Molecular and Cellular Endocrinology 546 (2022) 111572

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Short chain fatty acids: Microbial metabolites for gut-brain axis signalling

Kenneth J. O'Riordan [a], Michael K. Collins [a,b], Gerard M. Moloney [a,b], Emily G. Knox [a,c], María R. Aburto [a], Christine Fülling [a], Shane J. Morley [a], Gerard Clarke [a,d], Harriët Schellekens [a,b], John F. Cryan [a,b,*]

[a] APC Microbiome Ireland, University College Cork, Ireland
[b] Department of Anatomy & Neuroscience, University College Cork, Ireland
[c] School of Pharmacy, University College Cork, Ireland
[d] Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

ARTICLE INFO

Keywords:
Microbiota-gut-brain axis
Microbiota
Microbiome
Short-chain fatty acids

ABSTRACT

The role of the intestinal microbiota as a regulator of gut-brain axis signalling has risen to prominence in recent years. Understanding the relationship between the gut microbiota, the metabolites it produces, and the brain will be critical for the subsequent development of new therapeutic approaches, including the identification of novel psychobiotics. A key focus in this regard have been the short-chain fatty acids (SCFAs) produced by bacterial fermentation of dietary fibre, which include butyrate, acetate, and propionate. Ongoing research is focused on the entry of SCFAs into systemic circulation from the gut lumen, their migration to cerebral circulation and across the blood brain barrier, and their potential to exert acute and chronic effects on brain structure and function. This review aims to discuss our current mechanistic understanding of the direct and indirect influence that SCFAs have on brain function, behaviour and physiology, which will inform future microbiota-targeted interventions for brain disorders.

1. Introduction

The community of microbes within our gut has co-evolved with its human host over thousands of years and understanding this relationship is vital for appreciating how our microbiome contributes to our health and wellbeing (Llorens-Rico and Raes, 2019; Gomaa, 2020). There are over 100 trillion microbes residing in the human gastrointestinal (GI) tract, made up of bacteria, viruses, phages, and archaea, collectively known as the gut microbiome. Over recent years, they have been shown to affect physiological systems of the body, including our brain and behaviour, via direct and indirect mechanisms (Agus et al., 2018; Fan and Pedersen, 2021; Sekirov et al., 2010; Rutsch et al., 2020). Communication between the gut microbiome and the brain occurs along the gut-brain axis, a bidirectional signalling pathway comprising the immune system, tryptophan metabolism, vagus nerve activity, the enteric nervous system (Soret et al., 2010), as well as bioactives (microbial by-products or metabolites) produced by the gut microbiome (Vuong et al., 2017; van der Hee and Wells, 2021; Fung et al., 2017). Studies, largely in animal models, have examined the effects of bacterial interventions on behaviour using different bacterial strains, multiple administration techniques, and different life stages (for review see (Cryan et al., 2019)). However, we still lack an intricate mechanistic understanding of how these microbes and microbial metabolites affect our behaviour in health and disease.

The microbiota represents a rich reservoir of potential novel metabolites and bioactives, with pleiotropic functionalities for the host (Agus et al., 2021). It is thought that probiotics, live microorganisms that provide health benefits, can do so without having a major effect on microbiome composition, per se (Kristensen et al., 2016). Indeed, administration of certain probiotic strains of bacteria (mainly *Bifidobacterium* spp. and *Lactobacillus* spp.) has been shown to alter the metabolic profile of the host through production of metabolites that could be beneficial in certain contexts including serotonin, histamine, γ-aminobutyric acid (GABA), branched-chain amino acids (BCAAs), and SCFAs (Hemarajata and Versalovic, 2013; Chung et al., 2018). Indeed, accumulating evidence suggests that bacterial metabolites can act at multiple locations both local to and distant from their site of production, modifying host behaviour and health (Fung et al., 2017; Spichak et al., 2021a; Nikolova et al., 2021). For instance microbes can act locally, producing bioactives, including mediators normally associated with mammalian neurotransmission (Wall et al., 2014). It seems likely then

* Corresponding author. APC Microbiome Ireland, University College Cork, Ireland.
E-mail address: J.Cryan@ucc.ie (J.F. Cryan).

https://doi.org/10.1016/j.mce.2022.111572
Received 14 May 2021; Received in revised form 7 January 2022; Accepted 11 January 2022
Available online 20 January 2022

Abbreviations

5-HT	5-hydroxytryptamine or serotonin
5-HT_{3B}	Serotonin 3B receptor
AD	Alzheimer's disease
Aβ	β-amyloid
APP	Amyloid precursor protein
ASD	Autism spectrum disorder
BBB	Blood-brain barrier
BCAA	Branched-chain amino acid
CD41	Glycoprotein (Gp) IIb/IIIa integrin
CNS	Central nervous system
CSF	Cerebrospinal fluid
DC	Dendritic cells
DNA	Deoxyribonucleic acid
EAE	Experimental autoimmune encephalomyelitis
EEC	Enteroendocrine cell
ENS	Enteric nervous system
ERK	Extracellular signal-regulated kinase
FFAR	Free fatty acid receptor
FMT	Faecal microbiota transplant
GABA	γ-aminobutyric acid
GHSR-1a	Growth hormone secretagogue receptor 1a
GLP-1	Glucagon-like peptide-1
GPCR	G-protein coupled receptor
HDAC	Histone deacetylase
hCMEC/D3	Immortalised human cerebromicrovascular endothelial cell line
HPA	Hypothalamic-pituitary-adrenal
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IFN	Interferon
IL	Interleukin
i.c.v.	Intracerebroventricular
i.p.	Intraperitoneal
IPE	Inulin-propionate ester
JNK	c-Jun N-terminal kinase
LPS	Lipopolysaccharides
MCT1	Monocarboxylate transporter 1
MDD	Major depressive disorder
MS	Multiple sclerosis
mTOR	Mammalian target of rapamycin
NF_KB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFE2L2	Nuclear Factor, Erythroid 2 Like 2
NTS	Nucleus tractus solitarius (the nucleus of the solitary tract)
PBMC	Peripheral blood mononuclear cells
PD	Parkinson's disease
PTM	Post-translational modifications
PYY	Peptide YY
SCFA	Short-chain fatty acid
SMCT1	Sodium-coupled (Na(+)-coupled) transporter for l-lactate
SPF	Specific pathogen-free
Spp.	Several species
Foxp3	Forkhead box P3
TJP	Tight junction protein
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TNF-α/β	Tumour necrosis factor alpha/beta

that microbial metabolites could play a significant role in the behavioural changes noted after probiotic administration (Sarkar et al., 2016; van de Wouw et al., 2017), as well as regulating brain function in health, stress and ageing (van de Wouw et al., 2018; Boehme et al., 2021). In this review, we will focus on the microbial metabolites SCFAs produced by the gut microbiome to explore their potential as a key player in microbiota-gut-brain axis communication, and ability to act as a novel therapeutic for human disease. We will start by examining what SCFAs are, where they are located along the GI tract, and at what concentration.

2. Microbial metabolites - short-chain fatty acids

SCFAs are the most commonly studied gut microbial-derived metabolite. They are carboxylic acids with aliphatic tails of 1–6 carbon atoms (van der Hee and Wells, 2021; Parada Venegas et al., 2019). They are the product of bacterial fermentation of complex polysaccharides, which are otherwise non-digestible by the host (Brestoff and Artis, 2013). Over 95% SCFAs produced in the gut are acetate, propionate and butyrate (Parada Venegas et al., 2019; Rios-Covian et al., 2020), although valerate, iso-valerate, valproate, caproate, isocaproate, succinate, iso-butyrate, and hexanoate are also found in smaller quantities (Rios-Covian et al., 2020; Cook and Sellin, 1998). SCFAs can be sourced from, and correlate strongly with, our diet (van der Hee and Wells, 2021; Dalile et al., 2019). For example, SCFAs are found in high concentrations in foods such as butter and other dairy products (Stilling et al., 2016; Butler et al., 2020). Acetate is the smallest and most structurally simple with only a single carbon bound to the carboxyl group, followed by propionate and butyrate with two and three bound hydrocarbons, respectively (Ríos-Covián et al., 2016).

SCFAs have been associated with many different host physiological processes including GI function (Gill et al., 2018), the regulation of blood-pressure (Pluznick, 2017), circadian rhythms (Tahara et al., 2018), and innate and adaptive immune regulation, including microglial (the brains resident immune cells) maturation in the brain (Erny et al., 2017), and astrocyte gene expression in a sex-specific manner (Spichak et al., 2021b). Intriguingly, altered SCFA levels in faecal content have been seen in human disorders where brain physiology and behaviour are modified: decreased SFCA levels have been reported in anorexia nervosa (Morita et al., 2015) and Parkinson's disease (PD) (Unger et al., 2016), and increased SCFA levels in obesity (van de Wouw et al., 2017; Rahat-Rozenbloom et al., 2014), in children exposed to chronic psychosocial stress (Michels et al., 2017), and in autism spectrum disorder (ASD) (Wang et al., 2012). More recently, decreased faecal acetate and butyrate levels were seen in children with ASD (Liu et al., 2019). Preclinically, reduced levels of SCFAs have been seen to be associated with Alzheimer's disease (AD) (Zhang et al., 2017), and chronic stress (Maltz et al., 2018). Alterations in SCFA levels were also reported in depressed mice, relative to controls, which correlated with specific bacterial taxa (Wu et al., 2020a).

Studies examining physiological concentrations of SCFAs in the brain are scarce (Silva et al., 2020). However, the Human Metabolome Database (http://www.hmdb.ca/) reports cerebrospinal fluid SCFA concentrations as 0–171 μM for acetate, 0–5 μM for propionate, and 0–2.8 μM for butyrate (see Table 1). Tissue concentrations have also been examined and reported as 17.0 pmol/mg of tissue for butyrate, and 18.8 pmol/mg of tissue for propionate in the human brain (Bachmann et al., 1979). SCFA concentrations in the blood have been reported highest in the portal circulation, lower in the hepatic circulation and lowest in the peripheral circulation, where mean concentrations were 70 μmol/l for acetate, 5 μmol/l for propionate, and 4 μmol/l for butyrate (Cummings et al., 1987).

In one report, in-depth information on concentration variation from the proximal to distal intestine in humans was gathered post-mortem

Table 1
Normal concentrations of short chain fatty acids in adults >18 years old.

Tissue	Concentration	Refs
Acetate		
Blood	26.8–64.2 μM	[a] (Psychogios et al., 2011)
	30.4 (22.0–40.0) μM	[b] (Lentner, 1981)
	41.9 ± 15.1 μM	[a] (Psychogios et al., 2011)
	69.14(30.49) μM	[a] (Zordoky et al., 2015)
Cerebrospinal Fluid	58.0 ± 27.0 μM	[a] (Wishart et al., 2008)
	100.0 ± 30.0 μM	[a] (Commodari et al., 1991)
	116.0 ± 55.0 μM	[b] (Lentner, 1981)
Gut (wet faeces)	35.86 ± 16.8 μmol/g	[a] (Zheng et al., 2013)
	37.4 (12.8–103.4) μmol/g	[a] (Høverstad et al., 1984)
Butyrate		
Blood	1.0 (0.3–1.5) μM	[b] (Lentner, 1981)
Cerebrospinal Fluid	1.4 (0–2.8) μM	[b] (Lentner, 1981)
Gut (wet faeces)	4.44–11.9 μmol/g	[a] (Han et al., 2015)
	6.35 ± 3.13 μmol/g	[a] (Zheng et al., 2013)
	12.4 (4–53) μmol/g	[a] (Høverstad et al., 1984)
Propionate		
Blood	0.9 ± 1.2 μM	[b] (Lentner, 1981)
Cerebrospinal Fluid	2.8 ± 3.2 μM	[b] (Lentner, 1981)
Gut (wet faeces)	6.58–14.4 μmol/g	[a] (Han et al., 2015)
	11.4 ± 4.74 μmol/g	[a] (Zheng et al., 2013)
	12.5 (4.5–27.8) μmol/g	[a] (Høverstad et al., 1984)

[a] References collected from the human metabolome database (https://hmdb.ca/).
[b] References collected from the Geigy Scientific Tables.

from six individuals with causes of death ranging from coronary heart disease to road traffic accidents (Cummings et al., 1987). Here it was noted that concentrations of acetate and butyrate peaked in the caecum, while propionate peaked in the ascending colon. SCFA concentrations reduce as they pass through the large intestine, but each undergo a small increase upon reaching the rectum (Cummings et al., 1987). Levels of SCFAs in human faeces have been reported as approximately 60 g/kg (1 mol/kg) for acetate, 10–20 g/kg (136–274 mmol/kg) for propionate, and 3.5–32.6 g/kg (40–374 mmol/kg) for butyrate (McOrist et al., 2011; Macfarlane and Macfarlane, 2003); this is commonly cited as a 60:20:20 ratio (den Besten et al., 2013). SCFA faecal concentrations have been shown to increase with prebiotic and probiotic treatment (Nagpal et al., 2018; Baxter et al., 2019). SCFAs contribute to a wide range of processes including metabolism and immunity and can exert influence over neurological function and disease (Stilling et al., 2016; Sharon et al., 2014).

To help guide future therapeutics, the following SCFA-producing microbial genera that are commonly found in the gut should be considered in targeted approaches: *Akkermansia, Bifidobacterium, Lactobacillus, Lactocaseibacillus, Ligilactobacillus, Ruminococcus, Ruminoclustridium, Blautia, Bacteroides, Roseburia, Prevotella, Eubacterium, Fusicatenibacter, Faecalibacterium, Enterococcus, Clostridium* and *Coprococcus* (see Table 2) (Dalile et al., 2019; Takada et al., 2016; Valles-Colomer et al., 2019). In addition, other species that have been associated with increased SCFA levels are: *Alistipes*, *Bilophila*, and *Lachnospiraceae*. It is increasingly apparent that SCFAs play an important role in host physiology, therefore much more work is needed to fully elucidate this relationship. Firstly, we will examine how SCFAs arise in the gut through dietary intake, microbial metabolism, and host uptake.

2.1. SCFAs in the gut – influence of diet

While some foods contain SFCAs, the primary source is from colonic microbial fermentation of specific host-indigestible and non-absorbable dietary fibres (Macfarlane and Macfarlane, 2003; Baxter et al., 2019); examples include inulin, wheat bran, cellulose, and resistant starches. This is supported by the fact that germ-free animals (lacking a gut-microbiota and hence gut microbiota-derived SCFAs) and antibiotic treated mice (that have a strongly ablated gut-microbiota) have markedly lower SCFA levels (Backhed et al., 2007; Hoverstad and Midtvedt, 1986; Palleja et al., 2018; Zhao et al., 2016). Other sources of endogenous SCFAs include the breakdown of proteins by the microbiota (Yao et al., 2016), host metabolism of long-chain fatty acids and pyruvate into acetate (Knowles et al., 1974), as well as the consumption of alcohol (Sarkola et al., 2002). Minor amounts of SCFAs can also be attained by the consumption of fermented foods (Gill et al., 2018).

Given the importance of fibre in our diet (Berding et al., 2021; Reynolds et al., 2019), as the major supply for microbe-derived SFCAs to the host, research is increasingly focused on gut microbiota-derived modulation of gut SCFA levels depending on fibre type and

Table 2
SCFA producing bacteria. A list of SCFA-producing gut bacteria discussed in the literature. Notably *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, and *Bacteroides fragilis*, are thought to be among the primary producers of acetate, butyrate, and propionate, respectively.

SCFA Producer	Notes	Refs
Acetate		
Bifidobacterium adolescentis	Produces acetate, lactate and formate.	Flint et al. (2015)
The *Bacteroidetes* Phylum	The main producers of acetate in the gut.	(Macfarlane and Macfarlane, 2003; Hoverstad and Midtvedt, 1986; Levy et al., 2016)
Butyrate		
Interspersed species in the Lachnospiraceae and Ruminococcaceae families such as *Faecalibacterium prausnitzii.*	Dominant bacteria in human faecal samples capable of butyrate production.	(Louis and Flint, 2017; Parada, 2019)
Clostridium tyrobutyricum	Used for monocolonisation to introduce butyrate to germ-free mice.	Braniste et al. (2014)
Clostridiales sp. *SS3/4, Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia intestinalis, Roseburia inulinivorans,* and *Eubacterium hallii*	Data from a metagenomic large cohort of affected individuals with type 2 diabetes, which revealed a lack of butyrate-producing bacteria.	(Ríos-Covián et al., 2016; Qin et al., 2012)
Propionate		
Clostridium ramosum	Produced the greatest amount of propionate in comparison with several other species.	Smith et al. (2013)
The *Desulfovibrio* genus	Increased levels of this genus are associated children with ASD.	Finegold (2011)
The *Bacteroidetes* genus, such as *Prevotella copri*	Dominant bacteria in human faecal samples capable of propionate production. They may also be an important phylum in the contribution to the severity of symptoms in ASD.	(Louis and Flint, 2017; Finegold et al., 2010)
Bacteroides fragilis	Major propionate producing bacteria in the human intestine.	(Shimizu et al., 2018; Rios-Covian et al., 2015)
Acetate/propionate		
Bacteroides thetaiotaomicron	Used for monocolonisation to introduce acetate/propionate to germ-free mice.	Braniste et al. (2014)

bioavailability. Indeed, one intriguing study showed that a specific group of SCFA-producing microbes (*Bifidobacterium pseudocatenulatum*) was enhanced following a diet high in fibre (as a fermentable carbohydrate) and its availability in the colon, which was capable of modulating clinically-relevant host outcomes in Type 2 Diabetes (Zhao et al., 2018). The fibre-promoted SCFA-producing microbes were present in higher diversity and abundance, correlating with improvements in clinical outcomes including improved haemoglobin A1c levels and increased glucagon-like peptide-1 (GLP-1) production, and a reduction in metabolically detrimental compounds such as indole and hydrogen sulfide. *B. pseudocatenulatum* in particular, had profound effects in mice, where it significantly reduced weight gain, body fat, fasting glucose, and insulin resistance, as well as improved the postprandial glycemic response and increased the caecal acetate content (Zhao et al., 2018).

Diet-derived protein, the prime source of amino acids critical for synthesis of neurotransmitters and brain health in general, has been associated with increased levels of gut-derived SCFAs and BCAAs (Singh et al., 2017). The consumption of a pea protein increased intestinal SCFAs associated with anti-inflammatory effects and mucosal barrier maintenance (Swiatecka et al., 2011). A protein-rich diet has also been associated with increases in *Bacteroides* abundance, a microbial genus crucial for the initial gut-based proteolysis of protein into amino acids. Further, an animal-based protein diet showed significant increases in the bile-tolerant anaerobes *Alistipes, Bilophila* and *Bacteroides* (David et al., 2014; Cotillard et al., 2013). In a comparison of children fed animal protein in Italy to rural African children on an agrarian diet, the animal protein-based diet increased abundances of *Alistipes* and *Bacteroides* (De Filippo et al., 2010). This may be important given that data showed increased abundance of *Alistipes* correlated with depression (Jiang et al., 2015). In fact, it is possible that long-term animal-based diets could have a detrimental effect on gut microbiota (Moreno-Perez et al., 2018).

Access to dietary SCFAs during early-life development may be equally or more important than in adults and is now under greater scrutiny. It was shown that butyrate supplementation during the post-weaning phase in mice significantly altered social behaviour, sexual preference, and depression-like behaviours (Zhao et al., 2020). Furthermore, fibre in the maternal diet has the potential to regulate neurocognitive functions in the offspring (Yu et al., 2020), likely via modulation of gut-derived SCFA levels. Also, a high-fibre diet was capable of abrogating maternal obesity-induced cognitive and social deficits and synaptic impairments seen in the offspring (Liu et al., 2021). This evidence supports the use of SCFA-dependent perinatal intervention, potentially through dietary fibre supplementation, for improving offspring brain health. Overall, more work is needed in understanding the relative contribution of the effects of diet on the SCFA-producing microbiota and their impact on brain function, including the establishment of guidelines of safe levels of SCFA administration in humans.

2.2. Delivering SCFAs to the gut and impact on serotonin

Another innovation within the microbiome-gut-brain axis research field has focused on examining formulation approaches to get SCFAs to specific sites along the GI tract, such as the colon. Recent human studies show that colon-delivered SCFAs have the capacity to attenuate the male cortisol response following psychosocial stress (Dalile et al., 2020). However, a recent randomised crossover-designed healthy human study found no differences in blood glucose or insulin concentrations, nor changes in neuropeptide levels after targeted delivery of propionate (as an inulin-propionate ester: IPE) to the colon; although brain imaging fMRI indicated the IPE reduces anticipatory reward responses in the human striatum to high-energy foods (Byrne et al., 2016). On the other hand, preclinical evidence showed that acylated starches, which reach the colon without being absorbed, can substantially increase caecal acetate, butyrate, and propionate levels (Kimura-Todani et al., 2021). Indeed, acetylated, propionylated, and butyrylated high-amylose maize starches can deliver SCFAs directly to the colon (Annison et al., 2003). It has also been shown that mid-colon can be stimulated by SCFAs to secrete the neurotransmitter serotonin (5-HT) (Fukumoto et al., 2003), but this was not the case for the orad or caudad colonic compartments, highlighting the importance of spatial biogeographic differences along the colon, and in particular, relevance to local spatial microbial population abundance changes (Grider and Piland, 2007). Moreover, SCFAs failed to stimulate 5-HT secretion from primary mouse enterochromaffin cells (Martin et al., 2017), and acetate has been shown to modulate gut 5-HT response by decreasing serotonin receptor 5-HT_{3B} expression (Bhattarai et al., 2017). As a result, more research is warranted to examine the potential mechanisms involved in SCFA impact on colonic, systemic and central serotonergic signalling (Russo et al., 2019), as it is yet unclear if this is beneficial or harmful to the host. Having considered the concentration and location of SCFAs in the GI tract, we will now cover the uptake of SCFAs by the host, from the gut.

2.3. SCFA uptake

While it is clear that gut SCFA levels are high and concentrations fluctuate along the extent of the small intestine, what is less obvious is how that affects host-microbe interaction and SCFA uptake. Specifically, gut-derived SCFAs are absorbed by the host epithelium, after which predominantly butyrate is used as an energy source for colonocytes (Hamer et al., 2008; Clausen and Mortensen, 1994; McNeil et al., 1978), which can be taken up from the intestinal lumen in one of two ways: via passive diffusion through the epithelia as non-ionised SCFAs (Mascolo et al., 1991; Walter and Gutknecht, 1984), or through protein transporters (Kekuda et al., 2013; Tamai et al., 1995). Non-ionised passive uptake of SCFAs was the first route identified (for example: reviewed in (Kamp and Hamilton, 2006)). This non-ionic theory of SCFA uptake was initially challenged, as butyrate rapidly dissociates to its anionic form in the colon, thus facilitated diffusion through transporters must take place (Phillips and Devroede, 1979). Indeed, only a very small portion of SCFAs in the gut are present in their non-ionised form, making the role of passive diffusion rather minor (Sellin, 1999).

The remainder of butyrate, as well as the majority of propionate, is subsequently metabolised by hepatocytes, resulting in 1- to 15- μmol/L concentrations of propionate and butyrate in circulation, whereas acetate is found within a range of 100–200 μmol/L (Stilling et al., 2016; Cummings et al., 1987; Peters et al., 1992; Bloemen et al., 2009) (see Table 1). This is supported by reports showing that exogenously administered SCFAs are metabolised in the same SCFA-specific preferential manner (Boets et al., 2017): i.e., butyrate > propionate > acetate.

Most SCFA anions are co-absorbed with cations such as Na^+ or K^+ (for example: reviewed in (Stumpff, 2018)). Facilitated SCFA diffusion through epithelia uses transporters such as the sodium-coupled monocarboxylate transporter (SMCT1) (Miyauchi et al., 2004; Cuff and Shirazi-Beechey, 2002), and the pH dependent hydrogen-coupled monocarboxylate transporter (MCT) 1 and 4 (Keduka et al., 2013; Tamai et al., 1995; Thangaraju et al, 2008). Other transporters for SCFAs exist but are thought to be quantitatively less important (for example: reviewed in (Dalile et al., 2019)). It is relevant to note that SCFAs can exert effects on the gut before they are taken into the general circulation, through various G-protein coupled receptors (GPCRs) and hydroxycarboxylic acid receptor 2 (for example: reviewed in (Parada Venegas et al., 2019)), mediating an anti-inflammatory effect (for example: reviewed in (Thorburn et al., 2014)).

Both diet and the transit time of digesting food may play a role in SCFA uptake. A diet high in resistant starch was found to increase the expression of MCT1 in pigs (Haenen et al., 2013). Faster colonic transit times in an *in vitro* model have been found to increase the faecal SCFA content, which is possibly due to impeded absorption of SCFAs (El Oufir et al., 2000), an important fact to keep in mind when measuring faecal SCFA content as an experimental output. Mice and rats express MCT1 highest in the caecum and colon, while other regions have low MCT1 expression (Iwanaga et al., 2006). The capacity of the GI tract to take up

SCFAs is likely highest in these areas of high expression. In humans, it has been shown that the proximal colon and ileum have very low expression of SCFA transporters but, MCT1, MCT4, and MCT5 increase along the colon, reaching its highest level of expression in the distal colon (Iwanaga et al., 2006).

2.4. SCFAs metabolism

Once taken up by the host, SCFAs act as an important metabolic fuel (Inoue et al., 2014; Bogie et al., 2020) as they can be used for the synthesis of glucose and lipids as host energy sources (Cani et al., 2019; Hu et al., 2018). When absorbed by colonocytes they are used in mitochondrial β-oxidation and the citric acid cycle (Schönfeld and Wojtczak, 2016). This provides a vital energy source for colonocytes; butyrate alone has been shown to provide 70% of energy requirements for colonocytes in mice (Serpa et al., 2010), and acetate can account for about 60–75% of the total faecal SCFAs (Parada Venegas et al., 2019). Intriguingly, germ-free mice exhibit a deficit in mitochondrial respiration in colonocytes (Donohoe et al., 2011). Those SCFAs not metabolised by colonocytes are transported into portal circulation (Bloemen et al., 2009). A comparatively small fraction of SCFAs enter systemic circulation capable of reaching peripheral tissues (Boets et al., 2015). In humans, the complete energy contribution of SCFAs has been estimated to provide 10% of daily caloric requirements (Bergman, 1990). Unlike butyrate, propionate and acetate do not serve as a primary energy source for colonic epithelia, but instead are used as energy substrates for peripheral tissues (den Besten et al., 2013), where concentrations of SFCAs can reach 19–160 μmol/l for acetate, 1–13 μmol/l for propionate, and 1–12 μmol/l for butyrate (Canfora et al., 2015) (see Table 1). Aside from being a source of fuel for the body, SCFAs can play a role in treatment and protection against metabolic disease; they have functions in host insulin sensitivity and appetite regulation, and could aid prevention of diet-induced insulin resistance and obesity (Shimizu et al., 2019). SCFAs are also used as substrates for gluconeogenesis, and cholesterol synthesis (van de Wouw et al., 2017; Boets et al., 2015; Hellman et al., 1954).

SCFA metabolism can lead to possible effects on host behaviour and physiology (see Table 3). For example, the metabolism of SCFAs by the citric acid cycle subsequently increases levels of mammalian target of rapamycin (mTOR) which functions in regulatory pathways controlling ribosome biogenesis and cell growth (Dennis et al., 2001). mTOR has also been implicated in host behaviour (Xu et al., 2018) and brain physiology (O'Riordan et al., 2014).

While much has been learned about diet-delivered host-indigestible and non-absorbable dietary fibres, which are metabolised by gut microbes into metabolites such as SCFAs, that then interact with the host gut epithelium, and are taken up for host metabolism, much work is still

Table 3
SCFA effects on brain physiology. SCFAs have a wide range of effects on the host's brain. They influence BBB integrity, regulate normal development and function of microglia, participate in inflammation, and even alter levels of neurotransmitters and intracellular potassium levels. SCFAs carry out these processes through affecting intracellular pathways, affecting cellular epigenetics, and changing protein levels.

Effect	Model	Refs
Acetate		
Altered levels of glutamine, glutamate, GABA, and anorexigenic neuropeptide expression in the hypothalamus.	*In vivo* mouse model	Fung et al. (2017)
Butyrate		
Improved integrity of BBB associated with increased levels of tight-junction protein occludin in frontal cortex and hippocampus, but no effect on claudin-5. Increased histone acetylation in brain lysates.	Effect seen with (i) Oral gavage of germ-free mice with butyrate and (ii) mono-colonisation with butyrate-producing *Clostridium tyrobutyricum* or acetate/propionate producing *Bacteroides thetaiotaomicron.*	Braniste et al. (2014)
Gut microbiota-derived butyrate may contribute to histone crotonylation in the brain.	Microbiota depletion in mice (specific pathogen free/ABX).	Fellows et al. (2018)
Butyrate epigenetically regulates the microglia response through downregulation of pro-inflammatory mediators and upregulation of anti-inflammatory mediators.	Experimental mouse (C57BL/6NTac) model.	Patnala et al. (2017)
Triggered the reversible elongation of microglial processes in normal and inflammatory conditions, through Akt activation.	*In vitro/in vivo*	Wang et al. (2018)
Abolished LPS-induced depressive-like behaviours and microglia activation in the hippocampus.	Behavioural mouse model	Yamawaki et al. (2018)
Obese individuals (n = 35) had higher levels of SCFAs than lean individuals (n = 33), while treated (Roux-en-Y gastric bypass/gastric sleeve) obese individuals (n = 90) showed reduced SCFA levels in faeces (n = 80, 6 months post-op).	Clinical studies	Farup et al., 2016; Schwiertz et al., 2010; Liu et al., 2018; Kim et al., 2019)
Propionate		
Can modulate lung immune responses: high-dose propionate delivered to the murine lung, mimicking antibiotic exposure, altered SCFA levels resulting in a diminished immune containment of *Staphylococcus aureus* pneumonia.	Mouse models (Wild-type C57BL/6 and C3H/HeOuJ)/cell cultures	Tian et al. (2019)
i.c.v. application of high doses caused ASD-like behavioural changes in rats.	Long–Evans rats	Macfabe (2012)
Reduction in inflammation and oxidative stress through decreasing CD41 expression on hCMEC/D3 cells, and affected the translocalisation of NFE2L2, a transcription factor nuclear factor involved in the antioxidant pathway.	*In vitro* cell cultures	Hoyles et al. (2018)
Reduction of experimental autoimmune encephalomyelitis (EAE) and axonal damage through increased Treg differentiation.	*In vitro* cell cultures	Haghikia et al. (2015)
Propionate and butyrate		
Regulated the expression of tryptophan hydroxylase and altered intracellular potassium in the cells of the central nervous system.	Review	Oleskin and Shenderov (2016)
Acetate, Propionate, and Butyrate		
SCFAs are sufficient to normalise germ-free associated alterations in microglia gene expression, morphology, and abundance, as well as establish normal maturation of microglia in germ-free animals.	Post-natal supplementation to germ-free animals.	(Borre et al., 2014; Erny et al., 2015)

needed to track and trace SCFAs mobility from the gut epithelium to the brain. We now turn our focus to the potential SCFAs have as gut-brain-axis signalling molecules in the host.

3. SCFAs: microbial metabolites that modulate gut-brain signalling

3.1. SCFAs and their peripheral and CNS receptors

The host enteric nervous system (ENS) is one of the first host physiological interactions for SCFAs in the gut (see Fig. 1) (Fung et al., 2017; Dalile et al., 2019; Stilling et al., 2016; Borre et al., 2014). Butyrate, propionate, and acetate have been shown to activate several GPCRs including GPR109A, GPR164 and OR51E2, the best characterised of which are GPR43 and GPR41 (Dalile et al., 2019). Now commonly referred to as free fatty acid receptor 2 (FFAR2) and FFAR3, the specificity of these receptors is known to be influenced by the length of the SCFA carbon chain (Nohr et al., 2015). Both FFAR2 and 3 are located on chromosome 19, where there is about 50% sequence similarity; it has been shown that FFAR2 has a high affinity for the shorter carbon chain SCFAs acetate and propionate, while FFAR3 prefers longer fatty acid molecules such as butyrate (Brown et al., 2003). These receptors are known to be expressed in a wide variety of cell types, including immune cells such as neutrophils, monocytes, and lymphocytes (Brown et al., 2003), innate lymphoid cells (Sepahi et al., 2021), as well as tissues ranging from gut and vasculature to organs, such as the kidneys. Although widely expressed on many different cell types, for the purposes of this review we will focus on the role of these receptors in neurons and their associated tissues.

Neuronally expressed SCFA receptors have been found in both the peripheral and central nervous systems (Falomir-Lockhart et al., 2019). The ability of SCFAs to cross the blood brain barrier (BBB; the primary structural barrier between the blood and the brain) was confirmed when radiolabelled ^{14}C–SCFAs were injected into the carotid artery of rats and detected in the brain (Oldendorf, 1973), in a self-inhibitory manner, where butyrate reported in higher per-cent access, then propionate, followed by acetate, at the ratio of 4.6:3.1:1.4 (B:P:A). Although, such experiments are often carried out with concentrations of SCFAs far above physiological levels, it is known that SCFAs are detectable at appreciable concentrations in human CSF (Wishart et al., 2018), with acetate at 0–171 μM, propionate at 0–6 μM, and butyrate at 0–2.8 μM (see Table 1). Not only are SCFAs capable of crossing the BBB but they are also believed to be important for BBB integrity and function. Germ-free mice have been shown to have appreciably lower levels of the important BBB tight junction proteins (TJP) claudin-5 and occludin, which can be reversed by colonisation of these animals with a mixture of bacteria, including SCFA producing strains (Braniste et al., 2014). Interestingly, expression of FFAR3 has been confirmed in brain endothelial cells, tentatively suggesting a mechanism whereby butyrate may influence the structure and function of the BBB (Hoyles et al., 2018).

Activation of FFAR's leads to the suppression of orexigenic hypothalamic activity in neurons expressing neuropeptide Y, which has been linked to changes in appetite and circadian rhythms (Silva et al., 2020). Interestingly, microbial SCFA-mediated stimulation of FFAR's has a downstream inhibitory effect on ghrelin secretion (Mishra et al., 2020; Engelstoft and Schwartz, 2016; Engelstoft et al., 2013). Indeed, an acute increase in colonic SCFAs was associated with reduced ghrelin concentrations (Rahat-Rozenbloom et al., 2017). Noteworthy, recent evidence suggest that SCFAs may inhibit signalling through the ghrelin receptor or the growth hormone secretagogue (GHSR-1a) receptor (Torres--Fuentes et al., 2019). Both propionate and butyrate were able to attenuate ghrelin-mediated Gq signalling of the GHSR-1a receptor. Additionally, acetate, butyrate and propionate decreased ghrelin-mediated GHSR-1a internalisation, a measure of β-arrestin mediated GHSR-1a signalling. Thus, SCFA-producing gut microbes may indirectly impact on ghrelin signalling via FFAR2-mediated ghrelin regulation, or directly via either antagonism or allosteric modulation of the GHSR-1a (Leeuwendaal et al., 2021). It has also been shown that acute oral administration of butyrate leads to a drop in the activation of a cohort of hypothalamic neurons which express neuropeptide Y, leading to a suppression of food intake (Li et al., 2018).

FFAR's also have a role in the normal function of glial cells. Although the mechanisms are yet unknown, it has been shown that mice lacking FFAR2 have microglia that were similar in profile to those of germ-free animals (Silva et al., 2020). Moreover, butyrate has been found to signal through GPR109a, which has been found to be expressed in the substantia nigra of individuals with PD (Wakade et al., 2014). Using fluorescent microscopy this same work demonstrated that the expression of GPR109a showed significant co-localisation with microglia, thereby suggesting a role in neuroinflammation, which we describe elsewhere in this review.

SCFAs have also been shown to interact locally in the gut, regulating ENS function and motility (Soret et al., 2010), where butyrate has been suggested as a treatment for GI motility disorders, including Inflammatory bowel disease (IBD) (Harig et al., 1989; Scheppach et al., 1992). The local mechanism of action in the colon has been proposed to be via commensal microbe-mediated induction of functional regulatory T (Treg) cells in the colonic mucosa (Furusawa et al., 2013). Indeed, such work has led to the idea of the diet-microbiota axis as a regulator of host immunity and homeostasis (Nagai et al., 2016). Further, targeting the duodenum with bioactive gut molecules called bacterial SCFA-containing enterosynes, has become a novel treatment therapeutic for type 2 diabetes, specifically modulating smooth muscle cells of the duodenal ENS (Knauf et al., 2020). SCFAs not only interact with and signal through the ENS in the host gut epithelium, but they also act on colonocytes, which we will explore in the next section.

3.2. SCFA-mediated enteroendocrine signals in the microbiome-gut-brain axis

As mentioned previously (and see Table 4), SCFAs are probably best known for their effects on type-L enteroendocrine colonocytes, specifically (Leeuwendaal et al., 2021). In binding FFAR2 and FFAR3 receptors (Lu et al., 2018), SCFAs signal the secretion of the anorexigenic hormones peptide YY (PYY) and GLP-1 (Tolhurst et al., 2012; Psichas et al., 2015; Cani et al., 2009; Larraufie et al., 2018). These peptides are transported to the brain via vagal afferents (Goswami et al., 2018) or circulating blood (Freeland and Wolever, 2010), where they can influence appetite and food intake (De Silva and Bloom, 2012). Notably, acetate was shown to cross the BBB and signal into different brain areas including increasing hypothalamic neuropeptide expression regulating satiety (Frost et al., 2014). Further, increased levels of colonic propionate was associated with decreased subjective appeal of high-energy foods, a reduction in energy intake, and a decreased actifvity in reward centres, with no changes in PYY and GLP-1 levels (Byrne et al., 2016). However, it has been reported that an acute increase in colonic SCFAs had no effect on GLP-1 or PYY levels in lean or healthy overweight/obese subjects (Rahat-Rozenbloom et al., 2017); although they suggest that a chronic enhancement in SCFA levels in a larger sample size may result in different outputs. Yet, another study using the same propionate delivery method saw increased GLP-1 and PYY levels after acute but not chronic delivery (Chambers et al., 2015).

While early evidence indicates that both PYY and GLP-1 are expressed in different brain regions (Trapp and Richards, 2013; Alvarez et al., 2005; Morimoto et al., 2008; Katsurada and Yada, 2016), including the nucleus tractus solitarius (NTS; a projection area of the vagus nerve) (Trapp and Richards, 2013), and that both have been shown to mediate reward-related cognitive processes, to have anti-anxiety and anti-depressant properties, and to enhance memory and neuroplasticity (van Bloemendaal et al., 2014; Anderberg et al., 2016; Gil-Lozano et al., 2010; During et al., 2003; Isacson et al., 2011), more work is needed to provide stronger evidence that PYY is produced

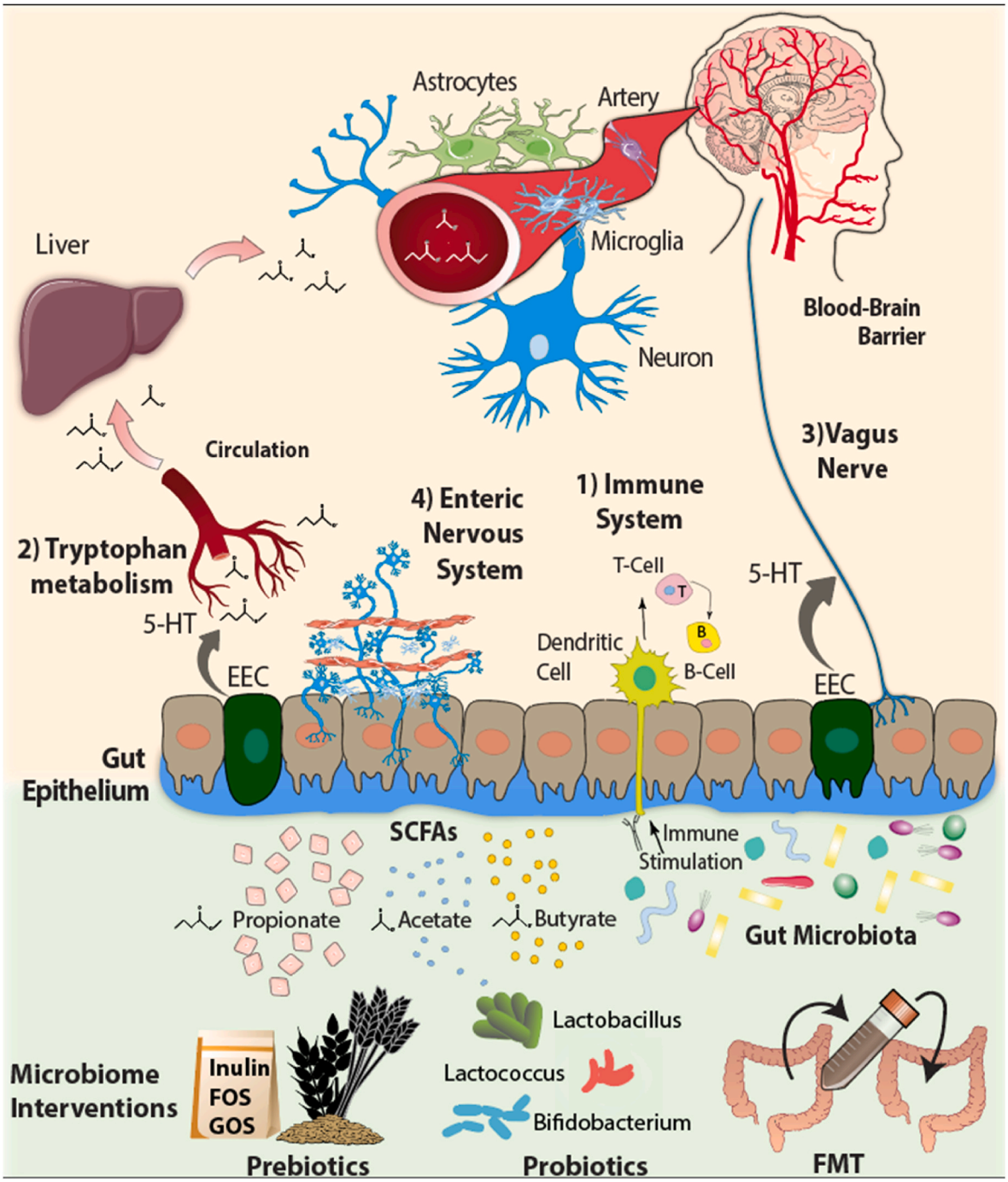

Fig. 1. The Microbiome-gut-brain axis. Communication between the gut microbiome and the brain occurs along the gut-brain axis, a bidirectional signalling pathway, comprising the 1) immune system, 2) tryptophan metabolism, 3) vagus nerve activity, 4) the enteric nervous system, as well as the bioactives (microbial by-products or metabolites) produced by the gut microbiome. FMT= Faecal microbiota transplant; FOS = Fructo-oligosaccharides; GOS = Galacto-oligosaccharides; SCFA = Short-chain fatty acids; EEC = Enteroendocrine Cell; 5-HT -5-hydroxytryptamine/Serotonin.

outside of the GI tract. Further, the extent to which SCFA-induced changes in these two appetite hormones could influence anxiety, stress or depression is still unclear.

SCFAs have also been associated with changes in the secretion of other hormones such as insulin and leptin; in particular, leptin secretion from adipocytes has been reported to be enhanced following SCFA stimulation (Xiong et al., 2004; Zaibi et al., 2010). Further, microbial derived SCFAs augmented FFAR stimulation and had a downstream inhibitory effect on ghrelin secretion (Engelstoft and Schwartz, 2016; Engelstoft et al., 2013). Interestingly, these hormones have been shown to influence brain function (Lee et al., 2016; Kullmann et al., 2016; Farr et al., 2015; Bali and Jaggi, 2016); thus, their possible involvement in SCFA-mediated cognitive processes constitutes an interesting avenue for further investigation. Both insulin and leptin have been shown to be differentially altered by SCFA supplementation regimes (Lin et al., 2012; Robertson et al., 2005), although some studies have reported no effects too (Zaibi et al., 2010; Perry et al., 2016; Frost et al., 2014). Not only have SCFAs been shown to interact with the ENS, CNS and gut epithelia, the have a potential influence on host epigenome. Next, we will review this association and potential avenue for microbial metabolite derived

Table 4
Role of SCFAs in enteroendocrine and neuropeptide signalling in the microbiome-gut-brain axis. SCFA interaction with their receptors on colonic enteroendocrine L-cells leads to the secretion of gut hormones such as PYY and GLP-1, both of which will signal to the brain via the vagus nerve or circulation. These hormones can in turn influence learning, memory and mood. SCFAs can also cross the BBB and influence central synthesis of some of these peptides. SCFAs have been shown to influence levels of other hormones, such as leptin, insulin and ghrelin. Finally, SCFAs are also able to cross the BBB and directly influence brain neuropeptide production and other aspects of brain function. FFAR-free fatty acid receptor; GLP-1- glucagon-like peptide-1; PYY-peptide YY; AMP- adenosine monophosphate; HDAC-histone deacetylase.

Target	Effect	Function	Refs
Acetate			
Hypothalamus	↑anorexigenic neuropeptide expression	Acetate suppressed appetite through phosphorylation-based changes in hypothalamic AMP-activated protein kinase and acetyl-CoA carboxylase activity, resulting in changes in downstream neuropeptide expression.	Frost et al. (2014)
Propionate			
Caudate and nucleus accumbens	↔GLP-1 ↔PYY plasma levels	Decreased appeal of subjective high-energy foods; reduced energy intake; decreased activity in reward centres. However, no differences in blood glucose or insulin concentrations, nor changes in neuropeptide levels, were found.	Byrne et al. (2016)
Butyrate, Propionate, and Acetate			
L-type enteroendocrine cells (*FFAR2, FFAR3*)	↑GLP-1 and ↑PYY secretion	Enhancement of GLP-1 release occurred via FFAR2 and FFAR3, while SCFA-induced release of PYY occurred in human enteroendocrine cells via HDAC inhibitory activity.	(Lu et al., 2018; Tolhurst et al., 2012; Psichas et al., 2015; Larraufie et al., 2018)
Adipocytes (*FFAR3*)	↑Leptin secretion	SCFAs stimulated leptin production through the G_i family by activating FFAR3 receptors. Increased SCFAs has been associated with reduced leptin levels and a suppression of body weight/fat gain.	(Xiong et al., 2004; Gabriel and Fantuzzi, 2019)
Ghrelin	↓↑Ghrelin secretion ↑PYY and GLP-1	Plasma ghrelin levels decreased after i.v. injection with all 3 SCFAs, and plasma glucose and insulin increased, but only with butyrate and propionate. Ghrelin, plasma PYY and GLP-1 were significantly increased after rectal acetate infusion in hyperinsulinaemic females.	(Freeland and Wolever, 2010; Fukumori et al., 2011)
Pancreas *(FFAR2, FFAR3)*	↓↑ Insulin secretion	Propionate, signalling by FFAR3 through a Gαi/o pathway, inhibited glucose-dependent insulin secretion. Acetate and propionate potentiated insulin secretion through FFAR2 in a mechanism coupled to Gq activation of phospholipase C and protein kinase C.	(Priyadarshini and Layden, 2015; Pingitore et al., 2019)

host epigenomic signalling.

3.3. SCFAs: signalling molecules at the interface between microbiome and epigenetics

The microbiome and the epigenome are dynamic systems that are in a constant state of flux dependent nutrient accessibility. Epigenetic mechanisms are required to respond to environmental stimulation, a process facilitated by several key enzymes. Many of these enzymes employ cellular metabolites as a source of acetyl, methyl or phosphate groups, which highlights the crucial role these metabolites may play in this epigenetic-microbiome crosstalk. It is at this juncture between the microbiome and epigenetic mechanisms that SCFAs have the potential to play a crucial role. In 1977, n-butyrate was shown to be a histone deacetylase (HDAC) inhibitor, providing early evidence of the importance of SCFAs in regulating host chromatin conformation (Riggs et al., 1977). Evidence for metabolic regulation of epigenetic signalling came from *in vitro* experiments showing that acetate was a putative marker for increased histone acetylation in adipocytes (Wellen et al., 2009), while experiments using propionate showed a reduction in HDAC expression in human colon cancer (HT-29) cells, and others showed increased histone acetylation (Hinnebusch et al., 2002). Using an organoid model, propionate and butyrate were shown to increase expression of HDAC3 and HDAC5 (Lukovac et al., 2014). Conversely, in HT-29 cells it was shown that butyrate was a potent inhibitor of HDAC activity in the colon (Waldecker et al., 2008).

Butyrate is a key metabolite capable of influencing epigenetic signalling; it was shown that dietary fibre could protect against tumour growth in the colon, which was consequently dependent on the presence of butyrate (Waldecker et al., 2008). Furthermore, when butyrate was supplemented to a high-fat diet given to obese C57BL/6J mice, it was capable of preventing and treating insulin resistance by promoting energy expenditure and stimulation of mitochondrial function (Gao et al., 2009). The gut microbiota also influences epigenetic programming as a function of colonisation status. Several post-translational modifications (PTMs) were shown to be dependent on the microbiome in germ-free, recolonised germ-free, and conventionally raised mouse studies. Intriguingly, these PTMs were noted in the liver and white adipose tissue as well as the colon, demonstrating that direct contact with the microbiome is not essential. Moreover, it was shown that the sensitivity of PTMs to colonisation was also influenced by diet with mice receiving a Western style diet displaying no changes in PTM composition (Krautkramer et al., 2016). A recent paper that examined the transcriptional landscape of the intestinal epithelial cell under homeostatic and inflammatory conditions, revealed that the methylome was shaped by the microbiome and that microbiome induced epigenetic changes were essential for maintaining homeostasis (Ansari et al., 2020; Pan et al., 2018). It is becoming clear that enzymes that modify histones have not only evolved to "recognise" endogenous metabolites but also metabolites derived from the gut microbiota.

Other histone PTMs include crotonylation, butyrylation and hydroxybutyrylation. Crotonylation in particular, is a PTM where a crotonyl group from crotonyl-coenzyme A is added to lysine residues that can both initiate and repress gene expression (Martinez-Moreno et al., 2020; Tweedie-Cullen et al., 2012). Crotonylation is found in the brain, and SCFAs are absorbed in the colon and enter the bloodstream (Fellows et al., 2018), which portends that SCFAs could influence neurophysiology and may have brain specific functions. Intriguingly, work involving butyrate producing bacteria such as *Clostridium butyricum* demonstrated a capacity to increase brain butyrate concentrations an order of magnitude higher than physiological levels (Sun et al., 2016). While it is clear that microbial metabolites can interact with the hosts epigenome directly, or indirectly, how much of an impact this has to modify the epigenome is less well understood. Nonetheless, a few studies have highlighted the affect the gut microbiome has on host physiological systems, both directly and indirectly, including brain function and behaviour, and the immune system, which we will now discuss.

3.4. SCFAs and host immunity

A single layer of epithelial cells constitutes a mucosal interface between the gut microbiome and host systemic immunity. This border is the setting for an interaction between metabolites produced by the

microbiome and immune cells from the host. It is here that our gut microbiota influences host immunity locally and in the periphery (Rooks and Garrett, 2016). SCFAs, through HDAC inhibition, can control the expansion of haematopoietic and non-haematopoietic cell lineages along with influencing their role in host immunity (Fellows et al., 2018). HDACs, when inhibited by SCFAs, promote tolerance and develop an anti-inflammatory phenotype that is important for maintenance of homeostasis and promote the concept that the microbiome can influence host physiology through epigenetic signalling (Rooks and Garrett, 2016). Many cells of the immune system are affected by SCFAs through HDAC inhibition; peripheral blood mononuclear cells (PBMCs), when stimulated with butyrate, decreased nuclear factor κB (Nf-κB) activation and tumour necrosis factor (TNF)-α secretion (Usami et al., 2008), while in neutrophils, acetate, propionate, and butyrate inhibited cytokine production and Nf-κB activation in a similar manner. Macrophages show a similar response to acetate and butyrate (Kendrick et al., 2010; Chang et al., 2014), while in dendritic cells (DC) butyrate and propionate block cell development and generate tolerogenic DCs (Singh et al., 2010; Trompette et al., 2014). These studies recognise HDAC inhibition by SCFAs as a crucial regulator of the host innate immune response through Nf-κB activation.

In another study examining the effect of gut-derived enrichment of propionate-producing gut bacteria, it was shown that this could modulate lung immune responses; although the same study reports that exposure of a high dose of propionate to the lungs directly, intended to mimic post antibiotic exposure status, reduced host immune containment of a *Staphylococcus aureus* pneumonia (Tian et al., 2019).

SCFAs can also influence the amount and function of immune cells such as T_{reg} cells in the periphery through HDAC inhibition *in vivo*. These functions have been shown to be essential in maintaining immune homeostasis. In mice, the T cell transcription factor, forkhead box P3 (Foxp3), which is normally suppressive, was increased in T_{reg} cells and supported the attenuation of colitis through inhibition of HDAC9 expression (Tao et al., 2007). In fact, many studies have shown that HDAC inhibition by SCFAs can influence the number of $Foxp3^+$ T_{reg} cells in the colon under normal conditions (Rooks and Garrett, 2016). Interestingly, maternal diet enriched with SCFAs was capable of influencing asthma by suppression of $Foxp3^+$ T_{reg} cells in the lung (Thorburn et al., 2015). Therapeutically, the use of HDAC inhibitors has been shown in many mouse models of inflammation, including lipopolysaccharide (LPS)-induced cytokine production from DCs where it reduced TNF-α, interleukin (IL)-1β, IL-6 and interferon (IFN)-γ, through impairment of Nf-κB (Wang et al., 2009). SCFAs also play a crucial role in the maintenance of mucosal immunity by strengthening the epithelial cells that line the mucosal layer (Said et al., 2017). For example, mucus production by goblet cells is enhanced in mice administered SCFAs, with increasing levels of *Muc2* gene expression and prostaglandin synthesis (Willemsen et al., 2003), while in germ-free mice colonised with SCFA-producing *Bacteroides thetaiotaomicron* or *Faecalibacterium prausnitzii,* differentiation of goblet cells and mucus production was increased (Wrzosek et al., 2013).

3.5. SCFAs and neuroimmune function

Under normal physiological conditions activation of immune cells and cytokine production has minimal impact on the CNS. Systemic infection though, can have a considerable impact on cognition and behaviour (Nutma et al., 2019; Cruz-Pereira et al., 2020), and the interaction of cytokines with neural processes can influence both mood and motivation (Capuron and Miller, 2011). While we have already discussed the role SCFAs play in host immunity at the luminal surface, it is also conceivable that alterations in the microbiome can influence SCFA supply. This in turn could influence peripheral immunity, and hence the brain; therefore, systemic inflammation could be reduced by improving barrier function, and be modulated by the interaction of SCFAs with immune cells (Dalile et al., 2019).

It is likely that SCFAs can also influence brain function through their interactions with the innate and adaptive arms of the immune system. One study observed a reduction in hippocampal neurogenesis following antibiotic treatment, which was subsequently reversed with a combination of probiotics and recolonisation with an unperturbed microbiota (Mohle et al., 2016). Of interest in this study was that $LY6C^{hi}$ monocyte levels in the brain correlated positively with neurogenesis (Mohle et al., 2016), thus positing a role for SCFAs in this relationship (Nastasi et al., 2015; Corrêa-Oliveira et al., 2016), which warrants further investigation.

It is perhaps obvious that systemic inflammation may play an important role in neuroinflammation (Dalile et al., 2019), but more work is needed to interrogate the role that SCFAs may play. Within the brain, microglia control innate immune function and are critical for brain development. Moreover, the gut microbiome has been shown to influence microglia. Under homeostatic conditions, a composite microbiome promotes the maintenance and function of the microglia while also contributing to maturation (Erny et al., 2015). Interestingly, in germ-free mice that normally possess underdeveloped microglia, supplementation with SCFAs (acetate, butyrate and propionate) enhanced maturation of underdeveloped microglia back to a structure similar to that of specific pathogen-free (SPF)/control mice (Erny et al., 2015). How SCFAs sourced from the gut influence microglia structure and function remains to be elucidated, but it is likely to involve FFAR's. Of interest, it was shown that FFAR2 knockout mice possess microglia similar in structure and stunted appearance to germ-free mice (Gautier et al., 2012). SCFAs can regulate many processes along the microbiota-gut-brain axis through direct and indirect methods, and epigenetic signalling, as discussed earlier, is central to this communication. Understanding this relationship may be key to developing therapeutic strategies for disorders of the CNS.

In rat primary microglia, LPS-induced inflammation was reduced by treatment with butyrate, indicating an anti-inflammatory mode of action. However, treatment of microglia with butyrate and propionate following an LPS challenge displayed a pro-inflammatory response (Huuskonen et al., 2004), by reducing IL-6 secretion by primary murine microglia and increasing IL-6 secretion from N9 microglia. Further, a SCFA mixture at "physiological" micromolar concentrations reduced the level of cytotoxins and cytokines secreted by THP-1 microglia-like cells, and the SCFAs formate and valerate specifically decreased the phagocytic activity of stimulated THP-1 cells (Wenzel et al., 2020). It is clear that much more research is needed to elucidate the precise mechanisms SCFAs produced by the gut microbiota could influence neuroinflammation. However, now we will consider the effect of the BBB on SCFA signalling to the brain.

4. SCFAs and the blood brain barrier

As mentioned earlier, the primary structural barrier between blood and brain, the BBB, plays a critical role of defence for the brain against a potentially detrimental attack. The BBB helps maintain brain homeostasis and is highly selective with very low paracellular permeability, preventing unwanted toxins and pathogens from entering the brain, and therefore must be a prime consideration of the direct effect of SCFAs on brain and behaviour. The BBB is a close connection of endothelial cells, astrocytes, pericytes, and the basement membrane, tied to one another through the tight junction proteins claudin-5, occludin, and zonula occludens-1. Barrier integrity is measured both through functional permeability of the barrier and expression of the tight junction proteins, which are known to greatly reduce paracellular permeability. The barrier function plays a crucial role in the microbiome-gut-brain axis, seeing that it is significantly more permeable in germ-free mice (Braniste et al., 2014) (see Fig. 2A), or in mice treated with antibiotics, when compared to control mice (Sun et al., 2020a; Wu et al., 2020b).

It is possible that SCFAs can affect BBB permeability and integrity through microbial metabolite interactions with the cellular components

of the BBB (see Table 3). Oral gavage of germ-free mice with sodium butyrate significantly improved BBB integrity through a reduction in permeability and an increase in TJP expression (Braniste et al., 2014). Additionally, mono-colonisation of germ-free mice with the butyrate producer *Clostridium tyrobutyricum,* and the acetate and propionate producers *Bacteroides thetaiotaomicron*, also reduced BBB permeability (Braniste et al., 2014) (see Fig. 2B). This was recapitulated *in vitro* where both butyrate and propionate, but not acetate, protected the BBB from LPS-mediated disruption (Hoyles et al., 2018) (see Fig. 2C).

As mentioned earlier, data thus far indicates that SCFAs can reach the brain, having been found in CSF in appreciable concentrations (Wishart et al., 2018) (see Table 1), and hence influence BBB integrity through modulation of the TJPs, but further understanding of the mechanisms have yet to be elucidated. Also mentioned earlier, one other potential mechanism is through interactions with the FFAR3 receptors present on brain endothelial cells. Propionate reduces inflammation and oxidative stress through decreasing CD41 expression on the surface of cells, and effecting the translocalisation of NFE2L2, a transcription factor nuclear factor involved in the antioxidant pathway (Hoyles et al., 2018). The involvement of other cellular structures and components remain unknown. It should be noted that only the SCFAs acetate, butyrate, and propionate have been explored for direct effects on BBB physiology. However, an additional microbial metabolite, methylamine trimethylamine N- oxide (TMAO) also has protective effects on BBB integrity, while its precursor trimethylamine (TMA) impairs BBB integrity (Hoyles et al., 2021). It is clear that much more work is still needed to elucidate the involvement of the BBB in SCFA-mediated brain and behaviour interactions.

Thus far we have assessed that gut-derived bioactive molecules such as SCFAs can signal to the brain, directly and indirectly, through interaction with GPCRs (FFARs) on the host gut epithelium (e.g. colonocytes), the brain and the BBB, and with immune cells, suggesting a role for SCFAs in neuroinflammation, as well as regulating appetite and food intake. One alternative route of communication between the gut and the brain where SCFAs could play a role is with vagus nerve activity, which we will address next.

5. SCFA-induced vagus nerve activation

Probably the fastest and most direct route of communication between the gut microbiota and the brain involves signalling via the vagus nerve (see Fig. 1). Much research has so far been conducted to help elucidate the mechanisms involved. For example, acetate can reduce the effect of food intake, which was shown when it was administered directly into the third ventricle of intracerebroventricular (i.c.v.) cannulated male Wistar rats and compared to intraperitoneal (i.p.) delivery (Frost et al., 2014). Further, when butyrate was administered via oral gavage to rodents, decreased food intake, and reduced neuronal activity in the NTS were seen. This effect was abolished in mice that had undergone subdiaphragmatic vagotomy, where they did not show a reduction in food intake relative to sham mice supplemented with sodium-butyrate enriched food for 7 weeks (Li et al., 2018). Moreover, an i.p. injection of SCFAs differentially reduced food intake, with butyrate being more effective than propionate, and both more so than acetate, which was attenuated following ablation of the hepatic branch of the vagus nerve (Goswami et al., 2018), although it should be noted that i.p. injections of SCFAs may potentially be noxious and thus have acted as a possible confounding factor in this study. However, it is as yet unknown if SCFAs themselves act on the vagus nerve directly, or indirectly. It has been shown that FFAR3 is expressed in the periportal afferent neural system, hinting at the possibility of FFAR3 expression in vagal afferents allowing for the potential of direct vagal activation by SCFAs (De Vadder et al., 2014). FFAR3 has been shown expressed in the enteric neural plexus and autonomic and sensory ganglia, supporting the hypothesis that SCFAs are able to directly mediate their effects via the vagus nerve or the ENS (Nohr et al., 2015; De Vadder et al., 2014; Kaji

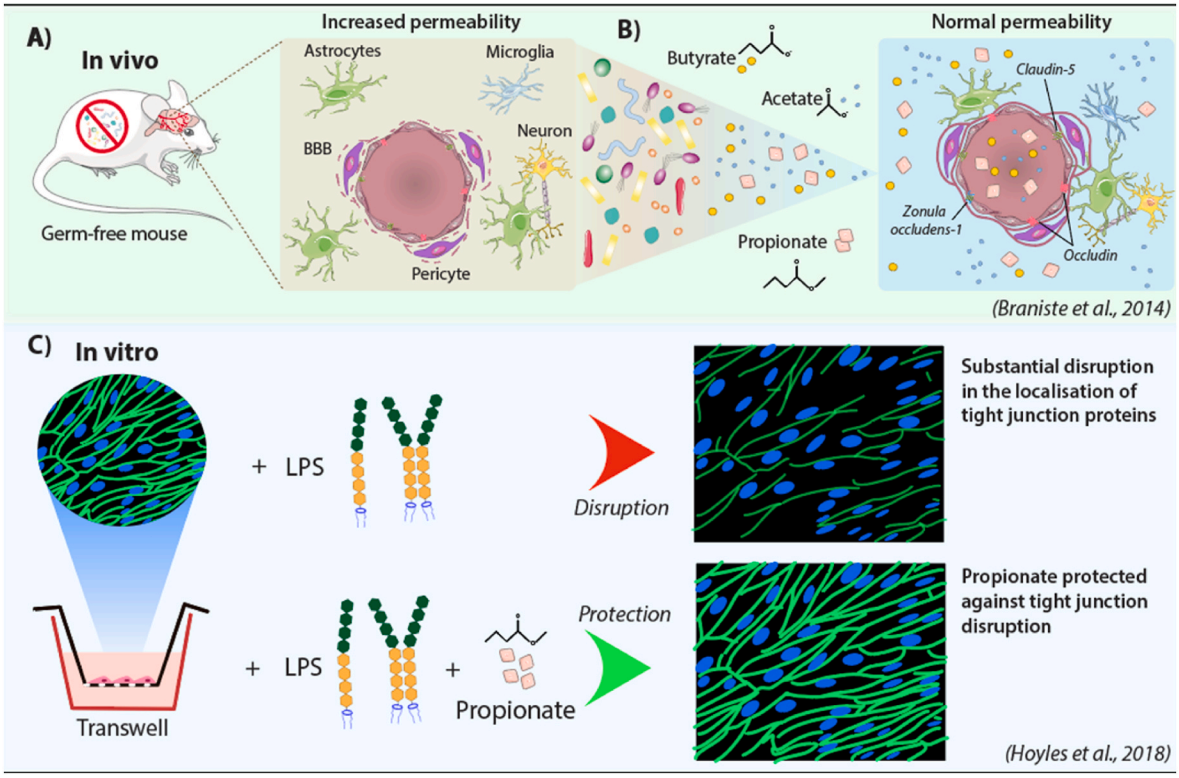

Fig. 2. Short chain fatty acids protect blood brain barrier structure and integrity. A) Germ-free mice have a disrupted BBB and, B) monocolonisation with bacterial strains producing mainly acetate and propionate, or butyrate, as well as oral gavage of sodium butyrate, improves BBB integrity. C) Cell culture BBB models have disrupted integrity when treated with LPS, but pre-treatment with propionate protects against BBB disruption. BBB = Blood-brain barrier. LPS = Lipopolysaccharide.

et al., 2016; Won et al., 2013).

It is clear that SCFA-induced vagus nerve signalling results in the activation of various neurons in the CNS. However, more research is needed to investigate the regulatory mechanisms occurring, and which specific neuronal populations are activated in SCFA-induced vagus nerve signalling throughout the brain, and how this relates to behaviour. While much of the discussion thus far has dealt with homeostasis and healthy scenarios, much work has uncovered a role for SCFAs in diseased or immunocompromised host states, which we will now explore.

6. SCFAs in disorders of the microbiota-gut-brain axis

Both preclinical and clinical evidence point to shifts in the composition of the gut microbiome being partially responsible for the exacerbation of several disorders of the CNS (see Table 5), including traumatic brain injury, AD and PD (Silva et al., 2020). Consequently, this implies that the microbiome and SCFAs can be a critical target in the treatment and improvement of core symptoms in these conditions (Long-Smith et al., 2020). Indeed, a range of disorders including ASD, anorexia nervosa, and multiple sclerosis (MS) have also been correlated with alterations in gut microbiota in humans and animal models (Spichak et al., 2021a; Dalile et al., 2019; Morita et al., 2015; Unger et al., 2016; Zhang et al., 2017; Deng et al., 2019; Sharon et al., 2019; Jackson et al., 2019; Cryan et al., 2020). Regarding PD, an alteration in SCFA levels has been noted in individuals with PD, and animal models. Orally administered SCFAs was shown to be sufficient to induce PD related deficits and promoted neuroinflammation in an α-synuclein-based mouse model of PD (Sampson et al., 2016). This is at odds with a growing literature from human studies that have seen decreased SCFA-producing bacteria and decreased levels of SCFAs in PD individuals (Unger et al., 2016; Nishiwaki et al., 2020; Vascellari et al., 2020; Wallen et al., 2020). Targeting this deficit by treating mesencephalic cell cultures with propionate in an *in vitro* model of PD, promoted cell survival of dopaminergic cells (Ostendorf et al., 2020). Further, amyloid uptake in humans positively associated with blood acetate levels, and negatively associated with blood butyrate levels (Marizzoni et al., 2020).

Decreased SCFA levels were found in both experimental and clinical models of AD (Zhang et al., 2017; Doifode et al., 2021). Acetate has been seen to have an anti-inflammatory effect in a mouse model of AD, through upregulation of FFAR3, and inhibition of ERK/JNK/Nf-κB intracellular signalling pathway (Liu et al., 2020). The butyrate producing *C. butyricum* protected against microglia mediated inflammation in a transgenic mouse model of AD (Sun et al., 2020b). Finally, SCFAs interfered with the formation of neurotoxic oligomers from amyloid-β peptides, one of the hallmarks of AD (Ho et al., 2018). However, it has

Table 5
Diseases associated with SCFA alterations/imbalance. SCFAs have been shown to associate with numerous diseases; however, these association are highly varied. SCFA supplementation appears to be a good candidate for disease amelioration in several cases, a theory bolstered by observations of reduced SCFA levels in some disease. However, some diseases feature increased SCFA levels and certain animal models of human diseases (e.g., ASD) associate with large concentrations of SCFAs in the gut. ASD-autism spectrum disorder.

Disease	Association	Refs
Autism Spectrum Disorder (ASD)	Children with ASD had higher faecal acetate, butyrate, isobutyrate, valerate, isovalerate and caproate than controls.	Wang et al. (2012)
	Children with ASD had much lower levels of acetate, propionate, and valerate than controls, and exacerbated further in children with autism taking probiotics.	Adams et al. (2011)
	The severity of ASD was affected by increases in propionate-producing bacteria and decreases in butyrate producing bacteria.	(Finegold, 2011; Finegold et al., 2010)
	Administration of high amounts of propionate to rodents through various routes, such as i.c.v., is used as an animal model of autism.	(Choi et al., 2018; Macfabe, 2012)
	Sodium butyrate increases sociability in autism mouse model (BTBR).	Kratsman et al. (2016)
Alzheimer's Disease (AD)	Amyloid uptake in humans positively associated with blood acetate levels and negatively associated with blood butyrate levels.	Marizzoni et al. (2020)
	The level of SCFAs is reduced in mouse models of AD.Concentrations of butyrate, and isobutyrate in particular, were reduced in both faeces and brain of AD ($APP^{swe}/PS1^{\Delta E9}$ (PAP)) transgenic male mice.	Zhang et al. (2017)
	In vitro SCFAs interfere with the assembly of β-amyloid (Aβ) peptides into the soluble neurotoxic aggregates seen in AD. In particular, the relative anti-Aβ aggregation efficacy in decreasing order was valerate ≫ butyrate > propionate.	Ho et al. (2018)
	Supplementation of SCFAs to germ-free APPPS1 mice nearly doubled the cerebral Aβ plaque load, potentially through modulation of the microglial phenotype.	Colombo et al. (2021)
Multiple Sclerosis (MS)	An animal model of MS found oral SCFA (butyrate, caproate, laurate) administration to be beneficial, reducing the severity of EAE.	(Haghikia et al., 2015; Mizuno et al., 2017)
	Acetate supplementation prevented the onset of clinical symptoms of EAE.	Chevalier and Rosenberger (2017)
	Oral administration of butyrate significantly ameliorated demyelination in mice fed oral antibiotics, which significantly enhanced cuprizone-induced demyelination. Further, *in vitro* (organotypic slice culture) butyrate treatment suppressed lysolecithin-induced demyelination and enhanced remyelination.	Chen et al. (2019)
Parkinson's Disease (PD)	Faecal butyrate levels in PD patients were reduced.	Unger et al. (2016)
	Faecal acetate, propionate, butyrate and n-valerate were all increased in a murine PD model over control mice, with acetate up 260.6%. FMT from control mice reduced these increases to lower than control levels.	Sun et al. (2018)
	Orally administered SCFAs promoted neuroinflammation and motor deficits in a mouse model of PD	Sampson et al. (2016)
	Butyrate supplementation attenuated behavioural impairments in mouse and *Drosophilia* models of PD.	(Liu et al., 2017; Laurent et al., 2013)
	Butyrate rescued dopaminergic cells from transcriptional deregulation and DNA damage induced by α-synuclein.	Paiva et al. (2017)
Major Depressive Disorder (MDD)	Faecal propionate content was lower and isocaproate was higher in depressed individuals; there was also negative correlations between acetate, propionate, and Beck's score and significant correlations between acetate and propionate and BDI somatic scores, as well as isocaproate, and both cognitive/affective and somatic scores. This work suggests that SCFAs may potentially contribute to the depression phenotype.	Skonieczna-Żydecka et al. (2018)
	Serum and cerebrospinal fluid SCFAs (including acetate and butyrate) levels were lower in a non-human primate model of depression.	Deng et al. (2019)
	Butyrate has been shown to have possible antidepressant effects in rodent models e.g. reducing depressive-like behaviour from chronic psychosocial stress, and reversing anhedonia and sociability impairments.	Resende et al. (2013)

been reported that SCFA supplementation to a germ-free AD mouse model was sufficient to nearly double cerebral Aβ plaque load (Colombo et al., 2021). There is also some evidence to show that butyrate can confer a neuroprotective effect in ischemic stroke by decreasing microglial activation, reducing levels of pro-inflammatory markers, and increasing the levels of anti-inflammatory markers (Patnala et al., 2017). Clearly more work is needed to categorically elucidate the role, either positive or negative, if any, for SCFA involvement in either PD, AD, or ischemic stroke.

Altered SCFA levels have also been seen in the pathophysiology of MS, although the picture is far from clear. Positive correlations between SCFAs and disease duration, and negative correlations between SCFA and disease starting age, have been found in individuals with untreated MS (Dominguez-Mozo et al., 2021). One study found that the serum and faeces of MS patients exhibited reduced propionate levels compared to healthy controls; however, the ratios of propionate/acetate and butyrate/acetate were significantly higher in healthy controls, leading them to conclude that there may be a possible dual role for propionate or butyrate, and acetate (Duscha et al., 2020). Interestingly while acetate has been shown to correlate positively with disability and immune response (Pérez-Pérez et al., 2020), acetate supplementation has been shown to prevent the onset of symptoms in an animal model of MS (Chevalier and Rosenberger, 2017).

Individuals with depression or a lower quality of life (using the RAND-36 health-related quality of life survey (Hays et al., 1993)) score, revealed an association between butyrate producing bacteria (*Coprococcus* and *Faecalibacterium*), and indicators of a higher quality of life (Valles-Colomer et al., 2019). Two SCFA producing bacterial genera *Prevotella* (Lin et al., 2017) and *Bifidobacterium* (Koh et al., 2016; Rong et al., 2019) were present in greater relative abundance in individuals with major depressive disorder (MDD), a metric that is easily measured and should be factored in to the diagnosis and therapeutic intervention in MDD. Specific bacterial families (Lachnospiraceae and Ruminococcaceae) from the Firmicutes phylum were shown to be reduced in individuals with MDD (Jiang et al., 2015), while increased in healthy controls (Hu et al., 2019). From the Lachnospiraceae family in particular, *Roseburia*, *Blautia*, and *Lachnospiraceae incertae sedis* genera, are known to be involved in the production of SCFAs from the breakdown of carbohydrates (Duncan et al., 2007), and *Roseburia,* and *Coprococcus* (Hu et al., 2019), along with *Faecalibacterium* (Painold et al, 2019), were reported in lower abundance in individuals with bipolar disorder. Not only has *Faecalibacterium* been associated with better self-reported health outcomes, it was associated with better sleep quality, and lower generalised anxiety and mania in a bipolar population (Evans et al., 2017), although see (Lu et al., 2019), where it was reported that *Faecalibacterium prausnitzii* was present in higher proportions in a bipolar population than healthy controls. This discrepancy may be explained by the fact that individuals in the first study (Evans et al., 2017) were on at least one or more medication for their condition at the time of testing, whereas individuals in the second study (Lu et al., 2019) had ceased medication for at least 3 months prior to testing, or had never received any psychotropic medication. Therefore, the state of medication and polypharmacy need to be taken into consideration for future human studies.

Further, recent work suggests that SCFAs may potentially contribute to the depression phenotype. Faecal propionate content was lower, and isocaproate higher, in depressed Polish individuals (Skonieczna--Żydecka et al., 2018); there were also negative correlations between acetate, propionate, and Beck's score, as well as significant correlations between acetate and propionate and BDI somatic score. Although the authors themselves point out that the group sizes were small (moderately heavy (n = 5) and severe (n = 7) depression), as well as the pharmacotherapy of hyperlipidemia and thyroid disease present in the tested population.

Given that SCFAs display neuroactive properties (Stilling et al., 2016), their potential to modulate autism-related behaviour cannot be overlooked. Indeed, transplantation of human gut-microbiota to mice from donors with ASD, induced ASD-related behavioural deficits (Sharon et al., 2019). Intraventricular infusions of relatively high doses of propionate have been proposed as an ASD model, where neurotoxic doses of propionate could induce autism-like behaviour in rodents (MacFabe et al., 2011; Shultz et al., 2015). These mice display impaired sociability, epileptic and convulsive responses, and increased repetitive behaviours. It is possible that an underlying mechanism of ASD is overproduction of propionate by gut-microbiota leading to elevated levels of propionate in the brain. Another study reported vastly altered brain physiology following high doses of propionate using various modes of administration (Choi et al., 2018). However, whether elevated levels of an individual SCFA such as propionate can play a part in what is clinically observed in ASD individuals is unknown. Conflicting findings from clinical studies show both increases (Adams et al., 2011) and decreases in faecal SCFA levels (Wang et al., 2012), confusing the picture of the exact relationship of SCFAs to ASD. Along with altered behaviours such as repetitive actions, and impaired sociability, they noted changes in gene expression, and increased microglial activation. Moreover, social behaviour was shown to be modulated via immunoregulation and microbiota maintenance (Chen et al., 2019). Further, a recent large ASD stool metagenomics study uncovered negligible direct associations between ASD diagnosis and the gut microbiome, querying whether gut-derived microbial signalling molecules have any driving role in ASD at all (Yap et al., 2021).

In humans, members belonging to the *Lachnospiraceae* family have been shown to be protective as an artificial stool preparation against antibiotic-resistant *Clostridium difficile* infection (Petrof et al., 2013) and metabolic disorders (Cho et al., 2012). In particular, one study (Petrof et al., 2013) reported associations with the abundance of the *Lachnospiraceae* family, but not direct evidence. Nonetheless, the members of *Lachnospiraceae* are potent producers of SCFAs (see Table 2) (Duncan et al., 2002), which suggests SCFA levels could act as potential drivers of protection against these ailments.

SCFA uptake and absorption can be affected by numerous factors including obesity. When a high concentration of SCFAs was generated in the rectum of human subjects', obese individuals were found to absorb more SCFAs than lean individuals (Rahat-Rozenbloom et al., 2014). However, most SCFAs are absorbed in the proximal colon, which in humans is as yet unexamined in this context. Inflammatory bowel disorder (IBD) features a decreased absorption of butyrate due to a downregulation of MCT1 (Thibault et al., 2007). A similar downregulation has also been seen in ulcerative colitis (Fisel et al., 2018), which likely has a similar effect on SCFA absorption.

In irritable bowel syndrome (IBS), abnormal faecal SCFA levels have been reported (Farup et al., 2016), indicating that faecal SCFA levels could be used as a possible diagnostic biomarker. However, there does appear to be non-uniform SCFA changes across different IBS subgroups (Farup et al., 2016; Gargari et al., 2018; Ringel-Kulka et al., 2015; Tana et al., 2010). For example, individuals with IBS had a higher proportion of faecal propionate than healthy controls (Sun et al., 2019). Further, faecal microbiota transplantation (FMT) from a single super-donor was given to individuals with IBS, which ameliorated symptoms and raised butyrate levels across all IBS groups, including diarrhea-predominant IBS, the subgroup that displayed a raised level of butyrate compared to healthy controls (El-Salhy et al., 2021), and identified as having significantly reduced levels of MCT1 and SMCT1 (Fredericks et al., 2020). However, not all research has reported SCFA level changes in IBS (Tian et al., 2020), although changes were reported in serum levels of butyrate and propionate. Such data indicates that further analysis of IBS subgroups is warranted, to ascertain different IBS subgroup SCFA profiles.

Chronic stress is a considerable risk factor for the development of neuropsychiatric disorders (Ramirez et al., 2017) and the microbiome-gut-brain axis has been shown to play a key role in the relationship between stress and the brain (Cruz-Pereira et al., 2020).

Recent clinical work has shown that colon-delivered SCFAs have the potential to modulate the core hypothalamic-pituitary-adrenal (HPA)-axis responsivity to psychosocial stress (Dalile et al., 2020). Preclinical experiments have now convincingly shown that chronic stress alters the composition of the gut microbiome and interventions that target the microbiota can reduce or eliminate the effects of stress on host physiology and brain function (Burokas et al., 2017; Bharwani et al., 2017). Pre-clinical work from our lab has shown that supplementation with acetate, butyrate and propionate in mice undergoing prolonged psychosocial stress had a positive effect on behaviour and stress-induced gut permeability (van de Wouw et al., 2018).

As the field of microbiome-gut-brain axis research matures, and microbiota-derived SCFA involvement in health and disease is accruing more evidence, we are still at a somewhat preliminary stage of understanding whether our observations are correlational or if there is strong support for a causal role. Interpretation and a full understanding of such data is proving difficult and conflicting. This only emphasises the pressing need for better designed and controlled longitudinal human studies in healthy and diseased populations, run in tandem with preclinical studies incorporating translational disease models, to fully uncover the underlying mechanisms and potential role for SCFAs as novel therapeutics.

7. Conclusion and future research

It is becoming increasingly clear that the gut-microbiota can act as key regulators of communication along the bidirectional gut-brain axis. While the communication pathways are facilitated via various routes including the immune system, the vagus nerve, and the enteric nervous system, the direct or indirect involvement of microbial metabolites such as SCFAs is being examined more closely, both as biomarkers of pathological states and for the development of novel therapeutic strategies. While a growing number of studies are examining the effects of gut derived SCFAs on host physiology, no consensus has yet been reached whether a specific SCFA signature exists, per se. Although there has been much warranted interest in the field, caution needs to be exercised as much of the available clinical data is largely derived from small cohorts and lacks consensus and a longitudinal perspective (McLoughlin et al., 2017). More mechanistic studies are needed to understand how changes in gut microbiota metabolite levels can moderate health and disease, to ascertain safety efficacy for potential therapeutic advice.

As it stands, SCFAs, circulating concentrations of which are heavily manipulable by diet, appear to be strong candidates with both direct and indirect effects on the brain. SCFAs can exert influence over intestinal barrier integrity and regulate host GI immunity, resulting in peripheral immunity modulation, ultimately protecting against disease states, which involves neuroinflammation, including obesity and affective disorders. SCFAs have also shown that they can protect against neurotoxin infiltration at the BBB through augmentation of BBB tight junction expression patterns. SCFAs have been shown to directly modulate luminal concentrations of neurotransmitters and neurotrophic factors, leading to the potential for neuronal growth and excitability regulation, in both the ENS and CNS. SCFAs have also been shown to modulate the HPA axis, regulating the stress responses in mammals.

However, even with a growing body of preclinical research supporting the hypothesis that SCFAs can be used as novel therapeutics to augment cognitive deficits, definitive evidence supporting translatability of these findings to a human population is lacking, although early evidence is encouraging (Dalile et al., 2020; Schellekens et al., 2021). There are only a few clinical observational and interventional studies to date, and more are needed, examining SCFA supplementation across the lifespan, including at the extremes of life. Much evidence is uncovering the involvement of SCFAs in brain health and function in offspring of maternal dietary interventions, and cognitive outcomes in an aging model. It is crucial that we gather more information that may inform if switching to a diet designed to increase/decrease SCFA levels in the body can improve cognitive outcomes. It may be that microbial accessibility (i.e., fermentability) is an important consideration in designing dietary needs for positive influence on cognition. Therefore, it is crucial that future research is designed to investigate the mechanisms involved, taking the individual's genetics, gut-microbiota profile, and other pertinent lifestyle factors into consideration.

Malnutrition is often associated with poor cognitive function; therefore, it is imperative that we examine whether supplementing impoverished societies with a microbiota-directed complementary food that modulates SCFA levels can improve neurodevelopment and cognitive function, especially in children. More research needs to be conducted to establish causality and understand the role SCFA-boosting foods or prebiotics can have in helping decipher mechanistic relationships. Better dietary habits supporting mental health need to be advocated, but an increase in understanding of the pathways are urgently needed. More high-quality data is needed on brain function, behaviour, and physiology, and should be championed to help establish evidence-based health claims aimed at developing therapeutic interventions for diseases associated with cognitive dysfunction and inform future microbiota-targeted interventions for brain disorders.

Acknowledgements

Prof. Cryan is funded by Science Foundation Ireland SFI/12/RC/2273_P2, the Saks Kavanaugh Foundation, EU H2020 project DLV-848228 DIS-COvERIE, and Swiss National Science Foundation project CRSII5_186346/NMS2068. Prof. Cryan has received research funding from 4D Pharma, Cremo, Dupont, Mead Johnson, Nutricia, and Pharmavite; has been an invited speaker at meetings organized by Alimentary Health, Alkermes, Ordesa, and Yakult; and has served as a consultant for Alkermes and Nestle.

References

Adams, J.B., Johansen, L.J., Powell, L.D., Quig, D., Rubin, R.A., 2011. Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 11, 22,. https://doi.org/10.1186/1471-230X-11-22.

Agus, A., Planchais, J., Sokol, H., 2018. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 23, 716–724. https://doi.org/10.1016/j.chom.2018.05.003.

Agus, A., Clement, K., Sokol, H., 2021. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut 70, 1174–1182. https://doi.org/10.1136/gutjnl-2020-323071.

Alvarez, E., et al., 2005. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. J. Neurochem. 92, 798–806. https://doi.org/10.1111/j.1471-4159.2004.02914.x.

Anderberg, R.H., et al., 2016. GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. Psychoneuroendocrinology 65, 54–66. https://doi.org/10.1016/j.psyneuen.2015.11.021.

Annison, G., Illman, R.J., Topping, D.L., 2003. Acetylated, propionylated or butyrylated starches raise large bowel short-chain fatty acids preferentially when fed to rats. J. Nutr. 133, 3523–3528. https://doi.org/10.1093/jn/133.11.3523.

Ansari, I., et al., 2020. The microbiota programs DNA methylation to control intestinal homeostasis and inflammation. Nat. Microbiol. 5, 610–619. https://doi.org/10.1038/s41564-019-0659-3.

Bachmann, C., Colombo, J.P., Beruter, J., 1979. Short chain fatty acids in plasma and brain: quantitative determination by gas chromatography. Clin. Chim. Acta 92, 153–159. https://doi.org/10.1016/0009-8981(79)90109-8.

Backhed, F., Manchester, J.K., Semenkovich, C.F., Gordon, J.I., 2007. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc. Natl. Acad. Sci. U. S. A. 104, 979–984. https://doi.org/10.1073/pnas.0605374104.

Bali, A., Jaggi, A.S., 2016. An integrative review on role and mechanisms of ghrelin in stress, anxiety and depression. Curr. Drug Targets 17, 495–507. https://doi.org/10.2174/1389450116666150518095650.

Baxter, N.T., et al., 2019. Dynamics of human gut microbiota and short-chain fatty acids in response to dietary interventions with three fermentable fibers. mBio 10. https://doi.org/10.1128/mBio.02566-18.

Berding, K., Carbia, C., Cryan, J.F., 2021. Going with the grain: fiber, cognition, and the microbiota-gut-brain-axis. Exp. Biol. Med. 246, 796–811. https://doi.org/10.1177/1535370221995785.

Bergman, E.N., 1990. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol. Rev. 70, 567–590. https://doi.org/10.1152/physrev.1990.70.2.567.

Bharwani, A., Mian, M.F., Surette, M.G., Bienenstock, J., Forsythe, P., 2017. Oral treatment with Lactobacillus rhamnosus attenuates behavioural deficits and immune

changes in chronic social stress. BMC Med. 15, 7,. https://doi.org/10.1186/s12916-016-0771-7.
Bhattarai, Y., et al., 2017. Human-derived gut microbiota modulates colonic secretion in mice by regulating 5-HT3 receptor expression via acetate production. Am. J. Physiol. Gastrointest. Liver Physiol. 313, G80–G87. https://doi.org/10.1152/ajpgi.00448.2016.
Bloemen, J.G., et al., 2009. Short chain fatty acids exchange across the gut and liver in humans measured at surgery. Clin. Nutr. 28, 657–661.
Boehme, M., et al., 2021. Microbiota from young mice counteracts selective age-associated behavioral deficits. Nat. Aging 1, 666–676. https://doi.org/10.1038/s43587-021-00093-9.
Boets, E., et al., 2015. Quantification of in vivo colonic short chain fatty acid production from inulin. Nutrients 7, 8916–8929.
Boets, E., et al., 2017. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. J. Physiol. 595, 541–555. https://doi.org/10.1113/JP272613.
Bogie, J.F.J., Haidar, M., Kooij, G., Hendriks, J.J.A., 2020. Fatty acid metabolism in the progression and resolution of CNS disorders. Adv. Drug Deliv. Rev. 159, 198–213. https://doi.org/10.1016/j.addr.2020.01.004.
Borre, Y.E., et al., 2014. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol. Med. 20, 509–518. https://doi.org/10.1016/j.molmed.2014.05.002.
Braniste, V., et al., 2014. The gut microbiota influences blood-brain barrier permeability in mice. Sci. Transl. Med. 6 https://doi.org/10.1126/scitranslmed.3009759, 263ra158.
Brestoff, J.R., Artis, D., 2013. Commensal bacteria at the interface of host metabolism and the immune system. Nat. Immunol. 14, 676–684. https://doi.org/10.1038/ni.2640.
Brown, A.J., et al., 2003. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J. Biol. Chem. 278, 11312–11319. https://doi.org/10.1074/jbc.M211609200.
Burokas, A., et al., 2017. Targeting the microbiota-gut-brain Axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biol. Psychiatr. 82, 472–487. https://doi.org/10.1016/j.biopsych.2016.12.031.
Butler, M.I., et al., 2020. Recipe for a healthy gut: intake of unpasteurised milk is associated with increased Lactobacillus abundance in the human gut microbiome. Nutrients 12. https://doi.org/10.3390/nu12051468.
Byrne, C.S., et al., 2016. Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods. Am. J. Clin. Nutr. 104, 5–14. https://doi.org/10.3945/ajcn.115.126706.
Canfora, E.E., Jocken, J.W., Blaak, E.E., 2015. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat. Rev. Endocrinol. 11, 577–591. https://doi.org/10.1038/nrendo.2015.128.
Cani, P.D., et al., 2009. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am. J. Clin. Nutr. 90, 1236–1243. https://doi.org/10.3945/ajcn.2009.28095.
Cani, P.D., et al., 2019. Microbial regulation of organismal energy homeostasis. Nat. Metabol. 1, 34–46.
Capuron, L., Miller, A.H., 2011. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Therapeut. 130, 226–238. https://doi.org/10.1016/j.pharmthera.2011.01.014.
Chambers, E.S., et al., 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut 64, 1744–1754. https://doi.org/10.1136/gutjnl-2014-307913.
Chang, P.V., Hao, L., Offermanns, S., Medzhitov, R., 2014. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc. Natl. Acad. Sci. U.S.A. 111, 2247–2252. https://doi.org/10.1073/pnas.1322269111.
Chen, K., et al., 2019. Drosophila histone demethylase KDM5 regulates social behavior through immune control and gut microbiota maintenance. Cell Host Microbe 25, 537–552 e538. https://doi.org/10.1016/j.chom.2019.02.003.
Chen, T., Noto, D., Hoshino, Y., Mizuno, M., Miyake, S., 2019. Butyrate suppresses demyelination and enhances remyelination. J. Neuroinflammation 16, 1–13.
Chevalier, A.C., Rosenberger, T.A., 2017. Increasing acetyl-CoA metabolism attenuates injury and alters spinal cord lipid content in mice subjected to experimental autoimmune encephalomyelitis. J. Neurochem. 141, 721–737. https://doi.org/10.1111/jnc.14032.
Cho, I., et al., 2012. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature 488, 621–626. https://doi.org/10.1038/nature11400.
Choi, J., et al., 2018. Pathophysiological and neurobehavioral characteristics of a propionic acid-mediated autism-like rat model. PLoS One 13, e0192925. https://doi.org/10.1371/journal.pone.0192925.
Chung, H.J., Sim, J.H., Min, T.S., Choi, H.K., 2018. Metabolomics and lipidomics approaches in the science of probiotics: a review. J. Med. Food 21, 1086–1095. https://doi.org/10.1089/jmf.2017.4175.
Clausen, M.R., Mortensen, P.B., 1994. Kinetic studies on the metabolism of short-chain fatty acids and glucose by isolated rat colonocytes. Gastroenterology 106, 423–432. https://doi.org/10.1016/0016-5085(94)90601-7.
Colombo, A.V., et al., 2021. Microbiota-derived short chain fatty acids modulate microglia and promote Abeta plaque deposition. Elife 10. https://doi.org/10.7554/eLife.59826.
Commodari, F., Arnold, D.L., Sanctuary, B.C., Shoubridge, E.A., 1991. 1H NMR characterization of normal human cerebrospinal fluid and the detection of methylmalonic acid in a vitamin B12 deficient patient. NMR Biomed. 4, 192–200. https://doi.org/10.1002/nbm.1940040407.
Cook, S.I., Sellin, J.H., 1998. Review article: short chain fatty acids in health and disease. Aliment. Pharmacol. Ther. 12, 499–507. https://doi.org/10.1046/j.1365-2036.1998.00337.x.
Corrêa-Oliveira, R., Fachi, J.L., Vieira, A., Sato, F.T., Vinolo, M.A.R., 2016. Regulation of immune cell function by short-chain fatty acids. Clin. Transl. Immunol. 5, e73. https://doi.org/10.1038/cti.2016.17 e73.
Cotillard, A., et al., 2013. Dietary intervention impact on gut microbial gene richness. Nature 500, 585–588. https://doi.org/10.1038/nature12480.
Cruz-Pereira, J.S., et al., 2020. Depression's unholy trinity: dysregulated stress, immunity, and the microbiome. Annu. Rev. Psychol. 71, 49–78. https://doi.org/10.1146/annurev-psych-122216-011613.
Cryan, J.F., et al., 2019. The microbiota-gut-brain Axis. Physiol. Rev. 99, 1877–2013. https://doi.org/10.1152/physrev.00018.2018.
Cryan, J.F., O'Riordan, K.J., Sandhu, K., Peterson, V., Dinan, T.G., 2020. The gut microbiome in neurological disorders. Lancet Neurol. 19, 179–194. https://doi.org/10.1016/S1474-4422(19)30356-4.
Cuff, M.A., Shirazi-Beechey, S.P., 2002. The human monocarboxylate transporter, MCT1: genomic organization and promoter analysis. Biochem. Biophys. Res. Commun. 292, 1048–1056. https://doi.org/10.1006/bbrc.2002.6763.
Cummings, J.H., Pomare, E.W., Branch, W.J., Naylor, C.P., Macfarlane, G.T., 1987. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 28, 1221–1227. https://doi.org/10.1136/gut.28.10.1221.
Dalile, B., Van Oudenhove, L., Vervliet, B., Verbeke, K., 2019. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat. Rev. Gastroenterol. Hepatol. 16, 461–478. https://doi.org/10.1038/s41575-019-0157-3.
Dalile, B., Vervliet, B., Bergonzelli, G., Verbeke, K., Van Oudenhove, L., 2020. Colon-delivered short-chain fatty acids attenuate the cortisol response to psychosocial stress in healthy men: a randomized, placebo-controlled trial. Neuropsychopharmacology 45, 2257–2266. https://doi.org/10.1038/s41386-020-0732-x.
David, L.A., et al., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563. https://doi.org/10.1038/nature12820.
De Filippo, C., et al., 2010. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc. Natl. Acad. Sci. U.S. A. 107, 14691–14696. https://doi.org/10.1073/pnas.1005963107.
De Silva, A., Bloom, S.R., 2012. Gut hormones and appetite control: a focus on PYY and GLP-1 as therapeutic targets in obesity. Gut Liver 6, 10–20. https://doi.org/10.5009/gnl.2012.6.1.10.
De Vadder, F., et al., 2014. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156, 84–96. https://doi.org/10.1016/j.cell.2013.12.016.
den Besten, G., et al., 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J. Lipid Res. 54, 2325–2340. https://doi.org/10.1194/jlr.R036012.
Deng, F.L., et al., 2019. Metabonomics reveals peripheral and central short-chain fatty acid and amino acid dysfunction in a naturally occurring depressive model of macaques. Neuropsychiatric Dis. Treat. 15, 1077–1088. https://doi.org/10.2147/ndt.s186071.
Dennis, P.B., et al., 2001. Mammalian TOR: a homeostatic ATP sensor. Science 294, 1102–1105.
Doifode, T., et al., 2021. The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. Pharmacol. Res. 164, 105314,. https://doi.org/10.1016/j.phrs.2020.105314.
Dominguez-Mozo, M.I., et al., 2021. Herpesvirus antibodies, vitamin D and short-chain fatty acids: their correlation with cell subsets in multiple sclerosis patients and healthy controls. Cells 10, 119.
Donohoe, D.R., et al., 2011. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metabol. 13, 517–526.
Duncan, S.H., Barcenilla, A., Stewart, C.S., Pryde, S.E., Flint, H.J., 2002. Acetate utilization and butyryl coenzyme A (CoA):acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. Appl. Environ. Microbiol. 68, 5186–5190. https://doi.org/10.1128/AEM.68.10.5186-5190.2002.
Duncan, S.H., Louis, P., Flint, H.J., 2007. Cultivable bacterial diversity from the human colon. Lett. Appl. Microbiol. 44, 343–350. https://doi.org/10.1111/j.1472-765X.2007.02129.x.
During, M.J., et al., 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat. Med. 9, 1173–1179. https://doi.org/10.1038/nm919.
Duscha, A., et al., 2020. Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism. Cell 180, 1067–1080.e1016. https://doi.org/10.1016/j.cell.2020.02.035.
El Oufir, L., et al., 2000. Relationships between transit time in man and in vitro fermentation of dietary fiber by fecal bacteria. Eur. J. Clin. Nutr. 54, 603–609.
El-Salhy, M., Valeur, J., Hausken, T., Gunnar Hatlebakk, J., 2021. Changes in fecal short-chain fatty acids following fecal microbiota transplantation in patients with irritable bowel syndrome. Neuro Gastroenterol. Motil. 33, e13983,. https://doi.org/10.1111/nmo.13983.
Engelstoft, M.S., Schwartz, T.W., 2016. Opposite regulation of ghrelin and glucagon-like peptide-1 by metabolite G-protein-coupled receptors. Trends Endocrinol. Metabol. 27, 665–675. https://doi.org/10.1016/j.tem.2016.07.001.
Engelstoft, M.S., et al., 2013. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. Mol. Metabol. 2, 376–392. https://doi.org/10.1016/j.molmet.2013.08.006.

Erny, D., et al., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18, 965–977. https://doi.org/10.1038/nn.4030.
Erny, D., Hrabe de Angelis, A.L., Prinz, M., 2017. Communicating systems in the body: how microbiota and microglia cooperate. Immunology 150, 7–15. https://doi.org/10.1111/imm.12645.
Evans, S.J., et al., 2017. The gut microbiome composition associates with bipolar disorder and illness severity. J. Psychiatr. Res. 87, 23–29. https://doi.org/10.1016/j.jpsychires.2016.12.007.
Falomir-Lockhart, L.J., Cavazzutti, G.F., Gimenez, E., Toscani, A.M., 2019. Fatty acid signaling mechanisms in neural cells: fatty acid receptors. Front. Cell. Neurosci. 13, 162,. https://doi.org/10.3389/fncel.2019.00162.
Fan, Y., Pedersen, O., 2021. Gut microbiota in human metabolic health and disease. Nat. Rev. Microbiol. 19, 55–71. https://doi.org/10.1038/s41579-020-0433-9.
Farr, O.M., Tsoukas, M.A., Mantzoros, C.S., 2015. Leptin and the brain: influences on brain development, cognitive functioning and psychiatric disorders. Metabolism 64, 114–130. https://doi.org/10.1016/j.metabol.2014.07.004.
Farup, P.G., Rudi, K., Hestad, K., 2016. Faecal short-chain fatty acids - a diagnostic biomarker for irritable bowel syndrome? BMC Gastroenterol. 16, 51,. https://doi.org/10.1186/s12876-016-0446-z.
Fellows, R., et al., 2018. Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. Nat. Commun. 9, 105,. https://doi.org/10.1038/s41467-017-02651-5.
Finegold, S.M., 2011. Desulfovibrio species are potentially important in regressive autism. Med. Hypotheses 77, 270–274.
Finegold, S.M., et al., 2010. Pyrosequencing study of fecal microflora of autistic and control children. Anaerobe 16, 444–453.
Fisel, P., Schaeffeler, E., Schwab, M., 2018. Clinical and functional relevance of the monocarboxylate transporter family in disease pathophysiology and drug therapy. Clin. Transl. Sci. 11, 352–364.
Flint, H.J., Duncan, S.H., Scott, K.P., Louis, P., 2015. Links between diet, gut microbiota composition and gut metabolism. Proc. Nutr. Soc. 74, 13–22.
Fredericks, E., Theunissen, R., Roux, S., 2020. Short chain fatty acids and monocarboxylate transporters in irritable bowel syndrome. Turk. J. Gastroenterol. 31, 840–847. https://doi.org/10.5152/tjg.2020.19856.
Freeland, K.R., Wolever, T.M., 2010. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin and tumour necrosis factor-alpha. Br. J. Nutr. 103, 460–466. https://doi.org/10.1017/S0007114509991863.
Frost, G., et al., 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 5, 3611. https://doi.org/10.1038/ncomms4611.
Fukumori, R., et al., 2011. Plasma ghrelin concentration is decreased by short chain fatty acids in wethers. Domest. Anim. Endocrinol. 41, 50–55. https://doi.org/10.1016/j.domaniend.2011.04.001.
Fukumoto, S., et al., 2003. Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 284, R1269–R1276. https://doi.org/10.1152/ajpregu.00442.2002.
Fung, T.C., Olson, C.A., Hsiao, E.Y., 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nat. Neurosci. 20, 145–155. https://doi.org/10.1038/nn.4476.
Furusawa, Y., et al., 2013. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504, 446–450. https://doi.org/10.1038/nature12721.
Gabriel, F.C., Fantuzzi, G., 2019. The association of short-chain fatty acids and leptin metabolism: a systematic review. Nutr. Res. 72, 18–35. https://doi.org/10.1016/j.nutres.2019.08.006.
Gao, Z., et al., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58, 1509–1517. https://doi.org/10.2337/db08-1637.
Gargari, G., et al., 2018. Fecal Clostridiales distribution and short-chain fatty acids reflect bowel habits in irritable bowel syndrome. Environ. Microbiol. 20, 3201–3213. https://doi.org/10.1111/1462-2920.14271.
Gautier, E.L., et al., 2012. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nat. Immunol. 13, 1118–1128. https://doi.org/10.1038/ni.2419.
Gil-Lozano, M., et al., 2010. GLP-1(7-36)-amide and Exendin-4 stimulate the HPA axis in rodents and humans. Endocrinology 151, 2629–2640. https://doi.org/10.1210/en.2009-0915.
Gill, P.A., van Zelm, M.C., Muir, J.G., Gibson, P.R., 2018. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. Aliment. Pharmacol. Ther. 48, 15–34. https://doi.org/10.1111/apt.14689.
Gomaa, E.Z., 2020. Human gut microbiota/microbiome in health and diseases: a review. Antonie Leeuwenhoek 113, 2019–2040. https://doi.org/10.1007/s10482-020-01474-7.
Goswami, C., Iwasaki, Y., Yada, T., 2018. Short-chain fatty acids suppress food intake by activating vagal afferent neurons. J. Nutr. Biochem. 57, 130–135. https://doi.org/10.1016/j.jnutbio.2018.03.009.
Grider, J.R., Piland, B.E., 2007. The peristaltic reflex induced by short-chain fatty acids is mediated by sequential release of 5-HT and neuronal CGRP but not BDNF. Am. J. Physiol. Gastrointest. Liver Physiol. 292, G429–G437. https://doi.org/10.1152/ajpgi.00376.2006.
Haenen, D., et al., 2013. A diet high in resistant starch modulates microbiota composition, SCFA concentrations, and gene expression in pig intestine. J. Nutr. 143, 274–283.
Haghikia, A., et al., 2015. Dietary fatty acids directly impact central nervous system Autoimmunity via the small intestine. Immunity 43, 817–829. https://doi.org/10.1016/j.immuni.2015.09.007.
Hamer, H.M., et al., 2008. Review article: the role of butyrate on colonic function. Aliment. Pharmacol. Ther. 27, 104–119. https://doi.org/10.1111/j.1365-2036.2007.03562.x.
Han, J., Lin, K., Sequeira, C., Borchers, C.H., 2015. An isotope-labeled chemical derivatization method for the quantitation of short-chain fatty acids in human feces by liquid chromatography–tandem mass spectrometry. Anal. Chim. Acta 854, 86–94. https://doi.org/10.1016/j.aca.2014.11.015.
Harig, J.M., Soergel, K.H., Komorowski, R.A., Wood, C.M., 1989. Treatment of diversion colitis with short-chain-fatty acid irrigation. N. Engl. J. Med. 320, 23–28. https://doi.org/10.1056/NEJM198901053200105.
Hays, R.D., Sherbourne, C.D., Mazel, R.M., 1993. The RAND 36-item health survey 1.0. Health Econ. 2, 217–227. https://doi.org/10.1002/hec.4730020305.
Hellman, L., Rosenfeld, R.S., Gallagher, T., 1954. Cholesterol synthesis from C 14—acetate in man. J. Clin. Invest. 33, 142–149.
Hemarajata, P., Versalovic, J., 2013. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Therapeut. Adv. Gastroenterol. 6, 39–51. https://doi.org/10.1177/1756283X12459294.
Hinnebusch, B.F., Meng, S., Wu, J.T., Archer, S.Y., Hodin, R.A., 2002. The effects of short-chain fatty acids on human colon cancer cell phenotype are associated with histone hyperacetylation. J. Nutr. 132, 1012–1017. https://doi.org/10.1093/jn/132.5.1012.
Ho, L., et al., 2018. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev. Neurother. 18, 83–90. https://doi.org/10.1080/14737175.2018.1400909.
Hoverstad, T., Midtvedt, T., 1986. Short-chain fatty acids in germfree mice and rats. J. Nutr. 116, 1772–1776. https://doi.org/10.1093/jn/116.9.1772.
Høverstad, T., Fausa, O., Bjørneklett, A., Bøhmer, T., 1984. Short-chain fatty acids in the normal human feces. Scand. J. Gastroenterol. 19, 375–381.
Hoyles, L., et al., 2018. Microbiome-host systems interactions: protective effects of propionate upon the blood-brain barrier. Microbiome 6, 55,. https://doi.org/10.1186/s40168-018-0439-y.
Hoyles, L., et al., 2021. Regulation of blood–brain barrier integrity and cognition by the microbiome-associated methylamines trimethylamine-N-oxide and trimethylamine. Preprint. https://doi.org/10.1101/2021.01.28.428430.
Hu, J., Lin, S., Zheng, B., Cheung, P.C., 2018. Short-chain fatty acids in control of energy metabolism. Crit. Rev. Food Sci. Nutr. 58, 1243–1249.
Hu, S., et al., 2019. Gut microbiota changes in patients with bipolar depression. Adv. Sci. 6, 1900752,. https://doi.org/10.1002/advs.201900752.
Huuskonen, J., Suuronen, T., Nuutinen, T., Kyrylenko, S., Salminen, A., 2004. Regulation of microglial inflammatory response by sodium butyrate and short-chain fatty acids. Br. J. Pharmacol. 141, 874–880. https://doi.org/10.1038/sj.bjp.0705682.
Inoue, D., Tsujimoto, G., Kimura, I., 2014. Regulation of energy homeostasis by GPR41. Front. Endocrinol. 5, 81,. https://doi.org/10.3389/fendo.2014.00081.
Isacson, R., et al., 2011. The glucagon-like peptide 1 receptor agonist exendin-4 improves reference memory performance and decreases immobility in the forced swim test. Eur. J. Pharmacol. 650, 249–255. https://doi.org/10.1016/j.ejphar.2010.10.008.
Iwanaga, T., Takebe, K., Kato, I., Karaki, S.-I., Kuwahara, A., 2006. Cellular expression of monocarboxylate transporters (MCT) in the digestive tract of the mouse, rat, and humans, with special reference to slc5a8. Biomed. Res. 27, 243–254.
Jackson, A., et al., 2019. Diet in Parkinson's disease: critical role for the microbiome. Front. Neurol. 10, 1245,. https://doi.org/10.3389/fneur.2019.01245.
Jiang, H., et al., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.
Kaji, I., et al., 2016. Neural FFA3 activation inversely regulates anion secretion evoked by nicotinic ACh receptor activation in rat proximal colon. J. Physiol. 594, 3339–3352. https://doi.org/10.1113/JP271441.
Kamp, F., Hamilton, J.A., 2006. How fatty acids of different chain length enter and leave cells by free diffusion. Prostaglandins Leukot. Essent. Fatty Acids 75, 149–159. https://doi.org/10.1016/j.plefa.2006.05.003.
Katsurada, K., Yada, T., 2016. Neural effects of gut- and brain-derived glucagon-like peptide-1 and its receptor agonist. J. Diabetes Investig. 7 (Suppl. 1), 64–69. https://doi.org/10.1111/jdi.12464.
Kekuda, R., Manoharan, P., Baseler, W., Sundaram, U., 2013. Monocarboxylate 4 mediated butyrate transport in a rat intestinal epithelial cell line. Dig. Dis. Sci. 58, 660–667. https://doi.org/10.1007/s10620-012-2407-x.
Kendrick, S.F., et al., 2010. Acetate, the key modulator of inflammatory responses in acute alcoholic hepatitis. Hepatology 51, 1988–1997. https://doi.org/10.1002/hep.23572.
Kim, K.N., Yao, Y., Ju, S.Y., 2019. Short chain fatty acids and fecal microbiota abundance in humans with obesity: a systematic review and meta-analysis. Nutrients 11. https://doi.org/10.3390/nu11102512.
Kimura-Todani, T., et al., 2021. Corrigendum to "Dietary delivery of acetate to the colon using acylated starches as a carrier exerts anxiolytic effects in mice. Physiol. Behav. 229, 113259,. https://doi.org/10.1016/j.physbeh.2020.113259.
Knauf, C., Abot, A., Wemelle, E., Cani, P.D., 2020. Targeting the enteric nervous system to treat metabolic disorders? "Enterosynes" as therapeutic gut factors. Neuroendocrinology 110, 139–146. https://doi.org/10.1159/000500602.
Knowles, S.E., Jarrett, I.G., Filsell, O.H., Ballard, F.J., 1974. Production and utilization of acetate in mammals. Biochem. J. 142, 401–411. https://doi.org/10.1042/bj1420401.

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., Backhed, F., 2016. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 165, 1332–1345. https://doi.org/10.1016/j.cell.2016.05.041.
Kratsman, N., Getselter, D., Elliott, E., 2016. Sodium butyrate attenuates social behavior deficits and modifies the transcription of inhibitory/excitatory genes in the frontal cortex of an autism model. Neuropharmacology 102, 136–145. https://doi.org/10.1016/j.neuropharm.2015.11.003. –.
Krautkramer, K.A., et al., 2016. Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues. Mol. Cell 64, 982–992. https://doi.org/10.1016/j.molcel.2016.10.025.
Kristensen, N.B., et al., 2016. Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. Genome Med. 8, 52,. https://doi.org/10.1186/s13073-016-0300-5.
Kullmann, S., et al., 2016. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. Physiol. Rev. 96, 1169–1209. https://doi.org/10.1152/physrev.00032.2015.
Larraufie, P., et al., 2018. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci. Rep. 8, 74. https://doi.org/10.1038/s41598-017-18259-0.
Laurent, R.S., O'Brien, L.M., Ahmad, S.T., 2013. Sodium butyrate improves locomotor impairment and early mortality in a rotenone-induced Drosophila model of Parkinson's disease. Neuroscience 246, 382–390.
Lee, S.H., Zabolotny, J.M., Huang, H., Lee, H., Kim, Y.B., 2016. Insulin in the nervous system and the mind: functions in metabolism, memory, and mood. Mol. Metabol. 5, 589–601. https://doi.org/10.1016/j.molmet.2016.06.011.
Leeuwendaal, N.K., Cryan, J.F., Schellekens, H., 2021. Gut peptides and the microbiome: focus on ghrelin. Curr. Opin. Endocrinol. Diabetes Obes. 28, 243–252. https://doi.org/10.1097/MED.0000000000000616.
Lentner, C., 1981. Geigy scientific Tables: units of measurement, body fluids, composition of the body. Nutrition 1 (Novartis (formerly Ciba Geigy).
Levy, M., Thaiss, C.A., Elinav, E., 2016. Metabolites: messengers between the microbiota and the immune system. Genes Dev. 30, 1589–1597. https://doi.org/10.1101/gad.284091.116.
Li, Z., et al., 2018. Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. Gut 67, 1269–1279. https://doi.org/10.1136/gutjnl-2017-314050.
Lin, H.V., et al., 2012. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS One 7, e35240,. https://doi.org/10.1371/journal.pone.0035240.
Lin, P., et al., 2017. Prevotella and Klebsiella proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. J. Affect. Disord. 207, 300–304. https://doi.org/10.1016/j.jad.2016.09.051.
Liu, J., et al., 2017. Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1. J. Neurol. Sci. 381, 176–181.
Liu, H., et al., 2018. Butyrate: a double-edged sword for health? Adv. Nutr. 9, 21–29. https://doi.org/10.1093/advances/nmx009.
Liu, S., et al., 2019. Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. Sci. Rep. 9, 287,. https://doi.org/10.1038/s41598-018-36430-z.
Liu, J., et al., 2020. Anti-neuroinflammatory effect of short-chain fatty acid acetate against Alzheimer's disease via upregulating GPR41 and inhibiting ERK/JNK/NF-κB. J. Agric. Food Chem. 68, 7152–7161. https://doi.org/10.1021/acs.jafc.0c02807.
Liu, X., et al., 2021. High-fiber diet mitigates maternal obesity-induced cognitive and social dysfunction in the offspring via gut-brain axis. Cell Metabol. 33, 923–938 e926. https://doi.org/10.1016/j.cmet.2021.02.002.
Llorens-Rico, V., Raes, J., 2019. Tracking humans and microbes. Nature 569, 632–633. https://doi.org/10.1038/d41586-019-01591-y.
Long-Smith, C., et al., 2020. Microbiota-gut-brain Axis: new therapeutic opportunities. Annu. Rev. Pharmacol. Toxicol. 60, 477–502. https://doi.org/10.1146/annurev-pharmtox-010919-023628.
Louis, P., Flint, H.J., 2017. Formation of propionate and butyrate by the human colonic microbiota. Environ. Microbiol. 19, 29–41.
Lu, V.B., Gribble, F.M., Reimann, F., 2018. Free fatty acid receptors in enteroendocrine cells. Endocrinology 159, 2826–2835. https://doi.org/10.1210/en.2018-00261.
Lu, Q., et al., 2019. Gut microbiota in bipolar depression and its relationship to brain function: an advanced exploration. Front. Psychiatr. 10, 784,. https://doi.org/10.3389/fpsyt.2019.00784.
Lukovac, S., et al., 2014. Differential modulation by Akkermansia muciniphila and Faecalibacterium prausnitzii of host peripheral lipid metabolism and histone acetylation in mouse gut organoids. mBio 5. https://doi.org/10.1128/mBio.01438-14.
Macfabe, D.F., 2012. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. Microb. Ecol. Health Dis. 23. https://doi.org/10.3402/mehd.v23i0.19260.
MacFabe, D.F., Cain, N.E., Boon, F., Ossenkopp, K.P., Cain, D.P., 2011. Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: relevance to autism spectrum disorder. Behav. Brain Res. 217, 47–54. https://doi.org/10.1016/j.bbr.2010.10.005.
Macfarlane, S., Macfarlane, G.T., 2003. Regulation of short-chain fatty acid production. Proc. Nutr. Soc. 62, 67–72. https://doi.org/10.1079/PNS2002207.
Maltz, R.M., et al., 2018. Prolonged restraint stressor exposure in outbred CD-1 mice impacts microbiota, colonic inflammation, and short chain fatty acids. PLoS One 13, e0196961. https://doi.org/10.1371/journal.pone.0196961.
Marizzoni, M., et al., 2020. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J. Alzheimers Dis. 78, 683–697. https://doi.org/10.3233/JAD-200306.
Martin, A.M., et al., 2017. Regional differences in nutrient-induced secretion of gut serotonin. Physiol. Rep. 5 https://doi.org/10.14814/phy2.13199.
Martinez-Moreno, J.M., et al., 2020. The contribution of histone crotonylation to tissue health and disease. Focus Kidney Health 11. https://doi.org/10.3389/fphar.2020.00393.
Mascolo, N., Rajendran, V.M., Binder, H.J., 1991. Mechanism of short-chain fatty acid uptake by apical membrane vesicles of rat distal colon. Gastroenterology 101, 331–338. https://doi.org/10.1016/0016-5085(91)90008-9.
McLoughlin, R.F., Berthon, B.S., Jensen, M.E., Baines, K.J., Wood, L.G., 2017. Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. Am. J. Clin. Nutr. 106, 930–945. https://doi.org/10.3945/ajcn.117.156265.
McNeil, N.I., Cummings, J.H., James, W.P., 1978. Short chain fatty acid absorption by the human large intestine. Gut 19, 819–822. https://doi.org/10.1136/gut.19.9.819.
McOrist, A.L., et al., 2011. Fecal butyrate levels vary widely among individuals but are usually increased by a diet high in resistant starch. J. Nutr. 141, 883–889. https://doi.org/10.3945/jn.110.128504.
Michels, N., Van de Wiele, T., De Henauw, S., 2017. Chronic psychosocial stress and gut health in children: associations with calprotectin and fecal short-chain fatty acids. Psychosom. Med. 79, 927–935. https://doi.org/10.1097/PSY.0000000000000413.
Mishra, S.P., Karunakar, P., Taraphder, S., Yadav, H., 2020. Free fatty acid receptors 2 and 3 as microbial metabolite sensors to shape host health: pharmacophysiological view. Biomedicines 8, 154,. https://doi.org/10.3390/biomedicines8060154.
Miyauchi, S., Gopal, E., Fei, Y.J., Ganapathy, V., 2004. Functional identification of SLC5A8, a tumor suppressor down-regulated in colon cancer, as a Na(+)-coupled transporter for short-chain fatty acids. J. Biol. Chem. 279, 13293–13296. https://doi.org/10.1074/jbc.C400059200.
Mizuno, M., Noto, D., Kaga, N., Chiba, A., Miyake, S., 2017. The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. PLoS One 12, e0173032.
Mohle, L., et al., 2016. Ly6C(hi) monocytes provide a link between antibiotic-induced changes in gut microbiota and adult hippocampal neurogenesis. Cell Rep. 15, 1945–1956. https://doi.org/10.1016/j.celrep.2016.04.074.
Moreno-Perez, D., et al., 2018. Effect of a protein supplement on the gut microbiota of endurance athletes: a randomized, controlled, double-blind pilot study. Nutrients 10. https://doi.org/10.3390/nu10030337.
Morimoto, R., et al., 2008. Expression of peptide YY in human brain and pituitary tissues. Nutrition 24, 878–884. https://doi.org/10.1016/j.nut.2008.06.011.
Morita, C., et al., 2015. Gut dysbiosis in patients with anorexia nervosa. PLoS One 10, e0145274. https://doi.org/10.1371/journal.pone.0145274.
Nagai, M., Obata, Y., Takahashi, D., Hase, K., 2016. Fine-tuning of the mucosal barrier and metabolic systems using the diet-microbial metabolite axis. Int. Immunopharm. 37, 79–86. https://doi.org/10.1016/j.intimp.2016.04.001.
Nagpal, R., et al., 2018. Human-origin probiotic cocktail increases short-chain fatty acid production via modulation of mice and human gut microbiome. Sci. Rep. 8, 12649,. https://doi.org/10.1038/s41598-018-30114-4.
Nastasi, C., et al., 2015. The effect of short-chain fatty acids on human monocyte-derived dendritic cells. Sci. Rep. 5, 16148,. https://doi.org/10.1038/srep16148.
Nikolova, V.L., et al., 2021. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. JAMA Psychiatr. 78, 1343–1354. https://doi.org/10.1001/jamapsychiatry.2021.2573.
Nishiwaki, H., et al., 2020. Short-chain fatty acid-producing gut microbiota is decreased in Parkinson's disease but not in rapid-eye-movement sleep behavior disorder. mSystems 5, e00797–720. https://doi.org/10.1128/mSystems.00797-20.
Nohr, M.K., et al., 2015. Expression of the short chain fatty acid receptor GPR41/FFAR3 in autonomic and somatic sensory ganglia. Neuroscience 290, 126–137. https://doi.org/10.1016/j.neuroscience.2015.01.040.
Nutma, E., Willison, H., Martino, G., Amor, S., 2019. Neuroimmunology - the past, present and future. Clin. Exp. Immunol. 197, 278–293. https://doi.org/10.1111/cei.13279.
O'Riordan, K., Gerstein, H., Hullinger, R., Burger, C., 2014. The role of Homer1c in metabotropic glutamate receptor-dependent long-term potentiation. Hippocampus 24, 1–6. https://doi.org/10.1002/hipo.22222.
Oldendorf, W.H., 1973. Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. Am. J. Physiol. 224, 1450–1453. https://doi.org/10.1152/ajplegacy.1973.224.6.1450.
Oleskin, A.V., Shenderov, B.A., 2016. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microb. Ecol. Health Dis. 27, 30971.
Ostendorf, F., Metzdorf, J., Gold, R., Haghikia, A., Tönges, L., 2020. Propionic acid and fasudil as treatment against rotenone toxicity in an in vitro model of Parkinson's disease. Molecules 25, 2502.
Painold, A., et al., 2019. A step ahead: exploring the gut microbiota in inpatients with bipolar disorder during a depressive episode. Bipolar Disord. 21, 40–49. https://doi.org/10.1111/bdi.12682.
Paiva, I., et al., 2017. Sodium butyrate rescues dopaminergic cells from alpha-synuclein-induced transcriptional deregulation and DNA damage. Hum. Mol. Genet. 26, 2231–2246.
Palleja, A., et al., 2018. Recovery of gut microbiota of healthy adults following antibiotic exposure. Nat. Microbiol. 3, 1255–1265. https://doi.org/10.1038/s41564-018-0257-9.

Pan, W.H., et al., 2018. Exposure to the gut microbiota drives distinct methylome and transcriptome changes in intestinal epithelial cells during postnatal development. Genome Med. 10, 27,. https://doi.org/10.1186/s13073-018-0534-5.
Parada Venegas, D., et al., 2019. Short chain fatty acids (SCFAs)-Mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front. Immunol. 10 https://doi.org/10.3389/fimmu.2019.00277.
Patnala, R., Arumugam, T.V., Gupta, N., Dheen, S.T., 2017. HDAC inhibitor sodium butyrate-mediated epigenetic regulation enhances neuroprotective function of microglia during ischemic stroke. Mol. Neurobiol. 54, 6391–6411. https://doi.org/10.1007/s12035-016-0149-z.
Pérez-Pérez, S., et al., 2020. Acetate correlates with disability and immune response in multiple sclerosis. PeerJ 8, e10220,. https://doi.org/10.7717/peerj.10220.
Perry, R.J., et al., 2016. Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome. Nature 534, 213–217. https://doi.org/10.1038/nature18309.
Peters, S.G., Pomare, E.W., Fisher, C.A., 1992. Portal and peripheral blood short chain fatty acid concentrations after caecal lactulose instillation at surgery. Gut 33, 1249–1252. https://doi.org/10.1136/gut.33.9.1249.
Petrof, E.O., et al., 2013. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. Microbiome 1, 3,. https://doi.org/10.1186/2049-2618-1-3.
Phillips, S.F., Devroede, G.J., 1979. Functions of the large intestine. Int. Rev. Physiol. 19, 263–290.
Pingitore, A., et al., 2019. Short chain fatty acids stimulate insulin secretion and reduce apoptosis in mouse and human islets in vitro: role of free fatty acid receptor 2. Diabetes Obes. Metabol. 21, 330–339. https://doi.org/10.1111/dom.13529.
Pluznick, J.L., 2017. Microbial Short-Chain Fatty Acids and Blood Pressure Regulation. Curr. Hypertens. Rep. 19, 25,. https://doi.org/10.1007/s11906-017-0722-5.
Priyadarshini, M., Layden, B.T., 2015. FFAR3 modulates insulin secretion and global gene expression in mouse islets. Islets 7, e1045182,. https://doi.org/10.1080/19382014.2015.1045182.
Psichas, A., et al., 2015. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int. J. Obes. 39, 424–429. https://doi.org/10.1038/ijo.2014.153.
Psychogios, N., et al., 2011. The human serum metabolome. PLoS One 6, e16957,. https://doi.org/10.1371/journal.pone.0016957.
Qin, J., et al., 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490, 55–60.
Rahat-Rozenbloom, S., Fernandes, J., Gloor, G.B., Wolever, T.M., 2014. Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans. Int. J. Obes. 38, 1525–1531. https://doi.org/10.1038/ijo.2014.46.
Rahat-Rozenbloom, S., Fernandes, J., Cheng, J., Wolever, T.M.S., 2017. Acute increases in serum colonic short-chain fatty acids elicited by inulin do not increase GLP-1 or PYY responses but may reduce ghrelin in lean and overweight humans. Eur. J. Clin. Nutr. 71, 953–958. https://doi.org/10.1038/ejcn.2016.249.
Ramirez, K., Fornaguera-Trías, J., Sheridan, J.F., 2017. Stress-induced microglia activation and monocyte trafficking to the brain underlie the development of anxiety and depression. Curr. Top. Behav. Neurosci. 31, 155–172. https://doi.org/10.1007/7854_2016_25.
Resende, W.R., et al., 2013. Effects of sodium butyrate in animal models of mania and depression: implications as a new mood stabilizer. Behav. Pharmacol. 24, 569–579. https://doi.org/10.1097/FBP.0b013e32836546fc.
Reynolds, A., et al., 2019. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 393, 434–445. https://doi.org/10.1016/S0140-6736(18)31809-9.
Riggs, M.G., Whittaker, R.G., Neumann, J.R., Ingram, V.M., 1977. n-Butyrate causes histone modification in HeLa and Friend erythroleukaemia cells. Nature 268, 462–464. https://doi.org/10.1038/268462a0.
Ringel-Kulka, T., et al., 2015. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. Am. J. Gastroenterol. 110, 1339–1346. https://doi.org/10.1038/ajg.2015.220.
Rios-Covian, D., et al., 2015. Different metabolic features of Bacteroides fragilis growing in the presence of glucose and exopolysaccharides of bifidobacteria. Front. Microbiol. 6, 825,. https://doi.org/10.3389/fmicb.2015.00825.
Ríos-Covián, D., et al., 2016. Intestinal short chain fatty acids and their link with diet and human health. Front. Microbiol. 7, 185. https://doi.org/10.3389/fmicb.2016.00185, 185.
Rios-Covian, D., et al., 2020. An overview on fecal branched short-chain fatty acids along human life and as related with body mass index: associated dietary and anthropometric factors. Front. Microbiol. 11, 973,. https://doi.org/10.3389/fmicb.2020.00973.
Robertson, M.D., Bickerton, A.S., Dennis, A.L., Vidal, H., Frayn, K.N., 2005. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. Am. J. Clin. Nutr. 82, 559–567. https://doi.org/10.1093/ajcn.82.3.559.
Rong, H., et al., 2019. Similarly in depression, nuances of gut microbiota: evidences from a shotgun metagenomics sequencing study on major depressive disorder versus bipolar disorder with current major depressive episode patients. J. Psychiatr. Res. 113, 90–99. https://doi.org/10.1016/j.jpsychires.2019.03.017.
Rooks, M.G., Garrett, W.S., 2016. Gut microbiota, metabolites and host immunity. Nat. Rev. Immunol. 16, 341–352. https://doi.org/10.1038/nri.2016.42.
Russo, E., et al., 2019. Immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Front. Immunol. 10, 2754,. https://doi.org/10.3389/fimmu.2019.02754.
Rutsch, A., Kantsjo, J.B., Ronchi, F., 2020. The gut-brain Axis: how microbiota and host inflammasome influence brain physiology and pathology. Front. Immunol. 11, 604179,. https://doi.org/10.3389/fimmu.2020.604179.
Said, H., et al., 2017. FFA3 activation stimulates duodenal bicarbonate secretion and prevents NSAID-induced enteropathy via the GLP-2 pathway in rats. Dig. Dis. Sci. 62, 1944–1952. https://doi.org/10.1007/s10620-017-4600-4.
Sampson, T.R., et al., 2016. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 167, 1469–1480 e1412. https://doi.org/10.1016/j.cell.2016.11.018.
Sarkar, A., et al., 2016. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci. 39, 763–781. https://doi.org/10.1016/j.tins.2016.09.002.
Sarkola, T., Iles, M.R., Kohlenberg-Mueller, K., Eriksson, C.J., 2002. Ethanol, acetaldehyde, acetate, and lactate levels after alcohol intake in white men and women: effect of 4-methylpyrazole. Alcohol Clin. Exp. Res. 26, 239–245.
Schellekens, H., et al., 2021. Bifidobacterium longum counters the effects of obesity: partial successful translation from rodent to human. EBioMedicine 63, 103176,. https://doi.org/10.1016/j.ebiom.2020.103176.
Scheppach, W., et al., 1992. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology 103, 51–56. https://doi.org/10.1016/0016-5085(92)91094-k.
Schönfeld, P., Wojtczak, L., 2016. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. JLR (J. Lipid Res.) 57, 943–954. https://doi.org/10.1194/jlr.R067629.
Schwiertz, A., et al., 2010. Microbiota and SCFA in lean and overweight healthy subjects. Obesity 18, 190–195. https://doi.org/10.1038/oby.2009.167.
Sekirov, I., Russell, S.L., Antunes, L.C., Finlay, B.B., 2010. Gut microbiota in health and disease. Physiol. Rev. 90, 859–904. https://doi.org/10.1152/physrev.00045.2009.
Sellin, J.H., 1999. SCFAs: the enigma of weak electrolyte transport in the colon. News Physiol. Sci. 14, 58–64. https://doi.org/10.1152/physiologyonline.1999.14.2.58.
Sepahi, A., Liu, Q., Friesen, L., Kim, C.H., 2021. Dietary fiber metabolites regulate innate lymphoid cell responses. Mucosal Immunol. 14, 317–330. https://doi.org/10.1038/s41385-020-0312-8.
Serpa, J., et al., 2010. Butyrate-rich colonic microenvironment is a relevant selection factor for metabolically adapted tumor cells *. J. Biol. Chem. 285, 39211–39223. https://doi.org/10.1074/jbc.M110.156026.
Sharon, G., et al., 2014. Specialized metabolites from the microbiome in health and disease. Cell Metabol. 20, 719–730. https://doi.org/10.1016/j.cmet.2014.10.016.
Sharon, G., et al., 2019. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. Cell 177, 1600–1618 e1617. https://doi.org/10.1016/j.cell.2019.05.004.
Shimizu, J., et al., 2018. Propionate-producing bacteria in the intestine may associate with skewed responses of IL10-producing regulatory T cells in patients with relapsing polychondritis. PLoS One 13, e0203657.
Shimizu, H., et al., 2019. Dietary short-chain fatty acid intake improves the hepatic metabolic condition via FFAR3. Sci. Rep. 9, 16574,. https://doi.org/10.1038/s41598-019-53242-x.
Shultz, S.R., et al., 2015. Intracerebroventricular injection of propionic acid, an enteric metabolite implicated in autism, induces social abnormalities that do not differ between seizure-prone (FAST) and seizure-resistant (SLOW) rats. Behav. Brain Res. 278, 542–548. https://doi.org/10.1016/j.bbr.2014.10.050.
Silva, Y.P., Bernardi, A., Frozza, R.L., 2020. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front. Endocrinol. 11, 25,. https://doi.org/10.3389/fendo.2020.00025.
Singh, N., et al., 2010. Blockade of dendritic cell development by bacterial fermentation products butyrate and propionate through a transporter (Slc5a8)-dependent inhibition of histone deacetylases. J. Biol. Chem. 285, 27601–27608. https://doi.org/10.1074/jbc.M110.102947.
Singh, R.K., et al., 2017. Influence of diet on the gut microbiome and implications for human health. J. Transl. Med. 15, 73,. https://doi.org/10.1186/s12967-017-1175-y.
Skonieczna-Żydecka, K., et al., 2018. Faecal short chain fatty acids profile is changed in Polish depressive women. Nutrients 10, 1939.
Smith, P.M., et al., 2013. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341, 569–573.
Soret, R., et al., 2010. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. Gastroenterology 138, 1772–1782. https://doi.org/10.1053/j.gastro.2010.01.053.
Spichak, S., et al., 2021a. Mining microbes for mental health: determining the role of microbial metabolic pathways in human brain health and disease. Neurosci. Biobehav. Rev. 125, 698–761. https://doi.org/10.1016/j.neubiorev.2021.02.044.
Spichak, S., et al., 2021b. Microbially-derived short-chain fatty acids impact astrocyte gene expression in a sex-specific manner. Brain Behav. Immun. Health 16, 100318,. https://doi.org/10.1016/j.bbih.2021.100318.
Stilling, R.M., et al., 2016. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem. Int. 99, 110–132. https://doi.org/10.1016/j.neuint.2016.06.011.
Stumpff, F., 2018. A look at the smelly side of physiology: transport of short chain fatty acids. Pflügers Archiv 470, 571–598. https://doi.org/10.1007/s00424-017-2105-9.
Sun, J., et al., 2016. Clostridium butyricum pretreatment attenuates cerebral ischemia/reperfusion injury in mice via anti-oxidation and anti-apoptosis. Neurosci. Lett. 613, 30–35. https://doi.org/10.1016/j.neulet.2015.12.047.
Sun, M.-F., et al., 2018. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: gut microbiota, glial reaction and TLR4/TNF-α signaling pathway. Brain Behav. Immun. 70, 48–60.
Sun, Q., Jia, Q., Song, L., Duan, L., 2019. Alterations in fecal short-chain fatty acids in patients with irritable bowel syndrome: a systematic review and meta-analysis. Medicine (Baltim.) 98, e14513,. https://doi.org/10.1097/MD.0000000000014513.
Sun, N., et al., 2020a. Antibiotic-induced microbiome depletion in adult mice disrupts blood-brain barrier and facilitates brain infiltration of monocytes after bone-marrow transplantation. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2020.11.032.

Sun, J., et al., 2020b. Effect of Clostridium butyricum against microglia-mediated neuroinflammation in Alzheimer's disease via regulating gut microbiota and metabolites butyrate. Mol. Nutr. Food Res. 64, 1900636. https://doi.org/10.1002/mnfr.201900636.
Swiatecka, D., Narbad, A., Ridgway, K.P., Kostyra, H., 2011. The study on the impact of glycated pea proteins on human intestinal bacteria. Int. J. Food Microbiol. 145, 267–272. https://doi.org/10.1016/j.ijfoodmicro.2011.01.002.
Tahara, Y., et al., 2018. Gut microbiota-derived short chain fatty acids induce circadian clock entrainment in mouse peripheral tissue. Sci. Rep. 8, 1395,. https://doi.org/10.1038/s41598-018-19836-7.
Takada, M., et al., 2016. Probiotic Lactobacillus casei strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models. Neuro Gastroenterol. Motil. 28, 1027–1036. https://doi.org/10.1111/nmo.12804.
Tamai, I., et al., 1995. Participation of a proton-cotransporter, MCT1, in the intestinal transport of monocarboxylic acids. Biochem. Biophys. Res. Commun. 214, 482–489. https://doi.org/10.1006/bbrc.1995.2312.
Tana, C., et al., 2010. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neuro Gastroenterol. Motil. 22, 512–519. https://doi.org/10.1111/j.1365-2982.2009.01427.x e114-515.
Tao, R., et al., 2007. Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat. Med. 13, 1299–1307. https://doi.org/10.1038/nm1652.
Thangaraju, M., et al., 2008. Sodium-coupled transport of the short chain fatty acid butyrate by SLC5A8 and its relevance to colon cancer. J. Gastrointest. Surg. 12, 1773–1781. https://doi.org/10.1007/s11605-008-0573-0 discussion 1781-1772.
Thibault, R., et al., 2007. Down-regulation of the monocarboxylate transporter 1 is involved in butyrate deficiency during intestinal inflammation. Gastroenterology 133, 1916–1927.
Thorburn, A.N., Macia, L., Mackay, C.R., 2014. Diet, metabolites, and "western-lifestyle" inflammatory diseases. Immunity 40, 833–842. https://doi.org/10.1016/j.immuni.2014.05.014.
Thorburn, A.N., et al., 2015. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. Nat. Commun. 6, 7320,. https://doi.org/10.1038/ncomms8320.
Tian, X., et al., 2019. Elevated gut microbiome-derived propionate levels are associated with reduced sterile lung inflammation and bacterial immunity in mice. Front. Microbiol. 10, 159,. https://doi.org/10.3389/fmicb.2019.00159.
Tian, Z., Zhuang, X., Luo, M., Yin, W., Xiong, L., 2020. The propionic acid and butyric acid in serum but not in feces are increased in patients with diarrhea-predominant irritable bowel syndrome. BMC Gastroenterol. 20, 73,. https://doi.org/10.1186/s12876-020-01212-3.
Tolhurst, G., et al., 2012. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes 61, 364–371. https://doi.org/10.2337/db11-1019.
Torres-Fuentes, C., et al., 2019. Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling. Faseb. J. 33, 13546–13559. https://doi.org/10.1096/fj.201901433R.
Trapp, S., Richards, J.E., 2013. The gut hormone glucagon-like peptide-1 produced in brain: is this physiologically relevant? Curr. Opin. Pharmacol. 13, 964–969. https://doi.org/10.1016/j.coph.2013.09.006.
Trompette, A., et al., 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat. Med. 20, 159–166. https://doi.org/10.1038/nm.3444.
Tweedie-Cullen, R.Y., et al., 2012. Identification of combinatorial patterns of post-translational modifications on individual histones in the mouse brain. PLoS One 7, e36980,. https://doi.org/10.1371/journal.pone.0036980.
Unger, M.M., et al., 2016. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Park. Relat. Disord. 32, 66–72. https://doi.org/10.1016/j.parkreldis.2016.08.019.
Usami, M., et al., 2008. Butyrate and trichostatin A attenuate nuclear factor kappaB activation and tumor necrosis factor alpha secretion and increase prostaglandin E2 secretion in human peripheral blood mononuclear cells. Nutr. Res. (New York, N.Y.) 28, 321–328. https://doi.org/10.1016/j.nutres.2008.02.012.
Valles-Colomer, M., et al., 2019. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat. Microbiol. 4, 623–632. https://doi.org/10.1038/s41564-018-0337-x.
van Bloemendaal, L., et al., 2014. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes 63, 4186–4196. https://doi.org/10.2337/db14-0849.
van de Wouw, M., Schellekens, H., Dinan, T.G., Cryan, J.F., 2017. Microbiota-gut-brain Axis: modulator of host metabolism and appetite. J. Nutr. 147, 727–745. https://doi.org/10.3945/jn.116.240481.
van de Wouw, M., et al., 2018. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J. Physiol. 596, 4923–4944. https://doi.org/10.1113/JP276431.
van der Hee, B., Wells, J.M., 2021. Microbial regulation of host physiology by short-chain fatty acids. Trends Microbiol. 29, 700–712. https://doi.org/10.1016/j.tim.2021.02.001.
Vascellari, S., et al., 2020. Gut microbiota and metabolome alterations associated with Parkinson's disease. mSystems 5, e00561–520. https://doi.org/10.1128/mSystems.00561-20.
Vuong, H.E., Yano, J.M., Fung, T.C., Hsiao, E.Y., 2017. The microbiome and host behavior. Annu. Rev. Neurosci. 40, 21–49. https://doi.org/10.1146/annurev-neuro-072116-031347.
Wakade, C., Chong, R., Bradley, E., Thomas, B., Morgan, J., 2014. Upregulation of GPR109A in Parkinson's disease, 10.1371/.
Waldecker, M., Kautenburger, T., Daumann, H., Busch, C., Schrenk, D., 2008. Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. J. Nutr. Biochem. 19, 587–593. https://doi.org/10.1016/j.jnutbio.2007.08.002.
Wall, R., et al., 2014. Bacterial neuroactive compounds produced by psychobiotics. Adv. Exp. Med. Biol. 817, 221–239. https://doi.org/10.1007/978-1-4939-0897-4_10.
Wallen, Z.D., et al., 2020. Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens. npj Parkinson's Dis. 6, 11,. https://doi.org/10.1038/s41531-020-0112-6.
Walter, A., Gutknecht, J., 1984. Monocarboxylic acid permeation through lipid bilayer membranes. J. Membr. Biol. 77, 255–264. https://doi.org/10.1007/BF01870573.
Wang, L., de Zoeten, E.F., Greene, M.I., Hancock, W.W., 2009. Immunomodulatory effects of deacetylase inhibitors: therapeutic targeting of FOXP3+ regulatory T cells. Nat. Rev. Drug Discov. 8, 969–981. https://doi.org/10.1038/nrd3031.
Wang, L., et al., 2012. Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. Dig. Dis. Sci. 57, 2096–2102. https://doi.org/10.1007/s10620-012-2167-7.
Wang, P., et al., 2018. Sodium butyrate triggers a functional elongation of microglial process via Akt-small RhoGTPase activation and HDACs inhibition. Neurobiol. Dis. 111, 12–25.
Wellen, K.E., et al., 2009. ATP-citrate lyase links cellular metabolism to histone acetylation. Science (New York, N.Y.) 324, 1076–1080. https://doi.org/10.1126/science.1164097.
Wenzel, T.J., Gates, E.J., Ranger, A.L., Klegeris, A., 2020. Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. Mol. Cell. Neurosci. 105, 103493,. https://doi.org/10.1016/j.mcn.2020.103493.
Willemsen, L.E., Koetsier, M.A., van Deventer, S.J., van Tol, E.A., 2003. Short chain fatty acids stimulate epithelial mucin 2 expression through differential effects on prostaglandin E(1) and E(2) production by intestinal myofibroblasts. Gut 52, 1442–1447. https://doi.org/10.1136/gut.52.10.1442.
Wishart, D.S., et al., 2008. The human cerebrospinal fluid metabolome. J. Chromatogr. B, Anal. Technol. Biomed. Life Sci. 871, 164–173. https://doi.org/10.1016/j.jchromb.2008.05.001.
Wishart, D.S., et al., 2018. HMDB 4.0: the human metabolome database for 2018. Nucleic Acids Res. 46, D608–D617. https://doi.org/10.1093/nar/gkx1089.
Won, Y.J., Lu, V.B., Puhl 3rd, H.L., Ikeda, S.R., 2013. beta-Hydroxybutyrate modulates N-type calcium channels in rat sympathetic neurons by acting as an agonist for the G-protein-coupled receptor FFA3. J. Neurosci. 33, 19314–19325. https://doi.org/10.1523/JNEUROSCI.3102-13.2013.
Wrzosek, L., et al., 2013. Bacteroides thetaiotaomicron and Faecalibacterium prausnitzii influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. BMC Biol. 11, 61,. https://doi.org/10.1186/1741-7007-11-61.
Wu, M., et al., 2020a. Associations between disordered gut microbiota and changes of neurotransmitters and short-chain fatty acids in depressed mice. Transl. Psychiatry 10, 350,. https://doi.org/10.1038/s41398-020-01038-3.
Wu, Q., et al., 2020b. Potential effects of antibiotic-induced gut microbiome alteration on blood-brain barrier permeability compromise in rhesus monkeys. Ann. N. Y. Acad. Sci. 1470, 14–24. https://doi.org/10.1111/nyas.14312.
Xiong, Y., et al., 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. Proc. Natl. Acad. Sci. U. S. A. 101, 1045–1050. https://doi.org/10.1073/pnas.2637002100.
Xu, D., et al., 2018. Hippocampal mTOR signaling is required for the antidepressant effects of paroxetine. Neuropharmacology 128, 181–195. https://doi.org/10.1016/j.neuropharm.2017.10.008.
Yamawaki, Y., et al., 2018. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res. 1680, 13–38.
Yao, C.K., Muir, J.G., Gibson, P.R., 2016. Review article: insights into colonic protein fermentation, its modulation and potential health implications. Aliment. Pharmacol. Ther. 43, 181–196. https://doi.org/10.1111/apt.13456.
Yap, C.X., et al., 2021. Autism-related dietary preferences mediate autism-gut microbiome associations. Cell 184, 5916–5931. https://doi.org/10.1016/j.cell.2021.10.015 e5917.
Yu, L., Zhong, X., He, Y., Shi, Y., 2020. Butyrate, but not propionate, reverses maternal diet-induced neurocognitive deficits in offspring. Pharmacol. Res. 160, 105082,. https://doi.org/10.1016/j.phrs.2020.105082.
Zaibi, M.S., et al., 2010. Roles of GPR41 and GPR43 in leptin secretory responses of murine adipocytes to short chain fatty acids. FEBS Lett. 584, 2381–2386. https://doi.org/10.1016/j.febslet.2010.04.027.
Zhang, L., et al., 2017. Altered gut microbiota in a mouse model of Alzheimer's disease. J. Alzheimers Dis. 60, 1241–1257. https://doi.org/10.3233/JAD-170020.
Zhao, X., et al., 2016. Sensitive and simplified detection of antibiotic influence on the dynamic and versatile changes of fecal short-chain fatty acids. PLoS One 11, e0167032. https://doi.org/10.1371/journal.pone.0167032.
Zhao, L., et al., 2018. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 359, 1151–1156. https://doi.org/10.1126/science.aao5774.
Zhao, P., et al., 2020. Long-lasting effects of postweaning sodium butyrate exposure on social behaviors in adult mice. Brain Res. Bull. 165, 209–217. https://doi.org/10.1016/j.brainresbull.2020.09.014.
Zheng, X., et al., 2013. A targeted metabolomic protocol for short-chain fatty acids and branched-chain amino acids. Metabolomics 9, 818–827. https://doi.org/10.1007/s11306-013-0500-6.
Zordoky, B.N., et al., 2015. Metabolomic fingerprint of heart failure with preserved ejection fraction. PLoS One 10, e0124844. https://doi.org/10.1371/journal.pone.0124844 e0124844.