TOPICAL REVIEW

Bugs, breathing and blood pressure: microbiota–gut–brain axis signalling in cardiorespiratory control in health and disease

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Karen M. O’Connor is currently a postdoctoral researcher in the Department of Physiology, University College Cork, Ireland working with Dr Fiona B. McDonald where she is investigating the effects of unstable patterns of oxygenation and infection on cardiorespiratory control in animal models of preterm infancy. For her doctoral studies, she researched the role of the gut microbiota in the control of breathing and cardiovascular function under the supervision of Professors Ken D. O’Halloran and John F. Cryan. This review summarises emerging findings in this field of research, and includes an overview of her original published studies of microbiota manipulation in rodent models performed during the course of her doctoral training in Cork.
Abstract  There is clear evidence of physiological effects of the gut microbiota on whole-body function in health and disease. Microbiota–gut–brain axis signalling is recognised as a key player in behavioural disorders such as depression and anxiety. Recent evidence suggests that the gut microbiota affects neurocontrol networks responsible for homeostatic functions that are essential for life. We consider the evidence suggesting the potential for the gut microbiota to shape cardiorespiratory homeostasis. In various animal models of disease, there is an association between cardiorespiratory morbidity and perturbed gut microbiota, with strong evidence in support of a role of the gut microbiota in the control of blood pressure. Interventions that target the gut microbiota or manipulate the gut–brain axis, such as short-chain fatty acid supplementation, prevent hypertension in models of obstructive sleep apnoea. Emerging evidence points to a role for the microbiota–gut–brain axis in the control of breathing and ventilatory responsiveness, relevant to cardiorespiratory disease. There is also evidence for an association between the gut microbiota and disease severity in people with asthma and cystic fibrosis. There are many gaps in the knowledge base and an urgent need to better understand the mechanisms by which gut health and dysbiosis contribute to cardiorespiratory control. Nevertheless, there is a growing consensus that manipulation of the gut microbiota could prove an efficacious adjunctive strategy in the treatment of common cardiorespiratory diseases, which are the leading causes of morbidity and mortality.

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Abstract figure legend  A schematic representation of the proposed pathways by which the gut microbiota influences cardiorespiratory control in health and disease. Red text highlights potential sources of altered microbiota–gut–brain communication due to a perturbed gut microbiota that may result in adverse cardiorespiratory control, i.e. altered afferent vagal activity, sympathetic nervous system hyperactivity, modulated short-chain fatty acid (SCFA) signalling and increased inflammation. HPA, hypothalamic–pituitary–adrenal axis; NA, noradrenaline; SNS, sympathetic nervous system. Images were obtained from Smart Servier Medical Art, to create a new composite figure, and are used under the terms of the Creative Commons Attribution 3.0 Licence (creativecommons.org).

Overview

Whereas the influence of the gut microbiota on the brain and behaviour is well recognised (Dinan & Cryan, 2017), there is emerging evidence that the gut microbiota may also serve as a major player in homeostatic neurocontrol systems critical for life, through a bidirectional pathway termed the microbiota–gut–brain axis (Rhee et al. 2009; Cryan et al. 2019). Recent studies have focused on the potential link between the gut microbiota and nervous system control of breathing and blood pressure. These studies are the focus of this review.

Cardiovascular and respiratory diseases are leading causes of morbidity and mortality worldwide (Benziger et al. 2016; Thomas et al. 2018). Animal models of disease elaborating cardiorespiratory morbidity, together with models incorporating manipulation of the gut microbiota, reveal a link between the gut microbiota and cardiorespiratory control. There are gaps in the understanding of the mechanistic links, but strong evidence in favour of a pivotal role for short-chain fatty acids (which are produced by gut microbiota from dietary fibres) in the control of blood pressure. Importantly, there is evidence of a disrupted gut microbiota signature in people with obstructive sleep apnoea, asthma, cystic fibrosis and hypertension. Animal models reveal the beneficial effects of manipulation of the gut microbiota axis on cardiorespiratory physiology, suggesting that adjunctive therapies that target the gut microbiota may have therapeutic application in the treatment of common cardiorespiratory diseases.

The gut microbiota

The microbiota refers to the substantial community of commensal, symbiotic and pathogenic microbes that populate the skin, lungs, urogenital and gastrointestinal tract. It includes bacteria, viruses, fungi and archaea. The gastrointestinal tract possesses an extensive and diverse ecosystem containing trillions of microorganisms, harbouring 1000–1150 prevalent bacterial species that combine to dominate the microbial population (Qin et al. 2010). The intestinal bacterial population alone is estimated to establish a 1:1 ratio of host: bacterial cells (Sender et al. 2016). Evolution of the gut microbiota is sensitive to early life influences. Colonisation of an infant commences during parturition, where perinatal
As mode of delivery, nutritional influences, gestational age at birth and antibiotic exposure shape the maternal microbiota imprint (Penders et al. 2006; Moya-Perez et al. 2017; Stewart et al. 2018; Fouhy et al. 2019). Caesarean delivery leads to reduced microbiota richness and diversity compared with vaginally delivered infants (Azad et al. 2013; Shao et al. 2019). Furthermore, compared with full-term delivered infants, premature babies have diminished microbiota diversity, decreased Bifidobacterium and Bacteroides abundance as well as increased proliferation of the Proteobacteria phyla, at least over the first 2 months of life, a consequence of insufficient gastric secretion, antibiotic administration and physical immaturity (Sondheimer et al. 1985; Barrett et al. 2013; Dahl et al. 2017; Korpela et al. 2018). The microbiota signature of premature babies appears to be diverse, highly specific to the individual, and capable of switching from one dominating pattern of microbiota to another within days (Barrett et al. 2013; Korpela et al. 2018). Importantly, a normal microbiota can be expedited in premature, caesarean-delivered, hospitalised babies in 2018). Importantly, a normal microbiota can be expedited in premature, caesarean-delivered, hospitalised babies in the first months of life by breast milk feeding (Korpela et al. 2017; Stewart et al. 2018). Breastfed infants are colonised with skin contact and the mother’s unique breast milk microbial pattern with increased levels of Bifidobacterium evident compared with formula-fed infants (Roger et al. 2010; Azad et al. 2013). Vaginally delivered, full-term babies that were breastfed, born to healthy non-antibiotic-treated mothers have optimal progression of infant microbiota (Penders et al. 2006). These perinatal factors result in perpetual microbiota evolution at least up to 4 years after birth (Fouhy et al. 2019), a critical time during childhood development. Remarkably, the diverse and highly complex gut microbiota community continuously evolves and adapts over an entire lifetime (Borre et al. 2014; McVey Neufeld et al. 2016; Kundu et al. 2017). Distinctive functional and compositional hallmarks are evident across various life periods, including neonatal, early life, puberty, adulthood and ageing, with large interpersonal differences evident (Kundu et al. 2017). Notwithstanding the vast degree of interpersonal variation, the adult gut microbiota is primarily dominated by Firmicutes and Bacteroidetes (Kurokawa et al. 2007; Arumugam et al. 2011). More recently, the adult gut microbiota was classified into three different enterotypes: Prevotella, Ruminococcus and Bacteroides (Arumugam et al. 2011). Furthermore, microbiota diversity and composition are influenced by nutrition, life-style, hormones and health status, ageing, environment, stress and medication, amongst other factors (Woodmansey, 2007; O’Mahony et al. 2011; Albenberg & Wu, 2014; Panda et al. 2014; Golubeva et al. 2015; Kelly et al. 2015; Foster et al. 2017; Boehme et al. 2019). A growing body of evidence now points to the gut microbiota as a potent contributor to whole-body homeostasis in both health and disease (Cryan & O’Mahony, 2011; Grenham et al. 2011; Kelly et al. 2016; Lynch & Pedersen, 2016; Sarkar et al. 2016; Dinan & Cryan, 2017; Gilbert & Lynch, 2019).

Microbiota–gut–brain axis communication pathways

The gut microbiota functions in a multimodal bidirectional communication pathway termed, the microbiota–gut–brain axis, enabling microbes to share information with the brain and the gut to communicate with the gut (Rhee et al. 2009; Cryan et al. 2019). There is compelling evidence to illustrate that dysregulated microbiota–gut–brain axis signalling affects homoeostatic neurocontrol systems, with consequences for behaviours such as anxiety, depression, social interactions, and learning and memory (Bercik et al. 2011a; Hsiao et al. 2013; Desbonnet et al. 2014; Hoban et al. 2016; Burokas et al. 2017; Dinan & Cryan, 2017). Furthermore, many of these maladies are associated with neurodegenerative, neurodevelopmental or biopsychosocial disorders such as Parkinson’s disease, autism and irritable bowel syndrome (Cryan & O’Mahony, 2011; Dinan & Cryan, 2017; Cryan et al. 2020). The mechanisms of bidirectional microbiota–gut–brain axis signalling are multifaceted, comprising both afferent and efferent pathways of the central, enteric and autonomic nervous systems, as well as the hypothalamic–pituitary–adrenal (HPA) axis (Burokas et al. 2015). Currently, a number of afferent (neuronal, immune system, gut microbiota metabolites, tryptophan metabolism and neurotransmitters) and efferent (neuronal and HPA axis) pathways have been proposed (Fig. 1). Despite the considerable amount of experimental evidence from rodent and human studies supporting the role of the gut microbiota in regulating physiological homeostasis and brain functions, signalling pathways have not been entirely elucidated. As such, whilst multiple correlations between microbiota factors and health and disease have been described, the collective understanding of the putative link between the gut microbiota and the brain is still in its infancy. Proposed pathways are described next.

Short-chain fatty acids. The principal short-chain fatty acids (SCFAs), acetic, propionic and butyric acid, are end-products of microbial fermentation of partially digestible and indigestible polysaccharides (Macfarlane & Macfarlane, 2012). Functioning as major signalling mediators of host–microbiome communication, SCFAs play a crucial role in the maintenance of physiological homeostasis and brain functions (Stillings et al. 2014a; Canfora et al. 2015).

SCFAs are either utilised by colonocytes or transferred by diffusion and monocarboxylate transporters into
the circulation (Kekuda et al. 2013; Vijay et al. 2015). Free-fatty-acid receptors (FFARs), especially FFAR2 and 3, are located on an extensive range of cells throughout the body (Sina et al. 2009; Tolhurst et al. 2012; Nohr et al. 2015; Lu et al. 2018b). SCFAs can bind to FFARs expressed on epithelial enteroendocrine cells of the gastrointestinal tract, stimulating the release of gut hormones such as glucagon-like peptide 1 (Tolhurst et al. 2012). SCFA binding to FFAR3 on autonomic neuronal ganglia results in neuronal activation (Kimura et al. 2011; Nohr et al. 2015). Additionally, it is apparent that FFAR2 is highly expressed in immune cells, suggesting a role for SCFAs in immune system regulation (Sina et al. 2009; Smith et al. 2013b). Furthermore, SCFAs may directly influence neurotransmitters; for example, butyrate and propionate modify tyrosine hydroxylase gene expression in PC12 cell lines, which affects dopamine and noradrenaline synthesis (DeCastro et al. 2005; Nankova et al. 2014; Stilling et al. 2016). SCFAs affect microglia of the central nervous system (Erny et al. 2015; Mosher & Wyss-Coray, 2015). Germ-free mice, born and raised in sterile environments, have defects in microglia maturation, morphology and function (Erny et al. 2015), increased blood–brain barrier (BBB) permeability and decreased expression of brain tight junction proteins (Braniste et al. 2014). SCFA supplementation reversed these microglial deficits (Erny et al. 2015), up-regulated brain tight junction proteins and reduced BBB permeability (Braniste et al. 2014). The

**Figure 1. The microbiota–gut–brain axis**

The microbiota–gut–brain axis permits microbes to communicate with the brain and influence CNS regulation of the gut, and other physiological systems. A number of complex communication pathways are proposed mechanisms of microbiota–gut–brain axis signalling. A growing body of evidence suggests vagally mediated communication is the primary signalling pathway between the gut microbiota and the brainstem (Fulling et al. 2019). SCFAs, metabolites of the gut microbiota, can bind freely to free-fatty-acid receptors located throughout the body (Sina et al. 2009; Tolhurst et al. 2012; Nohr et al. 2015; Lu et al. 2018b). Gut hormones are released as a consequence of SCFAs binding to free-fatty-acid receptors on enteroendocrine cells (Tolhurst et al. 2012). The gut microbiota can facilitate central neurotransmitter regulation by synthesising and releasing neurotransmitters from bacteria directly or by altering levels of neurotransmitter precursors, i.e. tryptophan (Desbonnet et al. 2010; Lyte, 2013, 2014; O’Mahony et al. 2015). The immune system also functions as a communication pathway of the microbiota–gut–brain axis (El Aidy et al. 2014b). Cytokines signal to the brain via numerous pathways, including detection by vagal afferent fibres (Goehler et al. 2000; Johnston & Webster, 2009). EEC, enteroendocrine cell; ENS, enteric nervous system; HPA, hypothalamic–pituitary–adrenal; SCFA, short-chain fatty acid. Images were obtained from Smart Servier Medical Art, to create a new composite figure, and are used under the terms of the Creative Commons Attribution 3.0 Licence (creativecommons.org).
relationship between SCFAs and microglia modulation has also been described in a rodent model of sleep-disordered breathing. Ganesh and colleagues report reduced acetate and increased microglia activation in a rat model of obstructive sleep apnoea (OSA). Probiotic or prebiotic supplementation prevented the decrease in acetate levels and the augmented microglial activity; indeed, acetate administration into the caecum prevented OSA-induced gut inflammation (Ganesh et al. 2018).

Interestingly, under healthy physiological conditions a limited amount of SCFAs may cross the BBB (Stilling et al. 2014a). FFARs are sparsely distributed in the brain. However, persistent secretion of SCFAs may result in epigenetic modulation through histone deacetylase (Stilling et al. 2014b, 2016). For example, butyrate can inhibit the activity of histone deacetylases, resulting in hyper-acetylation of histones (Waldecker et al. 2008; Kratsman et al. 2016; Dalile et al. 2019).

Tryptophan metabolism and neurotransmitters. The gut microbiota is interconnected to the serotonergic system, which orchestrates the modulation of various complex physiological functions (Clarke et al. 2013; O’Mahony et al. 2015). Interestingly, 95% of serotonin synthesis occurs within the gastrointestinal tract, with only 5% produced in the brain (Spiller, 2008). The gut microbiota facilitates central neurotransmitter regulation by either altering levels of neurotransmitter precursors or synthesising and releasing neurotransmitters directly from bacteria (Desbonnet et al. 2010; Lyte, 2013, 2014; O’Mahony et al. 2015).

Tryptophan, a serotonin precursor, was increased in the plasma of germ-free mice, whilst gut microbial colonisation normalised plasma tryptophan concentrations. The absence of microbiota in germ-free mice also affects the central serotonergic system within the brain; heightened tryptophan levels correlate with elevated hippocampal serotonin concentrations and turnover in a sex-dependent manner (Clarke et al. 2013). A probiotic strain, *Bifidobacterium infantis*, increased tryptophan concentrations in plasma, with subsequent effects on central 5-hydroxyindoleacetic acid, a serotonin metabolite (Desbonnet et al. 2008). *Candida, Escherichia, Streptococcus* and *Enterococcus* species are also capable of producing serotonin (Lyte, 2013, 2014). Indeed, microbial species can produce several other neurotransmitters: *Bacillus* species produce dopamine, *Lactobacillus* species produce acetylcholine, *Bifidobacterium* and *Lactobacillus* species produce γ-aminobutyric acid (GABA) and *Bacillus, Escherichia* and *Sacccharomyces* species produce noradrenaline (Lyte, 2013, 2014; Strandwitz, 2018). Microbially synthesised neurotransmitters access the blood through the mucosal layer of the intestines; however, these neurotransmitters cannot cross the BBB under normal physiological conditions. It is noteworthy that tryptophan is capable of passing through BBB capillaries, which may stimulate serotonin production within the raphé nuclei of the brainstem (Le Floc’h et al. 2011). It is plausible that neurotransmitters predominantly influence brain function through activation of the enteric nervous system; however, there is a paucity of information regarding signalling mechanisms. Stimulation of serotonin type 3 receptors on vagal afferents, prompting neuronal activation, offers a potential mechanism (Glatzle et al. 2002; Raybould et al. 2003).

**Immune system.** The immune system is a key communication pathway of the microbiota–gut–brain axis (El Aidy et al. 2014). Immune cells within the gastrointestinal tract play a crucial regulatory role at the host–microbiome interface, influencing whole-body health (Macpherson & Uhr, 2004; Sonnenburg et al. 2006; Belkaid & Hand, 2014). Commensal gut microbes frequently reside in regions enriched in immune cells, which produce mucus, antimicrobial peptides and immunoglobulin A (Belkaid & Hand, 2014). Mucus produced by goblet cells limits interactions between host tissue and gut microbiota and prevents microbial translocation (McGuckin et al. 2011; Belkaid & Hand, 2014). Additionally, an antimicrobial peptide, regenerating family member 3 γ (Reg3γ) depletes gram-positive bacteria, whereas colonisation of germ-free mice with gram-negative bacteria augments Reg3γ expression (Cash et al. 2006; Sonnenburg et al. 2006). Similarly, intestinal dendritic cells in concert with T and B lymphocytes of Peyer’s patches mediate immunoglobulin A production, specifically for commensal-derived antigens (Macpherson & Uhr, 2004). Thus, when functioning optimally, an important regulatory interaction exists at the luminal surface between the gut microbiota and the host tissue, which is vital for integrative body systems.

Sensory vagal afferent fibres can detect cytokines and other inflammatory mediators and inform the brain of inflammation in the periphery (Goehler et al. 2000; Johnston & Webster, 2009). However, the mechanism by which these inflammatory mediators are detected remains unclear. In situations of dysregulated intestinal permeability such as stress, bacterial components including lipopolysaccharide (LPS) can translocate from the intestinal lumen into the circulatory system. Systemic LPS prompts peripheral immune system stimulation and HPA axis activation (Kelly et al. 2015; Araujo et al. 2017). Under healthy physiological conditions, it is unlikely that immune molecules, such as chemokines, cross the BBB. However, recent studies suggest an increased potential for chemokines to cross a dysregulated BBB, suggesting microbiota-induced immune modulation may directly affect brain function (Banks & Erickson, 2010).
**Neuronal pathways.** The neuronal pathways of microbiota–gut–brain communication include central, enteric and autonomic nervous systems (Houlden et al. 2016; Kigerl et al. 2016; Breit et al. 2018; Fulling et al. 2019). Animal and human studies suggest the vagus nerve is the most direct communication pathway of the microbiota–gut–brain axis (Fulling et al. 2019). The vagi are the principal nerves of the parasympathetic nervous system, consisting of 80% afferent and 20% efferent fibres. Emerging from the medulla oblongata of the brainstem and terminating within the colon, the vagi are a likely conduit for the microbiota to directly modulate brainstem function (Berthoud & Neuhuber, 2000). Vagal efferent fibres of preganglionic neurones arise from the dorsal motor nucleus of the vagus nerve and supply muscular and mucosal layers in the lamina propria and in the muscularis externa of the gut wall (Berthoud & Neuhuber, 2000). Afferent cell bodies of the nodose ganglia convey sensory cues from the periphery to the nucleus tractus solitarii (NTS) of the brainstem, projecting afferent signals to multiple regions within the central nervous system, including the ventrolateral medulla and locus coeruleus of the pons, which are involved in cardiovascular control and central chemosensitivity, respectively (Berthoud & Neuhuber, 2000).

Studies in mice report that administration of *Lactobacillus rhamnosus* modifies GABA receptor expression in the brain and mitigates anxiety and depressive-related behaviours (Bravo et al. 2011). These behavioural and neurochemical outcomes were abolished in vagotomised mice, suggesting vagal-mediated communication between the gut microbes and the brain (Bravo et al. 2011). Furthermore, oral administration of *Campylobacter jejuni* in mice elevated anxiogenic behaviour and induced neuronal activation within the NTS, parabrachial and paraventricular nuclei and amygdala, critical components of the respiratory control and/or central autonomic networks (Gaykema et al. 2004; Goehler et al. 2008). Additionally, anxiolytic benefits of probiotic *Bifidobacterium longum* were eradicated after vagotomy in mice (Bercik et al. 2011b). Furthermore, vagotomy in young patients minimised the risk of developing neurodegenerative disorders (Svensson et al. 2015). Indeed, it has been suggested that vagal afferents respond to many stimuli within the gut, including nutrients, cytokines, gut hormones and metabolites, and neurotransmitters (Goehler et al. 2000; Raybould et al. 2003; Johnston & Webster, 2009; Kimura et al. 2011; Nohr et al. 2015; Bharwani et al. 2020).

**Overview of cardiorespiratory control**

The cardiorespiratory control network within the brainstem is a highly complex tightly regulated homeostatic system. The pontomedullary regions of the brainstem consist of interconnected neuronal networks that are vital for the production of rhythmic breathing, detection of metabolic imbalance, and regulation of autonomic outflow involved in cardiovascular homeostasis (Guyenet, 2014). Neuromodulators such as serotonin, noradrenaline, glutamate, GABA and glycine have multiple functions at various levels of the control network. Some modulators can exert differential effects on activity by acting on different G-protein receptors. Disturbances in neuromodulation can significantly affect cardiorespiratory control (Doi & Ramirez, 2008; Harris-Warrick & Johnson, 2010; Ramirez et al. 2012; Abbott et al. 2013; Smith et al. 2013a). These networks depend on critical feedback from the periphery such that sensory-guided modulation of respiratory and autonomic centres shape respiratory motor drive and sympathetic and parasympathetic outflow evoking appropriate cardiorespiratory reflex control (Guyenet, 2006, 2014; Garcia et al. 2011). Sensory afferent cues from peripheral chemoreceptors, pulmonary and airway vagal afferents, and arterial baroreceptors project to the NTS within the brainstem. The NTS integrates and relays information to other cardiorespiratory regions where appropriate cardiorespiratory autonomic responses are generated to maintain oxygen, acid–base and blood pressure homeostasis (Corderidge & Corderidge, 1984; Widdicombe, 2003; Prabhakar & Peng, 2004). Notwithstanding the homeostatic control governing breathing and blood pressure, there is remarkable potential for adaptive and maladaptive plasticity, which can occur at multiple regions within the cardiorespiratory control system, including peripheral and central levels. Maladaptive plasticity results in unfavourable outcomes for cardiorespiratory control, including breathing instability and the establishment of hypertension, with deleterious consequences for integrative body systems (Julien et al. 2008; Fournier et al. 2013; Joseph et al. 2013; Kinkead et al. 2013; Golubeva et al. 2015; Soliz et al. 2016; O’Connor et al. 2019a). Stress debilitates the cardiorespiratory control network, at various life stages, which can persist depending on duration, intensity and timing of the stressor. Perinatal and early life stress dampens the capacity to achieve adequate ‘fine-tuning’ of breath-to-breath ventilatory control increasing the apnoea index, respiratory frequency variability, as well as influencing hypoxia ventilatory responsiveness; moreover, sympathetic nervous system activity is augmented, a major contributor to the hypertensive phenotype (Genest et al. 2004; Gulemetova & Kinkead, 2011; Fournier et al. 2013; Golubeva et al. 2015).

**Gut microbiota and cardiorespiratory control**

**Blood pressure.** Elaborate mechanisms of blood pressure regulation are slowly being unravelled. Several studies using models that manipulate the gut microbiota,
including faecal microbiota transplant strategies, antibiotic and probiotic administration, demonstrate substantial interplay between the gut microbiota and blood pressure homeostasis (Ganesh et al. 2018; Lucking et al. 2018; Marques et al. 2018; Toral et al. 2019). Perturbed gut microbiota composition and diversity, specifically elevated Firmicutes: Bacteroidetes ratio, and decreased microbial richness and evenness have been associated with hypertension in multiple animal models (Durgan et al. 2016; Adnan et al. 2017; Santisteban et al. 2017; Toral et al. 2019). Recently, it was reported that the gut microbiota and/or gut microbiota metabolites function in autonomic control of the heart (Kim et al. 2018).

Hypertension is an independent risk factor for cardiovascular disease and stroke, and 90–95% of hypertensive cases are classified as primary idiopathic hypertension, i.e. the cause of hypertension is unknown (Carretero & Oparil, 2000; Mancia et al. 2013). Research in humans and animal models has linked the development of hypertension to aberrant gut microbiota composition and diversity (see Fig. 2) (Yang et al. 2015; Durgan et al. 2016; Adnan et al. 2017; Li et al. 2017; Santisteban et al. 2017; Yan et al. 2017; Toral et al. 2019). Hypertensive patients host decreased species richness and evenness in addition to a distinct diversity cluster compared with normotensive individuals (Yang et al. 2015; Li et al. 2017; Yan et al. 2017). In the gut of hypertensive patients, there was lower metabolism of amino acids, cofactors, vitamins and SCFA-producing enzymes, steroid degradation, trimethylamine-producing enzymes and membrane transport compared with controls (Yan et al. 2017). Faecal transplant from two hypertensive patients into recipient germ-free mice produced hypertension and tachycardia in the recipient animals (Li et al. 2017). Faecal microbial transfer from normotensive donor rats to hypertensive recipient rats decreased blood pressure in the hypertensive recipients (Toral et al. 2019). An increase in the Firmicutes: Bacteroidetes ratio develops in spontaneously hypertensive rodents, which was also evident when the hypertensive phenotype was transferred via oral gavage into normotensive animals (Yang et al. 2015; Adnan et al. 2017). Intriguingly, this shift was not observed in pre-hypertensive rodents (Santisteban et al. 2017) or when an anti-hypertensive agent, minocycline, recovered the Firmicutes: Bacteroidetes ratio (Yang et al. 2015). Furthermore, hypertensive rodents have reduced bacterial diversity as evident by a decrease in microbial evenness and richness (Yang et al. 2015).

In hypertensive rats, butyrate- and acetate-producing bacterial taxa, such as Clostridiaceae families and Bifidobacterium, respectively, were significantly reduced whereas lactate-producing bacterial taxa, such as Streptococcaceae and Coriobacteriaceae families, were increased (Yang et al. 2015; Durgan et al. 2016; Santisteban et al. 2017; Ganesh et al. 2018; Kim et al. 2018). The relative abundance of lactate-, butyrate- and acetate-producing bacterial taxa were all associated with systolic blood pressure (Adnan et al. 2017; Toral et al. 2019). Lactobacillus, a lactate-producing genus, positively correlated with systolic blood pressure, whereas the butyrate-producing families, Clostridiaceae and Odoribacteraceae, and members of the acetate-producing genera, Holdemania and Coprobacillus, were negatively correlated with systolic blood pressure (Adnan et al. 2017; Toral et al. 2019). Additionally, minocycline administration tended to increase acetate- and butyrate-producing bacteria, demonstrating that an increase in these bacterial taxa is associated with normal blood pressure (Yang et al. 2015). These studies highlight that specific bacteria are, at least in part, either responsible for, or sensitive to, changes in blood pressure.

In rodent models, propionate, acetate and butyrate administration attenuated cardiac fibrosis, cardiac hypertrophy and hypertension in chronic angiotensin II-induced and mineralocorticoid excess-induced hypertension (Marques et al. 2017; Kim et al. 2018; Bartolomaeus et al. 2019). Additionally, acetate supplementation decreased the Firmicutes: Bacteroidetes ratio (Marques et al. 2017) and butyrate treatment normalised gut barrier dysfunction (Kim et al. 2018), two pathologies of hypertensive models (Adnan et al. 2017; Santisteban et al. 2017). Remarkably, probiotic (Clostridium butyricum) or prebiotic (Hylon VII) administration prevented the development of hypertension in a high-fat diet (HFD) and obstructive sleep apnoea (OSA) rat model, increasing the abundance of several SCFA-producing taxa and caecum acetate, which were decreased in the hypertensive model. Furthermore, probiotic or prebiotic administration prevented epithelial goblet cell loss, mucus barrier thinning and microglia activation, which were evident in the HFD+OSA hypertensive model. Impressively, chronic acetate administration into the caecum of rats during exposure to HFD+OSA not only restored caecal acetate concentrations, but also prevented the development of hypertension and gut inflammation (Ganesh et al. 2018). Probiotic (Lactobacillus rhamnosus) administration prevented the development of hypertension in a high-salt diet + OSA animal model, reducing blood trimethylamine oxide levels (Liu et al. 2019). Moreover, probiotics (Lactobacillus fermentum and Bifidobacterium breve) increased butyrate-producing bacteria and prevented the development of high blood pressure, endothelial dysfunction and gut microbiota disturbances in hypertensive rats. Interestingly, oral administration of butyrate or acetate administration prevented the development of hypertension and alterations to the gut microbiota (Robles-Vera et al. 2020). Butyric acid administered into the colon exerted a hypotensive effect. Intriguingly, this reduction in blood pressure was diminished by
The precise mechanism by which perturbed gut microbiota and microbial metabolites contribute to hypertension has yet to be elucidated (see Fig. 3). At present, sympathetic neuronal communication between the hypothalamic paraventricular nucleus and the gut has been proposed as a player in blood pressure regulation (Santisteban et al. 2017). Faecal microbiota transfer from normotensive donor to hypertensive recipient rats decreased blood pressure, gut inflammation and plasma LPS, as well as the production of NADPH oxidase-dependent reactive oxygen species and neuroinflammation in the hypothalamic paraventricular nucleus. Additionally, decreased plasma noradrenaline concentrations and blunted pentolinium-induced hypotensive responses were evident in recipient rats, indicative of blunted sympathetic nervous system excitation (Toral et al. 2019). This proposed mechanism may also have relevance in hypertensive animal models with autonomic nervous system imbalance, such as chronic intermittent hypoxia (CIH)-exposed animals (Li et al. 2018). Furthermore, studies have recurrently identified altered lactate-, butyrate- and acetate-producing bacterial taxa in hypertensive animal models (Yang et al. 2015; Durgan et al. 2016; Santisteban et al. 2017; Ganesh et al. 2018). These SCFAs reduce BBB permeability and influence brain microglia, neurotransmitter production and immune system regulation (DeCastro et al. 2005; Braniste et al. 2014; Erny et al. 2015; Stillling et al. 2016). Moreover, SCFAs can cause neuronal activation (Lal et al. 2001; Nohr et al. 2015), influencing the autonomic nervous system. When considered together, these studies suggest that hypertension, at least in part, results from the influence of perturbed gut microbiota on central cardiovascular control regions. Aside from the influence of the sympathetic nervous system on the cardiorespiratory...
control network, microbiota-mediated dysfunction of vago-vagal signalling may contribute to the development of hypertension (Onyszczewicz et al. 2019).

**Breathing.** The gut microbiota has been recently linked with the respiratory control network, a homeostatic neural system which maintains oxygen and acid–base balance, vital for whole-body health. Pre-natal stress disturbs the gut microbiota composition in rat offspring with associated adverse effects on respiratory control, resulting in elevated variability of breathing frequency during normoxia and altered ventilatory responsiveness to hypoxic and hypercapnic chemostimulation. Of interest, breathing frequency responsiveness to hypercapnia positively correlated with *Anaerotruncus* and *Oscillibacter* genera and enhanced variability of breathing frequency during normoxia correlated with *Mucispirillum* and *Papillibacter* (Golubeva et al. 2015). Notably, these observed associations may well be interdependent due to the effects of systemic stress on the microbiota (O’Mahony et al. 2011; Foster et al. 2017; van de Wouw et al. 2018), which will be described in more detail below. Moreno-Indias et al. (2015, 2016) demonstrated that respiratory dysregulation and alterations to the gut microbiota structure develop in an animal model of intermittent hypoxia. Until recently, there was no other report investigating the potential regulatory role of the gut microbiota on the control of breathing. We performed the first comprehensive assessment of respiratory control in animal models of manipulated gut microbiota, as well as sleep-disordered breathing with altered gut microbiota, revealing a link between gut microbiota and neural control of breathing. Considering that deleterious respiratory behaviours are evident in adult rats with disrupted gut microbiota following...
antecedent pre-natal stress (Golubeva et al. 2015), and that dysregulated microbiota–gut–brain axis signalling promotes the development of aberrant brain behaviours, such as anxiety, depression and altered learning and memory (Hoban et al. 2016; Burokas et al. 2017; Foster et al. 2017), we aimed to investigate if the gut microbiota has a modulatory role in respiratory homeostasis.

In O’Connor et al. (2019a), two approaches were utilised to manipulate the gut microbiota. Adult male rats were treated with broad spectrum antibiotics (ABX) designed to deplete the gut microbiota. Additionally, rats received a faecal microbiota transfer (FMT) of pooled sham faeces in an attempt to reverse antibiotic-induced gut microbiota disruption. However, instead of normalising the gut microbiota profile, this FMT strategy created a second model of gut microbiota perturbation with a unique gut composition and increased gut microbiota diversity. Similar outcomes were evident in clinical FMT administration to irritable bowel syndrome patients (Halkjaer et al. 2018). Using the technique of whole-body plethysmography, assessment of respiratory control and whole-body metabolism in unrestrained, unanaesthetised animals revealed aberrant respiratory phenotypes in response to chemostimulation in ABX and FMT rats, with no change evident during basal normoxic breathing. Normal ventilation under baseline conditions indicates a remarkable capacity for the maintenance of respiratory homeostasis within the control network, despite observed changes in brainstem neurotransmitter levels. However, deficits in respiratory control were revealed during challenges to the homeostatic system. ABX and FMT rats had depressed respiratory frequency and minute ventilation during the initial hypoxic ventilatory response (O’Connor et al. 2019a), similar to the blunted hypoxic ventilatory response evident in adult rats exposed to pre-natal stress (Golubeva et al. 2015). These studies suggest that a disrupted gut microbiota signature either blunts chemosensory cues from the dominant peripheral oxygen sensors, the carotid bodies, or impairs central integration of chemoafferent neural traffic from the periphery. Although the initial hypoxic ventilatory responses were depressed in ABX and FMT rats, the phase 2 steady-state response to hypoxia remained unchanged (O’Connor et al. 2019a).

Intriguingly, ABX and FMT rats had depressed ventilatory responsiveness to hyperoxic hypercapnia, revealing that modifications to the gut microbiota are associated with blunted central chemoreflex control of breathing. This striking observation is physiologically significant as systemic acidosis develops during episodes of hypoventilation with reduced clearance of carbon dioxide. Hypercapnia is sensed by central chemoreceptors residing in the brainstem. Therefore, we assessed brainstem monoamine and monoamine metabolite concentrations in brainstem homogenates from ABX and FMT rats, as altered brain neurochemistry is evident in various models of disrupted gut microbiota (Clarke et al. 2013; Desbonnet et al. 2015; Hoban et al. 2016), and central carbon dioxide chemosensitivity is heavily influenced by brainstem neuromodulators (Eldridge & Millhorn, 1981; Gourine, 2005; Doi & Ramirez, 2008; Corcoran et al. 2009; Guyenet, 2014). High-performance liquid chromatography revealed that brainstem neuromodulators relating to the dopaminergic pathway were modified in ABX and FMT groups. Notably, a number of bacterial genera, predominantly from the Firmicutes phylum, correlated with brainstem neurochemistry, which in turn may be responsible for the perturbed chemoreflex control of breathing evident in ABX and FMT rats. Using two different models of perturbed gut microbiota, O’Connor et al. (2019a) suggests that dysregulated microbiota–gut–brain axis signalling culminates in deleterious outcomes for brainstem neurochemistry and respiratory control, extending previous work linking the gut microbiota to the control of breathing (Golubeva et al. 2015).

Dysregulated intestinal permeability has been associated with systemic inflammation and the transfer of bacterial metabolites such as LPS into the periphery (Araujo et al. 2017). Intestinal barrier dysfunction frequently occurs in models of perturbed gut microbiota, such as rodent models of maternal separation stress, hypertension and antibiotic administration (Gareau et al. 2007; Tulstrup et al. 2015; Ganesh et al. 2018; Kim et al. 2018). Consistent with these observations, ABX and FMT rats had increased permeability in the distal ileum, but not colon. It is conceivable that disrupted intestinal integrity contributed to altered brain neurochemistry and in turn the aberrant respiratory control in ABX and FMT rats. Considering its dominant role in the gut–brain axis, the vagus nerve presents as a potential player in the establishment and progression of cardiorespiratory disturbances evident in the ABX and FMT rats. Interestingly, no notable differences in cardiorespiratory responses to pulmonary vagal C-fibre stimulation were evident between groups, but vagal afferent stimulation from other peripheral sites such as the gut were not examined (O’Connor et al. 2019a). In summary, these studies clearly demonstrate that perturbation to the gut microbiota is associated with altered respiratory control evident in response to chemojunctional stimulation. Mismatches in ventilation and metabolism have consequences for acid–base balance with potential consequences for whole-body systems. These recent observations revealed a link between gut microbiota and the integrative control of breathing with potential implications for a variety of respiratory control disorders across the lifespan, including sleep-disordered breathing (see Fig. 2).
Sleep-disordered breathing. Chronic sleep disruption, an indirect stress that also features in sleep-disordered breathing, disturbs gut microbial diversity and composition in mice and remains altered for the duration of sleep fragmentation (Poroyko et al. 2016). Chronic sleep disruption increases the Firmicutes: Bacteroidetes ratio, an index of gut microbial imbalance, and is associated with various pathologies (Poroyko et al. 2016). Sleep disruption specifically promoted growth of Lachnospiraceae and Ruminococcaceae families with contrasting reductions in Lactobacillaceae and Bifidobacteriaceae families that consist of many beneficial species (Poroyko et al. 2016). Exposure to CIH, which is a dominant pathological hallmark of respiratory control disorders, including OSA, leads to disrupted gut microbiota in mice. CIH-exposed mice develop a Prevotella enterotype and altered bacterial genera, including proliferation of obligate anaerobes, an increased Shannon index, and a distinct diversity cluster compared with control mice (Moreno-Indias et al. 2015). Similarly, exposure to intermittent hypercapnic-hypoxia and a HFD alters the gut microbiota and gut microbiota metabolites (Tripathi et al. 2018). Additionally, CIH exposure elevates concentrations of endogenous LPS (Moreno-Indias et al. 2015), indicative of increased intestinal permeability, conceivably a consequence of sympathetic hyperactivity driven by CIH (Fletcher et al. 1992a,b; Santisteban et al. 2017). In a follow-up study, CIH-exposed mice were afforded 6 weeks of normoxia as a recovery strategy to mimic treatment for sleep-disordered breathing; however, after this recovery period, the systemic presence of endotoxins and CIH-induced gut microbiota perturbations persisted (Moreno-Indias et al. 2016). Exposure to CIH caused gut inflammation, oxidative stress and decreased tight junction expression, compromising intestinal barrier function (Wu et al. 2016), maladies associated with disrupted gut microbiota (Kelly et al. 2015; Santisteban et al. 2017). As such, CIH can affect the gut microbiome indirectly via autonomic dysregulation and/or by direct effects on the gut microbiota (Moreno-Indias et al. 2015, 2016). Therefore, the gut microbiota is a potential contributor to CIH-induced cardiorespiratory dysregulation via altered microbiota–gut–brain axis signalling initiated by changes in gut microbiota composition (see Fig. 2).

In CIH-exposed rodents, modelling human sleep apnoea, the influence of exposure to CIH on the gut microbiota and resultant effects on cardiorespiratory physiology are complicated by CIH-induced carotid body sensitisation and resultant alterations in autonomic control. Carotid body chemoreceptors are proposed to be critical in the development of numerous CIH-induced cardiorespiratory morbidities, including hypertension and elevated hypoxic ventilatory responsiveness (Huang et al. 2009; Peng et al. 2009; Del Rio et al. 2016; Iturriaga et al. 2017). Systemic stress and exposure to CIH provoke sympathetic nervous system hyperactivity, a derangement correlated to disrupted gut microbiota composition and diversity (Wu et al. 2016; Santisteban et al. 2017). Lucking et al. (2018), explored the effects of exposure to CIH on gut microbiota and cardiorespiratory control in guinea-pigs, a rodent with hypoxia-insensitive carotid bodies. Using a CIH paradigm that evokes hypertension in rats, it was reasoned that if cardiorespiratory impairments presented in CIH-exposed guinea-pigs in the absence of carotid body sensitisation, then structures other than the carotid bodies are potential contributors to development of CIH-induced morbidity.

CIH-exposed guinea-pigs displayed lower respiratory variability in concert with reduced frequency of sighs and central apnoeas assessed by whole-body plethysmography. In light of these adverse respiratory behaviours, brain-stem neuromodulators involved in the control of breathing were assessed. High-performance liquid chromatography revealed decreased concentrations of noradrenaline in the pons and medulla oblongata. Lower brainstem noradrenaline concentrations and reduced apnoea/sigh frequency are congruent observations, considering that noradrenaline promotes respiratory instabilities in mice exposed to intermittent hypoxia (Zanella et al. 2014) and elevated central noradrenergic terminals are noted in CIH-exposed rats (Mody et al. 2011), which have increased propensity for generation of apnoea (Edge et al. 2012). Exposure to CIH in guinea-pigs did not induce hypertension, but tachycardia was evident together with impaired baroreflex responsiveness. Separate studies convincingly demonstrated that exposure to an extended duration of severe CIH in guinea-pigs manifested in the establishment of hypertension and tachycardia, without carotid body sensitisation (Docio et al. 2018). These observations illustrate that sites other than the carotid bodies contribute to cardiorespiratory and autonomic impairments following exposure to CIH (Docio et al. 2018; Lucking et al. 2018; AlMarabeh et al. 2019; O’Connor et al. 2019b), which could reasonably arise from effects at the level of the microbiota.

Indeed, 16S rRNA sequencing revealed that CIH-exposed guinea-pigs exhibited altered gut microbiota composition and diversity, in the likely absence of carotid body sensitisation and elevated sympathetic nervous system activity (Lucking et al. 2018), consistent with observations of altered gut microbiota in other CIH-exposed animal models (Moreno-Indias et al. 2015, 2016; O’Connor et al. unpublished observations in CIH-exposed rats). It is conceivable that dysregulated microbiota–gut–brain axis signalling may have culminated in aberrant autonomic control of the heart, undesirable respiratory phenotypes and reduced noradrenaline concentrations in CIH-exposed...
guinea-pigs. This is particularly intriguing in the light of evidence that ABX and FMT rats exhibit respiratory control deficits and altered brainstem neurochemistry (O’Connor et al. 2019a). Butyrate, a metabolite of the gut microbiota, modified the gut microbiota, reduced blood pressure and normalised baroreflex activity and cardiac autonomic control in a hypertensive mouse model with perturbed gut microbiota (Kim et al. 2018). Considering that dysregulated autonomic control occurs in CIH-exposed guinea-pigs with altered gut microbiota (Docio et al. 2018; Lucking et al. 2018), these studies implicate disruption to the gut microbiota as a causal factor in the development of cardiovascular and autonomic dysfunction evident in CIH-exposed rodent models, with relevance to sleep-disordered breathing.

Given that ABX and FMT perturbed the gut microbiota and altered respiratory behaviours and brainstem neurochemistry (O’Connor et al. 2019a) and that CIH-exposed guinea-pigs, modelling human sleep apnoea, have a disturbed gut microbiota as well as perturbed respiratory and autonomic control (Lucking et al. 2018), it is reasonable to postulate that beneficial manipulation of the gut microbiota may have potential application as an adjunctive treatment in human cardiorespiratory disease. Considering the governing role of the vagus nerve, it presents as a plausible link between disturbed gut microbiota and adverse cardiorespiratory and autonomic outcomes. This is illustrated in Fig. 3. Studies are required to investigate if microbiota–gut–brain axis signalling via the vagus nerve has a modulatory role in the control of breathing and cardiovascular function. A complex interplay of microbiota–gut–brain axis signalling mechanisms may play a regulatory role in cardiorespiratory and autonomic control. Although links have recently been made between the gut microbiota and cardiorespiratory control, at present there is paucity of information regarding the gut microbiome and microbiota metabolites in patients with cardiorespiratory disease. Next, we will briefly summarise recent studies characterising the microbiota profile in patients with cardiorespiratory disorders.

**Cardiorespiratory disease**

**Obstructive sleep apnoea.** OSA is the most common form of sleep-disordered breathing and has devastating consequences for integrative body systems, emerging as a major health crisis worldwide (Garvey et al. 2015). OSA is characterised by repetitive collapse of the pharyngeal airway exclusively during sleep, leading to the development of episodic oxygen fluctuations manifesting in exposure to CIH. Compelling evidence exists for an association between OSA and cardiorespiratory, metabolic and neurocognitive morbidities, with CIH established as the primary pathogenic driving force behind the host of well-characterised morbidities associated with OSA (O’Halloran, 2016).

It has recently been shown that OSA patients fall into one of the three enterotypes: Bacteroides, Ruminococcus and Prevotella (Ko et al. 2019). Using an apnoea–hypopnoea index greater than 15, it was established that sleep architecture including arousal time and index, N1 sleep stage, and sleep latency were altered in Prevotella enterotype OSA patients compared with patients with Bacteroides and Ruminococcus (Ko et al. 2019). It is interesting to note that CIH exposure in mice also resulted in the development of a Prevotella enterotype (Moreno-Indias et al. 2015). Moreover, in the urine of OSA patients a number of metabolites were different compared with controls, and five of these metabolites related to the gut microbiota (Xu et al. 2018).

Although much remains to be known about the gut microbiota in OSA patients, recent advances have shown that oral, nasal and lung microbiota are significantly altered in OSA (Wu et al. 2018; Xu et al. 2018; Lu et al. 2018a). Firmicutes, Proteobacteria and Fusobacteria were significantly different in both lung and oral samples from people with OSA compared with controls (Xu et al. 2018; Lu et al. 2018a). Interestingly, seven genera of the nasal microbiota correlated with apnoea–hypopnoea index (a measure of disease severity) in OSA (Wu et al. 2018). Continuous positive airway pressure, the gold standard for treatment of sleep-disordered breathing, did not alter nasal microbiome diversity in OSA patients (Wu et al. 2018).

**Apnoea of prematurity and bradycardia.** Premature babies often develop apnoea of prematurity and bradycardia, and it is established that the gut microbiota is distinct from that of full-term babies (Barrett et al. 2013; Korpela et al. 2018). Apnoea of prematurity and bradycardia occur due to immature respiratory centres and an underdeveloped nervous system (Cohen & Katz-Salamon, 2005). Furthermore, in preterm infants there is early deficit of neuroprotective hormones including progesterone, the lack of which has implications for brain development (Berger & Soder, 2015; Bairam et al. 2019), which is also observed in animal models during the postnatal period (Lefter et al. 2007; Bairam et al. 2013; Joseph et al. 2018). The gut microbiota is involved in the early programming of brain circuits (Sudo et al. 2004; Diaz Heijtz et al. 2011; Clarke et al. 2013; Desbonnet et al. 2014). Progesterone supplementation alters the gut microbiota; for example, it increases *Bifidobacterium* abundance during the third trimester of pregnancy in humans and rodents (Nuriel-Ohayon et al. 2019). Decreased *Bifidobacterium* is evident in preterm infants, in tandem with reduced progesterone levels (Bairam et al. 2019). It is interesting to speculate that there may be an interplay between the gut microbiota and progesterone in the control of breathing, at least during neonatal life.
Organisms such as *Staphylococcus aureus* often colonise the infant’s gastrointestinal and respiratory tract and may cause or aggravate cardiorespiratory dysfunctions (Hofstetter et al. 2008). CIH is a dominant pathological feature of apnoea of prematurity and directly or indirectly influences the gut microbiota (Moreno-Indias et al. 2015, 2016). Perhaps the gut microbiota under the influence of progesterone may, to some extent, contribute to maturation of the cardiorespiratory centres within the brain and have relevance for apnoea of prematurity and bradycardia.

**Asthma.** Several studies have linked alterations to the gut microbiota during early life with increased risk of asthma in later life (van Nimwegen et al. 2011; Abrahamsson et al. 2014; Arrieta et al. 2015). Caesarean section delivery increases the risk of developing airway sensitivity up to 12 years of age (Keag et al. 2018). Asthmatic children had reduced gut microbiota diversity at 1 week and 1 month of age compared with non-asthmatic children (Abrahamsson et al. 2014). Furthermore, the relative abundance of faecal *Veillonella, Faecalibacterium, Rothia* and *Lachnospiraceae* were reduced in children at high risk of asthma (wheezzy and atopy). Interestingly, faecal acetate was also decreased in these children (Arrieta et al. 2015). Lack of gut microbiota diversity is also evident in asthmatic adults compared with healthy controls (Wang et al. 2018). Proteobacteria enrichment of the lung microbiota was observed in asthmatic patients (Hilty et al. 2010; Huang et al. 2015) and an abundance of *Haemophilus* was evident in patients with moderate-to-severe asthma (Hilty et al. 2010), with *Klebsiella* or *Moraxella catarrhalis* species present in patients with severe asthma (Huang et al. 2015).

Pregnant mice receiving acetate supplementation had suppressed expression of genes linked to human asthma and mouse allergic airways disease in the offspring (Thorburn et al. 2015). Gut and lung dysbiosis and dysregulated bidirectional signalling across the gut–lung axis appear to contribute to the increased emergence of asthma (Hufnagl et al. 2020). In asthmatic children, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* improved lung function and reduced asthmatic exacerbations (Gutkowski et al. 2011).

**Chronic obstructive pulmonary disease.** Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease characterised by persistent airflow limitation, with concomitant impairment in pulmonary gas exchange, leading to the development of hypoxaemia. To date, there is a paucity of studies investigating the gut microbiome in COPD patients. Smoking, which is a leading cause of COPD, has significant impact on gut microbiota structure. Smoking increases the abundance of Proteobacteria and Bacteroidetes phyla, as well as the *Clostridium, Bacteroides* and *Prevotella* genera (Benjamin et al. 2012; Wang et al. 2012), whilst reducing the Actinobacteria and Firmicutes phyla, as well as *Bifidobacterium* and *Lactococcus* (Tomoda et al. 2011; Savin et al. 2018). Additionally, it is well-established that potentially pathogenic taxa, including *Pseudomonas aeruginosa*, *Haemophilus influenza* and *Streptococcus*, colonise the lungs in COPD patients (Garcia-Vidal et al. 2009; Simpson et al. 2016; Wang et al. 2016). The non-pathogenic *Bacillus* species were decreased in the lungs of COPD patients (Simpson et al. 2016). There is a high prevalence of sleep-disordered breathing in people with COPD, presenting the so-called overlap syndrome (McNicholas, 2018). In addition, antibiotic administration is a central component of treatment for pulmonary diseases (Lopez-Campos et al. 2020). It is very likely that disruption to lung and gut microbiota populations in COPD influences cardiopulmonary physiology and respiratory control, with implications for disease progression.

**Cystic fibrosis.** Cystic fibrosis is an autosomal recessive disease manifesting from a mutation of the cystic fibrosis transmembrane conductance regulator gene. Cystic fibrosis patients have decreased gut microbiota diversity and altered composition compared with healthy controls. These compositional changes include increased Firmicutes: Bacteroidetes ratio as well as *Staphylococcus, Propionibacterium acnes, Clostridium difficile* and *Clostridiacaeae* (Burke et al. 2017; Vernocchi et al. 2018). Decreased abundance of healthy gut taxa including *Roseburia, Bifidobacterium* and *Faecalibacterium* was also evident (Burke et al. 2017). Moreover, gut microbiota differences were reported between various stages of cystic fibrosis (mild, moderate, severe) (Burke et al. 2017). Interestingly, *Lactobacillus* GG administration to cystic fibrosis patients promoted beneficial gut microbiota and decreased pulmonary exacerbations and hospital admissions (Bruzese et al. 2007).

**Summary and conclusion**

The gut microbiota signals via an intricate bidirectional communication pathway termed the microbiota–gut–brain axis. Perturbed microbiota–gut–brain axis signalling has detrimental consequences for homeostatic regulation of neurocontrol systems contributing to deleterious behaviours and other disease states. To date, dysregulated communication between the gut microbes and the brain has been associated with multiple maladies including stress-related pathologies such as anxiety, depression, irritable bowel syndrome and neurodevelopmental disorders, such as autism. Recent findings
from our group and others add to the emerging field exploring microbiota–gut–brain axis signalling in homeostatic systems, extending investigations to autonomic behaviours predominantly regulated by the brainstem (pons and medulla oblongata), specifically related to cardiorespiratory control. Considering that aberrant microbiota–gut–brain axis signalling extends to the homeostatic neural control systems responsible for the maintenance of adequate oxygen and acid–base balance, and whole-body health, recent data described in this review support a fundamental role for dysregulated microbiota–gut–brain axis signalling in cardiorespiratory disorders, including sleep-disordered breathing. It is increasingly evident that a disturbed gut microbiota signature is implicated in an ever-expanding portfolio of pathologies associated with neurocontrol networks. At present, there are many unresolved questions concerning the interplay between the gut microbiota, cardiorespiratory and autonomic control. Additional research is required to understand the elaborate signalling mechanisms of the gut–brain axis. If this can be achieved, it may shape therapeutic strategies for the treatment of human cardiorespiratory disorders.

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**Additional information**

**Competing interests**

None declared.

**Author contributions**

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