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How Bacteria in the Gut Influence Neurodegenerative Disorders

Understanding the role of the microbiome may lead to better treatments for Parkinson's, Alzheimer's

WASHINGTON, DC — Humans have roughly as many bacterial cells in their bodies as human cells, and most of those bacteria live in the gut. New research released today reveals links between the gut microbiome — the population of microorganisms living in the gastrointestinal tract — and brain diseases such as Parkinson's and Alzheimer's, including potential new ways to track and treat these diseases. The studies were presented at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Almost 100 trillion microbes — some beneficial and some harmful — live in the human gastrointestinal tract at any time, helping to regulate immune function and inflammation, two factors hypothesized to play a role in neurodegenerative diseases like Parkinson's and Alzheimer's. As brain-focused cures for such diseases remain elusive, scientists are looking to the microbiome for new insight and novel strategies.

Today's new findings show that:

- Metabolites derived from the microbiome block protein misfolding in test tubes and prevent neurodegeneration in a fly model of a disease related to Parkinson's, hinting that gut-derived metabolites may hold therapeutic promise (Lap Ho, abstract 573.23, see attached summary).
- A rat model of Parkinson's disease displays increased levels of an inflammatory protein in the colon, identifying a possible new biomarker for the disease (Doris J. M. Doudet, abstract 133.13, see attached summary).
- Nonhuman primates that received stomach injections of a protein associated with Parkinson's disease show signs of the disease in their brains, revealing that pathology can spread from the gut to the brain (Erwan Bezard, abstract 131.02, see attached summary).
- A gene associated with risk for Alzheimer's disease influences the gut microbiome of mice, potentiating a novel treatment strategy (Ishita Parikh, abstract 476.02, see attached summary).
- Probiotic treatment corrects memory problems in an Alzheimer's mouse model, suggesting that altering the microbiome may help delay the disease (Harpreet Kaur, abstract 126.23, see attached summary).

"The results presented today add to the growing body of evidence showing the influence of the gut on the brain and the crucial relationship between the two," said press conference moderator Tracy Bale, PhD, of the University of Maryland School of Medicine and Center for Brain Development and Maternal Mental Health. "Targeting the gut introduces a different and promising angle to tackle brain disorders across the lifespan."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about the microbiome and the brain on *BrainFacts.org*.

Related Neuroscience 2017 Presentation
Presidential Special Lecture: The Gut Microbiota and Childhood Undernutrition
Monday, Nov. 13, 5:15–6:30 p.m., WCC, Hall D

Abstract 573.23 Summary

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Gut-Derived Compounds May Block Protein Misfolding Seen in Neurodegenerative Diseases

Flies treated with specific metabolites show reduced age-related degeneration

Compounds made by bacteria in the gut may block the problematic protein misfolding characteristic of many neurodegenerative diseases, such as Parkinson's disease, according to new research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Many neurodegenerative diseases are thought to be caused by a misfolded protein that acts as a seed, triggering other proteins to misfold and the disease to spread throughout the brain. For example, in the case of Parkinson's and related diseases (called Parkinson-plus syndromes), alpha-synuclein misfolds, causing other alpha-synuclein species to misfold and clump together in toxic aggregates. Compounds that interfere with misfolding may prevent the aggregates from forming, halting the disease's spread.

To try to identify such compounds, researchers tested six gut-derived metabolites. In test tube experiments, three of the compounds inhibited the aggregation of alpha-synuclein. Researchers then conducted tests in a fly model in which a segment of a gene (C9orf72) associated with Parkinson-plus syndromes is longer than usual, causing the photoreceptors in the fly's eyes to degenerate with age. Flies were given food supplemented with one of the compounds and tested for photoreceptor degeneration. All six of the compounds reduced degeneration in the fly model, with two almost completely preventing it.

"Outcomes from our studies link gut microbiota metabolism with protective mechanisms against Parkinson-plus syndromes," said lead author Lap Ho, PhD, of the Icahn School of Medicine at Mt. Sinai. "Our new evidence suggests the feasibility of developing gut microbiota-derived compounds to simultaneously target both alpha-synuclein misfolding and C9orf72 gene mutation to increase the likelihood of therapeutic efficacy."

Research was supported with funds from the National Center for Complementary and Integrative Health and the Office of Dietary Supplements.

Scientific Presentation: Tuesday, Nov. 14, 3–4 p.m., WCC Halls A–C

Abstract 16274. Role of gut microbiota-derived metabolites in neurodegenerative disorders involving protein misfolding and C9orf72 expansion
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TECHNICAL ABSTRACT: There is growing evidence that in many neurodegenerative disorders, cell-to-cell transmission of a pathological, misfolded protein, such as misfolding of α-synuclein (α-syn) in Parkinson's disease (PD), may be a vehicle for the spreading of pathology throughout the brain. This misfolded protein, or seed, further induces misfolding of native proteins within the cell. Pathological misfolded proteins may exist in diverse conformations with distinct cellular and biochemical properties. We investigate whether microbiota-derived metabolites may help to attenuate the misfolding of α-syn and thereby promote resilience against PD phenotypes. We identified 6 biologically available, gut microbiota-derived compounds (GMP10, GMP11, GMP26, GMP28, GMP39, and GMP44) for investigation. Using independent *in vitro* protein aggregation assays (e.g., photo-induced cross-linking of unmodified proteins assay, thioflavin-T, fluorescence assay, and electron microscopy) we demonstrated that three of the compounds (GMP26, GMP44, GMP28) potently inhibit aggregations of monomeric α-syn (or monomeric β-amyloid peptides) into neurotoxic protein aggregates, *in vitro*. Based on evidence linking the c9orf72 gene with expansions of GGGGCC hexanucleotide repeats and PD, as well as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), we continue to test the neuroprotective ability of our compounds *in vivo* using a Drosophila model with overexpression of GGGGCC hexanucleotide repeats. Overexpression of 30 GGGGCC repeats in the Drosophila eye causes age-dependent photoreceptor neurodegeneration (Zhang K. et al, Nature 2015; 525:56). We treated Drosophila by mixing individual test compounds into the food and found all six compounds significantly suppressed eye degeneration at 10 μM, with compounds GMP26 and GMP11 almost completely suppressing the eye phenotype. The comparative efficacy of the six compounds are GMP26 = GMP11 > GMP39 > GMP10 > GMP44 > GMP28. Outcomes from our studies link gut microbiota with mechanisms underlying PD and suggest the feasibility of developing GMP26 as a means to simultaneously target both α-syn misfolding and C9orf72 expansion to increase the likelihood of therapeutic efficacy in PD, ALS, FTD patients with C9orf72 expansion.

Abstract 133.13 Summary

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Parkinson's Disease Rat Model Shows Elevated Inflammation in the Gut

Gastrointestinal inflammation may be an early marker of disease

The gut may reveal the presence and progression of neurodegenerative diseases such as Parkinson's disease, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. In the future, changes in the levels of inflammatory markers in gastrointestinal tract tissue may be used as an early biomarker of disease.

Parkinson's disease is typically characterized as a disease of the brain, but recent studies have suggested it may also be diagnosed by changes in the gastrointestinal tract, such as the presence of Lewy bodies — abnormal clumps of proteins within cells. Inflammation in the gut may also serve as a marker of disease, but previous studies have only examined small, localized samples of human gut tissue.

In this pilot study, researchers looked for signs of inflammation in colon tissue from 10 control rats and 12 rats exposed to a neurotoxin that produces Parkinson's disease–like symptoms. All of the Parkinson's disease model rats had elevated levels of the inflammatory marker CD68, compared to just one of the control rats.

"Inflammation in the lining of the gut may be indicative of Parkinson's disease development as much as brain inflammation," said senior author Doris Doudet, PhD, of the University of British Columbia. "This study is a first step to map the progression of inflammation in the gut along the timeline of the development of other neurodegenerative disease-related symptoms in a new progressive animal model."

Research was supported with funds from the Weston Foundation.

Scientific Presentation: Sunday, Nov. 12, 8–9 a.m., WCC Halls A–C

Abstract 14154. Inflammation in the gut of a new progressive rat model of PD
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TECHNICAL ABSTRACT: Pathophysiology of the gastrointestinal tract is increasingly being explored as a possible means to diagnose and to measure the progression of Parkinson's Disease (PD). While the presence of Lewy bodies is seen as the primary marker of neurodegenerative disease-related gut pathophysiology, recent publications theorize that gut inflammation may serve as a reliable indicator and precipitating condition of PD as well (1). A previous study using human biopsies failed to find a "significant difference in the expression of pro-inflammatory cytokines or glial marker between patients with and without enteric Lewy pathology" (2). However, it has been suggested that the fact that biopsies take only a small highly localized sample of gut tissue causes results derived from these samples to be unrepresentative of overall pathophysiology. To explore the hypothesis that gut inflammation is a reliable indicator of PD, we ran a small pilot experiment: the gut of 6 experimental BSSG-induced PD rat (a novel progressive rodent model of PD (3)) and of 4 control rat were prepared as swiss rolls, paraffinized, sectioned, and immunohistochemically stained using an anti-CD-68 primary antibody and a goat anti-mouse secondary antibody visualised using Vector Red. Preliminary results demonstrated that elevated inflammation was present in the submucosa in the colon of all six experimental rats in comparison to only one out of four control rats. These data support further exploration of increased inflammation of gut submucosa in PD as well as in this novel progressive rodent model of PD. Further experiments to evaluate the colonic colocalization of synuclein aggregates with CD68 in BSSG rat model are ongoing in larger subgroups. These data further support the hypothesis that gut submucosa inflammation is indicative of PD development as much as brain inflammation. This will be a first step to map the progression of inflammation in the gut along the timeline of the development of other pathophysiological symptoms. 1) Houser & Tansey, Parkinson's Disease, 2016 2) Devos et al., Neurobiology of Disease, 2013 3) VK et al. PLOS one, 2015

Abstract 131.02 Summary

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Parkinson's Disease Pathology Spreads From Brain to Gut in Nonhuman Primates

Study shows disease-associated protein moves in both directions

Toxic forms of alpha-synuclein, a protein that goes awry in Parkinson's disease, may spread from the brain to the gut, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Understanding how Parkinson's disease pathology propagates may lead to better strategies for intervening and halting the spread of toxic proteins.

Parkinson's disease is characterized by Lewy bodies — aggregated clumps of the protein alpha-synuclein — and eventual neuronal cell death. Studies in rodents have shown that alpha-synuclein pathology spreads from the gut up to the brain, where it leads to neurodegeneration and symptoms such as shaking, rigidity, and trouble moving. However, whether alpha-synuclein could also move in the opposite direction, from the brain to the stomach, was unexplored.

To test whether alpha-synuclein can spread both upward (from stomach to brain) and downward (from brain to stomach), researchers injected baboons with Lewy bodies derived from Parkinson's patients. The Lewy bodies were injected into the stomach of one set of animals and the brain of another set. Two years later, the brains and small intestines of both sets of animals were examined for neuronal death and alpha-synuclein pathology. Regardless of the site of injection, the animals had lesions and pathology in both their brains and their small intestines.

"The findings from this study establish that alpha-synuclein species might move up and down the neural axis in nonhuman primates," said senior author Erwan Bezard, from the Institute of Neurodegenerative Diseases in Bordeaux, France. "Although moving up was expected, it is the first demonstration in primates. Moving down is totally unexpected and groundbreaking."

Research was supported with funds from the Michael J. Fox Foundation.

Scientific Presentation: Sunday, Nov. 12, 9–10 a.m., WCC Halls A–C

5415. Bidirectional gut-to-brain and brain-to-gut propagation of alpha-synuclein pathology in nonhuman primates
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TECHNICAL ABSTRACT: The prototypic synucleinopathy Parkinson's disease (PD) is hypothesized to spread out from the enteric nervous system (i.e. the gut) via the vagal nerve up to the central nervous system. Such popular hypothesis is supported by indirect clinical evidences and by experimental data showing gut-to-brain transfer of synucleinopathy using either viral vector delivery of synuclein or recombinant synuclein preformed fibrils. We here aimed at testing the alternate hypothesis that synucleinopathy can indeed develop upward but also downward, i.e. from the gut to brain and from the brain to the gut. To this end, we used our primate model of synucleinopathy obtained with administration of α-synuclein species contained in PD-derived Lewy bodies (LB) (Recasens et al., 2014). We examined in nonhuman primates (i) if LB administration in the ventral wall of the stomach (n=5) leads to central nervous α-synuclein aggregation and possibly nigrostriatal degeneration and (ii) if LB administration in the striatum (n=6) might lead to synucleinopathy into the enteric nervous system of the duodenum.Two years after injection, extensive analysis was performed to assess qualitatively, quantitatively and spatially in the whole brain and in the enteric nervous system the extent and pattern of lesion as well as the occurrence of synucleinopathy using both biochemical and histochemical procedures. Stomach-LB injected nonhuman primates showed enteric nervous system pathology and nigrostriatal lesion in keeping with the well-accepted hypothesis. However, striatum-LB injected animals, in addition to the expected nigrostriatal degeneration, showed also enteric nervous system pathology in the duodenum. This study establishes that α-synuclein species might move up and down the neural axis in nonhuman primates questioning (i) the hypothesis of a peripheral origin of synucleinopathies (ii) and the specificity of enteric nervous system as biomarkers of PD.

Abstract 476.02 Summary

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Alzheimer's Disease-Related Gene Affects Gut Microbiome in Mice

Manipulating bacterial populations may be a new way to reduce risk

A gene associated with risk for Alzheimer's disease may also affect the gut microbiome, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. By identifying disease-associated bacterial populations, scientists can explore ways to alter the microbiome, and thus disease risk, with diet or drugs.

The greatest genetic risk factor for Alzheimer's disease is the APOE allele. Compared to people carrying the most common allele — APOE3 — those with APOE4 have an increased risk of Alzheimer's disease, while APOE2 carriers have decreased risk. APOE status may also influence the gastrointestinal system, but in the opposite way: Mice carrying APOE4 were better protected from parasitic stomach infection compared to APOE3 mice. In developing countries, APOE4 carriers had the best outcomes after childhood diarrheal diseases, while APOE2 carriers had the worst.

To determine whether APOE affects the gut microbiome, researchers examined mice expressing APOE2, APOE3, or APOE4 alleles. Sequencing DNA isolated from fecal samples revealed the populations of bacteria living in the animals' guts. The bacterial populations varied significantly between mice expressing APOE2, APOE3, or APOE4 alleles; for example, bacteria from the Ruminococcaceae family were most abundant in APOE2 mice and the least abundant in APOE4 mice.

"These results suggest that APOE alleles may differentially affect the gut microbiome, which could contribute to the actions of APOE in modulating Alzheimer's disease risk," said lead author Ishita Parikh, PhD, of the University of Kentucky. "Since the gut microbiome may be manipulated by factors such as probiotics and antibiotics, this study may lead to novel ways to reduce the risk of Alzheimer's disease."

Research was supported with funds from the National Institutes of Health and the BrightFocus Foundation.

Scientific Presentation: Tuesday, Nov. 14, 9–10 a.m., WCC Halls A–C

Abstract 5763. Gut microbiome association with APOE genotype in EFAD mice
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TECHNICAL ABSTRACT: Although the microbiome is emerging as a modulator of the human condition, the role of the microbiome in Alzheimer's disease (AD) is unclear. The *APOE4* genotype is the greatest genetic risk factor for AD and yet has been associated with improved gastrointestinal recovery after insult in human and murine studies. These observations lead us to hypothesize that *APOE* genotype impacts the gut microbiome. To assess this hypothesis, we compared 16S ribosomal RNA gene amplicon-based microbiome profiles in EFAD mice, homozygous for *APOE2, APOE3, or APOE4* with both carriers and non-carriers of the 5xFAD mutations at 4 and 6 months of age. Ordination (principal coordinate analyses) of the multivariate data revealed that combining carriers and non-carriers, *APOE* genotype is associated with distinct microbiome profiles, with *APOE3* intermediate between *APOE2* and *APOE4*. Comparisons of the underlying bacterial differences showed that the relative abundance of multiple bacterial families were significantly altered in a step-wise fashion from *APOE4* to *APOE3* to *APOE2*, including bacteria from the family Ruminococcaceae (Clostridia) which were highest with *APOE2*. Bacteria from this family can be induced by resistant starch diets, and are key for digesting resistant starch to increase short chain fatty acid levels. In summary, we report that the *APOE* genotype is correlated with specific gut microbiome profiles in a murine model, though the mechanism of action is not yet understood. The effect of sex, FAD carrier status and age are important modulators of *APOE* effects and will be investigated, clarifying the potential for translational impact of these data. As well, these data will be strengthened if replicated in other murine model organisms and humans.

Abstract 126.23 Summary

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Probiotics Reduce Memory Deficits in Mouse Model of Alzheimer's Disease

Changing the composition of the microbiome may delay disease development

Taking probiotics that alter the species of bacteria living in the gut might slow down the progression of Alzheimer's disease, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Probiotics — live bacteria with known health benefits — can change the composition of the gut microbiome, helping healthy species outnumber harmful ones. Previous research in rodents has shown that the presence of certain species of bacteria in the gut might accelerate the progression of Alzheimer's disease, suggesting that substances like probiotics that reduce the ratio of these species may also help treat the disease.

To test whether probiotics could slow disease progression, the researchers fed control mice and mice with genetic mutations associated with Alzheimer's disease either a diet supplemented with a probiotic or a regular diet for two months. Alzheimer's model mice on the normal diet displayed memory problems compared to control mice, but Alzheimer's model mice that were fed the probiotic had fewer memory problems. Additionally, the Alzheimer's model mice were found to have leakier guts — their intestines were more permeable to substances flowing in and out — compared to control mice, and this too was corrected with probiotic treatment.

"Our study suggests that gut bacteria can contribute to the pathological features associated with Alzheimer's disease and that probiotic supplementation can help to slow down the progression of disease," said lead author Harpreet Kaur, PhD, of the University of North Dakota. "This is exciting news because probiotics are widely available in the form of foods and food supplements."

Research was supported with funds from the National Institute on Aging, the North Dakota Established Program to Stimulate Competitive Research, and the National Institute of General Medical Science.

Scientific Presentation: Sunday, Nov. 12, 10–11 a.m., WCC Halls A–C

Abstract 8698. Probiotic supplementation improved cognitive and intestinal function in a mouse model of Alzheimer's disease
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TECHNICAL ABSTRACT: It has been demonstrated that changes in intestinal microbiota may not only influence gastrointestinal function but also affect the central nervous system. An altered intestinal microbial ecosystem has been associated with the pathogenesis of various brain disorders in which inflammation is implicated including mood disorder, multiple sclerosis, and depression, to name a few examples. However, it is unclear whether alteration of the intestinal microbiota affects progression or inflammatory aspects of Alzheimer's disease (AD), one of the most common dementing neurodegenerative diseases. In order to test this idea, littermate control wild type C57BL/6 mice were compared to the newly characterized APP knock-in transgenic mouse line that has the human Aβ sequence knocked in to the mouse APP gene along with three disease causing mutations (APP NL-G-F). The animals at 7 months of age were randomly divided into two groups and orally treated with vehicle (control) or probiotic (VSL#3) for 8 weeks. VSL#3 is a medical food containing 8 strains of live, freeze-dried lactic acid producing bacteria. The vehicle treated APP (NL-G-F) mice demonstrated impaired memory and increased anxiety-like behavior when compared to vehicle treated wild type mice using a cross maze and light-dark box behavioral test, respectively. This correlated with increased intestinal permeability in the vehicle treated APP (NL-G-F) but not wild type mice. However, no differences were observed in gastric emptying and intestinal motility in APP (NL-G-F) compared to wild type mice. Importantly, probiotic (VSL#3) supplementation to APP (NL-G-F) animals for 8 weeks significantly reduced intestinal mucosal permeability and improved memory performance. Our results support a role for intestinal microbes in the pathophysiology of AD and suggest that enrichment with beneficial bacteria could potentially help in treatment or prevention of AD. Further research is needed to understand the molecular mechanism of action attributed by these beneficial bacteria in CNS disorders.