Nutrition Research Reviews

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Digging deep for nutrients and metabolites derived from high dietary protein intake and their potential functions in metabolic health

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Review Article

Cite this article: Gilsenan S, Leong D, Cotter PD, Brennan L, and Nilaweera KN (2025) Digging deep for nutrients and metabolites derived from high dietary protein intake and their potential functions in metabolic health. *Nutrition Research Reviews* **38**: 586–598. doi: 10.1017/S0954422424000374

Received: 30 November 2023
Revised: 8 November 2024
Accepted: 6 December 2024
First published online: 13 December 2024

Keywords:
metabolic health; metabolites; microbiota; proteins

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Abstract

Intake of high quantities of dietary proteins sourced from dairy, meat or plants can affect body weight and metabolic health in humans. To improve our understanding of how this may be achieved, we reviewed the data related to the availability of nutrients and metabolites in the faeces, circulation and urine. All protein sources (≥20% by energy) increased faecal levels of branched-chain fatty acids and ammonia and decreased the levels of butyrate. Some metabolites responded to dairy and meat proteins (branched-chain amino acids) as well as dairy and plant proteins (*p*-cresol), which were increased in faecal matter. Specific to dairy protein intake, the faecal levels of acetate, indole and phenol were increased, whereas plant protein intake specifically increased the levels of kynurenine and tyramine. Meat protein intake increased the faecal levels of methionine, cysteine and alanine and decreased the levels of propionate and acetate. The metabolite profile in the faecal matter following dairy protein intake mirrored availability in circulation or urine. These findings provide an understanding of the contrasting gut versus systemic effects of different dietary proteins, which we know to show different physiological effects. In this regard, we provide directions to determining the mechanisms for the effects of different dietary proteins.

Introduction

All living organisms require a constant supply of nutrients that can be metabolised in tissues, acting as fuels for growth and development, as well as regulators of nutrient (energy) homeostasis. This process is controlled, in part, by the small intestine by allowing digestion to take place, breaking complex nutrients into forms that can easily be absorbed into the circulation and/or by producing signalling molecules that communicate the availability of nutrients in the gastrointestinal tract to other tissues [1–3]. By contrast, the colon receives much less nutrient load compared with the small intestine because of absorption through the latter tissue. Yet, a diverse range of metabolites are produced in the colon from metabolism of dietary nutrients by the gut microbiota inhabiting this tissue, resulting in a range of metabolic health outcomes (Fig. 1) [4–9]. In this article, we focused on the nutrient and metabolite profiles created by high dietary protein (HDP) intake, which differ in source, to improve our understanding of how the different dietary proteins influence body weight and metabolic health.

Effects on physiology and metabolic health

A renewed focus to understand the relationship between diet and metabolic health has arisen in part due to the increased prevalence of obesity and associated comorbidities over the past 100 years, mostly due to high calorie intake, particularly an increased intake of dietary fat, which affects metabolic health [10–15]. A particular interest in protein intake has emerged with many weight loss or weight maintenance recommendations promoting increased protein intake, generally above 20% of total energy intake within the 10–30% acceptable macronutrient range for proteins [16]. Data show that HPD intake reduced body weight gain or cause weight loss up to 10%, with a reduction in fat mass and an increased lean mass in overweight and obese individuals of both sexes (Table 1) [14,30–32]. The effects extended to include reduction in plasma insulin levels, triacylglycerol, high-density lipoproteins and blood pressure (Table 1). Notably, whilst these effects have been shown relative to baseline measurements or in comparison with carbohydrate intake (Table 1), there is evidence that the quality of the protein also impacts metabolic health (Table 1). For instance, whey protein (WP) intake reduced waist circumference and circulating ghrelin and insulin-like growth factor (IGF)1 levels in obese

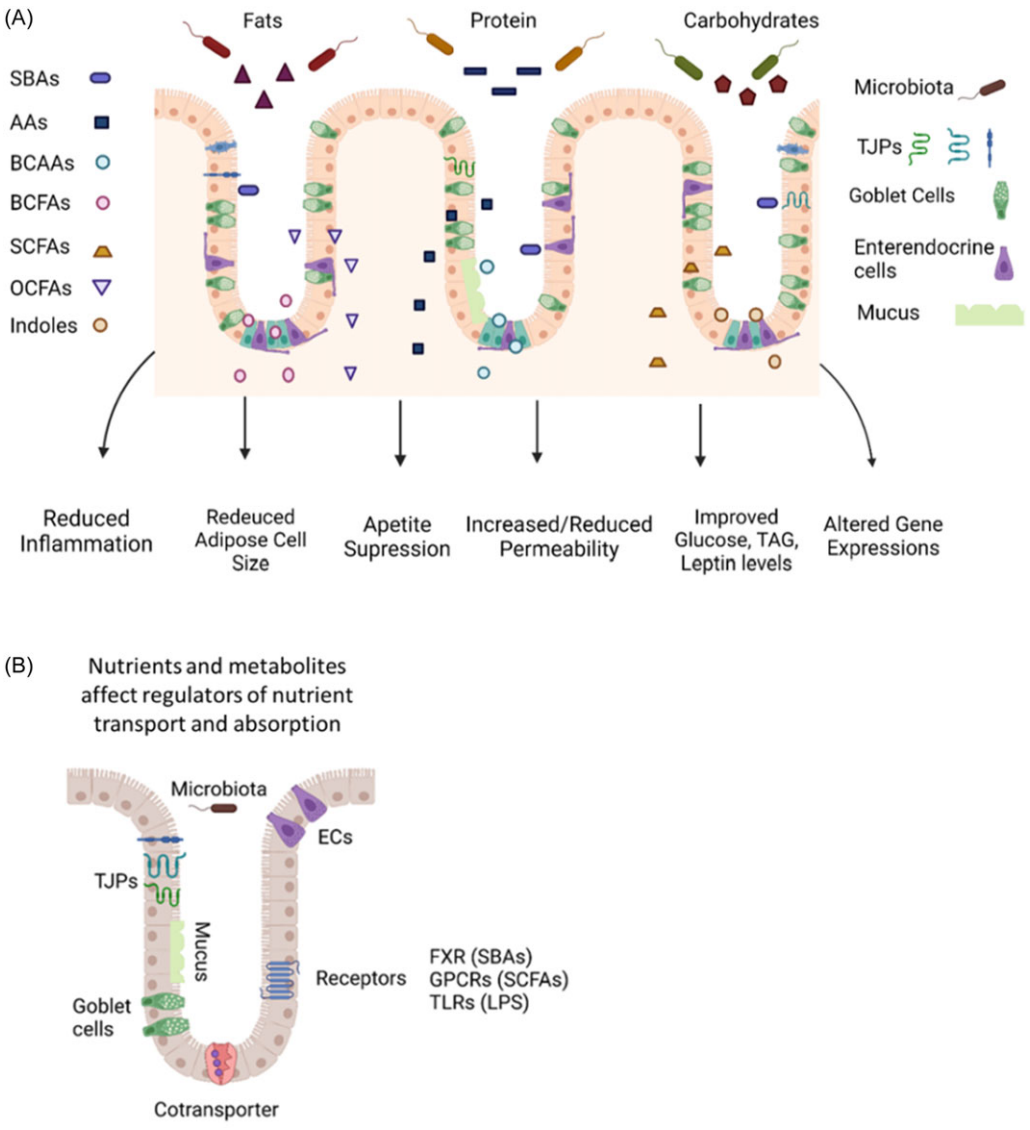

Figure 1. The impact of nutrients on the colonic epithelium. (A) Digested macronutrients either pass through the epithelium or they are metabolised by the gut microbiota, resulting in different metabolites been produced, with diverse roles. (B) A colon intestinal crypt, and associated cells and receptors that respond to nutrients and metabolites involved in many signalling mechanisms. AA, amino acids; BCAA, branched-chain amino acids; BCFA, branched-chain fatty acids; EC, enteroendocrine cells; FXR, Farnesoid X receptor; GPCR, G-protein-coupled receptors; OCFA; odd-chain fatty acids; SBA, secondary bile acids; SCFA, short-chain fatty acids; TAG, triacylglycerol; TLR, Toll-like receptors; LPS, lipopolysaccharides; TJB, tight-junction-associated proteins.

humans in comparison with soy intake (Table 1). Relative to collagen, WP caused a reduction in visceral fat, with similar effects shown for milk proteins, containing both WP and casein, compared with controls fed milk proteins and soy (Table 1). These effects reported for *ad libitum* intake have been extended to include calorie restriction, with WP showing a greater improvement of metabolic health than other protein sources (Table 1), but there are few exceptions (Table 1) [26,29]. It is also important to highlight that there are data showing unhealthy outcomes of HPDs. For instance, red meat intake has been associated with increased risk of colorectal cancers and kidney disease [33,34]. The different effects of proteins on metabolic health can be related to the quantity and composition of the amino acids, how the proteins are digested and absorbed through the gut and the impact on the gut microbiota and their functional capacity to produce metabolites, which ultimately affects host health [35–38]. For this review, we focused attention on dairy, meat or plant protein intake and their impact on the abundance of metabolites produced in the gut (and, hence, detected in faeces) as well as that emerge in circulation/urine to better understand how different proteins affect host metabolic health. Our focus was on data related to human studies, but in a few cases we have mentioned rodent studies to draw conclusions. The search includes effects of HPD, where the protein content was equal or greater than 20% of total energy intake.

Effect on the gut microbiota

The gastrointestinal tract is inhabited by the microbiota, with the colon containing a much higher density of microbiota (10^{10}–10^{11} cells per millilitre of contents), as well as a much more diverse microbial composition compared with other parts of the intestine [39,40]. This complexity in microbial communities is further supported by the colonic structure and functions. Notably, the colon is made up of a number of colonic epithelial cells (Fig. 1), with many of these cells, particularly goblet cells, capable of producing enzymes contributing to the metabolism of nutrients in the intestinal mucosa before they reach the circulation [41]. The colonic microbiome also acts as a vital part of the digestive process by breaking down complex carbohydrates, proteins and fats, which are not broken down enzymatically in the preceding parts of the digestive system [42]. The transit rate in the colon is much slower

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

Table 1. Impact of protein quantity and quality on body weight and metabolic health in humans

	Test protein	Control	Dur	BMI	Sex	Diet	Health outcomes	Ref
Impact of protein quantity	WP	CHO	23W	~31·1	M/F	Ad lib:	↓ Body mass, fat mass, weight circumference and plasma insulin	[17]
	Soy	CHO	23W	~31·1	M/F	Ad lib:	↓ Plasma insulin	[17]
	Soy	CHO	3W	25–30	M/F	Ad lib:	↓Systolic blood pressure	[53]
	WP	Baseline	16W	~28	M/F	Ad lib:	↓Body weight, body fat, plasma triacylglycerol and HDL	[18]
	Casein	Baseline	12W	~30·5	F	Ad lib:	↑ Total abdominal body fat and subcutaneous fat	[19]
	MP	Baseline	20W	~29	M/F	Ad lib:	↓Body weight, visceral fat and subcutaneous fat and systolic blood pressure	[20]
	Soy	Baseline	20W	~29	M/F	Ad lib:	↓Diastolic blood pressure	[20]
	Red/white meat	High v Low proteins	64W	~32·8	F	CR+ WMD	↑Weight loss	[21]
Impact of protein quality	WP	Soy	23W	~31·1	M/F	Ad lib:	↓Waist circumference, circulatory ghrelin and IGF1	[17]
	MP	Soy + MP	20W	~29	M/F	Ad lib:	↓Visceral fat	[20]
	WP	Collagen	8W	30·9–31·1	F	Ad lib:	↓Visceral fat	[22]
	WP	Casein	12W	~31·3	M/F	Ad lib:	↓Augmentation index (arterial stiffness)	[23]
	WP	Soy	2W	28–50	M/F	CR	Decline in muscle protein synthesis reduced	[24]
	MP + amino acids	Pea + casein	12W	~33	M/F	CR	↓Visceral fat and ↓ subcutaneous fat	[25]
	Gelatin	Whey	8W	~36	F	CR	↓Waist circumference	[26]
	WP + EAA	Casein	8W	~31·3	M/F	CR	↓Body fat	[27]
	WPH	WP	8W	24–35	F	CR	↓HOM-IR	[28]
	Whey	Soy	32W	27·6–40·4	M/F	CR + WMD	CR induced metabolic improvement were not influenced by protein source	[29]

The direction of change is shown by arrows, as increase (↑), decrease (↓) or no change (↔).Ad lib, *ad libitum*; CHO, carbohydrate; CR, calorie restriction; Dur, duration; EAA, essential amino acids; F, female; HDL, high-density lipoproteins; IGF, insulin-like growth factor; M, male; MP, milk proteins; WMD, weight maintenance diet; WP, whey proteins; WPH, whey protein hydrolysate; W, weeks.

compared with the small intestine, allowing increased microbial action on the food material [43]. Indeed, microbial metabolism of digested dietary proteins results in the production of a range of nutrients and metabolites, which have diverse physiological functions (see below).

The microbiota composition plays an important role in metabolic health [37,44,45]. Notably, the alpha and beta microbial diversity, measured by the richness of diversity and evenness and relative differences in the overall diversity of taxa, respectively, highlight the similarities and differences in the microbiota across the different interventions, and associated metabolic states. A rich and diverse gut microbiota composition generally reflects a microbiota that is more resilient and capable of functioning better, with a loss in species diversity a common finding in several disease states [46]. The importance of the gut microbiota in mediating protein effects was highlighted by recent work showing that WP reduced body weight gain in high-fat-fed mice and that this effect can be transferred via faecal matter onto mice fed casein [6,47,48]. In contrast to animal studies [49], only few studies show an impact of dietary proteins on the gut microbiota in humans in the overweight and obese categories (Table 2). Of note, subjects ingesting varied quantities of dietary fats, whilst co-ingesting proteins at 25% energy from various sources (red and white meat and plants), show no effect on the alpha or beta diversities [50]. However, in the latter study, when the main effect of dietary fat on the gut microbiota was removed, an effect of dietary proteins can be seen on these micro-organisms, which were largely due to any source of protein rather than the quality of the protein consumed (Table 2). Similar data have been generated to show an impact of protein quantity on the composition of the gut microbiota (e.g. with or without fish intake or high and low gluten intake; Table 2). Where the impact of the source of proteins was investigated (pork versus chicken intake), the only changes in the gut microbiota was seen relative to baseline intake for each protein type [54] (Table 2). Imposing a calorie restriction for 8 weeks also did not affect the gut microbiota regardless of the hydrolysed state of the WP proteins [28,53] (Table 2). In contrast to the above studies, which used 16S rRNA sequencing to uncover microbial changes, a study by Bel Lassen *et al.* [25] used Metagenomics sequencing to explore the impact of an extended calorie restriction (12 weeks) on subjects consuming milk proteins supplemented with amino acids. The latter intervention was found to increase the microbial potential to produce amino acids compared with pea and casein intake (Table 2). This suggests that the interaction between the quality of the protein and the gut microbiota may be more subtle (at a functional level), requiring a greater depth of sequencing to uncover, but with the potential to influence the luminal pool of amino acids and their derivatives that are accessible by the host.

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

Table 2. Impact of protein quantity and quality on the composition and functional potential of the gut microbiota in humans

Test protein	Comparison	Dur	BMI	Sex	Intervention:	Impact on gut microbiota	Ref
Red meat, white meat, and plant proteins	High versus low fat	18W	18–26	M/F	Ad lib:	-Dietary fat main driver of changes in the gut microbiota.	[50]
						-Within each level of fat, dietary proteins, regardless of the source, affected *Akkermansia*, *Bacteroides*, *Sutterella*, *Cantenibacterium*, *Faecalibacterium*, *Megasphaera*, *Oscillospira* and *Methanobrevibacter*	
Salmon	No fish	8W	~31	M/F	Ad lib:	-[↓] *Bacteroidetes* Phylum, *Clostridiales* order of *Firmicutes*	[51]
						-[↑] *Selenomonadales* order of *Firmicutes.*	
Low Gluten	High Gluten	22W	~28	?	Ad lib:	-No changes in diversity.	[52]
						-[↓] *B. longum, B. angulatum, B. pseudocatenulatum, B. adolescentis, D. longicatena, B. wexlerae, Lachnospiraceae 1, A. hadrus, E. hallii.*	
						-[↑] Clostridiales, Lachnospiraceae 2	
						-[↓] Functional potential for carbohydrate degradation	
Casein	Soy	3W	25–30	M/F	Ad lib:	-No changes in diversity.	[53]
Pork	Chicken	3W	~30	M/F	Ad lib:	-No changes in diversity.	[54]
						-[↑] *Ruminiclostridium 5* pre versus post pork group and [↓] pre versus post chicken group	
MP + amino acid	Pea + casein	12W	~32	M/F	CR	[↑] Microbial function potential to synthesis amino acids	[25]
WPH	WP	8W	24–35	F	CR	No effect on the gut microbiota	[28]

The direction of change is shown by arrows, as increase (↑), decrease (↓) or no change (↔).Ad lib, *ad libitum*; CR, calorie restriction; Dur, duration; F, female; M, male; MP, milk proteins; WP, whey proteins; WPH, whey protein hydrolysate W, weeks.

Effects on nutrients and metabolites

Most digested proteins are absorbed in the small intestine as amino acids, but some undigested proteins, especially following HPD intake, reach the colon where they are further broken down by proteolytic bacteria for the synthesis of other amino acids and/or into amino acid derivatives that have been associated with numerous health outcomes, including regulating digestion and absorption (Table 3). Of note, lysine, arginine, glycine and the branched-chain amino acids (BCAA), namely leucine, iso-leucine and valine, are the most preferred amino acid (AA) substrates of colonic microbiota [83].

BCAA and their derivatives

BCAA are building blocks of lean tissue and are capable of modulating gene expression and signalling pathways, including regulating dietary nutrient absorption, partake in lipolysis, lipogenesis, glucose metabolism and intestinal barrier function [84–86]. However, BCAA have also been shown to have negative effects on metabolism, with increased consumption of BCAA correlated with a more unhealthy metabolic state [87], although these effects may be mediated somewhat by changing the levels of individual BCAAs [88]. Increased BCAA intake has been shown to result in increased insulin resistance [89–91]. Negative effects of BCAA intake may also include an increased risk of cancer [92]. Conversely, a reduction in BCAA intake has been shown to have positive effects on metabolic health [93].

Intake of HPD increased faecal levels of BCAA, specifically following dietary casein and red and white meat intake (Table 4). By contrast, circulating levels of BCAA increased regardless of the type of protein consumed in both fasted and non-fasted states after prolonged intake (3–4 weeks) as well as after acutely challenges, where the post-prandial plasma increase was higher after milk protein consumption compared with plant protein intake (within 5 h), WP intake compared with casein intake (3 h) and following red meat intake compared with baseline measurements (within 4 h) (Table 5). It is interesting that HPD and BCAA have both positive and negative outcomes on metabolic health. Whilst this suggests a potential functional relationship in the way dietary proteins affect metabolic health, it is important to highlight the role of the gut microbiota as a modulator of the effects. This is because these micro-organisms can convert BCAA into short-chain fatty acids (SCFA) and branched-chain fatty acids (BCFA) (Table 3), which have diverse metabolic health effects (discussed below). Indeed, in agreement with the BCAA availability in the faeces and circulation, HPD intake also increases BCFA in faeces with some reaching the urine (Tables 4 and 5). By contrast, the availability of SCFA in faeces and urine was either unaffected or decreased, with the exception of acetate, which was increased in faeces and urine following casein intake (Tables 4 and 5 and further detailed below). The data suggest a potential microbial preference for conversion of amino acids into BCFA over SCFA in a background of HPD intake, which generally accompanies a low carbohydrate intake [53,106,107].

Aromatic amino acids (AAA) and derived metabolites

Tryptophan: Evidence is emerging that the dietary supply of tryptophan affects host metabolic health directly or indirectly, the latter following microbial fermentation into numerous metabolites [71,72,108]. Indole, a tryptophan metabolite, acts as a signalling molecule capable of modulating the secretion of the satiety

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

Table 3. Metabolic effects of dietary protein or microbial-derived amino acids and their metabolites

Dietary protein-derived nutrient	Metabolites	Host metabolic effects of metabolites	References
AA	Microbial-derived AA	Protein synthesis; Immunity; regulation of metabolic pathways; energy homeostasis.	[35,55–63]
Aromatic AA: tryptophan	Tryptamine	Neurotransmitter (immunity and intestinal motility).	[59,60,64–72]
	Indole	Improves intestinal barrier and satiety.	
	Kynurenine/ quinolinic	Immunity.	
	Serotonin	Neurotransmitter (mood, appetite and immunity).	
Aromatic AA: tyrosine	Tyramine	Neurotransmitter linked to hypertension.	[59]
	Phenol	Reduces integrity of gut epithelium.	
	p-Cresol-derivatives	Reduces integrity of gut epithelium.	
Aromatic AA: phenylalanine	Phenylethylamine	Neurotransmitter. Releases catecholamine/serotonin.	[59]
Glutamate, arginine	GABA	Neurotransmitter (stress modulation).	[59,60]
Basic AA: arginine	Agmatine	Anti-inflammatory and inhibits intestinal cell proliferation.	[59]
	Putrescine	Promotes intestinal cell proliferation.	
	Spermidine/ spermine	Reduces oxidative stress.	
Basin AA: histidine	Histamine	Neurotransmitter (wakefulness and learning).	[59,60]
Sulphur AA: cysteine, methionine	H_2S methanethiol	Impedes cellular respiration and cause apoptosis.	[60,73]
Basic AA: lysine, histidine, aromatic AA: tyrosine, tryptophan	Ammonia	Reduces intestinal activity.	[60,73]
BCAA: leucine /isoleucine	BCFA: isovalerate/ isobutyrate	Lipid and glucose metabolism	[74,75]
Glutamine, glutamate, alanine, histidine, serine, threonine cysteine, methionine, lysine	Butyrate (SCFA)	Reduces intestinal permeability and affects cell proliferation; energy source for gut cells; mucin production; immunity; epigenetic effects.	[76–78]
Glutamine/glutamate, alanine, glycine, histidine, serine, threonine, cysteine, proline, lysine	Acetate (SCFA)	Colonic calcium absorption; appetite suppression; liver lipogenesis and cholesterol metabolism	[79,80]
Aspartate, alanine, threonine methionine	Propionate (SCFA)	Production of satiety hormones and appetite suppression; intestinal permeability; impedes liver gluconeogenesis; cholesterol metabolism [60].	[81,82]

AA, amino acids; BCAA, branched-chain amino acids; BCFA, branched-chain fatty acid; GABA, gamma-aminobutyric acid; SCFA, short-chain fatty acid.

hormone, glucagon-like peptide (GLP)-1 from colonic enteroendocrine L cells [67]. Indole improves the intestinal epithelial barrier, upregulating genes responsible for tight-junction organisation, actin cytoskeleton, mucin production and adherens junction, suggesting the strengthening and maintenance of the epithelial barrier, which directly affects intestinal permeability [64]. The tryptophan breakdown also produces indole-3-propionic acid (IPA), indole acetic acid (IAA) and kynurenine, which are also associated with several positive health outcomes (Table 3). Of note, like indole, IPA improves epithelial barrier function and reduces inflammation and body weight [69]. This molecule also improves insulin sensitivity, as does IAA [69]. These effects are in part due to the indole moiety, which acts as a ligand for the aryl hydrocarbon receptor [109], whereby receptor activation can suppress inflammatory response and affect energy metabolism [110]. Serotonin can be synthesised by the gut microbiota from tryptamine, a metabolite of tryptophan, and the latter amino acid and its derivative regulate the serotonin levels in the colon and blood [71,111]. Tryptamine is also capable of inducing the release of serotonin from enteroendocrine cells as well as potentiating the inhibitory response of cells to serotonin [112,113]. While there are many health benefits of breakdown of tryptophan, in host cells and by microbial activity, the co-production of ammonia is a concern because of the damage caused to the mucosal layer in the colon, which impairs the absorptive capacity of the tissue [73].

In relation to protein source, intake of high quantities of proteins increased the faecal levels of indole derivatives (milk proteins) and ammonia (all protein sources; Table 4). This raises the possibility that these dietary proteins increase the microbial activity related to metabolism of tryptophan in the gut. In support of this suggestion, the intake of milk proteins supplemented with amino acids was found to increase the gut microbial potential to produce amino acids (Table 2). Beyond the gut, indole derivatives have been found to increase in urine following dairy protein (casein) intake (Table 5), whilst other tryptophan metabolites, namely kynurenine and quinolinic acid, show no consistency in

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

Table 4. Impact of dietary proteins on the metabolite profiles in the faeces in humans

Nutrient or metabolite		High-protein diets			Reference
		Dairy	Meat	Plant	
BCAA		↑CAS $_{(3W)}$	↑RED/WHT $_{(4W)}$	?	[53,94]
EAA: methionine		?	↑ RED/WHT $_{(4W)}$	?	[94]
Non-EAA: cysteine, alanine		?	↑ RED/WHT $_{(4W)}$	?	[94]
Non-EAA: tyrosine		?	↔ RED/WHT $_{(4W)}$	↔GLTN $_{(22W)}$	[52,94]
BCFA		↑ MP $_{(1W)}$	↑ RED/WHT $_{(4W)}$	↑ SOY$_{(3W)}$	[52,53,95–97]
		↑CAS $_{(3W)}$		↔ GLTN $_{(22W)}$	
SCFA: butyrate		↓ CAS $_{(3W)}$	↓ RED/WHT $_{(4W)}$	↓ SOY$_{(3W)}$	[52,53,96–98]
		↔ DAIRY/MEAT $_{(1·5W)}$		↔GLTN $_{(22W)}$	
		↔ DAIRY/ANIMAL/PLANT $_{(48W)}$			
SCFA: propionate		↔ CAS $_{(3W)}$	↓RED/WHT $_{(4W)}$	↔ SOY$_{(3W)}$	[52,53,96–98]
		↔ DAIRY/MEAT $_{(1·5W)}$		↔GLTN $_{(22W)}$	
		↔ DAIRY/ANIMAL/PLANT $_{(48W)}$			
SCFA: acetate		↑ CAS $_{(3W)}$	↓ RED/WHT $_{(4W)}$	↔ SOY$_{(3W)}$	[52,53,96–98]
		↔ DAIRY/MEAT $_{(1·5W)}$		↔GLTN $_{(22W)}$	
		↔ DAIRY/ANIMAL/PLANT $_{(48W)}$			
Tryptophan derivatives	Indole derivatives	↑ MP $_{(1W)}$	↔ RED/WHT $_{(4W)}$	↔ GLTN $_{(22W)}$	[52,95–97]
	Kynurenine	?	?	↑ GLTN $_{(22W)}$	[52]
	Quinolinic	?	?	↔ GLTN $_{(22W)}$	[52]
Tyrosine derivatives	Phenol	↑ MP $_{(1W)}$		?	[95,98]
		↔ DAIRY/MEAT $_{(1·5W)}$			
		↔ DAIRY/ANIMAL/PLANT $_{(48W)}$			
	p-Cresol-derivatives	↑ MP $_{(1W)}$	↔ RED/WHT $_{(4W)}$	↑ SOY$_{(3W)}$	[53,95,96]
	Tyramine	↔ CAS $_{(3W)}$	?	↑ SOY$_{(3W)}$	[52,53]
				↔GLTN $_{(22W)}$	
Tryptophan, lysine, histidine, tyrosine derivative	Ammonia	↑ MP $_{(1W)}$	↑RED $_{(3W)}$	↔ SOY$_{(3W)}$	[53,95,97–99]
		↔ CAS $_{(3W)}$	↔ RED/WHT $_{(4W)}$		
		↑ DAIRY/MEAT $_{(48W)}$			
		↑ DAIRY/ANIMAL/PLANT $_{(48W)}$			
Cysteine, methionine derived	Methanethiol	↑ MP $_{(1W)}$	?	?	[95]

The direction of change is shown by arrows, as increase (↑), decrease (↓) or no change (↔) of metabolites. The length of the dietary challenge is shown in subscript in weeks (W). BCAA, branched-chain amino acids; BCFA, branched-chain fatty acids; CAS, casein; EAA, essential amino acids; MP, milk proteins; RED, red meat; SCFA, short-chain fatty acids; GLTN, gluten; WHT, white meat.

terms of availability in faeces and circulation/urine based on the source of the protein consumed (Tables 4 and 5). The presence of indole in faeces and circulation/urine following chronic intake of dairy proteins (>1 week; Tables 4 and 5), is striking, and this contrasts with the intake of non-dairy proteins, which only seem to increase indole levels only in urine (by soy or meat/plant protein intake; Table 5). The difference may be related to the differential impact of dairy and plant proteins on the functional potential of the gut microbiota (mostly affected by dairy proteins; Table 2) combined with the host tissue accessibility and metabolism of tryptophan that we know to be higher in quantity in milk proteins compared with plant proteins [38].

Tyrosine: Microbial metabolism of tyrosine can lead to the production of phenols, *p*-cresol derivatives and tyramine (Table 3) [59]. Tyramine is a neurotransmitter facilitating norepinephrine release, which is known to affect respiration and glucose levels in blood (Table 3). Both phenol and *p*-cresol are known to decrease the integrity of the gut epithelium [59]. Similar to tryptophan, the faecal availability of this AAA was not influenced by protein source, but the related metabolites, phenol, *p*-cresol derivatives and tyramine were increased in faecal matter by dairy (phenol and *p*-cresol) and plant (*p*-cresol and tyramine) intake (Table 4). Data are limiting on the availability of tyrosine-derived metabolites in circulation, except for the increased urinary levels of *p*-cresol detected following dairy (casein) protein intake (Table 5). The data suggest that the quality of protein associated with HPD, which can deliver high quantities of tryptophan and tyrosine, can provide beneficial effects (by producing indoles) as well potential harmful effects (by producing ammonia, phenol and *p*-cresol).

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

Table 5. Impact of dietary proteins on the metabolite profiles in circulation or urine in humans

Nutrient or metabolite		High-protein diets			References
		Dairy	Meat	Plant	
EAA: BCAA		↑CAS (3W:PLASMA: FASTED)	↑RED (4H:PLASMA; POSTPRANDIAL)	↑SOY (3W:PLASMA:FASTED)	[94,53,100–103]
		↑ WP (4W:PLASMA; FASTED)	↑RED/WHT (4W:SERUM: NOT FASTED)	↑ MIX PLANT (5H;PLASMA: POSTPRANDIAL)	
		↑ WP (3H:PLASMA; POSTPRANDIAL)			
		↑MP (5H;PLASMA: POSTPRANDIAL)			
EAA: threonine		↑ MP (5H;PLASMA: POSTPRANDIAL)	↑RED (4H:PLASMA; POSTPRANDIAL)	↑ MIX PLANT (5H;PLASMA: POSTPRANDIAL)	[94,102,103]
			↔ RED/WHT (4W:SERUM: NOT FASTED)		
EAA: tryptophan, methionine, lysine		↑ MP (5H;PLASMA: POSTPRANDIAL)	↑ RED (4H:PLASMA; POSTPRANDIAL)	↑ MIX PLANT (5H;PLASMA: POSTPRANDIAL)	[94,102,103]
			↔ RED/WHT (4W:SERUM: NOT FASTED)		
Non-EAA: tyrosine		↑ MP (5H;PLASMA: POSTPRANDIAL)	↑ RED (4H:PLASMA; POSTPRANDIAL)	↑ SOY (3W:PLASMA:FASTED)	[94,53,102,103]
		↑ CAS (3W:PLASMA: FASTED)	↔ RED/WHT (4W:SERUM: NOT FASTED)	↑ MIX PLANT (5H;PLASMA: POSTPRANDIAL)	
Non-EAA: glycine		↑ MP (5H;PLASMA: POSTPRANDIAL)	↑RED (4H:PLASMA; POSTPRANDIAL)	↑ MIX PLANT (5H;PLASMA: POSTPRANDIAL)	[94,102,103]
			↔ RED/WHT (4W:SERUM: NOT FASTED)		
BCFA		↑ CAS (3W:URINE: FASTED)	↑ RED/WHT (4W:SERUM:NOT FASTED)	↑ SOY (3W:URINE:FASTED)	[52,53,94]
				↔ GLTN (22W:URINE;FASTED)	
SCFA: butyrate		↓ CAS (3W:URINE: FASTED)	?	↓ SOY (3W:URINE:FASTED)	[52,53]
				↔ GLTN (22W:URINE;FASTED)	
SCFA: propionate		↔ CAS (3W:URINE: FASTED)	?	↔ SOY (3W:URINE:FASTED)	[52,53]
				↔ GLTN (22W:URINE;FASTED)	
SCFA: acetate		↑CAS (3W:URINE: FASTED)	?	↔ SOY (3W:URINE:FASTED)	[52,53]
				↔ GLTN (22W:URINE;FASTED)	
Tryptophan derivatives	Indole derivatives	↑ CAS (3W:URINE: FASTED)	↔ RED/WHT (4W:SERUM: NOT FASTED)	↑ SOY (3W:URINE:FASTED)	[52,53,94,104,105]
				↔ GLTN (22W:URINE;FASTED)	
			↑ MEAT/PLANT (2W:URINE/SERUM;FASTED)		
	Kynurenine	?	↔ RED/WHT (4W:SERUM: NOT FASTED)	↓ GLTN (22W:URINE;FASTED)	[52,94]
	Quinolinic	?	?	↔ GLTN (22W:URINE;FASTED)	[52]
Tyrosine derivatives	*p*-Cresol derivatives	↑CAS (3W:URINE: FASTED)	↔RED/WHT (4W:SERUM:NOT FASTED)	↔SOY (3W:URINE:FASTED)	[53,94,104]
			↔MEAT/PLANT (2W:URINE/SERUM;FASTED)		
Tryptophan, tyrosine, histidine-Derivatives	Ammonia	↔CAS (3W:URINE:FASTED)	?	↔SOY (3W:URINE:FASTED)	[53]

The direction of change is shown by arrows, as increase (↑), decrease (↓) or no change (↔) of metabolites. The length of the dietary challenge is shown in subscript in weeks (W) or hours (H) along with the medium in which the metabolite was detected and whether the subjects were fasted or non-fasted. BCAA, branched-chain amino acids; BCFA, branched-chain fatty acids; CAS, casein; EAA, essential amino acids; MP, milk proteins; RED, red meat; SCFA, short-chain fatty acids; GLTN, gluten; SCFA, short-chain fatty acids; WHT, white meat.

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Non-essential amino acids: Dietary AAs are absorbed through the gut or act as substrates for microbial production of AAs, for their own utilisation and/or for supply to the host (Table 3). For instance, glutamine supplementation is found to impact the overall AA composition and content in the gastro-intestine, including raising the concentration of Asp, Glu and Ala in the blood [114–116]. Similarly, in the host, serine can be used to produce glycine or this process can be reversed [117]. Glycine has many biological effects, including being used for protein synthesis and bile acid metabolism and, hence, contributing to the digestion and absorption of dietary lipids and vitamins, as well as reducing body weight and fat and leading to an associated improvement in insulin sensitivity [117]. Given the wide range of routes of amino acid synthesis (host tissue metabolism and the gut microbiota), it is no surprise that the intake of dietary proteins should cause an increase in the levels of tyrosine and glycine in circulation following chronic and acute challenges (all protein sources; Table 5). Interestingly, whilst intake of red and white meat did not cause any changes in circulatory levels of these amino acids, it should be noted that the related data were generated from non-fasted state following 4 weeks of intervention [94] (Table 5), contrasting with other studies showing a post-prandial increase in the AAs (4–5h) following an acute dietary protein challenge (Table 5), presumably reflecting a greater absorption in the small intestine.

Short-chain fatty acids: There is a large body of evidence relating to the beneficial health impacts of SCFA, namely acetate, butyrate and propionate, in particular in regulating energy metabolism, specifically in reducing hepatic glucose production and adiposity and stimulating the release of satiety related hormones such as peptide YY [79,81,118,119]. The SCFA also partake in the maintenance of the gut, including improving the integrity of intestinal epithelial cells, promoting the expression of tight-junction-associated proteins, cell proliferation and increasing mucin production [120,121]. These effects are dependent upon the type of SCFA produced and how and where they act. Of note, SCFA are absorbed into the colonocytes or those that escape metabolism in cells are transported into the liver via the portal system. It should be mentioned that only a minor fraction of SCFA produced in the colon reach the circulatory system. Despite this, some contrasting responses of SCFAs need to be highlighted. Of note, acetate can be utilised for cholesterol synthesis, while propionate decreases the activity of the related pathway in the liver [60]. The higher levels of SCFA also decrease the production of hydrogen sulphide, which is well established to be detrimental to colonic health (Table 2), including as a contributing factor to ulcerative colitis [122,123] and as a potential trigger of colorectal cancer [124]. The effects of SCFA are mediated by G-protein-coupled receptors, namely GPR41, GPR43 and GPR109a, which are expressed in different tissues within the body [125]. It should also be noted that some SCFA have negative effects on health. Notably, propionate has been shown to increase liver lipogenesis [126]. In addition, acetate, propionate and butyrate have been shown to reduce gut dysbiosis-driven lung inflammation, as well as cause a pro-inflammatory response in human primary lung fibroblasts [126].

The SCFA synthesised in the colon are produced mainly by the microbial fermentation of indigestible carbohydrates such as fibre, with increasing fibre intake increasing SCFA-producing bacteria and colonic SCFA [127–130]. However, AA can also function as synthetic precursors of SCFA in the colon [60], with the type and quantity of SCFA produced depending on the AA substrate available (Table 1) as well as the microbiota present [131–133]. Likely, as a result of the availability of AA in the colon, HPD with low carbohydrates have been shown to influence the production of SCFA [53,106,107]. Of note, proteins from dairy (casein), meat (red and white meat) and plant (soy) all decreased butyrate-producing microbiota, and further decreased butyrate levels in faeces (Table 4). By contrast, dairy (casein) proteins increased acetate levels in the faecal matter (Table 4) and also in urine (Table 5). Available evidence suggests that the source of protein influences the type of SCFA produced in the gut, with some (acetate) reaching the urine, presumably via the circulation.

Branched-chain fatty acids (BCFAs): Further microbial fermentation of BCAA results in the formation of branched SCFA (BSCFA) or BCFA, including isovalerate and isobutyrate. The latter can also be produced from bacterial fermentation of some amino acids such as glycine (which can produce acetate), threonine (which can produce butyrate) or alanine (which can produce propionate) [60]. The levels of BCFA in the colon highlight proteolytic fermentation, as BCFA are elevated when saccharolytic fermentation is minimal and protein fermentation is significantly enhanced in the colon [73,134]. Similarly to SCFA, BCFA are shown to have positive impacts on metabolic health (Table 3), being associated with weight loss and maintenance [75] as well as showing an inverse correlation with lipotoxicity and improved insulin sensitivity [74,75]. Likely due to the availability of BCAA in the colon (Table 4), HPD increased the levels of BCFA in the faecal matter and circulation, including urine (Tables 4 and 5). This effect was seen for proteins sourced from dairy, meat and plants, with the exception of gluten (Table 5). The largely similar effects of different proteins on the availability of BCFA both in faecal matter and in circulation suggest an important role for these metabolites in mediating the metabolic health effects of HPDs.

Exploring the potential mechanisms

All protein sources increased BCFA in faecal content, probably from the increased gut availability of BCAA (Fig. 2A), suggesting a greater bacterial conversion of BCAA to BCFA with the intake of different proteins, but we cannot exclude the contribution of other amino acids for this process. Dairy protein intake specifically increased faecal levels of indole and acetate (Fig. 2A). Alongside these health-promoting metabolites, several other metabolites emerge in faecal matter with known unhealthy outcomes. These were phenol (dairy), *p*-cresol derivatives (dairy and plant), ammonia (all protein sources) and tyramine (plant). In circulation, and regardless of the source of proteins, amino acids, including BCAA, increased (Fig. 2B). In addition, for dairy proteins, the impact on the faecal availability of acetate, indole, *p*-cresol, BCFA and butyrate mirrored availability in the circulatory system or urine (Fig. 2B), suggesting both gastro-intestinal and systemic effects of these metabolites. This contrasts with metabolites produced following plant and meat protein intake, which show fewer common responses in faecal matter and circulation (and urine) (Fig. 2). The contrasting levels of metabolites in the gut and circulation/urine following dairy, meat or plant protein intake could be related to the differences in the amino acid composition and the three-dimensional structure of the proteins accessible for enzymatic digestion and how the resulting digested peptides and amino acids are utilised by the dietary protein-sensitive gut microbiota to produce metabolites, which ultimately reach the gut and/or enter the circulatory system [35–38].

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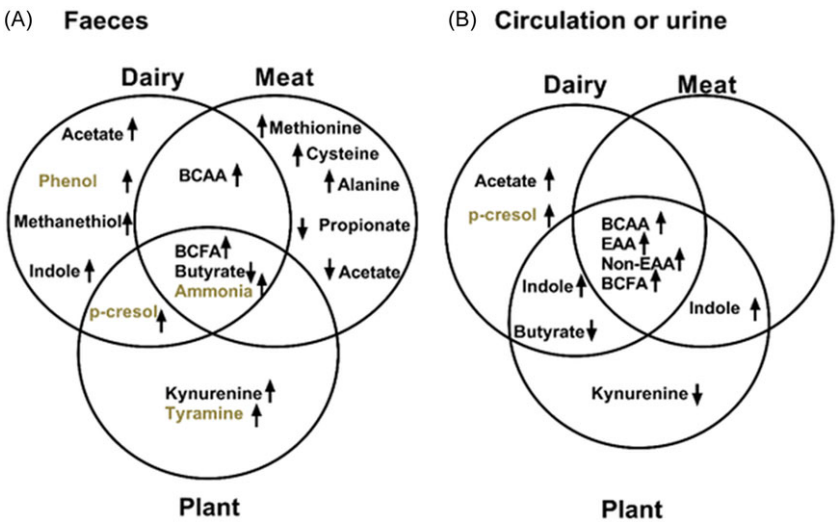

Figure 2. Impact of protein quality on the metabolites in (A) faeces and (B) circulation or urine. The direction of change is shown by arrows, as increased (↑) or decreased (↓). Metabolites highlighted in red colour are known to cause unhealthy outcomes in humans. BCAA; branched-chain amino acids; BCFA, branched-chain fatty acids; EAA; essential amino acids.

In exploring the mechanisms for the physiological outcomes of HPD intake, the post-prandial increase in circulatory levels of AA including BCAA is notable because their increase has been associated with increased satiety in human subjects, in particular following WP consumption compared with casein intake. The effect can be related to increased circulatory levels of satiety related hormones, namely cholecystokinin, (GLP)-1 and glucose-dependent insulinotropic polypeptide [101]. Whilst these data have emerged from acute challenges, the long-term intake of HPD does not appear to cause changes in energy intake in humans, suggesting that there are other mechanisms at play [135]. In this regard, the increased availability of indole in the gut lumen by dairy protein intake is interesting because this metabolite and its derivatives are known to increase the release of GLP-1 from enteroendocrine cells [69], and the activity of GLP-1 has been linked to roles beyond the reduction in food intake to include effects on adiposity [136]. In addition, and separate from effects on GLP-1, indoles and their derivatives have a direct impact on adiposity, reducing adipogenesis and increasing thermogenesis [69], and their detection in urine following dairy (and plant) protein, presumably by the crossover from circulation, supports circulatory effects. Given that BCFA have been associated with a reduction in body weight [75], it is not surprising that these should also increase in circulation following HPD intake (Fig. 2). The data suggest that indole and BCFA generated by HPD intake may contribute to the reduction in body weight through effects on intake, effects on energy expenditure and/or direct effects on lipid metabolism. These metabolites could account, at least in part, for the greater impact of dairy proteins on metabolic health compared with other sources of proteins. In contrast to body weight and adiposity, the effect of HPD on insulin sensitivity is inconstantly reported [14,21,137,138]. This may be due in part to increased circulatory levels of BCAA and increased faecal and circulatory levels of *p*-cresol and its derivatives, which are known to reduce insulin sensitivity [89,90], counterbalanced by the increased levels of acetate detected mainly following dairy protein intake. Whilst HPD intake is known to reduce or cause no change in butyrate and propionate levels, the increased acetate level in faecal matter is significant because of important roles of these SCFA in energy balance regulation and insulin sensitivity [139–141]. Overall, it is clear that proteins from different sources produce common and distinct metabolites, and their unique mechanisms of actions in the gut and/or via circulation presumably underlie the differences in physiological and metabolic outcomes of HPD.

Future directions

There are limited data on the effect of high protein intake on the composition and functional potential of the gut microbiota. Further studies are also needed to ascertain how plant proteins other than soy and gluten influence the nutrients and metabolite profiles in the gut, given the increased focus on these proteins as a sustainable production source for human consumption [142]. Extending these lines of investigation, work is also needed to clarify the role of sex, since this parameter influences the protein quantity consumed, the composition and the functional potential of gut microbiota and physiological and metabolic parameters [143–145]. While the focus of our review was on human data, cross-species investigations can provide a greater understanding of the role played by nutrients and metabolites identified here as potential mediators of metabolic health effects of HPD. These studies could involve the transfer of faecal matter from humans to other species such as rodents within each sex and/or supplementation or depletion of the nutrients or metabolites in the diet to ascertaining their biological significance.

Conclusions

The amino acids derived from dietary proteins play important roles in physiological processors and, in turn, in metabolic health and, in some instances, in the pathophysiology of metabolic disorders. This functional relationship extends to include metabolites formed in the gut by the activity of the microbiota. A comparison of HPD, which included the limited number of studies on plant proteins (soy and gluten), revealed similarities and differences in the metabolite profiles in faeces and circulation/urine, highlighting the contrasting gut versus circulatory effects of protein source within HPD. This understanding will help to elucidate the complex mechanisms of action of HPD and, in turn, improve the efficacy of the interventions.

https://doi.org/10.1017/S0954422424000374 Published online by Cambridge University Press

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