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Review

Exposure to non-nutritive sweeteners during pregnancy and lactation: Impact in programming of metabolic diseases in the progeny later in life

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ABSTRACT

The nutritional environment during embryonic, fetal and neonatal development plays a crucial role in the offspring's risk of developing diseases later in life. Although non-nutritive sweeteners (NNS) provide sweet taste without contributing to energy intake, animal studies showed that long-term consumption of NSS, particularly aspartame, starting during the perigestational period may predispose the offspring to develop obesity and metabolic syndrome later in life. In this paper, we review the impact of NNS exposure during the perigestational period on the long-term disease risk of the offspring, with a particular focus on metabolic diseases. Some mechanisms underlying NNS adverse metabolic effects have been proposed, such as an increase in intestinal glucose absorption, alterations in intestinal microbiota, induction of oxidative stress and a dysregulation of appetite and reward responses. The data reviewed herein suggest that NNS consumption by pregnant and lactating women should be looked with particular caution and requires further research.

Contents

Abbreviations: ADI, acceptable daily intakes; MS, metabolic syndrome; NNS, non-nutritive sweeteners; T1R, taste receptors type 1; T1R1, taste receptors type 1 subunit 1; T1R3, taste receptors type 1 subunit 3.

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1. Introduction

Both epidemiologic and clinical studies have provided evidence that consumption of a diet rich in nutritive sweeteners or sugars, such as fructose and sucrose, may be an important explanation for the increased prevalence of metabolic syndrome (MS) observed in humans [1–4]. MS is a cluster of abnormalities including insulin resistance, visceral obesity, hypertriglyceridemia, low serum high-density lipoprotein (HDL) cholesterol, and hypertension, which increase the risk of cardiovascular disease and type 2 diabetes [1]. Most of these alterations have also been found in rats fed a high-fructose [5] or a high-sucrose diet [6], suggesting that, similarly to humans, rodents are also susceptible to develop MS induced by nutritive sweeteners.

Predisposition to develop MS may be acquired in early stages of life [7]. In fact, exposure to an aberrant nutritional environment during critical periods of development, such as the intrauterine period, has a great impact in programming the risk of the fetus to develop MS later in life [7–9]. Besides the evidence resulting from the Dutch famine birth cohort study regarding this programming effect in humans [10], this has also been well demonstrated in animal studies, in which feeding female rodents with fructose or sucrose-rich diets during the perigestational period – which extends from conception throughout pregnancy till the end of lactation-induced offspring hyperinsulinemia, impaired glucose tolerance, increased adiposity [11,12] and hyperleptinemia (which positively correlates with fat mass) [13,14], compared with offspring from females fed a standard chow.

Because nutritive sweeteners consumption is associated with adverse health outcomes, non-nutritive sweeteners (NNS) have been proposed as an alternative to them [1]. NNS are food additives used in *diet* or *light* foods, particularly beverages, yogurts, candies and baking products, that provide sweet taste and palatability without significantly contributing to caloric intake [15–17] and, consequently, without contributing to weight gain, adiposity, hyperglycemia and other related metabolic alterations [18–20]. However, the safety of their long-term ingestion, especially when starting from early development throughout life, has been questioned by a considerable number of studies [21–25]. Due to this, we aimed to review the available information about the impact of NNS exposure during the perigestational period on the later in life offspring's risk of developing diseases (in particular metabolic diseases), and to discuss the mechanisms involved in the potential fetal programming effects of NNS.

2. Non-nutritive sweeteners (NSS) consumption

Currently, seven NNS are approved to be used in foods and to be consumed by the general public, including pregnant and lactating women: aspartame, acesulfame-K, saccharin, sucralose, neotame, stevia [15,16,26,27], and advantame [28]. Among them, aspartame and acesulfame-K are the most widely used in foods, and both children and women of childbearing age are considered their major consumers [17,25,29]. The intake of NNS is difficult to estimate due to their widespread inclusion in many foods and because a blend of different NNS is normally present in a single food product [15,16]. However, crude estimates of the average intake of aspartame and acesulfame-K in adults was found to be inferior to their *acceptable daily intake* (ADI; the maximal amount of a non-nutritive sweetener considered safe to consume every day without adverse effects in humans [15]). However, in children, the estimated intake of both NNS was found to be superior to their ADI (14% and 69%, respectively) [30]. For aspartame the ADI is 40 and 50 mg/kg of body weight/day (in the US and European Union, respectively) and for acesulfame-K is 15 mg/kg of body weight/day [16,28]. Both of these NNS are approximately 200 times sweeter than sucrose [15].

3. NNS and long-term adverse health outcomes

Although NNS consumption is not associated with major short-term adverse health effects for the fetus [15–18,31–34], except for a mild risk of preterm delivery [35,36] (as it will be discussed in Section 3.3), the safety of its long-term ingestion has been questioned by animal studies (reviewed by [16,23]). In the following sections, we will present and discuss the data linking NNS long-term exposure, starting during early stages of life, with later in life adverse health outcomes for the offspring.

3.1. Cancer

Published studies on the long-term exposure to NNS, starting during the fetal period, upon later in life development of cancer are scanty and are restricted to aspartame and to animal models (no large-scale, randomized and long-term clinical studies have been performed in humans) [24,25].

Although in genetically altered mice models ($p53^{+/-}$, Cdkn2a-deficient and ras-activated oncogene models) long-term exposure to aspartame at doses equivalent to 7500 mg/kg body weight/day was not able to induce neoplasms [31], Soffritti et al. (2006) demonstrated that aspartame induced carcinogenic lesions in multiple tissues (peripheral nerves, renal pelvis, ureter, blood and lymphatic organs) when administered to wild-type rats from 8 weeks of age onwards, at levels close or even lower than the ADI for humans (4–100 mg/kg of body weight /day) [37]. Additionally, when rat fetuses were exposed to similar levels of aspartame from the 12th day of fetal life, an increased incidence of lymphomas, leukemias and breast tumors were observed later in life [25]. Furthermore, the incidence of lymphomas and leukemias occurred earlier in life in female offspring when aspartame exposure started prenatally compared with adult life [25]. Another study demonstrated that aspartame increased the incidence of hepatocellular and alveolar/bronchiolar carcinomas in adult mice when exposure started during fetal life, but the results from that study must be interpreted with caution, as the amount of aspartame consumption was well above the ADI for humans [24].

Given that aspartame is hydrolyzed by esterases and peptidases in the intestinal lumen to L-phenylalanine, aspartic acid and methanol, its carcinogenic effect might not be caused by aspartame itself but rather by its metabolites, in particular methanol [16,24,38], which was shown to generate formaldehyde adducts in cellular proteins and DNA [39].

As a whole, the results from these studies suggest that in animal models, exposure to aspartame starting during the intrauterine period can increase the incidence of malignant tumors later in life, particularly lymphomas and leukemia (Table 1).

3.2. Metabolic and neurologic diseases

Whilst NNS do not significantly contribute to energy intake, some epidemiological (reviewed by [1,15,20,40]) and animal studies (reviewed by [41–43]) found that long-term consumption of NNS-containing foods, or NNS itself, was associated with an increased risk of developing overweight, obesity, type 2 diabetes and MS. However, in some of these epidemiological studies, failure to adjust for potential demographic and clinical confounding factors inherent to the study population, such as level of education, baseline body mass index, waist circumference and reverse causality (individuals at higher risk of weight gain choosing to