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Orally Administered Probiotics Modulate Gut Microbiota and Restore Glucose Homeostasis in a Mouse Model of Alzheimer's Disease

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ABSTRACT

Cerebral glucose homeostasis deregulation has a role in the pathogenesis and the progression of Alzheimer's Disease (AD). Current therapiesdelay the decline in cognitive capabilities and reminiscence loss without definitively curing AD.

Recent studies have focussed on the role of the gut microbiota in disorders associated with the central nervous system, with special interest in the modulation of the gut-brain axis.

Using 3xTg-AD triple transgenic AD mouse model, we have demonstrated that the oral administration of a formulation of lactic acid bacteria and bifidobacteria (namely SLAB51) counteracts cognitive decline, reduces Aβ aggregates and brain damages and partially restores the impaired neuronal proteolysis. Improvement of cognitive function is supported by enriched gut content of anti-inflammatory Short Chain Fatty Acids (SCFAs) and increased plasma concentrations of neuroprotective gut peptide hormones that play a role in modulating neuronal functions like learning and memory. In detail, probiotics oral administration influences energy metabolism and glycolysis-gluconeogenesis in AD mice, enhancing Glucagon Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) plasma concentrations. Probiotics oral administration improves glucose uptake in 3xTg-AD mice by restoring the brain expression levels of key glucose transporters (GLUT3, GLUT1) and insulin-like growth factor I receptor β (IGF-IR β), in accordance with the diminished phosphorylation of AMP-Activated Protein Kinase (AMPK) and protein-kinase B (Akt). In parallel, phosphorylated tau aggregates decrease in treated mice. Probiotics counteract the time-dependent increase of glycated haemoglobin and the accumulation of Advanced Glycation End-products (AGE) in AD mice, consistently with memory improvement. Collectively, our facts elucidate the mechanism *via* which intestine microbiota manipulation ameliorates impaired glucose metabolism in AD, ultimately delaying the disorder development.

Keywords: Alzheimer's disease; Probiotics; Glucose metabolism; AGE's

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INTRODUCTION

Alzheimer's Disease (AD) is the maximum common form of dementia. However, the etiopathogenesis of this devastating disease is not fully understood [1]. Recent studies in rodents endorse that alterations in the intestine microbiome can also make contributions to amyloid deposition, but the microbial groups related to AD have no longer been characterized in humans. Towards this end, we characterized the bacterial taxonomic composition of fecal samples from participants with and without a diagnosis of dementia due to AD. Our analyses revealed that the gut microbiome of AD members has decreased microbial range and is compositionally distinct from control age-and sex-matched people. We classify phylum-*via* genus-wide variations in bacterial abundance along with decreased firmicutes, expanded bacteroidetes and decreased bifidobacterium inside the microbiome of AD participants. Furthermore, we observed correlations between levels of differentially abundant genera and Cerebrospinal Fluid (CSF) biomarkers of AD [2]. These findings upload AD to the growing list of illnesses associated with intestine microbial alterations, as well as an advocate that intestine bacterial communities can be a goal for corrective intervention.

DESCRIPTION

Microbiota-Host Interact ons Involved in the Nervous Control of Glucose Metabolism

From the mouth to the large intestine, a large, rich, diverse and complex prokaryotic community live in straight contact with the host. Between 2000 and 2010, numerous studies pointed out the importance of the microbiota in the energetic metabolism regulation. It was showed that Germ-Free (GF) mice are leaner and have a better glucose tolerance than their Conventionally-Raised counterpart (Conv-R). The colonization of GF mice with an intestinal microbiota coming from a Conv-R resulted in a worse insulin tolerance and a 60%-increase of body fat induced by a higher lipogenic activity within the liver.

The microbiota can interact with the host through different mechanism. By digesting fibers and nutrients, the microbiota can produce exceptional molecules as 1) Small-Chain Fatty Acids (SCFA) with the most well-known byturate, propionate and lactate but additionally succinate, 2) indole and its derivatives, 3) some neuro-hormones or mimetics as GABA, ClpB (α MSH mimetic) and 4) others molecules affecting the host as imidazole propionate. The microbiota also modifies and transforms the biliary acids secreted in the intestinal lumen to secondary biliary acids by using deconjugation, dehydrogenation, dihydroxylation of epimerization. One the other hand, the microbiota interacts through its own components as Lipopolysaccharides (LPS) or RNA and DNA fragments through the transmembrane and cytosolic receptors TLR and as peptidoglycanes through the receptor NOD [3].

During the last decades, numerous studies contributed to improve the knowledge about the microbiota-host interactions particularly in the metabolism context. It was shown 1) that LPS, through TLR4 and CD14, participates to the low-grade inflammation observed during the metabolic diseases and aggravating the diseases and it was called endotoxemia and peptidoglycans through NOD2 can modulate colonization and intestinal inflammation influencing the sensitivity to insulin, 2) the importance of dietary fibers and the SCFA production in the metabolism regulation through a GLP-1-dependant mechanism and 3) the role of secondary biliary acid through TGR5 and FXR. More recently, it was observed that succinate is a critical molecule produced essentially by prevotella in the regulation of glucose metabolism and the weight in mice [4]. Also, it was observed that E. coli produces ClpB, an α MSH mimetic, controlling than the food intake. Indole and its interaction with the receptor AhR plays also a critical role in the regulation of intestinal immune system activity and glucose metabolism through a GLP-1-dependant mechanism. Similarly, a study observed that akkermansia, a mucin-degradating bacteria and particularly a membrane protein, prevented obesity and associated complications in mice. Finally, recently, a new bacterially-produced molecule in a context of type 2 diabetes, imidazole propionate, was identified to modulate the liver activity and impair glucose metabolism [5-7].

The microbial influence on the ENS homeostasis and activity can be mediated by TLR4. NOD2 as TLR4 are critical for the ENS sensitivity to the intestinal neuro-hormone as GLP-1. In the tongue level, LPS, through TLR4, decrease the neuronal response of taste buds to saccharose.

Another kind of microbial influence should be more investigated. It is recently observed that SCFA can modulate epigenetics of the cells of the liver, adipose tissue and the colon. On the other hand, epigenetics is critical for neuronal homeostasis and activity. For example, MeCP2 (methyl CpG bonding protein) is a protein influence by epigenetic modifications and a mediator of synaptic development and plasticity [8]. An alteration of MeCP2 expression induces Rett syndrome in human beings characterizing with the major role of vital neuronal deficiency however additionally due to the fact its miles expressed by using enteric neurons, a crucial dysregulation of the intestinal transit and nitric oxide manufacturing.

CONCLUSION

Since nitric oxide is an important mediator of GLP-1 action for the control of glucose metabolism, MeCP2 could influence glucose metabolism. On the other DNA methylation is also critical for the expression of N-myc Downstream-Regulated Gene 4 (NDRG4). This protein is critical for brain morphogenesis through BDNF production and neurites outgrowth and myelinisations.

Its expression level is reduced in Parkinson's disease and this protein is expressed in the enteric neurons, particularly the nNOS-positive neurons. The other epigenetic modification is histone deacetylations. Histone deacetylase (Hdac) can be critical for neuronal homeostasis and plasticity. Hdac6 modulate alpha-tubulin, a critical protein in axon formation, expression. Hdac dysregulation is also observed in neurodegenerative disorders. Interestingly, it was observed that Hdac6 inhibition protects against vincristine-induced peripheral neuropathy. Thus, by understanding better the microbiota-induced epigenetic modifications within the neurons of the VN or of the intestine could increase the knowledge about the molecular link between microbiota and neurons.

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