Amino acids at the intersection of nutrition and insulin sensitivity

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A systems network that is coordinated in the sensing and management of nutrient signals is paramount to energy homeostasis, and its dysfunction induces metabolic stress and insulin resistance. Amino acids have recently emerged as a collection of signaling metabolites that underlie the metabolic impacts of different dietary patterns and life styles. This relationship is beginning to be understood from the close coupling of immune and metabolic systems, and serves to enrich our understanding of metabolic diseases, such as type 2 diabetes mellitus. In this review, we provide an overview of several amino acids or their metabolites that link nutrients with insulin sensitivity and discuss how they integrate into organ crosstalk pathways to influence physiological or pathological metabolic states.

Introduction

Elaborate processing of nutrients is among the most fundamental requirements for survival and health. After food intake, various organs are intimately synchronized to ensure proper disposal of the nutrients for energy harvest, storage, and expenditure. In states of famine or starvation, similarly, the metabolic responses should be reprogrammed at multiple tissues to mount an integrated calorie restriction response. A well-known example is the fine-tuned regulatory systems to ensure glucose homeostasis, which is evolutionarily important in unexpected episodes of food surplus and shortage. In modern society, the loss of such a coordinated response is seen in the etiology of T2DM and obesity epidemics, which entail system maladaptions to the chronic stress of nutrient overload and impaired insulin responses [1]. To restore metabolic health, understanding interorgan signaling in metabolic balance and disturbance has been an exciting frontier for pharmacologists.

The concept that nutrients and their metabolites have a role in determining insulin sensitivity was noted more than five decades ago, when it was recognized that lipids and fatty acids reduced insulin-induced glucose uptake in isolated heart muscle [2]. To date, a large list of regulatory lipids in insulin sensitivity are known, as have been discussed by several excellent reviews [3–5]. By contrast, although the report of elevated serum amino acid levels with obesity and insulin resistance dates as early as the end of the 1960s [6], the association of amino acids and metabolites in the regulation of insulin sensitivity has seen relatively slow progress. Efforts to understand the effects of amino acids on insulin action initially concentrated on direct actions in insulin target sites, typically the liver, skeletal muscle, and white adipose tissue [7]. Interest in the mechanistic link between amino acids and insulin resistance has renewed in recent years, and a major impetus in this direction is the results from several clinical studies in patients with T2DM or obesity [8,9], which provided new insight into amino acids in the context of the integrated whole-body regulation of insulin resistance. These conceptual advances promise a new approach to predict, prevent, and treat insulin resistance and metabolic disorders by targeting amino acid-related signaling networks.

Here, we summarize current knowledge of amino acids as signaling metabolites in the systems control of insulin sensitivity. Specifically, we highlight how these metabolites are integrated into the tissue crosstalk network of energy metabolism, and discuss several questions pertaining to the translational prospects of these new findings (Fig. 1).

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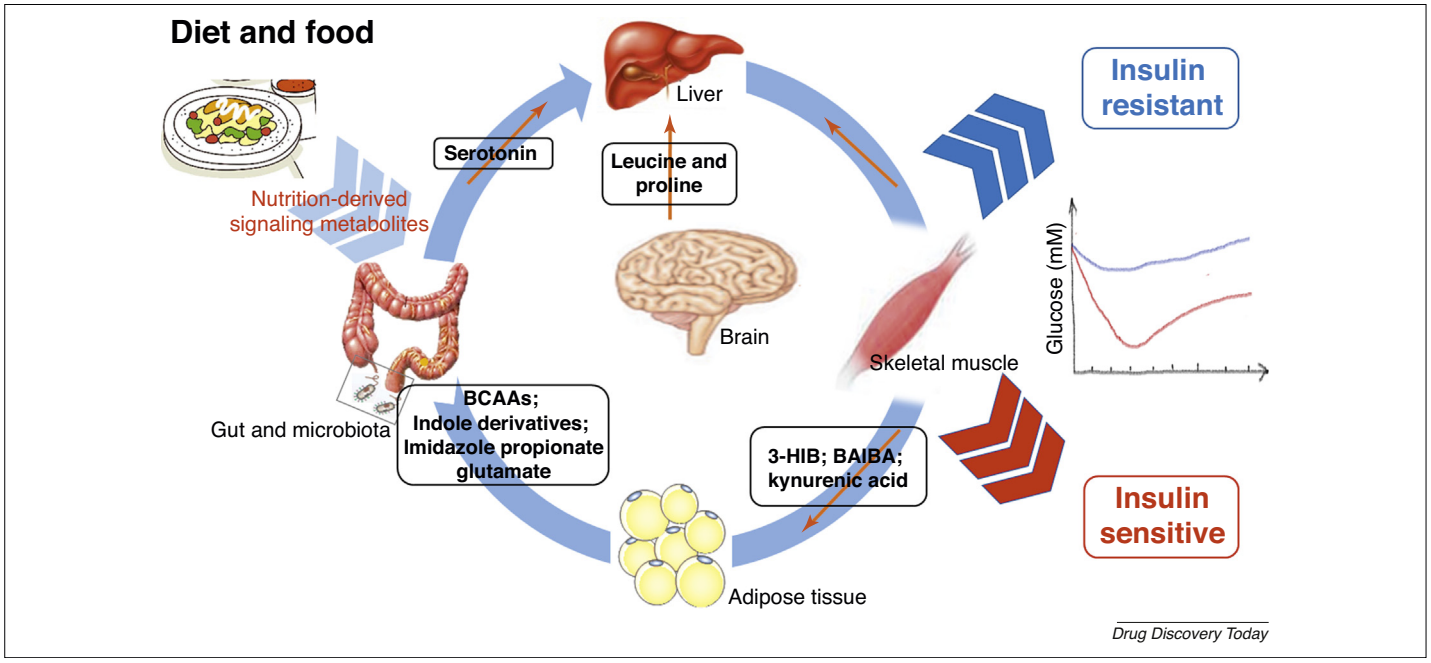

FIGURE 1

Amino acids as signaling metabolites connecting nutrition, tissue crosstalk, and insulin sensitivity. Diet and food serve as the source of myriad small-molecule metabolites that are sensed and processed by an integrated organ network. Amino acids have emerged as new players in this signaling network, fine-tuning insulin sensitivity. Typical examples include tryptophan metabolites (serotonin and indole derivatives), branched-chain amino acids (BCAAs), microbial histidine metabolites (imidazole propionate), and glutamate in the gut; BCAA metabolites [3-hydroxyisobutyrate [(3-HIB) and beta-aminoisobutyric acid (BAIBA)] and kynurenine metabolite (kynurenic acid) in the skeletal muscle; leucine and proline metabolites in the brain, as well as serotonin reaching the liver and adipose tissue. Therefore, amino acids serve as key signaling metabolites in the integrated organ network to control insulin sensitivity in energy metabolism.

Amino acid signals from the gut

The gastrointestinal system is the first site where nutrients are sensed and processed, and it is clear that complex interorgan crosstalk involving metabolic, endocrine, immune, and neural mechanisms is engaged to mount multidimensional responses to food intake [10,11]. Recent studies have revealed the role of food-derived amino acids or their metabolites, especially from gut microbial metabolism, as novel mediators in local and distant energy metabolism. These insights are adding to the therapeutic potential of gut-based targets for metabolic diseases.

Host metabolism of tryptophan to serotonin

Tryptophan (TRP) is an aromatic amino acid (AAA), a group that also includes tyrosine and phenylalanine. Supplied by dietary protein, most TRP undergoes transformation in the digestive tract by several routes, resulting in a variety of biologically active compounds. A major pathway of TRP catabolism in the host is the serotonin (5-hydroxytryptamine, 5-HT) pathway in enterochromaffin cells via TRP hydroxylase 1 (TPH1) and the kynurenine pathway (KP) in both immune and epithelial cells via indoleamine 2,3-dioxygenase (IDO) 1 [12].

Enterochromaffin cells generate >90% of all the peripheral 5-HT, which makes the gut an essential 5-HT reservoir [13]. Genetic or chemical ablation of *Tph1*, which suppresses peripheral 5-HT synthesis, protected mice from high-fat diet-induced obesity, insulin resistance, and nonalcoholic fatty liver disease (NAFLD) [14]. Recently, gut-derived 5-HT was shown to exert direct actions on the liver lipogenic pathway via serotonin receptor 2A (HTR2A) signaling, and gut/liver-specific *Tph1* knockout or HTR2A antagonism (sarpogrelate) ameliorates hepatic steatosis [15]. These reports highlight a pathogenic role of 5-HT along the gut–liver axis in states of overnutrition. However, a more complicated role of 5-HT might be anticipated given its versatile actions on other organs, such as the adipose tissue and pancreas [16].

Microbial metabolism of tryptophan to indole derivatives

Since the early observation of *Escherichia coli* generation of indole from TRP in 1897 [17], several bacterial species have been reported to be able to convert TRP into diverse indole and indole derivatives. Two recent reviews summarized the biochemistry of such transformations and their health impacts [18,19]. In light of the intimate crosstalk of the gut with other metabolic organs [10], it is perhaps not surprising to see a growing number of reports on their role in systems energy metabolism. A recent study identified that, in both preclinical and clinical settings, metabolic syndrome was associated with the reduced capacity of the microbiota to metabolize TRP into derivatives that are able to activate the aryl hydrocarbon receptor (AhR) [20]. Typically, supplementation with a *Lactobacillus* strain, with high AhR ligand-production capacity, leads to improved dietary- and genetic-induced metabolic impairments, particularly glucose disturbance and liver steatosis.

Given that the fraction of TRP that reaches the colon is subjected to the metabolism of gut mucosal IDO, there is potential competition between the host and gut bacteria in TRP metabolism. A recent study reported that obesity in mice was associated with increased intestinal IDO activity, which tipped the balance of TRP metabolism from indole derivative toward kynurenine production [21]. This metabolic shift contributed to reduced interleukin (IL)-

22 production, the compromise of gut mucosal barrier, and endotoxemia. Notably, IDO deletion or inhibition improved insulin sensitivity and lipid metabolism in liver and adipose tissues. These findings highlight the role of the gut microbiota–AhR–IL-22 axis in the control of metabolic disease and reveal intestinal IDO as a basis for novel preventative or therapeutic interventions.

Microbial metabolism of branched chain amino acids

Leucine, valine, and isoleucine are branched-chain amino acids (BCAAs) that account for 35% of essential amino acids. As early as the 1960s, high BCAA signatures were found in the blood of patients with obesity and insulin resistance [6]. To date, elevations in BCAAs have been associated with numerous systemic diseases, including cancer, diabetes, and heart failure. Bacteria have been known for some time to synthesize BCAAs alone [22], but their involvement in shaping host BCAA reservoirs remained unclear for years [23]. The direct impact of the gut microbiome on circulating BCAAs and insulin resistance in humans was recently revealed by a study by Pedersen *et al.*, which included 277 nondiabetic Danish individuals [24]. In particular, increased levels of circulating BCAAs were correlated with *Prevotella copri* (*P. copri*) and *Bacteroides vulgatus* (*B. vulgatus*) in the gut microbiome, which has an enriched biosynthetic potential for BCAAs. Importantly, *P. copri* was directly shown to induce insulin resistance, aggravate glucose intolerance, and augment circulating levels of BCAAs. A later study in a cohort of 257 Chinese patients further confirmed that serum concentrations of AAAs (phenylalanine and tyrosine) and BCAAs (leucine, isoleucine, and valine) were considerably higher in obese individuals than in lean controls [8]. Of interest, this increase was linked to the depletion of species of *Bacteroides* (e.g., *B. thetaiotaomicron* and *B. ovatus*), which have the ability to ferment AAA to produce phenylacetic acid.

Microbial metabolism of glutamine

A study in 2001 indicated that *B. thetaiotaomicron* colonization in germ-free mice modulates the expression of genes involved in nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis, and postnatal intestinal maturation [25]. One of the changes, in particular, was increased mRNAs encoding glutamate transporter and glutamate decarboxylase in epithelial cells, suggesting the impact of bacteria on host glutamate level. This link was recently confirmed by Liu *et al.*, who showed that serum glutamate was inversely correlated with the abundance of *B. thetaiotaomicron*, which could convert glutamate to GABA via decarboxylation [8]. Meanwhile, *Ruminococcus gnavus*, *Dorea longicatena*, and *Coprococcus comes,* bacteria that produce glutamate from glutamine, are specifically enriched in obesity. In 23 obese individuals who underwent sleeve gastrectomy, a weight-loss surgery with well-confirmed metabolic benefits, considerably decreased circulating glutamate levels and an increased abundance of *B. thetaiotaomicron* were detected 3 months post surgery [8]. Together, these findings support the role of *B. thetaiotaomicron* metabolism of glutamine in shaping the systemic pool of glutamate and the resulting metabolic outcomes.

Microbial metabolism of histidine

Histidine is a semiessential amino acid in humans, and its degradation produces urocanate and glutamate, which are well conserved in both bacteria and humans [26]. However, the generation of imidazole derivatives, such as imidazole propionate, is only found in bacteria. Although histidine supplementation was shown to improve insulin resistance and to confer metabolic benefits in obese women with metabolic syndrome [27], recent studies have reported a complicated role of histidine resulting from microbial metabolism. A previous study in mice with glucagon-like peptide-1 (GLP-1) resistance suggested that the bacterial pathway modules involved in the metabolism of several amino acids, including histidine, are enriched, potentially blocking the gut–brain axis signals to trigger insulin secretion [28]. It was recently found that imidazole propionate, a bacterial product of histidine, was present in higher concentrations in the portal blood of patients with T2DM. Notable, two bacterial strains *Streptococcus mutans* and *Eggerthella lenta*, which produce imidazole propionate, were more abundant in patients with T2DM [26]. Therefore, increased microbial transformation could explain the low serum level histidine in patients with diabetes. Moreover, this highlights the potential metabolic risk of histidine overconsumption, especially in patients with high bacterial metabolic capacity.

Amino acid signals from the skeletal muscle

Skeletal muscle accounts for >80% of insulin-stimulated glucose uptake, and dysfunction of this energy consumption underlies insulin resistance and T2DM. In addition to this local effect, skeletal muscle also synthesizes and secretes multiple factors, known as myokines, to exert effects on adjacent and remote organs, such as the adipose tissue and brain [29]. It is becoming clear that several amino acids from the skeletal muscle constitute new players in this broad network of systems energy metabolism.

Valine metabolism

Under physiological conditions, BCAAs are rapidly oxidized into the tricarboxylic acid (TCA) cycle in most tissues, most significantly in muscle. It was recently found that BCAA oxidation was further shunted toward muscle in mice with insulin resistance [30]. These findings highlight muscle as having a central role in determining the circulating BCAA pool. Recent years have seen major advances in our understanding of the role of BCAA metabolites as signaling molecules from skeletal muscle. Two salient examples are 3-hydroxyisobutyrate (3-HIB) and beta-aminoisobutyric acid (BAIBA) from valine oxidation. 3-HIB is secreted by muscle and serves as a paracrine regulator of *trans*-endothelial fatty acid transport and lipid accumulation in muscle, which induce insulin resistance [31]. This provides a mechanistic explanation for a recent finding in a study in humans that showed that increased plasma levels of 3-HIB were associated with incident T2DM [32]. Interestingly, BAIBA was identified as another endocrinal signal from skeletal muscle that transmits the beneficial effect of exercise from skeletal muscle to other tissues and organs [32]. After secretion from muscle under the control of PGC-1α, BAIBA induces energy expenditure in adipocytes and distal fat tissues, and β-oxidation of hepatic fatty acids in part via activation of peroxisome proliferators-activated receptor α (PPARα) [33]. Notably, in humans, plasma BAIBA concentrations increase with exercise and are inversely associated with metabolic risk factors.

Kynurenine metabolism to kynurenic acid

The KYN pathway of TRP metabolism regulates several host biological processes involving neurotransmission, inflammation, and immune response [34]. Meanwhile, roles in metabolic diseases are emerging. Kynurenic acid (KA) is generated from KYN via kynurenine aminotransferase (KAT) expressed in several tissues, including brain, liver, and skeletal muscle. The antidepressive benefits of exercise have been linked to increased KAT expression in skeletal muscle in a PGC-1α-dependent manner [35]. More recently, exercise training-induced KA production in skeletal muscles was found to confer metabolic benefits by acting on GPR35 in adipocytes. KA activation of GPR35 stimulated lipid metabolism, and thermogenic and anti-inflammatory gene expression in adipose tissue, which suppressed weight gain and improved glucose tolerance in animals fed a high-fat diet. Therefore, the KA/GPR35 axis provides another dimension to understanding the metabolic impacts of exercise and KYN pathway metabolism [36].

Amino acid signals from the brain

The whole-body energy status is finely sensed and regulated by a neural network in which the brain actively communicates with peripheral organs to coordinate metabolism. Not surprisingly, brain insulin resistance commonly associates with metabolic disturbances in the liver, and a 'gut–brain–liver' axis has been proposed to explain how nutrients and drugs in the gut affect glucose metabolism in the liver [37]. In line with these connections, recent studies have uncovered several amino acids in the brain that regulate hepatic glucose production, highlighting new regulatory roles in systems energy metabolism.

Leucine and proline

The brain has an indispensable role in coordinating energy metabolism by sensing peripheral nutrient signals [38]. Circulating leucine is transported from the blood into the central nervous system (CNS) via the large neutral amino acid transporter 1 (LAT1), potentially informing the brain of nutrient intake. Seminal work in 2006 revealed that intracerebroventricular administration of L-leucine, but not L-valine, activated the mammalian target of rapamycin (mTOR) pathway in the hypothalamus, inducing anorexia and significant weight loss [39]. Further investigation of leucine metabolism in the brain indicated that it undergoes transamination to α-ketoisocaproic acid, which further transforms to acetyl- and malonyl-CoA. This metabolic transformation within the mediobasal hypothalamus (MBH) coupled the central sensing of leucine with hepatic glucose production via the vagus nerve, and inhibiting such a central transformation blocked the glucoregulatory effect of systemic leucine [40]. A later study from the same research group reported that astrocyte-mediated proline metabolism to pyruvate could act in a similar manner to lower hepatic glucose production [41]. Together, these studies expand the former list of signaling nutrient metabolites that act on the brain to balance their direct stimulatory action on hepatic gluconeogenesis [42].

Metabolic impacts of amino acids: what are the mechanisms?

Ample evidence has established that amino acids exert profound effects on insulin action, glucose metabolism, and metabolic outcome [43]. However, the mechanistic underpinnings behind these effects are not yet fully understood. Current findings largely appear to support both direct and indirect effects of amino acids on insulin actions and glucose metabolism. As a well-known mechanism, amino acids or their metabolites might function at the level of insulin receptor signaling. As a typical example, mTOR is an important energy sensor that transmits signals related to amino-acid sufficiency and protein synthesis. Activation of the mTOR pathway by nutrient signals is known to induce insulin resistance [44]. As a potent activator of mTORC1 activity, leucine promotes protein synthesis and impairs the action of insulin at the liver and skeletal muscle [45]. This partially explains the close link between the BCAA-related metabolite signature and insulin resistance. Of interest, a similar mechanism was recently revealed for imidazole propionate, a bacterial metabolite of histidine, which activates p38γ MAPK to induce mTORC1 activation, subsequently impairing insulin signaling at the level of insulin receptor substrates [26]. These findings enrich our understanding of direct, cell-autonomous actions of amino acids in muscle, liver, and white adipose tissue that affect insulin sensitivity.

In line with an integrated regulatory network, non-cell autonomous factors have been proposed to induce insulin resistance. A growing body of literature suggests that gut barrier compromise is closely associated with metabolic diseases. Therefore, microbial TRP catabolites could contribute to systemic metabolic homeostasis via the fortifying effect on barrier integrity. For example, indole-3-propionic acid was found to regulate intestinal barrier function in mice by acting as a ligand for the pregnane X receptor (PXR), possibly contributing to reduce endotoxemia and insulin resistance [46]. By contrast, indole-3-aldehyde-mediated activation of AhR and IL-22 secretion was proposed to underlie microbial regulation of gut permeability, hormone secretion, and metabolism [47].

It is now clear that metabolic stress induced by nutritional surplus could be sensed by immune receptors to trigger the progression of obesity, insulin resistance, and T2DM [48]. In fact, in addition to actions on gut barrier function, indole metabolites of TRP catabolism have shown immunoregulatory effects, also known to induce the systemic immune response [49], inhibiting hepatic and CNS inflammation [50,51]. Thus, it will be intriguing to further understand the contributions of immune responses in the gut as well as systemic circulation in the regulatory effects of indole derivatives. Indeed, an exciting new field, dubbed 'immunometabolism', aims to understand the mutual relationship between systemic metabolism and immune factors [52]. These conceptual advances underscore that metabolism and immunity are evolutionarily interwoven, and are helpful to understand how immune factors at distant sites regulate the incidence of insulin resistance.

Drug discovery and translational considerations

The emerging effects of amino acid and their metabolites on host metabolism herald a new area for future pharmacological research. Overall, current findings suggest that amino acid signaling could be explored to diminish insulin resistance and reduce the incidence of cardiometabolic disorders. Generally, this could be directly achieved by the use of specific metabolites, or by targeting their receptors, or by indirectly manipulating the gut microbiota. Also, the pharmacological potential of amino acids transporters has recently been suggested [53].

To therapeutically target metabolism, it is important to clarify the metabolic pathways required for their production and elimination, both biochemically and at the whole-body level. For example, modifying BCAA levels in insulin resistance and other pathologies requires knowledge of the biochemistry and physiology of mammalian BCAA metabolism [54]; Meanwhile, it is helpful to know how BCAA metabolism is shaped by different organs and their relative contributions under different pathophysiological conditions. In this regard, a recent study using *in vivo* isotopic tracing in mice revealed that chronically insulin-resistant mice showed blunted BCAA oxidation in adipose tissues and liver, and that BCAA oxidation shifted toward the muscle in *db*/*db* mice. This provides a quantitative framework highly valuable for drug design and discovery [30]. By contrast, if the therapeutic strategy is focused on modifying the microbial production of BCAAs, the major bacterial source and precise microbial enzymatic pathways involved need to be described. *P. copri* and *B. vulgatus*, which were previously identified as producers of BCAAs, would be good starting points for pharmacologists.

However, for most bacterial metabolites, the metabolizing microorganisms, as well as the associated biochemical pathways, remain to be fully characterized. Combining different methods, particularly metabolomics, with metagenomics appears to be a promising strategy to identify the microbes and microbial genes involved. This is perhaps best exemplified by a recent report of a reversible, gut microbe-targeted nonlethal inhibitor of trimethylamine oxide (TMAO) production that shows great potency and selectivity to reduce thrombosis potential [55]. This would not be possible without insights into the major microbial TMA-generating enzyme pair (Cut C/D) [56].

Exploiting signaling metabolites as drug templates is a fruitful strategy for drug discovery, but a current hurdle lies in the ambiguity in their targets. Understanding of amino acid-modulated signaling in insulin sensitivity remains limited, with several outstanding questions. For example, although microbial catabolites of amino acids are causally linked with insulin sensitivity, the direct targets are largely elusive. Given that G-protein-coupled receptors (GPCRs) have been known for many years as sensors of multiple metabolites generated from nutrients [57], the identification of amino acids or their metabolites as endogenous GPCR ligands requires more research. Also, whether amino acids could activate neural mechanisms to induce metabolic changes is an open question, although this mode of action has been revealed for lipids derived from nutrients.

The exciting promise of circulating amino acids in predicting insulin resistance and intervention outcomes suggests a new perspective to understand the metabolic benefits of exercise [58] and therapeutic drugs. Advances could reveal endogenous mechanisms for metabolic homeostasis that could be strengthened by pharmacological means. This is exemplified by a recent clinical study linking *Bacteroides fragilis* and intestinal FXR signaling with the metabolic benefits of metformin [59]. The mechanistic insights led to the discovery of glycoursodeoxycholic acid, an endogenous antagonist of intestinal FXR, that improved various metabolic endpoints in mice with established obesity.

Despite these prospects, the causative roles of amino acids in the development of insulin resistance are not conclusive and, in some cases, are controversial, as seen in the case of histidine. This is not unexpected given the diverse signaling roles of amino acids and organ-specific contributions to energy metabolism. Therefore, metabolic impacts of amino acids should be understood in both a context- and disease-dependent manner. For example, dietary methionine restriction produces a highly beneficial metabolic phenotype in mice, and this is mechanistically linked to a combination of direct effects on hepatic insulin signaling and indirect effects in other peripheral tissues, such as adipose tissue [60]. However, in the presence of choline deficiency, methionine deficiency induces nonalcoholic fatty liver disease and worsens insulin resistance.

Concluding remarks and future perspectives

Since the first reports that circulating AAAs and BCAAs are elevated in individuals with obesity and insulin resistance, there has been growing interest in understanding the role of these small molecules derived from nutrients. Amino acids and their metabolites function not only as exchangeable energy sources between tissues, but also as signaling molecules integrated into the multiorgan regulatory network of energy metabolism. Understanding the mechanisms underlying altered amino acid level and how they modify disease pathophysiology will keep researchers busy for the foreseeable future.

The emergence of sensitive and high-throughput metabolomic platforms for global assays of small-molecule metabolites, coupled with well-designed clinical studies, are likely to provide important new insights into amino acids in metabolic disease in the years ahead. Further studies will be needed to uncover the biological basis for the correlational relationship, determine the signaling programs, and integrate these processes at an organismal level. Given the interplay of amino acids, it would be necessary to clarify how a specific amino acid affects the metabolism and function of other amino acids as well as the host metabolism.

Diet affects multiple facets of human health and is inextricably linked to chronic metabolic conditions, such as obesity, T2DM, and cardiovascular disease [61]. The modulation of signaling amino acids from nutrients might be realized from diet intervention alone or in combination with drugs to target several pathways. To date, several dietary patterns, such as a ketogenic or paleolithic diet, have shown health benefits or therapeutic potentials in several diseases. It will be intriguing to explore how amino acid metabolism is mechanistically involved in different dietary approaches, knowledge from which might inform the design of precision dietary interventions for metabolic disorders.

The pharmacological potential of gut microbiota has received significant research interest and remains to be fully explained. Given that the microbiota has been intimately implicated in amino acid metabolism, further investigations are needed to elucidate the role of amino acid metabolism in the intricate gut microbiota–host relationship. To find a selective nonlethal drug targeting gut microbial enzymes linked to host metabolism, enriching our understanding of the bacterial pathway of amino acid catabolism is an urgent need, which will determine the extent to which we could realize the potential of gut microbiota-targeted strategies. In the pursuit of these goals, it is important to appreciate the great resilience and complexity of the gut microbiota, the functions of which vary in different contexts and in response to different environmental factors [62–64].

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References

1 Johnson, A.M. and Olefsky, J.M. (2013) The origins and drivers of insulin resistance. *Cell* 152, 673–684
2 Randle, P.J. *et al.* (1963) The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1, 785–789
3 Glass, C.K. and Olefsky, J.M. (2012) Inflammation and lipid signaling in the etiology of insulin resistance. *Cell Metab.* 15, 635–645
4 Yue, J.T. and Lam, T.K. (2012) Lipid sensing and insulin resistance in the brain. *Cell Metab.* 15, 646–655
5 Yang, Q. *et al.* (2018) Metabolites as regulators of insulin sensitivity and metabolism. *Nat. Rev. Mol. Cell Biol.* 19, 654–672
6 Felig, P. *et al.* (1969) Plasma amino acid levels and insulin secretion in obesity. *N. Engl. J. Med.* 281, 811–816
7 Petersen, M.C. and Shulman, G.I. (2018) Mechanisms of Insulin Action and Insulin Resistance. *Physiol. Rev.* 98, 2133–2223
8 Liu, R. *et al.* (2017) Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. *Nat. Med.* 23, 859–868
9 Wang, T.J. *et al.* (2011) Metabolite profiles and the risk of developing diabetes. *Nat. Med.* 17, 448–453
10 Zhang, X. *et al.* (2016) Treatment of insulin resistance: straight from the gut. *Drug Discov. Today* 21, 1284–1290
11 Winer, D.A. *et al.* (2016) The Intestinal Immune System in Obesity and Insulin Resistance. *Cell Metab.* 23, 413–426
12 Cervenka, I. *et al.* (2017) Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. *Science* 357 eaaf9794
13 Matthes, S. and Bader, M. (2018) Peripheral serotonin synthesis as a new drug target. *Trends Pharmacol. Sci.* 39, 560–572
14 Crane, J.D. *et al.* (2015) Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. *Nat. Med.* 21, 166–172
15 Choi, W. *et al.* (2018) Serotonin signals through a gut–liver axis to regulate hepatic steatosis. *Nat. Commun.* 9, 4824
16 Ohara-Imaizumi, M. *et al.* (2013) Serotonin regulates glucose-stimulated insulin secretion from pancreatic beta cells during pregnancy. *Proc. Natl. Acad. Sci. U. S. A.* 110, 19420–19425
17 Smith, T. (1897) A modification of the method for determining the production of indol by bacteria. *J. Exp. Med.* 2, 543–547
18 Roager, H.M. and Licht, T.R. (2018) Microbial tryptophan catabolites in health and disease. *Nat. Commun.* 9, 3294
19 Agus, A. *et al.* (2018) Gut microbiota regulation of tryptophan metabolism in health and disease. *Cell Host Microbe* 23, 716–724
20 Natividad J.M., *et al.* Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. *Cell Metab.* 28, 737-749
21 Laurans, L. *et al.* (2018) Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health. *Nat. Med.* 24, 1113–1120
22 Neinast, M. *et al.* (2019) Branched chain amino acids. *Annu. Rev. Physiol.* 81, 139–164
23 Shoaie, S. *et al.* (2015) Quantifying diet-induced metabolic changes of the human gut microbiome. *Cell Metab.* 22, 320–331
24 Pedersen, H.K. *et al.* (2016) Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 535, 376–381
25 Hooper, L.V. *et al.* (2001) Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 291, 881–884
26 Koh, A. *et al.* (2018) Microbially produced imidazole propionate impairs insulin signaling through mTORC1. *Cell* 175, 947–961 e917
27 Feng, R.N. *et al.* (2013) Histidine supplementation improves insulin resistance through suppressed inflammation in obese women with the metabolic syndrome: a randomised controlled trial. *Diabetologia* 56, 985–994
28 Grasset, E. *et al.* (2017) A specific gut microbiota dysbiosis of type 2 diabetic mice induces GLP-1 resistance through an enteric NO-dependent and gut-brain axis mechanism. *Cell Metab.* 25, 1075–1090 e1075
29 Iizuka, K. *et al.* (2014) Skeletal muscle is an endocrine organ. *J. Pharmacol. Sci* 125, 125–131
30 Neinast, M.D. *et al.* (2018) Quantitative analysis of the whole-body metabolic fate of branched-chain amino acids. *Cell Metab.* 29, 1–13
31 Mardinoglu, A. *et al.* (2018) Beta-aminoisobutyric Acid, l-BAIBA, is a muscle-derived osteocyte survival factor. *Cell Rep.* 22, 1531–1544
32 Roberts, L.D. *et al.* (2014) beta-Aminoisobutyric acid induces browning of white fat and hepatic beta-oxidation and is inversely correlated with cardiometabolic risk factors. *Cell Metab.* 19, 96–108
33 Zang, X. *et al.* (2018) Regulation of proinflammatory monocyte activation by the kynurenine-AhR axis underlies immunometabolic control of depressive behavior in mice. *FASEB J.* 32, 1944–1956
34 Agudelo, L.Z. *et al.* (2014) Skeletal muscle PGC-1alpha1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell* 159, 33–45
35 Agudelo, L.Z. *et al.* (2018) Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. *Cell Metab.* 27, 378–392
36 Duca, F.A. *et al.* (2015) Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats. *Nat. Med.* 21, 506–511
37 Augustine, V. *et al.* (2018) Peripheral and central nutrient sensing underlying appetite regulation. *Trends Neurosci.* 41, 526–539
38 Cota, D. *et al.* (2006) Hypothalamic mTOR signaling regulates food intake. *Science* 312, 927–930
39 Su, Y. *et al.* (2012) Hypothalamic leucine metabolism regulates liver glucose production. *Diabetes* 61, 85–93
40 Arrieta-Cruz, I. *et al.* (2005) Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat. Med.* 11, 320–327
41 Tremblay, F. *et al.* (2007) Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. *Annu. Rev. Nutr.* 27, 293–310
42 Hotamisligil, G.S. and Erbay, E. (2008) Nutrient sensing and inflammation in metabolic diseases. *Nat. Rev. Immunol.* 8, 923–934
43 Newgard, C.B. *et al.* (2009) A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* 9, 311–326
44 Venkatesh, M. *et al.* (2014) Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity* 41, 296–310
45 Zelante, T. *et al.* (2013) Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* 39, 372–385
46 Jin, C. *et al.* (2013) Innate immune receptors: key regulators of metabolic disease progression. *Cell Metab.* 17, 873–882
47 Dodd, D. *et al.* (2017) A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature* 551, 648–652
48 Krishnan, S. *et al.* (2018) Gut microbiota-derived tryptophan metabolites modulate inflammatory response in hepatocytes and macrophages. *Cell Rep.* 23, 1099–1111
49 Rothhammer, V. *et al.* (2016) Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat. Med.* 22, 586–597
50 Hotamisligil, G.S. (2017) Inflammation, metaflammation and immunometabolic disorders. *Nature* 542, 177–185
51 Kandasamy, P. *et al.* (2018) Amino acid transporters revisited: New views in health and disease. *Trends Biochem. Sci.* 43, 752–789
52 Brosnan, J.T. and Brosnan, M.E. (2006) Branched-chain amino acids: enzyme and substrate regulation. *J. Nutr.* 136, 207S–211S
53 Roberts, A.B. *et al.* (2018) Development of a gut microbe-targeted nonlethal therapeutic to inhibit thrombosis potential. *Nat. Med.* 24, 1407–1417
54 Koeth, R.A. *et al.* (2013) Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* 19, 576–585
55 Husted, A.S. *et al.* (2017) GPCR-mediated signaling of metabolites. *Cell Metab.* 25, 777–796
56 Duft, R.G. *et al.* (2017) Metabolomics approach in the investigation of metabolic changes in obese men after 24 weeks of combined training. *J. Proteome. Res.* 16, 2151–2159
57 Sun, L. *et al.* (2018) Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. *Nat. Med.* 24, 1919–1929
58 Stone, K.P. *et al.* (2014) Mechanisms of increased *in vivo* insulin sensitivity by dietary methionine restriction in mice. *Diabetes* 63, 3721–3733
59 Gentile, C.L. and Weir, T.L. (2018) The gut microbiota at the intersection of diet and human health. *Science* 362, 776–780
60 Suez, J. *et al.* (2018) Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* 174, 1406–1423
61 Singh, V. *et al.* (2018) Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. *Cell* 175, 679–694
62 Rothschild, D. *et al.* (2018) Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555, 210–215