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Microbiota-Gut-Brain Axis as a Regulator of Reward Processes

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ABSTRACT

Our gut harbours trillions of microorganisms essential for the maintenance of homeostasis and host physiology in health and disease. In the last decade, there has been a growing interest in understanding the bidirectional pathway of communication between our microbiota and the central nervous system. With regard to reward processes there is accumulating evidence from both animal and human studies that this axis may be a key factor in gating reward valence. Focusing on the mesocorticolimbic pathway, we will discuss how the intestinal microbiota is involved in regulating brain reward functions, both in natural (i.e., eating, social or sexual behaviours) and non-natural reinforcers (drug addiction behaviours including those relevant to alcohol, psychostimulants, opioids and cannabinoids). We will integrate preclinical and clinical evidence suggesting that the microbiota-gut-brain axis could be implicated in the development of disorders associated with alterations in the reward system and how it may be targeted as a promising therapeutic strategy.

Abbreviations

5-HT, Serotonin; α-MSH, Melanocyte-stimulation hormone; AN, Anorexia nervosa; BBB, Blood-brain barrier; CCK, Cholecystokinin; CIE, Chronic intermittent vaporised alcohol exposure; ClpB, Caseinolytic protease B; CNS, Central nervous system; D1, Dopamine 1 receptor; D2, Dopamine 2 receptor; DA, Dopamine; DOPA, Dihidroxyphenylalanine; DOPAC, 3,4-Dihydroxyphenylacetic acid; EEC, Enteroendocrine cell; FFAR, Free fatty acid receptor; FMT, Faecal microbiota transplant; FOS, Fructo-oligosaccharide; GABA, γ-aminobutyric acid; GHSR-1a, Ghrelin receptor 1; GHSR, Growth hormone secretagogue receptor; GLP-1, Glucagon-like Peptide-1; GLP-1R GLP-1 receptor; GOS, Galacto-oligosaccharide; HVA, Homovanillic acid; LPS, Lipopolysaccharide; NA, Noradrenaline; NAc, Nucleus accumbens; NPY, Neuropeptide Y; NTS, Nucleus tractus solitarii; PFC, Prefrontal cortex; PVN, Paraventricular nucleus; PYY, Peptide YY; SCFA, Short chain-fatty acids; SPF, Specific-pathogen free; THC, Δ^9-tetrahydrocannabinol; TLR, Toll-like receptor; VTA, Ventral tegmental area.

1. INTRODUCTION

The reward system is a set of neuronal structures responsible for the processing of a number of psychological components, such as 'wanting', 'liking' and associative learning (Berridge and Robinson 2003). These three processes occur together, 'wanting' dominates the initial appetitive phase, 'liking' dominates the consummatory phase, and learning occurs through the reward-behavioural cycle (Berridge *et al.* 2016). Both phenomena are underpinned by different brain circuits and neurotransmitter systems. The 'wanting' component is largely controlled by the dopaminergic system, whereas the 'liking' component is thought to be more mediated by opioid and GABAergic systems (Berridge and Robinson 2003). The neural circuitry constituting the anatomical and neurochemical substrate for reward and pleasure was described several decades ago by Olds and Milner, who, after implanting electrodes in certain areas of the central nervous system (CNS) and administering electrical microstimuli, demonstrated a pleasure response in the animals (Olds and Milner 1954). Following this, it was proposed that the monoaminergic activity could underlie the neurochemical basis of pleasure, with the monoaminergic system playing an important role in drug reinforcement (Fibiger 1978; Arbuthnott *et al.* 1970; Poschel and Ninteman 1963). This system connects the ventral part of the midbrain with the ventral and anterior part of the brain. One of its best characterised pathways is the mesocorticolimbic projection, especially the dopaminergic pathway (Ikemoto 2010).

The reward pathway is initiated by the activation of dopaminergic neurons located in the ventral tegmental area (VTA), which project to the nucleus accumbens (NAc), the prefrontal cortex (PFC), and the amygdala, where dopamine (DA), together with other neurotransmitters, are released promoting learning and the sensation of pleasure (Bardo 1998). Another brain structure important role in reward processing is the habenula. This small structure receives inputs from the limbic system and send signals to the VTA, regulating DA levels in the striatal region playing an important role in reward and reward-associated learning (Velasquez *et al.* 2014; Baker *et al.* 2016; Proulx *et al.* 2014). Drugs of abuse (non-natural stimuli) have the ability to induce DA release of greater amplitude and duration than those induced by natural rewards (Wise and Rompre 1989). Despite the capacity of non-natural rewards to hijack the brain circuits in which natural rewards act, a high degree of overlap has been observed in the brain regions that process both stimuli (Olsen 2011). Plasticity in these circuits may be responsible for behavioural alterations (affecting motivation, executive function, and reward processing) characteristic of addiction and dependence (Kalivas and O'Brien 2008; Koob and Volkow 2010; Kelley and Berridge 2002).

There has been an increasing emphasis on the contribution of factors outside the brain in regulating central processes. Indeed, a growing body of research focuses on the ability of both the endocrine and the immune system on modulating reward processes (Anisman *et al.* 1996; Ye *et al.* 2001; Goeders 2002; Adam and Epel 2007; Montesinos *et al.* 2016; Greene *et al.* 2019). Over the past decade a new player has emerged as another key factor

in sculpting reward circuits across the lifespan, namely, the gut microbiome, which encompasses the trillions of bacteria in our gut. This review will focus on the emerging data that demonstrates how gut microbes may be involved in regulating brain reward functions influencing feeding, social and addictive behaviours (Figure 1). First, we will provide a brief overview of microbiota-brain connections explaining the main pathways of communication. Then, we will discuss the role of gut microbiota as a regulator of the reward system integrating new preclinical and clinical evidence on both natural and non-natural rewards. We will describe potential mechanisms of action and the implications for the development of psychiatric disorders. Finally, we will examine the emergent evidence of microbiome-driven interventions and its therapeutic effects in psychiatric disorders associated with reward alterations.

2. THE MICROBIOTA-GUT BRAIN AXIS

By definition, the microbiome is considered a community of microorganisms - the bacteria, fungi, virus, and other single cell microorganisms living together in a particular habitat (Ursell *et al.* 2012). One of the most exciting advances in biology has been the understanding of how the microbiome influences host physiology and behaviour (Cryan and Dinan 2012; Gilbert *et al.* 2018). Not only do humans, animals and plants have their own unique microbiome (Butler *et al.* 2019; Compant *et al.* 2019; Knight *et al.* 2017); but soils, forests and oceans do as well (Sunagawa *et al.* 2015; Baldrian 2017; Lakshmanan *et al.* 2014), which demonstrates the importance of microorganisms in the overall functioning of life. The human body harbours about 100 billions microbes, outnumbering the human cells in the body by a ratio of 1.3 to 1 (Sender *et al.* 2016). The majority of these microorganisms are found in the gastrointestinal tract, resulting in a complex symbiotic relationship that is acquired immediately at birth (Robertson *et al.* 2019; Tamburini *et al.* 2016). Although there has been some reports of existence of microbiota in the placenta and in utero colonization in the foetus (Collado *et al.* 2016; Jiménez *et al.* 2008; Aagaard *et al.* 2014), these findings have been disputed by others suggest limited evidence by a lack of contamination controls, maintaining the idea that the placenta and womb are sterile (Lauder *et al.* 2016; Lim *et al.* 2019; Milani *et al.* 2017; Rackaityte *et al.* 2020; Perez-Muñoz *et al.* 2017). The gut is densely populated with greater diversity of microorganisms that any other organ. The interaction between the microbiota and the host is intricate, creating a mutually beneficial relationship. On the one hand, the microbiota has the ability to contribute to a multitude of physiological processes such as protection against pathogens, modulation of the immune system, fermentation of undigestible dietary fibres and production of active peptides and proteins that regulate energy metabolism in the host (Rooks and Garrett 2016; Kennedy *et al.* 2017; Mayer *et al.* 2015). On the other hand, the host provides protection and nutrients necessary for the development of the microbiological ecosystem (Foster *et al.* 2017; Mushegian and Ebert 2016), highlighting the mutualistic relationship between the host and the microbiome.

Although a basic understanding of the interaction between the microbiota and the host dates back to ancient times, recently, the interest on the impact of intestinal microbiota on health and disease has re-emerged. This has largely been due to advances in sequencing technologies coupled with the appropriated bioinformatic tools (Gevers *et al.* 2012; Hao *et al.* 2017). Moreover, there has been a growing awareness of the crosstalk between our intestinal bacteria, the CNS and behaviour. The microbiota-gut-brain-axis is a bidirectional pathway throughout which the brain regulates the activity of the gut and *vice versa* and is critical for the homeostasis of the host system (Rhee *et al.* 2009; Collins *et al.* 2012; Cryan *et al.* 2019) (Figure 1). Signals from the gastrointestinal tract to the brain are able to influence a number of brain functions, and the brain responds by executing decisions that determine seeking, intake, and behaviours (eating, social, activity), which shows that both organs are constantly communicating and influencing each other. Communication in the microbiota-gut-brain axis does not only depend on neuronal signals (neurotransmitters), it also depends on endocrine (hormones and gut peptides) and immune signals (cytokines), and microbiota derived metabolites, acting together to regulate host physiology and microbiota composition.

2.1 The vagus nerve

The vagus nerve is one of the major modulatory constitutive communication pathways between the microbiota and the brain (Fülling *et al.* 2019). The vagal afferent nerves are in contact with all the layers of the digestive wall, but do not cross the intestinal epithelial barrier so they are not in direct contact with the intestinal microbiota (Bonaz *et al.* 2018). Thus, these nerve fibres can respond only to indirect microbial signals, such as neurotransmitters or short chain-fatty acids (SCFA), which will diffuse through the epithelial walls or through interaction with enteroendocrine cells (EECs) (Raybould 2010; Ye and Liddle 2016). It has also been described that gastrointestinal hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) or ghrelin can act on the CNS through the vagus, thanks to the presence of specific receptors on these fibres (Ye and Liddle 2016). Evidence suggests that the microbiota has the ability to alter host behaviours throughout the vagus nerve, transducing beneficial microbial-derived effects (Bravo et al. 2011; Bercik et al. 2011; Vazquez et al. 2016; Sgritta et al. 2019), and modulating anxiety-related behaviours (Goehler *et al.* 2005).

2.2 Immune system

Another important role of the microbiota is its contribution as an immune system modulator. The gastrointestinal tract represents the major interface between the immune system and the microorganisms, and the ability to discriminate commensal from pathogens can be considered as the driving force of immune system evolution (Mezouar *et al.* 2018). Cytokines (key mediators of immune system function) can signal to the brain indirectly via the vagus nerve or directly throughout the blood-brain barrier (BBB). Lipopolysaccharide (LPS), the largest component of the external membrane of Gram-negative bacteria, plays an important role in activating the immune system as it comprises the most important surface antigen of this type of bacteria. This component present in the

cell wall activates toll-like receptors (TLRs), which are widely expressed in immune cells. Once these receptors are activated, they can recruit inflammatory mediators, cause cytokine production, and chemokine-mediated recruitment of acute inflammatory cells (Daulatzai 2014). Released cytokines can act on the CNS via slow transmission, involving cytokines produced by different tissues and diffusing into the brain (Banks 2008) or via fast transmission, involving afferent nerves innervating the body and signalling the brain (Goehler *et al.* 2005). The activation of the brain cytokine system is associated with changes in sickness behaviour altering sleep, sociability, eating, cognition and motivation (Konsman *et al.* 2002). For example, the administration of the VSL#3 (composed of various *Lactobacilli*, *Bifidobacteria* and *Streptococcus*) attenuated sickness behaviours and inflammation, demonstrating that the microbiota is able to modulate inflammatory responses, which can affect brain function and behaviour (D'Mello *et al.* 2015). The gut microbiota has also been implicated in microglial maturation and function (Erny *et al.* 2015), or the increased neuroinflammatory responses at middle age and at advanced age (inflammaging) (Thevaranjan *et al.* 2017; Xia *et al.* 2016; Boehme *et al.* 2020), reinforcing the idea of the microbiome as an essential modulator of a healthy immune response.

2.3 Bacterial metabolites: Short-chain fatty acids and neurotransmitters

Under anaerobic conditions, undigested carbohydrates are fermented mainly into short-chain fatty acids (SCFA), the most extensively studied molecules with respect to how the gut microbiota influence host physiology. These molecules have multiple effects in the host, principally as an energy source (Dalile *et al.* 2019). It has also been demonstrated that SCFA can elicit intracellular signalling by binding to G-protein coupled receptors (e.g., free fatty acid receptors or FFARs). These receptors are involved in controlling anorexigenic hormones (i.e. PYY and GLP-1), providing a potential link between SCFA and appetite control (Byrne *et al.* 2015). Recently, it was also shown that SCFA can attenuate ghrelin receptor signalling (Torres-Fuentes *et al.* 2019), a key receptor at the interface of appetite regulation and food reward (Schellekens *et al.* 2012). In addition, microbial-derived SCFAs can also influence brain physiology and behaviour directly. Circulating SCFAs, such as butyrate, acetate and propionate, are able to cross the BBB throughout monocarboxylate transporters (Maurer *et al.* 2004), and enter the CNS to exert their effects on neurons and glial cells (Joseph *et al.* 2017). Systemic administration of sodium butyrate has also been reported to induce transient acetylation of histones in the frontal cortex and hippocampus, inducing antidepressant-like effects in mice (Schroeder *et al.* 2007). Evidence suggests that SCFAs are capable of modulating neurotransmission (DeCastro *et al.* 2005; Shah *et al.* 2006; Nankova *et al.* 2014), for example increasing the expression of tyrosine hydroxylase and decreasing the expression of dopamine-β-hydroxylase (Mally *et al.* 2004; DeCastro *et al.* 2005). Also, it has been observed that propionic acid modulates serotoninergic, GABAergic and dopaminergic neurotransmission *in vivo* (El-Ansary *et al.* 2012). In particular, the hippocampus and striatum -crucial areas for reward behaviours- seem to be influenced by gut-derived SCFAs (van de Wouw *et al.* 2018; Byrne *et al.* 2015).

The microbiota has been shown to synthesize and respond to several neurochemical compounds associated with the host mood and behaviour (i.e., DA, serotonin (5-HT), γ-aminobutyric acid (GABA), etc) (Strandwitz 2018; Wall *et al.* 2014). These neuroactive compounds can enter into the circulatory system reaching distal areas such as the brain. Therefore, the gut-mediated regulation of these different neurotransmitters may have a crucial role in brain processes. Catecholamine levels have been shown to be altered in germ-free mice when compared with specific pathogen free, suggesting the ability of the gut microbiota to produce these compounds (Asano *et al.* 2012). However, the possibility that these catecholamines can act distally in the brain is highly questionable, since they are not able to cross the BBB. In spite of this, there is evidence suggesting that the gut microbiota is capable of inducing changes at the catecholaminergic level in the brain. A clear example has been observed in germ-free animals, which showed a decrease in the amino acid tyrosine (essential amino acid for the synthesis of noradrenaline (NA) and DA) when compared to recolonized germ-free mice, which induced an increase in the brain DA levels (Matsumoto *et al.* 2013). Some gut microbes are also able to metabolise tryptophan (the precursor of 5-HT). It has been observed in germ-free mice a reduction 5-HT levels in plasma, colon and caecum (Hata *et al.* 2017; Clarke *et al.* 2013; Wikoff *et al.* 2009), and the conventionalization of germ-free mice resulted in an increase of intestinal 5-HT. Indeed, bacterial species such as *Clostridium perfringens* modulates host colonic 5-HT synthesis via host tryptophan hydroxylase, highlighting the role for the host-microbiota in regulating 5-HT-related biological processes (Yano *et al.* 2015). Gut microbiota is also able to covert the amino acid glutamate into GABA. Interestingly, certain *Escherichia*, *Lactobacillu*s and *Bifidobacterium* have been shown to synthesize GABA. Gut-derived GABA, unlike catecholamines, is able to reach the CNS due to the presence of specific GABA transporters expressed in the BBB (Takanaga *et al.* 2001).

2.4 Enteroendocrine signalling

EECs are specialised cells distributed throughout the gastrointestinal tract and represent approximately 1% of the epithelial cells (Latorre *et al.* 2016). EEC secretory products such as CCK, GLP-1 and PYY are released in response to diverse stimuli to influence physiological functions in the host such as control of intestinal secretion and motility, regulation of food intake and metabolism (Latorre *et al.* 2016; Rehfeld 2004). Hormones and gut peptides secreted by EECs act on receptors present on the vagus nerve that bring stimuli to the brain and may mediate satiety and other behavioural responses. However, it is unclear whether some of these peptides interact directly with the brain or how the brain interprets the information coming from the gut. Recently, a new route of communication between EECs and the enteric nervous system has been described (Bohórquez *et al.* 2014; Bohórquez *et al.* 2015; Kaelberer *et al.* 2018). A basolateral elongation, called neuropod, has been observed in some of the EECs, and is capable of establishing a functional synapse with enteric glia and vagal afferents (Kaelberer *et al.* 2020; Liddle 2019; Kaelberer *et al.* 2018). This interesting connection suggests that the intestinal signals from the EECs to the brain may be more precise and faster than

expected, and that the CNS may have the ability to interact with the EECs through these connections. Additionally, receptors for gut peptides have been described in central brain regions such as hypothalamus and nucleus tractus solitarii (NTS), indicating that these peptides might modulate their responses acting directly in the brain (Ohkubo *et al.* 1990; van Bloemendaal *et al.* 2014; Göke *et al.* 1995; Dourish *et al.* 1989; Ballaz 2017). Although inconsistencies exist, different microbiome-targeted studies have demonstrated that the microbiota modulates EECs signalling (Covasa *et al.* 2019; Plovier and Cani 2017). Preliminary evidence demonstrates that germ-free animals exhibit attenuation of gut peptides expression, suggesting that the microbiota may be responsible for stimulation and production of satiety peptides (Duca *et al.* 2012). Furthermore, the administration of oligofructose and inulin (dietary fructans) promote satiety in rats, increasing GLP-1 and decreasing ghrelin in the gut (Cani *et al.* 2004), indicating that modulations of the gut bacteria regulates gut peptides. Moreover, the existing association between microbiome changes and ghrelin levels were recently highlighted (Schalla and Stengel 2020). In theory, SCFAs may have the capability to modulate these peptides, through their interactions with FFAR receptors present in EECs promoting the release of gut hormones (Nøhr *et al.* 2013).

2.5 Hypothalamic-pituitary-adrenal axis (HPA)

The HPA axis is a complex set of pathways and interactions among the hypothalamus, the pituitary gland, and the adrenal glands. Neurons in the hypothalamus release corticotrophin-releasing factor and vasopressin stimulating the release of the adrenocorticotrophic hormone in the pituitary gland which in turn promotes the release of glucocorticoid hormones from the adrenal glands (Besedovsky *et al.* 1991). The HPA axis has an important role regulating homeostatic systems in the body (i.e., CNS, immune system, metabolic system, reproductive system, mood and emotion) and is the main coordinator of stress response. It has been observed that different types of stress can alter the composition of the gut microbiota (Bailey 2014; Bharwani *et al.* 2016; De Palma *et al.* 2014), but also gut microbiota can influence HPA responses (Frankiensztajn *et al.* 2020; Wall *et al.* 2014). Studies in germ-free animals demonstrated an exaggerated HPA response (elevated adrenocorticotrophic hormone and corticosterone) when exposed to stressors (Clarke *et al.* 2013; Sudo *et al.* 2004), suggesting the relationship between the gut microbiota and stress altering HPA axis. Gut microbiota seems to activate HPA axis through modulations of the immune system or microbial metabolites (i.e., SCFAs or neurotransmitters) inducing a dysfunctional response to the host and contributing to the development of CNS disorders (Rea *et al.* 2016; Moloney *et al.* 2014).

3. THE MICROBIOTA AS A REGULATOR OF THE REWARD PATHWAY

It is well known that microbes resident in the gastrointestinal tract are capable of influencing host functions and behaviours, demonstrating that the host and its symbiotic microbes can behave as one evolutionary entity called holobiont (Margulis, 1991). This close interaction between the host and the microbiome has provided a clear evolutionary advantage that has favoured survival and fitness for both. Such microbiota-driven

alterations in host behaviour have led to the hypothesis that some symbionts manipulate the host for their own purposes (Sampson *et al.* 2016; Johnson and Foster 2018). For example, some authors suggest that microorganisms could influence individual´s nutritional aspects modifying feeding decisions or even making us more sociable to promote contact between hosts and increase their own transmission (Alcock *et al.* 2014; Leitão-Gonçalves *et al.* 2017). Behavioural changes induced by microbes have also been traced to specific subsets of the microbiota. Evidence suggests that *Lactobacillus* and *Bifidobacterium* species can relieve anxiety and depressive symptoms in animals and humans (Aizawa *et al.* 2016; Desbonnet *et al.* 2008; Jang *et al.* 2018). In addition, *Bacteroides* species have been shown to improve repetitive and anxious behaviours and communication deficiencies in mice, purportedly by restoring specific bacterial metabolites (i.e., 4-ethylphenylsulfate and indolepyruvate) (Hsiao *et al.* 2013). These microbiome-induced alterations show that they could play a role in regulating one of the most important and oldest systems in our brain, the reward system (Figure 1). Growing evidence indicates that perturbations in the microbiota can influence monoaminergic neurotransmission (i.e. dopaminergic neurotransmission) in the mesocorticolimbic circuit, which is involved in natural and non-natural rewards (González-Arancibia *et al.* 2019). Such perturbations also appear to be a signature in psychiatric disorders in which the mesocorticolimbic circuit is highly involved (Skosnik and Cortes-Briones 2016).

4. NATURAL REWARDS

4.1 The microbiota as a regulator of food reward

Food has been one of the most studied rewarding stimuli in the scientific literature. Eating behaviour is a complex mechanism involving appetite, motivation and energy demands, and is regulated by numerous central and peripheral factors (Ursell *et al.* 2012). Feeding behaviour is regulated mainly by the integration of two neural circuits: the homeostatic, necessary to maintain weighty and metabolic functions, and the hedonic, driven by the sensation of pleasure (Rossi and Stuber 2018). The close connection between feeding and reward demonstrates that both neural circuits are activated simultaneously during eating behaviours. Peripheral signals from the adipose tissue, the pancreas and the gut providing information on the energy balance are received by the hypothalamus and the VTA (Alonso-Alonso *et al.* 2015) (Figure 2). Both regions are responsible for coordinating these signals in order to maintain the metabolic needs and to promote food seeking (DiLeone *et al.* 2012). The VTA acts as an integration node of these peripheral, hypothalamic and vagal signals to promote motivation and food consumption, supporting the role of the reward system in regulating eating behaviours (Meye and Adan 2014). Evidence suggests that gut microbiota might be an important modulator of these pathways of communication in the host brain, influencing host metabolism and mesolimbic reward circuits and altering feeding behaviours (Murray *et al.* 2014; van de Wouw *et al.* 2017) (Figure 2).

4.1.1 VTA as a target for gut-derived signals

Ball was the first researcher to provide evidence of the role of the gut in reward by stimulation of the lateral hypothalamus. The stimulation of this region promoted feeding behaviour, an effect that was blocked following a subdiaphragmatic vagotomy in rats (Ball 1974). Recently, it has been shown that optogenetic right-node vagus stimulation produces reward behaviours, resulting in increasing dopaminergic activity in the brain (albeit in the substantia nigra) (Han *et al.* 2018), and suggesting that the vagus nerve is involved in nutrient sensing via gastrointestinal communication. There are approximately 20 regulatory peptides produced by the EECs, which are distributed in the gastrointestinal mucosa controlling digestion, appetite and metabolism (Sam *et al.* 2012; Murray *et al.* 2014). Gut peptides target the brain via sensory nerves and the circulation (Covasa *et al.* 2019) encoding hunger and satiety signals modulating the brain reward circuit in a multitude of ways.

Ghrelin is the only known peripherally-derived orexigenic peptide and it is released during fasting by the stomach into the circulatory system and crosses the BBB promoting food intake due to its ability to activate its receptor expressed on neurons in the arcuate nucleus that produce neuropeptide Y (NPY) and agouti-related peptide (Perry and Wang 2012; Howick *et al.* 2017). Interestingly, ghrelin signalling plays a key role at the interface of homeostatic appetite control and food reward signalling (Schellekens *et al.* 2012). Elevated circulating levels of ghrelin signal an increase in appetite while at the same time modulate food 'liking' and 'wanting' (Perello and Dickson 2015; Druce *et al.* 2005). Ghrelin also appears to stimulate appetite through actions on the vagus nerve (Date *et al.* 2002). In humans and rats, the presence of the ghrelin receptors (GHSRs) on neurons attached to the nodose ganglia suggests that the vagus nerve can transmit the ghrelin signal from the stomach to the CNS (Burdyga *et al.* 2006; Sakata *et al.* 2003). Interestingly, increased endogenous levels of ghrelin have been shown to increase central dopamine levels (Kawahara *et al.* 2013), while functional magnetic resonance imaging in human subjects has shown that ghrelin administration enhances the activation of the central reward circuitry in response to food visual cues (Goldstone *et al.* 2014). On one hand, ghrelin increases the value of reward by exerting its effects on the reward system, acting on GHSRs in the VTA (Abizaid *et al.* 2006), favouring DA concentrations and dopaminergic receptor activity in the NAc. In addition, ghrelin has been shown to alter the expression of dopaminergic and acetylcholinergic receptors in the VTA and NAc (Jerlhag *et al.* 2012). On the other hand, actions of this peptide on reward are not limited exclusively to the catecholaminergic system, it is also capable of altering the expression of opioid receptors (μ opioids) in the VTA, increasing motivation and favouring eating behaviours (Skibicka *et al.* 2012; Kawahara *et al.* 2013). These findings demonstrate that ghrelin not only exerts its role on homeostatic feeding but can also alter the hedonic value by acting on the VTA, activating the reward system and promoting food-seeking behaviours.

Anorexigenic peptides such as CCK, GLP-1 and PYY are released from different parts of the gastrointestinal tract in response to the presence or absence of nutrients regulating

appetite via the gut-brain axis pathways. CCK is released in response to fatty acids and amino acids that interacts with specific G-coupled receptors present in the EECs cells (McLaughlin *et al.* 1998). CCK acts on vagal afferents that terminate in the NTS, activating pathways that control feeding behaviours, and altering food intake by interacting with dopaminergic system (Bednar *et al.* 1991). In addition, CCK stimulates pancreatic secretion of insulin, a peptide with a strong influence on the reward system due to the presence of receptors for this molecule in dopaminergic neurons in the VTA (Figlewicz *et al.* 2003). Although the mechanism of action is completely unknown, it seems that insulin is able to raise the threshold of neuronal activation of the reward system by suppressing the excitatory transmission of VTA (Labouèbe *et al.* 2013) and reducing the expression of opioid receptors (Figlewicz *et al.* 2008), decreasing motivation and food consumption.

Another gut peptide with an important role regulating food intake is GLP-1. This peptide activates GLP-1 receptors (GLP-1R) present in the dendritic terminals of the vagal afferents acting on the CNS and suppressing food intake (Krieger *et al.* 2015). Pharmacological activation of GLP-1R in the VTA and NAc reduced intake of highly palatable food without suppressing the intake of standard diet in rats that were provided with both diets simultaneously (Alhadeff *et al.* 2012). Also, systemic administration of GLP-1 agonists activate GLP1-R in the VTA reducing food intake and body weight in rats (Mietlicki-Baase *et al.* 2013). Taken together, these results indicate that the activation of GLP-1 signalling in the mesolimbic system can mediate the hedonic and rewarding value of food (Dickson *et al.* 2012; Dossat *et al.* 2011). PYY is another peptide released in the colon and ileum of relevance for food intake regulation. This peptide, apart from inducing its effects through the vagus nerve, can effectively cross the BBB and act on the hypothalamus exerting anorectic effects (Nonaka *et al.* 2003). However, the action of PYY is not only restricted to the hypothalamus. Indeed, it has been shown that systemic administration of PYY inhibit food intake in rodents and humans (Batterham *et al.* 2002) altering the neuronal activity of VTA (among other regions) in human volunteers (Batterham *et al.* 2007), suggesting modulation of the reward pathway.

4.1.2 Food reward signalling

The gut contains numerous bacteria that are dependent on the feeding behaviour of the host to receive nutrients necessary for their growth and adequate maintenance. Likewise, bacteria contribute to host physiology digesting fibre, shaping the host immune system and producing essential metabolites (Zheng *et al.* 2020; Holscher 2017). EECs are able to secrete peptides that regulate satiety and appetite in response to bacterial metabolites (Raybould 2010), demonstrating that the microbiota composition and richness might be responsible for host eating behaviour and appetite (Alcock *et al.* 2014; Urrutia-Piñones *et al.* 2018).

Changes in eating behaviour have been related to alterations in intestinal microbiota in a process called ‘molecular mimicry’. The microbiota is capable of producing amino acid

sequences homologous to endogenous neuropeptides regulating appetite and emotion. One of the clearest examples is with *Bacteroides* that produce molecules homologous to insulin, NPY, melanocyte-stimulation hormone (α-MSH) showing their impact on appetite and emotion by mimicking these molecules (Fetissov *et al.* 2008a). These bacterial peptides have homologous sequences that are capable of inducing immunological cross-reactions with immunoglobulins (auto-antibodies) present in the circulatory system (Chervonsky 2013). Under physiological conditions, auto-antibodies are found to act directly against hormones or peptides (e.g. ghrelin, leptin, insulin, PYY and NPY among others) regulating appetite. Auto-antibodies have been detected in humans and rats (Fetissov *et al.* 2008b), although the levels of these have been significantly decreased in germ-free animals altering motivational behaviours (Fetissov *et al.* 2008a). In addition, it has been observed that *Rikenellaceae* and *Clostridiaceae* are capable of producing a peptidase called Caseinolytic protease B (ClpB) in humans (Arnoriaga-Rodríguez *et al.* 2020), that can mimic α-MSH increasing satiety (Tennoune *et al.* 2014). This protease may produce auto-antibodies that act against α-MSH reducing its anorexigenic effects, which can causes a decrease in the effects of satiety in the animal promoting food intake (Tennoune *et al.* 2014).

Metabolites produced by the intestinal microbiota such as SCFAs are able to modulate eating behaviours (Byrne *et al.* 2015; Dalile *et al.* 2019). At a local level, it has been described that SCFA improve the production and secretion of 5-HT in the colon, as well as promote the release of anorectic hormones such as GLP-1 and PYY into the bloodstream, thanks to their interaction with FFA2 and FFA3 receptors (Dalile *et al.* 2019). These receptors are also present in the adipose tissue, where they are able to release leptin (Gabriel and Fantuzzi 2019), reducing food intake via homeostatic and hedonic mechanisms (Fulton *et al.* 2006; Hommel *et al.* 2006) and in the vagus nerve (Nøhr *et al.* 2015). De Vadder and colleagues demonstrated that propionate increased the activity of the dorsal vagal complex, which receives inputs from the vagus nerve and hypothalamus, key brain structures in appetite control (De Vadder *et al.* 2014). In addition, the administration of dietary compounds that increase the production of propionate by the microbiota in the colon of healthy humans attenuated the rewarding effects on feeding behaviours (Byrne *et al.* 2015) via the striatal pathway, decreasing caudate and NAc activity.

4.1.3 Implications for eating disorders

There is growing evidence suggesting that modulation of gut microbes affects food and reward-seeking behaviours. A clear example of how the microbiota is able to modulate food choices is found in research utilising the *Drosophila melanogaster* (Leitão-Gonçalves *et al.* 2017). The lack of essential amino acids in *D. melanogaster* diet increased their appetite for foods containing these compounds. However, *D. melanogaster* receiving an appropriate microbiota transfer do not show appetite for foods rich in essential amino acids, suggesting that the microbiota is responsible for mediating this type of response. The authors demonstrated that suppression of this feeding behaviour

was associated with *Acetobacter pomorum* and *Lactobacilli*, showing that they might be modulators of feeding choices.

The communication between the host and the microbiota has an impact on satiety signalling and host food consumption by altering the optimal energy consumption requirements, which are different for both the host and the microbiota. An increase in energy consumption above the optimal levels for the individual can provide an excess of substrates that favour the explosive growth of certain microbial populations to the detriment of others (Ierardi *et al.* 2016; Tomas *et al.* 2016; Lin *et al.* 2019; Hildebrandt *et al.* 2009). These alterations can result in a reduction in bacterial α diversity, causing the manipulation of the host to consume an excess of energy. Despite the intestinal microbiota is considered a community of symbiotic and mutualistic microorganisms (Bäckhed *et al.* 2005; Schluter and Foster 2012; Ley *et al.* 2008), the evolutionary conflict between both has not been well explored. Some studies argue that microbial genes have evolved to be able to manipulate their hosts and host genes have evolved to prevent microbial manipulation that conflicts with their own interests (Alcock *et al.* 2014; Kurokawa *et al.* 2007; Qin *et al.* 2010). Alterations in the bacterial community can turn the initial beneficial interaction into an unbalance relationship contributing in the development of a wide range of disorders (i.e., eating disorders) (DeGruttola *et al.* 2016; Glenny *et al.* 2017). From an evolutionary perspective, foods with a high content of fats and sugars are more attractive since they can be quickly converted into energy (de Macedo *et al.* 2016). Furthermore, the consumption of this type of high-energy diet (western diet) has been associated with dysregulations in feeding behaviour (Avena and Gold 2011), the reward system (Avena and Gold 2011) and the gut microbiota (Zinöcker and Lindseth 2018).

Binge eating occurs in some eating disorders promoting overweight associated with a loss of control over eating, specially of highly palatable and caloric foods that are rich in sweets, fats, and have little nutritional value (Avena 2007). Moreover, a growing body of research is showing that highly palatable and hyper-processed foods activate the reward system triggering adaptations similar to those induced following drug consumption (Koob and Moal 1997; Lenoir *et al.* 2007; Vendruscolo *et al.* 2010; Moore *et al.* 2017), altering eating patterns that might result in the development of "food addiction". In the long term, excessive consumption of palatable energy-dense food can dysregulate the reward system, causing overeating and contributing to changes in feeding behaviours that might lead to the development of disorders such as obesity (Frank 2013), supported by marked alterations in the intestinal microbiota found in obese individuals (Turnbaugh *et al.* 2009). Human and mouse models of obesity have shown alterations in the gut microbiome composition, associated with an increase in the relative abundance of *Firmicutes* and a decrease in *Bacteroidetes* when compared with lean controls (Ley *et al.* 2005). Several studies demonstrated that germ-free mice are resistant to the obesogenic effects induced by high-fat diets (Kübeck *et al.* 2016; Rabot *et al.* 2010; Logan *et al.* 2020). A clear example was reported by Bäckhed and collaborators, where they observed

a decrease in body fat despite showing an increase in food intake in germ-free mice (Bäckhed *et al.* 2004). Increases in sucrose consumption have also been observed in germ-free mice, associated with an increase in the expression of specific glucose transporters in the gut (Swartz *et al.* 2012), which may be responsible for regulating the release of gastrointestinal peptides (Samuel *et al.* 2008; Hirasawa *et al.* 2005). In line with this, an increase in preference and intake for fats has been observed in germ-free mice, associated with a decrease in the gut expression of satiety signals (i.e., CCK, PYY and GLP-1), as well as a decrease in the plasmatic levels of ghrelin and leptin (Duca *et al.* 2012), suggesting that gut microbes are able to influence feeding decisions targeting homeostatic and hedonic systems. Nutrient sensing throughout the gastrointestinal tract plays an important role in the rewarding aspect of food intake and could be strongly influenced by gut microbes. Eating disorders such as obesity is associated with low responsiveness to sweet and fat foods, favouring the liking for these types of food (Berthoud and Zheng 2012). Taken together, these results show that microbiota can induce alterations in nutrient sensing through peptide regulation that can favour the intake of highly palatable food by inducing alterations in the reward system (Sclafani and Ackroff 2012; Furness *et al.* 1999; de Macedo *et al.* 2016). Moreover, excessive consumption of obesogenic diet is not only associated with an increase in obesity, but also evokes changes in social behaviour and dopaminergic alterations in the mesolimbic pathway (Davis *et al.* 2008). A recent study demonstrated that intermittent consumption of a hypercaloric diet induced physiological changes in brain (expression of mRNA associated with reward and neuroplasticity) and gut microbiota (alteration in *Lachnospiraceae*, *Ruminococcaceae* and *Clostridiales*), that may be associated with the social alterations observed in rats (Reichelt *et al.* 2020).

Another disorder associated with alterations in feeding behaviours with a strong link to the gut microbiota is anorexia nervosa (AN) (Kleiman *et al.* 2015; Borgo *et al.* 2017). This disorder is characterised by an abnormally low body weight, an intense fear of gaining weight, and a distorted body image. AN has been associated with significant dysfunctions in the reward system (Frank *et al.* 2012; Scheurink *et al.* 2010; Cha *et al.* 2016). Several studies have found alterations in gut peptides such as PYY or ghrelin in patients with AN, which could contribute to the abnormal eating behaviours of these patients by altering homeostatic and hedonistic eating habits (Eddy *et al.* 2015; Otto *et al.* 2001). In addition, increases in *Methanobrevibacter smithii*, a decreased in the microbial richness of specific genera (*Streptococcus*, *Clostridium* and *Bacteroides*), and reduced concentrations of certain SCFAs (specifically acetate and propionate) have been reported in patients with AN (Armougom *et al.* 2009; Morita *et al.* 2015). These alterations in SCFAs induced by changes in the bacterial community could be responsible for alterations in gut peptides changing feeding patterns. Also, AN patients show an increased in plasma ClpB, which may be associated with lower body weight and lower food consumption (Breton *et al.* 2016). Taken together, these results suggest that the intestinal microbiota may exert effects on food consummatory behaviour which might contribute to the development of eating disorders, associated in part with alterations in the reward system, in a multitude of ways.

4.2 The microbiota as a regulator of social reward

Social interactions are powerful, positive, and pleasurable stimuli in animals and humans that are beneficial for a vast array of aspects of life. Sociability has many advantages in terms of reproduction, defence and foraging, demonstrating that it is a key aspect of a mammals' longevity and survival. The brain has evolved to accommodate for social behaviour and some studies have speculated that natural selection has favoured microbes that increase their own transmission through social interactions (Lombardo 2008; Montiel-Castro *et al.* 2013). These facts lead us to think that the endosymbiont intestinal microbiota could have influenced the evolution of sociability and social interactions. The social transmission of the microbiota between conspecifics differs among species (Sherwin *et al.* 2019a). In invertebrates, coprophagia (consumption in faeces) and trophallaxis (transfer of food or pheromones from mouth to mouth or rectum to mouth, frequent in social insects) play an important role in the microbial transmission (Engel and Moran 2013; Martinson *et al.* 2012; Koch and Schmid-Hempel 2011). Also, in rodents, coprophagy is an important mechanism not only for feeding, but also for the transmission of microbiota, favouring social interactions (Archie and Tung 2015). In humans this social transfer of microbiota occurs with individuals who share certain environments or lifestyles (i.e., share the same microbial sources or diet), showing that frequent contact with cohabitants shape the composition of our microbial communities (Song *et al.* 2013; Lax *et al.* 2014).

The neuropeptides oxytocin and vasopressin released by the paraventricular nucleus (PVN) of the hypothalamus have been highlighted as important modulators of social behaviours (Meyer-Lindenberg *et al.* 2011). Some evidence indicates that these social hormones are modulated by the gut microbiota (Erdman and Poutahidis 2016; Desbonnet *et al.* 2015; Sgritta *et al.* 2019; Buffington *et al.* 2016), suggesting that the microbiome could induce its effects on social behaviour, favouring the rewarding effects of social interaction (Krach 2010; Preston 2017; Bhanji and Delgado 2014). The PVN projects to regions rich in oxytocin receptors, such as those associated with dopaminergic signalling in the mesolimbic system (VTA and NAc) engaging the social reward circuit. Maternal care, social play and sexual behaviour are the most studied social interactions in mammals due to their importance and highly rewarding effects. These behaviours induce a sense of well-being and pleasure, they motivate approach behaviours to specific social stimuli and elicit associative learning to positive past experiences. In the last decade, there has been a growing interest in understanding the role of the microbiome in these three branches of sociability (Figure 3).

4.2.1 Maternal care, social play and sexual behaviour

In mammals, maternal behaviour and care involves input from several factors including sensory cues (auditory and olfactory signals) emitted by the infant and received by the mother, as well as proper oxytocin system functioning. This behaviour motivated during the postpartum period is highly adaptive and functions to drive the bond between the

mother and pup by seeking out and interacting with the pups which is essential for the development and survival of the offspring (Fleming *et al.* 1994; Fleming *et al.* 1999). Oxytocin facilitates the motivation to approach new-born pups through connections with the VTA (Kohl *et al.* 2017). Oxytocinergic signalling drives contact with the offspring, helping to establish this memory for the pups and reinforce the mother-pup bond (Pedersen *et al.* 1982; Albin-Brooks *et al.* 2017). The rewarding properties arising from this bond during the postpartum period could result in a unique state of reward responsiveness during which pups are the most rewarding stimulus to the mother (Seip and Morrell 2007), and changes in the dynamic mother-pup interaction due to hormonal fluctuations in mothers or changes in the pups needs may alter this maternal behaviour (Wansaw *et al.* 2008). The gut microbiota has emerged as a critical regulator in the early postnatal period, being essential for the appropriate development of the offspring (Cowan *et al.* 2020), but the microbiota can also influence postnatal development by regulating maternal factors. It has been reported that mothers who deliver vaginally-born offspring display greater activity in the striatum when compared to a mother that delivered by caesarean-section, indicating that oxytocin may help to increase maternal caregiving through activation of the dopaminergic reward system (Swain *et al.* 2008). It has been observed that antibiotic administration to dams results in abnormal behaviour, suggesting a clear role of the microbiome in regulation of maternal care. Indeed, cross-fostering by conventional dams can rescue the behavioural phenotype in offspring born from antibiotic-treated dams (Tochitani *et al.* 2016). Although the mechanism behind this and the involvement of the microbiota have not been fully elucidated, it has been suggested that this social experience due to the maternal behaviour early in life may epigenetically shape offspring brain development and later adult behaviour (Champagne and Curley 2005).

After weaning, social play with juvenile peers helps in the development of communicative skills, acquisition of cognitive and social competence, and development of behavioural flexibility (Panksepp *et al.* 1984; Spinka *et al.* 2001; Trezza *et al.* 2010). Interestingly it has been demonstrated that social interactions confer a reinforcing nature. They confirmed that new social interactions are linked with the release of oxytocin from the PVN to VTA, increasing excitability of dopaminergic projections that target the NAc, releasing DA and reinforcing the social interaction (Hung *et al.* 2017). Interestingly, social behaviours across the animal kingdom appear to be influenced by the microbiota (Sherwin *et al.* 2019b). Studies performed in germ-free animals demonstrated that mice spent less time interacting with a novel conspecific mouse when compared with a conventionally colonised mouse (Buffington *et al.* 2016; Desbonnet *et al.* 2014; Sgritta *et al.* 2019; Stilling *et al.* 2018). Moreover, conventionally colonised mice prefer to spend more time interacting with a novel conspecific over a familiar one, while germ-free mice are unable to distinguish between the novel and familiar animals, demonstrating difficulties in the identification of social novelty (Desbonnet *et al.* 2014; Stilling *et al.* 2018). Studies with antibiotics have been associated with deficits in social behaviour demonstrating that the microbiome plays an important role in shaping social interactions (Desbonnet *et al.* 2015). Although the mechanisms by which the microbiota regulates

social behaviour is unknown and likely involves a multitude of pathways, the reward system could be a key hub due to its ability to integrate multiple stimuli including those associated with sociability.

During adulthood, sexual behaviour is mainly associated with reproduction and is essential for the survival of the species. Like other rewarding stimuli, sexual behaviour elevates mesolimbic DA (Meisel *et al.* 1993; Mermelstein and Becker 1995). In this form of interaction, oxytocin has been strongly implicated. It has been observed that the density of oxytocin receptors in NAc is higher in monogamous prairie voles when compared with non-monogamous. Indeed, the monogamous behaviour is prevented when oxytocin receptors are blocked (Young *et al.* 2001) or D2 receptors are antagonised in NAc (Wang *et al.* 1999; Gingrich *et al.* 2000), demonstrating an important role of both systems in bond formation. Furthermore, oxytocin and DA have been implicated in facilitating sexual behaviour in males (e.g., penile erections) and females (e.g., lordosis and male receptivity) (Carter 1992). Another crucial aspect in the initiation of sexual behaviours are pheromones or sex hormones. Several studies suggest that the microbiota is able to regulate sexual behaviours such as odour discrimination in urine where it was abolished in germ-free animals demonstrating a clear role of the microbiota (Singh *et al.* 1990). In this line, it has been observed that germ-free status interferes with normal reproduction in both sexes, and these effects were reversed after microbial colonisation (Shimizu *et al.* 1998). In addition, it has been described that commensal bacteria can favour mating preference in *Drosophila melanogaster* altering the cuticular levels of hydrocarbon sex pheromones (Sharon *et al.* 2010). Furthermore, in this study the authors observed that antibiotic treatments blocked mating preference, suggesting that these commensal bacteria are able to alter mating behaviour by modifying pheromone levels. Sexual dimorphism in the gut microbiota may play an important role in modulating the gut-brain signalling and the reward system (Hayes *et al.* 2020; Jaggar *et al.* 2020; Audet 2019). One of the major differences between males and females is the different balance of sexual hormones (i.e., androgens, estrogens, oxytocin and vasopressin), which may be responsible for the sexual dimorphism of the gut microbiome (Yurkovetskiy *et al.* 2013; Org *et al.* 2016). Sex hormones regulate the reward system in multitude of ways due to the presence of specific receptors for these molecules in the mesolimbic pathway, having important consequences in drug abuse vulnerability and sexual behaviours (Tobiansky *et al.* 2016; Becker 1999; Hull *et al.* 1999). The gut microbiome also appears to have the ability to modulate sex hormones and a clear example was provided by transferring an adult male's gut microbiota to a female, which led to an increase in testosterone levels (Markle *et al.* 2013). Although evidence supporting the role of the gut microbiota in social behaviours is becoming more clearer, it has also been observed that the microbiome from other regions (i.e., the reproductive system) may also play a key role in reproductive function by influencing sexual selection (Rowe *et al.* 2020). Sexually transmitted microbes have deleterious effects on host health, but new evidence suggests that reproductive microbiome may have significant positive effects on reproductive function and performance in both sexes (Rowe *et al.* 2020). Several hypotheses have proposed that favouring sexual behaviours would encourage the transmission of beneficial reproductive

microbes by favouring the horizontal transmission of these microorganisms (Lombardo 1999; Smith and Mueller 2015), which could favour such behaviours by acting on the reward system to promote sexual interactions (Fiorino and Phillips 1999; Mitchell and Stewart 1990; Mitchell and Gratton 1994; Hull *et al.* 1999).

4.2.2 Implications for social disorders

Social experiences are able to elicit powerful emotional responses (Baumeister and Tice 1990). However, social rejection or exclusion, are emotionally negative experiences that impede the access to social resources and rewards essential for the individuals' survival and reproduction (Baumeister and Leary 1995; Brewer 2004). Social anxiety disorder is a chronic psychiatric disorder characterised by fear of social situations which leads to high levels of stress, anxiety and social avoidance (American Psychiatric Association, 2013). The oxytocinergic system seems to play a role in the behavioural manifestations of this disorder (Bartz et al. 2011; Heinrichs et al. 2003). Another neurotransmission system that seems to be altered is the dopaminergic system (Carlton *et al.* 2020). In particular, social anxiety disorder has been associated with alterations in the functional connectivity of the reward system, including markedly decreased functional connectivity between reward regions and between reward regions and the lateral prefrontal cortex (Manning *et al.* 2015). As previously mentioned, the microbiota seems to be a key player in the development of appropriated social behaviours, and alterations in its composition appear to contribute to the appearance of such disorders. Numerous preclinical evidence show that the intestinal microbiota can be altered under different chronic psychosocial stressors (Cussotto *et al.* 2018). Chronic social stress is a risk factor in the development of anxiety and depression (Cryan and Slattery 2007) and it has been associated with increases in social avoidance behaviour. Mice exposed to a chronic social defeat stress paradigm that elicited higher rates of social avoidance displayed an association with grater changes in gut microbiota taxas when compared to controls (Szyszkowicz *et al.* 2017). In another study performed in rats, the authors reported that animals more vulnerable to social defeat stress had an increase in the expression of immune-modulating microbiota (i.e., *Clostridia*) when compared with more resilient animals (Pearson-Leary *et al.* 2020). Future studies should focus on translating findings in animal models to humans focusing on the reward system.

Autism spectrum disorder is a neurodevelopmental disorder characterised by deficits in sociability, restricted and repetitive behaviours, communication and cognitive disturbances. Among other factors, these behavioural alterations have been associated with aberrant brain growth and development linked to neuroinflammatory processes, alterations in neurotransmission and changes in pro-social hormones (i.e., oxytocin and vasopressin) (Marotta *et al.* 2020; Madore *et al.* 2016). One of the aspects that has attracted most attention has been the impact of motivational factors on the development of social cognition (Chevallier *et al.* 2012). It has been observed that deficits in social reward can alter different aspects of social behaviours including social orientation, social interactions and social bonding (Chevallier *et al.* 2012). Regions related to the reward system have been altered in autistic patients (Izuma *et al.* 2011) in response to social

stimuli such as faces (Schultz *et al.* 2000), social approval (Scott-Van Zeeland *et al.* 2010) or social rejection (Masten *et al.* 2011). At a molecular level, these social alterations in autism have been linked to oxytocinergic (Modi and Young 2012) and glutamatergic systems (Peça *et al.* 2011; Bozdagi *et al.* 2010) which are highly related to the reward pathways. Despite the fact that autism shows numerous neurological alterations, it also presents alterations in the gastrointestinal system as well as alterations in the microbiota (Rosenfeld 2015). In a study of children with autism, it was observed that treatment with the broad spectrum antibiotic vancomycin showed an improvement in the behavioural symptoms associated with the disorder (Kang *et al.* 2017; Sandler *et al.* 2000). These studies showed that the intestinal microbiota may contribute at least in part to the negative effects associated with this neurodevelopmental disorder. In addition, several studies have shown a reduction in the abundance of the genus *Bifidobacterium*, and an increase in the abundance of potentially pathogenic genera such as *Desulfovibrio* and *Clostridia* in children with autism (Finegold 2011; Finegold *et al.* 2010; Kang *et al.* 2018; Parracho *et al.* 2005). Preclinical animal models based on clinical risk factors for autism (i.e., maternal exposure to valproic acid, diet-induce obesity, maternal immune activation, BTBR animal models or knockout mice for the shank 3 gene) have shown alterations in intestinal microbiota, providing important insights into how microbiota may be related to autism (Buffington *et al.* 2016; de Theije *et al.* 2014; Hsiao 2013; Golubeva *et al.* 2017; Sgritta *et al.* 2019; Tabouy *et al.* 2018). Furthermore, alterations in microbial metabolites such as SCFA have been observed in autistic patients (Wang *et al.* 2012). Neurotoxic doses of propionic acid induced autism-like behaviour in rats (Thomas *et al.* 2012), while butyrate administration showed improvements in repetitive behaviour in a murine model of autism (Kratsman *et al.* 2016). These results show that SCFA's may play an important role in modulating autistic behaviours, but their role in different regions such as the reward system needs further investigation as it has been observed in other studies that these molecules can alter regions of the striatum and mesolimbic system (Dalile *et al.* 2019; Byrne *et al.* 2015). Another bacterial metabolite produced by *Clostridioides* and linked to autism is p-cresol (Altieri *et al.* 2011; Gabriele *et al.* 2014). In rats, p-cresol administration induced changes in glutamatergic and GABAergic receptors in NAc that were reversed following oxytocin administration, suggesting that mesolimbic system may be important in the development of p-cresol-dependent neurological disorders (Tevzadze *et al.* 2019). Recently, it has been shown that p-cresol induced social deficits, stereotypes and perseverant behaviours (core autism symptoms) in mice associated with changes in VTA dopaminergic activity, suggesting alterations in social reward processing (Bermudez-Martin *et al.* 2020),

5. NON-NATURAL REWARDS

5.1 The microbiota as a regulator of drug reward

Neural circuits involved in the processing of natural rewards are hijacked by drugs of abuse, inducing changes in plasticity associated with increases in drug-seeking and craving as addiction progress (Kalivas and O'Brien 2008; Kelley 2004; Kelley and Berridge 2002). These plasticity changes have been reported in several regions associated

with motivation, executive function and reward (Kalivas and O'Brien 2008; Koob and Volkow 2010; Berridge and Robinson 2003). It is well known that a complex overlap between drug addiction and other types of rewards such as food and social reward exists (Olsen 2011). Preliminary evidence indicates that drug-induced perturbations in the gut microbiota relate to reward response (Lee *et al.* 2018; Kiraly *et al.* 2016), which warrants for further research investigating the role of microbiome alterations in driving drug-seeking behaviour (Figure 4).

5.1.1 CNS neurotransmission

Drugs of abuse act on the mesocorticolimbic DA circuitry activating the reward pathway. This pathway is crucial not only for reward but also for reinforcement processes, motivation and goal-direct behaviours (Schultz 1998). Drugs have the ability to act on this system, favouring DA release (preferentially in the NAc) from the VTA, activating the reward pathway of the brain (Di Chiara and Imperato 1988). Most drugs of abuse increase DA levels in this pathway through different mechanisms. Nicotine causes release of DA in VTA activating nicotinic receptors (Maskos *et al.* 2005). Opioids, cannabinoids and benzodiazepines inhibit GABAergic interneurons in the VTA reducing the inhibition of dopaminergic neurons (Spyraki *et al.* 1983; Phillips *et al.* 1983; Szabo *et al.* 2002; Lupica *et al.* 2004; Vashchinkina *et al.* 2014; Riegel and Kalivas 2010). Psychostimulants increase extracellular DA interacting with dopamine transporters inhibiting DA reuptake (Dietz *et al.* 2009).

The gut microbiota has also been reported to produce catecholamines. Some of the first evidence was observed in *in vitro* experiments whereby relatively high levels of norepinephrine were found to be produced by different bacterial species, demonstrating exogenous neurotransmitter production (Tsavkelova *et al.* 2000). *Escherichia coli* K-12 has also been observed to carry enzymes able to produce and degrade monoamine neuromodulators as well as having dihydroxyphenylalanine (DOPA), 5-HT, DA and noradrenaline (NA) in culture fluids in concentrations able to bind with their receptors (Shishov *et al.* 2009). Several brain regions where the gut microbiota may influence dopaminergic neurotransmission have been described in the literature (González-Arancibia *et al.* 2019). Alterations in dopaminergic pathways have been reported in germ-free mice when compared with specific-pathogen free (SPF) mice, demonstrating that dopaminergic circuits are sensitive to gut microbiome alterations. A clear example was observed by Diaz Heijtz and collaborators, they reported an increase in DA metabolism in the striatum of germ-free mice (increased DOPAC/DA ratio), as well as decreased expression of the dopamine 1 receptor (D1 mRNA), when compared to SPF (Heijtz *et al.* 2011). Conversely, it has been reported that a decrease in DA turnover (decrease HVA/DA ratio) occurs in the striatum of germ-free mice when compared to recolonised control mice (Nishino *et al.* 2013). In line with this study, a decrease in the DA turnover (decrease HVA/DA ratio) in the striatum of germ-free rats was demonstrated, illustrating that the absence of the gut microbiota can induce dopaminergic alterations in areas related to the reward system (Crumeyrolle-Arias *et al.* 2014).

The use of antibiotics as a means to alter the composition of the microbiota is a widely used tool to investigate the microbiota-gut-brain axis. However, an important consideration in the use of antibiotics is to take into account their absorption route by the gastrointestinal system. Non-absorbable antibiotics offer an advantage in this regard since they modulate the microbiome without entering in the circulatory system, avoiding systemic and CNS effects (Tochitani *et al.* 2016). However, their antimicrobial effects may not be as broad-spectrum. In contrast, the use of absorbable antibiotics (i.e., metronidazole or minocycline) can enter the CNS having direct actions on the brain and behaviour (Fröhlich *et al.* 2016) but more recently, no trace of antibiotics at effective antimicrobial doses were observed in the brain as measured by liquid chromatography-mass spectrometry (Dodiya *et al.* 2020). It has been observed that ampicillin administration induced an increase in tyrosine hydroxylase levels in the prefrontal cortex as well as alterations in the expression of D1 and D2 mRNA, and there was a trend towards increased tyrosine hydroxylase in the striatum, although this was not significant (Lotan *et al.* 2014). In addition to this, the administration of an antibiotic cocktail to adult male Sprague-Dawley rats reduced the DA turnover (decrease HVA/DA ratio) when compared with control rats (Hoban *et al.* 2016), demonstrating that gut dysbiosis alters levels of neuromodulators in the brain via the microbiota-gut-brain axis. Also, it has been observed that the administration of antibiotics was able to reduce the loss of dopaminergic neurons in the striatum in animals treated with 6-OHDA, which implies the gut microbiota as a potential contributor to alterations in the dopaminergic system and in the development of neurodegenerative diseases such as Parkinson's Disease (Koutzoumis *et al.* 2020). Another neurotransmitter highly studied in the microbiota field is GABA, the main inhibitory neurotransmitter in the CNS. It has been observed that in germ-free animals, there is a reduction of GABA levels in the lumen and serum without changes in brain tissue (Matsumoto *et al.* 2013). *Escherichia*, *Lactobacillus* and *Bifidobacterium* genera have been reported to synthesise GABA (Yunes *et al.* 2016; Smith *et al.* 1992; Patterson *et al.* 2019), although the importance of this GABA production in the lumen of the gut is unclear. Other intriguing data has recently emerged with an association between the composition of GABA modulating bacteria and major depression. Functional magnetic resonance in patients with major depressive disorder (diseases associated with GABAergic alterations) was negatively correlated with the relative abundance of Bacteroides, a bacterial specie associated with GABA production in human healthy individual (Strandwitz *et al.* 2019).

5.1.2 Peripheral mediators

In recent years, there has been a growing interest in the role of ghrelin in the drug addiction field. As mentioned previously, ghrelin has been described as a modulator of hedonic feeding behaviour (Davis *et al.* 2012; Naleid *et al.* 2005; Perelló and Zigman 2012; Schellekens *et al.* 2013) and in general reward processing (Mason *et al.* 2014; Vengeliene 2013; Stievenard *et al.* 2017). It has been observed in preclinical models that ghrelin has the ability to alter dopaminergic transmission acting on GHSR-1a in the

reward pathway forming heterodimers with dopaminergic receptors (Abizaid *et al.* 2006; Jiang *et al.* 2006; Jerlhag *et al.* 2012; Schellekens *et al.* 2013). Ghrelin has been implicated as a key player in alcohol consumption (a calorically appetising and highly reinforcing substance). An increase in ghrelin during withdrawal and a decrease after alcohol intake may also be seen (Calissendorff *et al.* 2005; Szulc *et al.* 2013), suggesting an important role of this peptide in non-natural rewards (Leggio *et al.* 2012; Farokhnia *et al.* 2019). Indeed, ghrelin exerts a role in other types of drugs apart from ingestible and caloric drugs such as alcohol. Manipulation of the ghrelin system through the administration of agonists and antagonists demonstrates its role in addictive behaviours. Exogenous ghrelin administration enhanced cocaine-induced motor activity (Wellman *et al.* 2005), cocaine place preference (Schuette *et al.* 2013), as well as increased motivation to self-administer heroin in rats (Maric *et al.* 2012). GHSR-1a antagonist such as JMV2959 attenuates cocaine, amphetamine, nicotine and morphine conditioned place preference, locomotor activity and NAc DA release in rats (Jerlhag *et al.* 2010; Jerlhag and Engel 2011; Wellman *et al.* 2011; Sustkova-Fiserova *et al.* 2014; Engel *et al.* 2015), highlighting the role of central ghrelin in regulating drug-reward responses. Interestingly, bacteria (i.e., *Bifidobacterium* and *Lactobacillus* genera) have been shown to produce metabolites (SCFAs and lactate) that affect G-Protein coupled receptors including the GHSR-1a, suggesting the potential ability of the intestinal microbiota in modulating motivation and reward through the ghrelin system (Torres-Fuentes *et al.* 2019).

The gut microbiota has the ability to modulate intestinal, peripheral and brain immune cells. Perturbations in the intestinal microbiota and in the gut epithelial barrier alter immunological responses inducing inflammation in the entire body including the brain (Caricilli 2014). Neuroinflammatory processes are characterised by an increase in microglial activation and are linked to the production of neuroexcitatory and proinflammatory cytokines (Minagar *et al.* 2002). These products enhance neuronal excitation and potentiate drug-induced changes in the mesocorticolimbic system (Coller and Hutchinson 2012). Alcohol and its metabolites alter gut permeability acting on tight-junction proteins. In particular, alcohol and its metabolites are able to destabilise (Dunagan *et al.* 2012), alter the expression of (Wang *et al.* 2014), and redistribute tight-junction proteins altering the gut barrier (Elamin *et al.* 2013). These barrier alterations result in gut and systemic inflammation affecting neuronal function (Schulzke *et al.* 2009). Pro-inflammatory cytokines disrupt the BBB, starting a vicious cycle perpetuating alcohol effects on the brain (Banks *et al.* 2015). Opiates have also been associated with alterations in gut permeability as well as alterations in the immune system (Meng *et al.* 2013), suggesting that the gut microbiota could mediate their effect on drug of abuse through immune alterations. Despite the potential importance of the neuroinflammatory response in drug reward, the exact mechanism on how the microbiota is contributing to this response is not fully understood. SCFA derived from bacterial metabolites could be in part responsible, as it has been determined that they control microglial homeostasis (Erny *et al.* 2015), induce anti-inflammatory cytokines (Cox *et al.* 2009) as well as reduce

the production of pro-inflammatory cytokines (Patnala *et al.* 2017; Yamawaki *et al.* 2018).

5.1.3 Implication for substance use disorders

Alcohol

A significant number of studies have investigated the relationship between the gut microbiota and alcohol use disorders (AUD). Chronic alcohol consumption has been associated with alterations in gut diversity, increased intestinal permeability and hepatic inflammation in preclinical models (Bull-Otterson *et al.* 2013; Yan *et al.* 2011; Mutlu *et al.* 2012; Keshavarzian *et al.* 2009; Ferrier *et al.* 2006). Studies in rodents demonstrated that mice intragastrically fed with alcohol develop alcohol liver disease, associated with a bacterial overgrowth in the small intestine and dysbiosis in the caecum (i.e., reduction of *Firmicutes* and increase *Verrucomicrobia* and *Bacteroidetes*) (Yan *et al.* 2011). In another study performed in rats, intragastric alcohol administration induced colonic microbiome dysbiosis (Mutlu *et al.* 2012), suggesting that changes in the microbiome alters gut permeability and liver damage (Keshavarzian *et al.* 2009). The effects of chronic intermittent vaporised alcohol exposure (CIE, a murine model to control confounding variables such as caloric intake, dose and gastrointestinal nutrient absorption) has been shown to have quite a profound effect on the gut microbiome in mice. It was observed that CIE exposure alters gut microbiota (increased genus *Alistipes* and reduced genera *Clostridium* IV and XIVb, *Dorea* and *Coproccocus*) when compared with control mice (Peterson *et al.* 2017). Also, alterations in the gut microbiota induced by alcohol were associated with an increase in impulsivity, as well as striatal alterations of D1 and D2 receptors (Jadhav *et al.* 2018).

The increase in gut permeability, inflammatory responses and liver damage has been observed in AUD patients (Ciocan *et al.* 2018; Dubinkina *et al.* 2017; Rao *et al.* 2004; Jiang *et al.* 2015). Leclercq and collaborators demonstrated that alterations in gut permeability and microbiome composition (principally decreases in genera from Ruminococcaceae family) were associated with craving, a hallmark of addiction (Leclercq *et al.* 2012; Leclercq *et al.* 2014). More recently these authors have shown that gut microbiota induce changes in metabolism linked to alterations in sociability and depression in AUD (Leclercq *et al.* 2020). Recently, we have proposed a framework of how emotional dysregulation and alcohol-related microbiome dysbiosis could contribute to accelerate the addiction cycle in AUD (Carbia *et al.* 2020), highlighting the importance of integrating disparate aspects such as microbiota for advancing in the understanding of addiction.

Psychostimulants

In the same vein, studies focused on the effects of other substances of abuse in gut microbiota demonstrated similar results, particularly regarding psychostimulants, such as cocaine. Stool samples from cocaine users presented a higher relative abundance of

Bacteroidetes when compared with non-users (Volpe *et al.* 2014), but it is unclear whether these differences could participate in and/or mediate some of the behavioural consequences induced by cocaine administration. Kiraly and collaborators demonstrated that administration of non-absorbable antibiotics in mice enhanced cocaine conditioned place preference and locomotor sensitivity at low doses when compared with non-antibiotic treated mice (Kiraly *et al.* 2016), demonstrating that gut microbiota affects drug-seeking behaviours. In this line, a recent study reported a significant correlation of *Lachnispiroceae* and *Ruminococcaceae* families with addiction-related behaviours such as reward learning, increased impulsivity, and inattention deficits (Peterson *et al.* 2020). Also, an increase in the relative abundance of *Proteobacteria* and *Fusobacteria* was observed in methamphetamine treated rats (Ning *et al.* 2017). Indeed, the authors determined a reduction in the propionate-producing genus *Phascolarctobacterium* and an increase in *Ruminococcaceae* family in this methamphetamine treated rats. Another psychostimulant studied with implications on the gut microbiota is MDMA. An increase of *Proteus mirabilis* in the caecum has been observed after the administration of MDMA in rats (Ridge *et al.* 2019). Moreover, in this study it was observed a reduction of MDMA-induced hyperthermia in animals treated with antibiotics, indicating a role of the microbiota in the hypothalamic thermoregulatory circuits, presumably by modulating the dopaminergic and serotoninergic activity (Rusyniak and Sprague 2005; Hargreaves *et al.* 2007; Benamar *et al.* 2008; García-Cabrerizo and García-Fuster 2015).

Opiates

Opiates have also been studied and associated with alterations in the intestinal microbiota. A recent study reported that the gut microbiome and its metabolites, such as SCFAs, are crucial mediators of morphine reward, providing evidence for the role of the microbiome in morphine addictive behaviours and mechanistic insights of the gut-brain signalling in substance use disorders (Hofford *et al.* 2020). Apart from their negative effects on addiction, alterations to the gastrointestinal system and on immune activation levels have been described in opiate users (Hilburger *et al.* 1997; Docherty *et al.* 2011; Juurlink and Dhalla 2012). Morphine disrupts epithelial gut barrier function by damaging tight junction proteins via TLR receptor activation in mice (Meng *et al.* 2013), and this might induce sepsis and dysregulation of the immune system (Banerjee *et al.* 2013). Short-term morphine exposure induced rapid gut microbial alterations (an increase in communities with pathogenic function and a decrease in communities associated with stress tolerance) and metabolic changes, in an opiate receptor-dependent manner (Wang *et al.* 2018). Moreover, a correlation was observed between *Enterococcus faecalis* and gut dysbiosis following morphine treatment, and inoculation of *E. faecalis* via oral gavage augmented morphine analgesic tolerance in a tail flick test. Further evidence demonstrating that the gut microbiota modulates the behavioural effects of opioid use was observed in germ-free and antibiotic-treated mice. These animals exhibited a decrease in tolerance to morphine analgesic effects, which were reversed after a faecal microbiota transplant (FMT) from naïve mice, restoring the tolerance (Zhang *et al.* 2019). In addition, they observed that tolerance was associated with a depletion of *Bifidobacteria* and *Lactobacillaeae* genus.

Cannabinoids

Cannabinoids such as Δ^9-tetrahydrocannabinol (THC), the major psychoactive constituent of cannabis, has been associated with certain antimicrobial activity in *in vitro* experiments (Appendino *et al.* 2008). Chronic THC consumption changed gut microbiota composition in mice (Cluny *et al.* 2015). These results were associated with a reduction in energy intake as well as a reduction in body weight and adiposity in mice treated with a high fat diet. Human studies reinforced this preliminary evidence; in particular, it was noted that cannabis users had approximately 13-fold higher *Prevotella:Bacteroides* ratio than non-users (Panee *et al.* 2018).

Despite these apparent connections, future research will need to investigate mechanisms of action of gut dysbiosis and reward alterations to understand how these changes in the microbiota affect reward learning, locomotor sensitivity and reinforcement of addictive behaviours, and if it is the substance use that drives microbiota changes or if the microbiota can contribute to the continued use and addiction propensity via hijacking of reward neurocircuitries.

6. TARGETING THE MICROBIOME TO IMPROVE REWARD-RELATED ALTERATIONS?

The significant involvement of the gut microbiota in health and disease suggests that manipulation of commensal bacteria using "psychobiotics" (beneficial bacterial or probiotics-, and the substrates for these bacteria or prebiotics) and fecal transplants as novel interventional approaches in reward disorders (Long-Smith *et al.* 2020). Although other interventions such as diet or exercise may have a synergistic or coadjuvant effect on the gut microbiota, we will focus exclusively on microbiome-targeted intervention, that is psychobiotics and faecal transplants.

6.1 Prebiotics

Prebiotics are non-human-digestible compounds used by intestinal microorganisms that can modify the composition and metabolism to confer health benefits at a physiological level for the host. Inulin, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are the most widely used prebiotics. The administration of diets rich in fibre has been shown to benefit the growth of bacteria such as *Bifidobacterium* and *Lactobacillus*, inducing anti-obesity effects and preventing the expression of genes related to obesity and inflammation (Torres-Fuentes *et al.* 2015). It has been shown that inulin is capable of increasing the number of *Bifidobacteria* in genetically obese or diet-induced animals and increase the number of EECs in rodents by promoting the release of GLP-1 (Delzenne *et al.* 2005), altering appetite by modifying feeding behaviours (increasing satiety and reducing caloric intake). FOS supplementation in mice has also been associated with a reduction of intake of highly palatable foods, suggesting alterations in the hedonic or motivational state for palatable rewards (Delbès *et al.* 2018). A double-blind, placebo-

controlled study showed that the combination of a casein/gluten-free diet along with the prebiotic B-GOS led to an improvement in social behaviour in autistic children (Grimaldi *et al.* 2018). These behavioural changes were accompanied by an increase in the relative abundance of the beneficial strain *Bifidobacterium longum* in the microbiota of the autistic children. The study of the effects of prebiotics on drug-related disorders is also limited and has focused mainly on effects at the gut and hepatic levels. Oat supplementation was associated with a decrease in intestinal leakage and improvement in alcohol-induced liver damage in rats (Keshavarzian *et al.* 2001). In addition, the administration of FOS reduced bacterial overgrowth and enteric dysbiosis in a mouse model of alcohol liver disease (Yan *et al.* 2011). Regarding the effects of prebiotics in the brain, the administration of FOS and GOS increased brain-derived neurotrophic factor levels and N-methyl-D-aspartate receptor signalling via the involvement of gut peptides in rats (Savignac *et al.* 2013), which intervene in behaviours associated with depression, anxiety and addiction among others. These results demonstrate that the beneficial effects of prebiotics are largely mediated by the production of bacterial metabolites. This is supported by the fact that the administration of SCFAs mediated the behavioural effects induced by the microbiota in response to cocaine and morphine in mice (Kiraly *et al.* 2016; Hofford *et al.* 2020).

6.2 Probiotics

Probiotics are live bacteria that, when ingested in adequate amounts, exert beneficial health effects for the host. Dietary interventions using probiotics have been used to reduce obesity. In animal studies probiotics have been associated with weight loss (Mazloom *et al.* 2019). In general, *Lactobacillus* and *Bifidobacterium* strains can reduce body weight in response to high-fat diets. These bacterial strains have shown anti-obesity effects, reductions in inflammation, adiposity, body weight and energy intake (Torres-Fuentes *et al.* 2015). *Hafnia alvei* (a commensal species from the *Enterobacteriales* order) has been described as a probiotic with anti-obesity properties. *H. alvei* affects the expression of the ClpB gene (synthetizes the α-MSH-mimetic ClpB protein), which has the ability to reduce food intake, body weight and fat mass gain in hyperphagic and obese mice (Legrand *et al.* 2020). In humans, these studies are more limited; VSL#3 has been found to have positive effects against fat consumption and accumulation (Osterberg *et al.* 2015). *Lactobacillus* has also been found to have a beneficial effect on autism-related disorders. *Lactobacillus reuteri* supplementation has been associated with increases in oxytocin expression in diverse autism spectrum disorder animal models validating the efficacy and the mechanism of action of this probiotic in preclinical studies (Buffington *et al.* 2016; Sgritta *et al.* 2019; Tabouy *et al.* 2018). In humans, *Lactobacillus plantarum* WCSF1 improved antisocial behaviours in autistic children (Parracho *et al.* 2010). Similarly, the administration of multi-strain probiotics (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus* and *Bifidobacteria longum*) improved behavioural and gastrointestinal symptoms in autistic children (Shaaban *et al.* 2018). As for drug addiction, little is known about the role that probiotics may play. Most studies have focused on assessing the effects of probiotics on other negative aspects related to drugs of abuse. Preclinical

supplementation of *Lactobacillus rhamnosus GG* prevented the pathogenic changes induced by ethanol in mice (Bull-Otterson *et al.* 2013). The probiotic VSL#3 attenuated morphine analgesic tolerance in mice associated with a partial restoration of gut microbiota components and a decrease in proinflammatory cytokines (Zhang *et al.* 2019). However, despite these relationships, much remains unknown about the underlying mechanisms on which psychobiotics influence host physiology and behaviour.

6.3 Fecal Microbiota Transplantation

A new strategy to target the composition of the intestinal microbiota is the FMT, a procedure that involves the transfer of the intestinal microbiota from one individual to another to restore the normal gut microbial community and functionality (Li *et al.* 2016a). This technique has been successfully applied in patients to treat recurrent *Clostridium difficile colitis,* demonstrating the potential therapeutic effect of this technique for treating other microbiome-related diseases (Li *et al.* 2016b). An interesting preclinical study demonstrated for the first time that FMT donors (with normal diet and exercise) confer beneficial effects to high fat diet-fed mice associated with the bacterial genera *Helicobacter* and *Odoribacter*, suggesting a potential therapeutic treatment for obesity (Lai *et al.* 2018). In humans, the transfer of gut microbiota from healthy donors to obese individuals diagnosed with type 2 diabetes increased insulin sensitivity (Vrieze *et al.* 2012), demonstrating that FMT is an interesting technique to influence gut microbiota and alter host metabolism (Lee *et al.* 2019). These promising results have increased the interest in the use of this technique to treat autism and improve gastrointestinal and behavioural outcomes. It has been reported in EphB6-deficient mice (mouse model of autism-like behaviour) transplanted with faecal material from wild-type mice an amelioration of the autistic-like behaviours in these deficient rodents (Li *et al.* 2020). In human studies, a modified FMT protocol (Microbiota Transfer Therapy), which consist in an intensive daily FMT exposure up to 7-8 weeks, improved gastrointestinal symptoms, autism-related symptoms and normalised the microbiota profile in autistic patients (Kang *et al.* 2017). The use of the FMT to treat drug-related disorders has been limited. It has been reported in mice exposed to chronic alcohol that FMT from healthy donors alleviated alcohol-induced anxiety and depression, providing a new target for treating alcohol use disorders (AUD) (Xu *et al.* 2018). In the same line, it has been observed that FMT prevent liver lesions in mice associated with alcohol exposure, demonstrating that microbiota manipulation can prevent alcohol-induced liver injury, considering it a new approach to treat alcoholic-liver disease (Ferrere *et al.* 2017). Intriguing results come from a recent FMT trial in AUD-related cirrhosis (Bajaj *et al.* 2020). The FMT (with deficient taxa in this population) was associated with short-term improvement in inhibitory control and reduced craving. Although promising, larger clinical trials are needed to confirm and extend these findings.

7. CONCLUSIONS

Over the past few decades, much knowledge has been generated about how reward processing works and the neural substrates that govern these responses. Nevertheless,

much still remains to be learned, and more aspects than just the molecular and cellular mechanisms in the brain must be integrated to better understand the workings of this complex system. Accumulating evidence from preclinical and clinical studies highlights the role of the gut microbiota in the gut-brain axis and its implications on central brain reward modulation. Certain tools and animal models (germ-free, antibiotic treatment, FMT) have shown us that microbiota alterations might influence natural (i.e., food, sex, social relations) and non-natural reinforcers (drugs of abuse). Moreover, associations between gut microbiota composition and psychiatric disorders are becoming apparent, with alterations in the reward system being noted (i.e., obesity, autism or drug addiction). Therefore, from a treatment perspective, there is a significant potential for the microbiome as a translational research target for the above-mentioned psychiatric disorders but further studies in this area are warranted, especially in dissecting the mechanisms of action of bacterial strains upon behaviour. As presented in this review, considerable variability exists in the microbiome profile depending on the psychiatric disorder evaluated. This might be due to differences in the animal strains and models, age, doses, duration of the interventions and tests used to evaluate behavioural outcomes. Psychobiotic approaches are well positioned as a future first-line therapeutic intervention, but much work is required to test optimal doses, strains and timing in the therapeutic application. A special effort needs to be done to improve the specificity (precision pre- and probiotics) (Veiga *et al.* 2020) based on microbial signatures characteristic of particular disorders.

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Figure Legends

Graphical abstract: Over the past decade the gut microbiome has emerged as a surprising new player in sculpting reward circuits across the lifespan. Focusing on the mesocorticolimbic pathway, we discuss how the gut microbiota is involved in regulating brain reward functions, both in natural and non-natural reinforcers. Also, we integrate preclinical and clinical evidence suggesting that the microbiota-gut-brain axis could be implicated in the development of disorders associated with alterations in the reward system and how it may be targeted as a promising therapeutic strategy.

Figure 1: Potential pathways by which the intestinal microbiota influences brain reward processes. The main communication pathways of the microbiome-gut-brain axis are the vagus nerve, the immune system, HPA axis, bacterial metabolites and enteroendocrine cells. Gut microbes are able to produce various metabolites, such as neurotransmitters or neuroactive compounds, SCFAs, mimetic peptide sequences and toxins. These metabolites act on enteroendocrine cells, the vagus nerve or by translocation throughout the gut epithelium into the systemic circulation. Neurotransmitters and neuroactive peptides produced or altered by the gut microbiota can be released to the systemic circulation and may have an impact on host physiology altering the reward system. Stimulation of enteroendocrine cells by SCFAs release gut hormones such as CCK, GLP-1 and PYY, and can increase the concentration of peripheral hormones such as ghrelin, leptin and insulin targeting different areas on the brain reward system. These peripheral hormones can be affected by auto-antibodies interacting with microbial mimetic peptides as ClpB. Alterations in the gut epithelium ("leaky gut") has an impact in the presence of gut microbial toxins such as LPS. This molecule activates the immune response (IL, TNF) crossing the blood-brain barrier or activating the vagus nerve altering brain reward functioning. Abbreviations: PFC prefrontal cortex, Nac nucleus accumbens, VTA ventral tegmental area, CCK cholecystokinin, GLP-1 glucagon-like peptide, PYY peptide YY, IL interleukin, TNF tumor necrosis factor, ClpB caseinolytic protease B, LPS Lipopolysaccharide.

Figure 2: Microbiome-gut-brain axis in feeding behaviour. Feeding is a complex behaviour integrated by the homeostatic and the reward system. The gut microbiota together with other peripheral signals regulates both systems promoting food intake. From the lateral hypothalamus, signals are sent via orexin, neurotensin and MCH. ARC sends signals through the AgPR or NPY from AgRP neurons and α-MSH from POMC neurons. In addition, the NTS sends signals releasing GLP-1 peptide. Abbreviations: MCH Melanin concentrating-hormone neurons, POMC
pro-opiomelanocortinal neurons, α-MSH melanocyte-stimulating hormone, NPY neuropeptide Y, AgRP agouti-related peptide, NTS nucleus tractus solitarii, VTA ventral tegmental area, NAc nucleus accumbens, CCK cholecystokinin, GLP-1 glucagon-like peptide, PYY peptide YY.

Figure 3: Schematic representation of the most well studied social interactions in mammals and its links with the reward system. The gut microbiota is depicted as a key mediator in the development and function of the social brain. Gut microbes are capable of modulating the mesolimbic system through the release of metabolites into the circulatory system or via the vagus nerve modifying social behaviours. Olfactory stimuli from pheromones or from the pups stimulate the olfactory bulb sending signals to the reward system favouring sexual or maternal behaviours. In addition, visual, auditory or physical stimuli processed by various regions of the cortex can send signals to the reward system promoting socialization. Abbreviations: OB olfactory bulb, PVN paraventricular

nucleus, VTA ventral tegmental area, NAc nucleus accumbens, NTS nucleus tractus solitarii, AMYG amygdala.

Figure 4: Schematic representation of the brain reward circuit and key neurobiological targets for the action of the most common substances of abuse. At the periphery, microbiota and gut-derived components can alter the reward system through hormonal, immune or vagal pathways. Neurotransmitters produced by the gut microbiota can be released to the systemic circulation and may have an impact on host physiology altering the reward system. Peripheral hormones, such as ghrelin, are able to target different areas of the brain's reward system by acting on ghrelin receptors present in these regions. Damage to the gut epithelial barrier causes the increased permeability ("leaky gut") of bacterial products such as LPS that can enter the blood inducing systemic alterations. In response, immune cells secrete cytokines that via the blood stream are transported to the brain causing neural damage or targeting the vagus nerve inducing alterations in the reward response. Abbreviations: PFC prefrontal cortex, VTA ventral tegmental area, NAc nucleus accumbens, AMYG amygdala, NTS nucleus tractus solitarii, IL interleukin, TNF tumor necrosis factor, LPS lipopolysaccharide.