Neurodegenerative Pathogenesis

Subjects: Neurosciences

Contributor: Sachchida Nand Rai

Current research in medicine in several parts of the world has attempted to establish a link between the occurrence of neurodegenerative pathologies, microbiota dysbiosis, and the incidence of obesity. The body's response to different physicochemical factors has also been influenced by the proper assimilation of bioactive compounds contained in the food that is ingested. Oxidative stress is one of the major factors that directly affects the functioning of the human microbiota.

Keywords: gut-brain axis ; neurotransmitter ; dysbiosis ; obesity

1. Introduction

Recovery from dysbiosis (the imbalance in gut microbial population) and the establishment of eubiosis are currently being investigated in research regarding a demonstration of a direct relationship between the nervous system and the colon's microbial fingerprint [1]. Considered to be the second brain (enteric nervous system), the structure of enteric neurons is the key factor that controls the physiological response to the environment [2]. Increased administration of antibiotics determines the prevalence of antibiotic resistance genes in gut bacterial strains, and sustains dysbiosis [3]. Molecular interactions between microbial strains play an essential role in the stress response, in developing pathologies, and in reducing inflammatory progression, and are a significant factor in supporting and maintaining dysbiosis [4].

Oxidative stress represents one major factor that directly affects the structure (microbial pattern) of human microbiota [5]. The perturbed pattern determines the incidence of degenerative diseases, obesity, and other physiological modifications [6].

The regenerative (modulatory) function of microbiota has been recently demonstrated in research to reduce significant pathology symptoms, mainly those involved in degenerative diseases [7]. This aspect results from microbiota-targeted therapies that modulate the microbial pattern and influence the host homeostasis [8]. Restoring the microbiota will lead to better overall functioning, which also helps maintain the functionality of other tissues or organs [7].

This evidence linking gut microbiota to degenerative pathologies is known, and new links between these are needed in the current epidemiological context. A newly identified aspect was obesity, based on its connection with the microbiota's role. Identifying critical mediators of this process is a novelty that will open up the possibility of new therapeutic approaches by correcting dysbiosis and reducing the inflammatory response.

From clinical trials in patients with neurodegenerative diseases, the effect of these products has been unclear. Positive results tend to be the improvement of other physiological parameters (anxiety reduction or biochemical parameters [9]) that act indirectly on the cognitive status [10]. SCFAs were just key mediators, which modulate the colon's integrity. The initial stages are developed, in many cases, at the level of the nervous system by its improper function that influences gut microbiota status.

2. Microbiota Role in the General State of Health

These regenerative aspects are closely related to inflammatory progression, as microbial profile dynamics can ensure host homeostasis. A clear picture could be represented by microbial species' differences to observe the microbial balance in various chronic pathologies. An example of correspondence between the microbial population of microbiota, obesity, and neurodegenerative pathologies could be the variation ofAkkermansia muciniphilapopulation [11]:In obesity, there was an increase in theFirmicutes:Bacteroidetesratio (number of the cells/mL) The differences in microbial composition determined the increased abundance of pathways involved in alpha-linolenic acid metabolism, electron transfer carriers, bacterial motility proteins, Parkinson's disease, and Prion diseases [12].

The colonic microbiota activity and the metabolic function's modulation depend on bioactive compounds' bioavailability [13]. Modulation by functional products influences both the microbial fingerprint, which has a xenobiotic effect, and the products of microbial metabolism. Reducing the xenobiotic impact is a complex process that affects the regenerative function [14]. The functioning of these two systems is based on an interdependence that expresses a capacity (the physiological barrier's function) to maintain an optimal state of health [15].

3. Oxidative Stress and Microbiota in Neurodegenerative Processes

Maintaining a well balanced relationship between intestinal microbiota and the nervous system is essential in promoting homeostasis [16]. The onset of dysbiosis influences the occurrence of cognitive disorders (depression, anxiety, and associated dysfunction, such as multiple sclerosis [17]) that coincide with the onset and establishment of irritability, sensitivity, and minor neurological diseases [18]. These manifestations are sustained by inflammatory processes that characterize intestinal dysbiosis [19]. Modulation of the microbial pattern eliminates these symptoms (as multitarget strategy) [20], and classical medication of neurodegenerative pathology as AD only determines an improvement of cognitive status [21].

Inflammatory progression and aggravation reduce the natural process of neuronal protection [22], resulting in premature neuronal aging. This phenomenon frequently leads to the establishment of neurodegeneration [23]; modulation of the microbiota contributes to improving these complex processes and reducing accumulations of proinflammatory factors [7].

Nutraceuticals can be the key to this process, which controls the overall health status with long-term effects [24]. The control of these functions is also a way of reducing the natural aging process 's impact strictly related to cell oxidation and the action of oxidative stress [25]. This aspect demonstrated an imbalance between free radicals and the human body's

Thus, antioxidants directly attenuate biological factors that can cause inflammatory progression [26]. The use of classical drugs, on the other hand, may generate toxicity and adverse reactions. Antioxidant products reduce this toxicity by the scavenging activities of free radicals. These compounds, which are often polyphenol carboxylic compounds, have other effects and, after administration, are identified as prebiotic-like products [27].

The complex relationship between biotransformation at the microbiota level and the protection against neurodegeneration results in reducing oxidative stress (an increase in antioxidant protection) and preventing the aging of nerve cells. Changing bowel motility, increased intestinal permeability, and increased drug consumption with side effects is another essential factor that correlates (or absorptive dysfunction represents) critical factors. They associate the natural aging process with a reduced immune response and an increased inflammatory progression. The interconnections between physiological processes associated with old age progressively lead to the establishment of the neurodegeneration process [1].

The regenerative function is expressed at two levels:Modulation (correction) of the disturbing pattern (dysbiosis);Modulation (correction) of physiological processes resulting from restoring the balance along the gut–brain axis.

Even if the microbiota's regenerative role is not widely accepted in clinical practice, its unbalanced metabolism favors the onset of the pathological state where oxidative stress has a more pronounced character (such as in the cardiovascular or neuronal systems) [28]. The critical point is the establishment of eubiosis, which could influence both mechanisms [29]. Metabolic correction provides a biochemical explanation for optimizing physiological functions, and the oxidative cause of stress can be eliminated [30].

Clinical relevance was determined by exo- and endogenous factors. The modulators' chemical structure is an essential element that influences the gut-brain (biochemical signaling) balance [31]. Disruption of two-way communication is investigated in recent research, the source of neurological dysfunctions, and the cause of a decreased body immune response [32].

Microbiota activity can be controlled through the gut-brain axis using different compounds with particular functionalities based on several pathways [33] called neurotransmitters; for example, identifying the neurotransmitter pattern's role is crucial in explaining the interaction with different exogenous factors [28][34][35].

Neuroendocrine systems also interact with the gut microbiome, controlling physiological functions in response to oxidative stress by the hypothalamic-pituitary-adrenal (HPA) axis. As different microbiota-gut-brain axis pathologies are associated with the HPA axis dysfunction [36], this interaction is significant. In PD, the triggering of limb tremors disrupts dopamine

synthesis, which controls and regulates muscle movements through the gut–brain axis. The phenomenon is linked to the microbiota pattern; therefore, the microbial profile's control determines a secondary (indirect) regulation of dopamine synthesis [37].

Recent studies have shown that microbiota plays a significant role in the pathogenesis and therapy of PD [37]. The dysbiosis of microbiota may indicate the progression of PD [38]. Several patients with PD exhibit dysbiosis and gastrointestinal problems even before the onset of motor symptoms and their diagnosis [39]. Before the clinical onset of PD symptoms, leaky gut was observed due to gastrointestinal symptoms like constipation, hypersalivation, and dysphagia [38].

The population of pathogenic bacteria like Enterobacteria, Streptococci, Staphylococci,Shigella, andH. pyloriwas also increased in PD cases [40][41]. Gut microbes affect the synthesis of dopamine [42], deposition of α-synuclein enhances oxidative stress, induces local inflammation, enhances intestinal permeability, and causes constipation in PD [43][44][45]. ; therefore, gut microbiota can be explored for the early diagnosis of PD, as suggested by current studies, which are very reliable and noninvasive [46]. In PD,Helicobacter pyloriare mentioned, with increasing levels of Enterobacteriaceae and a lower number ofPrevotellaceae[45].

The Mediterranean diet can also sustain a healthy microbiome pattern and reduce the risk of PD by enhancing the growth of beneficial strains [39][47]; however, several side effects may be mentioned at a preprolonged administration of these functional products: intestinal bacterial overgrowth, D-lactate acidosis, brain fogginess, and horizontal gene transfer [48]. The dysbiosis of microbiota may represent an early sign of PD by identifying the microbiota pattern. The gastrointestinal tract initiates a spread of α-Syn, which means that initial nonmotor symptoms like constipation might be an early sign of the disease. Several probiotics, prebiotics, and their combination might restore healthy microbiota patterns and prevent further progression of PD [37][39][49].

In AD, neurotransmitters' activity that influences neuroinflammation directly relates to the metabolic activity [50]. [50][51], and are located, especially, around the essential internal organs (e.g., liver or heart) [52]. Microbiota activity influences the formation of amyloid plaque, which progressively causes the death of neuronal cells [53]. In vivo studies have shown a decrease in certain bacteria such asEubacterium rectaleandBacteroides fragilisand an increase inEscherichia coli[54].

Other compounds with a negative effect are proinflammatory cytokines that cause severe inflammatory responses [55]. Increased synthesis of proinflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-6, and IL-18 has been identified in people diagnosed with AD. Of these, two proinflammatory cytokines (TNF and IL-1β) were determined to have elevated values demonstrating the severity of AD [56]. The presence of these cytokines is correlated with the loss of the ratio betweenE. coliandE. rectale(the ratio is different between target groups, daily habits, etc.), which supports a typical microbial pattern in the case of degenerative diseases [57].

Amyotrophic lateral sclerosis (ALS) determines changes in the microbiota structure and dysfunction of the gut-brain axis [58]. It has been demonstrated thatAkkermansia muciniphilareduces ALS symptoms by accumulating nicotinamides that improve motor function. An inverse effect was associated with the presence ofRuminococcus torquesandParabacteroides distasonis[59].

Based on this knowledge, we could consider that modulation of microbiota could sustain neuronal health as an alternative strategy for the population's target group. Unbalanced metabolism favors the onset of the pathological state where oxidative stress has a more pronounced character (such as in the cardiovascular or neuronal systems). The control through the gut-brain axis involves several molecules from different pathways that do not have a well described mechanism. It is necessary to identify new biomarkers and therapeutic strategies for early diagnosis and innovative treatments, especially in preventing neurodegenerative diseases.

Food addiction and drug use have a negative influence, leading to a disturbance of the neural system's functionality. This behavior, doubled by the high degree of food processing, leads to obesity and other degenerative pathologies [60]. The initiation of dysbiosis, a result of fast-food consumption, is related to disruption in dopamine release [61][62].

Recent studies have shown a connection between obesity, type 2 diabetes, and neurodegenerative diseases. Modulation of the microbiota associated with weight loss is among the new therapeutic strategies against neurodegenerative disorders [63]. Obesity is a risk factor in developing neurodegenerative diseases (e.g., AD or PD), with common causes such as oxidative stress and mitochondrial dysfunction, both of which are supported by inflammatory progression. From a molecular perspective, early aging causes an increase in the blood-brain barrier's permeability and intestinal permeability in the elderly, which has a proinflammatory effect [64][65].

The relationship between different bacterial strains and a dysbiotic microbiome state responds to exogenous factors and inflammatory processes generated by oxidative stress inE. colihave been reported in overweight women [66]. These data are correlated with recurrent infections caused by this strain in the urinary tract in people diagnosed with type 2 diabetes who are also overweight [67]. A reduction in oxygen consumption and overexpression of proinflammatory mediator genes (e.g., IL-6) has been demonstrated [5].

Such processes induce oxidative stress, which controls several genes' expression including those responsible for producing various cytokines [37]. The cellular level of ROS conditions the physiological response that controls inflammatory processes. For neurodegenerative diseases (e.g., AD), redox balance is a crucial factor, andLactobacillusstrains play an essential role in maintaining the gut–brain axis homeostasis. The different physiological dysfunction (degenerative process) is closely linked to pathogenesis of inflammatory diseases (e.g., obesity or inflammatory bowel disease)

The host homeostasis was influenced not only by the level of SCFA but through other cellular components. LPS are toll-like receptors (TLR) expressed by immune cells. Maintaining intestinal health and healing the possible lesions implies microbiota-mediated TLR signals. A new approach to the influence on the microbiota may be related to the amount of lipopolysaccharides produced by bacteria (determined by the perturbed intestinal permeability), given that the amount of lipopolysaccharides in the blood was correlated with diabetes, cell death, or other diseases such as sepsis, atherosclerosis, inflammatory bowel disease, nonalcoholic fatty liver disease or neurodegenerative diseases [68][69].

Other components, such as secondary bile acids produced by microbiota action, play an essential role in controlling the production of bile acids and immunity [70]. Studies show that SCFAs and conjugated primary bile acids act differently, the first with an anti-inflammatory role, the second with the opposite role [71]. Some of these compounds act as aryl hydrocarbon receptor ligands, and their low levels are indicators of metabolic disorders. Simultaneously, through SCFAs and bile acids, gut microbiota also modulates the metabolism of tryptophan to serotonin; the final product of its degradation is another parameter in metabolic diseases [72].

The point of connection of neurodegenerative diseases (e.g., AD) with the intestinal microbiota is the microbial diversity changes that are often encountered with age. Research conducted in vitro supports these data, which indicates a dysbiotic condition in type 2 diabetes, which is related to obesity [67]. In ALS, the results were significant becauseA. muciniphilais considered part of a new type of functional product used to control weight and associated pathologies (reduce glucose intolerance) These data indicate another link between degenerative pathologies (e.g., ALS) with a decrease in the abundance of bacterial strains that help control obesity.

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