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Improving healthspan via changes in gut microbiota and fermentation

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Abstract Dietary resistant starch impact on intestinal microbiome and improving healthspan is the topic of this review. In the elderly population, dietary fiber intake is lower than recommended. Dietary resistant starch as a source of fiber produces a profound change in gut microbiota and fermentation in animal models of aging. Dietary resistant starch has the potential for improving healthspan in the elderly through multiple mechanisms as follows: (1) enhancing gut microbiota profile and production of short-chain fatty acids, (2) improving gut barrier function, (3) increasing gut peptides that are important in glucose homeostasis and lipid metabolism, and (4) mimicking many of the effects of caloric restriction including upregulation of genes involved in xenobiotic metabolism.

Keywords Resistant starch · Gut microbiota · Gut peptides · Healthspan · Prebiotic · Gut health · Short-chain fatty acids · Butyrate · Age-related anorexia · Caloric restriction mimetic

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Gut health and aging

After many years of disrepute, research into connections between the intestinal microbiome and general health of elderly persons has re-emerged robustly (Britton and McLaughlin 2013) based on solid preclinical and clinical investigations (Claesson et al. 2012; Biagi et al. 2010; Rampelli et al. 2013). Perturbations of intestinal microbiota have now been strongly linked to immune, metabolic, and neurological diseases (Blumberg and Powrie 2012; Sekirov et al. 2010; Qin et al. 2012).

Intestinal microorganisms include approximately 100 trillion cells, which is 10 times greater than the number of human cells (Steinhoff 2005; Sears 2005), and these have 100 times as many genes on aggregate as the human genome (O'Hara and Shanahan 2006), representing over 1000 different species that perform numerous beneficial functions in healthy individuals (Sekirov et al. 2010). In effect, the diverse and highly populated microbiota in the gut functions as a metabolic organ modulating nutrition, metabolism, and immunity (Dethlefsen et al. 2007).

The distal gut of young healthy adults is typically dominated by bacteria in the phyla *Firmicutes* (60–80 % of total bacteria) and *Bacteroidetes* (20–40 % of total bacteria) (Dethlefsen et al. 2007). End-products of bacterial metabolism include the short-chain fatty acids (SCFA) acetate, butyrate, and propionate, which are

important for energy metabolism and signaling in the gut (Cuervo et al. 2013), as well as immune homeostasis (Claesson et al. 2012; Biagi et al. 2010; Rampelli et al. 2013; Smith et al. 2013). Among the elderly, however, proportions of these phyla differ compared with younger individuals (Cuervo et al. 2013). At the genus level, depletion of specific beneficial gut bacteria, such as *Bifidobacterium* and *Akkermansia* spp., has been observed in elderly individuals (Cuervo et al. 2013; Dethlefsen et al. 2007). Enrichment in Proteobacteria has been associated with poor health outcomes in elderly persons, related to low-grade inflammation as evidenced by bacteria-induced cytokine responses resulting from age-related increases in the permeability of the gut (Biagi et al. 2010). Even in animal models such as *Drosophila melanogaster*, this "leaky gut syndrome" has been linked to metabolic and inflammatory markers of aging and mortality (Rera et al. 2012). Indeed, a recent study (Rera et al. 2012) indicated that the lifespan of individual flies could be predicted by intestinal barrier failure as indicated by measurement of antimicrobial peptides (AMPs). A summary of studies of gut microbiota in the elderly is given in Table 1.

Fermentable carbohydrate and gut health

Diet composition is a critical factor in regulating the chemostatic culture in the gut (David et al. 2014). Dramatic changes in the processing of foods during the modern era have led to an altered microbiome that could have negative health consequences especially for older persons (Claesson et al. 2011; Cotillard et al. 2013; van Tongeren et al. 2005). As one prime example, the levels of fermentable carbohydrate (FC) in human diets have been progressively decreased due to modern milling and food preparation methods. Calculations of FC intake in medieval Europe were as high as 50–100 g/day (Birkett et al. 1997). FC intake in developing countries today is estimated to be 30–40 g/day (Birkett et al. 1997). However, measurements of FC intake in developed countries are only 3–8 g daily from commonly consumed foods (Birkett et al. 1997; Baghurst and Baghurst 1994). Recent literature reviews have documented significant relationships between the amount of FC in the diet and health indicators including blood lipid levels, glucose intolerance in diabetes, and cancer risks (Slavin 2013; Flint 2012). Our preclinical studies in rodent models have shown health benefits when FC is added to the diet including improved metabolic syndrome, glucose tolerance, and lower blood lipid levels (Keenan et al. 2013, 2006; Zhou et al. 2008; Keenan et al. 2012; Shen et al. 2011).

High-amylose starch

It is unlikely that Western societies will ever return to a diet of coarsely ground grains and legumes high in FC. To counter this trend, FC is now available as a relatively inexpensive ingredient that can be incorporated into foods that are acceptable to modern tastes. HAS has a range of 40–60 % FC and can be used in breads, cereal products, and other baked goods (Goldring 2004).

Most starches are ~80 % amylopectin and 20 % amylose. Amylose molecules are able to fold tightly into a starch granule and resist amylase action in the gut by not allowing as many sites for digestion (Brown 2004). Since amylose is only partially digested in the small intestine, it is available for fermentation in the

Table 1 Summary of gut microbiota studies of the elderly

Gut microbiota in elderly	Health implication	References
Reduction in abundance of Ruminococcus and Prevotella	Correlated to frailty and calf circumference	Claesson et al. 2012
Enriched in Proteobacteria	Increased inflammation	Biagi et al. 2010
Function analyses of gut microbiota	Loss of genes for short-chain fatty acid production and a decrease in the saccharolytic potential	Rampelli et al. 2013; McLaughlin et al. 2015
Lower Clostridium cluster IV and Bifidobacteria, while higher levels of Bacteroides	Linked to reduced formation of short-chain fatty acids and higher inflammation	Zwielehner et al. 2009
Reduced proportion of cultivable Bacteroides	Correlated to elevated blood glucose levels	Sepp et al. 2014
Lower levels of *Faecalibacterium* spp.	Fecal lipopolysaccharides (LPS) was significantly higher, greater inflammatory burden	Park et al. 2015

large intestine. Thus, it has been proposed that plant foods with high-amylose content are potential prebiotics (Ao et al. 2007). Genetic selection of plants has generated a high-amylose low-cost cornstarch. In addition to selection for this trait, some laboratories are using modern biotechnology to increase amylose content of rice (Kumar and Khush 1986) and wheat (Sestili et al. 2010; Regina et al. 2006). This form of prebiotic is now being incorporated into many food types, a process which should expand in the future. Thus, we have proposed that increased use of HAS might be a viable dietary strategy for improving the health of frail elderly.

HAS enhances the gut microbial profile

Technology for analyzing bacterial DNA has only recently been applied to the field of nutrition and aging. We have shown in aged C57BL/6Nia (B6) mice that HAS diets increase the proportion of *Bacteroidetes* in a dose-dependent manner (0 % control and 18 and 36 % HAS by diet weight) (Tachon et al. 2012). The relative amounts of Actinobacteria (*Bifidobacterium*) and Verrucomicrobia (*Akkermansia*) were also significantly increased in the guts of aged B6 mice fed HAS. Proportions of *Bifidobacterium* and *Akkermansia* were positively correlated with mouse-feeding responses, gut weight, and expression levels of the proglucagon gene (Tachon et al. 2012). Proportions of the Firmicute *Lactobacillus* were also significantly increased in a dose-dependent manner. *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* are target organisms for enrichment in the intestine because their amounts decline in the elderly (Steinbaugh et al. 2012; Sekirov et al. 2010; Shamliyan et al. 2013; Smith et al. 2013; Berg et al. 1996; Zwielehner et al. 2009) and known associations with good health and immune function have been established (Drago et al. 2012; Everard and Cani 2013; Ventura et al. 2009; Bron et al. 2012; Kimura et al. 2011). Overall, changes in the gut microbiota in response to HAS indicate an intricate food-web network by which beneficial bacteria are enhanced and HAS is metabolized to SCFA.

Improved motor coordination in aged mice fed HAS

A major feature of frailty is severely reduced motor and postural control (Morley 2009; Fairhall et al. 2011). In further support of the potential health benefits of HAS in elderly and frail individuals, we have reported that motor function is improved in male B6 mice (24 months) fed HAS diets (18 or 36 % FC) for 9 weeks (Zhou et al. 2013). Specifically, the mice were evaluated on an accelerating rotarod with latency to fall across three trials as the primary measure of motor coordination. This task is highly age-sensitive in mice (Graber et al. 2013; Ingram 1985). Rotarod performance was significantly improved in mice fed the HAS diet compared to age-matched control fed mice. Further tests are needed that can assess function in elderly and frail mice to reflect HAS diet effects on healthspan.

HAS attenuates age-related anorexia

Frailty is also marked by major changes in appetite (Wurtman 1988). An extensive literature describes aspects of the age-related decline in appetite and energy intake even in *healthy* people (Hays and Roberts 2006). Elderly persons are less hungry and feel full before a meal, and then become more rapidly satiated after eating a meal than younger subjects (Morley 1997). This age-related reduction in energy intake and nutrient sensing has been termed *the anorexia of aging* (Morley 2009). Older people fail to respond to over- or underfeeding with the compensatory changes in eating that are observed in younger people. For example, after being underfed for 21 days, young men overate and quickly returned to normal weight; whereas, the older men did not compensate, returned only to their baseline intake, and did not regain the weight that they had lost (Roberts 1994). This failure of response to acute undernutrition means that the elderly have impaired homeostatic regulation of energy balance. This apparent insensitivity to metabolic cues can lead to inappropriate weight loss in response to acute or chronic illness or other stressors, resulting in greater morbidity and mortality in geriatric populations. Compared with young counterparts, aged male rats fail to increase food intake after a fast and are slow to regain lost body weight on re-feeding (Gruenewald et al. 1996). In rhesus monkeys, an age-related decrease in food intake begins shortly after maturity and is accompanied by a reduced motivation to work for food (Mattison et al. 2005; Kaneda et al. 2001). The reduced ability to defend body weight in rats is associated with a blunted fasting-induced increase in neuropeptide Y (NPY) gene expression (Wolden-

Hanson et al. 2004) and agouti-related protein (AgRP) gene expression. We have shown that gene expressions of these two neuropeptides are controlled by the energy status of the cell and specifically via AMPK signaling (Lee et al. 2005). In addition, we have conducted extensive studies of the metabolic/neuronal mechanisms associated with food intake control and weight regain after caloric restriction (Lee et al. 2005; Harris and Martin 1984; Kasser et al. 1989; Beverly and Martin 1991; He et al. 1998; Clegg et al. 2003). However, there is a lack of knowledge of how diet impacts age-associated decline in nutrient sensing. Initial studies indicate that HAS feeding can enhance the response to fasting in elderly mice (Zhou et al. 2013). Following HAS feeding for 9 weeks, the same male B6 mice used for motor coordination testing were fasted from 9:00 p.m. to 10:00 a.m., and their food intake was measured for 4 h after re-feeding. As noted in comparison to the control fed group, the mice fed HAS (18 and 36 %) exhibited significantly greater food intake following the fast. These findings provide support for the hypothesis that consumption of HAS enhances brain signaling of energy status in aged mice.

Chronic kidney disease and HAS

Nearly 50 % of individuals 70 years or older meet the definition of chronic kidney disease, and 38 % of this age group has stage 3 or stage 4 chronic kidney disease (Johansen 2010). It is known that foods with added fiber lower serum creatinine levels in patients with chronic kidney disease (Salmean et al. 2013). In addition, the intake of a pre- and probiotic mixture composed of resistant starch significantly lowered the colonic generation and the renal excretion of toxic [(15)] ureide and functions as an ammonia shift from urinary to fecal (15) N excretion (Wutzke and Scholübbers 2010) . Recently, it has been shown that feeding HAS to hemodialysis patients may reduce the plasma levels of the colon-derived solutes indoxyl sulfate and possibly p-cresol sulfate (Sirich et al. 2014). The HAS improvement of kidney function may also be related to the higher levels of butyrate production by the large intestine microbes (Keenan et al. 2006) since butyrate attenuates gentamicin- induced nephrotoxicity (Sun et al. 2013). The utility of HAS in reducing the burden of chronic kidney disease in the elderly is worthy of further investigation.

Possible mechanisms of action

Based on the studies cited, we propose that a HAS diet acts to improve functional outcomes through four primary mechanisms: (1) stimulate gut microbial fermentation to upregulate genes involved in xenobiotic metabolism. (2) restore *Lactobacillus* levels to improve markers of gut barrier function, (3) increase levels and actions of butyrate to improve markers of healthspan, and (4) increase GLP-1 secretion from the gut leading to multiple actions on tissues to improve metabolic status. A schema of these mechanisms is presented in Fig. 1.

HAS-induced changes in beneficial microbiota

The primary consequences of increased HAS intake are modifications to the composition and functionality of the intestinal microbiota which use the carbohydrates as fermentable substrates for growth (Salonen et al. 2014). We have shown that dietary alterations result in significantly different adaptive responses by probiotic lactobacilli in the human and mouse intestine (Baghurst and Baghurst 1994; Marco et al. 2007, 2009, 2010). Dietary supplementation of HAS has produced numerous health benefits directly linked to increases in certain members of the native intestinal microbiota, particularly *Bifidobacteria*, *Lactobacillus*, *Akkermansia*, and butyrate-producing bacteria, such as *Allobaculum* and certain *Clostridium* species (Tachon et al. 2012; Everard et al. 2014; Schwiertz et al. 2002). The prebiotic action of HAS can possibly restore microbiota to physiologically beneficial levels in aging individuals.

HAS upregulates genes involved in xenobiotic metabolism

A transcriptional gene array analysis of cecal tissue from rats fed a HAS-enhanced diet was recently published by our group (Keenan et al. 2012). The following genes were found to be significantly upregulated in cecal mucosa: (1) cytochrome P450 family 2; (2) cytochrome P450 family 3; (3) cytochrome P450 family 4, flavin-containing monooxygenase 2; and (4) epoxide hydrolase 1. Elevation of these phase I xenobiotic-metabolizing enzymes has been called “a hallmark of

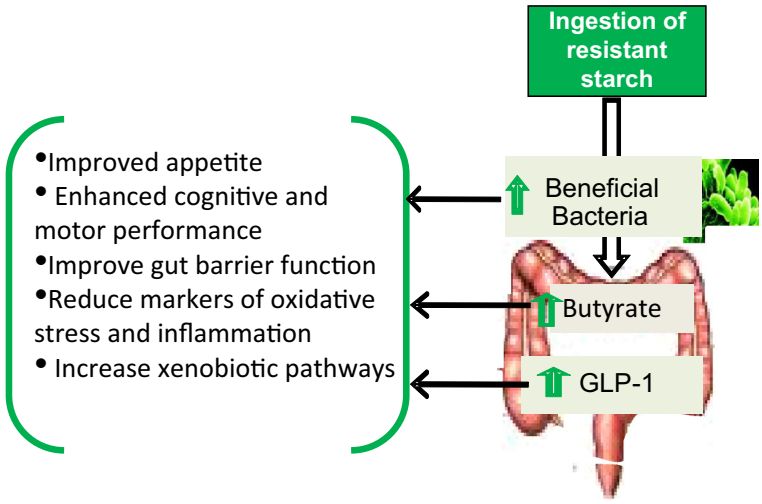

Fig. 1 Proposed mechanisms of HAS and Improved healthspan. Ingestion of high-amylose starches increases beneficial microbiota and stimulates the production of butyrate and increases GLP-1 release from the gut

long-lived mice," characterizing a shared signature of mouse models with extended lifespan (Steinbaugh et al. 2012).

HAS increases butyrate

Enhancing gut microbial production of butyrate could also lead to improved healthspan (Canani et al. 2011). We have established that diets containing HAS increase gut microbial production of butyrate (Zhou et al. 2008; Keenan et al. 2012; Charrier et al. 2014; Vidrine et al. 2013). The following points underscore the potential health benefits of this action:

- Quantification of butyryl CoA:acetate CoA-transferase genes reveals different butyrate production capacity in individuals; the elderly had significantly fewer copies of the butyryl CoA:acetate CoA-transferase gene than young (Hippe et al. 2011).
- Sodium butyrate improves memory function in a mouse model of Alzheimer's disease when administered at an advanced stage of disease progression (Govindarajan et al. 2011).
- Post-training systemic administration of sodium butyrate ameliorates age-related memory decline in rats (Reolon et al. 2011).
- Sodium butyrate alters the mortality rate of the senescent span of *Drosophila melanogaster* by decreasing its vulnerability or short-term risk of death, in a manner similar to that of dietary restriction (Vaĭserman et al. 2012).
- Tributyrin (source of butyrate) attenuates the production of TNFα and IL-1 by peritoneal macrophages and their expression in adipose tissue and also reduces the expression of MCP-1 and infiltration by leukocytes (Vinolo et al. 2012).
- Feeding butyrylated starch increases the levels of cecal and portal blood butyrate several fold and leads to improved gut health (Clarke et al. 2011; Bajka et al. 2010).

In summary, enhanced butyrate production by gut microbiota should lead to marked improvements in healthspan.

HAS increases GLP-1

GLP-1 is a gut-secreted hormone shown to have multiple biological functions. The primary clinical functions of GLP-1 and its analogs are to stimulate pancreatic insulin secretion and improve peripheral tissue insulin sensitivity (Yu and Wang 2008). However, the role of GLP-1 on brain function has recently attracted more attention (Hölscher 2012, 2014). GLP-1 has been shown to prevent the degenerative process and to ameliorate neurodegenerative changes in cellular and animal models of Alzheimer's disease (Ghosal et al. 2013; McIntyre et al. 2013; Ma et al. 2012). Also, GLP-1 is known to increase GK expression in pancreatic beta-cells (Burcelin et al. 2006), evidence that it improves pancreatic glucose sensing.

More importantly, GLP-1 has been shown to decrease intracerebral glucose content by activating hexokinase and changing glucose clearance during hyperglycemia (Burcelin et al. 2006). In addition, GLP-1 enhances GK activity in neurons in a glucose-dependent manner via GLP-1 receptor (GLP-1R) (Gejl et al. 2013). Thus, we speculate that GLP-1 might be important in the cascade of signaling events affecting brain aging and that HAS enhancement of GLP-1 levels and signaling should attenuate brain aging and consequently, improve cognition, motor behavior, and anorexia of aging.

Regarding support for a role of GLP-1 in responses to HAS, several important lines of evidence can be cited. First, we reported that aged male B6 mice (18–20 month) fed HAS showed increased levels of active GLP-1 in sera collected after 9 weeks on HAS diet compared to controls (Zhou et al. 2012). The proglucagon gene is responsible for GLP-1 expression in the gut (Holst 2007). We showed increased expression of proglucagon mRNA measured by quantitative RT-PCR in cecal epithelia cells obtained from aged B6 mice on the HAS diet in a dose-responsive manner as well as in young mice (3 months) (Zhou et al. 2012). HAS feeding has been reported to increase insulin sensitivity even in pre-diabetic subjects and also increases GLP-1 in serum (Bodinham et al. 2014). Thus, beneficial effects of HAS feeding in rodents appear to translate well to humans.

HAS as a caloric restriction mimetic

There has been increasing interest in the development of calorie restriction mimetics, or treatments that can mimic the life-lengthening and health-promoting effects of calorie restriction (CR) by activating the same cellular pathways that are activated by low-calorie diets (Lane et al. 2007; Ingram and Roth 2011). The exact mechanism linking calorie restriction and longevity is still a matter of debate. HAS diets mimic many of the short-term effects of CR. Table 2 provides a comparison of known effects of caloric restriction and HAS feeding (Higgins 2004; Higgins et al. 2004; Keenan et al. 2006; Shen et al. 2011; Zhou et al. 2008). HAS feeding mimics caloric restriction by reducing body fat, increasing fatty acid oxidation, reducing oxidative stress and inflammation, improving glucose clearance and insulin sensitivity, and preventing cancer.

Summary

HAS has the potential for improving healthspan in the elderly through multiple mechanisms as follows: (1) enhancing gut microbiota profile and production of short-chain fatty acids, (2) improving gut barrier function, (3) increasing gut peptides that are important in glucose homeostasis and lipid metabolism; and (4) mimicking many of the effects of caloric restriction including upregulation of genes involved in xenobiotic metabolism.

Table 2 Summary of the effects of diet restriction and high-amylose starch

	Diet restriction	High-amylose starch	HAS references
Longevity	↑	?	
Inflammation	↓	↓	Zhou et al. 2012; Le Leu et al. 2013
Glucose clearance	Improved	Improved	Zhou et al. 2008; Shen et al. 2011
Insulin sensitivity	Improved	Improved	Robertson et al. 2005; Johnston et al. 2010; Robertson 2012
Blood lipids	↓	↓	Keenan et al. 2006, 2013; DeJonge et al. 2009
Oxidation of fatty acids	↑	↑	Higgins et al. 2004; Zhou et al. 2009
Lipogenesis	↓	↓	Higgins et al. 2006; Higgins and Brown 2013
Body fat	Reduced	Reduced	Keenan et al. 2006, 2013; Charrier et al. 2014
Cancer risk	↓	↓	Toden et al. 2007; Clarke et al. 2008
Oxidative Stress	↓	↓	Kwak et al. 2012

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