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Important roles of amino acids in immune responses

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Abstract

This commentary highlighted the background, take-home messages, and impacts of our 2007 *British Journal of Nutrition* paper entitled "Amino acids and immune function". In 2003–2004, there was an outbreak of severe acute respiratory syndrome (SARS) caused by SARS coronavirus-1 (CoV-1) in Asian countries. By the mid-2000's, clinical and experimental evidence indicated important roles for amino acids (AA) in improving innate and adaptive immunities in humans and animals. Based on our long-standing interest in AA metabolism and nutritional immunology, we decided to critically analyze advances in this nutritional field. Furthermore, we proposed a unified mechanism responsible for beneficial effects of AA and their products (including nitric oxide, glutathione, antibodies, and cytokines) on immune responses. We hoped that such integrated knowledge would be helpful for designing AA-based nutritional methods (e.g., supplementation with glutathione, arginine and glutamine) to prevent and treat SARS-like infectious diseases in the future. Our paper laid a framework for subsequent studies to quantify AA metabolism in intestinal bacteria, determine the effects of functional AA on cell-mediated and humoral immunities, and establish a much-needed database of AA composition in foodstuffs. Unexpectedly, COVID-19 (caused by SARS-CoV-2) emerged in December 2019 and has become one of the deadliest pandemics in history. Notably, glutathione, arginine and glutamine have now been exploited to effectively relieve severe respiratory symptoms of COVID-19 in affected patients. Functional AA (e.g., arginine, cysteine, glutamate, glutamine, glycine, taurine and tryptophan) and glutathione, which are all abundant in animal-sourced foodstuffs, are crucial for optimum immunity and health in humans and animals.

Keywords: **Amino acids: Nutrition: Immunology: Health: Disease**

Amino acids (AA) are organic substances containing both amino and acid groups. These nutrients are the building blocks of proteins and also have regulatory roles in cell metabolism and functions[1]. Fifteen years ago, we published an article entitled 'Amino acids and immune function' in the *British Journal of Nutrition* (*BJN*)[2]. Consistent with the increasing recognition of AA in the health of humans and animals, this paper has attracted the 10th highest number of citations in the Journal's 75 years of rich history[3]. At the kind invitation of Prof. John C. Mathers (Editor-in-Chief of *BJN*), we would like to highlight here: the background for our 2007 *BJN* paper, the take-home message of the paper and why it has been so highly cited; and how the paper has influenced the scientific development of the field. Given the current global COVID-19 pandemic[4], this invited commentary will contribute to developments of new effective nutritional strategies to fight the infectious disease, while improving the health of humans and animals[5].

Why did we write the 2007 British Journal of Nutrition paper?

There was an outbreak of severe acute respiratory syndrome (SARS) in China and four neighbouring countries in 2003–2004[4]. This highly infectious respiratory illness was caused by SARS coronavirus-1 (CoV-1), an enveloped, positive-sense, single-stranded RNA virus that infects the epithelial cells of the lungs. Because it was known in the early 2000s that glutathione (a tripeptide formed from glutamate, cysteine and glycine) inhibits the proliferation of the influenza virus[6] and also has potent immunomodulatory effects through cellular redox signalling[7], Wu *et al.* proposed that enhancing glutathione synthesis through improved AA nutrition would play an important role in preventing and treating a plethora of human diseases, including SARS[8]. Furthermore, much evidence indicated that dietary AA intake regulates the production of nitric oxide (NO; a regulator of immune responses) from arginine in cells of the immune system (including macrophages and lymphocytes[9]. Additionally, NO was reported to kill pathogens and suppress the replication cycle of SARS-CoV-1 within host cells[10]. These findings provided compelling cellular and molecular mechanisms responsible for the beneficial effects of dietary AA in improving both innate and adaptive immunities in humans and animals. Because we had a long-standing interest in AA metabolism in macrophages and lymphocytes, as well as its role in immune responses[11–18], we decided to critically analyse these exciting advances in nutritional sciences for readers of *BJN*, a leading journal of the field. It was hoped that such knowledge would be helpful for

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designing AA-based nutritional methods to prevent and treat SARS-like infectious diseases in the future.

What did our 2007 British Journal of Nutrition paper highlighted and why it became so highly cited?

Our 2007 *BJN* paper started with an overview of the immune system (innate (non-specific) and adaptive (acquired) immunities) to clear invading pathogens (e.g. bacteria, parasites, fungi and viruses), as well as assessments of immune function in cells and the whole body. This was followed by the description of the metabolism of all the twenty proteinogenic (protein-creating) AA in immunocytes (T-lymphocytes, B-lymphocytes, macrophages and related cell types). These biochemical and immunological aspects include (a) the catabolism of arginine, glutamine and tryptophan; the oxidation of arginine by NO synthase to NO plus citrulline; and the synthesis of glutathione from glutamate, cysteine and glycine; (b) the interorgan metabolism of AA for the endogenous formation of arginine, glutamine and alanine from branched-chain AA that involves the skeletal muscle, small intestine and kidneys; and (c) crucial roles of individual AA in innate and adaptive immunities. In addition, we summarised compelling clinical and experimental evidence that a deficiency of dietary protein or AA reduces the concentrations of most AA (including arginine, cysteine, glutamine, glycine and tryptophan) in plasma, impairs immune responses in humans and animals and increases their susceptibility to infectious pathogens[19–23].

Furthermore, we comprehensively summarised findings that dietary supplementation with specific AA (e.g. arginine, branched-chain AA, cysteine, glutamate, glutamine, glycine and tryptophan) to humans and animals with malnutrition and infectious disease enhances AA nutrition and immune status, thereby reducing the rates of morbidity and mortality. Because AA imbalances and antagonisms have negative impacts on nutrient intake and utilisation, optimal ratios and amounts of dietary AA are crucial for both enteral and parenteral nutrition. Finally, we discussed, in great detail, the underlying cellular and molecular mechanisms for the actions of individual AA in the immune system. Many lines of clinical and experimental evidence supported the notion that AA modulate immune responses in immunocytes and the whole body by regulating: (a) the activation of T-lymphocytes, B-lymphocytes, natural killer cells and macrophages; (b) cellular redox state, gene expression and lymphocyte proliferation; (c) the production of antibodies, cytokines and other cytotoxic substances by specific immunocytes (e.g. B-lymphocytes, $CD4^+$ T-lymphocytes and $CD8^+$ T-lymphocytes); and (d) the coordination among the integrated network for innate and adaptive immunities. We expected such knowledge to be critical for the development of effective means to improving health and preventing infectious diseases in humans and animals (including rats, pigs, cattle, birds and fish).

Several reasons may explain why our 2007 *BJN* paper has been highly cited in the literature. First, the article comprehensively reviewed the cell-specific and interorgan metabolism of AA that support immune responses in humans and animals under various nutritional, physiological and immunological conditions. Second, published clinical and experimental findings regarding the effects of protein or AA nutrition on immune functions were interpreted and integrated on the basis of our updated knowledge of AA biochemistry, physiology and nutrition, with the roles of AA being nicely summarised in tables. Third, we proposed a unified mechanism responsible for the beneficial effects of dietary AA in improving both innate and adaptive immune systems, with our concepts being clearly illustrated in self-explanatory figures. Fourth, our review highlighted a knowledge gap in our understanding of roles of AA in immunity. We also provided 'food for thought' on the use of emerging high-throughput, high-efficient technologies (e.g. genomics, transcriptomics, metabolomics, proteomics, bioinformatics, systems biology and epigenetics) to design AA-related experiments in nutritional immunology research. Finally, the knowledge about the functional roles of AA in killing pathogens (including viruses) as highlighted in our 2007 *BJN* paper has been very helpful for the timely and effective use of glutathione and certain AA (e.g. arginine and glutamine) to alleviate severe syndromes of COVID-19 (one of the deadliest pandemics in history) caused by SARS-CoV-2 (see below). This infectious disease, which started in December 2019, has infected more than 245 million people and killed 4·97 million of them worldwide as of 29 October 2021[4]. Various nutritional strategies are now being developed to prevent and treat COVID-19[5].

What happened after our 2007 British Journal of Nutrition paper was published?

The 2007 *BJN* paper has laid a framework for our subsequent studies of AA-related nutritional immunology in collaboration of colleagues. Specifically, our basic research focused on the metabolism of AA (including arginine, glutamine and tryptophan) in the bacteria of the small intestine of farm and laboratory animals[24–33], which is crucial for understanding the interaction between dietary AA and the gut microbiota for maintaining intestinal immunity and health. In addition, we conducted some applied research in nutritional immunology, which included dietary supplementation with functional AA (e.g. arginine, glutamine, glycine and proline) to: (a) enhance the production of antibodies by immunologically activated B-lymphocytes[34,35], (b) reduce mortality in vaccine-immunised animals[36–38] and virus-infected rodents[39], (c) alleviate immune-mediated intestinal and hepatic inflammation in endotoxin-treated animals[40] and (d) improve the immunity, survival and growth of mice[41,42] and weanling piglets[31,32,43]. Our 2007 *BJN* paper also stimulated our interest in: (a) the role of bacterial AA metabolism in mammalian utero-placental inflammation and pregnancy outcomes[29,44,45]; (b) dietary supplementation with proline to modulate the production of inflammatory cytokines at the placenta and fetus interface of mice[45] and to enhance embryonic survival and growth[44]; and (c) the use of AA (e.g. glutamine, glutamate and glycine) to enhance the intestinal immunity and survival of aquatic animals (e.g. fish, shrimp and crabs)[11,46–49]. The use of functional AA to improve the mucosal immunity and

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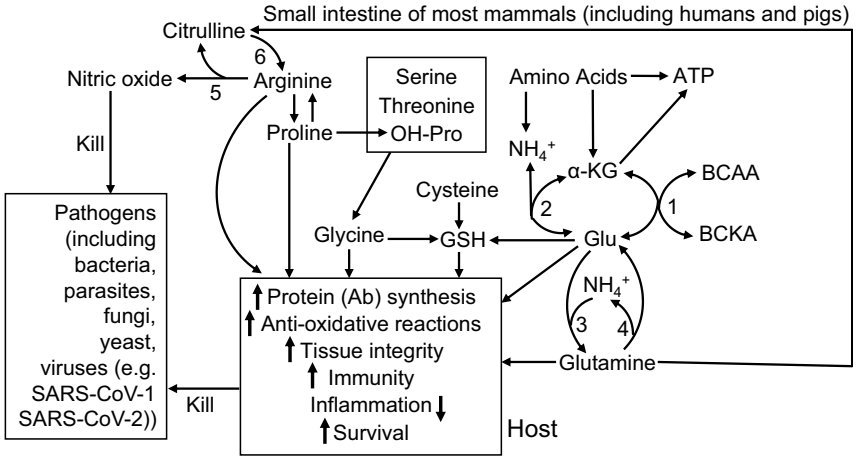

Fig. 1. A unifying mechanism responsible for the beneficial effect of amino acids in improving innate and adaptive immunities in animals. Diet provides animals with amino acids, some of which (e.g. arginine, proline, glycine, glutamate and glutamine) are synthesised *de novo* in a cell- and tissue-specific manner. In certain tissues (e.g. the small intestine of mammals, birds and fish) and cell types (e.g. lymphocytes and macrophages), amino acids (particularly glutamine, glutamate and aspartate) are major energy sources to maintain their integrity and functions. In addition, nitric oxide (a metabolite of arginine) can kill pathogens (including viruses). Furthermore, glutathione (formed from glutamate, cysteine and glycine) and some amino acids (e.g. arginine, glycine, glutamate and glutamine) enhance: (a) innate immunity through optimising cellular antioxidative responses and inhibiting inflammation and (b) adaptive immunity via promoting the production of antibodies. Enzymes that catalysing the indicated reactions are: 1, branched-chain amino acid transaminase; 2, glutamate dehydrogenase; 3, glutamine synthetase; 4, glutaminase; 5, nitric oxide synthase and 6, argininosuccinate synthase and lyase. Ab, antibodies; BCAA, branched-chain amino acids; BCKA, branched-chain α-ketoacids; GSH, glutathione; α-KG, α-ketoglutarate; OH-Pro, 4-hydroxyproline; NO, nitric oxide; SARS-CoV, severe acute respiratory syndrome-coronavirus.

the survival of aquatic animals is critical for aquaculture[11,47,48], because these species are continuously challenged in an environment rich in potential pathogens[50]. Furthermore, to provide scientific rationale for the inclusion of protein ingredients in the diets of humans and farmed animals to improve their immunity and health, we established a much-needed database of all proteinogenic AA plus key non-proteinogenic AA and nitrogenous nutrients in common foodstuffs for humans (including meat, wheat and rice)[51,52] and animals (including feather meal, insect meal, mucosal products and poultry by-product meal)[12,53,54]. Animal-sourced ingredients contain relatively high amounts of functional AA (e.g. arginine, cysteine, glutamine, glycine, methionine, proline, 4-hydroxyproline, tryptophan and taurine), as well as glutathione, creatine and carnosine with potent immunomodulatory and anti-inflammatory effects[1,55].

Our 2007 *BJN* paper has also guided AA-based clinical and experimental research of other investigators in the field of nutritional immunology. This is indicated by the fact that our article has been cited for over 1200 times in Google Scholar by researchers from hundreds of laboratories worldwide[56]. Of particular note, since the outbreak of COVID-19, our original proposition for the use of glutathione or its precursor (N-acetylcysteine) to mitigate SARS-CoV-1[2,8] has been exploited to effectively relieve severe respiratory symptoms of COVID-19 in affected patients[57–59]. Because viruses require the activation of the NF-κB signalling pathway within host cells to replicate[60], glutathione improves redox balance to inhibit viral growth. In addition, NO has recently been reported to kill SARS-CoV-2 within host cells[61], further substantiating the suggestion that increasing dietary arginine provision can reduce risk for infections by pathogens, including bacteria and SARS-CoV-2[2,62]. Interestingly, the concentrations of arginine, glutamine and glycine in the plasma of patients with COVID-19 were reduced by 37, 40 and 38 %, respectively, compared with healthy individuals[63]. Consistent with this recent report, adding oral arginine ($2 \times 1{\cdot}66$ g daily) to standard therapy in patients with severe COVID-19 reduced the frequency of respiratory support during the first 10 d after starting the treatment, as well as the length of their hospitalisation from 46 to 25 d[64]. Likewise, because glutamine can augment immune responses and alleviate inflammation[2,23], supplementing glutamine (3×10 g daily) to the normal enteral diet of adult humans during the early period of COVID-19 infections shortened their hospital stays from 10·4 to 8·9 d and could also eliminate a need for patient management in intensive care units[65]. Finally, there is a suggestion that intravenous or oral administration of glycine may be effective in ameliorating tissue inflammation and damage in COVID-19 patients[66]. The mechanisms for the actions of the functional AA are illustrated in Fig. 1. Animal-sourced foodstuffs are excellent sources of these nutrients that can improve immunity and health in both humans and animals[1,49,54,55].

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The authors' contributions were as follows: G. W. wrote the manuscript and P. L. assisted in its revisions. All authors approved the final manuscript. G. W. has the primary responsibility for the final content.

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British Journal of Nutrition

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