ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové
Department of Pharmacology and Toxicology

Candidate: Mgr. Veronika Váchalová
Supervisor: prof. PharmDr. František Štaud, Ph.D.
Title of doctoral thesis: Physiological and pharmacological perspectives of monoamine regulation in the fetoplacental unit

During pregnancy, the placenta is a vital organ for fetal growth and development, and its proper formation and function are essential for a successful gestational course. Current research indicates that maternally derived factors, such as disease or pharmacotherapy, may alter the functions of its key structure, the trophoblast. This layer, consisting of terminally differentiated syncytiotrophoblasts and their progenitor cells, the cytotrophoblasts, plays a significant role in the regulation of primary monoamine homeostasis. Monoamines such as serotonin, norepinephrine, and dopamine are involved in fetal organ development, including that of the brain. Thus, maintaining proper monoamine homeostasis in the fetoplacental unit is critical for healthy fetal programming, with implications for later life.

To ensure this balance, the trophoblast is equipped with regulatory proteins like those found in the brain. Monoamine synthetic and degradation enzymes, along with monoamine transporters, regulate monoamine homeostasis in the fetoplacental unit. However, the functional characteristics of these systems in the trophoblast layer, as well as their activity in undifferentiated cytotrophoblast progenitor cells, remain incompletely understood. Additionally, the gestation-related regulation of monoamine pathway components in the placenta is not well characterized. Moreover, monoamine transporters are known to be susceptible to drugs commonly used during pregnancy, such as antidepressants and antidiabetics (metformin).

Therefore, in this work, we aimed to 1) investigate the regulation of trophoblast monoamine transporters and monoamine handling during the cyto-/syncytiotrophoblast transition, 2) evaluate the synthesis, transport, and metabolism of monoamines in the fetoplacental unit based on gestation age, and 3) examine the effects of pharmacotherapy commonly used in pregnancy (antidepressants and metformin) on monoamine transport in the placenta.

To achieve our aims, we employed a range of experimental approaches, including cell models of syncytium development (primary human trophoblasts, BeWo, and JEG-3 cells), fresh villous human term placenta isolated fragments, and human term placenta isolated placental membrane vesicles. Additionally, rat placenta-derived HRP-1 cells and rat term placenta perfusions were used as animal models. Gene and protein expression of key monoamine transporters were assessed via quantitative PCR and Western blotting, respectively. The effects of trophoblast differentiation and inhibitors on monoamine uptake were investigated through functional studies.

The outcomes of this research elucidate monoamine transport alterations in differentiating trophoblasts and describe the expression patterns of monoamine regulatory components in the fetoplacental unit during gestation. Furthermore, this study highlights the expressional and functional differences between placenta-derived cell models, which is crucial for selecting the optimal model for monoamine research. Lastly, our findings indicate that several drugs commonly used during pregnancy interact with monoamine transport systems, inhibit their function, and thereby alter monoamine homeostasis in the fetoplacental unit.