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A novel role for maternal stress and microbial transmission in early life programming and neurodevelopment

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ABSTRACT

Perturbations in the prenatal and early life environment can contribute to the development of offspring stress dysregulation, a pervasive symptom in neuropsychiatric disease. Interestingly, the vertical transmission of maternal microbes to offspring and the subsequent bacterial colonization of the neonatal gut overlap with a critical period of brain development. Therefore, environmental factors such as maternal stress that are able to alter microbial populations and their transmission can thereby shape offspring neurodevelopment. As the neonatal gastrointestinal tract is primarily inoculated at parturition through the ingestion of maternal vaginal microflora, disruption in the vaginal ecosystem may have important implications for offspring neurodevelopment and disease risk. Here, we discuss alterations that occur in the vaginal microbiome following maternal insult and the subsequent effects on bacterial assembly of the neonate gut, the production of neuromodulatory metabolites, and the developmental course of stress regulation.

1. Introduction

Early life perturbations such as stress, inflammation, or infection produce long-term effects on the developing brain, increasing subsequent risk of neuropsychiatric disorders throughout life. Despite advances in understanding the mechanistic roles of the maternal milieu in normal and pathological neurodevelopment, significant progress in biomarker discovery and the treatment of neuropsychiatric disorders has not been made. This is in part due to the multifactorial presentation of neuropsychiatric conditions and common comorbidities, including chronic gastrointestinal (GI) dysfunction. As a growing body of evidence suggests that a critical window for neurodevelopment overlaps with microbial colonization of the gastrointestinal tract, it is likely that environmental perturbations could similarly impact both systems (Borre et al., 2014; Stilling et al., 2014).

In particular, maternal stress during pregnancy has been associated with an increased incidence of neurodevelopmental disorders and gastrointestinal dysfunction (Chrousos, 2009; Mawdsley and Rampton, 2006; O'Mahony et al., 2009). Among the many maladaptive effects it exhibits on the mother, chronic stress during pregnancy alters vaginal host immunity and resident bacteria composition (Culhane et al., 2001; Wadhwa et al., 2001; Witkin et al., 2007). The vaginal ecosystem is a dynamic community shown to be sensitive to a variety of factors such as body composition, diet, infection, antibiotic treatment and stress (Bennet et al., 2002; Cho et al., 2012; Turnbaugh et al., 2009; Ravel et al., 2011; Koenig et al., 2011), and is poised to communicate information about the state of the pending external environment. Maternal vaginal microflora is ingested into the neonatal gut during parturition, establishing the initial microbial population. Therefore, perturbations to the vaginal ecosystem could have significant consequences for offspring development and disease risk. For example, dysbiosis of vaginal microflora can impact the microbial assembly of the neonatal gut where decreased diversity and stability of microbial populations could promote disruption of key processes involved in host metabolism, immune function, and neurodevelopment (Round and Mazmanian, 2009; Nicholson et al., 2012; Maslowski and Mackay, 2011; Cryan and Dinan, 2012). The hypothalamic-pituitary-adrenal (HPA) stress axis may be particularly sensitive to gut microbial disruption as its development overlaps with the initial colonization of the neonatal gut (Borre et al., 2014; Walker et al., 1986). Critically, HPA axis dysregulation has long been recognized as a hallmark of inflammatory and psychiatric disorders, where both hyper- and hypo-responsivity have been reported (Bale et al., 2010; Howerton and Bale, 2012; Moghaddam, 2002; Lupien et al., 2009).

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In this review, we discuss the influence of maternal-infant microbial transmission on early life programming, and the ability for stress to alter this process (Fig. 1). Specifically, we will highlight a potential mechanistic role for the neonate gut microbiome to contribute to nutrient metabolism, thereby linking itself to the developing brain. We outline the bidirectional communication between the HPA stress axis and gut microbiota, and consider the implication of early microbial dysbiosis during critical neurodevelopmental windows, emphasizing potential sex-specific consequences across a number of behavioral domains. We conclude by providing some perspectives on future directions in this area.

2. The vaginal microbiome

The female reproductive tract and its microflora form a dynamic ecosystem, with the vaginal mucosal environment determining the survival of specific bacterial species, and the microflora in turn contributing to the vaginal environment. The hormonal control of vaginal glycogen content is believed to be a major factor shaping the microbial composition and stability within the female reproductive tract. Upon estradiol stimulation, glycogen is deposited onto mature vaginal epithelium where it is metabolized to glucose by the epithelial cells and bacterial enzymes (Linhares et al., 2011; Redondolopez et al., 1990). *Lactobacillus* was the first bacterial genus identified with the capacity to metabolize vaginal glucose into lactic acid and hydrogen peroxide, and it is predominantly these H_2O_2-producing strains that thrive in low vaginal pH conditions. By maintaining low vaginal pH and producing H_2O_2, as well as by stimulating the immune system and preventing further colonization through competitive exclusion, healthy *Lactobacillus* populations protect the female reproductive tract from infection by opportunistic pathogens. Indeed, overgrowth of *Gardnerella vaginalis*, a harmful toxin-producing bacterium, has been associated with increased vaginal pH and loss of H_2O_2-producing *Lactobacillus* (Hawes et al., 1996; Mijac et al., 2006; Soper, 1997; Tomas et al., 2003; Vallor et al., 2001).

During pregnancy, steroid hormones such as progesterone and estradiol stimulate high levels of glycogen deposition onto vaginal epithelium further promoting the growth of favorable acidophilic vaginal bacteria like *Lactobacillus*. However, these hormones also play a significant role in immunosuppression during pregnancy. While this effect is adaptive as it allows tolerance of the developing offspring, it may also increase maternal vulnerability to environmental challenges (Trowsdale and Betz, 2006; Zuk and Stoehr, 2002). Stress during pregnancy can exaggerate the normal physiological immunosuppression, thereby increasing maternal vulnerability to genitourinary infection and its related obstetrical risks including associations with neurodevelopmental disorders. For instance, in a recent epidemiological study, mothers of children with autism spectrum disorder reported greater frequency and severity of vaginal bacterial infections during pregnancy (Zerbo et al., 2013). Importantly, recurrent vaginal bacterial and fungal infections can trigger a variety of local and global responses that may result in the eventual loss of the beneficial *Lactobacillus*-dominant vaginal ecosystem (Gupta et al., 1998; Ehrstrom et al., 2005). The downstream effects of stress-related *Lactobacillus* depletion on maternal-infant microbial transmission, host metabolism, and immune function remain to be examined, but likely include important consequences for the developing brain.

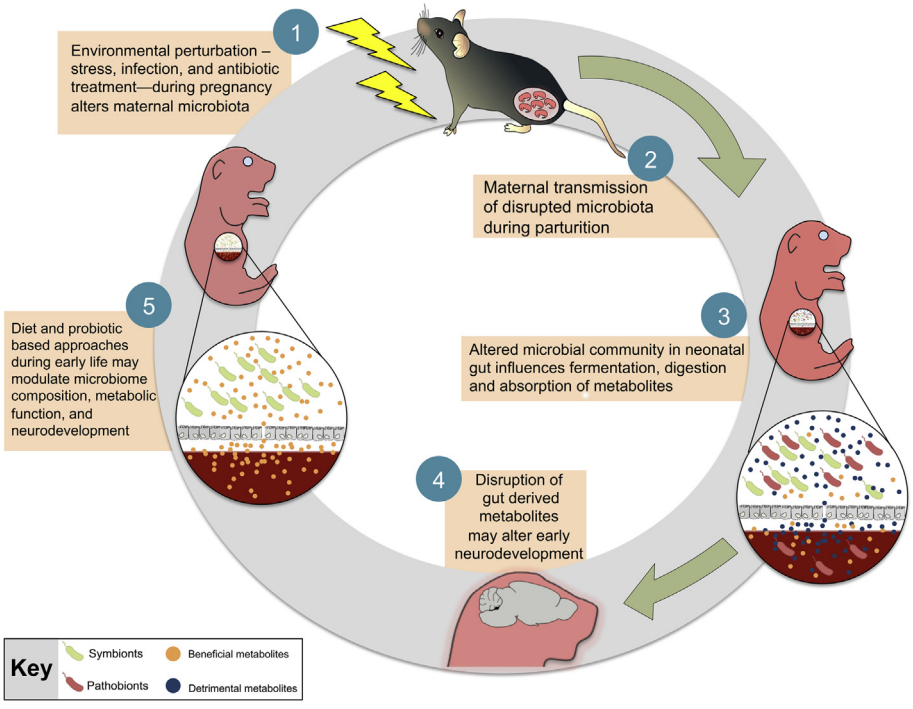

Fig. 1. A proposed model for the role of maternal microbial transmission in early life programming and neurodevelopment. Environmental perturbations, such as stress or infection, during pregnancy destabilize the vaginal ecosystem that may lead to dysbiosis of the vaginal flora characterized by a shift from a *Lactobacillus*-dominant (symbionts) environment to overgrowth of opportunistic pathogens (pathobionts). Vertical transmission of a disrupted microbiota may compromise key developmental processes of the neonate, including the synthesis and absorption of microbe-derived metabolites, maturation of the gastrointestinal tract, and immune function. Outcompetition by pathobionts in the neonatal gut may increase production of detrimental metabolites and alter downstream neurodevelopmental events, including development of the hypothalamic-pituitary-adrenal (HPA) stress axis, as its development overlaps with early colonization patterns of the neonatal gut. Disruption during this critical window may result in long-term programming that persists even after stable core microbiota has been established. Administration of probiotics or dietary factors that promote maturation of the neonatal gut provide a promising avenue of therapeutic treatments by which to modulate microbiota composition, metabolic function, and neurodevelopment of the host.