MEDIA RELEASE

Compounds produced by gut bacteria alter immune function and energy metabolism in autism

Further validates long-held caregiver perceptions of gut-diet-behaviour links

Underscores importance of nutrition, microbiome in human development, health, behaviour

March 12, 2018 (London, Ontario, Canada): Two recent papers, one in *Translational Psychiatry* and another in *Frontiers in Immunology* by a longstanding Canada-US research collaboration, have found further evidence that compounds produced by bacteria contained in the *microbiome*, the trillions of bacteria in the digestive tract, have major effects altering the way our bodies function.

These compounds, known as *short chain fatty acids*, can fine tune our gut, immune system and metabolism. They may even alter our brain function and behaviour and may offer a potential link with the growing incidence and peculiar association of digestive, immune, metabolic and dietary issues, early infections, hospitalizations and microbiome alterations often found in persons with autism spectrum disorders (ASD).

Autism rates have skyrocketed from affecting 0.01% of children half a century ago to currently up to 2% of children in the most recent studies – a 200-fold increase.

Using immune cells derived from children with ASD and controls without neurodevelopmental disorders, the team found evidence these short chain fatty acids exerted profound effects on cellular energy metabolism, immune activity and genes that regulate learning and memory. Immune cells from children with ASD were found to respond quite differently from those from children without ASD, particularly when these cells were first challenged with an inducer of oxidative stress, suggesting that exposure to early stressors can alter the function of immune cells in children with ASD.

Short chain fatty acids, known as propionate, butyrate and acetate, are produced by many gut bacteria through the fermentation of foods, and are present naturally or as additives in the diet.

These compounds have broad effects on cellular development and function through:

- alteration of cellular signaling,
- alteration in fat metabolism,
- the switching on and off of important genes, and
- the modulation of mitochondrial function, the energy power plant of cells.

Cells with high energy requirements, particularly those in the brain, immune system and gut, appear particularly affected. Thus these gut derived compounds, particularly propionate, are in a position to link anecdotal and scientific evidence of gut motility problems, early antibiotic exposure, altered gut bacteria, whole body immune issues, food cravings, and regression in a large subset of persons with ASD.

Not all short chain fatty acids are created equal. Their effects may vary at different types and doses, at what time in development they are exposed, diet, microbiome composition, and with inherited and acquired alterations in immune and mitochondrial function, including those found in persons with ASD.

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Regarding the latter, Dr. Richard Frye, Medical Director, Neurodevelopmental Disorders Program, Barrow Neurological Institute at Phoenix Children's Hospital a world expert in mitochondrial disorders and neurodevelopmental conditions, has shown that blood samples and mitochondria obtained from persons with ASD often have abnormal function which cannot be explained solely by genetic alterations in the majority of cases.

Dr. Frye has found that these abnormalities, termed acquired and/or secondary mitochondrial dysfunction, may partly occur through a host of environmental factors associated with autism.

In parallel, in Canada, Dr. Derrick MacFabe, Director of the Kilee Patchell-Evans Autism Research Group, has found evidence that propionate has broad effects on brain function and behaviour.

Interestingly, propionate is produced in excess by ASD-associated antibiotic resistant bacteria and is also present as a food preservative in refined carbohydrates and dairy foods. Propionate was capable of producing reversible repetitive, antisocial and tic behaviours, coupled with brain inflammatory and metabolic effects consistent with those found in ASD patients when administered to laboratory rodents.

With Dr. Frye, the team previously found similar metabolic findings which paralleled the rat model in a subset of persons with ASD.

Drs. Shannon Rose, Frye and MacFabe examined the role of propionate and butyrate as environmental modulators of mitochondrial function in lymphoblastoid cell lines derived from boys with ASD and neurotypical controls.

Initial studies found a complex picture, that propionate, as a fatty acid, was capable of being utilized as a fuel, but also could induce oxidative stress at higher doses and exposures. However, cells from some ASD patients were "supermetabolizers" of propionate but suffered excessive metabolic impairments when subjected to an oxidative stress challenge. Thus propionate could have beneficial as well as detrimental effects on the cell, depending on dose, timing and presence of increased oxidative stress, which often occurs during a variety of illnesses.

In the first of two recent studies, published in *Frontiers in Immunology*, the team found propionate administration to these cell lines produced broad changes in genes involved in cell inflammatory pathways and immunoglobulin (antibody) production, which was more profound in cells from ASD patients.

These findings relate to the increased innate neuroinflammation and brain autoimmunity found in children with ASD and their mothers. The study also found activation of learning and memory pathways, which was also seen in the propionate rat model of ASD and is suggestive of the obsessional behaviours and enhanced memory found in persons with ASD.

In the second collaborative study, published in *Translational Psychiatry*, the team found that the lymphoblastoid cells' response to the related short chain fatty acid butyrate was also dose and time dependent, but the response was quite different than propionate, improving mitochondrial energy metabolism and the activation of genes involved in mitochondrial fission, the body's response to stress, as well as learning and memory pathways in a subset of ASD children.

Although preliminary, the study suggests that butyrate may have a "restorative" effect on mitochondrial function during periods of oxidative stress, including that occurring in ASD, and may have therapeutic implications.

Although promising, the authors strongly caution that the effects of these gut bacterial metabolites are complex.

Short chain fatty acids, often touted in the media, are not “good” or “bad”, but have varying effects at different doses, modes of delivery, in different tissues and at different developmental periods through the lifecycle. Indeed, these studies suggest individuals including those with ASD, may have unique mitochondria that respond quite differently to these bacterial compounds, as well as other environmental agents.

The authors stress the need for further translational research and properly orchestrated clinical trials examining behaviour, as well as bacterial and metabolic biomarkers. Nonetheless, these collective studies from this group and others have provided further mechanistic support for the long-held notion of families and caregivers of persons with ASD, that there are dietary and gastrointestinal links to the condition, and the potential for improvement in ASD symptoms with dietary treatments and treatments that heal the gastrointestinal tract.

These collaborative studies performed over the last decade, are noteworthy as they have largely been funded through charities from families of persons with ASD, who wished more evidence-based research was directed toward potential environmental contributors to the condition. This compliments more traditional studies which have largely focused on genetics over the last decade.

Funding for these and related studies have largely been provided from Autism Research Institute (San Diego, CA) and Mr. David Patchell-Evans, CEO of GoodLife Fitness, who has provided over $5.5 million toward the Kilee Patchell-Evans Autism Research Group for open sharing of evidence-based research into gut related links to ASD.

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