Amino Acids (2012) 42:1553–1582
DOI 10.1007/s00726-011-0915-1

INVITED REVIEW

Nutritional and medicinal aspects of D-amino acids

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Received: 27 January 2011 / Accepted: 6 April 2011 / Published online: 26 April 2011

Abstract This paper reviews and interprets a method for determining the nutritional value of D-amino acids, D-peptides, and amino acid derivatives using a growth assay in mice fed a synthetic all-amino acid diet. A large number of experiments were carried out in which a molar equivalent of the test compound replaced a nutritionally essential amino acid such as L-lysine (L-Lys), L-methionine (L-Met), L-phenylalanine (L-Phe), and L-tryptophan (L-Trp) as well as the semi-essential amino acids L-cysteine (L-Cys) and L-tyrosine (L-Tyr). The results show wide-ranging variations in the biological utilization of test substances. The method is generally applicable to the determination of the biological utilization and safety of any amino acid derivative as a potential nutritional source of the corresponding L-amino acid. Because the organism is forced to use the D-amino acid or amino acid derivative as the sole source of the essential or semi-essential amino acid being replaced, and because a free amino acid diet allows better control of composition, the use of all-amino-acid diets for such determinations may be preferable to protein-based diets. Also covered are brief summaries of the widely scattered literature on dietary and pharmacological aspects of 27 individual D-amino acids, D-peptides, and isomeric amino acid derivatives and suggested research needs in each of these areas. The described results provide a valuable record and resource for further progress on the multifaceted aspects of D-amino acids in food and biological samples.

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Keywords D-Amino acids · D-Peptides · Amino acid derivatives · Nutritional evaluation · Bioavailability · Toxicity

Introduction

Most amino acids of importance in nutrition exist as L-isomers. Natural proteins are exclusively built from L-amino acids. During food processing, the L-amino acids may be racemized to their mirror image configuration, the D-isomers (Friedman et al. 1981; Masters and Friedman 1979). D-amino acids (DAA) can also be synthesized by microorganisms (Arlorio et al. 2009; Friedman 2010; Friedman et al. 1981), marine invertebrates (Zagon et al. 1994), and to a very limited extent, other animals (Nagata et al. 2006). Racemization of L-amino acid residues to their D-isomers in food and other proteins is pH, time, and temperature dependent. Although racemization rates of the 18 different L-amino acid residues in a protein vary, the relative rates in different proteins are similar (Friedman and Liardon 1985; Kuge et al. 2004; Liardon and Friedman 1987; Liardon et al. 1991). Racemization of amino acids and formation of D-peptide bonds and the crosslinked amino acid such as lanthionine (LAN) and lysinoalanine (LAL) can impair digestibility and nutritional quality (Friedman 2009b; Friedman 2010).

Two pathways are available for the biological utilization of D-amino acids: (a) racemases or epimerases may convert D-amino acids directly to L-isomers or to (DL) mixtures; or (b) the degradative enzymes, D-amino-acid oxidase (DAAO) and D-aspartate oxidase (DDO), may catalyze oxidative deamination of the α-amino group to form α-keto acids, which can then be specifically reaminated to the L-form (Brückner and Fujii 2010). DAAO acts on neutral and basic

DAA, whereas DDO acts on acidic DAA (Katane and Homma 2010). In mammals, conversion by the oxidases predominates over the racemases or epimerases. The amounts and specificities of these oxidases vary in different animal species. In some, the oxidase system may be rate limiting in the utilization of a D-amino acid as a source of the L-isomer. Consequently, the kinetics of transamination of D-enantiomers would be too slow to support optimal growth. In addition, growth depression could result from nutritionally antagonistic or toxic manifestations of D-enantiomers.

The nutritional effectiveness of protein-associated essential D-amino acids depends on the amino acid composition, digestibility, and physiological utilization of released amino acids. Since an amino acid must be liberated by digestion before nutritional assimilation can occur, the decreased susceptibility to enzymatic proteolysis of D-D, D-L, and L-D-peptide bonds in DAA-containing proteins to digestion is a major factor adversely affecting the bioavailability of protein-associated D-amino acids (reviewed in Borg and Wahlstrom 1989; de Vrese et al. 2000; Friedman 1991, 1999; Man and Bada 1987).

In this review, we present techniques used in our laboratory to assess the nutritional and toxicological effects of D-amino acids on mice. The presented protocol evaluated free amino acid diets. It does not address the issue of impairment of digestibility caused by protein-associated D-amino acids. Also covered are dietary and pharmacological aspects of D-amino acids and derivatives.

Nutritional aspects of DAA

As part of a program to evaluate the chemistry and the nutritional and toxicological potential of novel amino acids, including D-amino acids, crosslinked amino acids, and amino acid derivatives formed during food processing, we compared the weight gain in mice fed free amino acid diets in which the test compound was substituted for the relevant L-isomer. The results obtained reflect the ability of mice to utilize unnatural amino acids in the complete absence of the L-form. In the case of essential (L-His, L-Ile, L-Lys, L-Met, L-Phe, L-Thr, L-Trp, L-Val) or semi-essential (L-Cys, L-Tyr) amino acids (Mercer et al. 1989), the mice must meet the entire metabolic demand from the D-isomeric forms or derivatives.

All of the L-amino acid residues in a protein and additional new derivatives formed during food processing can undergo racemization simultaneously, but often at differing rates. Assessment of the extent of racemization in a protein is a difficult task that requires quantitative measurement of $\sim$40 L- and D-optical isomers (Zahradnícková et al. 2005). There are a number of challenges to measuring DAA in biologic samples (Waldhier et al. 2009). Except for aromatic amino acids, amino acids are not detectable spectrophotometrically, nor are they volatile for GC analysis, so they are often derivatized before or after separation. In column chromatography, there is often poor resolution of isomers, leading to poor sensitivity because the small DAA peak can be lost in the shoulder of the LAA peak. Traditional analysis by GC (Schurig 2001) or GC/MS (Brückner and Westhauser 2003) is considered by some to be too cumbersome for small volume samples due to the multiple steps necessary for sample cleanup and derivatization (Kirschner and Green 2009). To improve chromatographic resolution, DAA are often analyzed on a chiral or ligand column, or are derivatized before separation with reagents that convert the enantiomers to diastereomers, the configurations of which are more easily separated (B'Hymer et al. 2003). Two-dimensional HPLC (Hamase et al. 2009), immunocytochemical techniques (Mangas et al. 2007), and microchip electrophoresis (Huang et al. 2009) have recently been developed to increase separation and improve sensitivity. Methodologies continue to be improved with novel techniques explored. See Ilisz et al. (2010) and Kirschner and Green (2009) for good reviews of DAA methods of analysis.

Experimental procedures for nutritional evaluation

Animals

Weanling male mice were of Swiss Webster strain (Simonsen Laboratories, Gilroy, CA). For convenience, Table 1 shows reported bioavailability studies in other animals and humans. Mice were housed in polycarbonate cages with stainless steel wire tops and pine shavings for litter.

Animal care

The animals were housed into one or two per cage. The growth assay was standardized with six mice per group and potency estimated based on the response of two to seven groups (growth data from 12 to 42 mice). Mice were assigned to each treatment based on initial body weight blocks. Mice were grouped into blocks according to weight and then an animal from each block was assigned to each treatment, with the end result that each group had nearly the same initial average body weight. The environment was maintained at 22.2 $\pm$ 1.1°C and 50 $\pm$ 10% humidity. The light–dark cycle of 0,600–1,800 h light and 1,800–0,600 h dark was regulated by an automatic timer. Feed and water were provided ad libitum. Mice were weighed after 14 days.

Diets

Standard diets were formulated from the ingredients listed in Table 2. A balanced array of amino acids replaces the

Table 1 Summary of reported utilization of D-amino acids by different animal species and humans, adapted from (Borg and Wahlstrom 1989)

D-Amino acid	D-Utilization (% relative to L-isomer)						
	Rats	Mice	Poultry	Humans	Pigs	Dogs	Cats
Lys	0	0	0	0			
Trp	75	0	<10	<10	60	35	
	100		17–40		70		
			20				
Thr	0	0	0	0			
			100				
Met	100	100	100	0	50	100	100
			100	36	100		
Cystine	0		0				
Arg	100		0				
	0						
His	>90	0	<10				
			20				
Phe	68	100	20	50			
	0		100				
			0				
Tyr	100			0			
Leu	100	0	100	0			
			Partial				
Val	0	0	Partial	0			
	50		100				
Ile	0	0	Partial	0			
			0				
			100				

Table 2 Composition of amino acid diet used for nutritional analysis

Ingredient	%
L-Ala	0.35
L-Arg · HCl	1.35
L-Asn	0.60
L-Asp	0.35
L-Glu	3.50
Gly	2.33
L-His · HC1	0.41
L-Ile	0.82
L-Leu	1.11
L-Lys · HC1	1.35
L-Met	1.17
L-Phe	1.51
L-Pro	0.35
L-Ser	0.35
L-Thr	0.82
L-Trp	0.174
L-Val	0.82
Cellulose	3.00
Corn oil	8.00
Cornstarch	20.00
Dextrose	38.33
Salts USP XIV	5.00
Zinc	0.0125
Cobalt	0.00057
Sodium acetate	1.31
Water (added)	5.00
Complete vitamin mixture	2.00
Total	100.00

Amino acids were replaced as needed to study alternate compounds, as directed in the text

protein in the diet. The diet is similar to the commercially available amino acid diet available from MP Biomedicals (Solon, OH), but lacks L-cystine and L-Tyr. This diet predates the current AIN 93 standard. AIN 93 adopted changes in the content of vitamins and minerals, and in the ratio of complex versus simple carbohydrates, and now includes added linolenic acid. Amino acids should be 97% pure or better (Sigma Chemical Co. St. Louis, MO).

Alphacel™ from MP Biomedicals was used as the source for cellulose. The salt mixture, U.S.P. XIV, is available commercially (MP Biomedicals: Solon, OH). It contains calcium carbonate (6.86%), calcium citrate (30.83%), calcium biphosphate monobasic (11.28%), manganese carbonate (3.52%), magnesium sulfate·$7H_2O$ (3.83%), potassium chloride (12.47%), dipotassium phosphate (21.88%), sodium chloride (7.71%), copper sulfate·$5H_2O$ (0.00777%), ferric citrate (16–17% Fe) (1.52815%), manganese sulfate·H_2O (0.02008%), potassium aluminum sulfate (0.00923%), potassium iodide (0.00405%), and sodium fluoride (0.0507%). AIN 93 mineral mixes, now common for mice studies, contain the additional minerals: zinc, chromium, selenium, molybdenum, silicon, nickel, boron, lithium, and vanadium, as well as other changes in composition.

The typical diet was supplemented with zinc and cobalt, 125 and 5.7 mg/kg, respectively. However, because these two minerals may interact negatively with sulfur amino acids, for diets containing these amino acids, these minerals were reduced to 6.25 and 0.29 mg/kg diet, respectively.

In our studies, we used a standard vitamin mixture that contained (per kg vitamin mix): 900,000 IU vitamin A acetate, 100,000 IU cholecalciferol, 5,500 IU DL-α-tocopherol, 100 g choline chloride, 1 g menadione, 4.5 g nicotinic acid, 1 g riboflavin, 1 g pyridoxine HCl, 1 g thiamine HCl, 3 g calcium pantothenate, 0.02 g D-biotin, 0.2 g folic acid, 5 g inositol, 45 g ascorbic acid, and 1.35 mg vitamin B-12 (crystalline). The currently

commercially available vitamin mixes vary slightly from this mix. MP Biomedicals has a very similar mix with the following differences: levels of α-tocopherol are about four times higher; levels of menadione are about two times higher; levels of folic acid are about one-half as high; and *p*-aminobenzoic acid is now included in the mix.

Comments about test diet

To test the efficacy of D-amino acid, we replaced the comparable or interchangeable L-amino acid in the diet in full and/or in part. Each amino acid (natural and unnatural) should be added back to the diet at graded concentrations, typically 0, 12.5, 25, 50, and 100% of the ideal concentrations required for maximum growth. A more complex design would include both the L- and the D-isomers in the same diet. For example, the L-isomer may be held constant at 25% of optimal, while varying the D-isomer to 0, 25, 50, and 100% of an optimal amount of the L-isomer. Some amino acids may require special consideration. When studying interchangeable amino acids, such as L-Met and L-Cys, one must be careful to control the amount of both in the diet. For example, to test the availability of D-Cys, L-Met must be eliminated or reduced in the diet to prevent or minimize conversion of L-Met to L-Cys.

The above procedure was also followed to test the efficacy of amino acid derivatives and dipeptides. In all cases, molar equivalents of the test compound to the L-amino acid were used.

Calculations

The mean body weight gain for each experimental group of six animals was determined. Mean body weight gains were compared by Duncan's multiple range test using individual values (Duncan 1955). Efficacy of the test compound was determined by the following four overlapping techniques: relative response, % maximum growth response, replacement value, and relative potency. No one method was ideal for all cases. Multiple methods were often useful in a single study. Understanding the behavior of compounds in the growth assay can often be complicated by other factors such as sparing the effects of one amino acid for another, competition, and toxicity. Additional studies may be needed to further define the interactions of the unnatural amino acids in vivo.

Relative response of D-amino acids and amino acid derivatives

This parameter is defined as the growth response of the test amino acid relative to the equivalent amount of L-amino acid. At any given level of feeding, the average net weight gain (relative to 0% L-amino acid in the diet) of mice on the test compound diet is divided by the average net weight gain of animals on the comparable L-amino acid diet, and the result is multiplied by 100 to obtain % relative response. This method can be used to calculate the relative response at any given feeding level. Note, however, that the response is likely to change as % amino acid in the diet increases. This is due to the fact that the control diet reaches maximum growth before the test diet (Fig. 1). In this example, L-Phe reaches a maximum response at a faster rate than D-Phe, so at low dietary levels there is a larger difference between the two isomers. As dietary levels of D-Phe increase and weight gain improves, the relative response of D-Phe to L-Phe increases as well. At 100% of the required dose of L-Phe in the diet (1.51% absolute concentration), the relative response of D-Phe is 62%. Figure 1 is an example of a simple growth model where D-Phe is converted in vivo to L-Phe with no complicating dynamics such as antagonism or toxicity.

Percent maximum growth response

This parameter is defined as the growth response of a test diet relative to the maximum growth from the relevant L-amino acid diet. The test diet may be a combination of compounds and may be fed at varying concentrations. This method entails dividing the average net weight gain of the mice on the test diet by the average net maximum weight gain on the control (100% of the L-amino acid) diet, and then multiplying the ratio by 100. Molar concentration is not a component of this equation. Figure 2 plots the percent maximum growth response when varying two dependent

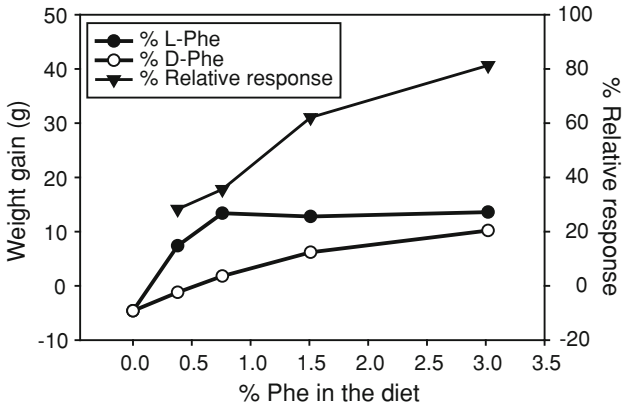

Fig. 1 Relationship of weight gain to % L- or D-Phe in amino acid diets fed to mice. The *triangles* represent the calculated relative response of D-Phe to L-Phe (average net weight gain of mice on the test compound diet divided by the average net weight gain of animals on the comparable LAA diet, and the result multiplied by 100). The *graph* shows the relative response at any given feeding level. The relative response of D-Phe to L-Phe increases not because the rate of response of D-Phe increases, but because the rate of response of L-Phe levels out while D-Phe is still increasing

nutrients in the diet, L-Phe and L-Tyr. The response is complicated by the sparing effect of L-Tyr on L-Phe. The data show that L-Tyr exhibits only a partially sparing effect for L-Phe and may even be inhibitory to mice at high L-Tyr to L-Phe ratios. This method is useful when studying the effect of more than one compound on growth or components that are mutually dependent, as it compares the growth induced by any given diet with the maximal growth by the optimal control diet.

Replacement value (bioavailability)

Replacement value is defined as the relative concentration of the L-amino acid (obtained from a standard curve) that would produce the same weight gain observed with the molar equivalent of the test compound. It is especially useful when evaluating amino acid derivatives or peptides, as it is calculated on a molar basis. The equation for the standard curve of the control may be determined using regression analysis with a semi-logarithmic model with an empirical constant (Fig. 3). This plot is used to calculate the L-amino acid equivalent, and the result is then divided by the molar equivalent concentration of the L-amino acid to obtain the percent replacement value.

Relative potency

Relative potency of the test compound is calculated as the ratio of the best fitting linear slope of the test compound to the best fitting linear slope of the standard control L-amino acid. This calculation is useful, as it provides a concentration-independent value that compares the nutritional value of the test compound to the L-amino acid control. Slope ratio analyses of growth data were performed as

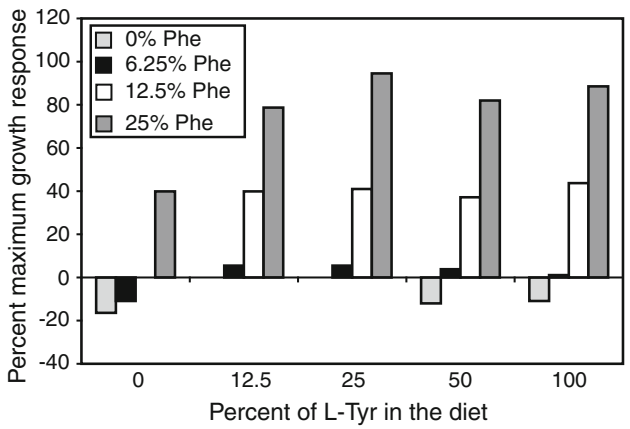

Fig. 2 *Bar graph* of the calculated percent maximum growth response of mouse diets with variable amounts of interdependent L-Tyr and L-Phe. The graph compares variable concentrations of two nutrients to maximal growth achieved when both nutrients are supplied at nutritional adequate levels. L-Tyr has a sparing effect on L-Phe

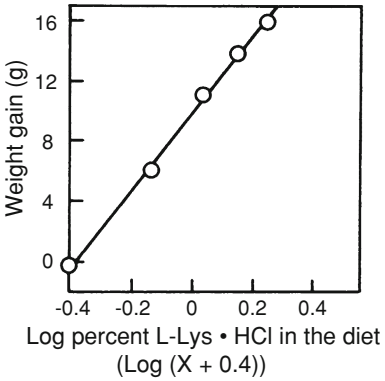

Fig. 3 Linear plot of mean weight gain versus log of L-Lys in the diet of mice used for calculating replacement value (bioavailability). The empirical constant, 0.4, gives an optimum regression coefficient of 0.999. This plot is used to calculate the LAA equivalent of various related test compounds. See Table 3 for results from corresponding growth studies with D-Lys and four lysine derivatives

described by Finney (1978). Growth curves were constructed from the average weight gains per group versus the molar concentrations of the test or control compound. Figure 4 is an example of such growth curves. The most linear part of the curve is situated between 1 and 5 mmoles/100 g diet. The slopes were estimated from the best fitting linear part of the growth curve with the aid of the general linear model (GLM) using SAS software (SAS Institute Inc. 1982). Confidence intervals of potencies relative to the corresponding L-amino acid were estimated using Fieller's theorem (Duncan 1955; Zerbe 1978).

Mice provide a good in vivo model to study the nutritional utilization and biological effects of unnatural amino acids (Friedman and Gumbmann 1979, 1981, 1984a, b, 1988; Friedman et al. 1982). Tables 3, 4, 5 list the nutritional values of specific D-amino acids, D-peptides, and amino acid derivatives as sources of the corresponding L-isomers. Here, we briefly discuss findings with specific unnatural amino acids.

Nutritional utilization of D-amino acids or amino acid derivatives

Lysine derivatives

L-Lys is a nutritionally limiting amino acid in cereal grains such as maize, barley, rice, and wheat. The nutritional value of these grains can be improved by fortification or genetic modification to increase the lysine content (Friedman and Atsmon 1988; Friedman and Finot 1990). The ε-NH_2 group of L-Lys residues in proteins is subject to chemical modification both in vivo and in vitro. Modifications in vivo include post-translational methylation to mono-, di-, and tri-methyl-L-Lys and interaction with

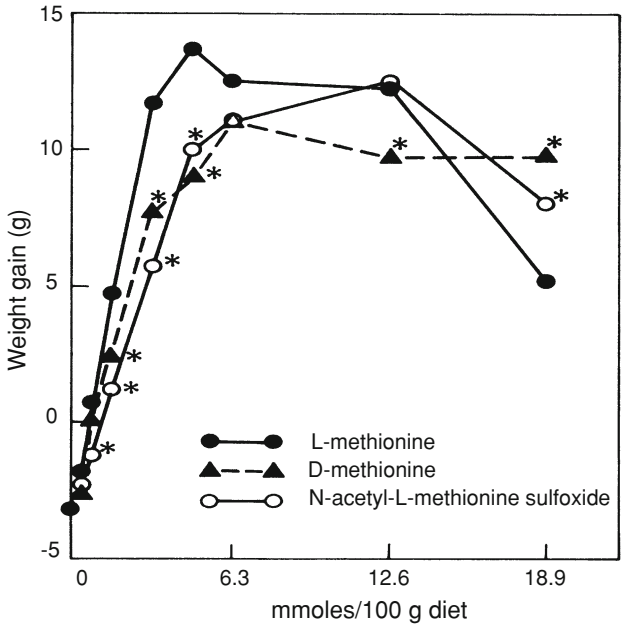

Fig. 4 Weight gain in mice fed increasing dietary levels of L- and D-Met and *N*-acetyl-L-Met sulfoxide for 14 days. Plotted are mean values ($n = 6$), SEM = ± 0.6 g; *asterisk* indicates significant difference from L-Met at the same dietary concentration, $P < 0.05$. Relative potency is measured as the slope at the most linear portion of the plot. The resulting values are a concentration-independent comparison to the LAA

Table 4 Relative L-Met potency of unnatural Met, Met derivatives, and Met peptides, adapted from (Friedman and Gumbmann 1988)

Test compound	Relative potency
D-Met	73.1
L-Met sulfoxide	85.4
D-Met sulfoxide	28.7
DL-Met sulfone	0
N-acetyl-L-Met	89.1
N-acetyl-D-Met	23.7
N-acetyl-L-Met sulfoxide	58.7
N-acetyl-D-Met sulfoxide	1.7
N-formyl-L-Met	86.8
L-Met hydroxy analog	55.4
D-Met hydroxy analog	85.7
L-Met-L-Met	99.2
L-Met-D-Met	102.9
D-Met-L-Met	82.1
D-Met-D-Met	41.5

Relative potency calculated as a ratio of the slope of the line best representing the test compound to the slope of the line best representing the control compound

glucose (Maillard browning), especially in diabetics (Friedman 1982). Modifications in vitro include acylation, methylation, and lysinoalanine formation. Chemical

Table 3 Relative growth response of mice to D-Lys and L-Lys derivative diets by two measures: % replacement value and relative response, adapted from (Friedman and Gumbmann 1981)

Test compound	Relative response	% Replacement value
D-Lys · HCl	−11.8	−4.4
ε-*N*-methyl-L-Lys · HCl	12.3	7.5
ε-*N*-dimethyl-L-Lys · HCl	9.4	4.6
ε-*N*-trimethyl-L-Lys · HCl dioxalate hemihydrate	8.2	3.8
LL-, DL-Lysinoalanine	8.3	3.8
α-*N*-acetyl-L-Lys	0.8	0.6
ε-*N*-acetyl-L-Lys	6.6	3.3

Relative response, net growth of mice on test compound/net growth of mice on control compound. % Replacement value, percent amino acid equivalent/% molar equivalent of control

modifications of lysine have been extensively studied to prevent Maillard browning reactions and lysinoalanine formation, as well as to protect proteins against reduction in nutritional quality and degradation by ruminant microorganisms. The replacement values of a number of Lys derivatives determined with the aid of the standard curve in Fig. 3, as well as their calculated relative response, are listed in Table 3. The derivatives seem to be poorly utilized, with replacement values ranging between 0.6 and 7.5% L-Lys equivalents.

D-Lys appears to not be utilized as a source of L-Lys in mice. Previous studies have shown that DAAO did not convert D-Lys to the keto acid in vivo, and that D-Lys was largely excreted unchanged in rats (Neuberger and Sanger 1944). D-Lys is also not utilized as a nutritional source of L-Lys by chicks, dogs, and humans (Borg and Wahlstrom 1989). We found that ε-NH_2-acetylated protein-associated L-Lys was utilized by rats as a nutritional source of L-Lys (Friedman 1978). Evidently, deacylase enzymes remove the acetyl group more rapidly from protein-associated acetylated L-Lys residues than from free L-Lys. In contrast, ε-NH_2-succinylated-L-lysine, which may be a new intermediate in the citric acid cycle (Tsuchida et al. 2010; Zhang et al. 2011), and ε-NH_2-succinylated-L-lysine residues in casein and soy proteins were not utilized by mice as a source of L-lysine.

The extent of nutritional damage from alkali treatment, associated with loss of lysine, may depend on the original lysine content of a protein. Decrease in lysine due to racemization and LAL formation in a high-lysine protein such as casein, high-lysine corn protein, or soy protein isolate may have a less adverse effect than in a low-lysine protein, such as wheat gluten or corn protein, where lysine is a nutritionally limiting amino acid (Friedman 1996; Friedman and Finot 1991).

Table 5 Growth response of mice as affected by dietary sulfur amino acids and derivatives in suboptimal L-Met (25%) diets

Test substance	Molar % of optimal L-Met	Weight gain (g)			% Max growth response	
		0% L-Met	25% L-Met	100% L-Met	Relative to 100% L-Met[a]	Change from 25% L-Met[b]
None	–	−3.4	7.7	16.0	58	–
L-Cys	100	−3.6	13.2		86	28
D-Cys	100	−4.2	5.6		47	−11
L-Cystine	100	−1.8	11.8		79	21
	80	–	14.5		90	32
	40	–	16.0		98	40
	20	–	13.0		82	24
D-Cystine	100	−2.5	5.0		43	−14
	25	–	10		71	13
DL + meso-Lan	100	−3.2	9.4		66	9
N-Acetyl-L-Cys	100	−3.0	15.8		99	42
L-Cysteic acid	100	−3.6	11.4		76	19
L-Cys sulfinic acid	100	−3.0	9.0		64	7
S-Methyl-L-Cys	100	−4.0	1.0		23	−35

Test substances were added at a 100% molar equivalent of optimal L-Met

[a] Net weight gain from diet containing the test compound divided by net weight gain from diet containing only 100% L-Met, e.g., (13.2–(−3.6))/(16.0–(−3.4)) = 86%

[b] Subtract % max growth response of test compound from % max growth response with no added test compound, both at the same supplemented L-Met level

Methionine derivatives and isomeric dipeptides

L-Met is the nutritionally limiting amino acid in legumes, but is abundant in cereals and nuts. Cereals (low in L-Lys and high in L-Met and L-Cys) and legumes (low in L-Met and high in L-Lys) consumed together are known to complement each other to provide high-quality protein in the diet. The availability of both these amino acids is important in diets of primarily vegetable origin. During food processing, L-Met can be chemically modified. Modifications include oxidation to L-Met sulfoxide and L-Met sulfone, racemization to D-Met, and degradation to sulfur compounds with undesirable flavors. Additionally, we found that excessive amounts of L-Met could inhibit growth. Therefore, there is an interest in bioavailability of L- and D-Met substitutes to overcome these problems.

Table 4 lists the relative potency in mice of Met, Met derivatives, and peptides we tested. Supplementation with L-Met of a diet devoid of other sulfur amino acids to a maximum between 3.15 and 6.3 mmol/100 g markedly stimulated the growth of mice, after which additional L-Met inhibited growth. Derivatization of L-Met generally lowered potency. However, D-Met, the three isomeric dipeptides LL-, LD-, and DL-Met-Met, *N*-acetyl-L-Met, L-Met sulfoxide, *N*-formyl-L-Met, and D-Met hydroxy analog were all well utilized as nutritional sources of L-Met. By contrast, the relative potency of the L-Met hydroxy analog derivative, and the double derivative *N*-acetyl-L-Met sulfoxide was 55–59%. The relative potencies of D-Met sulfoxide, *N*-acetyl-D-Met, and DD-Met-Met ranged from 24 to 42%. *N*-Acetyl-D-Met sulfoxide and DL-Met sulfone were essentially not utilized. Several of the analogs were less growth inhibiting at high concentrations in the diet than was L-Met.

The nutritional value of D-Met in mice approaches that of the L-Met (Table 4). By contrast, D-Met appears to be poorly utilized by humans when consumed either orally or during total parenteral nutrition (TPN) (Printen et al. 1979). One factor giving rise to inconsistencies in the utilization of D-Met is the dose dependency of the apparent potency of D-Met relative to its L-isomer, i.e., the dietary level of the D-form for any given growth response relative to that of the L-form, which would produce the same growth response. This dose dependency is a result of the non-linear nature of the dose–response curves (Fig. 4). This complicates attempts to compare results from mice with those of other animal species. The results imply that some Met derivatives may be better candidates for fortifying foods than L-Met because they are not as toxic at elevated concentrations.

Cysteine derivatives

L-Cys is a non-essential amino acid in the diet because it can be synthesized in vivo from the essential amino acid

L-Met. L-Cys can supplement or spare dietary L-Met when that amino acid is limiting (Gumbmann and Friedman 1987). Study designs can be complicated by this sparing effect. We found that in a diet containing no L-Met, addition of Cys or related sulfur-containing derivatives did not promote growth (Table 5). However, in the presence of suboptimal L-Met levels (25%), many of these compounds stimulated growth. Thus, *N*-acetyL-L-Cys, L-Cys, and LL-Cystine were particularly effective growth promoters. D-Cys, DD-Cystine, and *S*-Methyl-L-Cys were growth depressing at 100% equivalent molar concentration. At 25%, DD-Cys-Cys was growth promoting. L-Cystine was also more effective at somewhat lower concentrations than the molar equivalent of L-Cys. Concentration responses to D-Cys and *S*-methyl-L-Cys were not measured. These growth-depressing effects, at equivalent molar concentrations to optimal L-Met, imply that these sulfur-containing amino acids and peptides may be toxic. The results with these amino acids demonstrate the complexity that may be encountered when test compounds are partially sparing for essential amino acids and also exhibit some toxicity (growth depression).

D-Phenylalanine and D-tyrosine

L-Tyrosine is a non-essential amino acid in the diet because it can be synthesized in vivo from the essential amino acid L-Phe. L-Tyr can supplement or spare part of the dietary need for L-Phe in the diet. This aspect is important for the management of the metabolic disease phenylketonuria, in which L-Phe cannot be converted to L-Tyr, leading to physiologically damaging concentrations of L-Phe in the body.

Protein bound L-Phe and L-Tyr racemize rapidly to D-isomers (Friedman and Liardon 1985; Liardon and Friedman 1987) upon treatment with alkali and heat. In our studies, we examined the ability of the D-isomers to replace L-Tyr and L-Phe, both individually and in combination (Friedman and Gumbmann 1984a). Higher concentrations of D-Phe can replace the need for L-Phe in the diet (Fig. 1), possibly due to a lag in the in vivo conversion (pharmacokinetics) of D- to L-isomers. D-Phe does not appear to be toxic at the concentrations tested.

L-Tyr can replace some of the requirement for L-Phe in the diet (Fig. 2). A small increase in the level of L-Tyr (12.5%) doubled the growth of mice on an L-Phe-poor diet. Additional supplementation had no effect. In fact, at the higher levels, L-Tyr appeared to negatively impact L-Phe-deficient mice. D-Tyr had no similar sparing effect on L-Phe. Addition of D-Tyr to amino acid or casein diets greatly depressed weight gain in mice (Fig. 5). This growth inhibition was significantly reduced by increasing the L-Phe content of the amino acid diets or the protein content of casein diets. Our results demonstrate that D-Tyr cannot be utilized as a partial replacement for L-Phe. It creates a metabolic stress that becomes evident when D-Tyr and L-Phe are present in equimolar amounts. The potential of subchronic and chronic effects following exposure to lower levels of D-Tyr merits study.

D-Tryptophan

L-Trp is a nutritionally limiting amino acid in maize (Friedman and Cuq 1988). Replacement of L-Trp with D-Trp in the diet followed a simple pattern, similar to the L- and D-Phe responses, not influenced by toxicity or by sparing effects (Fig. 6). Growth increased rapidly as L-Trp in the diet was increased and rapidly leveled off at a maximum. The growth curve for D-Trp relative to L-Trp had a shallow slope. Maximum growth was not achieved until the concentration of D-Trp was 2.5 times the corresponding level of L-Trp. Considerable species variation exists for the nutritive value of D-Trp (Borg and Wahlstrom

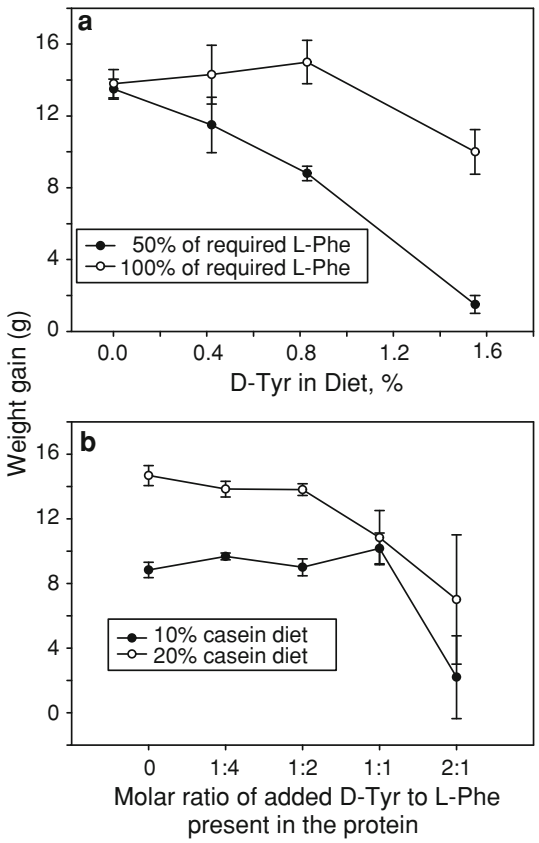

Fig. 5 D-Tyr significantly depresses growth in mice in both amino acid and casein diets. The adverse effect is reduced in diets with higher amounts of L-Phe and/or with high-quality protein. **a** Effect on growth of D-Tyr added to diets containing sufficient (100%) and insufficient (50%) L-Phe. **b** Effect on growth of added D-Tyr in high and a low casein diets

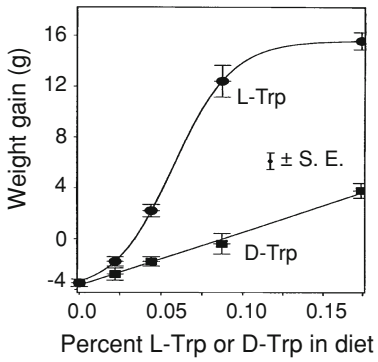

Fig. 6 Relationships of weight gains to percent of L- and D-Trp isomers in amino acid diets fed to mice. Growth increases rapidly with added L-Trp in the diet, rapidly leveling off at a maximum. The growth curve for D-Trp relative to L-Trp has a shallow slope

1989) (Table 1). In chicks' diets, relative potency of the D- to the L-isomer has been reported to be 20%. D-Trp was well utilized by growing pigs (Arentson and Zimmerman 1985). The value for humans is about 10%. Rats utilize D-Trp as efficiently as L-Trp. D-Trp can serve as a niacin precursor in rats to the same extent as does the L-form (Carter et al. 1982; Shibata et al. 2000). These studies also showed that D-Trp has one-sixth of the activity of niacin.

In summary, mice provide a good animal model to study the biological utilization and biological effects of DAA, both free and protein associated. A major advantage of mouse bioassays is that they require about one-fifth of the test substance needed for rats and can be completed in 14 days (Friedman and Gumbmann 1979, 1981, 1984a, b, 1988; Friedman et al. 1982).

Medicinal uses of D-amino acids

Most biologic processes are stereospecific. Conformational identity is essential when molecules fit together or interact. However, there are some non-specific processes that do not depend on stereospecificity. Many LAA have physiologic uses beyond their obvious nutritional use. DAA may have effects on biologic systems in a number of ways.

- They may be converted to LAA, and thus provide a pool for the amino acid.
- They may act stereo-specifically independently from LAA.
- They may act similarly to LAA in a non-specific process.
- They may act similarly to LAA in a specific process, but at a slower rate of activation.
- They may act antagonistically to LAA by binding to a site without activation.

DAA are often used as tools to differentiate between specific and non-specific endogenous processes. This can aid in understanding metabolism, but can also be complicated by some of the above points. Some DAA are taken up by diseased tissue differently than by healthy tissue, leading to potentially better diagnostic approaches and new therapeutic targets (McConathy and Goodman 2008; Tsukada et al. 2006). Recent advances in analytical techniques have allowed more accurate measurement of small amounts of DAA among much larger pools of LAA in biological fluids and tissues (Ilisz et al. 2010; Kirschner and Green 2009).

Transmembrane transport of DAA

Amino acid transport across cell membranes is essential for cell nutrition, as well as for maintenance of homeostasis in interstitial spaces for systems, which use amino acids as neurotransmitters and synaptic modulators (Palacín et al. 1998). Transfer of amino acids across cell membranes is mediated by membrane transport proteins (transporters) also known as carrier proteins. These proteins are integral to the membrane, spanning the width of the membrane between extra- and intra-cellular spaces. There are a variety of amino acid transporters, categorized by mode of action and activity (e.g., Na+ dependent/independent) and by the amino acid group transported. The transporters are not specific to a particular amino acid, but rather to a group of amino acids with common characteristics (cationic, anionic, branched chain, Me-substituted, etc.) (Christensen 1990). Likewise, any particular amino acid may be transported by a variety of transporter systems. This mild specificity of the transporters, less than the specificity found in typical enzyme systems, may allow D-amino acids to be transported into cells, although normally less preferentially than their L-counterparts.

Transporter systems have variable affinity for DAA. In competitive inhibition studies, D-isomers were found to be less effective at inhibiting Gly uptake by the Gly transport system than the L-isomer: D-Asn (50% as effective); D-Met and D-Nor-Leu (40%); D-Ala (30%); D-Nor-Val and D-Phe (20%); D-AAB, D-Val, D-Ile, and D-Leu (10%); and His (0%) (Oxender 1965; Paine and Heinz 1960). D-Ala transport in the rabbit proximal renal tubule by both Na+-dependent and independent processes was inhibited by L-Ala, suggesting that the normal pathways were designed for the L-configuration (Jessen et al. 1988). D-Ala and D-Val were found to have 1/30th the affinity of the corresponding L-isomers in the Ehrlich tumor cells, yet over time the cell interior came to near equilibrium with the exterior, indicating that transport rates out of the cell were even more stereospecific (Oxender 1965). The fact that the X-AC transport system serving Asp and Glu can transport D-Asp,

but not D-Glu can be accounted for by steric considerations (Christensen 1990). D-Asp, L-Asp, L-Glu, and L-cysteate all had similar affinities for the X-AG transporter EAAT2 (excitatory amino acid transporter 2) (Dunlop 2001).

X-AG transporters such as the EAAT group, of which D-Asp is a substrate, maintain synaptic homeostasis in the central nervous system (Shigeri et al. 2004). DAA have the potential to be used as both a tool for mechanistic discovery and as a source of therapies of the CNS (Dunlop 2006).

Absorption of DAA from the diet may be controlled differently from peripheral utilization. The intestinal enterocytes, responsible for nutrient absorption, appear to have nearly the same compliment of transporters as other cells in the body, but in the interest of nutrition are regulated for maximal absorption (Kilberg et al. 1993).

The ability to utilize DAA to some degree may have adaptive advantages. A transporter found in Drosophila, specific for a broad range of neutral amino acids, was found to equally or even preferentially transport the D-isomers (Miller et al. 2008). Presumably, the fly has adapted to form symbiotic relationships with DAA producing microbes. Specific examples of potential advantages in humans will be covered in the amino acid specific section below.

Individual activities

To facilitate understanding the complex nature of biological activities of DAA, we briefly summarize results of published studies on the following nutrition- and health-related aspects of DAA in alphabetical order. It should be emphasized that nutrition may impact on health and vice versa.

D-Alanine

Despite being found in human bodily fluids and tissues (Nagata et al. 1992, 2006, 2007), D-alanine (D-Ala) is not formed in the body because it is believed that humans lack D-Ala racemase. D-Ala is the most prevalent D-amino acid in higher plants (Robinson 1976), is found in high concentrations in certain mollusks (Zagon et al. 1994), and is an integral part of the structure of bacterial cell walls (Zagon et al. 1994). Thus, plants, animals, and processed food can serve as dietary sources of D-Ala and other DAA. Human intestinal microflora is also an important source of DAA (Konno et al. 1990). The submandibular gland and oral epithelial cells, not ingested food, or oral bacteria appear to be the source of high levels of D-Ala and D-Asp in human saliva, suggesting that these specialized cells may have undiscovered alanine racemase or aminotransferase (Nagata et al. 2006). Large amounts of D-Ala in urine of mice are of bacterial and not dietary origin (Konno et al. 1990).

Because D-Ala is a structural component of bacterial cell walls, it is a possible indicator of bacterial contamination, excessive heat treatment, and prolonged shelf storage of fruit juices and other foods (Gandolfi et al. 1994; Voss and Galensa 2000). D-Ala is a major component of teichoic acid found in Gram-positive bacteria such as *Staphylococcus aureus*, where it imparts zwitterionic properties to the cell wall, leading to cell wall rigidity and resilience as well as providing sites for bacterial attachment to mucosal membranes and to each other for biofilm formation. Changes in the structure of teichoic acid may alter the virulence of pathogenic bacteria as well as avoid formation of biofilms on food and tissues (Latteyer et al. 2010). Modification of the dipeptide termini of the peptidoglycan cell wall precursors from D-alanyl-alanine to D-alanyl-D-lactate seems to enhance the susceptibility of vancomycin-resistant enterococci to inactivation by telavancin (Hill et al. 2010; Nannini et al. 2010; Shiratsuchi et al. 2010).

D-Ala may have potential for use in diseases of the human brain. D-Ala appears to be an agonist of the glycine site on the *N*-methyl-D-aspartate (NMDA) subtype glutamate receptor, the function of which is associated with memory function and synaptic plasticity. Hypofunction of this receptor has been associated with schizophrenia (Tsai et al. 2006). Oral administration of D-Ala improves cognitive symptoms of patients with schizophrenia (Hatano et al. 2010; Tsai et al. 2006). Antibiotic-induced psychosis may be linked to a depletion of D-Ala production by microflora (Mehdi 2010). D-Ala was also found to selectively induce cytotoxic oxidative stress in brain tumor cells (Stegman et al. 1998).

D-Ala has a number of other potential medical uses. D-Ala can be used in studies of molecular imaging (Shikano et al. 2007). Changes in D-Ala content of the rat pancreas are related to their diurnal and nocturnal (circadian) habits (Morikawa et al. 2008). D-Cycloserine, an analog of D-Ala, has shown promise for the treatment of tuberculosis by inhibiting the enzyme D-alanine-D-alanine ligase that catalyzes the formation of the dipeptide D-alanyl-D-alanine in *Mycobacterium tuberculosis* bacteria (Bruning et al. 2011). Patients with liver cirrhosis had a smaller increase in D-alanine aminotransferase during portal clamping than those with a normal liver (Sugiyama et al. 2010).

D-Arginine

D- and L-Arg mixtures can be separated by selective crystallization using their copper-diastomeric complexes (Bacarea et al. 2010). Both L- and D-Arg protected against oxygen radical-induced injury of rat heart tissue (Suessenbacher et al. 2002) and against endotoxin shock in

rabbits (Wiel et al. 2000). D-Arginine (D-Arg) and other DAA inhibited cell proliferation and tumor growth in rats (Szende 1993), acted as a central nervous system stimulant, and exhibited anticonvulsant activity in humans (Navarro et al. 2005). Nona-D-Arg amide suppresses corneal cytokines responsible for *Pseudomonas aeruginosa* keratitis (eye inflammation) (Karicherla et al. 2010). Deamino-8-D-Arg vasopressin augmented platelet function and reduced blood loss during cardiac surgery (Jámbor et al. 2010). A novel two-component amino acid racemase inverts D- to L-Arg, facilitating D-Arg utilization through the L-Arg metabolic pathway (Li and Lu 2009). D-Arg attenuates the effectiveness of L-Arg infusion during resuscitation for hemorrhagic shock (Arora et al. 2010). The inhibition of the enzyme arginine decarboxylase by D-Arg improves the activity of the drug agmatine against anxiety and depression (Taksande et al. 2009, 2010). D-Arg containing thrombin inhibitors exhibited antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*, presumably by suppressing trypsin-like proteinases that govern the infection process (Poyarkov et al. 2010). A poly (oligo-D-arginine) carrier with the heme oxygenase-1 gene is a potential non-viral vector for gene therapy to protect brain cells from neuronal injury, including stroke (Hyun et al. 2010).

D-Aspartic acid

Masters and Friedman (1980) demonstrated for the first time that commercial processed foods contain D-aspartic acid (D-Asp) and other DAA. This and later studies (Friedman 2010) indicate that processed foods contain high amounts of D-Asp.

Like D-Ala, D-Asp is part of peptidoglycan structure of bacterial cell walls (Zagon et al. 1994). D-Asp is widespread in marine invertebrates (Zagon et al. 1994) and is an endogenous amino acid present in nervous and endocrine tissues in mammals (Furuchi and Homma 2005). It is the precursor for the important neurotransmitter agonist, NMDA. Aspartate racemase is one of only two racemases found in mammals (Topo et al. 2010a), indicating a native ability to regulate levels D-Asp. Additionally, DDO activity has been found in the kidney, liver, and brain of mammals (Katane and Homma 2010). The ability of mammalian cells to regulate D-Asp implies that D-Asp is a novel type of messenger in the mammalian body (Furuchi and Homma 2005).

To study the regulation of D-Asp, mice strains were developed to be deficient in DDO (Errico et al. 2006; Huang et al. 2006). With DDO deficiency, D-Asp accumulated in the kidney, brain, and spleen at levels 10–26 times normal (Errico et al. 2006). With the increased D-Asp, NMDA also significantly increased in the brain. D-Asp was found to accumulate in the pituitary with concurrent diminished synthesis and levels of pituitary pro-opiomelanocortin (Huang et al. 2006),

D-Asp shows potential for pharmacologic use. It was involved in cell-to-cell signaling in neuron-containing ganglia of the California sea slug (Scanlan et al. 2010), behaved as a neurotransmitter in the central nervous system of vertebrates and invertebrates (D'Aniello et al. 2011; Topo et al. 2010b), regulated the growth of nerve cells, learning, and memory (Kim et al. 2010), and exhibited neuromodulatory action at glutamatergic synapses that might play a beneficial role in conditions related to mammalian brain pathology (Errico et al. 2009).

D-Asp also regulated reproductive activity in animals and humans and improved semen quality in rabbit bucks (Macchia et al. 2010). D-Asp prevented potassium and magnesium depletion in rats induced by diuretics (Iezhitsa et al. 2004). The D/L-Asp ratio can be used to estimate the age of teeth and elastin from human arteries in forensic science (Dobberstein et al. 2010; Ohtani and Yamamoto 2010).

Excessive D-Asp can have negative effects in the body. D-Asp activated antioxidative, cytoprotective effects in the kidney and enhanced caspase levels, indicative of apoptosis in brain and heart tissues (Burrone et al. 2010). It also aggravated nephritis in rats induced by *Staphylococcus aureus* bacteria (Koyuncuoglu et al. 1988). D-β-Asp-containing proteins were found to accumulate in macular degeneration of the eyes associated with aging (Kaji et al. 2010). DDO activity increased the production of H_2O_2 in the thyroid glands of mice and rats (Topo et al. 2010a).

D-Cysteine

As discussed previously in the "Nutritional utilization of D-amino acids or amino acid derivatives", D-cysteine (D-Cys) does not replace L-Cys. In fact, it appears that D-Cys may be nutritionally antagonistic or toxic.

D-Cys but not *N*-acetyl-D-Cys lowered rat blood cyanide levels derived from acrylonitrile (Benz et al. 1990). D-Cys is also reported to be involved in the detoxification and/or prevention of toxicities caused by cyanides (Huang et al. 1998), the drug paracetamol (McLean et al. 1989), and other drugs (Friedman 1973, 1994; Takahashi et al. 1994). L-Cys-glutathione disulfide, but not the D-Cys analog, protected mice against acetaminophen-induced liver damage (Berkeley et al. 2003). D-Cys desulfhydrase catalyzes the elimination of H_2S form D-Cys, presumably to form dehydroalanine (Todorovic and Glick 2008). The natural antibiotic thiostrepton contained D-Cys (Schoof and Arndt 2009). An assessment of olfactory properties in 20 human subjects of L- and D-amino acids suggests that D-Cys and other D-amino acids may affect the perceived flavors of

foods, both as taste and olfactory stimuli (Laska 2010). D-Cys induces sleep and abnormal behavior during stress in neonatal chicks (Yamane et al. 2009) and exhibits anti-HIV activity (Nakatani et al. 2008). D-Cys and D-Cys copolymers-gadolinium chelates can serve as MRI contrast agents for magnetic resonance angiography and cancer imaging (Zong et al. 2009). D-Cys-capped CdSe(ZnS) quantum dots were used to separate carnitine enantiomers (Carrillo-Carrion et al. 2009).

The *S*-nitrosothiol, *S*-nitrosocysteine (SNC), is a primary nitric oxide carrier plasma. NO is an important signaling molecule for biologic systems related to vasodilation and platelet aggregation. Impairment of NO metabolism is associated with numerous chronic diseases such as atherosclerosis and hypertension. SNC is an important regulator of NO metabolism, but its mode of action is not fully elucidated. Intracellular delivery of NO from SNC is complex, so SNC cannot be viewed as a simple NO donor (Gordge and Xiao 2010). Because cellular uptake of D-Cys and D-SNC is reduced from the L-counterparts, these isomers have been used to explore the targets of SNC, be they intra- or extracellular.

Both L- and D-SNC equally degrade to NO, but have different biologic potencies, indicating specific and nonspecific effects (Davisson et al. 1996). In conscious rats, intravenous L-SNC was a more potent hypotensive and vasodilator agent within the mesenteric and sympathetically hindlimb beds, while D-SNC was more effective than L-SNC in inhibiting baroreceptor reflex-mediated tachycardia (Davisson et al. 1996). When injected intracerebroventricularly into rats, L-SNC and L-Cys caused a fall in arterial pressure, but D-SNC, D-Cys, and the *S*-nitrosothiol, *S*-nitroso-L-glutathione did not, indicating possible specific responses (Davisson et al. 1997). Both L- and D-SNC equally decreased human platelet aggregation in vitro by cGMP-independent mechanisms, possibly by extracellular release of NO (Tsikas et al. 1999). Both D- and L-SNC enter red blood cells, but L-SNC at more than twice the rate of D-SNC (Sandmann et al. 2005). SNC enters cells stereospecifically by transporters of the L system, namely LAT1 and LAT2 (Li and Whorton 2005).

The role of free Cys as a precursor to SNC in NO metabolism also appears complicated. Cys can be converted to SNC extracellularly by *S*-transnitrosylation of *S*-nitrosoproteins. While intravenous injections in rats of L- or D-Cys had no effect on NO-mediated systems (Davisson et al. 1996), when preceded by injections of *S*-nitrosoalbumin, the isomers temporarily and equally reduced arterial pressure (Warnecke et al. 2009). High levels of Cys could drive *S*-transnitrosylation to SNC in the extracellular space (Zhang and Hogg 2005). Conversely, Cys inhibited uptake of cellular SNC, suggesting that both use the same transporter and that the blood concentration of one can affect metabolism of the other (Sandmann et al. 2005). There is huge potential in this area of research for understanding and for development to new drugs potentially effective against metabolic syndrome, of which D-Cys will no doubt play a role.

D-Cystine

Although L-cystine is not an essential amino acid for rodents, less L-Met is needed for growth if the diet contains L-cystine (Friedman and Gumbmann 1984b). Our results also show that L-cystine is somewhat more efficient in sparing D-Met than in sparing L-Met in diets containing low levels (0.29%) of the two isomers. Supplementation of D-Met with an equal sulfur equivalent of L-cystine doubled growth. Thus, the overall response was equal to that produced by L-Met in the presence of L-cystine. In contrast, supplementation of suboptimal levels of L-Met with increasing concentrations of D-cystine reduced the growth rate of mice. Excess D-cystine in the diet is toxic.

Other studies indicate that D-cystine can be transformed into dimeric and monomeric surfactants that can be used to lower surface tension (Faustino et al. 2010) and that it inhibits aspartate-beta-semialdehyde dehydrogenase by covalently binding to the essential ^{135}Cys of the enzyme, probably by sulfhydryl-disulfide interchange (Alvarez et al. 2004).

Dehydroalanine

Dehydroalanine is an intermediate in the racemization of protein-associated amino acids. We found that its content (in g/16 g N) in alkali-treated casein was 0.33 and in alkali-treated acetylated casein 1.39 (Masri and Friedman 1982). Dehydroalanine can, in principle, act as a biological alkylating agent similar to that suggested for processing-induced acrylamide (Friedman 2005; Friedman and Levin 2008).

Chemical mutagenesis provides a route for the introduction of dehydroalanine residues into proteins which react with various nucleophiles to form new protein-associated natural, unnatural, and modified amino acids (Chalker and Davis 2010). Antibiotics of the thiocillin and thiostrepton class contain dehydroamino side chains derived from Ser and Cys and methyl-dehydroamino side chains derived from Thr (Walsh et al. 2010). Lantibiotics, a class of ribosomally synthesized and posttranslationally modified peptide antibiotics, contain dehydroalanine, dehydrobutyrine, lanthionine, and methyl-lanthionine residues (Zhang and van der Donk 2009).

D-Glutamic acid

Free L-Glu is found in many foods, contributing to the Umami taste perception of those foods (Kurihara 2009). The receptors for Umami are considered chiral specific because monosodium-D-Glu does not contribute to Umami taste (Hettinger et al. 1996). Because Umami has some role in appetite (Uematsu et al. 2011), could it be that isomerization could alter that effect? As with D-Ala and D-Asp, D-glutamic acid (D-Glu) is part of bacterial peptidoglycan in the cell wall (Zagon et al. 1994), thus is found in fermented foods such as cheese and yogurt (Rundlett and Armstrong 1994). The fact that the virulent *Bacillus anthracis* uses poly-γ-D-Glu in its capsule to evade immune response in its hosts is being capitalized for vaccine development (Lee et al. 2009). *N*-methyl-D-glutamate, the glutamate equivalent to the neurochemical agonist NMDA, was found in mollusks (Tsesarskaia et al. 2009).

Although Glu has a critical role in cellular metabolism (citric acid cycle), neuronal transmission, and cellular oxidation, it is a non-essential amino acid because it can be produced endogenously by transamination of other amino acids. Glu is a significant component of dietary proteins, but much of dietary Glu is metabolized in the intestinal mucosa as fuel and as a source for other amino acids and glutathione, thus dietary levels have little effect on circulating Glu (Janeczko et al. 2007; Reeds et al. 2000). Glu concentrations in the circulation and brain are tightly controlled by the blood brain barrier which allows whole brain concentration to be 100 times higher and extracellular brains fluids 100 times lower than blood levels (Hawkins 2009). Considering the tightly controlled Glu levels, the question is what effect does exogenous Glu, and for that matter derivatives and isomers, have on biologic functions?

Mammals have the innate ability to degrade and form D-Glu. DDO acts on D-Glu, but to a lesser extent than on D-Asp or NMDA (Katane and Homma 2010). In rat tissues, the level of D-Glu correlated well, although consistently higher, to the level of D-Asp, suggesting that DDO may be responsible for the presence of these isomers (Kera et al. 1995).

Glutamate receptors, abundant in the brain, are present in the peripheral body, and because of the blood brain barrier, there may be a greater potential for exogenous Glu to affect the periphery (Julio-Pieper et al. 2011). There is evidence that Glu may act in the periphery to stimulate nerves to affect other body systems remotely (Kondoh et al. 2009). Luminal Glu appears to plays a role in the neuronal response for digestive activity (Akiba and Kaunitz 2011). It may also have a role in satiety and appetite (Kondoh et al. 2009). Because D-Glu is a significant part of the human diet, and because Glu has very profound effects in the mammalian body, it is surprising to find that very little research has been done on D-Glu in the body.

D-Glu was found in the kidney, liver, and brain of rats, with higher concentrations, especially in the liver, in males compared to females (Kera et al. 1995). L-Glu is the most important neurotransmitter in the brain. D-Glu was found in the rat brain, but not in human cerebrospinal fluid, whereas D-Asp was found in both (Huang et al. 2009). D-Glu was taken up by neuronal cells of only specific areas of the rat brain, as opposed to L-Glu and D-Ser which were found more widely in the brain (Mangas et al. 2007). Apparently D-Glu is taken up by glial cells but is quickly converted by glutamine synthetase to D-glutamine (D-Gln) and subsequently released to be taken up by neuronal cells (Pow and Crook 1996). D-Glu is not utilized by the X-AC cell membrane transport system that transports L-Glu into cells (Christensen 1990), so there may be other transport systems specific to cells in certain parts of the brain. The findings imply that D-Glu may have very specific functions. Because of its location in the brain, D-Glu may be involved in visual, auditive, and analgesic mechanisms (Mangas et al. 2007).

With the importance of Glu in many functions of the body, there is an undiscovered potential to use D-Glu for medical and scientific uses.

D-Histidine

Enantioselective potentiometric membrane electrodes can be used for analysis of D-histidine (D-His) in pharmaceutical preparations (Stefan-Van Staden 2010). D-His enhanced zinc accumulation and reduced the fraction of zinc that was retained and absorbed by fish (Glover and Hogstrand 2002). Both D- and L-His enhance DNA degradation by hydrogen peroxide and ferric ions (Tachon 1990). D-His-induced cell injury is mediated by an iron-dependent formation of reactive oxygen species (ROS) (Rauen et al. 2007; Yokel 2006). D-His and D-Ala can protect against infection by *Bacillus anthracis* spores (Hu et al. 2007). Addition of iron to D-His-containing solutions protects against cell injury in organ preservation solutions (Rauen et al. 2007). Elevated D-His impaired absorption of L-His by rainbow trout intestine (Glover and Wood 2008). D-His facilitated brain zinc uptake may contribute to metal-induced neurodegeneration (Yokel 2006). D-His containing peptides exhibit antibacterial and antifungal activities (James Mason et al. 2009). D-His residues protect the antimicrobial peptide poly(arginyl-histidine) secreted by fungi against enzymatic hydrolysis (Nishikawa and Ogawa 2004).

D-Homocysteine

Hyperhomocysteinemia is a proven cardiovascular risk factor. Circulating Hcy levels are related to acute

myocardial infarction, stroke, dementia, and venous thrombo-embolic disease. They may also have a role in age-related macular degeneration, cognitive abnormalities, osteoporosis, neural tube defects, depression, schizophrenia, inflammatory bowel disease and colon tumors (de Jaeger et al. 2010). Dietary contributions appear insignificant (Pexa et al. 2008) as Hcy is manufactured from and degraded to Met in vivo (Selhub 1999).

Early dietary studies showed that L-Hcy was better utilized than D-Homocysteine (D-Hcy). In studies with chicks, L-Hcy was found to spare L-Cys and L-Met in the diet by 100 and 28%, respectively. The sparing effect of D-Hcy was only 68 and 7%, respectively (Harter and Baker 1978). These results show that D-Hcy is not well utilized in the normal metabolic pathway of L-Hcy.

There has been much interest in Hcy, and apparently most experimenters have used DL-Hcy for their investigations. What little work that has been done on pure isomers would indicate that D-Hcy is not very active in human Hcy metabolism. Because of this D-Hcy may be a useful tool to elucidate information on the etiology of L-Hcy. L-Hcy, but not D-Hcy, induced mRNA expression of the proinflammatory cytokines, monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8l), in cultured human aortic endothelial cells (Poddar et al. 2001). Excess L-Hcy caused accumulation of *S*-adenosylhomocysteine and reduced transmethylation reactions leading to neural tube defects in rat embryos, whereas D-Hcy did not (van Aerts et al. 1993), presumably due to D-Hcy's poor specificity for the enzyme *S*-adenosylhomocysteine hydrolase (van Aerts et al. 1994). L-Hcy, but not D-Hcy, promotes the formation of ROS primarily by a biochemical mechanism involving endothelial nitric oxide synthase (Weiss 2005).

Isoleucine stereoisomers (D-Ile, L-allo-Ile, and D-allo-Ile)

Ile exists as 4 stereoisomers, L- and D-Ile and L- and D-allo-Ile. D-Ile and D-*allo*-Ileu form crystalline 1:1 complexes with D-2-aminobutyric acid (Görbitz et al. 2009). This method can be used to spontaneously resolve DL-*allo*-Ileu into D-*allo*- and L-*allo* isomers (Dalhus and Görbitz 2000). Sensitive methods using derivatization followed by HPLC/MS (Zhao et al. 2006) or 2-dimensional HPLC (Hamase et al. 2007) were able to detect all 4 isomers at low levels in biologic samples. D-*Allo*-Leu was found in human urine (Zhao et al. 2006) and in rat, dog, and mouse urine and kidneys (Hamase et al. 2007). D-Ile was found in the urine, but not in the brain, kidney, or liver of the rat (Hamase et al. 2007). Relatively small amounts of L-*allo*-Ile were found in human plasma (Zhao et al. 2006) and in the brain, kidney, liver, and plasma of the rat (Hamase et al. 2007). It appears D-*allo*-Ile is more prevalent than L-*allo*-Ile in mammals.

Addition of D-Ile to the culture medium strikingly promoted mycelial growth of Matsutake mushrooms (Kawagishi et al. 2004). D-Leu, D-Ile, and D-Val enhanced the activity of prolinase in erythrocytes of a prolidase-deficient patient (Wang et al. 2004). A group of antibiotic peptides isolated from amphibian skin contain D-*allo*-Ile in their amino acid sequence (Kreil 1994). The bicyclic depsipeptide histone deacylase, which inhibits spiruchostatins, contains D-*allo*-isoleucine-D-cysteine as well as D-Ala and D-Val segments in its amino acid sequence. The peptide exhibited cell growth inhibitory activity at nanomolar levels (Narita et al. 2009).

Lanthionine

Lanthionine (LAN) isomers are formed during the biosynthesis of microbial-derived peptide antibiotics (Sahl and Bierbaum 1998) and during exposure of proteins to alkali and heat. Reaction of the SH group of Cys with the double bond of dehydroalanine gives rise to one pair of optically active D- and L-isomers and one diastereomeric (*meso)* form of LAN (Friedman et al. 1979). LAN and cystathionine form radioactive rhenium complexes which are promising renal imaging agents (He et al. 2007; Lipowska et al. 2006). We developed a method for the analysis of LAN isomers and numerous other sulfur amino acids by ion-exchange chromatography (Friedman et al. 1979).

Base-catalyzed formation of LAN and LAL does not affect bioactivity of bovine somatotropin (Tou et al. 2009). Heat- and base-catalyzed formation of LAN in wheat proteins may enhance network formation during bread formation and the production of bioplastics made from gluten (Lagrain et al. 2010). Exogenous LAN and cystathionine can replace diaminopimelic acid in cell wall peptoglycans of *E. coli* bacteria (Mengin-Lecreulx et al. 1994). It is not known whether the replacement will affect the virulence of the pathogens. The mixture of DL + *meso*-LAN has a nutritionally sparing effect on L-Met, as evidenced by a 27% greater weight gain when the two amino acids were fed together, than when fed suboptimal L-Met (Friedman and Gumbmann 1984b; Friedman and Gumbmann 1988).

D-Leucine

Sterilized alkali-treated olives contain significant amounts of D-leucine (D-Leu) and other DAA (Casado et al. 2007). D-Leu in proteins can be used to control coordination of metal ions to diastereopeptides (Peacock et al. 2008). D-Leu inhibits the growth of cultured human breast cancer cells (Shennan and Thomson 2008). A stereospecific mechanism exists for the transfer of D-Leu across the in vitro human placenta (Schneider et al. 1979).

D-Lysine

A plant lysine racemase that converts L-Lys to D-Lysine (D-Lys) is a novel marker for selectable plant transformations (Chen et al. 2010). Concentrations of D-Lys and other DAA in wine increase with fermentation time (Kato et al. 2011). D-Lys inhibited the growth of cyanobacteria (Zimba et al. 2001) and the enzymatic glycation of proteins that may accompany diabetes (Lubec et al. 1989). Both oral and intravenous administration of D-Lys reduced renal uptake of radioactive peptides used in tumor therapy (Verwijnen et al. 2005). Because of its low toxicity, D-Lys may be a better candidate to reduce radioactivity uptake by the kidneys during cancer therapy with radionuclides than is L-Lys (Bernard et al. 1997; Boyd et al. 2006; Lin et al. 2007). Poly-D-lysine stimulates the proliferation of human chondrocytes (Scheller et al. 2004) and brain astroglial cells (Benfenati et al. 2010).

Lysinoalanine isomers

The crosslinked amino acid lysinoalanine (LAL), formed concurrently with DAA in alkali-treated proteins, has two asymmetric C-atoms, making possible four diastereoisomeric forms: DD, DL, LD, and LL (Friedman 2009a). We previously developed a widely used ion-exchange method for the analysis of LAL in soy protein hydrolysates (Friedman et al. 1984). The nutritional value of the individual isomers as a source of L-Lys is not known. Table 3 shows that a mixture of LL and LD isomers has a value for the mouse, equivalent on a molar basis to 3.8% of L-Lys. LAL can serve as marker of protein damage in heat-treated liquid infant formulas, milk, and cheese (Calabrese et al. 2009; Cattaneo et al. 2009; Pellegrino et al. 2010). Serine racemase contains a catalytically active LAL residue, showing that LAL can also be biosynthesized in vivo (Yamauchi et al. 2009).

We have examined the affinity LAL toward a series of metal ions, of which copper (II) was chelated the most strongly. The four LAL isomers differ in their ability to chelate metal ions such as copper (Friedman and Pearce 1989; Pearce and Friedman 1988). On this basis, we suggested a possible mechanism for kidney damage in the rat involving the interaction of LAL with copper within the epithelial cells of the proximal tubules. The direct relationship between the observed affinities of the two LAL isomers for copper (II) ions in vitro and their relative toxic manifestation in the rat kidney suggests that LAL exerts its biological effect through chelation of copper in body fluids and tissues. The observed binding of LL- and LD-LAL to cobalt (II), zinc (II), and other metal ions imply that LAL could also influence cobalt utilization.

LAL, ornithinoalanine (OAL), and LAN are formed during alkaline treatment of wool during skin unhairing of sheep and other processes designed to enhance the strength of wool, and possibly also human hair, via crosslinking reactions (Danalev et al. 2008; Friedman 1977a). These compounds can be used as indicators of changes in the structure and properties of wool keratin during skin unhairing processes in sheep (Koleva et al. 2009). We found that wool fibers treated at high pH contained large amounts of LAN (Friedman 1977b).

D-Methionine

High levels of L-Met (but not of D-Met) are toxic since they inhibited growth of mice (Garlick 2006). D-Methionine (D-Met) was completely transformed to the L-form in vitro by 4 enzymes isolated from different bacteria (Findrik and Vasic-Racki 2007). Chiral inversion of D-Met in rats occurs primarily in the kidneys (Hasegawa et al. 2010).

Other investigators found that D-Met inhibited tumor cell growth in vitro (Sasamura et al. 1999), protected cancer patients against mucosal injury caused by radiation therapy (Hamstra et al. 2010; Vuyyuri et al. 2008) as well as against hearing loss by blocking pro-cell-death signal pathways (Cheng et al. 2008; Dinh and Van De Water 2009; Samson et al. 2008). Unlike L-Met, D-Met was not toxic in isolated mouse hepatocytes (Dever and Elfarra 2008).

D-Ornithine

Analytical methods were developed for Orn isomers that may be present in processed foods (Martínez-Girón et al. 2008; Martínez-Girón et al. 2009). D-Ornithine (D-Orn) has been found in nature on few occasions. A new compound isolated from the larva of the dobsonfly (*Protohermes grandis* Thunberg) was shown to be a cyclic dipeptide of D-Orn (Tanaka and Oda 2009). D-Orn is present in the structure of the *Staphylococcus aureus* siderophore staphyloferrin A that allows the bacteria to grow in iron-restricted environments (Cotton et al. 2009). In an effort to increase the incorporation of non-natural amino acids into proteins, it was found that D-Orn appears to be a direct precursor for biosynthesis of the natural but rare amino acid pyrrolysine (Namy et al. 2007).

D-Orn has proven valuable in studying ornithine decarboxylase (ODC), the first enzyme in eukaryotic polyamine biosynthesis. Inhibition of this enzyme shows promise for cancer treatment. Substituting D-Orn for L-Orn during X-ray crystallography has given insights into substrate binding and ODC conformational flexibility (Jackson et al. 2004; Jackson et al. 2003). A racemic derivative of ornithine, DL-difluoromethylornithine, as well as D-Orn itself to

a lesser extent, inhibit the activity of human ODC (Qu et al. 2003). Surprisingly, the D-derivative was as active as the L-derivative, even though the enzyme has a high degree of stereospecificity for L-Orn. This characteristic could potentially be exploited in drug development.

D-Phenylalanine

D-Phenylalanine (D-Phe) has supposed analgesic, antidepressant, and anti-attention deficit activity (Young 1996). There is little evidence in the scientific literature of this. The proposed mode of action is by two possible mechanisms: (1) steric alteration and inhibition of the carboxypeptidase-like enkephalin degrading enzymes (Christianson et al. 1989; Halpern and Dong 1986); and (2) as a precursor to neurologically active peptides. D-Phe was found to have no analgesic activity in several studies (Klinger 1996; Walsh et al. 1986). Evidence for antidepressant effects is largely anecdotal and may be due to placebo effect (Young 1996). There seems little evidence supporting D-Phe use for attention deficit disorder (Rucklidge et al. 2009). Scientific pursuit in this area has been largely abandoned.

Oral administration of D-Phe caused blood levels to rise rapidly, followed by 1/3 or the dose excreted in the urine and 1/3 of the dose converted to L-Phe (Lehmann et al. 1983). A similar dose of L-Phe showed very little of it was excreted in the urine. The utility of D-Phe and other DAA in stable isotope studies in humans depends on the age of the subject and the nature of the amino acid tracer (Tomlinson et al. 2010). Dietary administration of a novel chromium D-Phe complex [Cr(D-Phe)$_3$] exhibited beneficial effects in insulin-resistant pre-diabetic mice (Dong et al. 2008). D-Phe derivatives were effective in the management of type 2 diabetes (Mavian et al. 2010).

Subcutaneous inoculation of mice with radioactive 2-iodo-D-Phe reduced growth rates of sarcoma tumors in mice by at least 33% without adverse side effects (Bauwens et al. 2010). D-Phe can trap ROS and reactive nitrogen species (RNS) in the rat brain by forming hydroxylation and nitration products (Oeckl and Ferger 2009). D-Phe and D-Trp elicit a chemotactic response in human neutrophils via activation of a G protein-coupled receptor (Irukayama-Tomobe et al. 2009). D-Phe analogs enhance the antibiotic profile of the antimicrobial peptide gramicidin (Solanas et al. 2009).

D-Phe and hydroxyproline define the native structure and presumably virulence of conotoxin, a toxic peptide obtained from the venom produced by cone snails (Huang and Du 2009). Results from exposure of taste fibers of the calf to D-Phe and other sweetening agents suggest that the taste world of cattle is different from other species (Hellekant et al. 2010).

Phenylethylaminoalanine

The amino group of phenylethylamine, a biogenic amine present in food, reacts with the double bond of dehydroalanine to form DL-phenylethylaminoalanine (PEA). Jones et al. (1987) found that oral administration of this compound induces kidney damage in rats, similar to that observed with LAL. We developed an analytical method for separating the two PEA isomers (Friedman and Noma 1986) and discovered that it inhibits metalloenzymes (Friedman et al. 1986a, b). It would be of interest to test the biological properties of the individual isomers, D- and L-PEA.

D-Proline

Analysis by an amperometric D-amino acid biosensor prepared with D-Proline (D-Pro) dehydrogenase showed that rice wine and vinegar contained, respectively, 0.02 and 0.55 mmol/liter of D-Pro (Tani et al. 2009). Mixing D-Pro and other DAA with the corresponding L-isomers results in heat release in the range of 0.6–6 cal/mol, suggesting that chiral solutions contain entrapped energy (Shinitzky et al. 2007).

D-Pro serves as a substrate for *Helicobacter pylori*, a bacterium associated with gastric inflammation and peptic ulcers (Tanigawa et al. 2010). D-Pro peptides in cell wall of the parasite *Trypanosoma cruzi* impart resistance against host proteolytic enzymes (Chamond et al. 2009; Coatnoan et al. 2009). Substitution of D-Pro into a 23 amino acid peptide isolated from *Arabidopsis* leaves causes loss of ability to induce the expression of genes encoding defense proteins against phytopathogens (Pearce et al. 2008).

Oral feeding of an aqueous solution of D-Pro for 1 month to rats induced fibrosis and necrosis of kidney liver cells and elevation of serum enzymes (Kampel et al. 1990). By contrast, orally fed D-Pro and D-Asp did not induce acute toxicity in rats (Schieber et al. 1997). A novel *bis*(D-Pro) drug reduced serum amyloid P component and prolonged renal survival of patients with hereditary fibrinogen amyloidosis (Gillmore et al. 2010). A *bis*-D-Pro compound depleted amyloid deposits in human patients (Bodin et al. 2010). Injection of D-Pro induces sedative effects in chicks (Hamasu et al. 2010).

Selenomethionine

Selenomethionine (Se-met) is an analog of Met, with selenium substituting for the sulfur atom. Se-met is produced in plants analogously to Met at levels relative to available selenium. tRNA^{met} in plants is not selective between Met and Se-met, so incorporation into plant tissues appears to relate to soil selenium levels (Schrauzer

2000). Se-met satisfies the nutritional requirement for selenium and is a major source of selenium in the diets of both animals and humans. Se-met also acts as an antioxidant in vivo. Se-met is not synthesized in humans, so the only source is dietary. D-Se-met and L-Se-met were found in infant formula, but only L-Se-met was found in breast milk (Gómez-Ariza et al. 2004).

Selenium in any form is toxic in excess, but D-Se-met may be less so than L-Se-met. D-Se-met was retained in the tissues rats as strongly as L-Se-met and both were equally toxic at high supplementation levels (McAdam and Levander 1987). But another study found that in rats D-Se-met was less toxic than L-Se-met (Hermann et al. 1991). Comparison of the effects of oral consumption of L-Se-met, DL-Se-met, and selenized yeast on the reproduction of mallard ducklings revealed that although both Se-met preparations were of similar toxicity, their potency was greater than that of selenium present in yeast (Heinz et al. 1996). The survival of day-old ducklings consuming L-Se-met after 2 weeks was significantly lower (36%) than that of ducklings consuming the DL-isomer (100%) (Heinz et al. 1996). D-Se-met was less cytotoxic than L-Se-met in cultured human and murine lymphoid cells and was not a substrate for methionine adenosyltransferase indicating that Se-met enzymatic metabolism are involved in the cytotoxicity (Kajander et al. 1991). The differential responses of normal cells to L- and D-Se-met appear attributable primarily to the initial steps of Se-met metabolism involving stereospecific transsulfurization enzymes (Schrauzer 2000).

Supplementation of broiler diets with D- and L-Se-met improved selenium deposition and antioxidant status of the meat, but L-Se-met was a more effective antioxidant (Wang et al. 2011). D-Se-met protected against adverse effects induced by space radiation (Esaki et al. 1989; Kennedy et al. 2004). An HPLC method was developed to analyze chiral forms of Se-met in human serum and urine (Moreno et al. 2010).

D-Serine

Serine racemase (SRR) was the first of two racemases found in vertebrates (Wolosker et al. 1999). The gene for SRR has been characterized in humans (Xia et al. 2004), suggesting that D-serine (D-Ser) has an essential biochemical role in the body. Dietary exposure to D-Ser may be greater than with other D-amino acids because protein-associated L-Ser racemizes faster to the D-isomer than the other amino acids (Friedman and Liardon 1985).

D-Ser has been reported to enlarge rat kidney cells (cytomegaly) similar to that observed with LAL. Several approaches were used in an attempt to elucidate possible mechanisms of D-Ser renal toxicity (Maekawa et al. 2005; Williams and Lock 2004; Williams et al. 2005). Sodium benzoate (Williams and Lock 2004; Williams et al. 2005), protein-deficient diets (Levine and Saltzman 2003), and α-aminoisobutyric acid (Krug et al. 2007) attenuated D-Ser nephrotoxicity in rats. D-Ser-induced kidney damage may be due to a lowering of the concentration of renal glutathione (GSH) that protects the kidneys against kidney-damaging ROS (Krug et al. 2007). The decrease in glutathione concentration takes place during the metabolism of D-Ser by DAAO. Because nephrotoxicity induced by D-Ser is similar to that caused by LAL, the question arises as to whether effects of these two amino acids on the rat kidney are competitive, additive, or synergistic.

DAAO inhibitors increase the D-Ser concentration in mammalian blood and brain (Smith et al. 2010) and ameliorate pain in rats (Gong et al. 2011). Oxidation of D-Ser by DAAO produced hydroxypyruvate, which was selectively cytotoxic to astroglial cells (Chung et al. 2010). A consequence of rat liver injury is a sharp decrease in renal DAAO activity, possibly resulting in metabolic acidosis (Zhang et al. 2010b). Intrastriatal administration of D-Ser-induced lipid peroxidation and decreased oxidative defense of rats (Leipnitz et al. 2010).

The content of D-Ser, D-Asp, D-Asn, and D-Thr in proteins of human cataract lenses was significantly higher than in age-matched normal lenses (Hooi and Truscott 2010). The increased rates of in vivo racemization may contribute to the opacity of human lenses. Does consumption of racemized proteins with a high content of the indicated DAA contribute to this and other adverse effect in the human eye? Can DAAO be used therapeutically to decrease the content of DAA in the lenses?

D-Ser has potential as a therapeutic agent for neurological disorders. D-Ser can serve as a substitute for glycine as a co-agonist of the NMDA receptor, which mediates glutamatergic neurotransmission (Kleckner and Dingledine 1988). Deficiencies in the activity of the NMDA receptor have been associated with neuropsychiatric deficiencies (Coyle 2006). Thus, several studies have found an association between the activity of serine racemase and schizophrenia (Labrie et al. 2009), Alzheimer's disease (Hashimoto et al. 2004), and age-related memory loss (Mothet et al. 2006). D-Ser may also be useful as an innovative pharmacologic strategy in the treatment of these diseases (Coyle et al. 2010; Sethuraman et al. 2009), as well as for ameliorating pain (Muth-Selbach et al. 2004) and treating anxiety disorders (Matsuda et al. 2010). Further research is needed to clarify the consequences of D-Ser exposure on pathways implicated in neuronal functions and neurodegenerative disorders (Davidson et al. 2009).

Other studies indicate that D-Ser performs a variety of additional specialized functions in nature. These include the following events. A strain of protozoa (*Drosophila*

melanogaster) has developed a transport mechanism with adaptive specialization in the absorption, and gut and brain functions of D-Ser and other DAA which may be involved in neuronal functions (Miller et al. 2008). The D-configuration of Ser maintains the toxic conformation of the mushroom poison viroisin (Zanotti et al. 1999). D-Ser inhibits the growth of *Pasteurella pestis* (Smith and Higuchi 1960) and can be enzymatically transformed to L-Trp (Shimada et al. 2009). The recent discovery that D-Ser governs signaling pathways in the fertilization process of plants, analogous to what is observed in animal neurons mentioned above (Michard et al. 2011), will undoubtedly stimulate studies on the role of D-Ser in plant physiology.

Threonine stereoisomers (D-Thr, L-allo-Thr, and D-allo-Thr)

L-Thr is nutritionally important because it is the second limiting amino acid in maize (corn) protein. The utilization of D-Thr by the chick, rat, mouse, or humans as a nutritional source of the L-isomer is insignificant (Borg and Wahlstrom 1989). Thr exists as four stereoisomers because it has two chiral centers. Reversal of the chiral center at the α-carbon produces D-*allo*-Thr, at the *β*-carbon produces L-*allo*-Thr, and at both centers, D-Thr. An amino acid racemase was isolated from *Pseudomonas putida* bacteria, which racemized L- to D-*allo*-Thr and D- to L-*allo*-Thre (Lim et al. 1993). D-*Allo*-Thr has been found in several natural antibiotics (Winkelmann et al. 1980; Zink et al. 1992). The enzyme D-threonine aldolase isolated from *Arthrobacter* catalyzes the cleavage of D-Thr into Gly and acetaldehyde. Both D-Thr and D-*allo*-Thr act as substrates with different kinetic parameters. Because the aldolase reaction is reversible, the enzyme can produce nearly equimolar amounts of D-Thr and D-*allo*-Thr via carbon–carbon bond formation between Gly and acetaldehyde (Kataoka et al. 1997; Liu et al. 1998). Until recently, L-Thr was the only isomer thought to be naturally present in mammals.

D-Thr has been found at very low levels in human urine (Brückner and Schieber 2001). Newer analytical techniques have allowed the determination of trace levels of D-Thr in other physiologic tissues amidst excessive L-isomers (Hamase et al. 2009; Waldhier et al. 2010). The four isomers of Thr were resolved using a two-dimensional HPLC system and measured in various tissue of mammals (Hamase 2007; Zhao et al. 2004). D-*Allo*-Thr was found in the brain and the urine at much higher levels than D-Thr. L-*Allo*-Thr was not detected, suggesting that the epimerization of the chiral center of the α-carbon predominantly occurs, compared with the epimerization of the *β*-carbon (Zhao et al. 2004). Another technique of derivatization combined with GC/MS allowed simultaneous determination of L- and D-Thr in a single run (Waldhier et al. 2010). They were able to determine with this technique that patients suffering from renal failure were found to have significantly higher ratios of D-Thr to L-Thr than healthy controls (Waldhier et al. 2010).

D-Tryptophan

Next to D-Ala, derivatives of D-Tryptophan (D-Trp) are the most prevalent D-amino acids in higher plants (Robinson 1976). Apples contain about 0.8 mol/g (Robinson 1976). As discussed previously in the "Nutritional utilization of D-amino acids or amino acid derivatives", D-Trp may replace L-Trp in mice, but must be used at approximately 2.5× greater levels. Both D-Phe and D-Trp taste sweet (Finley and Friedman 1973; Friedman and Cuq 1988; Maehashi et al. 2007; Manita et al. 2006). D-Trp aldolase is involved in the biosynthesis of vitamin B6-dependent enzymes (Paiardini et al. 2003).

Copper complexes of D- and L-Trp bind to and cleave DNA of human carcinoma cell lines, especially to pancreatic cancer cells. The L-enantiomeric form exhibited greater binding affinity than did the D-form (Arjmand and Muddassir 2011). The aryl hydrocarbon receptor (AHR) mediates toxic and adaptive responses to xenobiotic compounds. DAAO catalyzes the production of AHR agonists through the enzymatic conversion of D-Trp to indole-3-pyruvic acid (Nguyen et al. 2009). This observation shows that D-Trp can modulate the endogenous AHR activity and presumably detoxifications pathways. D-Trp-containing peptides may be useful in the treatment of Parkinson's disease (Shaltiel-Karyo et al. 2010). 1-Methyl-D-Trp is a useful immunotherapeutic agent for combination use with chemotherapy (Jia et al. 2008). D-Trp can serve as a nitrogen source for *Cryptococcus gatti meningoencephalitis* (Gutierrez et al. 2010).

D-Tyrosine

As discussed in the "Nutritional utilization of D-amino acids or amino acid derivatives", D-tyrosine (D-Tyr), this amino acid has a depressive effect on the growth of mice eating an otherwise balanced diet. The depressive effect can be somewhat ameliorated by added L-Phe, which may be converted to L-Tyr in vivo. The potential for chronic toxicity following exposure to lower levels of D-Tyr remains unknown. The antimetabolic manifestation of D-Tyr may be ascribed to interference with the biosynthesis of vital neurotransmitters and proteins in vivo (Anonymous 1985; Friedman and Gumbmann 1984a).

Studies with mice suggest that D-Tyr-tRNA(Tyr) deacylase may be involved in Alzheimer's associated pathology (Liu et al. 2010b). Formation of D-tyrosyl-tRNA^{Tyr} may be responsible for the toxicity of D-Tyr toward *E. coli* (Soutourina et al. 2004). D-Amino acid-tRNA deacylases

protect cells against invasion by DAA (Sheoran et al. 2008; Wydau et al. 2009; Zheng et al. 2009).

D-Valine

Administration of TPN containing D-Leu, D-Met, D-Phe, and D-valine (D-Val) to hepatoma-bearing rats showed that D-Val inhibited tumor growth without negative effects on the host. D-Leu and D-Met also improved the nutritional status of the sick rats (Sasamura et al. 1998). These observations suggest that some DAA diets may benefit cancer patients. Replacement of D-Val by *N*-methyl-D-Leu reduces toxicity without affecting antitumor activity of actinomycin D (Zhang et al. 2010a). The calcium release-inhibiting depsipeptide malevamide E isolated from cyanobacteria contains a D-Val residue (Adams et al. 2008).

D-Peptides

Naturally occurring and synthetic DAA-containing peptides are reported to exhibit numerous beneficial effects. Although detailed discussion of this aspect of DAA chemistry and biology is beyond the scope of the present overview, here we briefly outline selected recent observations that are relevant to the theme of this paper. These provide an entry into the literature of the multifaceted, potential beneficial effects of D-peptides.

The following observations suggest that some D-peptides exhibit high antimicrobial and antiviral activity. A synthetic all-D-peptide was bacteristatic against *E. coli* (MIC < 1 μM) (Ryadnov et al. 2002). Cell-surface studies suggest that D-peptides have the potential to be used for intravenous injection and direct-surface application as anti-infectives (Monk et al. 2005). A potent new lipopeptide antibiotic isolated from *Streptomyces fradiae* contains three D-amino acids (Gu et al. 2010). A designed D-peptide shows promise as a potent antiviral candidate against HIV (Welch et al. 2010). A current approach uses peptide engineering strategies to create bioactive peptides with D- and other unnatural amino acids (Nagao et al. 2011; Wang et al. 2009). Antibiotic peptides isolated from amphibian skin that contain D-*allo*-Ile in their amino acid sequence are mentioned above under D-*allo*-Ile.

D-Ala, D-Glu, D-Leu, and D-Met regulate DAA-containing bacterial cell wall peptidoglycan peptide remodeling in the stationary phase and cause biofilm dispersal in aging bacterial communities (Cava et al. 2011; Kolodkin-Gal et al. 2010). A better understanding of the factors that regulate the biosynthesis of cell wall peptidoglycans and degradation of biofilms that anchor bacteria to food and tissue surfaces may facilitate development of improved antibiotics based on food-compatible natural products, including tea catechins (Friedman 2007), chitosans (Friedman and Juneja 2010), and plant essential oils (Friedman et al. 2002).

A D-nanofiber peptide induced rapid hemostasis (reduced blood loss) in a wounded rabbit liver model (Luo et al. 2011). D-Peptides inhibited brain amyloids and reduced amyloid-induced cytotoxicity in cell culture. (Esteras-Chopo et al. 2008; Wiesehan et al. 2008). D-Peptide inhibitors can be used for targeted therapy of malignant neoplasms (Liu et al. 2010a).

Conclusion and research needs

There is a need to standardize methods designed to ascertain the role of DAA in nutrition. Because the organism is forced to use the DAA as the sole source of the L-form, the use of all-amino-acid diets in which the L-isomer is completely replaced with different levels of the corresponding DAA may be preferable to supplementation of proteins with DAA. DAA along a peptide chain may be less utilized than the L-forms. The utilization of any DAA may be affected by the presence of other DAA in the diet.

Additionally, largely unresolved are the following questions:

(a) How do biological effects of D-amino acids vary, depending on whether they are consumed in the free state or as part of a food protein?
(b) Do metabolic interactions, antagonisms, or synergisms among D-amino acids occur in vivo?
(c) Do free and protein-associated D-amino acids interact (bind) differently than L-amino acids in the digestive tract with active sites of the proteolytic enzymes, such as chymotrypsin, pepsin, and trypsin?
(d) Do D-amino acids and D-peptides alter the normal microflora of the intestine?
(e) Does racemization of toxic bacterial, plant, and venom proteins alter protein conformations, charge distributions (isoelectric points), and affinities for cell membranes, resulting in protective effects against protein-induced in vivo toxicities (Friedman 2001; Rasooly et al. 2010a, b, c)?
(f) Will DAA disassemble biofilms produced by pathogenic bacteria such as *E. coli* and *Salmonella* in food (Cava et al. 2011; Kolodkin-Gal et al. 2010)?
(g) Can analytical methods and preparative HPLC methods be developed for determining the content and biological functions of four possible isomeric forms (LL, LD, DD, DL) of crosslinked amino acids with two asymmetric C-atoms (lysinoalanine, ornithinoalanine, histidinoalanine) and of eight isomeric forms (DDD, DDL, DLD, DLL, LLL, LLD, LDL, LDD) of amino acid derivatives with three asymmetric carbon atoms

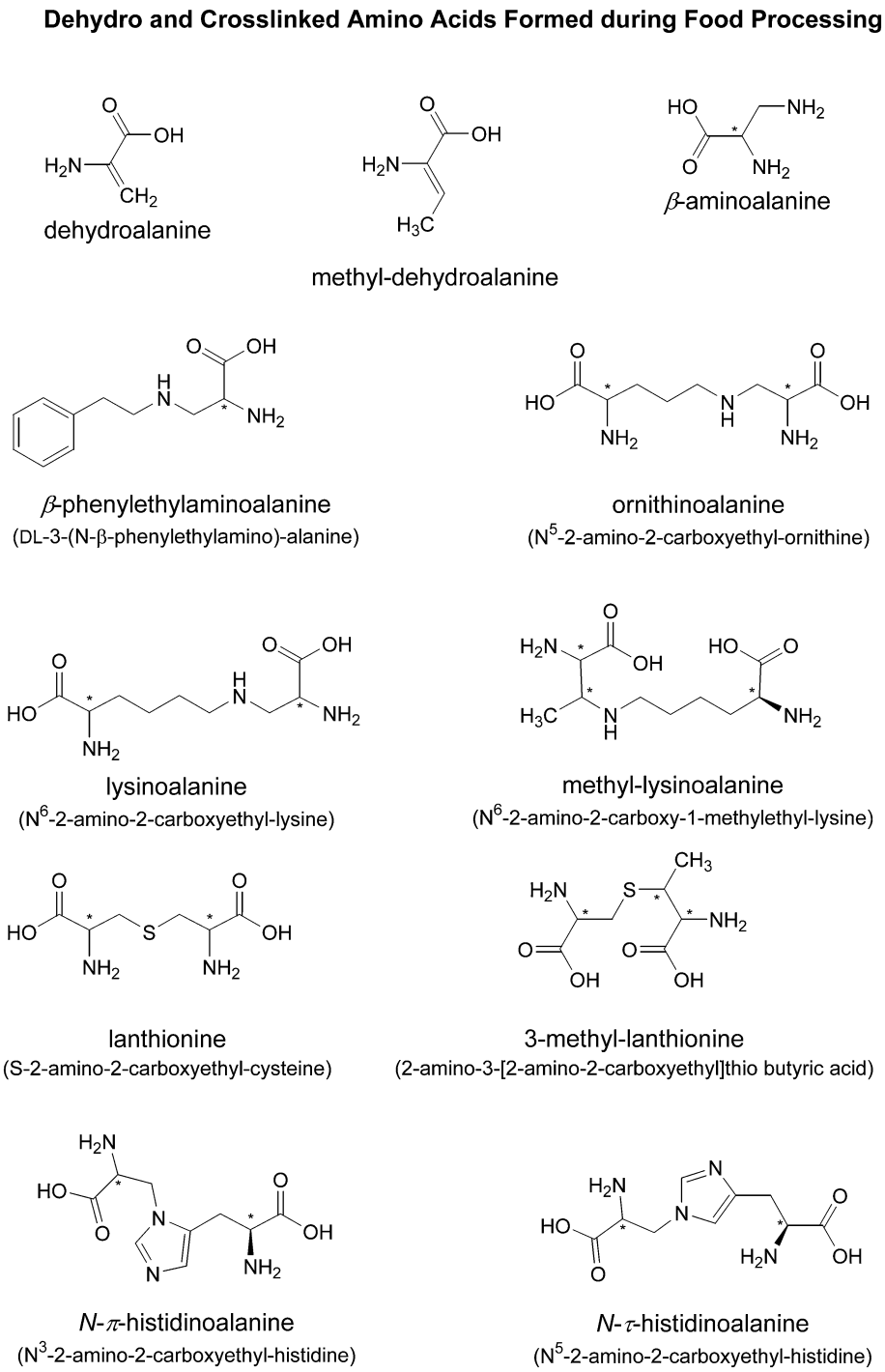

Fig. 7 Structures of dehydro amino acids involved in the formation of crosslinked amino acids with one, two, or three asymmetric C-atoms marked with *asterisks*

(methyl-lanthionine; methyl-lysinoalanine) (Boschin et al. 2002) that may be present in food and in vivo (Friedman 1977a) (Fig. 7)? Answers to these questions will help further define the roles of DAA in nutrition and medicine.

Conflict of interest The authors declare that they have no conflict of interest.

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