Primary Hyperoxaluria Type 1 in Japan

Arata Ichiyama,* 1 Toshiaki Oda,2 and Eiko Maeda-Nakai3

13 First Department of Biochemistry, Hamamatsu University School of Medicine,
3600 Handa-cho, Hamamatsu, Shizuoka 431-3192, Japan.
1 E-mail: ichiyama@hama-med.ac.jp; 2 E-mail: odat129@hama-med.ac.jp;
and 3 E-mail: namaeiko@hama-med.ac.jp

ABSTRACT

Glyoxylate is an immediate precursor of oxalate, but in its metabolism the conversion into glycine catalyzed by serine:pyruvate/alanine:glyoxylate aminotransferase (SPT/AGT) appears to be the main route. When SPT/AGT is missing as in the case of primary hyperoxaluria type 1 (PH1) more glyoxylate is used for the oxalate production, resulting in calcium oxalate urolithiasis and finally systemic oxalosis. SPT/AGT is a unique enzyme of species-specific dual organelle localization; it is located largely in mitochondria in carnivores and entirely in peroxisomes in herbivores and man. For herbivores, the peroxisomal localization of SPT/AGT is indispensable to avoid massive production of oxalate, probably because liver peroxisomes are the main site of glyoxylate production from glycolate, and plants contain glycolate much more than animal tissues. Recently, we took charge of laboratory examination for 8 cases of primary hyperoxaluria in Japan, and felt that symptoms of some of the Japanese PH1 patients are apparently milder than those of Western patients. The reason of this is not clear, but from the above mentioned seemingly indispensable association of grass-eating with the peroxisomal localization of SPT/AGT it may be related, at least in part, to the food habit of Japanese, especially that of old generation, that they prefer boiled greens rather than frying or raw vegetables.

Index Entries: Primary hyperoxaluria type 1; oxalate; glyoxylate; glycolate; liver peroxisomes; serine:pyruvate/alanine:glyoxylate aminotransferase (alanine:glyoxylate aminotransferase).

INTRODUCTION

Oxalate is an apparently useless end product of metabolism, at least in mammals, and is even toxic, because its insoluble calcium salt easily deposits in tissues. Although the absorption of dietary oxalate and the nonenzymic formation from diketogulonic acid, an intermediate of ascorbate metabolism, also contribute to urinary oxalate, about 50% of it is known to reflect endogenous oxalogenesis (1), which is believed to occur mostly in the liver by way of glyoxylate. Glyoxylate is thought to be formed primarily from glycolate in liver peroxisomes (2), but the origin of glycolate still remains to be elucidated.
Apart from the oxidation to oxalate, glyoxylate is converted to glycine by alanine:glyoxylate aminotransferase (AGT) or serine:pyruvate/alanine:glyoxylate aminotransferase (SPT/AGT). Since this aminotransferase was discovered as serine:pyruvate aminotransferase (3), and is involved in both the metabolism of serine and glyoxylate, we usually call it SPT/AGT, but when only the glyoxylate or serine metabolism is concerned, the shorter name AGT or SPT is also relevant. Usually, the conversion to glycine catalyzed by SPT/AGT appears to be the chief route of glyoxylate metabolism, and when this enzyme is missing, as in the case of primary hyperoxaluria type 1, more glyoxylate is utilized for the oxalate production, resulting in hyperoxaluria, calcium oxalate urolithiasis, nephrocalcinosis, and systemic oxalosis, with massive deposition of insoluble calcium oxalate in kidney, bone, and other tissues. Primary hyperoxaluria type 1 is a progressive and lethal disease. In many cases, patients die from renal failure or heart block caused by deposition of calcium oxalate in the myocardium. The only effective therapy available at present is combined hepatorenal transplantation (4).

Recently, the authors took charge of laboratory examination for eight cases of primary hyperoxaluria in Japan, and had an impression that clinical symptoms of Japanese primary hyperoxaluria type 1 patients seem to appear later than those in Western countries. This article discusses the presumed origin of glycolate with reference to the apparently milder symptoms of Japanese primary hyperoxaluria type 1 patients.

MATERIALS AND METHODS

The SPT activity of SPT/AGT was determined essentially as described previously (5). Oxalate in urine and plasma was determined by the oxalate oxidase method previously described (6), except that a microplate reader (EL 340, Bio-Tek) was used, instead of a spectrophotometer. Creatinine was determined by the Jaffe reaction, using the microplate reader.

RESULTS AND DISCUSSION

Glyoxylate Metabolism in Mammals

One of the distinctive features of glyoxylate metabolism in mammals is that most enzymes concerned have other functions. Three enzymes known to catalyze the oxidation of glyoxylate to oxalate in vitro are glycolate oxidase, lactate dehydrogenase (LDH), and xanthine oxidase, among which LDH may be mostly responsible for the oxalate production in vivo (2). Since the first two enzymes are short chain α-hydroxy acid oxidase and dehydrogenase, respectively, it is important that glyoxylate in aqueous solutions exists in a hydrated form, and is structurally similar to an α-hydroxy acid. As already stated by Richardson and Tolbert for glycolate oxidase (7), the oxalate formation from glyoxylate by glycolate oxidase and LDH may be an unnecessary occurrence, because, for both enzymes, their presence is needed for other purposes. Oxalate production from glyoxylate probably occurs as a consequence of an evolutionary limit in the development of an enzymatic site that would be specific for glycolate or lactate, and which would not attack the hydrated glyoxylate molecule of nearly similar structure. Two other enzymes known to act on glyoxylate, SPT/AGT and D-glycerate dehydrogenase/glyoxylate reductase (DGDH/GR), appear to play dual roles in the metabolism of glyoxylate and serine. In primary hyperoxaluria type 2 caused by a deficiency of DGDH/GR, for example, L-glyceric acid is produced from accumulated hydroxypyruvate, an intermediate of serine metabolism, by the action of LDH, and is excreted into urine (8).

Species-Specific Organelle Distribution of SPT/AGT

The enzyme deficient in primary hyperoxaluria type 1, SPT/AGT, is a unique enzyme of dual subcellular localization and functions. In 1978, Takada and Noguchi (9,10) found that, in carnivores and herbivores including man, it is located in mitochondria and perox-