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Intergenerational effects of sucralose and stevia on intestinal and hepatic gene expression and gut microbiota in mice

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Statement of the Problem: Non-nutritive sweeteners (NNS) are questioned for their potential role in chronic non-communicable diseases. However, it remains unclear whether their metabolic effects can be transmitted across generations and whether the gut microbiota (GM) plays a mediating role. This study evaluated whether parental intake of sucralose or stevia affects GM composition, fecal short-chain fatty acids (SCFA) levels, and the expression of intestinal (Tlr4,Tnf,Tjp1) and hepatic (Srebp1) genes, and whether these changes persist in F1 and F2 offspring.

Methodology: F0 mice received plain water or water supplemented with sucralose or stevia (0.1 mg/mL) for 16 weeks (N=6/group). F0 mice were crossed to generate the F1 generation (N=6/group), and F1 mice to generate the F2 (N=6/group). F1 and F2 animals did not receive NNS. GM composition was assessed via 16S rRNA gene sequencing, SCFA levels via gas chromatography, and gene expression via RT-qPCR.

Findings: No changes in glucose tolerance were observed in F0, but decreased glycemic tolerance was detected in F1 and F2 sucralose- exposed males. Alpha-diversity was higher in F0 and F1 animals exposed to stevia, and in F1 and F2 animals exposed to sucralose. Microbiota compositional changes were more pronounced in F0 and F1, particularly in the sucralose group, which showed increased abundance of pathobionts and a reduction in beneficial symbionts. F0 animals from both NNS groups had lower SCFA concentrations, a change that persisted in F1 and F2. Sucralose led to sustained overexpression of intestinal Tlr4 and Tnf (F0- and F1) and persistent downregulation of hepatic Srebp1 (F0,F1 and F2). Stevia induced a transient increase in Tlr4 and Tnf in F1, which normalized in F2.

Conclusion & Significance: NNS consumption can trigger intergenerational physiological and molecular changes. Sucralose exerted stronger and more persistent effects on the GM, SCFA production, and inflammatory and metabolic gene expression than stevia.

Recent Publications:

1. Concha F, Perez-Bravo F, Gotteland M. Sucralose and stevia consumption leads to intergenerational alterations in body weight and intestinal expression of Histone Deacetylase 3. Nutrition. 2024, 112465.
2. Concha F, Sambra V, Caceres P, López-Arana S, Carvajal B, Gotteland M. Maternal consumption, and perinatal exposure to non-nutritive sweeteners: should we be concerned? Front. Pediatr. 2023.11:1200900.
3. Ramírez AL, Quezada J, Duarte L, Concha F, Poblete-Aro C, Escobillana L, Rincón-Cervera MA, Pérez-Bravo F, Elorza A, Bravo-Sagua R, García-Diaz DF. The administration of an extract from berberis microphylla modulates energy expenditure, thermogenesis and mitochondrial function and dynamics on brown adipose tissue from obese mice.
4. Concha F, Villanueva V, Vásquez K, Orellana JF, Escobillana L, Méndez A, Soto M, Stevenson A, Meneses P, Cid V, Delgado M, Fuenzalida F, García-Diaz DF. El consumo de un extracto de Calafate (Berberis microphylla) modifica marcadores de respuesta inmune en ratones delgados y obesos".
5. Sambra V, Concha F, Cavada G, Gotteland M. La exposición materna a edulcorantes no nutritivos, afectan el metabolismo y el microbioma de la descendencia. Rev. Chil. Endocrinol. Diabetes 2019; 12 (4)

Biography

Francisca Concha, Biological Anthropologist and currently an Assistant Professor at the University of Chile. I hold a Master's degree in Genetics and a Ph.D. in Nutrition and Food Sciences (2024). My research focuses on nutriepigenetics, microbiota, and intergenerational inheritance. In 2024, I obtained three competitive grants as principal investigator: (1) evaluating the intergenerational effects of sucralose and stevia on intestinal epigenetic markers in mice; (2) determining contextual factors influencing non-nutritive sweetener consumption in Chile; and (3) evaluating sweet taste receptor gene polymorphisms in healthy and type 1 diabetic children. I have published 10 scientific papers and have actively presented my research at national and international conferences. At this conference, I will present research based on the results of my Ph.D. thesis.

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