Distinction of Dicarboxylic Aciduria Due to Medium-Chain Triglyceride Feeding From That Due to Abnormal Fatty Acid Oxidation and Fasting in Children

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Increased amounts of dicarboxylic acids are excreted in human urine under conditions of medium-chain triglyceride (MCT) feeding, abnormal fatty acid oxidation (FAO) and fasting. Criteria to distinguish dicarboxylic aciduria originating from MCT feeding and other conditions are needed in urinary organic acid profiling for detecting inborn errors of metabolism. Patterns of dicarboxylic aciduria in children under various conditions were compared. The relative amounts of medium-chain saturated dicarboxylic acids in urine are not reliable for identifying MCT-induced dicarboxylic aciduria. On the other hand, low ratios of unsaturated to saturated dicarboxylic acids (<0.1) and 3-hydroxydecenedioic to 3-hydroxydecanedioic acids were found to be useful in identifying dicarboxylic aciduria due to MCT ingestion. Additional unique features of dicarboxylic aciduria from MCT are low ratios of 3-hydroxydodecanedioic to 3-hydroxydecanedioic acid (<0.14) and 3-hydroxyadipic to adipic acid (<0.02).

DETECTION OF specific disorders in fatty acid metabolism using urinary organic acid analysis is less definitive than detection of disorders in amino acid metabolism.[1-4] Part of the reason is that the abnormal urinary organic acid profiles of patients with disordered fatty acid oxidation (FAO) may occur only during acute episodes of hypoglycemia and/or fasting. Under these conditions, plasma concentration of fatty acids increases, leading to an elevated urinary excretion of medium-chain dicarboxylic acids, a condition generally termed "nonketotic dicarboxylic aciduria." These medium-chain saturated metabolites usually include adipic (DC6), suberic (DC8), and sebacic (DC10) acids.[5]

Another problem encountered in the analysis of urinary organic acids is the distinction of dicarboxylic aciduria of dietary origin from that of abnormal fatty acid metabolism. Nonketotic dicarboxylic aciduria from medium-chain triglyceride (MCT) oil ingestion has been characterized previously by several investigators.[6-13] The pattern of relative abundance of saturated dicarboxylic acids and the appearance of medium-chain ω-1 hydroxy fatty acids in urine have been proposed as characteristic features of dicarboxylic aciduria due to MCT oil ingestion. In urine from subjects on MCT, the abundance of dicarboxylic acids has been described as DC10 > DC8 > DC6 or DC8 > DC10 > DC6, in contrast to the sequence of DC6 > DC8 > DC10 found in normal fasting subjects and patients with disorders of FAO. However, dicarboxylic aciduria resulting from deficiency of medium-chain acyl-CoA dehydrogenase (MCAD) also has the sequence of DC10 > DC8 > DC6 or DC8 > DC10 > DC6 in some cases.[6] In addition, subjects who are on MCT oil may have a normal pattern of DC6 > DC8 > DC10.[14] The present investigation was designed to establish criteria to distinguish dicarboxylic aciduria due to MCT ingestion from that due to abnormal endogenous FAO.

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SUBJECTS AND METHODS

Study Design

Urine samples were obtained from routine urinary organic acid screening for the detection of possible inborn errors of metabolism. Initially, seven subjects on MCT oil were identified by review of medical records. The ages of these hospitalized children ranged from 3 to 10 months (5 ± 2); they were on various MCT-containing formulas, which included Pregestimil (Mead Johnson), Alimentum (Ross, Columbus, OH), Portagen (Mead Johnson, Evansville, IN), and added MCT oil (Mead Johnson). Spot urine samples were collected because these subjects presented with failure to thrive or developmental delay and were screened for possible metabolic disorders. Subsequent investigation of these subjects ruled out possible defects in FAO or other identifiable metabolic defects. Age-matched subjects (n = 10; aged 6 ± 3 months; range, 1 to 10) with FAO disorders were selected on the basis of nonketotic dicarboxylic aciduria without associated MCT intake. This group of subjects includes three patients with MCAD deficiency,[15] three with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, and one with an electron transport-chain defect, as determined by enzymatic analysis or by the specific organic acid pattern; the remaining three subjects had undetermined causes of impaired FAO.[16] All of these urine samples were collected when the subjects were sick. Control fasting subjects (n = 7) previously described were between 2 and 8 years of age and were evaluated for possible hypoglycemia, which was not detected.[17] Samples were selected with significant dicarboxylic aciduria comparable to that of the other two groups, usually obtained after 24 to 36 hours of fasting. Another set of control urine samples (n = 14) used for comparison of urinary excretion of 3-hydroxybutyrate to that of the MCT group were randomly selected samples from age-matched subjects who had apparently normal urinary organic acid profiles. Data are presented as the mean ±SD.

Analysis of Urine

Urine samples (volume equivalent to 0.05 mg creatinine up to a maximum of 0.5 mL) were mixed with pentadecanoic acid (20 μg) as the internal standard; the mixture was acidified with concentrated hydrochloric acid to pH 1 and extracted with 2 mL ethyl acetate–diethyl ether (1:1) three times. The combined extract was dried and converted to trimethylsilyl derivatives by bistrimethylsilyltrifluoroacetamide containing 1% trimethylchlorosilane. A Hew-

lett-Packard (Avondale, PA) 5890A gas chromatograph with dual capillary columns was used for quantitative analysis of the derivatized samples. The columns used were a 30-m nonpolar SPB-1 (bonded dimethylpolysiloxane phase; Supelco, Bellefonte, PA) and a 30-m intermediate-polar SPB-35 (bonded 35% diphenyl:65% dimethylpolysiloxane phase; available now from Supelco only through special custom order); both columns were 0.25-mm ID and had 0.25-mm film thickness. A temperature program from 60°C to 250°C increasing at a rate of 4°C/min and a split injection ratio of 50:1 were used for the analysis. Metabolites in the urine were determined as the weight equivalent to the internal standard based on area ratios. No correction for flame ionization detector response and extraction recovery was made; however, we have determined that the detector responses and recoveries of metabolites were close to 1.[18,19] Identities of metabolites were confirmed or assigned by comparison to synthetic authentic samples as described previously for 3-hydroxyadipic acid,[18] 3-hydroxydicarboxylic acids,[16,19] and saturated and unsaturated dicarboxylic acids.[15,20,21] 5-Hydroxyhexanoic acid was confirmed by comparison to a sample synthesized from sodium borohydride reduction of acetylbutyric acid (from Aldrich, Milwaukee, WI). 7-Hydroxyoctanoic acid was assigned based on comparison of the mass spectrum to that published.[9] Confirmation of structural identities of the metabolites was made with a Hewlett-Packard 5985B gas chromatograph–mass spectrometer. Samples (trimethylsilyl derivatives) were introduced through a capillary column (SPB-1) gas chromatographic inlet with the same temperature program used for gas chromatographic analysis. The electron-impact (70 eV) mode was used to ionize the molecules.

RESULTS

Urinary Metabolites Resulting From MCT Oil

Urine samples from subjects on MCT contained saturated dicarboxylic acids (adipic, suberic, and sebacic), ω-1 hydroxy fatty acids (5-hydroxyhexanoic and 7-hydroxyoctanoic), and 3-hydroxydicarboxylic acids (3-hydroxydecanedioic and 3-hydroxyoctanedioic). These urine samples had slightly elevated 3-hydroxybutyrate (52 ± 54 mmol/mol creatinine) relative to randomly selected age-matched children without dicarboxylic aciduria or other abnormalities of urinary metabolites (22 ± 20, n = 14, $P < .05$). A typical urinary organic acid profile from a subject on MCT oil is compared with a profile from a subject with abnormal fatty acid oxidation resulting from LCHAD deficiency (Fig 1).

Saturated Dicarboxylic Acids

In all three groups of subjects (MCT, FAO disorders, and fasting controls), urinary excretion of saturated dicarboxylic acids consists mostly of adipic, suberic, and sebacic acids (Fig 2). In the MCT group, the amount ranged from 123 to 853 mmol/mol creatinine for DC6, from 119 to 1,848 for DC8, and from 54 to 6,943 for DC10. The corresponding data were 229 to 5,018, 69 to 2,639, and 82 to 1,884 for the FAO-disorders group, and 92 to 983, 45 to 326, and 7 to 59, respectively, for the fasting group. Because the absolute amount of excretion of these metabolites changed with the metabolic condition of the subjects, the ratios of metabolites proved to be the most useful parameters for comparison, as shown in Fig 2.[15,16,18] Fasting control subjects had an unequivocal profile of dicarboxylic acids generated from endogenous fatty acid metabolism; the profiles of these samples were all in the order of DC6 > DC8 > DC10 (DC6/DC8 > 1 and DC8/DC10 > 1). Samples from the FAO-disorders group mostly showed the same order as the fasting controls, but a few samples had higher DC10 than DC8, including samples from patients with MCAD deficiency. In contrast, samples from the MCT group mostly had profiles in the order of DC10 > DC8 > DC6. However, one of these samples had a ratio of DC6/DC8 of 2, and the ratio of DC8/DC10 was greater than 1 in three samples. Since there was overlap in these ratios between MCT and FAO-disorder groups, the relative amounts of these dicarboxylic acids cannot be used alone as a reliable criterion for distinguishing a possible MCT oil ingestion or disordered fatty acid metabolism.

7-Hydroxyoctanoic and 5-Hydroxyhexanoic Acids

Urinary excretion of 7-hydroxyoctanoate is normalized to excretion of adipate for comparison among the three groups (Fig 3). There was some overlap of these ratios between MCT and FAO-disorder groups. All of these samples overlapping with the MCT profile came from patients with MCAD deficiency. The fasting controls did not have detectable 7-hydroxyoctanoate. In those samples from MCT and FAO-disorder groups with detectable 7-hydroxyoctanoate, the amount of 5-hydroxyhexanoate was 5% to 40% that of 7-hydroxyoctanoate. Therefore, a large excretion of 7-hydroxyoctanoate might suggest MCT oil ingestion, but a definite conclusion can not be drawn, since FAO disorders that affect metabolism of medium-chain fatty acids, such as MCAD deficiency, may have the same profile.

Saturated 3-Hydroxydicarboxylic Acids

3-Hydroxydodecanedioate (3OHDC12), 3-hydroxydecanedioate (3OHDC10), 3-hydroxyoctanedioate (3OHDC8), and 3-hydroxyadipate (3OHDC6) were excreted in fasting controls and FAO-disorder subjects with dicarboxylic aciduria. In contrast, the MCT group excreted mainly 3OHDC10 and 3OHDC8. The ratios of 3OHDC10/3OHDC8 were the same for all three groups. However, the ratios of 3OHDC12/3OHDC10 were consistently lower for the MCT group (< 0.14) than for FAO-disorder subjects or fasting controls (Fig 3). Urinary 3-hydroxyadipic acid lactone was not elevated in the MCT group. This compound remained at a baseline level less than 2 mmol/mol creatinine. Therefore, the ratio of 3-hydroxyadipic acid lactone to adipate was less than 0.02 in all samples from the MCT group. In contrast, this ratio was 0.21 ± 0.19 in the fasting group and between 0.06 and 1.07 in the FAO-disorder group, with the lowest ratios usually from patients with MCAD deficiency and the highest ratios from patients with LCHAD deficiency.[16]

Unsaturated Dicarboxylic and 3-Hydroxydicarboxylic Acids

Urine samples from FAO-disorder and fasting groups contained unsaturated dicarboxylates that are not present in significant amounts in urine from the MCT group (Fig 4). The amounts of these unsaturated metabolites, ie, unsaturated octenedioic acids (*cis*-3, *trans*-3, and *cis*-4 isomers), unsaturated decenedioic acids (*cis*-4 and *cis*-5 isomers), and

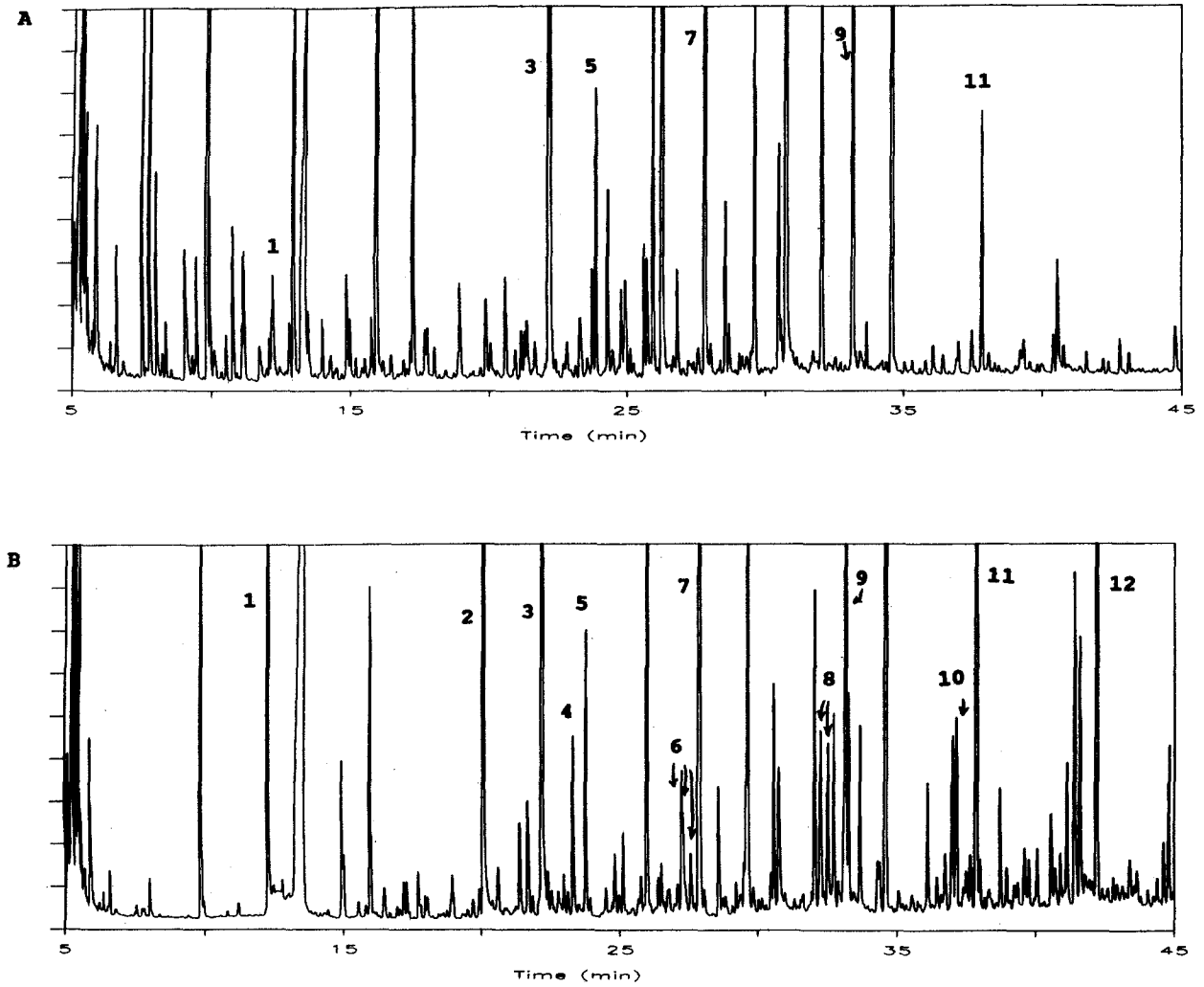

Fig 1. Urinary fatty acid metabolites from (A) MCT feeding and (B) disordered FAO (in this particular example from a child with LCHAD deficiency). (1) 3-hydroxybutyric, (2) 3-hydroxyadipic acid 3,6-lactone, (3) adipic, (4) *trans*-2-hexenedioic, (5) 7-hydroxyoctanoic, (6) octenedioic (in sequence, *cis*-3, *cis*-4, and *trans*-3), (7) suberic, (8) decenedioic (*cis*-5 and *cis*-4), (9) sebacic, (10) 3-hydroxydecenedioic, (11) 3-hydroxydecanedioic, and (12) 3-hydroxydodecanedioic acids.

unsaturated 3-hydroxydecenedioic acid (*cis*-5 isomer only), are shown normalized to their individual saturated counterparts (suberic, sebacic, and 3-hydroxydecanedioic acids, respectively). For dicarboxylic acids, the highest ratio in the MCT group was 0.014; in contrast, the lowest ratio in the other two groups was 0.24. The lowest ratio of 3-hydroxydecenedioate and 3OHDC10 for FAO-disorder and fasting groups was 0.1; in contrast, no 3-hydroxydecenedioic acid was detectable in the MCT group. Therefore, we concluded that a ratio less than 0.1 for each of these unsaturated/saturated metabolites would be indicative of MCT feeding.

Confirmation of Validity of the Recommended Criteria in Identifying Urine Samples From Subjects With MCT Ingestion

Based on these criteria of low ratios of unsaturated to saturated dicarboxylic acids, we identified from our routine urinary organic acid analysis program 41 of 693 urine samples with dicarboxylic aciduria that was characteristic of ingestion of MCT. Of these 41 samples, 31 were from 31 subjects whose hospital records were available for review. Ingestion of MCT within 24 hours before sample collection was confirmed in all of these subjects. Sources of MCT included Portagen, Pregestimil, Enfamil Premature Formula, Nutramigen, Alimentum, and supplemental MCT oil. In addition, 41 samples from 31 individuals were identified as reflecting possible defects in FAO, based on nonketotic dicarboxylic aciduria distinguished from the MCT pattern by these criteria. Review of the medical records available for 30 of these samples confirmed that none of these subjects were receiving identifiable sources of MCT during or 24 hours before the sample collection.

DISCUSSION

Recommended Criteria for Identification of Dicarboxylic Aciduria Due to Ingestion of MCT Oil

Our data show that low ratios (<0.1) of unsaturated to saturated dicarboxylic acids (both DC8 and DC10) and

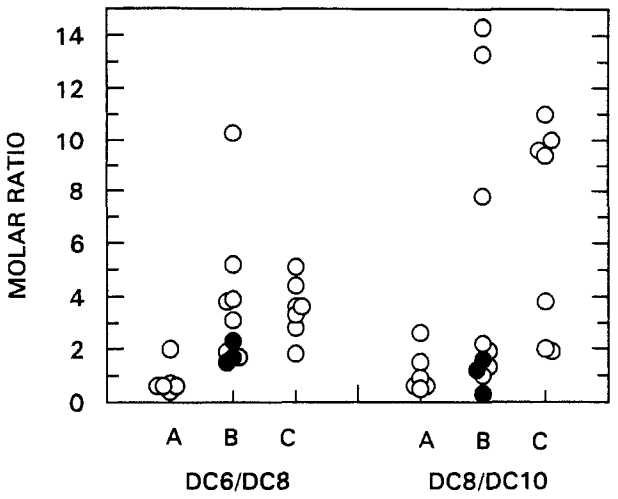

Fig 2. Relative amounts (molar ratio) of adipate to suberate (DC6/DC8) and suberate to sebacate (DC8/DC10) excreted in urine from three groups of subjects. (A) MCT feeding (n = 7; 0.8 ± 0.6 for DC6/DC8; 1.1 ± 0.8 for DC8/DC10; mean ± SD); (B) disorders of FAO (n = 10; 3.5 ± 2.7; 4.5 ± 5.3); (C) fasting (n = 7; 3.5 ± 1.1; 5.4 ± 4.1). (●) Samples from patients with MCAD deficiency.

unsaturated 3-hydroxydecenedioate to saturated 3OHDC10 are reliable criteria for identifying dicarboxylic aciduria due to MCT oil. Additional consistent criteria are a low ratio of 3OHDC12/3OHDC10 (<0.14) and the near absence of 3OHDC6 (<0.02).

Rationale for the Urinary Organic Acid Patterns in Different Groups

The characteristic urinary profile of fatty acid metabolites from MCT oil can be explained by the unique metabolic pathways of medium-chain fatty acids. MCTs used in formulas consist mainly of (saturated) decanoate (33%) and octanoate (66%).[22]

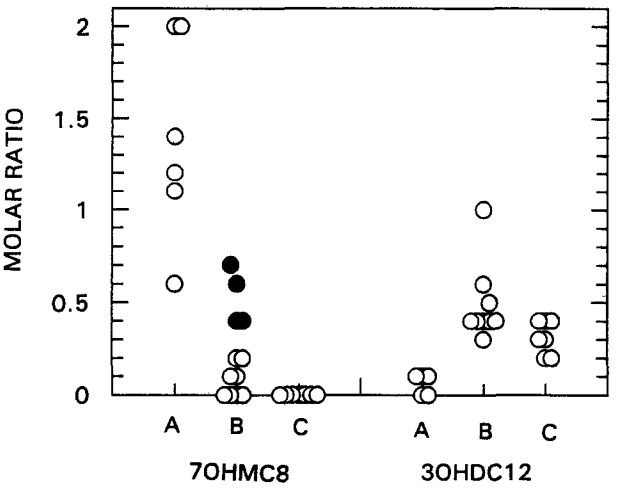

Fig 3. Relative amounts (molar ratio) of 7-hydroxyoctanoate/adipate (7OHMC8) and 3-hydroxydodecanoate/3-hydroxydecanoate (3OHDC12) excreted in urine from three groups of subjects. (A) MCT feeding; (B) disorders of FAO; (C) fasting. (●) Samples from patients with MCAD deficiency.

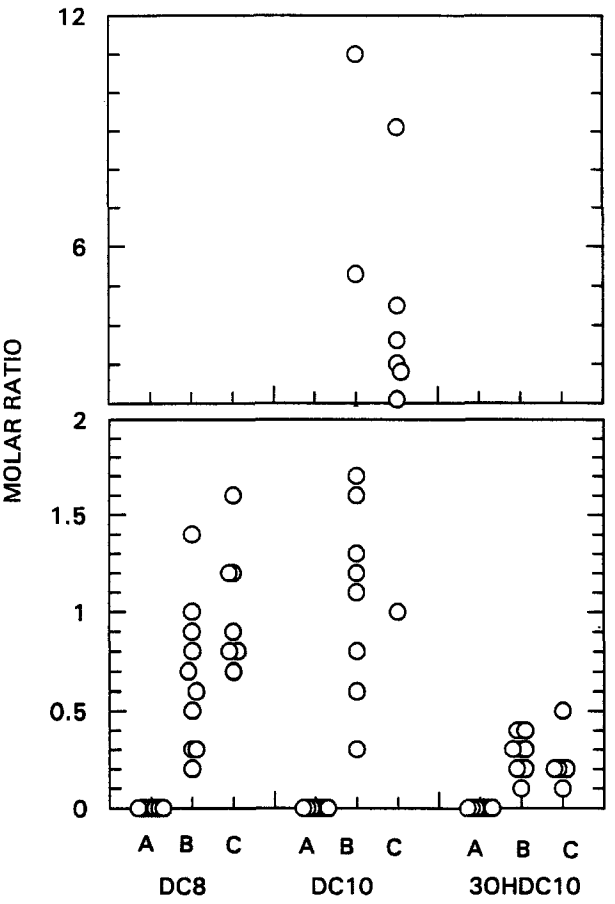

Fig 4. Ratios of unsaturated dicarboxylates and 3-hydroxydicarboxylates to their saturated counterparts in three groups of subjects. (A) MCT feeding (n = 7); (B) disorders of FAO (n = 10); (C) fasting controls (n = 7). DC8, ratios of unsaturated octenedioates (sum of *cis*-3, *cis*-4, and *trans*-3 isomers) to suberate; DC10, ratios of unsaturated decenedioates (sum of *cis*-5 and *cis*-4 isomers) to sebacate; 3OHDC10, ratios of unsaturated 3-hydroxydecenedioate (*cis*-5 isomer) to 3-hydroxydecanedioate. The absence of unsaturated dicarboxylates and 3-hydroxydicarboxylates in urine samples from the MCT group (highest ratio for these samples, 0.014) distinguishes this group from the other two groups (lowest ratio, 0.10).

Metabolism of Decanoate and Octanoate

The main route for the disposition of decanoate is β-oxidation, which releases 3-hydroxydecanoate as a result of incomplete metabolism[16] (Fig 5). 3-Hydroxydecanoate is converted to 3OHDC10 by ω-oxidation, which produces, via its CoA derivatives, 3OHDC8 through further β-oxidation. In addition, decanoate is also a good substrate for ω-oxidation, yielding sebacic acid, which is then metabolized by sequential β-oxidation to suberate and adipate.[5] The pattern of accumulation of dicarboxylic acids produced from decanoate is generally in the order of DC10 > DC8 > DC6.[23] Children with MCAD deficiency accumulate medium-chain fatty acids in plasma as a result of impaired medium-chain fatty acid oxidation.[24] The urinary saturated dicarboxylic acid profile from these patients is the closest to that resulting from MCT.[15]

Octanoate, the major component in MCT, is not a good substrate for ω-oxidation.[23,25] In addition to β-oxidation,

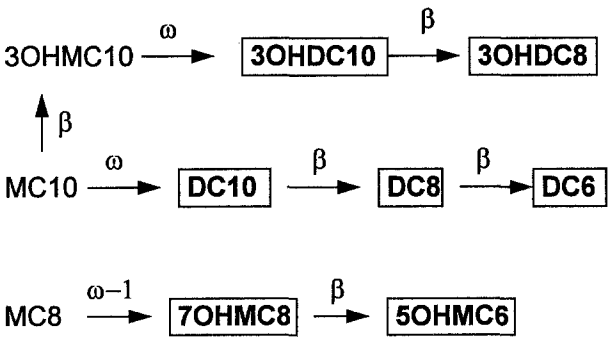

Fig 5. Schematic representation of oxidative pathways from decanoate (MC10) and octanoate (MC8) to characteristic urinary metabolites (in boxes). 3OHMC10, 3-hydroxydecanoate; 3OHDC10, 3-hydroxydecanedioate; 3OHDC8, 3-hydroxyoctanedioate; DC10, sebacate; DC8, suberate; DC6, adipate; 7OHMC8, 7-hydroxyoctanoate; 5OHMC6, 5-hydroxyhexanoate; β, β-oxidation; ω, ω-oxidation; and ω-1, ω-1 oxidation. β-Oxidation requires activation of acids to their CoA esters, which is omitted from the graph for clarity.

octanoate is oxidized by ω-1 hydroxylation to 7-hydroxyoctanoate,[23] which may be further metabolized to 5-hydroxyhexanoate via β-oxidation. Therefore, the oxidation of decanoate and octanoate from MCT yields 3OHDC10, 3OHDC8, 7-hydroxyoctanoate, and 5-hydroxyhexanoate, as well as sebacate, suberate, and adipate in urine.

Metabolism of Long-Chain Fatty Acids

In ordinary diets and standard formulas, the majority of fat is in the form of long-chain triglycerides. Long-chain fatty acids also may undergo incomplete oxidation to release 3-hydroxy fatty acids[19] and ω-oxidation to produce dicarboxylic acids.[23,26] Under conditions of fasting and defects of FAO, elevated plasma long-chain fatty acids leads to increased production, via alternate pathways, of dicarboxylates and 3-hydroxydicarboxylates.[15,16,18] In addition to saturated medium-chain dicarboxylates, urine samples from subjects under these conditions also contain 3OHDC10, 3-hydroxyadipate, 3OHDC12, and 3OHDC8 in decreasing relative amounts. 3-Hydroxyadipate is produced from β-oxidation of long-chain 3-hydroxydicarboxylates.[16] Since ingestion of MCT oil–containing formulas does not elevate plasma long-chain fatty acids, 3-hydroxyadipate and longer-chain 3OHDC12s are not produced in significant amounts in these subjects.

Unsaturated dicarboxylates and 3-hydroxydicarboxylates with *cis*-4 and *cis*-5 structures are produced from oxidation of unsaturated fatty acids, ie, oleate and linoleate.[20] Since ingestion of MCT-containing formulas does not elevate plasma long-chain unsaturated fatty acids,[27] urinary excretion of these unsaturated metabolites is not increased. Other unsaturated fatty acids with *cis*-3 and *trans*-3 structures are probably produced from metabolism of long-chain saturated fatty acids, such as palmitate and stearate, via isomerization of *trans*-2-enoyl-CoA catalyzed by isomerase.[28] Production of *cis*-3 and *trans*-3 fatty acids occurs only from long-chain substrates[29]; these long-chain unsaturated fatty acids then undergo ω- and sequential β-oxidation to *cis*-3 and *trans*-3 octenedioates. Therefore, metabolism of fatty acids derived from MCT does not produce significant amounts of *cis*-3 and *trans*-3-octenedioates.

These metabolic pathways provided a rational explanation for the empirical observations that distinguish the urine organic acid pattern associated with dietary MCT ingestion from disorders of FAO and fasting. Although the previous criteria have been generally helpful, these additional criteria proposed in the present investigation are more definite. The ready identification of dicarboxylic aciduria as due to dietary origin during urinary organic acid analysis for detection of inborn errors of metabolism can prevent false suggestion of a defect in FAO.

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