



Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood



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Summary Early-life adverse experiences, including prenatal stress (PNS), are associated with a higher prevalence of neurodevelopmental, cardiovascular and metabolic disorders in affected offspring. Here, in a rat model of chronic PNS, we investigate the impact of late gestational stress on physiological outcomes in adulthood. Sprague-Dawley pregnant dams were subjected to repeated restraint stress from embryonic day 14 to day 20, and their male offspring were assessed at 4 months of age. PNS induced an exaggeration of the hypothalamic–pituitary–adrenal (HPA) axis response to stress, as well as an elevation of blood

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pressure and impairment of cognitive function. Altered respiratory control was also observed, as demonstrated by increased variability in basal respiratory frequency and abnormal frequency responses to both hypoxic and hypercapnic challenges. PNS also affected gastrointestinal neurodevelopment and function, as measured by a decrease in the innervation density of distal colon and an increase in the colonic secretory response to catecholaminergic stimulation. Finally, PNS induced long lasting alterations in the intestinal microbiota composition. 16S rRNA gene 454 pyrosequencing revealed a strong trend towards decreased numbers of bacteria in the *Lactobacillus* genus, accompanied by elevated abundance of the *Oscillibacter*, *Anaerotruncus* and *Peptococcus* genera in PNS animals. Strikingly, relative abundance of distinct bacteria genera significantly correlated with certain respiratory parameters and the responsiveness of the HPA axis to stress. Together, these findings provide novel evidence that PNS induces long-term maladaptive alterations in the gastrointestinal and respiratory systems, accompanied by hyper-responsiveness to stress and alterations in the gut microbiota.

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1. Introduction

The prenatal period is a critical stage of development for all major physiological systems. Consequently, exposure to an adverse environment *in utero* can alter foetal developmental trajectories that increases the risk for neuropsychiatric, metabolic and cardiovascular disorders in affected offspring later in life (Fowden et al., 2005; Markham and Koenig, 2011; Mastorci et al., 2009). One form of *in utero* adversity that has received a growing appreciation is maternal psychosocial stress during pregnancy or prenatal stress (PNS). PNS, including maternal depression and anxiety, affects a significant number of pregnant women (Bennett et al., 2004) and is associated with a higher prevalence of neurodevelopmental disorders such as autism spectrum disorder, attention deficit hyperactivity disorder and schizophrenia (Boersma et al., 2014; Ronald et al., 2011). While the causative molecular basis of these associations is still the subject of intensive research, it is clear that the hypothalamic–pituitary–adrenal (HPA) stress axis is shifted towards a hyperactive mode (Glover et al., 2010; Weinstock, 2008), which is therefore likely to affect many physiological systems in the offspring. Indeed, in animal models of early-life postnatal stress, hyper-responsiveness of the HPA axis is coupled with altered plasticity of respiratory control, increased visceral pain sensitivity and impaired intestinal barrier function (Dumont et al., 2011; O'Mahony et al., 2009; Söderholm et al., 2002). To our knowledge, these associations have not been investigated in the context of PNS to date.

There is growing awareness that the composition of an individual's gut microbiota influences their health status, suggesting that PNS-induced alterations to gut microbiome could dramatically impact on physiological function in affected offspring. Indeed, animal studies demonstrate that exposure to PNS disturbs intestinal colonisation of neonates (Jašarević et al., 2015). Furthermore, in a recent study PNS was shown to affect the composition of the human infant gut microbiota over the first 110 days after birth (Zijlmans et al., 2015). Moreover, there is growing evidence that chronic stress can alter the vaginal microbial ecosystem in the mother, which in turn impairs the initial microbial colonisation of the neonatal intestine (Gur

et al., 2015; Jašarević et al., 2015). The maintenance of microbial diversity is important for the normal development of the CNS, as well as gastrointestinal (GI) and respiratory function (Borre et al., 2014; Collins et al., 2014; Desbonnet et al., 2015; Moreno-Indias et al., 2015). However, whether maternal stress during pregnancy has a long-term impact on microbiota composition and whether these changes in microbiota are associated with functional physiological outcomes in the PNS offspring is largely unknown.

To address these questions, we used a rat model of maternal stress to examine the impact of PNS on (a) the plasticity of respiratory control, (b) colonic innervation and secretomotor function, (c) the reactivity of the stress response and (d) on the composition of the gut microbiota in adult offspring.

2. Methods

2.1. Animals

Animal protocols were approved by the Animal Experimentation Ethics Committee of University College Cork and performed in accordance with EU Directive 2010/63/EU. Sprague-Dawley (SD) rats (Harlan, UK) were housed on a 12 h light/12 h dark cycle; standard rodent chow and water were given *ad libitum*.

2.2. PNS protocol

Pregnant SD females were housed individually and randomly assigned to the PNS ($n=6$) or control ($n=5$) group. The PNS protocol was adapted from (Ward and Weisz, 1984) and performed during the last week of pregnancy (embryonic days 14–20). Pregnant dams were placed 3 times \times 45 min daily into transparent plastic restrainers (8.6 cm in diameter \times 21.6 cm in length, LABEX of MA, US) under bright light (1200 lx) at 10:00 am, 14:00 pm and 18:00 pm. Control dams were left undisturbed in their home cages. After birth pups were raised with their mothers. Male offspring were weaned on postnatal day 21 and group housed with the same-sex littermates.

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