

We are what we eat: Can our diet shape communication between gut microorganisms and the brain to determine disease development?

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Autism Spectrum Disorder (ASD) encompasses autism, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger's disorder. These neurodevelopmental conditions present clinically as impairments in social interaction and communicative abilities, as well as through strong tendencies towards repetitive interests and behaviors.¹ Using a sample of 11 children, Leo Kanner was the first to document observations of severe communication problems, abnormal social interactions, and stereotypical behaviours, such as repetitive rocking.² Kanner's initial description of this "syndrome" set the framework for the subsequent compartmentalization of afflicted children into the realm of ASD.

The incidence of ASD has increased significantly in the past two decades; in 1992, 19 in every 10,000 American children were estimated to suffer from ASD,³ with that number increasing to 90 cases in 10,000 as of 2006.⁴ Population-based studies of ASD prevalence in Canada are limited; however, one study suggested 65 per 10,000 children to be afflicted.⁵ It is becoming evident that there are increasing rates of ASD and other neurodegenerative disorders in

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Dr. Derrick MacFabe Enhanced diagnostic procedures, as well as

increasing societal awareness of ASD and associated disorders, may contribute to enhanced detection in this country, but many experts agree that other factors must be at play. Dr. Derrick MacFabe, a leading researcher at the University of Western Ontario (UWO), agrees, saying:



There are increasing rates of ASD and other neurodegenerative disorders in countries around the world that have adopted westernized eating and lifestyle habits, including increased consumption of processed carbohydrates. (Flickr: cindy1379)

"There are a lot of changes happening in human health over the recent years, and the effects of such are staring us in the face." Indeed, the changes alluded to can include the overconsumption of carbohydrates, misuse of antibiotics, and exposure to such things as environmental pollution, heavy metals, and herbicides. Dr. MacFabe himself has spearheaded research initiatives aimed at characterizing a link between Canadian nutrition habits and the effects on the resident gastrointestinal (GI) microbiota, as well as the resulting impact on the development of ASD.⁷ He credits pioneers in the field, such as Dr. Sidney Finegold, for establishing connections between perturbed microbial populations in the guts of children with regressive forms of ASD.

Dr. MacFabe readily agrees that the examination of a link between bacteria in the gut and pertinent effects within the central nervous system may seem far-fetched – at least upon first thought. However, he became increasingly interested in following documentation in the literature recognizing abnormal populations of certain bacterial groups, including clostridia and desulfovibrio, in stool samples of patients with autism. It was here that he began to question the possible outcomes that such changes in the gut may have in the brain. It was on this quest that Dr. MacFabe recognized the importance of defining metabolic markers, particularly from gut microbial populations characteristic of children with ASD, that can be isolated and tested for effects in animal models of disease. ►

MacFabe defines particular short-chain fatty acids (SCFAs) as natural forms of metabolites that are produced by members of the gut bacterial microbiota upon ingestion of carbohydrates.⁷ He particularly focuses on propionic acid (PPA), as it is an intermediate SCFA that is a normal part of carbohydrate metabolism.⁷ Dr. MacFabe points out "...that there is a higher concentration of PPA in stool samples from children with autism than in their healthy counterparts." Consequently, for his research group the question quickly became whether PPA provided a link between dietary carbohydrate intake, altered microbiota, and effects within the central nervous system capable of producing ASD-associated symptomology.

"A good model of disease is one which can link findings from multiple models," says Dr. MacFabe, who also emphasizes the initial importance of determining a central effect of PPA in the brain. Indeed, Dr. MacFabe says, "We were shocked to see in adult animals with intact nervous systems [that] small amounts of PPA administered into the brain proved to have a central effect by eliciting significant hyperactive, repetitive, and ignoring behaviors," typical of observations from many behavioral models of ASD. This work is groundbreaking in its demonstration that a broad level, common metabolite of gut bacteria can elicit significant behavioral effects.

Subsequent studies performed by MacFabe and his team have shown additional changes in the immune profile of animals administered PPA; these changes are seen in both innate and neuro-inflammatory markers. The study, released by the *Journal of Translational Psychiatry* in January 2013, identified a large sub-group of ASD patients exhibiting biomarkers for abnormal fatty-acid metabolism.⁶ These findings have begun to bring much of the work done in the PPA-administered rat model full-circle, as they suggest an important overlap between a promising animal model and a real life disease situation.

The work done by Dr. MacFabe and his team has illustrated the complexity of the human body's interactions with the materials that are ingested from the outside environment,

as well as the potential detriments of the carbohydrate overconsumption that is prevalent in our society. The observations have also raised questions about antibiotic administration in the early years of childhood. Dr. MacFabe, however, is quick to shoot down common misconceptions in the media that his research suggests we stop using antibiotics: "These drugs save lives, and I do not condone the ablation of their use." Instead, he suggests looking at the bigger picture and using his observations as a template to help with asking the questions about the mechanisms behind disease development, which requires cross talk in the medical and research communities. Additional misconceptions propagated by the media can also cloud the reality of scientific progress; the result is desperate parents looking for quick cures to their child's ASD. "Many desperate parents may not appreciate what is needed ethically before treatments are accessible," says Dr. MacFabe. This further highlights the need for additional research in the areas surrounding the impact of our environment on the human body; it also highlights the need to exploit novel model systems – animal *and* *in vitro* – to help give us a glimpse behind important initiation events leading to neurological conditions such as ASD. ■

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