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No detriment in taste response or expression in offspring of mice fed representative levels of sucrose or non-caloric sucralose while pregnant

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ABSTRACT

Recent studies in mice indicate that consumption of acesulfame K (a high intensity sweetener) while pregnant, can lead to deficits in taste or enhanced sweet consumption in the offspring, leading to concerns the same may be common in human populations. However, this work employed a relatively unpopular sweetener, fed in quantities amounting to over 20 × the FDA's Acceptable Daily Intake (ADI). The aims of this study were to test the effects of sucralose, the USA's most popular high intensity sweetener, along with sucrose, on the taste system of the offspring of mice supplemented at a level commensurate with ADIs while pregnant. The hypothesis was that feeding a dam intensely sweet solutions would produce offspring with enhanced response to sweet taste, when compared to offspring of dams given only water. Females were mated following a 4-week period in which one group was given a measured ration of sucrose or sucralose in addition to chow and water, with the control group given chow and water only. Sucrose and sucralose solutions were removed two weeks after parturition to prevent direct consumption by the offspring. The offspring at 8 weeks of age for both the sucrose and sucralose supplementation showed no change in their taste response to sucrose or sucralose. No effect of maternal sweet supplementation was detected at the taste bud level, with fungiform taste bud density and taste bud gene expression remaining unchanged. Overall, this study suggests that sucrose and sucralose consumption at human-relevant levels during pregnancy and lactation do not produce any long-term changes to the offspring's peripheral taste system.

1. Introduction

1.1. The maternal diet and its influence on the offspring

There exists an evolutionary advantage to food preferences being susceptible to input from the mother's diet during the perinatal period. Resultantly, offspring may be innately drawn to already familiar, “safe” foods. However, a number of medical issues are linked to the maternal diet. Gestational diabetes is associated with greater cravings and preferences for sweetened foods in the pregnant mothers [1]; although it remains unknown how a heavy sugar diet may affect taste responses in the offspring. Consumption of non-nutritive sweeteners is associated with increased body weight and a higher prevalence of obesity in adults [2,3,4], with artificially sweetened beverage consumption during pregnancy also linked to a higher body mass index in the offspring [5]. Studies feeding 10% sucrose to rats after weaning for 3 weeks resulted in an increased sucrose preference when tested at 9 weeks old, relative to control rats receiving just water [6]. To our knowledge, a human study of maternal sucrose treatment during pregnancy and lactation, and its effects on the offspring's preference for sucrose has yet to be carried out. Although a number of studies have already looked at the impact of non-nutritive sweeteners during pregnancy and lactation, and their impact on offspring metabolism or metabolic disease [7,8], a better understanding of how sweet taste can be modulated through the maternal diet may be helpful in improving juvenile obesity outcomes, as a reduction in sugar-sweetened beverage consumption efficiently reduces the prevalence of obesity and obesity-related diseases [9].

Taste is linked in a somewhat complex manner to flavor acceptance, via both the peripheral and central nervous system. In neonates, sweet, umami, and low concentrations of salty substances are innately preferred, whereas bitter and sour substances are rejected. Exposure to certain flavor stimuli during infancy and early childhood can modify these innate tendencies and alter dietary preferences in children years later [10–14]. This influence on infants is often referred to as “flavor

Abbreviations: FDA, Food and Drug Administration; USA, United States of America; ADI, Acceptable Daily Intake; ace-K, acesulfame-K; T1R2, (taste 1 receptor 2); T1R3, (taste 1 receptor 3); HED, human equivalent dose; NHANES, National Health and Nutrition Examination Survey

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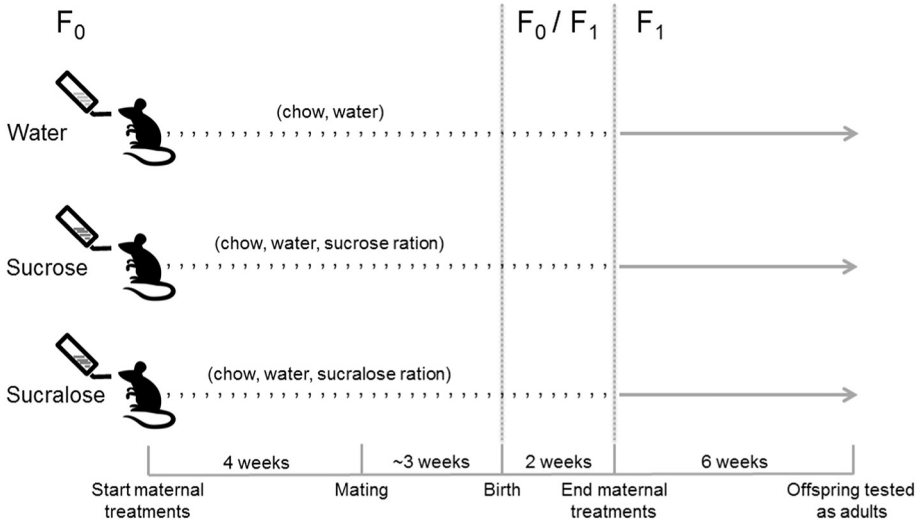

Fig. 1. Timeline of treatments. Female mice at 8 weeks of age, in addition to ad libitum water and normal chow, were randomly assigned to receive distilled water, 2 mL of 0.623 M sucrose (in solution), or 2 mL of 6.7 mM sucralose (in solution) daily for 4 weeks. Females were then mated, continuing to receive their respective supplements throughout the gestation and lactation period until 2 weeks postpartum. Offspring were weaned at 3 weeks of age (and thus had no direct contact with treatment solutions) onto ad libitum water and normal chow until testing at 8 weeks old.

programming" or "flavor imprinting" [15,16]. Clinical studies by Mennella et al. [17] reveal that mothers fed carrot juice during the third trimester pass carrot flavor acceptance to their offspring. Follow-up studies also demonstrated that babies of mothers who consumed more fruit during lactation were more likely to accept fruits than babies fed formula; though vegetable consumption did not have the same effect [18]. Another study investigating formula-fed infants (less than a month old) given either a cow milk-based formula control or hydrolyzed protein hydrolysate formula (which had relatively more bitter, sour, and savory tastes) for up to 8 months found infants that consumed the treatment formula exhibited greater acceptance and increased consumption of the savory broth relative to plain [19]. Thus, the question is posited whether the exposure to a sweet stimulus prenatally can lead to an enhanced preference for flavors containing more sweetness during later life, and further if the source of such modulation lies within the taste bud itself.

1.2. Sweet taste modulation from maternal acesulfame-K exposure

Rodent studies by Zhang et al. [20] demonstrate that acesulfame-K (ace-K), a non-nutritive sweetener, can be ingested prenatally through the mother's amniotic fluid, as well as postnatally through breast milk. This early ace-K exposure was capable of increasing the offspring's preference for ace-K by ~25%, as well as for sucrose by ~30% in two-bottle preference testing. Although follow-up studies focused on early intraoral exposure in pups, instead of in utero exposure, the same group was able to show altered gene expression in taste buds of the offspring for sweet taste transduction elements including T1R2, leptin, and endocannabinoid (CB1) receptors [21]. Interestingly, the expression of Gα-gustducin, believed to be a reliable marker for chemosensitive cells, was also increased in fungiform taste buds [22]. This also associated with more taste buds, and Gα-gustducin-positive labeled cells in 7 and 9-week-old adult mice. These findings strongly imply that maternal ingestive behavior can impact fetal taste buds. Despite these implications, it should be noted that ace-K was provided to dams ad libitum in these studies, therefore the resultant total intake equated to > 20-fold the FDA's average daily intake levels [3].

1.3. Sucralose – a non-nutritive sweetener

Sucralose is a relatively new non-nutritive sweetener, approved in 1999 by the United States Food and Drug Administration (21 C.F.R. § 172). Despite its recent introduction, sucralose already accounts for the majority of non-nutritive sweetener consumed in the USA, and is expected to increase further in the near future, as regulatory and consumer trends shift against competitors [23]. Like ace-K, sucralose can be detected in breast milk [24]. The perception of sweet taste by both sugars and artificial sweeteners is peripherally mediated by T1R2 and T1R3 heterodimers on the tongue [25]. Most artificial sweeteners bind to taste receptors with greater affinity than does sucrose [26], thus by weight, sucralose is about 600 times sweeter than sucrose [27]. Not only is sucralose sweet at low doses, but it is also excreted almost entirely unchanged, overall producing two minor metabolites as measured in mouse urine [28], which contributes to its negligible contribution to caloric intake and presumed overall safety for consumption [29]. Sucrose activates taste pathway regions in the brain more intensely than sucralose, suggesting that sucrose and sucralose may result in varying physiological brain responses, despite it being difficult for participants to distinguish the difference in taste between sucrose and sucralose [30]. A preference for sucralose can predict behavioral responses to sweet and bittersweet tastants [31] and has been correlated with less obvious phenomena such as drug seeking behavior, impulsivity, and risk-taking behavior [32–35].

The aims of this study were first, to test the effects of sucrose supplementation in pregnant mice on the taste system of their offspring and second, to test if these same effects could be elicited using supplementation of the non-nutritive sweetener sucralose, both at levels relevant to the human diet.

2. Methods

2.1. Animals

All procedures were approved by Cornell University's Institutional Animal Care and Use Committee. In-house bred virgin C57BL/6 female mice at 8 weeks of age, originally purchased from Jackson Laboratories, in addition to ad libitum water, were randomly assigned to receive distilled water, 2 mL of a 0.623 M sucrose ration (Sigma-Aldrich, St. Louis, Missouri) to represent 426.5 mg/kg sucrose daily, or 2 mL of a 6.7 mM sucralose ration (Sigma-Aldrich, St. Louis, Missouri) to represent 5.331 mg/kg sucralose daily for 4 weeks, then mated, continuing to receive their respective supplements throughout the gestation and lactation period, until 2 weeks postpartum (Fig. 1). The offspring were weaned at 3 weeks and maintained on normal chow and water until testing at 8 weeks of age. Both male (control n = 5–7, sucrose n = 11–14, sucralose n = 9–13) and female (control n = 7–10, sucrose n = 6, sucralose n = 8) offspring were used and analyzed together (see Supplement 3 for sex breakdown).

To mimic the daily consumption of a sweetened beverage, sucrose and sucralose treatments were administered orally via a liquid ration