Doc. MUDr. Ivana Kacerovská Musilová, Ph.D.
Department of Obstetrics and Gynecology
University Hospital Hradec Králové
Sokolská 581, 500 05 Hradec Králové
Charles University, Faculty of Medicine in Hradec Králové
Šimkova 870, 500 03 Hradec Králové
E-mail: ivana.musilova@fnhk.cz

DISSERTATION THESIS REVIEW

submitted to Faculty of Pharmacy in Hradec Králové, Charles University

TITLE: Physiological and pharmacological aspects of tryptophan and serotonin homeostasis in the fetoplacental unit

AUTHOR: Mgr. Rona Karahoda

SUPERVISOR: Prof. PharmDr. František Štaud, Ph.D.

1. INTRODUCTION

This dissertation presents a comprehensive study of placental tryptophan metabolism. Placental utilization of this essential amino acid plays an important role in fetal development. Alterations in tryptophan homeostasis during pregnancy (e.g., pharmacotherapy) might represent harmful mechanisms that influence fetal development, which might determine long-term outcomes resulting from modified fetal programming.

2. THESIS EVALUATION

2.1. General description

The thesis is organized as an annotated set of four research articles and one invited review.

The text is logically structured and stratified into chapters according to the requirements for this type of scientific document. The Theoretical Background chapter presents a comprehensive literature review, supporting the formulation of the aims of the dissertation. The Results and Discussion are merged into one chapter, consisting of detailed article annotations. The Summary and Conclusion chapters provide a complex recapitulation of all findings with respect to their potential clinical impact. The citations referred in the text represent a list of relevant information sources.

The thesis was written in excellent English with correct formal adjustment of the text. It contains a number of well-prepared figures and schemes supporting the text, which makes the thesis easy to follow.

2.2. Scientific content

This thesis addresses the placental and fetal metabolism of tryptophan, characterizes placental serotonin handling, and evaluates the potential effect of antidepressants on this system. These studies have been performed using advanced methodological approaches applied to animal models and human placentas.

This thesis contains four research articles and one invited review. At present, one of the research articles is a submitted manuscript, while the rest have been published in top international journals with high impact factors. The candidate is the first author of three articles, with two of them in the shared first-author position. The candidate contributed

extensively to all articles, and her contribution included performing the experiments, data analysis, data interpretation, and manuscript preparation.

The results substantially extend our knowledge on tryptophan and serotonin homeostasis in the materno-fetal interface and provide clinically valuable data that suggest the potential adverse effects of some maternal medications (e.g., antidepressants and oral anti-diabetic agents) on fetal development and programming.

The scientific content of this thesis is current and relevant. The high quality and novelty of the content are supported and highlighted by the acceptance of the constituent articles in high-ranking journals.

3. QUESTIONS TO THE DEFENDANT

3.1. Article 4.1., wherein the role of placental drug transporters is discussed, mentions the possible deterioration of these transporters by some maternal disorders, such as inflammation. It is widely known that inflammation represents a highly common underlying pathology of preterm birth. Is there any evidence that preterm delivery is associated with alterations in the function of placental drug transporters?

3.2. In article 4.2., it is mentioned that serotonin uptake by OCT3 is inhibited by endogenous molecules, such as glucocorticoids. From the point of view of obstetrics, it raises the question of whether a course of corticosteroids (betamethasone or dexamethasone) for lung maturation, which is commonly administered in the management of preterm delivery, could affect serotonin homeostasis.

4. CONCLUSION

This thesis presents interesting and important results with potential clinical impact that have been obtained in the framework of consistent experimental studies. The author has demonstrated the ability to perform independent, high-level scientific work.

The thesis fulfills all criteria for a Ph.D. dissertation, and I recommend it for defense. After a successful defense, I recommend granting the academic title of "Ph.D." to Mgr. Rona Karahoda.

In Hradec Králové, March 3, 2021 Ivana Kacerovská Musilová