Role of urocortin in pregnancy: An update and future perspectives

Salvatore Giovanni Vitale, Antonio Simone Laganà, Agnese Maria Chiara Rapisarda, Maria Giovanna Scarale, Francesco Corrado, Pietro Cignini, Salvatore Butticè, Diego Rossetti

Salvatore Giovanni Vitale, Antonio Simone Laganà, Francesco Corrado, Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood “G. Barresi”, University of Messina, 98100 Messina, Italy

Agnese Maria Chiara Rapisarda, Department of General Surgery and Medical Surgical Specialties, University of Catania, 95124 Catania, Italy

Maria Giovanna Scarale, Department of Clinical and Community Sciences, University of Milan, 20122 Milan, Italy

Pietro Cignini, Department of Prenatal Diagnosis, Altamedica Fetal Maternal Medical Center, 00198 Rome, Italy

Salvatore Butticè, Unit of Urology, Department of Human Pathology, University of Messina, 98100 Messina, Italy

Diego Rossetti, Department of Maternal and Child Health, Gavardo Hospital, 25085 Brescia, Italy

Author contributions: Vitale SG and Laganà AS made equal contributions to this work and the writing of the manuscript; Scarale MG, Butticè S and Rossetti D participated in the compilation of the manuscript and its drafting; Rapisarda AMC, Corrado F and Cignini P collected the literature data and edited the manuscript.

Conflict-of-interest statement: All authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Antonio Simone Laganà, MD, Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood “G. Barresi”, University of Messina, Via C. Valeria 1, 98125 Messina, Italy. antlagana@unime.it Telephone: +39-090-2212183 Fax: +39-090-2937083

Received: February 12, 2016 Peer-review started: February 18, 2016 First decision: March 25, 2016 Revised: May 10, 2016 Accepted: May 17, 2016 Article in press: May 27, 2016 Published online: July 16, 2016

Abstract

The activities of corticotropin-releasing factor (CRF) and related peptides are mediated a number of receptors with seven transmembrane domains that are coupled to the Gs and Gq proteins. These receptors are known as CRF-Rs. In vitro studies have evidenced that urocortin (UCN) and CRF provoke an increase in the contractility of the uterus which is induced by endometrial prostaglandin F2α. Furthermore, through trophoblasts, it stimulates the secretion of adrenocorticotropic hormone (ACTH) and prostaglandin PGE2 and has a vasodilatory effect on the placenta. While it is well known that the placenta produces considerable quantities of CRF, several studies have, however, excluded that the placenta can generate significant quantities of UCN. In the short term, the human fetal adrenal gland produces more cortisol and dehydroepiandrosterone sulfate. The gestational tissues express UCN3 and UCN2 mRNA in cytotrophoblast and syncytiotrophoblast cells, while UCN2 is only to be found in the maternal and fetal vessels and amniotic cells. Nevertheless, gestational tissues express UCN2 and UCN3 differentially and do not stimulate placental ACTH secretion. In term pregnancies, maternal plasma levels of CRF and UCN are lower than at the beginning of pregnancy and are correlated to labor onset. Conversely,
they do not decrease in post-term pregnancies. This evidence would seem to indicate that the fine-regulated expression of these neuropeptides is important in determining the duration of human gestation. In this scenario, low concentrations of UCN in the amniotic fluid at mid-term may be considered a sign of predisposition to preterm birth.

Key words: Urocortin; Corticotropin-releasing factor; Obstetrics; Gynecology; Inflammation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Low concentrations of urocortin (UCN) in the amniotic fluid may be a sign of predisposition to preterm birth, since it correlates with a pro-inflammatory state. UCN is present at higher serum concentrations in women with endometriomas. Therefore, the measurement of UCN could be useful in distinguishing between endometriosis and other benign ovarian cysts. The therapeutic treatment with UCN decreases serum levels of proinflammatory cytokines in several experimental situations, so it is plausible that the same effects may occur in different obstetric and gynecological diseases in which inflammation plays a key role in the onset and progression of the disease.

INTRODUCTION

The urocortin (UCN) is a molecule composed of 40 amino acid residues belonging to the family of peptides related to corticotropin-releasing factor (CRF). Accumulating evidence suggests a key role for UCN in several physiological as well as pathological obstetric conditions. Nevertheless, so far no robust data are available in current literature which can be helpful to elucidate its possible therapeutic application(s). Considering these assumptions, the aim of this paper was to collect data about this topic in order to review the role of UCN during pregnancy. The MEDLINE data base between 1970 ± 2016 was searched by using the terms UCN combined with each of the following terms: Gynaecology, obstetrics, delivery, birth, placenta, and uterus. The relevance of articles was screened on the basis of information in the title and abstract.

BIOCHEMICAL AND GENETIC ASPECTS

The activation of CRH receptors type 1 (CRH-R1) by CRH or UCN stimulates multiple G proteins which influences various signaling cascades in a tissue-specific manner. In human myometrium and human embryonic kidney, the binding of UCN to CRH-R1 receptors activates both the Gs and Gq. These activate the adenylyl cyclase/protein kinase A and the phospholipase C/protein kinase C and ERK1/2 signaling pathways, respectively.[1]

In this family, UCN1, UCN2 and UCN3 have been identified. UCN1 has a high affinity for both CRHR1 and CRHR2 receptors. Human UCN1 mRNA is present in different central nervous system cells and various peripheral tissues including placenta, decidua, fetal membranes, endometrium, heart and gastrointestinal tract. UCN2 is mainly expressed in the heart. UCN2 has a number of various cardiovascular effects and due to fact it protects the myocardium against ischemic injury, it has provoked considerable interest recently. UCN2 also activates mitochondrial ATP-sensitive potassium channels and also blocks the opening of the mitochondrial permeability transition pore.

UCN3 was expressed in the pancreatic beta cells during mice embryonic development. UCN3 can be secreted from pancreatic alpha and beta cells and may have possible paracrine and/or autocrine effects in the islet. Its potent biological action is mediated by CRF receptor type 1 (CRF-R1) and receptor type 2 (CRF-R2), causing adrenocorticotropic hormone (ACTH) release, vasodilation,[2] increased cardiac inotropism, reduction of vascular permeability[3], appetite suppression[4] and increased secretion of atrial natriuretic peptide and brain natriuretic peptide[5]. The UCN sequence is 45% homologous to that of CRF[6].

The human UCN consists of 124 amino acids, 80 of which form the “precursor peptide”. The amino acids Arg-Arg in position 81-82 and Lys-Gly in position 123-124 undergo a process of proteolysis, constituting respectively the site of detachment from the precursor and the C-terminal sequence. The UCN binds to the same protein in plasma, the CRF-BP (CRF-binding protein) that carries the CRF. The actions and the tissue distribution of CRF-BP have led to the hypothesis that this protein may modulate the action of UCN in different time frames and in different parts of the brain. UCN3 mRNA expression is found in areas of the brain including the hypothalamus, amygdala, and brainstem, but is not evident in the cerebellum, pituitary, or cerebral cortex. The inactivation of CRF-BP induces an increase of CRF and free UCN[7]. The UCN gene is located on the short arm of chromosome 2 (2p23-p21). The gene structure is similar to that of CRF, articulated on two exons and an intron. The coding region is located entirely on the second exon. Moreover, the UCN and CRF have common sites of transcription initiation, such as the TATA-box, the CRE (cAMP response element), GATA binding sites and C/EBP[8]. Conversely, the regional distribution of immunoreactive UCN has been studied with radioimmunoassay techniques in the human brain and is partly different from that of the CRF, although
it has been demonstrated that the UCN mRNA is expressed in every brain region\textsuperscript{[9]}. Indeed, UCN has been found in several brain regions, including the hypothalamus, bridge, cerebral cortex and cerebellum, whereas CRF is present in higher concentrations in the frontal and parietal cortex and the hypothalamus, while its concentration at the pontine level is minimal. CRF activity and their related peptides are mediated by receptors with seven transmembrane domains that are coupled to the G protein\textsuperscript{[10,11]}. Compared to the CRF, the UCN binds with six times greater affinity to CRF-R1 and with forty times greater affinity to CRF-R2\textsuperscript{[12]}. Another mechanism of UCN action is its effect on calcium channels. In mouse spermatogenic cells, UCN has been shown to act by reducing L-type calcium currents of acute isolated cardiac myocytes and T-type calcium currents through the inhibition of the calcium channel instead of binding to its CRF-R2. Secondly, UCN may also reduce intracellular calcium through the inhibition of calcium channels in vascular smooth muscle cells. In this way, UCN could increase the gene expression of ATP-sensitive potassium channels\textsuperscript{[13]}. As already mentioned, elevated levels of UCN are correlated with the reduction of appetite and blood pressure through an increase in cardiac contractility, activity and anxiety\textsuperscript{[14-16]}. The human cardiovascular system also expresses high numbers of CRF receptors. Therefore, both UCN2 and UCN3 have been found to produce potent, sustained, direct and endothelium-independent vasodilating effects in an in vitro human internal mammary artery model of endothelin-1 induced constrictions. UCN1 also produced endothelium-dependent vasodilating effects in this model, which were putatively mediated (unlike in vivo rodent studies) by nitric oxide and, downstream, by the cyclic guanine 3′,5′ monophosphate-dependent stimulation of calcium-activated K+ channels in vascular smooth muscle.

The NO/cGMP signaling pathway seems to be important in vascular adaptation and placental physiology during pregnancy and labor because it mediates the vasodilatory effects of agonists in resistance vessels, especially the stem villous arterioles, and this helps maintain the low vascular resistance of the fetoplacental circulation. There is considerable evidence which indicates that this NO/cGMP pathway mediates the vasodilatory actions of CRH and UCN in human fetoplacental circulation\textsuperscript{[14,17]}. UCN also correlates with the onset of labor, spontaneous abortion and preeclampsia\textsuperscript{[14]}. Endometrium, myometrium, ovaries and/or placenta are also known to express CRF and UCN\textsuperscript{[16,18]}.  

**IMPLICATIONS IN OBSTETRICS DURING PREGNANCY**

**Reproductive UCN**

Evidence that the concentration of free CRF increases during pregnancy and that CRF increases placental vasodilation and myometrial contractility has led several researchers to investigate whether UCN has a similar role during gestation. In *in vitro* studies have demonstrated that both UCN and CRF increase uterine contractility induced by the endometrial prostaglandin F2α. This mechanism is probably due to the accelerated procontractile effect of PGE2 by up-regulating the expression of PGE2 receptor and by increasing the prostaglandin alfa receptor. Furthermore, it stimulates ACTH and prostaglandin PGE2 secretion by the trophoblast and has a vasodilatory effect on the placenta. In addition to stimulatory effects on prostaglandin production, UCN also up-regulated myometrial expression of proinflammatory cytokines via CRH-R2. A positive feedback loop between UCN and inflammatory cytokines therefore probably exists because UCN expression was increased by the inflammatory stimulus tumor necrosis factor alpha, probably through NF-kB signaling\textsuperscript{[15]}. Moreover, UCN decreases placental gene and protein expression of 15-hydroxyprostaglandin dehydrogenase, a PGE metabolizing enzyme, an effect that is reversed by selective CRH-R2 antagonist astressin. These effects echo the stimulatory effect of UCN on prostaglandin production. All of these effects are inhibited by astressin, a CRF receptor antagonist. While there is a substantial similarity in action of CRF and UCN regarding myometrial contractility and placental functions, similar relationships were not observed when investigating the ability of the placenta to produce UCN\textsuperscript{[19]}. It has already been demonstrated that the placenta synthesizes considerable quantities of CRF, but studies have shown that the placenta does not produce significant quantities of UCN. This excludes the possibility that greater amount of free CRF present in circulation during pregnancy may be a result of a dislocation of the CRF from CRF-BP by UCN\textsuperscript{[20]}. On the other hand, the possible role of UCN in ovarian steroidogenesis is still far from being completely elucidated.

**Ovarian cycle**

Immunohistochemical methods were adopted to detect UCN1 in both granulosa and theca cells of dominant and non-dominant follicles, as well as in atretic follicles\textsuperscript{[21]}. UCN1 was also found in luteinized granulosa and thecal cells in the mid- and late-phase corpus luteum\textsuperscript{[21]}. Synthesized locally, it acts on steroidogenic luteal cells, in particular, during luteal regression, through the CRF–R\textsuperscript{[21]}. Immunohistochemistry methods also revealed that mRNA levels of CRF and CRF-R1 were significantly higher in the regressing corpus luteum compared to either the mid-luteal phase or pregnant corpus luteum\textsuperscript{[21]}. However, no significant difference was revealed between the expression of these genes in the mid-luteal phase of the menstrual cycle and early pregnancy\textsuperscript{[21,22]}. Nevertheless, no evidence was found concerning the potential role of UCN 2 and 3 in the ovary in those studies\textsuperscript{[21,22]}.  

**Menstrual cycle**

During the menstrual cycle, UCN mRNA has been shown...
to be expressed in endometrial epithelial and stromal cells during both endometrial phases (proliferative and secretory phase)\[23\]. The highest concentrations of UCN1 and mRNA were found in the secretory phase, while they were higher in the late phase compared to the early secretory phase\[24\].

**Placental and myometrial UCN**

Placental and myometrial UCN2 may play a role in the endocrine-inflammatory processes of parturition, thus representing a potential target for treating inflammation-induced obstetric complications\[25\]. In the short term, the human fetal adrenal gland increases the production of cortisol and dehydroepiandrosterone sulfate (DHEA-S). DHEA-S, which acts as a substrate for the production of placental estrogen, induces important changes involved in childbirth. CRF, UNC, ACTH stimulate all elements of the pathway of DHEA-S and also activated synthetic CRF-R1. The consequential increase in levels of DHEA-S may be used for the synthesis of estrogens in the placenta and contribute to the process that leads to birth\[26\]. The estradiol E2 increases the activity of the promoter UCN via ER- α and decreases the activity of the human UCN promoter through ER-α. There is evidence that estrogens exert a direct transcriptional regulation and differential gene UCN\[27\]. The placenta, decidua and fetal membranes express mRNA UCN2-UCN3, localized in cytotrophoblast and syncytiotrophoblast cells, while only in the maternal and fetal vessels and amniotic cells can UCN2 be found. Gestational tissues differentially express UCN2 and UCN3 and do not stimulate the secretion of placental ACTH\[28\].

**UCN and delivery**

In term pregnancies, maternal plasma levels of CRF and UCN are lower and correlated to labor onset. Conversely, they do not decrease in post-term pregnancies (when the labor did not physiologically occur). The fine-regulated expression of these neuropeptides would, therefore, seem to be important in determining the length of human gestation\[29\]. In this view, low concentrations of UCN in the amniotic fluid at mid-term may be considered a sign of predisposition to preterm birth\[30\].

Furthermore, placental CRF ant its receptors are highly expressed during the premature rupture of membranes (pPROM) with chorioamnionitis, suggesting that placental expression of stress-related pathways is activated in infective processes\[31\]. Interestingly, a report in a recent paper\[32\] illustrates the results of a cohort study which was carried on pregnant women at a gestational age of 28-36 wk. The subjects were admitted to a labor ward with spontaneous preterm labor. A blood sample was obtained from all participants and serum UCN was measured. The women were monitored up to delivery in order to compare serum UCN in women with preterm delivery with those delivering at term (37 wk or more). This study demonstrates that serum UCN cannot be used to differentiate between women who delivered preterm and women with signs of preterm labor. Furthermore, UCN1 concentrations in midtrimester amniotic fluid were analysed in 22 pregnant women with preterm deliveries and 45 women who delivered at term using an enzyme-linked immunosorbsent assay. This study\[33\] indicates the possibility that low UCN1 concentrations in midtrimester amniotic fluid may be used as an indicative marker of preterm birth.

**UCN and preeclampsia**

An investigation was also carried out to study the possible role of the molecule in the prediction of preeclampsia. Syncytiotrophoblast cells express UCN1 during pregnancy and this has been found to provoke the vasodilation of placental vascular tissue through paracrine or endocrine mechanisms\[34,35\]. Vascular endometrial cells express CRF-R2 and this makes UCN a strong vasodilator\[36\]. Pregnancies characterized by abnormal placental function (e.g., preeclampsia) have high maternal plasma CRF levels and reduced CRF-R1 expression\[37\]. This is why changes of this kind may lead to abnormal vascular resistance and preeclampsia\[38,39\]. In two interesting papers\[40,41\] it was demonstrated that CRF, UCN1 and UCN2 may positively regulate the placentai pathway of nitric oxygen (NO)/cGMP, thus provoking a poorly perfused feto-placental unit, dysregulation of the vascular resistance balance and, finally, preeclampsia.

One interesting paper reported that placental UCN2 and UCN3 expression are sensitive to O2 tensions and mediated by HIF-1α. During early pregnancy, UCN2/UCN3 could influence the proliferation of trophoblast and the establishment of pregnancy. In preeclampsia placentae, the increased expression of both peptides possibly indicate a response to oxidative stress\[42\]. Finally, human endometrium expresses both UCN and CRF, CRF-R1 and CRF-R2. The activation of CRF-R1 inhibits cell development and the proliferation of a line of tumor cells that derive from the human endometrium. Furthermore, it has been suggested that the signaling pathway of UCN is involved in the tumorigenesis of different tissues\[43\]. In fact, increased numbers of highly activated mast cells were observed in peritoneal endometriosis tissue. Affected tissue was also found to stain strongly for CRH or UCN, which indicates they might be associated with activated mast cells. These processes could play a role in fibrosis, inflammation, low fertility or spontaneous abortions associated with endometriosis. UCN increases in women with endometriomas, and measuring it might be of use to differentiate between endometriosis and other benign ovarian cysts\[44\].

**Data from animal studies which indicate possible therapeutic applications**

Gonzalez-Rey et al\[22\] refers, in a study conducted in 2006, to the therapeutic effects of UCN and adrenomedullin (AM) on the colonic mucosa of mice. The use of...
UCN or AM considerably reduced the mRNA expression of inflammatory cytokines (TNF-α, IFN-γ, IL-6, IL-1α, IL-1β, IL-12, IL-18, IL-17, IL-15), macrophage migration inhibitory factor, chemokines (RANTES), macrophage inflammatory protein (MIP-1α, MIP-1β, MIP-3β), monocyte protein (MCP-1, MCP-3), inducible protein (IP-10 and MIP-2), and chemokine receptors (CCR-1, CCR-2, CCR-3, CCR-5 and CCR-7) in the colonic mucosa of pathological rats. Furthermore, after the two points had been treated with AM/UCN there was a rise in the levels of the anti-inflammatory cytokine IL-10 and receptors CCR-4 and CCR-8. In vitro, lymphoid peripheral mononuclear cells, that had been isolated from mice treated with AM or UCN, reduced their levels of pro-inflammatory factors (TNF-α, IL-6 and MIP-2). This suggests that UCN/AM administers the deactivation of the inflammatory response of the colonic mucosa. Treatment with UCN/AM provoked a drop in the serum levels of proinflammatory cytokines TNF-α, IL-1β, IL-6, and MIP-2 and ASA, which is a hepatic acute phase protein involved in inflammatory tissue damage. The therapeutic effect of UCN and AM works by reducing the local and systemic levels of a wide range of inflammatory mediators, including cytokines, chemokines and the acute phase serum amyloid protein A. UCN and AM could be utilized for therapeutic septic shock, also in combination with other immunomodulatory agents. Alternatively, they could be used together with other anti-inflammatory factors in other therapies[36]. UCN is not currently commercially available for administration despite its promising role in reducing the inflammatory phenomena typical of several obstetrics and gynecological diseases. These interesting considerations could lead to its use in clinical practice if these data are confirmed by further studies.

CONCLUSION

UCN plays a significant role in human reproduction influencing the mechanisms of steroidogenesis in the ovary, the maintenance of placental function and labor (summarized in Table 1). Low concentrations of UCN in the amniotic fluid may be a sign of predisposition to preterm birth, since it correlates with a pro-inflammatory state. UCN can be found at higher concentrations in women with endometriomas, and measuring it could be important in differentiating between endometriosis and other benign ovarian cysts. The therapeutic treatment with UCN and AM decreases serum levels of proinflammatory cytokines in several experimental situations, so it is plausible that the same effects may occur in different obstetrics and gynecological diseases in which inflammation plays a key role in the onset and progression of the disease. Nevertheless, more pre-clinical studies are needed which may clarify the possible therapeutic effect(s) of UCN and its side effect(s), before hypothesizing its possible role in clinical practice.

REFERENCES

1 Papadopoulos N, Chen J, Randeva HS, Levine MA, Hillhouse EW, Grammatopoulos DK. Protein kinase A-induced negative regulation of the corticotropin-releasing hormone R1alpha receptor-extracellularly regulated kinase signal transduction pathway: the critical role of Ser301 for signaling switch and selectivity. Mol Endocrinol 2004; 18: 624-639 [PMID: 14657255 DOI: 10.1210/me.2003-0365]
2 Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull A V, Lovejoy D, Rivier C. Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. Nature 1995; 378: 287-292 [PMID: 7477349 DOI: 10.1038/378287a0]
3 Parkes DG, Vaughan J, Rivier J, Vale W, May CN. Cardiac inotropic actions of urocortin in conscious sheep. Am J Physiol 1997; 272: H1215-H1222 [PMID: 9176276]
4 Spina M, Merlo-Pich E, Chan RK, Basso AM, Rivier J, Vale W, Koob GF. Appetite-suppressing effects of urocortin, a CRF-related neuropeptide. Science 1996; 273: 1561-1564 [PMID: 8703220 DOI: 10.1126/science.273.5281.1561]
5 Ikeda K, Tojo K, Sato E, Ebisawa T, Tokudome G, Hosoya T, Harada M, Nakagawa O, Nakao K. Urocortin, a newly identified corticotropin-releasing factor-related mammalian peptide, stimulates atrial natriuretic peptide and brain natriuretic peptide secretions from neonatal rat cardiomyocytes. Biochem Biophys Res Commun 1998; 250: 298-304 [PMID: 9753624 DOI: 10.1006/bbrc.1998.9297]
Vitale SG et al. Urocortin in pregnancy

6 Bamberger CM, Wald M, Bamberger AM, Ergün S, Beil FU, Schulte HM. Human lymphocytes produce urocortin, but not corticotropin-releasing hormone. J Clin Endocrinol Metab 1998; 83: 706-710 [PMID: 9467598 DOI: 10.1210/jcem.83.2.4693]

7 Vale W, Spinjic J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981; 213: 1394-1397 [PMID: 6267699 DOI: 10.1126/science.6267699]

8 Donaldson CJ, Sutton SW, Perrin MH, Corrigan AZ, Lewis KA, Rivier JE, Vaughan JM, Vale WW. Cloning and characterization of human urocortin. Endocrinology 1996; 137: 2167-2170 [PMID: 8612563 DOI: 10.1210/en.137.5.8612563]

9 Takahashi K, Totsane K, Sone M, Murakami O, Satoh F, Arihara Z, Sassoano H, Iino K, Mouri T. Regional distribution of urocortin-like immunoreactivity and expression of urocortin mRNA in the human brain. Peptides 1998; 19: 643-647 [PMID: 9622018 DOI: 10.1016/S0196-9781(98)00012-6]

10 Chang CP, Pease RV, O’Connell S, Rosenfeld MG. Identification of a seven transmembrane helix receptor for corticotropin-releasing factor and sauvagine in mammalian brain. Neuron 1993; 11: 1187-1195 [PMID: 8274282 DOI: 10.1016/0896-6273(93)90230-O]

11 Chen R, Lewis KA, Perrin MH, Vale WW. Expression cloning of a human corticotropin-releasing-factor receptor. Proc Nail Acad Sci USA 1993; 90: 8967-8971 [PMID: 7692441 DOI: 10.1073/pnas.90.19.8967]

12 Kostich WA, Chen A, Sperle K, Largent BL. Molecular identification and characterization of a novel human corticotropin-releasing factor (CRF) receptor: the CRF2 gamma receptor. Mol Endocrinol 1998; 12: 1077-1085 [PMID: 9717834 DOI: 10.1210/endo.12.8.0145]

13 Tao J, Li S. Effects of urocortin via ion mechanisms or CRF receptors? Biochem Biophys Res Commun 2005; 336: 731-736 [PMID: 16061206 DOI: 10.1016/j.bbrc.2005.07.078]

14 Latchman DS. Urocortin. Int J Biochem Cell Biol 2002; 34: 907-910 [PMID: 12000762 DOI: 10.1016/S1357-2725(02)00010-1]

15 Sanz E, Monge L, Fernández N, Martínez MA, Martínez-León JB, Diéguez G, García-Villalón AL. Relaxation by urocortin of human saphenous veins. Br J Pharmacol 2002; 136: 90-94 [PMID: 11976272 DOI: 10.1038/sj.bjp.07064670]

16 Leitch IM, Boura AL, Botti C, Read MA, Walters WA, Smith R. Vasodilator actions of urocortin and related peptides in the human perfused placenta in vitro. J Clin Endocrinol Metab 1998; 83: 4510-4513 [PMID: 9851801]

17 Lewis K, Li C, Perrin MH, Blount A, Kuniata KE, Donaldson C, Vaughan J, Reyes TM, Gulyas J, Fischer W, Bilezikjian L, Rivier J, Sawchenko PE. Vale WW. Identification of urocortin II, an additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF2 receptor. Proc Nail Acad Sci USA 2001; 98: 7570-7575 [PMID: 11416224 DOI: 10.1073/pnas.121165198]

18 Florio P, Vale W, Petraglia F. Urocortins in human reproduction. Peptides 2004; 25: 1751-1757 [PMID: 15476942 DOI: 10.1016/j.peptides.2004.05.026]

19 Petraglia F, Florio P, Benedetto C, Marozio L, Di Blasio AM, Tecconi C, Piccinone E, Luisi S, Genazzani AR, Vale W. Urocortin stimulates placental adrenocorticotropin and prostaglandin release and myometrial contractility in vitro. J Clin Endocrinol Metab 1999; 84: 1420-1423 [PMID: 10199789 DOI: 10.1210/jcem.84.5.5358]

20 Glynn BP, Wolton A, Rodríguez-Liñares B, Phaneuf S, Linton EA. Maternal plasma corticotrophin-releasing factor and urocortin levels during mid pregnancy. J Soc Gynecol Investig 1999; 6: 533-540 [PMID: 10211674 DOI: 10.1012/josi.1999.540]

21 Kashanian M, Bahasadi S, Ghaseshi A, Bahaei S. Value of serum urocortin concentration in the prediction of preterm birth. J Obstet Gynecol Res 2013; 39: 26-30 [PMID: 22639902 DOI: 10.1111/j.1470-5753.2012.01887.x]

22 Karaer A, Celik E, Celik O, Simsek OY, Ozorol IH, Yilmaz E, Turkcuoglu I, Duz SA. Amniotic fluid urocortin-1 concentrations for the prediction of preterm delivery. J Obstet Gynecol Res 2013; 39: 1236-1241 [PMID: 23803066 DOI: 10.1111/j.1470-5753.2012.01877.x]

23 Florio P, Cobelli L, Luisi S, Ciampol G, Severi FM, Bocchi C, Petraglia F. Changes in inhibins and activin secretion in healthy and pathological pregnancies. Mol Cell Endocrinol 2001; 180: 123-130 [PMID: 11451581 DOI: 10.1016/S0303-7207(01)00503-2]

24 Petraglia F, Florio P, Gallo R, Simoncini T, Savozioli M, Di Blasio AM, Vaughan J, Vale W. Human placenta and fetal membranes express human urocortin mRNA and peptide. J Clin Endocrinol Metab 1999; 81: 3807-3810 [PMID: 8855842 DOI: 10.1210/jcem.81.11.8855842]

25 Simoncini T, Apa R, Reis FM, Miceli F, Stornati M, Driel L, Lanzone A, Genazzani AR, Petraglia F. Human umbilical vein endothelial cells: a new source and potential target for corticotropin-releasing factor. J Clin Endocrinol Metab 1999; 84: 2802-2806 [PMID: 10443683 DOI: 10.1210/je.84.5.8575]

26 Florio P, Petraglia F, Severi FM, Torricelli M, Bocchi C, Fiore G, Linton EA, Petraglia F. Redoubled maternal plasma urocortin concentrations and impaired uterine artery blood flow at human mid pregnancy. J Soc Gynecol Investig 2005; 12: 191-194 [PMID: 15784504 DOI: 10.1016/j.jsgi.2004.11.002]
Perkins AV, Linton EA, Eben F, Simpson J, Wolfe CD, Redman CW. Corticotrophin-releasing hormone and corticotrophin-releasing hormone binding protein in normal and pre-eclamptic human pregnancies. Br J Obstet Gynaecol 1995; 102: 118-122 [PMID: 7756202 DOI: 10.1111/j.1471-0528.1995.tb09063.x]

Karteris E, Goumenou A, Koumantakis E, Hillhouse EW, Grammatopoulos DK. Reduced expression of corticotropin-releasing hormone receptor type-1 alpha in human preeclamptic and growth-restricted placentas. J Clin Endocrinol Metab 2003; 88: 363-370 [PMID: 12519878 DOI: 10.1210/jc.2002-020375]

Karteris E, Vatish M, Hillhouse EW, Grammatopoulos DK. Preeclampsia is associated with impaired regulation of the placental nitric oxide-cyclic guanosine monophosphate pathway by corticotropin-releasing hormone (CRH) and CRH-related peptides. J Clin Endocrinol Metab 2005; 90: 3680-3687 [PMID: 15784708 DOI: 10.1210/jc.2004-2210]

Gude NM, King RG, Brennecka SP. Role of endothelium-derived nitric oxide in maintenance of low fetal vascular resistance in placenta. Lancet 1990; 336: 1589-1590 [PMID: 1979408 DOI: 10.1016/0140-6736(90)93374-X]

Imperatore A, Rolfo A, Petraglia F, Challis JR, Caniggia I. Hypoxia and preeclampsia: increased expression of urocortin 2 and urocortin 3. Reprod Sci 2010; 17: 833-843 [PMID: 20616367 DOI: 10.1177/1933719110373147]

Florio P, De Falco G, Leucci E, Torricelli M, Torres PB, Toti P, Dell’Anna A, Tiso E, Santopietro R, Leoncini L, Petraglia F. Urocortin expression is downregulated in human endometrial carcinoma. J Endocrinol 2006; 190: 99-105 [PMID: 16837614 DOI: 10.1677/joe.1.06726]

Florio P, Reis FM, Torres PB, Calonaci F, Toti P, Bocchi C, Linton EA, Petraglia F. Plasma urocortin levels in the diagnosis of ovarian endometriosis. Obstet Gynecol 2007; 110: 594-600 [PMID: 17766605 DOI: 10.1097/01.AOG.0000278572.86019.ae]

Wan R, Guo R, Chen C, Jin L, Zhu C, Zhang Q, Xu Y, Li S. Urocortin increased LPS-induced endothelial permeability by regulating the cadherin-catenin complex via corticotrophin-releasing hormone receptor 2. J Cell Physiol 2013; 228: 1295-1303 [PMID: 23168683 DOI: 10.1002/jcp.24286]
