Disorders of Proline and Serine Metabolism

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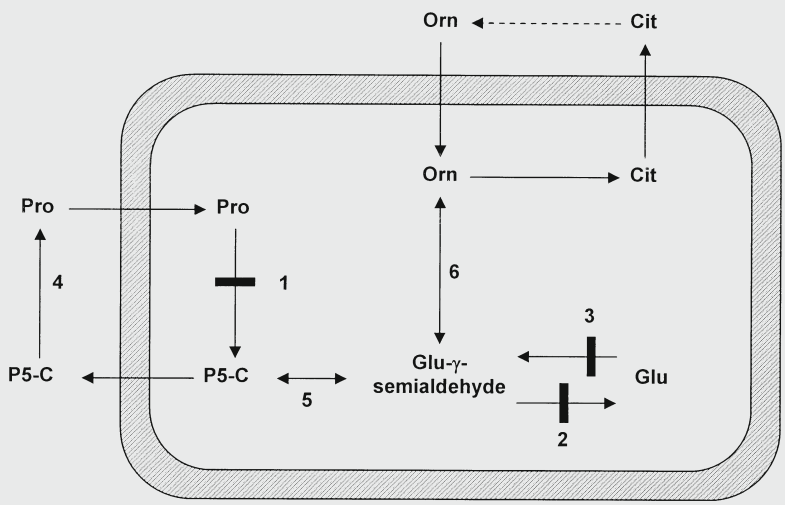
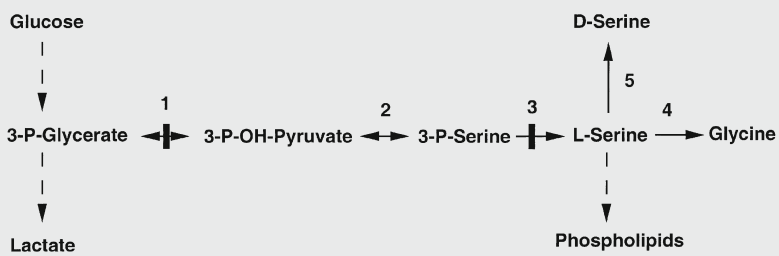
Proline and Serine Metabolism

Proline and serine are non-essential amino acids. Unlike all other amino acids (except hydroxyproline), **proline** has no primary amino group (it is termed an imino acid) and uses, as a consequence, a specific system of enzymes for its metabolism (◘ Fig. 25.1). Δ^1-Pyrroline 5-carboxylate (P5-C) is both the immediate precursor and the degradation product of proline. The P5-C/proline cycle transfers reducing/oxidising potential between cellular organelles. Owing to its pyrrolidine ring, proline (together with hydroxyproline) contributes to the structural stability of proteins, particularly collagen, with its high proline and hydroxyproline content.

Serine also has important functions besides its role in protein synthesis. It is a precursor of a number of compounds (partly illustrated in ◘ Fig. 25.2), including D-serine, glycine, cysteine, serine phospholipids, sphingomyelins and cerebrosides. Moreover, it is a major source of N^5,N^{10}-methylene-tetrahydrofolate (THF) and of other one-carbon donors that are required for the synthesis of purines and thymidine. Serine is synthesised de novo from a glycolytic intermediate, 3-phosphoglycerate, and can also be synthesised from glycine by reversal of the reaction catalysed by serine hydroxymethyltransferase, which thereby converts N^5,N^{10}-methylene-THF to THF (◘ Fig. 24.1).



◘ **Fig. 25.1.** Proline metabolism. *Shaded area* represents mitochondrial membrane. *Cit,* citrulline; *Glu,* glutamine; *Orn,* ornithine; *Pro,* proline; *P5-C,* Δ^1-pyrroline 5-carboxylate. **1**, Proline oxidase (deficient in hyperprolinaemia type 1); **2**, P5-C dehydrogenase (deficient in hyperprolinaemia type 2); **3**, P5-C synthase (deficient in P5-C synthase deficiency) **4**, P5-C reductase (deficient in P5-C reductase deficiency) **5**, nonenzymatic reaction; **6**, ornithine aminotransferase (deficient in gyrate atrophy). *Bars* across *arrows* indicate defects of proline metabolism



◘ **Fig. 25.2.** Pathway of de novo serine synthesis. *P,* Phosphate. **1**, 3-phosphoglycerate dehydrogenase; **2**, 3-phosphohydroxypyruvate transaminase; **3**, 3-phosphoserine phosphatase; **4**, serine hydroxymethyltransferase (utilises tetrahydrofolate); **5**, serine racemase. Glycine is synthesised from serine, but also from other sources. *Bars* across *arrows* indicate the known defects in serine synthesis

Four disorders of **proline** metabolism are known: two in its catabolism (hyperprolinaemia type I, which is due to proline oxidase deficiency, and hyperprolinaemia type II, which is due to Δ^1-pyrroline 5-carboxylate dehydrogenase deficiency) and two in its synthesis (Δ1-pyrroline 5-carboxylate synthase deficiency and Δ^1-pyrroline 5-carboxylate reductase deficiency). Hyperprolinaemia type I is generally considered a nondisease, while hyperprolinaemia type II appears to be associated with a disposition to recurrent seizures. The deficiency of the proline-synthesising enzyme, Δ^1-pyrroline 5-carboxylate synthase, which is also involved in ornithine synthesis, is described in ► Chapter 22.

Five disorders of **serine** metabolism are known. Three are in its biosynthesis: 3-phosphoglycerate dehydrogenase deficiency, phosphoserine aminotransferase deficiency and phosphoserine phosphatase deficiency. Patients with 3-phosphoglycerate dehydrogenase deficiency have congenital microcephaly, psychomotor retardation and intractable seizures and are partially responsive to L-serine or L-serine and glycine. One patient with an association of Williams syndrome and phosphoserine phosphatase deficiency has been reported. Another, unexplained, serine disorder has been reported in a patient with decreased serine in body fluids, ichthyosis and polyneuropathy but no central nervous system manifestations. There was a spectacular response to L-serine. Recently, hereditary sensory neuropathy type 1 has been found to be associated with mutations of serine palmitoyltransferase, the initial step in the **de novo** synthesis of sphingolipids.

25.1 Inborn Errors of Proline Metabolism

25.1.1 Proline Oxidase Deficiency (Hyperprolinaemia Type I)

- **Clinical Presentation**

Hyperprolinaemia type I is a very rare disorder; it is generally considered a benign trait, but recent work suggests that it may be associated with a subset of schizophrenic patients [1-4].

- **Metabolic Derangement**

Hyperprolinaemia type I is caused by a deficiency of proline oxidase (a mitochondrial inner-membrane enzyme), which catalyses the conversion of proline into P5-C (◘ Fig. 25.1, enzyme 1). Hence, in hyperprolinaemia type I, there are increased levels of proline in plasma (usually not above 2000 μM; normal range 100-450 μM), urine and cerebrospinal fluid (CSF). Hyperprolinaemia (as high as 1000 μM) is also observed as a secondary phenomenon in hyperlactataemia, possibly because proline oxidase is inhibited by lactic acid. Remarkably, and in contrast to hyperprolinaemia type II, heterozygotes have hyperprolinaemia.

- **Genetics**

The mode of inheritance is autosomal recessive. *PRODH*, the gene encoding proline oxidase, maps to 22q11, in the region deleted in the velocardiofacial syndrome/DiGeorge syndrome. At least 16 missense mutations have been identified [4, 5].

- **Diagnostic Tests**

The diagnosis is made by amino acid analysis. Direct enzyme assay is not possible, since the enzyme is not present in leukocytes or skin fibroblasts. Mutation analysis is thus necessary to confirm the diagnosis [4].

- **Treatment and Prognosis**

Since the prognosis is generally excellent, dietary treatment is not indicated.

25.1.2 Δ^1-Pyrroline 5-Carboxylate Dehydrogenase Deficiency (Hyperprolinaemia Type II)

- **Clinical Presentation**

This is a relatively benign disorder, though a predisposition to recurrent seizures is highly likely [2].

- **Metabolic Derangement**

Hyperprolinaemia type II is caused by a deficiency of pyrroline 5-carboxylate (P5-C) dehydrogenase, a mitochondrial inner-membrane enzyme involved in the conversion of proline into glutamate (◘ Fig. 25.1, enzyme 2). Hence, in hyperprolinaemia type II there are increased levels of proline in plasma (usually exceeding 2000 μM; normal range 100-450 μM), urine and CSF, as well as of P5-C. Heterozygotes do not have hyperprolinaemia. Evidence has been presented that the accumulating P5-C is a vitamin B_6 antagonist (owing due to adduct formation) and that the seizures in this disorder may be due at least in part to vitamin B_6 inactivation [6, 7].

- **Genetics**

This is an autosomal recessive disease. The gene *ALDH4A1* maps to 1p36. Mutations have recently been reported in four patients (two frame shift mutations and two missense mutations) [8].

- **Diagnostic Tests**

The accumulation of P5-C in physiological fluids is used to differentiate between type II and type I hyperproli-

naemia. This compound can be qualitatively identified by its reactivity with ortho-aminobenzaldehyde and can be quantitatively measured by several specific assays [2]. P5-C dehydrogenase activity can be measured in skin fibroblasts and leukocytes.

▪ Treatment and Prognosis

The benign character of the disorder does not justify dietary treatment (which, in any case, would be very difficult). Seizures are B_6 responsive.

25.1.3 Δ^1-Pyrroline 5-Carboxylate Reductase Deficiency

▪ Clinical Presentation

Forty patients from 24 families have been reported [9, 10]. They showed a cutis laxa type 2 syndrome comprising intrauterine growth retardation, progeroid appearance (wrinkly loose skin most prominent over the dorsum of the hands and feet, and craniofacial dysmorphy), joint laxity, psychomotor retardation, hernias, osteopenia, and less consistent features such as cataracts and athetoid movements. This disorder resembles pyrroline 5-carboxylate synthase deficiency, the other disorder of the proline synthesis pathway, but the latter disorder shows a more severe neurological phenotype.

25.2 Inborn Errors of Serine Metabolism

25.2.1 3-Phosphoglycerate Dehydrogenase Deficiency

▪ Clinical Presentation

At least nine patients belonging to four families are known with this disease, which was first reported in 1996 [11, 12]. They presented at birth with microcephaly and developed pronounced psychomotor retardation, severe spastic tetraplegia, nystagmus and intractable seizures (including hypsarrhythmia).

In addition, one patient showed congenital bilateral cataract, two siblings, growth retardation and hypogonadism, and two other siblings, megaloblastic anaemia. Magnetic resonance imaging of the brain revealed cortical and subcortical atrophy and evidence of disturbed myelination.

Recently, a much milder phenotype has been reported in two siblings [13]. Absence seizures occurred after the ages of 5 and 9 years, and there was moderate psychomotor retardation without microcephaly.

▪ Metabolic Derangement

The deficiency of 3-phosphoglycerate dehydrogenase, the first step of serine biosynthesis (◘ Fig. 25.2, enzyme 1), causes decreased concentrations of serine and, to a lesser extent, of glycine in CSF and in fasting plasma. Serine thus becomes an essential amino acid in these patients. A significant accumulation of the substrate, 3-phosphoglycerate, is unlikely since it is an intermediate of the glycolytic pathway. Therefore, the deficiency of brain serine seems to be the main determinant of the disease. Serine plays a major role in the synthesis of important brain and myelin constituents, such as proteins, glycine, cysteine, serine phospholipids, sphingomyelins and cerebrosides.

In the two patients with megaloblastic anaemia, decreased methyltetrahydrofolate was found in CSF. This can be explained by the fact that serine is converted to glycine by a reaction that forms methylenetetrahydrofolate (◘ Fig. 24.1), which is further reduced to methyltetrahydrofolate (► Chapter 28).

▪ Genetics

This is an autosomal recessive disease. The gene for 3-phosphoglycerate dehydrogenase has been mapped to 1q12. Several mutations have been identified [12, 14]. Prenatal diagnosis is only possible by mutation analysis, as there is a lack of data on enzyme activity in chorionic villi and amniocytes [15].

▪ Diagnostic Tests

The diagnosis should be suspected in patients with encephalopathy who have congenital microcephaly. Plasma amino acids must be measured in the fasting state (range for serine in patients: 28-64 μM; normal range: 70-187 μM), since serine and glycine levels can be normal after feeding. In CSF, serine levels are always decreased (6-8 μM; control range 35-80 μM), as are glycine levels, albeit to a lesser extent. The diagnosis is confirmed by finding deficient activity of 3-phosphoglycerate dehydrogenase in fibroblasts (reported residual activities of 6-22%). In patients with the milder juvenile phenotype, the metabolite and enzymatic findings were indistinguishable from those in patients with the severe phenotype [13].

▪ Treatment and Prognosis

Treatment with L-serine has a beneficial effect on the convulsions, spasticity, feeding and behaviour. Oral L-serine treatment (up to 600 mg/kg/day in six divided doses) corrected the biochemical abnormalities in all reported patients and abolished the convulsions in most patients, even in those in whom many anti-epileptic treatment regimens had failed previously. During treatment with L-serine, a marked increase in the white matter volume was

observed, and in some patients a progression of myelination [16]. In two patients, convulsions stopped only after glycine (200 mg/kg/day) was added.

In a girl diagnosed prenatally, because of decelerating head growth, L-serine was given to the mother at 190 mg/kg/day in three divided doses from week 27 of gestation. This normalised fetal head growth, and with subsequent postnatal therapy the girl showed normal psychomotor development at the age of 3 years [15].

Patients with the milder phenotype have been diagnosed as teenagers and responded favourably to low dosages of L-serine therapy [13].

25.2.2 Phosphoserine Aminotransferase Deficiency

This disorder has been reported in a brother and sister, who showed decreased concentrations of serine and glycine in plasma and CSF [17]. The index patient presented with intractable seizures, acquired microcephaly, hypertonia and psychomotor retardation, and died at the age of 7 months despite supplementation with serine (500 mg/kg/day) and glycine (200 mg/kg/day) from the age of 7 weeks. The younger sibling received treatment from birth, which led to a normal outcome at the age of 3 years. Enzyme activity measured in cultured fibroblasts was inconclusive, but mutation analysis revealed compound heterozygosity in *PSAT1* in both children.

25.2.3 Phosphoserine Phosphatase Deficiency

Decreased serine levels were found in plasma (53-80 μM; normal range 70-187 μM) and CSF (18 μM; control range 27-57 μM) of one patient with Williams syndrome [18]. Phosphoserine phosphatase activity in lymphoblasts and fibroblasts amounted to about 25% of normal (◘ Fig. 25.2, enzyme 3). Oral serine normalised plasma and CSF levels of this amino acid and seemed to have some beneficial clinical effect. The gene was mapped to 7p11, and the patient was found to be a compound heterozygote for two missense mutations, excluding a link with Williams syndrome [19].

25.2.4 Serine Deficiency with Ichthyosis and Polyneuropathy

A remarkable new serine deficiency syndrome has been discovered by De Klerk et al. [20] in a 15-year-old girl. She had ichthyosis from the 1st year of life and growth retardation from the age of 6 years, and presented at the age of 14 years with walking difficulties and areflexia, symptoms of an axonal polyneuropathy. Psychomotor development and magnetic resonance imaging of the brain were normal. Fasting plasma and CSF serine levels were decreased, but the CSF glycine level slightly increased. Oral ingestion of serine (400 mg/kg/day) cured the skin lesions and the polyneuropathy. It is hypothesised that this patient exhibits increased conversion of serine into glycine, possibly owing to hyperactivity of serine hydroxymethyltransferase (◘ Fig. 25.2, enzyme 4).

25.2.5 Serine Palmitoyltransferase Defects

They cause the most frequent subtype of hereditary sensory and autonomic neuropathy, HSAN type 1 (HSAN1), an autosomal dominant disease. The disorder has been shown to be caused by mutations in the *SPTLC* genes, encoding three subunits of serine palmitoyltransferase (SPT), the first step in the de novo synthesis of sphingolipids (► Chapter 37).

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