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Nonprotein Amino Acids of Plants: Significance in Medicine, Nutrition, and Agriculture

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Those nonprotein amino acids found in food and fodder plants and known to be toxic to man and domestic animals are described. These include toxins from many legume genera including *Lathyrus*, from other higher plant families, from seaweeds, and from fungi. Some inhibit protein synthesis, while others are incorporated into proteins with toxic effects. Basic processes such as urea synthesis and neurotransmission may be disrupted. The probable roles of nonprotein amino acids in protecting plants against predators, pathogens, and competing plant species are considered. The need to learn more of the nutritive value of nontoxic nonprotein amino acids and to explore the potential of others either as drugs or as leads to drugs in human and veterinary medicine is emphasized.

Keywords: Nonprotein amino acids; toxic amino acids; lathyrism; shellfish poisons; ecological significance; nutritional value

INTRODUCTION

The biological and nutritional importance of those 20 amino acids (plus selenocysteine and pyrrolysine) that are incorporated into proteins in accordance with the genetic code cannot be overstated. But what of the hundreds of other naturally occurring amino acids (*1*, *2*) that are not normally found as products of protein hydrolysis? Some of these, such as ornithine and homoserine, are readily recognizable as intermediates or end products of primary metabolism in both plants and animals. The majority, most of which have been isolated from plants, fungi, and microorganisms, may more properly be considered as secondary compounds. This distinction is not always clear however. For example L-5-hydroxytryptophan, the precursor of 5-hydroxytryptamine (serotonin) in the human brain, has a secondary storage role in seeds of *Griffonia* species, where it can account for as much as 14% of the dry seed weight (*3*, *4*). Similarly, L-3,4-dihydroxyphenylalanine (L-DOPA), which serves as a precursor of dopamine in the brain, and has been used as a drug in the treatment of Parkinson's disease, constitutes 6−9% of the dry seed weight of *Mucuna* species (**Figure 1**). Both amino acids are toxic to seed-eating beetle larvae at these concentrations (*5*), and evidence that certain nonprotein amino acids act as antimetabolites when introduced into organisms to which they are foreign (*6*) suggests that some at least fulfill an ecological role in the plants that sequester them. Their presence may, for example, confer a selective advantage by deterring potential predators and/or pathogens or by inhibiting the growth of competing plant species.

The nutritional and agricultural importance of nonprotein amino acids lies in the fact that many occur in plants grown for food and fodder, in wild species harvested inadvertently with crop plants, and in wild species to which domestic animals have occasional access. They are also found in seaweeds eaten by man and in microalgae that from time to time contaminate shellfish used for food. They also occur in toxic fungi.

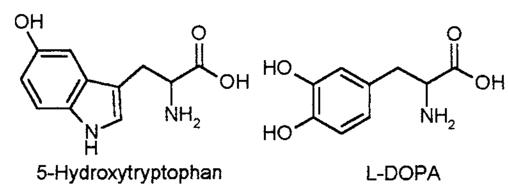

Figure 1. Primary metabolites or secondary compounds?

The primary purpose of this review is to raise awareness of the nonprotein amino acids that are present in food and fodder plants and bring together information relating to those that are known to be toxic to man and/or domestic animals. A secondary purpose is to emphasize how little we know of the nutritive value of those found in food plants or the ways in which the known toxicity of some to microorganisms and insects might be exploited in medicine and agriculture. Compounds such as proline, pipecolic acid, and kainic acid are referred to here as amino acids even though they are, in the strictest sense, imino acids.

TOXINS OF *LATHYRUS*

The legume genus *Lathyrus* contains approximately 130 species that are distributed through the north temperate regions and the mountains of tropical Africa and South America. Several species are of economic importance: *L. odoratus* (sweet pea) and *L. latifolius* (everlasting pea) are cultivated as ornamentals, while others such as *L. sativus* (chickling pea, grass pea), *L. cicera*, and *L. clymenum* are sources of food for man and domestic animals. The seeds, or foods made from the seeds, of these last three species have been implicated as causes of neurological disorders in both man and animals. Neurolathyrism

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in man is characterized by a progressive and irreversible spastic paralysis of the legs. It has been known since antiquity and affects populations in the Middle East, China, Ethiopia, and the subcontinent of India. Serious outbreaks of the disease usually coincide with periods of famine when other foods are in short supply and *Lathyrus* seeds make a major contribution to the diet (*7*). One such outbreak was reported recently in Ethiopia (*8*).

A study of free amino acids and related compounds in the seeds of 49 species of *Lathyrus* (*9*, *10*) showed that the genus could be subdivided on the basis of seed chemistry. Those species implicated as causes of human neurolathyrism were all found to belong to a single chemically defined subgenus, the seeds of which were characterized by the presence of two nonprotein amino acids which had not previously been found in nature.

L-Homoarginine (2-amino-6-guanidinohexanoic acid) was isolated from *L. cicera* (*11*) and *L. sativus* (*12*). It was identical with the synthetic compound previously prepared by Stevens and Bush (*13*) and shown by them to be a substrate for rat liver arginase. In the presence of this enzyme homoarginine undergoes hydrolysis to give lysine, an essential dietary requirement for man, and urea. The same workers also reported that homoarginine elicited a growth response in rats (which are also dependent on dietary lysine) when these animals were maintained on a lysine-deficient diet. It is therefore possible that the homoarginine present in *Lathyrus* seeds may act as a valuable precursor of lysine when dietary protein is in short supply. It has however been reported to induce a hypersensitivity and mortality in rats when administered intraperitoneally at 10 mmol/kg of body weight but not at 5 mmol/kg of body weight (*14*), while Tews and Harper (*15*, *16*) found that homoarginine fed to rats on a lysine-deficient diet reduced both growth and food intake and depressed the concentrations of ornithine, lysine, and arginine in the brain. More recently, it has been reported that the oral administration of homoarginine depressed feed intake in chickens (*17*). Clearly, further information on the potential toxicity of different concentrations of dietary homoarginine to animals (including man) is required. L-Homoarginine does not appear to inhibit nitric oxide synthase, which catalyzes the production of the neurotransmitter nitric oxide from arginine in mammalian vascular endothelial cells. It does however inhibit the uptake of L-arginine by those cells (*18*) and could presumably slow nitric oxide synthesis by depriving the enzyme of its substrate. The observation that skeletal alkaline phosphatase in canine serum is strongly inhibited by 10 mM L-homoarginine (*19*) raises the interesting possibility that this compound could be a contributory factor in some forms of osteolathyrism, reference to which will be made later. There is no evidence that the seeds of *Lens culinaris* (lentil), which also contain L-homoarginine (*20*), have adverse effects in man. The concentration of the free amino acid in the seeds of this legume is however lower than that found in the seeds of *L. sativus*.

β-N-Oxalyl-L-α,*β*-diaminopropionic acid (*β*-ODAP, 2-amino-3-oxalylaminopropanoic acid), sometimes referred to as *β*-oxalylaminoalanine or BOAA, was isolated from seeds of *L. sativus* (*21*−*23*), characterized as *β*-ODAP, and shown to be neurotoxic in higher animals. *L. sativus* is the most widely cultivated species of *Lathyrus* and a valuable source of food and fodder in some of the poorer regions of the world. As a nitrogen-fixing legume, the plant requires no added nitrogen fertilizer. It thrives on poor soils that will not support many other crop species; it is also resistant to both flooding and drought. The concentration of *β*-ODAP in the seeds is subject to genetic control, and progress has been made in identifying, conserving, and using low-*β*-ODAP varieties in breeding programs (*24*). The concentration of *β*-ODAP may also be influenced by environmental factors. In ripe seeds, water stress causes an increase and salinity a decrease in the concentration of the toxin (*25*). Similar increases and decreases are induced by zinc and ferrous ions, respectively (*26*).

The elucidation of the biosynthetic pathway to *β*-ODAP via *β*-(isoxazolin-5-on-2-yl)-L-alanine (BIA) and α,*β*-diaminopropionic acid (DAPA) in seedlings of *L. sativus* (*27*) holds out the possibility that a variety without *β*-ODAP may be developed by eliminating one or more of the genes coding for an enzyme or enzymes involved in its biosynthesis. BIA has also been found in seedlings of *Pisum sativum* (garden pea), *Lens culinaris* (lentil), and *L. odoratus* (sweet pea) but is not metabolized to *β*-ODAP in these species.

When *β*-ODAP occurs in *Lathyrus* seeds, it is accompanied by lower concentrations of α-oxalyldiaminopropionic acid (α-ODAP, 3-amino-2-oxalylaminopropanoic acid). In solution the individual isomers undergo spontaneous rearrangement to give a mixture of both forms (*28*), and the mechanism of this rearrangement has been investigated (*29*). In nerve cells *β*-ODAP, which is a close structural analogue of glutamic acid, acts as an agonist at "glutamate-preferring" receptors (*30*, *31*). No such activity is shown by α-ODAP, and the methods of preparation and cooking that favor the isomerization of *β*-ODAP may well reduce the toxicity of food made from *L. sativus* seeds or flour.

The seeds of a second group of 12 *Lathyrus* species analyzed by Bell (*9*, *10*) lacked homoarginine but contained not only α- and *β*-ODAP but also α,*γ*- diaminobutyric acid (DABA, 2,4-diaminobutanoic acid, aminobutyrine) together with its α-*N*- and *γ*-*N*-oxalyl derivatives α-ODAB and *γ*-ODAB (*28*). Seeds of these species are not used for food or fodder but have proved highly toxic in experimental animals. One species of the group (*L. sylvestris*) is however considered to have potential as a forage crop for ruminants (*32*). In this context it is worth remembering that the leaves have been reported (*33*) to contain no only DABA, but also *β*-ODAP, *γ*-ODAB, and *O*-oxalylhomoserine.

DABA was first identified in *Polygonatum multiflorum* (*34*) and subsequently isolated from *L. latifolius* by Ressler et al. (*35*), who demonstrated its acute neurotoxicity in rats. O'Neal et al. (*14*) showed that DABA, which is a lower homologue of ornithine, induces ammonia toxicity in these animals by inhibiting the liver enzyme ornithine transcarbamylase and disrupting the urea cycle.

γ-*N*-Oxalyl-L-α,*γ*-diaminobutyric acid (*γ*-ODAB, 2-amino-4-oxalylaminobutanoic acid) acts at glutamate receptor sites in isolated neuronal preparations. Unlike *β*-ODAP, however, which is an agonist, *γ*-ODAB is a depressant which antagonizes *N*-methyl-D-aspartate (NMDA)-induced depolarization of frog motor neurons (*36*).

The seeds of a third group of *Lathyrus* species which includes *L. odoratus* (sweet pea) were characterized by the presence of the two osteolathyrogens *β*-*N*-(*γ*-L-glutamyl)aminopropionitrile (*γ*-glutamyl-BAPN) and free *β*-aminopropionitrile (BAPN). The seedlings of *L. odoratus* are, on the other hand, a rich source of a novel group of isoxazolin-5-on-2-yl amino acids and related compounds with physiological activity.

γ-Glutamyl-BAPN was originally isolated from seeds of *L. odoratus* (*37*, *38*) and *L. pusillus* (*39*) and identified chromatographically in seeds of *L. hirsutus* and *L. roseus* (*10*). Dasler (*40*) showed that the physiologically active part of the molecule was the BAPN moiety. The compound produces severe skeletal

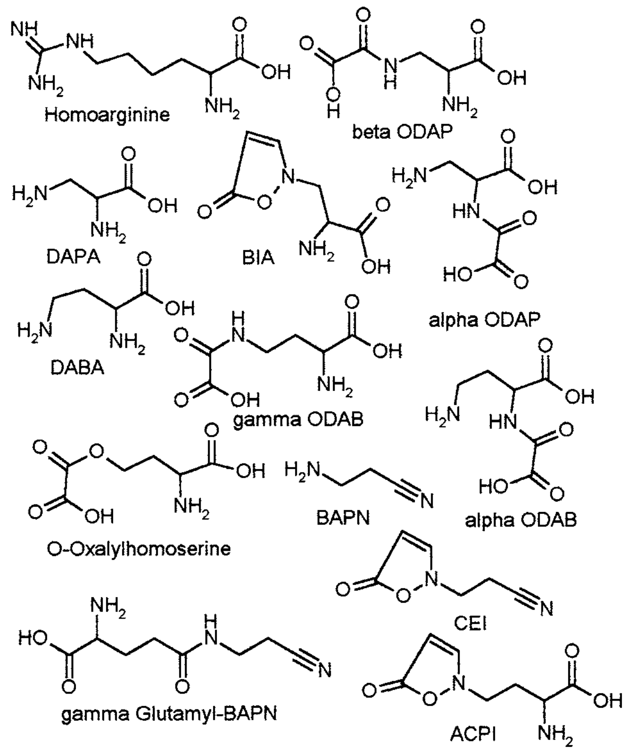

Figure 2. Amino acids and cyano compounds from *Lathyrus* species.

abnormalities when fed to young rats (*37*) and aortic aneurisms in both rats and chicks (*41*). Both γ-glutamyl-BAPN and BAPN exercise their toxicity by inhibiting the formation of cross linkages between the polypeptide chains during the synthesis of collagen (*41*) and elastin (*42*).

α-Amino-γ-(isoxazolin-5-on-2-yl)butyric acid (2-(3-amino-3-carboxypropyl)isoxazolin-5-one, ACPI) was one of eight different isoxazolin-5-one derivatives reported (*43*) to be present in the seedlings of *L. odoratus*. On hydrolysis or photolysis it yielded DABA, and when fed to day-old chicks produced the same neurotoxic effects as DABA. Indeed, DABA appeared to be the major metabolite of ACPI and was found in the chick brain and excreta. A second compound, though not an amino acid, was 2-cyanoethyl-isoxazolin-5-one (CEI), which on hydrolysis or photolysis yielded BAPN. When given CEI, chicks showed symptoms of osteolathyrism. Free BAPN, together with unchanged CEI, was found in the excreta.

While BAPN and its γ-glutamyl derivative are not found in seeds of *L. sativus* (*10*), β-ODAP, its precursor BIA, ACPI, and CEI have been found in the seedlings (*44*). As it is the practice in certain areas of the world to eat the green parts of the plant when in season, the skeletal abnormalities (osteolathyrism) observed among some patients suffering from neurolathyrism in both India and Bangladesh (*45*, *46*) may result from the ingestion of CEI. Low concentrations of CEI in the seeds have also been suggested as a possible cause of osteolathyrism (*47*). The inhibition of skeletal alkaline phosphatase by L-homoarginine (*19*), to which reference was made earlier, raises the possibility that yet another compound could be involved (**Figure 2**).

TOXIC AMINO ACIDS OF OTHER LEGUME GENERA

β-Cyanoalanine (2-amino-3-cyanopropanoic acid, BCNA) and γ-glutamyl-BCNA are found in the seeds of *Vicia sativa* (common vetch), a species grown for fodder (*48*, *49*), and in 15 other species of the same genus (*50*). Accumulation of BCNA has also been reported in a cyanide-resistant strain of *Enterobacter* (*51*), and both BCNA and the γ-glutamyl derivative occur in the neurotoxic mushroom *Clitocybe acromelalga* (*52*).

BCNA can be hydrolyzed to asparagine in a number of plant species, and it is probable that BCNA is present in many higher plants, but at concentrations too low to cause toxicity in animals. The administration of BCNA by stomach tube to weanling male rats at a concentration of 15 mg/100 g of fresh weight produced reversible hyperactivity, tremors, convulsions, and rigidity. When injected subcutaneously at a concentration of 20 mg/100 g of fresh weight, convulsions, rigidity, and prostration were followed by death (*48*). The γ-glutamyl derivative was as toxic (on a molar basis) as the free amino acid to male Sherman rats, but only about half as toxic to White Leghorn chicks. When fed to the chicks, as part of their diet, at concentrations equivalent to half of those present in the seeds of *V. sativa*, both compounds produced a terminal convulsive state within a week (*49*). BCNA acts as an inhibitor of cystathionase in the pyridoxal phosphate requiring conversion of cystathionine to cysteine (*53*), of aspartate decarboxylase (*54*), and of asparaginase and glutaminase in some procaryotes (*55*). There has been renewed interest in the potential toxicity of BCNA to man and livestock as a result of increased *V. sativa* production and seed export from Australia (*56*).

Canavanine (2-amino-4-guanidinoxybutanoic acid) occurs in over 350 species of the Papilionoideae, a subfamily of the Leguminosae (*57*). Seeds are a particularly rich source of the amino acid, and concentrations as high as 13% dry weight have been reported in those of *Dioclea megacarpa* (*58*).

Canavanine is an analogue of arginine and acts as an antimetabolite in many biological systems (*1*, *59*). Evidence of its toxicity to mammals in vivo is limited. It is perhaps significant however that monkeys (*Cynomolgus macaques*) fed on the seeds and sprouts of *Medicago sativa* (alfalfa), which contain canavanine, develop hematological and serological abnormalities. These abnormalities are similar to those seen in human systemic lupus erythematosus (SLE), an autoimmune disease that adversely affects the kidney and skin. This syndrome can be reactivated in monkeys by feeding them canavanine (*60*). Reactivated SLE was also observed in people who had eaten alfalfa tablets over a prolonged period (*61*). Prete (*62*) showed that canavanine can affect β-lymphocyte function, accelerating the disease of autoimmune mice and inducing antibody-mediated autoimmune phenomena in normal mice. She also showed (*63*) that canavanine affected the charged surface membrane properties of autoimmune β cells and suggested that such alterations may be associated with abnormal (auto)immune response. These and other results have been reviewed (*64*). Morimoto et al. (*65*) showed that canavanine acts on human suppressor-inducer T cells to regulate antibody synthesis and that the lymphocytes of SLE patients are specifically unresponsive to canavanine.

Canaline (2-amino-4-aminoxybutanoic acid), which is formed by the action of arginase on canavanine, is highly toxic to insects, but little is known of its activity in higher animals. Canaline has been isolated from two legume species and could possibly occur in all canavanine-synthesizing species (*58*).

Indospicine (2-amino-6-amidinohexanoic acid) has been identified as the cause of Birdsville disease, a neurological syndrome found in horses that have eaten *Indigofera linnaei*, a legume which occurs widely in the Northern Territory of Australia. Indospicine was originally isolated from *I. spicata*, a native of Africa and Asia, and shown by Hegarty and Pound (*66*) to be a potent antimetabolite of arginine. It is both teratogenic and hepatotoxic in laboratory animals and ruminants

(*67*). Birds fed on seeds of *I. spicata* do not develop liver damage however (*68*), and it has been suggested that being uricotelic they are less susceptible to the effects of indospicine, an arginase inhibitor, than ureotelic animals (*66*). Indospicine is not broken down by arginase, and it has been shown to block the incorporation of arginine, and consequently other amino acids, into rat liver protein (*69*, *70*).

Even among mammals there are marked differences in both sensitivity to and the effects produced by indospicine. This is clearly illustrated by the contrasting responses of horses and dogs to the compound. In 1984 30 dogs were reported to have died in Alice Springs after eating horse meat from locally slaughtered horses. One of these horses was known to have been a clinical case of Birdsville disease, which is characterized by neurological, but not hepatic, abnormalities. Postmortem examinations of seven of the dogs revealed "severe liver damage, icterus and other evidence of liver failure". In subsequent experiments it was shown that the meat of an apparently healthy horse that had eaten *I. linnaei* contained sufficient indospicine to cause liver damage when fed to dogs (*71*). Purified indospicine (administered intraperitoneally and as a dietary additive) was used to confirm that the liver damage was due to indospicine and not to some other toxin that might have been present in the horse meat (*72*).

Mimosine (β-[*N*-(3-hydroxy-4-pyridone)]-α-aminopropionic acid) was first isolated from *Mimosa pudica* (*73*), but it was its presence in high concentrations in the leaves and seeds of *Leucaena leucocephala* (Lam.) de Wit (leucaena), formerly known as *Leucaena glauca*, that led to the recognition of its toxicity. The young leaves of this leguminous shrub, which has great potential as a fodder crop in the tropics, may contain as much as 8−10% dry weight of mimosine (*74*), while even higher concentrations can occur in the seeds (*75*). The ingestion of leaves and seeds of leucaena has been held responsible for the loss of hair in both animals and man. Crounse et al. (*76*) demonstrated that hair growth was inhibited in mice fed on a diet containing either the ground seed of leucaena or purified mimosine. In addition to its depilatory effects mimosine interferes with reproduction (*77*) and acts as a teratogen in rats (*78*).

In ruminants the toxicity of leucaena is dependent on the rate and degree of mimosine breakdown, first by plant enzymes, during the mastication of fresh (but not dried) plant material, and second by bacteria in the rumen (*79*). This breakdown gives rise to 3-hydroxy-4(1*H*)-pyridone (DHP, 3,4-DHP), a powerful goitrogen (*80*) which may itself undergo transformation to the isomeric 2,3-DHP, which is also a goitrogen (*79*).

The chronic toxic effects, due to DHP, seen in cattle grazing on leucaena in Australia were not observed in ruminants feeding on leucaena in Hawaii and Indonesia. While the rumen of the Australian animals contained bacteria able to degrade mimosine to DHP, those present in the rumen of the Hawaian and Indonesian animals were also able to break down the pyridone ring of DHP to nontoxic products. By transferring DHP-degrading bacteria, isolated from the rumen of Indonesian goats, to the rumen of Queensland goats and cattle, it has been possible to protect Australian ruminants feeding on leucaena against both the depilatory effects of mimosine and the goitrogenic effects of DHP (*79*, *81*). Four strains of a bacterium able to degrade DHP have been isolated from the rumen contents of a goat in Hawaii. The bacterium has been designated *Synergistes-jonesii*, indicating a new genus and species (*82*). The leucaena psyllids (jumping plant lice) which infest *L. leucocephala* are also able to break down mimosine and DHP (*83*).

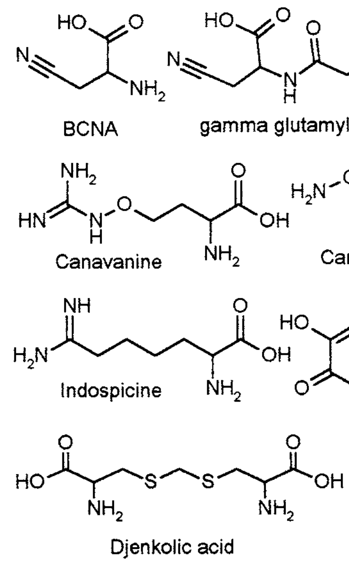

Figure 3. Toxins of other legume genera.

Endemic goiter is widespread among the people of Indonesia, and it has been suggested (*84*) that this may be related to the use of the young shoots, pods, and green seeds of leucaena in salads. Whether these contain toxic concentrations of DHP remains to be demonstrated, but it has been shown (*85*) that mimosine in leucaena can be broken down after harvesting, by enzymes present in the plant tissues. Clearly, if significant breakdown occurs in shoots, pods, or seeds before they are eaten, then the possibility of DHP intoxication in nonruminants must exist.

Djenkolic acid (*S*,*S′*-methylenebiscysteine) occurs widely in the Mimosoideae, a subfamily of the Leguminosae, but derives its name from a particular species, *Archidendron pauciflorum* (*Pithecellobium lobatum*), the djenkol bean. The bean, which contains 1−2% djenkolic acid (*86*), is eaten in Indonesia, where its consumption can cause acute kidney malfunction and impaired urine flow (*87*). The toxic effects result from the low solubility of the amino acid under acid conditions, which leads to the formation of crystals in the kidney and urinary tract (**Figure 3**).

TOXINS OF OTHER PLANT FAMILIES

Hypoglycin (hypoglycin A, α-amino-β-(2-methylenecyclopropyl)propionic acid, 2-amino-3-methylenecyclopropylpropanoic acid) is found in the fruit of *Blighia sapida* (Ackee). This tree, a native of West Africa, was reputedly brought to Jamaica in 1793 by Captain Bligh, and its fruits continue to be eaten by the people of that island. It is now grown elsewhere in the West Indies and in various countries on the Atlantic coast of Central America but is not commonly used for food except in Jamaica. The fruit is a three-lobed capsule (7−10 cm long) which when ripe splits open to reveal three black seeds attached to the edible cream-colored arils (*88*). If unripe arils are eaten, they rapidly cause vomiting, which may be followed by convulsions, coma, and death. The concentration of hypoglycin in the unripe arils may be as much as 0.1% dry weight, which is 10 times the concentration found in ripe arils (*89*). When ingested, the amino acid causes a dramatic fall in blood glucose levels from normal values of between 80 and 100 mg % to 10 mg % or less. In addition to free hypoglycin, the fruit but not the aril contains γ-glutamylhypoglycin, which was originally designated hypoglycin B. In rats this compound elicits effects comparable to those of hypoglycin when given at twice the concentration (*90*).

It appears that the cause of hypoglycemia is not the amino acid itself but a metabolite, methylenecyclopropylacetic acid, which is formed in the liver and acts by blocking fatty acid metabolism (*91*, *92*). The inhibition of fatty acid oxidation increases the organism's dependence on glucose as a source of energy, but the replacement of glucose by gluconeogenesis is itself dependent on the availability of acetyl-CoA, NADH, and ATP, which are products of hepatic fatty acid oxidation (*92*, *93*). Methylenecyclopropylacetic acid therefore induces rapid carbohydrate breakdown while simultaneously inhibiting carbohydrate synthesis.

In addition to the "vomiting sickness" caused in adults, the fruit of *B. sapida* has been implicated as a possible cause of birth defects in children. Hypoglycin proved to be teratogenic in rats but not in chicks. It has been suggested that the abnormalities induced in rat embryos are caused by competition between hypoglycin and the essential amino acid leucine of which it is a close analogue. In a chick, however, the embryo develops within the egg, which is "preloaded" with necessary nutrients. In these circumstances the hypoglycin would be unable to compete successfully with the large pool of leucine available for normal development (*94*).

β-*N*-Methyl-α,β-diaminopropionic acid (MeDAP, 2-amino-3-methylaminopropanoic acid), sometimes referred to as β-methylaminoalanine (BMAA), is a possible cause of amyotrophic lateral sclerosis−parkinsoism dementia (ALS−PD), a motor neuron disease found among Chamorro Indians in Guam and adjacent islands of the Marianas group. The similarity of this disease to neurolathyrism suggested that it might be associated with a dietary factor in the seeds of *Cycas circinalis*, which are processed and eaten by the people of the islands (*95*). The seeds contain the carcinogen cycasin and also MeDAP (*96*, *97*). MeDAP was found to be acutely neurotoxic when administered in relatively high concentrations to experimental animals, but no chronic toxicity was caused by injecting lower concentrations into growing rats over a period of 78 days (*98*).

The relatively low concentrations of MeDAP in the seeds led Rosenthal and Bell (*58*) to question whether MeDAP could be responsible for ALS−PD, and the same doubt was later expressed by Duncan et al. (*99*). Primates nevertheless appear more sensitive to MeDAP than rodents, and cynomologous monkeys showed signs of motor neuron dysfunction after dosing with MeDAP at 100−350 mg/kg for several weeks (*100*). It is therefore possible, but far from certain, that MeDAP when ingested at low concentration over a prolonged period may be responsible for ALS−DP in Guam. MeDAP, like β-ODAP, acts as a glutamate agonist at *N*-methyl-D-aspartate (NMDA)-preferring receptors of the neuron. Its toxicity depends however on the presence of bicarbonate (*101*) with which it forms a stable carbamate that is a close analogue of glutamate (*102*). Using concentrations of MeDAP similar to those used by Vega et al. (*97*), Seawright et al. (*103*) showed selective degeneration of cerebellar cortical neurons in rats. All cells showing degeneration were GABAergic, although not all were known to be NMDA receptors.

Cattle eating large amounts of *Brassica oleracea* var. *acephala* (marrowstem kale) tend to develop hemolytic anemia, which can be fatal. The kale contains *S*-methylcysteine sulfoxide (SMCO), which in the rumen is converted to the active hemolytic factor dimethyl disulfide (*104*, *105*). SMCO, which also occurs in other species of *Brassica* (*106*, *107*), is not toxic to nonruminant animals including man and may indeed be beneficial as it lowers the level of plasma cholesterol in rats (*108*). The presence of SMCO is an important deterrent to the exploitation of forage and root *Brassica* crops (*109*).

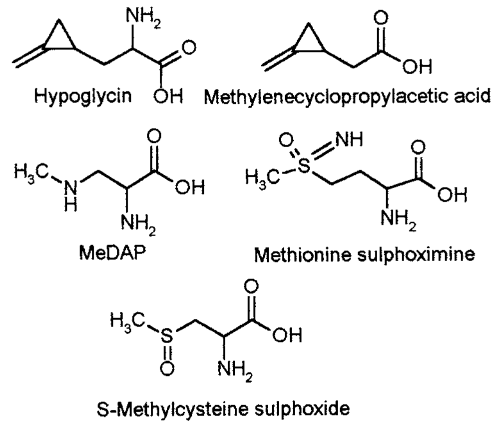

Figure 4. Toxins of other plant families.

L-Methionine sulfoximine (MSO) was first discovered as the toxic principle in "agenized" wheat flour that caused hysteria in dogs (*110*). The neurotoxin was subsequently found to occur naturally in three species of the Connaraceae, *Cnestis polyphylla*, *Cnestis glabra*, and *Rourea orientalis* (*111*). The seeds of a third *Cnestis* species, *Cnestis palala* (a climbing shrub of Southeast Asia), are reputedly used in Malaya and Thailand to poison dogs. These seeds have been shown (*112*) to contain high concentrations (524 μmol/g of dry weight) of MSO, and their acute toxicity to dogs has been confirmed (oral administration of ground seed (347 mg/kg) being fatal within 24−25 h). The absolute configuration of the isolated amino acid was established as 2(*S*)-methionine *S*(*S*)-sulfoximine [(2*S*,*SS*)-2-amino-4-(*S*-methylsulfonimidoyl)-*n*-butanoic acid] (**Figure 4**).

SELENIUM-CONTAINING AMINO ACIDS

A number of selenium analogues of sulfur-containing amino acids are found in plants (*113*). Traces of selenium (ca. 0.01 ppm) are beneficial to animals (*114*), and indeed, selenocysteine is an essential component of a few important enzymes found in organisms throughout the living world (*115*). Dietary concentrations of selenium greater than 1 ppm are likely to prove toxic to animals, however (*116*). Less sensitive than animals, plants such as *Trifolium repens* (white clover) and *Lolium perenne* (perennial rye grass) will tolerate concentrations of 5 ppm selenium in their tissues before growth retardation occurs, while others such as *Triticum vulgare* (wheat) will tolerate concentrations as high as 30 ppm before they are affected. In all these "nonaccumulator" species the majority of the selenium occurs as protein-bound selenocystine and selenomethionine (*116*).

In contrast there are "accumulator" species that grow exclusively on seleniferous soils. These may contain as much as 15000 ppm selenium. Selenium is not only nontoxic to these species but is an essential requirement. The accumulator species do not incorporate selenium into their proteins but sequester the element principally in the form of *Se*-methyl-L-selenocysteine or selenocystathionine. The first of these is found in plants such as *Astragalus bisulcatus* (Leguminosae) and *Oonopsis condensata* (Compositae) and the second in plants such as *Neptunia amplexicaulis* (Leguminosae) and *Morinda reticulata* (Rubiaceae), while both occur in the crucifer *Stanleya pinnata* (*117*).

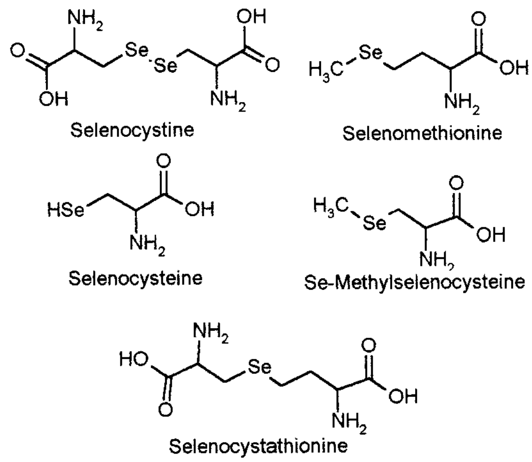

Figure 5. Seleno amino acids.

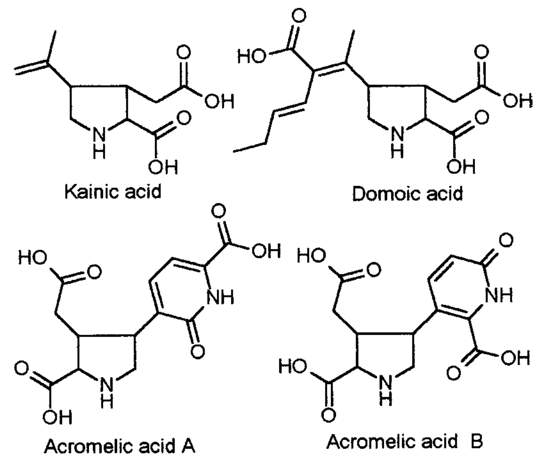

Figure 6. Kainoid amino acids.

Selenium present in nonaccumulator species growing on seleniferous soils can give rise to a condition known as "alkali disease" in grazing animals. This condition, which involves loss of hair, emaciation, and sloughing of the hooves, is caused by ingesting maize, wheat, barley, oats, and other grasses containing between 10 and 30 ppm selenium (*118*). The poisoning of human beings after the ingestion of grain grown on selenium-rich soils in Columbia has also been reported (*119*).

A second type of toxicity in grazing animals, which has in the past been attributed to selenium poisoning, is referred to as "blind staggers". Animals suffering this disease "appear to have affected vision, wander, stumble and show loss of appetite". Death is preceded by respiratory distress and paralysis. It now appears however that these symptoms, as seen in sheep after feeding on the accumulator species *A. bisulcatus*, involve a combination of chronic selenium poisoning with poisoning by the polyhydroxy alkaloid swainsonine (*120*).

The nuts of the large deciduous tree *Lecythis ollaria* (Lecythidaceae) are eaten by people in Central and South America. In certain areas of Venezuela however they are known to cause abdominal discomfort, nausea, vomiting, and diarrhea. A remarkable feature of the syndrome is the temporary loss of hair from the scalp and body a week or two after the ingestion of the nuts and after the first acute sickness has terminated. The toxin responsible has been identified (*121*) as selenocystathionine (**Figure 5**).

KAINOID AMINO ACIDS OF ALGAE AND FUNGI

Kainic acid (3-carboxymethyl-4-isopentylproline), from which the group takes its name, is a neurotoxin first isolated, together with the epimeric allokainic acid, from *Digenea simplex*, a seaweed which has been used for centuries in the islands of Japan as an ascaride for the treatment of roundworm infestation (*122*). It has since been identified in other algae (*123*−*126*) including some strains of the seaweed *Palmaria palmata*, which has been used as a vermifuge in Ireland and as a food supplement in other coastal countries of the north Atlantic (*125*). Kainic acid is a potent excitatory amino acid, being a close chemical analogue and agonist of the neurotransmitter glutamic acid. Its signficance in medicine has been primarily as a tool in neurophysiological research. In this respect it resembles *N*-methyl-D-aspartic acid (NMDA), another algal amino acid (*126*). It is of interest that the physiological properties of NMDA, like those of L-homoarginine, were originally studied using synthetic material before it was realized that the amino acids occurred naturally.

Domoic acid (3-carboxymethyl-4-(2-carboxy-1-methylhexa-1,3-dienyl)proline) was first isolated from the seaweed *Chondria armata*, which, like *D. simplex*, has been used as an ascaricide in remote islands of Japan (*122*). It has since been found in other algae (*126*). In 1987, however, an outbreak of gastrointestinal and neurological illness occurred among individuals who had eaten mussels collected from three estuaries of Prince Edward Island in eastern Canada. The cause of this outbreak was traced to the presence in the mussels of domoic acid (*127*). The ultimate source of the toxin was *Pseudonitzschia pungens* (*Nitzschia pungens*), a pennate phytoplanktonic diatom on which the mussels had been feeding. The diatom, which was in extensive bloom at the time of the outbreak, was isolated from the digestive glands of the mussels and shown to synthesize domoic acid in cell culture (*128*, *129*). It was estimated that the most severely affected patients had ingested 290 mg of domoic acid with the mussels, a great deal more than the 20 mg present in a dose of *C. armata* extract used for killing intestinal worms in Japan (*130*). Domoic acid has also been found in shellfish and phytoplankton from the Gulf of Mexico (*131*) and in razor clams on the western seaboard of the United States (*132*). Domoic acid is a close chemical analogue of both the neurotransmitter glutamic acid and kainic acid. Five other amino acids closely related to domoic acid have been reported in fish tissue contaminated with the same microalga (*133*). Domoic acid toxicity and β-ODAP-induced neurolathyrism present a common pattern of neuronal hyperexcitation followed by chronic loss of function in neural systems susceptible to excitotoxic degeneration (*134*).

Acromelic acids A and B were isolated from the highly poisonous Japanese mushroom *Clitocybe acromelalaga* and subsequently synthesized (*135*). Reference has already been made to this mushroom as a source of BCNA and its γ-glutamyl derivative (*52*). Ingestion of the mushroom causes sharp pain and red edema of the hand and foot after several days, and these effects may last for a month or more. Both acromelic acids are more potent as neuroexitatory amino acids than domoic acid. The importance of stereochemistry in determining the biological activity of kainoid amino acids, both natural and synthetic, is emphasized by Parsons (*136*) in an excellent review (**Figure 6**).

TOXICITY TO INSECTS

The observed toxicity of nonprotein amino acids (including canavanine) from various legume seeds to the larvae of the seed-eating beetle *Callosobruchus maculatus* (the cowpea weavil) and also to those of *Prodenia eridania* (the southern army worm) suggested a defensive role for the compounds (*5*, *137*). Clearer evidence of such a role was the observation that the larvae of another beetle (*Carydes brasiliensis*), which feed on the canavanine-rich seeds of the legume *Dioclea megacarpa*, possess an arginyl-tRNA synthetase which discriminates against canavanine and prevents its damaging incorporation into the insect's protein in place of arginine (*138*). Clearly, biochemical adaptation in the successful predator has enabled it to circumvent the seed's chemical defense. Homoarginine, however, is incorporated into the protein of *Manduca sexta* (the tobacco hornworm) but unlike canavanine does not appear to affect larval growth (*139*). In a study of the effects of seven nonprotein amino acids on the lysozyme activity of the same insect (*140*), Rosenthal showed that canavanine, azetidine-2-carboxylic acid, selenomethionine, and 2-aminoethylcysteine caused significant loss of lysozyme activity. He also found that the concurrent administration of canavanine and 2-aminoethylcysteine markedly intensified their individual capacities to inhibit the enzyme.

ρ-Aminophenylalanine, previously reported as a growth inhibitor of *Escherichia coli* (*141*), has been found in the seeds of a restricted number of *Vigna* species. When screened for resistance to the larvae of the old world bruchid beetle *Callosobruchus maculatus* and the new world bruchid *Zabrotes subfasciatus*, both of which are generalists and important pests of *Vigna* and *Phaseolus* crops, it was found that no live adults emerged from any of the seeds containing *ρ*-aminophenylalanine on which eggs had been laid. Using artificial seeds into which the amino acid was incorporated, it was shown that 0.3% was lethal to *Z. subfasciatus* and 0.75% to *Ca. maculatus* while lower concentrations (0.075−0.1%) "markedly increased development times in both insect species indicating ecologically significant sub-lethal effects of this compound" (*142*). These experiments also showed that *ρ*-aminophenylalanine was 4 times as toxic to larvae of *C. maculatus* as was L-DOPA (*5*).

INFLUENCE ON FEEDING IN INSECTS

The presence of compounds that deter a potential predator from feeding may be as important, or more important, to the survival of a plant than the presence of compounds that are toxic to that predator. The study of nonprotein amino acids as feeding deterrents has been restricted largely to insects. Navon and Bernays (*143*) using the Acridids *Locusta migratoria migratorioides* (R. and F), *Chortoicetes terminifera* (Walker), and *Schistocerca americana gregaria* (Dirsh.), which are, respectively, graminivorous, less strickly graminivorous, and polyphagous, showed that the first two were inhibited from feeding by most of the nonprotein amino acids used, the majority of which had been isolated from legumes, while the third was little affected. Low concentrations of α-aminoadipic acid and *β*-alanine stimulated feeding, but these two nonprotein amino acids may more properly be regarded as primary metabolites than as secondary compounds. Further studies (*144*) using the nymphs of *Anacridium melanorhodon*, which feed on the leaves of *Acacia* species and the graminivorous *L. migratoria*, showed that concentrations of homoarginine, pipecolic acid, and 4-hydroxypipecolic acid comparable to those found in the leaves of *Acacia* species inhibited feeding by *L. migratoria* but not by *A. melanorhodon.* Feeding by *A. melanorhodon* was inhibited by some of the nonprotein amino acids found in the seeds, but not the leaves, of *Acacia* species. Using the larvae of *Spodoptera littoralis* (African leaf worm), it was shown (*145*) that the nonprotein amino acids found in the leaves of *Lathyrus latifolius* (the everlasting pea) could act either as feeding deterrents or as phagostimulants. *γ*-ODAB and *O*-oxalylhomoserine were antifeedants, *β*-ODAP (the cause of neurolathyrism in man) and homoserine were phagostimulants over the concentration range used. DAPA was a phagostimulant at low concentrations and an antifeedant at higher concentrations. The insect's reaction to this compound was reminiscent of our own to mustard or jalapeño peppers.

Study of the effects of nonprotein amino acids from species of the legume genus *Calliandra*, including *S*-(*β*-carboxyethyl)-cysteine, pipecolic acid, and various hydroxylated pipecolic acids, on the aphid *Aphis Fabae* (*146*) provided evidence that certain combinations of amino acids were more effective in inhibiting feeding, survival, and fecundity in this sucking insect than were individual compounds. While most plants probably do not rely on one secondary compound or even one group of secondary compounds as protection against potential predators, it is clear that nonprotein amino acids, singly or acting synergistically, can be significant weapons in their chemical armories.

TOXICITY TO PLANTS AND ORGANISMS OF THE RHIZOSPHERE

In an early paper Fowden (*147*) described the effects of a number of nonprotein amino acids on the growth of *Vigna* (formerly *Phaseolus*) *aureus* (mung bean) seedlings. Azetidine-2-carboxylic acid caused the greatest growth inhibition, and subsequent studies (*148*, *149*) showed that this lower homologue of proline was replacing proline in the protein of susceptible species but not in the protein of synthesizing species. These latter possessed a prolyl-tRNA synthetase that discriminated against azetidine-2-carboxylic acid. It is also of interest (*150*) that the tyrosyl-tRNA synthetase of *V. aureus* (a nonproducer of 3-(3-hydroxymethylphenyl)alanine) activates that close analogue of tyrosine 5 times faster than the tyrosyl-tRNA synthetase of another legume, *Caesalpinia tinctoria* (a producer species). Growth of *V. aureus* was also inhibited by mimosine, although the mechanism of inhibition was not a simple replacement of phenylalanine in protein synthesis (*151*). Using *Lactuca sativa* (lettuce), Wilson and Bell (*152*, *153*) showed that at 1 mM concentration 15 nonprotein amino acids from legume and cycad species suppressed hypocotyl growth, radicle growth, or both, by more than 50% and root exudates of *Neonotonia (Glycine) wightii* leucocephala, containing canavanine, produced marked inhibition of both hypocotyl and radicle growth (*154*). BIA, found in the root exudates of *Pisum sativum* (pea) and *Lathyrus odoratus* (sweet pea), inhibits germination in a number of plant species (*155*). The same compound shows broad-range antifungal activity (*156*), suggesting that this and other nonprotein amino acids found in root exudates may play a significant role in determining the composition of the rhizosphere by discouraging potential pathogens and possibly supporting the growth of beneficial organisms such as nitrogen-fixing bacteria. It has also long been known that some nonprotein amino acids can inhibit pollen tube development in nonproducer species, effectively providing a barrier to cross pollination between producer and nonproducer species (*157*). The recently reported ability of the cover crops *Mucuna pruriens* and *Canavalia ensiformis* to suppress the growth of cogon grass (*158*) may well be related to the presence L-DOPA and canavanine in their respective root exudates (**Figure 7**).

NUTRITIONAL SIGNIFICANCE IN MAN AND DOMESTIC ANIMALS

Free amino acids (protein and nonprotein) and their water-soluble derivatives of low molecular weight frequently play a major role in the storage of nitrogen by plants, and methods

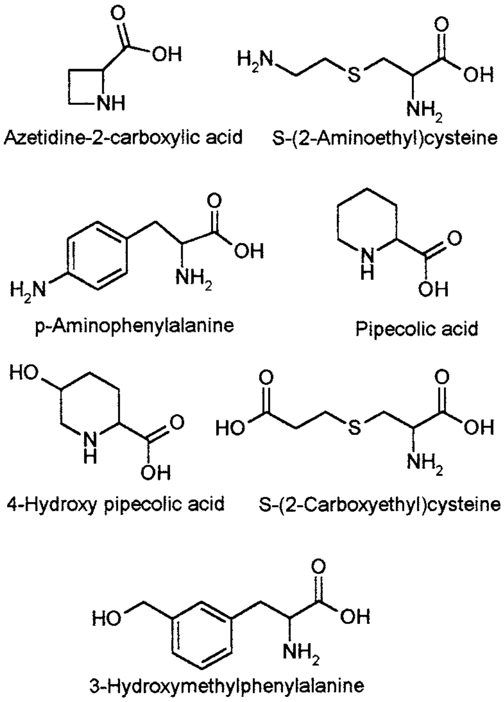

Figure 7. Other nonprotein amino acids of ecological significance.

for their detection and determination have been reviewed (*159*). It is not unusual to find a single free amino acid accounting for 5% or more of the dry weight of a legume seed. Whether the major stored amino acid is arginine as in the seeds of *Vicia faba* (broad bean) or γ-hydroxyarginine as in the seeds of *Lens culinaris* (lentil) (*20*, *160*), their fate during food processing and after ingestion is a matter of importance. While the toxicity of various nonprotein amino acids to man and his domestic animals has been described, virtually nothing is known (possibly due to a lack of commercially available compounds) of the positive contributions that others may make to the nutritional value of the plants in which they occur. This is particularly true of those which may be precursors of essential amino acids such as lysine or physiologically active amines such as serotonin.

CONCLUSIONS

Some nonprotein amino acids found in food and fodder plants are a threat to human and animal health. Others, forming a significant part of a plant's free amino acid pool, may make an important, though little recognized, contribution to the nutritive value of a crop plant. Some are toxic to potential insect predators but not necessarily to man or grazing animals. Some are incorporated, with damaging effect, into the proteins of organisms to which they are foreign or interfere with their primary metabolic pathways. Some act as agonists or antagonists in the neurotransmission of higher animals. Others influence the growth of fungi and bacteria. Clearly, a better understanding of how different microorganisms, plants, and animals (including man) deal with, or fail to deal with, these compounds metabolically is a matter of importance in both agriculture and medicine. The presence in a crop plant of an amino acid that is metabolized by man but acts as a feeding deterrent to potential insect predators is clearly advantageous to a farmer, as is the presence in its root exudate of a compound that suppresses the growth of competing plant species. Some, such as L-DOPA, have already been used in the treatment of human disease. Other amino acids with antibacterial or antifungal activity could not only benefit the plants that synthesize them but provide drugs, or leads to drugs, of value in human or veterinary medicine. Much more needs to be learned of the biological activity, the relative toxicities of these compounds to different organisms, and their nutritional value if we are to make the best use of them and the plants in which they are synthesized.

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