Gut Microbiome in Association with Diet and Neurodegenerative Diseases

by

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The human colon has the most significant population of bacteria in the entire body.

It is believed that microoraganisms came into existence over 1.5 billion years ago. They are the most abundant organism on this planet surviving an array many various and fulfilling many important purposes. They can be found in a variety of environments such from lakes and oceans to hot springs. Microogranisms include bacteria, archaea, and viruses and while some serve a negative purpose other benefit us greatly. One notable location that bacteria tend to live in is the human body. Microorganisms live in every part of the human body on the skin they form a biofilm on our teeth, and most notably the gut otherwise known as the gastrointestinal tract.

The gut microbiome can be defined as the sum of microorganisms that take residence in the gastrointestinal tract. These microorganisms include bacteria, archaea, and fungi. A majority of the microogranisms that take residence in our gastrointestinal tract provide many great benefits such as aiding in digestion and producing certain aliments that the body needs to protecting itself against pathogens, such as making Vitamin B and K which are Vitamins that the body does not produce, and fermenting undigested carbohydrates. A healthy gut microbiome can also increase your life span and the number of healthy years lived on this planet. But there are some that impact us negatively such as releasing toxins, increasing our likelihood of contracting certain diseases, and putting the balance of our gastrointestinal system in complete disarray. This can lead to a state of gut dysbiosis which is a state in which there is an imbalance of microorganisms within our intestines. And since 80 percent of our immunity exists in our intestines this can have quite a negative impact. There are many factors that shape and characterize our gut microbiome such as our mode of delivery, the microbes we are exposed to prior to and following birth, the environment we are raised in, as well our diet and lifestyle. Although all of these factors synonymously play a role diet and lifestyle is probably the greatest and most definitive factor.

Bacteria posses many different classifications and they come in a variety of shapes and sizes. There are two different type of bacteria; gram negative and gram positive. There are many differences between them but the most notable one would be the fact that the structure of their cell wall differs greatly. Gram Negative have substantially thinner cell wall but their cell is much harder to penetrate. Many gram negative bacteria are resistant to antibiotics which makes quite difficult to eliminate from its host. Gram positive bacteria have a very thick cell wall, that of which mainly consist of multiple layers of peptidoglycan. Peptidoglycan is a macromolecule that is composed of amino acids and sugars. Peptidoglycan gives shape and support to the bacterial cell, giving it great protection. Gram positive bacteria also possess chains of teichoic acid which protrudes from the cell membrane and through the cell wall. Teichoic acid are a chain of molecules that are made of sugars. Teichoic acid aids in the bacteria infect other cells and causes infectious disease. Gram negative bacteria have a cell wall is made of a thin layer of peptidoglycan. Although the cell wall is thinner it is far more complex in nature. Gram positive bacteria have an outer membrane that is located outside of the peptidoglycan layer. These bacteria also possess a molecule called lipopolysaccharide on the outer membrane. This protects the bacteria from the harsh external environment.

Bacteroides are anaerobic which are bacteria that grow only when oxygen is not present they are resistant to bile, they are non-spore forming which means that they do not form spores, and they are gram negative bacteria, and they are rod shaped. Bacteroides may be passed from the mother to the child during vaginal birth and thus become part of the human flora in the earliest stages of life. They can cause significant pathology if they escape the gut such as an abscess in the abdomen in the brain, the pelvis, liver and lungs. They utilize simple complex sugars and polysaccharides for their growth. Many bacteria have transport linked phosphorylation systems that allow sugars to be transported across the cell membrane by these phosphotransfer systems can immediately enter metabolic or biosynthetic pathways. There are a number of reports during the last two years discussing the relations between the ratio of Bacteroidetes and the Firimcutes are linked to obesity in humans and mice. The microbiota of

these individual are more heavily enriched with Firmicutes and less with Bacteroidetes. And in some studies they found that the abundance of Bacteroidetes increases as obese individuals lose weight. When the microbiota of obese mice are transferred to germ free mice these mice gain more fat than the control group than the lean mice did. A recent study found that diets that are based on a high intake of protein but a low intake of fermentable carbohydrates. This includes many popular diet such as Atkins and the South beach diet, this resulted in an alteration in the gut flora. They found that proportions of Bacteroides and and several clusters of Clostridia were not altered but the numbers Roseburia, Eubacterium rectale, and bifidobacteria decreased significantly as carbohydrate intake decreased. Showed an increase in ability to use a variety of starches.

The subject of the microbiome is a topic of great interest within the field of modern biology because of what it is we can learn about human organisms by studying it. The state of the microbiome can provide markers for various different disease but one myriad of diseases that remains to be somewhat of a mystery are neurodegenerative diseases. Much is known about the neurodegenerative diseases in terms of the progression of the disease and its stages but very little known as to why it happens or what exactly triggers it.

Neurodegenerative diseases which are diseases in which neurons are affected in the brain; this includes Parkinson's Disease, Alzheimer's disease, and Huntington's disease. Parkinson's disease is a neurodegenerative disorder that affects dopaminergic neurons (which are neurons that produce dopamine) in a specific part of the brain called the substantia nigra. The substantia nigra is the nucleus of the midbrain. It contains two components: the pars compacta and the parts reiculata. Destruction of the pars compacta of the substantia nigra causes lower availability of dompamine. This creates a reduction in motor movement, this reduced functioning of the substantia nigra is a result of Parkinson's Disease. In a normal adult brain the substantia nigra is black but in patients with Parkinson's disease their substantia nigra turns white this can be observed following death. There are many symptoms of

this disease to contend with. Tremors which are involuntary movement typically of the hands, arms, and legs. Difficulty with balance coordination which makes walking and many everyday basic activities a challenge, which makes falling which commonly happens. Muscle rigidity which is stiffness that usually occurs in the limbs of the body such as the arms, shoulder, and neck. With the disease these patients experience an eventual decline in spontaneous movement this often leads to a decrease in mental skills, or their reaction time and a decrease in facial expression.

Alzheimer's Disease is the 6th leading cause of death in the United States. Alzheimer's disease was discovered by Dr. Alois Alzheimer. And in 1906, she observed the brain tissue of a woman who had a recently died of some sort of unknown mental illness. This woman was reported to have symptoms such as memory loss, difficulty with language and speech, and radical behavior. Upon examination she found many abnormal clumps which are now called amyloid plaques and bunches of tangled fibers which are now called neuro fibrillary. Amyloid plaques and neurofibrillary tangles are known as one of the major hallmarks of this disease. Amyloid plaque is a collection protein(amyloid) that forms between nerve cells in the brain of Alzheimer's patients. It is believed that it interferes with connections between neural cells and contributes to the progression of this disease. Neurofibrillary tangles are bunches of tangled fibers found inside the brain's cells. These tangles are made of a protein called tau, which is component that is used to create microtubules in the body's cells. The microtubule aids in the transportation of nutrients and other key substances from one part of the cell to another. Although tau is something that everyone posseses this protein is found to be abnormal in patients with Alzheimer's disease. Alzheimer's disease has seven stages no impairment, very mild decline, mild decline, moderate decline, moderately severe decline, severe decline, and lastly very severe decline. In no impairment there are not any present signs of the disease or any memory loss. With very mild decline the individual may experience minor memory problems but nothing significant or abnormal. In the stage of Mild Decline the individual may be begin to experience memory problems to the point that their family members notice and it would be detectable by a doctor. With Moderate Decline, the

individual begins having difficulty remembering simple details and they begin to experience a great deal of confusion. With Severe Decline, the patient becomes confused, cannot recognize faces other than those of close family and friends. They also cannot remember personal details about themselves, and begin to experience incontinence as well extreme changes in personality and mood. And in the final stage this person is nearing death, they can only speak very few words and phrases and cannot appropriately respond to their environment. They also may lose the ability to swallow their food. Alzheimer's disease also has many cognitive symptoms. The degradation of nerve cells results in many significant. This created radical changes in mood and behavior, they lose their ability to think and to reason logically, and eventually complete cognitive decline. These individuals lose their memory progressively over time and once they reach the late stages of this disease they must completely depend on a caretaker for even the simplest of needs. This also affects their speaking so they have great difficulty with that. And because they suffer from great memory loss often times they do not recognize people they once knew prior to the progression of the disease, even family and loved ones. Huntington's disease is a disease that causes a mutation in Chromosome 4 in the human genome and it is a dominant gene meaning that both parents must be carriers. This mutation is in a gene that codes for a protein called huntingtin. This disease is genetic meaning that it must be inherited from one of your parents in order to contract the disease. This disease causes the death of various brain cells in the body, especially those that aid in voluntary and involuntary movement. This disease is characterized by uncontrolled movement of the limbs and body, a decline in reasoning skills, and changes in mood such as anxiety and depression. As previously stated the causes of this disease are not yet entirely understood and there is currently no cure. Huntington's disease differs in many ways in comparison to the other neurodegenerative disease that have been mentioned. Huntington's not only is a genetically inherited disease but it also has a much earlier onset. Huntington's disease is typically diagnosed between the ages of 30 and 50 years old and in some cases although it is rare the onset can be under the age of 20. With Alzheimer's and Parkinson's disease the onset is usually much later in life and is more

prevalent in elderly people. Symptoms of Huntington's disease can be described as having Alzheimer's and Parkinson's disease combined. Symptoms include muscle rigidity, slow movement, involuntary muscle movement, and seizures.

As a result scientists are trying to study diet, lifestyle, and activity with the belief that it there is a correlation with these factors and the progression of this debilitating neurodegenerative disease. Therefore studying the gut microbiome may provide clues as to what triggers these diseases. Nutrition is vital to our health and it is vital to the health of our gut microbiota. Many people believe that neurodegenerative are caused by genetic and environmental factors and although these factors are certainly valid there is one aspect of health that hasn't been entirely considered. Many think that what we eat and our nutrition does not affect our likelihood to contract certain diseases such as Parkinson's disease or Alzheimers. But it seems there is an undeniable connection between diet and one's health status. In this paper I will demonstrate the relationship between diet, status of gut microbiota, and the development of neurodegenerative diseases and that the state of the gut microbiome does contribute to neurodegenerative disease.

Since scientists have concluded that dysbiosis has a definite correlation with disease but the long standing question remains what constitutes a healthy gut microbiome. Although there is a great deal of research that is required to fully determine this there are some common factors that have been commonly identified. These factors include integrity of the mucus membrane, integrity of the diet, stress, tight gap junctions, as well as many other major lifestyle factors. The mucous barrier is a layer of mucous produced by goblet cells that lines the epithelium of the GI tract, and acts as an immune defense against invading pathogens (Conlan 2014). Bacteria are able to adhere to the mucous layer and degrade it and penetrate the body's defenses that way. A loss of gut bacteria function has been attributed to many diseases such as Parkinson's Disease. There are many gut bacteria that can be easily recognized such as: Bifidobacterium, Lactobacillus, Bacteroides, Clostridium, Escherichia, and

Ruminococus. And about 60 percent of the bacterial organisms that reside in the gut belong to the phyla Bacteriodetes or Firmicutes. The ratio between the two indicate many things about one's health especially their diet, and it is believed that there are three enterotypes as they are called that exist. Enterotypes are a classification of organisms that are defined by the phyla of bacteria that mainly reside in the ecosystem of the gastrointestinal tract. Enterotype 1 is mainly dominated by the Bacterioidetes phyla, Enterotype 2 is mainly dominated by Prevotella, and Enterotype 3 Ruminococcus. Studies have shown substantial evidence that Western diets (a diet that is high in salt, sugar, and saturated fat) have a strong association with microbial populations that are dominated by a Bacterioides Enterotype. There is an association between a high ratio of Bacteriodes and the development of many disease such as Parkinson's Disease, Diabetes, colorectal cancer, and low grade inflammation (Conlan 2014). It has been found that organisms associated with carbohydrate metabolism are overrepresented within this Enterotype. Conversely, the fecal microbiota of African and South American children consuming a plant rich diet is found to be very rich in the Prevotella enterotype as well as species of bacteria that are associated with fiber utilization and are known to use cellulose as substrates such as Xylanibacter. Enterotype 3 which is characterized by an overrepresentation of Firmicutes specifically Ruminococcus. These types of bacteria are enriched with membrane transports designated for sugar, suggesting an uptake of simple sugars by these genera. Tight gap junctions are space between cells that is located between the intestinal cells and the epithelium. The tight junction is key in maintaining the integrity of the gut microbiome. Tight gap junctions affect the permeability of the gut mucous lining including leaky gut syndrome and plays a key role in maintaining human health. Many diseases have been associated with tight gap junction and their loss of integrity, specifically neurodegenerative diseases. There are also many lifestyle factors that can influence the composition of your gut microbiome. The microbes you are exposed during childhood certainly play a factor. It has been shown that if children do not obtain sufficient exposure to pathogens and microbial organisms such as the gut microbiota this can significantly increase their

chance of contracting an autoimmune disease or an allergy related disease. The bacteria of the gut microbiome can give signals and direct the immune system to endure many different antigens, to make intestinal epithelial cells, and immune cells to respond to these signals. Host immune defenses along the intestine, including a mucus barrier, help prevent potentially harmful bacteria from causing damage to tissues. The maintenance of a diverse and thriving population of beneficial gut bacteria helps to keep harmful bacteria at bay by competing for nutrients and sites of colonization. Dietary means, particularly the use of a range of fibers, may be the best way of maintaining a healthy gut microbiota population.

Smoking for example has a significant impact on the gut microbiome and increases your risk of colorectal cancer. Air-borne toxic particles can also reach the large bowel via mucociliary clearance from the lungs, and increased environmental pollution associated with industrialization can contribute to increase Irritable Bowel Disorder (Conlan 2014). Stress also plays a huge factor since it affects your colonic motor activity, which takes place via the gut-brain axis. The gut brain axis contains hormonal and neural pathways so it is believed that changes in the the gut microbiome may affect brain activity as well as mood. Another huge factor would be one's level of physical activity. As it is already known people who are not physically are more likely to be overweight, more likely to have cardiovascular issues, and more likely to develop diabetes. It is clear based on the evidence that physical activity has a positive impact on the characterization of the gut microbiota. A recent showed that individuals who are professional athletes demonstrated an increase in microbial diversity in response to exercise and a healthy diet.

As previously stated the cause of these neurodegenerative diseases remains unknown. But there are many factors relating to the composition of the gut microbiome that provide great insight into this topic. Out of all these neurodegenerative diseases there appears to be many commonalities and underlying themes. In all of these disease these patient all have been microbiome that has been disturbed and is out of balance. And in one study it was confirmed that all of these Alzheimer's

patients that were tested experienced dysbiosis prior to contracting the disease. Patients with Parkinson's disease all had a mucosal gut lining that had been degraded and depleted. And as it well known the mucosal lining of the intestine is key in maintaining the integrity of the microbiome as well as the integrity of the body. Although there are many modes in which bacteria and viruses can enter the body the one of the most effective would be via the intestinal mucosal lining. Bacteria invade the body by releasing toxins, degrading this mucus lining and eventually penetrating it which can cause inflammation as well as a host of other diseases.

It has been found that microbial organisms present in the fecal samples of PD patient differs greatly from healthy individuals. It was also observed that bacteria that belong to the Blautia genera, Corpocpcccus and Roseburia were reduced in these samples belong to PD patients. Bacteria that belong to the Blautia genera are produce Butyrate which reduce inflammation in the body. Upon comparison the fecal samples of healthy individuals they found that there was an abundance of bacteria from the Raulstonia genus in PD patients which are bacteria that encourage inflammation. There was also a significant increase in the abundance of Eubacterium eligens, Eubacterium rectale, and *Eubacterium hallii, and Enterobacteriae* that were positively correlated in PD patients which indicated a worsening of the disease. A reduced abundance of Prevatella appears to be a common factor in PD patients. Reduced levels of *Prevotella* are also associated with diminished mucin production (Bergstrom and Xia 2013). Mucin proteins are high molecular weight O-linked glycoproteins, which line mucosal surfaces and aid in maintaining the integrity of the epithelial barrier.

The fermenting of non-digestable starches such as those found in plants provide the host with a great source of nutrients as well SCFA's. These include formate, acetate, proprionate, and butyrate. SCFA's also act as signaling molecules between other microogranisms, they are a great energy source for human cells and tissues (Morrison and Preston 2016). The SCFAs acetate and proprionate have been shown to reduce adipocyte lipolysis (which is the breakdown of triglycerides found in adipose fat cells

into glycerol and fatty acids), regulate appetite, improve leptin secretion by adipocytes, and enhance whole-body glucose maintainence ; thereby SCFAs impact the maintenance of the overall energy balance in humans.

SCFAs also act as signaling molecules from bacteria to host cells and they play a vital role by maintaining the stability of the epithelial lining of the intestines. This is achieved by regulating the expression of tight junction proteins in the epithelium. Tight junction proteins such as zonula occludens (ZO)-1 and claudin-1 by intestinal epithelial cells. This increase in tight junction protein expression can hinder the release of lipopolysaccharide (LPS) into the submucosae, this reduces the changes of an inappropriate immune response taking place. Gut microbiota also seems to play a huge role in the regulation of brain health. A study was done involving mice that were given oral antibiotics, these mice were pathogen free in order to observe this involvement. The result was an increase in expression of brain-derived neurotrophic factor(BDNF) in the hippocampus, and a decrease in expression of BDNF in the amygdala, indicating the relationship between the microbiota and central nervous system (CNS) is complex. Brain-derived neurotrophic factor is a neurotrophin. Neurotrophins are proteins that are involved in the development, differentiation, and growth of neurons or brain cells. A lot of communication between the microbiome and the brain takes place via the Vagus nerve, this nerve begins in the medulla oblongata of the CNS and extends into the peripheral nervous system supplying the gut, heart, lungs, and other organs of the chest and abdomen with input from the parasympatheric nervous system. Acetylcholine is one of the neurotransmitters that are primarly used with in the Vagus nerve. Acetylcholine is released at neuromuscular junctions to active muscle action. The thoracic and abdominal organs also feed the CNS sensory information, this information is mediated by hormones and peptides(chain of amino acids) such as ghrelin, cholecystokinin, glucagon-like peptide 1. Ghrelin is a hormone that is released primarily by the stomach as well as the small intestines, brain, and the pancreas. It also increases hunger, foot intake, and fat storage. Cholecystokinin is a peptide hormone that is released by the cells of the duodenum, and their function

principally it to stimulate fat and protein digestion. Glucagon like Peptide 1 is a hormone that increases feelings of satiety between meals and during meals by slowing down the emptying of the stomach. The somatic sensory ganglia express free fatty acid receptor three, this is activated by proprionate. These receptors are located in the islet cells of the pancreas, immune cells, and in the brain, and are vital to immunity and metabolism. This receptor is activated by products of dietary fiber digestion and short chain fatty acids, which greatly influences intestinal immunity. Since SCFAs are produced by the microbes of the intestine, is it possible that these signaling pathways associated with this receptor could be used for communication between the gut microbiota and the central nervous system. So it is evident that short chain fatty acids that are produced in the intestinal tract, affect the brain and neural function. For example, the application of proprionate, to neuronal cells, as well as glial cells, leads to temporary intracellular acidification, and in the case of neurons, this intracellular acidification impacts their excitability(the ability of a neuron to respond to a stimulus and for ions to move across the membrane) and signaling potential. More specifically, the application of hippocampal neurons led to rapid intracellular acidification, which caused various decreases in excitatory postsynaptic current. The gut microbiota is involved in the development and mediation of endocrine signaling in the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic-pituitary-adrenal (HPA) axis sends and receives signals by transporting hormones across the Blood Brain Barrier and the circulatory system. For example, Germ free mice exhibited higher expression of brain corticotropin releasing hormone lower expression of glucocorticoid receptors, compared to pathogenic mice. Corticotropin-releasing hormone is a hormone that is made by the hypothalamus which stimulates the release of Corticotropin from the anterior pituitary gland, and is also involved in the body's response to stress. Glucocorticoid receptors bind cortisol and glucocorticoids, these cells are expressed in every cell in the body and they also control genes that regulate metabolism and immune response. There was a significant correlation with germ free mice with high corticosterone concentration and anxiety after the introduction of stress

as opposed to the other mice. This demonstrates that at least some amount of “good intestinal bacteria” may be key in the normal human stress response.

It is quite apparent in my eyes that what we eat influences not only the state of gut microbiome but our overall health. Although there are many factors that influence the characterization of our gut microbiota such as our mode of delivery, the microbiota we are exposed to in the womb, and the microogranisms we are exposed to as children, there is one factor that stands to carry great influence. Long term changes in our eating and dietary patterns can produce significant changes in composition of gut microbiota. Those that consume a diet that is rich in various plant sources, non-digestable starches found in vegetables such as fiber exhibit many markers of a healthy gut microbiome. They demonstrate a higher prevalence of Prevotella these bacteria which have positive association with overall health. These bacteria also reduce inflammation, which is vitally important since low grade inflammation is a huge indicator of the presence of many diseases. Healthier individuals also have a gut microbial profile that demonstrates great diversity in reference to species of bacteria present. Individuals who were involved in various studies regarding this topic possess gut microbial profiles which lack species diversity. They demonstrated a higher abundance of bacteria belonging to the Firmicutes genera. High prevalence of this genera is associated with an unhealthy diet essentially. A diet that would be characterized as the following: being high in sugar, high in processed foods, high in saturated fat, and high in meat consumption which would be identified as the Western diet. Many Alzheimer’s and Parkinson’s disease patients experienced dysbiosis prior to the onset of the disease. The release of compounds in the intestine such SCFA’s have many affects and interacts with the gut brain axis, and even affect the neurotransmitters that we release. A higher prevalence of bacteria of this type also increase permeability of the intestinal thus increasing exposure to bacterial endotoxins which wreak havoc on the body. Patients with Parkinson’s disease indicated high levels of Lipopolysaccharides binding in the blood due to its high absorption. Lipopolysaccharides also cause

systematic inflammation by producing cytokines through the toll like receptor pathway. Increase in Enterobacteriaceae and the presence of Lipopolysaccharides has been associated with the presence and the progression of Parkinson's disease (Sarkar 2019). It is clear that diet affects the progression because bacterial organisms compete for resources in whatever environment they reside in. And in the gastrointestinal tract there is competition for resources as well. The bacteria that are produced is based on the products that are available in this microbial ecological environment or in other words that amount of substrate that is present. So if there is a higher amount of fermented carbohydrates for example bacteria such as Prevotella will be more abundant. This is the case because there will be plenty of product as a result of the fermented carbohydrates that were digested to utilize this product as an energy source and carry out all of its necessary cellular activities. Conversely, if more foods that are high in saturated fat such as whole milk and meat is consumed, or high in sugar then bacteria that use these products as substrates for its biological processes such as those belonging to the Firmicutes genera will have a greater presence in the microbial population in the gut. The fact that these patients with Parkinson's disease and Alzheimer's disease had dysbiosis suggests that their microbiome was of incredibly poor status. Poor status of the microbiome indicates that the diet was being consumed played a part in triggering the onset of this disease.

It is believed that microogranisms came into existence about 1.5 billion years ago. They live in a multitude of environments and they serve a multitude of purposes. There are billions of microogranisms that reside in the gastrointestinal tract of humans. This can also be defined as the gut microbiome. Many of the microogranisms residing in our intestines offer many great benefits such as increasing the integrity of the gut lining, producing Vitamins such as Vitamin K that the body does not otherwise produce on its own, and aiding in digestion. But there are also many that impact us negatively such increasing our likelihood of disease. This can create a state of dysbiosis of imbalance of microorganisms within the gut. Many disease have been associated with the state of dysbiosis most notably neurodegenerative diseases. Neurodegenerative diseases have been correlated with dysbiosis

without seeking further explanation but at the root of dysbiosis are a poor diet and poor food choices. What we eat determine our mental status, the bacteria that colonize within our bodies, and our overall health. Neurodegenerative diseases could potentially be avoided if better food choices were made and higher level of awareness was exercised when it comes to diet and wellness, and it is up to us and only us to chose. We can chose health and well being or chose the potential pitfalls of disease.

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