Maternal gut microbiome alteration has enduring effects on offspring's metabolic programming and neuroendocrine plasticity

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Maternal gut microbiome alteration has enduring effects on offspring's metabolic programming and neuroendocrine plasticity

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The alarmingly high prevalence of obesity and type 2 diabetes, particularly in children, highlights the need to better understand the mechanisms involved in the development of these pathological conditions. Previous studies showed that alterations in the maternal nutritional environment disrupt the development of hypothalamic circuits with enduring metabolic consequences in the offspring. Recent evidence also linked maternal gut microbiome with offspring's brain development and behavior. Nevertheless, whether the maternal gut microbiome(mGM) affects the development of offspring's hypothalamic circuits with short- and long-term consequences on hypothalamic function remains unknown. Here, we examined the consequences of impairment of mGM on physiological and neurodevelopmental outcomes in the offspring. To this aim, we developed a mouse model of maternal dysbiosis during gestation and lactation by administering a cocktail of large spectrum antibiotics(ABX) in dams. The aim was to target critical phases of the hypothalamic development,that include embryonic neurogenesis,postnatal circuit formation and hypothalamic barriers maturation. We first validated the model by confirming that during gestation, lactation and up to weaning the abundance of gut bacteria was markedly reduced in ABX-treated dams compared to controls. Maternal body weight during gestation,litter size or litter sex ratio were not affected by the treatment. A battery of metabolic tests were performed to examine the consequence of maternal dysbiosis on the offspring's metabolic regulation. mGM alteration slows pre-weaning offspring body weight gain. However,the offspring of antibiotic-treated dams(off_ABX) display a catch-up growth between weaning and adulthood,mainly due to an increase in longitudinal growth. At adulthood,male off_ABX develop metabolic alterations. Adult female off_ABX exhibit delayed puberty onset,but no metabolic impairments. In addition,preliminary results suggest that off_ABX present neuroanatomical changes of the blood-hypothalamic barrier in the median eminence, which is at the crossroad between the brain and the periphery and plays a crucial role in regulation of metabolism. Together, these results support the hypothesis that mGM contributes to the development of the neuroendocrine hypothalamus with both short-and long-term consequences on metabolic regulation and reproductive functions in the offspring associated with structural changes of the blood-hypolathamic barrier