GASTRO INTESTINAL TRACT: THE WORLD OF SECOND BRAIN

Prajwal Toragal[1], Seema Sankeshwari[2] , Nagaraja Puranik[3]

[1]Final year Postgraduate student, [3]Professor, Department of Physiology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka State.

[2]Assistant Professor, Department of Physiology, Apollo Institute of Medical Sciences and Research Centre, Chittoor, Andhra Pradesh.

ABSTRACT

Mothers gift not just life but also a microbial profile to their babies, i.e., for vaginally delivered babies, these communities resemble the specific microbial communities found in the mother's birth canal; for babies delivered by caesarean section, the communities resemble the skin communities of the mother. These gut microbiota, via a complex bidirectional communication system, interact with the Central Nervous System, the enteric nervous system, and the hypothalamo-pituitary-adrenal axis (HPA) (cognitive and emotional centers), referred to as the Gut-Brain axis. Though in contemporary societies microbes have a strong negative connotation and are viewed in a warlike context, not all are harmful but beneficial and indeed crucial for a normal healthy life. As many ongoing research studies link the pathogenesis of various diseases to altered gut microbiota, many studies on the other hand show dramatic recovery with faecal microbiota transplantation, confirming the earlier

Keywords: Faecal microbiota transplantation; Gut-brain axis; Gut microbiota; HPA axis.

INTRODUCTION

The human gut has evolved over millions of years and harbours several cohabiting complex communities of microbes which are collectively referred to as micro biota. These microbiotas include various archaea, viruses, protists, yeast, and fungi belonging to more than 1,000 species of bacteria. Altogether making a count of over one billion microorganisms. Normally, the words "health" and "microbes" are not used in the same sentence. In modern society, there is a strong negative connotation and a warlike setting when it comes to microbes. Since the beginning of the study of microorganisms, there has been a legitimate focus on the substantial hazards that disease-producing bacteria provide to human health.

Most interactions between humans and bacteria, meanwhile, are benign or even helpful rather than harmful. The members of the microbiota perform as overt pathogens, commensals, and mutualists, each of which benefits from the other's presence while the host and microbe appear to be unaffected (one partner benefits and the other is harmed).

The homo sapiens genome is >99% identical, and there are many ways in which people are highly similar to one another. However, microbial populations vary greatly within a single human body as well as between habitats and between individuals. John Donne wrote that "no man is an island." From a microbial perspective, however, each individual is made up of an entire archipelago of diverse habitats that exchange bacteria with one another and with the outside at some subtle level, rather than simply one isolated island. The variation between the microbial communities that live in a person's mouth and those that live in their gut is comparable to the difference between the communities found in soil and seawater. The variation is highest between bodily sites. Even within a single body region, there are obvious variances across individuals: bacterial species differences in gut and hand communities can range from 80 to 90%, whereas the degree of variation in the mouth seems to be considerably lower.

In the same way, in the realm of microbes, the same is probably true. The communities with the highest degree of similarity are those descended from the same individual, according to studies of bacterial diversity in faeces taken from young adult female mono and dizygotic twin pairs and their mothers over time.

1. Adult monozygotic twin pairs gut bacterial communities are similar to those of dizygotic twin pairs in a manner that is not noticeably different.
2. Members of the same family have more in common with one another than members of other families.
3. These results emphasise the importance of early environmental exposures in influencing the adult gut's microbial ecology.

The mode of delivery affects early exposures in people. Within 20 minutes after delivery, mouth, skin, and gut

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Correspondence: Dr Prajwal Toragal, Final year Postgraduate student, Department of Physiology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka state. E-mail:drprajaykims@gmail.com, Cell: 9686321986

samples from babies reveal highly uniform microbial communities. These communities reflect the particular microbial communities found in the mother's vagina for babies delivered vaginally; for babies delivered via caesarean section, the communities resemble the mother's skin communities. Over the first three years of life, the infant's gut microbiota evolves to match the adult gut microbiota, and it may alter again later on (figure.1). It is unknown at what stages various body habitat communities develop into their highly distinct adult forms. The gut microbiota communicates with ENS and CNS primarily via the vagus nerve and also by producing active metabolites.

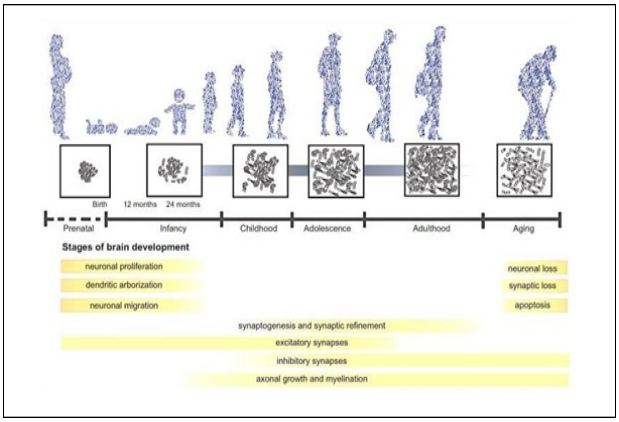

Figure 1 : Timeline graph showing changes in microbial diversity over the course of the human life cycle, from conception to old age, including infancy, childhood, adolescence, and adulthood, along with typical changes in neural development, indicating concurrent neuronal processes taking place at particular stages of life [1].

Absorption of tryptophan which is an immediate precursor of serotonin. It is an established fact that serotonin is a major mood regulatory chemical substance. Short chain fatty acids from the microbiota can pass the blood-brain barrier and have been demonstrated to modulate microglia functioning, which is necessary for healthy brain development and behaviour regulation. Immune response against these commensals is modulated by the release of various cytokines and cortisol via HPA axis. (figure.2).

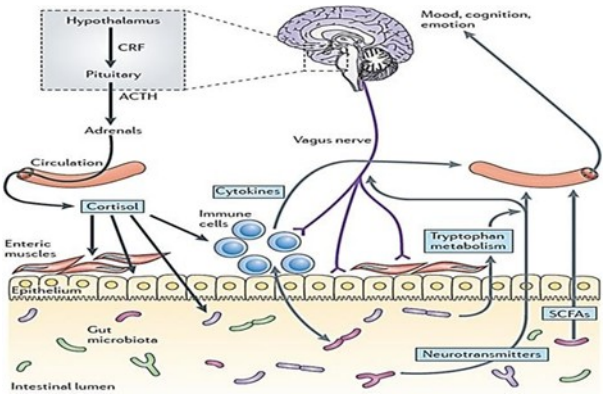

Figure 2: Diagram depicting the bidirectional interaction between gut microbiota and brain Serotonin, GABA, Melatonin, Histamine, Acetylcholine, Catecholamines, Brain derived neurotrophic factor (BDNF) [2].

Numerous human microbiome projects are looking into how the composition of the microbiota and microbiome, as well as how they relate to human diseases. In many cases, gnotobiotic mouse models serve as the basis for hypotheses about a connection between the microbiota and the microbiome and disease (mice raised in germ free environments- with no exposure to microbes- and then colonised at specific stages of life with different microbial communities). Germ-free animals are contrasted with conventionally raised animals of comparable genotype or with germ-free mice who have received a microbiota from a donor routinely raised mouse with a specific phenotype. These comparisons have demonstrated the importance of the gut microbiota in the development of both the innate and adaptive immune systems, the microbiota's role in the development of inflammatory bowel disease in animals carrying mutations in genes linked to disease risk in humans, and the ability of certain gut microbiota members' surface components to specifically alter immune system activity to reduce or prevent disease. This discovery adds more support to the idea that this microbial community plays a role in the pathogenesis of specific types of autoimmune diseases by altering the likelihood of developing type one diabetes in genetically predisposed mice.

Gnotobiotic mice offer a great way to regulate host genotype, microbial community composition, nutrition, and living circumstances. It is possible to ascertain the effects of these communities on previously germ-free recipients as well as the impact of the recipients on the transplanted microbiota and its microbiome using microbial communities isolated from donor mice of specific genotypes and physiological characteristics [3]. These studies have shown that the gut microbiota regulates the efficiency of nutrient and energy absorption from the diet. It does this not only by breaking down otherwise indigestible diet components but also by controlling host genes that control adipocytes' ability to store energy. The microbiota modifies the formation of the complex microvasculature that underlies the pace of epithelial turnover in the gut. The effects of the gut microbiota go beyond the digestive system. Heart weight in germ-free mice is considerably lower than in germ-containing animals, whether evaluated by echocardiogram or as wet mass and normalised to tibial length or lean body weight. This difference disappears two weeks following colonisation with gut bacteria. Certain aspects of behaviour, such as locomotion, are influenced by the presence or absence of gut bacteria. This finding begs the question of whether bacteria in this co-evolved relationship have learned how to manipulate specific aspects of host behaviour for mutual gain. For instance, it is intriguing that routinely reared mice than in germ free animals have plasma levels of serotonin that are several folds greater [4].

Enteric nervous system's developmental and evolutionary characteristics: The enteric nervous system was discovered in the middle of the 19th century, was a significant scientific advance in our understanding of how the neurological system and the digestive system interact. The enteric nervous system has historically been referred to as the second brain due to its size, complexity, and closeness in neurotransmitters and signalling molecules

to the brain. Early researchers have observed top down modulation of gastrointestinal function by stress and emotions as well as bottom-up signalling from visceral afferent to the brain in stomach pain disorders as well as potential emotion control5 .Since the 1990s, this subject has drawn more attention, partly as a result of a number of independent but related scientific findings from a variety of research areas, including enteric neuroscience, neuroimaging, intestinal microbiology, host microbial interactions, and most recently, gut brain transmission [5].

One of our body's most important systems is the digestive system. We have a gut-wrenching experience sometime, isn't it? Similarly, stressful situations make us feel butterflies in our stomach. Don't we often make decisions on gut instinct? Emotions like anger, worry, sorrow and happiness are known to have physical action GIT. The gate control hypothesis is what experts name it. Gut receptors communicate pain to the brain. A huge network of neurons that line our gut, sometimes referred to as our second brain, are responsible for this sensation. Our gut nerves are very important for controlling our emotions.

Normal functioning of CNS is essential to keep the gut healthy by releasing various biologically active substances like NTs and hormones. In their key study published in 2004, Sudo and colleagues postulated the existence of the gut-brain axis [6].

It is obvious from an evolutionary perspective that the enteric nervous system is not just a feature of humans. Insects, snails, etc., are among the animals in the animal kingdom that have an enteric nervous system that is analogous [7]. It has been hypothesised that the more primitive but related intestinal nerve circuits are indeed the source of the ganglia that later give rise to the primitive brains of helminthes and higher animals. Thus, the neuronal circuitries and transmitter systems that have evolved to assure the best responses to the challenges presented by our internal environment, such as the luminal environment, may have been created in the central nervous system. In the course of development, precursor cells leave the neural crest and travel along the Vagus to the gut where they settle and differentiate give rise to the enteric nervous system [8]. The enteric nervous system can be seen as a peripheral extension of the limbic system into the gut. This is based on its close bidirectional connections with the limbic and autonomic regions of the brain. Alternative views of the central nervous system include views of its pontine, autonomic, and link circuits as an encephalized element of the enteric nervous system.

Important concepts in brain-gut viscera interactions

William James and Carleton Lange developed the first comprehensive scientific theory of the relationship between the brain and the viscera in 1880. It was based on the idea that the autonomic nervous system's output from stimuli that elicit emotions like anger, fear, or love first causes changes in visceral function, and that the afferent tract feedback of these visceral organs to the brain is crucial in the production of a particular emotional response. This hypothesis states that we experience anxiety when we see our heart rate increasing, notice our breathing becoming shallower and more frequent, or experience stomach butterflies.

The James Lange idea was contested by Walter Canon in the late 1920s, who posited that emotional responses are directly appreciated by subcortical regions of the brain rather than as a result of feedback from circumstantial physiological changes. According to his theory, these bodily changes that are connected to emotional states are merely the consequence of these brain changes, and visceral reactions are too delayed to have any bearing on how an individual subjectively experiences emotional sentiments.

The importance of interoceptive feedback in emotional states and cognitive processes has been emphasised again in modern theories of emotion and consciousness that were proposed in the form of somatic marker hypothesis by Antonio Damasio and homeostatic emotion hypothesis by A. D. Craig [9]. These theories have also largely resolved the long-standing debate about the directionality of brain viscera interactions in the generation of emotions. Damasio persuasively argued that visceral and other physical reactions to particular contextual events are linked to either positive or negative emotional states, which in turn give rise to the somatic markers. In accordance with this notion, these body loops or their meta-representations in the orbitofrontal cortex may impact future planning and intuitive decision-making in addition to how someone feels at any particular time. For example, according to Damasio, somatic markers may secretly lead to the introduction of bias in the choice of an appetitive mode of behaviour, the unintentional repression of previously learned responses, and other outcomes [10].

The brain-gut signaling: The enteric nervous system's reflex circuits involve the insular cortex and anterior cingulate cortex that make up the brain-gut axis. Most cases of gastric reflux and reflexes involving spatially separate parts of the gastrointestinal tract involve mesenteric reflexes and vago-vagal reflexes, although many local physiological responses of the gut to stretch or chemical stimulation solely involve enteric reflexes. Spinal and supraspinal reflexes are frequently triggered by nociceptive stimuli, eliciting significant emotional and autonomic reactions. In order to improve homeostatic control of intestinal function, circuits outside the gut wall are activated. These circuits integrate the information obtained from the external environment and the internal environment. The impulses that originate in prefrontal regions can control sympathetic and vagal outputs as well as alter the dorsal horn through descending influences, pontomedullary nuclei have a tonic inhibitory influence on the gain of these reflexes.

The sense of emotional sensations, such as agony, discomfort, or well-being, is linked to the conscious awareness of interoceptive information that is either created by signals from the gut or by the recall of interoceptive memories. The dorsal nucleus of the vagus transmits signals to the vagal promoter neurons in the nucleus tractus solitarius, which is the vagal relay nucleus in the medulla. The dorsal vagal complex is made up of the NTS and DMNV. Medullary catecholaminergic nuclei A1, A2, and A5 are located in the ventromedial medulla (VMM) and rostral ventrolateral medulla (RVM). The parabrachial nucleus as well as from forebrain areas, such as the hypo-

thalamus, amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC), send signals to the periaqueductal grey. The PFC supplies the insula (INS) and autonomic nervous system with the highest cortical modulatory input [11].

Homeostatic signals from the brain to the stomach Through a number of parallel pathways, including the two limbs of the ANS, the HPA axis and sympathoadrenal axis, and descending monoaminergic tracts, the brain communicates with the viscera, including the gastrointestinal tract [12]. The hypothalamus and amygdala are two important subcortical regions that produce these effects. They were given inputs from the medial prefrontal cortex network, which is a network of cortical regions, including the anterior cingulate cortex and its subregions. While pre-genual ACC regions (BA 24) project to the periaqueductal grey, ventral ACC regions (sub-genual cingulate cortex and Broadmann area 25-BA25) project largely to the medullary vehicle complex. The orbitofrontal cortex network and lateral PFC give integrated multi-sensory information concerning the depiction of complex homeostatic body states, such as those related to gut regulation, dietary habits, and visceral pain, to the medial PFC network. With the help of the mesencephalic PAG, different motor neurons are combined with outputs from the amygdala, hypothalamus, and medial network sub regions.

The finding that eating reduces pain-related behaviours in rats, analgesic mechanism linked to engagement of descending serotonergic pain modulation pathways, is an illustration of the gut-related involvement of the medial component of the enteric nervous system [13]. Other behaviours and motivating states, including alertness and panic, can potentially influence the pathways that regulate descending opioid-dependent pain. However, the lateral system (which includes the central nucleus of the amygdala, red nucleus of the striae terminalis, lateral hypothalamus, and pontine locus coeruleus complex as well as subregions of the PAG) may be involved in the execution of various regional motor patterns of the viscera through the activation of purpose-specific subsets of sympathetic and parasympathetic pathways.

In response to internal or external demands, the autonomic nervous system can be reflexively activated by ascending signals from the gut or by descending cognitive stimuli. When the body's homeostasis is in danger, when there is a great deal of external stress, or when one is experiencing powerful emotions like rage, fear or grief, for instance, top down modulation can take the place of local reflex function [14].

Model of illness that accounts for changing brain-gut interactions: A fundamental function of changed appraisal and prediction inaccuracy has been hypothesized, similar to cognitive theories of anxiousness. This is supported by the fact that, in many functional gastrointestinal illnesses, anxiety and poor coping mechanisms (such as catastrophizing) play a key role in determining how severe the symptoms are. Based on a negatively balanced interoceptive recall of such experiences, this model postulates a mismatch between the actual interoceptive image of the digestive system recorded in the insula and the projected condition. The mismatch causes ANS responses to be activated, anxiety toward gut-related feelings and emotional arousal, and maybe heightened sensory perception. The suggested model assumes that there is a mismatch between the predicted reward and the actual reward delivery in the case of obesity and dietary obsession. This discrepancy encourages compulsive overreaction in an effort to receive the anticipated degree of reward. The processes that underlie the failure to repair the mismatch by updating the expected state are yet to be known [15].

Faecal microbiota transplantation as a novel therapeutic tool: Given its capacity to affect distant organs and systems, the gut microbiota resembles an endocrine organ in many ways [16]. The treatment of recurrent Clostridium difficile infection with FMT has been proven effective. There are early signs that it may potentially have therapeutic potential for other illnesses such as obesity, metabolic syndrome, inflammatory bowel disease, and functional gastrointestinal disorders [17] The infusion of a solution of faecal matter from a donor into the digestive tract of a recipient is known as faecal microbiota transplantation (FMT), which aims to directly alter the recipient's microbial makeup and provide health benefits [18]. Ge Hong, a physician in fourth-century China, is credited with describing the use of faeces as therapy for a number of ailments, including diarrhea [19] . In 1958, Eiseman and colleagues described the use of faecal enemas as a treatment for pseudomembranous colitis, ushering FMT into the realm of mainstream medicine [17]. First, a donor without a family history of autoimmune, metabolic, or cancerous illnesses is usually chosen, and any potential pathogens are screened for. After combining the faeces with water or regular saline, they are then ready for use. A filtration process is then added to get rid of any particulates. Through a nasogastric tube, nasojejunal tube, esophagogastroduodenoscopy, colonoscopy, or retention enema, the mixture can be delivered. The majority of FMT's clinical experience has come from managing recurrent or resistant Clostridium difficile infections (CDI) [20]. The main finding of the faecal transplantation study conducted by Oleg V. Goloshchapov et al. was that FMT in healthy participants confirmed the long-term conversion of microbiota composition. The microbiota composition among recipients shifted in favour of the donor profile. The relative increase in donorderived bacteria in the stomach of healthy receivers was the most significant discovery [21].

CONCLUSION

Our knowledge of the two-way communication between the brain and the digestive system has come a long way. This includes our understanding of how the brain modifies these enteric nervous system pathways and gut functions, our extraordinary progress in mapping the functional neuroanatomy of the enteric nervous system, and our ability to decipher the intricacy of gut brain signaling through numerous interconnected communication pathways. In contrast, a lot of the features of gut-brain signaling discussed in this article, particularly their significance in emotional and cognitive function, are still hypothetical at this time but may serve as a roadmap for future research. There are several crucial questions that need to be answered. What contribution does gut to brain transmission play in adult brain development and maturation com-

pared to its involvement during early brain development? Does the development of adult injective actions, visceral pain sensitivity, mood and affect, memory, and intuitive judgment depend on early gut-to-brain communication? What functions do the microbiota and taste receptors have in this interoceptive signaling? Does brain development involve mucosal-driven vagal input to the brain? Is there a connection between the pathophysiology of anxiety and depression and changes in microbial signaling from the gut to the brain, as suggested by the frequent co-occurrence of various brain gut diseases with mood and affective disorders? And how can interoceptive memories and mistaken predictions affect the onset of human diseases?

The majority of these ideas can be examined in humans, which is one of the major benefits of answering these issues. The centre of conversation nowadays is research analysis related to this concept of the combined gut brain axis. In the next days, we may expect much more in-depth theories, more current research, and more sophisticated correlation studies about this second brain realm, which will result in significant advancements in all the aforementioned areas.

Thus, a microbiological scan could end up being a required element of routine physicals or a tool for forensic scientists. All of these hypotheses raise concerns about the proper archiving and distribution of volunteer-obtained microbial communities and strains.

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