

34 Amino Acid Metabolism in Helminths

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34.1 Abstract

Metabolism of amino acids is better known in nematodes than in other helminths, particularly in parasites of mammals and humans. There are differences between species and also life-cycle stages, so that the presence of genes encoding the proteins does not ensure functional enzymes, e.g. there are differences in expression of glutamate synthase, arginine decarboxylase and Δ^1 -piperidine-carboxylate reductase between the two closely related species or life-cycle stages of sheep abomasal nematode parasites. The main differences in metabolism of amino acids from that in other animals are in properties of individual enzymes, rather than the absence or presence of pathways. Unusual features are the lack a full ornithine-urea cycle in many helminths, the presence of creatinase activity, synthesis of polyamines from either ornithine or agmatine and incorporation of ammonia into glutamate.

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34.2 Introduction

Cestodes (tapeworms) of the Phylum Cestoda, trematodes (flukes and schistosomes) of the phylum Platyhelminthes and roundworms of the phylum Nematoda, although anatomically very different, are generally grouped as helminths. All cestodes are parasitic, whereas there are both parasitic and free-living species of trematodes and nematodes. Trematodes have both an absorptive tegument and an incomplete gut (Asch and Read, 1975; Hanna, 1980; Pappas, 1988), whereas nematodes have digestive tracts and absorption occurs across their outer cuticles, which are structurally unlike typical absorptive surfaces (Bird and Bird, 1981; Page, 2001), except in a few species in which there are microvilli on the cuticle (Riding, 1970). Adult cestodes consist of a head (the scolex) and segmental proglottids generated by the scolex, which mature as they move distally as new proglottids are formed and break off at the posterior end. As there is no digestive tract, absorption occurs only across the tegument, which resembles a brush border (Pappas *et al.*, 1973).

34.3 Overview

Since the extensive reviews of helminth nitrogen metabolism of McManus (1987) and Barrett (1981, 1983, 1991), most work has been carried out on parasitic nematodes, with a focus on

identifying novel anthelmintic targets. Biochemical studies, supplemented with annotated gene sequences in public databases, of a limited range of species has resulted in only a partial picture of amino acid metabolism in helminths. Further, even closely related species have shown notable differences in enzyme properties and there are examples of enzymes not being expressed at some life-cycle stages.

Proteolytic enzymes on the intestinal brush border and/or secreted by many parasitic nematodes of plants (Vanholme *et al.*, 2004) and animals (Sajid and McKerrow, 2002) break proteins to peptides and amino acids. Uptake of nitrogenous compounds in helminths can be as ammonium, peptides (Meissner *et al.*, 2004) and amino acids (Isseroff *et al.*, 1976; Jeffs and Arme, 1985, 1987; Veljkovic *et al.*, 2004) and also through the γ -glutamyl cycle (Dass and Donahue, 1986; Abidi and Nizami, 1995). Excess nitrogen is excreted by free living and parasitic nematodes as approximately 80% ammonia and 20% urea (Rogers, 1952; Wright, 1975a; Simpson *et al.*, 2009).

Amino acids are commonly oxidised (Grantham and Barrett, 1986a; Umair *et al.*, 2011c, 2012a) or decarboxylated (Singh *et al.*, 1983; Umair *et al.*, 2011d) by nematodes and helminth aminotransferases are able to transaminate a large number of L-amino acids, usually using the glutamate - 2-oxoglutarate (2-OG) system (Singh and Srivastava, 1983; Barrett, 1991; Walker and Barrett, 1991a,b). Amino acids contribute to nematode energy metabolism (Bruce *et al.*, 1972; Davies and Köhler, 1990) (Fig. 34.1) and some species are reported to survive *in vitro* with glutamine or alanine as the sole carbon source. The malate synthase - isocitrate lyase glyoxylate cycle in nematodes (Rothstein and Mayoh, 1964, 1966; Barrett *et al.*, 1970; Grantham and Barrett, 1986b) allows all amino acids to be glucogenic (Fig. 34.1). Early studies of the interconversion of radio-labeled amino acids suggested there may be no essential amino acids for nematodes (Rothstein and Tomlinson, 1961; Rothstein, 1965), however, *in vitro* cultivation of helminths requires supplementation with the L-amino acids arginine, isoleucine, tryptophan, valine and histidine (Brockelman and Jackson, 1978; Hata, 1994) and also leucine, lysine, methionine, phenylalanine and threonine (Hata, 1994). Incorporation of ammonia via the glutamine synthetase (GS) - glutamate synthase (GOGAT) pathway (Umair *et al.*, 2011a) may reduce the number of amino acids essential for parasitic nematodes.

34.4 Glutamate

Glutamate is incorporated into proteins, involved in synthesising other amino acids, a source of excreted ammonia and a link between nitrogen and energy metabolism through interconversion of glutamate and 2-OG, catalysed by glutamate dehydrogenase (GDH) and a large group of transaminases (Barrett, 1991).

34.4.1 Glutamate dehydrogenase

GDH catalyses the reversible oxidative deamination of glutamate to ammonium and 2-OG and can either function in ammonia assimilation or generation of ammonia and 2-OG (Goldin and Frieden, 1971; Hudson and Daniel, 1993). GDHs appear to be universally present in helminths and many can use either NAD⁺ or NADP, although not with equal efficiency (Grantham and Barrett, 1986a; Muhamad *et al.*, 2011, Umair *et al.*, 2011b). Allosteric regulation of *Haemonchus contortus* and *Teladorsagia circumcincta* GDH differed from mammalian GDH: ADP and ATP were more stimulatory, GTP was strongly inhibitory and ATP stimulated *H. contortus* GDH amination more markedly than deamination (Umair *et al.*, 2012b).

34.4.2 Glutamine Synthetase (GS) - Glutamate Synthase (GOGAT)

GS, a universal enzyme which catalyses the formation of glutamine from glutamate and ammonia, has been described in *Heligmosomoides polygyrus*, *Panagrellus redivivus* (Grantham and Barrett, 1988) and both L3 and adult *T. circumcincta* (Muhamad, 2006). GOGAT, which catalyses the formation of two glutamate molecules from glutamine and 2-OG (Vanoni and Curti, 1999), is present in plants, microorganisms and some insects (Hirayama *et al.*, 1998; Scaraffia *et al.*, 2005), in which it supports assimilation of ammonia from low concentrations, provided ATP is available (Fisher and Sonenshein, 1991, Mifflin and Habash, 2002). In contrast, GDH is able to assimilate ammonia only from higher concentrations (Helling, 1998). *In vitro*, there was re-uptake by L3 *T. circumcincta* of excreted ammonia (Simpson *et al.*, 2009) and GOGAT activity was increased by incubation of L3 with ammonia for a similar time period (Umair *et al.*, 2011a). GOGAT activity has been detected in homogenates of L3 and adult *T. circumcincta* (Muhamad, 2006; Umair *et al.*, 2011a) and adult, but not L3, *H. contortus* (Umair *et al.*, 2011a) and databases contain GOGAT gene sequences for free-living and many parasitic nematodes.

34.4.3 Glutaminase

Glutaminase hydrolyses glutamine to glutamate and ammonia. High glutaminase activity was detected in *T. circumcincta* (Muhamad, 2006), low activity in *H. polygyrus* and *P. redivivus* (Grantham and Barrett, 1986a), but was undetectable in *Litomosoides carinii* (Davies and Köhler, 1990).

34.4.4 GABA (γ -aminobutyrate) shunt

The nematode neurotransmitter GABA (Feng *et al.*, 2002; Schuske *et al.*, 2004) is formed by irreversible decarboxylation of L-glutamate by γ -aminobutyrate decarboxylase, the first step of the three enzyme GABA shunt, which forms succinate from glutamate and bypasses part of the TCA cycle (Balazs *et al.*, 1970). The other two enzymes are GABA-transaminase and succinic semialdehyde dehydrogenase. Although demonstrated in specific tissues (Monteoliva *et al.*, 1965; Singh *et al.*, 1983), all enzymes of the shunt were detected in homogenates of only some parasitic helminths, particularly larger species living in more anaerobic environments (Monteoliva *et al.*, 1965; Rasero *et al.*, 1968; MacKenzie *et al.*, 1989), suggesting the GABA shunt may not be important in the metabolism of many helminths.

34.5 Proline

The proline required for synthesis of collagen, an important component of the cuticle, can either be synthesised from ornithine or glutamate or obtained directly from the host. A fully functional mammalian-type ornithine-proline-glutamate pathway has been demonstrated in many helminths (Grantham and Barrett, 1986b; Mohamed *et al.*, 2008; Umair *et al.*, 2011c).

34.6 Arginine

In helminths, arginine is a substrate for synthesis of polyamines, agmatine, nitric oxide, phosphoarginine, proline, glutamate and urea via the ornithine urea cycle (OUC). Umair *et al.* (2011d) found no evidence in sheep abomasal nematodes of the non-mammalian arginine deiminase or dihydrolase pathways, which generate ATP, ornithine, ammonia and CO₂ (Zúñiga *et al.*, 2002).

34.6.1 Arginase

Arginase, which irreversibly generates ornithine from arginine, has been described in numerous helminth species (Barrett, 1991). The *H. contortus* and *T. circumcincta* arginases were unusual in not requiring added Mn^{2+} or another bivalent metal ion for activity, in contrast to rat liver arginase (Kuhn *et al.*, 1991). Other divalent cations tested were inhibitory to the arginases of both species, as is also the case for *Fasciola hepatica* arginase (Mohamed *et al.*, 2005). The optimal pH of 8-8.5 for the arginases of the gastric nematode parasites (Muhamad, 2006; Umair *et al.*, 2011d) may relate to the acidity of their environment, as the arginase of gastric pathogen *Helicobacter pylori* also has an exceptionally low optimal pH of 6.1 (McGee *et al.*, 2004).

34.6.2 Ornithine urea cycle

In ureotelic animals, excreted urea is formed by the OUC, however, helminths generally lack a fully functional urea cycle (Janssens and Bryant, 1969) and urea is a minor excretory product (Rogers, 1952; Wright, 1975a). Although arginase is present, the other OUC enzymes, carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL) have not been detected consistently. All OUC enzymes were detected in *P. redivivus* (Wright, 1975b), *Dicrocoelium lanceatum* (Rijavec and Kuralec, 1965) and *F. hepatica* (Rijavec and Kuralec, 1965; Mohamed *et al.*, 2005) and in *P. redivivus*, although ASS and ASL activities were very low (Wright, 1975b).

34.6.3 Nitric acid synthase (NOS)

Nitric oxide is a neurotransmitter in helminths and NOS activity can be demonstrated histochemically in the central and peripheral nerves of cestodes and trematodes (Gustafsson *et al.*, 1996, 1998) and adult *H. contortus* (Umair *et al.*, 2011d). In contrast to neuronal activity, NOS was undetectable in homogenates of whole adult or L3 *T. circumcincta* or *H. contortus* (Umair *et al.*, 2011d).

34.6.4 Agmatine

Agmatine is formed from arginine by arginine decarboxylase (ADC), which was detected in *H. contortus*, but not in *T. circumcincta* (Umair *et al.*, 2011d). In *H. contortus*, ADC appeared to be distinct from ornithine decarboxylase (ODC) (Umair *et al.*, 2013b). Agmatine is metabolised to putrescine and urea by agmatinase, an enzyme which is generally present in non-mammalian tissues (Tabor and Tabor, 1985), including both *H. contortus* and *T. circumcincta* (Umair *et al.*, 2011d). This was surprising for *T. circumcincta*, in which ADC was not found, however, this apparent activity may be due to arginase, which is capable of using either arginine or agmatine as substrate (Ahn *et al.*, 2004).

34.6.5 Polyamines

The polyamines putrescine, spermidine and spermine, which regulate cell growth, survival and differentiation, are universally synthesised from ornithine by ODC (Pegg, 1986), whereas putrescine is also formed from agmatine by ADC in microorganisms and plants (Slocum *et al.*, 1984). All three polyamines are actively transported in nematodes (Sharma *et al.*, 1989). *Filaria* appear to acquire putrescine from the host (Wittich *et al.*, 1987) and very low or negligible ODC activities have been reported in many other nematodes (Singh *et al.*, 1983; Wittich *et al.*, 1987; Sharma *et al.*, 1989). Unusually, putrescine was generated from arginine by both the ODC and ADC pathways in *H. contortus*, but not *T. circumcincta* (Umair *et al.*, 2011d) and there was direct oxidation of spermine and spermidine in *Ascaris suum* (Müller and Walter, 1992). There were also unusual substrate specificities of the putrescine N-acetyltransferases of

A. suum and *Onchocerca volvulus* (Wittich and Walter, 1989, 1990) and the ODC of *Caenorhabditis elegans* (Schaeffer and Donatelli, 1990) and *H. contortus* (Klein *et al.*, 1997) were membrane-bound, rather than cytosolic.

34.6.6 Arginine kinase

Phosphoarginine and arginine kinase are the usual phosphagen and phosphagen kinase in nematodes (Platzer *et al.*, 1995, 1999; Umair *et al.*, 2013a), but not in adult cestodes or digeneans (Barrett and Lloyd, 1981).

34.7 Serine, threonine and glycine

34.7.1 Glycine

The metabolism of glycine, serine and threonine appear to be consistent with that in other animals. There are few reports on helminth glycine metabolism, apart from its interconversion to serine by L-serine hydroxymethyltransferase in *Nippostrongylus brasiliensis* (Walker and Barrett, 1991b), *Brugia pahangi* and *Dirofilaria immitis* (Barrett, 1983).

34.7.2 Serine

L-serine is metabolised to phospholipids, glycine, taurine, cysteine and the mammalian neurotransmitter D-serine (Kalhan and Hanson, 2012), as well as providing methyl groups to tetrahydrofolate (THF), and subsequently to Adomet (*S*-adenosylmethionine), for methylation of proteins, DNA and RNA. Serine is obtained from the breakdown of protein, glycine-serine recycling and from pyruvate using phosphoenolpyruvate carboxykinase and is metabolised to pyruvate by serine dehydratase, serine aminotransferase or serine hydroxymethyltransferase. L-serine dehydratase, which deaminates serine to pyruvate, is active in *N. brasiliensis* (Walker and Barrett, 1992), *H. polygyrus* and *P. redivivus* (Grantham and Barrett, 1986a). L-serine hydroxymethyltransferase, which catalyses the reversible conversion of serine and THF to glycine and 5,10-methylenetetrahydrofolate (Schirch and Peterson, 1980), is present in *N. brasiliensis* (Walker and Barrett, 1991b), *B. pahangi* and *D. immitis* (Barrett, 1983). The gene is present in the *H. contortus* genome and in *C. elegans* is encoded by the *mel-32* gene, in which it is maternally essential (Vatcher *et al.*, 1998). Reversible conversion of serine to cysteine is carried out by the helminth *trans*-sulphuration enzyme cystathionine β -synthase (Walker and Barrett, 1997).

34.7.3 Threonine

There is no evidence that threonine can be synthesised in helminths from aspartate, as in micro-organisms and plants (Azevedo *et al.*, 1997), suggesting that its reported synthesis from labelled precursors by *Caenorhabditis briggsae* (Rothstein and Tomlinson, 1961) and *H. contortus* (Kapur and Sood, 1984) may be due to bacterial contamination or symbionts. Threonine is converted to pyruvate by threonine dehydrogenase; an encoding gene is annotated in the *H. contortus* genome. An intermediate in this pathway reacts with CoA to produce acetyl-CoA and glycine. There is an active threonine dehydratase in *N. brasiliensis* (Walker and Barrett, 1991b), *H. polygyrus* and *P. redivivus* (Grantham and Barrett, 1986a) and serine dehydratase can also metabolise threonine.

34.7.4 Sarcosine

Sarcosine (N-methylglycine) is degraded to glycine either by sarcosine dehydrogenase (SarDH) or sarcosine oxidase (SOX). Whereas in mammals, SarDH activity is essential to prevent sarcosinaemia (Reuber *et al.*, 1997), there was no SarDH activity in L3 and adult *H.*

contortus and *T. circumcincta* and sarcosine was demethylated by SOX. Genes encoding SOX have been annotated in *C. elegans*, *Ancylostoma caninum* and *H. contortus*.

Bacteria and plants generate sarcosine during the metabolism of creatinine by several pathways, including one using creatinase as the last enzyme (Wyss and Kaddurah-Daouk, 2000). Creatinase, which catalyses the conversion of creatine to sarcosine and urea, was demonstrated in adult, but not L3, *H. contortus* and in both L3 and adult *T. circumcincta* (Muhamad, 2006; Umair *et al.*, 2013c). The enzyme appears to be present in many nematodes, as genes encoding creatinase are reported from *H. contortus*, *A. suum*, *Toxocara canis*, *Brugia malayi*, *C. elegans* and *C. briggsae*.

34.8 Methionine and cysteine

Walker and Barrett (1997) comprehensively reviewed the metabolism of sulphur amino acids by parasitic helminths and concluded that it generally resembled that of their hosts; the pathways investigated included the methionine cycle and AdoMet metabolism, *trans*-sulphuration, transaminative catabolism of methionine, oxidative catabolism of cysteine and glutathione synthesis. There were unusual properties of some nematode enzymes, such as the biochemical properties and amino acid structures of some methionine cycle enzymes, differences in AdoMet decarboxylases from the corresponding mammalian enzymes (Ndjonka *et al.*, 2003) and a cystathionine β -synthase in *N. brasiliensis* which catalysed the non-mammalian 'activated l-serine sulphhydrase' reaction (Walker and Barrett, 1992).

34.8.1 Glutathione

The tripeptide glutathione (L- γ -glutamyl-L-cysteinylglycine) (GSH) is formed by successive additions to glutamate of cysteine and glycine by the enzymes γ -glutamylcysteine and GSH synthetases, then degraded by four enzymes, together forming the γ -glutamyl cycle (Meister, 1981), which acts as an amino acid transporter. Glutathione has many cellular functions, particularly as an antioxidant, in leukotriene, steroid and prostaglandin metabolism and as a conjugate of toxic compounds and xenobiotics (Meister, 1981). It is a cellular detoxifying agent which reduces the efficiency of anthelmintic drugs.

Glutathione S-transferases (GSTs), which are responsible for conjugation of compounds to glutathione, have been identified and characterised or the encoding genes sequenced in many parasitic helminths. GSTs are secreted/excreted proteins (Moreno *et al.*, 2011) under investigation as targets for vaccine or chemical treatment of parasitic trematodes and nematodes. Differences in nematode and host GSTs (Campbell *et al.*, 2001) have allowed, vaccines to be developed to reduce parasite burdens and fecundity (Balloul *et al.*, 1987; Da Costa *et al.*, 1999).

34.9 Leucine, isoleucine and valine

P. redivivus and *H. polygyrus* catabolise branched chain amino acids (BCAAs) by pathways similar to those in rat liver (Grantham and Barrett, 1986b): ^{14}C -labelled leucine, isoleucine and valine were reduced to CO_2 and branched chain aminotransferases (BCATs) transaminated each to their keto-acids. BCATs have been identified in *N. brasiliensis* (Walker and Barrett, 1991b), *F. hepatica* (Lee *et al.*, 1983) and *Ascaridia galli* (Singh and Srivastava, 1983) and Singh *et al.* (1983) detected decarboxylase activity for leucine and valine in the intestines, ovaries and cuticle of *A. galli*. The interaction of the three BCAAs seen in vertebrates did not appear to operate in *C. elegans* (Perelman and Lu, 2000).

34.10 Tyrosine, phenylalanine and tryptophan

The aromatic amino acids have been studied extensively as precursors of nematode neurotransmitters that are targeted by many chemical anthelmintics (Köhler, 2001). Dopamine, catecholamines, tyramine and octopamine are formed from tyrosine, serotonin from tryptophan and histamine from histidine (Blenau and Baumann, 2001). Octopamine is synthesised by conversion of tyrosine to tyramine by tyrosine decarboxylase, then to octopamine by tyramine β -hydroxylase. Octopamine inhibits pharyngeal muscle pumping and egg laying and is an antagonist to serotonin (Horvitz *et al.*, 1982). Tyramine also inhibits egg laying in *C. elegans* (Alkema *et al.*, 2005). In *C. elegans*, phenylalanine hydroxylase is involved in synthesizing a melanin-like pigment (Calvo *et al.*, 2008).

Phenylalanine hydroxylase, tyrosine hydroxylase and tryptophan hydroxylase make up the aromatic amino acid hydroxylase family (Fitzpatrick, 2003). L-phenylalanine is catabolised to L-tyrosine in *C. elegans* by phenylalanine hydroxylase (Calvo *et al.*, 2008). Tyrosine is catabolised in eukaryotes, including *C. elegans* (Fisher *et al.*, 2008), by a 5 step pathway, the first of which is the removal of the amino group by tyrosine aminotransferase, then 4 steps to produce fumarate and acetoacetate. The synthesis of tetrahydrobiopterin, an electron donor for these decarboxylases (Fitzpatrick, 2012), requires GTP-cyclohydrolase, the gene encoding which has been sequenced and expression monitored during development in *T. circumcincta* and *Dictyocaulus viviparus* (Baker *et al.*, 2011).

34.10.1 Tyrosinase

Tyrosinases have mono- and di-phenol oxidase activity and are involved in the synthesis of DOPA from tyrosine, melanin synthesis and protein crosslinking. Trematode tyrosinases have been extensively studied because of their role in eggshell sclerotinisation and potential for chemotherapy or as vaccine candidates (Fitzpatrick *et al.*, 2007; He *et al.*, 2012; Bae *et al.*, 2015).

34.10.2 Chorismate mutase (CM)

CM, the last enzyme of the seven step shikimate pathway which synthesises tyrosine and phenylalanine in plants and microorganisms, is expressed by plant parasitic nematodes of the genera *Meloidogyne* (Lambert *et al.*, 1999; Long *et al.*, 2006), *Globodera* (Jones *et al.*, 2003) and *Pratylenchus* (Haegeman *et al.*, 2011). There is no report of a complete shikimate pathway in nematodes and CM is suggested to have been acquired from microorganisms through horizontal gene transfer (Yan *et al.*, 1998). Expression of CM in the *Globodera pallida* suboesophageal gland (Jones *et al.*, 2003; Long *et al.*, 2006) supports the proposal that it is secreted to assist the nematodes in penetrating the root nodule through the development of feeding sites, although *Pratylenchus coffeae*, which also expresses the protein, does not form feeding sites. This enzyme may have a role in the suppression of the host response to the parasites (Curtis, 2007).

34.11 Alanine

Helminths very actively transaminate L-alanine reversibly to pyruvate using 2-OG as the amino group donor, whereas D-alanine was transaminated at extremely low rates by *H. contortus* and *T. circumcincta* (Walker and Barrett, 1991a). Alanine may not be used as substrate by other enzymes, such as alanine racemase, which was not detected in adult *N. brasiliensis* (Walker

and Barrett, 1991a). Alanine transaminase (AlaAT) activity has been reported in all helminth groups (Barrett, 1991; Walker and Barrett, 1991a; Muhmad, 2006) in both cytosolic and mitochondrial forms; mAlaAT was responsible for 80% of activity in adult *N. brasiliensis*, whereas in *H. contortus* 54% of activity was cytosolic and 22% was associated with the cell debris and cuticle fractions (Walker and Barrett, 1991a). *H. contortus* cAlaAT was less tolerant of temperatures of 45°C than the rat liver enzyme and responded differently to protective agents. Low host vitamin B₆ levels reduced AlaAT activity in *L. carinii* (Beg *et al.*, 1995) and *Hymenolepis diminuta* (Platzer and Roberts, 1970).

34.12 Aspartate and asparagine

High aspartate transaminase (AspAT) activity has been reported in cestodes (Wertheim *et al.*, 1960; Rasero *et al.*, 1968), digeneans (Watts, 1970) and nematodes (Rasero *et al.*, 1968; Walker and Barrett, 1991b; Muhamad, 2006). The properties *T. circumcincta* AspAT were consistent with those of AspAT from other organisms (Muhamad, 2006).

Asparagine synthesis from aspartate by glutamine-dependent asparagine synthetase was identified in *P. redivivus* by Grantham and Barrett (1988). Asparagine can be catabolised by asparaginase or by transamination: asparaginase generates aspartate and ammonium, whereas the transamination produces 2-oxosuccinamate. Asparagine transaminase activity was present in *H. diminuta*, *Hymenolepis citelli* (Wertheim *et al.*, 1960), *P. redivivus* and *H. polygyrus* (Grantham and Barrett, 1986a). Asparaginase activity was localised to the cuticle of *D. immitis* and an active recombinant protein expressed (Tsuji *et al.*, 1999).

34.13 Lysine

L-lysine cannot be synthesised in animal tissues, but is metabolised through either the pipecolate or saccharopine pathways (Broquist, 1991). A bifunctional enzyme (Gaziola *et al.*, 1997) with both lysine-ketoglutarate reductase (LKR) and saccharopine dehydrogenase (SacDH) activity (Galili *et al.*, 2001) forms the saccharopine pathway, the major route for lysine regulation and catabolism in plants and animals (Broquist, 1991; Tang *et al.*, 1997; Arruda *et al.*, 2000). This was the sole route for lysine catabolism in L3 abomasal nematodes, as Δ^1 -piperidine-carboxylate reductase activity resulted in an incomplete pipecolate pathway, whereas this pathway was functional in adult worms (Umair *et al.*, 2012a). Nematode gene sequences deposited in databases are consistent with a bifunctional LKR-SacDH enzyme. Both LKR and SacDH were dual co-factor enzymes and not specific for either NAD⁺ or NADP⁺, as is the case in other organisms, in which there are NADPH-specific LKR activity and NAD⁺-specific SacDH activity (Tang *et al.*, 1997).

34.14 Conclusions

Amino acid metabolism has been investigated in depth mainly in nematodes, particularly parasitic species, making it difficult to compare pathways over the many groups of helminths. As there are species and life-cycle stage differences in expression of enzymes, the presence of genes encoding the proteins does not ensure enzyme activity. The main differences in metabolism of amino acids from that in other animals are in the properties of individual enzymes, rather than the absence or presence of pathways. Unusual features, at least in some helminths, are the lack a full ornithine-urea cycle, the presence of creatinase activity, synthesis of polyamines from either ornithine or agmatine and incorporation of ammonia into glutamate through the GS-GOGAT pathway. There were differences between closely related species,

such as common sheep abomasal nematode parasites, which were not identical in expressing glutamate synthase, arginine decarboxylase and Δ^1 -piperidine-carboxylate reductase. Overall, helminth metabolism was more flexible than generally seen in animals, particularly in the ability to synthesise amino acids from ammonia and degradation of all amino acids to glucose, because of a functional glyoxylate shunt.

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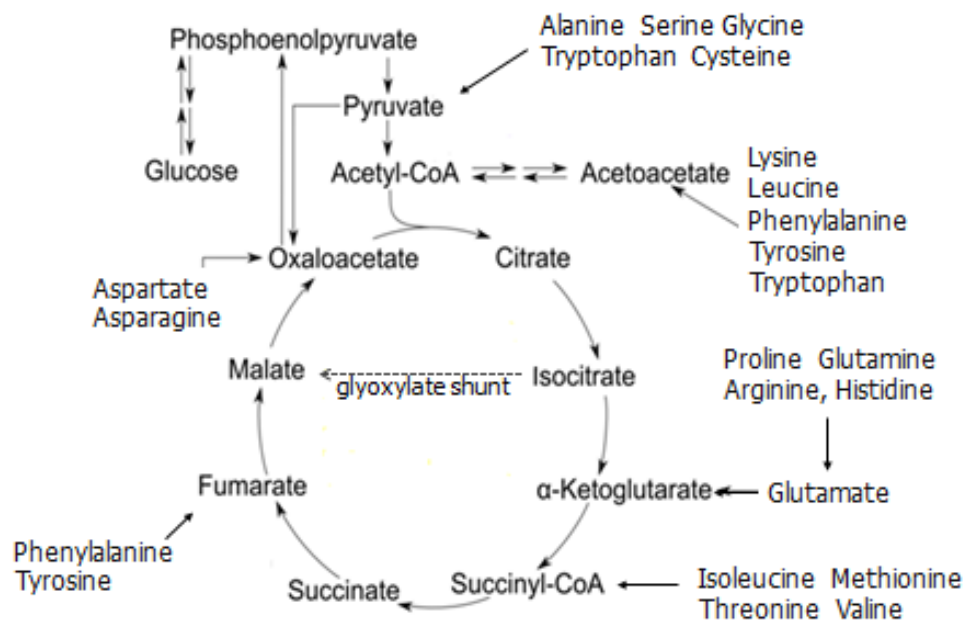


Fig. 34.1. Entry points of amino acids into energy metabolism. All amino acids are glucogenic, at least in nematodes, because of a functional glyoxylate cycle.