Nature Reviews Neuroscience | Published online 7 Jul 2016; doi:10.1038/nrn.2016.93

GUT–BRAIN COMMUNICATION

Making friends with microbes

> addition of *L. reuteri* to drinking water of MHFD offspring rescued PVN oxytocin expression and social behaviour deficits

Maternal obesity is associated with changes in the composition of the gut microbiota in the offspring. However, how such gut-bacteria differences may affect the brain and behaviour of offspring is not clear. Now, Costa-Mattioli and colleagues show that maternal obesity leads to social and synaptic deficits in the offspring that are caused by a reduction in certain gut-bacterial species.

The authors fed female mice a high-fat diet (HFD) for 8 weeks to induce obesity before pregnancy, and fed all offspring a regular diet. At 7 weeks of age, unlike maternal regular diet (MRD) offspring, maternal HFD (MHFD) offspring did not spend more time in a chamber containing another mouse than in a chamber containing an empty cage, indicating a lack of sociability. In addition, MHFD offspring showed no preference for a chamber containing a novel mouse over one containing a familiar mouse — indicating a lack of preference for social novelty.

Using ribosomal RNA sequencing, the authors found that the gut-bacteria profiles of MHFD offspring and MRD offspring differed considerably. MHFD offspring that were co-housed with MRD offspring (and that were therefore exposed to the gut bacteria of the MRD offspring) at weaning for 4 weeks showed similar gut-bacteria profiles to MRD offspring, and showed no social impairments. Thus, certain gut bacteria may influence social behaviour development.

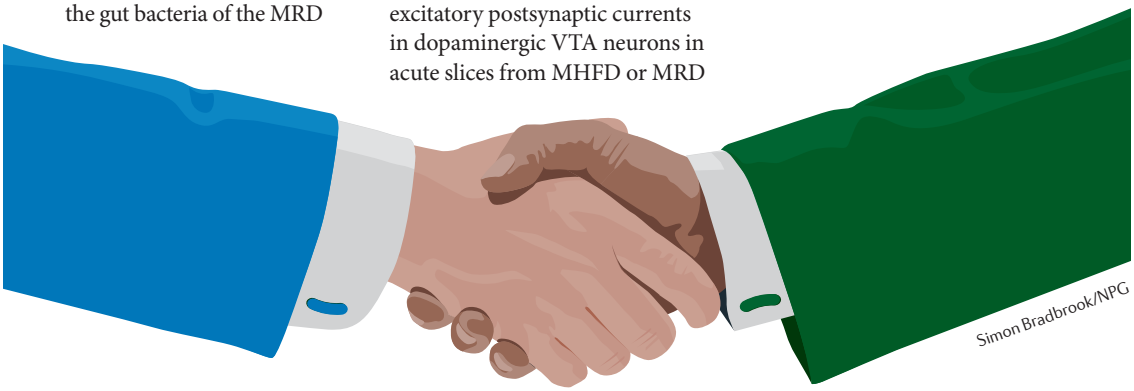
Metagenomic shotgun-sequencing analysis of faecal samples revealed that levels of *Lactobacillus reuteri* were more than ninefold lower in MHFD offspring than in MRD offspring. Previous work has shown that the presence of *L. reuteri* in the gut increases plasma levels of oxytocin, a hormone that is important for social interactions. Here, the authors found that oxytocin was expressed in fewer cells in the hypothalamic paraventricular nuclei (PVN) of MHFD offspring than of controls. Strikingly, addition of *L. reuteri* to drinking water of MHFD offspring rescued PVN oxytocin expression and social behaviour deficits in these animals, indicating that a paucity of oxytocin in MHFD offspring may mediate the social deficits found in these animals.

Oxytocin-positive PVN neurons project to the ventral tegmental area (VTA), which processes reward, and the reward associated with a novel social interaction induces synaptic potentiation in the VTA. The authors recorded glutamatergic excitatory postsynaptic currents in dopaminergic VTA neurons in acute slices from MHFD or MRD offspring 24 hours after a 10-minute interaction with a familiar or novel mouse. In MRD offspring, but not in MHFD offspring, interaction with a novel mouse induced long-term potentiation. However, this social behaviour-induced synaptic plasticity was observed in MHFD offspring that had been treated with *L. reuteri* at weaning or with intranasal oxytocin 30 minutes before the social interaction. Furthermore, both of these treatments increased the social preference of the MHFD offspring for a novel mouse over a familiar mouse, indicating that the synaptic and behavioural deficits in MHFD offspring may be linked.

Together, these data suggest that MHFD induces differences in the gut microbiota that are associated with impaired social development and deficits in the synaptic plasticity that is involved in social reward processing. These findings may have implications for neurodevelopmental disorders that involve social behaviour deficits, such as autism spectrum disorder.

Natasha Bray

ORIGINAL ARTICLE Buffington, S. A. *et al.* Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* **165**, 1762–1775 (2016)



Simon Bradbrook/NPG