

March 14-15th, 2015, Barcelona

Fact sheet #2

What's good for the gut is good for the brain: A new perspective on autism

Autism is often associated with gut impairment and changes of the intestinal microbiota. Some beneficial gut microbes offer the potential to restore the balance inside the gut and thus improve the psychiatric symptoms significantly. At the Gut Microbiota for Health World Summit in Barcelona (March 14-15, 2015) Prof. Elaine Y. Hsiao presented the audience with studies that provide a large body of evidence in support of this promising approach.

At least one child in 160 suffers from an autism spectrum disorder (ASD), according to the World Health Organisation (WHO).

These brain development disorders are characterized by deficits in social interaction, communication difficulties, restricted and repetitive behavioural patterns and sometimes also by linguistic impairments and delayed cognitive processing.

Therapeutical approaches have been limited so far, but recent findings indicate that novel pathways are opening up with the gut microbiota playing a key role. Prof. Elaine Y. Hsiao (California Institute of Technology, Pasadena / USA) presented a study, based on animal trials, that sheds light on the close links between microbial composition, gut conditions and ASD and the large therapeutical potential that these connections imply¹.

A leaky gut: harmful metabolites enter the bloodstream

The researchers injected pregnant mice with artificially created virus-like DNA. This activated the animals' immune system and induced ASD in their offspring. The new generation of mice then showed all the behavioural patterns typical of ASD: They spent less of their time in the middle of an open space than normal mice, were more easily startled by sounds, were less sociable, produced fewer vocalizations and clinged to stereotypic actions. In addition the gut microbiota composition of the ASD mice was altered and the permeability of their intestines was significantly increased as compared to healthy mice. Such a "leaky gut" allows potentially harmful substances

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to escape the interior of the intestine into the bloodstream. As Prof. Hsiao pointed out, similar processes have been observed in subsets of children with ASD, who often have gastrointestinal problems, such as constipation or diarrhoea. Even more remarkable than the changes in the microbial population of the affected mice are the products of the bacteria's metabolic activities. The researchers found that the serum of the ASD mice contained 46 times the normal amount of a molecule called 4-ethylphenyl sulfate (4-EPS), which is a metabolite of gut bacteria. Also, it is chemically similar to *p*-cresol, a gut microbial metabolite found at high concentrations in the urine of autistic children.

In order to establish the psychiatric role of 4-EPS Prof. Hsiao and her colleagues administered the metabolite to healthy mice which resulted in their showing some of the same behavioural symptoms as ASD mice. This suggests that indeed leaked 4-EPS and similar molecules might reach the brain via the bloodstream and – at high concentrations – shape the behaviour in an abnormal manner.

“It is important to note that our findings are restricted to mice, but we are hopeful that this approach will also be fruitful for developing new approaches to treatment of humans..”

Prof. Elaine Y. Hsiao

Which therapeutic options for mental disorders?

Based on the immunological and gastrointestinal abnormalities observed in the autism mouse models, the researchers decided to test whether probiotic treatment with the *B. fragilis* could improve symptoms. *B. fragilis* is a commensal microbe present in the healthy human intestine. Previous studies revealed that probiotic treatment with *B. fragilis* effectively treats gastrointestinal abnormalities and immune problems in mouse models of intestinal disease and multiple sclerosis. The hypothesis could be confirmed: After the ASD mice had been treated with *B. fragilis*

their increased intestinal permeability and high 4-EPS levels went back to normal. The probiotics had probably caused a closing of the leaks, thus keeping the 4-EPS in the intestine.

“Our study results provide a mechanism by which a human commensal bacterium can improve ASD-related gastrointestinal deficits and associated behavioural abnormalities related to autism.



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It is important to note that our findings are restricted to mice, but we are hopeful that this approach will also be fruitful for developing new approaches to treatment of humans. Much more research needs to be done to determine whether microbiota-mediated therapies might be a safe and effective treatment for neurodevelopmental conditions”, said Prof. Hsiao.

Reference:

1. Hsiao, Elaine Y. et al. (2013): Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders, *Cell* (2013), <http://dx.doi.org/10.1016/j.cell.2013.11.024>

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