Vol 6 | Issue 1 | Pages 143-153

Journal of Neurodegenerative Disorders
ISSN: 2642-4274

Review Article

DOI: 10.36959/459/610

Parkinson´s Disease, Diet and GM Alterations

*David Armando Guach-Hevia, MD**

Medical Sciences University of Holguin, Cuba

Abstract

A wide research was made about the brain-GM axis and its implications in metabolic, endocrine, intestinal and neurological issues. Dysregulation of the brain-GM axis due to gastrointestinal alterations has been recently associated with the pathogenesis of several neurodegenerative diseases, including Parkinsonism, supporting the hypothesis that the pathological process is spread from the gut to the brain. Diet induced metabolic disorders, through immunological, bacterial and intestinal parameters variations may induce systemic inflammation, stimulating the alpha-synuclein misfolding and the dopaminergic impairment seen in patients with shakiness paralysis' risk, favoring the Parkinsonism genesis and progression. The close relationship between GM dysbiosis, diet induced metabolic damage and neurological dysfunction suggests that the GM modification through diet prebiotic and probiotic based may provide a promising preventive and therapeutic option in Parkinsonism and other neurodegenerative disorders.

Keywords

GM, Brain-GM axis, Diet induced disorders, Parkinson´s disease

List of Abbreviations

GMBA: Gut Microbiota Brain Axis, GM: Gut Microbiota, PD: Parkinson's Disease, SCFAs: Short Chain Fatty Acids, ANS: Autonomic Nervous System, VN: Vagus Nerve, ENS: Enteric Nervous System, HPA: Hypothalamus–Pituitary–Adrenal Axis, MCP-1: Monocyte Chemotactic Protein 1, TLRs: Toll Like Receptors, CRH: Corticotrophin Releasing Hormone, GI: Gastrointestinal, SIBO: Small Intestine Bacterial Overgrowth, DMCN: Dorsal Motor Nucleus of the Vagus, EGCs: Enteric Glial Cells, BBB: Brain Blood Barrier, BDNF: Brain Derived Neurotropic Factor, CREB: Cyclic AMP-Response Element Binding Protein, WAT: White Adipose Tissue, ATMs: Adipose Tissue Macrophages, ROS: Reactive Oxygen Species, MDA: Malondialdehyde, CNS: Central Nervous System, LP: Lipopolysaccharide, IL: Interleukin, TNF: Tumoral Necrosis Factor.

Introduction

For the longest time, microbiology and neuroscience used to be studied independently and with limited overlap. Recently, however, with the advancement in sequencing technology and the subsequently growing interest in metagenomics, the effect of microbial colonization on host physiology, metabolism and even behaviour has raised the question if hosts are dependent on masses of associated microorganisms [1]. In 2013, after the results of the Human Microbiome Project, the United States National Institute of Mental Health launched a special research project on GM-brain axis (GMBA), in views to develop new medications or noninvasive treatments for mental diseases. Since then, studies on the influence of GM (GM) on the brain have been increasing, and the GMBA, novel mechanism used to name the bi-directional connection, has become one of the focuses on current neuroscience [2]. The latest research showed that changes in GM could affect the brain's physiological, behavioral, and cognitive functions [3]. Although the exact mechanism of GMBA has not yet been fully understood and clarified, the evidence from animals and human studies has showed that GM can play an important role in brain behavior and cognitive development through metabolic, immunologic, endocrine and nervious pathways, by producing hormones, immune factors, and metabolites which also indicated that altering the GM could improve or even cure brain diseases [4].

Both functional and compositional GM alterations have been recently associated with the genesis and progression of several neurodegenerative diseases, including Multiple Sclerosis, Alzheimer´s disease, Lateral Amyotrophic Sclerosis and Parkinson´s disease. The main disturbed mechanisms include different grades of chronic or acute inflammation, oxidative stress, neurotransmitters misbalance, nutrients

***Corresponding author:** David Armando Guach-Hevia, Medical Sciences University of Holguin, Cuba

Accepted: April 18, 2023

Published online: April 20, 2023

Citation: Guach-Hevia DA (2023) Parkinson´s Disease, Diet and Gut Microbiota Alterations. J Neurodegener Disord 6(1):143-153

deficit and abnormal bacteria´ strains overgrowth [5]. Although further studies need to be done, these outcomes situate the GM as a possible target on the prevention, treatment or even cure of these and other intestinal microbiota related pathologies.

In addition there are multiple current studies focused on the paper of diet induced benefits or damage on individual cognition, through GM diet altering homeostasis. There has been proposed that poor diet consumption, mainly high fat or sugar based diet, eventually leads to cognition deficit and nervous disorders, due to the stimulation of a "GM dysbiosis" status, together with chronic metaflammation, insulin resistance and oxidative stress increase [6]. These findings strongly suggest that diet composition might influence the genesis and even the evolution of Parkinsonism through the modulation of GM, favoring the idea that Parkinson´s disease clinic and physiopathology features might be primarily caused by diet induced disorders on individuals at risk. Considering such hypothesis, several questions were formulated in order to summarize the consulted materials:

How does GM promote Parkinsonism genesis and evolution?

What is the influence of diet properties on microorganism composition and physiology?

Is there any association between GM dysbiosis based on poor diet consumption and Parkinsonism etiology?

GM Climbing the Human Pyramid

GM is a complex community located along the intestinal tract that helps to maintain dynamic metabolic ecological balance. There are an estimated of 100 trillion (1 × 1013 to 1 × 1014) bacteria in an adult's body, 80% of which exist in the gut, about ten times as many as cells in human body [7]. The gut microbiome hosts more than 100 bacterial species and more than 5000 strains of microbes, encoding 150 times as many genes as the human genome [8]. The bacteria, mainly anaerobic bacteria, dominate this environment followed by others microorganisms that include virus, protozoa, archaea, and fungi. The microbiome is mainly defined by two bacterial phylotypes: Bacteroidetes and Firmicutes, which represent around 70-75% of the totality, followed by amounts of *Proteobacteria, Actinomyces, Fusobacterium, and Verrucomicrobia* in smaller proportions [9].

GM has multiple functions. Firstly, it constitutes the intestinal barrier, stimulates intestinal epithelial cell regeneration and protection trough mucus and cell´s metabolites production, nourishes mucosa by producing short-chain fatty acids (SCFAs) and its implications on the gut´s homeostasis promotes the continuous regeneration of GM members [10]. GM is also involved in the maturation of immune system by stimulating innate immune responses in the early stage of life, which leads to the maturity of intestinal related lymphoid tissue, inspires the acquired immunity by stimulating local and systemic immune responses, intestinal synthesis and metabolism of certain nutrients, hormones and vitamins, and plays an important role in drug and poison removal [11]. Under physiological conditions, GM continuously stimulates the immune system leading to a state of "low degree of physiological inflammation", which is a rapid and effective mechanism for defending against pathogens. In addition, it also plays a role of protective competition against gut pathogenic microorganism colonization, by decreasing nutrition for the survival of the pathogen agent and by producing cytokines that can inhibit the growth of the microorganism [12].

GM changes with human physical and cognitive development and is constantly influenced by various stress factors. Babies receive the initial microbiome from their mothers, and after one-year-old, the infants form a complex gut microbiome like adults [10]. The compositions of GM are not fixed, and change with increasing age and stress factors exposition. The functional or compositional changes of beneficial bacteria due to multiple factors that include infection, drug intake, systemic or located illness, stress exposure and diet variations can significantly affect the health of individuals through altering multiple physiological parameters, some of which have been found involved in the nervous system homeostasis [13].

How Does GM Affect the Brain?

After the results of the Microbiome Project, the bidirectional communication between the gut and the brain was updated, been currently referred to as the GMBA, novel mechanism that connects Central Nervous System (CNS) structures with the intestinal microflora through multiple pathways, allowing the brain to exert influence over the GM and vice versa. Although the exact mechanism of reciprocal communication has not yet been fully understood, there has been already proposed that GM exerts effects on the brain not only through the intestinal nervous system pathway, but also through the endocrine, immune and metabolic system.

Neuroanatomical pathways

The gut can interact with the brain through two neuroanatomical pathways. The one is mutual information exchange directly between gut and brain by the autonomic nervous system (ANS) and vagus nerve (VN) in the spinal cord; another one is a bidirectional communication between gut and brain through the bi-communication between enteric nervous system (ENS) in the gut and ANS and VN within the spinal cord [14]. The neural anatomical pathways for controlling gut functions form a hierarchic four-level integrative organization: The first level is the ENS, including myenteric ganglia, submucous ganglion, and gut glial cells, integrated both in the Meissner submucous plexus and the Auerbach mienteric plexus; the second level is prevertebral ganglia regulating peripheral visceral reflex responses; the third level is the ANS in the spinal cord (from T5-L2 sympathetic nerve and S2-S4 parasympathetic nervous system) and brain stem nucleus tractus solitarius and dorsal motor nucleus of VN, which receive and give the origin of afferent and efferent fiber of VN, respectively; finally, the fourth level includes the higher brain centers [15]. Information from cortex and subcortical centers including basal ganglia downs to brainstem nuclei, that control many gut functions. The afferent fiber of

VN stops at the brain stem nucleus tractus solitarius, which then gives fiber upward to thalamus, lobus limbicus, and insular cortex through parabrachial nucleus. Spinal afferent fiber goes upward within spinothalamic tract and spinal tract to the thalamus and gracile nucleus and cuneate nucleus of medulla oblongata, respectively, then project fiber to thalamus through lemniscus medialis. Fiber is gave from thalamus and projected to the primary sensorimotor areas and insular cortex. Damages and abnormalities at the above mentioned levels can influence the regulation of intestinal function, including local intestinal reflexes, and external neural control [14]. Through these neuroanatomical structures brain exerts its influence on the gut´s microorganism's homeostasis, but GM also uses these pathway to exertaction on the brain.

Neuroendocrine hypothalamic-pituitary-adrenal axis

The hypothalamus-pituitary- adrenal axis (HPA) regulates cortisol secretion, and cortisol can affect immune cells (including cytokine secretion) both locally in the gut and systemically, therefore affecting nervous structures involved. Cortisol can also alter gut permeability and barrier function, and change GM (GM) composition [16]. Cortisol secretion by the adrenal cortex is mainly induced through stress exposure. *In vivo* exams using lab´s mice showed that early stress and maternal separation could lead to a long-term change of HPA, and also had a long effect on the microbiome. When compared with rats nonseparated from the mother, the diversity of 16S ribosomal RNA in adult rats, who received mother separation for 3 h/day from day 2 to day 12 after birth, revealed that stress significantly changed microbiome in feces [17]. Microbiome composition in mouse exposed to a long-term restraint stress was significantly different from that of a nonstressed mouse. Stress can reduce the quantity of Bacteroides at cecum and increase the number of Clostridium [18]. It also increased interleukin-6 and monocyte chemotactic protein 1 (MCP-1) levels in blood, and MCP-1 was significantly related with the changes of three kinds of stress-induced bacteria of *Enterococcus faecalis*, *Pseudobutyrivibrio*, and aerogenic bacteria Dorea strain [19]. Strengthening the idea that GM alterations is related to psychological stress, mediated by HPA pathway.

Gut immune system

Development of gut immune system significantly depends on GM. *In vivo* studies have shown germ free mice almost had no immune activity, but they could generate immune function when giving certain microbiota [20]. Bacteria communicate with the host through a variety of immune ways, and the toll like receptors (TLRs) of host cell play a key role in this communication. There are ten kinds of TLRs in the human innate immune system, which have been identified as pattern recognition receptors [21]. These receptors are a part of the innate immune system, which is the first step to produce cytokine response and is also widely distributed on neurons. Hence, neurons also respond to bacterial and viral components fluctuations. The balance of GM may change the regulation of inflammatory response, and this mechanism may also get involved in the regulation of emotion and behavior. Systemic inflammation is represented by increased levels of serum pro-inflammatory cytokines, such as Interleukin (IL-1), Interleukin (IL-6) and Tumoral Necrosis Factor alpha (TNF-α) which are associated with depression and sickness symptoms [22]. IL-1 and IL-6 stimulate the release of corticotrophin releasing hormone (CRH), the regulator of the HPA, which as stated earlier can be linked to depression. Thus, inflammation can be directly linked to depression. Recognition of the gut microbe's structural components, such as lipopolysaccharide (LPS), by the host's innate immune receptors results in the production of pro-inflammatory cytokines [20]. Showing how the GM can cause cognition deficits via inflammation. Kang, et al. showed that an increase in anxiety levels and declined cognitive levels are positively correlated with increased bacterial numbers in the phyla Bacteroidetes and Proteobacteria, both Gram-negative and LPS producers, while bacteria of the Gram positive family of *Lachnospiraceae* are associated with a reduced anxiety phenotype [23]. These findings support the connection of the gut to the brain via the immune response.

Additionally, in the brain-GM bidirectional interaction there are also involved many different molecules and substances both sides synthetized, and structures like the BBB and the intestinal layer (barrier system) that contribute to regulate the communicative flow.

Neurotransmitters and neural regulators synthesized by intestinal bacteria

GM produce many types of metabolites which have an effect on the CNS, specifically D-lactate, ammonia and SCFAs. In chronic fatigue syndrome patients with cognitive dysfunction and neurological impairment, increased levels of D-lactate producing bacteria such as *Enterococcus* spp. and *Streptococcus* spp. were found in their stools, indicating that D-lactate might have a modulatory role on cognition [24].

Ammonia (NH3) is a well-known neurotoxic molecule. Bacterial urease converts urea to ammonia and carbon dioxide. Hyperammonemia, the state of increased levels of NH3 in the blood is related to impaired BBB integrity, intracerebral productions of the neurotransmitters serotonin and dopamine and the production of abnormal neurotransmitters octopamine and phenylethylamine [25]. Therefore, several studies suggest that the presence of species which produce bacterial urease in the GM may cause these detrimental effects in the CNS.

In addition, SCFAs such as acetate, propionate and butyrate, are bacterial fermentation products that play a crucial role in the development of the host's gut immune homeostasis. The metabolism of dietary fibre to SCFAs by some gut bacteria is an important energy source for humans and these metabolites are relevant for gut motility, having a trophic effect on epithelial cells, influencing immune system development and modulating enteroendocrine hormone secretion. Propionate promotes regulatory T cells, which have anti-inflammatory effects and can prevent excessive inflammation in the gut mucosal tissue [26]. However, MacFabe and colleagues proposed that propionate has

been linked to autism-like behaviours. An intraventricular administration of this SFCA in adult rats caused impaired behaviour, such as abnormal motor movements, cognitive deficits, repetitive interests and impaired social interactions. These behaviours were also linked to neuroinflammation, suggesting that inflammation was the central mediator between the SFCAs and the outcome. Certain faecal SCFAs (acetic, butyric, isobutyric, valeric, and isovaleric) are significantly increased in children who suffer from autism spectrum disorder (ASD) when compared to control groups [27]. This evidence supports the role of gut microbial products as a communication pathway connecting the gut and the brain.

Another possible influence of gut microorganism over brain function is that some bacterial strains have been found to produce neurotransmitters such as gamma-amino butyrate acid, serotonin, 5-hydroxytryptamine, dopamine, epinephrine, norepinephrine and histamine which can access the CNS via the Enteric Nervous System (ENS) [28]. The underneath mechanism conceives a mimicry process in which bacteria copy neurotransmitters structures altering therefore its serum levels. These gut microbe-derived neurotransmitters can affect CNS functions with both positive and negative outcomes.

Intestinal mucosal barrier and blood brain barrier

Evidence from rodent studies showed that stress changed intestinal mucosal barrier function, made LPS and other cytokines entering blood circulation, and stimulated TLR4 and other TLRs producing inflammatory cytokine [29]. In addition, peripheral produced inflammatory factors could increase the permeability of blood-brain barrier (BBB), thus make it possible for peripheral produced inflammatory factors to directly influence the brain [30]. Therefore, vast evidence of animals and human studies showed that GM plays a critical role in the brain development and function.

Parkinson´s Disease and GM-Brain Axis

Parkinson'sdisease(PD)isamulticentricneurodegenerative disorder characterized by the accumulation and aggregation of alfa-synuclein (α-syn) in the substantia nigra in the CNS and in other neural structures [31]. The classical motor symptoms like bradykinesia, resting tremor, rigidity and late postural instability result from the death of dopamine generating cells in the substantia nigra. There is also a wide spectrum of non-motor manifestations involving for example olfactory (loss of smell), gastrointestinal (GI), cardiovascular, and urogenital systems [32]. It has become evident that the different levels of the brain-gut axis including the ANS and the ENS may be affected in PD, due to the influence of the GM. Dysregulation of the GMBA in PD may result in GI dysfunction, which is present in over 80% of PD subjects, that could significantly contribute to the pathogenesis of PD itself, supporting the hypothesis that the pathological process is spread from the gut to the brain [33].

Among many causes of parkinsonism, including multiple system atrophy, progressive supranuclear palsy or corticobasal degeneration, GI symptoms have been best characterized in the classical PD. In the study of Edwards, et al. evaluating the frequency of various GI symptoms in 98 patients with PD, abnormal salivation, dysphagia, nausea, constipation and defecatory dysfunction were present in 70%, 52%, 24%, 29%, and 66% of subjects, respectively [34]. Delayed gastric emptying with reduced amplitude of stomach contractions may also have potentially relevant pharmacokinetic implication causing an impaired absorption of L-dopa and thus worsening motor fluctuations. All of these GI alterations that lead to intestinal dysmotility and evacuation delay may predispose for small intestinal bacterial overgrowth (SIBO), proposing new insights into the phatogenesis of the disease, due to there are studies that support that the α-synucleopathy might start in the ENS rather than in other structures [35]. In addition, PD has been interestingly associated with a higher prevalence of peptic ulcer disease due to *Helicobacter pylori* infection, that could be related to the gut alterations beginning or worsening [36].

Alpha-Synucleopathy spread along the GMBA

Under physiological conditions, α-syn is abundantly expressed in the CNS and involved in the regulation of neurotransmission, although aggregation of insoluble fibrils of phosphorylated α-syn have been implicated in several neurodegenerative disorders, such as PD and Alzheimer's disease [37]. Recent reports have shown that lesions in the ENS occurred at a very early stage of the disease, even before the involvement of the CNS. This led to Braak's hypothesis according to which α-syn pathology starts in the submucosal plexus of the ENS and propagates retrogradely to the CNS via vagal preganglionic axons of the dorsal motor nucleus of the vagus (DMVN). From the DMVN there would be predictable caudo-rostral spread of pathology to other areas of the brainstem including the substantia nigra and finally to the basal forebrain and neocortex [33]. This retrograde transport (from gut to brain) of α-syn can be concomitant with anterograde (from brain to gut) diffusion.

Additionally, accumulating evidence shows that α-syn plays a crucial role in neuroinflammation by triggering and/or potentiating astroglial and microglial activation. Recent studies have also shown that dysfunction of enteric glial cells (EGCs) at the ENS level occurs in PD. EGCs, which represent in the digestive tract counterpart for brain astrocytes, may be critically involved in gut inflammation and modulation of intestinal epithelial barrier integrity [38]. Devos, et al. found that expression of pro-inflammatory cytokines and glial markers are increased in colonic biopsies from PD patients and they are correlated with the disease duration [39]. Both clinical and neuropathological evidences indicate that neurodegenerative changes are accompanied by GI symptoms that may precede or follow the CNS impairment. Based on these observations a mechanistic hypothesis presenting the gut as the gateway in neurodegenerative diseases has been proposed. Accordingly, the ENS and the GM fluctuations seem to play a critical role in the pathophysiology of PD representing a rout of entry for a putative environmental factor to initiate the pathological process. Furthermore, regarding the parallel manifestations of neuropathologies in the ENS and CNS, the ENS may provide a more accessible target for studies of neural

function, histopathology, and biochemistry in PD. Thus, the ENS can be considered not only as "the second brain", but also as a window towards "the first brain [40].

Parkinson´s disease and GM dysbiosis

Although the causal relationship between the microbiota changes and the pathogenesis of PD remains unclear, it has been suggested that the GM changes associated with intestinal inflammation, alterations in the gut barrier function and intestinal permeability misbalance may contribute to the initiation of α-syn misfolding, propossing that the GM alterations precede or occur during the course of PD [33]. The interesting concept of molecular mimicry involving the microbiota in neurodegeneration has been also proposed. Indeed, Friedland suggested that bacterial proteins may elicit cross-seeded misfolding, inflammation and oxidative stress, and cellular toxicity in neurodegeneration, initiating or otherwise influencing the development of PD, Alzheimer's disease and other related disorders [41]. In addition, priming of the innate immune system by the microbiota (residing in the gut and oral/nasal cavities) may enhance the inflammatory response to cerebral amyloids such as α-syn. Trudlerand, et al. postulated that cerebral amyloid may mimic viral or bacterial infection resulting in glial cell activation through TLRs. Specifically, it has been documented that neuroinflammation in PD is associated with upregulation of TLR2 signaling and activation of microglia. TLR2, playing an important role in the regulation of intestinal barrier integrity, has been also found to activate microglial cells in the CNS, and its activation has been related to microbial influences [42]. It has been suggested that the peripheral immune response characterized by the presence of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-8 in the serum induces a disruption of the BBB and promotes microglia-mediated inflammation and neurotoxicity [20]. The GM influences the BBB permeability associated with reduced expression of the tight junction proteins in a homological way as it affects the intestinal epithelial barrier, showing its influence on brain damage [30].

Sui, et al. proved that a bidirectional transport of α-syn into and out of the brain by the BBB is possible and suggested that microbial LPS induced inflammation could increase α-syn uptake by the brain by disrupting the BBB. In an animal model of PD, peripherally induced inflammation was shown to induce the microglial complement pathway to damage dopaminergic neurons [33]. Several studies have demonstrated that pro-inflammatory factors associated with chronic GI diseases related to GMdysbiosis induce brain inflammation and the death of dopaminergic neurons and could eventually be responsible for parkinsonism [37].

Interestingly, Scheperjans and colleagues have showed a reduced abundance of the *Prevotellaceae* bacteria family in PD patients compared with healthy controls, and greater abundance of *Enterobacteriaceae* among those patients with the postural instability and gait difficulty phenotype compared to those with tremor-dominant PD. *Prevotellaceae* bacteria as commensals are involved in mucin synthesis in the gut mucosal layer and production of neuroactive SCFAs through fiber fermentation [43]. Thus the reduced abundance of *Prevotellaceae* could result in decreased mucin synthesis and increased intestinal permeability leading to a greater local and systemic exposure to bacterial antigens and endotoxins, which in turn would trigger or maintain excessive α-syn expression in the colon or even promote its misfolding, favoring the afore mentioned dysregulations. Another suggested possibility, by which the GM could affect α-syn pathology, is that α-syn intra- and extraneuronal clearance mechanisms are impaired by SCFA-dependent modulation of gene expression [37].

Recent studies reported high prevalence of SIBO in PD, ranging from 54% to 67%. PD being associated with gastroparesis and impaired GI motility may predispose to SIBO. In the study by Fasano, et al., the presence of SIBO reported in 54% of PD subjects, was associated not only with the GI symptoms but also with the motor symptoms. Interestingly, the improvement in the motor fluctuations following treatment with the antibiotic rifaximin was observed. According to that report, SIBO was not associated with worse GI function, but independently predisposed to worse motor function [35]. It is possible that SIBO contributes to motor dysfunction by disrupting small intestinal integrity leading to immune stimulation and/or alteration in L-dopa absorption. SIBO may cause changes in the gut permeability which promotes translocation of bacteria and endotoxins across the intestinal epithelium, inducing the pro-inflammatory response. A recent study involving newly diagnosed PD patients confirmed that intestinal permeability in these subjects was markedly increased compared with healthy controls, and this was associated with more intense staining of *Escherichia coli* in the intestinal mucosa and with systemic exposure to LPS. Noteworthy, these alterations were correlated with abnormal accumulation of α-syn in enteric neurons [44]. LPS is a gut-derived, pro-inflammatory bacterial endotoxin that may cause delayed and progressive nigral pathology when administered systematically and serves even as a progressive model of PD. These data reinforce the link between gut dysbiosis, intestinal permeability and neurological dysfunction.

Importantly, some genetic risk factors may play a crucial role in the interactions between the brain-gut-microbiotaaxis respecting gut inflammation. The methylation status in the SNCA promoter region may affect α-syn expression and the risk for PD. Therefore, a potential role of the GM as an epigenetic factor influencing DNA methylation may be speculated. The ε4 allele of apolipoprotein E (ApoE) has been shown to increase the risk for dementia in synucleinopathies such as PD. Potentially, ApoE genotype, by influencing bile acid secretion, could affect the composition of the GM favoring the development of organisms triggering misfolding. Moreover, three single nucleotide polymorphisms in CARD15 gene, known to be associated with Crohn's disease, have been also shown to be over-expressed in PD patients, supporting the observation that GI inflammation contributes to the pathogenesis of PD [45].

The previously discussed investigative outcomes promoting an obvious connection between GM induced synucleinopathy and PD physiopathology, have generated a considerable interest in the potential role of antibiotic

therapy in improving motor symptoms, although well designed treatment trials are needed to fully elucidate a causal link between SIBO and motor dysfunction in PD. These results should also encourage further studies on a new therapeutic approach based on the manipulation of the GM with probiotics, prebiotics, or even fecal microbiota transplantation. Interestingly, considering the relevance of GM in the evolution of diseases, many current studies relate poor diet habits with cognitive decline, due to diet induced GM alterations.

Diet Induced Nervous Disorders through Microbiota dysbiosis

There has been highly documented that long term consumption of high-fat and high-sugar diets or poor diets has a detrimental effect on cognition. This abnormality could be due to the disturbance of the physiology of gut-brain axis through microbiota altering. A poor diet is known to cause obesity and has then been linked to a decline in the microbiota's composition, termed "gut dysbiosis" [6]. A change in diet has been shown to have an impact on the composition of the GM within 24 h of the diet change. Long term consumption of a high-fat diet increases the ratio of Firmicutes to Bacteroidetes. This increase has been linked to obesity in the adults, although there has been observed a decrease in the elderly, suggesting that the reduced ratio might be related to the decline in cognition seen in the elderly. In addition, high carbohydrate together with a high glycemic index diet showed a correlation with an increase in faecal Bacteroidetes, whilst a high carbohydrate but low glycemic diet led to an enhanced growth of *Faecalibacterium prausnitzii* [46]. These observations suggest that each specific change in bacterial population due to different diets can alter the GM in different ways, thus resulting in the variation of individual GM profiles. There is, also, one study that illustrates the connection between the GM and whether the individual's diet is plant or animal-based. The short-term consumption of a diet composed entirely of animal or plant products alters the gut microbial gene expression rapidly. Animal-based diet consumption led to increased bile-tolerant microbiota (Alistipes spp., Bilophila spp. and Bacteroidetes spp.) and decreased dietary plant polysaccharide fermenters, like Firmicutes (*Roseburia* spp., *Eubacteriumrectale* and *Ruminococcusbromii*) in the gut [47]. These studies suggest that an animal-based diet could result in diseases linked with an inflamed gut, by promoting the growth of a microbiota population which specializes in protein degradation.

Reported cognitive disturbances due to a poor diet include depression, memory impairment, decreased planning and problem solving abilities, decreased mental flexibility and altered inhibitory processes, related with changes in the hippocampus and the frontal lobe in obese human models [48]. Many studies have related this to a decrease in brain derived neurotrophic factor (BDNF) levels in the hippocampus. This nerve growth factor is a key survival signal for striatal neurones in the brain and is released by cortical neurones. BDNF uses synapsin 1 and CREB (cyclic AMP-response element binding protein) to modulate the synaptic plasticity, so these proteins therefore drive learning and memory. BDNF, synapsin 1, CREB and mRNA for protein neurite growth have all been found to have decreased levels after continued consumption of a high-fat diet [49].

Insuline resistance, body mass index and hyperinsulinemia are strongly related to Obesity, Diabetes Mellitus, Metabolic Syndrome and other poor diet induced diseases. Recently, insulin resistance has been associated with a decrease of Bacteroidetes and Bifidobacterium species, together with reduced cognition (poor memory, slower processing speed and prefrontal inhibitory control), changes in microglia morphology, synaptic loss in the prefrontal cortex and decreased levels of corticosterone, indicating that insulin resistance, perhaps through its influence on microbiota balance might be the main driving component of poor diet induced cognitive defects [50].

Obesity induced inflammation has also been linked to altered cognition. In the obese state, the brain, liver, adipose tissue and pancreas are all exposed to higher levels of pro-inflammatory cytokines, such as (TNF-α), (IL-6), interleukin-1β (IL-1β) and (MCP-1), followed by other metabolic molecules such as resistin, visfatin, retinol binding protein-4, plasminogen activator inhibitor1 and serum amyloid A, all secreted by adipocytes activating macrophages in the white adipose tissue (WAT), that can affect the immune response [51]. Resistin is known to induce insulin resistance. Logically, having more WAT due to a high-fat diet consumption raises inflammation levels via the release of pro-inflammatory cytokines. In addition, the WAT of the obese individuals has increased macrophage infiltration, termed "adipose tissue macrophages" (ATMs), wich are a major source of pro-inflammatory cytokines in obese subjects. ATMs can be "metabolically activated" by certain factors such as glucose, insulin and palmitate and all of these markers have increased levels in individuals with obesity and Metabolic syndrome. Furthermore IL-1β produced by ATMs causes insulin resistance by disrupting insulin signalling in peripheral tissues or inducing the dysfunction of beta-cells, thus resulting in decreased insulin levels. Finally, the state of chronic low-grade inflammation found in obesity has been termed "metaflammation", related to excessive stimulation of the innate immune system resulting from gut dysbiosis and/or SIBO and increased intestinal permeability that may produce systemic and/or CNS inflammation [6].

A possible consequence of a high-fat diet consumption which may cause systemic inflammation could be an increase in the numbers of Gram-negative bacteria seen in an obese gut. Long-term high-fat diet consumption enhances the growth of gram negative bacteria from the Proteobacteria phylum, whose outer membranes are composed of LPS, a ligand of a human innate immune TLR4, which is found on gut epithelia and immune cells. Recognition of bacterial LPS by TLR4 results in increased levels of pro-inflammatory cytokine secretion, increasing gut inflammatory tone and gut epithelium disruption by decreasing tight junction protein expression; thus allowing more gut luminal LPS to diffuse into the gut tissue vasculature and therefore cause systemic inflammation and insulin resistance [52].

Interestingly, an excess of pro-inflammatory cytokines, which are increased during insulin resistance, such as TNF-α and IL-1 are known to have an altering effect on dopamine function in the subcortical brain structures, especially in the basal ganglia. The basal ganglia plays a major role in motivation and motor activity regulation, both parameters modulated by dopamine. Therefore, dysregulation of the basal ganglia and dopamine function can lead to depression, fatigue, anxiety and psychomotor symptoms [53]. Thus, poor diet induced inflammation due to gut dysbiosis via increased numbers of LPS containing bacterial species, may be a crucial risk factor for altered cognition states such as depression, inhibitory misbalance and abnormal eating patterns, three states often found both in patients suffering from Metabolic Syndrome and neurodegenerative Parkinsonism.

The oxidative stress with a higher production of brain reactive oxygen species (ROS) have also been shown increased after consumption of a high-fat diet. The ROS enhancement result in a decrease in spatial learning capacity, reduced dendritic spine density in the hippocampus, perirhinal cortex and the prefrontal cortex, and reduced long term potentiation in neuronal synapses [5]. Another proposed cognitive deficit caused by long term consumption of a high-fat diet is a reduction in neurogenesis, due to an increase in malondialdehyde (MDA), that is quite toxic to neural progenitor cells, and therefore inhibits neurogenesis [48]. A high-fat diet is also thought to decrease cognition levels by impairing the BBB, recently linked to the development of Alzheimer's disease and related memory disorders. A highfat diet increases the BBB's permeability and reduces the rate of leptin and ghrelin's active transport across the BBB, both anorexigenic hormones whose resistance promotes uncontrolled eating patterns, inhibitory misbalance and behavioral alterations [6].

Finally, Bocarsly and colleagues found that obesity has a correlation with decreased brain volume, notably in the hippocampus, anterior cingulate and prefrontal cortex areas of the brain which have been linked to impulsivity and poor inhibitory prefrontal regulation [54]. This could be another reason for the impulsive altered behaviors caused due to poor diet induced obesity (See Figure 1).

Taken together, these studies demonstrate the relevant role of diet in the Nervous System wellbeing or collapse, suggesting that diet quality might be an important risk factor in the genesis and progression of nervous illnesses, including neurodegenerative processes. According to this, multiple clues might link the Parkinsonism etiology and evolution with poor dietetic habits, considering diet induced microbiota dysbiosis as a relevant intermediary.

Parkinson´s disease, diet and GM alterations

The studies previously discussed propose a wide range of results in which GM alterations has been related both with diet induced metabolic disorders and PD. Thus, these findings make possible the association between diet induced disorders and the pathogenesis of PD itself, through the microbiota dysbiosis status seen in both processes. The first microbiota distortion´s convergence point might be that a high animal´s fat and sugar diet leads to a decrease in the ratio of bile tolerant Bacteroidetes in the elderly population, which has been related with cognition decline [38]. On PD patients, with high prevalence after the 40-years-old, even

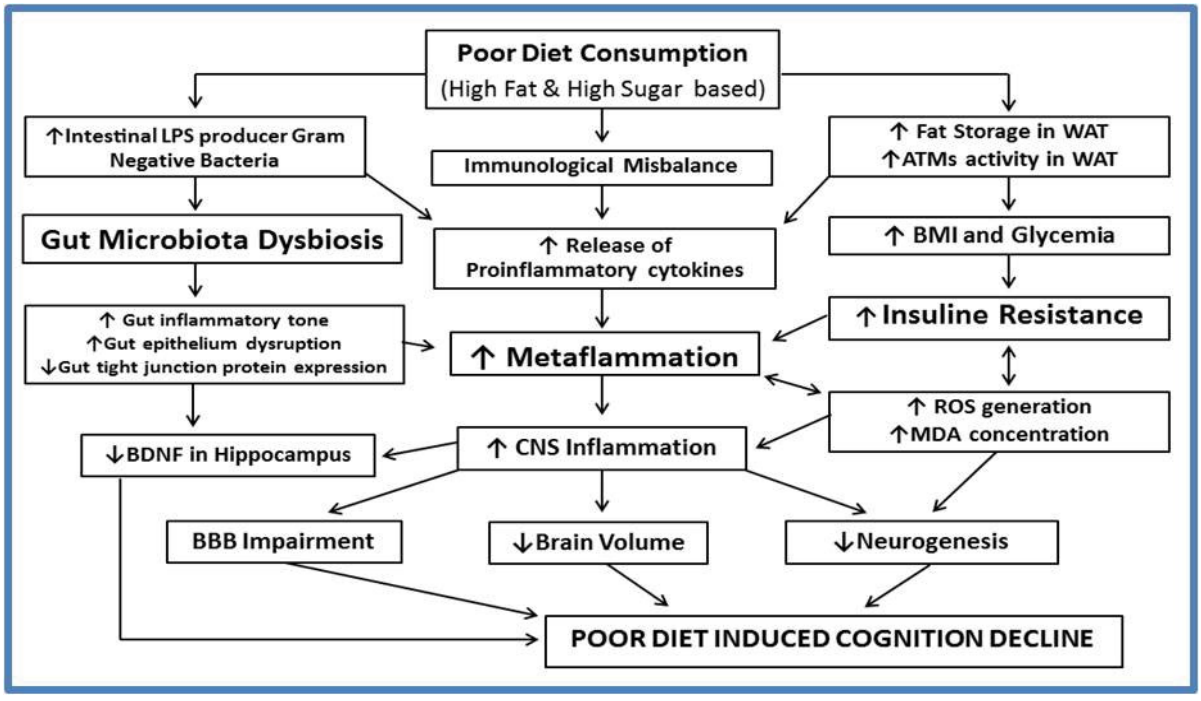

Figure 1: Poor diet consumption can lead to cognition decline.

WAT: White Adipose Tissue; LPS: Lipopolysaccharide; ATMs: Adipose Tissue Macrophages; BDNF: Brain Derived Neurotrophic Factor; BMI: Body Mass Index; ROS: Reactive Oxygen Species; MDA: Malondialdehyde; CNS: Central Nervous System.

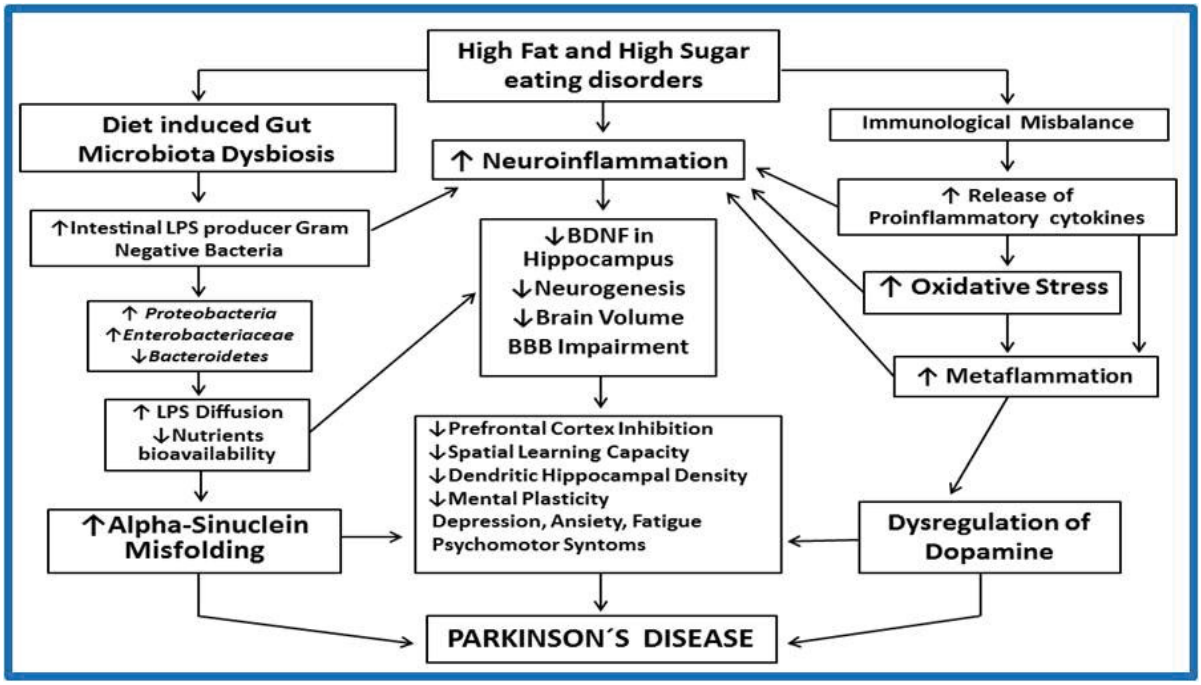

Figure 2: Proposed mechanisms through which poor diet consumption might lead to Parkinson´s Disease genesis. LPS: Lipopolysaccharide; BDNF: Brain Derived Neurotrophic Factor.

greater after 65-years-old, the Prevotellaceae family that belongs to the Bacteroidetes phylum has also been found decreased, showing a possible relation between the high fat and sugar diet and PD [37].

In addition, an animal based diet has been link with metaflammation (chronic low grade inflammation due to GI dysfunction) with excessive stimulation of innate immune system that promotes the growth of microorganisms, mostly Gram negative Proteobacteria specialized in protein degradation [50]. Besides, animal based diet increases the gut´s permeability that facilitates the diffusion of Proteobacteria LPS and the activation of proinflammatory cytokine secretion, currently related with dysregulation of dopamine function at the subcortical basal ganglia, which has been related to depression, fatigue, anxiety and psychomotor symptoms [53].

GI dysfunction has been associated with around 80% of PD patients [36]. Together with SIBO, related with an increase of Enterobacteriaceaea [37]. Proteobacteria´s phylum family, LPS producer, that contributes to gut inflammation and intestinal permeability disorders, increasing the alphasinucleinopathy misfolding, the brain degeneration through neuroinflammation and death of dopaminergic neurons [33]. *Helicobacter pylori*, microorganism related to the PD etiology, also belongs to Proteobacteria phyla. These findings support the association between poor diet and PD, due to the animal based diet seems to be related with the PD´s Proteobacteria overgrowth, that enhances the metaflammation, the gut membrane damage, the LPS diffusion, the neurodegeneration because of the production and aggregation of phosphorylated alpha-synuclein, and the dopamine dysfunction.

Another consequence related to the high fat and sugar consumption is the decrease of the BDNF, found in Obesity, Alzheimer, Huntington´s disease and also PD [6].

Additionally, the secretion of pro-inflammatory cytoquines due to high fat diet induced metaflammation, such as TNF-α, IL-1β and IL-8, has been related with BBB impairment, allowing a greater pass of LPS, ROS, MDA and other toxic neurodegenerative promoters to the brain, decreasing brain volume and cognition inhibition [6,37]. All these alterations have been found in PD patients, increasing the amount of proves that associate PD and poor diet induced disorders (See Figure 2).

This analysis might suggest new preventive and therapeutic strategies in which through diet management, GM might be profitably shaped, in views to prevent through early natural therapies the genesis and development of PD and other neurodegenerative disorders. With that purpose, food prebiotic and probiotic based seems to be a promising preventive and therapeutic natural via.

Prebiotic and Probiotic based diet. The promising joker

Multiple novel investigative outcomes have shown that there are many probiotic strains which are capable to limit excessive amounts of ROS *in vivo*, contributing to prevent and to control several diseases associated with oxidative stress, like Parkinsonism itself. Prebiotics and probiotics are defined as “live microbes which, when administered in adequate amounts, confer a health benefit to the host” [55]. There are many different strains of prebiotic and probiotic bacteria, historically related to the consumption of lactic

acid products, but specifically probiotic strains belonging to the genera Lactobacillus and Bifidobacterium have been reported to have a wide range of health promoting capacities [56]. Although prebiotic and probiotic molecular mechanisms have not yet been fully understood, probiotic are well known because of their modulation of the GM´s composition and function, together with antibacterial substance production, improvement of the epithelial barrier and reduction of the intestinal inflammation. Many studies have shown that selected probiotic strains, mainly lactobacilli and bifidobacteria have developed important antioxidative properties [57] a minuscule can be used to prepare probiotic based fermented food that may improve total antioxidative capacity decreasing markers of oxidative stress in both healthy and sick people [58].

The antioxidant mechanisms of probiotics could be assigned to metal ion chelation, enzyme inhibition, the activity reduction and inhibition of ascorbate autoxidation metabolic activities and the scavenging of oxidant compounds or the prevention of their generation in the intestine [59]. Some researchers have found that probiotic strains colonize the colon decreasing the fecal pH promoting the saccharolytic metabolism and the subsequent acidification of feces, due to the fermentation of carbohydrates to SCFAs [60]. Other investigators have hypothesized that probiotic exert their protective antioxidative effect by restoring GM composition and function [61]. Contributing to the transformation of dietary compounds, thus increasing the bioavailability of dietary antioxidants.Other promising prebiotic and probiotic bacteria belong to the genus Lactococcus and to the species *Streptococcus thermophilus*, that presented high levels of intracellular glutathione and superoxide dismutase activity [62].

Considering that along with inflammation, oxidative stress seems to be one of the main inducers of Parkinson´s neurodegeneration, causing excitotoxicity, neuronal loss and axonal damage [63]. The usage of prebiotic and probiotic based food in order to positively modify the antioxidative balance regarding the above mentioned properties, specially the GM related, promises to be a strategic joker on the prevention of the disease appearing or aggravation, or even a joker in the cure of the disease itself. Notwithstanding, further studies are necessary to confirm and extend the prebiotic and probiotic health promoting features in patients suffering neurodegeneration.

Conclusion

A better understanding of the GMBA interactions should bring a new insight in the pathophysiology of PD and other neurodegenerative disorders, allowing an earlier diagnosis with a focus on peripheral biomarkers within the ENS, as well as lead to novel therapeutic options in PD. Dietary or pharmacological interventions should be aimed at modifying the GM composition and enhancing the intestinal epithelial barrier integrity in PD patients or subjects at higher risk for the disease. This could influence the initial step of the following cascade of neurodegeneration in PD. Further studies on a new preventive and therapeutic approach in PD based on the modification of the GM with probiotics and prebiotics based diet, or even fecal microbiota transplantation, awaits a higher association between neurosciences and microbiology' specialties.

Acknowledgements

To my family, friends and colleagues for their precious support.

Relevant Conflicts of Interests

Nothing to report.

Funding

Nothing to report.

Author Contributions

Conception, design, literature searches, drafting the article and critical revision of the manuscript for important intellectual content: DAG-H. Final manuscript was read and approved by the autor.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author on request.

References

1. Stilling M, Cryan J (2015) The brain´s geppetto microbes as puppeteers of neural function and behavior. J Neuroviro 22: 14-21.
2. Schmidt C (2015) Mental Health: Thinking from the gut. Nature 518: S12.
3. Smith PA (2015) The tantalizing links between gut microbes and the brain. Nature 526: 312-314.
4. Ogbonnaya ES, Clarke G, Shanahan F, et al. (2015) Adult hippocampal neurogenesis is regulated by the microbiome. Biol Psychiatry 78: e7-e9.
5. Guo C, Sun L, Chen X, et al. (2013) Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen Res 21: 2003-2014.
6. Proctor C, Thiennimitr P, Chattipakorn N, et al. (2016) Diet, GM and cognition. Metab Brain Dis 32: 1-17.
7. Lozupone CA, Stombaugh JI, Gordon JI, et al. (2012) Diversity, stability and resilience of the human GM. Nature 489: 220-230.
8. Blekhman R, Goodrich J, Huang K, et al. (2015) Host genetic variation impacts microbiome composition across human body sites. Genome Biol 16: 191.
9. Donaldson G, Lee M, Mazmanian S (2016) Gut biogeography of the bacterial microbiota. Nat Rev Microbiol 14: 20-32.
10. Forsythe P, Kunze W (2012) Voices from within: Gut microbes and the CNS. Cell Mol Life Sci 70: 55-59.
11. de Vos WM, de Vos EA (2012) Role of the intestinal microbiome in health and disease: From correlation to causation. Nutr Rev 70: S45-S56.
12. Sekirov I, Russell SL, Antunes LC, et al. (2010) GM in health and disease. Physiol Rev 90: 859-904.
13. Stilling RM, Dinan TG, Cryan JF (2014) Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. Genes Brain Behav 13: 69-86.

14. Schemann M, Neunlist M (2014) The human enteric nervous system. Neurogastroenterol Motil 1: 55-59.

15. Grenham S, Clarke G, Cryan JF, et al. (2011) Brain-gut-microbe communication in health and disease. Front Physiol 2: 94.

16. Hsiao W, Metz C, Singh D, et al. (2008) The microbes of the intestine. An introduction to their metabolic and signaling capabilities. Endocrinol Metab Clin North Am 37: 857-871.

17. Bangsgaard Bendtsen KM, Krych L, Sørensen DB, et al. (2012) GM composition is correlated to grid floor induced stress and behavior in the BALB/c mouse. PLoS One 7: e46231.

18. Tortorella C, Neri G, Nussdorfer G (2007) Galanin in the regulation of the hypothalamic-pituitary-adrenal axis. Int J Mol Med 19: 639-647.

19. Bailey MT, Dowd SE, Galley JD, et al. (2011) Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. Brain Behav Immun 25: 397-407.

20. Hooper LV, Littman DR, Macpherson AJ (2012) Interactions between the microbiota and the immune system. Science 336: 1268-1273.

21. Duerkop BA, Vaishnava S, Hooper LV (2009) Immune responses to the microbiota at the intestinal mucosal surface. Immunity 31: 368-376.

22. Nell S, Suerbaum S, Josenhans C (2010) The impact of the microbiota on the pathogenesis of IBD: Lessons from mouse infection models. Nat Rev Microbiol 8: 564-577.

23. Kang SS (2014) Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol Neurodegener 9: 36

24. Galland L (2014) The gut microbiome and the brain. J Med Food 17: 1261-1272.

25. Skowronska M, Albrecht J (2012) Alterations of blood brain barrier function in hyperammonemia: An overview. Neurotox Res 21: 236-244.

26. Smith PM (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341: 569-573.

27. MacFabe DF (2012) Short-chain fatty acid fermentation products of the gut microbiome: Implications in autism spectrum disorders. Microb Ecol Health Dis 23: 10.

28. Tillisch K (2014) The effects of GM on CNS function in humans. Gut Microbes 5: 404-410.

29. Carabottia M, Scirocco A, Maselli M, et al. (2015) The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28: 203-209.

30. Kortekaas R, Leenders KL, van Oostrom JC, et al. (2005) Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Ann Neurol 57: 176-179.

31. Lees AJ, Hardy J, Revesz T (2009) Parkinson's disease. Lancet 373: 2055-2066.

32. Dickson DW, Fujishiro H, Orr C, et al. (2009) Neuropathology of non-motor features of parkinson disease. Parkinsonism Relat Disord 15: S1-S5.

33. Holmqvist S, Chutna O, Bousset L, et al. (2014) Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol 128: 805-820.

34. Cersosimo MG, Raina GB, Pecci C, et al. (2013) Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms. J Neurol 260: 1332-1338.

35. Tan AH, Mahadeva S, Thalha AM, et al. (2014) Small intestinal bacterial overgrowth in Parkinson's disease. Parkinsonism Relat Disord 20: 535-540.

36. Nielsen HH, Qiu J, Friis S, et al. (2012) Treatment for Helicobacter pylori infection and risk of parkinson´s disease in Denmark. Eur J Neurol 19: 864-869.

37. Mulak A, Bonaz B (2015) Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterology 21: 10609-10620.

38. Pfeiffer RF (2011) Gastrointestinal dysfunction in Parkinson's disease. Parkinsonism Relat Disord 17: 10-15.

39. Devos D, Lebouvier T, Lardeux B, et al. (2013) Colonic inflammation in Parkinson's disease. Neurobiol Dis 50: 42-48.

40. Drouard A, N Guyen JM, Chaumette T, et al. (2010) Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. PLoS One 5: e12728.

41. Friedland RP (2015) Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. J Alzheimers Dis 45: 349-362.

42. Trudler D, Farfara D, Frenkel D (2010) Toll-like receptors expression and signaling in glia cells in neuro-amyloidogenic diseases: Towards future therapeutic application. Mediators Inflamm 2010: 497987.

43. Scheperjans F, Aho V, Pereira PA, et al. (2015) GM are related to Parkinson's disease and clinical phenotype. Mov Disord 30: 350-358.

44. Fasano A, Bove F, Gabrielli M, et al. (2013) The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov Disord 28: 1241-1249.

45. Surana NK, Kasper DL (2014) Deciphering the tête-à-tête between the microbiota and the immune system. J ClinInvest 124: 4197-4203.

46. David LA, Maurice CF, Carmody RN, et al. (2014) Diet rapidly and reproducibly alters the human gut microbiome. Nature 505: 559-563.

47. Flint HJ, Scott KP, Duncan SH, et al. (2012) Microbial degradation of complex carbohydrates in the gut. Gut Microbes 3: 289-306.

48. Cordner ZA, Tamashiro KL (2015) Effects of high-fat diet exposure on learning & memory. Physiol Behav 152: 363-371.

49. Wu A, Ying Z, Gomez-Pinilla F (2004) The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. Eur J Neurosci 19: 1699-1707.

50. Cox AJ, West NP, Cripps AW (2015) Obesity, inflammation, and the GM. Lancet Diabetes Endocrinol 3: 207.

51. Kratz M (2014) Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab 20: 614-625.

52. Cryan J, Dinan T (2012) Mind altering microorganisms: The impact of the GM on brain and behavior. Nat Rev Neurosci 13: 701-712.

53. Felger JC, Miller AH (2012) Cytokine effects on the basal ganglia and dopamine function: The subcortical source of inflammatory malaise. Front Neuroendocrinol 33: 315-327.

54. Bocarsly ME (2015) Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proc Natl Acad Sci USA 112: 15731-15736.

55. (2001) FAO/WHO working group. Report of a joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Córdoba, Argentina.

56. Rossi M, Amaretti A (2010) Probiotic properties of bifidobacteria. In: Mayo B, van Sinderen D, Bifidobacteria: Genomics and Molecular Aspects. Microbiol Mol Biol Rev, 97-123.

57. Amaretti A, di Nunzio M, Pompei A, et al. (2012) Antioxidant properties of potentially probiotic bacteria: in vitro and in vivo activities. Appl Microbiol Biotechnol 97: 809-817.

58. Virtanen T, Pihlanto A, Akkanen S, et al. (2007) Development of antioxidant activity in milk whey during fermentation with lactic acid bacteria. J Appl Microbiol 102: 106-115.

59. Azcárate-Peril MA, Sikes M, Bruno-Bárcena JM (2011) The intestinal microbiota, gastrointestinal environment and colorectal cancer: A putative role for probiotics in prevention of colorectal cancer? Am J Physiol Gastrointest Liver Physiol 301: G401-G424.

60. Pompei A, Cordisco L, Raimondi S, et al. (2008) In vitro comparison of the prebiotic effects of two inulin -type fructans. Anaerobe 14: 280-286.

61. Nardone G, Compare D, Liguori E, et al. (2010) Protective effects of Lactobacillus paracasei F19 in a rat model of oxidative and metabolic hepatic injury. Am J Physiol Gastrointest Liver Physiol 299: G669-G676.

62. Lutgendorff F (2009) Probiotics prevent intestinal barrier dysfunction in acute pancreatitis in rats via induction of ileal mucosal glutathione biosynthesis. PLoS One 4: e4512.

63. Chiurchiù V, Orlacchio A, Maccarrone M (2016) Is modulation of oxidative stress an answer? The State of the Art of Redox Therapeutic Actions in Neurodegenerative Diseases. Oxid Med Cell Longev 2016: 7909380.

DOI: 10.36959/459/610