Disorders of Intermediary Metabolism

A1

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Key Facts

- The classical inborn errors of metabolism are defects in enzymes of the metabolism of amino acids, carbohydrates and fatty acids or in mitochondrial energy metabolism (Fig. A1.1).
- Disorders of intermediary metabolism are often dynamic, they fluctuate with changes in the metabolic state of the patient and frequently allow successful therapeutic intervention.
- Most disorders of intermediary metabolism are readily diagnosed through basic metabolic investigations which include blood gases, glucose, lactate, ammonia, plasma amino acids, urinary organic acids and an acylcarnitine profile.

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A1.1 Disorders of Amino Acido Metabolism

Typical aminoacidopathies result from abnormalities in the breakdown of amino acids in the cytosol. In addition, several disorders involving mitochondrial enzymes such as branched-chain ketoacid dehydrogenase (maple syrup urine disease) or ornithine aminotransferase (gyrate atrophy of the choroidea) are classified as aminoacidopathies as they do not involve CoA-activated metabolites. This distinguishes aminoacidopathies from the organic acidurias, which are considered a separate group of disorders affecting mitochondrial enzymes, CoA-activated metabolites, and which have effects on other mitochondrial functions. Clinical symptoms of the aminoacidopathies may be thought of as caused by the accumulation of toxic intermediates that cause specific organ damage. Several defects of amino acid metabolism such as histidinemia are benign because

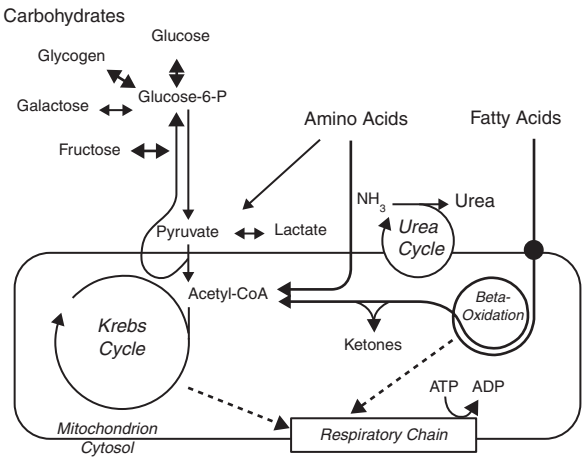

Fig. A1.1 Main pathways of intermediary metabolism

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the metabolites that accumulate are not toxic. The pathogenetic relevance of an inborn error of amino acid metabolism is not always easy to ascertain as clinical symptoms observed in the child may be coincidental or the reason for performing the analysis in the first place. Aminoacidopathies are diagnosed through the analysis of plasma (or urinary) concentrations of amino acids and sometimes of urinary organic acids. A majority is treatable through dietary restriction of protein and of the amino acid involved in the defective pathway and by the avoidance or prompt treatment of catabolic states that lead to the breakdown of large amounts of protein. Another therapeutic strategy that has been successful in hepatorenal tyrosinemia is the inhibition of a biochemical step before the actual genetic deficiency, thereby changing a harmful disease into a more benign amino acid accumulation without the accumulation of the more damaging substances downstream.

A1.2 Organic Acidurias

The classical organic acidurias are deficiencies of enzymes in the mitochondrial metabolism of CoA-activated carboxylic acids, most of which are derived from amino acid breakdown. In this way, they are distinguished from disorders of fatty acid oxidation, which not only involve CoA esters but also present different diagnostic and therapeutic challenges. The term organic acidurias is preferred to the alternative term organic acidemias as they are most often detected by analysis of the urine. Biochemically, some of the reactions impaired in the organic acidurias are parallel to the dehydrogenase, hydratase, or ketothiolase reactions of the mitochondrial β-oxidation cycle. Clinical features are caused not only by the accumulation of toxic intermediates but also by a disturbance of mitochondrial energy metabolism and carnitine homeostasis; they may include encephalopathy and episodic metabolic acidosis. Organic acidurias are diagnosed through the analysis of organic acids in the urine or acylcarnitines in the blood. Treatment is similar to that of the aminoacidopathies and involves the dietary restriction of the relevant amino acid(s) and the avoidance of protein catabolism. However, as the defective enzymes are distant (more downstream) from the respective amino acids, restriction may not lead to a stoichiometric reduction of pathological metabolites, although it does in methylmalonic aciduria. Unexpected fluctuations occur and complete return to normal intermediary metabolism is usually impossible. Supplementation with carnitine and sometimes other substances such as glycine (e.g., to form isovalerylglycine in isovaleric aciduria) are very useful adjuncts to the treatment.

Disorders of biotin metabolism are included among the organic acidurias. Biotin is a cofactor of the mitochondrial carboxylases and a deficiency of biotinidase or holocarboxylase synthetase leads to multiple carboxylase deficiency. It is also usually diagnosed through urinary organic acid analysis. Biotinidase enzyme analysis of dried blood spots has been included into programs of neonatal screening as it is well treated with biotin supplementation.

A1.3 Disorders of Ammonia Detoxification

The breakdown of protein produces large amounts of nitrogen in the form of ammonia that is highly neurotoxic but is normally converted to urea and excreted in the urine. Defects in enzymes of the urea cycle and other disorders of ammonia detoxification present clinically with encephalopathy and other symptoms of hyperammonemia. Metabolic investigations should include analysis of the amino acids in plasma and urine and urinary orotic acid. Treatment requires the reduction of protein intake in conjunction with the supplementation of essential amino acids, the avoidance of catabolic states and the administration of benzoate or phenylacetate/phenylbutyrate, which remove nitrogen in the form of alternative conjugates of amino acids such as glycine and glutamine.

A1.4 Disorders of Fatty Acid Oxidation and Ketogenesis

Mitochondrial fatty acid oxidation is required for the provision of energy during fasting, either through complete oxidation or through production of ketones in the liver that then serve as an alternative energy source for the brain. Disorders in this pathway typically present as hypoketotic hypoglycemia precipitated by

fasting, leading to coma or convulsions. In addition, some disorders cause severe hepatopathy and (cardio-) myopathy, probably as results of the accumulation of toxic metabolites. The diagnosis is best reached in the acute situation through the analysis of free fatty acids and the ketone bodies 3-hydroxybutyrate and acetoacetate as well as the acylcarnitine profile and urinary organic acids. The diagnosis may be missed if samples are obtained in the normal interval between episodes or after the patient has been treated with intravenous glucose. Treatment consists of avoidance of fasting. Carnitine supplementation is mostly unessessary and must be carefully balanced in some defects, particularly those that cause cardiomyopathy or hepatopathy.

A1.5 Disorders of Carbohydrate Metabolism and Transport

The disorders in this group display a relatively wide range of clinical features and may cause clinical symptoms because of toxicity, deficiency of energy, hypoglycemia, or storage.

- *Disorders of Galactose and Fructose Metabolism*: Defects in the cytosolic metabolism of galactose and fructose for glycolysis cause disease through accumulation of pathogenic metabolites. Children with galactosemia and fructosemia typically develop evidence of severe damage to the liver and/or kidney after dietary intake of lactose (milk, milk products) or fructose (fruit, sucrose), respectively. Treatment requires the elimination of the intake of galactose or fructose.
- *Disorders of Gluconeogenesis and Glycogen Storage*: Typical metabolic features are hypoglycemia after relatively short periods of fasting and lactic acidemia. There may be variable organ dysfunction, most frequently hepatopathy. Glycogen storage leads to hepatic enlargement, which in infancy may be massive. In some disorders such as glycogenosis type III there are elevations of the transaminases and creatine phosphate kinase, and there may be clinical myopathy. Treatment includes frequent meals, cornstarch supplementation, or continuous overnight tube feeding to avoid hypoglycemia.
- *Disorders of Carbohydrate Transport*: There are a number of different glucose and other carbohydrate carriers, and clinical symptoms differ greatly depending on the tissue localization of the individual defect. Symptoms are frequently gastrointestinal or renal but also include the central nervous system (deficient glucose transport across the blood/brain barrier).

A1.6 Mitochondrial Disorders

Disorders of energy metabolism (usually summarized as mitochondrial disorders although enzymes deficient, e.g., in organic acidurias or fatty acid oxidation defects are also located in the mitochondrion) include genetic defects of the pyruvate dehydrogenase complex, the Krebs cycle and the respiratory electron transport chain, comprising the final pathways of substrate breakdown and the production of ATP. Mitochondrial disorders manifest clinically with symptoms and signs of energy deficiency and a highly variable pattern of organ dysfunctions. In many cases, there are lactic acidemia and progressive neurodegenerative disease. Periods of metabolic stress such as intercurrent infections may trigger a deterioration of the patient's condition. The diagnostic work-up may be difficult and should include frequent measurements of blood lactate levels, CSF lactate, plasma amino acids and alanine, and often a search for mutations in mitochondrial DNA. Repeated, careful examinations of organ functions as well as imaging are essential. Treatment options are limited but usually include various vitamins and cofactors such as riboflavin, coenzyme Q, or thiamine. Heterozygous mutations in the genes of some Krebs cycle enzymes (e.g., fumarase) cause inherited cancer predisposition syndromes.

A1.7 Disorders of Cobalamine and Folate Metabolism

Genetically determined or nutritional deficiencies of vitamin cofactors may affect various metabolic pathways and cause a wide range of clinical symptoms. They can frequently be satisfactorily treated by supplementation of the deficient substance. Of particular importance in intermediary metabolism are cobalamin (vitamin B_{12}) and folate which are essential for cytosolic methyl group transfer. The cellular methylation reactions require methyl group transfer from serine to *S*-adenosylmethionine involving the folate cycle,

cobalamin (vitamin B_{12}) and the methionine–homocysteine cycle. A disturbance in this pathway may be caused by methylcobalamin deficiency, a disturbance of the folate cycle, or by deficient remethylation of homocysteine to methionine. Most disorders of cobalamin metabolism as well as nutritional deficiency of vitamin B_{12} cause methylmalonic aciduria. Clinically, disorders of cytosolic methyl group transfer cause an encephaloneuropathy, often with additional hematological problems such as megaloblastic anemia and thrombembolic complications of hyperhomocysteinemia. The diagnosis involves the analysis of urinary organic acids, plasma amino acids (homocysteine), and levels of folate and cobalamin. Treatment includes supplementation of cobalamin and folate, in some situations with addition of betain and methionine.

A1.8 Disorders of Amino Acid Transport

Deficiencies in the intestinal and/or renal transport of amino acids may be nonsymptomatic or cause symptoms because of deficient absorption of essential amino acids (e.g., tryptophan in Hartnup disease) or because of increased urinary concentration of unsoluble amino acids which causes nephrolithiasis (e.g., cystein in cystinuria). These disorders are diagnosed by the quantitative analysis of amino acids in plasma and urine. Treatment depends on the clinical picture. Deficiency of essential amino acids is treated by supplementation with large amounts of these compounds, or in the case of tryptophan deficiency, supply of the cofactor nicotinic acid that is normally synthesized from tryptophan. Renal calculi in cystinuria can be prevented by treatment with a chelating agent such as penicillamine, which forms mixed disulfides with cysteine, and calculi once formed can be resorbed if they have not incorporated too much calcium.

A1.9 Disorders of Peptide Metabolism

- The tripeptide *glutathione* and the *gammaglutamyl cycle* have multiple functions in cellular metabolism, ranging from amino acid transport across membranes to detoxification of peroxides. Deficiencies may cause neurological and hematological as well as metabolic problems. Investigations should include the determination of organic acids in the urine and glutathione in various body fluids. Treatment is largely symptomatic; certain drugs should be avoided.
- Defective breakdown of *dipeptides* of histidine such as homocarnosine or carnosine may be found in patients with mental retardation, although the causative relationship is not always proven. Ulcers of the skin, particularly of the legs are seen in prolidase deficiency. Investigations should include amino acid and peptide analysis of the urine. Treatment is symptomatic; some individuals with disorders of dipeptide metabolism are asymptomatic and do not require treatment.

A1.10 Disorders of the Transport or Utilization of Copper, Iron, and Zinc

- *Disorders of copper metabolism*: Wilson disease causes a chronic hepatopathy and symptoms of central nervous dysfunction, while patients with Menke disease suffer from neurological problems in conjunction with abnormalities of hair, connective tissue, and bones. Diagnosis involves the analysis of copper and coeruloplasmin in serum, urine, and liver tissue. Treatment in Wilson disease is aimed at reducing copper load, while copper should be parenterally substituted in Menke disease.
- *Disorders of iron metabolism*: Patients affected with such disorders may present with iron-deficient anemia, e.g., due to insufficient intestinal absorption of iron, or with iron overload and liver dysfunction as in hemochromatosis. Secondary iron overload may be observed in some hemolytic anemias. Treatment is directed at substitution or removal of iron.
- *Disorders of zinc metabolism*: Acrodermatitis enteropathica is characterized by chronic skin problems, alopecia, and central nervous symptoms. It is diagnosed through reduced levels of zinc and alkaline phosphatase and is treated with supplementation of zinc.