REVIEW

The placenta controls the physiology of pregnancy by increasing the half-life in blood and receptor activity of its secreted peptide hormones

Philip Lowry and Russell Woods

School of Biological Sciences, University of Reading, Reading, UK

Correspondence should be addressed to P Lowry: p.j.lowry@reading.ac.uk

Abstract

An efficient functioning placenta is essential for a healthy pregnancy and yet the way this is achieved has been the subject of much discussion and confusion, particularly with the occurrence of pathological conditions such as preeclampsia, morning sickness and hyperemesis/ptyalism gravidarum. We will attempt to explain the underlying physiology and the potential roles played by the placental tachykinins, neurokinin B and endokinin.

Key Words

- ▶ tachykinins
- ▶ C-reactive protein
- ▶ morning sickness
- ▶ preeclampsia
- ▶ placenta

*Journal of Molecular
Endocrinology*
(2018) **60**, R23–R30

Introduction

The placenta is a consummate endocrine organ as it secretes many biologically active peptide hormones at various times throughout the whole pregnancy. Unlike regulated secretion from other endocrine tissues, secretion from the placenta is constitutive: the synthesis and release of each peptide hormone being controlled at the level of transcription. It follows that many peptide hormones can be released differentially from even one placental cell type.

As simple peptide hormones generally have short half-lives (<10 min) in the circulation, under normal circumstances, this would be a considerable metabolic burden for the placenta to maintain significant blood concentrations of each peptide throughout the whole pregnancy. However, a number of known and many

unidentified potential placental peptide hormones have been found to carry a posttranslational modification (PTM) containing phosphocholine (Lovell *et al.* 2007) that *per se* would lengthen the half-life.

C-reactive protein (CRP), an acute-phase protein that binds strongly to phosphocholine, is normally secreted by the liver as a stable pentamer in response to a microbial infection or to an autoimmune disease such as rheumatoid arthritis (Pepys & Hirschfield 2003). CRP concentrations are also elevated in the blood during pregnancy and more so in preeclampsia (Cebesoy *et al.* 2009, Ertas *et al.* 2010) with the placenta recently being identified as the source (Parchim *et al.* 2015). As the half-life of CRP in the circulation is some 19 h (Vigushin *et al.* 1993), this would lead to a substantial increase in the half-life of

any CRP-bound phosphocholinated placental peptide accompanied by an increase in bioactivity due to their ability to cluster their respective receptors potentially into pentamers. This topical review will attempt to elucidate in detail how these mechanisms are exploited by the placenta, particularly in relation to phosphocholinated tachykinins, to ensure a healthy pregnancy but also can cause pathological situations such as preeclampsia and hyperemesis/ptyalism gravidarum.

Placental tachykinins

The tachykinins are an ancient family of biologically active peptides and examples can be found throughout the animal and microbial kingdoms. They are distinguished by containing the common C-terminal motif: Phe-X-Gly-Leu-Met-amide. In humans, there are four members of the tachykinin family: substance P (SP), endokinin (EKA/B) also known as hemokinin, neurokinin A (NKA) and neurokinin B (NKB). They signal through three G-protein-coupled neurokinin receptors (NK1-3R). SP and EKA/B have the same hexapeptide sequence (Gln-Phe-Phe-Gly-Leu-Met-amide) at their C-terminal (Fig. 1) and have preference for the NK1R. NKA has preference for the NK2R and NKB for the NK3R but there is a degree of crosstalk. NK1Rs and NK2Rs are found in the brain and in the periphery but the NK3Rs are mainly found in the periphery.

As examples of biologically active peptides, the tachykinins are unique in being expressed throughout the nervous, immune and endocrine systems and are involved in the regulation of a diverse range of physiological and pathological processes (Steinhoff *et al.* 2014); NKB and EKB in particular are found in the placenta (Page *et al.* 2000, 2003).

Placental neurokinin B

The first tachykinin gene found to be expressed in the human placenta was the TAC3 gene that encodes the

NKB precursor. A radioimmunoassay for the processed NKB decapeptide detected material in the extracts of the human placenta and in the blood of pregnant women. Elevated concentrations of the peptide in the nanomolar range were found in blood of women suffering from preeclampsia (Page *et al.* 2000), an observation confirmed by others (Geissbuehler *et al.* 2007, Zulfikaroglu *et al.* 2007).

In a healthy pregnancy, normal stimulation of maternal peripheral NK3Rs would cause a modest increase in heart rate (Thompson *et al.* 1998), contraction of the hepatic portal vein (Mastrangelo *et al.* 1987) and mesenteric blood vessels (D'Orleans-Juste *et al.* 1991). This would conspire to improve the mother's blood circulation to other organs such as the uterus. The poorly implanted placenta seen in preeclampsia responds by hypersecreting NKB with overstimulation of NK3Rs resulting in hypertension. NKB has also been shown to cause lung and liver oedemas similar to that seen in preeclampsia (Grant *et al.* 2002). However, the NKB placental peptide did not react with some antibodies raised against the natural brain form of the peptide and mass spectrometric analysis revealed that it has a larger mass and indicated that it contained a PTM containing phosphocholine (Lovell *et al.* 2007). Further mass spectrometric analysis suggested that the PTM was a variant of desacetyl platelet activating factor attached by an ester bond to the side chain of the aspartate residue at position 4 in the NKB decapeptide (Lowry 2011). Although NKB has always been assumed to be the natural ligand for the NK3R, the simple decapeptide is only a partial agonist and most receptor studies use synthetic homologues such as senktide that is a full NK3R agonist. Thus, it was initially assumed that the phosphocholinated PTM added by the placenta to NKB converted it into a full agonist for the NK3R. Significantly, there is a candidate phosphocholine transferase B enzyme which is uniquely expressed in the placenta in the pregnant female where it is associated with the endoplasmic reticulum, the site of secretory peptide synthesis (Lykidis *et al.* 1998, 1999).

	VIVALE
Endokinin A	DGGEQTLSTEAEWEGAGPSIQLQLQEVKTGKASQFFGLM-NH2
Endokinin B	DGGEQTLSTEAEWEGAGPISIQLQLQEVKTGKASQFFGLM-NH2
Substance P	RPKPQQFFGLM-NH2
Neurokinin A	HKTDSFVGLM-NH2
Neurokinin B	DMHDFVGLM-NH2

Figure 1

Primary structures of human tachykinins: EKA, EKB substance P, NKA and NKB. 'Unprocessed human hemokinin' is underlined in EKA and EKB.

As a phosphocholinated protein, ES62, secreted by a filarial parasitic nematode had previously been shown to aid its survival in the host, with the phosphocholine moiety conferring the activity (Harnett *et al.* 2003), it was also thought that the placental secretion of phosphocholinated NKB may help the placenta to avoid surveillance by the mother's immune system (Lowry 2008).

NKB however is not the only placental peptide/protein that carries a phosphocholine PTM. In the rat, placental pro-corticotropin-releasing factor (CRF), pro-activin, follistatin and pro-hemokinin (endokinin) were also found to be modified, as well as a significant number of other as yet unidentified placental peptides/proteins (Lovell *et al.* 2007) suggesting that this PTM represents a fundamental mechanism that regulates peptide hormone longevity in blood and potentially modulates their biological activity.

The significance of placental CRP

CRP, an acute-phase protein normally synthesised in the liver, naturally binds strongly to phosphocholine, and in healthy individuals the blood concentrations are very low. CRP levels do however increase rapidly in response to inflammation, whether from microbial infection or by tissue damage (Pepys & Hirschfield 2003). Figure 2 shows the structure of CRP with five protomers formed into a stable pentamer. It is important to note that all five binding sites for phosphocholine on each protomer face in the same direction (Thompson *et al.* 1999) so that any bound phosphocholinated placental peptides would follow suit. CRP circulates as this pentamer and binds to phosphocholine on the surface of microbes, the resulting aggregation initiating the immune response. Binding to exposed phosphatidylcholine on damaged tissue cell membranes assists in their removal but high levels of CRP can persist under such conditions as rheumatoid arthritis.

Elevated concentrations of CRP are also found in the blood of pregnant women and more so in preeclampsia (Cebesoy *et al.* 2009, Ertas *et al.* 2010) but notably it has recently been shown that the main source in pregnancy is the placenta where it appears to be synthesised in the same region of the syncytiotrophoblast as NKB (Parchim *et al.* 2015). It was found that infusion of CRP into mice to mimic the concentrations found in human preeclampsia resulted in only pregnant animals showing symptoms of preeclampsia, namely hypertension, proteinuria, kidney and placental damage and increased levels of sFlt-1. More importantly, it was found that these CRP-induced

symptoms in the pregnant mice were attenuated by administration of either an NK3R antagonist or inhibition of the placental phosphocholine transferase B enzyme and lead to the conclusion that it is the coordinate action of CRP and PC-NKB that causes the symptoms of preeclampsia (Parchim *et al.* 2015). The simple binding of circulating PC-NKB to CRP, a protein with a half-life of 19 h (Vigushin *et al.* 1993), would result in a very significant increase in the half-life of this small placental tachykinin peptide from just a few minutes to several hours permitting the placenta to maintain significant blood concentrations at relatively low secretion rates.

Receptor clustering is a common trigger for a number of signalling events. It is known that aggregation or clustering of peptide hormone receptors can increase potency and/or change downstream signalling and significantly alter the physiological response (Caré & Soula 2011, Dustin & Groves 2012, Goyette & Gaus 2016). This could be the case with CRP/PC-NKB at the NK3Rs. PC-NKB bound to CRP could also prevent receptor endocytosis leading to an increase in potency.

To summarise in a normal healthy pregnancy, low concentrations of CRP-bound PC-NKB at peripheral NK3Rs result in mild NK3R clustering into pentamers in the heart, hepatic portal vein and mesenteric vessels leading to the changes in the mother's vasculature to the benefit of the uterus and placenta. Oversecretion of PC-NKB and CRP by a distressed placenta to improve survival of the feto/placental unit would lead to overstimulation and clustering of NK3Rs which would then give rise to the symptoms of preeclampsia. The observation that inhibiting the synthesis of placental phosphocholine transferase and/or blocking the NK3R reduced the severity of symptoms of preeclampsia in CRP-treated pregnant mice (Parchim *et al.* 2015) lends considerable weight to this hypothesis.

Placental endokinin

Although the gene for substance P is not expressed in the human placenta, the TAC4 gene for the stronger NK1R agonist, endokinin, is expressed. There are four splice variants: α -TAC4, β -TAC4, γ -TAC4 and δ -TAC4 which are expressed in many tissues throughout the body. The γ -TAC4 and δ -TAC4 variants are highly expressed in the placenta (Page *et al.* 2003). The translated pro-endokinin peptide precursor is unusual as it does not contain the classical double basic consensus sequence upstream of the main tachykinin peptide region. Thus, rather than being processed to an eleven- or ten-residue-long peptide

Figure 2

Space-filled 3D model (courtesy of Mark Pepys) of the choline-reactive protein pentamer showing phospho-choline bound to each protomer (Thompson *et al.* 1999).

as with substance P and NKB, it has a long N-terminal extension. The α -TAC splice variant would give rise to the 47mer peptide, EKA (Fig. 1). The more widely expressed β -, γ - and δ -TAC splice variants would lead to the secreted mature processed peptide, EKB, some 41 residues in all. EKA contains six extra residues inserted between Trp¹⁵/Glu¹⁶ with the rest of the sequence, the same as EKB (Fig. 1). In both EKA and EKB, the arginine position (37 in EKA and 31 in EKB) has been substituted with threonine that automatically removes the double basic processing site which is found upstream of the tachykinin motif in the SP, NKA and NKB precursors. The so-called human hemokinin (Thr-Gly-Lys-Ala-Ser-Gln-Phe-Phe-Gly-Leu-Met-NH₂), the last 11 residues underlined in EKA and EKB (Fig. 1) originally proposed (Kurtz *et al.* 2002) would not exist *in vivo* as processing at single lysine residues, has never been reported. Thus, it is not surprising that despite the availability of a commercial immunoassay to the 11mer hemokinin, there have been no reports of significant concentrations of hemokinin in human samples. However, a two-site immunometric

assay (one antibody raised against residues 12–30 and the second raised against residues 32–41 of EKB) detected significant concentrations of EKB immunoreactivity in human placental extracts (Page *et al.* 2003). Like its rat equivalent, placental human EKB was also found to be phosphocholinated and being a longer peptide (41mer vs 10mer) eluted much later than placental NKB on C8 HPLC (D Butlin & P Lowry, unpublished observations). In fact, the natural N-terminal extension would increase potency of EKB at the NK1R, as a synthetic EKB-32mer with an extended N-terminal, EKB (10–41), was considerably more potent than substance P at this receptor (Page *et al.* 2003). Both the human endokinin and the rat N-terminally extended endokinin/hemokinin have a single aspartate residue (the amino acid with the PTM attached in placental NKB (Lowry 2011)) at their respective N-terminals for the potential attachment of the phosphocholine containing PTM by the placenta. Again, like PC-NKB, PC-EKB being bound to CRP would lead to a significant increase in its half-life in the circulation and result in clustering of its preferred receptors, the NK1Rs.

Tachykinins in vascularisation and vasodilation

Although NKB was originally proposed to be the tachykinin secreted by the placenta that would cause local beneficial vasodilation via NK1Rs (Brownbill *et al.* 2003, Laliberte *et al.* 2004), the much stronger placental NK1R agonist, EKB, is clearly a more suitable candidate. Moreover, phosphocholinated EKB in consort with placental CRP would increase its half-life from minutes to several hours and also result in NK1 receptor clustering which could be the stimulus that creates the important neovascularisation in both the placenta and the uterus that is vital for efficient diffusion of gases, nutrients and waste products throughout pregnancy. Thus, both placental phosphocholinated tachykinins, complexed with CRP, in stimulating NK1 and NK3 receptors could also be responsible for the beneficial changes seen in the mother's peripheral blood flow in a healthy pregnancy. This involves improved cardiac output, general arterial compliance, an increase in renal plasma flow and a reduction in vascular resistance and blood pressure. These alterations begin soon after conception, peak by the beginning of the second trimester and persist throughout gestation. The resulting fall in ventricular afterload initiates the large increase in cardiac output and, subsequently, the expansion of plasma volume: changes that are associated with a healthy pregnancy (Conrad & Lindheimer 1999).

NK1Rs in morning sickness and chemotherapy-induced emesis

Vomiting or emesis has been recognised for centuries as a protective reflex after ingesting poisonous materials. The one condition in which emesis has been the cause of much distress and confusion (particularly regarding what benefit it can impart) is pregnancy. In extreme cases (hyperemesis gravidarum), it can lead to the death of both mother and foetus.

However, it has been reported that systemic administration of the NK1R agonist, substance P, into experimental animals causes emesis (Carpenter *et al.* 1984, Knox *et al.* 1993) and its topical application to the area postrema (the part of the medulla oblongata below the blood-brain barrier) in the ferret induced retching after a latency of about 30s (Andrews 1994) and in the dog induced firing in neurones in about 48% of the neurones tested (Carpenter *et al.* 1983).

Although the TAC1/substance P gene is not expressed in the human placenta (Page *et al.* 2003), the potent activity of CRP-bound PC-EKB released by the placenta clustering both local NK1Rs and those in the area postrema would provide an explanation for the putative link between a healthy placenta and emesis of pregnancy. In fact, a recent comprehensive study showed that women who experienced morning sickness had healthier pregnancies and concluded that the viability of the placenta was linked to emesis (Hinkle *et al.* 2016). It is intriguing to note here that there is a remarkable coincidence in the timing of emesis and changes in the mother's vasculature (Conrad & Lindheimer 1999) covered in the previous section adding to the notion of the involvement of placental EKB stimulating systemic NK1Rs for a healthy pregnancy.

Another supportive coincidence is the observation that women who do not experience emesis during pregnancy, presumably due to natural downregulation or reduced sensitivity of their brain NK1 emesis receptors, have a much better tolerance to chemotherapy for the treatment of cancer later in life (Bouganin *et al.* 2012) suggesting that the same NK1 receptors are involved. Patients, who do experience chemotherapy-induced emesis, do however respond well when treated with NK1R antagonists such as aprepitant (Diemunsch *et al.* 2009, Dos Santos *et al.* 2012).

Salivation

The excessive salivation during pregnancy (ptyalism gravidarum), which invariably accompanies hyperemesis gravidarum, provides further evidence for the secretion of the NK1R agonist EKB by the placenta. The sialagogic action of substance P was first recognised 50 years ago, when a peptide with this activity was isolated from the hypothalamus and was found to have the same amino acid composition as substance P isolated from the gut (Leeman & Hammerschlag 1967). More recent pharmacological studies have confirmed that salivation is mediated through the NK1 receptor (Giuliani *et al.* 1988).

Drug treatment

Given the many physiological roles of tachykinins, the use of freely diffusible small-molecule NK1R antagonists for the alleviation of the symptoms of morning sickness and salivation should be avoided as they could have adverse effects on the development of both the placenta and the foetus. However, in women previously diagnosed

with diabetes insipidus, the use of the orally administered peptide, DDAVP (desmopressin), is safe during pregnancy. Enough DDAVP survives digestion (due to its resistant D-amino acid content) to be efficacious, but it does not cross the placenta into the foetus in appreciable amounts. Similarly, sendide, an NK1R antagonist, is also a protected peptide and reduces cisplatin-induced emesis in ferrets by targeting NK1Rs in the gut and the area postrema (Minami *et al.* 1998). As sendide would not be expected to cross into the foetus, could it become the drug of choice to treat morning sickness and sialorrhoea? In view of possible negative effects in the mother and feto/placental unit, it may not be advisable for 24-h dosage in extreme cases of hyperemesis gravidarum, but it may provide enough temporary relief for pregnant women to have nourishment by mouth, avoiding intravenous feeding/rehydration and enabling arrest of the self-sustaining vomiting reflex. A sendide-containing mouthwash could however be a safe treatment for sialorrhoea.

Lung EKB, smoking in pregnancy and chemotherapy

Unlike TAC1 (the substance P gene), the TAC4 splice variants, as well as being expressed in most body tissues, were also expressed in all but one of the 15 tumour (including the placental BeWo) cell lines studied (Page *et al.* 2003), suggesting that EKA and EKB would be synthesised and released from the associated tissue. Of particular interest was the expression of β -TAC4 and γ -TAC4 in normal lung tissue and in both lung tumour cell lines screened, γ TAC4 in A549 and β -TAC4, γ -TAC4 and δ -TAC4 in U937. Humans as well as animals generally try to escape from smoke (and thus avoid getting burnt in forest fires, etc.) as inhalation induces nausea. This is probably the reason why many people never take up smoking tobacco or inhale the smoke as they have sensitive NK1Rs in their area postrema that are easily stimulated making them feel nauseous. Thus, could it be the potent NK1R agonist, EKB, released from the lungs into the circulation during smoke inhalation, stimulating the NK1 receptors in the area postrema that initiates this nausea? In a recent preliminary study, the concentration of plasma EKB immunoreactivity increased nearly 30-fold in a non-smoker after inhalation of tobacco and remained elevated two hours later when nausea was still being experienced (Vaiyapuri *et al.* 2017). Why some individuals can keep on inhaling tobacco smoke without experiencing nausea maybe due to downregulation or natural insensitivity of the same NK1 receptors while simultaneously they become

addicted to nicotine. Indeed, it is well known that women who smoke during pregnancy are afforded considerable protection against morning sickness (Klebanoff *et al.* 1985, Little & Hook 1979) and preeclampsia (Conde-Agudelo *et al.* 1999) suggesting that both NK1 and NK3 receptors have been downregulated and desensitised, respectively. Vomiting and nausea induced by chemotherapy are also lower in people who smoke tobacco, again suggesting the same NK1Rs that are involved (Bouganin *et al.* 2012).

The offspring of women who smoke during pregnancy suffer from pre- and postnatal growth retardation and increased risks of placental mortality, morbidity and behavioural anomalies (Abel 1980). The poor placental outcome may be due to the same EKB released from the lungs during smoking downregulating the NK1Rs or displacing PC-EKB from local placental/uterine NK1Rs, preventing the coordinated action of CRP/PC-EKB and clustering these receptors into pentamers, the proposed event necessary for the stimulation of neovascularisation and a healthy placenta. It is also possible that the high lung endokinin concentrations in uterine blood disrupt the local concentration gradient of placental endokinin that may be necessary for the correct directional growth of the spiral arteries in the small finger-like projections that ensure the efficient exchange of nutrients, gases and waste products at the placental/uterine interface.

Other placental phosphocholinated neuropeptides

Other placental peptide precursors that were found to contain the phosphocholine immunoreactivity were pro-opiomelanocortin, follistatin, pro-activin and pro-CRFs, but in the latter two, neither of the processed active peptides, activin and CRF, possessed the PTM (Lovell *et al.* 2007). In the case of placental CRF, it circulates and is bound to a specific inhibiting binding protein that is also expressed in the human placenta (Petraglia *et al.* 1993). In late pregnancy, concentrations of the CRF-inhibiting binding protein decrease, leading to a rapid increase in circulating levels of free bioactive CRF at the onset of parturition (McLean *et al.* 1995).

In the Lovell *et al.*'s (2007) study, there did however seem to be many other placental peptides which were immunoreactive for phosphocholine, with the probability of their coordinate action with CRP at target receptors in the mother. Thus, it is possible that the cumulative effect of certain cocktails of phosphocholinated neuropeptides bound to CRP of placental origin could stimulate certain brain receptors sufficiently enough to be responsible

for changes of behaviour that are experienced by many women during pregnancy. Withdrawal of this stimulus postpartum could contribute to postnatal depression.

Concluding comments

The placenta as an endocrine organ, and particularly as a source of peptide hormones, is widely acknowledged. The potential futility of expending energy on the continual production of molecular messengers that possess such short survival times in the plasma has not, however, been considered. We propose that the placenta modulates physiology through a unique PTM of the hormones that it produces. This not only extends the half-life of placental-derived hormonal signals, but changes the nature or enhances their actions. While this appears to form a fundamental mechanism that controls physiological changes required for healthy pregnancy, overreactivity in some may underlie some of the most prevalent pregnancy-related disorders.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors wish to thank Sir Mark Pepys FRS for the picture of the 3D model of CRP, Drs A Bicknell and W Kaiser for helpful discussion and Profs. J Gibbins and F Cunningham for critical reading of the manuscript.

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Received in final form 17 November 2017

Accepted 24 November 2017