Editorial

Amino Acid Nutrition and Metabolism in Health and Disease

Adam J. Rose

Nutrient Metabolism & Signalling Laboratory, Department of Biochemistry and Molecular Biology, Metabolism, Diabetes and Obesity Program, Biomedicine Discovery Institute, Monash University, Clayton 3800, Australia; adam.rose@monash.edu

Received: 28 October 2019; Accepted: 30 October 2019; Published: 1 November 2019

Abstract: Here an overview of the special issue “Amino acid nutrition and metabolism in health and disease” is given. In addition to several comprehensive and timely reviews, this issue had some original research contributions on fundamental research in animal models as well as human clinical trials exploring how the critical nutrients amino acids affect various traits.

Keywords: amino acid; nutrition; metabolism; dietary protein restriction; supplements; exercise; D-amino acids

Of the three major macronutrients, protein is critical for vitality [1]. Protein can be digested and absorbed as amino acids [2] and short peptides [3], both of which have important somatic effects. Amino acids are the building blocks of our cellular machinery in the form of proteins and protein complexes. In addition, many important metabolites (i.e., purine/pyrimidines, neurotransmitters etc.) are products of cellular amino acid metabolism. In contrast to that of fats (lipid droplets in adipose tissue) and carbohydrates (glycogen in liver and muscle), there is no dedicated storage depot of protein in the body, and body protein is conserved during periods of total nutrient deficiency or withdrawal [4]. This is achieved by cellular mechanisms such as recycling of amino acids via autophagy and processing of proteins within the lysosome [5], as well as physiological processes such as the dampening cellular turnover of amino acid consuming tissues [5], the inhibition of protein synthesis in quiescent tissues [6,7], and fine control of ureagenesis matched to dietary protein supply [8]. Nevertheless, some important biochemical pathways require that the amino acid amine group is lost and thus there is then an obligatory loss of amino acids which needs to be replaced via food consumption [9]. Thus, adequate protein nutrition is paramount to supply such indispensable amino acids [10]. In this special issue on “Amino Acid Nutrition and Metabolism in Health and Disease” we highlight new information as well as review several important topics within this sub-field of nutrition.

Preclinical studies have shown that dietary protein restriction can promote metabolic health [11–16]. In their paper, Javed and Bröer [17] show that mice lacking the neutral amino acid transporter B0AT1 have a serum amino acid profile resembling that of mice fed a low protein diet. Given that B0AT1 is the major transporter of neutral amino acids across the intestinal lumen and reabsorbs neutral amino acids in the renal proximal tubules [18], this reinforces that the inhibition of this transporter might be an attractive strategy to mimic the effects of dietary protein restriction to improve health and retard age-related disease [19].

Branched-chain amino acids (BCAA) have been implicated as a major contributor to the effects of dietary protein supply on metabolic health [20,21]. In their paper, Ribeiro et al. [22] assessed and directly compared the relationship between circulating BCAs, body composition, and intake in older mice and men. They found that protein intake was correlated with circulating BCAA levels, and that body weight and body fat were positively associated with circulating BCAA levels, in both mouse and human. In their paper, David et al. [23] examined the relationship between circulating...
BCAA levels, body composition and tissue BCAA catabolic capacity in rats made insulin resistant by high-fructose feeding. In this model, the high BCAA levels in insulin-resistant rats were not associated with differences in body composition, but were correlated with altered skeletal muscle BCAA catabolic capacity.

The dietary restriction of sulphur containing amino acids (SCAA), in particular L-methionine and L-cysteine, confer health benefits to age-related disease [24]. The regulation and role of signaling pathways, particularly the integrated stress response, was reviewed in detail by Jonsson et al. [25]. They highlight a disconnect between canonical integrated stress response signaling and adaptive responses to SCAA restriction. In addition, two original contributions from clinical trials addressing the role of SCAA were published in this special issue. One by Olsen et al. [26] reported results of a pilot randomized clinical trial testing the combination of dietary SCAA restriction and high unsaturated fatty acid supply on feasibility and certain AA biomarkers, and another by Lee et al. [27] examined the relationship between acute and chronic exercise, insulin sensitivity, and plasma amino acid levels. The latter study [27] provided evidence that both acute and long-term exercise may influence trans-sulphuration and glutathione biosynthesis, and suggested a link between exercise-improved insulin sensitivity and oxidative stress/mitochondrial function.

There were further contributions of clinical trials investigating select amino acid supplements on traits. Of note, Tsuda et al. [28] studied the effects of combined L-arginine, L-valine and L-serine supplementation on exercise-induced fatigue in healthy volunteers using a randomized, double-blinded, placebo-controlled crossover design. They demonstrated that supplementation with the amino acid mixture reduced the feeling of fatigue during exercise. It will be interesting to see if such results affect actual exercise performance in future studies. On L-arginine, Hsu & Tian [29] reviewed the role of L-arginine synthesis and metabolism in pregnancy, with a focus on developmental programming of non-communicable diseases. They presented an overview of emerging evidence from experimental studies showing that targeting the L-arginine metabolic pathway has promise as a reprogramming strategy in pregnancy to prevent non-communicable diseases in the offspring. With the premise that the amino acids L-arginine and L-citrulline can affect nitric oxide, a well-described vasodilatory substance [30], Khalaf et al. [31] reviewed the effects of these amino acids on blood pressure regulation. They provided evidence that oral L-arginine supplementation can lower blood pressure to a comparable extent to that of exercise and diet interventions, effects that are not well understood and perhaps deserve greater attention, particularly as deaths and burden due to hypertension rival that of cancer [32,33].

On cancer, Bastings et al. [34] provided an intriguing review of the various sources of D-amino acids, their metabolism, and their contribution to physiological processes and diseases, with a focus on cancer. Once considered to be non-functional or not even present in living organisms, these enantiomeric counterparts of L-amino acids are now acknowledged to play important roles in numerous physiological processes in the human body.

In addition to the paper by Ribeiro et al. [22], other contributions also examined the role of dietary protein/amino acid supply in age-related disease. As menopause is associated with a spike in age-related disease incidence in women [35], Lin et al. [36] examined the potential beneficial effects of soy protein supplementation and exercise training on ‘postmenopausal’ mice. They found that a combination of soy protein supplementation and exercise reduced fatigue and improved bone function in ovariectomized mice.

With our ageing population, age-related dementias are a prominent health issue. In their review, Glenn et al. [37] described the current understanding of dietary protein and amino acids and the preventative roles they play with regard to age-related dementias, and provide future directions to follow for this field.

Even though there are several cellular pathways such as GCN2 and mTORC1 which signal amino acid availability with appropriate cellular responses and fates, peptide hormones also play an equally important role in conveying dietary amino acid availability with traits and behaviors. On this topic, Rose [38] reviewed the regulation and roles of certain peptide hormones in response to altered dietary protein supply, with focus on glucagon, PYY and FGF21.
Going forward, the future is bright concerning the topic of protein/amino acid nutrition in health and disease, and particular promising directions—such as inter-organ amino acid nutrition, tissue/niche heterogeneity of amino acid metabolism, and the role of the microbiome and epigenome in the interaction of amino acid supply/metabolism with various traits such as immunity—should be considered for future study. Indeed, with the advent and application of new technologies and ‘big data’, many new interesting and pivotal interactions will undoubtedly be uncovered.

Author Contributions: A.J.R. wrote the manuscript.

Conflicts of Interest: The author declares no conflict of interest.

References
1. Rose, W.C., II. The sequence of events leading to the establishment of the amino acid needs of man. *Am. J. Public Health Nat’l’s Health* 1968, 58, 2020–2027. [CrossRef] [PubMed]
2. Rose, W.C. The amino acid requirements of adult man. *Nutr. Abstr. Rev.* 1957, 27, 631–647. [PubMed]
3. Rutherford-Markwick, K.J. Food proteins as a source of bioactive peptides with diverse functions. *Br. J. Nutr.* 2012, 108 (Suppl. 2), S149–S157. [CrossRef] [PubMed]
4. Cahill, G.F., Jr. Fuel metabolism in starvation. *Amnu. Rev. Nutr.* 2006, 26, 1–22. [CrossRef]
5. Carroll, B.; Korolchuk, V.I.; Sarkar, S. Amino acids and autophagy: Cross-talk and co-operation to control cellular homeostasis. *Amino Acids* 2015, 47, 2065–2088. [CrossRef]
6. Rose, A.J.; Richter, E.A. Regulatory mechanisms of skeletal muscle protein turnover during exercise. *J. Appl. Physiol.* 2009, 106, 1702–1711. [CrossRef]
7. Millward, D.J.; Garlick, P.J. The pattern of protein turnover in the whole animal and the effect of dietary variations. *Proc. Nutr. Soc.* 1972, 31, 257–263. [CrossRef]
8. Meijer, A.J.; Lamers, W.H.; Chamuleau, R.A. Nitrogen metabolism and ornithine cycle function. *Physiol. Rev.* 1990, 70, 701–748. [CrossRef]
9. Reeds, P.J.; Biolo, G. Non-protein roles of amino acids: An emerging aspect of nutrient requirements. *Curr. Opin. Clin. Nutr. Metab. Care* 2002, 5, 43–45. [CrossRef]
10. Reeds, P.J. Dispensable and indispensable amino acids for humans. *J. Nutr.* 2000, 130, 1835S–1840S. [CrossRef]
11. Maida, A.; Zota, A.; Sjoberg, K.A.; Schumacher, J.; Sijmonsma, T.P.; Pfenninger, A.; Christensen, M.M.; Gantert, T.; Fuhrmeister, J.; Rothermel, U.; et al. A liver stress-endocrine nexus promotes metabolic integrity during dietary protein dilution. *J. Clin. Invest.* 2016, 126, 3263–3278. [CrossRef] [PubMed]
12. Maida, A.; Zota, A.; Veggioopoulos, A.; Appak-Baskoy, S.; Augustin, H.G.; Heikenwalder, M.; Herzig, S.; Rose, A.J. Dietary protein dilution limits dyslipidemia in obesity through fgf21-driven fatty acid clearance. *J. Nutr. Biochem.* 2018, 57, 189–196. [CrossRef] [PubMed]
13. Kitada, M.; Ogura, Y.; Suzuki, T.; Monno, I.; Kanasaki, K.; Watanabe, A.; Koya, D. A low-protein diet exerts a beneficial effect on diabetic status and prevents diabetic nephropathy in wistar fatty rats, an animal model of type 2 diabetes and obesity. *Nutr. Metab. (Lond.)* 2018, 15, 20. [CrossRef] [PubMed]
14. Kitada, M.; Ogura, Y.; Suzuki, T.; Sen, S.; Lee, S.M.; Kanasaki, K.; Kume, S.; Koya, D. A very-low-protein diet ameliorates advanced diabetic nephropathy through autophagy induction by suppression of the mtorc1 pathway in wistar fatty rats, an animal model of type 2 diabetes and obesity. *Diabetologia* 2016, 59, 1307–1317. [CrossRef]
15. Fontana, L.; Cummings, N.E.; Arriola Apelo, S.I.; Neuman, J.C.; Kasza, I.; Schmidt, B.A.; Cava, E.; Spelta, F.; Tosti, V.; Syed, F.A.; et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep.* 2016, 16, 520–530. [CrossRef]
16. Solon-Biet, S.M.; McMahon, A.C.; Ballard, J.W.; Ruohonen, K.; Wu, L.E.; Cogger, V.C.; Warren, A.; Huang, X.; Pichaud, N.; Melvin, R.G.; et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab.* 2014, 19, 418–430. [CrossRef]
17. Javed, K.; Broer, S. Mice lacking the intestinal and renal neutral amino acid transporter slc6a19 demonstrate the relationship between dietary protein intake and amino acid malabsorption. *Nutrients* 2019, 11, 2024. [CrossRef]
18. Broer, A.; Juelich, T.; Vanslambrouck, J.M.; Tietze, N.; Solomon, P.S.; Holst, J.; Bailey, C.G.; Rasko, J.E.; Broer, S. Impaired nutrient signaling and body weight control in a Na\textsuperscript{+} neutral amino acid cotransporter (slc6a19)-deficient mouse. *J. Biol. Chem.* 2011, 286, 26638–26651. [CrossRef]

19. Jiang, Y.; Rose, A.J.; Sijmonsma, T.P.; Broer, A.; Penninger, A.; Herzig, S.; Schmoll, D.; Broer, S. Mice lacking neutral amino acid transporter b(0)at1 (slc6a19) have elevated levels of fgf21 and glp-1 and improved glycaemic control. *Mol. Metab.* 2015, 4, 406–417. [CrossRef]

20. Arany, Z.; Neinast, M. Branched chain amino acids in metabolic disease. *Curr. Diabetes Rep.* 2018, 18, 76. [CrossRef]

21. Tremblay, F.; Lavigne, C.; Jacques, H.; Marette, A. Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. *Ann. Rev. Nutr.* 2007, 27, 293–310. [CrossRef] [PubMed]

22. Ribeiro, R.V.; Solon-Biet, S.M.; Pulpitel, T.; Senior, A.M.; Cogger, V.C.; Clark, X.; O’Sullivan, J.; Koay, Y.C.; Hirani, V.; Blyth, F.M.; et al. Of older mice and men: Branched-chain amino acids and body composition. *Nutrients* 2019, 11, 1882. [CrossRef] [PubMed]

23. David, J.; Dardevet, D.; Mosoni, L.; Savary-Auzeloux, I.; Polakof, S. Impaired skeletal muscle branched-chain amino acids catabolism contributes to their increased circulating levels in a non-obese insulin-resistant fructose-fed rat model. *Nutrients* 2019, 11, 355. [CrossRef]

24. Parkhiko, A.A.; Jouandin, P.; Mohr, S.E.; Perrimon, N. Methionine metabolism and methyltransferases in the regulation of aging and lifespan extension across species. *Aging Cell* 2019, e13034. [CrossRef] [PubMed]

25. Jonsson, W.O.; Margolies, N.S.; Anthony, T.G. Dietary sulfur amino acid restriction and the integrated stress response: Mechanistic insights. *Nutrients* 2019, 11, 1349. [CrossRef] [PubMed]

26. Olsen, T.; Ovrebo, B.; Turner, C.; Bastani, N.E.; Refsum, H.; Vinknes, K.J. Combining dietary sulfur amino acid restriction with polyunsaturated fatty acid intake in humans: A randomized controlled pilot trial. *Nutrients* 2018, 10, 1822. [CrossRef] [PubMed]

27. Lee, S.; Olsen, T.; Vinknes, K.J.; Refsum, H.; Gulseth, H.L.; Birkeland, K.I.; Drevon, C.A. Plasma sulphur-containing amino acids, physical exercise and insulin sensitivity in overweight dysglycemic men. *Nutrients* 2018, 11, 10. [CrossRef] [PubMed]

28. Tsuda, Y.; Yamaguchi, M.; Noma, T.; Okaya, E.; Itoh, H. Combined effect of arginine, valine, and serine on exercise-induced fatigue in healthy volunteers: A randomized, double-blinded, placebo-controlled crossover study. *Nutrients* 2019, 11, 862. [CrossRef]

29. Hsu, C.N.; Tain, Y.L. Impact of arginine nutrition and metabolism during pregnancy on offspring outcomes. *Nutrients* 2019, 11, 1452. [CrossRef]

30. Stamler, J.S.; Meissner, G. Physiology of nitric oxide in skeletal muscle. *Physiol. Rev.* 2001, 81, 209–237. [CrossRef]

31. Khalaf, D.; Kruger, M.; Wehland, M.; Infanger, M.; Grimm, D. The effects of oral l-arginine and l-citrulline supplementation on blood pressure. *Nutrients* 2019, 11, 1679. [CrossRef] [PubMed]

32. Disease, G.B.D.; Injury, I.; Prevalence, C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the global burden of disease study 2016. *Lancet* 2017, 390, 1211–1259. [CrossRef]

33. Collaborators, G.B.D.C.o.D. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: A systematic analysis for the global burden of disease study 2016. *Lancet* 2017, 390, 1151–1210. [CrossRef]

34. Bastings, J.; van Eijk, H.M.; Olde Damink, S.W.; Rensen, S.S. D-amino acids in health and disease: A focus on cancer. *Nutrients* 2019, 11, 2205. [CrossRef] [PubMed]

35. Wells, G.L. Cardiovascular risk factors: Does sex matter? *Curr. Vasc. Pharmacol.* 2016, 14, 452–457. [CrossRef]

36. Lin, C.L.; Lee, M.C.; Hsu, Y.J.; Huang, W.C.; Huang, C.C.; Huang, S.W. Isolated soy protein supplementation and exercise improve fatigue-related biomarker levels and bone strength in ovariectomized mice. *Nutrients* 2018, 10, 1792. [CrossRef] [PubMed]

37. Glenn, J.M.; Madero, E.N.; Bott, N.T. Dietary protein and amino acid intake: Links to the maintenance of cognitive health. *Nutrients* 2019, 11, 1315. [CrossRef]

38. Rose, A.J. Role of peptide hormones in the adaptation to altered dietary protein intake. *Nutrients* 2019, 11, 1990. [CrossRef]

© 2019 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).