Gut dysbiosis by HFD: Effect on Distant Organs

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Contributor: Dagmara Kociszewska , Srdjan Vlajkovic , Jeffrey Chan , Peter R Thorne

The gastrointestinal (GI) tract protects the body from environmental challenges by blocking access to the host's blood circulation for many pathogens, including fungi, bacteria, and parasites. This GI firewall comprises various structures and shielding mechanisms to fulfil its protective function, constituting an intestinal barrier (IB). The IB includes mucosal and submucosal layers, tight junctions (TJ), continuously renewing epithelium, and microbiota. The intestinal epithelial cells (IECs) are a barrier between the immune system and GI lumen, maintaining a limited IB permeability. Nonetheless, the GI tract has an arduous task. The constantly changing environment requires the IB to continually respond to new challenges, yet maintain its integrity while protecting the host from pathogens. Failure of the IB leads to intestinal hyperpermeability (leaky gut), allowing pathogens and their metabolites to enter the bloodstream. The metabolites then can affect distant organs, such as brain and inner ear.

gastrointestinal tract high-fat diet obesity

1. Gut Microbiota

Intestinal (gut) microbiota can be considered a first line of defence against GI pathogens, as it stimulates the immune system, synthesises amino acids and vitamins, and breaks down toxic compounds found in food [1]. The human microbiome contains 3.8×10^{13} microorganisms, including thousands of various species of bacteria, fungi, parasites, and viruses [2], accounting for up to 3% of body weight [3]. The majority of the microbiota inhabit the distal bowel, where they help process materials otherwise indigestible for humans [2]. Each person has a distinctive and unique microbiome [4], and alterations in the gut microbiota can benefit or harm the host [5][6]. The microbiome can react dynamically in response to changing conditions such as diet or medications. When the balance between the different microorganisms is disturbed, it leads to dysbiosis, affecting the regular, necessary interactions between the body and microbiota and altering the IB, thus making the host's body more prone to illness. When this barrier is compromised, the host immune system can initiate a cascade of inflammatory responses to the intestinal milieu, turning the symbiotic relationship between the host and gut microbiome into a pathological one [7]. The most frequent sources of dysbiosis are antibiotics, bacteria-depleting medications, infectious diseases, or prolonged, poor diet [8].

1.1. Gut Microbiota and Inflammation

In eubiosis (healthy microbiome), the gut is protected by the outer mucus layer, anti-inflammatory microbial products and elements of the immune system, such as immunoglobulin A (IgA), regulatory T cells (Tregs), and

eosinophils. The human microbiome consists of the five main phyla of bacteria: *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia* and *Archaea*, with the most dominant being *Bacteroides, Prevotella*, and *Ruminococcus* [9].

Bacteria can have pro- and anti-inflammatory properties. As an example of an anti-inflammatory bacterium, *Akkermansiamuciniphila* is a mucin-degrading strain belonging to the phylum *Verrucomicrobia.* In eubiosis, *Akkermansiamuciniphila* enhances mucin production [10], and supports the expression of TJ proteins such as occludin, thus maintaining IB integrity [11]. It is also associated with leanness, reduced inflammation and insulin sensitivity [12][13][14][15][16].

In contrast, pro-inflammatory bacteria produce endotoxins. In dysbiosis, the increase in Gram-negative and lipopolysaccharide (LPS)-producing bacteria can be observed [17][18]. It is well established that a HFD is closely linked with DIO-related dysbiosis, which manifests in a decrease in overall microbiota, and increased gut permeability [19][20]. Several studies using murine and human models have associated DIO and a HFD with enhanced endotoxemia, which leads to the increased permeability of the IB and increased penetration of the luminal LPS into the circulation [21][22][23][24][25].

Therefore, intestinal hyperpermeability can cause a leak of toxic substances (such as pro-inflammatory microbial solutes) into the bloodstream [26]. In response to pathogens spreading through the bloodstream, the body launches an acute inflammatory response by activating the innate and adaptive immune systems [27]. If the inflammatory response fails to resolve, it will lead to a state of chronic inflammation that could potentially reach the inner ear. Moreover, this chronic inflammation can result in complications such as diabetes or IBD [28].

IBD is an umbrella term used to describe disorders that involve chronic GI inflammation, such as Crohn's disease (CD) and ulcerative colitis (UC) [29], which are also characterised by a leaky gut. The prevalence of genetic causation of IBD is relatively low, making environmental factors a key suspect. Moreover, factors that are known to positively impact gut microbiota, such as early exposure to animals, having many siblings [30][31], natural mode of delivery [32] and breastfeeding [33], decrease the chances of developing IBD. In contrast, factors such as C-section [32][34], excessive paediatric hygiene [35] and early-life antibiotic therapies [36][37][38] appear to increase the risk of developing IBD. This is further supported by the incidence of IBD being higher in urban areas rather than rural areas [39][40]. Diet is also an important factor, where multiple studies have described the association between diet and the incidence of IBD [41][42][43][44][45][46].

Although the complex aetiology of IBD is not fully understood, IBD and sub-clinical manifestations of inflammatory gut diseases have been associated with gut dysbiosis and significantly increased levels of bacterial products such as LPS [21][47][48]. Previous studies have shown that healthy subjects can generally tolerate autologous microbiome; however, in susceptible individuals, the breakdown of this symbiosis is associated with chronic intestinal inflammation [49][50]. Treatments that typically affect microbiota, such as faecal diversion and antibiotic therapy, are often used for IBD management [51][52][53][54][55][56]. Interestingly, the intestinal lesions in IBD are usually located at sites of higher concentrations of commensal bacteria [57][58]. Moreover, IBD patients have an altered gut mucus

layer [59], which would further implicate microbiota in the pathophysiology of IBD. IBD patients also present higher yields of antibodies against commensal bacteria than healthy individuals [60].

In eubiosis, *Bacteroides fragilis* is a commensal, anti-inflammatory bacterium of the gut. Many strains of *B. fragilis* produce polysaccharide A (PSA), which binds to TLR2, promoting secretion of the anti-inflammatory cytokine interleukin 10 (IL-10) from the regulatory T cells. Outside the gut (due to surgery or leaky gut), *B. fragilis* can cause systemic inflammation. A particular *B. fragilis* strain (ETBF) produces metalloprotease enterotoxin, which is thought to be involved in the aetiology of IBD [61][62][63].

1.2. Lipopolysaccharides

Lipopolysaccharides (LPS) are components of the cellular wall of Gram-negative bacteria. Under physiological conditions, the IB prevents bacterial LPS from entering the bloodstream [64]. Pathological conditions can increase the number of Gram-negative bacteria in the GI tract [21] and the levels of LPS circulating in the bloodstream, leading to metabolic endotoxemia [65], as shown in mice on a HFD [22]. The increased levels of LPS are also found in metabolic diseases and DIO [66][21][22][67][68]. LPS activates inflammatory responses after binding to Toll-like receptor 4 (TLR4) on the immune cells [67]. LPS also induces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor in macrophages and stimulates these cells to release inflammatory cytokines such as interleukin 1 beta (IL-1β) and tumour necrosis factor alpha (TNFα) [69]. In turn, TNFα can suppress scavenger receptor function in macrophages [70]. In addition, LPS can increase the production of intracellular reactive oxygen species (ROS) [71].

Resulting from the disbalance of ROS metabolism, OS is recognised as a mediator of inflammation-induced disorders, including age-related hearing loss (ARHL) and other forms of SNHL [72][73][74][75][76]. In human studies, administration of LPS resulted in suppression of insulin receptors and increased insulin resistance [77], which has been associated with hearing loss [78].

1.3. Short-Chain Fatty Acids

Commensal, anti-inflammatory gut microbiota metabolises complex carbohydrates into short-chain fatty acids (SCFA). SCFA fulfil various roles, including activating and inhibiting the inflammatory response and different metabolic pathways [79]. SCFA levels vary between obese and lean individuals [80]. Butyrate, a type of SCFA, contributes to the prevention of metabolic disorders [81] and helps retain the IB's integrity, thus reducing the rate of LPS translocation through the intestinal epithelium [81]. SCFA can also prevent HFD-induced obesity in mice by altering gut microbiota [82]. Furthermore, butyrate stimulates nuclear transcription factor-peroxisome proliferator-activated receptor gamma (PPAR-γ), which in turn inhibits the pro-inflammatory NF-κB pathway [83][84]. It also inhibits interferon-gamma (IFN-γ) signalling to suppress inflammation [85].

2. Interactions between the Gut and Distant Organs

Gut microbiota communicates with the brain through several communication channels known as the microbiota–gut–brain axis. The communication routes include tryptophan metabolism, the vagus nerve, microbial metabolites, and the immune system [86]. Even though the notion of a gut–brain axis is relatively new, the evidence is exponentially rising [87][86][88][89][90][91][92].

Interaction between microbiota and the host's tissues within the IB can result in the secretion of chemokines, cytokines, neurotransmitters, endocrine messengers, neuropeptides, and microbial by-products such as LPS [86]. These molecules can then penetrate the vascular and lymphatic systems, impact neural messages carried out by vagal and spinal afferent neurons, communicate with the brain regarding the host's health status and influence behaviour [86]. Most of the host–microbiota interactions occur within the IB, where the exchange of molecules mediates communication between the gut and immune system [93]. The intestinal epithelium also houses enterocytes, secretory cells, chemosensory cells and gut-associated lymphoid tissue, participating in the immune response [94].

The enterocytes play a vital role in the innate immune system response by releasing pro- and anti-inflammatory cytokines and chemokines, whereas B lymphocytes in Peyer's patches produce immunoglobulins [95]. Intestinal epithelial pattern recognition receptors (PRRs) identify molecular patterns unique to the specific microorganisms [96][97]. These include Toll-like receptor (TLR) family members, which mediate pro-inflammatory responses [98]. In addition, some metabolites of commensal bacteria (such as LPS) can activate the innate immune system and, thus, modulate neural responses [86][99].

The integrity of the blood–brain barrier (BBB) can be affected by systemic pro-inflammatory signalling induced by a HFD [100][101][102], leading to brain inflammation and injury. This may not be linked to obesity, as transplantation of microbiota from mice fed a HFD caused significant disruptions in exploratory, cognitive, and stereotypical behaviour in non-obese recipient mice fed a standard diet [103]. This study provided direct evidence that HFD-induced changes to the gut microbiome are sufficient to disrupt brain function in the absence of obesity. Furthermore, previous studies have shown that germ-free mice exhibit increased BBB permeability, with downregulation of TJ proteins claudin-5 and occludin. Nevertheless, exposure of germ-free mice to specific-pathogen-free mice followed a reduction in BBB permeability and upregulation of TJ proteins [104].

The gut microbiota can also modulate the host's behaviour and brain function [89][105][106][107][108]. Of interest, germ-free mice displayed cognitive deficits, similar to mice infected with *Citrobacter rodentium* and exposed to acute stress [109][110]. Several studies have reported gut microbiota as a critical player in neuroinflammation, neurodegeneration and mental illness development [111][112]. Gut dysbiosis has been said to play a role in the aetiology of neurodegenerative diseases such as Alzheimer's disease (AD) [113], Parkinson's disease (PD) [114], multiple sclerosis [115] and amyotrophic lateral sclerosis [116]. In AD, an imbalance in the microbiome is associated with the co-localisation of LPS with amyloid β-protein (Aβ) 1–40/42 in amyloid plaques and around blood vessels [117]. LPS binds to microglial receptors (TLR2, TLR4 and CD14), activating the NF-κB (p50/p60) complex, which initiates neuroinflammatory processes [118][119].

Regarding PD, bowel inflammation can provoke the progression of the disease [120]. Colonic hyperpermeability in PD patients has been linked with increased α-synuclein and *E. coli* accumulation in the sigmoid colon [121]. The microbiome landscape in PD is significantly shifted, with decreased levels of bacteria that produce anti-inflammatory mediator butyrate (*Blautia*, *Coprococcus*, and *Roseburia*) and increased levels of LPS-producing bacteria (*Oscillospira* and *Bacteroides*) [114]. Furthermore, specific changes in the gut microbiome have been linked with the severity of symptoms and elevated serum cytokine levels seen in PD [122]. This further supports a link between changes in gut microbiota, systemic inflammation and PD.

IBD has also been linked with a higher incidence of neurodegenerative disorders, including dementia [123][124]; however, the mechanisms are not well understood.

In summary, factors such as a HFD can cause gut dysbiosis, hyperpermeability of the IB and infiltration of pathogens and microbial solutes into the circulation, thus contributing to chronic systemic inflammation [125]. Chronic inflammation can disrupt the BBB's integrity, facilitating the infiltration of pathogens and pro-inflammatory cytokines into the brain, resulting in neuroinflammation and neurodegeneration [126][127][128][129] (**Figure 1 and Figure 2**).

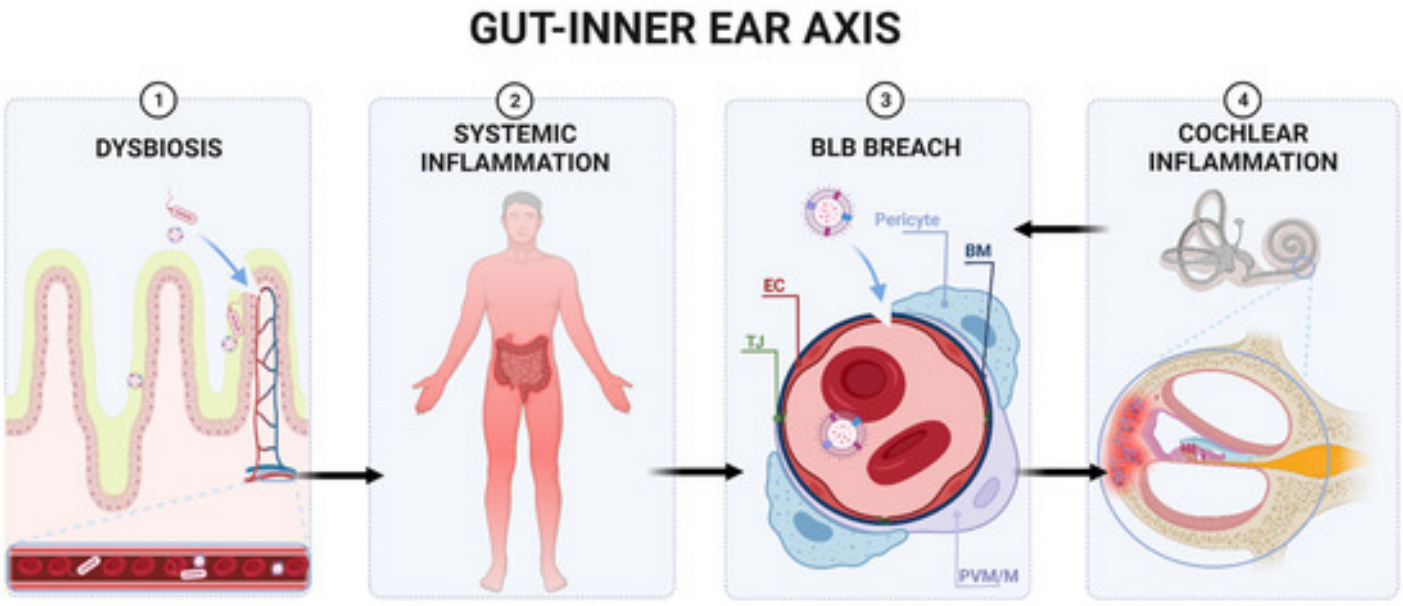

Figure 1. Proposed gut–inner ear axis resulting in sensorineural hearing loss (SNHL). (**1**) Gut dysbiosis induced by a high-fat diet can damage the intestinal barrier and cause a leaky gut. (**2**) This allows gut microbiota and bacterial toxins such as lipopolysaccharide to infiltrate the bloodstream and cause a systemic inflammatory response. (**3**) Pathogens and inflammatory cytokines reaching the inner ear can damage the blood–labyrinth barrier (BLB). (**4**) Infiltration of pathogens to the inner ear leads to the activation of resident macrophages, the release of pro-inflammatory cytokines, and the overproduction of reactive oxygen species (ROS), causing apoptosis of damaged cells and immune cell infiltration in the lateral wall of the cochlea (spiral ligament and stria vascularis). Inflammatory processes in the cochlea might further increase the BLB's permeability, perpetuating inflammation. Unresolved inflammation leads to damage of sensorineural structures, eventually causing SNHL. Abbreviations: EC,

endothelial cell; TJ, tight junction; BM, basement membrane; PVM/M, perivascular-resident macrophage-like melanocytes.

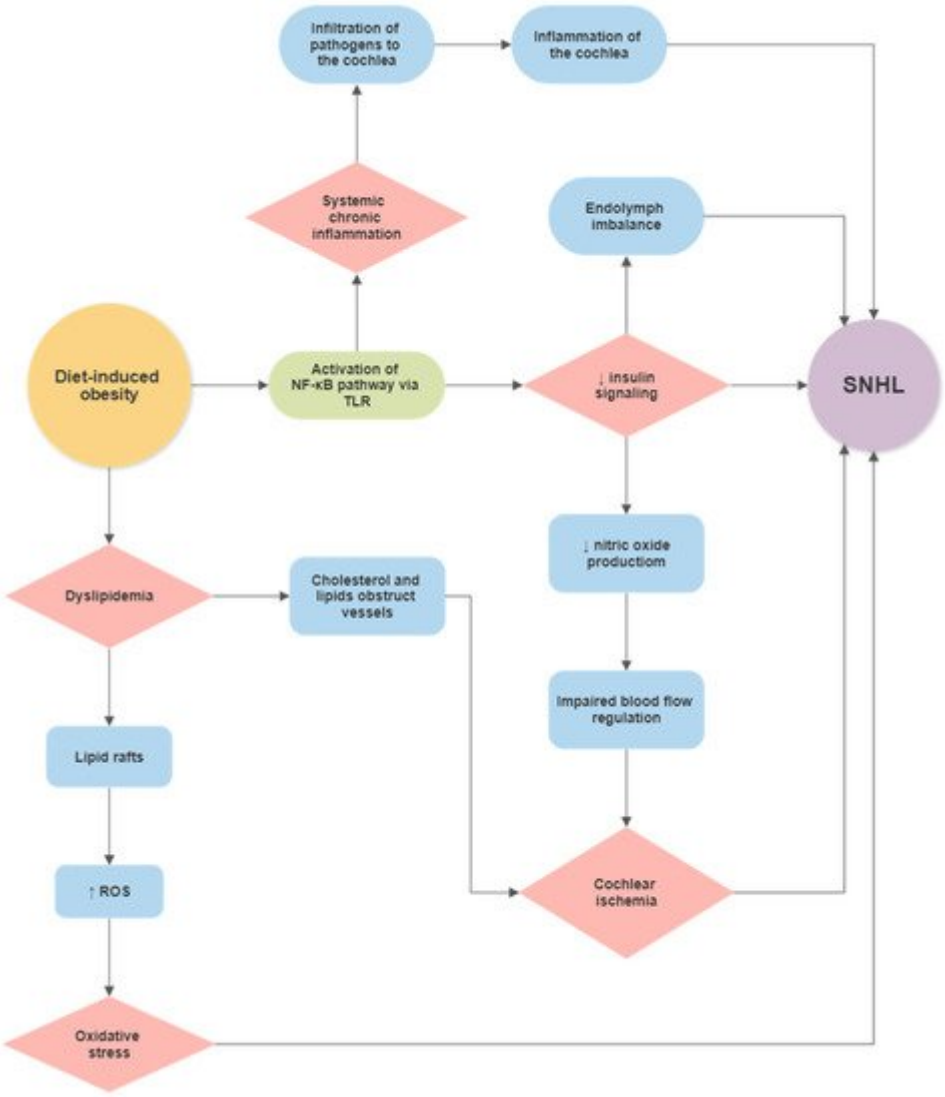

Figure 2. Flowchart showing the potential link between a high-fat diet and sensorineural hearing loss (SNHL) based on current literature.

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