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The Not so Sweet Side of Added Sugar

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Abstract

Consumption of sugar in its many forms produces energy required by the brain and body yet can also confer harmful health effects. Chronic sugar ingestion can lead to the development of Type 2 diabetes, metabolic syndrome, cardiovascular illness and neurodegenerative disorders. Although there is a wealth of knowledge about the negative human health effects of added dietary sugar, there is limited understanding about the effects on the bacteria enriched in the human digestive tract. This human microbiome is highly complex, diverse, and has been linked to disease and poor health.

Keywords: Chronic sugar ingestion • Anti glycation compounds • RT-PCR • Coronary • GFP reporter analyses

Commentary

In the study of Kingsley et al. (2021), we employ a *C. elegans E. coli* system, where we are able to directly alter the environment (added sugar) of the microbiota (*E. coli*) and examine the health consequences on the host (*C. elegans*). Importantly, *C. elegans* are bacterivores and therefore have an obligatory symbiotic relationship with their microbial food source. Our *C. elegans E. coli* system also allows the possibility of modifying either the host/*C. elegans* or the diet/*E. coli* in response to environmental changes and takes advantage of the many genetic and molecular tools available in both model organisms [1-3].

To model the effects of a high sugar diet, prior *C. elegans* research used several different methods (Figure 1). Previous protocols have used different concentrations of glucose, tested various developmental stages of the animal, and varied the duration of the exposure of *C. elegans* to glucose. In all of these studies, the application of glucose was either added directly to the top of the agar growth plate or added to the media prior to pouring into the growth plate dish [4-9]. Since the bacteria and animals were both in contact with added sugar, the mechanism underlying the effects of the high glucose was unclear (Figure 1). Were the effects due to the direct contact of the glucose with *C. elegans*? Were the effects due to the direct contact of the glucose with *E. coli*? Were the effects due to the animals eating the sugary bacteria? Or a combination?

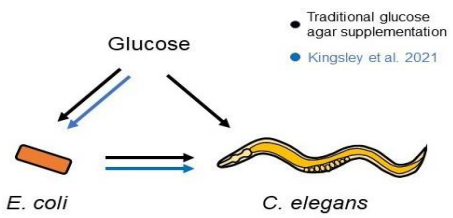

Figure 1. Model showing the method used in Kingsley et al versus other methods.

In Kingsley et al. (2021) [3], our experimental procedure was developed based on previous studies from Pepper et al. [10] who showed chronic glucose exposure significantly changed bacterial viability and promoted bacterial glycation. We incubated *E. coli* for 3 days with/without added glucose, and then inactivated the bacteria to pause further bacterial metabolism of the glucose. Therefore, the *C. elegans* consuming the glucose fed bacteria were never in direct contact with the glucose and only in contact with byproducts of the bacterial processing of the glucose. Interestingly, our method of a high glucose diet led to a decreased lifespan, reduced healthspan (locomotion, stress resistance) similar to results with the agar plate method [3-9].

Our experimental protocol involves incubating *E. coli* with glucose. Together with our previous studies [10], these data suggest that the glucose fed bacterial diet has an increased level of advanced glycation end products (AGEs). A group of heterogeneous compounds, AGEs are produced through non-enzymatic reactions where the carbonyl group of reducing sugars is covalently coupled to proteins, lipids, and/or nucleic acids. Anti glycation compounds such as the prebiotic carnosine have been shown to reduce the amount of AGEs within the bacteria [10]. Interestingly, in Kingsley et al. (2021) [3], we found that carnosine supplementation to the bacterial diet abrogated the negative health effects of the added glucose. Therefore, reduction of bacterially derived AGEs from a high sugar diet has the potential to increase host health.

Consumption of the high sugar/AGE diet by the host *C. elegans* led to a reduction in oxidative stress resistance coupled with changes in gene expression. We found that expression of the glutathione S transferase, *gst-4*, was suppressed as observed by RT-PCR and GFP reporter analyses. Furthermore, reduction of function mutation in *gst-4* blunted the response to the high sugar/high AGE diet. Together, these data solidify *C. elegans gst-4* as a key component in the regulation of a high sugar diet.

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Our data clearly suggest that the effects of a high glucose diet are mediated through the bacteria. Previous studies used a bacterial pts mutant to examine the bacterial contribution of the high glucose diet on lifespan. However, although pts is a gene that encodes for the major bacterial glucose transporter 8, these mutants still transport sugar but at reduced rates [11,12]. In Kingsley et al. [3], we assessed the bacterial contribution to the high sugar diet by two different methods. First, we compared the effect of *E. coli* supplemented with glucose either at the start of the bacterial culture or after the 3 day incubation (Pre glucose vs. Post glucose). Although the amount of glucose available to *C. elegans* in the post glucose supplementation was significantly higher, lifespan was shortened and healthspan (locomotion, oxidative stress resistance) was reduced only when the *E. coli* could process the glucose. Secondly, we supplemented the *E. coli* with the synthetic glucose analog 2-Deoxy-D-glucose (2-DG). When consumed, 2-DG is phosphorylated by hexokinase rendering it incapable from being further processed. Therefore, 2-DG can be used as a glycolytic inhibitor. *C. elegans* consuming a bacterial diet supplemented with 2-DG exhibit both wildtype lifespan and wildtype healthspan. Together, both methods revealed that bacterial processing of glucose causes negative effect on host health and longevity.

Conclusion

Our findings illuminate the importance of the bacterial diet to the host *C. elegans*. Altering the bacterial health with a diet of added sugar directly negatively impacts health and longevity within the host. We believe that across multiple methods these data support the negative impact of dietary AGEs. Since *C. elegans* consume the *E. coli* that become the microbiota, future experiments may involve examining the importance of a dynamic microbiota and its impact on health.

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