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CYSTEINE, ITS METABOLISM AND TOXICITY

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The complex and confusing intermediary metabolism of the sulfur-containing amino acid, cysteine, has been unravelled and succinctly reviewed. Its pathways of synthesis and breakdown in mammals have been closely examined and a balanced account presented. Additionally, the deleterious effects arising from the presence of too little or too much cysteine within the cell have been discussed.

Keywords: Cysteine; cystine; cysteinesulfinic acid; metabolism; toxicity

CONTENTS

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1. INTRODUCTION

L-Cysteine (2-amino-3-mercaptopropionic acid) is a thiol containing amino acid imperative to the growth and function of all living organisms. Over a hundred years ago, cysteine was obtained by reduction of crude cystine preparations, thereby demonstrating that cystine was a dimer and establishing cysteine as a compound in its own right.[1] Up until the 1940's, L-cysteine was considered to be an essential dietary amino acid in mammals. However, it was later concluded that this was not the case.[2] Microorganisms and plants are able to synthesise L-cysteine in a two step reaction involving the *O*-acetylation of serine with coenzyme A, followed by displacement of the acetyl group with inorganic sulfide. In comparison, animals obtain L-cysteine exogenously from the diet, through the breakdown of proteins or, alternatively, synthesis *de novo* via methionine transsulfuration. Thus, by definition, and in contrast to the essential sulfur amino acid methionine, L-cysteine is a non-essential amino acid in animals.

What must be considered is the implication that L-cysteine will remain a non-essential amino acid as long as dietary methionine intake sufficiently meets total sulfur amino acid needs. If this is not achieved L-cysteine can become an 'acquired indispensable' amino acid. It has been demonstrated that L-cysteine can supplement fifty percent of the total dietary sulfur amino acid requirement of growing dogs[3] and that a third of the methionine requirement of the growing rat can be satisfied by L-cysteine.[4] However, the picture is not quite so simple and it has been concluded that L-cysteine is an essential amino acid for the human foetus presumably owing to the lack of development of enzymes necessary for methionine transsulfuration.[5]

2. BIOSYNTHESIS OF L-CYSTEINE

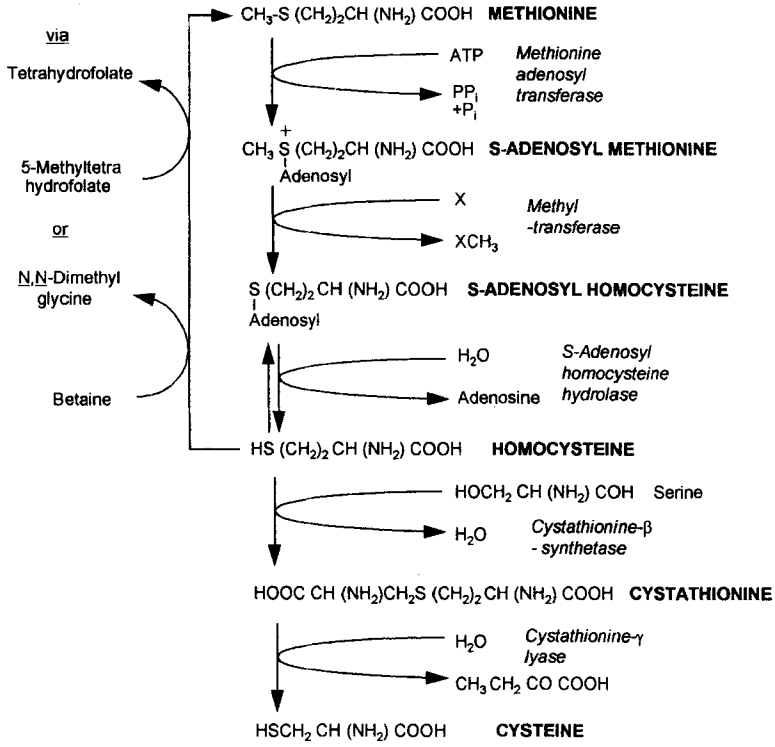
A number of classical studies have established that during synthesis the carbon skeleton and nitrogen of the L-cysteine molecule were derived from serine and that the sulfur was transferred from methionine.[6] Earlier reviews on methionine emphasise this transsulfuration as its major route of metabolism[7,8] but more recently importance has also been placed on the transamination pathway.[9,10]

Although the formation of L-cysteine via transsulfuration, and its further metabolism, could supply a metabolic route for methionine, the transsulfu-

ration pathway exhibits the characteristics of a biosynthetic rather than catabolic pathway. The transsulfuration pathway has a relatively high requisite for metabolic energy and the initial rate limiting step has low activity. Transsulfuration may not be the major catabolic pathway it was once thought to be, but it can be said that the synthesis of L-cysteine is one of the most important metabolic fates of methionine. This is implied by a number of observations. L-Cysteine is able to replace a substantial portion of dietary methionine on a nearly equimolar basis[3,4,11,12] and the incorporation of methionine sulfur into L-cysteine precedes its incorporation into cysteinyl residues of proteins and glutathione.

The first step of the transsulfuration pathway is the formation of *S*-adenosylmethionine (Scheme 1), a high energy sulfonium compound. Methionine adenosyl transferase catalyses the transfer of an adenosyl moiety from adenosine triphosphate (ATP) to the sulfur atom of methionine. The methyl group of *S*-adenosylmethionine is transferred to a nitrogen, oxygen or sulfur atom of a wide range of acceptor molecules; biological methylations catalysed by methyltransferases. The co-product of such transmethylations is *S*-adenosylhomocysteine which is subsequently hydrolysed to yield homocysteine and adenosine. This reaction is catalysed by *S*-adenosylhomocysteine hydrolase and is reversible. Equilibrium of the enzyme favours *S*-adenosylhomocysteine, thus proper flux through the cycle is dependent upon the maintenance of low *in vivo* homocysteine and adenosine concentrations. After the formation of homocysteine a branch point in the pathway occurs with homocysteine either being remethylated back to methionine or irreversibly condensed with serine to form cystathionine. Homocysteine and methionine are readily interconvertible and remethylation of homocysteine completes what is referred to as the 'methionine cycle' of transmethylation (Scheme 1), this branch point being a regulatory locus where methionine levels can be controlled to a fine degree.[13]

Transsulfuration proper begins with condensation of homocysteine, catalysed by cystathionine β-synthetase to produce cystathionine (Scheme 2). Cystathionine β-synthetase is activated by *S*-adenosylmethionine,[14] and it has been demonstrated that supplementation of a low methionine diet with L-cysteine results in less hepatic cystathionine β-synthetase activity.[15] Possible explanations for this include less activation of cystathionine β-synthetase by *S*-adenosylmethionine, or a primary effect in which L-cysteine alters the utilisation of methionine at the level of protein syn-

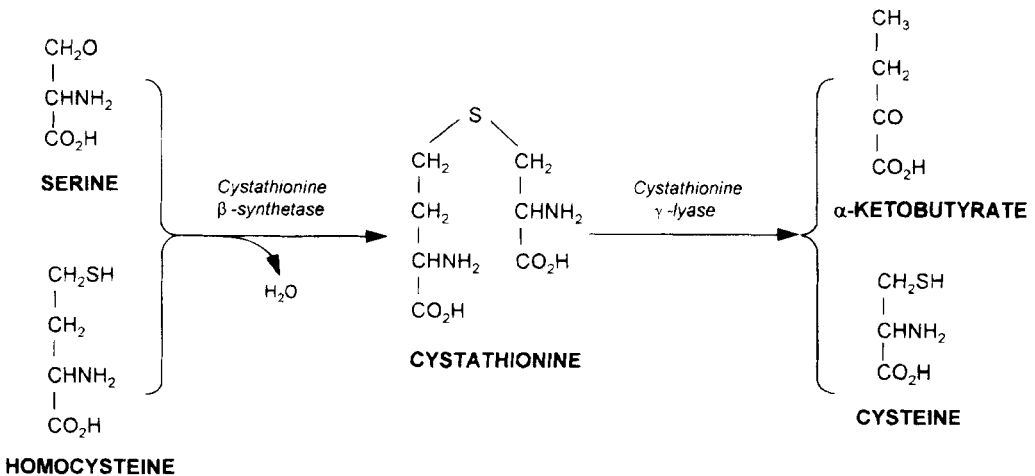


SCHEME 1 Biosynthesis of cysteine. The transsulfuration-transmethylation pathway of methionine in mammals, incorporating the 'methionine cycle'.

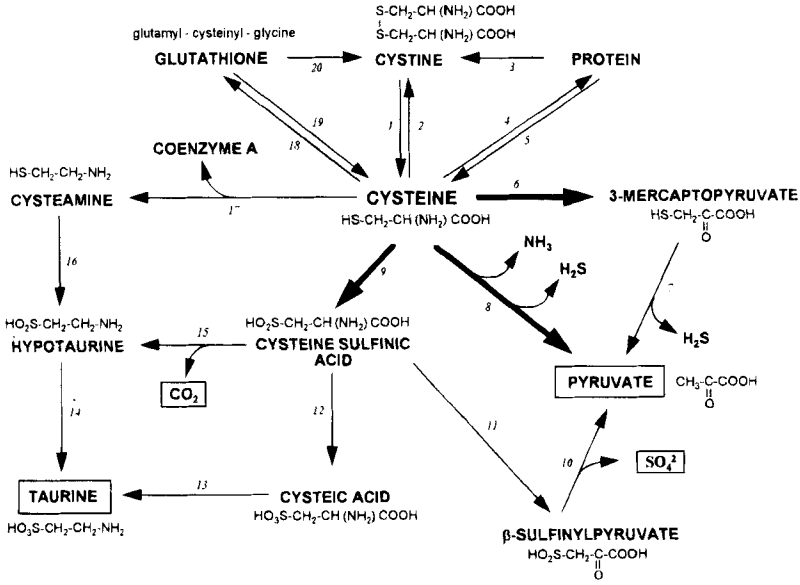
thesis.[16] The final step is the formation of L-cysteine and α-ketobutyrate by γ-cleavage of cystathionine. The enzyme responsible for catalysing this reaction is cystathionine γ-lyase (γ-cystathionase); its action is reversible and cystathionine can be synthesised from L-cysteine and homoserine (Scheme 2).

3. BREAKDOWN OF L-CYSTEINE

The intermediary metabolism of L-cysteine is complex. L-Cysteine participates in a wide variety of reactions and pathways leading to at least a dozen intermediates and end products (Scheme 3). Some of these metabolic pathways are well understood, whilst others remain somewhat of an



SCHEME 2 Mammalian transsulfuration. The sulfur atom of homocysteine is transferred to cysteine and the carbon skeleton to α-ketobutyrate. The carbon skeleton and nitrogen atoms of cysteine are derived from serine. Cystathionine β-synthetase catalyses an irreversible step, whilst cystathionine γ-lyase catalyses a reversible reaction.



SCHEME 3 Mammalian cysteine metabolism. Bold arrows represent the principle catalytic pathways of cysteine catabolism. Taurine, carbon dioxide, pyruvate and sulfate are boxed in order to emphasise that they are the major catalytic products of cysteine. The numbers refer to the enzyme or metabolic process corresponding to that particular reaction, as described.

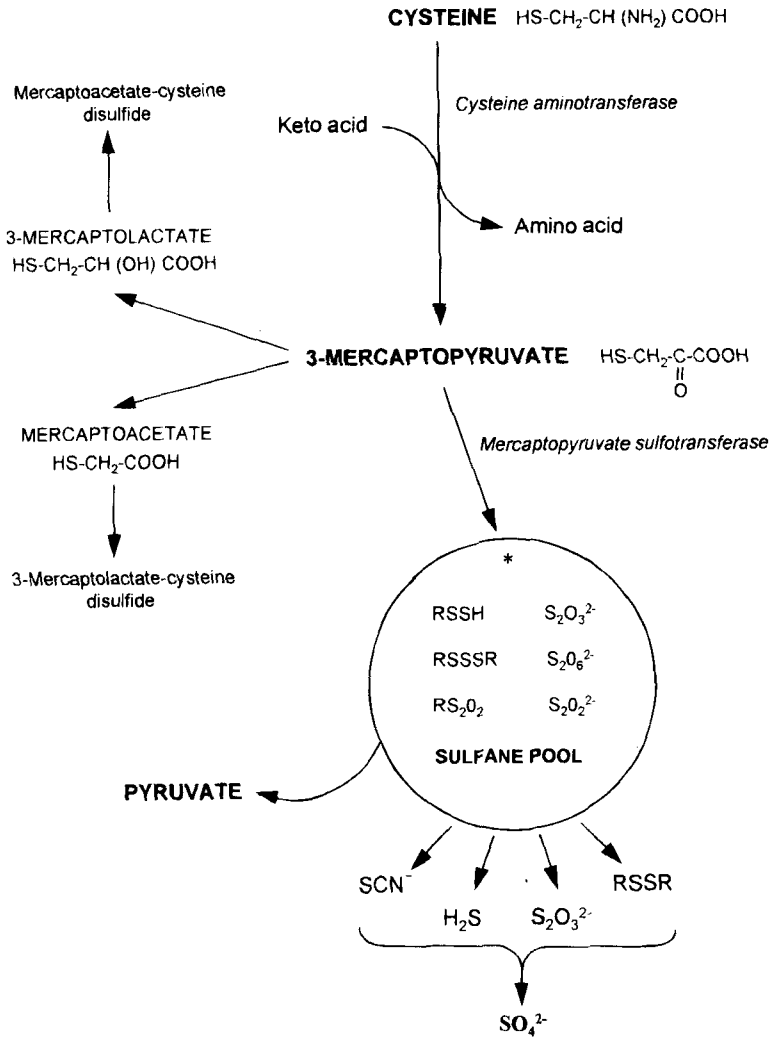
Reaction Number	Enzyme or Metabolic Process
1	Thiol oxidase or autoxidation
2	Enzymatic or non-enzymatic transhydrogenations
3	Disulfide bond formation
4	Ribosomal protein synthesis
5	Protein degradation
6	Cysteine transaminase
7	3-Mercaptopyruvate sulfotransferase
8	γ-Cystathionase
9	Cysteine dioxygenase
10	Spontaneous reaction
11	Aspartate aminotranferase
12	Non-enzymatic reaction
13	Cysteine sulfinic acid decarboxylase
14	Hypotaurine dehydrogenase
15	Cysteine sulfinic acid decarboxylase
16	Cysteamine dioxygenase
17	Coenzyme A biosynthesis and catabolism
18	Glutathione synthesis
19	γ-Glutamyl transpeptidase
20	Oxidation of glutathione followed by enzymatic cleavage

enigma. Although a pathway may be quantitatively minor this does not confer functional minority and until the physiological/biochemical roles of such pathways and their intermediary products are known they must be regarded as potentially important. Despite this complexity, the major catabolic products of L-cysteine are taurine, carbon dioxide, sulfate and pyruvate. These products arise from the currently considered principal reaction pathways, formally initiated by transamination (3-mercaptopyruvate pathway), desulfhydration, decarboxylation (cysteamine pathway) and oxidation (cysteine-sulfinic acid pathway).

Early work on the relative importance of these pathways indicated that the major catabolic route was the *S*-oxidation of L-cysteine through the cysteinesulfinic acid pathway. Experiments carried out on intact male rats suggested that 70–80% of L-cysteine catabolism leads to the formation of taurine via this route.[17,18] Recently, however, work has been undertaken which intimates the importance of L-cysteine catabolism pathways not involving cysteinesulfinic acid and reports have been published demonstrating that less than 10% of L-cysteine degradation in isolated rat hepatocytes leads to the formation of taurine.[19,20] It is unclear whether the discrepancies in the literature are a result of false assumptions or whether metabolism in rat hepatocytes is not representative of the whole animal. However, what is clear is that the roles of various pathways need to be further elucidated.

3.1. The 3-Mercaptopyruvate Pathway

L-Cysteine undergoes transamination with oxoglutarate, yielding 3-mercaptopyruvate. This reaction is mediated by a pyridoxal phosphate-dependent enzyme and takes place in the mitochondria. Several transaminases able to utilise L-cysteine have been isolated from mammalian tissues and much of the evidence attributes cysteine transaminase activity to that of aspartate transaminase, despite its high K_m value (22 mM) for L-cysteine. 3-Mercaptopyruvate then undergoes desulfuration to form pyruvate and a reduced sulfur species, whilst in the presence of glutathione, hydrogen sulfide is formed. This reaction is catalysed by 3-mercaptopyruvate sulfotransferase, found both in the cytosol and mitochondria. If suitable nucleophilic acceptors are present (eg. cyanide, sulfite, a thiol) the enzyme will catalyse the transulfuration of sulfur from 3-mercaptopyruvate to the nucleophile. L-Cysteine sulfur which enters the sulfane pool thus has a relatively long half-life before it is oxidised to sulfate and excreted (Scheme 4).



SCHEME 4 The transamination pathway. *Transfer of sulfur into and out of the sulfane pool. Sulfane formation and interconversion occurs readily under the auspices of mercaptopyruvate sulfotransferase and thiosulfate sulfotransferase. The major excretory form of such sulfur is sulfate.

The relative importance of the 3-mercaptopyruvate pathway to L-cysteine catabolism is still in doubt. Despite reports that direct transamination is quantitatively minor, with less than 0.5% of total sulfur excretion originating from 3-mercaptopyruvate metabolites,[20,21] there is ample evidence to support the physiological importance of this pathway *in vivo*. It has been postulated that the 3-mercaptopyruvate pathway may be significant to the D-isomer of L-cysteine, with conversion of D-cysteine to 3-mercaptopyruvate by D-amino acid oxidase.[22,23] 3-Mercaptopyruvate is the proximate source of sulfane sulfur in mammals, utilised as part of normal metabolic processes and in defence against such toxins as cyanide. Similarly, an inborn error of L-cysteine metabolism, β-mercaptolactate-cysteine disulfidurea, is due to a deficiency in 3-mercaptopyruvate sulfotransferase and can lead to mental retardation.[24]

3.2. Desulfhydration of L-Cysteine

L-Cysteine may be cleaved directly to form pyruvate, ammonia and hydrogen sulfide (Eq. 1) and early investigators ascribed this to the activity of an L-cysteine desulfhydrase. However, no such enzyme has ever been isolated from mammalian tissues. This apparent activity was later credited to rat liver cystathionine γ-lyase (γ-cystathionase).[25] Cystine is also a substrate for cystathionine γ-lyase yielding pyruvate, ammonia and thiocysteine (Eq. 2), the latter of which undergoes dismutation with cystine to produce cysteine (Eq. 3). If a sulfane acceptor is present, the thiocysteine sulfur is released into the sulfane pool and then reduced in conjunction with oxidation of L-cysteine to form cystine and hydrogen sulfide (Eqs. 4, 5). It is this sequence of reactions that provides an explanation of the old idea of a desulfhydrase activity.

$$\text{cysteine} + H_2O \longrightarrow \text{pyruvate} + NH_3 + H_2S \quad (1)$$

$$\text{cysteine} + H_2O \longrightarrow \text{pyruvate} + NH_3 + \text{thiocysteine} \quad (2)$$

$$\text{thiocysteine} + \text{cystine} \longrightarrow \text{thiocystine} + \text{cysteine} \quad (3)$$

$$\text{thiocysteine} + \text{sulfane acceptor} \rightleftharpoons \text{cysteine} + \text{sulfane}-S \quad (4)$$

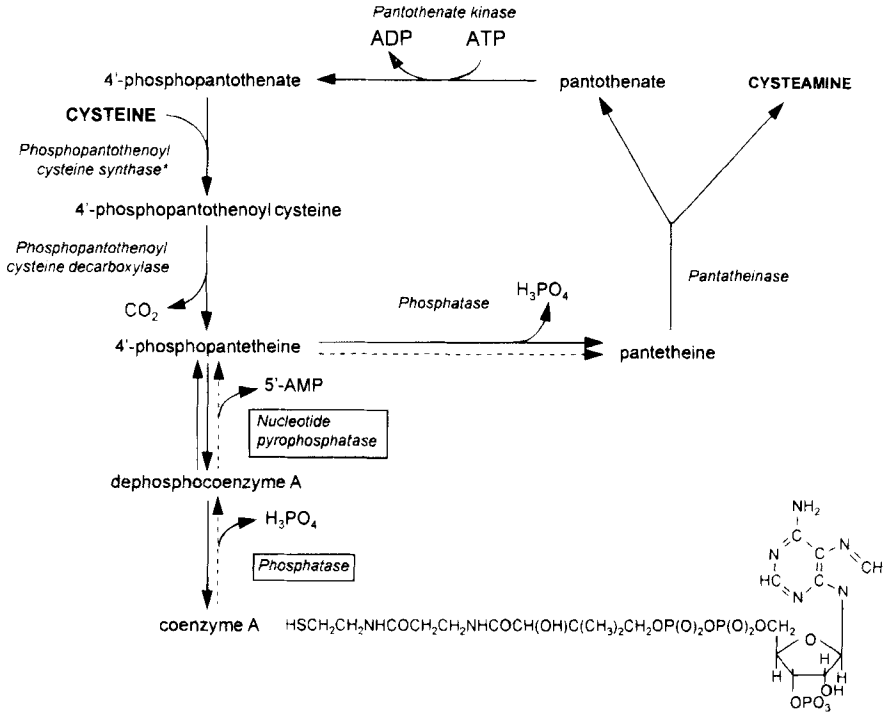
$$2\,\text{cysteine} + \text{sulfane}-S \rightleftharpoons \text{cystine} + H_2S \quad (5)$$

What is paradoxical is that the same enzyme appears to be involved in both the synthesis (from cystathionine) and breakdown of L-cysteine. Initially, desulfhydration was considered to be a minor metabolic route,[21,22] yet there are data to indicate that the majority of L-cysteinesulfinic acid independent catabolism of L-cysteine is attributable to cystathionine γ-lyase. As much as 50% of L-cysteine catabolism by hepatocytes may be accounted for by cystathionine γ-lyase activity.[19,20]

3.3. The Cysteamine Pathway

The conversion of L-cysteine to cysteamine and further oxidation to hypotaurine, hence taurine, has been demonstrated in a number of rat organs including liver, kidney and heart where it is present in low concentrations.[26] Cysteamine is the decarboxylated analogue of cysteine, yet there is no evidence that a cysteine decarboxylase exists. What has been proposed is that the formation of cysteamine from L-cysteine is a part of a series of complex reactions involved in the synthesis of coenzyme A[27] (Scheme 5). Condensation of 4′-phosphopantothenate with L-cysteine yields 4′-phosphopantothenoylcysteine, catalysed by 4′-phosphopantothenoylcysteine synthase. The next step is the decarboxylation of the cysteinyl residue on 4′-phosphopantothenoylcysteine, mediated by 4′-phosphopantothenoylcysteine decarboxylase, to form 4′-phosphopantetheine. At this point 4′-phosphopantetheine (regulated by a phosphatase) will either be committed to form coenzyme A or dephosphorylated to give pantetheine. The latter is then cleaved by pantetheinase to yield pantothenate and cysteamine. Cysteamine can also be formed by the catabolic hydrolysis of coenzyme A, a reversal of its synthesis (Scheme 5). Cysteamine is then *S*-oxidised to form hypotaurine catalysed by cysteamine dioxygenase, the enzymology of which is well understood. The further oxidation of hypotaurine to taurine can occur non-enzymatically, although a hypotaurine oxidoreductase has been discovered in rat tissue.[28]

The cysteamine pathway is a putative route of taurine formation. It is the only metabolic sequence available for taurine synthesis in the heart and the only cysteinesulfinic acid independent route. Further indications as to the importance of this pathway are demonstrated by a comparison of cysteamine and cysteine dioxygenase activities in mammalian organs, with cysteamine dioxygenase being comparable to, and in some instance greater than, cysteine dioxygenase activity.[29]



SCHEME 5 The synthesis of coenzyme A and the pantothenate cycle. Cysteine is decarboxylated to form cysteamine, via the pantothenate cycle. Cysteamine can also be formed by the breakdown of coenzyme A, represented by the dashed arrows and boxed enzymes.

3.4. The Cysteinesulfinic Acid Pathway

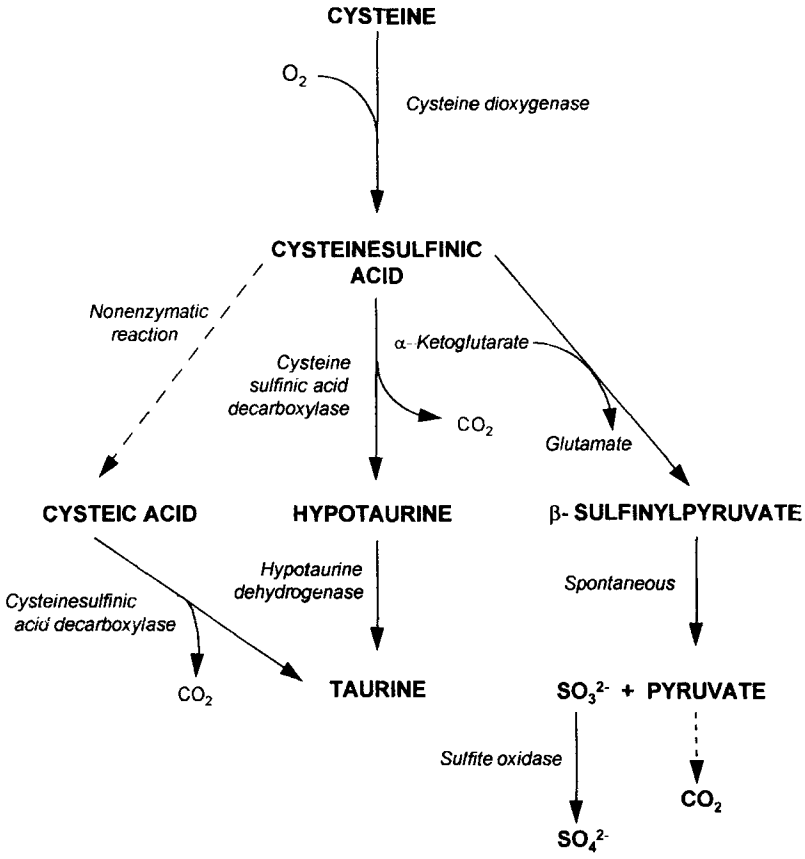
L-Cysteine is rapidly oxidised in rat liver cystosol to its *S*-oxidation product, cysteinesulfinic acid. This reaction is catalysed by the action of cysteine dioxygenase. The turnover of cysteinesulfinic acid is very fast and it is rapidly metabolised through a number of possible pathways. Cysteinesulfinic acid lies at a metabolic branch point of its own degradation. It may be transaminated to give β-sulfinylpyruvate, it can undergo further oxidation to produce cysteic acid or it can be decarboxylated to form hypotaurine.

The transamination of cysteinesulfinic acid is mediated by cysteinesulfinic acid aminotransferase. This enzyme is not fully characterised and it is generally assumed to be identical to aspartate aminotransferase. The reaction takes place in mitochondria and once cysteinesulfinic acid enters the organelle it is

quickly transaminated. The major amine acceptor is α-ketoglutarate, the reaction yielding glutamate and, transiently, β-sulfinylpyruvate.[30,31] The latter compound is unstable and spontaneously desulfinates to form sulfur dioxide and pyruvate. It has been suggested that this occurs whilst β-sulfinylpyruvate is still enzyme bound, thus β-sulfinylpyruvate is not released into solution.[32] The sulfur dioxide formed is toxic and it is rapidly oxidised to sulfite and thence sulfate by sulfite oxidase, this occurs in the mitochondrial intermembrane space (Scheme 6).

Cysteinesulfinic acid may be oxidised non-enzymatically to cysteic acid, but the rapid transamination and decarboxylation of cysteinesulfinic acid is thought to prevent this from occurring extensively. Whether this reaction occurs enzymatically in mammals is unclear. Some reports have indicated the enzymic conversion of cysteinesulfinic acid to cysteic acid[33,34] and despite low cysteinesulfinic acid decarboxylase activity in the embryo, taurine production from cysteic acid occurs readily.[35] It has been suggested that cysteic acid can also arise through sulfation involving adenosine 3′-phosphate 5′-phosphosulfate (PAPS) transferase; the evidence for this pathway, however, is tenuous.[22] The only metabolic reaction known for cysteic acid is its decarboxylation to form taurine, thought to be mediated by cysteinesulfinic acid decarboxylase but sometimes called cysteic acid decarboxylase. In general, the pathway is considered to be minor in the catabolism of L-cysteine and the synthesis of taurine.[36] Controversy surrounding the existence of cysteic acid as a true mammalian metabolite (as opposed to a chemical oxidation product) would tend to support this view.

The cysteinesulfinic acid decarboxylase route provides not only a catabolic pathway but is also the metabolic origin of taurine. Cysteinesulfinic acid is decarboxylated in the mammalian brain and liver, but rates vary between both tissue and species. The reaction is cytosolic, mediated by cysteinesulfinic acid decarboxylase, a pyridoxal phosphate-dependent enzyme, to form hypotaurine. Initially, it was unclear whether cysteinesulfinic acid decarboxylase and glutamate decarboxylase activities were expressed by the same protein and hence identical enzymes. Purification of activities from the hog brain clearly identified the existence of distinct enzymes, although glutamate decarboxylase is capable of catalysing the decarboxylation of cysteinesulfinic acid.[37,38] Hypotaurine exists in low concentrations in liver and brain of adult mammals, at least 90% of hypotaurine is readily oxidised to taurine.[39,40] The mechanism of oxidation of hypotaurine remained elusive,



SCHEME 6 Cysteinesulfinic acid dependent pathways. The non-enzymatic reaction via cysteic acid is, generally, considered to be of minor importance to cysteine catabolism.

both enzymatic and non-enzymatic formation were considered and it was not until recently that the reduced nicotinamide adenine dinucleotide phosphate (NADPH) dependent hypotaurine dehydrogenase was identified.[41]

4. PARTITIONING OF CYSTEINESULFINIC ACID

Transamination is generally considered a minor fate of cysteinesulfinic acid. It has been demonstrated, in both whole rodents and isolated rat hepatocytes, that about 80% of cysteinesulfinic acid is decarboxylated to

hypotaurine (reports range from 70–95%).[17,20,39,42] Therefore, in rodents, cysteinesulfinic acid catabolism occurs primarily through decarboxylation to hypotaurine.

The quantitative significance of taurine production in L-cysteine catabolism and the metabolic partitioning of cysteinesulfinic acid between transamination and decarboxylation shows extensive species variation. Rodents possess a very high capacity for taurine synthesis through cysteinesulfinic acid decarboxylation, whilst the amount of cysteinesulfinic acid decarboxylated in humans is much less.[43] Cats are deficient in cysteinesulfinic acid decarboxylase, which is associated with their nutritional requirement for taurine;[44,45] its absence can lead to blindness.

There is a general correlation between cysteinesulfinic acid decarboxylase activity and the ability of animals to form taurine.[44–46] In animals given an excess of dietary L-cysteine or protein a decrease in cysteinesulfinic acid decarboxylase activity is observed.[17,19,47] In isolated rat hepatocytes this occurs in conjunction with a decrease in the catabolism of cysteinesulfinic acid to hypotaurine and taurine. However, an increase in the catabolism of L-cysteine to hypotaurine and taurine was also seen.[48] In the developing rat cysteinesulfinic acid decarboxylase activity and amounts of taurine are inversely related. Whilst taurine levels are high in the developing brain, decreasing after development, cysteinesulfinic acid decarboxylase activity is initially low, increasing with age. Similarly, foetal liver cysteinesulfinic acid decarboxylase activity is low, yet a third of taurine in the pup at birth has been synthesised *in utero*.[49,50] This evidence demonstrates that cysteinesulfinic acid decarboxylase activity is not rate limiting in the oxidation of L-cysteine to hypotaurine and hence taurine in mammals. It also challenges assumptions that the regulatory locus for the partitioning of L-cysteine catabolism occurs at the cysteinesulfinic acid branchpoint, between transamination and decarboxylation.

Studies have indicated that cysteinesulfinic acid independent pathways also play a major role in L-cysteine metabolism and suggest changes in cysteine dioxygenase activity have a greater regulatory effect on the catabolic flux of L-cysteine to taurine than cysteinesulfinic acid decarboxylase. In contrast to cysteinesulfinic acid decarboxylase activity, animals fed on an excess of methionine, L-cysteine or protein exhibit an increase in cysteine dioxygenase activity which parallels an increase in hepatic L-cysteine concentration and precedes both an increase in hepatic taurine concentration and taurine excretion.[47,51,52] Thus, cysteine dioxygenase

indubitably has an adaptive role to play in the catabolism of excess L-cysteine sulfur and is regulatory to the normal degradation of L-cysteine in mammals.

5. CRITICAL L-CYSTEINE CONCENTRATIONS—THE DOUBLE-EDGED SWORD

Regardless of the metabolic importance of L-cysteine, its normal intracellular concentration is amongst the lowest known for any protein amino acid in mammals, within the rage of 30–250 μM.[51,53,54] L-Cysteine is also one of the most toxic amino acids and it has been suggested that low intracellular L-cysteine concentration is a reflection of its inherent reactivity and serves to protect the cell.[22] The possible reasons underlying the essentiality of mechanisms for cysteine metabolism and homeostasis have recently become more apparent. Cysteine levels which are too low or too high both lead to physiological dysfunction which can be reflected in chronic disease states.[55,56]

Breathing high levels of oxygen for longer than four hours will lead to respiratory distress and death. This toxicity is largely due to the production of 'reactive oxygen species', comprising superoxide anions, hydrogen peroxide and hydroxyl free radicals. Such reactive entities are produced normally by the body, about two percent of inhaled oxygen produces 'reactive oxygen species', but usually their rate of production is less than the capacity of the body to remove them. If however, these natural defence mechanisms are not functioning then cell damage will result. This process can be seen in cases of 'stroke' where the long-lasting dysfunction which may ensue is thought to be due to 'reactive oxygen species' generated after the thrombus has blocked veins or arteries. Such 'reactive oxygen species' are also thought to play a part in cancer induction and also enable the mediator, nitric oxide, to form damaging peroxynitrite ions. Against these harmful oxidants, thiols, especially cysteine, play a major role, catalysing reduction of 'reactive oxygen species' to less or even non-toxic forms. Levels of cysteine also control the plasma concentrations of glutathione, a tripeptide central to defence from oxidative stress and ensuing tissue damage.

High levels of cysteine are also known to be dangerous. Although the basis for L-cysteine toxicity is not fully defined, evidence for L-cysteine induced

toxicity is well documented. Rats fed diets containing excess L-cysteine soon showed weight loss and general degeneration before death.[57] Free L-cysteine is neurotoxic, particularly in developing mammals and subcutaneous injection or oral administration of L-cysteine to neonates has led to degenerative changes in the central nervous system.[58,59] Perfused rat liver became discoloured and patchy when challenged with excess L-cysteine[60] and cultured cells also exhibited L-cysteine toxicity.[61]

Suggested mechanisms by which L-cysteine toxicity is manifested include the reaction of L-cysteine with pyridoxal 5′-phosphate to form stable thiazolidine and hemithioacetal derivatives, thus depleting cells of the coenzyme. In relation to this, L-cysteine has been shown to inhibit various pyridoxal 5′-phosphate dependent enzymes, forming a relatively stable thiazolidine derivative of vitamin B_6.[62–64] L-Cysteine undergoes rapid auto-oxidation to form cystine which is insoluble and toxic if allowed to accumulate.[65] Paradoxically, considering its antioxidative properties, auto-oxidation of L-cysteine, in the presence of transition metals, generates reactive oxygen species such as hydrogen peroxide, which are cytotoxic.[66,67] It is possible that high levels of L-cysteine alone may produce considerable alteration of the disulfide-thiol status of the cell or that they may interfere with certain metal functions.[62] Neurotoxicity of L-cysteine has been linked to that of the excitatory amino acids, glutamate and aspartate, but L-cysteine damage is more widespread. It has been suggested that the lipophilic nature of cysteine allows it to penetrate the brain easily where it is oxidised to cysteinesulfinic acid (presumably by cysteine dioxygenase) which is also an excitatory amino acid and the actual toxic agent.[21] L-Cysteine has been shown to react positively in the commonly used short-term Ames test for mutagenicity where thiol free radicals are thought to be the most likely candidates for the active species.[68]

The plethora of pathways of L-cysteine catabolism appear to function in the regulation and maintenance of narrow and physiologically acceptable L-cysteine levels. Unfortunately, drifting either above or below this fine control can lead to toxicity and deleterious consequences.

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