ABSTRACT

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Title of Doctoral Thesis **Physiological and pharmacological aspects of tryptophan and serotonin homeostasis in the fetoplacental unit**

The placenta is an ephemeral organ inevitable for the successful course of pregnancy. As the main link between the mother and the fetus, the placenta fulfills numerous roles during gestation, including endocrine, transport, and immunoprotective processes. Proper functioning of the placenta is critical for the normal growth and development of the embryo/fetus. Importantly, the latest research has associated perturbations of maternal conditions (such as pharmacotherapy, malnutrition, diseases, stress, or inflammation) with alterations of the trophoblasts' endocrine, transport, and metabolic functions. Of note is the placental utilization of the essential amino acid tryptophan, suggested as a potential mechanism contributing to fetal programming of adulthood diseases. Tryptophan flux along the serotonin and kynurenine pathways generates metabolites with neuroactive, immunosuppressive, and antioxidant properties. Current literature suggests that fine-tuning of tryptophan metabolite concentrations in the fetoplacental unit is crucial for successful pregnancy outcome. Nonetheless, a comprehensive characterization of the enzymes and transporters involved in the metabolism/transport of tryptophan, serotonin, and kynurenines is still lacking. Moreover, controversies remain in the regulation of serotonin homeostasis in the fetoplacental interface.
On these grounds, the aims of this thesis were manifold and included: 1) detailed assessment of placental serotonin and kynurenine pathways during gestation in humans and rats, 2) evaluation of contribution of fetal organs (brain, intestine, liver and lungs) to the prenatal tryptophan metabolism, 3) characterization of serotonin handling in human and rat term placenta, and 4) effect of antidepressants on the placental serotonin system. A wide range of methodological approaches was utilized including in vitro transport assays, in situ perfusion of rat term placenta, isolation of membrane vesicles and primary trophoblast cells from human term placenta, gene expression analysis by Quantitative- and Droplet Digital PCR analysis, protein expression by western blotting, and metabolic activity of rate-limiting enzymes.
We report that the placental homeostasis of tryptophan is subject to strictly regulated developmental changes during pregnancy. We show that placental production of kynurenine increases during pregnancy, with a low contribution of other fetal organs. On the other hand, placental tryptophan metabolism to serotonin is crucial in early-to-mid-gestation, with a subsequent switch to fetal brain and intestine serotonin synthesis. We further provide the first evidence that human and rat term placenta extract fetal-derived serotonin via the organic cation transporter 3 (OCT3). Correspondingly, increased expression and function of serotonin-degrading enzyme (MAO-A) and uptake transporters (SERT and OCT3) at term indicate efficient placental clearance of this monoamine, likely to prevent hyperserotonemia in the fetoplacental unit. We demonstrate that this orchestration between metabolizing enzymes and transporters is disrupted by antidepressants, which might at least partly explain the poor outcomes upon antidepressant use in pregnancy.