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Gut microbiota-related neuroinflammation at the crossroad of food reward alterations: implications for eating disorders

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ABSTRACT

The link between gut microbiome and eating behaviours, especially palatable food intake, is a growing focus of scientific investigation. The complex ecosystem of microorganisms in the gut influences host metabolism, immune function and neurobehavioural signalling. This review explores the role of neuroinflammation in dysregulations of food-induced reward signalling and the potential causal role of the gut microbiota on these proinflammatory processes. Particular attention is given to eating disorders (ED, specifically anorexia nervosa, binge eating disorder and bulimia nervosa) and potential links with the gut microbiota, food reward alterations and neuroinflammation. Finally, we propose gut microbiota modulation as a promising therapeutic strategy in food reward alterations and ED.

KEY MESSAGES

⇒ The gut microbiota impacts the hedonic and motivational aspects of food intake as well as the related signalling in the reward system.
⇒ The gut microbiota modulates neuroinflammation by impacting glial cell activation, proinflammatory processes and blood–brain barrier permeability.
⇒ Neuroinflammation is described in reward-related brain regions and associated with altered food reward responses.
⇒ Obesity and eating disorders (ED) present changes in gut microbiota composition, altered food reward processes and neuroinflammation events in reward-associated brain regions.
⇒ Gut microbiota modulation offers a promising therapeutic strategy against food reward alterations and ED.

INTRODUCTION

Two distinct yet interconnected regulatory systems control our eating behaviours to provide the necessary energy and nutrients while maintaining a stable body weight over the long term. First, food intake is regulated to cover energy expenditure, a process governed by homeostatic mechanisms and mainly orchestrated by the hypothalamus.[1] Alongside this fundamental regulation, food intake behaviours are also driven by the rewarding value of food. Food reward processes are complex and involve several aspects including the liking component amplifying the hedonic impact of palatable tastes and the wanting component generating incentive motivation to obtain and consume food rewards.[2] This non-homeostatic mechanism guides eating behaviours towards hedonic feeding, stimulating the consumption of palatable foods (rich in sugar and/or fat).[3] In the brain, the reward system is involved in the hedonic and motivational processing and it encompasses the mesocorticolimbic pathway, formed by dopaminergic neurons located in the ventral tegmental area (VTA) projecting to the striatum (Str), including the nucleus accumbens (NAc) and to the prefrontal cortex (PFC). Additionally, other brain structures such as the hippocampus (Hp) have also been implicated in reward processes.[4] It is important to acknowledge, nonetheless, that the homeostatic and the hedonic regulation of food intake are not completely independent but rather a complex interplay between both systems takes place both at central and peripheral levels to modulate food intake.[5]

Over these last decades, the gut microbiota has been shown to play a key role in eating behaviours mainly through the regulation of the homeostatic system.[6] This narrative review focuses on the effects of gut microbiota in the regulation of the reward system during hedonic and motivational aspects of food intake, from brain signalling to the associated behaviours. As neuroinflammation has been proposed as a potential mechanism behind aberrant brain activity,[7] the review summarises the evidence on the link between neuroinflammation and reward system (mal)adaptation during food intake and how the gut microbiota is able to modulate this neuroinflammation. We mainly selected preclinical studies since human evidence remains to be investigated. Finally, the review proposes the hypothesis of neuroinflammation in eating disorders (ED) by making a general picture of the link between ED and gut microbiota in humans and food reward alterations. Proposing new mechanisms in the crosstalk between gut microbes and food reward is of utmost importance to develop additional effective therapeutic strategies to tackle important public health concerns linked to altered food behaviours. As a conclusion, we propose the gut microbiota as a promising therapeutic approach in food reward alterations and ED.

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GUT MICROBIOTA REGULATES FOOD REWARD

Modulation of host behaviours related to food reward by gut microbes

The gut is now recognised as a major regulator of motivational and emotional states and relevant gut–brain circuitry has been highlighted through the vagus nerve.[8] The gut–brain axis is crucial in the regulation of food reward processes. For instance, gut-to-brain postingestion sensing signalling is critical for the development of sugar preference.[9] The gut microbiota is part of the gut–brain axis and has been shown to influence brain chemistry and host behaviour.[10] Therefore, several preclinical studies aimed to highlight the interaction between the gut microbial community and hedonic feeding behaviour. In this context, it has been demonstrated that the absence of gut microbiota in germ-free (GF) mice induced an increase in sucrose intake[11] and a higher preference for intralipid emulsions, in comparison with conventional mice.[12] In addition, antibiotic depletion of the gut microbiota in mice increased the consumption of high-fat high-sugar (HFHS) palatable food compared with vehicle-treated mice during a two-food choice paradigm.[13] Along the same lines, the study of Ousey *et al* confirmed that antibiotic-treated mice presented an increased intake of palatable food and an increased food reward-seeking behaviour compared with vehicle-treated mice. Furthermore, reconstitution of the gut microbiota using faecal material transplantation (FMT) from conventional mice suppressed the increase in palatable food intake. These behavioural changes were linked to alterations in the activity of brain regions implicated in reward response, such as the NAc and VTA.[14] Altogether, these results show a potential causal role of gut microbiota on food reward-related behaviours.

Moreover, the literature also indicates that the gut microbiota influences the reward system in the context of overeating and obesity. The role of gut microbes in triggering food reward-related behaviours during obesity has been recently demonstrated. Indeed, lean mice receiving FMT from high-fat diet (HFD)-induced obese mice showed similar changes in palatable food consumption to those observed in obese donor mice[13] whereas HFD animals treated with a cocktail of antibiotics presented a restoration of the preference for the sucrose solution.[15] Moreover, mice receiving FMT from obese donors presented impaired food reward-seeking behaviour to get sucrose rewards in an operant conditioning task compared with lean mice.[16] Interestingly, changes in dopaminergic signalling induced by HFD-induced obesity were also transferred through FMT.[13 17] In conclusion, these studies indicate that the gut microbiota is a key modulator of the food reward-related neurobehavioural manifestations observed in rodents under HFD feeding.

Gut microbiota impact reward signalling

Dopamine (DA) is the primary driver of both food and drug rewards.[18] On exposure to rewarding stimuli like palatable food, DA is released in the mesocorticolimbic pathway, reinforcing food-seeking behaviours. Interestingly, some preclinical studies in rodents highlighted the implication of gut microbiota on the brain dopaminergic system (table 1). Indeed, GF rodents presented a higher turnover of DA as reflected by an increased ratio of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) over DA[19] and decreased levels of DA and its metabolites in reward-related brain regions.[20 21] Moreover, antibiotic treatment induced increased levels of the DA

Table 1 Summary of gut microbiota implication on dopaminergic and opioid systems in reward-related brain regions

System	Model	Approach	Brain regions	Effect	Ref.
DOPAMINERGIC	NMRI mice	GF	Str	↑ DOPAC/DA	19
	F344 rats	GF	Hp, Str	↓ HVA	20
			FC	↓ HVA, DA, DOPAC	
	C57BL/6 mice	GF	Str	↓ DA, *Th*	21
			Hp	↓ DA, ↑ *Th*	
			FC	↓ DA	
	Lewis rats	Abx (ampicillin)	PFC	↑ TH	22
	Female Sprague-Dawley rats	Abx (neomycin, bacitracin, vancomycin and pimaricin)	Str	↓ DA	23
			VTA	↓ DOPAC, DRD2 ↑ DRD1, *Th*	
			NAc	↓ DRD2	
	Female C57BL/6 mice	GF+alive Lactobacillus plantarum PS128	Str	↑ DA, DOPAC, HVA	24
	C57BL/6 mice	Abx (kanamycin, gentamicin, colistin, metronidazole and vancomycin)	Str	↓ DOPAC	25
		Abx+Clostridium difficile	Str	↑ DA	
			PFC	↑ HVA	
			Hp	↓ DOPAC	
OPIOIDS	Fischer rats	GF	NAc	↑ OPRM1	28
	C57BL/6 mice	GF	NAc	↑ OPRM1	29
	NIH Swiss mice	GF	FC	↑ *Oprm1*	27
		Abx (ampicillin, vancomycin, neomycin, metronidazole and amphotericin)	FC	↓ *Oprm1*	

↑ depicts 'increase', ↓ depicts 'decrease'. Italicised words represent mRNA expression.
Abx, antibiotics; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; DRD1, dopamine receptor 1; DRD2, dopamine receptor 2; FC, frontal cortex; GF, germ-free; Hp, hippocampus; HVA, homovanillic acid; mRNA, messenger RNA; NAc, nucleus accumbens; OPRM1, μ-opioid receptor 1; PFC, prefrontal cortex; Str, striatum; Th, tyrosine hydroxylase; VTA, ventral tegmental area.

synthesising limiting enzyme (tyrosine hydroxylase, TH)[22] and dopamine receptor 1 (DRD1) and decreased levels of DA, DOPAC and dopamine receptor 2 (DRD2) in reward-related brain regions.[23] Interestingly, supplementation with alive *Lactobacillus plantarum* PS128 in GF mice increased DA and its metabolites in the Str.[24] *Clostridium difficile* colonisation in antibiotic-treated mice also induced a modification of the levels of DA and associated metabolites.[25] All these results support the implication of gut microbiota on the dopaminergic system, potentially involved in the modulation of food reward-related behaviours.

Furthermore, opioids also play an important role in the hedonic aspects of eating and reward mechanisms. Opioid signalling contributes to the reward system through the expression of opioid receptors and their natural ligands in various brain reward regions, including the VTA, NAc and FC.[26] Interestingly, few preclinical studies using GF mice or antibiotic gut microbiota-depleted mice reported potential effects of gut microbes on μ-opioid receptor 1 in reward-related brain areas[27–29] (table 1). However, the role of gut microbes in the modulation of opioid signalling remains to be clarified.

That said, even if preclinical models such as GF or antibiotic-treated mice are particularly interesting to study the role of gut microbes in different processes, it is also important to keep in mind the limitations of such models presenting numerous adaptations which limit the translation for humans.

Furthermore, other neurotransmitters also play a key role in the regulation of food reward-related behaviours including serotonin (5-HT), glutamate and γ-aminobutyric acid (GABA) but more research is needed to link such neurotransmitters with gut microbes. Finally, besides the capacity of gut microbes to modulate host food reward signalling, it is also important to mention that some bacteria have also been reported to produce neurotransmitters and thereby over-riding host control of sensory decision.[30] Therefore, we could also speculate that neurotransmitters produced by gut microbes impact host food reward signalling but this remains to be clearly demonstrated.

GUT MICROBIOTA MODULATES NEUROINFLAMMATION

Neuroinflammation and food reward processes

Neuroinflammation is a multifaceted physiological and pathophysiological response of the brain to stress stimuli and diseases[31] and the neuroinflammation hypothesis has been proposed as one of the processes that may trigger impairments in reward processing in some diseases.[32]

Neuroinflammation can arise either through the local activation of inflammatory pathways in the brain or by alterations in the blood–brain barrier (BBB) permeability (figure 1). The BBB is a protective barrier that regulates and controls the passage of substances between the general bloodstream and the brain and so providing the brain with an immune isolation state in physiological situations. However, persistent exposure to peripheral and local proinflammatory stimuli may promote alterations of the tight junction proteins, like claudin-1 (CLDN1) and 5 (CLDN5), occludin and zonula occludens 1 (ZO1), that normally ensure the integrity of the BBB.[33] This leads to an increased permeability that facilitates the migration of proinflammatory mediators from the peripheral circulation into the brain, like extravasation of leucocytes or proinflammatory cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)1β and IL6 or interferon γ.[34] In consequence, the increase in proinflammatory messengers in the brain coming from the periphery will stimulate the activation of brain-resident glial cells, which in turn will release further cytokines and chemokines leading to a vicious circle of inflammatory processes.[35]

The BBB responsiveness to stimuli, including proinflammatory mediators, is also influenced by astrocytes surrounding microvessels. Astrocytes can become activated by inflammatory mediators and adopt a proinflammatory phenotype associated with an increased expression of glial fibrillar acidic protein (GFAP).[36] On the other hand, microglia, the resident immune cells of the central nervous system (CNS), may also become activated and associated with an increased expression of ionised calcium-binding adaptor protein-1 (IBA1).[37]

Growing evidence in preclinical models suggests that reward-related regions involved in food reward processes present inflammatory states in the context of obesity. Hypercaloric diet induced increased levels of proinflammatory cytokines, activation of astrocytes and microglia in the NAc and dorsal Str of rodents.[38–41] Interestingly, the selective inhibition in the NAc of the NF-κB pathway, a transcription factor inducing the expression of various proinflammatory genes, led to a reduction in compulsive sucrose-seeking behaviours in HFD-fed mice[42] highlighting the causal role of neuroinflammatory processes in food reward-related behaviours in rodents during obesity.

From a mechanistical point of view, inflammation triggers a decrease in DA synthesis and release that could thereby alter food reward-related processes. Indeed, during inflammation, there is a reduced availability of the cofactor tetrahydrobiopterin (BH4,) which is necessary for the activity of the TH, the limiting enzyme in DA synthesis.[43 44] Some studies have also demonstrated that proinflammatory cytokines reduced the expression of the transporter VMAT2, resulting in a decrease in DA availability in releasing processes.[45] Moreover, the transcription factor NF-κB, involved in inflammatory signalling regulated the transcription of the DRD2[46] whereas cytokines attenuated the binding of DA to DRD2 receptors.[43] Finally, some molecular links between increased inflammation and altered dopaminergic corticostriatal circuitry have also been described in patients with depressive disorder (for review, see[47]). Altogether, these results highlight the link between neuroinflammation and DA signalling in the reward system but their effects in the alterations of eating behaviours during obesity and ED remain to be demonstrated in humans.

Gut microbiota modulates neuroinflammation

Intestinal microbes modulate the maturation and function of tissue-resident immune cells in the CNS[48] and modulation of inflammatory pathways in the brain is proposed as an important regulator of the interaction between gut microbes and behaviours. Interestingly, some preclinical evidence supports the roles of gut microbes in the modulation of neuroinflammation (figure 2).

First, GF mice exhibit increased BBB permeability compared with conventional mice which is reversed when GF mice are exposed to control gut microbiota, leading to upregulation of tight junction proteins.[49] Antibiotic-induced gut microbiota depletion also disrupted the BBB and increased monocyte infiltration into the brain which is decreased by FMT from conventional mice.[50]

Second, gut microbiota components, such as lipopolysaccharides (LPS), injected in mice activate microglial cells in the brain[51] as well as astrocytes,[52] increase proinflammatory cytokines Il-1β, TNF-α and NF-κB[51] and disrupt the BBB.[53] Hence, gut microbiota metabolites such as short-chain fatty acids (SCFAs) have

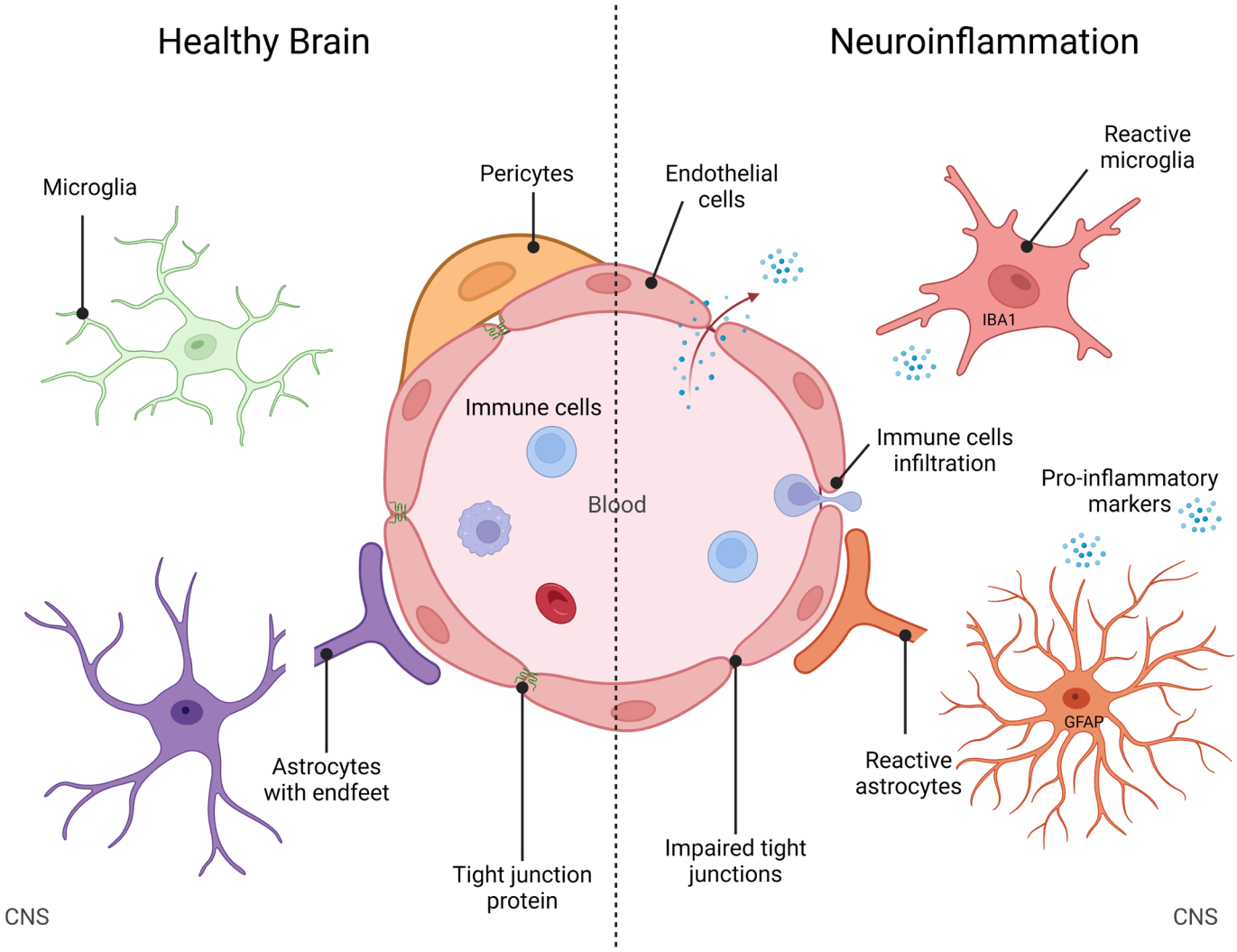

Figure 1 Neuroinflammation pathway. This figure illustrates how the interplay between immune cells, proinflammatory mediators and glial cells contributes to the pathogenesis of neuroinflammation. Increased permeability of the blood–brain barrier (BBB): proinflammatory mediators and cytokines, released in response to various stimuli, leading to the disruption of the BBB integrity, facilitating the entry of immune cells as macrophages or lymphocytes and inflammatory molecules into the brain. Activation of astrocytes: astrocytes, the supportive cells of the CNS, become activated in response to inflammatory signals. They undergo morphological changes, increased expression of glial fibrillar acidic protein (GFAP) and release inflammatory mediators further exacerbating neuroinflammation. Activation of microglia: microglia, the resident immune cells of the brain, become activated on encountering inflammatory stimuli and increase the expression of ionised calcium-binding adaptor protein-1 (IBA1). They undergo phenotypic changes and release proinflammatory cytokines, perpetuating the neuroinflammatory response. Created with BioRender.com. CNS, central nervous system.

been shown to modulate microglia maturation and function, thereby modulating neuroinflammation.[54]

Third, in the context of a hypercaloric diet, several preclinical studies highlighted the key role of gut microbiota in neuroinflammation. Using FMT from HFD or control donor mice into non-obese recipient mice, Bruce-Keller *et al* observed increased expression of *Iba*1, Toll-like receptor (*Tlr)2* and *Tlr4* and decreased expressions of *Zo1* and *Cldn5* in the PFC of recipient mice transplanted with faecal material from obese mice.[55] Using the same approach, Kim *et al* showed a significant increase in IBA1+immune cells in the nodose ganglia and in the nucleus of the tractus solitarius (NTS) of recipient rat transplanted with FMT from obese rats compared with rat receiving control gut microbiota.[56] Furthermore, oral antibiotic treatment rescued the increased expressions and protein levels of IL-1β and TNFα in the NAc of HFD mice.[57] These studies support the roles of gut microbes in the neuroinflammation associated with HFD feeding. Importantly, a mechanistic link between neuroinflammation and alterations in food reward during HFD feeding has been highlighted through the LPS-TLR4 signalling.[41] Indeed, TLR4 deletion partially protected HFD-induced obese mice from alteration in palatable food tropism and food-seeking behaviour whereas chronic low-dose LPS diffusion in the brain partially reproduced these alterations. In addition, another mechanism involved in the effects of gut microbes on neuroinflammation could rely on the modulation by gut microbes of the lipoprotein lipase expression in the mesocorticolimbic system thereby impacting the effect of lipids of DA-associated behaviours.[38 58] Finally, a recent study also demonstrated that a gut microbial tryptophan metabolite, the indole-3-acetic acid, was able to alleviate HFD-induced neuroinflammation in brain tissue via NF-κB signalling pathway blockade.[59]

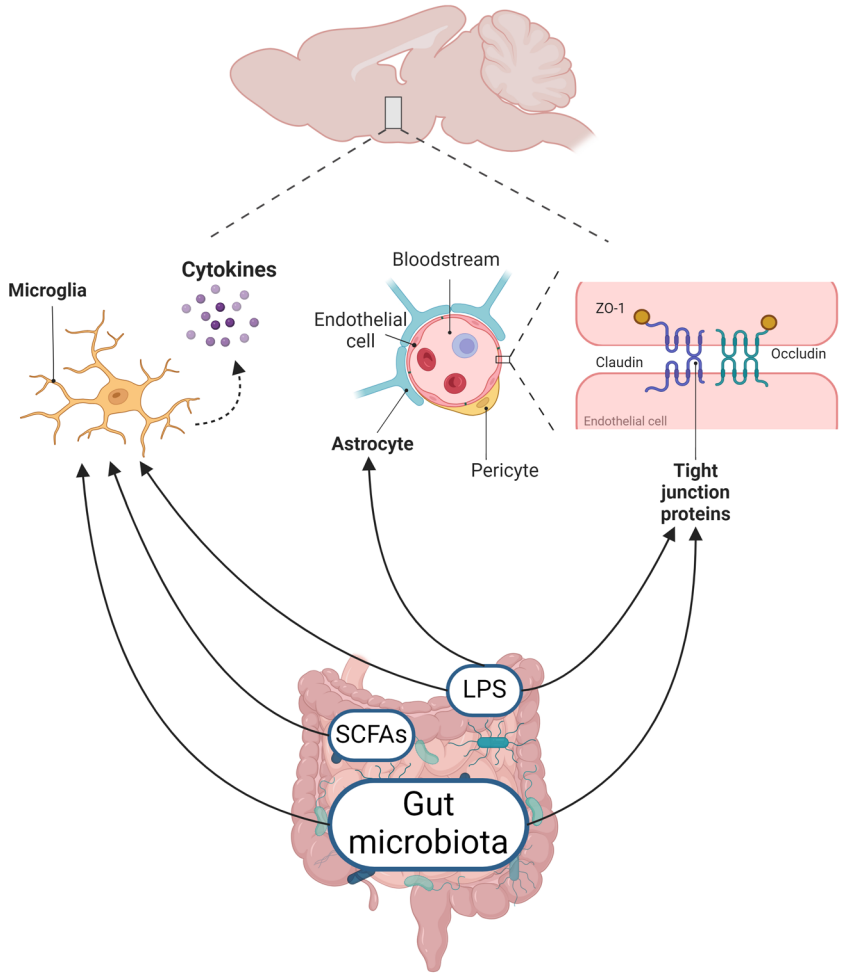

Figure 2 The gut microbiota modulates neuroinflammation. Recent studies on gut microbiota-depleted mice, through GF or antibiotic models, suggest that gut microbiota may regulate tight-junctions protein expression and microglia activation. Microbial products, such as lipopolysaccharides (LPS), a component of Gram-negative bacteria, or short-chain fatty acids (SCFA) can modulate microglial and astrocyte activation and decrease tight-junction protein expression. Altogether, this may result from a malfunctioning of the BBB, allowing the entrance of proinflammatory messengers to the CNS which in turn trigger signalling cascades, like proinflammatory cytokines production that may finally generate an inflammatory situation in the brain. Created with BioRender.com. BBB, blood–brain barrier; CNS, central nervous system; GF, germ-free.

In conclusion, emerging evidence suggests that the gut microbiota plays a pivotal role as a triggering factor for the modulation of neuroinflammation.

EATING DISORDERS

Definition and aetiology

ED are a group of psychiatric pathologies characterised by alterations of food intake-related behaviours, frequently leading to moderate or severe changes in body weight, shape, perception and other physiological parameters. Under the section 'Feeding and Eating Disorders', the Diagnostic and Statistical Manual of Mental Disorders-5 includes six main ED, among which anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) are the most prevalent, as well as the most investigated in research.[60]

AN is characterised by a decrease in energy intake triggered by a fear of gaining weight and a distorted body image. In consequence, AN patients frequently present extremely low body weight and body mass index, behaviours such as rigid diet control, excessive physical exercise or purging behaviours and inability to comprehend the severity of their state.[61] BN and BED are both binge-type disorders, defined as repetitive episodes of objectively large food intake in a short period of time accompanied by a sense of lack of control over this behaviour. While BN individuals engage in compensatory behaviours and manifest a disturbance in self-image, purging behaviours are absent in people with BED and body image perception is usually normal. However, they display other signs of psychological distress, such as shame about their eating problems or attempts to hide it. BED is frequently observed in overweight and obese individuals and it is the most prevalent ED among the general population.[60 62 63]

While the precise aetiology of ED remains unclear, ED seems to be associated with neuronal changes involving both the homeostatic and the hedonic systems implicated in food-related behaviours. Specifically, animal models have evidenced alterations in several neurotransmission systems[64] and disturbed patterns of activity in the reward-related brain regions.[65]

Given the multifactorial nature of ED, treatment relies on an interdisciplinary approach, including nutritional, psychological and pharmacological interventions.[62] However, several studies have pointed out the low success rate in recovery, considering that more than half of people affected by ED do not achieve full recovery and relapse and chronicity are common. Identifying additional effective therapeutic tools is therefore of utmost

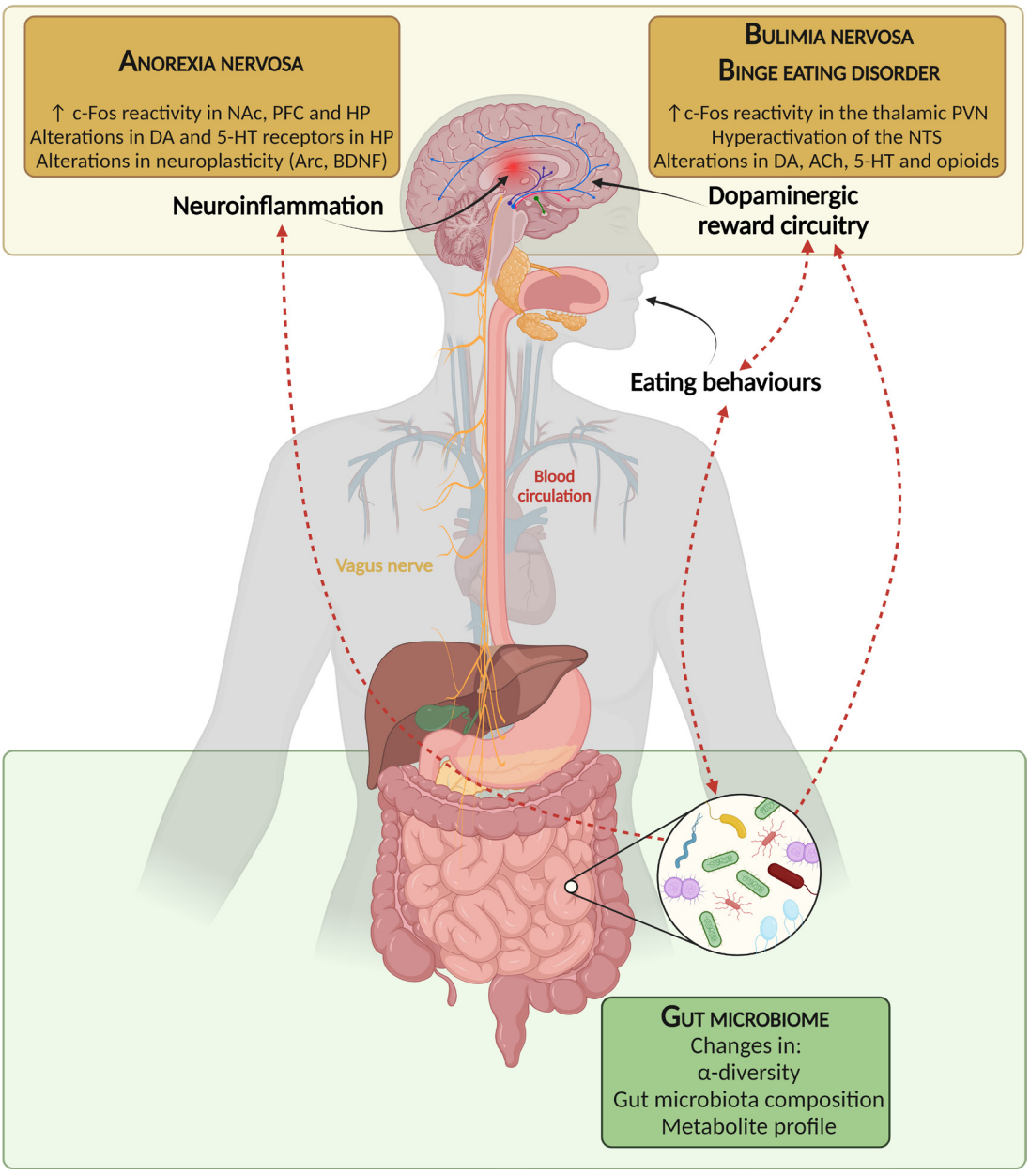

Figure 3 Alterations in the reward system and the gut microbiota in the three main ED. The literature offers evidence about the heterogeneous changes found in ED patients as well as in animal models. However, further research is needed to unequivocally link the CNS changes to the gut microbiota alterations as causal factors in these diseases. ↑ depicts 'increase'. Created with BioRender.com. 5-HT, serotonin; ACh, acetylcholine; Arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DA, dopamine; ED, eating disorders; HP, hippocampus; NAc, nucleus accumbens; NTS, nucleus of the tractus solitarius; PFC, prefrontal cortex; PVN, paraventricular nucleus.

importance for ED representing a major health concern due to the serious consequences for the physical health and psychosocial functioning of the patients.

ED and gut microbiota

The involvement of gut microbiota in ED has received increasing attention during the last decade but it still remains poorly understood. In this review, we focused on the available clinical results supporting changes in gut microbes during ED in humans (figure 3).

Various studies have pointed out that subjects suffering from AN showed a deviation of the gut microbiota composition compared with healthy controls, mainly in terms of diminished α-diversity and relative abundance of several different species (table 2; for review, see[66]). However, these results have not been reproduced in all studies.[67–69] Only, *Roseburia spp*, a SCFA-producer bacterium, has been repeatedly found to be diminished in AN patients compared with healthy subjects.[70–72] According to a systematic review, three bacterial species could differentiate patients from controls, namely *Alistipes*, *Parabacterioides* and *Roseburia*.[73] Interestingly, the gut virome has also been reported to be altered in AN.[74]

By using FMT approaches from AN patients to GF mice, the gut microbiome has been highlighted to contribute to the pathogenesis of AN.[74 75] Moreover, several Mendelian randomisation analyses on Genome-Wide Association Study data were performed to identify the causal association between gut bacteria taxa and AN.[70 71 76] One of these studies revealed the

Table 2 Microbiota characterisation in eating disorders

	Study population	Type of study and analysis	Changes in gut microbiota	Ref.
Anorexia nervosa	9 AN female patients versus 20 HC European cohort	Cross-sectional qPCR	↑ *Methanobrevibacter smithii*	78
	15 AN female patients versus 14 HC North American cohort	Longitudinal V1–V3 16S rRNA	↑ Bacilli ↑ Coriobacteriales ↓ Clostridia ↓ *Anaerostipes* ↓ *Faecalibacterium* ↓ α-diversity	80
	25 AN female patients (14 restrictive and 11 binge-purge subtype) versus 21 HC Japanese cohort	Cross-sectional 16S or 23S rRNA	↓ *Clostridium coccoides* ↓ *Clostridium leptum* ↓ *Bacteroides fragilis* ↓ *Streptococcus* ↓ *Lactobacillus plantarum* ↓ Total bacteria	79
	55 AN female patients versus 55 HC European cohort	Longitudinal V4 16S rRNA	↓ Bacteroidetes ↑ Firmicutes ↑ Actinobacteria ↑ *Methanobrevibacter smithii* ↑ Verrucomicrobia ↑ *Clostridium* ↓ *Roseburia spp.* ↑ β-diversity	67
	15 AN female patients versus 15 HC European cohort	Cross-sectional 16S rRNA qPCR	↓ Firmicutes ► ↓ *Ruminococcaceae* ► ↓ *Ruminococcus* ► ↓ *Roseburia* ► ↓ *Clostridium* ↑ Proteobacteria↑ *Enterobacteriaceae* ↑ *Methanobrevibacter smithii* ↑ Gram-bacteria	68
	18 AN female patients versus 26 HC and versus 20 AT European cohort	Cross-sectional V1–V2 16S rRNA	↑ *Coriobacteriaceae* ↓ Total bacteria (vs HC) ↓ α-diversity (vs AT)	111
	33 AN female patients versus 22 HC European cohort	Cross-sectional V3–V4 16S rRNA	↓ Strict anaerobic Gram+: ► ↓ *Eubacterium* ► ↓ *Roseburia* ► ↓ *Anaerostipes* ↓ *Peptostreptococcaceae* ↑ Turicibacter ↑ Anaerotruncus ↑ Salmonella ↑ Klebsiella ↑ Ruminococcus ↓ α-diversity	112
	Four 16S data sets from AN patients[67 68 80 112]	Meta-analysis	↑ *Alistipes* ↑ *Parabacteroides* ↓ *Roseburia* ↓ *Rominococcus* ↑ *Clostridium XVIII* ↑ *Akkermansia* ↑ *Eisenbergiella* ↑ α-diversity	73
	21 AN female patients (16 restrictive and 5 binge-purge subtype) versus 20 HC European cohort	Longitudinal V4 16S rRNA	↑ Bacteroidetes ↑ Actinobacteria ↑ *Weissella* ↑ *Coprococcus* ↓ Firmicutes ↓ Coriobacteriales ↓ *Parabacteroides* ↓*Oxalobacteraceae* ↓ α-diversity	113
	51 AN female patients versus 67 HC European cohort	Cross-sectional V3–V4 16S rRNA	↑ *Alistipes* ↑ Clostridiales ↑ *Christensenellaceae* ↑ *Ruminococcaceae* ↓ *Faecalibacterium* ↓ *Agathobacter* ↓ *Bacteroides* ↓ *Blautia* ↓ *Lachnospira* ↑ β-diversity	69
	19 AN female adolescent patients versus 20 HC European cohort	Longitudinal V1–V2 16S rRNA	↑ *Anaerostipes* ↓ *Romboutsia*	114
	93 AN female patients versus 98 HC North American cohort	Longitudinal Shotgun metagenomics	↓ *Bifidobacterium adolescentis* ↓ *Faecalibacterium prausnitzii* ↓ α-diversity	115
	30 AN female patients versus 30 HC Chinese cohort	Cross-sectional V3–V4 16S rRNA	↑ *Lachnospiraceae* ↓ *Ruminococcaceae* ↓ *Faecalibacterium* ↓ *Subdoligranulum* ↑ *Eubacterium hallii* ↑ β-diversity	116
	77 AN female patients versus 70 HC European cohort	*Cross-sectional Shotgun metagenomics*	↓ Bacteroid*etes* ↓ Actinobacteria ↑ Christensenellales CAG-138 ↓ *Ruminococcaceae* ↓ *Lachnospiraceae* ↑ *Lactobacillus* ↑ *Clostridium paraputrificum* ↓ *Roseburia intestinalis* ↓ *Roseburia inulinivorans* ↑ β-diversity	74
	Large-scale GWAS data	Mendelian randomisation analysis	↑ Actinobacteria	76
	63 AN female adolescent patients versus 41 HC European cohort	Longitudinal V1–V2 16S rRNA	↓ *Acinetobacter* ↓ *Dialister* ↓ *Faecalibacterium* ↓ Family XIII UCG 001 ↓ *Legionella* ↓ *Limnobacter* ↓ *Ralstonia* ↓ *Ruminococcaceae UCG 003* ↑ *Anaerostipes* ↑ *Anaerotruncus* ↑ *Bacteroides* ↑ *Bilophila* ↑ *Blautia* ↑ *Collinsella* ↑ *Eisenbergiella* ↑ *Erysipelotrichaceae_UCG_003* ↑ Family XIII AD3011 group ↑ *Lachnospiraceae* ND3007 group ↑ *Ruminococcacaea* UCG 009	117
	Large-scale GWAS data	Multiomics Mendelian randomisation analysis	↓ Firmicutes E ↓ RUG147 ↓ CAG-977 ↓ Desulfobacterota A ↓ CAG-269 sp002372935 ↓ *Klebsiella* ↓ Desulfovibrionia ↓ *Klebsiella pneumoniae* ↓ Desulfovibrionales ↓ CAG-776 ↓ *Desulfovibrionaceae* ↑ Parachlamydiales ↑ *Paenibacillus* ↑ *Gillisia* ↑ UBA1191 ↑ UBA7703 ↑ *Faecalicatena sp002161355* ↑ *Johnsonella ignava* ↑ *Staphylococcus aureus* ↑ *Comamonas* ↑ *Ruminococcus D* ↑ CAG-349 ↑ *Ruminococcus D bicirculans* ↑ CAG-177	71
Bulimia nervosa+binge eating disorder	38 obese patients with BED diagnosis versus 53 non-BED obese patients European cohort	Cross-sectional V5–V6 16S rRNA	↓ *Akkermansia* ↓ *Intestimonas* ↑ *Bifidobacterium* ↑ *Roseburia* ↑ *Anaerostipes*	83
	9 BN female adolescent patients versus 9 HC Chinese cohort	Cross-sectional V3–V4 16S rDNA	↓ *Faecalibacterium prausnitzii*	72
	21 AN female+9 BED female+17 BN female patients versus 28 HC European cohort	Cross-sectional V3–V4 16S rRNA	In binge-purge subtype: ↑ *Prevotella* In all ED: ↓ Actinobacteria: ↓ *Bifidobacterium* ↓ Collinsella	118

↑ depicts 'increase', ↓ depicts 'decrease'.
AN, anorexia nervosa; AT, athletes; BED, binge eating disorder; BN, bulimia nervosa; ED, eating disorders; GWAS, Genome-Wide Association Study; HC, healthy control; qPCR, quantitative PCR; rDNA, ribosomal DNA; rRNA, ribosomal RNA.

causal association of 25 gut microbiota taxa in AN, of which 12 were considered protective factors, including Firmicutes E or *Klebsiella*, while other 13 were considered as risk factors for AN, including *Staphylococcus aureus* or *Ruminococcus D*.[71] That said, it is important to mention that such kind of analyses limit the possibility of identifying specific bacteria species associated with AN.

Importantly, gut microbiota changes in AN could also be linked to a low-caloric diet. It has been shown in patients with AN that some taxa, such as Verrucomicrobia, may rise in response to dietary shortage since they are able to degrade the host mucins.[77] Moreover, the rise of the archaeon *Methanobrevibacter smithii*, which can reduce hydrogen and carbon dioxide into methane, has also been associated with caloric restriction in AN patients.[78 79]

Finally, it is also important to highlight that AN-induced alterations in gut microbiota may remain in later stages of life, even after clinical recovery or weight restoration.[80] A recent

Table 3 Summary of therapeutic approaches targeting the gut microbiota in obesity and ED to alleviate food reward dysregulations

Pathology	Model subject	Approach	Metabolite/bacteria	Effect	Ref.
Obesity	CT rats	Prebiotic	2′-FL	↑ Number of lever presses for pellet during operant conditioning test	98
	HFHS mice	Prebiotic	FOS	↓ Number of lever presses for sucrose pellet during operant conditioning test	99
		Prebiotic	Back to control diet+FOS	↓HFHS intake during 2-hour time restricted and overnight access	
	DIO mice	Prebiotic	Inulin	Improvement of sweet taste perception ↑ Sucrose preference	100
	Overweight women	Prebiotic	Inulin	↓ VTA and orbital cortex activation in response to very high caloric food ↓ self-report hunger sensation	102
	DIO mice	Probiotic	*Bifidobacterium pseudocatenulatum* CECT 7765	↑ Sucrose preference ↓ Hp and intestinal TLR2 and *Tlr2* mRNA up-regulated expression	101
Anorexia nervosa	AN adolescent patients	Probiotic	*Lactobacillus reuteri* DSM17938	↑ BMI ↑ Weight restoration ↑ Stool frequency	105
	Recurrent female AN patient	FMT	FMT from healthy donor	↑ Body weight ↑ Fat mass	106
Binge eating	Binge eating-subjected rats	Probiotic	*Bacteroides uniformis*	↓ Total caloric intake Restoration of NAc DA levels and of PFC DA receptor levels	109
	Stress-induced, binge eating-subjected female mice	Probiotic	*Faecalibacterium prausnitzii*	↓ Total caloric intake ↓ Preference for palatable food	72
	Abx-treated, binge-eating subjected mice	Probiotic	*S24-7 Bacteroidales family* *Lactobacillus johnsonii*	↓ Binge intake of high sucrose food	14
	Obese patients after bariatric surgery	Probiotic	*Lactobacillus acidophilus* NCFM *Bifidobacterium lactis* Bi-07	↓ Binge Eating Score ↓ Yale Food Addiction Score	110

↑ depicts 'increase', ↓ depicts 'decrease'.
Abx, antibiotics; AN, anorexia nervosa; BMI, body mass index; DA, dopamine; DIO, diet-induced obesity; 2-FL, 2′-fucosyllactose; FMT, faecal material transplantation; FOS, fructo-oligosaccharides; HFHS, high-fat high-sucrose diet; Hp, hippocampus; mRNA, messenger RNA; NAc, nucleus accumbens; PFC, prefrontal cortex; TLR, Toll-like receptor; VTA, ventral tegmental area.

longitudinal study performed in adolescent patients of AN showed that changes in gut microbiota were not fully resolved 1 year after hospital admission, not even in patients with weight restitution. Interestingly, some bacteria taxa could be potential positive prognosis markers in body weight gain since the better outcome was observed in patients that presented a higher abundance of *Sutterella*, a bacterium known to regulate inflammatory conditions.[81]

On the other hand, the literature about the relationship between the gut microbiota and BN or BED is more limited (table 2; for review, see[82]). BED disorder in obese subjects was characterised by changes in 11 genera, compared with obese subjects without the BED diagnostic. Specifically, *Akkermansia* and *Intestimonas* showed lower abundance in BED obese patients, while *Bifidobacterium, Roseburia and Anaerostipes* were increased.[83] Moreover, uncontrolled eating behaviour in obese patients was mostly characterised by low-diversity microbial steady states.[84] Recently a reduction in the abundance of *Faecalibacterium prausnitzii* has also been described in BN patients and its supplementation has been shown to control BED in mice.[72] That said, a Mendelian randomisation study analysing a cohort of individuals diagnosed with BN did not identify statistically significant associations.[70]

Lastly, even if it is not recognised as an ED, it is important to mention that vulnerability to food addiction has also been recently linked with gut microbiota signature in humans. A decrease in *Blautia wexlerae* was observed in addicted humans and of *Blautia* genus in addicted mice whereas a protective effect of *Blautia wexlerae* supplementation to develop food addiction has been shown in mice.[85]

Altogether these results highlight a potential associative link between gut microbes and ED whereas only very limited studies investigated potential causal association through FMT experiments in the AN model. Moreover, general limitations in most of the available studies include lack of control for diet, mental comorbidities, pharmacotherapies as well as heterogeneity in gut microbiota analysing techniques. Therefore, additional studies are required to confirm the causal role of gut microbes in the pathogenesis of AN and to highlight such causal roles of gut microbes in BN and BED in humans.

ED and food reward system

The neurobiology of ED relies on functional and structural changes involving both the homeostatic and the reward systems for food-related behaviours. Neuroimaging studies

have corroborated that ED patients show disturbed patterns of activity in brain regions implicated in cognitive control, emotional processing and reward value.[65] Indeed, increased food-related impulsivity and reward responsiveness to food cues and food intake is well established in BED patients.[86 87] This has been supported by highlighting an increased activity of the brain reward system when anticipating or receiving food in BED patients.[87] Brain reward response has also been shown to be altered in adolescents and young adults with AN.[88] In fact, animal models of the three main ED have evidenced alterations in several neurotransmission systems (dopaminergic, opioidergic,…) in the brain areas related to the reward system.[64] For this review, we will summarise the link between ED and the reward system (figure 3).

Various studies reported alterations in reward-related brain areas in preclinical models of AN. Female rats subjected to an activity-based anorexia protocol presented neuroplastic changes and higher neuronal activation in the NAc, Hp and PFC which in turn correlated with body weight loss.[89] Another important neuroplasticity mediator impacted by AN is brain-derived neurotrophic factor (BDNF), whose levels were altered in the PFC or VTA.[90]

In the context of BN or BED, the GABA and 5-HT neurotransmission seem to be implicated. In a paradigm of 2-hour restricted access to HFD, the administration of GABA receptor B ($GABA_B$) agonist, suppressed the binge-type intake of HFD in wild-type mice, while it showed no effect in knock-out mice for $GABA_B$ receptor in mesolimbic neurons.[91] In a similar approach, mice lacking functional serotoninergic 5-HT_{2C} receptor did not respond to the binge-inhibiting effects of drugs acting on serotoninergic receptors, but genetic re-expression of this receptor in dopaminergic neurons of the VTA was sufficient to rescue the suppression of the binge-eating behaviour.[92] Altogether, the evidence indicates that in the context of ED the mesocorticolimbic reward system suffers modifications contributing to the abnormalities in food intake behaviour and representing a target for a therapeutic approach.

However, we still lack a robust causal link that ties the tripartite relationship between gut microbiota, the reward system and ED. In a study with an activity-based anorexia model in mice, the antibiotic-induced depletion of gut microbiota triggered alterations in the messenger RNA levels of dopaminergic and serotoninergic receptors in the Hp in male mice. However, gut microbiota depletion did not affect food intake.[93] Regarding BED and BN, a recent study revealed hyperactivation of the paraventricular nucleus of the thalamus (involved both in reward response and homeostatic feeding) and NTS in animals subjected to an overeating paradigm compared with naïve controls, suggesting a heightened communication between the gut and the brain through the vagus nerve. Interestingly, kynurenic acid, an important regulator of glutamatergic neurotransmission, was decreased in the lumen of animals that underwent the overeating protocol, as well as in stool samples of patients diagnosed with BN. The decrease in this tryptophan metabolite correlated with a decrease in the bacterial species *F. prausnitzii*. Accordingly, colonisation with *F. prausnitzii* in overeating mice restored kynurenic acid levels and alleviated the overeating behaviours.[72] In conclusion, these studies highlight a link between gut microbes and reward systems in ED but further investigation is crucial to determine the potential use of the gut microbiota as a target for food reward processes modulation and their effect in the context of ED.

Neuroinflammation hypothesis for ED?

Literature on neuroinflammation in the context of ED is scarce but some preclinical studies highlight an increase of inflammatory markers in the brain during ED (figure 3). In an AN rat model, an increase of proinflammatory cytokines levels, activation of astrocytes and microglia have been reported in the Hp.[94] In a BED rodent model, an increase in the expression of the inducible isoform of the nitric oxide synthase (iNOS) has been shown in the hypothalamus.[95] Moreover, in a BED model with female mice, deletion of the IKKβ pathway in dopaminergic neurons reduced inflammation and binge-eating behaviours.[96] Even if these data reveal potential neuroinflammation in ED, further work is necessary to fully unravel the impact of neuroinflammation in the context of ED. That said since gut microbes could modulate inflammatory makers in the brain (see Gut microbiota modulates neuroinflammation) and signalling pathways involved in food reward (see Gut microbiota impact reward signalling), gut microbiota-targeted approaches are suggested as a potential interesting strategy in food reward alterations and ED.

GUT MICROBIOTA AS A SOURCE OF POTENTIAL THERAPEUTIC APPROACHES AGAINST FOOD REWARD ALTERATIONS AND ED

Therapeutic potential of gut microbiota-directed interventions in food-reward alterations during long-term HFD feeding

Patients suffering from obesity and overweight exhibited compromised food reward brain responses to palatable food. Importantly, these dysregulations persisted even after diet-induced weight loss,[97] therefore it becomes crucial to explore tools for restoring these brain responses. As a potential therapeutic strategy, we propose investigating the potential beneficial effects of gut microbes. Gut microbiota can be modulated by prebiotic- or beneficial microbe supplementation and some elements in the literature support the relevance of this strategy of targeting gut microbes in ED (table 3).

In lean condition, rats supplemented with 2'-Fucosyllactose presented an increase in food reward-seeking behaviour during an operant conditioning test compared with control group, while vagotomy restored the behaviour.[98] Investigating its effect in pathologic situations such as during obesity could be interesting. In that line of idea, mice under HFHS supplemented with fructo-oligosaccharides resulted in reduced food reward-seeking behaviour for sucrose pellets compared with HFHS mice and showed reduced intake of palatable food on returning to a control diet compared with mice without prebiotic supplementation.[99] Furthermore, supplementation with inulin partially improved the sweet taste perception and restored sucrose preference in obese mice.[100] These studies suggest that the prebiotic approach can ameliorate dysregulation in food reward behaviours associated with a hypercaloric diet.

In line with the probiotic approach, potential beneficial bacteria have been proposed in food reward dysregulations during long-term HFD feeding. *Bifidobacterium pseudocatenulatum* CECT 7765 supplementation in HFD mice regulated sucrose solution intake.[101] Moreover, daily administration of *Akkermansia muciniphila* in HFD mice improved food reward dysregulation possibly through modulation of neuroinflammation in reward brain areas.[38]

Finally, there is also evidence in human studies that gut microbiota modulation using the prebiotic impacts food reward processes during obesity. In overweight women, supplementation with the prebiotic inulin for 2 weeks decreased the activation

level of the VTA and orbitofrontal cortex in response to very high caloric food as well as self-reported hunger sensation.[102]

With all this evidence, we can say that the gut microbiota modulates the function of the reward system related to feeding behaviour during HFD feeding and obesity. However further studies are needed to identify the mediators and the more effective gut microbiota strategy to tackle food reward disorders.

Therapeutic potential of gut microbiota-directed interventions in ED

Given the important prevalence of ED and low rate of recovery after standard care, the search for alternative treatments against ED gains great relevance and the gut microbiota represents a clear potential target (table 3).[63 103]

Anorexia nervosa

Very few studies have been published regarding the impact of gut microbiota modulation in symptomatic changes in female AN patients (for review, see[104]). Investigation of the effects of *Lactobacillus reuteri* DSM17938 on AN adolescents reported an increase in body mass index, weight restoration and improved stool frequency in *L. reuteri* supplemented subjects.[105] Additionally, FMT shows promising proof of concept in treating AN through gut microbiota-targeted approaches. In a case report with a female patient suffering from recurrent AN, 36 weeks after the FMT treatment from a healthy donor, the patient showed an increase in body weight, fat mass and phylogenetic diversity. These changes were possibly mediated by an increase in the production of SCFA.[106] Furthermore, additional ongoing studies are further investigating if FMT from healthy donors would help to restore the gut microbiome of individuals with AN which in turn may aid patient recovery.[107] Lastly, it is worth mentioning the existence of an ongoing registered clinical trial to analyse the effects of supplementation with SCFA in anorectic patients on alterations in eating behaviour, among other physiological parameters, with the hypothesis of finding a switch towards a less restrictive diet.[108] Since AN is associated with altered food reward processes, additional gut microbiota strategies modulating the reward system could represent an interesting complementary therapeutic tool but this needs to be further evaluated.

BN and BED

A few studies have gathered preclinical evidence on the benefits of modulating the gut microbiota as a target for BED or BN treatment. The work of Agustí *et al* showed that oral administration of *Bacteroides uniformis* reduced the binge eating behaviours in a BED rat model, associated with changes in the extracellular DA concentration in the NAc and the restoration of DA receptor levels in the PFC.[109] In addition, oral administration of *F. prausnitzii* on female mice that were subjected to a BED model alleviated the BE episode as it decreased both the total amount of caloric intake and the preference for a highly palatable food.[72] In the same line, bacteria from the S24-7 Bacteroidales family (phylogenetically related to *F. prausnitzii*) and *Lactobacillus johnsonii* suppressed the binge-type intake of high sucrose food in mice induced by vancomycin gut microbiota depletion.[14]

On the other hand, the evidence from human studies on the potential benefits of probiotic treatment against BED or BN is still missing. There is only one study showing the possible effects of microbes on BED symptoms in obese patients after bariatric surgery. This randomised controlled trial showed that administration of *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07 for 90 days right after the gastric bypass surgery was more effective in diminishing the Binge Eating Score and the Yale Food Addiction Score (screening questionnaires to assess binge eating and food addiction, respectively) at 1 year follow-up, when compared with patients that received a placebo.[110] Although severe obesity is the key pathology in this cohort, these results open the door to possible use of gut microbes in primary ED-diagnosed patients.

In summary, the gut microbiota emerges as a promising source of potential therapeutic targets for addressing food reward alterations and ED, underscoring the significance of exploring gut microbiota-targeted interventions in the development of novel treatment approaches.

That said, even if such fundamental research provides new hopes for the development of novel clinical applications, it is also important to keep in mind that multiple and challenging steps still remain before translational applications in the clinic. Among these challenges, the validation of the causal role of gut microbes in patients suffering from ED remains of particular importance as well as the identification of the specific strains exerting beneficial effects and the underlying molecular mechanisms. Then, human interventions require large-scale production of microorganisms with their own specific needs, representing an additional obstacle to overcome. Furthermore, important gut microbiota interindividual variability may be responsible for variability in the efficacy of gut microbiome-targeting therapeutic approaches in larger cohorts of patients, challenging the bench-to-bedside development.

GENERAL CONCLUSIONS AND PERSPECTIVES

In conclusion, this review summarises the multifaceted role of gut microbiota in influencing food reward processes, reward signalling and neuroinflammation processes. It underscores the connection between alterations in gut microbiota composition, changes in food reward-related behaviour and the presence of neuroinflammation in relevant brain regions, particularly in the context of ED (figure 3). Importantly, these findings suggest that targeting the gut microbiota represents a promising therapeutic strategy to address food reward alterations and potentially mitigate the symptoms of ED. Further research in this area is warranted to fully elucidate the mechanisms involved and to explore the clinical applications of gut microbiota modulation in the treatment of ED and related conditions.

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