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Review Article

Brain Development and Microbiome Effect

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Received: September 13, 2016; **Published:** October 26, 2016

Abstract

• The human gut host contains1014 bacterial organisms, which is an amount that exceeds the cells within the body.

• Microbiota is the bacteria living both inside and on the human body (a community collectively known as, dwelling in the human microbiome), mostly are friendly and they outnumber the somatic and germ cells of the body by a factor of 10.

• Specific to the human gut are the commensal microflora which enter into an important symbiotic association with the human host beginning with the colonization of the gastrointestinal (GI) tract by the bacteria within half an hour after delivery and continue to develop depending on many factors. This is developmental process begins at birth and continue through early development, and remains for life.

• This developmental processing is actually active during vulnerable or sensitive developmental periods and thus it exerts influences that impact on the structure and function of organs (brain) that last throughout life.

• However, although the colonization of microbiota is due to postnatal environmental factors and is also affected by genetics and it is consistent and is difficult to change after reaching the adult form.

• It has a prenatal and postnatal effect on the developing of the infant brain.

• The microbiota are essential to the proper development of the mucosal and systemic immune systems and in nutrient uptake and metabolism as important contributors in making the individual's physiology and influence the function of the central nervous system (CNS) and behavior.

• Of particular interest is the impact of the microbiota on the functional development of the infant (mammalian) brain.

• The developing brain is susceptible to internal and external cues during its perinatal life, an important point when considering the association between common neurodevelopmental disorders (e.g. autism and schizophrenia) and microbial pathogen infections during this same period.

Breast feeding and probiotics are now being recognized in the brain -gut axis interaction.

Keywords: *Brain; Microbiome; Flora; Neurons; Immunity; Pathogen*

Introduction

In broad-spectrum, the spread of live bacterial vaccines to the environment is also a matter of concern. Though, attenuated human pathogens are usually not adapted to live outside its host. Therefore, survival in the environment is usually short. Vaccines based on

recombinantLactic Acid Bacteria (LAB) may result in the release of these bacteria in nature as they are more suited to survive in nature. Both attenuated bacteria like salmonella and food related LABhas been developed as live vaccines suitable for oral administration. Today, live vaccines based on attenuated Salmonellatyphi and Vibriocholerae are available. The development of bacterial vaccine vehicles carrying a heterologous gene or a DNA vaccine is more problematic and not yet into the market for use. Several bacteria have been suggested as vaccine vehicles and especially LABis promising. Their safety and immune modulating capacity have been tested using diverse vaccine components like antigens from infectious diseases, allergy-promoting proteins and therapeutic antibodies. However, considerable safety issues against live vaccine vehicles can be raised. We still need a better approachfor overall health and concern about safety during vaccination.

The gut is quite literally the second brain, both work in tandem, each influencing the other. It is the biggest lymphoid organ. This is why intestinal health has such a profound influence on mental health, and vice versa. Any changes in the pregnant mother microbial flora and diet may affect the development of the infant [4].

The brain and the gut

The brain and the gut have the same origin in embryogenesis. Pathological changes of one affect the other [1,2].

The human brain

The brain remains a mystery before and after birth. The human brain is the most complex three-pound organ in the universe. During some stage of growth, there is an increase of 250000 to 500000 neurons per minute. Neurons that fire together wire together. The connection synapsis has indefinite variation [5].

Brain growth

At birth, most neurons are present. There are approximately 100 billion neurons. By age 2 years, the brain is 80% of its adult size. Other brain cells (glial cells) and new neuron connections remain growing. The brain of a human fetus grows rapidly from the 10^{th} to 18^{th} week of pregnancy. Hence, maternal nutrition is vital. The brain also grows rapidly just before and for about 2 years after birth. There are about 1000 trillion connections by age 3 years [5].

Any malnutrition in the first few years will affect glial cell growth, as well as the development of neurons and myelin (which continues to form around axons for several years after birth). This implies that missing out on a particular nutrient at the time when a part of the brain is growing and needs that nutrient will cause a specific problem [6,7].

The microbial flora

The term “gut microbiome” is used to describe the complex ecosystem of bacteria that colonize the gut, including their genes, proteins, and metabolites. The microbiome is thought to interact with the brain through immunological, endocrine, and neural pathways. Consequently, nutritional components that may influence gut microbiota may also exert beneficial effects on the developing brain [8].

Microbial colonization

Human microbial colonization begins at birth and continues to develop and modulate in species for about 3 years, until the microbiota becomes adult-like. However, development of the microbiota begins well before the infant is born. Contrary to what was previously thought, amniotic fluid is not sterile [9,10]. This supports the notion that microbes in the amniotic fluid and placentas of full-term healthy infants have access to the unborn fetus [9,11]. The meconium is also not sterile, supporting the fact that microbes in the amniotic fluid also have access to the unborn fetus [11].

Microbial colonization induces anatomical development of the intestinal epithelium into the typical microvilli pattern. It increases epithelial cell turnover rates and kick-starts the maturation of the gut-associated lymphoid (immune) tissue (GALT) [12].

Gut microbiota serve the host by protecting against pathogens. They also participates in the intake of dietary nutrients and metabolizes certain drugs and carcinogens. Moreover, they influence the absorption and distribution of fat [13,14].

Factors influencing gut Microbiota

There are several factors that influence gut microbiota. These include: mode of delivery, type of feeding, hospitalization, gestational age, maternal disease, environment, genetics and antibiotics exposure [15,16].

Also, there is symbiosis between mother and infant, prenatally and postnatally, which affect the overall gut microbial flora of the growing infant such as: pregnant weight gain, antibiotics exposure of the mother during pregnancy, maternal smoking exposure, hygiene and social exposure, bacteria in the amniotic fluid, and gestational metabolic abnormalities.

As for the infant, high fat mother's milk, antibiotic exposure, admission to the intensive care unit, weight at birth, delivery and feeding modality all influence the gut microbiota [15,16].

Stages of microbial colonization

The intestine of the newborn is initially colonized by Enterobacteria. In the days after, strict anaerobic bacteria dominate the microbial community. During the first month, bifidobacterial species predominate the gut. The introduction of solid foods at 4-6 months promotes the expansion of clostridial species (Lachnospiracea, Clostridiaceae, and Ruminococcaceae). By 2-3 years of age, the composition is mainly Bacteroidaceae, Lachnospiraceae and Ruminococcaceae, which then remains stable into adulthood [17].

Gut microbiota and brain development

Microbiota are important to maintain homeostasis including brain development. Microbial colonization in the infant coincides with key neurodevelopment periods. Disruptions of early life gut colonization may be linked to central nervous system dysfunction [18].

The microbiota are essential to the proper development of the mucosal and systemic immune systems. They are also necessary in nutrient uptake and metabolism. These serve as important contributors in making the individual's physiology and influencing the function of the central nervous system (CNS) and behavior [19].

The developmental effect is bidirectional: gut microbiota-to-brain and brain-to-gut microbiota [19]. Gut microbiota has an effect on brain development, prenatally and postnatally since there are gut microbiota-to-brain communications during prenatal and postnatal development [20].

Prenatal and postnatal effect

The prenatal and postnatal periods in mammalian development are characterized by rapid changes in neuronal organization. Thus, providing a critical window of opportunity during which environmental factors could have long term influences on the brain and behavior outcome. The ability of microbiota to influence the fine maturation of the brain which has long lasting effects on its functions was recently revealed [20-22].

Prenatal effect

A rapidly growing infant brain supports the Barker hypothesis (1990) which states that environmental factors during prenatal and

postnatal life can have profound effects on the programming of intracellular signals, cell-to-cell interactions, and metabolic pathways. The developing brain has been shown to be susceptible to both internal and external environmental cues during prenatal life. The role of gut microbiota in modulating mood and behavior has been the focus of many research studies. Germ free mice display increased motor activity and decreased anxiety compared with conventionally raised mice [4,23].

The microbiota have the ability to influence the fine maturation of the brain, which may have long lasting effects on its functions [21,22]. They modulates the activity of HPA axis, normalize the high corticosterone concentrations and restore corticotrophin-releasing hormone [24].

There is a crucial role of the microbiota of the mother during pregnancy that might have programming effects later in life. The mechanism whereby microbiota influences the brain prenatally is yet to be determined, but the placenta is one of several possibilities [23].

The fetus lives in an almost sterile environment and communicates with the mother through the placenta. It is possible that maternal microbial metabolites could reach the growing fetus through the placenta and affect fetal brain development [4,23].

The placenta has an important role in shaping the fetus development. The placenta, nicknamed the fetal armor, has been shown to protect the fetus from damage when the mother is deprived of food by breaking down its own tissue (placental autophagy) to nourish energy demanding organs like the fetal brain [25,26].

The placenta appears also to provide the hormone serotonin essential for fetal forebrain development. The hormonal interaction between the placenta and the fetal hypothalamus- pituitary adrenal axis (HPA) was shown to be involved in regulating fetal brain development especially during stress. The effect of microbiota in modulating the activity of HPA axis normalized the high corticosterone concentrations and restored corticotrophin-releasing hormone [27].

Postnatal effect

The postnatal period is another critical period for brain development. For most vertebrates, the majority of organs and tissue development occurs during embryogenesis, and postnatal changes are primarily concerned with growth. However, the CNS is different in that a considerable amount of morphological development occurs. Cell differentiation and acquisition of function take place during postnatal development [28,29].

Colonization of the GI tract with microbiota begins postnatally at birth, overlapping with the critical period of brain development. Microbiota colonization is actually influenced to a great degree by mode of delivery and feeding patterns [28]. Clinical studies have shown that breast-fed infants have better neurodevelopment outcomes and higher scores on intelligence tests [29].

The microbiota of breast-fed infants appears to be more diverse and heterogeneous than the formula-fed according to a recent metagenomic study [21,22].

The gut-brain axis (GBA)

The gut-brain crosstalk is a complex bidirectional communication system. It ensures the proper maintenance of gastrointestinal homeostasis, and has multiple effects on motivation and higher cognitive functions. The GBA axis role is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as: immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling [20,30].

The GBA axis consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. This interaction occurs through signaling from gut microbiota to brain and from brain to gut microbiota by means of neural, endocrine, immune and humoral links.

The pathophysiological mechanisms involved were derived mainly from experiments on germ-free animal models, probiotics, antibiotics, and infection studies. The microbiota-GBA interactions come from the association of dysbiosis with central nervous disorders (i.e. autism, anxiety-depressive behaviors, and functional gastrointestinal disorders) [30].

The gut-brain crosstalk is a complex communication system that not only ensures the proper maintenance of gastrointestinal homeostasis, but is likely to have multiple effects on motivation, and higher cognitive functions. The GBA role is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as: immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling. The mechanisms underlying GBA communications involve neuro-immuno-endocrine mediators [20].

The exact mechanisms by which the gut microbiome communicates with the brain are not yet clear, but include: immunological, endocrine, and neural pathways.

The biochemical signaling takes place between the gut and the nervous system. This interaction involves the composition and function of the intestinal microbiota, which may alter hormones relating to neurochemical changes in the brain that can modulate the behavior of the host including: anxiety, cognition, stress, mood, energy-level and susceptibility to neurological disease [31,32].

Bidirectional communication: brain-gut pathways

Multiple pathways exist through which the gut microbiota can modulate the GBA. These include endocrine (cortisol), immune (cytokines), and neural (vagus nerve and enteric nervous system) pathways. The brain recruits these same mechanisms to influence the composition of the gut microbiota. Under conditions of stress, the hypothalamus-pituitary-adrenal axis regulates cortisol section. Cortisol can affect immune cells and alter gut permeability and barrier functions. Both the vagus nerve and modulation of systemic tryptophan levels are strongly implicated in relaying the influence of the gut microbiota to the brain. In addition, short-chain fatty acids are neuroactive bacterial metabolites of dietary fibers that can modulate brain behaviour [32].

This bidirectional communication network includes: the central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axis.

The autonomic system, with the sympathetic and parasympathetic limbs, drives both afferent and efferent signals. The afferent signals arise from the lumen and transmitted though enteric, spinal and vagal pathways to CNS. The efferent signals arise from CNS to the intestinal wall.

The HPA axis is considered the core stress efferent axis that coordinates the adaptive responses of the organism to stressors of any kind. It is a part of the limbic system, a crucial zone of the brain predominantly involved in memory and emotional responses.

Gut microbiota directly influence the immune system, nervous system and brain development during microbial colonization of the newborn and are controlled and modulated by different endogenous and exogenous factors. Of these factors, feeding with human milk creates a healthy microbiota in the infant gut and reduces incidence and severity of infections and promotes normal gastrointestinal function.

Microbiota and gut-brain axis interactions

From gut microbiota to brain, the interaction is by

Production, expression and turnover of neurotransmitters (i.e. serotonin, GABA), neurotrophic factor (BDNF), protection of intestinal barrier and tight junction integrity, modulation of enteric sensory afferents, bacterial metabolites and mucosal immune regulation.

From brain to gut microbiota, the interaction is by

Alteration in: mucus and biofilm production, motility, intestinal permeability and immune function [14,32].

Communication and effect

The gut-brain axis is based on top-down communication and how the neuro anatomy of the gut-brain axis has been affected [33]. The gut brain axis is focused not only on microbiome but also on other products and activity within this large lymphoid organ and immune system (GALT, MALT).

Microbiota is the key to maintaining homeostasis including brain development. Microbial colonization in the infant coincides with key neurodevelopment periods. Disruptions of early life gut colonization may be linked to central nervous system dysfunction.

Putative (supposed) mechanisms underlying microbiota brain axis

Bacterial metabolites and bacterial neuro-like peptides

Modulation of transmitters (i.e. serotonin, melatonin, gamma-aminobutyric acid, histamines and acetylcholine) secretes neuropeptide like molecules proposed to influence behavior and emotion.

Activation of the mucosal immune system

Immune cell populations induced within the gut could cross the blood-brain barrier and be reactivated within the CNS by the appropriate resident antigen presenting cell (APC) [34].

Stimulation of afferent system to CNS

Microbiota can elicit signals via the vagal nerve to the brain and vice versa [35,36].

Endocrine mechanisms

Enteroendocrine cells (EEC) are one of the largest endocrine systems in the body. They secrete gut hormones which control food intake and energy homeostasis. They act on the brain via vagal afferent fibers and through the circulation acting mainly on the hypothalamus (classical endocrine fashion) [37].

Probiotics

Probiotics, pre-biotic oligosaccharides, and certain amino acids are potential candidates for neuroprotection. They play a neuroprotective role against white matter injury, through modulation of inflammation and infection and through the influence of the microbiome-gut-brain axis [7].

Prebiotics may exert regulating effects on each of these communication pathways; adrenocorti- cotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) [21]. They may regulate anxiety, depression, stress, autism, learning, and memory [38].

Probiotics are potential neuroprotective agents for preterm infants.

By improving gut mucosal barrier integrity, regulation of appropriate bacterial colonization, enhancing mucosal IgA response, immunomodulation, thus leading to an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines [39]. Subsequently they induce changes in signaling pathways from the gut to the brain, which may ultimately modulate brain development [14].

Some probiotic mixtures induce beneficial psychological effects and decrease serum cortisol levels and result in reduced anxiety-like behavior (in rodents). The ability of probiotics to modulate the microbiome-gut-brain axis has been demonstrated to be strain-specific. There are no beneficial effects on neurodevelopmental performance or reductions in major impairments, such as hearing loss, cerebral palsy, visual impairment, and mental retardation have been reported [7,14,23].

Probiotics are micro-organisms that colonize the gut and provide health benefits to the host through improving gut mucosal barrier integrity, regulating appropriate bacterial colonization, enhancing mucosal IgA response, and immunomodulation. This leads to an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines [39]. Subsequently, this induces changes in signaling pathways from the gut to the brain, which may ultimately modulate brain development [14].

Brain and probiotics

Probiotics, pre-biotic oligosaccharides, and certain amino acids are potential candidates for neuroprotection. They play a neuroprotective role against white matter injury through modulation of inflammation and infection. Thus, may influence the microbiome-gut-brain axis. Probiotics may exert effects on each of these communication pathways: ACTH, adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH).

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Brain and prebiotics

Prebiotic oligosaccharides are indigestible food components that naturally occur in breast milk. They have antimicrobial, immunomodulatory, and anti-inflammatory functions. They provide benefits to the developing preterm brain [40].

Prebiotics improve the infant's intestinal microbiota by promoting growth of Bifidobacteria, (bifidogenic effect) which may in turn reduce the burden of potentially pathogenic micro-organisms in the gut with direct interaction with immune cells, supporting the immature immune system and establishing an immunologic balance [41]. So far, no studies have been undertaken to evaluate the effect of prebiotic oligosaccharides on brain development. (A mixture of pro- and prebiotics often referred to as synbiotics).

Short chain fatty acids

The microbiota early in life produces lower levels of short chain fatty acids (SCFAs) compared to adults, since they lack the prevalence of the microbes with the enzymes for their production and generally eat a diet low in complex dietary carbohydrates necessary for the production of SCFAs. Direct exposure of the SCFA (propionate) to animal brain tissue results in the development of autistic-like behavior

[42]. Thus, an increase in these metabolites may lead to alterations in brain function. This may occur when it is preceded with dysbiosis and in case of intestinal permeability.

Breast milk and brain

Breast milk is the source of healthy omega 3 fatty acids for healthy brain development. It is beneficial for baby's immune system and for mother's health. It increases mother-child bonding and emotional quotient (E.Q). It also has positive effects on intelligence quotient (I.Q) and behavior [44].

Breast milk and baby's gut and brain

The human breast milk has brain cell growth factors (neurotrophic factors), cytokines at varying concentrations, and protein extracts (which increase the amount of surviving enteric neurons as well as neurite outgrowth) [43,44].

Neurotrophic factors are proteins involved in the growth and survival of developing neurons. They are essential during the early development of the brain and help maintain healthy neuronal function throughout infant life. "Trophic" is actually derived from a Greek word meaning "to nourish", so neurotrophic factors are substances that nourish neurons. Cytokines are substances secreted by immune system cells. They play a role in cellular communication and behavior.

When is the brain fully developed?

Our brains are continually re-shaping themselves to meet the demands of everyday life, even throughout adulthood. There are certain aspects of brain structure and function that do level off during development. The number of neurons peaks even before birth. Some 100 billion are formed during the first five months of gestation. Recent evidence suggests that new neurons are produced throughout life, less rapidly, in numbers enough only to replace those that gradually die off [45,46].

There is great number of neurons present at birth, but brain size itself increases more gradually due to changes in individual neurons (like when trees add branches). Thus, each brain cell begins as a tiny sapling and only gradually sprouts its hundreds of long, branching dendrites [45,46].

Conclusion

Strong evidence suggests that gut microbiota has an important role in bidirectional interactions between the gut and the nervous system. It interacts with CNS by regulating brain chemistry and influencing neuro-endocrine systems associated with stress response, anxiety and memory function. Many of these effects (microbiome) appear to be strain specific, suggesting a potential role of certain probiotic strains as novel adjuvant strategy for neurologic disorders. The effect of CNS on microbiota composition is probably mediated by a perturbation of the normal luminal/mucosal habitat that can also be restored by the use of probiotics and possibly by diet.

Summary

The brain of a human fetus grows rapidly from the 10^{th} to 18^{th} week of pregnancy and for about 2 years after birth. Malnutrition during periods of rapid brain growth may have devastating effects on the nervous system and can affect not only neurons, but also glial cell development and growth with subsequent effects and sequels that persists into childhood and adolescence.

Growing evidence supports the existence of a micro biome-gut-brain axis. The microbiome interacts with the brain through immunological, endocrine, and neural pathways. The brain interacts with the gut through nervous and humeral action, prenatally and postnatally.

Probiotics, prebiotics, breast feeding (oligosaccharide) and certain amino acids with their immunomodulatory and/or antinflammatory effects may serve as neuroprotective agents and potential candidates for neuro protection against white matter injury.

Growing infants with abnormal microbial flora are more vulnerable to develop frequent and more severe common day-to-day infections. It will affect the growing brain thereby triggering a vicious cycle of abnormal behavior and gastrointestinal malfunction.

Acknowledgments

Many thanks to Miss Lubna Sinno, the secretary of the research department of the Makassed University General Hospital (Beirut Lebanon) for having the patience to correct all the manuscript and arrange the references, to Dr Majed koleilat (Evansville ,Indiana) To all the references which I used .

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Volume 2 Issue 4 October 2016