Metabolic tinkering by the gut microbiome
Implications for brain development and function

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Brain development is an energy demanding process that relies heavily upon diet derived nutrients. Gut microbiota enhance the host's ability to extract otherwise inaccessible energy from the diet via fermentation of complex oligosaccharides in the colon. This nutrient yield is estimated to contribute up to 10% of the host's daily caloric requirement in humans and fluctuates in response to environmental variations. Research over the past decade has demonstrated a surprising role for the gut microbiome in normal brain development and function. In this review we postulate that perturbations in the gut microbial-derived nutrient supply, driven by environmental variation, profoundly impacts upon normal brain development and function.

Introduction

The diverse community of microorganisms lining the gastrointestinal canal has co-evolved with its host to build a mutually beneficial relationship. This location supports resident microbes with a reliable supply of nutrients and favorable temperatures for biological and biochemical reactions. A major role of the gut microbiome is to digest dietary fiber, otherwise refractory to the host's enzymatic repertoire, into metabolic byproducts such as short chain fatty acids (SCFAs); acetate, propionate, and butyrate.[1] Throughout evolution, these products of bacterial fermentation were likely to have afforded significant metabolic and immune fitness advantages to the host-microbe entity, referred to as the holobiont.[2] Consequently, gut microbial metabolism is deeply intertwined with host metabolism[3,4] and is an important contributor to the dynamic transfer of energy from the diet to the host (**Fig. 1**). During early life (conception to adolescence), this transfer of energy is essential to the expansion of tissues that require vast amounts of nutritional support for

proper development, particularly the immune and central nervous system. Environmental perturbations which alter the collective metabolic capacity of the microbiome, and thus the availability of valuable metabolic precursors[5] may directly, or indirectly, modify brain developmental trajectories and function in later life.

Here we provide a survey of the current literature and convey our perspective on the metabolic communication between the host and gut microbiome to highlight its relevance to neurodevelopment and brain function. We will focus primarily on the potential of SCFAs to affect the brain through (1) directly modulating host chromatin structure and gene transcription, (2) use as an energy source for ATP generation, and (3) the incorporation of SCFAs into energy reserves. We will then examine the potential of gut microbial driven changes in host systemic metabolism to impact brain development and function.

In utero, the developing embryo receives a maternally dictated nutrient supply. Postnatally, the newborn is exposed to a vast number of microbes, vertically transmitted from the maternal microbiome, which, in combination with protective maternal antibodies and nutrients provided by the breast milk, secures the first dramatic growth expansion in immediate early life. Together with early host intestinal response genes, breast milk is likely to shape the initial repertoire of early colonising microbes[6,7] through it being both a source of microbes per se[8-10] and as a source of nutrients for the developing microbiome. These initial interactions are likely to be important steps in mediating infant development through shaping the efficacy of gut microbial nutrient harvest from the diet[11] and providing metabolites important for developmental progression.[12] Importantly, although the gut microbiome has been implicated as a modulator of normal brain development and function within an early life developmental window[13,14] (recently reviewed in refs. 15-17), the involvement of host-microbe co-metabolism in this processes remains largely unknown.

The early life environment plays a pivotal role in shaping the way an individual's brain develops and functions,[18] including variations in nutritional intake (recently reviewed).[19] Although the human brain represents 2% of the body's mass, it consumes 20% of the whole body energy budget, whereas in rodents, the brain mass represents only ~0.2% of body mass and thus
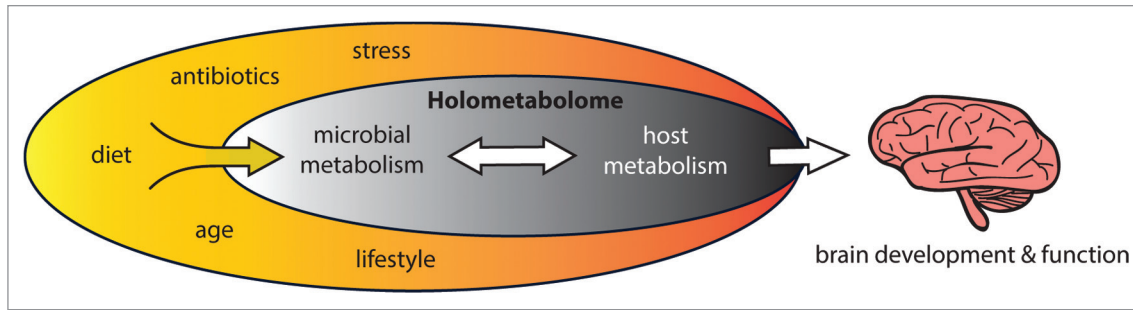
Figure 1. The host-microbe holometabolome. Environmental variations (yellow oval) leading to changes in the gut microbial metabolic capacity can induce alterations and compensations within the metabolic network. The consequence of a perturbed holometabolome will likely affect many different body systems, including brain development. The diet is likely to be a major environmental modulator of this system.

consumes only 2% of the body's energy budget.[20] This demonstrates the brain as being an incredibly energy demanding organ, regardless of species, but also that the human brain may be more vulnerable to metabolic dysfunction than rodents. Classic epidemiological studies on Dutch Hunger Winter sufferers revealed that nutrient deprivation within distinct gestational periods is associated with schizophrenia,[21,22] antisocial personality disorder,[23] and major affective disorders,[24] thus emphasizing the importance of adequate early-life nutritional support for normal brain development and function. For the developing brain, we hypothesize that changes in gut microbial metabolism during distinct critical developmental windows, such as in in early-life, may be key to understanding predispositions to various neurological disorders.

Endogenous Microbial Inhabitants: A Forgotten Organ

It is estimated that the number of microbial cells constituting the human gut microbiome outnumber the host's by 10:1 and the number of genes by 100:1. The microbiota contains a myriad of organisms including yeasts, protozoa, archaea, and bacteria, with estimations at over 1000 species.[25] Many of the beneficial effects that gut microbiota impart on host physiology is due to the production of SCFAs in the colon. Importantly, production of these metabolites is believed to be a major driving force behind the metabolic interactions between the host and gut microbiota.[4,26]

The significance of gut microbiota in host metabolism is perhaps best demonstrated by observations in mice lacking microbiota, referred to as germ-free, which are leaner than their colonised counterparts[27,] despite consuming more food[26,] and have a severely reduced survival rate upon starvation.[28] In addition, antibiotic treatment during early life increased adiposity, which was associated with shifts in the gut microbial composition in mice.[29] These data demonstrate that gut microbes aid in nutrient retrieval and storage to enhance the hosts ability to fulfil caloric requirements. It is therefore plausible that changes to the gut microbial composition, and consequently the production of SCFAs, may interfere with the vital nutrient supply

required for the intensely energy demanding process of brain development.

Microbial SCFA Production and Systemic Trafficking

The SCFA yield from a typical western diet constitutes 5–10% of a host's daily energy needs.[1,30] Factors limiting gut microbial production of SCFAs include (1) the availability of fermentable dietary fiber,[31] (2) microbiota expressing the necessary machinery to import, degrade and metabolise dietary fiber into SCFAs,[32,33] and (3) intra microbiome metabolic collaboration.[34] In addition, changes to the gut microbiome composition through antibiotic use,[3,6,35,36] mode of delivery,[36,37] caloric restriction,[38] age,[39-41] gastric surgery,[42,43] psychological stress,[44-46] geography,[41] and diet[6,47-54] are all either known to, or likely to, alter SCFA production throughout an individual's lifetime.

Once produced in the colon, SCFAs are then either used locally as an energy source by colonocytes (particularly butyrate[55]) or drained to the liver via the portal vein where their fate depends on the metabolic status of the host. Typically, SCFAs are incorporated into energy stores via lipogenesis or gluconeogenesis[4] however, they can also be distributed directly into the blood stream for dissemination to organs throughout the body,[56,57] including the brain (**Fig. 2**). Acetate, propionate and butyrate display decreasing penetration into the blood stream respectively. This may be due to the preferential use of butyrate as an energy source by colonocytes and possibly decreasing diffusion due to their respective increase in carbon chain length.[58] Consistently, acetate appears to be the most abundant of these metabolites in the peripheral circulation followed by propionate and then butyrate.[57,59-61] In humans, dietary manipulations designed to enhance colonic SCFA production lead to increases in serum acetate, propionate, and butyrate concentrations.[62,63] These changes can persist for hours as was demonstrated in men who ate a fiber rich evening meal and exhibited morning serum butyrate levels comparatively higher compared with those who ate a meal relatively low in fiber.[64] These findings indicate that the concentrations of serum SCFAs are dynamic and fluctuate in response to dietary fiber manipulation.

Transcriptional and Metabolic Regulation by SCFAs

In mitochondria, SCFAs can be oxidized to generate ATP via the TCA cycle. Through a series of intermediate steps the carbon backbones of acetate and butyrate are converted into acetyl-CoA which then enters the TCA cycle proximally, whereas propionate is converted to succinyl-CoA to enter at the distal end of the TCA cycle (**Fig. 3A**). In addition to their role as a source of ATP, SCFAs are also capable of host chromatin remodelling leading to global changes in host gene expression. In the nucleus, histones package host DNA into a conformational unit referred to as a nucleosome. Histone acetylation is accomplished by histone acetyl transferases (HATs). HATs transfer an acetyl groups onto histone lysine residues that neutralizes its positive charge and, in doing so, weakens the electrostatic interaction between histones and the negatively charged DNA (**Fig. 3B**). This loosening of the chromatin structure mediates active transcription by allowing greater access of transcription machinery to promoter regions. Conversely, transcription can be repressed by removal of the acetyl moieties from an acetylated lysine by a group of enzymes referred to as histone deacetylases (HDACs) (**Fig. 3B**). This latter form of transcription repression can be blocked by HDAC inhibitors (HDACi) (**Fig. 3B**). SCFAs, particularly butyrate and propionate, and even acetate (albeit at a far lower potency), are capable of inhibiting HDAC activity.[65,66] Therefore gut microbiota-derived SCFAs likely possess the capacity to influence host gene expression by remodeling host chromatin structure. It is thereby plausible that dietary induced fluctuations in colonic SCFA production reflected in host serum,[57,62,63] is capable of altering host gene expression far beyond the colon, including organs such as the liver, muscle, and brain.

Epigenetic regulation by histone acetylation has recently been shown to be intimately connected with host cell metabolism. In a landmark study, it was demonstrated that acetyl-CoA, derived from glucose and ATP-citrate lyase (ACL), can provide the acetyl substrate for histone acetylation[67] (**Fig. 3B**). Gut microbiota have been shown to modify the availability of circulating energy metabolites in blood, including glucose and other metabolites

Figure 2. Gut microbiota supply nutrients to the developing brain. This hypothetical model illustrates the route by which gut microbiota supply nutrients to the developing brain. Upon draining to the liver via the hepatic portal vein, SCFAs are incorporated into either lipogenic or gluconeogenic pathways for energy storage, depending on the metabolic state of the host, or disseminated directly into the bloodstream. Gut microbial regulation of blood metabolites, which are required to build a healthy brain, may modify developmental trajectories. In utero, nutrients for normal brain development are transported to the infant across the placental barrier via the umbilical vein. Two thirds of the nutrient and oxygen loaded blood passes through the liver while the remaining bypasses the liver via the ductus venosus and is diverted directly into the blood stream of developing fetus.

readily used to generate ATP via the TCA cycle.[68] It is therefore plausible that changes to the gut microbiota composition, and consequent perturbations in serum metabolite concentrations, can mediate changes to brain histone acetylation (**Fig. 3B**). This may be of particular significance if fluctuations in these circulating metabolites occur during early life when epigenetic control of developmental trajectories is vital to the later life function of a given organ, especially the brain due to its high energy demands. Similarly, during aging, a reduction in the availability of serum energy metabolites, as has been observed in a mouse model for
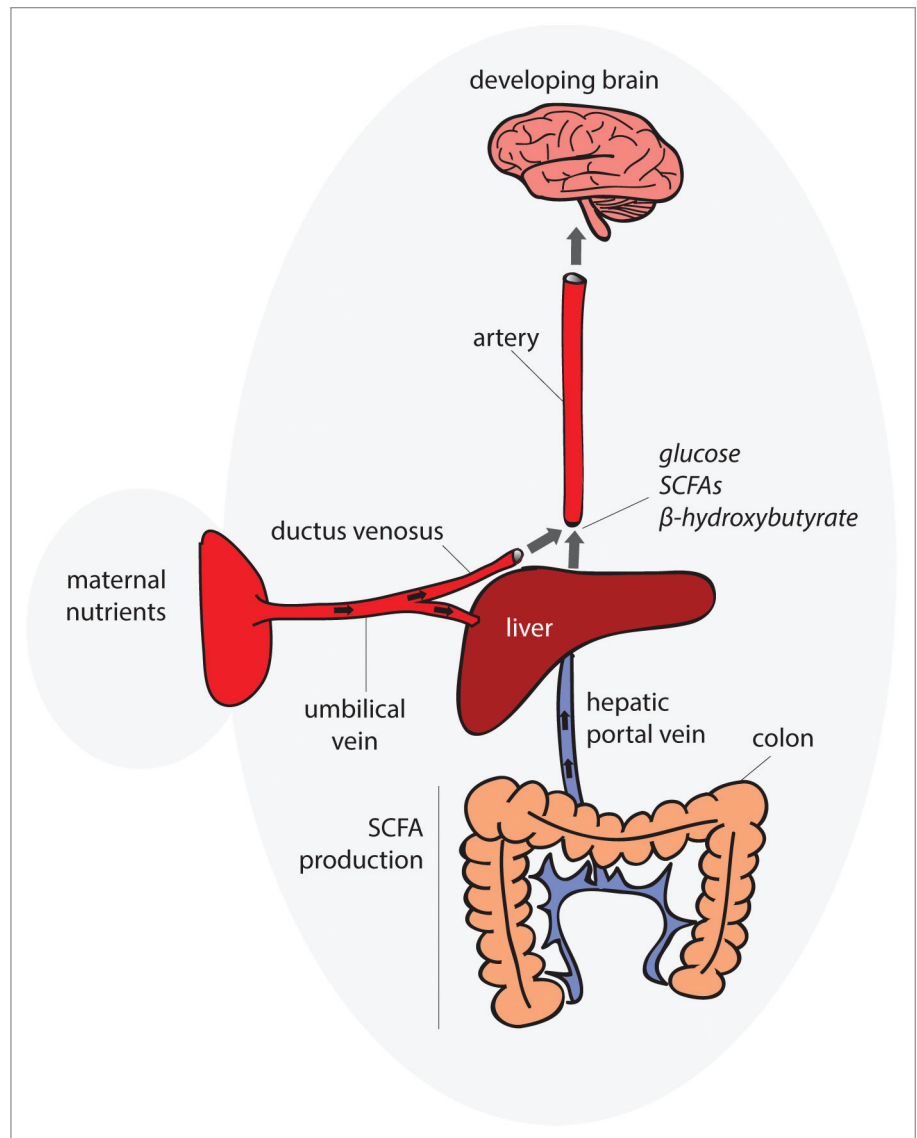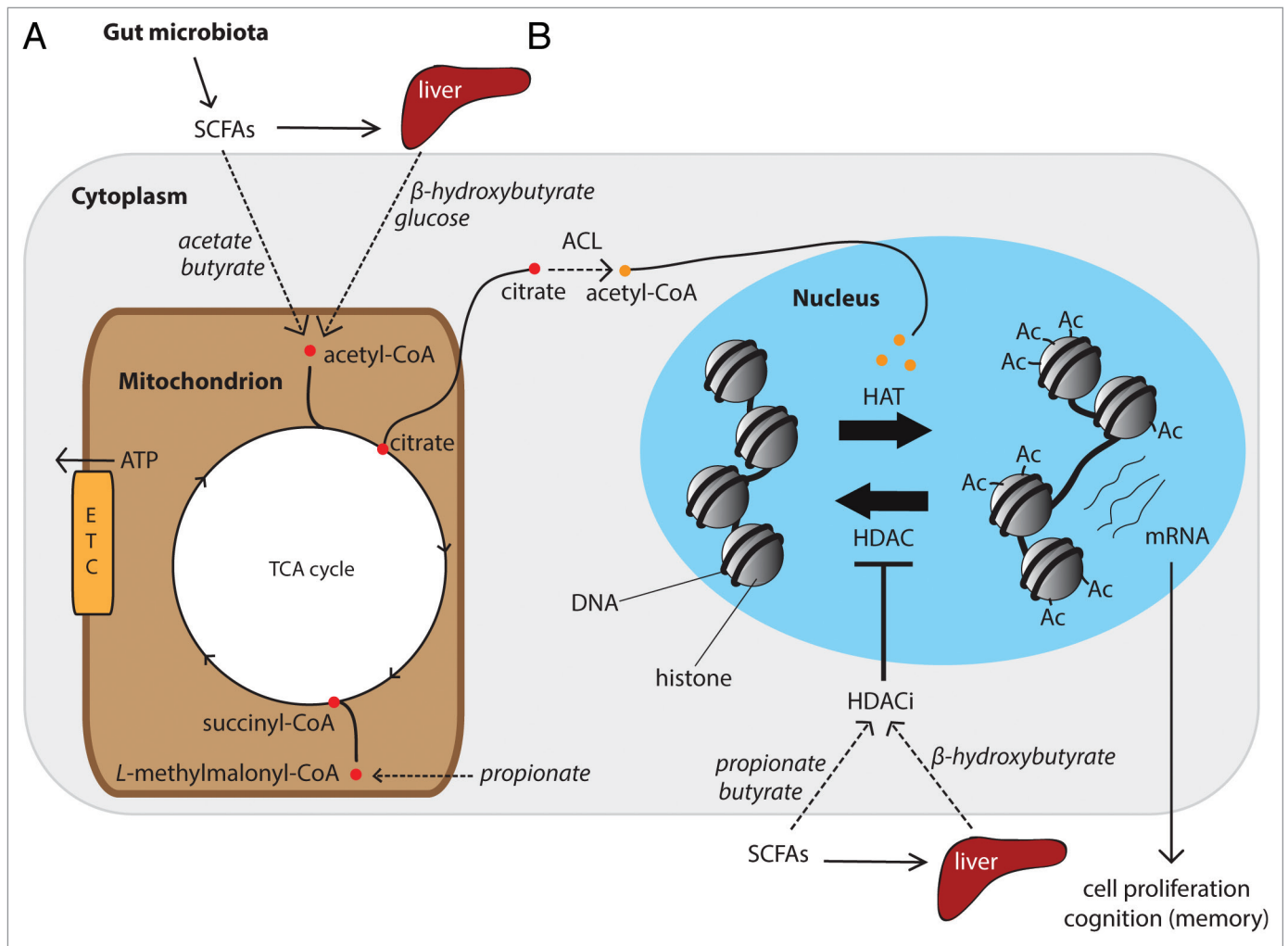
Figure 3. External metabolic cues regulate histone acetylation via the tricarboxylic acid (TCA) cycle. This hypothetical model illustrates how gut microbial regulated serum metabolites, which are readily used by mitochondria to generate ATP, may influence host cell gene transcription. (**A**) SCFAs are produced in the colon and disseminated directly into the blood stream or trafficked to the liver and released as glucose or β-hydroxybutyrate, depending on the host's metabolic status. These metabolites are then used by cells within the CNS to generate ATP via the TCA cycle. (**B**) ATP-citrate lyase (ACL) uses mitochondrial derived citrate to generate acetyl-CoA in the cytoplasm and nucleus. In the nucleus, histone acetyl-transferases (HATs) transfer the acetyl group from acetyl-CoA onto histone lysine residues to facilitate cell proliferation and the expression of genes important for learning and memory. Histone deacetylases (HDACs) remove acetyl groups from histones to suppress gene transcription. HDACs can be inhibited by a histone deacetylase inhibitors (HDACi), including gut microbial regulated serum metabolites, e.g., β-hydroxybutyrate, butyrate, and propionate. This is illustration is not to scale.

aging and cognitive decline,[69] may also mediate reduced histone acetylation observed in the aging mouse hippocampus.[70]

In vitro experiments demonstrate that butyrate can modify neuronal gene expression and signal transduction,[71,72] but to our knowledge, such high butyrate concentrations used in these experiments (1–6 mM) have not been reported in human or rodent blood under physiological conditions. In vivo models exploiting the potent HDACi activity of butyrate, again albeit at concentrations unlikely to be observed under normal conditions, has revealed its surprising ability to enhance cognitive function. Consistently, butyrate has been shown to reinstate histone acetylation in the mouse hippocampus (a brain region important for learning and memory) and was correlated with improved learning and memory.[73] Similar results were observed in models for depression,[49] age-associated cognitive decline,[70] Alzheimer disease,[74] and Huntington disease.[75] The corollary of these combined findings might suggest that reduced HDACi activity, potentially as a consequence of reduced gut microbial metabolite production or age dependent metabolite trafficking deficiencies of such metabolites,[76] may underlie changes to the way an individual's brain functions, including psychological state and neurodegenerative processes.

Gut Microbiota Regulation of Energy Reserves

At birth, newborns must adapt to a relatively high fat, low carbohydrate diet provided by the mother's milk instead of

a glucose rich nutrient supply across the placental wall. This metabolic shift relies heavily upon the infant being able to produce and utilize the ketone (D)-3-hydroxybutyrate as an energy source during intermittent feeding within the suckling and weaning period,[77] a process referred to as ketogenesis.[78] When blood glucose is low, ketones are produced through fatty acid β-oxidation in the liver and then disseminated via the blood stream. This glucose replacement ensures sufficient nutritional support for the body, especially the brain, during infant development. Similarly in adults, when blood glucose is low due to prolonged exercise, starvation or a ketogenic diet (low carbohydrate); millimolar concentrations of (D)-3-hydroxybutyrate are produced as an alternate energy source to support the adult's metabolic needs.[79,80] Gut microbiota play a key role in enhancing (D)-3-hydroxybutyrate production during starvation[81] and moderating the steady-state ketogenic profile and is thought to be a consequence of the enhanced stored energy afforded by gut microbial SCFA production.[27] Considering that (D)-3-hydroxybutyrate has recently been demonstrated as a potent HDACi,[82] it remains to be seen whether it and other gut microbial-regulated serum metabolites capable of HDACi (i.e., butyrate, propionate, and (D)-3-hydroxybutyrate) can alter brain development via its use as an energy source, HDACi or both.

Metabolite Sensing by G-Protein Coupled Receptors

Upon activation by an external ligand, G-protein coupled receptors (GPCRs) initiate an intracellular signaling cascade resulting in a specific host cell response. Gut microbiota derived SCFAs acetate, propionate and butyrate activate host cell G-protein coupled receptors (i.e., GPR43 [*FFAR2*], GPR41 [*FFAR3*], and GPR109A[HM74a{human}/PUMA-G{mouse}]) with different potencies. Activation of GPR43 and GPR41 expressed beyond the colon mediate host immune responses[83,84] and systemic metabolic regulation.[85-88] Blood SCFA concentrations can serve as a useful proxy for determining the physiological concentrations of circulating SCFAs to which many cells throughout the body are exposed. Serum acetate (~50–1000 μM) and propionate (~5–150 μM) concentrations capable of GPR43 and GPR41 activation respectively, have been observed during fasting and dietary fiber manipulation.[60-63,87,89] Serum butyrate concentrations observed after dietary fiber manipulation (1–5 μM)[62] however, are unlikely to cause significant activation of GPR109a in peripheral organs.[90] In peripheral tissue, GPR109a is activated by the ketone (D)-3-hydroxybutyrate which can reach as high as 6–8 mM during prolonged fasting.[78] These observations indicate that under certain physiological conditions where colonic SCFA production is enhanced, or (D)-3-hydroxybutyrate production is increased, gut microbial-regulated metabolites in the circulation are capable of directly mediating effects on host cells via GPCR signaling.

Metabolite Sensors in the Sympathetic and Central Nervous System

GPCRs are major facilitators of neural transmission through their role as neurotransmitter receptors in both the sympathetic and central nervous system. The SCFA receptor GPR41 is highly expressed in the sympathetic ganglia[91] and GPR109a expression has been demonstrated in the mammalian brain.[92,93] GPR41, also known as the free fatty acid receptor 3, has been shown to play a key role in the sympathetic nervous system (SNS)[91] including the regulation of blood pressure,[94] likely through mediating the release of the neurotransmitter norepinephrine (NE).[95] In addition, (D)-3-hydroxybutyrate, a metabolite also subject to gut microbial regulation,[27,81] was recently shown to antagonize GPR41-mediated SNS activation. Together, these observations demonstrate the potential for gut microbiota-regulated GPCR ligands in the blood to tweak neuronal activation of the SNS and potentially the central nervous system (CNS). A comprehensive characterization of SCFA receptor expression in the brain is needed to determine their relevance to direct CNS activation by gut microbial metabolites.

Gut Microbiota Dynamics during Brain Development

Pre and post-natal brain development is an intensely energy demanding process that progresses through distinct developmental windows.[5,96] The period of increasing brain weight, referred to as the "brain growth spurt," occurs at different times in different mammals.[5] The human brain growth spurt occurs perinatally whereas rat the rat brain growth spurt occurs comparatively later during the postnatal period. This intensely energy demanding process is mainly attributed to glial cell proliferation and myelination.[5]

Human infant brain growth is accelerated in the months leading up to, and directly after birth[97]; a temporal neurodevelopmental window paralleled by major shifts in the maternal[98] and infant microbiota composition.[39-41] Comparisons between 1st and 3rd trimester microbiota compositions from humans revealed an increase in species of Proteobacteria and Actinobacteria and an overall reduced microbial diversity.[98] Interestingly, gut microbiota from the 3rd trimester exhibited a distinct metabolic phenotype capable of promoting greater energy storage compared with first trimester microbiota.[98] This suggests an important role for the maternal microbiome in harvesting additional energy from the diet to sustain in utero infant development.

Postnatal neurodevelopment was examined using an animal model to compare Cesarean and vaginally delivered rats; two modes of delivery known to result in distinct microbial compositions.[37] Using a rat model, reduced neuronal spine density in pre-frontal cortex (PFC) neurons and hippocampal pyramidal neurons at postnatal day 35 (P35), which were then normalized by P70, was observed in Caesarean born animals compared with vaginally born controls.[99] Considering the likely differences in

gut microbial colonization in this model, it will be interesting to elucidate whether these phenotypes are a consequence of differing microbial composition or colonization kinetics.

Gut Microbiota-Host Co-Metabolism and Brain Development

The role of the gut microbiome, and manipulations thereof, in modulating brain function has seen a recent flurry of detailed reviews.[15,17,100-103] In particular, deregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a pathway implicated in several neurological disorders including depression and anxiety, has been demonstrated in various models of gut microbial manipulation and generally appears to be overactive in the absence of gut microbiota.[14,104-106] Pioneering work by Sudo and colleagues demonstrated that gut microbiota possess the capacity to modulate brain gene expression and that the HPA axis is programmed by microbial colonization during early-life.[14] However, the causal factors mediating gut microbial activation of the HPA axis remain unclear. The HPA axis can be programmed by dietary conditions in early-life (recently reviewed in 106). As the diet is also a strong modulator of gut microbial composition and its metabolic output, it is therefore worth considering the contribution of gut microbial derived metabolites in setting the parameters for HPA axis activation.

A recent demonstration of the vital role for SCFA production in host development was demonstrated using germ-free *Drosophila* mono-associated with the commensal *Acetobacter pomorum*. This powerful model revealed the striking observation that the absence of *Drosophila* microbiota results in developmental arrest at the larval stage when exposed to nutrient limiting conditions. This phenotype could be rescued by monocolonisation with *A. pomorum*.[12] This growth factor-like property of *A. pomorum* was shown to be indirectly related to the production of the SCFA acetate, which activated the insulin and/or insulin-like growth factor signaling (IIS) pathway. This remarkably thorough study clearly illustrates the fundamental importance of SCFA production by microbiota for invertebrate development, which may also be reflected in vertebrate development. Curiously, acetate production by *A. pomorum* was also implicated in the induced expression of *Drosophila* insulin-like peptides (*DILPs*) in the larval brain,[12] a pathway analogous to the mammalian IIS pathway and implicated in *Drosophila* peripheral and CNS development.[107] This demonstrates integration between microbial SCFA production and brain development.

Another microbial regulated metabolite relevant to brain development and function is tryptophan. Tryptophan is the metabolic precursor to the neurotransmitter serotonin, but unlike tryptophan, serotonin cannot cross the blood-brain-barrier and thus must be synthesized de novo in the brain from blood derived tryptophan. Thus, blood tryptophan provides the pool of available precursors for brain serotonin synthesis, which is modulated by gut microbiota.[108,109] Indeed, we have demonstrated higher serotonin turnover in the striatum of germ-free mice compared with conventional counterparts.[13] Others have

recently demonstrated gut microbiota-dependent changes to the hippocampal serotonergic pathway in germ-free male mice, but not females.[110] Considering the importance of serotonin for postnatal brain development,[111] it will be of great interest to decipher the role of gut microbial tryptophan metabolism in this process.

Under nutrient limiting conditions, energy is rationed out to organs where it is most needed, with the brain and muscle taking priority. The cognitive cost of this process was recently demonstrated using *Drosophila* where memory formation was disabled during starvation.[112] A germ-free mouse is somewhat reminiscent of a nutrient deprived animal as reflected by diminished fat stores,[26] a more ketogenic profile under non-stressed conditions,[27] lower serum glucose and metabolites available for ATP production.[68] As memory consolidation is an energy demanding process,[112] it will be of profound interest to determine whether this systemic scarcity of energy availability in germ-free mice is responsible for mediating impaired learning and memory observed in these mice.[106] Furthermore, cognitive enhancement has also been observed in mice treated with the probiotic bacterium *Lactobacillus rhamnosus* (JB-1).[105]

In a recent study, *Lactobacillus rhamnosus* (JB-1) was shown to alter GABA receptor expression in a brain region specific manner.[105] This differential gene expression was associated with reduced anxiety-like behavior and reduced stress induced corticosterone production.[105] Curiously, *L. rhamnosus* (JB-1) treated mice also displayed enhanced memory to an aversive cue. An important outcome of this seminal work was that specific neurochemical and behavioral effects were not observed in vagotomised mice, thus implicating the vagus nerve as an important communication route between gut microbiota and the brain. Although anxiety-like behavior in this model was shown to be mediated via the vagus nerve, it remains to be determined whether *L. rhamnosus* (JB-1) enhances cognitive function via the same route, or whether these effects are mediated by metabolic signals from the blood stream.

Separately, *L. rhamnosus* has been shown to suppress diet induced obesity in mice.[113] More recently, we demonstrated that *Lactobacillus paracasei* decreased fat storage and enhances serum very low-density lipoprotein (VLDL) concentrations and serum levels of the lipoprotein lipase inhibitor, ANGPTL4.[114] The ability of *L. paracasei* to induce ANGPTL4 expression in vitro was mediated by PPAR-γ and PPAR-α activation which may in part be attributed to the SCFA butyrate.[115] Both *L. rhamnosus* and *L. paracasei* have been shown to modify gut microbiota composition and SCFA production which was correlated with altered hepatic lipid metabolism and circulating lipoprotein levels.[116] It will be important to understand whether systemic metabolic changes that occur upon Lactobacilli administration are responsible for enhancing cognitive function, as was observed for *L. rhamnosus* (JB-1).[105]

Gut Microbial Modifications to Host Metabolism: Consequences for Brain Function

Gut microbiota have been implicated as major mediators of obesity and Type 2 Diabetes (T2D)[117,118] (reviewed in ref. 4).

Recently, insulin sensitivity was shown to be regulated via GPR43 activation by acetate.[87] Furthermore, dietary administration of butyrate was shown to improve insulin sensitivity and enhance mitochondrial function in peripheral tissue.[119] The brain is not entirely protected from metabolic disturbances and many of the molecular mediators of T2D, including insulin and leptin, have been associated with dementia[120-122] (reviewed in refs. 123,124). In support of this, a T2D mouse model, characterized by poor insulin sensitivity, exhibited hippocampal dysfunction and plasticity.[125] This phenotype could be ameliorated by maintaining normal physiological levels of corticosterone,[125] a hormonal mediator of the HPA axis which has independently been shown to be regulated by gut microbiota.[14,105]

Leptin is another T2D relevant hormone subject to gut microbial regulation and plays a role in brain function.[126,127] Leptin is a host derived hormone which acts as an appetite suppressant and is strongly implicated in obesity and T2D. In humans, higher levels of circulating leptin have been associated with a reduced risk of dementia and Alzheimer disease.[128] In support of this, leptin has been shown to increase adult mouse hippocampal neurogenesis[129] and rat hippocampal dendritic spine morphology.[130] Interestingly, germ-free mice display low levels of circulating leptin[126] and reduced cognitive function.[106] Perhaps, lower levels of circulating leptin levels in germ-free mice[126] reflect the lack of SCFA mediated GPR41 and/or GPR43 activation which has been shown to stimulate leptin production.[131,132] It will therefore be of profound interest to delineate the mechanism of gut microbial leptin regulation and its implications for host metabolism and brain function.

Regarding behavior and cognition, diets designed to enhance gut microbial fiber fermentation in the colon have provided useful insight. Using dietary manipulations that enhance gut microbial fiber fermentation in the cecum and colon, a positive correlation was observed between lactic acid and volatile fatty acid (VFA) production with anxiety-like behavior and aggression.[133] Subsequently, the same group demonstrated a positive correlation between serum lactate levels and the ability of rats to discriminate between a familiar and novel object,[134] suggesting improved cognitive performance. These results suggest that cognitive function may be modified by enhancing gut microbial fiber fermentation efficiencies. Considering that SCFAs can cross the blood-brain-barrier (BBB),[135,136] it will be worthwhile determining whether SCFAs, and associated metabolites such as lactate, in peripheral circulation can mediate direct effects on cognition.

Microbial Behavior

Different gut microbiota compositions have been shown to encode specific behavioral traits from inter-strain microbiota transplantation experiments.[137] These authors exploited the inherent high anxiety-like behavior of BALB/c mice by comparing them to the less anxious NIH Swiss mouse strain. Microbiota transplants of BALB/c microbiota into germ-free NIH Swiss mice increased their anxiety-like behavior whereby
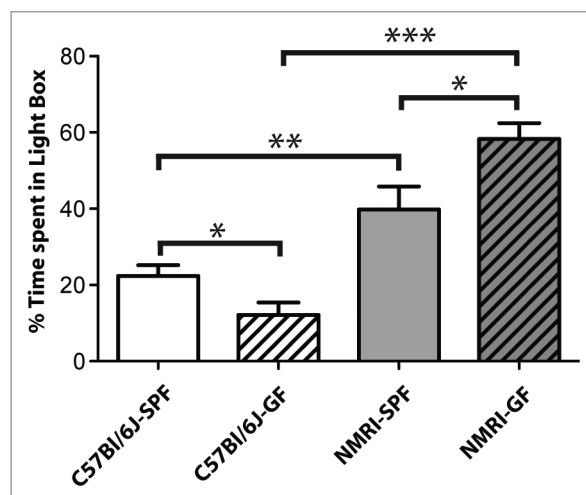

Figure 4. Strain differences in anxiety-like behavior between germ-free C57Bl/6J and NMRI mice. In the light-dark box test, a behavioral test for anxiety, mice were individually placed into a dark box and allowed 10 min of free exploration and the amount of time spent exploring the light box was recorded. An ANOVA showed significant main effects of strain of mice used and of being germ-free. Bonferroni-corrected t tests showed that within each strain, the C57Bl/6J and NMRI, the germ-free mice had significantly different anxiety-like behaviors from their SPF counterparts. Germ-free C57Bl/6J mice (n = 11) spent significantly less time exploring the light box compared with SPF counterparts (n = 14). NMRI germ-free mice (n = 5) spent significantly more time exploring the light box, and were significantly less anxious than their SPF counterparts (n = 7). $P \le 0.05$ (*), $P \le 0.01$ (**), $P \le 0.001$ (***).

the opposite was observed for the reverse transplantation into germ-free BALB/c mice. These data demonstrate that distinct gut microbiota compositions from individual mouse strains can impart behavioral functionality on the host. In support of these findings, we have also observed strain differences in relation to anxiety-like behavior when comparing germ-free NMRI and C57Bl6/J mice to conventionally raised specific pathogen free (SPF) counterparts (**Fig. 4**). This data supports previous observations that mouse strain specific differences in the gut microbiome composition can impose distinct behavioral characteristics and capable of either promoting or suppressing anxiety-like behavior.[137] More research designed to exploit the inherent behavioral traits of laboratory animals may yield more interesting insight into the role of gut microbiota in anxiety-like behavior.

An intriguing observation was recently made regarding the requirement of microbiota for social development in mice.[138] In these experiments, germ-free mice exhibited reduced social motivation and preference for social novelty. Although social cognition appeared to be established in the pre-weaning phase of this model, the development of social avoidance may be subject to microbial disturbances in later life. These findings may have clinical relevance to autism spectrum disorder (ASD), a developmental brain disorder characterized by deficits in social interaction which has been associated with differences in gut microbiota composition.[139] It remains to be addressed whether differences in gut microbiota composition[139] or elevated faecal

SCFA concentrations[140] observed in individuals diagnosed with ASD, are correlative or causative differences of this disorder. In support of elevated SCFA production by gut microbes playing a role in ASD etiology, direct administration of propionate into the brains of rats has been shown to induce ASD-like behavior.[141] Whether propionate overproduction by gut microbiota in ASD individuals can reach relevant concentrations in the human brain remains to be determined.

From an evolutionary perspective, host-host social interactions that are enhanced by gut microbiota will likely increase horizontal transfer of endogenous microbes between hosts. This is likely to be of benefit to the transferred microbe through increased access to novel niches and also to the host by enhancing resident microbial diversity, a property recently associated with significant benefits to host health.[142,143] Thus, gut microbial promotion of physical interaction between individuals may impart significant fitness advantages to both host and microbe. Perhaps a gut microbiome with a reduced capacity to potentiate host-host social interactions manifest as social deficits associated with ASD.

Another remarkable demonstration of gut microbiota influencing host-host behavior was revealed in a seminal paper using *Drosophila* to illustrate principals of the hologenomic theory of evolution.[144] Sharon and colleagues revealed that commensal microbiota are capable of inducing a preference in mate choice that persists for at least 37 generations.[144] Although altered cuticular hydrocarbon regulation was implicated as a potential molecular correlate upon which mate scrutiny may be based, exactly how an individual perceives another individual as preferable over another in this model remains unclear and suggests a rewiring of neuronal circuitry and/or cognitive function. This raises the unexpected possibility that preferences in mate choice, at least in part, may be driven by the endogenous microbial composition of an individual host.

Conclusions

Gut microbiota manipulation in humans has recently been shown to modify human brain function,[145] an observation which may instigate the tailoring of certain microbes to possible influence and attenuate certain psychiatric and cognitive disorders. This may prove to be a worthy pursuit for certain neurological mood disorders; however, neurodevelopmental and neurodegenerative disorders may be refractory to such interventions. Therefore, in depth profiling of the gut microbiome in a temporal and spatial manner as well as on individuals suffering various forms of human neurodevelopmental and neurodegenerative disorders is warranted, particularly those associated with metabolic and immune dysbiosis. To determine causation, germ-free animals reconstituted with microbiota from different developmental stages and diseased individuals, combined with robust paradigms to test relevant animal behavior, will be pivotal to deciphering the functional role of gut microbial variations in host brain development and later life function.

We hypothesize that environmental perturbations in gut microbiota composition will alter the metabolic activity of the gut microbiome which will result in changes in SCFA production. Consequently, this will ultimately impact on host organ development and function, including host brain development, via (1) changes in nutrient availability and (2) modifications in host transcription and cell function.

Similarly, we hypothesize that age associated changes in gut microbiota composition and concomitant changes in SCFA production,[146] may also play an important role in mediating age associated cognitive decline, and potentially dementia progression. Deciphering the details of how the gut microbiome participates in early life brain development and later life function will be an important facet in understanding how the environment shapes neurological outcomes. Such detail will be essential to designing novel strategies to treat gut microbial disturbances and restore systemic metabolic harmony,[147,148] an important underpinning of neurological health.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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