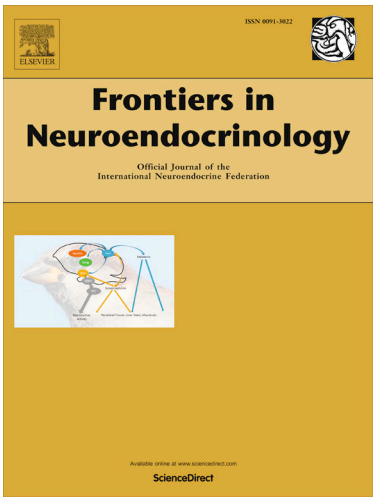

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PII: S0091-3022(18)30039-6
DOI: https://doi.org/10.1016/j.yfrne.2018.04.002
Reference: YFRNE 711

To appear in: *Frontiers in Neuroendocrinology*

Received Date: 2 October 2017
Revised Date: 23 April 2018
Accepted Date: 23 April 2018

Please cite this article as: S. Cussotto, K.V. Sandhu, T.G. Dinan, J.F. Cryan, The Neuroendocrinology of the Microbiota-Gut-Brain Axis: A Behavioural Perspective, *Frontiers in Neuroendocrinology* (2018), doi: https://doi.org/10.1016/j.yfrne.2018.04.002

The Neuroendocrinology of the Microbiota-Gut-Brain Axis: A Behavioural Perspective

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Invited Review: Frontiers in Neuroendocrinology

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Conflicts of interest:

JFC & TD have research funding from Mead Johnson Nutrition, Cremo, Dupont, Suntory Wellness, Danone-Nutricia and 4D Pharma; SC and KS report no financial interests or potential conflicts of interest.

Abstract

The human gut harbours trillions of symbiotic bacteria that play a key role in programming different aspects of host physiology in health and disease. These intestinal microbes are also key components of the gut-brain axis, the bidirectional communication pathway between the gut and the central nervous system (CNS). In addition, the CNS is closely interconnected with the endocrine system to regulate many physiological processes. An expanding body of evidence is supporting the notion that gut microbiota modifications and/or manipulations may also play a crucial role in the manifestation of specific behavioural responses regulated by neuroendocrine pathways. In this review, we will focus on how the intestinal microorganisms interact with elements of the host neuroendocrine system to modify behaviours relevant to stress, eating behaviour, sexual behaviour, social behaviour, cognition and addiction.

Keywords: neuroendocrine system, hormones, corticosterone, stress, HPA axis, eating behaviour, sexual behaviour, social behaviour, learning, addiction

1. Introduction

Our gut harbours trillions of symbiotic microorganisms that are essential and beneficial not only for the regulation of host physiology, but also for the appropriate development of central nervous system (CNS) and brain responses (Cryan and O'Mahony, 2011; Dinan and Cryan, 2013; Qin et al., 2010b). The microbiota-gut-brain axis is a bidirectional pathway through which the brain regulates the activity of the gut and *vice versa* and is critical for homeostasis of the host system (De Vadder et al., 2014; Dinan and Cryan, 2017; Holzer et al., 2012; Montiel-Castro et al., 2013; Rhee et al., 2009; Sherwin et al., 2017). A number of different mechanisms have been proposed in order to explain how the intestinal microbiota might influence the brain including the enteric nervous system (ENS: neurons in the intestine), the vagus nerve, inflammatory mediators, microbial metabolite production and the neuroendocrine system (Dinan et al., 2015; Mayer et al., 2015). Neural-endocrine interactions are also critical for regulating behavioural processes in the body in a system of neuroendocrine integration. A growing body of evidence is supporting the notion that the microorganisms present in the gut might interact with elements of the host neuroendocrine system therefore resulting in modifications of the host behaviour. Moreover, the gut microbiota produces several hormone-like metabolites that enter the circulation and act at distal sites and organs including the brain.

In this review, we will first provide a description of the neuroendocrine system and the microbiota-gut-brain axis and will focus on the mechanisms as to how the gut microbiota might influence neuroendocrine function. Furthermore, we will analyse the current scientific evidence on how the gut microbiota regulates different behavioural phenotypes via neuroendocrine integration, as summarised in *Table 1*. It is important to note that, as the majority of preclinical studies to date are performed in male animals, it is not always possible

to take into consideration the influence of sex differences in neuroendocrine-mediated behaviours. The different behavioural outcomes taken into consideration are as follows: stress-related behaviour, eating behaviour, sexual behaviour, social behaviour, cognition and addiction *(Fig.1)*. These behaviours have been selected for this review because they have been shown to be modulated by neuroendocrine routes (Bos et al., 2012; Carter, 1992; Kosten and Ambrosio, 2002; McCall and Singer, 2012; McEwen and Sapolsky, 1995; Murray et al., 2014; Sirinathsinghji, 1987; Smith et al., 2002; Tsigos and Chrousos, 2002b). The manuscript is organised in sections where each section corresponds to a behavioural outcome and the neuroendocrine component of each behaviour is also described.

Table 1. A list of correlations between gut microbiota, hormones and behaviour**.**

Host Response	*Species*	*Manipulation*	*Details*	*Reference*
Stress	Mouse	GF	GF mice show hyper-activation of HPA axis in response to restraint stress. Plasma ACTH and corticosterone are ↑ in GF compared to SPF mice. GF mice have ↓ BDNF expression levels in cortex and hippocampus	Sudo et al., 2004
			GF mice have ↓ anxiety-like behaviour and ↑ motor activity compared to SPF mice. GF mice also show altered expression of synaptic plasticity-related genes. However, plasma corticosterone is ↑ in GF mice, possibly indicating a stress response in GF mice to experimental conditions	Neufeld et al., 2011
			GF mice have ↓ anxiety-like behaviour, ↑ motor activity and ↑ corticosterone levels compared to normal mice	Diaz Heijtz et al., 2011
		FMT in GF	Colonization of GF mice with SPF microbiota early in life, but not at a later stage, restores the HPA functionality	Sudo et al., 2004
		CS + probiotic administration	2-week treatment with *L. helveticus* and *B. longum* attenuates HPA axis response to chronic stress. Plasma levels of corticosterone, adrenaline and noradrenaline are ↓ in stressed mice	Ait-Belgnaoui et al., 2014
		Probiotic administration	Chronic treatment with *L. rhamnosus* ↓ levels of stress-induced corticosterone levels and ameliorates anxiety-like behaviours thorugh the vagus nerve	Bravo et al., 2011
		Infection + Probiotic administration	Infection with *C. rodentium* induces stress-induced memory impairment that is prevented by a combination of *L. rhamnosus* and *L. helveticus.* Exposure to psychological stress ↑ serum corticosterone, which is ↓ by probiotics	Gareau et al., 2011
		Prebiotic administration	Sialyllactose administration ↓ intestinal microbial dysbiosis and anxiety-like behaviour induced by a stressor. This prebiotic, however, does not ↓ corticosterone levels	Tarr et al., 2015
			Chronic treatment with *FOS* and *GOS* ↓ stress-induced corticosterone release and improves anxiety- and depressive-like behaviour. Also gut microbiota composition is	Burokas et al., 2017

			normalised following treatment	
	Rat	MS + probiotic administration	*B. infantis* normalizes the immune response and behavioural deficits induced by MS but no differences in corticosterone concentrations between groups	Desbonnet et al., 2010
		Maternal probiotic administration	*B. animalis* and *P. jensenii* protect against immune dysfunction and disturbance of the gut microbiota provoked by MS and/or adult restraint stress. This combination also activates neonatal stress pathways (↑ neonatal corticosterone) which persists into adulthood (↑ ACTH)	Barouei et al., 2012
	Human	Probiotic administration	*L. helveticus* and *B. longum* in combination ↓ urinary cortisol levels suggesting an attenuation of HPA axis response to stressors	Messaoudi et al., 2011
		Prebiotic administration	*GOS* ↓ waking salivary cortisol levels	Schmidt et al., 2015
	Rhesus monkey	MS	MS causes a disruption of the gut microbiota and associated stress-like behaviour but does not alter cortisol secretion	Bailey and Coe, 1999
Eating behaviour and obesity	Mouse	Prebiotic administration +/- HFD	In normal mice, FOS ↓ epididymal fat mass and ↑ plasma GLP-1. In high-fat-fed mice, FOS ↓ energy intake, body weight, glycemia and epididymal fat mass	Delmee et al., 2006
		Prebiotic administration + HFD	β-glucan and inulin ↓ weight gain in high-fat fed mice	Arora et al., 2012
		Probiotic administration	VSL#3 ↓ weight gain and food intake. Glucose tolerance improves. GLP-1 levels ↑	Yadav et al., 2013
		GF	GF mice have ↓ total body fat than conventionally raised mice. Recolonization of GF mice ↑ body fat content and insulin resistance	Backhed et al., 2004
			GF mice have ↑ preference of fat intake. Intestinal levels of CCK, PYY and GLP-1 are ↓	Duca et al., 2012
	Rat	GF	Autoantibodies directed against appetite-regulating peptides are ↓ in GF rats compared to SPF rats	Fetissov et al., 2008
		Prebiotic administration	Inulin-type fructans ↓ food intake, body weight and fat mass. Plasma levels of ghrelin	Cani et al.,

			are ↓	2004
		Probiotic administration	Lactobacillus strains ↓ food intake. PYY levels ↑	Forssten et al., 2013
	Human	Administration of propionate-augmenting compound	Colonic propionate ↓ reward-based eating behaviour. Effect not accompanied by alterations in levels of PYY and GLP-1	Byrne et al., 2016
		Prebiotic administration	Oligofructose ↑ weight loss and improve glucose toleration in overweight adults. Ghrelin levels ↓ and PYY levels ↑	Parnell and Reimer, 2009
			Oligofructose ↑ satiety following breakfast and dinner and ↓ hunger following dinner. Mechanisms not fully understood, but it is known that oligofructose ↑ GLP-1 release	Cani et al., 2006
		Probiotic administration	*L. rhamnosus* CGMCC1.3724 ↑ weight loss in obese ♀. Circulating leptin ↓	Sanchez et al., 2014
		Probiotic administration in ♀	Probiotics ↓ body weight gain in Iraqi obese ♀. PYY levels ↑, ghrelin levels ↓	Alajeeli, 2016
Sexual behaviour	Rat	GF	GF rats do not have discriminative urinary odours needed for mating	Singh et al., 1990
	Locust	GF	Gut bacteria are responsible for the production of guaiacol, a key component of pheromones. Faecal pellets of GF locusts smell different from faecal pellets of normal locusts	Dillon et al., 2000, 2002
	Drosophila melanogaster	Antibiotic administration	Symbiotic bacteria influence mating preference by modulating levels of cuticular hydrocarbon sex pheromones. As a confirmation, antibiotic treatment abolishes the mating preference	Sharon et al., 2010
Social behaviour	Mouse	Antibiotic administration in adolescence	Antibiotic-treated mice have ↓ mRNA expression of oxytocin and vasopressin in the hypothalamus, ↓ anxiety, ↓ non-spatial memory and impaired performance in the social transmission of food preference test	Desbonnet et al., 2015
		HFD during pregnancy, probiotic administration	Offspring of high-fat-fed mothers have ↓ oxytocin immunoreactive neurons in the hypothalamus accompanied by social behavioural deficits and altered gut microbiome.	Buffington et al., 2016

			Administration of *L. reuteri* to the offspring improves sociability	
Learning and memory	Mouse	GF	GF mice display absence of non-spatial and working memory. Psychological stress ↑ serum corticosterone, which is ↓ by probiotics	Gareau et al., 2011
		Infection + probiotic administration	*C. rodentium* causes stress-induced impairment in memory. Pre-treatment of *C. rodentium*-infected mice with a combination of *Lactobacillus*-containing probiotics prevents stress-induced memory deficits and ameliorates serum corticosterone levels	Gareau et al., 2011
			L. rhamnosus enhances memory to an aversive cue and context and ↓ corticosterone	Bravo et al., 2011
		Antibiotic administration in adolescence	Antibiotic treatment induces non-spatial memory deficits and ↓ oxytocin mRNA levels (in the hypothalamus)	Desbonnet et al., 2015
Addiction	Mouse	GF	GF mice have ↑ HPA response. As stress is a major risk factor for addiction, this might be relevant for addiction	Sudo et al., 2004
			GF mice have ↓ levels of dopamine in the caecum compared to SPF mice. As dopamine is a central neurotransmitter involved in reward pathways, this might be relevant for addiction	Asano et al., 2012
		Antibiotic administration	Antibiotic-treated mice have ↓ mRNA expression of oxytocin in the hypothalamus. Given that oxytocin is a key neurotransmitter involved in addiction pathways, this might be relevant for addiction	Desbonnet et al., 2015
			Antibiotic-treated mice have ↑ sensitivity to cocaine reward	Kiraly et al., 2016

Abbreviations: ↑ increase, ↓ decrease, *AA* arachidonic acid, *ACTH* adrenocorticotropic hormone, *BDNF* brain-derived neurotrophic factor, *CCK* cholecystokinin, *CS* chronic stress, *DHA* docosahexaenoic acid, *FMT* faecal microbiota transplantation, *FOS* fructooligosaccharide, *GF* germ-free, *GLP-1* glucagon-like peptide-1, *GOS* galactooligosaccharide, *HFD* high-fat diet, *HPA* hypothalamic–pituitary–adrenal axis, *MIA* maternal immune activation, *MS* maternal separation, *PNS* prenatal stress, *PYY* peptide YY, *SPF* specific-pathogen-free, *VPA* valproic acid.

2. Neuroendocrine System

The nervous and endocrine systems are intricately connected to each other and are responsible for the regulation of various physiological processes in the human body. This neuroendocrine system has a crucial role in developmental processes and tissue function, and it is composed of the hypothalamus, pituitary gland and target organs. For the scope of this review, we will take into consideration four of the six major neuroendocrine pathways: the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–thyroid axis (HPT), the hypothalamic–pituitary–gonadal axis (HPG) and the hypothalamic–neurohypophyseal axis (HN). Two more pathways, the hypothalamic-pituitary-liver axis and the hypothalamic-pituitary-prolactin axis, also form the neuroendocrine system but will not be covered in this review due to the scarce evidence linking these to the gut microbiota.

In this section, we will briefly describe the main features of the HPA, HPT, HPG and HN axes and function of related hormones.

2.1 Hypothalamic–Pituitary–Adrenal Axis (HPA)

The HPA axis is one of the main neuroendocrine systems in the human body. In the presence of an external stimulus, neuroendocrine neurons in the paraventricular nucleus (PVN) of the hypothalamus synthesize and secrete vasopressin and corticotrophin-releasing factor (CRF) (Del Rey, 2008). These two peptides stimulate the secretion of adrenocorticotropic hormone (ACTH) from the corticotropic cells of the pituitary gland. As a result of ACTH secretion, the adrenal cortex produces glucocorticoid hormones: cortisol in humans and corticosterone in rodents (Stephens and Wand, 2012). These two hormones in turn act back on the hypothalamus and pituitary gland in a negative feedback cycle. The HPA represents the main coordinator of stress response, but it also regulates other body processes such as digestion, immune system, mood, emotions, sexuality, and energy expenditure (Del Rey, 2008). When a

threat is perceived, the HPA axis mounts a defensive response and restores the homeostatic balance in the organism (de Kloet et al., 2005; Frodl and O'Keane, 2013; McEwen, 2007; Sapolsky, 1996). The activation of the HPA axis ultimately results in the release of behaviour-altering glucocorticoids, mineralocorticoids and catecholamines (Smith and Vale, 2006a; Tsigos and Chrousos, 2002a). The activity of the HPA axis is regulated by several afferent sympathetic, parasympathetic, and limbic circuits (*e.g.* amygdala, hippocampus, and prefrontal cortex) innervating either directly or indirectly the PVN (Smith and Vale, 2006a). Interestingly, under physiological conditions the HPA axis has a continuous oscillatory activity synchronized with circadian and ultradian rhythms (Dallman et al., 1994; Dickmeis et al., 2013; Tsigos and Chrousos, 2002a). In the presence of a stressful stimulus, glucocorticoids enter the brain and bind to the mineralocorticoid receptors and glucocorticoid receptors. Receptors sensitive to glucocorticoids are expressed throughout the CNS including in the same brain regions involved in the mounting of a stress-mediated neuroendocrine response (Sapolsky et al., 1984). Interestingly, the HPA has been shown to interact with both the immune system (Leonard, 2005) and the gonadal axis (Viau, 2002). In the early 1990s, it became apparent that cytokines and other humoral mediators of inflammation are strong activators of the central stress response, forming the afferent branch of a feedback loop through which the immune/inflammatory system and the CNS communicate (Chrousos, 1995). For instance, the three inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) are known to activate the HPA axis (Chrousos 1995; Tsigos, 1997). Moreover, components of the HPA axis can inhibit the gonadal system, indeed CRF is able to suppress the GnRH (gonadotropin-releasing hormone) neurons of the hypothalamus *(see section 2.3)* (Chrousos et al., 1998).

2.2 Hypothalamic–Pituitary–Thyroid Axis (HPT)

The HPT axis is one of the central regulators of metabolism in the human body. When the hypothalamus senses low circulating levels of thyroid hormones [triiodothyronine (T_3) and thyroxine (T_4)], it releases thyrotropin-releasing hormone (TRH). The TRH acts on the pituitary gland and stimulates thyrotropic cells to produce thyroid-stimulating hormone (TSH). The TSH, in turn, stimulates the thyroid to produce T_3 and T_4 until levels in the blood return to normal (Zoeller et al., 2007). The major portion of T_3, however, is produced in peripheral organs such as liver, adipose tissue, glia and skeletal muscle by deiodination of circulating T_4. The deiodination process is controlled by several hormones and neurotransmitters including TSH, vasopressin and catecholamines (Mariotti and Beck-Peccoz, 2000). Thyroid hormones regulate the hypothalamus and the anterior pituitary gland via a negative feedback loop. They also directly affect metabolism, cardiovascular system and development. For instance, T_3 and T_4 are able to increase the basal metabolic rate and induce effects on almost all body tissues (Hall, 2011). Moreover, they influence appetite, absorption of substances (especially glucose) and gut motility. Thyroid hormones stimulate the breakdown of fats and also decrease cholesterol levels, by increasing the rate of secretion of cholesterol in bile (Hall, 2011). The cardiovascular effects of thyroid hormones include an increase in the rate and strength of the heartbeat, an increase in oxygen consumption, and an increase the activity of mitochondria (Hall, 2011). Finally, thyroid hormones have been proven to be essential for brain maturation and brain function throughout life (Bernal, 2000). Indeed, thyroid diseases in adults can lead to several clinical manifestations (Joffe and Sokolov, 1994). Thyroid hormones function by crossing the cell membrane and binding to intracellular receptors called 'thyroid hormone receptors' (TR; *e.g.* TR-α1, TR-α2, TR-β1, TR-β2). These receptors, together with corepressor molecules, bind DNA regions termed 'thyroid hormone response elements' (TREs) localised near genes and modulate gene transcription. This eventually leads to changes in cell function (Hall, 2011).

2.3 Hypothalamic–Pituitary–Gonadal Axis (HPG)

The HPG axis comprises of the hypothalamus, pituitary gland, and gonadal glands. This neuroendocrine axis plays a critical part in the development and regulation of different body processes, mainly the reproductive and immune systems (Corradi et al., 2016). Variations in this system can result in altered hormone production by the ovaries/testes resulting in different local and systemic effects. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) and, as a result of that, gonadotropic cells from the anterior pituitary gland produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH send signals to the gonads and trigger testosterone and estrogen production in the testes and ovaries. One of the most important functions of the HPG axis in females is to regulate reproduction by controlling the uterine and ovarian cycles (Plant, 2015). In females, the positive feedback between estrogen and LH helps to prepare the follicle in the ovary and the uterus for ovulation and implantation. Moreover, the activation of the HPG axis in both males and females during puberty induces individuals to acquire secondary sex features (Plant, 2015). In males, FSH and LH stimulate the production of testosterone, a hormone required for normal spermatogenesis (Huang et al., 2001; Walker and Cheng, 2005). At birth, FSH and LH levels are elevated with females having a lifetime supply of primary oocytes. High levels of estrogen and testosterone released from testes and ovaries inhibit the production of GnRH from the hypothalamus through a negative-feedback loop (Whirledge and Cidlowski, 2010). Moreover, sex steroids are also known to modulate brain function, development and behaviour (Vadakkadath Meethal and Atwood, 2005). Testosterone levels, for example, have been shown to relate to prosocial behaviour (Wibral et al., 2012). As mentioned in *section 2.1,* the HPG is also connected and influenced by the HPA axis (Viau, 2002).

2.4 Hypothalamic–Neurohypophyseal Axis (HN)

The posterior pituitary (or neurohypophysis) comprises a collection of axonal projections coming from the hypothalamus which secretes the hormones oxytocin and vasopressin into the neurohypophyseal capillaries, from where they reach the systemic circulation (Phelps, 2007). In addition to axons, the posterior pituitary also contains pituicytes, specialized glial cells assisting in the storage and release of the hormones (Hatton, 1988).

Oxytocin is a peptide hormone that has both peripheral and central action, which is mediated by specific oxytocin G-protein-coupled receptors. This hormone is crucial for stimulation of milk ejection, uterine contractions during labour and plays a key role in several behaviours including social recognition, pair bonding, anxiety and maternal behaviours (White BA, 2013). Oxytocin is a key mediator of social bonding (Carter et al., 1992). In humans oxytocin has been linked to parental behaviour and parent-infant bonding. For example, high endogenous oxytocin levels peri-partum are associated with increased mother-infant bonding (Feldman et al., 2007). Especially because of its role in mediating social behaviours, oxytocin has been implicated in the aetiology of autism (Jacob et al., 2007; Wermter et al., 2010). Finally, a large body of evidence links oxytocin to stress regulation. In rodents, peripheral and central oxytocin levels have been found to increase in response to a wide variety of stressful stimuli, such as conditioned fear stimuli and restraint stress (Neumann et al., 2000; Onaka, 2004). In humans, an increase in plasma oxytocin was found in response to several types of psychosocial stressors (Hoge et al., 2008; Marazziti et al., 2006; Taylor et al., 2010). Moreover, oxytocin administration in humans was able to decrease the subjective stress ratings (Heinrichs et al., 2003) as well as increase the parasympathetic cardiac control (Norman et al., 2011) and decrease the salivary cortisol levels (Ditzen et al., 2009; Linnen et al., 2012). Given the beneficial roles of oxytocin in social bonding and stress regulation, this hormone might be a promising therapeutic target for psychiatric symptoms (Striepens et al., 2011).

Vasopressin is responsible for the regulation of the body's water retention. When the body is dehydrated, vasopressin is released from axon terminals in the posterior pituitary and causes the kidneys to conserve water, thus concentrating the urine and reducing urine volume (Sands et al., 2011). In addition to this peripheral function, vasopressin in the brain acts in conjunction with CRF to modulate the release of corticosteroids from the adrenal gland in response to stress, particularly during pregnancy and lactation in mammals (Goland et al., 1991; Ma et al., 2005; Toufexis et al., 1999).

3. Gut Microbiota

As stated earlier our gut houses a staggering amount of microorganisms that estimates consider contains 150 times as many genes as our genome (Qin et al., 2010a). This population is mainly composed of bacteria belonging to 500-1000 different species (Qin et al., 2010a). Fungi, archaea, and viruses are also present in the gut but less is known about their underlying functions. The intestinal microbiota does not remain stable throughout lifespan, in fact the microbiota of newborn infants, acquired at delivery, is characterised by low diversity and a relative dominance of the phyla Proteobacteria and Actinobacteria (Kurokawa et al., 2007). The microbial composition of the neonatal gut is influenced by a number of factors including antibiotic use, diet, mode of delivery, environmental factors and the maternal microbiota (Dominguez-Bello et al., 2010; Faa et al., 2013; Koenig et al., 2011; Marques et al., 2010). Interestingly, the microbiota of formula-fed infants is significantly different from the microbiota of breastfed infants (Bezirtzoglou et al., 2011; Lee et al., 2015; Wang et al., 2015). Moreover, vaginally delivered infants acquire the vaginal microbiota of the mother, whereas infants delivered by caesarean section are colonised by other environmental sources (Dominguez-Bello et al., 2010). In the first months of life, the number of strict anaerobes such as *Clostridium*, *Bacteroides* and bifidobacteria increases gradually and after 1 year of age a complex adult-like microbiota is established. The adult microbiota is

more stable over time and more complex than the neonate microbiota (Hamady and Knight, 2009).

4. Microbiota-Gut-Brain Axis

The microbiota-gut-brain axis is a bidirectional pathway through which the brain regulates the activity of the gut and *vice versa*. This bidirectional axis functions through a series of different routes (Bercik et al., 2012; Dinan et al., 2015; Rhee et al., 2009) and comprises an afferent and an efferent pathway.

4.1 Afferent Signalling

The vagus nerve, the tenth cranial nerve that has both efferent and afferent divisions, is a major modulatory constitutive communication pathway between the bacteria exposed to the gut and the brain (Bercik et al., 2011b; Bravo et al., 2011). The immune system provides a further route of communication between gut microbes and the brain, in fact microbiota and probiotics have a direct effect on the immune system (Duerkop et al., 2009b; Forsythe and Bienenstock, 2010). Symbiotic bacteria are crucial for the maturation of the immune system in fact, they provide signals for the development of key lymphocyte subsets (Edelman and Kasper, 2008). Moreover, gut bacteria contribute to intestinal epithelial cell maturation and can induce alterations in the circulating levels of pro- and anti-inflammatory cytokines that directly affect brain function, especially areas such as the hypothalamus, where IL-1 and IL-6 provide a potent release of CRF (Duerkop et al., 2009a). Gut bacteria contribute to the host metabolism by production of metabolites such as bile acids, choline and short chain fatty acids (SCFAs, namely acetic propionic and butyric acid) that are able to influence a range of physiological and metabolic functions (De Vadder et al., 2014). The free SCFAs are also able to cross the blood-brain barrier (BBB) through monocarboxylate transporters and act in several brain regions (Tan et al., 2014). Although it remains to be established whether the

microbiota can produce neuropeptide-like compounds, it is capable of generating a number of neurotransmitters and neuromodulators (Cryan and Dinan, 2012; Nicholson et al., 2012). Members of the genera *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* synthesize 5-hydroxytryptamine (5-HT); members of the genera *Escherichia*, *Bacillus* and *Saccharomyces* generate dopamine and/or noradrenaline; members of the genus *Lactobacillus* produce acetylcholine; and members of the genera *Lactobacillus* and *Bifidobacterium* produce gamma-aminobutyric acid (GABA) (Barrett et al., 2012; Cryan and Dinan, 2012; Lyte, 2014; Nicholson et al., 2012; Wall et al., 2014). An example of the connection of the gut microbiome with the host neurophysiological systems is a study showing that the excitability of gut sensory neurons located within the myenteric plexus of the ENS relies on the presence of the normal commensal microbiota for proper functioning (Neufeld et al., 2011). Several studies have suggested that another mechanism involved in the gut-brain communication is tryptophan metabolism. Tryptophan is an essential amino acid and is a precursor to many biologically active agents, such as serotonin (Ruddick et al., 2006). Most of the tryptophan is metabolised to kynurenine and the disruption of this metabolic pathway has been linked to both gastrointestinal and brain disorders (Fitzgerald et al., 2008). The first rate-limiting step in the kynurenine metabolic cascade is catalysed by some enzymes (specifically indoleamine-2,3-dioxygenase and tryptophan 2,3-dioxygenase) whose activity can be induced by inflammatory mediators and by corticosteroids, respectively (Ruddick et al., 2006). Evidence suggests that a probiotic bacterium, *Bifidobacterium infantis*, can alter concentrations of kynurenine through modulation of the gut microbiota (Desbonnet et al., 2008). Another class of molecules, gut-derived peptides, can reach the systemic circulation and bind receptors on immune cells and vagus nerve terminals thereby enabling indirect gut-brain communication (Lach et al., 2017).

4.2 Efferent Signalling

The HPA axis represents the main efferent route from the brain to the gut. When activated, the resulting secretion of cortisol (in humans) or corticosterone (in rodents) affects immune cell activity; both locally in the gut and systemically (Del Rey, 2008). Neuronal efferent activation includes also the efferent branch of the vagus nerve that, when activated induces a release of acetylcholine which, in turn, affect the levels of cytokines (Paton et al., 1971).

Some of the key communication routes of the gut-brain axis are thought to be responsible for the communication between the gut microbiota and neuroendocrine function and will be examined exhaustively in the following chapter.

5. How does Gut Microbiota affect Neuroendocrine Function?

The mechanisms through which the gut microbiota might influence neuroendocrine function and consequently host behaviour have not yet been fully deciphered. However, increasing evidence suggests that the gut microbiota acts through direct production of neuroendocrine metabolites (hormone-like metabolites such as SCFAs, neurotransmitters, GI hormones, precursors to neuroactive compounds such as tryptophan & kynurenine) and, indirectly, as modulator of inflammatory responses, immune responses and hormonal secretion *(Fig. 2)*.

In this section, we will describe different mechanisms as to how the gut microbiota modulates neuroendocrine function.

5.1 Short Chain Fatty Acids

Butyric, propionic and acetic acids are the main short chain fatty acids (SCFAs) produced by bacterial fermentation of proteins and carbohydrates in the intestine (Macfarlane and Macfarlane, 2012) and their molar ratios in the colon are approximately 20:20:60

(Cummings, 1981). SCFAs act as direct mediators between the gut and the brain in fact they circulate far from their production site and are carried by monocarboxylate transporters, which are expressed also on the blood-brain barrier (BBB) (Kekuda et al., 2013; Nisha Vijay, 2015). Among the SCFAs, propionic acid is able to activate the FFAR3 (free fatty acid receptor 3) and exerts beneficial effects on body weight control and glucose metabolism (De Vadder et al., 2014). Increasing evidence is suggesting that SCFAs can directly affect brain function and behaviour. Interestingly, both butyric and propionic acid affect dopamine and noradrenaline synthesis via increase of tyrosine hydroxylase gene expression (DeCastro et al., 2005; Nankova et al., 2014; Stilling et al., 2016). Furthermore, propionic acid has also been shown to modulate serotonergic neurotransmission (Nankova et al., 2014) and lower levels of GABA, serotonin and dopamine *in vivo* (El-Ansary et al., 2012). The ability of SCFAs to directly influence neurotransmitters' synthesis and to inhibit the histone deacetylases may be responsible for their behavioural effects (Donohoe et al., 2012; Matis et al., 2013). In fact, one of the most recognised cellular mechanism of action of butyrate is its ability to inhibit the histone deacetylases (Kruh, 1982). Indeed, when administered systemically, sodium butyrate induced a transient histone acetylation in the frontal cortex and hippocampus, resulting in an antidepressant-like behaviour (Schroeder et al., 2007). Intriguingly, gut-derived SCFAs have also been shown to affect the maturation and function of microglia, the resident macrophages of the central nervous system (CNS) (Erny et al., 2015; Huuskonen et al., 2004). Thus, germ-free mice (born and raised in a sterile environment) display global deficits in microglia with altered cell proportions and an immature phenotype; while mice deficient for the SCFA receptor FFAR2 do not present alterations in microglia cell densities but have malformed microglia, with alterations in dendrite length, number of segments and cell volumes (Erny et al., 2015). Interestingly, long-term SCFAs treatment was able to reverse the microglia deficits present in germ-free mice (Erny et al., 2015). Similarly, dietary modulation of SCFAs was able to attenuate blood-brain barrier deficits in germ-free mice (Braniste et al., 2014). As

microglia are crucial for the shaping of neural circuits in the developing brain (Bilimoria and Stevens, 2015), gut-derived SCFAs might have some relevance in circuits regulating the CNS and hypothalamic function. Importantly, SCFAs are also directly implicated in the release of hormones and neuropeptides, such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) from intestinal enteroendocrine cells (Rooks and Garrett, 2016), all of which we will discuss in *Section 5.3*.

5.2 Neurotransmitters and Tryptophan Metabolism

The gut microbiota produces different neurotransmitters such as dopamine, noradrenaline and ɣ-aminobutyric acid (GABA) (Roshchina, 2016) that can enter the circulation and potentially reach distal sites. Neurotransmitters influence hypothalamic function and the major neuroendocrine axes in the host, therefore the gut-mediated production/regulation of these neurotransmitters may play a crucial role in neuroendocrine function. Noradrenaline (NA) and dopamine (DA) are two crucial neurotransmitters that regulate many physiological processes in the brain and the body. Levels of both the neurotransmitters have been shown to be reduced in the caecum of germ-free mice compared to the SPF mice (Asano et al., 2012), which suggests that the gut microbiota is a potential source of catecholamines. These results suggest that there might be a correlation between intestinal bacteria and dopamine levels in conditions such as Parkinson's disease, characterized by insufficient dopamine production in the brain. Moreover, *Helicobacter pylori* has been shown to affect L-DOPA levels (Pierantozzi et al., 2006) and neurologic improvement has also been reported in one patient with Parkinson's disease after faecal transplantation for chronic constipation (Ananthaswamy, 2011). However, it is unlikely that these microbial-derived catecholamines have any effect at a central level, as they are not able to cross the BBB (blood-brain barrier). Nevertheless, the microbiota also appear to be able to modulate central catecholaminergic neurotransmission. Analysis of cerebral metabolites from GF mice showed lower levels of the amino acid

tyrosine (the rate-limiting substrate for NA and DA synthesis) in comparison with ex-germ-free animals. This induced a greater level of DA in the brains of GF mice, suggesting that the gut microbiota is able to modulate the central levels of catecholamines (Matsumoto et al., 2013). Another study from Nishino and colleagues also confirmed the same (Nishino et al., 2013).

Some intestinal bacteria are also able to produce ɣ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the CNS that is also associated to pathological scenarios such as depression and anxiety (Mohler, 2012). Human intestinally-derived strains of *Lactobacillus* and *Bifidobacterium* have been shown to produce GABA, with *L. brevis* and *B. dentium* being the most efficient GABA producers among the strains tested (Barrett et al., 2012). GABA transporters are localized on the blood-brain barrier (BBB) and allow gut-derived GABA to reach the CNS (Takanaga et al., 2001). Moreover, administration of *L. rhamnosus* to mice altered the expression of GABA receptors in different brain regions, resulting in a decrease of anxiety- and depressive-like behaviour (Bravo et al., 2011). Whether the peripherally derived GABA is capable of crossing the BBB either through diffusion or through active transport remains a matter of dispute (Boonstra et al., 2015). According to Takanaga and colleagues (Takanaga et al., 2001), GABA transporters are expressed at the BBB and this might be a mechanism through which microbial-derived GABA reaches the brain.

Interestingly, some intestinal microbes are able to metabolise tryptophan, the precursor of serotonin (5-HT), an important neurotransmitter involved in adaptive responses of the CNS. The first direct effect of microbiota on 5-HT was demonstrated in germ-free mice, which have lower plasma levels of this neurotransmitter than conventional mice (Clarke et al., 2013; Wikoff et al., 2009). This might be due to reduction in the expression of tryptophan hydroxylase, the rate-limiting enzyme in 5-HT synthesis (Yano et al., 2015). Interestingly, the increase in tryptophan levels in germ-free mice was correlated with increased serotonin

levels and serotonin turnover in the hippocampus in a sex-dependent manner. Indeed, this effect was seen only in male germ-free mice, suggesting that the oestrous cycle might have affected the serotonergic system (Clarke et al., 2013). We have shown that chronic administration of *B. infantis* in rats was able to increase the plasma tryptophan levels and decrease the kynurenine-to-tryptophan ratio, suggesting a reduced activity of IDO in the probiotic-treated rats (Desbonnet et al., 2008). Moreover, the administration of *Lactobacillus johnsonii* in rats has been shown to lower circulating kynurenine levels with concomitant increase in serotonin levels (Valladares et al., 2013). Also *Streptococcus*, *Enterococcus* and *Escherichia* are able to produce 5-HT (Roshchina, 2016). Interestingly, data from our laboratory have shown that faecal microbiota transplantation from depressed patients into healthy rats caused a dysregulation in tryptophan metabolism as indicated by increased plasma kynurenine-to-tryptophan ratio (Kelly et al., 2016). In addition, the transplanted rats showed a significant increase in both circulating and central kynurenine metabolite levels, which were similar to levels reported in autism, schizophrenia, depression and neurodegenerative diseases (McFarlane et al., 2008; Schwarcz et al., 2012).

In the context of microbiota-derived neurotransmitters and brain function, there still is much work needed to tease apart the relative contribution of alterations in peripheral levels of such neurotransmitters either directly or indirectly on neuroendocrine function.

5.3 Enteroendocrine Signalling

Enteroendocrine cells (EECs) are broadly distributed throughout the gastrointestinal tract and exert regulatory effects on the bidirectional communication between the gut and the brain. EEC secretory products are released in response to diverse stimuli and influence a variety of physiological functions in the host such as control of intestinal secretion and motility, regulation of food intake and metabolism (Rehfeld, 2004). Hormones and peptides secreted by EECs act on receptors located on the vagal afferent pathways that bring stimuli to the

brain, specifically the nucleus tractus solitarii (NTS) (Raybould, 2010b). The main hormones secreted by EECs are cholecystokinin (CCK), peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). CCK and PYY are mainly secreted in response to fat and proteins ingestion, while GLP-1 is secreted after intake of carbohydrates and fats (Cummings and Overduin, 2007). Interestingly, there is a body of evidence suggesting that intestinal microbes modulate the secretion of these hormones, either directly or indirectly through production of SCFAs. Germ-free mice, have alterations in the number of EECs and lower levels of PYY, GLP-1 and CCK compared to conventionally colonized mice (Duca et al., 2012). Moreover, intestinal infusion of *E. coli* proteins was able to increase plasma PYY and GLP-1 levels enhancing satiety (Breton et al., 2016). Breton and colleagues have also suggested that caseinolytic protease B (ClpB), a protein produced by *E. coli*, might be responsible for the elevated secretion of satiety peptides from EECs. Finally, short chain fatty acids (SCFAs), whose production is in part mediated by intestinal microbes, bind to their receptors (FFAR1 and FFAR3) expressed on EECs and stimulate the secretion of peptides/hormones (Bellono et al., 2017; Nohr et al., 2013; Swartz et al., 2012).

5.4 Immune Signalling

The contribution of the gut microbiota as stimulator of the immune system is being widely investigated. Lipopolysaccharide (LPS), a constituent of the outer membrane of Gram-negative bacteria and activator of the Toll-like receptor 4 (TLR4), has been suggested to cross the intestinal epithelial barrier in response to certain conditions such as stress (Maes et al., 2008) or a high-fat diet (Cani et al., 2008; Moreira et al., 2012), leading to immune and HPA axis activation. Interestingly, while LPS is able to acutely activate the immune system and HPA axis, exposure of newborn rodents to these factors is able to induce long-lasting effects. Some evidence showed that neonatal exposure to LPS leads to elevated ACTH and corticosterone responses to restraint stress and a decreased glucocorticoid feedback inhibition

in adulthood (Shanks et al., 1995). Concordantly, neonatal LPS exposure decreases cerebral glucocorticoid-receptor density, whereas CRF expression is increased (Shanks et al., 1995). Moreover, neonatal exposure to LPS induces enhanced prostaglandin-mediated HPA axis reactivity to LPS in adulthood (Mouihate et al., 2010).

5.5 Vagus Nerve

The vagus nerve has received much attention as a conduit of signals from the gut to the brain and vice versa (Goehler et al., 2000; Goehler et al., 1999; Goehler et al., 2005). Intestinal microbes are able to interact with the CNS through the vagus nerve and control the production and/or release of neurotransmitters (Sivamaruthi et al., 2015). The neurochemical and behavioural effects of *Lactobacillus rhamnosus* administration were absent in vagotomised mice, identifying the vagus as a major modulatory pathway between gut bacteria and the brain (Bravo et al., 2011). Interestingly another probiotic, *L. reuteri*, was shown to enhance wound healing in mice by increasing central levels of oxytocin through a vagal pathway (Poutahidis et al., 2013), strengthening the concept that this nerve directly links the gut to the hypothalamic-neurohypophyseal axis. Moreover, transient inactivation of the dorsal vagal complex was shown to decrease social deficits that were induced by LPS administration (Marvel et al., 2004). Vagal afferent signaling has also been implicated in the modulation of emotional behaviour, anxiety and fear. For example, a reduced anxiety-like behaviour was shown in rats that underwent subdiaphragmatic vagal deafferentation and this was associated with region-dependent changes in noradrenaline and ɣ-aminobutyric acid (GABA) levels in key areas of the limbic system, but not with functional alterations in the HPA axis (Klarer et al., 2014). In addition to this, the anxiolytic effect of *Bifidobacterium longum* was blocked by vagotomy (Bercik et al., 2011b). However, when oral antimicrobials were administered to SPF mice, consequent changes in microbiota composition and anxiety-like behaviour were not mediated by vagal pathways (Bercik et al., 2011a). The most

important function played by the vagus nerve in the context of gut microbiota and endocrine function is its role as conduit of signals. As mentioned in *Section 5.3,* hormones and peptides secreted by EECs activate vagal afferent pathways (Bonaz et al., 2018; Maniscalco and Rinaman, 2018; Raybould, 2010b) however, it is unclear how the brain might "decipher" the information coming from the gut.

6. Gut Microbiota and Stress

The first scientific publication on "general adaptation syndrome", or as we know today "biologic stress" has been published in Nature in 1936 by the 29-year old Hans Selye. Selye described stress as a nonspecific and predictable response of the body to demands placed upon it (Szabo et al., 2017). Stress is a condition in which the homeostasis of an organism is disturbed by a threat that might be real or perceived (De Kloet et al., 1994; McEwen et al., 2015). While fear is the physiological response to a real threat, anxiety is an overreaction to a situation that is only subjectively perceived as menacing and is characterized by disproportionate feelings of fear (Sylvers et al., 2011). When anxiety becomes so overwhelming that normal daily functioning is impeded, it can be diagnosed as psychiatric disorder. Once a stressful stimulus is perceived and the homeostasis disturbed, an organism is able to restore its steadiness through the activation of the HPA axis and sympathetic-adrenomedullary axis, which ultimately induces the release of behaviour-altering hormones such as glucocorticoids, mineralcorticoids and catecholamines (Kudielka et al., 2004; Smith and Vale, 2006a). The gut microbiota mediates the production of immune mediators such as TNF-α, IL-1β and IL-6 that, in turn, reach the brain and stimulate the HPA axis (*Fig.3*). Moreover, the gut microbiota is able to directly influence the production of glucocorticoid hormones (Mukherji et al., 2013). Mukherji and colleagues have shown that the interaction between bacterial products and Toll-like receptors (TLR) expressed on the intestinal epithelium is crucial for maintaining homeostatic levels of corticosterone, in fact microbiota-depleted mice have exaggerated and sustained synthesis of corticosterone throughout the day (Mukherji et al., 2013). From a behavioural point of view, different stressors are able to evoke in the host the so-called fight-or-flight response (Jansen et al., 1995).

The activity of the HPA axis is regulated by multiple afferent sympathetic, parasympathetic, and limbic circuits (e.g., amygdala, hippocampus, and medial prefrontal cortex) innervating

either directly or indirectly the paraventricular nucleus (PVN) of the hypothalamus (Smith and Vale, 2006b). In response to stress, the sympathetic nervous system (SNS) increases the release of catecholamines into systemic circulation, while CRF is released from paraventricular neurons of the hypothalamus, which then stimulate the activation of the HPA axis ultimately resulting in a release of glucocorticoids from the adrenal cortex. Glucocorticoids ultimately reach the brain and mediate their effects through high affinity mineralocorticoid receptors and lower affinity glucocorticoid receptors, the latter being activated at higher stress intensity (Herman et al., 2016).

It has been shown that different types of psychological stressors including maternal separation, chronic social defeat, physical restraint and overcrowding can alter the gut microbiota composition (Bailey, 2014; Bailey et al., 2011; Bharwani et al., 2016; De Palma et al., 2015; De Palma et al., 2014; Hsiao et al., 2013; Moloney et al., 2014). The milestone paper by Sudo and colleagues was instrumental in linking a role for the gut microbiota in stress responses. In this study, germ-free mice exhibited altered HPA axis function, with elevated levels of plasma adrenocorticotropic hormone (ACTH) and corticosterone in comparison with specific pathogen free (SPF) mice in response to restraint stress (Sudo et al., 2004). Germ-free mice also had reduced brain-derived neurotrophic factor (BDNF) expression levels in the cortex and hippocampus when compared to SPF mice. Moreover, the recolonisation of germ-free mice with SPF microbiota early in life, but not at a later stage, was able to restore the HPA axis functionality. This suggests that there are functional windows when the exposure to indigenous microbiota is required for normal development of the HPA axis (Sudo et al., 2004). Several other studies have confirmed that germ-free animals have high levels of ACTH and corticosterone following a stressful stimulus (Clarke et al., 2013; Crumeyrolle-Arias et al., 2014; Neufeld et al., 2011; Sudo et al., 2004). In the absence of a stressful stimulus, germ-free mice display an anxiolytic-like phenotype. Indeed, germ-free mice have an increased motor activity and reduced anxiety, compared with SPF

mice with a normal gut microbiota (Diaz Heijtz et al., 2011). Around the same time, Neufeld and colleagues showed that germ-free mice have reduced anxiety-like behaviour compared to SPF (specific-pathogen free) animals, however, plasma corticosterone levels were higher in GF than SPF mice, possibly indicating a stress response in GF mice to experimental conditions (Neufeld et al., 2011). Of note, not only have gut microbiota changes been linked to alterations in the stress response, but also the opposite scenario has been demonstrated (Foster et al., 2017). Indeed this concept is far from new, over 40 years ago Tannock and Savage published a pivotal experiment demonstrating the influence of stressful conditions on intestinal microbial populations in mice (Tannock and Savage, 1974). Interestingly, Guo and colleagues have shown that exposure of mice to psychosocial stress induced an increase of *Helicobacter pylori* colonization in the gastric mucosa that was accompanied by increased serum corticosterone levels. In the same study, mice that underwent treatment with a glucocorticoid-receptor antagonist (to antagonize the effect of endogenous corticosterone) showed decreased colonization by *H. pylori* (Guo et al., 2009), corroborating the crucial role played by glucocorticoids. One animal paradigm that is often used to investigate the effects of early life stress exposure in rodents is the maternal separation model, which has been shown to induce long-term changes in behaviour, HPA axis activity and alterations of the intestinal microbiota diversity/complexity (Lehmann et al., 2002; O'Mahony et al., 2011; Plotsky et al., 2005). When comparing maternally separated (MS) to non-separated (NS) rats, we have shown that MS animals had marked population-based alterations in the faecal microbiota (O'Mahony et al., 2009). Such results are in line with previous work from Bailey and Coe that demonstrated that maternal separation in infant rhesus monkeys caused a disruption of the gut microbiota integrity (Bailey and Coe, 1999). In addition, these changes in the microbiota were correlated with the display of stress-like behaviours, but not with cortisol secretion. More recently, we showed that MS rats exhibit a robust depressive-like phenotype as assessed by the forced swim test (FST), decreased noradrenaline content in the

brain, and increased peripheral interleukin-6 release. Moreover, the administration of the probiotic *B. infantis* resulted in normalisation of the behavioural deficits and restoration of basal noradrenaline levels in the brainstem, however, there were no differences in corticosterone concentrations between groups (Desbonnet et al., 2008; Desbonnet et al., 2010). Interestingly, it has been demonstrated that maternal probiotic administration (*Bifidobacterium animalis* subsp. *lactis* and *Propionibacterium jensenii*) activated neonatal stress pathways (with increased neonatal corticosterone levels) which persisted into adulthood (with elevated levels of adult ACTH); but it also protected against immune dysfunction and to some extent against disturbance of the gut microbiota provoked by MS and/or adult restraint stress (Barouei et al., 2012).

In addition to neonatal stress, prenatal stress (PNS) also has powerful and enduring effects on behaviour (Beijers et al., 2010; Frye and Wawrzycki, 2003; Maccari et al., 2003; Morley-Fletcher et al., 2003). In our laboratory we recently demonstrated that chronic PNS in rats resulted in hyperactivity of the HPA axis and affected neurodevelopment and functionality of the gastrointestinal tract (Golubeva et al., 2015). Interestingly, PNS also induced long lasting alterations in the gut microbiota composition, with a strong trend towards decreased numbers of bacteria of the *Lactobacillus* genus. Strikingly, the relative abundance of specific bacteria genera significantly correlated with the responsiveness of the HPA axis to stress (Golubeva et al., 2015). In line with previous results, Bailey and colleagues have shown that moderate disturbance (PNS using an acoustical startle paradigm for 6 weeks) of female monkeys during pregnancy was sufficient to alter the intestinal microbiota in the newborn infants (Bailey et al., 2004). Other studies have shown that exposure to a stressor can alter the microbial community of the gastrointestinal tract (Bailey et al., 2011; Bailey et al., 2010). Interestingly, Bailey *et al.* have shown that the exposure to a prolonged stressor not only altered the composition of the intestinal microbiota but also increased the susceptibility to the

enteric pathogen *Citrobacter rodentium* (Bailey et al., 2010). Alterations in gut microbiota composition, accompanied by an increased anxiety-like behaviour and cognitive deficits, were found in adult female offspring of PNS-exposed dams (Gur et al., 2017). In a population-based study, maternal PNS was positively correlated with the infants' microbiota composition (Zijlmans et al., 2015), reinforcing the idea that PNS can affect microbial composition. Finally, it was recently shown that PNS alters the offspring microbiome in a sex-specific manner (Jašarević et al., 2017).

To better investigate the link between gut microbiota and stress-like behaviour, different strategies have been applied and include the use of probiotics, prebiotics and antibiotics. Probiotics are defined as living micro-organisms that, if administered in adequate amount, confer health benefits to the host (Butel, 2014). A combination of *Lactobacillus helveticus* and *B. longum* to both rats and humans resulted in an anxiolytic-like effect in rats and the probiotic combination reduced urinary cortisol levels 24 hours following administration in humans, suggesting a normalisation of the HPA axis response to stressors (Messaoudi et al., 2011). Based on this work, the central effect of the same probiotic combination in mice was investigated and was found that a 2-week treatment with the probiotic formulation attenuated the HPA axis and ANS (autonomic nervous system) response to chronic stress. This was reflected by a decrease in plasma levels of corticosterone, adrenaline, and noradrenaline in stressed mice (Ait-Belgnaoui et al., 2014). As a further confirmation of the interaction between the intestinal microbiota and the stress response, chronic treatment with *L. rhamnosus* was able to decrease the levels of stress-induced corticosterone and ameliorate anxiety-like and depressive-like behaviours in mice (Bravo et al., 2011). Interestingly, as stated previously, the neurochemical and behavioural effects were not observed in vagotomized animals, thus suggesting that the vagus nerve might play a key role in the communication pathway between *L. rhamnosus* and the brain (Bravo et al., 2011). Infection

with *C. rodentium* in mice caused a stress-induced memory impairment which was attenuated by pretreatment with a combination of probiotics (*L. rhamnosus* and *L. helveticus*) (Gareau et al., 2011). In the same study, HPA axis activation was assessed by measuring levels of serum corticosterone, with exposure to psychological stress (water avoidance stress) causing a significant increase in serum corticosterone levels that was ameliorated by probiotics administration (Gareau et al., 2011).

Prebiotics were first defined as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health" (Gibson and Roberfroid, 1995) but this concept has been expanded more recently (Bindels et al., 2015). The prebiotic sialyllactose reduced stress-induced intestinal microbial disruption and anxiety-like behaviour thus confirming the hypothesis that the gut microbiota may play a crucial role in response to stress exposure (Tarr et al., 2015). This prebiotic, however, was not able to reverse the increases of corticosterone caused by the stressor. Work from our laboratory has recently shown that healthy mice treated with the prebiotics fructooligosaccharide (FOS) and galactooligosaccharide (GOS) for 3 weeks exhibited a reduction in stress-induced corticosterone release and had anxiolytic effects. In addition, the prebiotic combination was able to normalise the effects of chronic psychological stress on the microbiota (Burokas et al., 2017). From a translational perspective, GOS intake by healthy volunteers was associated with decreased waking salivary cortisol levels and altered attentional bias compared to placebo (Schmidt et al., 2015). These results suggest that the prebiotic intake may modulate the HPA axis activity in a similar way as probiotics. Depletion of gut microbiota can also alter stress responses and behaviour. For example, perturbation of the maternal gut microbiota during pregnancy, induced by administration of antibiotics, was able to influence the behaviour of the offspring. Indeed, offspring born from antibiotic-treated dams displayed

anxiety-like behaviour thus suggesting that disruption of maternal gut microbiota during pregnancy may lead to alterations in the behaviour of their offspring (Tochitani et al., 2016). To corroborate the previous findings, an anxious or non-anxious phenotype can be induced with a microbiota transplant from an animal with a similar phenotype (Bercik et al., 2011a) and our lab has demonstrated that transplantation of faecal microbiota from depressed patients into healthy rats was able to induce an anxiety-like phenotype (Kelly et al., 2016). In these studies based on microbiota depletion and faecal transplantation, the neuroendocrine component is often missing. A deeper investigation will be needed to elucidate the role that neurohormones play in the different behavioural outcomes.

6.1 Psychotropic Drugs and Gut Microbiota

With regard to stress and stress-related disorders, it is relevant to mention that some brain-targeting drugs have been shown to possess antimicrobial properties. Chronic treatment with the atypical antipsychotic olanzapine, for example, was able to induce changes in gut microbiota composition in rats (Davey et al., 2013). These microbiota changes appear to be responsible for the metabolic impairment caused by olanzapine; in fact, co-administration of an antibiotic cocktail in olanzapine-treated rats attenuated the metabolic dysfunction induced by olanzapine alone (specifically: body weight gain, uterine fat deposition, macrophage infiltration of adipose tissue and plasma free fatty acid levels) (Davey et al., 2013). Antidepressants can also alter gut microbiota. Tricyclic antidepressants (TCAs) are reported to prevent the growth of intestinal pathogens such as *E. coli*, *Yersinia enterocolitica* (Csiszar and Molnar, 1992; Molnar, 1988) and the parasite *Giardia lamblia* (Weinbach et al., 1992). TCAs also present *in vitro* activity against the parasites *Plasmodium falciparum* (Basco and Le Bras, 1990; Salama and Facer, 1990) and *Leishmania* spp. (Zilberstein and Dwyer, 1984). Another class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), including sertraline, fluoxetine and paroxetine have been shown to have antimicrobial activity

especially against gram-positive bacteria such as Staphylococcus and Enterococcus (Ayaz et al., 2015; Coban et al., 2009). The antimicrobial activity of some antidepressants is further confirmed by the synergistic effect of some SSRIs in combination with antibiotics; as well as their effects against some antibiotic-resistant bacteria (Bohnert et al., 2011; Munoz-Bellido et al., 1996, 2000).

While the majority of the results to date derive from *in vitro* studies, they represent a preliminary step for a more comprehensive investigation of how brain-targeting drugs might influence gut microbiota and impact on neuroendocrine pathways.

7. Gut Microbiota and Eating Behaviour

Eating behaviour and appetite are regulated by a complex system of central and peripheral signals. Peripheral regulation includes satiety and adiposity signals, while central control is accomplished by several effectors, including the neuropeptidergic, monoaminergic and endocannabinoid systems. Satiety signals such as CCK, GLP-1 and PYY are produced in the EECs during a meal and, through the vagus nerve signal to the nucleus tractus solitarius (NTS) in the brain. From NTS, afferents fibres project to the arcuate nucleus (ARC), where satiety signals are integrated with adiposity signals, leptin and insulin, and with several hypothalamic inputs. Another brain area involved in appetite regulation is the PVN, responsible of producing anorexigenic peptides such as thyrotropin releasing hormone (TRH) (Guo et al., 2004), CRF (Krahn et al., 1988; Smith et al., 2001; Uehara et al., 1998) and oxytocin (Lawson et al., 2015). The most immediate mechanism through which the gut microbiota modulates food intake is through the production/alteration of appetite-regulating hormones *(see Section 5.5)*. EECs express Toll-like receptors which, when activated by binding with bacterial products (e.g., lipopolysaccharides (LPS) and flagellin), modify the secretion of hormones that regulate satiety and hunger (Raybould, 2010a). It is currently recognised that different dietary patterns and feeding behaviours exert a critical impact on gut

microbiota composition (Conlon and Bird, 2014; De Filippo et al., 2010; Queipo-Ortuno et al., 2013; Wu et al., 2011); however the converse might also be true. Increasing evidence supports the concept that the gastrointestinal microbiota composition and richness may be responsible, together with other factors, for the host eating behaviour and appetite (Alcock et al., 2014; Fetissov, 2017; Goyal et al., 2015; Norris et al., 2013). Indeed, the symbiotic microorganisms residing in the intestine are dependent upon host feeding behaviour to receive the nutrients necessary for their growth (Dethlefsen et al., 2007). The gut microbiota is characterised by its own circadian rhythmicity, which means it undergoes diurnal fluctuations in composition and in the production of key metabolic mediators (Leone et al., 2015; Liang et al., 2015; Thaiss et al., 2014; Zarrinpar et al., 2014). It has been shown that the consumption of a high-calorie diet in mice, affecting the gut microbiota, altered the function of the mammalian circadian clock and changed the period of the locomotor activity (Kohsaka et al., 2007). Healthy humans and rats normally display autoantibodies directed against appetite-regulating peptide hormones and neuropeptides, which may have physiologic implications in hunger and satiety pathways (Fetissov et al., 2008). Indeed, IgG and IgA autoantibodies directed against leptin, ghrelin, peptide YY, neuropeptide Y, and other appetite-regulating peptides were decreased in germ-free rats compared with specific pathogen-free (SPF) rats, thus involving a change in the behavioural outcome (Fetissov et al., 2008). Increasing evidence suggests that metabolites produced by the colonic microbiota, such as SCFAs, modulate feeding behaviour via central mechanisms (Frost et al., 2014; Shen et al., 2009; So et al., 2007). Indeed, administration of a dietary compound that selectively augments propionate production in the colon of healthy humans, attenuated reward-based eating behaviour via striatal pathways, thus suggesting a key role for the propionate-producing intestinal microbiota (Byrne et al., 2016). These beneficial effects, however, were not accompanied by alterations in hormonal levels of PYY and GLP-1, as initially hypothesized by the authors. Intriguingly, commensal bacteria are critical modulators of food

choice (Alcock et al., 2014). In *Drosophila melanogaster*, lack of any essential amino acid from the diet usually induces fruit flies to have a strong appetite for proteinaceous food. However, flies that receive an appropriate microbiome do not develop this protein appetite, suggesting that the microbiota is able to mediate appetite response. Specifically, the gut bacteria species that suppress protein appetite are *Acetobacter pomorum* and *Lactobacilli* (Leitao-Goncalves et al., 2017). In this intriguing study using *Drosophila*, the role of hormonal secretions in mediating the effect of microbial changes was not investigated per se.

The investigation of the connection between obesity, eating behaviour and the gut microbiota has involved the use of gut-targeting supplements such as prebiotics and probiotics (Torres-Fuentes et al., 2015, 2017). Among others, inulin, β-glucan and FOS are fermentable carbohydrates that have been shown to modulate the intestinal microbiota by increasing the proportions of bifidobacteria and lactobacilli in humans (Tuohy et al., 2001). Several studies have reported that the modulation of microbiota activity using different non-digestible carbohydrates affects appetite (Bird et al., 2010; Daud et al., 2014; Delzenne et al., 2013; Frost et al., 1999; Klosterbuer et al., 2012; Nilsson et al., 2013; Robertson, 2012; Tarini and Wolever, 2010). The role of FOS in mice fed a standard diet and in mice fed two distinct high fat diets (one of which carbohydrate-free) has recently been investigated. In normal mice, FOS induced an increase in total caecum weight, a significant decrease in epididymal fat mass and an increase in colonic and portal plasma GLP-1. In the high-fat carbohydrate-free diet group, FOS decreased energy intake, body weight gain, glycemia, and epididymal fat mass, suggesting that dietary oligosaccharides promote, in certain conditions, endogenous GLP-1 production with beneficial physiological consequences (Delmee et al., 2006). In a recent study the administration of both β-glucan and inulin attenuated weight gain in high fat fed mice (Arora et al., 2012), confirming findings of others (Cani et al., 2004; Cani et al., 2005; Choi et al., 2010). In another study, the administration of oligofructose to overweight

and obese humans was able to induce weight loss and improve glucose regulation in overweight adults. Interestingly, this was associated with decreases in ghrelin levels and increases in PYY (Parnell and Reimer, 2009). Similarly, food intake, body weight and fat mass were all decreased in male Wistar rats after administration of three different prebiotics (Cani et al., 2004). It was also found that microbial fermentation of oligofructose increased satiety, reduced hunger and reduced the desire to ingest food in humans (Cani et al., 2006). Although the mechanisms responsible for such effects were not fully understood, it is known that oligofructose stimulates the release of GLP-1 (Delzenne et al., 2007), thus this might be one mechanism through which it exerted its beneficial effects. The increased satiety and reduced hunger caused by highly fermented prebiotics were associated with changes in plasma GLP-1 and PYY levels (Cani et al., 2009).

Another means of targeting the microbiome to alter metabolic function is via probiotics. Several studies have shown that probiotic administration is able to influence host satiety and eating behaviour, as well as playing a role in obesity (Arora et al., 2013; Belguesmia et al., 2016; Delzenne et al., 2011; Forssten et al., 2013). Here from a neuroendocrine perspective we will focus our attention on evidence that links probiotic administration, and therefore microbiota composition/stability, to eating behavior per se. It was recently shown that the administration of certain probiotic *Lactobacillus* strains were able to modify the levels of circulating satiety hormones, thus affecting food intake in rats (Forssten et al., 2013). In a recent study, the probiotic *L. rhamnosus* CGMCC1.3724 was administered to obese men and women over a period of 24 weeks and produced a significant sex-dependent effect. In fact, only in women, the weight loss in the probiotic group was significantly higher than that the placebo group. Interestingly, this weight loss in females was associated with significant reductions in circulating leptin concentrations (Sanchez et al., 2014). In another study, the administration of the probiotic VSL#3 in mice suppressed body weight gain and insulin

resistance via modulation of the gut microbiota composition. In addition, VSL#3 promoted the release of the hormone GLP-1, resulting in reduced food intake and improved glucose tolerance (Yadav et al., 2013). In a study conducted on Iraqi obese females, the consumption of probiotics caused an increase in peptide YY, a decrease of ghrelin and a subsequent decrease in body weight (Alajeeli, 2016). The impact of prenatal exposure to probiotics on weight gain has also been assessed. *L. rhamnosus* administered to pregnant women has been found to modify the standard of weight gain in children during the first six months of life (Luoto et al., 2010) with no evidence, however, that this effect is mediated by the neuroendocrine component.

7.1 Obesity

Several factors are known to contribute to obesity and metabolic disorders, such as the environment, life style, diet and genetics (Naukkarinen et al., 2012). Emerging evidence supports the notion that changes in gut microbiota composition and/or richness are correlated to obesity and this can occur in a causative way (Backhed et al., 2004; Ley et al., 2006; Ridaura et al., 2013; Turnbaugh et al., 2009b). In a landmark study, Bäckhed *et al.* demonstrated that germ-free mice have less total body fat than conventionally reared mice and the colonisation of germ-free mice with a caecal microbiota harvested from conventionally raised animals produces an increase in body fat content and insulin resistance (Backhed et al., 2004). In addition, germ-free mice have an increased preference and intake of fats compared to normal mice. This is associated with decreased intestinal expression of satiety peptides CCK, PYY and GLP-1 (Duca et al., 2012). In the same study, germ-free mice had lower levels of circulating leptin and ghrelin, and altered plasma lipid metabolic markers indicative of energy deficits (Duca et al., 2012). Both obese humans and mice have been shown to have a specific microbial profile that is different from lean people, with the relative proportion of *Bacteroidetes* decreased in obese subjects (Ley et al., 2005; Ley et al., 2006).

Moreover, the obese microbiome showed an increased capacity to harvest energy from the diet, a trait that was transmitted through microbial transplantation. In fact, colonisation of germ-free mice with an obese microbiota resulted in a significantly greater increase in total body fat than colonization with a lean microbiota (Turnbaugh et al., 2006). Importantly, the contribution of hormonal signalling in the onset of metabolic changes following faecal transplantation needs further investigation. Turnbaugh and colleagues also showed that a core gut microbiome is shared within lean or obese twins (Turnbaugh et al., 2009a) and many other studies have confirmed the specificity of the obese microbiota (Le Chatelier et al., 2013; Million et al., 2013; Ravussin et al., 2012; Ridaura et al., 2013; Ussar et al., 2015). Nevertheless, it has been shown that, when obesity is driven by the diet, the intestinal microbiome does not play a role in the onset of the obese phenotype (Rabot et al., 2016). In a cohort study, a combination of delivery mode, maternal pre-pregnancy BMI (body mass index) and antibiotics in infancy influenced the risk of being overweight in later childhood (Ajslev et al., 2011). Several other studies have supported the idea that administration of antibiotics during childhood increases the risk of obesity, thus demonstrating that the gut microbiota composition/stability may play a key role in the onset of obesity (Azad et al., 2014; Scott et al., 2016; Trasande et al., 2013). Even though many studies support the role of Bifidobacteria on the host fatty acid metabolism, strain-strain differences are important factors influencing the modulation of the gut microbial community (Wall et al., 2012). Therefore, more studies should aim to clarify the role of specific Bifidobacterium species and strains in obesity and weight management (Wall et al., 2012). Circadian rhythms regulate several aspects of physiology including metabolism and play a critical role in obesity (Bray and Young, 2007; Froy, 2010). The gut microbiota has been shown to contribute to accelerated post-dieting weight regain. Thaiss and colleagues found an intestinal microbiota signature that persisted after successful dieting of obese mice and contributed to faster weight regain upon re-exposure to obesity-promoting factors (Thaiss et al., 2016).

7.2 Anorexia Nervosa

Anorexia nervosa is a complex psychiatric disorder characterized by aberrant eating behaviour aimed at maintaining a low body weight because of the patient's pathological fear of weight gain, associated with alterations in the perception of the body shape (Kaye et al., 2009). From a neuroendocrine perspective, several studies have shown that subjects with anorexia nervosa have altered concentrations of the appetite-regulating hormones PYY (Germain et al., 2007; Nakahara et al., 2007), leptin (Monteleone et al., 2000) and ghrelin (Harada et al., 2008; Monteleone et al., 2008). Interestingly, also CRF (Glowa et al., 1992; Hotta et al., 1986) and oxytocin (Demitrack, 1990; Lawson et al., 2011; Lawson et al., 2012) have been found to be altered in patients suffering from anorexia nervosa.

In a recent population-based study, it has been shown that in comparing the intestinal microbiota of patients with anorexia nervosa to that of healthy controls, the alpha diversity was significantly lower in patients with anorexia both before and after inpatient weight restoration (Kleiman et al., 2015). Moreover, the microbial composition in the anorexic cohort was correlated with mood (Kleiman et al., 2015). An increase in *Methanobrevibacter smithii* has been detected in the intestinal microbiota of anorexic patients as compared to lean humans (Armougom et al., 2009) while others reported a decreased richness in the microbiota of anorexic patients (Morita et al., 2015). Interestingly, the microbial perturbations and gastrointestinal symptoms seen in anorexic patients did not recover after weight gain and/or normalisation of eating behaviour (Mack et al., 2016).

8. Gut Microbiota and Sexual Behaviour

Unlike other behavioural fields, very little is currently known of the connection between the gut microbiota, neurohormones and sexual behaviour. Almost sixty years ago, in 1959, Karlson and Lüscher coined the term “pheromones” and defined them as “substances secreted

to the outside of an individual and received by a second individual of the same species in which they release a specific reaction, for example, a definite behaviour or developmental process" (Karlson and Luscher, 1959). Among the pheromones, sex pheromones are the ones responsible for sexual recognition, attraction and mating behaviour in several species. Interestingly, research now suggests that the gut microbiota may play a role in regulating sexual behaviour, with the discriminative urinary odours present in conventional housed rats being abolished in germ-free rats, indicating a key role of bacteria in determining the unique odours responsible for the host behaviour (Singh et al., 1990). Moreover, it has been shown that the gut bacteria of locusts are responsible for the production of guaiacol, a key component of pheromones responsible for mating. This was further confirmed by the fact that the faecal pellets of locusts grown in germ-free conditions smelled different from those from locusts with a normal gut microbiota and did not have guaiacol (Dillon et al., 2000, 2002). Even though some animals do not have a gut microbiota per se, they possess symbiotic bacteria that in some cases have been linked to sexual behaviour. Intriguingly, it has recently been demonstrated that symbiotic bacteria can influence mating preference by changing the levels of cuticular hydrocarbon sex pheromones in the *Drosophila* (Sharon et al., 2010). In this study, a population of *Drosophila melanogaster* was divided in two parts, one reared on a molasses medium and the other on a starch medium. When the isolated populations were mixed, "molasses flies" preferred to mate with other molasses flies and "starch flies" preferred to mate with other starch flies. Furthermore, antibiotic treatment was able to abolish the mating preference, suggesting that the fly microbiota was affecting host pheromone levels, which in turn affected mating behaviour (Sharon et al., 2010). Interestingly, administration of the probiotic *L. reuteri* has been shown to increase testosterone levels in aging mice (Poutahidis et al., 2014).

Oxytocin is released by the posterior pituitary gland, acts also as mediator of sexual behaviour (Argiolas et al., 1988; Behnia et al., 2014; Witt and Insel, 1994). Some evidence

suggests that the gut microbiota is able to directly modulate the levels of host oxytocin (Poutahidis et al., 2013; Varian et al., 2017) and so it is interesting to speculate as to whether the microbiota contributes towards regulation of sexual behaviour. These preliminary results suggest that the gut microbiota may play a key role in sexual behaviour. Importantly, most of the studies to date have been focusing on interactions between the microbiome and pheromones, and more effort will be needed to elucidate the role played by the conventional neuroendocrine routes.

9. Gut Microbiota and Social Behaviour

Sociability is a key aspect of mammals' lifespan. In the last decades, numerous studies have been focusing on how social interactions take place across different species and some studies have suggested that the endosymbiotic microbes shared in group living have influenced the evolution of social behaviour (Lombardo, 2008; Montiel-Castro et al., 2013; Troyer, 1984). The microbiota has been linked to social status across a variety of species including *Drosophila* (Lize et al., 2014; Venu et al., 2014), bumblebees (Koch and Schmid-Hempel, 2011), hyenas (Theis et al., 2013), non-human primates in the wild (Tung et al., 2015) and rodents.

Oxytocin and vasopressin are neuropeptides of the hypothalamus-neurohypophyseal axis and play a critical role in social bonding (Meyer-Lindenberg et al., 2011) and, as mentioned above, the gut microbiota is able to modulate levels of the hormone oxytocin (Erdman and Poutahidis, 2016; Varian et al., 2017) thus potentially impacting on social behaviour. In a recent study, we demonstrated that mRNA levels of oxytocin and vasopressin were significantly reduced in the hypothalamus of antibiotic-treated adolescent mice when compared to non-treated mice, suggesting that gut microbes are able to modulate the activity of these hormones (Desbonnet et al., 2015). These biological changes were accompanied by behavioural alterations including reduced anxiety, non-spatial memory deficits and impaired

performance in the social transmission of food preference test (Desbonnet et al., 2015). We also assessed the social motivation and preference for social novelty in germ-free mice through the three-chambered sociability test (Yang et al., 2011) and demonstrated that germ-free animals suffer a social impairment, which is reversed by re-colonisation with a normal microbiota (Desbonnet et al., 2014). The gut microbiota is crucial for the presence of a normal social behaviour in mice (Buffington et al., 2016b). Furthermore, offspring of high-fat-fed mothers have fewer oxytocin immune-reactive neurons in the hypothalamus associated with social behavioural deficits, which are mediated by alterations in the offspring gut microbiome (in which the relative abundance is dramatically reduced) (Buffington et al., 2016a). In the same study, the administration of *L. reuteri* in the drinking water of the offspring was able to restore oxytocin levels and improve sociability and the preference for social novelty.

9.1 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder defined by deficits in social interaction and communication and the presence of limited, repetitive stereotyped interests and behaviours (NIH, 2017). Very little is currently know about the neuroendocrinology of autism, however, some studies have addressed the role of sex differences in autistic symptomatology, the majority of which showing that males are more prone to develop ASD than females (Baron-Cohen et al., 2011; Pfaff et al., 2011). These data however, should be interpreted with caution as females girls tend to be more socially driven than males (Christov-Moore et al., 2014; Connellan et al., 2000), therefore some mildly affected females might go unrecognized. A factor responsible for gender differences in ASD might be that males are exposed to higher intrauterine testosterone levels than females (Hines, 2006; Hines et al., 2015), with fetal testosterone associated to autistic traits and inversely correlated with social behaviour (Baron-Cohen et al., 2009; Dabbs and Morris,

1990; Eisenegger et al., 2011). It is important to remember that one of the main features of ASD is social impairment, suggesting that the neuroendocrinology of autism and social behaviour might overlap. As mentioned above, the neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) are key mediators of complex social behaviours including attachment, social recognition and aggression (Dölen et al., 2013; Heinrichs et al., 2009; Neumann and Slattery, 2016). Indeed, central administration of OXT in the olfactory bulb facilitates and prolongs social recognition in male rats (Dluzen et al., 2000; Dluzen et al., 1998). Also in female rats and mice, OXT is a crucial factor in social cognition. In female rats, intracerebroventricular administration of an OXT antagonist interfered with the animals' ability to establish normal social memory (Engelmann et al., 1998). Vasopressin, on the other side, has primarily been implicated in male typical social behaviours, including aggression, pair-bond formation, and in stress response (Goodson and Bass, 2001).

Three recent studies using animal models based on clinically validated risk factors of autism [Maternal exposure to 1) valproic acid (VPA), 2) high fat diet and 3) inflammation] illuminate a role of the microbiome in mediating behavioural changes relevant to ASD (Buffington et al., 2016b; de Theije et al., 2014; Hsiao, 2013). In utero exposure to VPA induced deficits in social interaction in mice and had a transgenerational impact on gut microbiota in the offspring. Moreover, this was associated with changes in social behaviour scores (de Theije et al., 2014). The maternal immune activation (MIA) mouse model is known to display features of autism and social impairment. Hsiao *et al.* showed that administration of *Bacteroides fragilis* to MIA mice was able to ameliorate deficits in communicative, stereotypic, anxiety-like and sensorimotor behaviour. Moreover, treating naive mice with a metabolite that is increased by MIA and normalized by *B. fragilis* resulted in behavioural abnormalities, supporting the idea that gut bacteria exert a crucial impact on behaviour (Hsiao et al., 2013). A recent study also proved that behavioural abnormalities of adult male offspring following fetal exposure to MIA are mediated by maternal commensal

bacteria. Indeed, pre-treatment of MIA mothers with the antibiotic vancomycin prevents the development of behavioural deficits in the offspring (Kim et al., 2017). Studies of the gut microbiota in children with ASD are limited in quantity and quality; however, some have pointed out differences in the microbiota composition between ASD and healthy children (Finegold et al., 2010; Kang et al., 2013; Parracho et al., 2005). To decrease the heterogeneity of findings and strengthen them, future studies should enlarge sample sizes, standardize methods and assess relevant confounding variables among ASD populations. Finally, further investigations will be needed to better assess the role of neuroendocrine signalling in autistic-like behaviours mediated by the microbiota.

10. Gut Microbiota, Learning and Memory

Learning and memory are complex processes finely regulated by specialized neuronal networks. The hormones oxytocin and vasopressin play a fundamental role in this inter-neuronal communication and several studies have demonstrated the involvement of these hormones in cognitive processes (Bohus et al., 1978; Dantzer et al., 1987; Ibragimov, 1990; Till and Beckwith, 1985). Moreover, some evidence also suggests that glucocorticoids levels are linked to memory and learning (Hui et al., 2004; Oitzl et al., 1998; Roozendaal and McGaugh, 1997). Neuroendocrine mechanisms are very important in supporting cognitive function across the lifespan (Almey et al., 2015; Lupien et al., 2007; McEwen et al., 2015). Moreover, postnatal gut microbial colonisation occurs in parallel with cognitive development (Alexeev et al., 2017) and evidence has shown that colonisation by gut microbiota impacts mammalian brain development and subsequent adult behavior (Diaz Heijtz et al., 2011). Germ-free mice, with or without exposure to stress, have memory impairments, thus demonstrating a decisive role for the gut microbiota in cognition (Gareau et al., 2011). In the same study, it was shown that infection with *C. rodentium* in conventionally colonised mice was able to generate stress-induced memory dysfunction (Gareau et al., 2011). Moreover,

pre-treatment of *C. rodentium*-infected mice with a combination of *Lactobacillus*-containing probiotics prevented stress-induced memory deficits and ameliorated serum corticosterone levels. In another study, ingestion of *B. breve NCIMB702258*, but not *B. breve 6330*, significantly impacted brain fatty acid composition in mice, increasing arachidonic acid (AA) and docosahexaenoic acid (DHA) levels, with potential clinical implications, as these fatty acids play important roles in cognitive processes such as memory and learning (Wall et al., 2012). In a further preclinical study, a positive effect of probiotic supplementation on diabetes-induced cognitive impairments in rats was observed (Davari et al., 2013). We have shown that antibiotic-treated adolescent mice had non-spatial memory deficits and reduced oxytocin mRNA levels (in the hypothalamus) when compared to non-treated mice (Desbonnet et al., 2015). Moreover, administration of *L. rhamnosus* in mice was able to not only decrease the stress response *(see section 6)* but to also enhance memory of an aversive cue and context in comparison with broth-fed mice (Bravo et al., 2011), reducing the levels of corticosterone. Interestingly, it has recently been shown that germ-free mice are not impaired in the acquisition of a fear learning response but have marked deficits in fear recall (Hoban et al., 2017). In another study, it has been shown that dietary-induced shifts in bacterial diversity were correlated with changes in memory and learning in mice (Li et al., 2009). Administration of *E. coli* and subsequent alterations in the gut microbial composition in mice resulted in memory impairments (Jang et al., 2017). Work from our laboratory demonstrated that prenatal stress in rats not only induces marked changes in the gut microbiota composition but also impairs cognitive function (Golubeva et al., 2015). Moreover, the microbial changes present in aged mice might be mediators of impaired cognitive performance and anxiety-like behaviour characteristic in late life (Scott et al., 2017). It was recently shown that the microbiota composition of human infants at one year of age predicts cognitive performance at 2 years of age, mostly in the area of communicative behaviour. (Carlson et al., 2017). Intriguingly, we found that administration of the single probiotic *B. longum* 1714 in healthy

male volunteers improves visuospatial memory and produces an electroencephalography profile consistent with improved memory (Allen et al., 2016).

Taken together these data highlight a role for the gut microbiota in both baseline and stress-related cognitive changes. More work is needed to determine the interactions between neuroendocrine systems and the microbiome in determining these effects (Dinan and Cryan, 2017). Moreover, there is a growing body of evidence linking the microbiome to ageing processes and Alzheimer's disease. Though a causal association between gut microbes and cognitive decline in the elderly has not yet been reported, some studies have demonstrated the specificity of the core microbiota in elderly subjects as opposed to young subjects (Claesson et al., 2011; Claesson et al., 2012) and in animal models of ageing. Moreover, neither germ-free nor antibiotic-treated transgenic Alzheimer's mice develop the characteristic plaques (Harach et al., 2015; Minter et al., 2016). In light of the results to date, it is tempting to speculate that changes in the elderly microbiota may modulate inflammatory and hormonal processes that act in the brain and impact on cognitive decline.

11. Gut Microbiota and Addiction

Stress represents one of the major susceptibility factors for the development of addictive behaviour and substantial evidence shows that the HPA axis and corticosteroids play a crucial role in the process of addiction (Ambroggi et al., 2009; Mantsch et al., 2007a; Yang et al., 2004). Interestingly, CRF is involved in the onset/development of addiction (Koob, 2010; Sarnyai et al., 2001) but the data are not always consistent. For example, cocaine has been shown to stimulate the HPA axis through a CRF-mediated mechanism in male rats (Goeders, 1997, 2002), and both CRF mRNA levels and circulating corticosterone are increased on cocaine withdrawal (Mantsch et al., 2007b). In contrast, shock-induced reinstatement of heroin or alcohol seeking depends on CRF, but not on corticosterone (Le et al., 2000; O'Callaghan et al., 2005; Shaham et al., 1997). Regarding sex differences in addiction, some

studies have suggested that females are more susceptible than males (Devaud et al., 2003; Festa et al., 2004) and that this might be due to gonadal hormones (Festa et al., 2004), however more research is required to confirm this hypothesis. There is a complex overlap between the neurobiology of addiction and more prototypical neuroendocrine behaviours such as food intake, sexual and social behaviours. There is also a burgeoning literature on the influence of the microbiome on addictive behaviours. Several studies have shown that alcoholism and cocaine addiction induce changes in gut microbiota composition (Leclercq et al., 2014; Mutlu et al., 2009; Mutlu et al., 2012; Peterson et al., 2017; Volpe et al., 2014; Yan et al., 2011) while others suggest that the gut microbiota might influence to some extent the onset/development of addictive behaviours. For instance, it is well established that stress is one of the most significant risk factors for addiction (Sinha and Jastreboff, 2013) and, as described in *section 6*, the stress response is modulated by the functional state of the gut microbiota. Translating this finding to humans, perturbations of the gut-brain axis and therefore altered stress response could predispose an individual to addiction. Another known risk factor that can also be comorbid with addiction is depression (Polter and Kauer, 2014). One of the main neurotransmitters involved in depression is serotonin (Nemeroff, 2002; Owens and Nemeroff, 1994) and it is recognised that 90% of the body serotonin is synthetized in the gut (Yano et al., 2015). Thus, the microbiota-derived modulation of serotonin levels might indirectly influence the development or onset of addiction. Finally, it is now well established that most drugs of abuse affect the brain via central dopamine-reward pathways (Volkow and Baler, 2015) and that the gut microbiota is a source of dopamine. As a confirmation of this, germ-free mice display lower levels of dopamine in the caecum than specific-pathogen-free mice (Asano et al., 2012). These findings provide evidence of a link between gut microbiota and dopamine function, which could have implications for addiction. Oxytocin has been linked to addiction and chronic administration of drugs of abuse such as cocaine has been shown to substantially reduce oxytocin levels in some brain areas (Elliott et

al., 2001; Johns et al., 1997; Sarnyai et al., 1992). Indeed, individual differences in oxytocin levels may be responsible for the host resilience and the susceptibility to develop problematic drug and alcohol abuse (Buisman-Pijlman et al., 2014). At the same time, mounting preclinical evidence is suggesting that oxytocin might represent a novel treatment for addictive disorders (Lee et al., 2016; McGregor and Bowen, 2012). Given that the gut microbiota has been shown to be involved in modulation of oxytocin levels in the brain (Desbonnet et al., 2015), it is reasonable to suppose that intestinal microbes might play a role in addiction. Only one study has directly linked the gut microbiota to addictive behaviour and has shown that alterations of the gut microbiota in mice affect the behavioural response to cocaine. Following prolonged treatment with non-absorbable antibiotics, the animals showed an enhanced sensitivity to cocaine reward and enhanced sensitivity to the locomotor-sensitizing effects of repeated cocaine administration (Kiraly et al., 2016).

Even though the findings to date are not exhaustive, they provide some evidence of the link between gut microbiota, neuroendocrinology and addiction. Further investigation is required in order to assess which other neuroendocrine pathways are involved in addiction and in which cases the gut microbiota plays a causal role.

12. Conclusion

Increasing evidence suggests that the gut microbiota affects different physiological and behavioural outcomes through modulation of neuroendocrine pathways. The production of hormones and neuroactive metabolites from the gastrointestinal tract influences distal sites and ultimately results in central activation and behavioural changes. The aim of this review was to present and discuss different behavioural scenarios that have been linked, to certain extent, to modifications of the intestinal microbiota and neuroendocrine pathways. However, the results to date come mainly from preclinical studies and further clinical experimentation is required in order to better clarify in which cases the gut microbiota plays a causal role.

Moreover, future studies should address the contribution of sex differences in the behavioural outcomes mediated by endocrine routes. Intriguingly, some researchers have pointed out that the host gender represents a key variable in stress-related behaviours (Bale, 2011; Mueller and Bale, 2008; Shansky, 2009; Shansky et al., 2010) and, given the hormonal discrepancies present among males and females, a deeper investigation of this aspect is required. Finally, it is important to note that the neuroendocrine system comprises two more axes, namely the hypothalamic-pituitary-liver axis and the hypothalamic-pituitary-prolactin axis, that have not been taken into consideration in this review due to the lack of direct links with the gut microbiota and/or behavioural outcomes. However, given the expansive nature of how the microbiome affects the programming of all body systems it is probably only a matter of time before it is also implicated in these axes in addition to affecting the hypothalamus-pituitary-thyroid axis. The investigation of the interactions between gut microbiota and these neuroendocrine axes represents future direction for research.

Acknowledgements

The APC Microbiome Ireland is a research centre funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan. Sofia Cussotto and Kiran Sandhu are supported by SFI (grant numbers 12/RC/2273 and 07/CE/B1368). John Cryan and Timothy Dinan are supported by the Irish Health Research Board, Health Research Awards (HRA_POR/2011/23, HRA_POR/2012/32), and John Cryan is also funded by the European Community's Seventh Framework Programme (Grant FP7/2007–2013, Grant Agreement 201714).

Figures

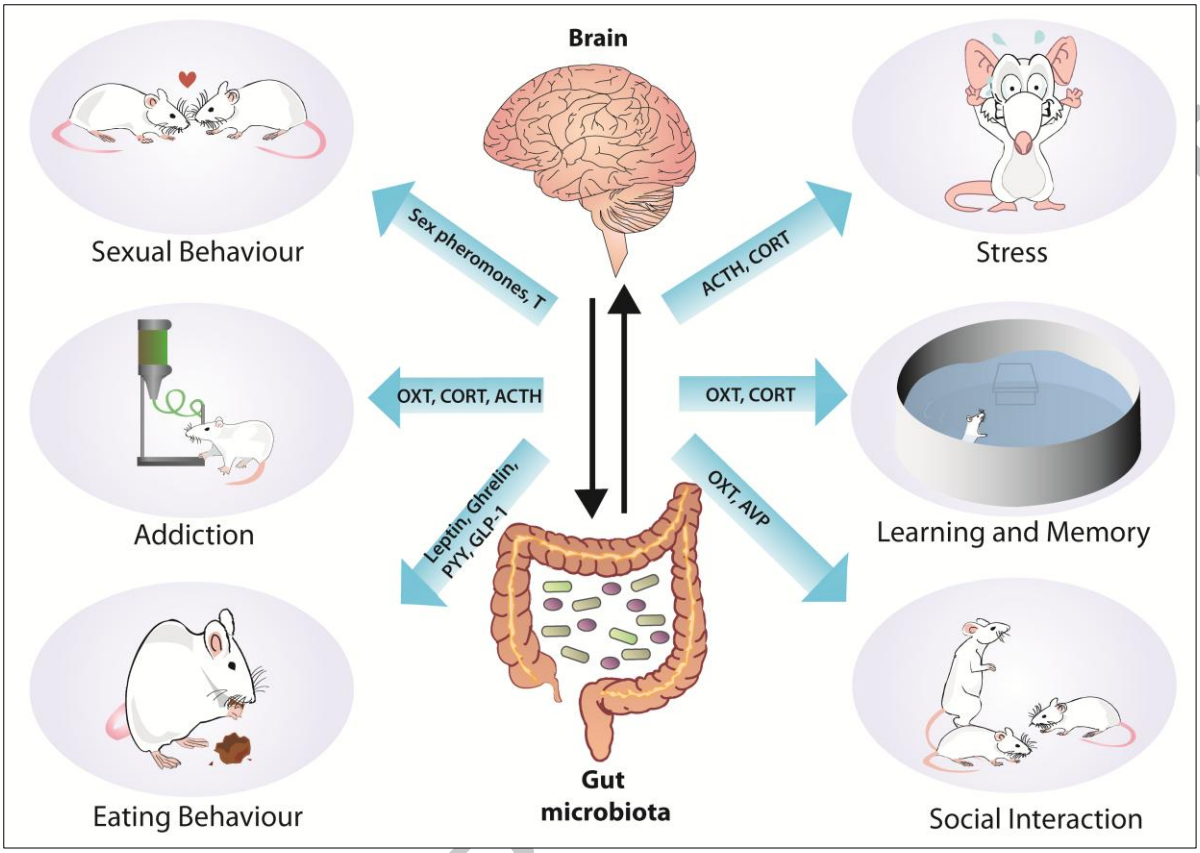

Figure 1. Using rodent models to assess the impact of the microbiota-gut-brain axis on host behaviour. Neuroendocrine pathways mediate the behavioural effects induced by manipulations/alterations of the gut microbiota. *Abbreviations: T* testosterone, *OXT* oxytocin, *CORT* cortisol (humans) corticosterone (rodents), *ACTH* adrenocorticotropic hormone, *PYY* peptide YY, *GLP-1* glucagon-like peptide 1, *AVP* arginine vasopressin.

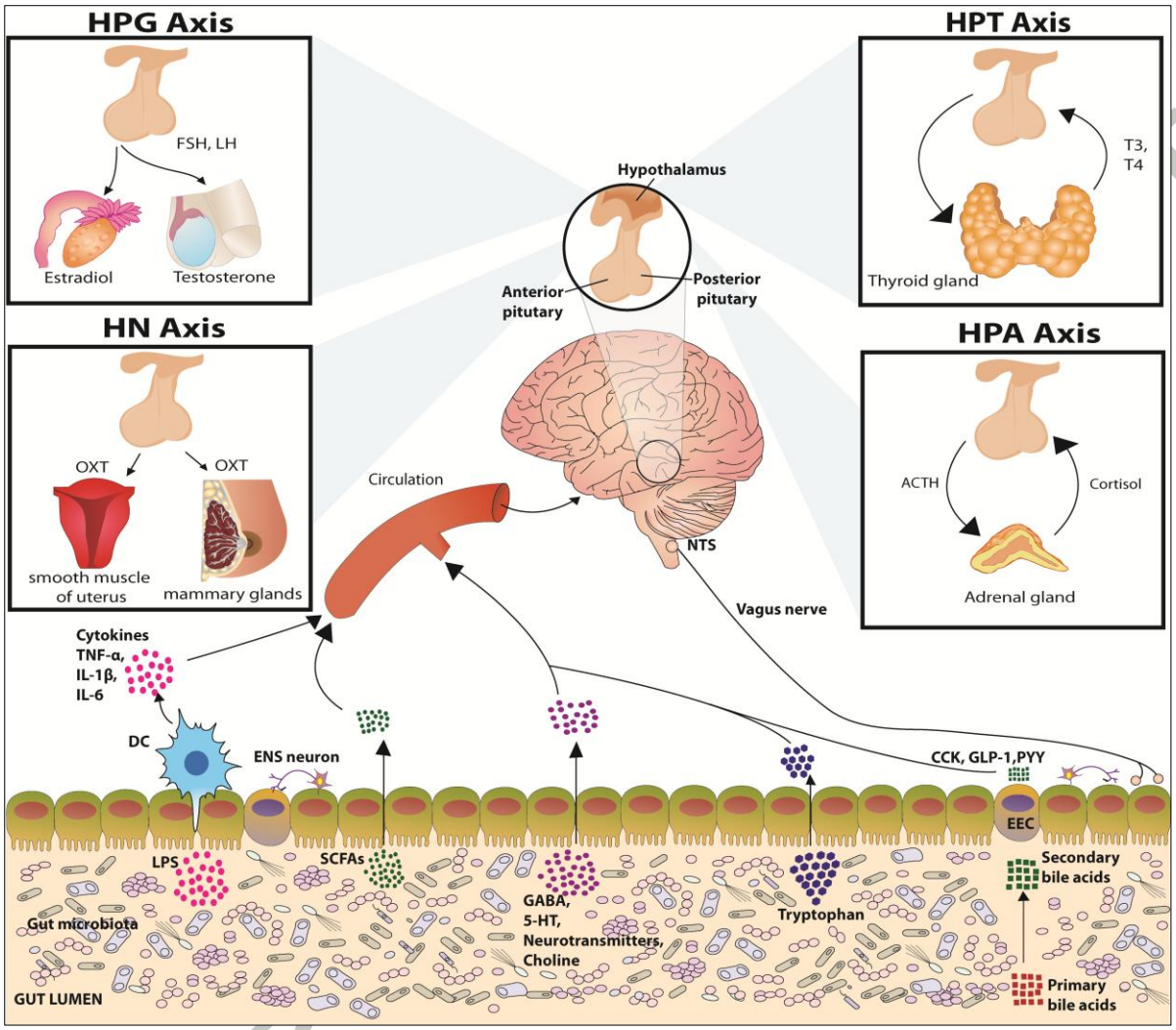

Figure 2. The gut microbiota influences neuroendocrine function through several routes that characterize the microbiota-gut-brain axis. These routes include the vagus nerve, production of SCFAs, immune activation with production of immune mediators, production of neurotransmitters and tryptophan. The gut microbiota is also able to convert primary bile acids into secondary bile acids, which activate receptors on EECs and stimulate the secretion of gut peptides. Neuroactive compounds produced by gut microbiota enter the circulation and reach the brain, subsequently affecting neuroendocrine function. *Abbreviations: 5-HT* (5-hydroxytryptamine) serotonin, *ACTH* adrenocorticotropic hormone, *CCK* cholecystokinin, *DC* dendritic cell, *EEC* enteroendocrine cell, *ENS* enteric nervous system, *FSH* follicle-stimulating hormone, *GABA* ɣ-aminobutyric acid, *GLP-1* glucagon-like peptide-1, *HN* hypothalamic-neurohypophyseal axis, *HPA* hypothalamus-pituitary-adrenal axis, *HPG* hypothalamus-pituitary-gonadal axis, *HPT* hypothalamus-pituitary-thyroid axis, *IL* interleukin, *LH* luteinizing hormone, *LPS* lipopolysaccharide, *NTS* nucleus tractus solitarii, *OXT* oxytocin, *PYY* peptide YY, *SCFA*s short chain fatty acids, *TNF-α* tumor necrosis factor alpha, T_3 triiodothyronine, T_4 thyroxine, *TSH* thyroid-stimulating hormone.

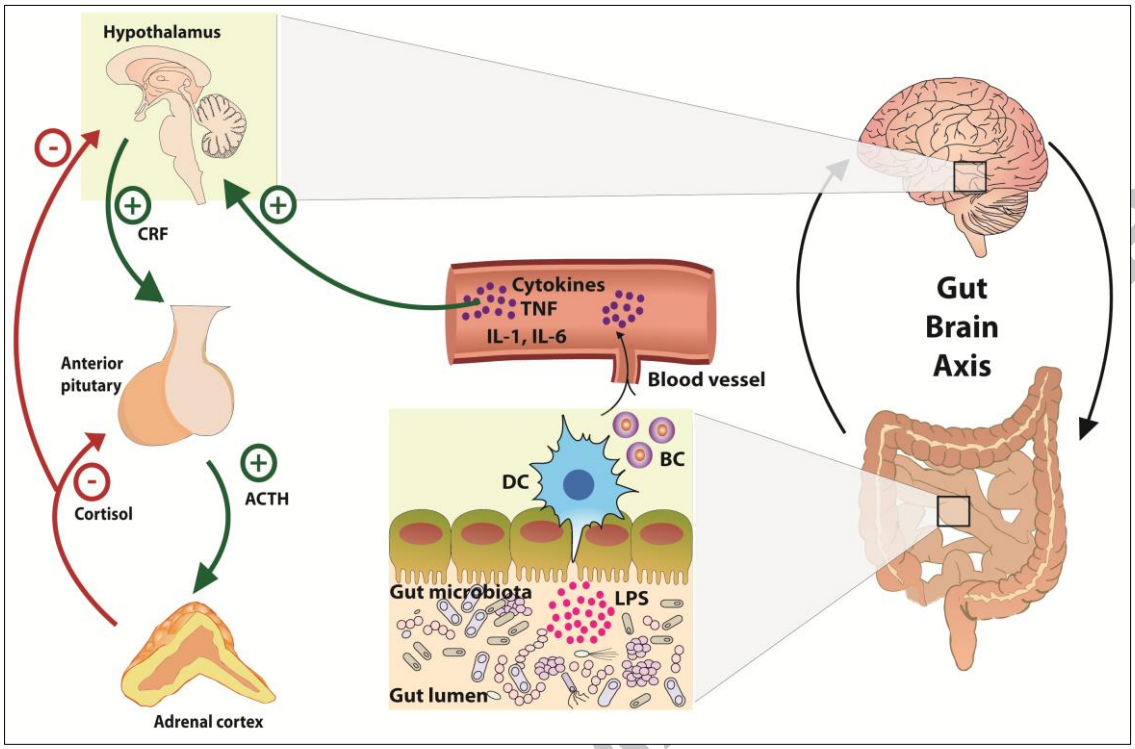

Figure 3. The immune system is a key mediator in the communication between the gut and the HPA (hypothalamus-pituitary-adrenal) axis. The gut microbiota regulates the release of cytokines TNFα, IL-1β and IL-6 into the circulation, which reach the brain and stimulate the release of CRF from the hypothalamus. This ultimately results in activation of the adrenal cortex and release of cortisol. *Abbreviations: ACTH* adrenocorticotropic hormone, *BC* B cell, *CRF* corticotrophin-releasing factor, *DC* dendritic cell, *IL* interleukin, *LPS* lipopolysaccharide, *TNF* tumor necrosis factor α.

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Highlights

- Intestinal microbes are components of the gut-brain axis, the bidirectional pathway between the gut and the brain
- The CNS is closely interconnected with the endocrine system to regulate many physiological processes in the human body
- The gut microbiota produces compounds of hormonal nature that influence distal sites such as the brain
- The gut microbiota interacts with elements of the host neuroendocrine system to modify host behaviours
- The following behaviours are examined: stress, eating behaviour, sexual behaviour, sociability, cognition and addiction