Medicine, Nishinomiya, Japan
[c] Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Japan
[d] Department of Pediatrics, National Hospital Organization Shimoshizu Hospital, Chiba, Japan
[e] Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba, Japan
[f] Niigata University of Pharmacy and Applied Life Sciences, Niigata, Japan
[g] Department of Cardiovascular Medicine, Graduate School of Medicine, Osaka University, Suita, Japan
[h] Division of Endocrinology and Metabolism, Saitama Children's Medical Center, Saitama, Japan
[i] Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan
[j] Department of Pediatrics, Nihon University School of Medicine, Tokyo, Japan
[k] Development of Pediatric Endocrinology and Metabolism, Osaka City General Hospital Children's Medical center, Osaka, Japan
[l] Department of Pediatrics, Okayama University Hospital
[m] Department of Clinical and Laboratory Medicine, Juntendo University, Tokyo, Japan
[n] Department of Pediatrics, Faculty of Medicine, Saitama Medical University, Saitama, Japan

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ABSTRACT

Background: Phenylketonuria (PKU) possibly leads to hypocholesterolemia and lowered vitamin D (VD) status. Metabolism of oxysterols linking with those of cholesterol and VD has never been examined in PKU.
Methods: Blood oxysterols along with blood phenylalanine, lipids and VD were examined for 33 PKU adults aged 21–38 years and 20 age-matched healthy controls.
Results: Total- and low-density cholesterols, and 25-hydroxy VD_3 were decreased significantly in the PKU group (cholesterols, 10% decrease; 25-hydroxy VD_3 35% decrease vs. the control group). 24S-hydroxycholesterol (24S-OHC) eliminating brain cholesterol, and 27-OHC and 7α-hydroxycholesterol (7α-OHC) representing peripheral and hepatic cholesterol elimination, respectively, were significantly decreased in PKU group: 24S-OHC, 25% decrease, $p<.01$; 27-OHC and 7α-OHC, 35–40% decrease, $p<.001$. 7β-Hydroxycholesterol (7β-OHC) reflecting oxidative stress was increased significantly in PKU group ($p<.05$). 7α-OHC and 27-OHC levels in PKU group always showed similar values, regardless of other parameters while the 24S-OHC and 7β-OHC levels decreased and increased, respectively, showing significant correlations with phenylalanine level ($p<.005$). 27-OHC level showed a significant positive correlation with the 25-hydroxy VD_3 level in this group ($p<.001$).
Conclusion: Blood oxysterol changes predominate over blood cholesterol changes and influence on VD status in adult PKU patients.

1. Introduction

Phenylketonuria (PKU: OMIM, 261600) is an autosomal recessive disorder caused by deficiency of hepatic phenylalanine hydroxylase (PAH; EC 1.14.16.1). Diverse unfavorable effects of hyperphenylalaninemia on the central nervous system in children have been well described [1–5]. Unless phenylalanine intake is restricted, they develop convulsions, developmental delay, and mental retardation. Additionally, evidence that high plasma phenylalanine concentrations possibly cause behavioral

Abbreviations: PKU, phenylketonuria; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; VD, vitamin D; PTH, parathyroid hormone; 7α-OHC, 7α-hydroxycholesterol; 7β-OHC, 7β-hydroxycholesterol; 24S-OHC, 24S-hydroxycholesterol; 27-OHC, 27-hydroxycholesterol.

* Corresponding author at: Department of Pediatrics, Takarazuka City Hospital, 4-5-1 Kohama-Cho, Takarazuka, Japan. Tel.: +81 797 87 1161; fax: +81 797 87 5624.
E-mail address: nagasa-hirono@k2.dion.ne.jp (H. Nagasaka).

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abnormalities, cognitive impairment, and emotional disturbance in adults has been reported increasingly [6,7].

Aside from the clinical presentations, various metabolic changes in PKU, particularly changes related to neurological manifestations, have been studied [1–5]. Among them, the most frequently explored are the low productions of neurotransmitters such as serotonin, dopamine and catecholamine, together with disturbance in the transport systems [1–5]. In addition, several studies have demonstrated the possibility that enhanced oxidative stress is, in part, associated with neurological manifestations in PKU [8–12]. Probably, multiple metabolic factors are associated with the clinical presentations of the disease. Nevertheless, information related to the biochemistry in PKU remains insufficient.

Oxysterols are metabolites originated from cholesterol, and some oxysterols have been implicated in the pathophysiology of neurological disorders [13–18]. Oxysterols are also metabolically connected to vitamin D (VD) (Fig. 1). In PKU, cholesterol and VD productions have

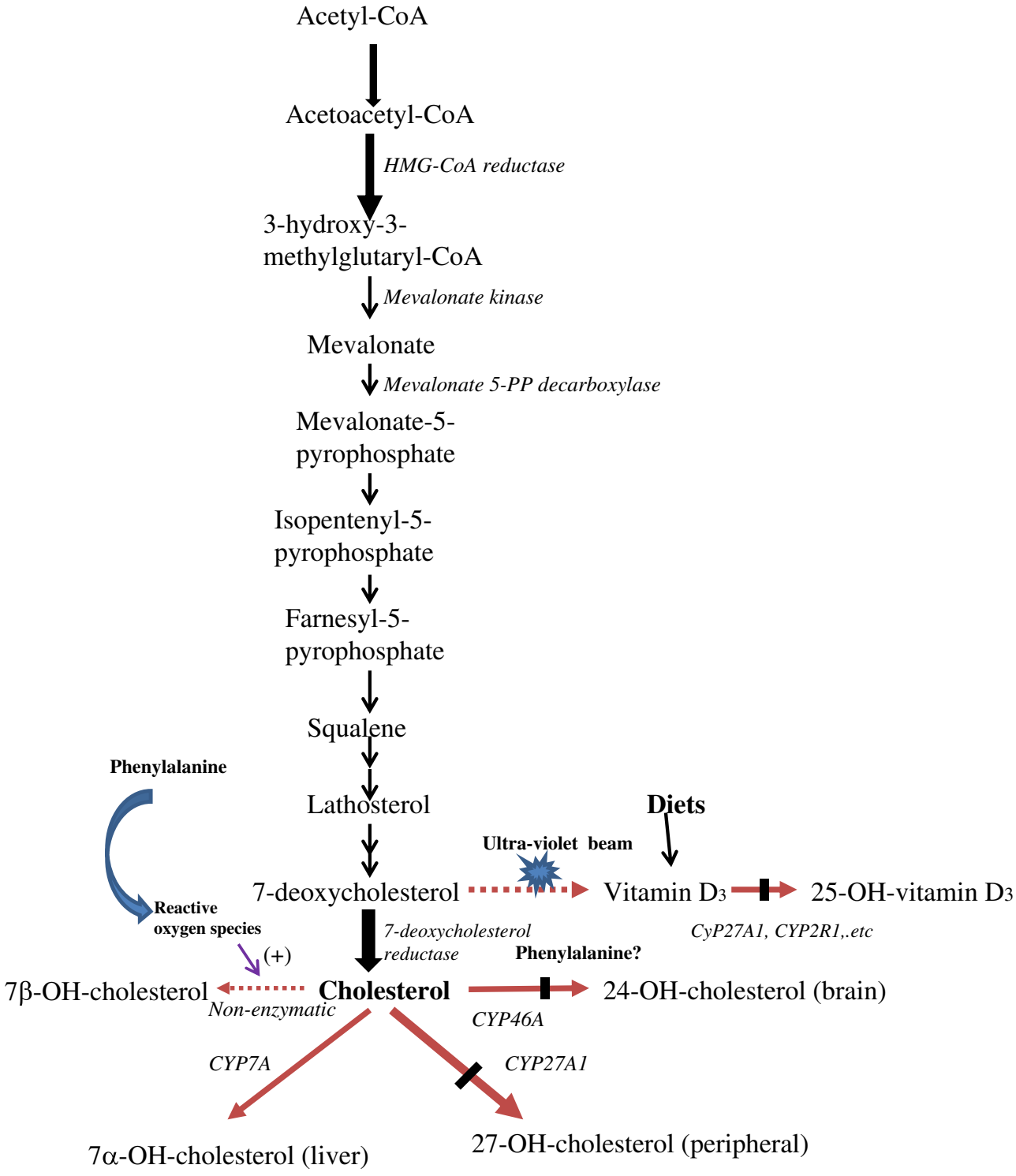

Fig. 1. Metabolic map illustrating cholesterol, oxysterol and vitamin D productions.