**REVIEW ARTICLE**

**L-Serine in disease and development**

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The amino acid L-serine, one of the so-called non-essential amino acids, plays a central role in cellular proliferation. L-Serine is the predominant source of one-carbon groups for the de novo synthesis of purine nucleotides and deoxythymidine monophosphate. It has long been recognized that, in cell cultures, L-serine is a conditional essential amino acid, because it cannot be synthesized in sufficient quantities to meet the cellular demands for its utilization. In recent years, L-serine and the products of its metabolism have been recognized not only to be essential for cell proliferation, but also to be necessary for specific functions in the central nervous system. The findings of altered levels of serine and glycine in patients with psychiatric disorders and the severe neurological abnormalities in patients with defects of L-serine synthesis underscore the importance of L-serine in brain development and function. This paper reviews these recent insights into the role of L-serine and the pathways of L-serine utilization in disease and during development, in particular of the central nervous system.

Key words: amino acids, brain, disease, glycine, d-serine, L-serine.

**HISTORICAL OVERVIEW**

Cramer [1] first discovered the amino acid serine in 1865 by analysing the contents of raw silk. He found that at least two proteins were present in silk; one was silk fibroin and the other, a gelatinous material, he called serecine. By further analysing the latter material, Cramer discovered a new substance that was either L-amino-β-hydroxypropionic acid or L-hydroxy-β-amino-propionic acid, and he gave this new substance the name serine. Many years later, in 1902, Fischer and Leuchs [2] clarified the structure of serine as 2-amino-3-hydroxypropionic acid. At first only the racemic mixture of D- and L-serine could be isolated by hydrolysis of different protein sources, but Fischer finally isolated the optically active L-isomer in 1907 [3]. It was very cumbersome to isolate L-serine from protein hydrolysates, and it was not until 1942 that Bergmann and colleagues [4] developed a relatively simple procedure for the isolation of L-serine (for a detailed historical overview of the isolation of serine, see [5]).

In that same year, Rose, Haines and Johnson [6] reported their first nutritional data on the amino acid requirements of human subjects. Previously, so-called dispensable and indispensable amino acids had been studied by evaluating growth in laboratory animals fed with synthetic amino acid combinations. Rose and colleagues investigated the nitrogen balance in healthy volunteers and the neuromodulators glycine and L-serine, and the neuromodulators glycine and D-serine.

**L-SERINE BIOSYNTHESIS**

L-Serine may be derived from four possible sources: dietary intake; biosynthesis from the glycolytic intermediate 3-phosphoglycerate; from glycine; and by protein and phospholipid degradation. Few data are available on the relative contributions of each of these four sources of L-serine to serine homoeostasis. It is very likely that the predominant source of L-serine will be very different in different tissues and during different stages of human development. For instance, the majority of L-serine synthesized by the foetal liver is from glycine via the combined action of the glycine cleavage system and serine hydroxymethyltransferase (SHMT) [11]. By contrast, the kidney synthesizes most of its L-serine from 3-phosphoglycerate [12].

Historically, two possible pathways of L-serine synthesis have been identified: a ‘phosphorylated’ pathway, involving 3-phos-
phosphoglycerate, phosphohydroxypyruvate, l-serine and l-serine, and a ‘non-phosphorylated’ pathway [13,14]. The latter pathway involves d-glycerate, hydroxypyruvate and l-serine. Rowsell et al. [15] and Cheung et al. [16] suggested simultaneously in 1969 that the non-phosphorylated pathway is not a synthetic pathway, but rather is involved in its reverse direction in gluconeogenesis, and that the phosphorylated pathway is the primary route for l-serine biosynthesis. Indeed, it was shown that the phosphorylated pathway plays no role in gluconeogenesis, because of irreversibility of the final step, the dephosphorylation of phosphoserine [17]. Consistent with this view is the presence of the enzymes of the phosphorylated pathway in many tissues, whereas the enzymes of the non-phosphorylated pathway are restricted to liver and kidney [18].

In the biosynthetic pathway, the glycolytic intermediate 3-phosphoglycerate is converted into phosphohydroxypyruvate, in a reaction catalysed by 3-phosphoglycerate dehydrogenase (3-PGDH; EC 1.1.1.95) (Scheme 1). Phosphohydroxypyruvate is metabolized to phosphoserine by phosphohydroxypyruvate aminotransferase (EC 2.6.1.52) and, finally, phosphoserine is converted into l-serine by phosphoserine phosphatase (PSP; EC 3.1.3.3) (Scheme 1).

In liver tissue, the serine biosynthetic pathway is regulated in response to dietary and hormonal changes. Of the three synthetic enzymes, the properties of 3-PGDH and PSP are the best documented. The activity of rat liver 3-PGDH and, to a lesser degree, of PSP is inversely related to the protein content of the rat diet. The activity of both enzymes is low on a high-protein/low-carbohydrate diet, and that of 3-PGDH is high on a low-protein/high-carbohydrate diet [18]. The sulphur-containing amino acids methionine and cysteine play an important role in mediating the effects of protein on 3-PGDH activity [19,20]. Hormonal factors such as glucagon and corticosteroids also influence 3-PGDH and PSP activities in interactions dependent upon the animal’s diet [18]. In tissues other than the liver, no such relationship between dietary intake and enzyme activity exists [18]. The flux through the serine biosynthetic pathway in rat and rabbit liver is regulated at the level of PSP, the irreversible and rate-limiting step in serine biosynthesis [21]. In contrast with ‘classical’ feedback, this amino acid biosynthetic pathway is regulated at its final step and is thus controlled by the cellular demand for the serine product. For instance, the enzymes of the serine biosynthesis pathway are up-regulated in rapidly proliferating tissues, such as neoplastic tissues, to meet the cellular demands for increased l-serine utilization [22]. According to some authors, the role of PSP is not limited to simply supplying precursors, but, in parallel with the function of other housekeeping genes in carcinogenesis, a role for PSP in endometrial carcinogenesis has been suggested [23]. Strunck et al. [23] suggested that the up-regulation of PSP in an in vitro model of endometrial adenocarcinoma was possibly related to the formation of phospholipids involved in signal transduction, as well as providing building blocks for peptide synthesis.

Enzymes of the serine biosynthetic pathway are present in many organs and tissues, in addition to the liver. High activities of these enzymes are present in kidney, testis, spleen and brain, whereas low activities are found in skeletal and heart muscle [18]. It has been shown that up-regulation of 3-PGDH takes place at the level of mRNA transcription, and that the down-regulatory effect of the sulphur amino acid cysteine involves mRNA destabilization [20,24]. Interestingly, studies of 3-PGDH mRNA expression in human tissues showed the presence of different transcripts in tissues known to have a high or low enzyme activity [25]. Although little is known about the relative quantitative contributions of the different sources of l-serine in different tissues, the data suggest that, in tissues with a high activity of the synthetic enzymes, biosynthesis via 3-phosphoglycerate is likely to represent an important supply of l-serine.

L-SERINE UTILIZATION

Although l-serine has a well recognized central role in cellular proliferation, multiple pathways of l-serine utilization are present, and these pathways do not relate only to the supply of
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Scheme 2  Pathways of human L-serine utilization

Enzyme systems are as follows: I, 'non-phosphorylated' serine pathway, involved in gluconeogenesis; the formation of hydroxypyruvate is catalysed by SPT/AGT; II, glyoxylate pathway; III, d-serine and pyruvate formation via d/L-serine racemase; IV, SHMT; V, glycine cleavage system; VI, transmethylation pathway of methionine metabolism; VII, trans-sulphuration pathway of methionine metabolism; VIII, formation of phosphoglycerols from L-serine and cytidine diphosphodiacylglycerol; IX, formation of sphingolipids; sphingosine is synthesized from L-serine and palmitoyl-CoA. Direct formation of pyruvate by SDH does not appear to play a role in human metabolism (indicated by ?). MTHF, methylenetetrahydrofolate.

nucleotide precursors. The various pathways of L-serine utilization are discussed below.

L-Serine and gluconeogenesis

In mammals, two pathways are involved in gluconeogenesis from L-serine. One involves the direct formation of pyruvate from L-serine by serine dehydratase (SDH; EC 4.2.1.13) (Scheme 2). The other pathway involves the formation of hydroxypyruvate by serine:pyruvate/alanine:glyoxylate aminotransferase (SPT/AGT; EC 2.6.1.51) (Scheme 2). Considerable differences exist between species in the relative contributions of these two gluconeogenic pathways, depending upon the dietary composition of the food consumed by the animals. Furthermore, SPT/AGT displays a species-specific organelle distribution; it is localized in mitochondria in carnivores, whereas it is present in peroxisomes in herbivores and humans, and in both organelles in rodents. In rodents the flux through SDH appears to be the major gluconeogenic route [26], whereas in dogs the predominant pathway appears to be through the aminotransferase [27]. In human liver SPT/AGT seems dominant, and in fact SDH does not appear to play a role in human metabolism [27]. The main role of SDH and SPT/AGT may be in the disposal of serine and glycine as the metabolic exits for spillover from these amino acid pools [26]. Notwithstanding the particular route involved, data from amino acid balance studies across the cannulated liver showed that serine is a net contributor to hepatic gluconeogenesis, but is of lesser significance than alanine and glutamine [28,29].

An important exception to these observations might be the brain. In a recent report by de Miranda et al. [30], the formation of pyruvate via D/L-serine racemase has been reported, linking the serine pathway to cellular energy metabolism.

The formation of hydroxypyruvate by SPT/AGT is the first step of the biosynthetic pathway of glyoxylate formation, and this step is impaired in hyperoxaluria type 1. Hydroxypyruvate cannot be converted into D-glycerate in hyperoxaluria type 2, and finally D-glycerate cannot be phosphorylated in D-glycerate kinase deficiency [31,32]. Consequently, L-serine may potentially aggravate the biochemical and clinical symptoms of these three inborn errors of metabolism.

SMHT

The pathway of L-serine catabolism initiated by SMHT is the major source of one-carbon groups, providing formyl groups for purine synthesis and methyl groups for pyrimidine synthesis, the remethylation of homocysteine and many other methylation
reactions involved in cellular homeostasis. SHMT (EC 2.1.2.1) catalyses the formation of glycine from serine, thereby generating 5,10-methylene-tetrahydrofolate (Scheme 2). Two isoenzymes of SHMT exist: a mitochondrial enzyme (mSHMT) and a cytosolic enzyme (cSHMT). The reversible l-serine-to-glycine interconversion by the different isoenzymes plays a role in maintaining the intracellular concentrations of one-carbon groups in the different cellular compartments. The exchange of l-serine, glycine and formate through the mitochondrial membrane is likely to be the main pathway for the equilibrium of intramitochondrial one-carbon groups such as 5,10-methylene-tetrahydrofolate, and l-serine, glycine and formate are the key metabolites in this transfer [33,34]. The two isoenzymes mSHMT and cSHMT have distinctive functions. Although the literature is not conclusive, it appears that in mitochondria l-serine is the major donor of one-carbon groups via mSHMT [35], whereas in the cytosol, cSHMT is involved in the supply of one-carbon units for thymidylate synthesis and is an important regulator of S-adenosylmethionine synthesis [36].

In neoplastic tissues, the serine synthetic enzymes and SHMT are significantly up-regulated [22]. Moreover, the gluconeogenic pathways of serine utilization are absent from these tissues, and this couples serine synthesis directly to nucleotide precursor formation in cancer cells. Therefore this area of the metabolic biochemistry of cancer cells is a potential target for anti-cancer therapy, either by antagonizing the pyridoxal phosphate cofactor or by direct inhibition of SHMT [37–39].

L-Serine and cystathionine formation

The l-serine utilization pathway through SHMT produces 5,10-methylene-tetrahydrofolate which, after reduction, yields 5-methyl-tetrahydrofolate, the methyl donor for the remethylation of homocysteine to methionine. However, l-serine itself plays a direct and essential role in the trans-sulphuration pathway, because it is required for the synthesis of cysteine, and subsequently taurine and sulphate. Homocysteine and l-serine combine to form cystathionine, catalysed by the enzyme cystathionine β-synthase (EC 4.2.1.22) (Scheme 2). This enzyme is deficient in classical homocystinuria. Surprisingly, the levels of serine and glycine are low in the cerebrospinal fluid (CSF), but not in the plasma, of untreated patients with classical homocystinuria, indicating either a compensatory decrease in l-serine synthesis or an increased utilization in brain tissue in this disorder [40]. The fact that the sulphur-containing amino acids are important in the hepatic regulation of serine synthesis suggests that low plasma levels of serine and glycine might be expected [20]. This was not the case, and the regulatory mechanisms causing the low serine and glycine CSF concentrations remain unclear. Plasma serine is only deficient in homocystinuria patients treated with folates, and this is thought to be secondary to the treatment via an increased flux through folate-dependent pathways [41].

Two products of l-serine metabolism, cysteine and glycine, are precursors for the synthesis of glutathione. Insufficient availability of glutathione causes haemolytic anaemia and neurological abnormalities in patients with defects in glutathione synthesis, as well as reduced cell survival in vitro. The symptoms and changes observed in cell cultures may also relate to increased demands for glutathione that cannot be met [42–46]. Lastly, taurine and sulphate can be considered as end-products of the trans-sulphuration pathway. Both of these metabolites have important functions in brain tissue. Multiple functions of the amino acid taurine are known in the central nervous system. Taurine is an inhibitory neurotransmitter, displays trophic functions on neuronal cells and is an important osmoregulator [47,48]. Depletion of taurine results in reduced migration of neurons [49]. Sulphate is an important component of complex molecules, such as glycosphingolipids and steroid hormones. A decreased availability of sulphate that occurs in the inborn error of metabolism sulphite oxidase deficiency may be related to the severe neurological symptoms observed in this disorder [50].

L-Serine and phospholipid synthesis

As well as having a central role in the synthesis of phosphoglycerols and complex macromolecules such as sphingolipids and glycolipids. The phosphoglycerol phosphatidylserine is synthesized from l-serine and cytidine diphosphodiacylglycerol (CDP-diacylglycerol) (Scheme 2), and can be converted into phosphatidylcholine via phosphatidyl-ethanolamine. Phosphatidylserine is an important lipid messenger and a key molecule in the apoptosis signalling pathway [51]. The backbone of sphingolipids, sphingosine, is synthesized from l-serine and palmitoyl-CoA (Scheme 2). Sphingosine can be converted into ceramide, the precursor of sphingomyelin and gangliosides. These l-serine-derived sphingolipids are important membrane components and myelin constituents, and play a role in cellular differentiation, proliferation and apoptosis [52]. The role of the release of ceramide from phospholipids by the action of sphingomyelinases in determining cell fate is well established, and this source of ceramide is probably very important in cellular signalling [53,54]. Caveolae and sphingolipid-rich domains respond to cellular responses to stress by recruiting sphingomyelinases, and thus induce the localized production of ceramide [55]. The actions of ceramide include permeabilization of lipid bilayers leading to vesicle aggregation and fusion, as well as reorganization of caveolae into active signalling compartments. These roles of ceramide in cellular signalling were reviewed recently by Kolesnick and co-workers [55,56]. Moreover, cells with null mutations in serine palmitoyl-transferase (EC 2.3.1.50), which catalyses the first step in the synthetic pathway of sphingosine, are not viable, indicating an essential role for ceramide synthesis from l-serine in cell survival [57,58]. Impaired neuronal survival and increased apoptosis were also observed in cerebellar Purkinje cells in culture when ceramide synthesis was inhibited [59].

The l-serine-derived sphingolipids play important roles in the central nervous system, and several inborn errors of metabolism due to disturbed sphingolipid breakdown are known. Patients suffering from these conditions are affected by progressive neurological deterioration [60]. At present, no human metabolic disorder involving the biosynthesis of l-serine-derived phospholipids has been reported; however, in patients with a defect in l-serine synthesis due to 3-PGDH deficiency, severe abnormalities of the cerebral white matter are present which may well relate to altered phospholipid metabolism [61].

L-Serine and formation of the neuromodulators D-serine and glycine

The formation of glycine from l-serine is an important reaction; not only does it result in the transfer of a one-carbon group to folates, but also the glycine itself has important functions, particularly in the central nervous system. Glycine is a well recognized inhibitory neurotransmitter, as well as an N-methyl-D-aspartate (NMDA) receptor co-agonist [62]. The neuromodulator D-serine appears to be an even more potent NMDA receptor co-agonist [63]. Recently a D/l-serine racemase has
been reported, thereby linking the formation of two important neuromodulators, glycine and D-serine, to L-serine catabolism (Scheme 2) [64–66].

With the description of a D/L-serine racemase, observations made by Krebs in 1935 [67] finally fell into place. He reported the presence of a D-amino acid oxidase (EC 1.4.3.3) in brain tissue. At present, new and exciting observations link the synthesis of D-serine to pyruvate synthesis. De Miranda et al. [30] reported the production of pyruvate in brain tissue via D/L-serine racemase. These findings relate the L-serine pathway and the synthesis of a D-amino acid to energy production in astrocytes. The role of pyruvate synthesis in the astrocyte, or its role in astrocyte–neuron interaction, needs to be determined.

Deficiencies of glycine and D-serine may be involved in the seizures observed in patients with 3-PGDH deficiency, as supplementation with L-serine and glycine in such patients ameliorates their seizures [68]. The role of L-serine metabolism in relation to the neuromodulators glycine and D-serine is discussed in more detail below.

**L-SERINE IN DEVELOPMENT, PARTICULARLY OF THE CENTRAL NERVOUS SYSTEM**

The metabolism of the amino acids L-serine and glycine during foetal development appears to be somewhat different from that of other amino acids, because the foetus synthesizes the majority of these two amino acids itself. The transport of both serine and glycine from the mother to the foetus seems to be limited. In foetal sheep neither serine nor glycine is transported across the placenta in significant amounts from mother to foetus [69,70]. This observation was confirmed for glycine in human pregnancies [71]. A shuttle appears to exist between the foetal placenta and the foetal liver. In *in vitro* studies in sheep showed that the foetal placenta produces significant amounts of glycine, and that this is used in the foetal liver to produce serine [69,70,72]. The enzymes of the serine biosynthetic pathway have a very high activity in the foetal liver, which decreases in the perinatal period, followed by a further fall to attain the low adult values. Observations by others suggest that L-serine formation via 3-phosphoglycerate is of importance in foetal serine production at this developmental stage [18,73]. This hepatic serine production during foetal life probably reflects the role of the serine pathway in providing precursors for DNA and RNA synthesis for cellular proliferation. A dysfunction of the foetal serine-to-glycine interconversion has been proposed in intrauterine growth retardation, where low foetal plasma serine and glycine concentrations have been observed [74,75].

Serine concentrations are high in all body fluids in early foetal development (measured by standard amino acid analysis and thus comprising both D- and L-serine). However, once a blood–brain barrier has been established, differences in serine concentrations between plasma and the CSF emerge [76]. It is very likely that, when a blood–brain barrier is present, the brain has to rely on its own synthesis of L-serine. The affinity of the neutral amino acid transporter for the transport of serine and glycine across the blood–brain barrier is low [77]. The presence of a serine synthesis pathway in brain tissue was established a long time ago [78]. 3-PGDH is highly expressed in foetal tissues, including brain tissue [25]. This means that, although plasma serine concentrations are high and the liver synthesizes significant amounts of L-serine, L-serine is also synthesized *de novo* in many tissues. Data from *in situ* hybridization of 3-PGDH during development of the central nervous system showed a very strong expression of 3-PGDH mRNA during early foetal development, especially in the ventricular and subventricular zones of the foetal brain (T. J. de Koning, O. Heinonen, L. W. J. Klomp, B. T. Poll-The, R. Surtees and A. J. Copp, unpublished work). Again, this probably relates to the fact that the ventricular and subventricular zones are tissues with a high rate of cell proliferation. Impairment of neuronal proliferation in early foetal life has been associated with microcephaly [80]. It is not unlikely that impairment of neuronal proliferation is related to the development of microcephaly observed in patients with a defect in serine biosynthesis (T. J. de Koning, O. Heinonen, L. W. J. Klomp, B. T. Poll-The, R. Surtees and A. J. Copp, unpublished work).

The role of L-serine in the central nervous system is not restricted to providing nucleotide precursors required for cell proliferation. Savoca et al. [81] showed that L-serine itself clearly had trophic effects on neurons in culture. They demonstrated that the addition of L-serine in physiological concentrations had a marked effect on dendritogenesis and axon length in these cells, whereas these effects were not observed when D-serine or glycine was added to the cultures. These observations have been confirmed by others in later experiments [82,83].

The metabolism of the L-serine-derived neuromodulators glycine and D-serine is similar to that of glutamate, being restricted to glial cells [83–86]; T. J. de Koning, O. Heinonen, L. W. J. Klomp, B. T. Poll-The, R. Surtees and A. J. Copp, unpublished work). These cells clearly provide the microenvironment for optimal neuronal development and neuronal functioning, and it is likely that L-serine homeoeostasis plays a pivotal role in maintaining this optimal microenvironment. A model describing how astrocytes and neurons interact and how D-serine is released by astrocytes was proposed by Snyder and Kim [87]. They suggested that glutamate not only binds to the NMDA receptor complex, but also triggers the release of D-serine from nearby astrocytes via activation of non-NMDA receptors. Subsequently, both glutamate and D-serine will activate the post-synaptic NMDA receptor complex.

Of the two neuromodulators glycine and D-serine, the role of glycine in neurotransmission has long been known. It is the major inhibitory neurotransmitter in the spinal cord and brain stem, and its functions include the regulation of locomotor behaviour [88]. Recently, the importance of glycine and the activation of glycine receptors during foetal brain development was established, and a function in cellular signalling for neuronal development and the maturation of synapses has been suggested [88].

Both glycine and D-serine are obligatory co-agonists of the NMDA receptor complex. Activation of the NMDA receptor complex is important during the development of the foetal brain [89]. However, little information is available on the presence and concentrations of D-serine during brain development. In human foetal brain tissue, concentrations appear to be high in the frontal cortex throughout foetal development, and become lower after birth [90]. At present, it is not clear from the literature whether D-serine is present during human development in organs other than the brain. The presence of D-serine was established in rodent tissues, where it was shown that D-serine is present almost exclusively in brain tissue, with low concentrations being observed in kidney and testis [91].

Although both D-serine and glycine are ligands for NMDA receptors, regional differences in their concentrations occur, and in postnatal rodent brain different developmental ‘profiles’ are found in the forebrain and cerebellum [85,92]. For instance, D-serine co-localizes with the NR2A/B NMDA receptor subtype in distinct areas of the brain, and in most areas with a high immunoreactivity for D-serine a low immunoreactivity for glycine is observed, and vice versa [92]. Not only are D-serine and glycine distributed unevenly throughout the brain, they also have...
distinct developmental profiles during postnatal development of the cerebellum. In the rat, d-serine concentrations in the cerebellum are high at birth and decline with age, whereas glycine concentrations rise with age, and in the adult cerebellum the main neurotransmitter appears to be glycine [92].

Interestingly, in some areas of the rat brain both d-serine and glycine are present at high concentrations. In the olfactory bulb a high immunoreactivity for both d-serine and glycine was demonstrated [92]. 3-PGDH is highly expressed in the olfactory bulb as well, indicating that extensive biosynthesis takes place (T. J. de Koning, O. Heinonen, L. W. J. Klomp, B. T. Poll-The, R. Surtees and A. J. Copp, unpublished work). The functions of l-serine, d-serine and glycine in the olfactory bulb remain to be elucidated.

Not only do astrocytes metabolize l-serine, it is likely that these cells release a significant amount of the l-serine synthesized to supply neurons with the necessary precursors for phospholipid synthesis. Neurons in culture use exogenous l-serine for the synthesis of l-serine-derived phospholipids. The biosynthesis of these phospholipids is severely decreased in the absence of l-serine or glycine [93].

Taken together, the important roles of l-serine and l-serine-derived neuromodulators in neurotransmission and phospholipid synthesis during foetal and postnatal development require that the synthetic and catabolic pathways of l-serine are tightly regulated. To date, sparse data are available on the regulation of these pathways in different cell types [94–96].

It will be clear from these observations that the synthesis and metabolism of l-serine are important in foetal development, especially of the foetal brain, and that these pathways will have specific roles in brain function. Therefore one will expect serious brain dysfunction when the l-serine biosynthesis pathway or pathways of l-serine catabolism are compromised or altered.

L-SERINE AND DISEASE
Disorders of amino acid catabolism are among the most frequent inborn errors of metabolism in humans, and have been recognized for many years. The clinical phenotypes are variable, but are often accompanied by extensive neurological dysfunction, illustrated by the natural history of untreated patients with phenylketonuria [97]. The hallmark of the biochemical diagnosis of these aminoacidopathies is the detection of characteristic metabolites accumulating in body fluids. No such inborn errors of l-serine catabolism resulting in markedly elevated serine concentrations have been identified. This is in contrast with errors of glycine catabolism, of which non-ketotic hyperglycinenaemia is a severe neurodegenerative disorder associated with intractable seizures due to a defect of the glycine cleavage system, accompanied by very high glycine concentrations in CSF and plasma [98]. However, moderately elevated serine and glycine concentrations have been associated with schizophrenia, indicating altered serine/glycine metabolism and pointing towards a specific genetic defect in some families [99]. More recently, the first disorders of serine biosynthesis were reported in human disease [100]. These patients were severely affected with neurological symptoms, and once again illustrate the importance of the serine biosynthesis pathway for brain development and function.

Serine and glycine in psychiatric disorders
Elevations in the plasma levels and urinary excretion of serine and glycine have been reported in patients suffering from schizophrenia and psychosis [101–103]. Subsequent studies showed the plasma activity of SHMT to be low, and serine and glycine concentrations to be elevated in some brain areas, in schizophrenic patients. A lowered SHMT activity was observed in the temporal lobes of schizophrenic patients [99,104,105]. Unfortunately, in these studies no discrimination was made between the enzyme activity of the different SHMT isoforms, but the above findings suggested an alteration in the regulation or specific activity of SHMT [106]. Animal models have been generated to study these interesting observations in more detail [107].

However, this area is controversial. The findings of abnormal concentrations of serine and glycine associated with psychiatric disorders have not been confirmed by other studies [108,109]. An alternative hypothesis for the biological origin of these disorders is exactly the opposite, namely that hypofunction of the glutamatergic system and NMDA receptors may exist. Stimulation of the NMDA receptors with glycine, d-serine or d-cycloserine may thus be beneficial to patients with schizophrenia [110–112].

In any event, the psychiatric disorders in which serine and glycine metabolism have been investigated are likely to be heterogeneous in their pathogenesis. To resolve the causative role of the amino acids, more detailed information on the regulation of the pathways involved and the specific activity of particular enzymes, as well as a better understanding of the biological functions of l-serine, d-serine and glycine, are necessary. A recent breakthrough in this area of research again points towards involvement of the NMDA receptor complex and d-serine in patients with schizophrenia. Chumakov et al. [113] observed a genetic association between schizophrenia and d-amino acid oxidase in a large series of patients, suggesting that the NMDA receptor pathway plays a role in this disorder.

Serine deficiency disorders
Jaeken et al. [100,114] were the first to report disorders of l-serine synthesis in patients with neurological symptoms. In contrast with the disorders of amino acid catabolism, these patients were identified because of very low concentrations of serine and glycine in plasma and CSF. Two disorders of serine biosynthesis have been reported so far: 3-PGDH deficiency and PSP deficiency.

3-PGDH-deficient patients suffer from serious neurological symptoms, such as congenital microcephaly, seizures and severe psychomotor retardation [114]. Magnetic resonance imaging of the brains of patients with 3-PGDH deficiency shows a characteristic attenuation of white matter volume and hypomyelination [61]. The seizures do respond to oral treatment with high dosages of l-serine alone or in combination with glycine [68,114,115]. Long-term follow-up of these patients showed that not all patients remained free of seizures, and that the outcome is likely to be much better if the disorder is diagnosed and treated early in life [116].

The diagnosis can be made relatively easily by analysing plasma and/or CSF amino acid levels in the fasting state, where low concentrations of serine and glycine will be detected. The biochemical abnormalities are more pronounced in CSF than in plasma, and for this reason CSF analysis is preferable, whereas urine analysis has no value. 3-PGDH deficiency can be confirmed in cultured skin fibroblasts. Recently, genetic defects have been identified in patients with 3-PGDH deficiency; so far, only missense mutations in the C-terminal region of the gene have been identified [25]. Expression studies and expression of a mutant protein lacking the last 209 amino acids of the C-terminal region demonstrated considerable residual enzyme activity, a finding similar to that in fibroblasts from patients [25,117]. These data suggest that the mutations observed in patients to date are
relatively mild. One may speculate that mutant proteins with less residual activity might not be compatible with life.

The second disorder of serine biosynthesis, PSP deficiency, has only been reported in a single patient [118]. This boy, who also suffered from Williams syndrome, had low CSF serine levels, but the deficiency was less pronounced than what is usually observed in 3-PGDH deficiency. A deficiency of PSP activity was detected in skin fibroblasts, and a favourable response to treatment with l-serine was reported.

Finally, there is another interesting case report of a patient with serine deficiency of unknown cause [119]. The patient was a girl with a progressive polyneuropathy combined with ichthyosis, growth retardation and delayed puberty. However, the activities of the three l-serine biosynthetic enzymes were normal in cultured skin fibroblasts, and the basic defect remains to be resolved. Nevertheless, treatment with l-serine resulted in an impressive improvement in muscle strength, and the girl's ichthyosis also resolved.

Not only have patients with low serine concentrations been reported, but also a patient with glycine deficiency has been described recently, and it is very likely that further disorders of amino acid synthesis will be discovered [120]. The existence of these serine and glycine deficiency disorders underscores the need for careful evaluation of amino acid concentrations in body fluids in patients with disorders of the central nervous system. It is clear from the disorders discussed above that when amino acids in body fluids are investigated, low concentrations are equally as important as elevated concentrations.

CONCLUSIONS
Almost 150 years have passed since the discovery of the amino acid serine. Although many of its functions in the human have been unravelled, a complete understanding of the effects of an excess or a deficiency of serine is still far away. Its undisputed role in cerebral function warrants continued research into the excess or a deficiency of serine is still far away. Its undisputed role in cerebral function warrants continued research into the effects of an excess or a deficiency of serine.

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