OCT3 ROLE IN PLACENTAL SEROTONIN HANDLING; EFFECT OF FETAL SEX AND INHIBITION BY ENDO- AND EXOGENOUS SUBSTANCES

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Serotonin (5-HT) is a crucial monoamine for proper fetal development/programming. Research on the placental handling of 5-HT has been ongoing for the last six decades but has yielded strikingly inconsistent results. Placenta is often viewed as a "donor" of 5-HT for the fetus, but many studies ignore the fact that at the later stages of gestation, the fetus can produce its own 5-HT from maternally-derived tryptophan. Recently, we have discovered a new pathway of placental serotonin handling: placental extraction of excess 5-HT from fetal circulation through organic cation transporter 3 (OCT3). This transporter is known to be inhibited by several endo- and exogenous compounds. We hypothesize that hormonal disbalance or pharmacotherapy during pregnancy may affect fetal serotonin levels. In addition, since fetal sex has been implicated in fetal development and programming, we study how placental OCT3 function may be affected in a gender-dependent manner.

5-HT transport studies were carried out *in situ* using the dually perfused rat term and *ex vivo* in placental basal membrane vesicles isolated from human term placenta. Rat fetal sex determination was performed using end-point PCR analysis for amplification of X-chromosome and Y-chromosome specific genes. For gene expression analysis of OCT3 expression in human and rat term placenta, qRT- and Digital Droplet PCR methods were employed.

We unveiled a so far unobserved finding that 5-HT uptake by placenta from the fetal circulation is significantly inhibited by various endo- and exogenous molecules (cortisol, progesterone, estrogen), antidepressants (paroxetine, venlafaxine), and cimetidine. In addition, remarkable differences between male and female fetuses were observed in placental 5-HT extraction. At physiological 5-HT levels, male fetuses were able to extract up to 80% of fetal 5-HT while female fetuses only 54%. At supraphysiological 5-HT levels, this gender-dependent effect was diminished.

Term placenta plays a protective role against excessive 5-HT levels in fetal circulation by taking it up into trophoblast cells (through OCT3). Genetic, endocrine or pharmacological insults may compromise this protective role of term placenta and affect fetal development/programming.

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