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Neonatal abstinence syndrome and the gastrointestinal tract

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ABSTRACT

Development of a healthy gut microbiome is essential in newborns to establish immunity and protection from pathogens. Recent studies suggest that infants who develop dysbiosis may be at risk for lifelong adverse health consequences. Exposure to opioid drugs during pregnancy is a factor of potential importance for microbiome health that has not yet been investigated. Since these infants are born after an entire gestation exposed to mu opioid receptor agonists and have severe gastrointestinal and neurological symptoms, we hypothesize that these infants are at risk for dysbiosis. We speculate that opioid exposure during gestation and development of NAS at birth may lead to a dysbiotic gut microbiome, which may impair normal microbiome succession and development, and impact future health of these children.

Introduction

Development of a healthy gut microbiome is essential in newborns to establish immunity and protection from pathogens [1]. Conditions known to impact the developing microbiota in infants include birth delivery method [2], diet [3,4], early hospitalization [5], antibiotic use, and country of origin [6]. Recent studies suggest that infants who develop dysbiosis may be at risk for lifelong adverse health consequences [7–9]. Much work has been completed to describe the microbiome of the healthy, term infant. The early studies were limited by sample size and diverse characteristics, but consistently reported Bifidobacterium as the dominant organism [4,10–12]. Eggesbo and colleagues [13] optimized design in a study of 85 infants delivered vaginally during the first 4 months of life, providing an excellent reference for the colonization process. Infants were exclusively breast fed for the first month, and were partially or exclusively breastfeeding at 4 months in their native Norway. Bifidobacterium was confirmed to be the most prevalent constituent, findings which have been replicated in more recent investigations [14,15]. Although microbiome characteristics have been generally described in the healthy newborn, there is some evidence that differences exist among different countries [6], illustrating the gut sensitivity to the environment. There is also new concern that the built environment (that in which we live) greatly influences the human microenvironment in ways not fully understood [16]. Many people live in a structure that has limited air circulation with the outdoors, and often air conditioning that probably limits the types of microbiota that can thrive in them [16]. Given the extreme sensitivity of microbiome development to external factors, it is logical to suggest that a fetal gut chronically exposed to opioids during gestation will be negatively impacted after birth. This is supported by the finding that opioids are associated with both decreased diversity and increased numbers of virulent and antibiotic resistant pathogens in the adult gut microbiome [17].

Untreated pregnant women who are opiate-dependent are at great risk for numerous pregnancy complications (low birth weight, preeclampsia, bleeding, malpresentation, fetal distress and meconium aspiration). These pregnancy effects are combined with serious infant morbidity and a 74-fold increase in sudden infant death syndrome [18]. Pregnant women addicted to opioids are treated with methadone because it improves important perinatal outcomes such as birth weight [19]. Pregnant women are administered methadone or buprenorphine, long acting μ opioid agonists, as a mechanism to reduce exposure of the fetus to repeated cycles of opioid exposure. These opiates, however, are not innocuous and have short term effects on infant's nervous system and neurobehavior [18] and put the infant at risk for withdrawal symptoms after birth.

Withdrawal from methadone causes neonatal abstinence syndrome (NAS) [20–22], and infants suffer from inconsolable crying and gastrointestinal (GI) distress [23]. This distress is manifested as diarrhea, cramping, and poor feeding, suggesting alterations in normal gastrointestinal function. Long term effects of prenatal opioid exposure include developmental delays, poor fine motor coordination [24], and attention deficit hyperactivity disorder [25,26]. Although the literature is silent on any associations of prenatal opioid exposures with physical health problems, it has been postu-

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lated that prenatal exposure could affect gut development, immune function, and neurobehavior [27]. NAS affects more than 10,000 infants annually, and the rate has increased significantly since 2004 ($p < 0.001$) [28]. The costs of hospitalization for NAS have been estimated to have increased from $190 million to $720 million between 2000 and 2009 [28], increasing again in 2013 to $1.5 billion with 80% paid by Medicare [29]. The most well-known outcome of any opioid exposure is NAS, reported to occur in 75–90% of exposed infants [30].

The hypothesis

A factor of potential importance for microbiome health that has not yet been investigated is exposure to opioid drugs during pregnancy. Since these infants are born after an entire gestation exposed to mu opioid receptor agonists and have severe gastrointestinal and neurological symptoms, we hypothesize that these infants are at risk for dysbiosis. We speculate that opioid exposure during gestation and development of NAS at birth may lead to a dysbiotic gut microbiome, which may impair normal microbiome succession and development, and impact future health of these children. Our model of the proposed mechanism of action is illustrated in Fig. 1. The maternal opioid abuse (or treatment with methadone/buprenorphine) activates the fetal gut mu receptors, which results in altered (decreased) gut motility and presumed effects on transcription pathways across time. The decreased gut motility is expected to alter development of a normal microbiome. Once withdrawal symptoms appear as a newborn, gut motility drastically increases, causing pain, distention, and behavioral stress in the newborn. The effects on transcription pathways across time may also alter the responsiveness of the gut to opioids, resulting in altered gut motility, as well as contributing to an altered microbiome. There is emerging evidence that genetic and/or epigenetic factors may provide some protection against NAS [31,32].

The impact of prolonged prenatal exposure to opioids during embryogenesis on MORs and gut physiology/motility and the potential impact on the microbiome are unknown. The MORs in the gut are involved in physiological and pathophysiological phenomena such as feeding [33], obesity [34], and immunosuppression [35]. These receptors are widely dispersed in the gut during gestation [36–38] and play an important role in motility and secretion. Gut motility then plays an important role in the determination of number and diversity of bacteria [39]. Motility has a bidirectional relationship with the commensal microbiome [40], in that microflora exerts an effect on motility, and motility impacts diversity. Gut motility is decreased by activation of MORs, and increases beyond normal rates during withdrawal. Since gut motility has a bidirectional relationship with the microbiome [39], it is unclear if motility changes are due to decreased MOR binding, changes in the microbiome, or a combination of both. Activation of MORs in the gut decreases motility by slowing peristalsis [36], potentially impacting or altering the microbiota. Normally, anaerobic organisms thrive in the distal gut with slow peristalsis, while aerobic organisms are more commonly found in the proximal gut where peristalsis is more rapid [39], but with motility changes, this balance is likely to be disrupted. The common symptom of abdominal cramping experienced by adults in withdrawal are likely to manifest as irritability and distress in newborns with NAS. We have reported signs of infant distress that interrupted feeding in infants with NAS, and many times accounted for more than half of the feeding session [41].

The gut has more neurons than any organ other than the central nervous system, and is considered by many to be a neurological organ (a "second brain"). The enteric nervous system (ENS) supplies all layers of the gut, and thus autonomously regulates virtually every aspect of digestion, including secretion and motility. Motility, secretion and absorption are largely mediated by transmembrane G protein-coupled receptors in the gastrointestinal tract which are responsive to many different messenger molecules, including opiates such as methadone. MOR agonist binding results in receptor endocytosis, and pre- and post-synaptic effects, including potassium channel activation, membrane hyperpolarization, calcium channel inhibition and decreased cyclic adenosine monophosphate. These effects interrupt normal enteric propulsion and water and electrolyte secretion, leading to chronic constipation, bloating and pain. Like many receptors, MORs respond by desensitization and resensitization [42]. Genes involved in coding MORs are subject to epigenetic influences such as methylation, which has been observed in infants with NAS [32]. The gene promoter coding for MOR is methylated (and thus silenced to some degree) in heroin addicts [43] and in addicts maintained on methadone [44]. MORs can become desensitized when chronically exposed to opioids, and signaling is decreased [45]. Yet, with chronic use of MOR agonists, while receptors may be desensitized, there is still often a significant inhibitory effect of opioids on gut motility and secretion. This may be related to refractoriness of the colon to MOR desensitization.

The interactions between gut microbiome and motility are bidirectional [40]. Disruption of the delicate balance leads to local and systemic consequences such as diarrhea or constipation [40]. The mechanisms that have been implicated from the microbiota side are release of end products of bacterial fermentation, intestinal neuroendocrine factors, and release of GI immune system mediators [40]. These products can reach and affect many tissues, including the brain. Dysbiosis in mice has been reported to be associated with down regulated MORs, and increased colonic contractility [46]. The modulatory mechanism of action through which MORs affects gut motility and secretion involves inhibition of acetyl-

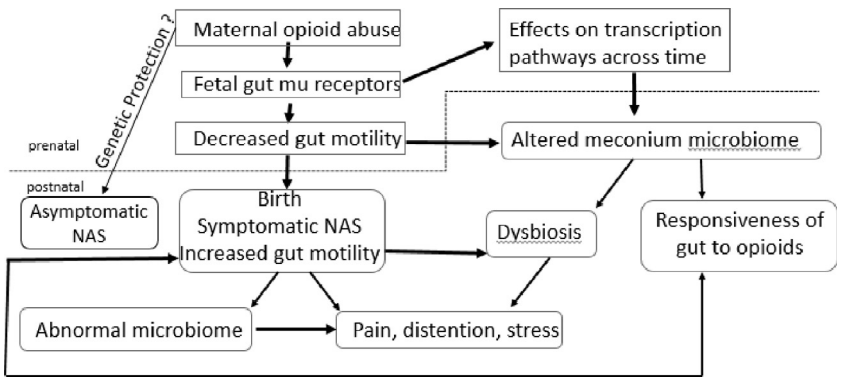

Fig. 1. Model of the proposed mechanism of action.