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Role of microbiota function during early life on child's neurodevelopment

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ABSTRACT

Background: There are critical periods during pregnancy and early life when child's neurodevelopment can be altered, where different factors including hormones, stress, genetics, and diet have an important role. Novel studies are indicating that also gut microbiota and maternal obesity can influence child's neurodevelopment.

Scope and approach: This review summarises the current concepts related to microbiota-gut-brain axis, including microbiota modulation of the eating behaviour, child's cognitive function and brain structure, microbiota analysis techniques and neurodevelopment assessment in children. Further, we propose and present knowledge about potential mechanisms of action and ways to intervene for disease prevention and treatments, opening up an exciting area with important medical and industrial applications.

Key findings and conclusions: This novel and fast developing research area is indicating that gut microbiota in association with body weight might have an important impact on foetal and child neurodevelopment. However, the exact mechanisms are not known and further research in the field is warranted. Within the MyNewGut Project we aim to analyse the impact of microbiota in association with body weight on cognitive and behaviour development in children. We will study the phylogeny and function of the gut microbial communities in overweight, obese and gestational diabetes pregnancies and in their progeny, in association with infants and children's cognitive and behavioural outcomes. As well, the impact of gut microbiome on brain structure and function during childhood will be evaluated. Results from this study will shed light on the impact of maternal and offspring gut microbiome and body weight on child's neurodevelopment, brain structure and function, and will suggest potential mechanisms for intervention.

1. Introduction

There are vulnerable periods during early life when neurodevelopment can be altered by factors of diverse nature. Environmental factors such as diet, hormones, stress and genetic factors, among others, are candidates to affect offspring neurodevelopment *in utero* or during the postnatal period. Maternal obesity has demonstrated to have an impact on infant neurodevelopment (Torres-Espinola et al., 2015), and although the causal pathway still remains to be elucidated, an integrated mechanism involving inflammation has been proposed (van der Burg et al., 2015).

Gut microbiota also seems to have an impact on infant neurodevelopment (Keunen, van Elburg, van Bel, & Benders, 2014). Gut-brain axis is not a new concept (Track, 1980), and it can be defined as the crosstalk between gastrointestinal motor and sensory components and central nervous system and the return response to the intestine (Jones, Dilley Jb Fau - Drossman, Drossman D Fau - Crowell, & Crowell, 2006). However, extensive reports in the

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literature have also associated gut microbiota with neurodevelopment and mental health, and given the importance of the gut microbiota in modulating health, the microbiota-gut-brain axis has been recently adopted (Collins, Surette, & Bercik, 2012; O'Mahony, Hyland, Dinan, & Cryan, 2011; Rhee, Pothoulakis, & Mayer, 2009). Besides, obesity can alter the composition of the gut microbiome (dysbiosis), although it is not yet clear if the alteration in the composition of gut bacteria occurs as a result of an obesogenic diet or if it is a causal factor in the development of obesity (Harley & Karp, 2012).

Obesity has become a worldwide epidemic impacting negatively the health of millions of people. The increase in the prevalence of obesity in young adults runs in parallel to an increase in the prevalence of obesity and diabetes during pregnancy, and given the adverse effects that these conditions have on both the mother and offspring's health, maternal obesity has become a very important topic of study (Haslam & James, 2005).

The ‘normal’ physiology during pregnancy differs between obese and normal-weight women. It is well known that obesity is associated, among others factors, with increased insulin resistance, and the same applies in pregnancy. Thus, early in pregnancy, obese mothers are more insulin resistant than lean women. These factors can lead to potential adverse effects in implantation and placentation processes (O'Reilly & Reynolds, 2013), and alter growth, development and metabolism of the foetus and even impact offspring neurodevelopment (Camprubi Robles et al., 2015; Torres-Espinola et al., 2015). Moreover, a maternal obesogenic condition has been related to dysbiosis, potentially altering the offspring's gut microbiota composition (Collado, Isolauri E Fau - Laitinen, Laitinen K Fau - Salminen, & Salminen, 2010). Gut microbiota solely or in combination with maternal obesity and others factors could have an impact on offspring's neurodevelopment (Borre et al., 2014) and also increase the risk of becoming obese during infancy or into adulthood (Gohir, Ratcliffe, & Sloboda, 2015) (Fig. 1). Until now, studies focused on the origins of obesity were oriented toward dietary excesses or host genes (Hollopeter, Erickson, & Palmiter, 1998). Experimental studies indicate an important function of the gut microbiota in promoting obesity (Delzenne & Cani, 2011). Some phyla and classes of bacteria are able to metabolise nutrients more efficiently than others, increasing the amount of energy usable for the host and increasing the absorption of calories from the diet, contributing to fat deposition (Turnbaugh, Backhed, Fulton, & Gordon, 2008a,b). Higher concentration of Bacteroidetes has been associated with a lean phenotype in several studies while Firmicutes have been found in higher amounts in obese subjects (Turnbaugh et al., 2006). These results were further confirmed in pregnant women (Santacruz, Collado, et al., 2010). It is necessary to identify the active bacteria that cause dysbiosis in the intestinal microbial community in order to design therapeutic strategies for long term protection against obesity and to prevent potential impairment in offspring's neurodevelopment. In recent years, improved high performance technologies and cultivation-independent methods have made it possible to characterize the composition of microbial community more accurately. This fact has enabled to link obesity with the intestinal microbial composition, demonstrating that a diversity of organismal assemblages can yield a core microbiome at a functional level, and that deviations from this core are associated with different physiological states (Santacruz, Collado Mc Fau - Garcia-Valdes, et al., 2010; Turnbaugh, Backhed, Fulton, & Gordon, 2008a,b; Turnbaugh et al., 2009).

Several studies have shown that microbiota disruption in children, as result of the type of delivery (i.e. colonization of the neonate is disrupted by C-section delivery (Blustein et al., 2013)) and by low-dose antibiotic exposure during maturation (Cox et al., 2014; Vrieze et al., 2014) can alter host metabolism and adiposity. However, the potential relationship between maternal and offspring microbiota composition and neurodevelopmental outcomes needs to be elucidated.

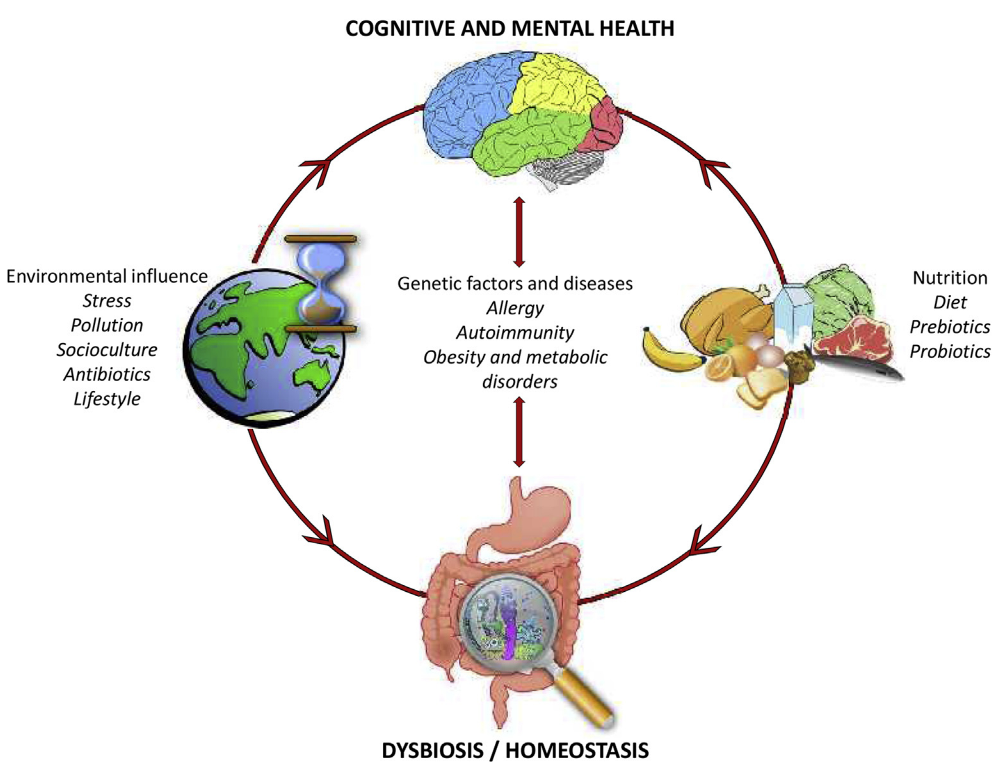

Fig. 1. Microbiota-gut-brain axis. Bidirectional crosstalk between gut microbiota and cognitive and mental health. Dysbiosis, diet and others external factors as mediators of obesity and related diseases and as key modulators of the bidirectional signalling pathways between the gut and brain that underlie neurodevelopmental disorders.