ABSTRACT

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Title of doctoral thesis: Effect of antidepressants on placental monoamine homeostasis

Depression in pregnancy is an increasingly common problem and it is reported that up to 25 % of pregnant women suffer from depression and approximately 13 % are prescribed antidepressants. Currently, the most commonly prescribed antidepressants in pregnancy are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, the safety of these treatments is still controversial, as poor pregnancy outcomes such as organ malformations, increased incidence of neurological disorders, and preeclampsia have been reported in pregnant women taking antidepressants. However, knowledge of the responsible mechanisms is still lacking at present as they have not been sufficiently investigated. Although the effect of antidepressants on the availability of serotonin (5-HT), dopamine (DA) and norepinephrine in brain tissue has been extensively characterized in the literature, the interactions of antidepressants with placental monoamine transporters have not received attention to date. However, appropriate levels of monoamines in the fetoplacental unit are critical for proper placental and fetal development, and any disruption can lead to changes in fetal programming.

For this reason, in this dissertation I have investigated the acute and chronic effects of antidepressants on fetoplacental monoamine homeostasis. To accomplish these goals, I first determined the transport mechanisms by which monoamines are taken from the maternal and fetal circulation up. After identifying serotonin transporter (SERT), norepinephrine transporter and organic cation transporter 3 (OCT3), the major transporters mediating monoamine uptake through microvillous (MVM) and basal membrane (BM), respectively, I confirmed the acute inhibitory effect of antidepressants on their transport function in the placenta. Subsequently, I confirmed the suitability of using a rat model to study the effect of long-term paroxetine treatment on monoamine homeostasis in the placenta and fetal brain and on uteroplacental and fetoplacental circulation, which was the last part of my research.

A wide range of experimental approaches has been used to obtain the results, including rat models, specifically *in situ* dual and umbilical perfusion of the rat placenta and long-term treatment of pregnant rats with paroxetine. In addition, accumulation studies using *ex vivo* isolated human placental

membrane vesicles, *in vitro* cell cultures (HRP-1, transfected MDCKII), molecular biology methods to determine relative and absolute gene expression, qRT-PCR and ddPCR, and western blotting to determine protein expression were used. Finally, a unique imaging technique, Doppler ultrasonography, was used to study the resistance of the uterine and umbilical arteries.

The results of this dissertation thesis provide, first, insight into the physiological aspects of 5-HT, DA, and norepinephrine transport across the human and rat placenta, and second, a previously undescribed mechanisms by which acutely and chronically administered antidepressants during pregnancy disrupt fetoplacental homeostasis of monoamine: 1) Antidepressants inhibit monoamine uptake from maternal circulation mediated by SERT and norepinephrine transporter and from fetal circulation mediated by OCT3. 2) Paroxetine administered throughout gestation in rats results in increased resistance of uterine and umbilical arteries, which may be due to the accumulation of monoamines in the bloodstream together with the predominance of the non-branching type of placental angiogenesis. 3) Paroxetine administered throughout gestation in rats downregulates the expression of all genes involved in placental homeostasis of 5-HT, DA and norepinephrine and upregulates dopamine-β-hydroxylase (DBH) and L-type amino acid transporter expression in the fetal brain. Given that there is currently no more appropriate choice of antidepressant therapy in clinical practice, our findings are pharmacologically relevant to ensure the safety of using these drugs during pregnancy.