The impact of gut dysbiosis on Parkinson's disease

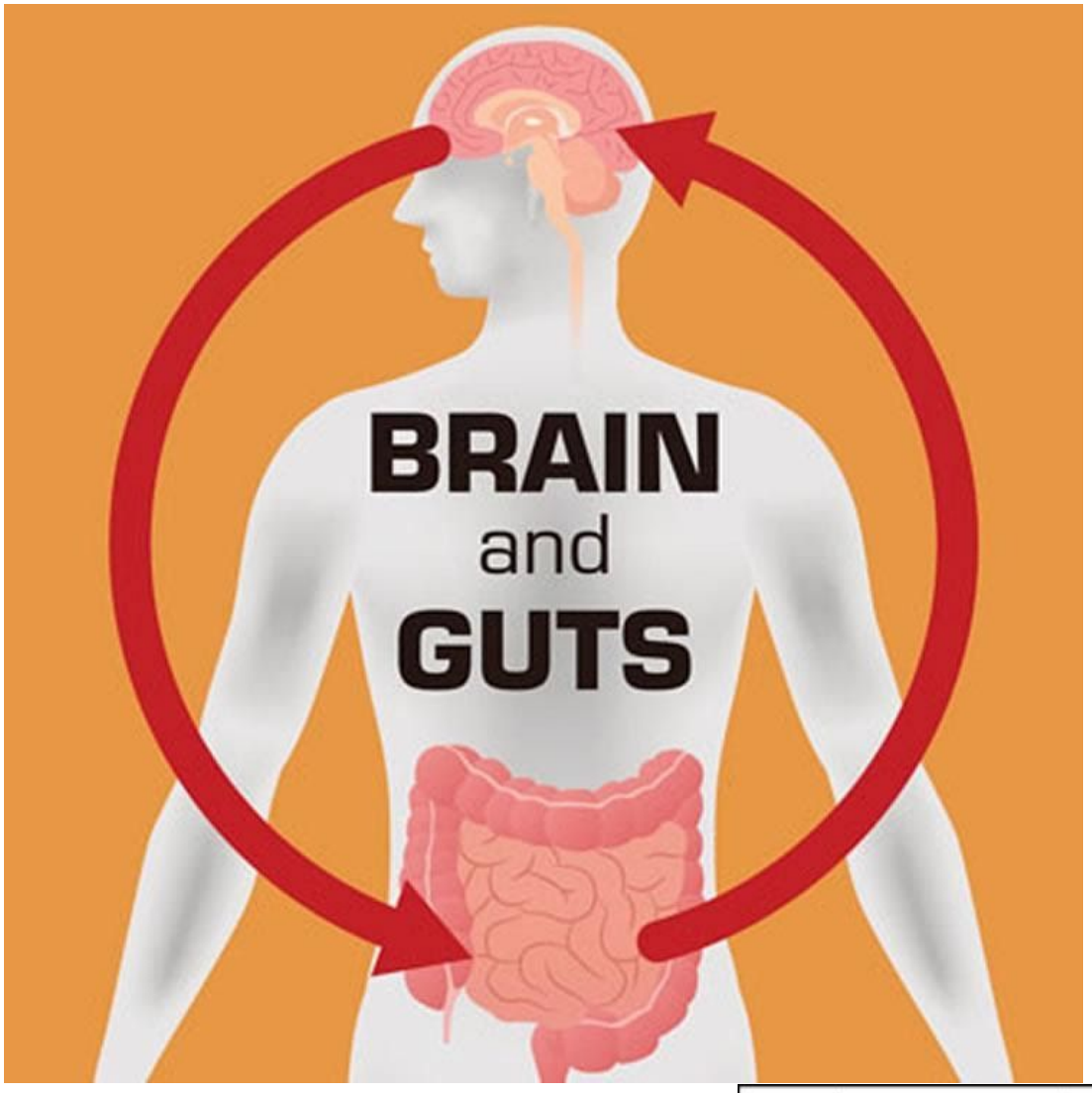

Figure 1 (Neuroscience news, 2017)

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Abstract

Parkinson's disease (PD) is after Alzheimer the neurodegenerative disorder with the highest prevalence in the world. Around the 2 percent of people aged over 65 years has been diagnosed with PD. This disorder has non-/motor symptoms like tremor, weak muscle strength, altered posture but also mood swings and dementia. Unfortunately, there is still no definitive underlying cause found for the development and/or progress of PD. Hence, a lot of research is done in finding this underlying cause to further understand the development of PD. A recently discovered possible cause of PD can be a dysbiosis in the gut microbiome which means an imbalance of gut microorganisms is present. The gut microbiome is always a highly interested topic because the gastrointestinal tract fulfills a lot of live depending functions such as metabolism, signaling and defensive pathways. The origin of dysbiosis in the gut microbiome can be induced due to the factors: α-Synuclein, short fatty chain acids, lipopolyssacharide, microglia and Toll like receptors. These factors are responsible for Lewy body forming through α-synucleinopathy, a higher permeability of the intestinal layer and more inflammatory responses. In order to cure PD patients a considerable amount of researches are performed through analyzing the effects of the therapeutic strategies as fecal transplantation, pro-, pre- and antibiotics on PD patients. All in all, it can be said that dysbiosis in the gut microbiome plays an important role in PD and a lot of effects are already known. Although, further research is necessary to develop effective therapeutic strategies to treat PD patients.

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Chapter 1: Introduction

Parkinson's disease (PD) was first described by the English surgeon James Parkinson who wrote a book named "An Essay on the Shaking Palsy" in the year 1817. In this book James described the newly discovered disease as an illness affecting the nervous system which resulted in tremor in the limbs, weak muscle strength and a differed body posture (Lees, 2017). PD is behind Alzheimer's disease the most neurodegenerative illness with around the 2 percent of all the people aged older than 65 having it (Poewe et al., 2017). A big problem that occurs due to a large amount of PD patients are the immense costs health care systems around the world have to cope with. The underlying cause is still not clear so a decrease in costs is not yet possible. Researchers keep investigating the effects of genetics and environmental factors on PD to better understand the development and/or progress of this disorder. Effective therapeutic strategies to really stop the progress of PD are also not found yet. So further research is necessary for less PD patients and costs.

All in all, it is necessary to conduct more researches to find the underlying cause. In this paper a more recently recognized origin of PD will be discussed namely the dysbiosis in the gut microbiome which is a highly interested topic. The gut microbiome is another term for all microorganisms living in the this tract. Eli Metchnikoff, Nobel prize winner in 1908 through altering the gut microbiome by changing bad bacteria for good bacteria, and sir Alexander Fleming , who discovered penicillin, were the first scientists describing the gut microbiome. In the last 10 years, a lot of research and technologies are used to get a better picture of the gut microbiome because the knowledge about the gut microbiome is important to restore the balance in bacteria populations in the gastrointestinal tract. A normal balance in the gut microbiome is responsible for a healthier life (Cresci et al., 2015).

In PD patients there is a loss of dopamine neurons which is probably through α-Synuclein Lewy body forming (Duffy et al., 2018). Research of Braak et al. resulted in findings linking the start of α-synucleinopathy and the enteric nervous system which is in close contact with the gut microbiome. So this could mean that the gut microbiome could be a potential starting source for PD because α-synucleinopathy through Lewy body forming is a hallmark for PD patients (Braak et al., 2006). Other factors that links PD and the gut microbiome are short fatty chain acids, lipopolyssacharide, microglia and Toll like receptors.

Linking these two subjects together this question is formed "What is the impact of dysbiosis in the gut microbiome on the development of Parkinson's disease?". In order to answer this question, a closer look will be taken on the correlation between Parkinson's disease and the dysbiosis in the gut microbiome through examining: α-Synuclein, short fatty chain acids, lipopolyssacharide, microglia and Toll like receptors. Furthermore, possible effective therapeutic strategies targeting the gut microbiome will be examined. So this paper will answer this question through explaining the development of Parkinson's disease through the examination of differences between a healthy gut and an altered microbiome on this neurodegenerative illness.

Chapter 2: Parkinson's disease

2.1 Location

PD is a neurodegenerative disorder and affects the central nervous system. In the brain PD affects the basal ganglia and in particular the substantia nigra (Calabresi et al., 2006) In addition, the outer layer of the cerebrum, known as cerebral cortex, is thinned. In elderly it is normal that the thickness of the cerebral cortex will decrease in comparison to young aged people (Fjell et al., 2012). However, according to research of Y. Yau et al in 2018 people suffering from Parkinson have a significant decreased thickness compared with a healthy control group (0.028mm vs 0.019mm reduction). Furthermore, it could be seen in three major parts of the cerebral cortex namely the right somatomotorsensory cortex, the left occipital lobe and bilateral frontal lobes. Finally, it is also known that cortical areas anatomically or functionally connected to the starting area in the brain in PD patients have a higher amount of cortical thinning during the first years measured (Yau et al., 2018).

2.2 Causes

The development of Parkinson is rather difficult because the main causes are not clear. The substantia nigra, located in the basal ganglia, is affected by PD through the atrophy of cells producing dopamine. Dopamine is rather important because it functions as messenger between the substantia nigra and other parts in the brain named basal ganglia. A differed balance between neurotransmitters, whereby there is more acetylcholine then dopamine, causes uncontrolled motor patterns PD is characterized for (Calabresi et al., 2006). It is found that Lewy body's, known as a-Synuclein, play a role in this degeneration. So if these Lewy body's are found in the cortex it can cause dementia (Duffy et al., 2018).

Different researches are done about the genetic and environmental factors which accelerate the disease. First of all, aging will definitely increase the chance on developing PD whereby a huge increase is perceptible in persons older than 50. Besides, every gender and ethnicity are susceptible to PD but the incidence rate in men seems to be two times higher than in women (Van den Eenden, 2003). Other notable causes are head injuries, earlier head diseases, contact with pesticides, traffic pollution or using certain medicaments (Dick et al., 2007). Finally, genetic factors play a role as well but in less than 10% it is caused due to familial history. However, most of time PD is induced through sporadic cases (Thomas et al., 2007).

2.3 Symptoms

PD symptoms can be divided into motor and non-motor symptoms. Firstly, the motor symptoms are uncontrollable movements, tremor in limbs, weak muscle strength, an abnormal altered body posture and difficulties in speech. Secondly, the non-motor symptoms are more apathy, sleeping problems, constipation, laziness, mood swings, taste & smell loss, hallucinations, pain in parts of the body and dementia (Sveinbjornsdottir, 2016).

Chapter 3: Gut Microbiome

3.1 Composition

The gut microbiome is defined as the more than trillion microorganisms living in the gastrointestinal tract. These microorganisms consist out of fungi, viruses, bacteria and archaea. The gut microbiome has with 50 percent the highest percentage of organisms in the body. (Sender et al., 2016). The gastrointestinal tract is very important for the uptake of nutrient out of food and needs a lot of organs to achieve this. The food comes in at the starting point which is the mouth and ends at the anus with passing through big organs as the stomach and intestines. The amount of microorganisms differ at each organ due to different pH levels or peristalsis movements. That is why the stomach and small intestine have a rather low amount of microorganisms because a low pH is present and it is a difficult place to colonize through the peristalsis movements. In the last part of the large intestine, the colon, are the most microorganisms of the gut mircrobiome (Clarke et al., 2014).

The development of the gut microbiome all starts when someone is still a fetus but the diversity of the microbiome is then still very low. A higher diversity of microorganisms in the gut microbiome starts to exist during childbirth due to contact with microbiota of the vagina. Therefore, a child born through caesarian section has contact with other bacteria such as Staphylococcus and Acinetobacteria not deriving from the vagina but hospital surfaces or skin contact. In addition, breastfeeding also contributes to more microbiome diversity (Collado et al., 2015). In the first years the newborns microbiome will be comparable with your mother but will change over time because of food and environment factors (Mackie et al., 1999). After the age of 3 the gut microbiome will consist mostly out of anaerobic bacteria with the bacteria Firmicutes and Bacteroidetes as most dominant species (Schloss et al., 2004).

3.2 Function

The metabolism, signaling and defense system of the human body are highly depending on a diverse gut microbiome. First of all, it is necessary that the present microbiota in the gastrointestinal tract can take in the nutrients, digest the digestible food and develop all kind of proteins and fats. In this way the products can help as example with enough energy supply (Gallo et al., 2016) Secondly, the signaling system is also an important function the gut microbiome has. It is in indirect contact with the central nervous system and produces signaling proteins, neurotransmitters, to transmit information all through the body (Scheperjans et al, 2016) Finally, the defense system is the third system depending on the gut microbiome. The pathogens in food entering the human body stumble firstly on the gut microbiota. The defensive system functions through the mucosal layer present in the intestines because of the innate immune system and by the favorable competence to bind supplements of food necessary for metabolism instead of the incoming pathogens (Bull et al, 2014)

Chapter 4: Gut dysbiosis and its effects on Parkinson's disease

If there is imbalance in the gut microbiome it has a negative effect on the human body and thereby on a person's health. The normal so important gastrointestinal tract, now has in some places like the small intestine immense growth of certain bacteria which outcompete smaller bacteria populations. So the gut microbiome does not work as it should be doing. Through all this, different illnesses are possible to develop during this dysbiosis, examples are : obesity, metabolic disorders, irritable bowel and Celiac disease (Carding et al., 2015). Furthermore, this dysbiosis can affect the central nervous system negatively through neuronal death or neuroinflammation and thereby can advance neurodegenerative disorders like Parkinson's and Alzheimer disease (Sun et al., 2018). As can been seen in figure 2, microbial dysbiosis seems to be the starting source of PD.

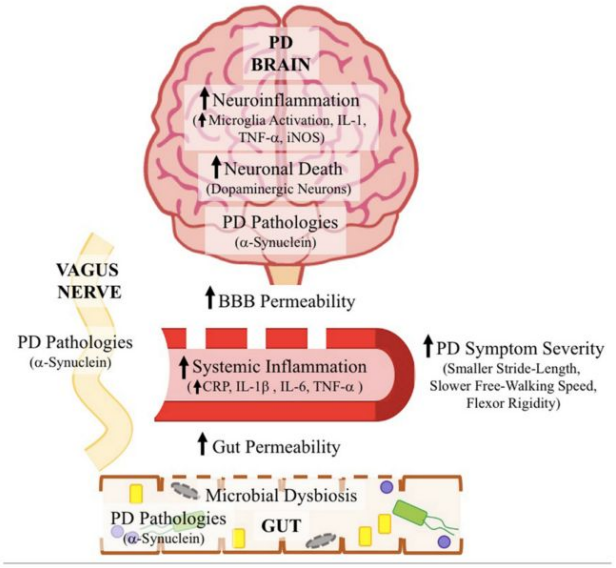

Figure 2: How microbial dysbiosis induces PD in the brain (Gazerani, 2019).

4.1 α-Synuclein

A-Synuclein is protein widely expressed in the central nervous system and in special in the brain.
This protein has two main functions. Firstly, it plays a key role in releasing certain neurotransmitters. Secondly, it affects the amount of dopaminergic neurons in the substantia nigra (Calo et al., 2016). Accumulation of protein α-Synuclein, α-synucleinopathy, in the substantia nigra and nervus vagus plays a part in different neurodegenerative disorders like Parkinson's and Alzheimer disease. The nervus vagus play an important role in digestion and motor control in organs in the gastrointestinal tract (Svensson et al., 2015). Mutations in genes for synthesizing α-Synuclein and Lewy bodies holding α-Synuclein are characteristics for PD (Burre et al., 2018).

In 2016 Sampson et al. investigated the correlation between motor deficits and gut microbiota. In this research there were two groups of mice that overly expressed α-Synuclein; the first group got fecal transplants from subjects with PD and the second group got fecal transplant from healthy subjects. The first group showed more severe pathology in motor assignments then the second group

(Sampson et al., 2016). This is a sign that an imbalance in gut microbiome present in PD patients can cause motor deficits.
Another research examined if α-Synuclein, which derives from a PD brain, injected in mice's enteric nervous system, will pass the nervus vagus on his way to the central nervous system. This result means that due to dysbiosis a protein crosses the gastrointestinal tract to the central nervous system and causing there damage in dopamine producing neurons (Holmqvist et al., 2014). Besides, there are even researches done that when a vagotomy is performed then there is a existing decrease in developing PD (Svensson et al., 2015).

4.2 Short fatty chain acids

Short fatty chain acids (SCFAs) are products of fibers which can't be digested by the gastrointestinal tract or they can derive from amino acids. The formal components are butyrate, acetate and propionate. SFCAs have multiple functions affecting the human metabolism and signaling. Some functions are; to create hunger feeling in the brain, to control insuline the pancreas and to provide enough sources for the muscles (Flint et al., 2015; Macfarlance et al., 2003) So SCFAs are necessary for a healthy gut microbiome and instability in SCFAs sources can cause have a diverse range of effects; the epithelial barrier will malfunction, metabolism disorders can appear and its anti-inflammatory functions on the mucosal layer deteriorate (Venegas et al., 2019).

In 2016 researcher Unger et al. examined if SCFAs and gut microbiome are altered between PD patients. Fecal samples were taken of two groups within the same age group divided into 34 healthy subjects and 34 subjects with PD. Afterwards, a link between the presence of certain bacteria phyla and components of SCFAs were investigated. The result was that the bacteria phyla Bacteroidetes and Prevotellaceae were reduced and the amount of Enterobacteriaceae was increased in the PD subjects. SFCA concentrations of butyrate, acetate and propionate were all decreased in the PD subjects. So if there is a dysbiosis in the gut microbiome then SCFAs are decreased and SCFAs are normally very important for a healthy metabolism (Unger et al., 2016). A directly causal link cannot be made yet but further research is necessary.

4.3 Lipopolyssacharide

Lipopolyssacharide (LPS) is a molecule which is a major cell wall component of gram negative bacteria. Lipopolyssacharide binding protein (LBP), which is synthesized in the liver, is necessary to bind to LPS to initiate an immune response. LPS normally goes through layers of the intestines if it is absorbed (Trent et al., 2009).

Researcher S. Hasewega et al. did research to lipopolyssacharide levels in the intestines of PD patients. Two groups were composed for fecal sampling: 52 subjects with PD and 36 healthy subjects. Fecal samples of PD subjects showed a decrease in bacteria count. Examples for decreased bacteria groups are C. coccoides and Bacteroides fragilis. Thereby there was a significant decrease in LBP but not in components of the intestinal mucosa layer. So this research concluded that the intestinal wall for LPS was increased but the intestinal layer was maintained. An altered gut microbiome can cause a higher intestinal permeability and vice verse a higher intestinal permeability can cause an altered gut microbiome (Hasewega et al., 2015). All in all, this has a negative effect on the further advancement of PD and even can have an effect on the development of PD. However, that cannot be concluded yet.

4.4 Microglia

In the central nervous system around 15% percent of the neuroglia cells are microglia. These microglia are the first to develop in the yolk sac and are one of the most present neuroglia cells. microglia are highly ramified with small cell soma, with their protrusion they watch over the brain

parenchyma for homeostatic disturbances and cell injury (Nayak et al., 2016). Microglia transforms from a small highly branched cell to a round less branched cell when activated (Erny et al., 2015). In the brain microglia fulfill diverse functions like creating inflammatory responses, contributing in signaling pathways and influencing the development of the CNS. The functions concerning homeostasis is all due to the capability of transforming easily. Imbalance in microglia are implicated in neurodegenerative disorders like Parkinson or Alzheimer disease (Nayak et al., 2016). Figure 3 shows that the activation of microglia acts as regulator in DA neuron loss in the substantia nigra.

In 2016 Sampson et al. did research after the microglia state in the substantia nigra and caudoputamen. They compared germ free (GF) to mice with specific pathogen free (SPF) mice and both groups had were expressing α-Synuclein in high amounts. The microglia in GF mice had longer and a higher amount of branches compared to the SPF mice which had larger rounder cell bodies with shorter branches. This result signifies that there are less activated or more matured cells in the SPF, which also means that the gut microbiota has an effect on the central nervous system. Thereby, they did a comparison between the two mouse groups if there is a difference in inflammatory products. The GF mice had decreased amounts of cytokines TNF-a and IL-6 compared to the other group. Normally, in activated state microglia have more inflammatory products. Besides, as was mentioned earlier the microglia activation state was decreased in the GF mice, thus also less inflammatory responses. This means a microbiome is necessary for microglia maturation. (Sampson et al., 2016). All in all, there are indications that a dysbiosis in the gut microbiome the development or progress of PD due to a dysbiosis in the gut microbiome inducing more activated microglia which can have α-synucleinopathy and inflammatory responses in the brain as consequence.

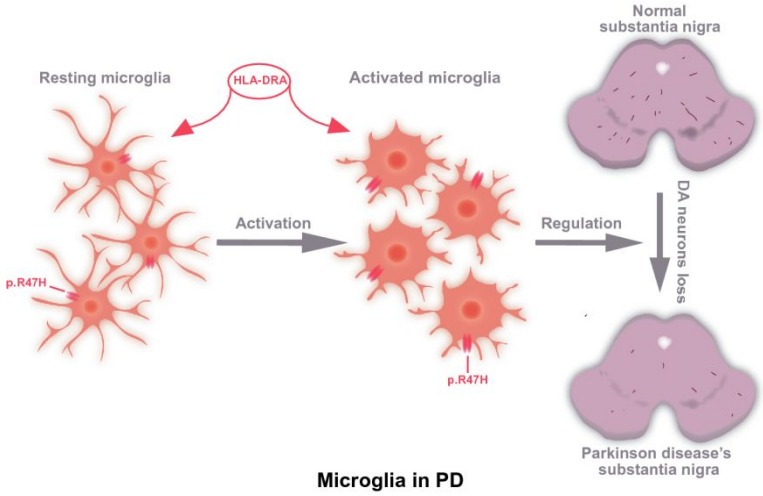

Figure 3: The activation of microglia is important for the regulation of DA neurons loss in the substantia nigra which is an hallmark for PD. (Verkhratsky et al., 2019)

4.5 Toll-like receptors

Toll-like receptors (TLR's) functions as a defensive system against viral and bacterial infections and can be found in diverse human tissues and neuroglia cells. Pathogen-associated molecular patterns (PAMPs) are identified by patter-recognition receptors of the TLR's and set the innate immune system in motion to remove infections through cytokines or lymphocytes (Lim et al., 2013).

A dysbiosis in the gut microbiome and a higher permeability of the intestinal layer will lead to a higher immune response due to more PAMPs crossing the intestinal layer. TLR's are more active to indentify these PAMPs of these growing amount of microorganisms. Fellner et al. analyzed the effects of TLR's on microglia and α-Synuclein. In this research two groups of mice were divided into

a group overly expressing TLR4 (TLR4+) and another group not expressing TLR4 (TLR-). Besides, both groups were given an overly expressing α-Synuclein gen to analyze the α-synucleinopathy. The TLR4+ group resulted in more microglia activation and inflammatory responses in comparison to the TLR- group which had less microglia activation and also less inflammatory responses (Fellner et al., 2013). So increased activation of TLR4 due to gut dysbiosis causes α-synucleinopathy and decreased dopamine levels in the substantia nigra which are characteristics of PD (Stefanova et al., 2011).

Chapter 5: Therapeutic strategies

At the moment there is not yet a curative treatment for PD but L-dopa or dopamine agonist work relatively well against α-synucleinopathy, Lewy bodies and non-/motor symptoms (Dorszewska, 2014). Diverse therapeutic strategies are examined by researchers to treat this big impact neurodegenerative disorder analyzing probiotics, prebiotics, antibiotics and fecal transportation on the development and symptoms of PD.

5.1 Probiotics

The gastrointestinal tract can be treated by the use of probiotics. These are “live microorganisms that can ameliorate a person’s health. Probiotics can be added in food, drugs or supplements. The cell surface of the mircroorganisms are important because they can have contact with the intestinal layer, TLR’s and mucosa layer (Hill et al.,2014) The normally used probiotics are the Lactobacillus, Bifidobacterium and Saccharomyces from these bacteria it is known that they decrease the permeability for microbes, benefit the immune system and decelerate bacteria growth (Derrien et al., 2015). Diverse non-motor symptoms such as depression, emotions and fear attacks caused by PD are decreased through the ingesting of probiotics with the bacteria lactobacillus and Bifidobacterium. A side note is that the vagus nervus requires to be undamaged because this is important for the signaling pathway between the gut and the brain. Further research on PD patients is necessary to see a direct correlation between probiotics and the amelioration of PD patients (Bravo et al., 2011; Sarkhar et al.,2016).

5.2 Prebiotics

Non fermentable food that promotes the gut microbiome in becoming healthier are called prebiotics. The most common examples are diverse polysaccharides, fibers and SCFAs. Prebiotics can decrease pH levels in the gut and thereby obstruct the growth of damaging microbes. In addition, the peristaltic movements and immune system are improved as due to fibers derived from food (Perez-Pardo et al., 2017; Gibson et al., 2017). Research also showed that some polysaccharides can boost the preservation and function of neurons in the central nervous system (H.E. Rasmussen et al., 2013; H.E. Savignac et al., 2014) Thus prebiotics seems to increase the gastrointestinal tracts immune response, peristaltic movements and protection of the neurons but this hasn’t be tried on PD patients yet.

5.3 Antibiotics

The intention of antibiotics is to stop the growth of bacteria or to demolish them. Currently, there is still a lot of uncertainty about the right treatment to make PD patients healthier with antibiotics. If there is a focus on improving the gut microbiome then Rifaximin could be the antibiotic needed. Rifaximin is used for the treatment of gastroparesis, constipation and small intestinal bacterial overgrowth (SIBO). This antibiotic can productive against the gram-positive and –negative bacteria causing dysbiosis in the gut microbiome through their SIBO (Barboza et al., 2015) Recently, another antibiotic named minocyline is already tested in PD patients and is now in further trials. Minocyline

re-established the balance between bacteria populations which stimulates the preservation of neurons (Parashar et al., 2017).

5.4 Fecal transplantation

The transplantation of fecal components from healthy persons to sick person is called fecal microbiota transplantation (FMT). This process can restore the imbalance in the gut microbiome and can heal someone's health (Choi et al., 2016). The infection caused through Clostridium difficile, which is a infectious bacteria in the gut, could be solved due to FMT (Rohlke et al., 2012). In figure 4 can be seen that a gut with C. difficile infection with microbial diversity gets a FMT from a healthy donor which results in a gut with increased microbial diversity. Thereby trials in alleviating the irritable bowel syndrome (IBS) resulted in clinical evidence that it decreases symptoms but was not yet statically proven. However, this could be potential for further research between the correlation of FMT and IBS (Halkjær et al., 2018) Another disease tested, which is comparable to PD, is multiple sclerosis (MS) and FMT to MS persons also resulted in less symptoms (Borody et al., 2011). All in all, FMT seems to restore the dysbiosis in the gut which causes diverse disorders. Nevertheless, direct evidence that PD patients can benefit from FMT is not yet established. Maybe the combination with probiotics can help but further research is necessary.

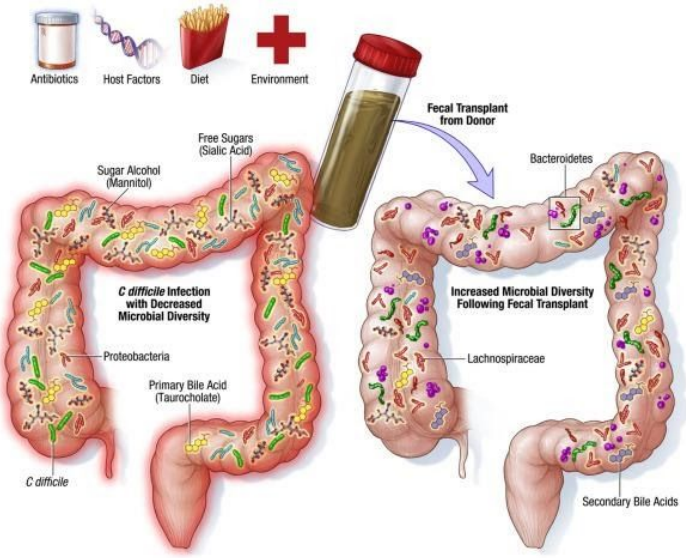

Figure 4: fecal transplantation from a donor given to a donor with a decreased microbial diversity which results in increased microbial diversity (Kelly et al., 2015).

Chapter 6: Conclusion/discussion

Parkinson's disease is a neurodegenerative disorder which affects a big amount of the world's population. It is known that the decrease of dopaminergic neurons in the substantia nigra induces PD because dopamine, which is a necessary neurotransmitter, cannot signal in the basal ganglia anymore. Motor symptoms of PD like tremor, weak muscle strength and altered body posture will develop due to the imbalance between acetylcholine and dopamine levels. Besides, there is a cortical thinning of the cerebral cortex that has a lot of functions including speech, sight and memory. The exact source responsible for these processes is not known but it has something to do with age because relatively 2% of the world population older than the age of 65 has PD. Moreover, men are also more susceptible than women and genetic factors are very important as well. Despite different researches done after the development and process of PD, there is still no significant evidence of the underlying cause and efficient therapeutics treatment found yet.

A hot topic concerning people's overall health is dysbiosis in the gut microbiome for the reason that a healthy lifestyle is very important for a healthy gastrointestinal tract. Furthermore, research of Braak et al., resulted in indications that α-Synuclein Lewy body forming starts in the enteric nervous system which is in close contact with the gut microbiome. So the gut microbiome could potential be the starting source for PD. A dysbiosis in the gut microbiome imbalances metabolism, signaling and defense systems of the human body which has an big impact on gastrointestinal tract and thereby on a person's health.

The dysbiosis of the gut microbiome might contribute to the development or progress of PD through diverse factors. Firstly, accumulation of protein α-Synuclein and Lewy body forming is a hallmark for PD and the source can be the gut microbiome. Sampson et al. performed fecal transplantation of a mice with PD to a healthy donor mice whereby a correlation between α-synucleinopathy and gut dysbiosis was found that induced motor deficits. The vagus nervus appeared important in the route α-Synuclein takes on its way to the CNS. Secondly, a reduction in SCFAs especially butyrate affects the metabolism in the human body. Unger et al. found a link between a reduction in SCFAs and PD but further research is necessary for significant evidence. Thirdly, a higher permeability of the intestinal layer for LPS through the decrease of LPB but the maintenance of the mucosa layer is very harmful for the reason that pathogens can pass the intestinal layer. As mentioned earlier there is pathway between the gut and the brain if permeability is higher in the gut then the pathogens can enter through this pathway the brain and do damage over there. Fourthly, dysbiosis in the gut activates more microglia with the result that an increase of inflammatory responses and α-synucleinopathy is noticed in the brain. Lastly, the increasing pathogens demand for higher

inflammatory responses. The TLRs respond to this inflammatory responses by increasing especially TLR4 which senses the PAMPs.

L-dopa works relatively well but real effective therapeutic treatments which decrease α-synucleinopathy, Lewy bodies and non-/motor symptoms is yet to be found. However, a lot of research is done to find therapeutic strategies for curing PD patients. Pro-/pre- and antibiotics seem to have a positive effect on decreasing symptoms but fecal transplantation of healthy donors into PD patients as well.

This is just the beginning in mapping the correlation between dysbiosis in the gut microbiome and PD. There are still a lot of ongoing researches on finding an effective therapeutic strategy. So are there researches done after effects of FMT on IBS and a combination of FMT with probiotics on PD patients. Maybe within a couple of years an effective therapeutic strategy is found and a considerable reduction in this age related neurodegenerative disorder is observed.

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