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RESEARCH PAPER

Low perinatal caffeine intake alters offspring thyroid function in a sex- and age-dependent manner

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Abstract

During perinatal period, some women limit caffeine intake to 300mg/day, following the WHO recommendation. Previously, using an animal model of low perinatal caffeine exposure, correspondent to 250mg/day for human, we observed a deleterious effect on thyroid hormone (TH), with low total T3 in dams and weaned male pups and high T3 in adult offspring of both sexes. The hypothesis of the present study is that this phenotype results from alterations in TH synthesis and metabolism. Pregnant Wistar rats received vehicle or caffeine (CAF, 25mg/kg/day) by gavage during gestation and lactation. We evaluated markers of TH synthesis in dams and offspring, such as gland morphology and mRNA expression. Here, at birth, CAF males presented higher total T4 (+96%; $P < .05$) and unchanged total T3 and TSH. At weaning, CAF dams presented only lower TSH. CAF male offspring presented lower colloid area, CAF female offspring presented greater thyroid epithelial height, and both sexes presented unchanged mRNA expression of TH synthesis markers, such as thyroid stimulating hormone receptor (Tshr), sodium-iodine symporter (Nis), thyroperoxidase (Tpo), dual oxidase (Duox), NADP oxidase 2 (Nox2) and iodothyronine deiodinase 1 (Dio1). Adult CAF males presented greater epithelial area, downregulation of *Nis* mRNA expression, and higher hepatic Dio1 mRNA expression. However, CAF females presented higher TSH, although genes of TH synthesis were downregulated. Perinatal low caffeine exposure promotes temporal adaptive changes in the pituitary-thyroid axis, thyroid gland and peripheral TH metabolism of offspring, supporting our hypothesis. These modifications contribute to changes in TH levels in an age- and sex-dependent manner.
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Keywords: Caffeine; Pregnancy; Lactation; DOHaD; Thyroid hormone synthesis; Thyroid gland morphology.

1. Introduction

The increasing incidence of metabolic and endocrine disorders has contribution of recent and past environments, especially the early life [1]. This is a sensitive period for maternal habits, in which epigenetic mechanisms promote a cascade of complex adaptive changes with short- and long-term consequences for offspring health, in agreement with the Developmental Origins of Health and Diseases (DOHaD) concept [2]. Interestingly, many of these adaptive changes depend on the age and sex of the offspring [3], contributing to differential susceptibility to some diseases.

Therefore, maternal nutrition during the pregnancy and lactation periods is a concern because of its impact on offspring tissue development and its consequences throughout the life of the child [4]. Consequently, the World Health Organization (WHO) has established several nutritional recommendations and limits the maternal intake of some bioactive compounds, such as caffeine [5]. This psychostimulant substance, which is found in coffee, tea, chocolate, beverages and some medications, is widely consumed, including by pregnant women [6]. Approximately 70% of American women continue to consume caffeine during pregnancy [6], with a median intake of 160–190 mg/day [6,7], and it is extrapolated that many women consume 300 mg of caffeine per day, which is the limit set by the WHO [7,8]. These heavy caffeine consumers have a 31% greater risk of miscarriage [9], and this level of caffeine consumption is strongly correlated with giving birth to babies with low birth weight [10,11]. In animal models, high caffeine intake also causes lower birth weights, as well as many physiological and behavioral changes in offspring [12,13].

During pregnancy, maternal caffeine metabolism is reduced, increasing its half-life [14]. In addition, caffeine is able to cross the placental and mammary barriers [15,16], thereby reaching babies, who are too immature to metabolize it [17]. Therefore, even an in-

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