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Review article

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Effects of dietary fibre on metabolic health and obesity

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Abstract

Obesity and metabolic syndrome represent a growing epidemic worldwide. Body weight is regulated through complex interactions between hormonal, neural and metabolic pathways and is influenced by numerous environmental factors. Imbalances between energy intake and expenditure can occur due to several factors, including alterations in eating behaviours, abnormal satiation and satiety, and low energy expenditure. The gut microbiota profoundly affects all aspects of energy homeostasis through diverse mechanisms involving effects on mucosal and systemic immune, hormonal and neural systems. The benefits of dietary fibre on metabolism and obesity have been demonstrated through mechanistic studies and clinical trials, but many questions remain as to how different fibres are best utilized in managing obesity. In this Review, we discuss the physiochemical properties of different fibres, current findings on how fibre and the gut microbiota interact to regulate body weight homeostasis, and knowledge gaps related to using dietary fibres as a complementary strategy. Precision medicine approaches that utilize baseline microbiota and clinical characteristics to predict individual responses to fibre supplementation represent a new paradigm with great potential to enhance weight management efficacy, but many challenges remain before these approaches can be fully implemented.

Sections

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Key points

- Obesity is a complex chronic progressive disease characterized by excess body weight and dysregulation in enteroendocrine and neurohormonal signalling pathways favouring increased appetite and energy storage.
- Therapeutics based on the manipulation of enteroendocrine pathways in the gastrointestinal tract are the most efficacious for weight loss and improving metabolic function.
- Prospective and epidemiological studies have demonstrated associations between fibre consumption and metabolic health, highlighting the role of the gut microbiota in linking dietary intake of fibre with beneficial effects.
- Microbiota-derived metabolites, including short-chain fatty acids, indole derivatives and bile acids, have been implicated in the pathogenesis of obesity and metabolic dysregulation.
- Heterogeneity exists between fibres in terms of their chemical and physical structures, which determines the effects of fibre on the gastrointestinal tract, the gut microbiota and energy homeostasis.
- Increased consumption of dietary fibre has the potential to induce structural, physicochemical and gastrointestinal site-specific benefits that are relevant for the treatment of obesity and metabolic syndrome.

Introduction

The obesity epidemic and associated rise in metabolic dysfunction together represent perhaps the greatest threats to human health of the twenty-first century[1]. World Health Organization (WHO) global data estimate that approximately 13%, or nearly 650 million, of the adult population of the world is currently affected by obesity[2]. To combat the epidemic, a pledge to achieve a net-zero increase in obesity prevalence from 2010 to 2025 was adopted in 2013 by the WHO's Global Action Plan for the Prevention and Control of Non-Communicable Diseases. Despite this relatively modest target, no country, to date, has been able to flatten the alarming trend. Worryingly, US models project that by 2030, one in two adults will be living with obesity, and nearly one in four adults in the USA are expected to be affected by severe obesity with a body mass index of >40 kg/m^2 (ref. 3). These figures highlight the critical need to pursue novel therapies that uniquely harness the complex pathways underlying obesity and metabolic syndrome to promote weight loss and regulation of metabolism and the immune system.

In this Review, we discuss the diverse hormonal, neural and metabolic mechanisms that underlie the obesity epidemic through the lens of two emerging therapeutic modalities: the gut microbiota and dietary fibre. Understanding current challenges and mechanisms underlying these promising strategies will help to usher in a new frontier for precision medicine and nutrition in metabolic disease.

Pathophysiology of obesity

Obesity is a complex chronic progressive disease characterized by excess adiposity and dysregulation in enteroendocrine and neurohormonal signalling pathways favouring increased appetite and energy storage[4,5]. Obesity has also been described as a chronic low-grade systemic inflammation with increased levels of circulating pro-inflammatory cytokines that negatively affect the central nervous system (CNS) and all organs involved in energy and metabolic homeostasis[6]. An increase in the size of the hypothalamus seen in individuals with obesity has been suggested to be owing to hypothalamic inflammation, which would serve to exacerbate the dysregulation of energy homeostatic mechanisms[7]. Increased visceral adipose tissue and the gastrointestinal tract seem to be the dominant contributors to systemic inflammation. A large body of evidence from animal models of obesity supports a role for increased amounts of gut microbiota-derived lipopolysaccharides entering the systemic circulation through either enhanced paracellular movement and/or via the transcellular route through chylomicron transport, resulting in the initiation of numerous pro-inflammatory pathways throughout the body, further propagating weight gain[8–10]. Although evidence from human studies is less clear than results obtained from animal models regarding an association between gut-derived lipopolysaccharides and obesity, several findings in humans have linked increased systemic lipopolysaccharides with obesity, particularly with metabolic disease risk associated with obesity[11,12]. Furthermore, findings from some human studies have shown that high levels of postprandial endotoxaemia precede the development of type 2 diabetes[13,14], suggesting a potential causative role.

Diet-based strategies: focus on fibre and gut microbiota

Increasing dietary fibre consumption has garnered extensive attention as a diet-based therapeutic for obesity owing to an extensive body of work in both animal models and humans demonstrating the benefits of fibre intake on host metabolism and weight loss[15–17]. Dietary fibres are carbohydrate polymers and oligomers that resist digestion by enzymes encoded in the mammalian genome; they reach the proximal colon in which they undergo different rates and degrees of saccharolytic fermentation by the gut microbiota, which is dependent on the fibre structure. The physiological benefits of fibre are diverse and dependent on both their physicochemical properties and the amount consumed, with the recommended dietary allowance for dietary fibre being 14 g per 1,000 kcal (25 g per day for adult women and 38 g per day for adult men). However, individuals consuming a Western-style diet typically consume less than 15 g per day of fibre or around half of the recommended amounts[18]. Because of this, the dietary guidelines for Americans have identified fibre as a nutrient of concern owing to this underconsumption.

Control of energy homeostasis

Dietary fibre has numerous effects on host physiology and energy balance. Under normal physiological conditions, energy homeostasis is tightly controlled through enteroendocrine and neurohormonal signalling pathways that regulate eating behaviour and energy storage. Beyond the production of insulin and glucagon from the pancreas, gastrointestinal and adipose tissues also generate signals primarily integrated within the hypothalamus to regulate food intake and energy expenditure[19]. Many of these are small, relatively short-lived enteroendocrine hormones released by specialized gastrointestinal enteroendocrine cells (EECs) throughout the gastrointestinal tract in response to nutrients and other signals[4]. These peptides act locally in the gastrointestinal tract and on distant organs, orchestrating the maintenance of energy homeostasis, including hunger, satiety, gut barrier integrity, gut transit, glycaemic control and overall energy balance[4]. Functions of

EEC-derived peptides can be broadly categorized by their orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) properties[20]. Cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP1), glucose-dependent insulinotropic polypeptide (GIP) and oxyntomodulin are anorexigenic hormones predominantly produced by EECs of the small intestine and released postprandially to induce satiety and reduce food intake through independent mechanisms, as described in Table 1. Ghrelin, released from the stomach, and insulin-like factor 5 (INSL5), released from EECs in the colon, act as orexigenic signals[21,22]. Leptin and adiponectin are released from

Table 1 | Major gut and adipose-derived hormones and their main effects on energy homeostasis

Hormone	Primary release site	Receptors and location	Molecular actions	Functional actions
Leptin[222]	Adipose tissue	Leptin receptors (brain, liver, pancreas, heart, perivascular intestinal tissue, immune cells)	↑POMC neurons ↓ AgRP–NPY neurons	↑Satiety Regulates energy storage
Adiponectin[223]	Adipose tissue	Adiponectin receptor (AdipoR1 and AdipoR2) (liver, muscle, adipose tissue, brain, heart, immune cells)	↑Neurogenesis ↓Gluconeogenesis ↓Lipogenesis ↑Glycolysis ↑Fatty acid oxidation ↑Glucose uptake ↑Insulin sensitivity	↑Satiety ↓Inflammation
Ghrelin[22]	Stomach	Growth hormone secretory receptors (stomach, intestine, pituitary, pancreas, vasculature, adrenal, brain, thyroid, heart, immune cells)	↑Glucagon secretion ↓Insulin secretion ↓POMC neurons in ARC nucleus ↑AgRP–NPY neurons ↓Lipid oxidation in adipocytes ↑Lipogenesis in adipocytes ↑Brain reward centres ↓Pro-inflammatory cytokine secretion	↑Gastric emptying ↑Gut motility ↑Food intake ↓Inflammation
GLP1 (ref. 224)	L cells in the ileum and colon	GLP1 receptor (pancreas, heart, kidneys, blood vessels, liver, lungs, CNS, stomach, intestine)	↑Insulin secretion ↓Glucagon secretion ↓Rate of nutrient absorption ↑Somatostatin secretion ↑Pancreatic β-cells ↑Neurogenesis ↑POMC neurons in the ARC nucleus ↓AgRP–NPY neurons	↓Gastric emptying ↓Gut motility ↓Appetite ↓Food intake ↓Inflammation
Oxyntomodulin[225]	L cells in the ileum	GLP1 receptor Glucagon receptor (pancreas, brain, stomach, intestine)	↑Insulin secretion ↑Glucagon secretion ↑POMC neurons in the ARC nucleus ↓ AgRP–NPY neurons ↑Hepatic gluconeogenesis ↑Lipolysis ↑Neuroprotection	↓Gastric emptying ↓Gut motility
Peptide YY[4]	L cells in the ileum and colon	Neuropeptide Y2 receptors (stomach, intestine, pancreas, adipocytes, brain)	↓Pancreatic and intestinal secretion ↓ AgRP–NPY neurons	↑Satiety ↓Gastric emptying ↓Gut motility
CCK[4]	I cells in the duodenum	CCK1 and CCK2 (pancreas, brain, gastric)	↓Gastric acid secretion	↓Gastric emptying ↓Food intake ↑Satiety
Glucose-dependent insulinotropic polypeptide[226]	K cells in the duodenum and jejunum	Gastric inhibitory polypeptide receptors (pancreas, CNS, adipose tissue, bone, heart, immune cells, adrenal, blood vessels)	↑Insulin secretion ↑Glucagon secretion ↑Lipid deposition in adipocytes ↑β-cell proliferation ↓Gastric acid secretion	↓Food intake ↓Inflammation ↓Oxidative stress ↑Neurogenesis
Insulin-like factor 5 (refs. 21,227)	L cells in the colon	G protein-coupled relaxin–insulin-like family peptide receptor 4 (brain, pituitary, pancreas)	↑Insulin secretion ↑GLP1 release ↑Hepatic glucose production	↑Food intake

AgRP, agouti-related peptide; ARC, arcuate nucleus; CCK, cholecystokinin; CNS, central nervous system; GLP1, glucagon-like peptide 1; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

adipose tissue and contribute to the regulation of eating behaviour and energy homeostasis. However, circulating levels of gut-derived appetite hormones do not necessarily correlate with energy intake[23,24]; furthermore, some studies have shown that hormonal responses in humans to acute diet challenges do not exhibit substantial adaptation to long-term differences in macronutrient intake[23]. These findings suggest that other factors, such as food energy density and the rate at which food is ingested, along with the palatability of the food, might contribute to increased energy intake in humans[24].

The CNS is an important site of action for several gut-derived hormones and a central regulator of hunger, satiety and energy storage through the integration of brain networks involving autonomic hypothalamic circuits, cortical executive circuits and corticolimbic reward pathways[25,26]. Within the arcuate nucleus of the hypothalamus are two separate and opposing neuronal populations: the orexigenic NPY–AgRP neurons (co-expressing neuropeptide Y and agouti-related peptide) and the anorexigenic POMC–CART neurons (co-expressing pro-opiomelanocortin and cocaine-regulated and amphetamine-regulated transcript)[27]. NPY–AgRP neurons are activated by energy deficits and signals such as ghrelin to stimulate food intake and inhibited by the presence of nutrients in the gastrointestinal tracts and satiation signals such as CCK and PYY[28]. By contrast, activation of POMC–CART neurons by signals such as leptin results in a suppression of feeding and altered glucose metabolism due to the release of α-melanocyte-stimulating hormone, which binds to brain melanocortin receptors[26]. Another identified population of GABAergic neurons in the hypothalamus that express prepronociceptin[27] has been shown to mediate hyperphagia and weight gain in mice[29] and has been postulated to have a substantial role in energy regulation[30]. There is evidence in adults with obesity that an impairment in post-ingestive nutrient signalling within the brain contributes to overeating and obesity. In a single-blinded, randomized, controlled, crossover study in 30 individuals with healthy weight and 30 individuals with obesity, results showed that individuals with obesity exhibited both global and nutrient-specific impairment in brain responses to ingested nutrients[31]. Together, gut and adipose-derived hormones and the CNS are fundamental targets for the therapeutic manipulation of energy homeostasis.

Seminal work over the past two decades has demonstrated an obesity metabolic profile characterized by increased levels of serum CCK, amylin, leptin, INSL5 and insulin, alongside decreased levels of ghrelin, GLP1 and PYY in humans[32]. Importantly, these plasma peptide levels were found to normalize with a resolution of obesity following bariatric surgery, thereby emphasizing their role as key therapeutic targets[33–35]. However, what remains to be clarified is whether these enteroendocrine and neurohormonal changes and endotoxaemia occur as a consequence of obesity or whether they are truly causal.

Pharmaceutical-based therapies

Drugs that target the endogenous neuroendocrine mechanisms underlying obesity are the most effective long-term pharmacotherapy for obesity and metabolic syndrome[36]. GLP1 agonists (semaglutide, liraglutide and sitagliptin) have demonstrated good efficacy for sustained weight loss and improvements in cardiometabolic function[37,38]. Clinical trials using double and triple hormone receptor agonists that act on GIP, GLP1 and/or glucagon receptors have shown exceptional efficacy in weight loss and improved metabolic parameters[39,40]. However, the use of these incretin-based therapies is currently limited by high costs, limited health-care coverage and problems with gastrointestinal tolerance. In addition, concerns have been raised about the long-term effects of these drugs on intestinal function[41,42]. Because of these limitations, there is growing interest in developing alternative incretin-targeted therapies, especially lower-cost dietary-based approaches, for treating obesity and preventing the onset of obesity-linked metabolic dysfunction by normalizing levels of incretin hormones such as GLP1 and GIP.

Fibre consumption and metabolic health

Several large prospective studies have demonstrated associations between fibre consumption and metabolic health, with current work highlighting the role of the gut microbiota in linking dietary intake of fibre with beneficial effects[43–51]. Evidence is rapidly accumulating that the gut microbiota profoundly affects all aspects of energy homeostasis through diverse mechanisms involving effects on immune, hormonal and neural systems[52], and that gut dysbiosis, or an abnormal composition of gut microbial taxa, might contribute to a disturbed energy metabolism through effects on adipose tissue, muscle and the liver[53]. Furthermore, gut microorganisms in both human studies and mouse models have been recognized as having a role in developing chronic low-grade inflammation and in the pathogenesis of insulin resistance[54,55]. Patients with obesity and metabolic syndrome have increased bacterial loads in plasma, the liver and omental adipose tissue, suggesting a breakdown of gut barrier function enabling bacterial translocation and resultant expansion and recruitment of pro-inflammatory immune cells into tissues[56,57]. Generally, studies have shown that individuals with obesity have decreased bacterial diversity and gene richness along with functional microbial metabolic alterations and specific changes in microbial profiles that are associated with host metabolic dysregulation[58–62]. A systematic review of 60 case–control studies evaluating the microbiota in patients with obesity and metabolic disorders (n = 4,551) compared with lean, healthy controls (n = 4,357) has identified *Faecalibacterium*, *Akkermansia* and *Alistipes* to be associated with a normal-weight phenotype, whereas Proteobacteria was the most consistently increased phylum seen in patients with obesity[58].

Fermentation of fibres by the gut microbiota results in the release of numerous metabolites, including short-chain fatty acids (SCFAs), phenolic and indole compounds, branched-chain fatty acids, lactate, succinate and various gases (hydrogen, carbon dioxide, methane, nitric oxide and sulfur-containing compounds). Although many of these metabolites benefit the host, others are considered toxic and detrimental to metabolic health[49,54,63–66]. The pathways and precursors used by gut microorganisms to produce metabolites are highly adaptable to dietary intake; therefore, targeting microbial metabolic function with specific dietary interventions such as fibre represents a key modifiable factor to improve metabolic dysfunction and obesity.

Short-chain fatty acids

SCFAs are the primary metabolites produced through fermentation from microbial-accessible fibres, with the relative molar ratio in the human gut lumen being ~60:20:20 for the primary SCFAs, acetate:propionate:butyrate[67]. SCFAs can mediate diverse local and peripheral effects through interactions with G protein-coupled receptors and by inhibiting histone deacetylation, resulting in epigenetically regulated changes in gene expression[68–70] (Fig. 1). Butyrate is used in the colon by colonocytes as an energy source, whereas propionate and acetate are absorbed through the portal vein to the liver in which propionate is primarily used as a substrate in gluconeogenesis and lipogenesis; conversely, acetate reaches the systemic circulation in substantially higher amounts[71].

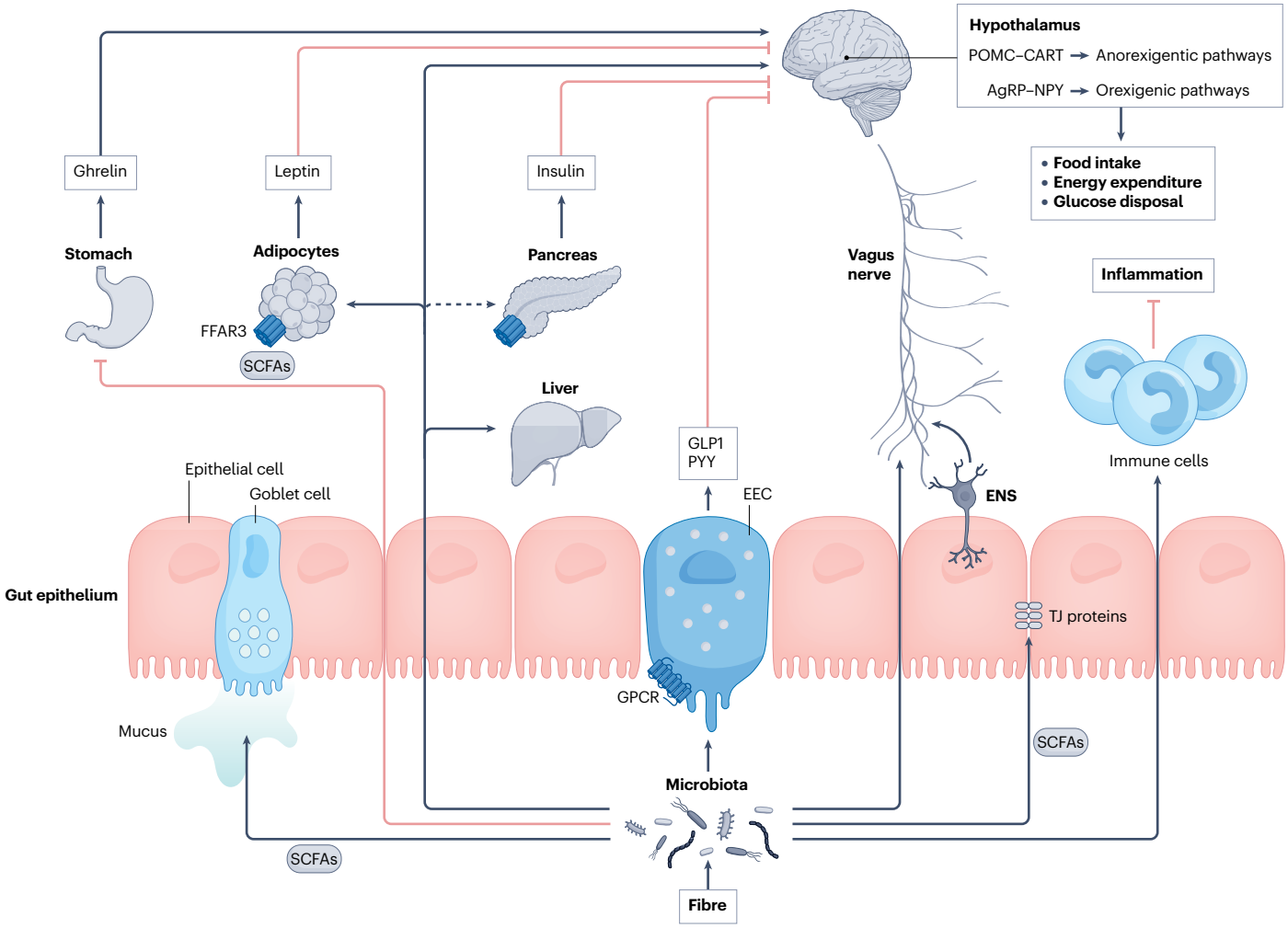

Fig. 1 | Mechanisms of action of short-chain fatty acids on energy homeostasis. Short-chain fatty acids (SCFAs) are produced from microbiota-accessible carbohydrates through fermentation by gut microbiota. Locally in the gut, SCFAs stimulate the secretion of glucagon-like peptide 1 (GLP1) and peptide YY (PYY) from intestinal enteroendocrine cells (EECs) and mucus from goblet cells and modulate immune cell function. SCFAs are used by colonocytes for energy and promote tight junction (TJ) protein expression to maintain gut barrier function. SCFAs interact with the enteric nervous system (ENS) and central nervous system to modulate gut motility and brain function. In distal organs, SCFAs modulate leptin production by directly interacting with free fatty acid receptor 3 (FFAR3) on adipocytes and inhibiting ghrelin-mediated cell signalling. SCFAs modulate hepatic metabolic and inflammatory function. AgRP, agouti-related peptide neuron; CART, cocaine-regulated and amphetamine-regulated transcript; GPCR, G protein-coupled receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin neuron.

It has been proposed that along with the well-documented effects of fibre on gastric emptying and inhibition of digestion, increasing fibre content in the diet might help in weight loss and glucose metabolism through the production of SCFAs[72,73]. A large body of in vitro and mouse studies has shown that SCFAs directly stimulate the secretion of GLP1 and PYY from enteroendocrine cells in the gut through the G protein-coupled receptors GPR41 and GPR43 (also known as FFAR3 and FFAR2)[70,74–77]. Supporting this mechanism in humans, in vivo studies have demonstrated that acute rectal infusions of acetate[73,78] or SCFA mixtures[72,79] increased systemic levels of PYY and GLP1. Furthermore, a human study has shown that in 20 healthy adults, acute oral intake of inulin-propionate ester increased the levels of systemic PYY and GLP1 and reduced food intake in comparison with inulin alone, suggesting a role for increased levels of propionate in modulating glucose metabolism[80].

SCFAs can also interact directly with the enteric nervous system, allowing for direct signalling between gut-derived SCFAs and the brain[81]. Mouse studies have demonstrated that SCFA administration suppresses appetite and energy intake through CNS-related mechanisms[82–85]. Furthermore, in vitro and mouse studies have shown that SCFAs can enhance the blood–brain barrier through various mechanisms, including reducing oxidative and pro-inflammatory pathways and increasing tight junction proteins[86–88]. In mouse studies, acetate and butyrate have been shown to cross the blood–brain barrier and stimulate the vagus nerve and hypothalamus, thereby regulating food intake and satiety[83,89]. Human studies using functional magnetic resonance imaging have

demonstrated that colonic propionate delivery reduced activity in brain regions linked with food cravings and reduced food intake[90]. However, although there are measurable concentrations of SCFAs found in the human brain and cerebrospinal fluid[91,92], uptake of circulating SCFAs by the human brain seems to be limited[93], suggesting that some of the documented effects of circulating SCFAs on brain activity might be owing to SCFA-induced interactions with immune and endocrine systems rather than direct interactions within the brain[94].

A decrease in the ability of adipose tissue to store lipids and buffer postprandial fatty acid fluxes has a role in the development of insulin resistance in humans through the resultant increase of fat storage in non-adipose tissues[95]. In cultured mouse and human adipocytes, acetate and propionate have been shown to inhibit lipolysis and enhance adipogenesis in a G protein-coupled receptor-dependent manner[96–98], thus potentially reducing systemic lipid circulation and fat accumulation in non-adipose tissue and improving insulin sensitivity. In human studies, rectal administration of SCFAs has demonstrated an inhibition of whole-body lipolysis[72], and in human adipocytes cultured in vitro, SCFAs have also been shown to stimulate leptin secretion[99,100]. SCFAs can also reduce pro-inflammatory cytokine secretion from human explant adipose tissue, therefore potentially contributing to a reduction in systemic low-grade inflammation associated with obesity[101,102].

However, despite this large body of work supporting a potential beneficial role for SCFAs in modulating weight gain and host metabolism, there is still a great deal of uncertainty in the field regarding the role of SCFAs in obesity, as many of the effects seen in primarily mouse models cannot be replicated in human studies[103,104]. Indeed, both increased[105–109] and decreased[110,111] levels of SCFAs have been reported to be associated with obesity. However, most human studies measure SCFAs in stool samples, which reflect the net result of production, absorption and utilization, and do not necessarily reflect systemic levels, which might be more relevant. Supporting this concept, in a cross-sectional study of 160 participants with BMI between 19.2 kg/m^2 and 41 kg/m^2 and with normal or impaired glucose metabolism, Muller and colleagues[112] have demonstrated that systemic SCFA levels negatively associated with fasting glycerol, triacylglycerols and free fatty acids and positively associated with fasting GLP1, whereas faecal levels showed no associations with any of these parameters. In addition, Muller and colleagues have also shown a negative association between circulating acetate and insulin sensitivity, whereas propionate had a positive association with insulin sensitivity[112]. Overall, the available human in vivo data examining the physiological effects of SCFA on host metabolism are still limited. Owing to the complexity underlying interactions between fibre, the gut microbiota and human metabolism, it remains unclear as to what beneficial effects of increasing fibre intake are due to microbial metabolism and production of certain metabolites, such as SCFA, or to other well-documented effects of fibre, including alterations in transit time, nutrient absorption, or faecal bulking and binding.

Lactate and succinate metabolism

Beyond SCFAs, gut microbiota also produces lactate and succinate during fibre fermentation[82,113,114]; however, these metabolites are often considered intermediates that support microbial production of SCFAs, such as acetate and propionate[115]. Lactate and succinate are present in blood and tissues at low concentrations[116], with increased levels detected in individuals with obesity and metabolic syndrome when compared with people without obesity[117,118]. Lactate is a host-derived product of glucose metabolism and can increase in the blood when flux through glycolysis exceeds mitochondrial oxidation[116]. Thus, it could be considered a biomarker of impaired glucose metabolism. In addition, in vitro and mouse studies have demonstrated that lactate can function as an active signalling molecule in regulating adipocyte function and metabolism, as well as reducing pro-inflammatory responses in adipose tissue and immune cell function through both GPR81-dependent and GPR81-independent mechanisms[119–121]. Owing to these beneficial findings, it has been suggested that targeting GPR81 through increasing fibre intake and resultant lactate production might represent a new therapeutic target in obesity and metabolic disorders.

Although succinate has traditionally been considered a metabolite of the tricarboxylic acid cycle, current work has demonstrated succinate to act as a metabolic signal involved in stress and tissue damage[122]. Low levels of succinate are found in the gut lumen, but studies in mice have shown that the concentration of extracellular succinate increases with increased fibre intake[113]. Succinate can act as a signalling molecule by binding to succinate receptor 1 (SUCNR1; also known as GPR91) on several different cell types, including adipocytes and immune cells[123,124]. In humans, negative correlations between plasma succinate levels, obesity and impairments in glucose metabolism were reported in cross-sectional studies[118,125]. Succinate was further reported to act as a thermogenic activator[126] and browning agent[127], as well as having an inhibitory effect on lipolysis[128]. A study using adipocyte-specific *Sucnr1*-knockout mice and isolated human adipocytes from people with obesity has identified a novel function for succinate-induced metabolic effects through regulating the circadian clock and leptin expression in adipocytes via interaction with SUCNR1 (ref. 129). There is also strong evidence that succinate–SUCNR1 signalling can act as a link between metabolic stress and inflammation[130]. Using human primary macrophages, Trauelsen and colleagues[131] have shown that extracellular succinate could induce an anti-inflammatory profile in macrophages. Interestingly, obesity has been linked with high levels of systemic succinate but reduced expression of the succinate receptor in adipose-tissue resident macrophages[130], which might help to explain why patients with obesity are often unable to control inflammation. In a mouse model, it has been shown that increased succinate produced by gut microbiota in response to fructooligosaccharide (FOS)-supplemented diets improved glycaemic control and energy metabolism by acting as a substrate for intestinal gluconeogenesis and subsequently reducing hepatic glucose production[132]. As more research is done examining succinate-induced physiological effects, it might help to illuminate the role of extracellular succinate and its local and systemic modes of action in modulating host metabolism and how best to target these pathways.

Intestinal gases

Microbial fermentation of fibre further produces gases such as H_2, CO_2 and CH_4. The effects of intestinal gases on human metabolism are poorly understood at the present time as most measurements of intestinal gases are usually indirect or highly invasive[133]. However, increased gas production during fibre fermentation can induce undesirable symptoms and is one of the main reasons underlying an individual's intolerance of high levels of fibre. Thus, dietary manipulations of fibre and macronutrient intake are used in clinical practice to alleviate gastrointestinal symptoms in patients with gastrointestinal disorders linked with gas production. More research to increase knowledge of the effect of gases in the intestinal tract on host physiology and metabolism would help in the design of therapies aimed at altering gas production.

Regulation of the gut–brain axis

The gut–brain axis constitutes a bidirectional communication pathway between the intestinal tract and the CNS and involves the enteric nervous system, the vagus nerve, the endocannabinoid system, and neuroimmune and neuroendocrine pathways[134,135]. Metabolites produced in the gut can modulate nervous system activity directly by acting locally on enteric neurons or vagal and sympathetic afferent nerve terminals or be transmitted to the brain via systemic circulation[136]. In addition, the gut microbiota produces several neurotransmitters, including serotonin, dopamine, acetylcholine and GABA, which can act within the enteric nervous system or the CNS through the vagus nerve[137]. A mouse study has shown that fragments of bacterial peptidoglycan called muropeptides interacted with NOD2 on hypothalamic neurons in the brain that regulate food consumption and body temperature, therefore causing an excessive hedonic intake of food by overriding homeostatic regulation of food take[138]. de Wouters d'Oplinter and colleagues[139,140] performed faecal microbiota transplantation (FMT) from lean or obese donor mice into lean recipient mice and demonstrated that FMT from obese donor mice could induce a hypofunctional brain reward system in lean recipients that was shown to be causally linked with a microbial-produced metabolite, 3-3′-hydroxyphenyl-propanoic acid, which affected dopaminergic and opioid markers in the brain responsible for compulsive behaviour and motivation regarding food. Further analyses have demonstrated that levels of *Akkermansia*, *Muribaculum*, Prevotellaceae and *Parabacteroides* correlated with 3-3′-hydroxyphenyl-propanoic acid plasma levels[139].

Together, these studies have demonstrated that the gut microbiota interacts with the host to modify metabolism through diverse autonomic and somatic neuroendocrine pathways and that substantial alterations are seen in these interactions in patients with obesity (Fig. 2). Indeed, each of these pathways represents a potential avenue that could be modulated through dietary interventions such as increasing fibre intake.

Dietary fibres: heterogeneous groups of non-digestible carbohydrates

Similarities and differences between dietary fibres

An appreciation of mechanisms that determine the physiological effects of fibre along the gastrointestinal tract, including the role of the gut microbiota, will support the development of efficacious fibre-based and complementary strategies for regulating immune, metabolic and body weight homeostasis. Common features shared among all dietary fibres is that their oligomeric or polymeric carbohydrate structures resist digestion in the small intestine and, if isolated and synthesized, show physiological benefits to human health[141]. However, tremendous heterogeneity exists between fibres regarding their chemical and physical structures and, therefore, physicochemical properties (Table 2). Linear carbohydrate structures with longer, unbranched chains, such as cellulose, are often insoluble in aqueous solvents and accessible to fewer gut microorganisms due to a (semi)crystalline crosslinked network that impedes fermentation by the human gut microbiota[142,143]. By contrast, oligomeric structures and polymers with mixed-linked or branched chains are generally soluble in water and more accessible to gut microorganisms[144]. Soluble fibres with increased degrees of polymerization and, therefore, high-molecular-weight fibres and microfibrillated insoluble fibres also tend to entrap water and other compounds within and between polymers, increasing viscosity in a concentration-dependent manner[142]. Molecular weight also influences microbial fermentation and rates of SCFA production; however, an association between molecular weight and fermentation are dependent on fibre structure and are not necessarily linear[145].

Although fibres are typically categorized based on physicochemical properties such as solubility, viscosity, binding capacity or fermentability, such classifications do not reflect the full spectrum of properties exhibited by discrete fibre structures. For instance, arabinoxylan oligomers or simple-structured polymers from grasses such as sorghum or rice are readily fermented, whereas complex-structured arabinoxylans are either fermented slowly throughout the colon (that is, corn bran) or poorly accessible to the human gut microbiota (that is, psyllium husk)[146,147]. Fibres are also seldom found isolated in nature. However, instead, they form complex three-dimensional extracellular matrices in foods with synergistic interactions between fibre types and other compounds such as phenolics and proteins[148,149]; although how these synergistic interactions affect gut microbiota and health remains unclear. Thus, an appreciation for the structure and physicochemical properties of fibres, especially once isolated or synthesized, is essential for more precise applications of fibres in the management of obesity.

Physiological effects along the gastrointestinal tract

Proximal gastrointestinal tract. The physicochemical properties of dietary fibres influence their behaviour along the gastrointestinal tract, which determines their effects on inflammation, metabolism and energy homeostasis (Fig. 3). Starting in the mouth, viscous fibres and large fibre particles such as cereal brans can prolong mastication and oro-sensory exposure by achieving a more firm and chewy food matrix, which alters endocrine cephalic phase responses towards satiation and reduced energy intake[150,151]. Fibres such as inulin, FOS and microfibrillated fibres can also maintain organoleptic characteristics (that is, sweetness and mouthfeel) when calorie-dense sugars and fats are reduced in food applications[152,153]. Fibre matrices in whole foods further act as barriers to digestive enzymes such as salivary amylase[148,149]. Maintenance of these three-dimensional plant cell wall structures during mastication influences the bioavailability of intracellular components such as starch along the gastrointestinal tract[154].

Fibres that increase chyme viscosity, such as higher-molecular-weight mixed-linked or branched polymers and microfibrillated fibres, promote gastric distension and delay gastric emptying. Increased digesta viscosity within the small intestinal lumen further delays nutrient absorption by limiting nutrient diffusion towards the mucosa[155] and the activity of endogenous digestive enzymes[156], which further slows proximal gastrointestinal transit by triggering the ileal break. Beyond viscosity, certain fibre structures can bind to or entrap compounds, such as macronutrients and micronutrients, phenolics and bile acids, which delay or prevent small intestinal absorption[149,154]. Bile-acid binding to dietary fibres interferes with the enterohepatic circulation of bile acids and impedes micelle formation, reducing the absorption and availability of lipids[157]. In addition, increased delivery of fibre-bound bile acids into the large intestine might result in increased conversion of primary bile acids into secondary bile acids by microbial bile salt hydrolases and 7α-dehydroxylase[158]. Studies in humans and mice, along with in vitro experiments using isolated human islets and mammalian cultured cells, have demonstrated that these secondary bile acids act as signalling molecules through several membrane and nuclear receptors, including G protein-coupled bile acid receptors (TGR5) and the farnesoid-X-receptor, that results in increased satiety, hepatic glycogen synthesis, insulin secretion and energy expenditure in the liver, brown adipose and muscle tissues[159]. Supporting a role for bile acids in glucose metabolism, a study in individuals with obesity and type 2 diabetes

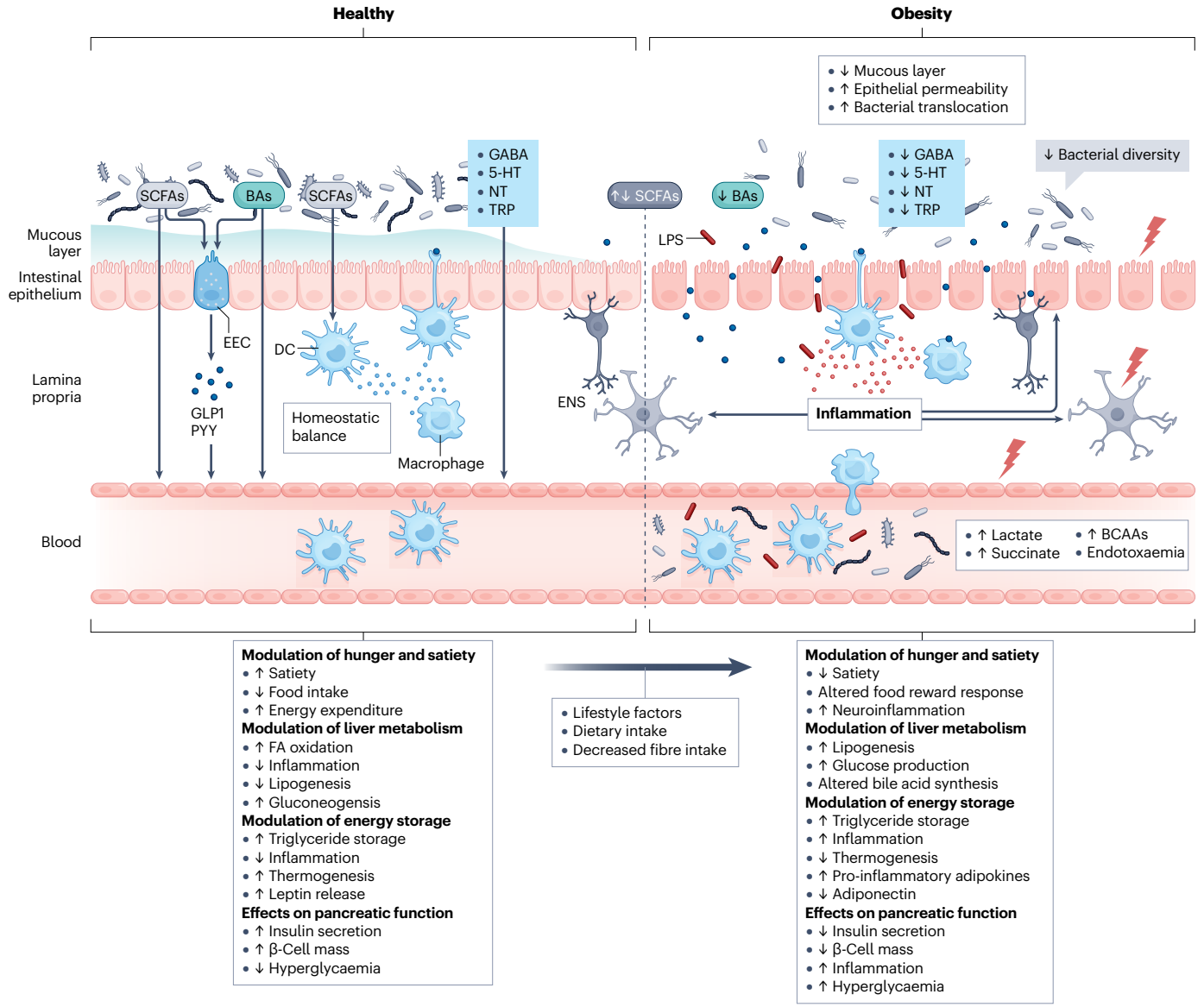

Fig. 2 | Interactions between the microbiota and the gut in obesity. The gut microbiota contributes to energy homeostasis and health by producing numerous metabolites, including short-chain fatty acids (SCFAs), lactate, succinate and secondary bile acids (BAs) that act locally and systemically on the brain, liver, adipose tissue and pancreas. Lifestyle factors, including unhealthy diets and a lack of fibre, are related to decreased bacterial diversity and associated reductions in microbial-produced metabolites. Loss of microbially produced metabolites can result in decreased enteroendocrine hormone secretion, a decrease in gut barrier function through loss of mucus and tight junctions, and an increase in inflammation. This decrease in barrier function can, in turn, lead to increased bacterial translocation and peripheral inflammatory tone throughout all the body organs. The use of dietary strategies such as fibre could beneficially affect obesity through a restoration of healthy microbiota and the production of microbial metabolites. BCAA, branched-chain amino acid; DC, dendritic cell; EEC, enteroendocrine cell; ENS, enteric nervous system; GABA, γ-aminobutyric acid; GLP1, glucagon-like peptide 1; 5-HT, 5-hydroxytryptamine; LPS, lipopolysaccharide; NT, neurotransmitter; PYY, peptide YY; TRP, trytophan metabolites.

(n = 23) has demonstrated that delivery of conjugated bile acids to the ileocolonic region decreased postprandial glucose and fasting insulin levels and increased GLP1 secretion[160].

Although poorly understood, dietary fibres might further alter resident small intestinal microbiota, which gradually increases in density from ~10^3 microbial cells per millilitre digesta in the duodenum to ~10^8 microbial cells per millilitre digesta in the ileum[161]. Such interactions were shown in a rat model to influence small intestinal nutrient sensing, particularly FOS-induced lipid sensing, which promoted the release of GLP1 from EECs to increase satiation[162]. Although precise mechanistic pathways remain to be elucidated, a large body of work in cultured cells, animal models and humans has also implicated microbial metabolites in the alteration of taste receptor expression and activity along the gastrointestinal tract, leading to altered taste preference and food

Table 2 | List of common isolated and synthesized commercial dietary fibres for use as complementary strategies in obesity and metabolic syndrome

Dietary fibres	General chemical structures	Common sources	Generalized physicochemical properties[a]		
			Solubility	Viscosity	Fermentability
Resistant dextrins					
Polydextrose	Highly branched, predominantly α-(1,6) or β-(1,6) glucose units, terminal sorbitol	Synthesized from dextrose	Soluble	Low	Slow to moderate
Resistant maltodextrin	Highly branched mixture of α-(1,6), α-(1,4), α-(1,3), α-(1,2) glucose units	Chemically modified starch	Soluble	Low	Slow to moderate
Resistant starches					
Crystalline RS (types II and III)	Linear α-(1,4) glucose units	Cereal grains, green banana, potato	Insoluble	Non-viscous	Slow to moderate
Crosslinked RS (type IV)	α-(1,4), α-(1,6) glucose units, often crosslinked with a phosphate group	Chemically modified starch	Insoluble	Non-viscous	Poor to moderate
Oligosaccharides					
Galactooligosaccharides	Varying α- or β-(1,6), (1,4), (1,3), or (1,2) galactose units, often terminal glucose	Synthesized from lactose (β-GOS), legume (α-GOS)	Soluble	Low	Fast
Fructooligosaccharides	Linear β-(2,1) fructose units, terminal glucose	Synthesized from sucrose	Soluble	Low	Fast
Xylooligosaccharides and arabinoxylooligosaccharides	Linear β-(1,4) xylose units. AXOS have side chains with primarily α-(1,2), α-(1,3), α-(1,5) arabinose units	Cereal grains, other grasses	Soluble	Low	Moderate to fast
Non-starch polysaccharides					
Microcrystalline, powdered cellulose	Linear β-(1,4) glucose units	Wood pulp, cotton and other lignocellulosic material	Insoluble	Non-viscous	Poor
Hydroxypropyl methylcellulose	Linear β-(1,4) glucose units substituted with hydroxypropyl and methyl groups	Chemically modified cellulose	Soluble	Moderate to high	Poor
Arabinoxylans	Linear β-(1,4) xylose units as a backbone with primarily α-(1,2), α-(1,3), α-(1,5) arabinose units as side chains; other monosaccharides are source dependent	Psyllium Cereal grains, other monocots	Soluble Insoluble to soluble	High Non-viscous to moderate	Poor Slow to moderate
β-Glucans	Linear or branched β-(1,3), β-(1,4) and/or β-(1,6) glucose units	Oat, barley Fungi	Soluble Insoluble to soluble	Moderate to high Non-viscous to moderate	Moderate Slow to moderate
Inulin-type fructans	Primary linear β-(2,1) and sometimes β-(2,6) fructose units, terminal glucose	Chicory, agave, sunchoke	Soluble	Low	Moderate to fast
Pectins[b]	Multiple pectic substances that are source dependent	Apple, citrus, sugar beets, other dicots	Soluble	Moderate to high	Slow to moderate
Gums and other fibres					
Alginate	Linear β-(1,4) mannuronic acid and α-(1,4) glucuronic acid units	Seaweed	Soluble	High	Poor to slow
Arabinogalactan	Linear β-(1,3) galactose units, β-(1,6) galactose and α-(1,5), α-(1,3) arabinose units as side chains	Acacia exudate, larch, component of pectin	Soluble	Low to moderate	Slow to moderate
Galactomannan[c]	Linear or slightly branched β-(1,4) mannose units with α-(1,6) galactose units as side chains	Fenugreek, guar, locust bean, tara	Soluble	Moderate to high	Slow to moderate
Glucomannan	Linear or slightly branched β-(1,4) mannose and glucose units	Konjac	Soluble	High	Slow to moderate
Xanthan gum	Linear β-(1,4) glucose units as a backbone with β-mannose–β-(1,4)–glucuronic acid–α-(1,2)-mannose side chains	*Xanthomonas campestris*	Soluble	High	Slow

Table 2 (continued) | List of common isolated and synthesized commercial dietary fibres for use as complementary strategies in obesity and metabolic syndrome

Dietary fibres	General chemical structures	Common sources	Generalized physicochemical properties[a]		
			Solubility	Viscosity	Fermentability
Gums and other fibres (continued)					
Mixed plant cell wall fibres[d]	A mix of non-starch polysaccharides with varying structures	Plant material	Variable	Variable	Variable

Further research is needed to ascertain the dose-dependent efficacy of purified fibres with discrete structures and mixtures thereof in the management of obesity and metabolic syndrome. AXOS, arabinoxylan; GOS, galactooligosaccharide; RS, resistant starch. [a]The physicochemical properties of isolated and synthesized commercial dietary fibres depend on variables such as source material and processing technology, which generate discrete fibre structures and molecular weights that determine the physicochemical properties of the ingredient. [b]Pectins are heteropolysaccharides comprising multiple pectic substances that can include arabinan, arabinogalactan, homogalacturonan, pectic galactan, rhamnogalacturonan I and rhamnogalacturonan II. [c]Partially hydrolysed guar gum is generated from the controlled enzymatic hydrolysis of guar galactomannan with β-endo-mannanase, generating a soluble, low viscous and moderately fermentable dietary fibre. [d]Several isolated dietary fibres in the market, such as oat hull fibre, citrus fibre, pea hull fibre or flaxseed mucilage, are considered mixed plant cell wall fibres, as they comprise more than one type of non-starch polysaccharide and will possess varying physicochemical properties dependent on composition and processing.

intake[163]. Finally, all dietary fibres, whether naturally occurring, isolated or synthetic, can reduce energy intake by simply replacing a portion of digestible compounds with non-digestible carbohydrates, which has relevance for lower viscous fibres capable of achieving higher levels in foods without altering organoleptic properties[142]. Collectively, nutrient absorption rates along the small intestine are hindered by increased fibre consumption through parallel, structure-dependent mechanisms, which promote satiety and attenuate postprandial glycaemic, lipidemic and inflammatory responses often dysregulated in obesity.

Supporting a role for the upper small intestine in metabolic dysregulation, randomized trials of duodenal mucosal resurfacing, which involves endoscopic hydrothermal ablation of mucosal tissue, have demonstrated durable improvements in metabolic parameters in patients with type 2 diabetes irrespective of body mass changes[164–166]. Together, these clinical responses indicate that the proximal gastrointestinal tract has a key role in regulating metabolic homeostasis and underlies its importance as a therapeutic target beyond weight loss. However, whether the distal gastrointestinal tract, including the colon, is also an effective target in humans for the treatment of obesity and metabolic remains to be answered.

Distal gastrointestinal tract and gut microbiota. Increased fibre intake equates to an expansion of unabsorbed nutrients that reach the proximal colon and are available to gut microbiota in humans. Fibres that associate with compounds in the small intestine further serve as platforms in the colon, bringing substrates and other growth factors close to the select microorganisms that utilize them[167]. Chemical and physical structures that are slowly or poorly fermented by gut microbiota, such as large fibre particles, cellulose or psyllium, serve other gastrointestinal benefits by stimulating peristalsis, mucosal secretions and resisting the reabsorption of entrapped water, which has been shown to add bulk and softens stool in humans[144]. By resisting microbial fermentation, these fibres might reduce colonic transit time, promoting the excretion of bound compounds and attenuating systemic inflammation[147]. Although fermentable fibres can also influence colonic transit time through increased microbial biomass and production of SCFAs and gases, dominant physiological effects of fibre fermentation are attributed to the structure-specific expansion of putatively beneficial microorganisms and subsequent production of SCFAs and other metabolites within the colon[167].

The arrival of fibre to the proximal colon initiates a highly complex cascade of cross-feeding interactions within a microbial consortium that collectively possesses traits for accessing, degrading and utilizing the discrete structures and metabolic by-products, ultimately enriching select members of the consortium. The fermentation cascade is initiated by primary degraders, which perform the keystone role by hydrolysing large polysaccharides to smaller polymers, oligosaccharides and sugars that become accessible to secondary fermenters[168]. Without the presence of structure-specific primary degraders, dietary fibres remain poorly accessible to gut microbiota[169]. During this process, by-products such as SCFAs, gases and other metabolites are released by primary degraders and secondary fermenters and further metabolized by metabolite utilizers, altering the pool of fermentation by-products that interact with human colonocytes[168]. Overall, multiple microbial community members are supported when fermentable fibre is consumed, which might explain why dietary patterns rich in diverse fibre structures are associated with more diverse microbial communities[170], which are considered a feature of healthy gut microbiomes[171]. However, the precise members of the consortium enriched and metabolic by-products promoted throughout the colon depend on the fibre structure, individual community and ecological factors such as colonic microenvironments. Utilizing a diet designed to deliver more dietary substrates to the colon and enhance gut microbiota (high in fibre, resistant starch, large food particle size and limited processed foods), Corbin and colleagues[172] have shown in 17 healthy adults that a specialized diet increased energy loss in faeces and resulted in lower metabolizable energy for the host compared with a Western-style diet. Although energy balance was maintained during both diets, the specialized diet reduced leptin secretion with a tendency for decreased fat mass and increased GLP1 without changes in food intake[172].

Although the predominance of by-products generated by microbial consortia during fibre fermentation occurs proximally within the colon, fermentation rates can be slowed by consuming fibres with crystalline or complex branching structures, which eases intestinal gas production and shifts SCFA outputs distally[173]. Extending SCFA distal production has been suggested to favourably influence satiety, glycaemia and energy metabolism in humans via the upregulation of enteroendocrine hormones such as PYY and GLP1 (ref. 79). Indeed, acetate administered in the distal colon increased fat oxidation and circulating PYY in six men with obesity; however, no effect was seen when acetate was administered in the proximal colon[73]. Although shifts towards increased fat oxidation and PYY production imply favourable energy metabolism, further research is needed to determine whether body weight and adiposity can be reduced through increasing fibre fermentation and production of SCFAs in the distal colon.

The expansion and extension of saccharolytic fermentation towards the distal colon further lessen the fermentation of dietary and mucosal proteins[174]. The suppression of proteolytic fermentation is partly driven

by a general preference for carbohydrates over amino acids as a source of energy for gut microorganisms and the fact that reductions in colonic pH during fibre fermentation from lactate and SCFAs inhibit proteolytic enzymes[175]. Diminished proteolytic fermentation in humans might subsequently decrease levels of putatively deleterious and pro-inflammatory pathobionts, such as *Desulfovibrio*, and metabolites, such as ammonia or p-Cresol[174]. The balance between fibre and protein fermentation has been demonstrated in humans, as increasing the dose of resistant starch and shifting diet patterns from high-protein, low-carbohydrate to a weight-maintenance diet has been shown to increase faecal SCFAs and reduce branched-chain fatty acids, metabolites generated by branched-chain amino acid fermentation[63,176]. Promoting SCFA production along the colon might additionally enhance gastrointestinal barrier integrity by stimulating mucus secretions, upregulating tight junction proteins, increasing antimicrobial peptide concentrations and regulating colonic epithelial proliferation, collectively mitigating the translocation of bacterial lipopolysaccharides and the ensuing metabolic endotoxaemia[177]. Together, these results support the targeting of the distal colon as a therapeutic target in the control of obesity.

Several ecological factors beyond fibre structure influence which health-relevant microorganisms and metabolites are promoted during fibre fermentation. Colonic transit time is recognized as a key factor influencing the gut microbiota and host metabolism, with slower transit times associated with reduced rates of fibre fermentation and fewer SCFAs, increased pH and proteolytic fermentation in the distal colon, and diminished recovery of faecal energy by gut microbiota[178]. Reductions in colonic pH have been further shown in vitro to shape the microbial consortium involved in fermenting a structurally distinct fibre by selecting against acid-sensitive microorganisms such as *Bacteroides*[179]. As most commensal microorganisms involved in colonic fibre fermentation are obligate anaerobes, increased oxygen concentrations across colonic microenvironments, as observed in inflammation, also shape consortium membership by supporting blooms of oxygen-tolerant microorganisms such as *Escherichia coli*[167]. Beyond environmental constraints, personal consortia can be determined by competitive interactions among microbial strains that utilize the same fibre or by-product owing to functional redundancy across unrelated strains or lack of phylogenetic niche conservatism among related strains[180]. As ecological factors shape individualized microbial responses to fibres, an ecological perspective is required when implementing fermentable fibre-based treatment strategies to prevent and treat obesity and metabolic syndrome.

Fibre-induced shifts in the gut microbiota are often reported as being restricted to a few dominant responding taxa with more personalized shifts in the remaining members and metabolic by-products[176,181–183]. For instance, decades of research in humans confirm that prebiotic oligosaccharides, such as FOSs and galactooligosaccharides, increase lactate and acetate by selectively promoting *Lactobacillus* and *Bifidobacteria* species often used as probiotics to confer health benefits in humans[184]. Butyrate-producers, such as *Anaerobutyricum*, *Eubacterium*, *Faecalibacterium* and *Roseburia*, have also been shown in in vitro studies to be enriched by cross-feeding lactate and acetate or by utilizing substrates such as crystalline-resistant

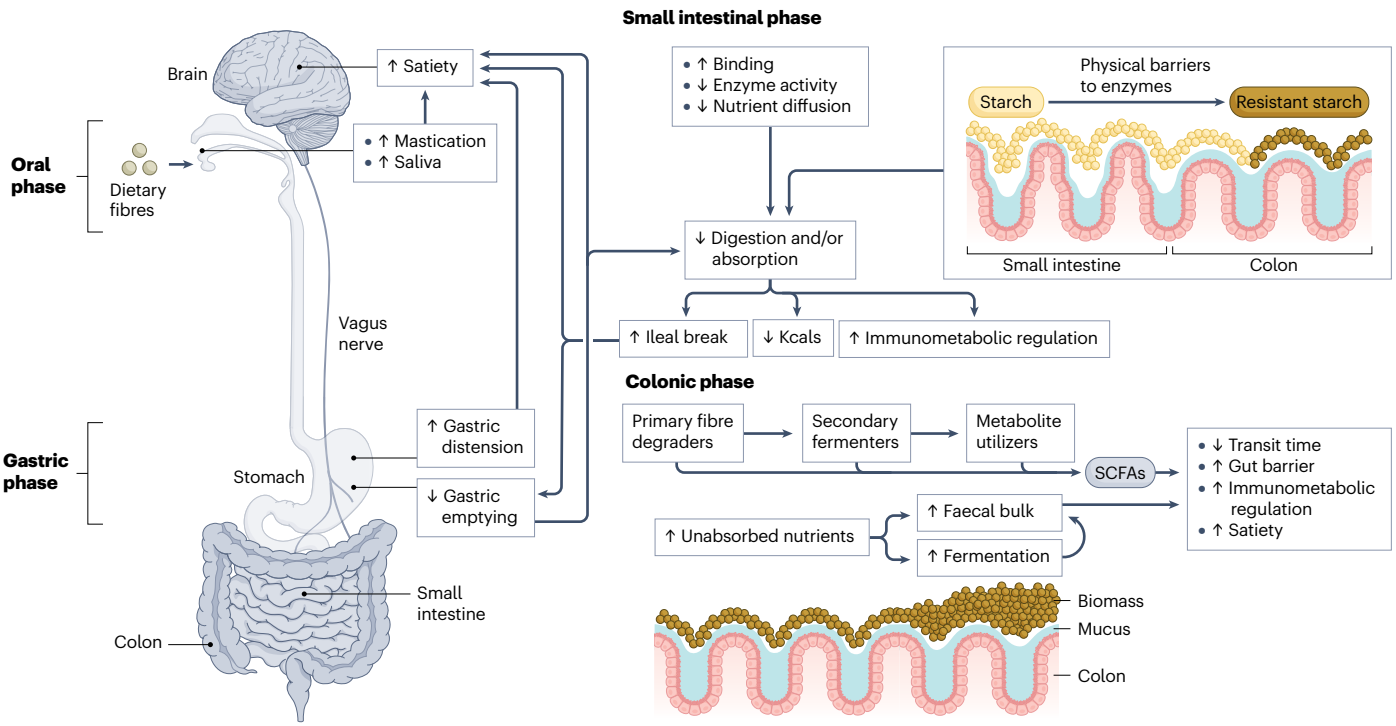

Fig. 3 | Physiological effects of dietary fibres along the gastrointestinal tract. Increased fibre consumption induces diverse physiological effects that are site and structure dependent, starting in the proximal gastrointestinal tract. In the oral and gastric phases, fibres can promote increased mastication and reduced gastric emptying for enhanced satiation. In the small intestinal phase, fibres can impede the digestion and absorption of nutrients by diverse mechanisms, improving immunometabolic regulation and satiety. In the distal gastrointestinal tract, colonic fermentation (or lack thereof) of fibres and unabsorbed nutrients favourably influences satiety, immunometabolism, gut barrier function and gastrointestinal transit time, in part, by supporting the production of short-chain fatty acids (SCFAs).

starch, xylan and inulin[115]. Alternatively, propionate producers, such as *Bacteroides*, *Parabacteroides*, *Phascolarctobacterium* and *Veillonella*, can be enriched by cross-feeding lactate and succinate or by degrading substrates such as esterified-resistant starch, pectin and xylan[115]. Promising metabolic improvements in adults with obesity and metabolic syndrome have been conferred by next-generation probiotics comprising *Akkermansia muciniphila* or *Anaerobutyricum soehngenii*[185–188], two bacterial species shown to be enriched by fibre supplementation. Thus, fermentable fibres can be applied to selectively expand health-relevant taxa within the gut microbiota. Additional research is, however, still needed to elucidate other commensal microorganisms and metabolites that are causally linked to obesity and metabolic dysfunction and can be targeted with select fibres.

In summary, increased consumption of fibres with distinct structures and physicochemical properties offers tremendous potential for the treatment of obesity and metabolic dysfunction. However, it remains uncertain whether the immunometabolic benefits of fibre are primarily caused by interactions along the proximal versus distal gastrointestinal tract and whether the gut microbiota serves a dominant causal role in these benefits.

Precision medicine approaches in the treatment of obesity

Dietary therapy personalized to the pre-treatment microbiome

High inter-personal variability in response to dietary interventions for weight loss can be attributed to multiple factors, including genetic background, microbiota composition and lifestyle factors (that is, meal timing, sleep, exercise and circadian rhythm)[189]. Identifying key factors that affect the response of an individual to dietary intake is required to implement personalized nutrition strategies to achieve weight loss. Baseline microbial metagenomic profiles, including the presence of several genes related to fibre degradation, have been shown to be associated with subsequent weight loss[190]. In a 6-month weight reduction study in 84 individuals, the baseline gut microbiota was the single best predictor of individual weight loss[191]. Furthermore, specific gut bacteria such as *Blautia wexlerae* and *Bacteroides dorei* have been shown to be the most predictive of weight loss when abundant at baseline, and weight loss correlated with a decrease in abundance in *Ruminococcus gnavus*, *Bacteroides massiliensis* and *Bacteroides finegoldii* and an increase in *Akkermansia*. Microbial taxa such as *Prevotella* are associated with fibre-enriched diets due to their ability to process complex fibres of plant origin, whereas individuals consuming low-fibre diets tend to have a higher level of *Bacteroides* than *Prevotella*[192]. In human weight-loss trials, people dominated by *Bacteroides* species were less likely to be able to lose weight or to maintain weight loss when consuming diets rich in fibre than individuals with higher levels of *Prevotella*[193–195]. These findings suggest that gut microbiota with high levels of fermentative metabolism, such as *Prevotella* species, might be more conducive to weight loss when increasing fibre intake[193,194,196]. Finally, data from the PREDICT 1 trial (n = 1,002) have shown that the gut microbiota composition was a good predictor of postprandial lipid and glycaemic responses and fasting cardiovascular metabolic markers[43,197]. However, it must be noted that gut microbiota composition only explained 5–7% of changes in postprandial rises in triglycerides, glucose and C-peptide, indicating that other factors were also clearly involved[197].

Phenotype-based interventions

Another method for applying precision medicine-based approaches to obesity and metabolic disorders is to use phenotype-tailored interventions based on the underlying pathophysiology and behavioural features of an individual. As proposed by Acosta and colleagues[198,199], obesity phenotypes can be categorized into four broad phenotypes: abnormal satiety, abnormal postprandial satiety, emotional eating and abnormal resting energy expenditure. A feasibility trial using specific tailored dietary interventions for each phenotype (abnormal satiation n = 28; abnormal postprandial satiety n = 13; emotional eating n = 26; abnormal resting energy expenditure n = 38) was carried out, including the use of high-fibre diets in those with abnormal satiety to switch off the brain hunger centre and produce maximal gastric distention. Supporting the concept, participants in the phenotype-tailored lifestyle intervention groups lost more weight and had a greater improvement in metabolic and clinical parameters than those participants receiving standard therapy[198].

Another approach based on metabolic phenotypes was developed based on the findings in the CORDIOPREV-DIAB trial (n = 642) that individuals with a predominant muscle-insulin-resistance phenotype responded better to a diet high in monounsaturated fatty acids, whereas individuals with predominantly liver-insulin resistance responded better to a low-fat, high-complex carbohydrate diet[200]. The personalized glucose optimization through nutritional intervention (PERSON) study was designed to test this approach of improving parameters of glucose homeostasis and cardiometabolic health through modulating dietary macronutrient content according to tissue-specific insulin-resistance phenotypes[201]. In a 12-week dietary intervention trial, people with muscle-insulin resistance or liver-insulin resistance were randomized to either a high-monounsaturated fatty acid diet or a low-fat, high-protein and high-fibre diet[201]. However, contrary to the findings from the initial CORDIOPREV-DIAB trial, individuals with muscle-insulin resistance (n = 149) had more improvement in metabolic parameters when consuming a low-fat, high-protein and higher-fibre diet, whereas individuals with liver-insulin resistance (n = 93) had more improvement when consuming the high-monounsaturated diet[201]. These conflicting results might have been due to differences in study populations and/or differences in the composition of the dietary interventions and clearly illustrate the challenges of designing precision dietary interventions based on certain phenotypes[202,203].

However, despite challenges associated with developing personalized nutritional interventions, these proof-of-principle studies overall support the underlying concepts of developing personalized dietary interventions using algorithms based on biological and phenotypic factors. In addition, understanding how gut microorganisms and their gene pathways interact with dietary components might help in the design of more effective personalized therapies and potentially increase the success of dietary interventions for weight loss.

Fibre-based strategies for obesity and metabolic syndrome

Together with the structural and physicochemical diversity between dietary fibres comes the potential for developing fibre-based strategies that complement current and emerging pharmacological and surgical therapies for obesity and metabolic syndrome. Although fibre-rich whole foods, such as whole grains, vegetables, fruits, legumes, nuts and seeds, provide mixed sources of non-starch polysaccharides and resistant starches for obesity-centred medical nutrition therapies, the concentrated and uniform features of isolated and synthetic fibres offer avenues for nutraceutical development to target metabolic syndrome pathophysiology and will be discussed further. Several purified food-grade dietary fibres are already marketed as food ingredients or supplements, many of which are accessed, degraded and utilized by

select microbial consortia[18]. A systematic review and meta-analysis including 22 randomized controlled trials with a total of 1,428 participants has shown that individuals using isolated soluble dietary fibre supplementation (inulin, FOS, resistant corn dextrin, guar gum, flaxseed mucilage, alginate powder, glucomannan and xanthan gum) for at least 12 weeks had a significantly higher reduction in body weight ($Z = -2.46$, $P = 0.01$) and improvement in metabolic function as estimated by HOMA-IR ($Z = -2.76$, $P = 0.01$) than the control interventions (digestible carbohydrates), supporting a role for isolated fibre supplementation in the control of obesity[204]. However, the reduction in body weight was relatively modest (mean difference −1.25 kg, 95% confidence interval −2.24), suggesting that isolated soluble fibres alone might not achieve substantial weight loss.

A challenge associated with using fibre-based strategies lies in what dosages might be required for beneficial effects and how individuals might react to these dosages. Often, dosages used in mouse and rat models translate to daily consumption of >100 g in humans[167], which can result in substantial adverse effects. Indeed, a longitudinal, randomized crossover study in 18 participants showed that 30 g of inulin supplementation increased levels of pro-inflammatory cytokines, such as IL-6 and TGFβ, and liver enzymes[205]. Another study using a combination of human tissue samples, ex vivo culture of human colonic biopsies and cell culture models has shown that dietary β-fructans triggered a pro-inflammatory response in human macrophages and biopsy samples from patients with inflammatory bowel disease with active gut inflammation[206]. The investigators speculate that in individuals lacking specific microbial taxa such as *Roseburia* and *Faecalibacterium prausnitzii* that are required to ferment fibres such as β-fructans, these unfermented fibres might induce an inflammatory response in the gastrointestinal tract [206]. These studies highlight the necessity of personalizing dietary therapy based on matching specific fibre blends with existing microbial functional characteristics in the host.

Fibre blends with precise physicochemical properties

With an understanding of how purified fibres behave along the gastrointestinal tract and interact with the human gut microbiota, fibres could be rationally selected based on their unique physicochemical properties, effect on the gut microbiota, and influence on satiety, glycaemic, lipidemic or inflammatory responses in obesity. Purified fibres with overlapping physiological effects on obesity could be intelligently paired to generate precision fibre blends. A commercialized example of such is PolyGlycopleX (InovoBiologic), a blend of sodium alginate, konjac gum and xanthan gum that interacts synergistically to form a highly viscous and gel-forming polysaccharide complex previously shown to promote satiety and lower total cholesterol levels[207]. One could speculate that pairing PolyGlycopleX with a mixture of fermentable fibres that favour propionate production might enhance clinical responses, as propionate supplementation in humans has been shown to have a favourable effect on satiety and cholesterol metabolism[80,208]. Consumption of a proprietary blend with seven fermentable fibres has been shown in 39 adults with high cardiometabolic disease risk to improve surrogate markers of glucose ($q = 0.04$) and cholesterol metabolism ($q = 0.004$) and significantly modulate compositional and functional features of the gut microbiota ($q < 0.1$)[209]. A blend of rapidly (inulin) and slowly (resistant starch) fermented fibres designed to extend acetate production towards the distal colon has also been shown postprandially to promote energy expenditure and attenuate glycaemic responses in healthy individuals ($n = 11$) but, interestingly, not in individuals with pre-diabetes ($n = 11$)[79]. These results highlight how an altered microbial fermentation capacity and differences in SCFA metabolism between individuals with normal weight and those with obesity or metabolic dysfunction might influence responses to fibre supplementation. Although fastidiously developed fibre blends are an emerging approach to partly overcome personalized responses to fibre supplementation, well-designed preclinical and clinical studies are needed to develop and determine the efficacy of such fibre blends alone and in combination with standard of care for the treatment of obesity and metabolic syndrome.

Aligning discrete fibre structures with health-relevant microbiota

Each proprietary technology developed to extract or synthesize a purified fibre has the potential to generate discrete fibre structures with varying molecular weights, monosaccharides and linkage types. A conceptual framework put forth by Hamaker and Tuncil[146] proposes that predictable and health-relevant changes in the gut microbiota could be obtained by aligning these discrete structures with gene clusters encoded in the genomes of target bacteria, with intricate fibre structures that are accessed, degraded and utilized by limited gut microbiota offering more predictable changes[210]. Fundamental aspects of the framework have been confirmed in 40 healthy adults by supplementing three chemically modified starches with similar yet distinct chemical structures and one digestible starch as crystalline and cross-linked resistant starches enriched for *Eubacterium rectale* (butyrate producer) and *Parabacteroides distasonis* (propionate producer) with dose-dependent increases in butyrate and propionate, respectively[176]. Using specific fibre combinations in a controlled diet study in 14 adults, Delannoy-Bruno and colleagues[211] have demonstrated that different fibre combinations elicited shared and fibre-specific responses in microbial functional gene expression and growth. For instance, combinations of pea fibre and inulin or pea fibre, inulin, orange fibre and barley bran both promoted several species of *Bacteroides* and increased pathways involved in the utilization of arabinooligosaccharides and xylooligosaccharides. Furthermore, fibre-induced changes in specific microbial genes could be linked with changes in host glucose metabolism, calcineurin and AKT signalling, apoptosis, kallikrein–kinin proteases and immune processes[211]. Although in vitro investigations have further demonstrated the potential of discrete fibre structures to intelligently manipulate the gut microbiome[210,212], additional randomized controlled trials in humans are needed to confirm the physiological effects of such precision fibre supplementation.

Synergistic synbiotics, live biotherapeutics and faecal microbial transplantation

Alignment between discrete fibre structures and the genomes of health-relevant bacteria suggests that the administration of live microorganisms, whether probiotics, live biotherapeutics or FMT, could be paired with the exact fibres selectively fermented by the co-administered microorganisms. Unlike complementary synbiotics, which combine probiotics and prebiotics, this precise pairing is the basis of synergistic synbiotic development, in which substrates are precisely developed to be selectively utilized by co-administered live microorganisms to confer a health benefit on the host[213]. However, some early preclinical[214] and clinical[215] findings suggest that synergistic synbiotics might not always interact predictably to promote health. For instance, supplementation with the prebiotic galactooligosaccharides, probiotic *Bifidobacterium adolescentis* or a synergistic synbiotic in 94 individuals with obesity has been shown to

Box 1

Key knowledge gaps limiting the application of dietary fibres as a complementary strategy

- Is the distal gastrointestinal tract an effective target in humans for the treatment of obesity and metabolic syndrome, or should complementary strategies focus on the proximal gastrointestinal tract?
- Which microbiota taxa and metabolites are causally linked to obesity and metabolic syndrome, can they be targeted with dietary fibres, and, if so, what doses are efficacious and are they well tolerated?
- Are there antagonistic, additive or synergistic effects between dietary fibres and current surgical, pharmaceutical and lifestyle-based therapies for obesity and metabolic syndrome?

similarly enhance gut barrier integrity, as estimated by the sucralose to lactulose ratio[215]. Synbiotic supplementation, or general pairing of prebiotic (or prebiotics) and probiotic (or probiotics), has, however, shown promise for the reduction of body weight[216] and correction of dysregulated metabolism in obesity, as reported by systematic reviews and meta-analyses[217]. A commercialized example of such is Pendulum Glucose Control (Pendulum Therapeutics), a proprietary blend of inulin, oligofructose, *A. muciniphila*, *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis* and *Anaerobutyricum hallii* that was shown to improve glucose metabolism in 21 individuals with type 2 diabetes being treated with either diet and exercise alone, or in combination with metformin with or without a sulfonylurea[218].

Administration of entire faecal microbial communities, or FMT, might further benefit from the co-administration of precise purified fibres that support health-relevant members within the community or modulate environmental constraints that prevent microbial engraftment. In a proof-of-concept study, FMT paired with non-accessible microcrystalline cellulose ($n = 17$), but not a fermentable fibre blend ($n = 17$) (resistant maltodextrin, type IV resistant starch and acacia gum), has been shown to improve insulin sensitivity in individuals with obesity and metabolic syndrome receiving standard-of-care therapies[219]. Microcrystalline cellulose supplementation with FMT supported an increase in community richness and engraftment and/or enrichment of several health-relevant taxa, such as *Akkermansia*, *Christensenellaceae* and *Phascolarctobacterium*, potentially by shifting colonic environments towards more favourable conditions, such as reductions in intestinal inflammation[147,219]. Diets consumed by donors before obtaining faeces further influence the efficacy of FMTs and should also be considered. For instance, Rinott and colleagues[220] observed that, in contrast to individuals receiving autologous FMT capsules following a weight-loss Mediterranean ($n = 16$) or health dietary guidelines ($n = 19$) diet, only individuals receiving autologous FMT capsules following a weight-loss Mediterranean diet with green tea and Wolffia globose green shake ($n = 19$) were shown to have attenuated weight gain 8 months post-weight loss relative to placebo capsules. Overall, the integration of next-generation probiotics, live biotherapeutic and FMT therapy development with the manufacturing of novel purified fibres with discrete structures would facilitate the development of innovative nutraceutical and pharmaceutical therapeutics that target metabolic syndrome pathophysiology by balancing dysbiotic gut microbiota.

Knowledge gaps impeding complementary fibre-based strategies

Although purified fibres have been shown to induce clinically relevant effects on obesity-related markers, several knowledge gaps limit their application as complementary therapies for obesity and metabolic syndrome (Box 1). There is a critical need to confirm whether the distal gastrointestinal tract and resident microbiota are an effective target in humans for treating obesity and metabolic dysfunction or whether complementary fibre-based strategies should focus on the proximal gastrointestinal tract to prolong mastication, absorption and transit time. To support this, clinical studies assessing the efficacy of purified fibres should characterize and report the structure and physiochemical properties of the fibre (or fibres) and include evaluations of transit time along the gastrointestinal tract[221]. Further research is needed to identify novel gut microbiota and metabolites that are causally linked to immune and metabolic homeostasis in humans and promoted by discrete fibre structures, as well as environmental constraints that prevent desired responses. As the effects of fibre supplementation are shown to be dose dependent[176], research should also determine which doses maximize physiological effects and whether such doses are well tolerated by humans in today's societies. Once discrete fibre structures and efficacious doses are identified, additional efforts are needed to commercialize the products, which includes developing cost-effective manufacturing technologies at scale and obtaining necessary regulatory approvals from each jurisdiction where the product will be marketed. Finally, further research is needed to determine whether synergistic, additive or antagonistic interactions are exhibited not only between different fibres but also between different dietary compounds such as proteins or phenolics, probiotic strains and live biotherapeutics, as well as concurrent pharmacological and surgical therapies for obesity and metabolic syndrome.

Conclusions

It is our newfound understanding of the complex interplay between enteroendocrine and neurohormonal processes underlying obesity that has helped dispel the once simple models of obesity as a mere disease of energy imbalance and has accelerated progress into effective therapeutic approaches for obesity. Overall, increased consumption of dietary fibre has the potential to induce structural, physicochemical and gastrointestinal site-specific benefits that are relevant for the treatment of obesity and metabolic syndrome. An appreciation of mechanisms that determine the physiological effects of fibre along the gastrointestinal tract, including the role of the gut microbiota, will support the development of efficacious fibre-based and complementary strategies for the regulation of immune, metabolic and body weight homeostasis. As preclinical and clinical research continues to explore which health-relevant microbiota and metabolites are reliably promoted by purified fibres, the cataloguing of such fibre–microbiota interactions would provide a framework for the development of fibre-based precision nutraceuticals for personalized, optimized therapy for obesity and associated metabolic comorbidities.

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