When Rhythms Meet the Blues: Circadian Interactions with the Microbiota-Gut-Brain Axis

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Abstract

The microbiota-gut-brain axis encompasses a bidirectional mode of communication between the microorganisms residing in our gut, and our brain function and behavior. The composition of the gut microbiota is subject to diurnal variation and is entrained by host circadian rhythms. In turn, a diverse microbiota is essential for optimal regulation of host circadian pathways. Disruption of the cyclical nature of this microbe-host interaction profoundly influences disease pathology and severity. This review aims to summarize current knowledge on this bidirectional relationship. Indeed the past few years have revealed promising data regarding the relationship between the microbiota-gut-brain axis and circadian rhythms and how they act in concert to influence disease, further research needs to be done to examine how they coalesce to modulate severity of, and risk for, certain diseases. Moreover, there is a need for a greater understanding of the molecular mechanisms underlying the close relationship between circadian-microbiome-brain interactions.

Introduction

The Human Microbiome

The human body exists in a constant, mutualistic relationship with a sizeable community of microorganisms known as the human microbiota (Lynch and Pedersen, 2016, Gilbert et al., 2018). Because of recent technological advances we are now able to study these trillions of microorganisms in greater detail than ever before, improving our understanding of the microbiota (the microorganisms themselves), the microbiome (the collective genetic material of all the microorganisms in and on the human body), and the environment in which they reside (Lynch and Pedersen, 2016, Gilbert et al., 2018). The highest concentration of our microbiota inhabit the human gastrointestinal tract, where they are responsible for dietary and xenobiotic compound metabolism (Cho and Blaser, 2012, Cryan et al., 2019a, Clarke et al., 2019). The two dominant groups of symbiotic bacteria found in the human gut are Bacteroidetes and Firmicutes, representing over 99% of the known gut microbiota (Ley et al., 2006, Maier et al., 2017) and alterations in their relative abundance has been associated with disorders such as obesity (Ley et al., 2006). Analyses of the microbiota composition of human subjects, combined with studies in antibiotic-treated or germ-free rodents, are beginning to uncover the functional contribution of the microbiota to the health of the mammalian host (Cho and Blaser, 2012, Franklin and Ericsson, 2017). It is important to note however, studies have not been able to identify a specific bacterial genus or species and attribute it to a disease state or physiological system. Instead, studies can state that the microbiota of one experimental group is different from a control group, or correlate certain bacterial classifications to these disease states or physiological systems. Even when a certain bacterial genus or species is associated with a disease, this observation is usually only correlative (Marin et al., 2017). Perturbation of the gut microbiota is associated with a growing list of diseases from gastrointestinal disorders such as inflammatory bowel disease (Zuo and Ng, 2018) to metabolic disorders (Wen et al., 2008, Turnbaugh et al., 2008). More recently, the concept of a microbiota-gut-brain axis (the bidirectional communication pathway between our brain and the microbiome in our gut) has emerged with implications for the gut microbiota involvement in psychiatric and neurological disorders including autism spectrum disorder, Alzheimer's disease, Parkinson's disease, and depression (Rhee et al., 2009, Bernstein, 2017, Cryan et al., 2019b, Tansey, 2019).

The Microbiota-Gut-Brain-Axis

Consideration of the microbiota-gut-brain axis has revolutionized how neuroscientists view the brain and behavior, and neural disease (Rhee et al., 2009, De Palma et al., 2014, Cryan et al., 2019a). There are multiple direct and indirect pathways through which the gut and brain communicate: the vagus nerve (Bonaz et al., 2018, Fulling et al., 2019), neuroactive monoamine neuromodulators (Liu et al., 2016, Valles-Colomer et al., 2019), the immune system (Cho and Blaser, 2012, Codagnone et al., 2019), the endocrine system (Farzi et al., 2018, Cussotto et al., 2018) and via microbial metabolites such as short-chain fatty acids (SCFAs, (van de Wouw et al., 2018, Liu et al., 2019b)) and bile acids (Wahlstrom et al., 2016, MahmoudianDehkordi et al., 2019). It is becoming clear that age, diet, and health and disease all differentially influence microbiome to brain signaling (Rhee et al., 2009, De Palma et al., 2014, Borre et al., 2014, Cryan et al., 2019a).

Our microbiota synthesize neurotransmitters such as γ-amino butyric acid (GABA), noradrenaline, and dopamine, in the gut (Lyte, 2014, Strandwitz et al., 2019), which is a potentially significant avenue of communication between the gut microbiota and their host. Neuroactive bacterial metabolites can modulate brain function and host behavior through a myriad of ways that are still being elucidated (Clarke et al., 2019). Known methods include interacting with gut epithelial cells altering gut barrier function (Allaire et al., 2018), activating enteroendocrine cells to stimulate the release of gut hormones (Latorre et al., 2016), and modulation of dendritic cells altering immune and microglial function (Lin and Zhang, 2017). To date however, the mechanisms involved remain to be defined.

Often, age-related diseases have a signature in the gut microbiota that has been shown to correlate with brain health (Cattaneo et al., 2017, Codagnone et al., 2019). Notably, birth mode (caesarean section or vaginal delivery) influences the composition of the early gut microbiota, which in turn may affect the brain and behavior (Dinan and Cryan, 2017b, Stinson et al., 2018, Montoya-Williams et al., 2018). Eating behaviors and diets can also have a significant influence on the gut microbiota population (Zarrinpar et al., 2014, Leitao-Goncalves et al., 2017, Ma et al., 2018, Singh et al., 2017). For instance, a high-fiber diet has been associated with enhancing the abundance of *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium,* which in turn have been positively associated with brain health, in particular demonstrating protection against psychiatric disorders (Heinritz et al., 2016, Baxter et al., 2019, Li et al., 2016). Conversely, a high-fat, obesity-inducing diet is strongly associated with an overgrowth in endotoxin-producing pathogens of the *Enterobacter* genus, including *Escherichia coli* (Fei and Zhao, 2013). Interestingly, such psychiatric disorders (Leone et al., 2015, Thaiss et al., 2014) and metabolic disorders such as obesity (Leone et al., 2015, Thaiss et al., 2014) have also been linked to circadian rhythms. In fact, due to the strong overlap of diseases related to the gut microbiota and physiological circadian cycles, researchers have begun to examine the interactions between the microbiota-gut-brain axis and circadian rhythmicity (Voigt et al., 2016a, Parkar et al., 2019, Tahara et al., 2018, Deaver et al., 2018).

Circadian Rhythms

Circadian rhythms are present in the majority of organisms, and synchronize important physiological activities at every level of organization in the body: from rest-wake timing to cellular-level metabolic processes (Scheiermann et al., 2013, Voigt et al., 2016a, Sollars and Pickard, 2015, Weger et al., 2019). The mammalian circadian clock follows an approximately 24-hour feedback loop of transcription and translation as described in **Figure 1** (Voigt et al., 2016a, Takahashi, 2017). The endogenous biological clock relies on zeitgebers, or environmental cues such as light (the primary zeitgeber), food timing, food type, exercise, temperature, and infection to keep the circadian clock synchronized with the environment (Tognini et al., 2017, Takahashi, 2017). The central circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which receives innervation from the retinohypothalamic tract (Brown, 1994). The SCN master clock can be reset by light (Wu et al., 2018a) and light-dark cycles. It is enhanced through a positive feedback loop with melatonin, a key hormone in sleep and circadian rhythmicity (Brown, 1994).

The SCN acts as the organizational hub of host circadian rhythms and regulates circadian pathways in peripheral tissues (peripheral clocks) via nerve impulses and hormones (Sollars and Pickard, 2015, Voigt et al., 2013). Most tissues in the human body express the same circadian rhythm genes and proteins as the SCN and have autonomous biological clocks that are linked to diurnal regulation of physiological functions. Approximately 5-10% of the genes in peripheral tissue are regulated by circadian oscillations (Sollars and Pickard, 2015). Therefore, synchronization of these peripheral circadian oscillations by the SCN is crucial to coordinate the operation of cells, tissues, organs and organisms in processes such as immune function, body temperature, blood pressure, energy allocation, metabolism, absorption of nutrients, insulin levels, and hormone secretion (Voigt et al., 2013, Potter et al., 2016). Different organisms have different circadian responses to the light-dark cycle; humans are diurnal, or active during the day (in response to light), and rodents are nocturnal, or active at night (in response to a lack of light). Indeed gut microbiome composition, sleep physiology, the immune system and cognition appear to have common linkages (Smith et al., 2019).

Many factors can disrupt the circadian rhythm, including environmental insults, gene polymorphisms, or behavior. Current social expectations impose negative environmental factors on circadian rhythm such as jet lag (Reid and Abbott, 2015, Inder et al., 2016), shift work (Reid and Abbott, 2015, Schilperoort et al., 2019), social jetlag (Roenneberg et al., 2012, Roenneberg et al., 2019), light or food at night (Burgess and Molina, 2014, Asher and Sassone-Corsi, 2015), inconsistent eating times (Asher and Sassone-Corsi, 2015, Tahara et al., 2018), and the “western” high-fat diet (Kohsaka et al., 2007, Leone et al., 2015). Many studies have examined circadian disruption in mice with knockouts or polymorphisms of genes involved in or related to the circadian cycle (Liang et al., 2015, Thaiss et al., 2014, Voigt et al., 2016b, Mazzoccoli et al., 2012, Patke et al., 2017).

Recent evidence also identifies the microbiota as both modulated by, and a modulator of, the central and peripheral clocks (Leone et al., 2015, Liang et al., 2015, Thaiss et al., 2014, Zarrinpar et al., 2014, Voigt et al., 2014, Voigt et al., 2016b, Mukherji et al., 2013, Thaiss et al., 2016). Altered circadian rhythms, irrespective of cause, have been implicated in a multitude of diseases including metabolic diseases such as obesity (Turek et al., 2005, Froy and Garaulet, 2018), sleep disorders (Patke et al., 2017, Ma et al., 2019), psychiatric disorders such as bipolar illness (Benedetti et al., 2003, Takaesu, 2018), and neurodegenerative diseases such as Alzheimer’s disease (Canevelli et al., 2016, Song et al., 2015).

Thus, given the influence of both the microbiota-gut-brain axis and circadian rhythms in host physiological processes, it is crucial to study the interplay between these two systems in health and disease (**Figure 1A**). The involvement of circadian rhythms on the microbiota-gut-brain axis and vice versa calls into question the potential mechanisms involved. Many studies implicate dysfunction as either instigators or enhancers of metabolic or endocrine disease, inflammation, and negative behavioral changes. This review will explore the relationship between circadian rhythms and the microbiota-gut-brain axis, and examine metabolic, endocrine, and immune

nodes of interaction particularly in the context of different diseases in which these two systems are implicated.

Bacterial Circadian Rhythm and Microbiota Compositional Oscillations

One of the earliest reported observations of a bacterial circadian rhythm was witnessed in a cyanobacteria in 1986 (Grobbelaar et al., 1986). More recently, it was reported that the swarming pattern of the human gut bacterium *Enterobacter aerogenes*, followed an endogenous circadian rhythm that was entrained by melatonin to a periodicity of 25.1 ± 1.4 hours (**Table 3A** (Paulose et al., 2016)). In another example of microbe-host symbiosis, the circadian-controlled luminosity of the symbiotic bacterium *Vibrio fischeri* was shown to regulate diurnal gene transcription in its host squid species, *Euprymna scolopes* (Heath-Heckman et al., 2013).

An extensive number of gut bacterial genera and species, as well as the microbial community as a whole, exhibit oscillatory behavior (**Table 3**) in response to both the time of day (Leone et al., 2015, Liang et al., 2015, Thaiss et al., 2014, Zarrinpar et al., 2014, Kaczmarek et al., 2017), and time of eating (Leone et al., 2015, Liang et al., 2015, Thaiss et al., 2014, Zarrinpar et al., 2014, Kaczmarek et al., 2017). Approximately 35% of the measured bacterial operational taxonomic units (OTUs) in humans undergo temporal rhythmicity, and these diurnal gut microbiota oscillations have also been found across multiple studies of human (Kaczmarek et al., 2017, Thaiss et al., 2014) and rodent gut microbiota (Leone et al., 2015, Liang et al., 2015, Thaiss et al., 2014, Zarrinpar et al., 2014). The microbial community composition and abundance also fluctuate as a function of time; the bacterial load in mice reaches a peak at 11 PM (active phase in nocturnal organisms), corresponding with a maximum in the *Bacteriodetes* population, and reaches a trough at 7 AM (rest phase) corresponding with a maximum in the *Firmicutes* population (Leone et al., 2015, Liang et al., 2015, Zarrinpar et al., 2014). However, it is perhaps surprising that such examples of bacterial circadian rhythm and microbiota compositional oscillations have yet to be studied in the context of brain health and cognitive function.

Effect of Host Circadian Rhythmicity on Gut Microbiota

Dysregulation of the microbiota host's circadian rhythm can significantly affect microbial oscillations (**Figure 2**). Preclinical examples include deleted circadian clock genes in mice (Thaiss et al., 2014, Voigt et al., 2014), the timing or restriction of food availability (Thaiss et al., 2014, Voigt et al., 2014), and light: dark phase change, or reversal in mice to examine the effect of jet lag and shift work in humans (**Figure 2, Figure 3** (Thaiss et al., 2014, Voigt et al., 2014).

Genetic Models of Circadian Circuit Modulation

Many studies have examined the effect of aberrant circadian clock genes on physiological functions and rhythmic activity in the body. *Bmal1* and *Per1/2*$^{-/-}$ knockout (KO) mice experience a significant reduction or ablation of gut microbiota diurnal oscillations compared to wild-type mice (Liang et al., 2015, Thaiss et al., 2014, Pagel et al., 2017), which also ablated circadian

rhythm behavior of the fecal microbiota (Liang et al., 2015), increased susceptibility to intestinal inflammation manifested as IBD (Pagel et al., 2017), and resulted in an aberrant microbial diurnal rhythm, driven by a disrupted feeding rhythmicity, as well as glucose intolerance and obesity (Thaiss et al., 2014). In *Bmal1* KO mice, this decrease in gut microbiota diurnal oscillations is associated with a complete eradication of diurnal oscillations in *Bacteriodetes* and *Firmicutes* compared to wild-type mice. *Clock*$^{\Delta 19}$ mice (dominant homozygous for the Δ19 allele, leading to a lengthened endogenous period and a loss of rhythmicity) have a less diverse gut microbiota than wild-type mice when fed a control diet, and a different microbial community structure when fed a high-fat diet (Voigt et al., 2014, King et al., 1997). Together, these experiments demonstrate that deficiencies in biological clock genes cause negative perturbations of the gut microbiota, independent of, but influenced by, diet. Interestingly, this change in the gut microbiota can be rescued by food restriction or timing (Thaiss et al., 2014).

Timed and Restricted Feeding

It has been shown that both timed feeding, or restriction of feeding, can induce drastic changes to the rhythmicity of the gut microbiota. Although *Per1/2*$^{-/-}$ mice fed *ad libitum* lack gut microbial diurnal rhythmicity, when fed on a schedule, they exhibit restored gut microbiota diurnal oscillations (Thaiss et al., 2014). Lean mice fed *ad libitum* showed strong microbial diurnal rhythmicity, which was abolished following a high-fat diet; however, when the mice were fed a time-restricted high-fat diet, they still maintained some gut microbiota diurnal rhythmicity and a lean phenotype (Zarrinpar et al., 2014). Mice on a high-fat diet that underwent intermittent fasting – a positive restriction of food timing – exhibited an altered gut microbiota and decrease in obesity only present when the microbiota was present, thus not seen in germ-free mice (Li et al., 2017).

Abnormal Light-Dark Cycle

Many studies alter the light-dark cycle to examine its effect on circadian rhythmicity, using either a phase shift (Thaiss et al., 2014, Schilperoort et al., 2019), a 24-hour light (Deaver et al., 2018), or a 24-hour dark paradigm (Wu et al., 2018a). Animals housed under either 24-hour conditions, combined with standard feeding, lost all gut microbial diurnal rhythmicity when compared to mice housed under normal conditions; the mice housed under a 24-hour dark cycle also manifested increased *Clostridia* abundance (Wu et al., 2018a, Deaver et al., 2018).

Both jet lag and shift work have been associated with a wide variety of metabolic, inflammatory, and stress-related diseases (Khalyfa et al., 2017, Scheer et al., 2009, Karatsoreos, 2014, Guerrero-Vargas et al., 2015, Inder et al., 2016).

High-fat diet-fed mice that underwent a light: dark phase reversal paradigm representative of shift worked, exhibited a change in their gut microbiota population and a reduced microbial diversity compared their counterparts (**Table 2A** (Voigt et al., 2014)). Standard-chow-fed mice that underwent a phase-shift paradigm representative of jet lag (8-hour shift) incurred a loss of both diurnal rhythmicity in their gut microbiota and oscillating OTUs (Thaiss et al., 2014). Furthermore, the jet lag paradigm also exacerbated the effect of a high-fat diet in mice, namely

increased weight gain and glucose intolerance. These results were corroborated in a human study during which two subjects underwent 8-10 hour flights to incur jet lag (**Table 2A** (Thaiss et al., 2014)). Their stool, 24 hours post-flight, encompassed a significantly altered microbiota composition characterized by a relative increase in *Firmicutes* compared to baseline and at recovery two weeks later (Thaiss et al., 2014).

It is becoming apparent that alterations in host circadian rhythmicity have a profound effect on our gut microbiota, potentially leading to a feedback mechanism of gut microbial modulation of further circadian rhythm-dependent activity. This avenue of communication needs much more investigation at both the preclinical and clinical levels to help elucidate potential therapeutic interventional strategies.

Effect of Gut Microbiota and its Metabolites on Host Circadian Rhythms

Much research has examined the impact of the gut microbiota and its metabolites on host circadian rhythm (**Figure 2**). Initial research queried how a change in the microbiota could affect peripheral circadian clocks, as well as the effect of microbiota-derived metabolites or diet-induced microbial changes may have on circadian clocks (Leone et al., 2015, Thaiss et al., 2016, Murakami et al., 2016, Govindarajan et al., 2016, Mukherji et al., 2013, Montagner et al., 2016).

Altered Peripheral and Gut Clocks due to Gut Microbiota Perturbation

Both germ-free and antibiotic-treated mice experience an alteration of their peripheral and gut clocks (Weger et al., 2019). Germ-free mice have significantly different mRNA expression of core circadian clock genes in the liver (*Bmal1, Per1, Per2,* and *Cry1*) compared to specific pathogen-free mice (Montagner et al., 2016). Furthermore, mice treated with antibiotics to ablate their gut microbiota had significantly altered levels of clock genes in the gut and periphery as well as a loss of rhythmicity of gut metabolites compared to wild-type mice (Mukherji et al., 2013, Thaiss et al., 2016). However, there are conflicting reports regarding the effect of antibiotic treatment on the expression of the core circadian clock genes in mice. Although one study (Mukherji et al., 2013) found that antibiotic-treated mice exhibited transcript-level changes in these genes, another (Thaiss et al., 2016) found that the oscillations of the core clock genes and their transcripts were independent of antibiotic-induced changes in the gut microbiota. These differences could be a result of methodological disparities between the studies; e.g. different cocktails of antibiotics for different lengths of time were used, and gut samples were prepared and stored differently (Mukherji et al., 2013, Thaiss et al., 2016).

Effect of Microbiota-Derived Metabolites and SCFAs on the Circadian Clock

Gut microbiota-derived metabolites including SCFAs (propionate, butyrate, acetate) and bile acids also alter circadian rhythms. For instance, not only do multiple bacterial metabolites oscillate, but the presence of the microbiota is crucial for metabolite rhythmicity, as germ-free and antibiotic-treated mice produce metabolites that do not oscillate diurnally (Thaiss et al., 2016). Intriguingly, removal of polyamines from the murine diet influenced an aberrant expression pattern in hundreds of circadian genes, resulting in an expression profile, which

resembled that seen with antibiotic-treated mice (Thaiss et al., 2016). They conclude that diet and the microbiota influence one another – the microbiota is necessary for rhythmicity of polyamines, and the absence of polyamines in the diet leads to a rhythmic pattern of circadian gene expression that is reminiscent of a depleted microbiota.

Oral administration of SCFAs and lactate to antibiotic-treated mice changed PER2 rhythms transiently in peripheral tissue (Tahara et al., 2018). The introduction of SCFAs such as butyrate or acetate *in vitro* to hepatic organoids also led to significant phase shifts and increases in the amplitude of PER2 and BMAL1 rhythms (Leone et al., 2015). Other microbiota-related metabolites, such as unconjugated bile acids, have been shown to both upregulate circadian rhythm genes in an *in vitro* cellular model, and alter circadian clock gene expression (Arntl, Clock, Npas2, Per1,2,3, Cry1,2), as well as regulators of these genes (*RORα, Nr1d1, Dbp, E4BP4*) in the mouse ileum, colon and liver, when given orally (Govindarajan et al., 2016). Furthermore, jet-lagged mice that received this treatment at the beginning of their shifted dark phase underwent an accelerated entrainment of clock genes to light compared to jet-lagged control mice (Tahara et al., 2018). SCFAs are introduced naturally into the body, usually with a high-fiber diet, which protects and encourages a healthy microbiota (Maslowski and Mackay, 2011, van de Wouw et al., 2018).

Conversely, a high-fat diet has detrimental effects on the microbiota and the circadian clock (Leone et al., 2015). Specific-pathogen-free (SPF) mice fed a high-fat diet had increased expression of *Bmal1* in the hypothalamus, and *Per2* in the liver during the dark phase, whereas germ-free mice on a high-fat diet showed no change (Leone et al., 2015). Thus, diet alone was only capable of inducing host circadian rhythmicity alterations when paired with a functional gut microbiota. Furthermore, the high-fat diet also altered diurnal microbiota oscillations, which associated with a dysregulation of circadian clock rhythmicity (Leone et al., 2015, Thaiss et al., 2014). Interestingly, a high-fat diet given to mice lengthened the circadian period, decreased clock gene oscillation amplitudes, and de-synchronized liver and fat expression of clock gene-controlled transcription factors, when compared to a standard diet (Kohsaka et al., 2007).

Ad libitum access to a high-fat diet significantly affected host bile acid profiles in mice (Oh et al., 2019). Specific bile acids impeded the activation of a circadian transcription factor and nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) that has been shown to mediate the relationship between a high-fat diet and resulting changes in hepatic oscillators (Kanemitsu et al., 2017, Murakami et al., 2016, Oh et al., 2019). Interestingly, mice fed a standard diet during their inactive period and mice fed a high-fat diet during their active period experienced similar changes in overall bile acid composition, indicating that both time of day and type of food consumed are important bile acid composition variables (Eggink et al., 2017). Furthermore, high-fat diet-fed mice subjected to timed feeding expressed higher levels of a principal ileal bile acid receptor farnesoid X receptor, with concomitantly reduced serum cholesterol levels compared to mice fed either a standard chow or a high-fat diet, *ad libitum* (Zarrinpar et al., 2014). The circadian-controlled signaling of bile acids through the farnesoid X receptor has also been linked to lipid metabolism.

It is widely accepted that diet is one of the main avenues of gut microbiota modulation; therefore, it is understandable that diet would alter and interact with the gut microbiota in a profound manner, and in a cyclical fashion due to the nature of natural feeding patterns. It has become even more important to study these interactions in light of the circadian rhythm entrainment associated with feeding patterns, and more in-depth and carefully controlled research is warranted.

Nodes of Interaction

The microbiota-gut-brain axis and circadian rhythm interact with one another via multiple nodes and appear to work synergistically. This bidirectional interplay between the host circadian clocks and microbiota oscillations is undoubtedly key to the maintenance of host homeostasis. Here we consider how such an interplay affects key physiological processes in the host.

Metabolism

Organisms generally consume food during their active phase and fast during their inactive phase (Reinke and Asher, 2019). Food eaten at different times provide different amounts of glucose during the active phase; a meal in the evening produces a plasma glucose spike with twice the magnitude of the spike produced when the same meal is eaten for breakfast (Van Cauter et al., 1997). The time of day at which we eat also influences which microbes are active in the gut (Parkar et al., 2019, Van Cauter et al., 1997). Different microbial populations are subject to change based on food timing; certain bacterial groups will reach a population maximum when their energy source is available, whether it be directly when the food enters the gut or hours later where they attain energy from metabolized food. Interestingly, the α-diversity (local species diversity) of the gut microbiota increases with feeding and decreases with fasting (Zarrinpar et al., 2014). The population of the gut microbiota further shows cyclical variation for different diets and feeding times, which is characterized by specific patterns of population fluctuation (Zarrinpar et al., 2014). For instance, mice fed a high-fat diet experienced a reduction in the Lactococcus genus (believed to be obesogenic) after they began time-restricted feeding that was particularly noticeable during the inactive phase (**Table 3B** (Zarrinpar et al., 2014)).

Interestingly, the presence of a gut microbiota has been found to directly regulate the expression of intestinal epithelial histone deacetylase 3 (HDAC3) (**Table 1** (Kuang et al., 2019). The gut microbiota promotes diurnal oscillations of HDAC3, whereas the lack of a gut microbiota, as seen in germ-free mice, results in stably high HDAC3 levels. When HDAC3 oscillates, it in turn rhythmically regulates histone acetylation, which regulates metabolic gene expression in a diurnally oscillatory manner (Kuang et al., 2019). Furthermore, the microbiota-induced oscillations of HDAC3 are positively associated with lipid absorption and high-fat diet-induced obesity via the lipid transporter gene *Cd36*, which is also regulated by *Rev-erbα*, a key circadian clock gene (Kuang et al., 2019).

Much work has focused on the interplay between circadian clock genes such as*, ROR, Clock, Crys, Pers*, *Bmal1 and Rev-erb* and metabolism (glucose, lipid and amino acid/protein) or

metabolic dysfunction (obesity, cardiovascular disease, diabetes) (Adamovich et al., 2014, Dang et al., 2016, Yin et al., 2006, Wang et al., 2017, Shi et al., 2019). For instance, RORα knockout mutant mice ($ROR\alpha^{sg/sg}$) have an inactive RORα gene, and display decreased adiposity, serum high-density lipoprotein cholesterol levels and serum and liver triglyceride levels (Lau et al., 2008). These mice are known as "staggerer" mice due to their uneven gait, imbalance and tremors, and display cerebellar defects (Lau et al., 2008). Furthermore, they did not gain weight when fed a high-fat diet compared to wild-type mice, demonstrating a role for RORα in fat accumulation (**Table 2A** (Lau et al., 2008)). However, these mice were more susceptible to atherosclerosis than wild-type mice, indicating RORα may play a protective role in atherosclerotic lesions (Lau et al., 2008). It is important to note that some of these phenotypes, such as the RORα, are quite severe, and caution exercised.

$Clock^{\Delta 19/\Delta 19}$ mutant mice also display smaller pancreatic islets, impaired insulin secretion, and decreased glucose tolerance (Marcheva et al., 2010), as well as hyperlipidemia, hyperglycemia, and hyperleptinemia (**Table 2A** (Turek et al., 2005)). The circadian gene *Cry-1* has been shown to regulate gluconeogenesis via fasting-induced inhibition of CREB in mice (Zhang et al., 2010). In humans, the *Cry1* mutation leads to a familial delayed sleep phase disorder, where individuals experience delayed sleep induction (Patke et al., 2017). Interestingly, a missense mutation in *Per2* leads to a familial advanced sleep phase disorder (Fu et al., 2001). *$Per2^{-/-}$* mice have changes in lipid metabolism and a decrease in both triglyceride and non-esterified fatty acid levels (Grimaldi et al., 2010). Interestingly, this relationship appears to be mediated by PPARγ, and *Per-2*'s control of PPARγ appears to be necessary in white adipose tissue for normal lipid metabolism (Grimaldi et al., 2010).

$Bmal1^{-/-}$ mice exhibited increased plasma levels of adiponectin and leptin, increased adiposity, and increased glucose production (Kennaway et al., 2013). *Rev-erbα* has also been shown to play a key role in adiposity; it represses an inhibitory pathway of brown adipocyte differentiation (Nam et al., 2015). *$Rev\text{-}erb\alpha^{-/-}$* mice exhibit a strong impairment in brown fat formation (Nam et al., 2015). The gut microbiota also indirectly acts through *Rev-erbα* to affect Nuclear Factor Interleukin 3 Regulator (NFIL3), which is a key regulator of lipid absorption and metabolism (Wang et al., 2017). When *Rev-erb α* is present, germ-free and antibiotic-treated mice have lower levels of NFIL3 than wild-type mice (Wang et al., 2017, Mukherji et al., 2013). In the absence of *Rev-erbα*, there was no effect of the gut microbiota on NFIL3 expression or lipid metabolism.

Although it is difficult to parse cause and effect elements of diet, feeding and microbial metabolite availability and their interaction with circadian mechanisms, and indeed several connections between modulators of the circadian rhythm and the gut microbiota are more distal connections and not necessarily causal, they may only constitute one mechanism of control amongst a plethora of systems at play. Therefore, it is critical for future studies to dissect out the relative contributions of these elements in both humans and model systems.

The Endocrine System

The microbiota-gut-brain axis and circadian rhythms often interact through the action of hormones. The SCN controls many of the endocrine glands both directly and indirectly (Bedrosian et al., 2016). Hormones secreted from these glands play a role in circadian rhythmicity and influence the gut microbiota, which can in turn influence the secretion of these hormones by feedback mechanisms (Bedrosian et al., 2016, Huo et al., 2017).

The pineal gland secretes the hormone melatonin, which is an effector of, and effected by, circadian rhythmicity (Brown, 1994). Melatonin is crucial to diurnal rhythms, can entrain the circadian rhythms of some gut bacteria, and cause negative chemotaxis of bacteria such as *Escherichia coli* (**Table 1** (Brown, 1994, Paulose et al., 2016, Lopes and Sourjik, 2018)). Directly innervated by the SCN, the paraventricular nucleus of the hypothalamus secretes the stress-related hormone corticotropin-releasing factor (CRF), which stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) (Bedrosian et al., 2016). Both hormones are key components of the hypothalamic-pituitary-adrenal axis (HPA axis), which regulates the body's response to stress (among other duties). The HPA axis oscillates under the control of the circadian clock, which is affected by changes in the gut microbiota (**Table 1** (Huo et al., 2017, Hoban et al., 2016, Shanks et al., 1995, Cussotto et al., 2018, Sudo et al., 2004)).

The adrenal glands respond to ACTH release by secreting glucocorticoids (Luo et al., 2018)(cortisol in humans, corticosterone in rodents), which are also key components of HPA axis activity (Bedrosian et al., 2016). Glucocorticoids act as a negative feedback messenger of this stress-response system and identify a link between circadian rhythms, the endocrine system, and the gut microbiota (**Table 1** (Agusti et al., 2018, Sudo et al., 2004)). Glucocorticoids are often prescribed as immunosuppressant and anti-inflammatory drugs, yet they have severe metabolic and neurological side effects, such as increased lipid accumulation, decreased gut microbiota diversity, and disrupted circadian rhythmicity in both the SCN and periphery (Wu et al., 2018b). In addition, work performed with germ-free mice has shown that the lack of a gut microbiome can regulate glucocorticoid receptor genes in the hippocampus, indirectly regulating cognitive function including depression (**Table 2** (Luo et al., 2018). However, it is important to note that the germ-free phenotype is severe, thus information gleaned from it should be regarded cautiously.

A recent study (**Table 1** (Weger et al., 2019)) found that growth hormone (key to sexual growth and dimorphism), testosterone (male-biased hormone), and estradiol (female-biased hormone) secretion were all altered in germ-free mice compared to wild types. The rhythmicity of these hormones that is typically present in wild-type mice, in a sex-biased manner, was abolished in germ-free mice, with blunted hormone levels (Weger et al., 2019). Furthermore, the secretion of ghrelin, a hormone upstream of growth hormone, was also reduced and non-rhythmic in germ-free mice (Weger et al., 2019). Ghrelin controls appetite and thus the timing of food, linking it with the gut microbiota (Lach et al., 2018). Serum ghrelin levels have been negatively associated with the amount of *Bifidobacterium*, *Lactobacillus*, and *B. coccoides – Eubacterium rectale*, and positively associated with the amount of *Bacteroides* and *Prevotella* in rats (Queipo-Ortuno et al., 2013). Ghrelin oscillates diurnally, is affected by alterations to the

circadian clock, and can rescue circadian rhythm deficits induced by a high-fat diet in mice (**Table 1** (Wang et al., 2018, Turek et al., 2005)). It has long been known that circadian rhythms and the SCN directly affect the endocrine system (Froy and Garaulet, 2018). Considering recent work describing the interaction between the endocrine system and the gut microbiota, this is of particular interest as it identifies the endocrine system as a node of interaction between circadian rhythms and the gut microbiota.

The Immune System and Inflammation

At birth, the formation of a well-functioning gut mucosal immune system depends on a healthy commensal bacterial population in the host's gut (Dinan and Cryan, 2017a). As the child ages, the immune system's interactions with the microbiota-gut-brain axis shifts toward an indicator of gut microbial stress. The majority of immune cells and cytokines oscillate diurnally (Labrecque and Cermakian, 2015, Keller et al., 2009), which affects how they respond to insults to their host, as well as immune cell population growth and activity, lymphocyte number and circulation, humoral response, macrophage transcriptome, and cytokine levels (**Table 1** (Labrecque and Cermakian, 2015, Keller et al., 2009)). Furthermore, phase-dependent responses have been seen in pathogen susceptibility, asthma, rheumatoid arthritis, and other autoimmune diseases (Keller et al., 2009, Labrecque and Cermakian, 2015). Studies have shown diurnal rhythmicity of both the expression of toll-like receptor 9 (TLR9) in response to bacterial or viral DNA (Labrecque and Cermakian, 2015, Silver et al., 2012), and the downstream signaling capacity of toll-like receptor 4 (TLR4) (Labrecque and Cermakian, 2015). Furthermore, TLR transcripts were lower in mice treated with antibiotics, and were directly associated with clock components (such as the binding of BMAL1 to the E box for *TLR9*) (Mukherji et al., 2013). Thus, TLR's are key converters of bacterial signals into rhythmic gene expression.

Neutrophils also exhibit circadian rhythmicity and are susceptible to gut microbiota perturbations (**Table 1** (Adrover et al., 2019, Zhang et al., 2015)). In particular, neutrophil aging is associated with increased anti-microbial activity and resistance to infection. However, this is also associated with vascular inflammation and reduced cardiovascular health (Adrover et al., 2019). T cells are also regulated by circadian rhythmicity and the gut microbiota (**Table 1** (Bollinger et al., 2011, Yu et al., 2013, Ren et al., 2017, Soto et al., 2017, Mazmanian et al., 2005)). T-cells undergo NFIL3-mediated (and mostly REV-ERBα-controlled) rhythmic development and differentiation from immature to mature T cells (Yu et al., 2013, Bollinger et al., 2011); mature T cells exhibit rhythmic production of cytokines (Yu et al., 2013, Bollinger et al., 2011). Furthermore, melatonin has been identified as a potent regulator of many types of T cells, including Th17, T regulatory cells, and memory T cells (Ren et al., 2017).

The microbiota is also involved in maintenance of a functioning immune system, and T cell development and lifespan (Soto et al., 2017, Lee et al., 2011). In fact, the microbiota is involved in the development of Th1, Th2, Th17, and Treg cells (Lee et al., 2011). Considering the importance of the gut microbiota in the development of the immune system, it is not surprising that germ-free mice exhibit decreased efficiency of T cells, B cells and neutrophils, and decreased production of CD4+ T cells and antibodies (Belizario et al., 2018). Furthermore, the

immune system is less effective in response to infection in germ-free mice (**Table 1** (Belizario et al., 2018)). Since the 1960s, studies have also found a relationship between the time of day of an infection – e.g. from *Escherichia coli*, *Streptococcus pneumoniae*, and *Salmonella enterica* Serovar Typhimurium – and both the body's immune response and infection colonization (**Table 1** (Halberg et al., 1960, Feigin et al., 1969, Bellet et al., 2013)). In fact, it has been hypothesized that inflammation may act as an intermediary between circadian rhythms, the gut microbiota, and these diseases (Voigt et al., 2016a). Additionally, negative changes in the gut microbiota or circadian rhythms are both associated with low-grade, sterile inflammation throughout the body, most likely due to a reduction of intestinal barrier integrity (Voigt et al., 2016a).

With the densest collection of immune cells in the human body, the GI tract is a critical target for immune system modulation, inflammation, and its involvement in centrally mediated events such as circadian rhythm control. It is critical that future research efforts are focused on examining the role of gut inflammation and the immune system's response to the gut microbiota in circadian rhythm control.

The involvement of circadian rhythms and the microbiota-gut-brain axis in disease

Metabolic Diseases

Accumulating evidence suggests that metabolic disorders can arise from the interaction between high-fat diet and other factors, including both circadian rhythm disruption (Parkar et al., 2019) or changes in the composition of the gut microbiota (**Table 2A** (Zinocker and Lindseth, 2018)). One large-scale study found that the gut microbiota of multiple metabolically-diseased populations (cardiovascular disease, type 2 diabetes, and obesity) had an increased inflammatory potential, meaning that the bacteria present in the microbiota of humans with these diseases are more likely to cause inflammation than the bacteria present in the microbiota of humans without the disease (Jie et al., 2017), suggesting a potential novel route of treatment. Mouse models of shift work (light/dark phase reversal) were associated with higher levels of HOMO-IR (a measure of insulin resistance), altered microbiota, increased gut permeability, and an increase in pro-inflammatory, and a decrease in anti-inflammatory immune cells (Khalyfa et al., 2017). This work suggests that both circadian rhythms and the gut microbiota could be mediators between a high-fat diet and metabolic disorders such as obesity, diabetes and cardiovascular disease.

Obesity

To date, the strongest link between circadian rhythms and the gut microbiota in disease has come from obesity research (**Table 2A** (Leone et al., 2015, Thaiss et al., 2014, Voigt et al., 2016b, Joyce et al., 2014a, Li et al., 2017, Shao et al., 2018, Yin et al., 2018, Stenvers et al., 2019, Froy and Garaulet, 2018)). The absence of a gut microbiota protects mice from the negative ramifications of a high-fat diet, and the induction of a circadian clock phase shift (in wild-type mice) exacerbates these negative ramifications (Leone et al., 2015, Thaiss et al., 2014). *Clock* mutant mice demonstrate the effect of circadian clock disruption on the gut

microbiota, and how this leads to metabolic dysfunction, such as obesity and diabetes (Voigt et al., 2016b, Turek et al., 2005). Interestingly, bile salt hydrolase (BSH), a key factor in lipid metabolism produced by certain bacteria in the gut, is a key mediator of the effect of a high-fat diet on obesity (Kanemitsu et al., 2017, Murakami et al., 2016). BSH is crucial for generating a diverse bile acid signature in the host, and its activity in the microbiota regulates host physiological processes including metabolism, circadian rhythmicity and immune response (**Table 1** (Yao et al., 2018, Joyce et al., 2014a, Joyce et al., 2014b)).

Further evidence for a close link between obesity, microbiota and circadian rhythms comes from the growing wealth of studies investigating the effects of intermittent fasting on metabolism and the gut microbiota (Li et al., 2017). Moreover, sleeve gastrectomy has also been shown to improve metabolism in animals fed a high-fat diet, which was mediated by change in the gut microbiota (Shao et al., 2018). Interestingly, oral administration of melatonin to mice fed a high-fat diet similarly resulted in an alleviation of weight gain and a change in the gut microbiota (Yin et al., 2018). The administration of the weight loss anti-angiogenic drug Fumagillin has also been shown to interact with both the microbiota and core circadian clock gene expression to elicit its metabolic effects (**Table 2A** (An et al., 2018)). It is worth noting that obesity can also be considered a brain disorder (Kure Liu et al., 2019, Liu et al., 2019a, Ziauddeen et al., 2012, Fletcher and Kenny, 2018), and there is a growing emphasis on the role of the microbiome-gut -brain axis in regulating central control of appetite, satiety, food choice, and obesity (Torres-Fuentes et al., 2017, Leitao-Goncalves et al., 2017, van de Wouw et al., 2017). Nonetheless, the role of circadian rhythms in regulating this axis in obesity deserves much more attention.

Diabetes

Human and animal models with both types of diabetes (I and II) display differences in gut microbiota composition compared to their healthy counterparts (**Table 2A** (Wen et al., 2008, Kieler et al., 2019, Stenvers et al., 2019, Karlsson et al., 2013)). Specifically, individuals with type II diabetes exhibit reduced oscillation amplitude of core clock genes and a general reduction in diurnally rhythmic genes in adipose tissue when compared to healthy controls (Stenvers et al., 2019). Also, although type II diabetic mice exhibited similar feeding and activity behaviors to wild-type mice, their gut microbiota showed a loss of diurnal oscillations in the genera *Akkermanisa, Bifidobacterium, Allobaculum* and *Oscillospira,* and a phase shift in the oscillations of the genus *Prevotella* and the phyla Proteobacteria and Actinobacteria (**Table 3B** (Beli et al., 2019). Interestingly, mice with deletions of either *Clock* or *Bmal1* have diminished glucose tolerance and insulin secretion, providing a link between circadian rhythm genes and diabetes (Marcheva et al., 2010).

Cardiovascular Disease

Much work has demonstrated the involvement of the gut microbiota in cardiovascular disease (Ma and Li, 2018, Jie et al., 2017), where a human cohort of patients with atherosclerosis demonstrated increased abundances of *Enterobacteriaceae* and *Streptococcus* spp. and expressed an increased inflammatory profile (Jie et al., 2017). Mouse models of cardiovascular

disease recovered faster in a 24-hour light-dark cycle compared to the those on a disrupted circadian rhythm, and an exacerbated heart condition (**Table 2A** (Martino et al., 2007)). Furthermore, mice with a 22-hour circadian cycle (due to a point mutation in casein-kinase 1ε, a circadian cycle regulatory gene) exhibited severe heart defects leading to early death, which was rescued by placing the animals in a 22-hour light-dark cycle (Martino et al., 2008). In humans, short-duration circadian misalignment resulted in increased 24-hour blood pressure the presence of inflammatory markers in the blood of healthy adults (Morris et al., 2016). Interestingly, either high-fiber or high-SCFA diets have been shown to not only positively modulate the gut (these mice exhibited a decrease in their Bacteroidetes: Firmicutes), but these diets also protect against cardiovascular disease and increase circadian rhythm regulation by upregulating circadian genes (**Table 2A** (Marques et al., 2017)).

Although studies examining the relationship between circadian rhythms and the microbiota-gut-brain axis are to date often correlational and not causal, their interaction is clear, and most apparent within the context of metabolic diseases. Across the spectrum, the gut microbiota and circadian rhythms can influence severity, and in the process, influence one another, and the brain.

Psychiatric Disorders

Much research has examined the relationship between circadian rhythms and psychiatric disorders, including major depressive disorder (MDD)(Ma et al., 2019, Murray, 2007), schizophrenia (Karatsoreos, 2014, Oliver et al., 2012), bipolar disorder (Takaesu, 2018), and anxiety (Fares et al., 2015) (**Table 2B**). Circadian rhythm disturbances (phenotypes) such as shift work, possessing an evening chronotype, or a phase delay in circadian rhythm onset, have all been associated with an increased prevalence or severity of MDD, which can be rescued by selective serotonin reuptake inhibitors (Karatsoreos, 2014, Takaesu, 2018, Vadnie and McClung, 2017, Fares et al., 2015, Bastiaanssen et al., 2020). Human subjects with MDD exhibit significant differences in their microbiota compared to healthy controls (Zheng et al., 2016, Aizawa et al., 2016, Jiang et al., 2015, Valles-Colomer et al., 2019). Interestingly, the administration of antibiotics such as minocycline (Miyaoka et al., 2012, Zheng et al., 2015), prebiotics (Burokas et al., 2017), or probiotics (Bravo et al., 2011) all exhibit antidepressant-like effects in animal models (**Table 2B**). Germ-free mice, like antibiotic-treated mice, exhibit decreased depressive and anxiety-like behaviors in response to stress when compared to their wild-type counterparts (Zheng et al., 2016, Clarke et al., 2013). Both depression and anxiety-like phenotypes were transferrable via a fecal matter transplant from human to rodent, or from rodent to rodent (Kelly et al., 2016, Zheng et al., 2016, De Palma et al., 2017), indicating the importance of a gut microbiota in the manifestation of these symptoms. The anxiety-like phenotype was alleviated with the administration of either prebiotics (Burokas et al., 2017) probiotics (Bravo et al., 2011), or via a *Clock* mutation (Roybal et al., 2007).

Similar to depression, a number of small studies in human subjects with bipolar disorder have also shown an altered gut microbiota compared to healthy controls (Evans et al., 2017, Dickerson et al., 2018). Moreover, probiotic administration alleviated symptoms and reduced

rehospitalization rates post-mania in a specific cohort (Dickerson et al., 2018). Interestingly, *Clock* gene polymorphisms in humans are associated with an increased recurrence risk in bipolar disorder (Roybal et al., 2007, Benedetti et al., 2003), and a mutation in the *Clock* gene in mice resulted in an increase in mania-like behavior compared to wild-type mice (Roybal et al., 2007, Benedetti et al., 2003). Mouse models of schizophrenia have an advanced-phase circadian cycle (melatonin releases earlier in the cycle than normal) and fragmentation of the cycle (Oliver et al., 2012). Studies have also found that a copy number variation in a human SCN gene is associated with a higher schizophrenia risk (Vacic et al., 2011).

Much of the evidence linking psychiatric illness to circadian rhythm disturbances comes from studies utilizing the mood stabilizer lithium (**Table 2B** (Roybal et al., 2007)). Lithium also affects sleep, circadian rhythms, the microbiota and inflammation. It is known to inhibit glycogen synthase kinase 3 (GSK3), thus causing REV-ERBα to degrade, activating the circadian feedback loop, and decreasing the pro-inflammatory effects of GSK-3β (Yin et al., 2006, Beurel and Jope, 2014). Lithium also interacts with sleep therapy and chronotherapy to increase potential efficacy of treatment (**Table 2B** (Karatsoreos, 2014, Benedetti et al., 2014)). One study found that the combination of sleep deprivation, light therapy and lithium resulted in a rapid and drastic decrease in suicidal symptoms in treatment-resistant bipolar depression (Benedetti et al., 2014). When administered to rats, lithium significantly increased species richness and diversity in the gut microbiota (Cussotto et al., 2019).

Whereas much research has been conducted on the effect of the microbiota-gut-brain axis, circadian rhythms, and their interplay in metabolic disorders, in comparison there is still a paucity of research on the interplay between the microbiota-gut-brain axis and circadian rhythms in psychiatric disorders. Although their independent effects on psychiatric disorders are apparent, more preclinical and clinical work needs to be done to examine how both systems may engage with one another to modulate psychiatric disorders, positively and negatively.

Neurodegenerative Disease

Elderly people with dementia or AD are known to exhibit “sundowning”, described as cognitive decline and increased confusion and agitation as the sun sets (Canevelli et al., 2016). These patients have lower melatonin levels, neurofibrillary tangle-induced damage to their SCN (in AD), and a dysregulated HPA axis (Canevelli et al., 2016). Mouse models of AD also exhibit a shortened period length (Canevelli et al., 2016, Oyegbami et al., 2017, Song et al., 2015), blunted *Cry1/2* cycle in the medulla (Canevelli et al., 2016, Oyegbami et al., 2017, Song et al., 2015), and altered expression of *Bmal1* and *Per2* (Canevelli et al., 2016, Oyegbami et al., 2017, Song et al., 2015). Humans with AD show increased abundance of pro-inflammatory *Escherichia/Shigella* and a decreased abundance of anti-inflammatory *E. rectale* compared to age-matched, healthy controls (Cattaneo et al., 2017). Furthermore, bacteria are capable of producing their own amyloid (for example, *E. coli*), which could cause an increase in proinflammatory markers and potentially initiate cross seeding of amyloid plaques (Cattaneo et al., 2017, Schwartz and Boles, 2013, Chapman et al., 2002, Kowalski and Mulak, 2019). Elderly individuals are also susceptible to Parkinson’s disease, the manifestation of which is preceded

by idiopathic rapid eye movement (iREM) sleep behavior disorder (RBD) (Heintz-Buschart et al., 2018). Interestingly, the gut microbiota of patients with RBD or Parkinson's disease are very similar, and both are significantly different to the gut microbiota of healthy, control patients (Heintz-Buschart et al., 2018).

Taken together, neurodegenerative diseases represent an exciting avenue of future research to study the interplay between the microbiota-gut-brain axis and circadian rhythms. The connection between Alzheimer's disease, circadian rhythms, and the microbiota-gut-brain axis (Hill et al., 2014) provides strong evidence that more research in this area is needed at the preclinical and clinical stages. Moreover, understanding the relative contribution of microbiota changes to RBD and circadian dysfunction may offer novel insights into the pathophysiology of Parkinson's Disease.

Conclusions and Future Directions

There is growing evidence supporting not only an interaction, but also bidirectional communication between circadian rhythms and the gut microbiota. However, it is clear that the precise underpinnings of the mechanisms involved are still unknown. Although the majority of the data supporting their interaction is transitive and through an intermediary, these nodes of incorporation of the two systems are powerful, grouping into metabolism, the endocrine system, and the immune system. Unfortunately, thus far research has mostly only examined the effect of either circadian rhythm or gut microbiota/microbiota-gut-brain axis independently, but not together. There is a similar state of affairs regarding disease models; the current understanding mostly deals with metabolic diseases, the correlative conclusions of which demonstrate the cumulative effect of circadian rhythm dysfunction and gut microbiota alteration. Strong data linking circadian rhythm and gut microbiota dysfunction lies with their interactions with psychiatric illness, and neurodegenerative disease. Here, there is a wealth of information examining diseases resulting from, or exacerbated by, interactions of the gut microbiota and circadian rhythm. Further, the examination into metabolic disorders is a crucial step in the right direction, and more work needs to be done to examine not only how both the microbiota-gut-brain axis and circadian rhythms influence disease, but also how they interplay with one another in the context of disease.

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Declaration of Interests

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. However, TGD has been an invited speaker at meetings organised by Servier, Lundbeck, Janssen, and AstraZeneca, and has received research funding from Mead Johnson, Cremo, Suntory Wellness, Nutricia, and 4D Pharma. JFC has been an invited speaker at meetings organised by Mead Johnson, Yakult, Alkermes, Ordesa, and Janssen, and has received research funding from Mead Johnson, Cremo, Suntory Wellness, Nutricia, Pharmavite, Dupont, and 4D Pharma. All other authors declare no competing interests.

Figures

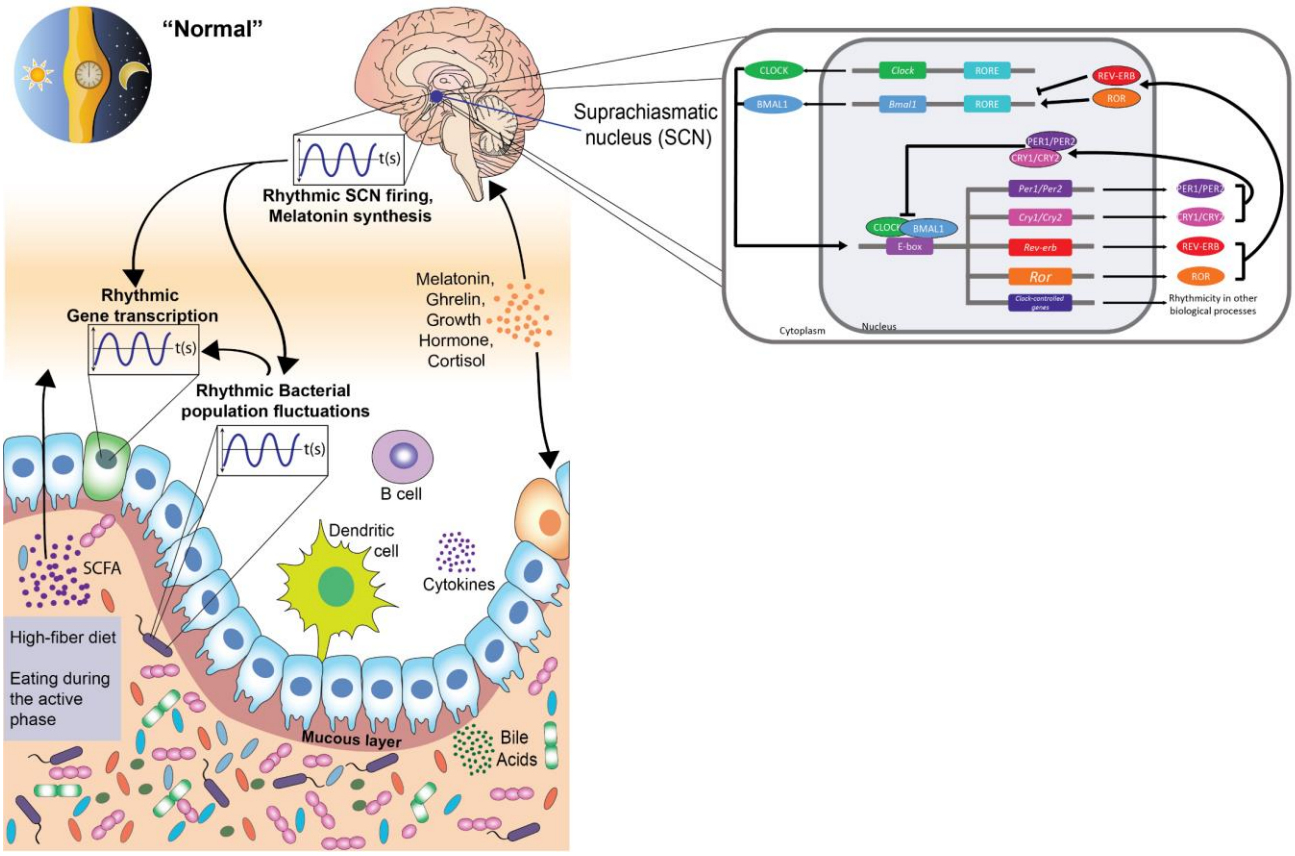

Figure 1. Depiction of circadian rhythms, the gut microbiota, and their interaction and effect on general physiology in a healthy individual

(A) An individual with a healthy microbiota, and a normal 24-hour light/dark cycle,

(B) Positive transcription factors, CLOCK (**c**ircadian **l**ocomotor **o**utput **c**ycles **k**aput) and BMAL1 (**b**rain and **m**uscle **a**ryl hydrocarbon receptor nuclear translocator-**l**ike protein **1**) heterodimerize in the cytoplasm, and translocate to the nucleus (Scheiermann et al., 2013). Once there, they bind to the E-box promotor region to initiate transcription and translation of the genes *Per1/2* (period) and *Cry1/2* (cryptochrome). PER1/2 and CRY1/2 then heterodimerize and initiate inhibitory feedback of CLOCK and BMAL1. As PER1/2 and CRY1/2 decrease due to CLOCK and BMAL1 repression, and as ubiquitin degrades the PER-CRY dimer, the cycle begins again. Additionally, the transcription factor REV-ERB suppresses BMAL1, and ROR (retinoic acid-related orphan receptor) activates BMAL1 (Scheiermann et al., 2013).

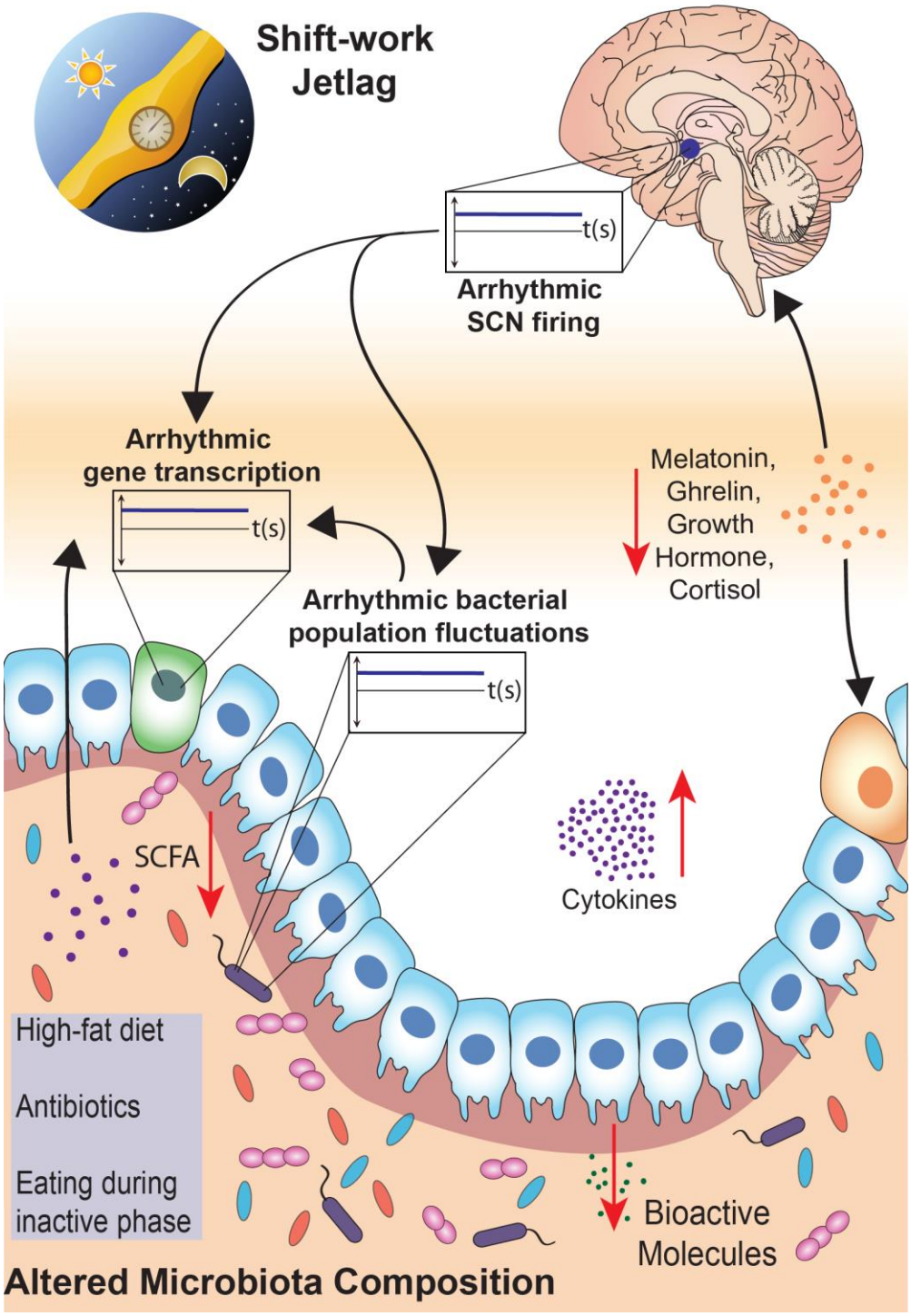

Figure 2. Effect of disturbances to either the circadian rhythm or the gut microbiota on host physiology

Potential physiological effects of either a compromised light/dark cycle due to shift work or jet lag, and/or an altered microbiota due to a high-fat diet, antibiotics or eating during the inactive phase. Such insults can cause loss of normal rhythmic SCN firing (Froy and Garaulet, 2018, Barclay et al., 2012), a loss in rhythmic gut epithelial gene transcription (Kuang et al., 2019), arrhythmic

bacterial population fluctuations (Beli et al., 2019, Tahara et al., 2018, Paulose et al., 2016), leading to a reduction in luminal bioactive molecule translocation across the gut epithelium (Turroni et al., 2018, Rea et al., 2017, Garrido et al., 2013), and a potential reduction in enteroendocrine activity (Larraufie et al., 2018, Larraufie et al., 2017, Plovier and Cani, 2017, Steinert et al., 2017), and a concomitant increase in luminal cytokine production (Rudzki et al., 2019, Hao et al., 2019, Hantsoo et al., 2019).

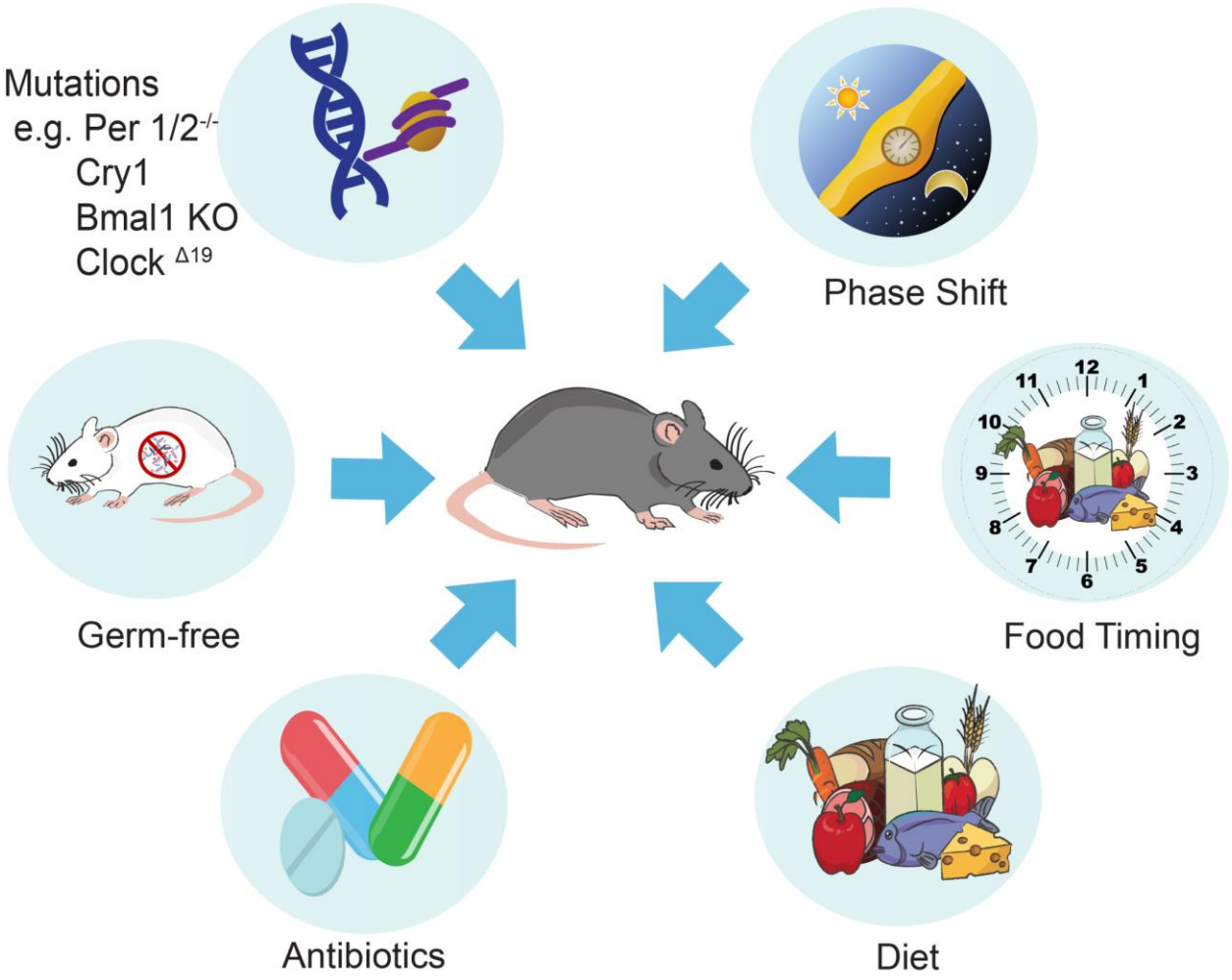

Figure 3. Pre-clinical methods currently utilized to study circadian rhythms and the microbiome-gut-brain axis.

Examples include the use of antibiotics to ablate the gut microbiota (Mukherji et al., 2013, Wang et al., 2017); altering diet to modulate type of food and caloric amount available to the host (Astafev et al., 2017, Leone et al., 2015); adjusting availability of food to the host animal (Wehrens et al., 2017); introducing a time phase-shift to perturb the circadian clocks (Tahara et al., 2018, Voigt et al., 2014); using congenital models of circadian circuit modulation (Voigt et al., 2016b, Thaiss et al., 2016); utilizing the germ-free mouse model (Montagner et al., 2016, Weger et al., 2019).

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