Placental and cord blood DNA methylation of the serotonin receptor type 2A gene: modulation by fetal sex and genotype and maternal metabolic state

P-01.4-03

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Serotonin receptor type 2A (HTR2A), a widely distributed G-protein-coupled receptor for multifunctional signaling molecule serotonin, has been implicated in many physiological processes and its dysregulation has been associated with a number of mental health and metabolic conditions. Different lines of evidence indicate that epigenetic modifications of the HTR2A gene play a role in molecular mechanisms through which early life environment influences development and lifelong health outcomes. The promoter region of the HTR2A gene contains a number of partially methylated cytosines that have been shown to modulate the gene's transcriptional activity. Here we investigated placental and cord blood HTR2A methylation levels in relation to fetal sex and genotype as well as maternal obesity and gestational diabetes mellitus. The study was performed on mother-infant dyads enrolled at the Clinical Hospital Center Zagreb as a part of our ongoing birth cohort study PlaNS (Placental and Neonatal Serotonin). All newborns were healthy, of normal birth weight and born at term by planned C-section. Cord blood samples were obtained via umbilical venipuncture and placental tissue samples were isolated from the fetal part of the placenta. DNA methylation levels were quantified at four CpG loci within the HTR2A promoter region using bisulfite pyrosequencing. In addition, samples were genotyped for two polymorphisms (rs6311, rs6306) in the respective gene region. The four targeted CpG cytosines were methylated to different degree in the cord blood and placental tissue. rs6311 and rs6306 genotypes as well as fetal sex were found to be significant predictors of the methylation levels in both tissues. Maternal metabolic parameters modulated placental HTR2A methylation in a sex-dependent manner. Taken together, data point to a complex interaction of genetic and environmental factors influencing HTR2A methylation levels during human fetal development.
Funded by HrZZ (IP-2018-01-6547).

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