11 Amino Acids in the Nutrition, Metabolism, and Health of Domestic Cats

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Abstract

Domestic cats (carnivores) require high amounts of dietary amino acids (AAs) for normal growth, development, and reproduction. Amino acids had been traditionally categorised as nutritionally essential (EAAs) or nonessential (NEAAs), depending on whether they are synthesized de novo in the body. This review will focus on AA nutrition and metabolism in cats. Like other mammals, cats do not synthesize the carbon skeletons of twelve proteinogenic AAs: Arg, Cys, His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Tyr, and Val. Like other feline carnivores but unlike many mammals, cats do not synthesize citrulline and have a very limited ability to produce taurine from Cys. Except for Leu and Lys that are strictly ketogenic AAs, most EAAs are both glucogenic and ketogenic AAs. All the EAAs (including taurine) must be provided in diets for cats. These animals are sensitive to dietary deficiencies of Arg and taurine, which rapidly result in life-threatening hyperammonemia and retinal damage, respectively. Although the National Research Council (NCR, Nutrient requirements of dogs and cats. National Academies Press, Washington, DC, 2006) does not recommend dietary requirements of cats for NEAAs, much attention should be directed to this critical issue of nutrition. Cats can synthesize de novo eight proteinogenic AAs: Ala, Asn, Asp, Gln, Glu, Gly, Pro, and Ser, as well as some nonproteinogenic AAs, such as γ-aminobutyrate, ornithine, and β-alanine with important physiological functions. Some of these AAs (e.g., Gln, Glu, Pro, and Gly) are crucial for intestinal integrity and health. Except for Gln, AAs in the arterial blood of cats may not be available to the mucosa of the small intestine. Plant-source foodstuffs lack taurine and generally contain inadequate Met and Cys and, therefore, should not be fed to cats in any age group. Besides meat, animal-source foodstuffs (including ruminant meat & bone meal, poultry by-product meal, porcine mucosal protein, and chicken visceral digest) are good sources of proteinogenic AAs and taurine for cats. Meeting dietary requirements for both EAAs

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and NEAAs in proper amounts and balances is crucial for improving the health, wellbeing, longevity, and reproduction of cats.

Keywords

Cats · Amino acids · Nutritional requirements · Protein deficiency

Abbreviations

AA	amino acid
BCAA	branched-chain amino acid
BCKAD	branched chain α-ketoacid dehydrogenease
CP	crude protein
DM	dry matter
FHL	feline hepatic lipidosis
IDO	indoleamine 2,3-dioxygenase
MAT	methionine adenosyltranferase
NO	nitric oxide
SAA	sulfur-containing amino acid
SAM	*S*-adenosylmethionine

11.1 Introduction

Domestic cats (*Felis silvestris*) are obligate carnivores (Zoran 2002). The word "obligate", which means "by necessity", is used to emphasize the fact that they are somewhat different than many other meat-eating predators. The cats eat "prey" or depend on nutrients [such as amino acids (AAs)] in animal tissues as their foods, and are also known as hypercarnivores (Adronie et al. 2013). Thus, the cats have evolved to lose an ability of synthesizing taurine (Sturman and Hayes 1980), which is an abundant AA in animals-source feedstuffs but absent from plant-source feedstuffs (Hou et al. 2019; Li and Wu 2020). Hypercarnivores require more dietary protein than omnivorous mammals (Holliday and Steppan 2004). Verbrugghe and Bakovic (2013) have suggested that cats have many physical and metabolic variations due to evolution pressure that includes the metabolism of one-carbon molecules and fatty acids. The requirements of carnivores for dietary protein are higher than omnivores and herbivores, because the former need AAs [e.g., Glu, Gln, Asp, Ala, and branched-chain AAs (BCAAs)] for ATP production by major tissues. The carnivorous mammals may be just like carnivorous fish in using Glu, Gln and Asp as the major metabolic fuels (Jia et al. 2017; Li et al. 2020a). In addition, AAs are used for glucose synthesis in all carnivores. During the deprivation of food, the gluconeogenic capacity of cats is maximized with the high expression of the needed enzymes in the liver (Rogers et al. 1977; Verbrugghe and Bakovic 2013).

Protein metabolism in domestic cats is different than that in omnivores (Wortinger 2010). This includes dietary requirements of cats for arginine and taurine (Wester et al. 2015; Wu 2018). Protein in the body cats consists of 20 proteinogenic AAs and other AA derivatives, including 4-hydroxyproline, 3-hydroxyproline, hydroxylysine, 3-methylhistidine, and methylarginines (Wu 2013). Like other mammals, cats do not synthesize the carbon skeletons of 12 proteinogenic AAs: Arg, Cys, His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Tyr, and Val (Jungnickel et al. 2018). These AAs have been traditionally classified as nutritionally essential AAs (EAAs) and must be included in diets for the cats of all age groups (Hou and Wu 2018a). Like other feline carnivores but unlike many mammals, cats do not synthesize citrulline de novo and have a limited ability to produce taurine. Taurine has a plethora of physiological functions (Wu 2020b) and must also be provided in their diets to prevent disorders, such as retinal, cardiovascular, muscular, and reproductive disorders. However, cats can synthesize de novo eight proteinogenic AAs: Ala, Asn, Asp, Gln, Glu, Gly, Pro, and Ser, as well as some nonproteinogenic AAs, such as γ-aminobutyrate, ornithine, and β-alanine with important physiological functions (Rogers et al. 1998). The biosynthesizable proteinogenic AAs had been historically classified as nutritionally nonessential AAs (NEAAs; see Hou et al. 2015 for review),

but this term has now been recognized as a misnomer in nutritional sciences and should not be used in nutrition research or practices (Hou and Wu 2017). Studies with pigs, rats, chickens, and fish have shown that these animals have dietary requirements for at least some of the NEAAs (Hou et al. 2015, 2016; Li et al. 2020a). This may also be true for cats (e.g., Gln and Gly), particularly those with cancers and intestinal damage (Morrison 2002).

Based on their metabolic fates, AAs are classified as glucogenic, ketogenic, or both glucogenic and ketogenic (Wu 2013). Glucogenic AAs are: Ala, Arg, Asp, Asn, Cys, Gln, Glu, Gly, His, Met, Pro, Ser, Thr, and Val that can produce pyruvate or an intermediate of the Krebs cycle (Burns et al. 1981; D'Mello 2003; NRC 2006; Saxton et al. 2016). Ketogenic AAs are Leu and Lys that produce acetyl-CoA and ketone bodies but no glucose (Harris et al. 2004; NRC 2006; Zhao et al. 2010). Amino acids that serve as both glucogenic and ketogenic are Ile, Phe, Thr, Trp and Tyr that can generate pyruvate or an intermediate of the Krebs cycle (substrates of glucose), as well as acetyl-CoA and ketone bodies (Hendriks 1996; Yu et al. 2001; NRC 2006). Furthermore, in domestic cats, cysteine, glycine, and glutamate [derived from branched-chain AAs (BCAAs)] participate in the syntheses of three unique sulfur-containing AAs (felinine, isovalthine, and isobuteine) through inter-organ metabolism that involves the liver and kidneys (Brosnan and Brosnan 2006; NRC 2006; Hand et al. 2010). The major objective of this article is to highlight the important roles of AAs in the nutrition, metabolism, and health of these companion animals.

11.2 Requirements of Protein and AAs for Growing and Adult Cats

Dietary AAs are required by cats for the growth and maintenance of body tissues and also for the production of nitrogen-containing organic compounds, including purines, pyrimidines, serotonin, creatine, polyamines, nitric oxide (NO), and glutathione (Hendriks 1996; Wu 2013). In practice, dietary protein is the primary source of AAs for the animals. Cats use a large amount of dietary protein for ATP production (Zoran 2002). The minimum requirement of growing and reproductive cats for dietary crude protein (CP) is 30% of the dietary dry matter and the minimum maintenance requirement of adult cats for dietary CP is 26% of the dietary dry matter (AAFCO 2014). Both EAAs and NEAAs are needed in the diets of animals (including cats) for their optimum health, growth and development (Wu 2018). Because some of the free AAs confer bitter, salty or unpleasant tastes and because it is expensive to prepare free AA-based purified diets, the cats that can eat and have a healthy digestive tract are generally provided with intact protein. Fully developed cats need dietary protein for the maintenance of digestive enzymes and proteins in tissues, such as those in blood, skeletal muscle, gastrointestinal mucosae, skin, hair, liver, and brain (Laflamme 2008). Growing cats and kittens need dietary protein for maintenance (just like adult cats), as well as the growth and development of tissues.

Cats can adapt to changes in dietary protein intake from 14% to 56% CP (Green et al. 2008; Rogers et al. 1998). This likely involves alterations in the activities of AA-metabolic enzymes and the rates of whole-body protein turnover (protein synthesis and degradation). Thus, cats fed a low-protein diet produce less ammonia, urea, and creatine than those fed a normal-protein diet (Zoran 2002). Animals can utilize excess protein as the source of energy if they are fed low-energy diets that contain relatively low levels of lipids and digestible carbohydrates (e.g., starch/glycogen). If dietary energy intake by animals is adequate, excessive dietary protein will be converted into lipids and glycogen, with nitrogen being excreted primarily as ammonia and urea in the urine (Wu 2013). The content of protein in meat is relatively constant. Of note, cats fed meats that naturally contain 70–75% CP [dry matter basis; about twice their minimum requirement for dietary CP (NRC 2006)] do not exhibit any adverse response. When their arginine intake is adequate and their

liver functions normally, healthy cats that consume meat do not exhibit ammonia toxicity. This indicates a high capacity of young and adult cats to catabolize dietary AAs.

Because Cys is formed from Met in the liver and Tyr is produced from Phe in both the liver and kidneys (Hou et al. 2020; Li et al. 2020d; Wu 2013), Cys and Tyr are generally not considered by some authors as EAAs (Verbrugghe and Bakovic 2013). However, a great dependence on Met for Cys provision will reduce the availability of Met as a methyl group donor for critical biochemical reactions (e.g., creatine synthesis and protein methylation) in the body. In addition, because the conversion of Phe into Tyr requires tetrahydrobiopterin (Wu 2013), which is readily oxidized and can be depleted under conditions of oxidative stress and disease (Shi et al. 2004), the degradation of Phe may not provide sufficient Tyr in a catabolic state. Cats that have genetic defects in Cys synthesis and Phe hydroxylation must obtain both Cys and Tyr from diets. To meet metabolic needs and reduce metabolic burdens on AA synthesis, all proteinogenic AAs should be provided to young and adult cats, just like livestock mammals and poultry (Wu 2014). In addition, cats of all age groups have a dietary requirement for taurine, as noted previously.

There are differences in the recommended requirement values of some EAAs for growing and reproductive cats between the 2006 and 2014 versions (Table 11.1). The requirements for His, Ile, Leu, Phe (+ Tyr), Phe and Val in the 2014 version are greater than those in the 2006 version. However, the recommended requirement values of most EAAs in the 2014 version are the essentially the same as those in the 2006 version. Interestingly, the recommended requirement value for Arg in the 2014 version is slightly lower by a 0.01% unit than that in the 2006 version. Of particular note, the recommended requirement values for Phe and Tyr in the 2014 version is substantially greater than those in the 2006 version to maintain the black hair color of the cats. Adequate intakes of Cys, Met and taurine are of exceptional concern in cat nutrition (Case et al. 2011). Deficiencies of

Table 11.1 Recommended requirements of cats for dietary protein and nutritionally essential amino acids

Nutrient (% of dry matter in diet)	AAFCO (2007); National Research Council (NRC 2006)			AAFCO (2014)		
	Minimum requirement for growth and reproduction	Minimum requirement for maintenance in adults	Maximum requirement	Minimum requirement for growth and reproduction	Minimum requirement for adult maintenance	Maximum requirement
Crude protein	30	26	–	30	26	–
Arginine	1.25	1.04	–	1.24	1.04	–
Histidine	0.31	0.31	–	0.33	0.31	–
Isoleucine	0.52	0.52	–	0.56	0.52	–
Leucine	1.25	1.25	–	1.28	1.24	–
Lysine	1.20	0.83	–	1.20	0.83	–
Methionine	0.62	0.62	1.5	0.62	0.20	1.5
Methionine (+ cysteine)	1.10	1.10	–	1.10	0.40	–
Phenylalanine (+ tyrosine)	0.88	0.88	–	1.92	1.53	–
Phenylalanine	0.42	0.42	–	0.52	0.42	–
Taurine	0.20	0.20	–			–
Threonine	0.73	0.73	–	0.73	0.73	–
Tryptophan	0.25	0.16	–	0.25	0.16	1.7
Valine	0.62	0.62	–	0.64	0.62	–
Total EAAs	8.11	7.44		9.25	7.38	

– Data are not available

EAAs nutritionally essential amino acids (including Cys and Tyr)

these AAs result in protein malnutrition in cats, leading to weight and lean tissue losses, poor work and reproductive performance, and insulin resistance (Case et al. 2011; Verbrugghe et al. 2012). The poor health of the animals may be caused by a deficiency of NO, which is a metabolite of Arg (Wu and Meininger 2009).

Compelling evidence shows that cats have dietary requirements for NEAAs (Verbrugghe and Bakovic 2013; Rogers et al. 1998). For example, growing kittens fed a 14% CP diet with all EAAs [1X NRC (1986) requirements] but without any NEAA lost body weight during a 10-day experimental period (Table 11.2). Additionally, kittens fed a 21% CP diet with all EAAs [2.8X NRC (1986) requirements] but without any NEAA grew poorly. Furthermore, kittens fed a 35% CP diet with all EAAs [4.7X NRC (1986) requirements] but without any NEAA grew at a suboptimal rate, as compared with the animals fed a 25% CP containing both EAAs and NEAAs. Disappointingly, the mixture of NEAAs used in the previous studies did not contain serine, and the ratios of NEAAs to EAAs were not consistent with those in meat (Wu et al. 2016) or the animal body (Wu 2013).

Unfortunately, nutritionists have generally considered only EAAs for cats (Table 11.1). However, the sum of these EAAs is less than 31% CP of the diet. Feeding only these EAAs to cats in any age group will not support their maintenance needs. Clearly, NEAAs should be included in the diets of cats at all of their developmental stages. At present, such data are not available. Based on the content (on the basis of dry matter) of true proteins, small peptides, and free AAs in the beef loin meat (Wu et al. 2016), as well as a lower metabolic rate in the adult than in

Table 11.2 Growth of kittens fed purified diets containing various rations of EAAs to NEAAs for 10 days[a]

CP content %	EAAs[b] : NEAAs[c]	(X) EAA requirement[d]	Number of animals	Weight gain (g/day)	AA in plasma (nmol/ml)		
					Glu	Arg	Pro
35	0.27 : 0.73	1.5	36	24.4	–	–	–
14[e]	1.00 : 0.00	1.9	12	– 4.7	60	136	75
14	0.47 : 0.53	1.0	12	14.7	102	107	199
21[e]	1.00 : 0.00	2.8	12	10.8	72	344	70
21	0.31 : 0.69	1.0	12	16.9	124	106	513
21	0.61 : 0.39	2.0	8	19.1	100	301	207
35[e]	1.00 : 0.00	4.7	12	21.5	72	290	67
35	0.18 : 0.82	1.0	12	13.3	182	78	1062
35	0.55 : 0.45	3.0	10	29.0	77	262	257
42	0.23 : 0.77	1.5	10	28.8	188	121	801
42	0.45 : 0.55	3.0	10	18.2	105	348	633
56	0.11 : 0.89	1.0	12	1.3	413	68	2165
56	0.17 : 0.83	1.5	10	16.5	228	98	1165
56	0.23 : 0.77	2.0	8	18.2	157	119	890
56	0.34 : 0.66	3.0	10	24.3	143	227	742

AA amino acid

[a]Adapted from Rogers et al. (1998). Cats (8 to 12 weeks of age; the initial body weights = 1.02 to 1.30 kg) were used for the experiments. Crude protein (CP) = nitrogen in the diet x 6.25. All diets contained 0.15% taurine

[b]Nutritionally essential amino acids (EAAs; L-isoform) used in the study are Arg, His, Ile, Leu, Lys, Met, Cys, Phe, Tyr, Thr, Trp, and Val

[c]The mixture of nutritionally nonessential amino acids (NEAAs) used in the study contained the following (%): was L-Ala, 17.5; Gly, 17.5; L-Gln, 17.5; L-Glu, 7.5; L-Asn, 15; L-Asp, 10; and L-Pro, 15. Note that: (1) the NEAA mixture did not provide Ser and therefore was incomplete; and (2) the proportion of NEAAs in the mixture was very different than that in meat or the animal body

[d]National Research Council (NRC 1986). The 1X EAA requirements (% of diet) are: Arg, 1.0; His, 0.3; Ile, 0.5; Leu, 1.2; Lys, 0.8; Met, 0.4; Cys, 0.35; Phe, 0.4; Tyr, 0.45; Thr, 0.7; Trp, 0.15; and Val, 0.6

[e]The diet contained only EAAs as the source of nitrogen

the young (Wu 2018), we recommend the minimum and maximum dietary requirements of cats for protein, NEAAs, and EAAs (Table 11.2) as references for feeding and a framework for future studies. The CP content (on the basis of dry matter) of the beef loin meat is 73.4% (Wu et al. 2016). The minimum and maximum requirements for dietary AAs are based on those for dietary protein (i.e., the minimum dietary requirements of young and adult cats for 30% and 26% CP, respectively, and the maximum dietary requirements of both young and adult cats for 73.4% CP; dry matter basis). To prevent or alleviate the loss of skeletal muscle in aging cats through enhancing NO synthesis, protein synthesis, and anti-oxidative reactions, as well as reducing white fat accretion, we recommend that elderly cats have higher minimum dietary requirements for Arg, Glu, Gly, and Trp than young adult cats. This is mainly because of the following considerations. First, Arg (Yao et al. 2008), Gly (Sun et al. 2016), and Trp (Cortamira et al. 1991; Dukes et al. 2015; Lin et al. 1988) enhance protein synthesis in skeletal muscle (Lin et al. 1988; Sun et al. 2016; Yao et al. 2008). Second, both Arg and Gly increase glutathione synthesis to protect cells from oxidative stress (Jobgen et al. 2009; Wang et al. 2014). Third, Arg, Gly and Trp improve intestinal immune function and health (Liang et al. 2018, 2019; Wang et al. 2014, 2015; Wu 2014). Fourth, Glu is a major energy substrate for the small intestine of animals (He et al. 2018; Hou and Wu 2018b; Jia et al. 2017; Li et al. 2020a) and plays an important role in maintaining intestinal integrity (Hou and Wu 2018a; Jiao et al. 2015) (Table 11.3).

Table 11.3 Recommended requirements of cats for dietary amino acids[a]

Crude protein and amino acid	Minimum dietary requirements of cats for amino acids			Maximum dietary requirements of young, adult, and elderly adult cats for amino acids
	Young cats	Young adult cats	Elderly adult cats	
Crude protein	30	26	30	73.4
Taurine	0.2	0.2	0.2	0.29
Proteinogenic amino acids that are not synthesized de novo by cats				
Arg	2.14	1.86	2.33	5.24
Cys	0.50	0.50	0.50	1.12
His	1.30	1.12	1.12	3.17
Ile	1.68	1.46	1.46	4.11
Leu	2.73	2.36	2.36	6.67
Lys	2.94	2.55	2.56	7.20
Met	1.03	0.90	0.90	2.53
Phe	1.37	1.19	1.19	3.35
Thr	1.51	1.31	1.31	3.70
Trp	0.41	0.35	0.44	1.00
Tyr	1.23	1.07	1.07	3.01
Val	1.94	1.68	1.68	4.74
Proteinogenic amino acids that are synthesized de novo by cats				
Ala	1.86	1.61	1.61	4.54
Asn	1.37	1.18	1.18	3.34
Asp	1.68	1.46	1.46	4.11
Glu	3.07	2.66	3.33	7.51
Gln	2.04	1.77	1.77	4.99
Gly	1.38	1.19	1.49	3.37
Pro[b]	1.42	1.23	1.23	3.47
Ser	1.45	1.25	1.25	3.54

[a]Values are % of dry matter in the diet

[b]Proline + 4-hydroxyproline (the ratio of proline to 4-hydroxyproline = 18.6:1.0; g/g)

11.3 Protein Deficiency in Cats

Protein deficiency occurs in cats when their dietary protein intake is less than their minimum protein requirement. Inadequate intake of protein can result in an insufficient provision of both EAAs and NEAAs (Agnew and Korman 2014). As noted previously, EAAs must be provided in the diet simply because they are not formed de novo in the animal body. Therefore, like other mammals (e.g., rats; Anonymous 1975), when a diet lacking protein is consumed by cats, there is a decrease in enzyme activity for EAA catabolism to conserve the AAs (Morris 2002). Clinical signs of protein deficiency in cats are: reduced lean body mass, hindered growth in young cats, loss of body weight, impaired reproduction, and reduced work performance (Case et al. 2011). This is because dietary protein is particularly important for not only "feline health", but also the prevention of various metabolic and infectious diseases (Backlund et al. 2011; Kantorosinski and Morrison 1988; Wu 2020a). If dietary protein deficiency happens with sufficient energy intake, plasma AA and albumin concentrations decrease, leading to edema or ascites (Agnew and Korman 2014; Case et al. 2011; Wester et al. 2015; Zoran 2002). Because cats depend on dietary protein for gluconeogenesis when their typical diets contain a small amount of digestible carbohydrate, low dietary AA intake may affect glucose provision and therefore, the function of the brain, red blood cells, retina, and kidney medulla (Verbrugghe and Bakovic 2013).

11.4 Glucogenic Amino Acids

As a carnivore, the domestic cat consumes diets rich in protein and fats. Thus, there are differences in glucose metabolism between cats and non-carnivorous mammals (Schermerhorn 2013). For example, healthy cats lack salivary amylase (for glycogen and starch hydrolysis), as well as hepatic glucokinase (for glycolysis and glucose sensing) and hepatic glucokinase regulatory protein, and are prone to periods of fasting hyperglycemia (Schermerhorn 2013). Glucogenic AAs, which are derived primarily from net protein degradation in skeletal muscle, can be converted into glucose through the biochemical pathway of gluconeogenesis (Brosnan 2003). Among them, Ala, Arg, Asp, Asn, Gln, Glu, Ile, Pro, Ser, Thr, and Val are quantitatively the most important glucogenic substrates in post-prandial and post-absorptive cats. The synthesis of glucose from AAs occurs in the liver and kidneys, and involves the degradation of AAs to their α-ketoacids and an intermediate of the Krebs cycle. This process is quantitatively substantial for AA catabolism and physiologically vital in cats under catabolic conditions, such as fasting and hunger (Young and Ajami 2001). Gluconeogenesis is used for the disposal of excess AA carbons (Case et al. 2011).

11.4.1 Arginine

Arginine is an EAA for cats (NRC 2006), because their small intestine has a very low activity of pyrroline-5-carboxylate synthase (Rogers and Phang 1985). This enzyme converts Glu into pyrroline-5-carboxylate, an intermediate in the formation of Arg from Gln, Glu, and Pro. There is likely little or no synthesis of citrulline from glutamine and glutamate in the enterocytes of the feline small intestine under physiological conditions. It is also possible that Pro oxidase, which generates pyrroline-5-carboxylate from Pro, is negligible or absent from the feline gut. Of note, Arg contains a positively charged nitrogen side chain as a binding site for negatively charged molecules (Burns et al. 1981). Cats have a high requirement for Arg to maintain the hepatic urea cycle in an active state and the whole-body nitrogen balance (Baker and Czarnecki-Maulden 1991). In the urea cycle (also known as the ornithine cycle), Arg is an allosteric activator of *N*-acetylglutamate synthase, which generates N-acetylglutamate to stimulate

carbamoylphosphate synthase-I (Wu and Morris 1998). The latter converts NH_3 and bicarbonate into carbamoylphosphate. In addition, Arg stimulates the secretion of some hormones (e.g., insulin, glucagon and gastrin) (D'Mello 2003) and the synthesis of NO in endothelial cells (Shi et al. 2004). Furthermore, Arg activates the mTORC1 cell signalling pathway to promote protein synthesis in skeletal muscle (Yao et al. 2008; Saxton et al. 2016), placenta (Kong et al. 2012), brown adipocytes (Ma et al. 2017), and mammary epithelial cells (Ma et al. 2018). Cats rapidly display hyperammonaemia within 2 to 5 h after consuming an arginine-free diet (Baker and Czarnecki-Maulden 1991), and the clinical syndromes of ammonia toxicity include vomiting, nausea, tremors, seizures and even death (Morris 1985).

Morris et al. (1979) reported that the inclusion of ornithine in the Arg-free diets could prevent the onset of hyperammonaemia in cats but could not restore their weight gains. Therefore, blood-borne ornithine can facilitate ammonia detoxification but is not a substrate for Arg synthesis in the body. This is explained by the complex compartmentation of ornithine metabolism in the small intestine to favour Pro production (Wu and Morris 1998). Note that there is no net synthesis of Arg via the hepatic urea cycle because Arg is rapidly hydrolyzed by arginase into urea plus ornithine. In contrast to ornithine, both extracellular and intracellularly generated citrulline are readily used for Arg synthesis by argininosuccinate synthase and lyase in cats (Baker and Czarnecki-Maulden 1991). Thus, citrulline can fully replace Arg in the diets for cats. This is important for those cats that genetically lack intestinal transporters for cationic AAs.

11.4.2 Threonine, Histidine and Valine

Threonine contains a hydroxyl group that is chemically reactive for phosphorylation by protein kinase (Wu 2018). This is an important mechanism for the regulation of enzyme or protein activity. In cats, neutral AA transporters are responsible for the absorption of threonine by the small intestine and the proximal tubules of the kidneys in Na^+-dependent and independent mechanisms. In addition, Thr may play a role not only in hepatic glucose synthesis but also insulin secretion or cell apoptosis (Depaoli-Bug et al. 1994).

Histidine contains a positively charged imidazole side chain. Basic AA transporters are essential for absorbing histidine by the small intestine, and the proximal tubule of the kidneys actively reabsorb plasma histidine in the Na^+-independent manner. Histidine is a structural component of proteins that plays a crucial part in oxygen exchange and is the precursor of biologically active compounds, such as histamine and carnosine (NRC 2006). Haemoglobin is present at a high concentration in the blood; the positive charge on the imidazole side chain of histidine facilitates oxygen exchange in the lungs and other tissues (Cianciaruso et al. 1981). As a neuroactive molecule, histamine plays a role in immune function and vasodilation. As a histidine-derived dipeptide, carnosine acts as a cellular antioxidant and a chelator of copper and zinc in animal cells (Boldyrev et al. 2013). Meat is rich in histidine (Wu et al. 2016).

Valine is a BCAA. It is catabolised in the body through the cooperation of multiple organs, including in the skeletal muscle, adipose tissue, kidneys, brain, and liver (Wu 2013). This AA is an abundant AA in both animal- and plant-source proteins (Hou et al. 2019; Li and Wu 2020). The carbon skeleton of Val is either oxidized for ATP production or used for hepatic glucose synthesis in cats, depending on their physiological states (Garlick and Grant 1988; Radford 2004). An intermediate of Val may be used as a precursor for the synthesis of a unique AA (isobuteine) in cats.

11.5 Ketogenic Amino Acids

Leucine and Lys are two strict ketogenic AAs that produce acetyl-CoA and acetoacetyl-CoA in the liver (D'Mello 2003). These two intermediates are metabolized to form acetoacetate and β-hydroxybutyrate in the liver, the ketone bodies that are major metabolic fuels in the extra-hepatic tissues, such as the brain, heart, skeletal muscle,

and kidneys (Eisert 2011). Ketogenic AAs cannot be converted into glucose in animals due to the absence of the glyoxylate cycle, and are oxidized to CO_2 plus water (Wu 2018). Hydroxylation of certain Lys residues in collagen is essential for its structure, whereas an intermediate of Leu is used as a precursor for the synthesis of a unique AA (isovalthine) in cats. Leucine is an abundant AA in both animal- and plant-source proteins (Hou et al. 2019; Li and Wu 2020). In contrast, Lys is abundant in animal-source proteins but is deficient in most of the plant-source proteins.

Leucine is metabolized through transamination in cats to form Glu, Gln, Ala and Asp (Baker and Czarnecki-Maulden 1991). Because of its large mass, skeletal muscle is the primary site for initiating Leu degradation to form α-ketoisocaproic acid via BCAA transaminase in animals (Wu 2013). In lactating mammals, BCAA transaminase is also highly active in their mammary tissues (Li et al. 2009), which helps to explain why the milk of mammals (including cats and sows) is highly abundant in Gln and Glu (Davis et al. 1994). The activity of this enzyme is nearly absent in the feline liver under physiological conditions. α-Ketoisocaproic acid is decarboxylated by branched-chain α-ketoacid (BCKA) dehydrogenease, which is highly active in the liver (Harris et al. 2004) and mammary tissue (Li et al. 2009; Zhang et al. 2019). In addition, Leu has been reported to enhance protein synthesis by increasing plasma insulin concentration (Anthony et al. 2002; Balage et al. 2001) and activating the MTOR cell signalling in skeletal muscle (Manjarín et al. 2018). Furthermore, Leu and α-ketoisocaproic acid inhibit protein degradation in skeletal muscle (Nagasawa et al. 2002). Therefore, dietary Leu exerts an anabolic effect in animals after absorption.

Lysine is degraded primarily in the liver of animals (Wu 2013). Caution should be taken to avoid an imbalance among basic AAs in diets, blood and cells, because these AAs share the same transporters in the plasma membrane. As a positively charged AA, Lys plays an important role in the methylation and acetylation of proteins, which contribute to the modulation of certain cytoskeleton-associated proteins (e.g., actin, tubulin, and small GTPases) and epigenetic regulation of gene expression (Ali et al. 2018; Wang et al. 2012; Zhao et al. 2010). Genetic defects in basic AA transporters can cause the poor absorption of Lys, as well as ornithine, Arg and His by the small intestine and the renal tubules, leading to Lys deficiency in animals (Hoppe et al. 1993).

11.6 Glucogenic and Ketogenic Amino Acids

11.6.1 Phenylalanine and Tyrosine

Phenylalanine and Tyr are the precursors for the syntheses of dopamine, noradrenaline and adrenaline in neurons, whereas Trp is the substrate for the production of serotonin, N-acetylserotonin, melatonin, and indoles in a cell-specific manner (Hendriks 1996; Wu 2013). Thus, the availability of these three aromatic AAs influences the health and behaviour of cats. Of note, Phe and Tyr are particularly important for cats to maintain their hair color (Rogers and Morris 1979). Phenylalanine is degraded by the tetrahydrobiopterin-dependent Phe hydroxylase to yield Tyr (Wu 2013). Tyrosine is also the precursor of thyroid hormones, melanin, and catecholamine neurotransmitters (dopamine, norepinephrine and epinephrine). Dietary restriction of Phe along with excess tyrosine results in decreased weight gain and negative nitrogen balance, compared with cats fed a Phe-adequate diet (Rogers and Morris 1979; Williams et al. 1987). About half of the requirement for aromatic AAs may be met by Tyr (Williams et al. 1987). A deficiency of dietary Tyr decreases the production of pigment substances (e.g., dopaquinone, trichochromes, eumelanin, and pheomelanin) in the skin (Anderson et al. 2002; Yu et al. 2001), and this phenomenon is reversed by dietary supplementation with Tyr (Anderson et al. 2002).

11.6.2 Tryptophan

Tryptophan is a large neutral AA. It shares the same transmembrane transporters with other

large neutral AAs, such as Leu, Val, Met, Ile, Tyr and Phe for uptake into cells (Hawkins et al. 2006). In the gastrointestinal tissue and brain, Trp is metabolized via the tetrahydrobiopterin-dependent Trp hydroxylase to generate serotonin and N-acetylserotonin. This pathway regulates the response of cats to environmental stress challenges and their behaviours (Da Graça Pereira and Fragoso 2010). In lymphocytes and macrophages, Trp is metabolized by indoleamine 2,3,-dioxygenase to form kynurenine, and this pathway plays an important role in intestinal and whole-body anti-inflammatory responses (Kato et al. 2012; Oxenkrug 2010). Furthermore, animals (including cats) can synthesize niacin from Trp (Baker and Czarnecki-Maulden 1991). However, Trp cannot fully substitute nicotinic acid in the diet of cats. Thus, these animals will die after they are fed a diet with adequate Trp level but a low level of nicotinic acid (NRC 2006). Of note, Trp is deficient in most of the plant-source proteins but abundant in animal-source proteins (Hou et al. 2019; Li and Wu 2020).

11.7 Carnitine

Carnitine is an AA derivative that is synthesized from Lys, Met and Ser in the presence of vitamin B_6, vitamin C, α-ketoglutarate, and iron (Wu 2013). Over the past two decades, there has been much interest in the role of carnitine in preventing and treating feline hepatic lipidosis (FHL), as well as enhancing white-fat loss in cats through stimulating fatty acid oxidation in the liver and other tissues such as skeletal muscle and white adipose tissue (Blanchard et al. 2002; Center et al. 2000). The FHL, also known as feline fatty liver syndrome, is one of the most common forms of liver disease in cats that are often obese. The clinical signs of this disease include dramatic weight loss, lethargy, vomiting, hepatomegaly, jaundice, and gastroparesis (Wills and Simpson 1994). Although carnitine is present in meat, dietary supplementation with this nutrient may be beneficial for mitigating the FHL in cats, which generally consume meat with a relatively high content of lipids.

11.8 Sulfur-Containing Amino Acids

Cats have high requirements for dietary Met and Cys (Burger and Smith 1987; Hendriks 1996) to maintain their dense hair and metabolic activities (MacDonald et al. 1984). Nutritional insufficiencies of Met and Cys occur in cats fed home-made vegetable-based diets, leading to reduced growth and crusting dermatitis in the mucocutaneous skin of the mouth and nose (Hoppe et al. 1993). Among the following four sulfur-containing AAs (i.e., Met, Cys, homocysteine, and taurine), only Met and Cys are precursors for protein synthesis (Brosnan and Brosnan 2006). Methionine is the initial AA for the formation of proteins in eukaryotic cells, whereas N-formyl methionine serves the same function in prokaryotes. In the liver of cats, Met is degraded via the transsulfuration pathway to generate Cys, with methionine adenosyltransferase (MAT) catalysing the initial step to form S-adenosylmethionine (SAM) (Teeter et al. 1978; Wu 2013). SAM is the major donor of the methyl group for protein and DNA methylation reactions in the body. Cys is either oxidized to CO_2 plus water or used for the synthesis of glutathione, a potent antioxidant (Stead et al. 2006). In addition, Cys contributes to disulfide linkages in proteins, thereby influencing their structure and biological activities. The formation of Cys from Met can substitute 50% of dietary Met requirement in cats (Hendriks et al. 1995). As an intermediate of Met catabolism, homocysteine (a potent oxidant) can be recycled into Met in the liver via the vitamin B_6-dependent Met synthase. Partial catabolism of Met may occur at a low rate in extrahepatic tissues, but generates little or no CO_2. Excessive intakes of Met and Cys are highly toxic to animals due to the production of their metabolites, such as H_2S, SO_2, and H_2SO_4 (Hou and Wu 2018a), and therefore must be avoided at all times.

11.8.1 Taurine

Taurine is a crucial nutrient for cats (Knopf et al. 1978; Morris et al. 1990). It is a sulfur-containing β-AA that is abundant in meat, fish and crustaceans (Li et al. 2020b,c) but is absent from proteins (Wu et al. 2016). In the liver of cats and dogs (Oberbauer and Larsen 2020), taurine is the only AA that conjugates with bile acid to yield bile salts, which are essential for the digestion and absorption of dietary lipids. Moreover, as an abundant antioxidant AA, taurine protects the eyes, brain, heart, skeletal muscle, reproductive tract, and immune organs from damage (Hand et al. 2010; Morris et al. 1990; Sturman and Lu 1997). In contrast to most species of dogs, cats have a very limited ability to produce taurine from Cys because of a low activity of cysteine dioxygenase and cysteinesulfinate decarboxylase, and therefore taurine must be included in the feline diets (Case et al. 2011; Knopf et al. 1978; Morris and Rogers 1992). Clinical syndromes of taurine deficiency in cats include retinal degeneration, poor reproductive performance, fetal and post-natal developmental abnormalities, and dilated cardiomyopathy (Hall et al. 2018; Hand et al. 2010; Markwell and Earle 1995). The recommended intake of cats for dietary taurine is 0.2% (NRC 2006), which is below taurine content in meat (0.23% to 0.29%) (Wu et al. 2016).

11.8.2 Production of Three Unique Sulfur-Containing AAs (Felinine, Isovalthine, and Isobuteine) by Domestic Cats

Domestic cats synthesize three unique sulfur-containing AAs (felinine, isovalthine, and isobuteine; Kodama et al. 1980; Kuwaki et al. 1963; Mizuhara and Oomori 1961; Oomori and Mizuhara 1962). The sources of the cysteine moiety and the remaining portion in these AAs are glutathione (formed from Glu, Gly and Cys) and an appropriate fatty acid, respectively. The latter is isopentenyl pyrophosphate (an intermediate of cholesterol biosynthesis) in felinine (Rutherfurd et al. 2002), isovaleric acid (a metabolite of leucine) in isovalthine (Rutherfurd-Markwick et al. 2005), and possibly isobutyric acid (a metabolite of valine) in isobuteine (Herring et al. 2020). In the liver of cats, glutathione is conjugated with isopentenyl pyrophosphate, isovaleric acid, and isobutyric acid to yield respective derivatives, which are transported in the blood to the kidneys. In the proximal renal tubules of the kidneys, the glutathione conjugates are metabolized via cauxin (a carboxylesterase), γ-glutamyl transferase and dipeptidases (e.g., aminopeptidase M) to release felinine, isovalthine, and isobuteine for excretion in the urine (Miyazaki et al. 2008). Because isopentenyl pyrophosphate is generated from acetyl-CoA from the oxidation of AAs, glucose and fatty acids, and because the skeletal muscle is the major site for initiating BCAA catabolism and therefore the production of isovaleric acid isobutyric acid, the inter-organ metabolism of macronutrients is crucial for the production of felinine, isovalthine, and isobuteine in cats.

Male cats produce more felinine than female cats (Hendriks et al. 1995; Rutherfurd-Markwick et al. 2005), but there is no gender-specific for the urinary excretion of isovalthine (Hendriks et al. 2004). There are reports that in both male and female cats, increasing dietary intake of Met or Cys enhances the synthesis of felinine and isovalthine (Hendriks et al. 1995; Hendriks et al. 2004). The biological significance of felinine, isovalthine, and isobuteine, as well as their derivatives remains largely elusive. These sulfur-containing AAs and metabolites may serve as non-toxic, non-reactive, and relatively stable end-products of Met and Cys to prevent excessive formation of toxic and highly toxic substances (e.g., H_2S, SO_2, and H_2SO_4) from Met and Cys (Herring et al. 2020). There are also suggestions that felinine is a territorial marker for intra-species communications and is a putative precursor of a pheromone that serves as a chemical signal to attract females (Miyazaki et al. 2008).

11.9 Summary

Dietary protein provides both EAAs and NEAAs for domestic cats to synthesize tissue proteins, peptides, neurotransmitters, and other AA derivatives (e.g., NO, GABA, polyamines, thyroid hormones, melanin, melatonin, and felinine) with enormous biological importance. Glutamate and Gln may be the major metabolic fuels for the feline small intestine to maintain its integrity and health. All of the proteinogenic AAs are nutritionally and physiologically essential for the growth, development, health, and survival of the animals. Because of an inability to synthesize Arg from Gln, Glu and Pro, cats are very sensitive to a deficiency of dietary Arg with very rapid onset of life-threatening hyperammonemia. Although dietary EAAs have been recommended to young and adult cats, little data are available on the dietary requirements of these animals for NEAAs. The present article fills this important gap of the knowledge to guide feeding practices and future studies. In addition, cats have a very limited ability to synthesize taurine (a non-proteinogenic AA), which must be included in their diets to prevent the eyes, brain, heart, skeletal muscle, reproductive tract, and other tissues from damage. Plant-based foods with inadequate or no taurine should not be fed to cats in any age group. Besides meat, animal-source foodstuffs (including ruminant meat & bone meal, poultry by-product meal, porcine mucosal protein, and chicken visceral digest) are excellent sources of proteinogenic AAs (in both amounts and balances) and taurine. New advances in AA nutrition and metabolism are expected to improve the health and wellbeing of cats in their life cycle.

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