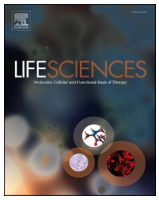
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Maternal low-dose caffeine intake during the perinatal period promotes short- and long-term sex-dependent hormonal and behavior changes in the offspring

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ABSTRACT

Aim: Maternal caffeine crosses the placenta and mammary barriers, reaching the baby and, because his/her caffeine metabolism is immature, our hypothesis is that even a low caffeine intake (250 mg/day), lower than the dose limit recommended by the World Health Organization, can promote caffeine overexposure in the offspring, leading to short- and long-term changes.

Main methods: Pregnant Wistar rats received intragastric caffeine (CAF) (25 mg/Kg/day) or vehicle during the gestation and lactation periods. We evaluated morphometrical, metabolic, hormonal, and behavioral parameters of male and female offspring at different ages.

Key findings: Even a low caffeine intake promoted lower maternal body mass and adiposity, higher plasma cholesterol and lower plasma T3, without changes in plasma corticosterone. Female CAF offspring exhibited lower birth weight, body mass gain and food intake throughout life, and hyperinsulinemia at weaning, while male CAF offspring showed reduced food intake and lower plasma T3 at weaning. At puberty and adulthood, male CAF showed higher preference for palatable food, aversion to caffeine intake and higher locomotor activity, while female CAF only showed lower preference for high fat diet (HFD) and lower anxiety-like behavior. At adulthood, both male and female offspring showed higher plasma T3. Male CAF showed hypertestosteronemia, while female CAF showed hypoinsulinemia without effect on glucose tolerance.

Significance: A low caffeine intake during the perinatal period affects rat's offspring development, promoting sex-dependent hormonal and behavior changes. Current data suggest the need to review caffeine recommendations during the perinatal period.

1. Introduction

Caffeine has central and peripheral effects, promoting metabolic alterations, alertness, and wakefulness behavior [1]. This substance is present in coffee, tea, soft drinks, energy drinks, chocolate, and some medications [2], being widely consumed in the world. Approximately 90 % of adults use caffeine regularity [2], with an average daily intake of 227–238 mg in countries such as the USA [3] and Brazil [4].

Caffeine and its metabolites cross biological barriers such as those present in the placenta and mammary gland [5], reaching the fetus and the baby. As caffeine acts as an antagonist of adenosine A2a and A1 receptors [6] and as a phosphodiesterase inhibitor [7], its ingestion during pregnancy can modulate fetal development, behavior, serum hormones and energy metabolism. Indeed, in animal models, a high caffeine intake during gestation (>60 mg/Kg/day) promoted intra-uterine growth restriction [8,9] and early hormonal changes, such as fetal hypoleptinemia [10], fetal hypothyroidism [11] and increased glucocorticoids at birth [9]. In addition, at adulthood, animals showed

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