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INVESTIGATING THE ROLE OF AQUAPORINS IN THE REGULATION OF UTERINE CONTRACTIONS AND THE PREVENTION OF PRETERM BIRTH

Ph.D. Thesis

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Investigating the role of aquaporins in the regulation of uterine contractions and the prevention of preterm birth

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1. INTRODUCTION

Aquaporins (AQPs) are small integral membrane proteins responsible for water transport across biological membranes, they are crucial for cell survival and metabolic processes. Their function can be regulated by genetic modification, phosphorylation, and environmental factors such as pH, temperature, and solute gradients. AQPs are widely distributed throughout the body, playing a key role in water homeostasis. Eleven AQP isoforms have been identified in mammalian reproductive systems. In females, AQPs regulate amniotic fluid flow, placental function, myometrial contractions, and cervical ripening. Water balance in the reproductive system is essential for a healthy pregnancy and childbirth.

AQP5, a classical aquaporin, selectively transports water but can also facilitate the passage of small molecules, such as H_2O_2 and CO_2. It is widely expressed in secretory tissues, internal organs, reproductive tissues, and neurological structures. In the reproductive system, AQP5 is highly expressed in the pregnant uterus and undergoes dynamic regulation during gestation, which is influenced by changes in progesterone levels. Changes in AQP5 expression correlate with uterine function and the onset of labor.

Preterm birth (PTB) is defined as birth before 37 weeks of gestation and is a leading cause of infant mortality and morbidity. Current clinical treatments for PTB include tocolytics such as beta-mimetics, COX inhibitors, calcium channel blockers, magnesium sulfate, and oxytocin receptor antagonists. However, these treatments only delay labor for a short period, which underlines the need for novel therapeutic targets. AQPs, particularly AQP5, may be promising targets in regulating uterine smooth muscle activity and labor onset.

The transient receptor potential (TRP) channel family consists of non-selective calcium-permeable proteins that act as molecular sensors for various stimuli. The TRPV subfamily includes six members (TRPV1-6), with TRPV4 playing a crucial role in osmotic regulation and mechanosensing. TRPV4 is widely expressed in smooth muscle cells, including the uterus, where it contributes to calcium homeostasis and contractility.

AQPs and TRPV4 channels interact in multiple physiological systems, including the brain, kidneys, and respiratory system. In the reproductive system, AQP5 and TRPV4 exhibit an inverse expression pattern during pregnancy, regulated by progesterone. AQP5 expression increases with progesterone, whereas TRPV4 is suppressed. Near labor, progesterone levels drop, leading to increased TRPV4 expression and calcium influx, which contributes to uterine contractions. This interplay suggests that targeting the AQP5-TRPV4 interaction could provide a novel therapeutic approach for preventing preterm birth.

2. AIMS

The main goal of this research is to investigate the role of AQP5 in uterine contractions and its potential involvement in preterm birth. Based on this, our first aim (**I.**) was to examine the osmotic pathway and the cooperation between AQP5 and TRPV4 channels in the rat uterus, using the natural TRPV4 antagonist citral in both *in vitro* and *in vivo* experiments. The second objective (**II.**) was to evaluate the physiological role of AQP5 in parturition, focusing on its influence on uterine contractions through a siRNA animal model. Our next aim (**III.**) was to explore the receptor-mediated pathway by studying the interaction between AQP5 and the adrenergic system, using terbutaline, doxazosin, and $HgCl_2$ as treatments. And our last goal (**IV.**) was to investigate the expression of AQP5 in human uterine and placental samples at different stages of pregnancy and in plasma, as well as its potential involvement in pregnancy complications related to obesity.

3. MATERIALS AND METHODS

3.1. ANIMAL STUDIES

Housing and Handling: Sprague-Dawley rats were housed in controlled conditions (22 ± 3 ºC, 30–70% humidity, 12/12 h light/dark cycle). They were provided with standard rodent diet and water *ad libitum*. All procedures followed ethical guidelines (EU Directive 2010/63/EU, Hungarian Act XXVIII). All experiments involving animal subjects were carried out with the approval of the National Scientific Ethical Committee on Animal Experimentation (registration number: IV/2767/2020). Mature rats were mated in cages with time-controlled doors. Vaginal smears confirmed pregnancy.

3.1.1. *In vivo* Studies

Citral Treatment and Preterm Birth Model: Rats were divided into five groups: control, vehicle control (olive oil, *per os*), citral (240 mg/kg, *per os*), LPS (50 µg, *i.p.*), and LPS+citral. Premature labor onset was monitored by changes in mobility, nest-building, and vaginal hemorrhage.

siRNA Treatment: AQP5 siRNA (1 mg/kg, *i.p.*) was administered on day 21 of pregnancy, and AQP5 expression was measured.

Terbutaline and Doxazosin Treatment: Rats were treated with terbutaline (10 mg/kg) and doxazosin (5 mg/kg), and then uterine tissue was collected 30, 60 and 90 minutes after the treatment.

3.1.2. *In vitro* Studies

Uteri from 22-day pregnant rats were isolated and applied to an organ bath. Myometrial contractions were measured, and the effects of citral, siRNA, and $HgCl_2$ were evaluated.

3.2. HUMAN STUDIES

Sample Collection: Normal and obese (BMI > 30 kg/m^2) pregnant women undergoing elective cesarean sections at the University of Szeged were recruited. Inclusion criteria: singleton pregnancies with fetal risk. The human study protocol was approved by the Clinical Research Ethics Committee of the University of Szeged (Ref. no. 57/2020-SZTE). This study was carried out according to the principles of the Declaration of Helsinki. We obtained written, informed consent from all participants. Uterus, placenta, and serum samples were collected.

3.3. MOLECULAR BIOLOGY STUDIES

RT-PCR Studies: Total cellular RNA was extracted from rat and human uterine tissues using the guanidinium thiocyanate-acid-phenol-chloroform extraction procedure, as described by Chomczynski and Sacchi. RT- PCR was used to analyze gene expression of AQP5 and TRPV4. RT-PCR was performed using the TaqMan RNA-to-CT-Step One Kit and ABI StepOne Real-Time cycler. Specific PCR products were confirmed by melting curve analysis. All samples were analyzed in triplicate, and fluorescence intensities were used to determine the threshold cycle (C_T).

Western Blot Analysis: Protein samples were homogenized, and a total of 50 micrograms of protein per well was subjected to electrophoresis on 4-12% NuPAGE Bis-Tris Gel in XCell SureLock Mini-Cell Units (Thermo Fisher Scientific). Proteins were transferred from gels to nitrocellulose membranes using the iBlot Gel Transfer System (Thermo Fisher Scientific). The blots were incubated overnight on a shaker with rat and human AQP5, rat TRPV4 and β-actin polyclonal antibodies in blocking buffer. Antibody binding was detected with the Western Breeze® Chromogenic Western Blot Immunodetection Kit (Thermo Fisher Scientific, Hungary).

ELISA Assays: AQP5 concentration were measured in human plasma and CREB levels in rat uterine tissue samples using ELISA kits. Blood samples were collected in EDTA-coated polyethylene tubes, centrifuged at 1500 g for 10 minutes at 5°C, and stored at -80°C for later analysis. AQP5 concentration in human plasma was measured using an ELISA kit (EH0968, FineTest, Wuhan Fine Biotech Co., Ltd.) according to the manufacturer's instructions. CREB levels in rat uterine tissue were measured using a specific ELISA kit (ER0865, Fine Test,

Wuhan Fine Biotech Co., Ltd.). Optical density values were obtained using a SPECTROStar Nano microplate spectrophotometer at 450 nm.

3.4. STATISTICAL ANALYSIS

Data were analyzed using Prism 10.2.1 software (GraphPad Software Inc., San Diego, CA, USA). Statistical significance was determined using either a one-way ANOVA test (with Dunnett's post hoc test) or an unpaired *t*-test, and results are presented as the mean ± standard error of the mean (SEM). A significance level of $p < 0.05$ was established.

4. RESULTS

4.1. RESULTS OF ANIMAL STUDIES

4.1.1. Citral treatment

4.1.1.1. Contractility studies

The KCl-induced contraction response was inhibited by citral treatment (10^{-8}–10^{-2} M) in the 22-day pregnant rat uteri (***Figure 1***). At lower concentrations (10^{-8}–10^{-5} M), the relaxing effect was less significant than at higher concentrations (10^{-4}–10^{-2} M), where the relaxant effect increased steeply. The maximum relaxant effect of citral was 62.9% ± 2.5, while the EC_{50} was $2.16 \times 10^{-4} \pm 6.07 \times 10^{-5}$ M.

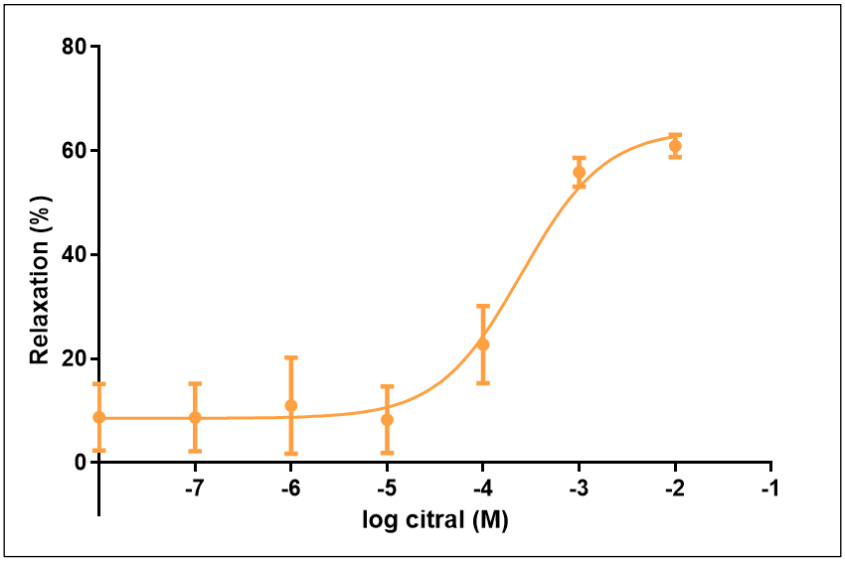

Figure 1. In vitro cumulative concentration-response curve of citral (10^{-8}–10^{-2} M) on 22-day pregnant rat uteri. The alteration in contraction was determined by the area under the curve (AUC) method and expressed in % ± S.E.M. as compared with the AUC of KCl-evoked control contractions. n = 6.

4.1.1.2. Molecular biology studies

Following *in vitro* citral treatment (10 μM for 2 h) of 22-day pregnant uteri the AQP5 mRNA and protein expression significantly increased compared to the control (***Figure 2A-B***). However, the expression changes in the TRPV4 expression were not significant (***Figure 2C-D***).

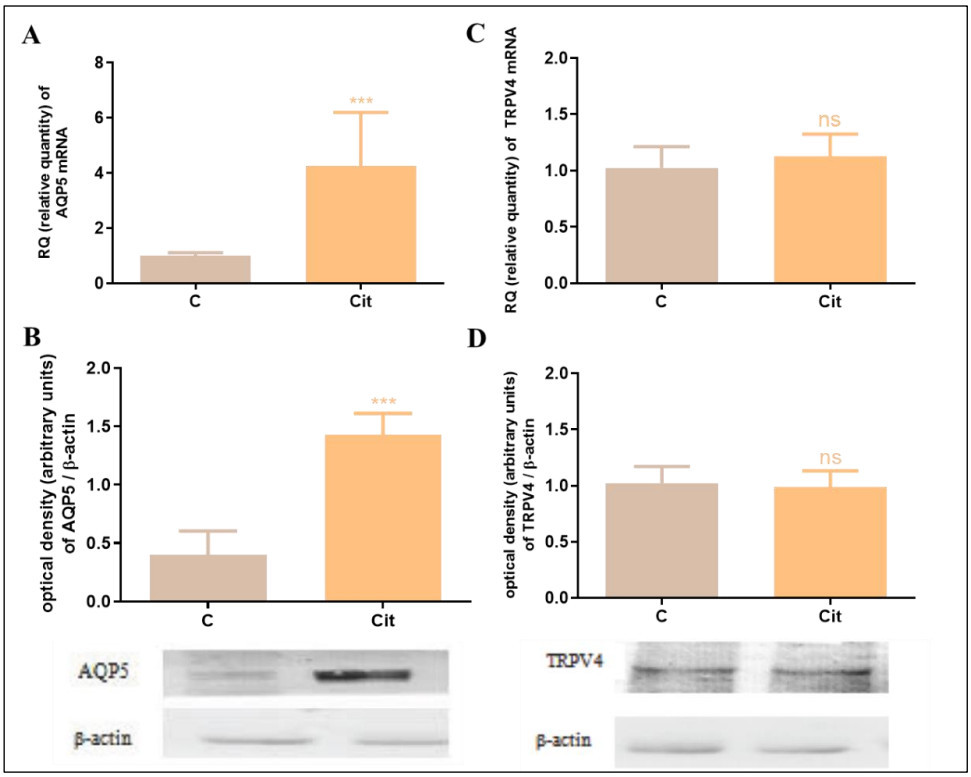

Figure 2. Changes in AQP5 mRNA (A) and protein (B, 35 kDa) and TRPV4 mRNA (C) and protein (D, 105 kDa) expression on gestational day-22 in pregnant rat uteri after citral treatment, in vitro. β-actin (43 kDa) was used as control. C: control uterus, Cit: citral-treated uterus, ns > 0.05; *** $p < 0.001$; compared to the control uterus sample. n = 6.

4.1.1.3. *In vivo* study of gestation length

In control rats, the calving date was usually the morning of gestation day 22 (t = 11.9 ± 0.5 h). The length of the gestational period significantly increased (mean time of birth on day 22: 15.9 ± 0.9 h) after vehicle (olive oil) treatment. After citral treatment, the gestational period was further extended (t = 28.6 ± 2.3 h) in normal pregnancy (***Figure 3A***). There were no adverse effects in any of the groups during the studies.

In the inflammatory-induced preterm birth model (treatment with LPS) the time of birth was during the night of the 20th day of pregnancy (t = 0.8 ± 1.5 h). No significant changes were observed in LPS-treated animals following vehicle control treatment at the time of parturition (t = 1.6 ± 1.0 h). Citral treatment resulted in a significantly longer gestational period in the LPS-

treated rat group, the time of delivery was extended to the dawn of the 22nd day of pregnancy (t = 54 ± 5.5 h) (***Figure 3B***).

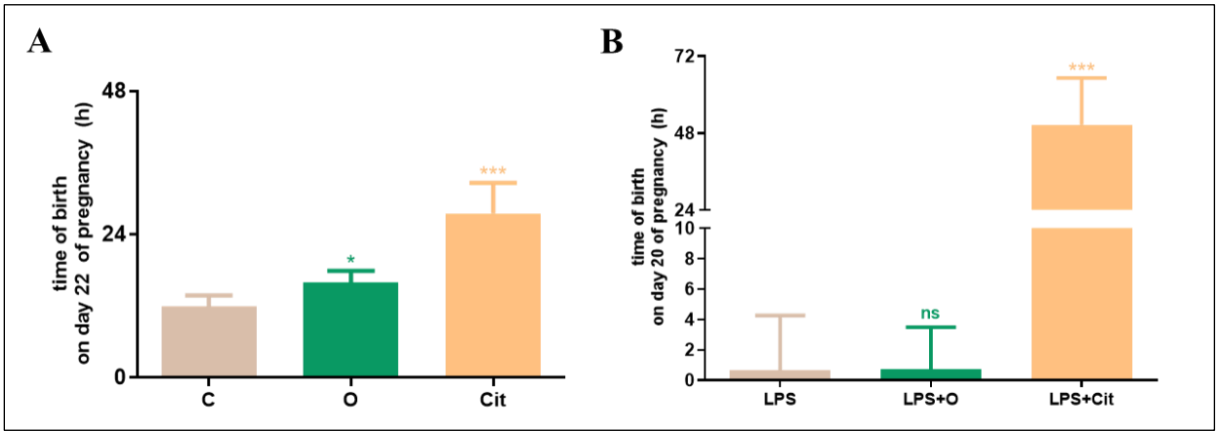

Figure 3. Changes in the time of birth of normal pregnancy (A) and bacterial lipopolysaccharide (LPS)-induced preterm birth (B). C: control, O: olive oil-treated, Cit: citral-treated, LPS + O: lipopolysaccharide and olive oil, LPS + Cit: bacterial lipopolysaccharide and citral treated animals. ns > 0.05, * $p < 0.05$, *** $p < 0.001$; compared to the control or LPS-treated animals. n = 6-8; control n = 16

4.1.2. siRNA studies

siRNA treatment significantly decreased AQP5 mRNA and protein expression compared to the control group (***Figure 4A***), indicating that the treatment worked, down-regulation of AQP5 channels occurred in the pregnant rat uteri. The control animals were administered with physiological saline solution and they gave birth on the morning of the 22th day of gestation (11.88 ± 0.4848 h), in contrast, the animals in the AQP5 siRNA-treated group had a shorter gestation period (7.95 ± 1.758 h), giving birth earlier than the control pregnant rats (***Figure 4B***). The treatment of rats with AQP5 siRNA significantly increased (difference: 148.2 ± 57.56 %) the KCl-evoked *in vitro* uterine contractions compared to the control animals (***Figure 4C***).

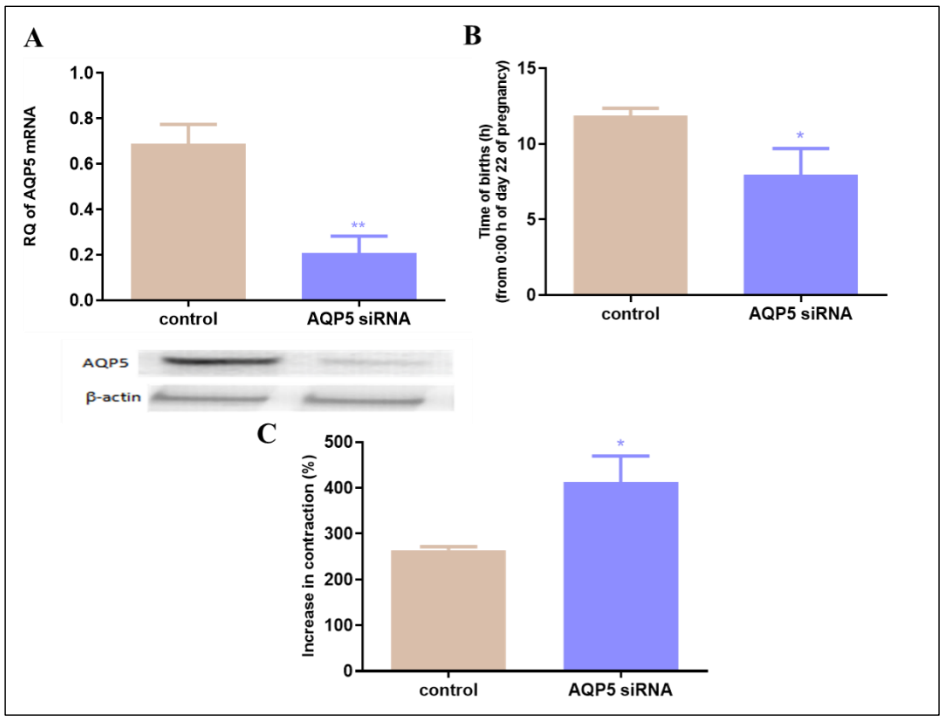

Figure 4. The effects of siRNA treatment. Changes in AQP5 mRNA and protein expression (**A**), the time of birth (**B**), and in vitro uterus contraction (**C**) in control and AQP5 siRNA-treated uterus. *p < 0.05 and **p < 0.01 compared to the control. n = 6

4.1.3. Terbutaline and doxazosin treatment

30 and 60 minutes following terbutaline administration, the AQP5 expression significantly increased in the pregnant rat uterus and significantly decreased in the 90th minute uterus samples (***Figure 5A***). The changes in the AQP5 protein expression followed the changes in mRNA expression, peaking 30 minutes after administration ***(Figure 5B***).

Following doxazosin administration, there was no significant change in the expression of AQP5 mRNA or protein (***Figure 5C-D***).

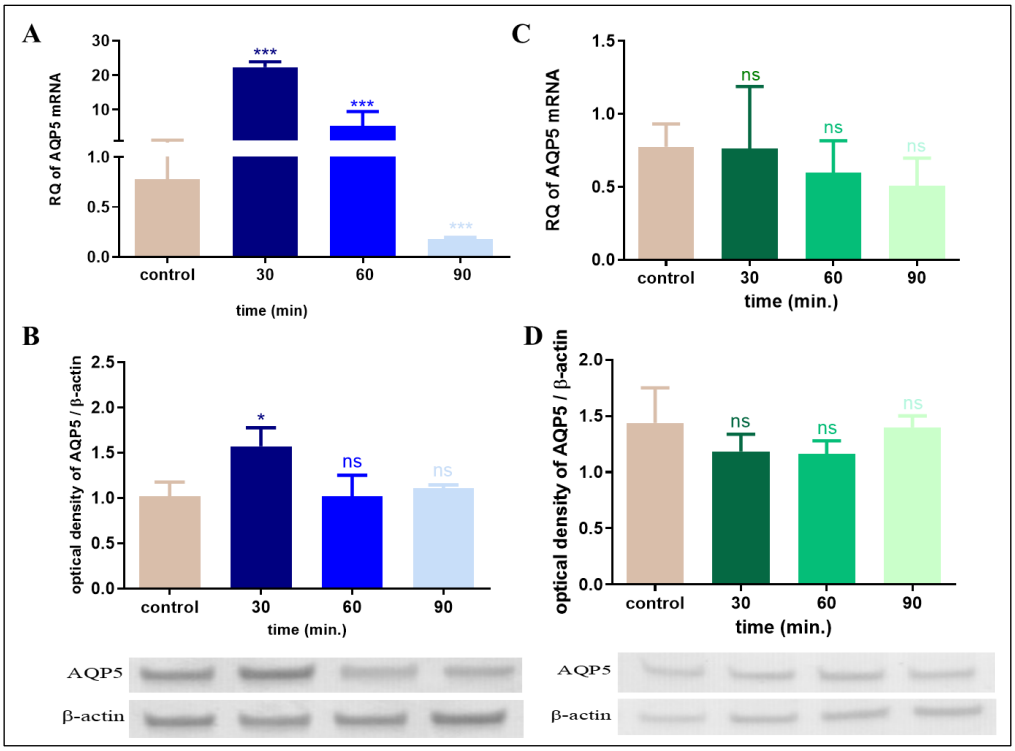

Figure 5. Changes in AQP5 mRNA (A) and protein expression after terbutaline (B) and doxazosin treatment (C, D) in pregnant rat uterus. ns > 0.05; *p < 0.05, ***p < 0.001; compared to the control uterine samples. n = 8

4.1.4. $HgCl_2$ studies

In the *in vitro* isolated organ bath study of 22-day-old pregnant rat uteri, $HgCl_2$ treatment increased the uterus' contractile activity, as measured by the enhanced AUC (area under the curve) values of spontaneous contractions. In the other group, following $HgCl_2$ treatment, the contractions caused by norepinephrine (NE) dramatically decreased (***Figure 6A***).

In the groups treated with $HgCl_2$ the AQP5 mRNA expression was significantly decreased compared to the control groups (***Figure 6B***). $HgCl_2$ significantly reduced protein expression in the presence of NE in comparison to the uteri in the NE treated control group (***Figure 6C***).

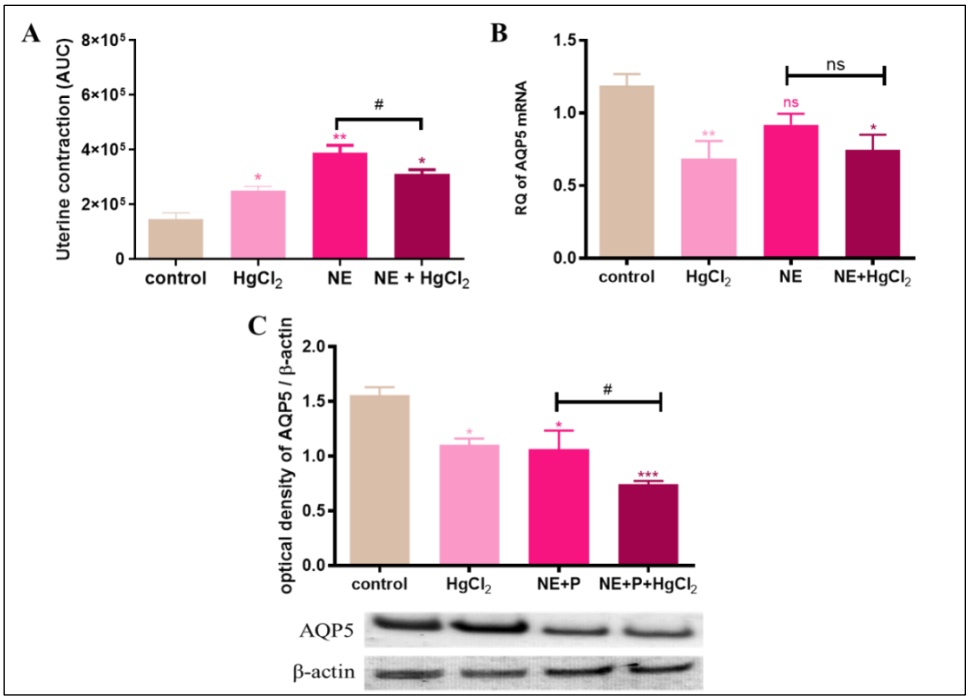

Figure 6. Changes in the area under the curve (AUC) values of uterus smooth muscle contraction (A), AQP5 mRNA (B), and protein expression (C) in spontaneous and NE-induced uterine contractions before and after $HgCl_2$ treatment. ns $p > 0.05$, *$p < 0.05$, **$p < 0.01$ compared to the control. #$p < 0.05$ compared to the NE-treated uterus.

NE elicited a concentration-dependent uterine contraction, which was reduced by $HgCl_2$ treatment. In the presence of terbutaline, the concentration-response curve of NE was shifted down, representing a concentration-dependent reduction in the relaxing effect. The $HgCl_2$ treatment ceased this concentration dependency of the relaxing action of NE in the presence of terbutaline (***Figure 7A***). Propranolol did not modify the stimulating effect of NE, but doxazosin shifted it down. In the presence of propranolol, the $HgCl_2$ treatment turned the NE effect to relaxation, which was not modified in the presence of doxazosin (***Figure 7B***).

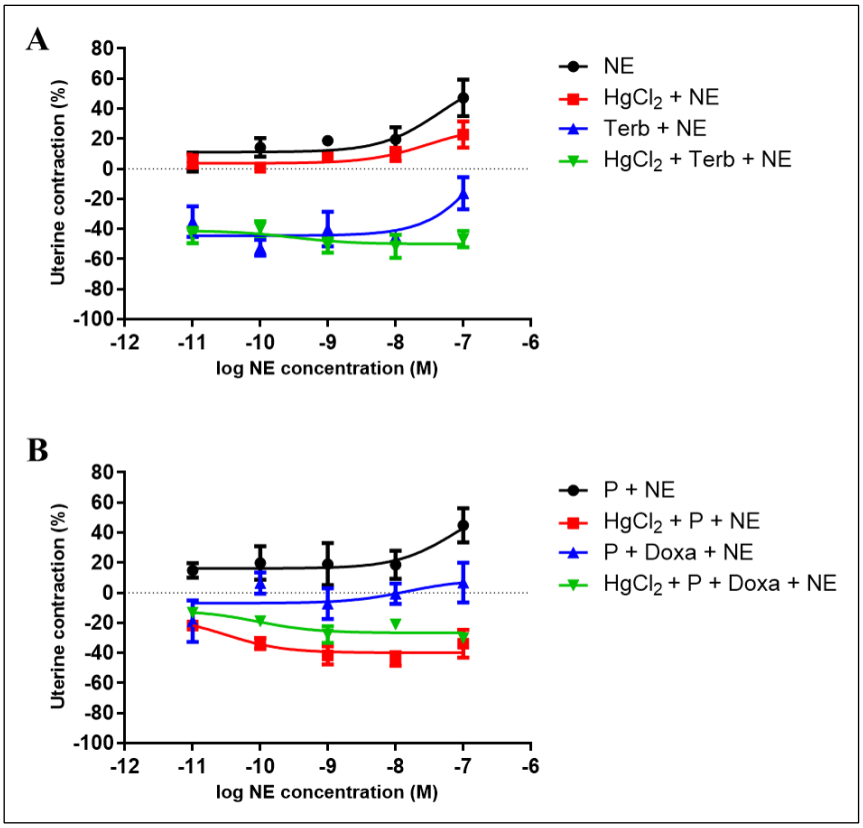

Figure 7. Dose-dependent effect of norepinephrine (NE, 10^{-11} – 10^{-7} M) on pregnant uterine contractions (day 22) alone or in combination with $HgCl_2$, terbutaline (Terb) 10^{-7} M, propranolol (P) and doxazosin (Doxa) 10^{-7} M.

Substance	EC50 (M)	Emax (%)
NE	$4.4 \pm 1.1 \times 10^{-8}$	62.9 ± 11.1
NE+T	$4.9 \pm 1.4 \times 10^{-7}$*	63.0 ± 9.7
NE+$HgCl_2$	$2.8 \pm 0.7 \times 10^{-8}$	28.1 ± 6.4**
NE+$HgCl_2$+T	$3.1 \pm 1.8 \times 10^{-10}$***	-50.8 ± 8.3***

Table 1. Changes in norepinephrine EC_{50} and E_{max} values without or after $HgCl_2$ treatment in the presence of terbutaline or alone. NE: norepinephrine (10^{-11}-10^{-7} M), T: terbutaline (10^{-7} M), EC_{50}: half maximal effective concentration, E_{max}: maximal contracting effect (a negative sign means relaxation), *p < 0.05, **p < 0.01, ***p < 0.001.

Substance	EC50 (M)	Emax (%)
NE+P	$7.5 \pm 1.9 \times 10^{-8}$	63.0 ± 15.6
NE+P+Doxa	$1.5 \pm 0.6 \times 10^{-8}$*	8.6 ± 3.1**
NE+P+$HgCl_2$	$3.0 \pm 1.2 \times 10^{-11}$***	-40.0 ± 8.1***
NE+P+$HgCl_2$+Doxa	$9.1 \pm 2.7 \times 10^{-11}$***	-26.7 ± 9.5***

Table 2. Changes in norepinephrine EC_{50} and E_{max} values without or after $HgCl_2$ treatment in the presence of propranolol or propranolol-doxazosin combination. NE: norepinephrine (10^{-11}-10^{-7} M), P: propranolol (10^{-7} M), Doxa: doxazosin (10^{-7} M), EC_{50}: half maximal effective concentration, E_{max}: maximal contracting effect (a negative sign means relaxation), p < 0.05, **p < 0.01, ***p < 0.001.

4.1.5. CREB assay

We examined cAMP response element binding protein (CREB) levels in uteri, which were treated *in vitro* with various combinations of norepinephrine (NE), $HgCl_2$, terbutaline and doxazosin. The $HgCl_2$ treatment did not induce changes in the CREB level in the NE-treated uterus, however the β_2-receptor agonist terbutaline, significantly decreased the CREB protein level after NE treatment, which was further enhanced by $HgCl_2$. In contrast, α_1-antagonist doxazosin did not cause significant changes in CREB protein levels with or without $HgCl_2$ (***Figure 8***).

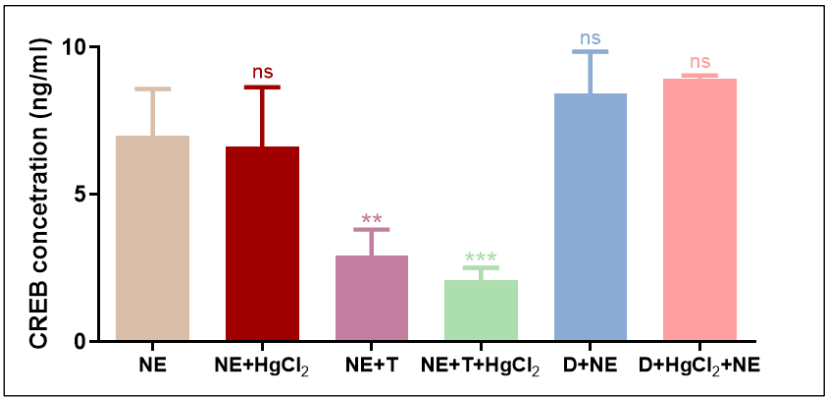

Figure 8. Changes in the concentration of cAMP response element binding protein (CREB) after $HgCl_2$, terbutaline (T) and doxazosin (D) treatment in norepinephrine (NE)-evoked contraction samples. ns $p > 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to the NE-treated uterus samples.

4.2. RESULTS OF THE HUMAN STUDIES

4.2.1. Alteration of AQP5 expression in the uterus and plasma

We examined the changes in AQP5 mRNA and protein expression in the human uterus at different gestational weeks. We found that both mRNA and protein expression of AQP5 significantly increased at week 34 compared to week 41 of gestation (***Figure 9A***). While during normal pregnancy weeks (36th to 41st weeks of gestation) the AQP5 expression did not change significantly, only protein expression was reduced at week 36 of gestation (***Figure 9B***).

The plasma samples from week 34 of pregnancy showed a considerable increase in AQP5 concentration when compared to the non-pregnant control and other weeks of normal pregnancy (***Figure 10***).

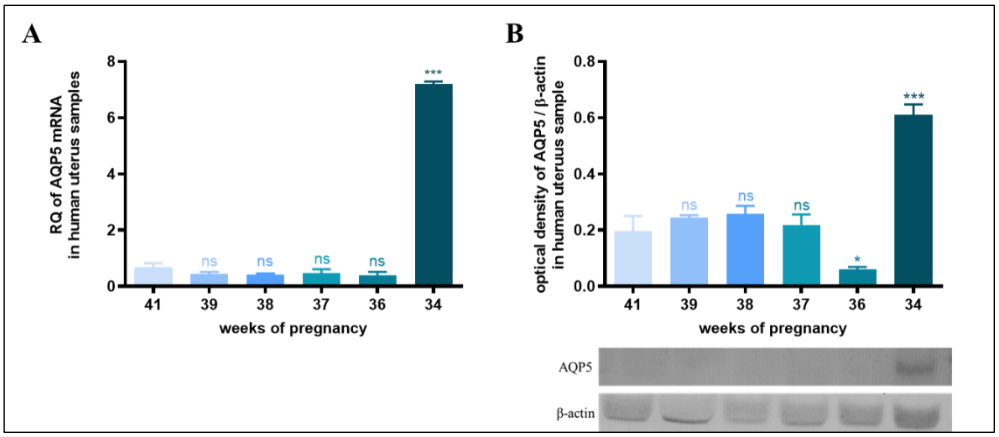

Figure 9. Changes in the AQP5 mRNA (A) and protein (B) expression during different weeks of normal pregnancy in human uterine samples. ns $p > 0.05$, * $p < 0.05$, *** $p < 0.001$ compared to the 41st week of pregnancy.

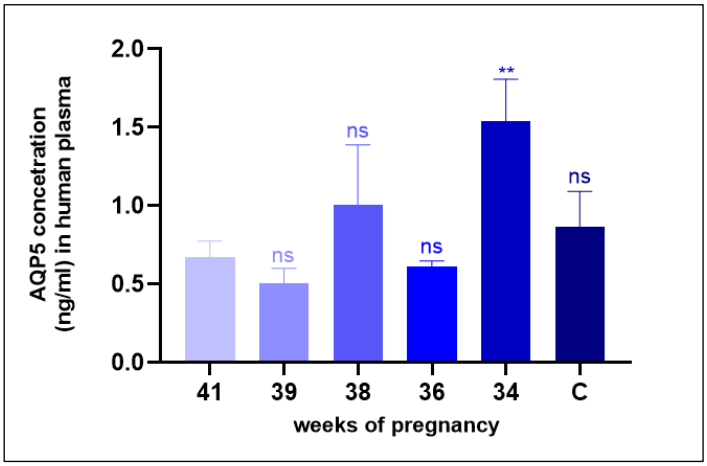

Figure 10. AQP5 concentration in the different weeks of normal pregnant and non-pregnant (C) human plasma samples. ns: $p > 0.05$, ** $p < 0.01$ compared to the control.

4.2.2. Alteration of AQP5 expression in the obese pregnant women

The uteri of obese mothers showed a significant increase in AQP5 mRNA and protein expression (***Figure 11***) compared to those of mothers of normal weight (control). When comparing the placental tissue of obese mothers to that of the control, no alterations in AQP5 mRNA and protein expression were observed (***Figure 12***).

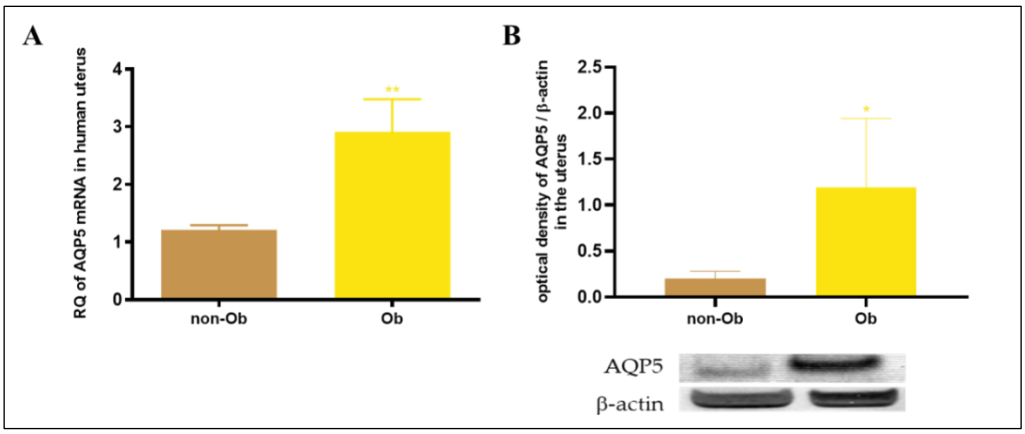

Figure 11. Changes in AQP5 mRNA (A) and protein (B) expression in uterine samples with normal weight (non-Ob) and obese (Ob) mothers in the third trimester of pregnancy; * $p < 0.05$, ** $p < 0.01$ compared to the control.

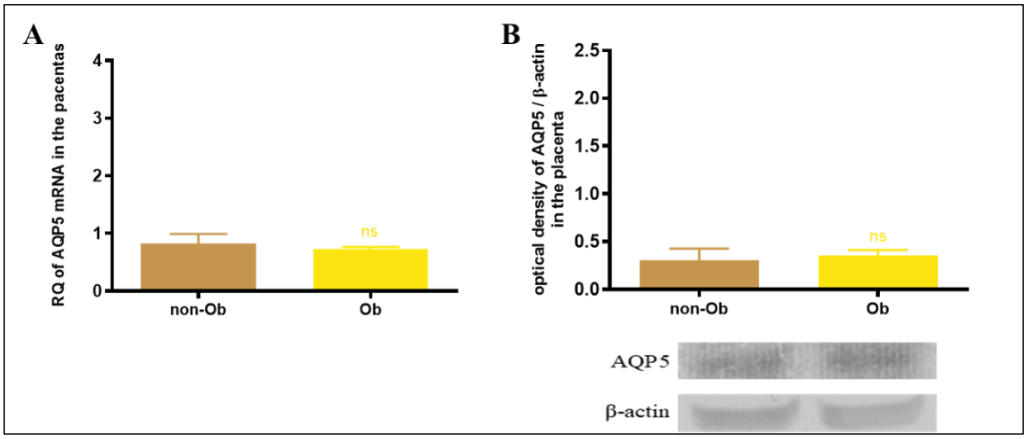

Figure 12. Changes in the AQP5 mRNA (A) and protein (B) expression in the placental tissue samples collected from obese (Ob) and non-obese mothers (non-Ob) in the third trimester of pregnancy; ns $p > 0.05$ compared to the non-obese mothers.

5. DISCUSSION

Premature birth (PTB) remains a critical global issue, being the leading cause of infant morbidity and mortality. Given the multifactorial causes of PTB, identifying effective prevention strategies is challenging. However, interdisciplinary research into the pathomechanisms of PTB, including understanding the role of the AQP5 channel in uterine contractility, may lead to potential therapeutic targets for tocolysis.

5.1. ANIMAL STUDIES

The previous work of the research group indicated an inverse correlation between AQP5 expression and uterine contractions. We proved, that the osmotic pathway is a key mechanism where changes in AQP5 influence osmotic balance in the late-pregnant uterus, affecting TRPV4 channel activity and modulating myometrial calcium levels. *In vivo* experiments in rats

confirmed this pathway, demonstrating that TRPV4 and AQP5 expression are interconnected. The use of citral, a natural TRPV4 inhibitor, allowed us to explore this mechanism in pregnant animals. Citral was chosen for its safety profile, as its pharmacokinetic parameters were well documented, unlike synthetic TRPV4 antagonists, for which data are lacking. Citral delayed pregnancy and induced dose-dependent uterine relaxation, further supporting the AQP5-TRPV4 interaction. Olive oil, particularly its component oleocanthal, also demonstrated uterine relaxant effects, possibly through modulation of the calcium/PGF_2 pathway. However, in the LPS-induced preterm birth model, olive oil's effects were absent, suggesting a complex interaction of factors in PTB.

We further examined the role of AQP5 in labor initiation using AQP5 siRNA, which successfully reduced AQP5 expression. This gene silencing led to increased uterine contractions and earlier parturition, supporting the hypothesis that reduced AQP5 expression induces labor.

The receptor-mediated pathway, potentially cooperating with the adrenergic system, represents another regulatory mechanism for AQP5. Direct *in vivo* examination of AQP5 remains challenging due to the lack of selective pharmacological tools. However, prior studies indicate that cAMP influences AQP5 expression, as seen in various tissues, including lung epithelial cells and myometrial tissues. In the pregnant uterus, AQP5 expression appears to be modulated by cAMP-elevating agents such as terbutaline, a β_2-adrenergic receptor agonist, which induces AQP5 translocation and increases expression through PKA activation. In contrast, doxazosin, an α_1-adrenergic receptor antagonist, does not significantly alter AQP5 expression, probably because it has no effect on cAMP levels. Additionally, $HgCl_2$, a known AQP5 inhibitor, increased spontaneous uterine contractions. In the presence of norepinephrine (NE), $HgCl_2$ reduced α_1-mediated contractions without affecting β-adrenergic responses, suggesting receptor-specific interactions. Terbutaline exhibited dose-dependent inhibition of uterine contractions, an effect potentiated by $HgCl_2$. Propranolol, a β-blocker, had no effect on α_1-mediated contractions, while doxazosin enhanced uterine relaxation, further intensified by $HgCl_2$, implying AQP5 involvement. These findings suggest that AQP5 expression modulates uterine contractility via adrenergic receptor pathways.

Furthermore, CREB, a transcription factor activated by cAMP, plays a critical role in cell differentiation and survival. Activation of β_2-adrenergic receptors by terbutaline led to increased cAMP levels and CREB phosphorylation, reducing uterine contractions. $HgCl_2$ treatment decreased CREB levels, suggesting a link between cAMP signaling, AQP5, and uterine relaxation.

5.2. HUMAN STUDIES

In human studies, we measured AQP5 expression between 34 and 41 weeks of pregnancy. AQP5 levels were elevated at 34 weeks but decreased significantly by 36 weeks and remained low until delivery, aligning with animal data suggesting AQP5's role in modulating uterine contractility. Changes in AQP5 expression were further explored in plasma samples, with notable alterations at 34 weeks, possibly influenced by glucocorticoid treatment (betamethasone) commonly given to preterm labor patients. Glucocorticoids are known to regulate AQP5 expression in various tissues, including the lung, where they increase AQP5 expression.

In obese women, the onset of labor is often delayed, and our data suggest that higher AQP5 expression in the uterus may contribute to this delay by inhibiting uterine contractions. This supports the hypothesis that elevated AQP5 levels in the uterus, along with other factors like oxytocin and progesterone, may influence labor timing. Interestingly, no significant changes in AQP5 expression were found in the placenta of obese women. These findings suggest that AQP5 could serve as a potential target for therapeutic strategies to manage labor timing in obese women.

6. CONCLUSION

Preterm birth remains a major global challenge, partly due to the limited understanding of its mechanisms. The results have highlighted a novel regulatory pathway involving the AQP5 channel, which may serve as a potential therapeutic target.

Our findings demonstrate that (**I**) inhibition of TRPV4 by citral reduces uterine contractions while increasing AQP5 expression in vivo, likely by suppressing cell volume expansion and delaying parturition. (**II**) Using an AQP5 knockdown rat model, we confirmed essential role of AQP5 in initiating labor. (**III**) We established a functional link between AQP5 and the adrenergic system via cAMP, as evidenced by terbutaline, doxazosin, and $HgCl_2$ experiments. (**IV**) Human studies, supported by our animal findings, demonstrate an inverse correlation between AQP5 expression and uterine contractility, suggesting potential implications for prolonged gestation in obese women.

These results provide strong evidence that AQP5 regulates uterine contractions through multiple pathways, including osmotic and receptor-mediated mechanisms. Our research may establish a foundation for future therapeutic strategies to modulate the onset of labor.

LIST OF PUBLICATIONS

1. Publications related to the Ph.D. thesis

I. Seres-Bokor A, **Kemény KK**, Taherigorji H, Schaffer A, Kothencz A, Gáspár R, Ducza E.: The Effect of Citral on Aquaporin 5 and Trpv4 Expressions and Uterine Contraction in Rat-An Alternative Mechanism. *Life (Basel). 2021 Aug 30;11(9):897.* ***[IF: 3,253; Q2 in Biochemistry, Genetics and Molecular Biology (miscellaneous) (2021)]***

II. Kemény KK, Ducza E. Physiological Cooperation between Aquaporin 5 and TRPV4. *International Journal of Molecular Sciences. 2022 Oct 1;23(19):11634.* ***[IF: 5,6; Q1 in Medicine (miscellaneous) (2022)]***

III. Kemény KK, Kozinszky Z, Altorjay ÁT, Kolcsár B, Surányi A, Ducza E. Effect of Obesity on Aquaporin5 Expression in Human Placental and Uterus Tissues. *Journal of Clinical Medicine. 2024;13(15):4490.* ***[IF: 3,0; Q1 in Medicine (miscellaneous) (2023)]***

IV. Kemény KK, Seres-Bokor A, Barna T, Mirdamadi M, Gáspár R, Surányi A, Ducza E. Cooperation of aquaporin 5 and the adrenergic system in the initiation of birth in rat model. *Heliyon. 2024;10(17):e37329.* ***[IF: 3,4; Q1 in Multidisciplinary (2023)]***

2. Presentations related to the Ph.D. thesis

I. Kemény KK, Seres-Bokor A, Schaffer A, Gáspár R, Ducza E. Effect of citral treatment on the length of rat gestation period - *Semmelweis Symposium 'Excellence in Clinical Research and Innovation' 2021* (poster presentation)

II. Kemény KK, Seres-Bokor A, Schaffer A, Barna T, Gáspár R, Ducza E. The possible role of AQP5 (and TRPV4) in the prevention of preterm birth - *17th RECOOP Bridges in Life Sciences Conferences 2022* (oral presentation)

III. Kemény KK, Seres-Bokor A, Barna T, Mirdamadi M, Gáspár R, Ducza E. Az AQP5 (és a TRPV4) csatorna lehetséges szerepe a koraszülés megelőzésében - *MGYT Gyógyszerkutatási Szakosztály Fiatal Kutatók Fóruma 2022* (oral presentation)

IV. Kemény KK, Surányi A, Altorjay ÁT, Németh G, Molnár A, Ducza E. AQP channels and pregnancy – molecular pharmacology studies in human samples - *18th RECOOP Bridges in Life Sciences Conferences 2023* (oral presentation)

V. Kemény KK, Surányi A, Altorjay ÁT, Németh G, Molnár A, Ducza E. Changes of AQP channels expression in pregnant human samples - *25. Tavaszi Szél Konferencia 2023* (oral presentation)

VI. Kemény KK, Ducza E. Az aquaporin 5 csatorna szerepének vizsgálata a koraszülés megelőzésében - X*V. Clauder Ottó Emlékverseny 2023* (oral presentation)

VII. Kemény KK, Surányi A, Altorjay ÁT, Ducza E. Investigation of obesity-related factors in human placental tissue samples - *19th RECOOP Bridges in Life Sciences Conferences 2024* (oral presentation)

VIII. Kemény KK, Surányi A, Altorjay ÁT, Ducza E. The relationship between obesity and pregnancy - molecular biology studies in human placental samples - *Congressus Pharmaceuticus Hungaricus XVII. and EUFEPS Annual Meeting 2024* (oral presentation)

IX. Kemény KK, Surányi A, Altorjay ÁT, Ducza E. Relationship between obesity-related factors and pregnancy complications - molecular biology studies - *EUGLOH Annual Summit 2024* (poster presentation)

3. Other publication unrelated to this thesis

I. Osman AA, Laczkó D, Vágvölgyi M, Seres-Bokor A, Sztojkov-Ivanov A, **Kemény KK**, Hunyadi A, Ducza E. Investigation of calonysterone and 20-hydroxyecdysone effects in high-fat, high-sugar diet-induced obesity rat model. *Heliyon, 11(3), e42435. (2025).* ***[IF: 3,4; Q1 in Multidisciplinary (2023)]***