Seminars in Fetal & Neonatal Medicine xxx (2016) 1–8

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Fetal, neonatal, and infant microbiome: Perturbations and subsequent effects on brain development and behavior

Rochellys Diaz Heijtz*

Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Keywords:
Commensal gut microbiota
Neurodevelopment
Germ-free mice
Autism spectrum disorder
Cognition
Antibiotics
Breastfeeding

SUMMARY

The human gastrointestinal tract harbors a diverse and complex community of microbes, termed gut microbiota, that normally assemble during the first postnatal years of life. This evolution-driven process has been shown to contribute to the developmental programming of epithelial barrier function, gut homeostasis, and angiogenesis, as well as the development and function of the immune system. Research over the last few years has revealed that the actions of the gut microbiota have much wider effects on host physiology and development than originally believed, including the modulation of brain development and behavior. This article briefly reviews recent findings on the impact of the gut microbiota on brain development, and how disturbances in the assembly and maturation of the gut microbiota may impact development of motor, social, and cognitive functions. The potential link between microbiota and metabolic requirements of the developing brain is also considered.

© 2016 Published by Elsevier Ltd.

1. Introduction

Human brain development is a protracted process that begins in utero and continues at least through late adolescence [1]. Critically, this process involves more than just a simple unfolding of a genetic blueprint, but rather a complex interaction between genetic and environmental factors. It is now recognized that the epigenome, through which environmental factors regulate gene expression, is responsible for long-lasting programming effects of environmental experiences (e.g. early life stress) on brain and behavior [2]. Over the past several decades, it has become clear that environmental influences during early life may profoundly affect brain development and later life structure and function. One such external environmental factor is the commensal gut microbiota that over evolutionary time has adapted to coexist not merely in a commensal, but rather a mutualistic relationship with mammals [3]. During birth and rapidly thereafter, the newborn is massively colonized with trillions of bacteria. This postnatal microbial colonization process has been shown to contribute to developmental programming of epithelial barrier function, gut homeostasis, and angiogenesis, as well as the development and function of the gut immune system [4]. A growing number of animal studies have revealed that the gut microbiota has effects on host physiology and development outside the gastrointestinal (GI) system, including the early-life programming of brain circuits involved in the control of stress response, motor activity, anxiety-like behavior and cognitive functions [5–10]. These findings have raised the possibility that perturbations of the developing infant gut microbiota may directly, or indirectly, modify developmental trajectories of the human brain and subsequent function in later life. The discovery of the size and complexity of the human microbiome (see other contributions in this issue of *Seminars*), in combination with the aforementioned preclinical studies have given way to a paradigm shift in our conceptualization of the origin of human neurodevelopmental and psychiatric disorders [11]. The precise mechanisms mediating the interactions between the gut microbiota and the developing brain remain largely unknown, but are likely to involve multiple direct and indirect pathways [12]. This article begins with a general overview of early postnatal human brain development and the impact of the gut microbiota on key neurodevelopmental processes, followed by a consideration of how some factors that perturb the developing gut microbiota might affect brain development and subsequent behavior. In addition, the potential link between the gut microbiota and metabolic demands of the developing brain is also considered.

* Address: Department of Neuroscience, Karolinska Institutet, Retzius väg 8, SE-171 77, Stockholm, Sweden. Tel.: +46 (08) 524 87886.
E-mail address: rochellys.heijtz@ki.se.

http://dx.doi.org/10.1016/j.siny.2016.04.012
1744-165X/© 2016 Published by Elsevier Ltd.

Please cite this article in press as: Diaz Heijtz R, Fetal, neonatal, and infant microbiome: Perturbations and subsequent effects on brain development and behavior, Seminars in Fetal & Neonatal Medicine (2016), http://dx.doi.org/10.1016/j.siny.2016.04.012

2. Gut microbiota acts as "environmental agent" shaping brain development

The first years of postnatal life represent a time of rapid changes in brain structure and function. The neonate brain grows from about 36% to about 80–90% of its adult volume by the age of 2 years [1,13]. During this period, there is massive outgrowth of dendrites and axons, followed by the formation of new synapses (synaptogenesis), expansion of glia cells, and myelination. Rapid overproduction of synaptic connections continues during the first two postnatal years, peaking between 3 and 24 months depending on the cortical region [14], before synaptic refinement and elimination occur in late childhood continuing beyond adolescence [15]. By the end of the second year, the overall pattern of adult myelination is established [16]. However, myelination continues, at a slower rate, into the second decade of life, with prefrontal regions being among the last brain areas to attain mature levels [17]. Interestingly, the maturation of the gut microbiota also occurs during the first two to three years of postnatal life, coinciding with this critical window of early brain development [18].

The importance of a normal gut microbiota for synaptogenesis is exemplified by our studies using the germ-free (GF) mouse model (devoid of any microbiota throughout development). These mice show higher expression of synaptic-related proteins, i.e. synaptophysin and PSD-95 in the striatum compared to conventionally raised mice (specific-pathogen-free; SPF) [5]. Conventionalization of GF mice early in life normalized the expression levels of these two synaptic-related proteins, suggesting that host microbes modulate synaptic development (either the production of new synapses or the pruning of existing ones). Recent evidence indicates that myelination in the prefrontal cortex can be affected by the commensal gut microbiota. In the absence of microbiota, mice displayed increased levels of several key myelin-associated genes (e.g. myelin basic protein, myelin oligodendrocyte protein, and myelin-associated glycoprotein), and hypermyelination as indicated by a decreased g-ratio (quantification of myelin thickness relative to axonal diameter) [19]. Although further experiments would be required to elucidate how the gut microbiota regulates synaptogenesis and myelination, these results indicate that brain regions important for motor control and cognitive functions are shaped during development by the host microbiota.

Interestingly, accelerated brain growth in infancy has been associated with a broad range of developmental delays in motor, language, and cognitive functions [20,21]. For example, neurodevelopmental disorders, including autism spectrum disorder (ASD), have been associated with "atypical brain connectivity patterns" involving higher-order association neocortical regions. Moreover, many children with ASD also suffer from gastrointestinal (GI) problems such as abdominal pain, gases, diarrhea, and constipation. In fact, some studies have found a strong positive association of autism severity with GI dysfunction [22,23]. The causes of ASD-associated GI problems remain unclear, but may be linked to an imbalance of commensal bacteria in the gut, as several studies have reported that children with ASD exhibit altered composition of the gut microbiota [24]. It will therefore be of great interest to investigate the potential link between the "relative degree of microbiota maturity" (both in terms of its composition and metabolic capacity) and the connectome of infants with low and high risk for autism in a multicenter prospective longitudinal study. In parallel, the use of gnotobiotic mouse models could provide a powerful tool to examine the effects of gut microbiota from these infants on underlying cellular and molecular determinants of atypical brain connectivity.

Previous studies have demonstrated that microglia, the resident immune cells of the central nervous system (CNS), play an important role not only during inflammation, but also in shaping neural circuits in the developing brain [25]. In a recent study, Erny et al. discovered that indigenous microbes control microglia maturation and function [26]. In the absence of microbiota, microglia display altered cell proportions and an immature phenotype, and they have a diminished response to bacterial (i.e. lipopolysaccharide) or virus (i.e. lymphocytic choriomeningitis virus) challenges, indicating that a microbiota is required to prime the innate immune system in both the periphery and central CNS. A breakthrough study by Clarke et al. [27] showed that commensal microbiota is a source of peptidoglycan (PGN; a major component of the bacteria cell wall) that systemically primes the innate immune system, enhancing killing by bone marrow-derived neutrophils of pathogens (e.g. *Streptococcus pneumoniae* and *Staphylococcus aureus*). The pattern recognition receptor (PRR) nucleotide-binding oligomerization domain-containing protein-1 (Nod1), which recognizes meso-diaminopimelic acid (meso-DAP)-containing PGN found predominantly in Gram-negative bacteria, was identified as the homeostatic regulator mediating the systemic effects of PGN. Interestingly, some Gram-negative bacteria from the Proteobacteria phylum, such as *Escherichia* and *Shigella* spp., are among the most abundant microbes during the first year of life [28]. It is therefore tempting to speculate that, during early postnatal development, the meso-DAP-containing PGN found in *Escherichia* and *Shigella* spp. may play a role in priming the host immune system, and the long-term programming of brain and behavior. In accordance with this hypothesis, we recently reported that during critical windows of development, PGN-derived from the commensal gut microbiota can be translocated into the developing brain, and sensed by specific PRRs of the innate immune system [29]. These findings underscore the need to further study and characterize the influence that endogenous microbial-derived products such as PGN may have on the developing brain.

3. Potential prenatal–maternal exchange of microbiota in utero

Until recently, the traditional view has been that the intrauterine environment of a healthy pregnancy is free of any bacteria. Recent studies, however, have challenged the idea of a sterile intrauterine environment by demonstrating the presence of bacterial DNA in the amniotic fluid, umbilical cord blood, meconium, placenta and fetal membranes from healthy pregnancies without any indication of infections or inflammation (for review, see [30]). For example, Satokari et al. found the presence of DNA derived from the commensal intestinal bacteria in full-term placenta from healthy pregnant women collected after elective cesarean section (C-section) without rupture of membranes [31]. Moreover, Aagaard et al. have demonstrated that the human placenta harbors a unique, low-abundance, but metabolically rich microbiome that is composed of commensal bacteria from the Firmicutes, Tenericutes, Proteobacteria, Bacteriodetes, and Fusobacteria phyla. The placenta microbiome, which resembles the oral microbiome, appears to be highly sensitive to the maternal health status, as its composition varies in association with maternal history of antenatal infection, antibiotic exposure, and preterm birth [30]. Consistent with these findings, previous studies have shown that oral inoculation of pregnant BALB/c mice with a genetically modified *Enterococcus faecium* strain resulted in a transfer of this strain to the amniotic fluid [32]. Although there is still some skepticism regarding some aspects of the human placenta microbiome concept, and about the origin and viability of the bacteria found in the intrauterine environment [33], the aforementioned findings do raise the intriguing possibility that transfer of maternal microbiota to the fetus may occur in utero, thereby initiating the colonization of the fetal gut. The potential role of the placenta microbiome on the developing fetal brain needs further investigation.

Please cite this article in press as: Diaz Heijtz R, Fetal, neonatal, and infant microbiome: Perturbations and subsequent effects on brain development and behavior, Seminars in Fetal & Neonatal Medicine (2016), http://dx.doi.org/10.1016/j.siny.2016.04.012

Download English Version:

https://daneshyari.com/en/article/5696919

Download Persian Version:

https://daneshyari.com/article/5696919

Daneshyari.com