Patho-mechanisms in the gut microbiota implicated in the immunological neuroendocrine gut-brain pathway

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***Abstract*- Human gastrointestinal tract consists of Bacteria, virus, fungi, protozoa, and archaea that make up the microbiota and maintains a mutual relationship with the host. Disruption of intestinal homeostasis may have a consequence on the gastrointestinal tract that affects the performance of some organs, one such organ is brain. The gut microbiota's importance in health and illness is becoming more widely understood. The microbiota of GI system connects the brain and the gastrointestinal system in a bidirectional mechanism with a mechanism known as Gut- brain axis. Our stomach bacteria can connect with our brain through a variety of processes that are still being researched. The vagus nerve, immune mediators, and microbial metabolites, for example, all influence central processes such as neurotransmission and behaviour. Changes in gut microbiota composition have been associated to IBD, autoimmune disease, and other neuropsychiatric diseases such as autism, schizophrenia, and depression. Disruption of the gut microbiota composition has been linked to IBD, autoimmune diseases, and a number of neuropsychiatric disorders such as autism, anxiety, and depression. We will look at how the gut-brain axis communicates via immune neuroendocrine pathways, as well as how intestinal microorganisms interact with host neuroendocrine system elements to modify stress, appetite, and other behaviors in this overview. A variety of circumstances can disrupt the GIT microbiome's homeostatic homeostasis, leading to dysbiotic microbiome configuration. Irritable bowel diseases (IBD), malnourishment, metabolic disturbances, asthmatic, and neurodegenerative diseases have all been associated with GIT microbiome taxonomic and/or functional dysbiosis. The current state of knowledge of microbial ecology homeostasis and dysbiosis in the human gut, as well as health complications linked to microbiome dysbiosis.**

Keywords: **Gut microbiome, factors, Dysbiosis, Diseases, Neurotransmitter gut-brain signaling, Neuro-endocrine gut-brain signaling, immune gut-brain signaling**

INTRODUCTION

The microbiome is a collective genome of microorganisms that live within or on the human body and thus are located in a specific habitat. The human microbiota, for example, is made up of bacteria, viruses, and fungus that live on the skin's surface and deep layers. Bacteria, viruses, and fungi all work together to form the human microbiota, with bacteria playing the most important role. Several gut microbiomes can be found throughout the body in various locations (Bull & Plummer, et al., 2014). The human body has around 30 trillion human cells, while our microbiome contains approximately 39 trillion microbial cells in total. Due to their small size, human cells make up about 43 percent of total cells within human body; these organisms make for only about one-three percent of our body weight, and we have around 2-20 million microbial genes and 20,000 human genes, but humans have only 1% of the total number of coding genes compared to microbial genes. Within the digestive system, there are diverse gut flora, or microbiomes, containing their genetic material. The gut microbiota seems to be significant in both food and mineral absorption, along with digestion, enzyme synthesis, vitamin and amino acid synthesis, and short-chain fatty acid biosynthesis (SCFAS) (Valdes, Walter, Segal, & Spector,et al., 2018)

These gastrointestinal microbiotas provide a critical capacity for the fermentation of non-digestible materials like food, fibers, and endogenous intestinal mucous are some of such substances. This fermentation aids in the growth of professional micro-organisms that creates SCFAS and gases. SCFAs are six-carbon fatty acids, the majority among which would be acetate, propionate, and butyrate. SCFAs are the most prevalent compounds generated from microbiota in the gut lumen. and They benefit from their great capacity to decrease tissue. and mucus layer damages, intestinal inflammation, and They stimulate insulin sensitivity through activating G-protein coupled receptors (GPCRs) by binding GPR41 and GPR43, which are important for gastrointestinal motility, and satiety, and also enhance insulin sensitivity, or by stimulating their inhibitory effects on histone deacetylases (HDACS), altering gene expression. Acetate, propionate, and butyrate, among the primary metabolites generated, are vital for gut health because they supply energy to epithelial cells, improve epithelial barrier integrity, and offer immunomodulation and protection against dangerous bacteria. When the immune cell penetrates the pathogen, the microbiota serves as a protector and grows the immune cell, giving the message to the immune cell (Belizario, J., Napolitano, M., et al., 2015)

Some examples that make the Microbiome

Bacteria	Fungi	Viruses	Archaea
Firmicutes	Candida	bacteriophages	methanogens

ORIGIN OF GUT MICROBIOME

Colonization of the gut through the human microbiome adapted by a little one with their first big dose of microbiota,duringthe childbirth as it travels through the start canal, that develops excess during breast feeding. When this exposure to micro-organisms occurs in advance than beginning, will lead to death of a fetus. Because this exposure causes difficulty in breath to the fetus as the respiration is provided entirely from mother's blood as a site of oxygen and vitamins, thus a new infant does not receive any uncertainty protected with micro-organism, that gives a brand-new microbiome. The maternal oral microbiome has been considered as the best to provide number one micro- organism that colonize infants (Bäckhed et al., 2015). There are different kinds of microbiome like normal microbiota that comes quicker and are eliminated soon after a half a day, week, or month, whereas, an exceptional microbiome that is obtained from environment and lives up to for a few years of age. In youngsters, the manner of delivery has a substantial impact on the intestinal flora in such a way that when a baby born vaginally, the mother's gut and vaginal microbiota colonize the baby first and when the child is added through Caesarean segment, it is much exposed to the pores, skin and health center that surrounds the microbiota first (Yatsunenko et al., 2012).

MODE OF DELIVERY THAT ALSO AFFECTS MICROBIOME

Delivery through vagina

Bifidobacterium, Parabacteroides, and certain Bacteroides are present inside the gut for children born via vaginal birth. A C-section baby's microbiome, on the other hand, contains Enterobacter, Haemophilus, and Streptococcus. Vaginal birth to a newborn expose infant to the mother's flora early on, which aids the development and diversity of the gut microbiome. Vaginal transfer allows the mother's microorganisms as well as bacteria from the environment to enter into the newborn infant's intestine as the child's first extensive contact to microorganisms comes from the mother's germs. The child's microbiome mimics that of the mother for around 6 months to a year, until the child's microbiome begins to evolve and mature. The bacteria of the Escherichia genus are attracted to the placenta, which does not differ for vaginal starting and C-segment, but may differ slightly in between women (Grölund, Lehtonen, Eerola, & Kero,et al.,1999) .

Section of the cesarean

Cesarean delivery is a medical technique in which a pregnant woman's abdomen is sliced open to extract the baby (CD). This procedure might be carried out in an emergency or on purpose, because the infant will not be able to move through the delivery canal, thus, there may be no first exposure to the mother's vaginal plant life, and the child's gut microbiota may not closely reflect her. Instead, the share of microorganisms from the environment, including those already existing in the room and the room itself, has increased. These distinctions have been suggested as possible causes of C-section births. Despite the fact that a mother's germs are often better at adapting to the child's system than other organisms, the lack of vertical transmission of bacteria from the mother to the child means that the intestines are colonized by a greater range and variety of bacteria from environment. Although the diversity of bacteria in an intestine of a kid born via C-section is initially higher, the delay in colonization reduces diversity, weakening the microbiome and its response to illnesses (Ferretti et al., 2018).

GUT MICROBIOME ROLE

Fiber metabolism, immunological guidance, and communication with the central nervous system are all roles that the gut microbiota can perform.

Digestion of foods

Enzymes produced by the microbiome aid in the digestion of carbohydrates. Nutrients must flow through the gut wall into the bloodstream after being broken down in the intestine, and they also help to digest and absorb food. The beneficial flora aids this process by allowing vitamins and minerals to travel to various tissues in the body. Lactobacteria is a type of beneficial bacteria that occurs in the small intestine. They facilitate in the digestion of dairy products and lactose, a sugar found in milk. Bifidobacteria, the other primary species of beneficial bacteria, reside in the colon. They make B vitamins, regulate bowel movements, and manufacture antibiotics to combat dangerous bacteria, among other things. Some foods include helpful flora and natural enzymes that aid in the digestion of meals in our intestines. However, many processed foods lack beneficial bacteria and enzymes.(Snelson & Coughlan,et al., 2019)

Metabolism of fiber

METABOLITES	GUT MICROBES	FUNTIONS	REFERENCE
Short chain fatty acids such as Valerate, Isovalerate, Acetate, Butyrate, Isobutyrate, Propionate, 2 methylpropionate, and hexanoate	Bacteroidetes, Firmicutes, Campylobacterjejuni, Staphylococcusaureus, Bifidobacteriumsp, Coprococcus, Clostridium, Roseburia, Faecalibacterium	• Host metabolic pathway control mediated by cell signaling. • Immunomodulation. • Energy homeostasis is maintained. • Glucose tolerance and insulin sensitivity have improved. • control of intestinal permeability	Y, Wang Y, Wang P, Huang Y, Wang F et al., 2018

Vitamins such as Vitamin B2, B6, B9, menadione, and vitamin K2	Gram positive bacteria, S.aureus, S. typhimurium, L. monocytogenes, Lactic acid bacteria, and Bifidobacterium,	• Participation in redox cycle. • DNA replication, methylation and repair • Cofactor of enzymatic reactions • Production of vitamins, nucleotides, and amino acids. • Defense against pathogens • Modulation of biofilm formation immunomodulation	Araki S, Suzuki M, Fujimoto M, Kimura M. et al.,1995
The metabolites of choline such as choline, methylamine, dimethylamine, betaine, dimethyl glycine, trimethylamine, and trimethylamine N-oxide,	Prausnitzii, Actinobacteria, Firmicutes, Bifidobacterium, Faecalibacterium,Proteobacteria,	• Biosynthesis phospholipids precursor • Modulation of lipid metabolism • Maintenance of glucosehomeostasis • Regulation of cell membrane function • Neurotransmission	Dawson PA, Karpen SJ.et al., 2015
Metabolites of bile acids (cholic acid, deoxycholic acid, taurocholic acid, lithocholic acid, glycocholic acid, ursodeoxycholic acid)	Enterobacter, Bifidobacterium, Bacteroides, Clostridium, Lactobacillus	• Control of the intestinal barrier. • Turn on nuclear receptors and cell Signaling pathways in the host. • Have antibacterial properties. • Controlling lipid absorption.	Pavlidis P, Powell N, Vincent RP, et al., 2015
Fatty acids that have been conjugated (sphingomyelin, acylglycerol, phosphatidylcholine, cholesterol, phosphoethanolamine)	Enterobacteria Clostridium, Citrobacter, Roseburia, Lactobacillus, Klebsiella, Bifidobacterium	• Controlling intestinal permeability. • Changes in cell size, weight, and fat content. • Bile acid and sterol production	Roche HM & Kelleher D et al., 2001

GUT MICROBIOME PLAY PROTECTIVE ROLE

The gastrointestinal tract connects the bacteria in the gut to the immune function in the stomach. The initial layer of the intestine immune system, involving gut-associated lymphoid as well as Peyer's patches, develops as a result of fundamental entanglement with gut commensals. The established immunological barrier and a collection of immune mechanisms prevent commensal bacteria from coming into direct contact with epithelial cells. The germs are quickly detected and killed by a second layer of protection that does not penetrate into the intestinal tissue. The 3rd type of immune system response was limited to the mucous and did not stimulate the systemic immune system. The innate immunological barrier is made up of mucous, antimicrobial peptides, as well as secretory IgA (Yoon, Lee, & Yoon, et al., 2014)

Microbiomes help to boost our immune system

The immune system defends the gastrointestinal tract against harmful pathogenic germs while allowing beneficial bacteria to colonize. These microorganisms help in supporting the gut microbiome for the correct development and operation for the immune system. Despite the fact is the specific mechanism is unknown, the SCFA butyrate appears to play a role in the formation (Rooks, 2016). Butyrate is created by the fermentation of fiber bacteria in the large intestine and aids in lining the intestine for the preservation, which devoid the digestive tract with the rest of the human body. Pathogens are unable to penetrate the immune system as a result of this.

According to new research, butyrate improves resistance by serving as a shift for the production of critical immune cells such macrophages and regulatory T cells. These cells keep the immune system from fighting microorganisms in the colon that are harmless or even beneficial(Million et al., 2018). According to scientists, both immune system as well as the gut microbiota are involved in establishing and maintaining gut homeostasis. These relationships can be established by researchers in mice studies. According to researchers studies, microbial imbalances can predispose people to immune-related disorders such as Inflammatory bowel disease and type 1 diabetes (Becker, Neurath, & Wirtz, et al., 2015).

FACTORS THAT AFFECT THE GUT MICROBIOTA

Genetics

The abundance of specific bacteria that establish throughout the gastrointestinal microbiota is determined by the host's genetic composition. which has an impact on human metabolism and, ultimately, health. microbial communities have more comparable members of the family than unrelated individualsand monozygotic twins had more similar gut microbiotas than dizygotic twins.Even though the fact that certain immune system genes have been linked to inflammatory bowel disease, no genomic sequence research has been carried out to identify the genes expression patterns that influence the structure of intestinal microbiota (Thompson-Chagoyán, Maldonado, & Gil, et al., 2005).

Diet

Diet can have a substantial impact even over short periods of time. The gut bacteria ferments amino acids after eating a western diet, as a result, short-chain fatty acids are produced as an energy source, along with dangerous chemicals. This is inhibited by a vegetarian diet, which promotes glucose fermentation as the microbiota's primary role. A non-vegetarian (western) diet has also been correlated to an increase in Bacteroides and a reduction in firmicutes (Cresci & Bawden, et al., 2015). The zinc-deficient diet produces a decrease in gut microbial diversity in hens, which is associated to reduced SCFA synthesis, according to a recent study (Reed et al., 2015).

Sweeteners made from artificial sources

Specific foods and dietary patterns can all affect the prevalence of different types of bacteria in the gut, which can have a negative impact on health. High-intensity sweeteners are often used as sugar substitutes since they are several times sweeter than sugar and have fewer calories. Despite the fact that these sugar substitutes are "generally recognized as safe" by regulatory bodies, animal research have indicated that they may have deleterious effects on the gut microbiome (Nettleton, Reimer, & Shearer, et al., 2016).

Stress

The complete response of an organism to environmental demands or pressures is characterized as stress. Stress adds to disease and disability susceptibility, posing a significant economic cost and physical stressors both stimulate the functions of hypothalamic-pituitary-adrenal (HPA) axis. These initiates cascades of hormonal reactions, such as the secretion of corticotrophin-releasing hormone, this also promotes the synthesis of glucocorticoids (cortisol) in the adrenal cortex. and induces systemic corticotrophin release (de Oliveira, Burini, & Jeukendrup, et al., 2014).

Exercise—physiological stress

High-intensity exercise causes GI distress since it is a physiological stress (Brock-Unte & Norman, et al., 1988). According to some statistics, 30 percent to 90 percent of long-distance runners have encountered digestive difficulties as a result of their training. Some of the symptoms of intestinal pain, which can fluctuate from minor to severe, include nauseous, vomiting, abdominal angina, and bloody diarrhoea. In contrast to the advantages of regular physical activity, excessive exertion may have a negative impact on intestinal health. Intestinal ischemia can occur as a result of chronic intestinal hypoperfusion caused by high-intensity exercise. As a result, increased intestinal permeability occurs, exposing the gut to endotoxin transmission (Øktedalen, Lunde, Opstad, Aabakken, & Kvernebo, et al., 1992).

Critical illness—physiological stress

As indicated by high-intensity workouts, intestinal hypoperfusion induced by splanchnic circulation redistribution severe enough just to elicit gut ischemia and mucosal destruction is widespread in the critically ill. (Mittal & Coopersmith, et al., 2014). The gut plays an important role in the spread of infectious complications and multiple organ failure syndromes in critically ill patients. A reduced gut immune response, a damaged intestinal epithelium, and defective commensal bacteria metabolic pathways all contribute to this (Shimizu et al., 2011).

Gastric acid suppression is a condition in which the stomach acid is suppressed.

Intestine dysmotility, altered gastrointestinal anatomic characteristics, immunological inadequacies, and hypochlorhydria are all factors increase the risk for bacterial overgrowth in the small intestine. While Helicobacter pylori infection and aging can induce hypochlorhydria, many patients often take medications to reduce their gastric acid secretion in stressful ulceration protection or gastroesophageal reflux disease (Ratuapli et al., 2012)

Medications

Antibiotics are frequently administered treatments that have saved millions of lives by preventing infections; yet, emerging data suggests that antibioticshave a substantial impact on the natural intestinal flora. It has an immediate effect that can persist for a long time.Antibiotics with a broad spectrum of action reduce the number of bacteria in the body, increasing the number of germs available for opportunistic infections while reducing the number of beneficial bacteria (Ge et al., 2017). Broad-spectrum antibiotics, such as clindamycin, have also been demonstrated to have the longest-lasting influence just on gut microbiota composition in newborns and young adults. Neonatal antibiotic exposure can result in microbial dysbiosis. Antibiotics changed the gut microbiota of the hosts without modifying their metabolism, according to a new study. According to studies on experimental mice, Antibiotic therapy influenced secondary bile acid and serotonin metabolism in the colon, resulting in delayed intestinal motility due to microbiota depletion (ge et al., 2017).

Ageing

One potentially fruitful method to the purpose of studying the activities of the gut microbiota in human aging is to collect age-related alterations in the gut microbiota and observe but these changes have any biological implications. Age-related variations in gut microbial community composition and diversity were observed in cross-sectional studies of faeces samples from people of various ages (Claesson et al., 2011). In general, as people get older, their gut microbiota becomes more diverse and unpredictable. However, when biological age is adjusted for chronological age, the total richness of the population decreases. Dysbiotic alterations are transmitted to the host through several regulatory pathways and bioactive substances, that can either delay but rather stimulate pro-inflammatory immune function (Kim & Jazwinski, et al., 2018).

GUT MICROBIOME DIVERSITY IS MAINTAINED AND IMPROVED

Foods high in probiotics

Food having rich is probiotics contains live microbes that gives health benefits. According to Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are "live bacteria that, when taken in adequate amounts, confer health benefits on the host". Because they provide a low pH environment for probiotic bacteria to thrive in

(Anandharaj et al., 2014).Most probiotic bacteria are found in the Lactobacillus and Bifidobacterium genera. The micro-organisms source for probiotics are Lactic acid bacteria (Vrese & Schrezenmeir,et al., 2008).

Brand name	Food product	Stains	Function	References
Aciforce	Freeze-dried product	Lactococcus lactic, Lactobacillus acidophilus, Enterococcus faecium, Bifidobacterium bifidum	Irritable bowel syndrome, cold, lactose intolerance, vaginal infection, gut health, and digestion are all symptoms of irritable bowel syndrome.	(Vrese & Schrezenmeir,et al., 2008)
Actimel	Probiotic yoghurt drink	Lactobacillus casei Immunitas	Colds and flues, diarrhoea, and the immune system	
Proviva	Natural fruit drink and yoghurt	Lactobacillus plantarum	Irritable bowel syndrome, inflammation, and a cold	
Yakult	Fermented Milk drink	Lactobacillus casei Shirota	Assist the immunological and digestive systems	(Anandharaj et al., 2014
Rela	Yoghurt, cultured milk and juice	Lactobacillus reuteri	Antibiotic-induced diarrhoea and immune system support	
Activia	Creamy yoghurt	Bifidus Actiregularis	Diarrhea, gastrointestinal disorder, immunological system, and weight loss are all symptoms of a weakened immune system.	

Foods that is high in prebiotics

There are different kinds of plant fibre that contain the good bacteria in the gut are called as prebiotics. Foods like natural oats and Jerusalem artichoke andingredients like barley, apples, leeks, bananas, asparagus, flaxseeds,onions, wheat bran,garlic, and contain prebiotics. Non-digestible carbohydrates, non-digestible oligosaccharides, and so on (Macfarlane, Steed, & Macfarlane, et al., 2008).An effective prebiotic should have been resistant to the effects of stomach acids, bile salts, and certain other hydrolyzing enzymes in the gut, no longer be absorbed into the better digestive tract, and easier to digest by the healthy intestinal microbes (kuo et al., 2013)

Symbiotic

Synbiotics is a term he used to describe a mixture of prebiotics and probiotics (devrese and schrezenmeir et al., 2008).Thus, "synbiotics" positively affect the host by increasing survival and selectively supporting the growth and/or stimulation of metabolites from one or a restricted amount of strength and conditioning microorganisms in the gastrointestinal system. Synbiotics have a few of the many health benefits, including increased gut microbiota balance, enhanced liver health in patients with cirrhosis, the development of immune-modulating capability, the prevention of bacterial proliferation, and a reduction in nosocomial infections in surgical patients (Zhang et al., 2010)

Starch that is resistant to attack

Normally resistant starch is a type of prebiotic and dietary fiber that "refuses" to be digested. It is digested in the large intestine and incited by gut bacteria as the small intestine refuses to digest it. It has been associated to weight loss, blood sugar management, and digestive health in studies. It can be found in cooled potatoes and cooked, grains and pasta, oats, lentils, and young bananas (Yoon et al., 2014)

Fermented Foods

Lactobacilli, which is the beneficial bacteria involves in breaking down the meals by bacteria and yeast that contributes to the development process. Basic, natural yoghurt, kefir, kimchi, sauerkraut, miso, and tempeh are just a few examples of fermented foods. According to research, eating 138 grammes of fermented kimchi every day for eight weeks modified the gut microbial composition of 24 obese women. Fermented kimchi has been shown to have extremely constructive effects on body fat percentage,blood pressure, fasting glucose levels, and optimal cholesterol levels in various studies (Leeuwendaal, Stanton, O'Toole, & Beresford,et al., 2022)

THE DEVELOPMENT OF DYSBIOSIS IN THE GUT MICROBIOTA GIT DISORDERS

Inflammatory bowel disease (IBD)

Inflammatory bowel disease is a gastrointestinal inflammatory illness. It affects around 3.6 million people globally. Ulcerative Colitis. Crohn's disease and the illnesses, caused by changes in the gut microbiota's interactions with the intestinal immune system (Kostic, Xavier, & Gevers, et al., 2014). Those symptoms are caused by a combine effect of the host, gut flora, and environmental factors. The changes in gut microbial composition, and an increase in facultative anaerobes thus low obligate anaerobic SCFA producers, are typical in IBD patients. One of the most noticeable differences is a considerable reduction in species biodiversity, with fewer species from the two most common phyla in the healthy microbiome firmicutes and bacteroidetes. This includes species

like f. Prausnitzii and roseburia, which assist to enhance anti-inflammatory IL-10 while reducing inflammatory cytokines like IL-12 and IFN-γ Mutations in the nod2 gene make people more susceptible to CD. PRRS, which also include toll-like receptors (TLRs), nod-like receptors (NLRs), and others are essential in innate immune system by recognizing pathogen-associated molecular patterns from a variety of microbial pathogenic (Nagao-Kitamotoet al., 2016).

Irritable bowel syndrome

Irritable bowel syndrome is defined by stomach discomfort, alterations in bowel movements, and an increase in proinflammatory cytokines as just a result of severe and chronic stimulation of a Hypothalamic - pituitary. According to the study, the luminal and mucosa microbiome of irritable bowel syndrome patients alter, and these differences are related to the kind of aggravation, including diarrhea or constipation. Low levels of Lactobacilli and Bifidobacteria in the feces, as well as increased concentrations of facultative anaerobic bacteria like Escherichia coli and increased Firmicutes: Bacteroidetes ratios, all, lead to a loss of microbiome diversity (Jeffery et al., 2012).

AUTOIMMUNE DISORDERS ARE CAUSED BY GUT DYSBIOSIS.

Rheumatoid arthritis

Anti-rheumatoid factor (RF) and anti-citrullinate peptide antibodies are present in Ra, which is a chronic autoimmune disorder characterized by infection and joint pain with varying degrees of systemic involvement (ACPA). Although genetics has a role, other risk factors such as cigarette use and infection are also important. The development of the condition has been connected to weight loss, smoking, and infections (Tobón, Youinou, & Saraux, et al., 2010). The changing microbiota has recently piqued the curiosity of many experts. Many researchers have recently been interested in the change of microbiota. However, a few studies have found that RA patients have distinct gut microbiota signature patterns. Anti-rheumatoid factor (RF) and anti-citrullinate peptide antibodies are present in Ra, which is a chronic autoimmune disorder characterized by infection and joint pain with varying degrees of systemic involvement (ACPA). Although genetics has a role, other risk factors such as cigarette use and infection are also important (Brusca, Abramson, & Scher, et al., 2014).

Multiple sclerosis

These investigations have showed enrichment or depletion of particular bacterial species in contrast to HCS. In industrialized countries, multiple sclerosis (MS), an inflammatory illness of the relevant frightened device, is on the increasing. According to the incidence of MS-associated single nucleotide polymorphisms in genes implicated in cellular immune responses and the efficacy of immune-targeted medical therapy, MS is a T cell-mediated autoimmune disorder. In terms of the pathophysiology of immune-mediated disorders, the relationship amongst the gut microbiota and systemic immunological responses, along with autoimmune reactions, has recently received a lot of interest. Clostridial species from clostridia clusters XIVA and IV, as well as Bacteroidetes, made up the majority of these taxa (de Oliveira, Leite, Higuchi, Gonzaga, & Mariano, er al., 2017).

Diabetes mellitus type 1

Two SCFAs, butyrate and acetate, have also been connected to a connection between type 1 diabetes and the gut flora. Meals thatcontainacetate and butyrate which comes from bacterial fermentation have increased Treg levels expression. Treg cells reduce the inflammatory response in the gut by suppressing effector T cells (Mariño et al., 2017).The energy required for colon cells are given by butyrate. These rich diets will reduce the permeability of intestine through providing sufficient energy in tight junction development. This butyrate is also been demonstrated in helping with insulin resistance treatment, representing the lack of butyrate-producing bacteria in the gut that may raise the risk of type 2 diabetes. Colorectal cancer risk is reduced by butyrate-rich diets, according to research (Säemann et al., 2000).

Metabolic syndrome and Obesity

The gut microbiota has already been associated with metabolic syndrome and obesity because of its importance in the digesting process. The Western pattern diet appears often to nurture as well as prolong irregularities throughout the gut flora, altering the amount of energy taken from food and the amount of energy utilized (Boulangé, Neves, Chilloux, Nicholson, & Dumas, et al., 2016). A healthy gut flora needs fiber and other complex carbohydrates to thrive, and changes in intestinal bacteria in response to a Western-style diet dramatically increase the amount of energy produced by that the gut bacteria, which might also lead to obesity and metabolic syndrome. (Schneiderhan, Master-Hunter, & Locke, et al., 2016). A complicated interplay between host nutrition, genetics, and microbiome compositional changes has been revealed in studies on the link between gut microorganisms, obesity, insulin resistance, and metabolic syndrome. Several studies have discovered that a prolonged inflammatory process caused by the translocation of gut bacterial LPS into the blood leads to a silent metabolic endotoxemia, which leads to obesity-related diseases (Mazidi, Rezaie, Kengne, Mobarhan, & Ferns, et al., 2016).

Disorders on the Autism Spectrum

Abnormal communication and social behaviours are hallmarks of ASDs, which occur during early childhood neurodevelopment. The development of disease is aided by gut disorders or a history of gastrointestinal disturbances such as infection and anti- or pro-biotic consumption in early life. GI symptoms and dietary issues are common, and they are usually proportional to the severity of an autistic spectrum disorder (ASD).Alterations in gut microbiota and oxidative stress have also been proposed as etiologies, in addition to genetics and environmental factors. Multiple studies have also linked ASD to higher quantities of Ruminococcus and Bacteroides, along with relatively low levels of firmicutes. In the faeces of children with ASD, Short-chain fatty acids (SCFA), acetic acid, propionic acid, and butyric acid levels are low, indicating problems in the gut flora. (Martin & Mayer, et al., 2017).

Depression & Anxiety

The etiology of depression and anxiety-like behavior has been connected to the gut microbiome. Depressive symptoms are associated with dysfunctional HPA activation in stress response. (Peirce & Alviña, et al., 2019). In germ-free mice, the HPA stress

response is hyperactive, although Bifidobacterium infants are capable of counteracting this hyperactivity. When stress is applied to GF mice, plasma ACTH and corticosterone levels are greater than in SPF mice. Increased production of brain-derived neurotrophic factor (BDNF) and lower serotonin 1A receptor levels in the hippocampus were similarly found to be associated with anxiolytic behaviour in GF mice. Anxiety and depression are common consequences in people with irritable bowel syndrome (IBS), and IBS patients have a greater incidence of these disorders than healthy people. IBD patients have modest verbal memory problems in addition to anxiety and despair (Foster & Neufeld, et al., 2013).

WHAT IS DYSBIOSIS AND HOW DOES IT AFFECT YOUR HEALTH?

Dysbiosis is defined as a shift in the microbiota's local distribution, modifications in their functional structure and metabolic activity, or an imbalance in the microflora causing a disruption in the microbiota's equilibrium. This imbalance is considered as an unbalance or mal-adaptation which occurs on or within the body, like a disturbed microbiota. The skin flora, stomach flora, or vaginal flora is all examples of human microbiota. Microbiota is colonies of bacteria that are harmless to humans. The majority of these bacteria are beneficial to your health and aid in your body's natural operations. Dysbiosis can occur when one of these bacterial colonies is out of balance. This dysbiosis causes unbalancing in either stomach or intestines. Gut dysbiosis seem to have a negative influence on host health through the qualitative and quantitative abnormalities in the area of intestine, variations in metabolic activity, and/or impact on local distribution. Certain commensal bacteria can produce SCFA, which alters the pH of the intestine and reduces the development of opportunistic infections (Myers & Hawrelak, et al., 2004)

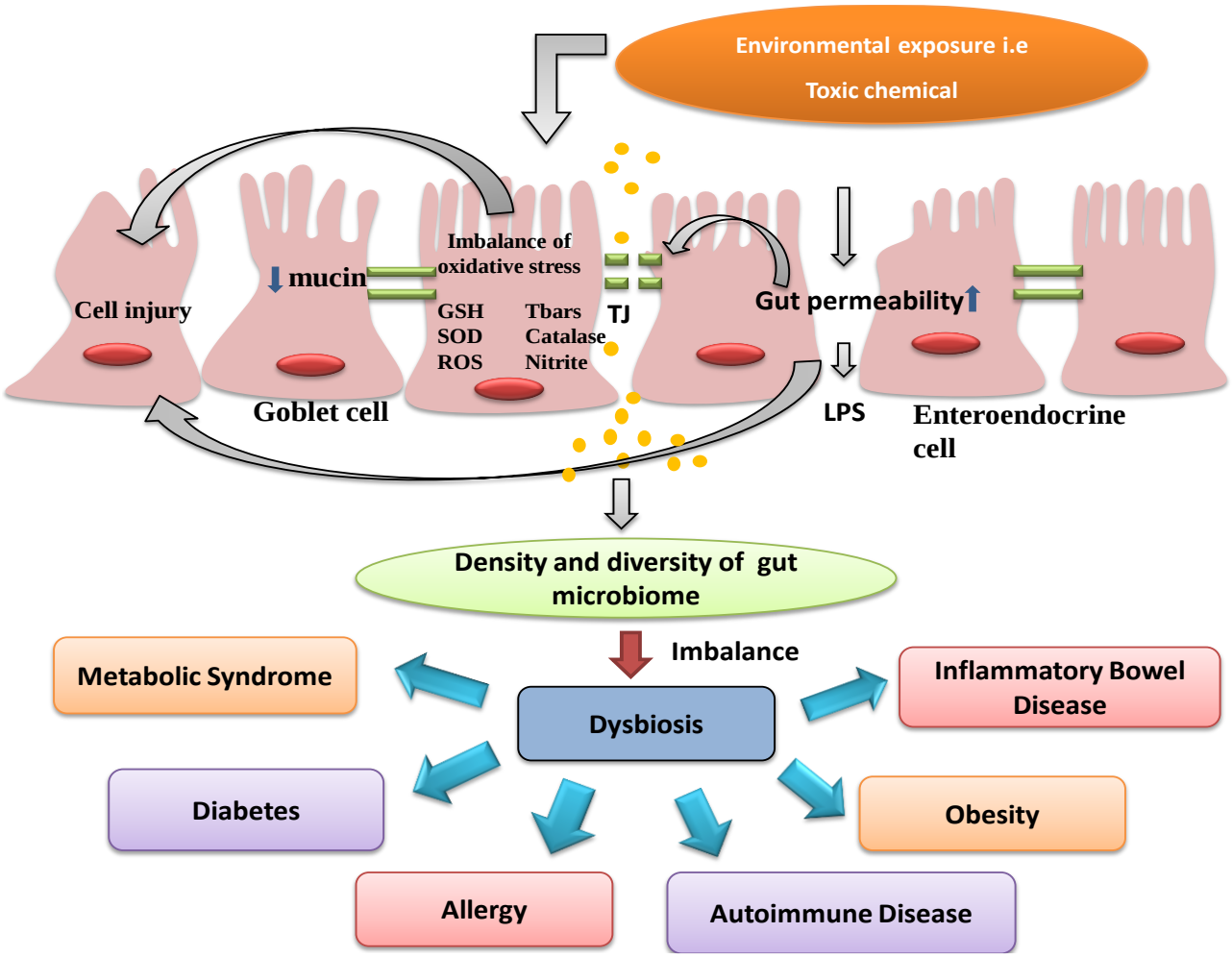

Fig.1:- Dysbiosis of Gut Microbiome

Some dysbiosis symptoms, including stomach upset, are just temporary. Without treatment, your body may be able to correct the imbalance. If your symptoms worsen, though, you should consult a doctor. Continue reading to learn more about dysbiosis, including what causes it, how to recognize the symptoms, and how to treat and prevent it. Dysbiosis isn't always linked to an increase in pathogen abundance; in the absence of important commensal bacteria, even if infections aren't present, it can be damaging (Levy, Kolodziejczyk, Thaiss, & Elinav, et al., 2017)

Who is at risk of dysbiosis and what causes it?

Dysbiosis in the gastrointestinal tract is usually caused by:-

- ❖ A dietary shift that increases your protein, sugar, or food additive intake.
- ❖ Unintentional chemical ingestion, such as pesticide residue on unwashed fruit.

- consuming two or more alcoholic beverages on a daily basis new medications that alter your gut flora, such as antibiotics
- Poor dental hygiene, which permits bacteria in your mouth to proliferate out of control.
- High amounts of stress or anxiety might cause your immune system to deteriorate.
- Unprotected intercourse, which can expose you to bacteria that are hazardous.

Symptoms that are common include:- Bad breath (halitosis), nausea, constipation, diarrhoea, difficulty urinating, itches in the vaginal or rectal area, bloating, chest discomfort, rash or redness, exhaustion, difficulty thinking or focusing, anxiety, sadness.

Gut barrier indicators as potential biomarkers

S.No.	Biomarkers for gut dysbiosis	mechanism	Description	References
1	ZO1	Integrity of Tight Junctions	IBD patients (n=50) had lower levels in the intestinal mucosa than controls (n=31). Tight junction strands are lost in mouse epithelial cell lines when the gene is knocked out.	(Bertiaux-Vandaële et al., 2011)
2	CLDN1	Integrity of Tight Junction	On comparison to ulcerative colitis and normal tissue (n=39), the expression of CLDN1was higher in both ulcerative colitis-associated CRC tissue and high-grade dysplasia(n=6). Claudin-1 over-expression in transgenic mice activates the Notch signaling system by inducing p-ERK and signaling MMP-9.	(Kinugasa et al., 2010)
3	I-FABP	Permeability of the intestine	Higher plasma concentrations are seen in patients with severe ulcerative colitis (n = 42).	(Salo et al., 2007)
4	Zonulin	Permeability of the intestine	In patients with Crohn's disease (n=37), faecal levels were higher than in controls (n=40). In comparison to bovine serum albumin-treated controls, zonulin treated micedemonstrated enhanced permeability in small intestine and gastroduodenum.	(Malíčková et al., 2017)
5	Calprotectin	Inflammation	Increased faecal calprotectin levels have been linked to IBD and intestinal inflammation.	(Bjarnason, 2017)
6	IFN-ϒ, IL10, IL12p70, IL13, IL1beta, IL2, IL4, IL6, IL8, TNF- α) are cytokine indicators.	Inflammation	In ApcF/WTmice, it elicited activation of the tumor inflammation driven by IL23/IL17 and early barrier loss that act additively and sequentially to genetically controlled events that governs the development and progression of CRC. TNF-α and IFN-γ alters the intestinal epithelial barrier properties and increases the epithelial paracellular permeability.	(Grivennikov et al., 2012)
7	Short chain fatty acids (SCFA)	permeability of Intestinal	A cross-sectional study found that CRC patients (n=19) had significantly lower stool levels of SCFA than healthy controls (n=16). In stool samples, the levels of bacteria generating SCFA were lower in CRC patients (n=15) than in controls (n=12).	(Weir et al., 2013)

The etiology of intestinal and extra-intestinal illnesses is linked to dysbiosis of the gut microbiota. Increased abundance of potentially harmful gram-negative bacteria and their related metabolic processes changes can lead to decreased microbial component, compositions, and function, as well as disruption of the epithelial barrier and increased susceptibility to infections, due to an impaired interaction between the relationship of gut microbiota and gut barrier disruption and link with gut immune system. In addition to producing discomfort, oxidative stress, and insulin resistance, gut dysbiosis can also disrupt immunological responses. Persistent dysbiosis and the translocation of microorganisms and their metabolic products through the mucosal barrier have been associated with type-2 diabetes, cardiovascular disease, inflammatory bowel disease, autoimmune disease, and several tumors. Allergies, bronchial asthma, metabolic syndrome, cardiovascular disease, and weight difficulties are examples of extra-intestinal

difficulties, while celiac disease, irritable bowel syndrome (IBS), and inflammatory bowel disease are examples of intestinal disorders (Toor D, Wsson MK,et al.,2019).

COMMUNICATION BETWEEN GUT AND BRAIN PATHWAYS

The amount of metabolic health in the colon is communicated to the brain via both neuronal and circulatory channels. Appetite regulation and satiety signals are coordinated by bidirectional gut brain neuronal relays. The vagus nerve, hormones and neurotransmitters produced by epithelial cells, as well as neurological channels, such as neuroepithelial connections, convey information to the brain about luminal compounds recognized by enteroendocrine cells in the intestine. Dietary metabolites and soluble substances produced by epithelial cells may find their way to the Blood Brain Barrier, where BMECs (Brain microvascular endothelial cells) express different kinds of specific receptors and nutrient transporters that aid in the specific nutrient's translocation (e.g., glucose, lactate) transversely the barrier and the binding of circulating peptide hormones and other factors that can modulate brain activity. Enteroendocrine, immunological cells in the kidneys, brain, gut, liver, and pancreas can be affected by microbial metabolites like amino acid metabolites, SCFAs, TMAs, and vitamins that pass through or modify these processes (Wang & Wang,et al., 2016).

Microbes are increasingly being demonstrated to be capable of creating neuroactive chemicals that directly contribute to the gut-brain connection. Bacteria such as Lactobacillus, Bifidobacteria, Enterococcus, and Streptococcus generate neurotransmitters such as acetylcholine, GABA, and serotonin, which can alter brain cell function both directly and indirectly. Surprisingly, the stomach produces 90% of the serotonin required for mood, behaviour, sleep, and a variety of other actions in the CNS and GI tract. The release of cytokine-carrying exosomes is triggered by serotonin binding to 5-HT receptors on microglia, offering another route for gut-driven neuroinflammation control. Another microbial substance that affects microglia function is tryptophan, a serotonin precursor (Keightley, Koloski, Talley, & Psychiatry, et al., 2015)

Neurotransmitter gut- Brain Signalling

Gamma-aminobutyric acid (GABA), which is produced by a range of Lactobacillus and Bifidobacterium species, is the most important inhibitory neurotransmitter in the brain. Candida, Escherichia, and Enterococcus create serotonin, while some Bacillus species produce dopamine (Mittal R, Debs LH.et al., 2017)

Serotonin

The gut mucosa and enteric neurons both make and release 5-HT in the colon. The release of 5-HT from these many sites can have a wide range of physiological effects. Enterochromaffin (EC) cells, which line the GI mucosa, produce the vast bulk of intestinal 5-HT. Among other things, this 5-HT source has been established to convey messages and induce peristaltic and secretory responses. The CNS receives sensory afferent connections, such as those that mediate nausea and pain. Two distinct isoforms of the same rate-limiting enzyme, tryptophan hydroxylase, drive 5-HT. TPH1 in EC cells, on the other hand, produces 5-HT in the mucosa of the intestine. 5-sHT is carried intracellularly, largely through the presynaptic serotonin reuptake transporter (SERT; Slc6a4), after being released into the GI lumen or synaptic cleft, where it is inhibited by intracellular monoamine oxidase (MAO). As a result, SERT (serotonin reuptake transporter) expression can rise or fall, resulting in lower or higher 5-HT levels available for neurotransmission. This can happen when tryptophan is transformed to 5-HT or degraded to kynurenine. After TPH (Tryptophan hydroxylase) converts tryptophan to 5-hydroxytryptophan (5-HT), aromatic amino acid decarboxylase turns 5-HTP to 5-HT (AADC). The tryptophan-2, 3-dioxygenase enzyme in the liver or the ubiquitous enzyme indoleamine-2, 3-dioxygenase are used to break down tryptophan through the kynurenine pathway (IDO). Despite the fact that it is outside the scope of this article, (Mittal et al., 2017)

Receptors

The scientific community has published a detailed report that divides the 18 receptors into seven categories ($5\text{-}HT_1$ to $5\text{-}HT_7$) that are found not only in the CNS and GI tract, but also in other systems like the cardiovascular and immunological systems. Except for the $5\text{-}HT_3$ receptor family, G-protein-coupled receptors make up the majority of the serotonin receptor family. The five subtypes of $5\text{-}HT_1$ are $5\text{-}HT_{1sA}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1D,}$ $5\text{-}HT_{1E}$, and $5\text{-}HT_{1F.}$ They're important in CNS illnesses like anxiety. The $5\text{-}H_{T2}$ family consists of three members: $5\text{-}HT_{2A,}$ $5\text{-}HT_{2B,}$ and $5\text{-}HT_{2C}$. $5\text{-}HT_{2A}$ and $5\text{-}HT_{2B}$ receptors can be found in myenteric neurons in the brain, where they may affect central processes Memory and cognition, for example, may be linked to the central and peripheral neural systems. $5\text{-}HT_{2C}$ is a neurotransmitter that is primarily expressed in the central nervous system and has a role in several central processes, namely limbic system function and motor behavior. The $5\text{-}HT_3$ receptor family consists of five receptors ($5\text{-}HT_{3A\text{-}D}$), each of which functions as an ion channel similarly to GABA receptors. The malfunctioning of the 5-HT3 family has been linked to psychosis, anxiety, and eating disorders. $5\text{-}HT_3$ receptors can be found in the CNS and the GI tract, where they help with intestinal motility, absorption, and secretion (Hannon J, Hoyer D.et al., 2008)

5-HT6 plays a significant role in mental diseases including psychosis, as well as cognition and learning, at the CNS level. 5-HT5A and 5-HT5B are two kinds of 5-HT5 that are only expressed in the nervous system, according to researchers. Memory and pain are both known to be enhanced by these receptors. The circadian rhythm is regulated by the 5-HT7 receptor, and its malfunction can lead to sadness. SERT activity and intestinal motility are both affected by 5-HT7 in the GI tract. The hypothalamus and limbic system are engaged when the brain stem receives data from the intestine end vispinal and vagal sensory neurons (responsible for the regulation of emotions).The gut's autonomic activity is influenced by descending projections from the limbic system (activated by stress) (Jones, Davis, & Sfanos, et al.,2020)

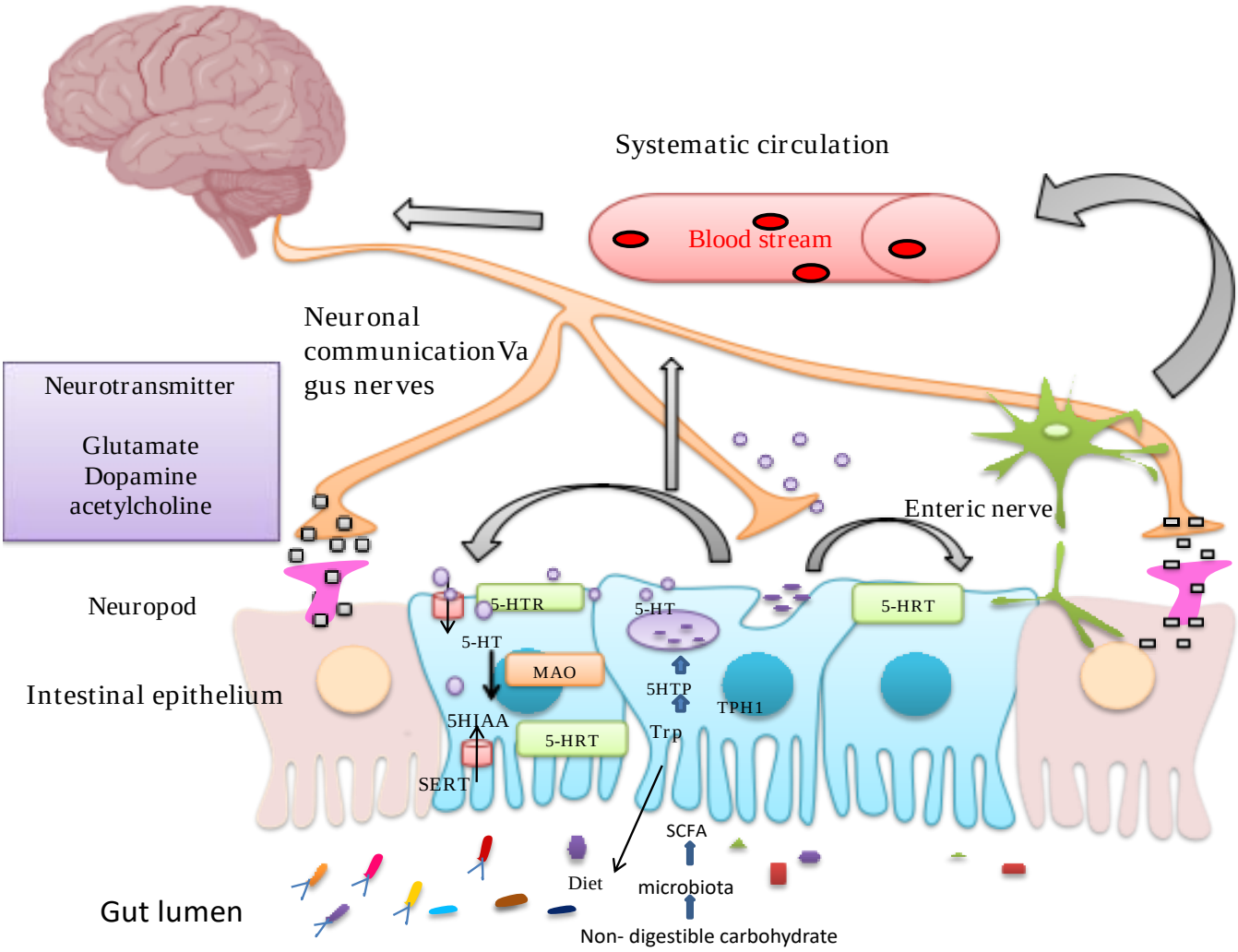

Fig.2:- Microbes that create serotonine and other neurotransmitters like dopamine, norepinephrine, and metabolites like butyrate, acetate, and propionate SCFA in the intestinal mucosa enterochromaffin cells and Enteric Nerves System neurons. Extrinsic neuronal activation en route to the circulation or local receptor-mediated effects on intrinsic ENS neurons (e.g., vagal sensory afferents) These make their way to the brain, where most are capable of passing through to the blood-brain barrier, whereas others influence cell activity at the barrier (Chen Y, Xu J, Chen Y. et al.,2021).

Catecholamines

Catecholamines are monoamines with an amine side chain on one end and a catechol group on the other. The synthesis and breakdown of these amines has been well discussed in the literature, and they also have a significant impact on the human body. Norepinephrine (norepinephrine), epinephrine (adrenaline), and dopamine are the three most common catecholamines. Norepinephrine and epinephrine are peripheral catecholamines, whereas dopamine is a central catecholamine. The reward circuit in the nucleus accumbens is one of the brain regions involved. The 'pleasure system,' which is responsible for emotions of pleasure and excitement, is affected by dopamine (Shiman R, Akino M,et at.,1971).

synthesis

All catecholamines start with L-tyrosine as a precursor.This molecule, together with the cofactors, is used by tyrosine hydroxylase. Which produces epinephrine using the cofactor S-adenosylmethionine and the cofactors oxygen and ascorbate are subsequently used by phenylethanolamine N-methyltransferase. Catecholamines (dopamine, norepinephrine, and epinephrine) are the biosynthetic pathway's final three products, each with unique features and functions in diverse organ systems. The most important enzyme in the catecholamine synthesis pathway is tyrosine hydroxylase. The regulation of this enzyme, which is ultimately responsible for the production of all three catecholamines, has received a lot of attention. The primary mechanism is endogenous neuropeptide Y. (NPY). The mechanism is complicated, but it basically works by lowering Ca2+ intake via the PKC pathway, which reduces neuronal depolarization and catecholamine synthesis (McCullough and Westfall, 1996). Other tyrosine hydroxylase inhibitors, such alpha-methyl-p-tyrosine, have been demonstrated to diminish total catecholamine synthesis. (Thompson et al., 1983).

Receptor

Numerous studies have been carried out on the receptor of choice for norepinephrine and epinephrine. Their preferences do not change in the intestines. This minute difference determines the effects of each catecholamine on the entire gut, including absorption, blood flow, and motility.

Dopamine

Dopamine appears to have receptors despite being the precursor to epinephrine and norepinephrine (D1 to D5). Dopamine, a newly discovered catecholamine involved in gut homeostasis, is another important catecholamine. D4 receptors are still only expressed in the mucous membrane, although D1, D3, and D5 receptors can be found in the nerve terminal layer of the intestinal wall as well as the gut. Only the nerve terminal layer of the gut wall contains D2 receptors. The D2 receptor appears to be the principal mediator of dopamine's endogenous activities, according to a study (Sclafani, et al., 2001).

AMINOBUTYRIC ACID

The inhibitory neurotransmitter GABA is the most well-known and crucial in the central nervous system. GABA signalling and transmission problems have been linked to anxiety and depression, among other mental diseases (Cryan, et al., 2005). The microbiota's role in GABAergic signalling in the CNS is still being investigated. According to a significant body of research, GABA also mediates the enteric neuronal system and hence has a role in gastrointestinal function. GABA regulates neuronal excitability in the ENS, particularly through the GABA-GABAA receptor pathway. It has no effect on the brain, unlike its role in the CNS (Seifi et al., 2014). GABA assists the peristaltic reflex in the colon as well GI motility is the movement of food from the stomach to the ileum (Auteri et al., 2015). GABAA receptors have also been found to regulate the control of T cell responses, suggesting that GABA has a second function as a natural T cells immunomodulator (Tian et al., 1999; Bjurstöm et al., 2008). Manipulation of GABAergic signalling and GABA receptors, as a well-known enteric immunomodulatory mediator, has attracted interest because of their potential to treat inflammatory GI diseases like IBD. Alprazolam, a benzodiazepine, for example, was shown to reverse the increase in the force of spontaneous colonic contractions in stress-induced rats by increasing the two subunits of the GABAA receptor on enteric corticotropin-releasing hormone (CRH) neurons (Seifi et al., 2014).

Neuroendocrine gut-brain signalling

The relationship between gut microbiota and enteroendocrine cell peptide production has long been known. The gut microbiota produces short-chain (six-carbon) fatty acids (SCFAs) such as acetate, propionate, and butyrate from non-digestible carbohydrates (fiber, starch) that remain in our colon. L-cells, which are intestinal enteroendocrine cells that create gut peptides that resemble "endocrine" signalling molecules and generate gut peptides that resemble "endocrine" signalling molecules and are strategically positioned to detect the presence of nutrients, bacteria, and their metabolites. EECs have been intensively investigated for their vital role in controlling gastrointestinal motility, secretion, and synthesis of peptide hormones that govern hunger, insulin release, energy expenditure, and other functions and adiposity through central mechanisms, as well as inhibiting histone deacetylation, which allows gene transcription. They have been shown to act on GPCRs — GPR_{43}/FFA_2 and GPR_{43}/FFA2. GPR_{41}/FFA_3, which is widely expressed in a variety of tissues, By increasing intracellular Ca2+ levels, it activates a range of processes that modify gene expression and/or enhance exocytosis, including pancreatic cells and transporters (Hong Y.H., Nishimura Yet al., 2005).

SCFAs bind to G-Protein-Coupled, Nutrient-Sensing Receptors, causing them to produce endocrine hormones.

Enteroendocrine L-cells regulate PYY and GLP-1 secretion. Food and bacterial products are detected by GPCRs, which are luminal substance receptors found on L-cells. The proteins FFAR2 and FFAR3, which are expressed in the apical and basolateral membranes, respectively, detect SCFAs. When Gs stimulate adenylyl cyclase, elevate cyclic AMP levels, activate PKA, which controls gene expression, and stimulate adenylyl cyclase, GLP-1 and PYY are activated. The PLC pathway is stimulated by Gi/o, while the Gs cAMP pathway is suppressed. When Gq activates the PLC pathway, DAG and IP3 are produced when PIP2 is hydrolyzed. IP3 activates voltage-gated Ca2+ channels, which release intracellular Ca2+. PKC, a critical modulator of cellular activity and gene expression, is stimulated when DAG is expressed. GPR119 and TGR5, both Gs-coupled receptors, are involved in hormone synthesis.

TLRs detect microbial substances and trigger inflammatory responses via the NF-kB pathway. Transporters that inhibit KATP channels in the cell generate membrane depolarization and calcium entry in glucose sensing. By secreting and regulating gut peptides such as GLP-1 and PYY, these pathways allow L-cells to communicate with other cells. The release of gastrointestinal hormones, which might regulate food intake, is influenced by the vagus nerve, brainstem, and hypothalamus. The orexigenic NPY/AgRP neurons and the anorexigenic POMC neurons are hypothesised to be important conduits for integrating peripheral signals into the hypothalamus' arcuate nucleus and modulating hunger. Increased connections between the hypothalamus nuclei and higher brain locations could change the hedonic aspects of food intake (van Son, J.; Koekkoek, L.L.;et al.,2021)

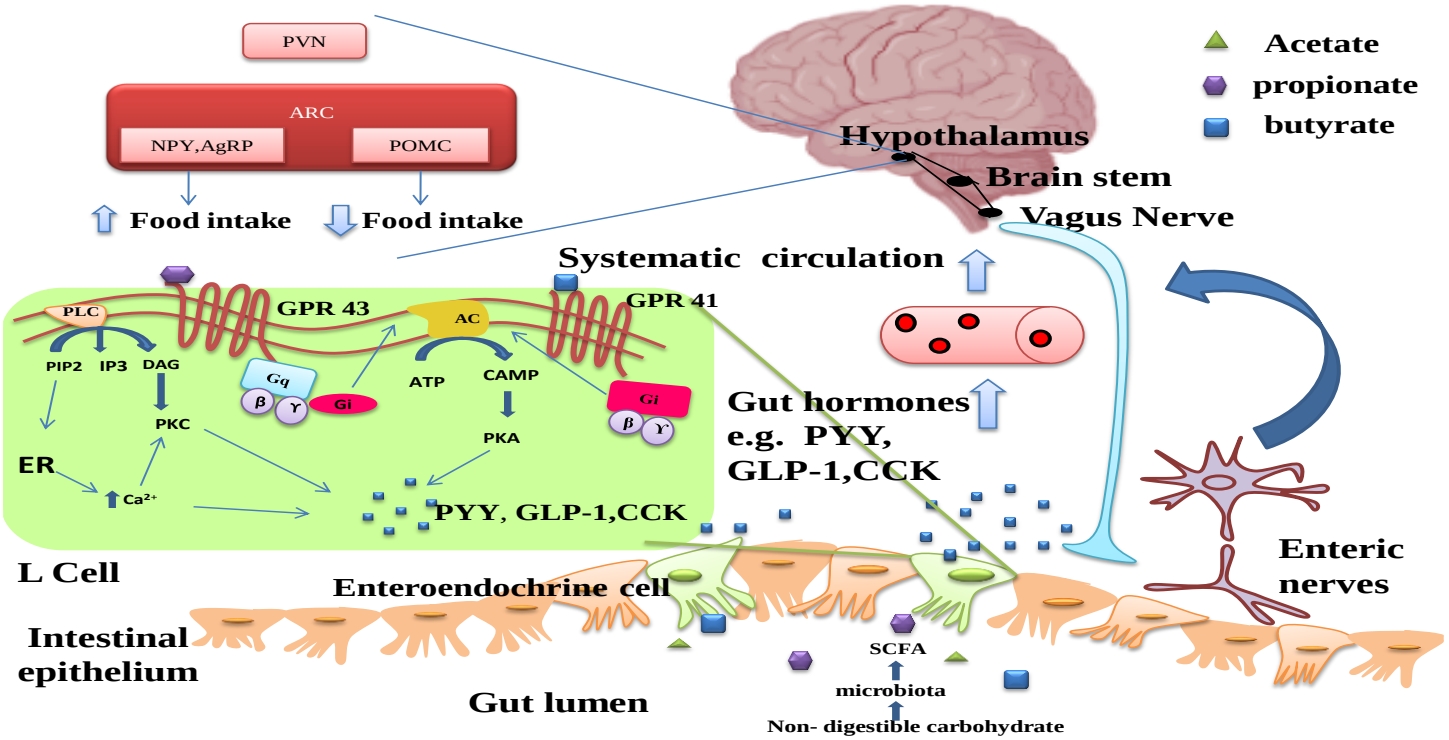

Fig.3:- Enteroendocrine cells (EECs) are known to be stimulated by microbe by-products that communicate also with gut epithelium, They produce neuropeptides such as peptide YY and neuropeptide Y (NPY), as well as cholecystokinin (CCK), glucagon-like peptide-1 and -2, and substance P. The same neuropeptides are thought to spread across the lamina propria. which would be inhabited by several immune cells on their way to the circulation or a specific receptor Extrinsic neural innervation (e.g., vagal sensory afferents) that delivers signals to the brain is mediated by intrinsic ENS neurons (Cani et al., 2013, Cani and Knauf, et al., 2016)

YY Peptide

L cells in the small intestine and colon generate the peptide YY (PYY). After being digested by dipeptidyl peptidase IV, the peptide circulates in two forms: Two PYY genes are PYY_{1-36} and PYY_{3-36}. PYY_{1-36} is the most common kind in the blood. After peripheral injection, Through binding to the Y_2 receptor, PYY has been proven to reduce food intake in both animals and humans. Both the Y_2 antagonist $BIIE_{0246}$ and Y_2 receptor deletion in rodents reduced the anorexigenic effects of the peptide. (Burdyga G, De Lartigue G,et al.,2008)

The anorexigenic gut-brain mode of action may involve the vagus nerve and humoral pathways. The Y2 receptor is present in vagal afferents, and vagotomy prevents PYY from acting anorexigenic. PYY can also flow through the blood-brain barrier without saturating it. The solitary tract nucleus and hypothalamus nuclei, which govern food intake, have been shown to be affected by PYY or PY_{3-36} given into the peripheral nervous system. Food intake is reduced in the brain When PYY is consisting essentially directly into the arcuate nucleus, a location implicated in food intake monitoring and expressing the Y2 receptor, the results are promising. This is performed by inhibiting the activity of neurons that produce neuropeptide Y. while boosting the activity of proopiomelanocortin-containing cells (Batterham RL, Cowley MA, et al., 2002).

Glucagon-Like Peptide 1 is a peptide that is similar to glucagon.

GLP-17-36 amide and GLP-17-37 are two physiologically active forms of glucagon-like peptide (GLP-1) produced by small intestinal endocrine L cells, with GLP-1736 amide being the most common in human circulation of the pro-glucagon gene in the nucleus of the solitary tract, which stimulates excess weight and food consumption. GLP-1 synthesis is biphasic post prandially: an early peak occurs 15 minutes after meal intake and is associated with humoral and vagal stimulation, whereas a later and higher peak is associated with direct L cell contact with food components. In addition to the well-known incretin activity, GLP-1 injections in the peripheral and central nervous systems reduce food intake in both humans and animals. Furthermore, the slowing of gastric and intestinal transit is expected to aid in the reduction of food consumption (Mojsov S, Heinrich G,et al.,1986). The vagus nerve, which expresses the GLP-1 receptor, delivers GLP-1 to the brain, as indicated by the diminished anorexigenic action of peripherally administered GLP-1 after vagotomy. The PVN-projecting nucleus of the solitary tract also expresses GLP-1, and Food intake and weight gain are stimulated by local suppression of the solitary tract pro-glucagon gene in the nucleus of the solitary tract. The gut-vagal-brainstem-hypothalamus circuit is crucial for GLP-1's food intake-suppressing effect to be mediated, as lesioning these pathways reduces the anorexigenic effect of peripherally given GLP-1. Despite this, GLP-1 can easily pass through the blood-brain barrier via diffusion. GLP-1 has the ability to control a variety of stress reactions. According to other research, inhibiting the GLP-1 receptor in single-minded 1-expressing PVN neurons reduces the hypothalamic-pituitary-adrenal axis responses to acute and

chronic stress, which has been linked to reduced anxiety and the prevention of body weight loss in chronic stress situations (Larsen PJ, Tang-Christensen M, et al., 1997)

Cholecystokinin

I cells in the upper small intestine, with a higher concentration in the duodenum, are the ones that produce the most CCCK. CCK comes in a variety of forms, including CCK-5, 7, 8, 18, 22, 25, 25, 33, 39, and 58, which indicate the amount of amino acids, with CCK-8 being the most commonly investigated. The identification of CCK-58 as the only form in circulation employing a modern blood processing technique suggests that shorter forms of degradation products exist (Sayegh AI.et al., 2013)

CCK binds to two types of receptors: CCKA (gastrointestinal) and CCKB (nervous system) (brain). CCKA (gastrointestinal) is located mostly on vagal afferents and in the gastrointestinal tract, CCKB, and from the other side, is largely present in the brain. CCK is secreted postprandially by duodenal I cells, with proteins and lipids functioning as the most effective stimulators. CCK is released from the vagus nerve It binds to afferents that express CCKA, activating neurons in the nucleus of the solitary tract to reduce food intake, Anorexigenic impact and CCK-induced neuronal activity in the brain are both eliminated after vagotomy. (Smith GP, Jerome C,et al., 1981)

Microbiota immune gut-brain signalling

Immune cells in the brain and spinal cord, despite the fact that the CNS is frequently thought to be immune privileged, the permeable brain–blood barrier (BBB) and the functional lymphatic vasculature (in the Dural meningeal membrane surrounding the brain) and could serve as a signaling doorway, implying that immune cells play a role in the CNS through challenges. Resident immune cells such as macrophages, CD8+ cells, Tregs, and various CD4+ T helper (Th) cell subsets, play a key role in innate and adaptive immune responses in addition to glial cells. The gut microbiota has been found to increase numerous subsets of CD4+ T lymphocytes when antigen stimulation and activation of immunological signaling pathways are used. SFB also increases the activation of innate lymphoid cells and Th17. Th17 in the intestine cell activation has been linked to certain bacterial antigens from SFB (Ma Q, Xing C, Long W,et al., 2019).

In contrast, Acinetobacter baumannii and Porphyromonasuenonis will involve in playing an important role in the activation of Th17 cells present in the gut. CD4+ T lymphocytes play a significant rolein experimental autoimmune encephalomyelitis (EAE) models in MS. Th1 cells that create IFN are harmful in MS, but Th2 cells that produce IL-4 and IL-10 are helpful. Animals lacking IL-23, a key cytokine for Th17 cell maturation, are protected from EAE, suggesting that Th17 cells play a role in disease progression. Tregs that express Foxp3 are involved in CNS inflammation control impede the EAE model by secreting the anti-inflammatory cytokines such as TGF and IL-10. Immunecells are known to activate by microbial metabolites for a long time. Interactions reduce colitis by stimulating the inflammasome through GPR-dependent mechanisms, while SCFAs reduce colitis by activating the inflammasome through GPR-dependent processes.between the GPR and the inflammasome are also critical for SCFA-induced suppressive Treg differentiation. By altering histones, SCFAs boost Foxp3+ Treg proliferation by increasing acetylation and decreasing deacetylation at the Foxp3 promoter region.

Furthermore, the gut microbiota's large-scale synthesis of propionic acid and butyrate protects against inflammatory reactions by raising the number of Treg cells through changing the Foxp3 promoter. SCFAs have been shown to stimulate retinoic acid synthesis in the gut, which inhibits Th17 cell differentiation and enhances Treg proliferation, resulting in anti-inflammatory benefits and a preclinical MS model. Increased Th1 and Th17 cell differentiation and proliferation, as well as expression of mRNA pro-inflammatory factors including as IFN,TNF, and Csf2, caused a severe phenotype in MS rats. It's critical to concentrate on gut-derived immune-regulating metabolites and its involvement in brain functioning and disease since a defective BBB allows these compounds to flow through (Erny D, Hrabe de Angelis AL,et at., 2015)

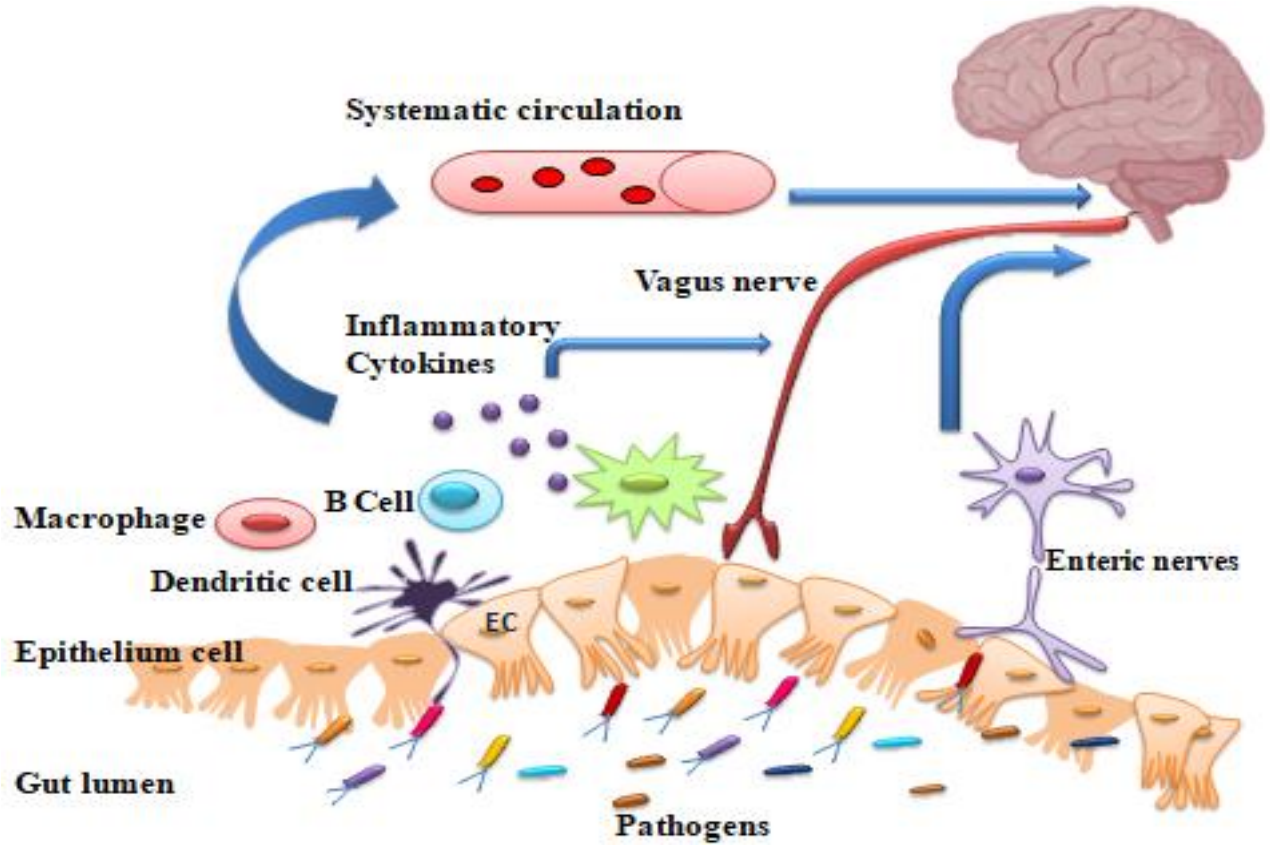

Fig.4:- Microbiomes communicate between immune cells in the gut, causing them to produce cytokines that travel from the bloodstream to the brain through the use of the vagus nerves (Elisei C, de Castro AP et al., 2017)

Conclusions and future prospects

We have learned more during the last year about how bacterial metabolites play a role in microbial interactions in health and disease as a result of the obvious sequencing and analysis of a large number of human microbiomes, as well as the development of their metabolic pathways. Individual functional differences in gut microbiomes have proven the importance of anabolic and catabolic pathways in the maintenance of fundamental community structures for whole-body homeostasis. New biomarkers with specific phylum and species discrimination are on the way, Evidence of microbial participation in type 2 diabetes, obesity, metabolic diseases, inflammatory bowel disease, and even certain malignancies has been confirmed. By influencing microbiome metabolism, gut microbiome dysbiosis influences inflammatory responses and adaptive immunity, as well as contributing to metabolic disorders. and thus host metabolism. Early Childhood education and The use of trying to cut pharmaceutical and nutraceutical products in adulthood to maximize microbial colonization and the building of a healthy gut microbial ecology may assist to prevent the onset of common inflammatory and metabolic illnesses. Eventually, in the not-too-distant future, The next step in metabolic treatments will be the discovery and development of drugs that target metabolic pathway enzymes while also triggering pro- and anti-inflammatory responses in immune cells.

Acknowledgements

RE and MSD acknowledge the award of Senior Research Fellowships by the Department of Pharmaceuticals, Ministry of Chemical and Fertilizer, Government of India. SN was further supported by the Women Scientist Scheme (WOS-A), Department of Science and Technology, Government of India (grant number SR/WOS-A/LS- 1224/2015).

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