The role of neurokinin B in pre-eclampsia

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Pre-eclampsia, a life-threatening disease unique to pregnancy, has been called a disease of theories. To date, there has been no widely accepted predictive test or therapeutic intervention to prevent or delay pre-eclampsia. The discovery of a new placental hormone, neurokinin B, may finally help to answer some of the past mysteries.

Pre-eclampsia is a principal cause of maternal morbidity and mortality, accounting for almost 15% of pregnancy-associated deaths (Department of Health, 1998). The mild form of pre-eclampsia most commonly presents with the features of maternal hypertension and proteinuria but can swiftly and unpredictably become severe with many extensive complications, which can involve the maternal liver, kidneys, lungs, blood vessels and nervous systems. These clinical problems normally become apparent only in the second half of pregnancy but are believed to start during the first trimester.

The diverse symptoms of pre-eclampsia have made it a difficult disease not only to define but also to identify a causative agent for the symptoms. It has therefore proved difficult to develop specific drugs that can be used to manage the condition in the clinic. Therapeutic intervention, so far, has been primarily aimed at combating the two main symptoms of pre-eclampsia — the hypertension and seizures (eclampsia). Better treatment is needed that can treat the root cause of the disease and not only the secondary symptoms.

DEFINING PRE-ECLAMPSIA AND ITS CAUSE

At the present time, pre-eclampsia is defined as hypertension, normally occurring after the 20th week of gestation, accompanied by proteinuria. In the absence of proteinuria, the condition is suspected if the hypertension is accompanied by headache, visual disturbances, abdominal pain, rapid weight gain or with abnormal laboratory tests. Also, eclamptic seizures may develop in a woman with pre-eclampsia that cannot be attributed to any other cause. The hypertension and other symptoms of pre-eclampsia are found to ultimately resolve by 12 weeks postpartum. Pre-eclampsia can also be superimposed on chronic hypertension and is often recognized by new onset proteinuria after the 20th week of gestation or sudden increases in blood pressure of previously controlled hypertension (National Institutes of Health, 2000).

Current dogma proposes a two-stage model in the development of pre-eclampsia. The first stage appears to involve the defective trophoblastic invasion of the placental bed, resulting in hypoperfusion and an ischaemic placenta. The second stage appears to involve the release of an unknown factor(s) into the maternal circulation from the placenta in response to the first stage that then causes the multi-system complications. The identity of this unknown placental factor has proved a much-debated medical mystery.

PROBLEMS WITH CURRENT THERAPIES

There are two main current therapies used to control the symptoms of pre-eclampsia: the antihypertensive and the anticonvulsant drugs. The goal of each treatment is to reduce the maternal risk in pre-eclampsia, allowing the pregnancy to proceed for as long as safely possible. The use of antihypertensive drugs during pregnancy has increased and at the same time coincided with a fall in the frequency of cerebral and hepatic lesions occurring during pre-eclampsia (Department of Health, 1998).

There are positive benefits to receiving therapy for severe hypertension. Nevertheless, pre-eclampsia is more than just hypertension, and a large study conducted in the UK reported an incidence of eclamptic seizures in 4.9/10 000 pregnancies (Douglas and Redman, 1994). A

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number of important and interesting points emerged from this report. It was demonstrated that 11% of eclamptic incidences were not linked to either hypertension or proteinuria, and a further 10% had proteinuria but no hypertension. Thirty-four per cent of women only had mild hypertension and only 19% presented with severe hypertension. In essence, high blood pressure does not correlate with the incidence of eclampsia or other symptoms of pre-eclampsia, and therefore a different course of action other than antihypertensive drugs needs to be undertaken. In the case of eclampsia, this means the need for anticonvulsant therapy.

To date, there is little evidence to suggest that any of the current therapies alters the underlying pathophysiology of pre-eclampsia or attenuates perinatal morbidity or mortality. Trials on pharmacological prevention, including aspirin (Heyborne, 2000), have been disappointing. Good pregnancy management providing continual maternal and fetal monitoring as well as non-pharmacological regimens, such as bed rest and early delivery, remain at the basis of pre-eclampsia treatments. Symptoms such as hypertension would appear secondary to the cause of the disease and should be viewed as clinical features only. In fact, antihypertensive therapy may even heighten the disease by hiding the changes in blood pressure and giving the impression that the disease is being controlled. If a placental factor linking all the symptoms of pre-eclampsia could be found, it might be possible not only to treat the symptoms at the same time as the cause, but also to do so with a single drug.

A ROLE FOR NEUROKININ B

The authors believe that the recently discovered placental peptide, neurokinin B (NKB) (Page et al, 2000) is, at present, the most promising candidate that can explain many of the symptoms of pre-eclampsia and therefore represent a true contestant for an eventual specific treatment. NKB belongs to a family of neuropeptides called the tachykinins; the first and most well known is substance P (SP), the other is neurokinin A (NKA). They activate the neurokinin (NK) receptors, of which there are three: NK1, NK2 and NK3. The order of affinity of these receptors for their peptide agonist is as follows:

NK1: SP > NKA > NKB
NK2: NKA > NKB > SP
NK3: NKB > NKA > SP

Traditionally, SP and NKA have both been described as hypotensive (Bury and Mashford, 1977). However, it has been shown in the rat that NKB causes contraction of the hepatic portal vein (Mastrangelo et al, 1987), venoconstriction of the mesenteric beds (D'Orleans-Juste et al, 1991) and increases in heart rate (Thompson et al, 1998). These are all potentially hypertensive effects.

The complementary DNA sequence of the human NKB gene from the placenta has been cloned to reveal its amino acid sequence. NKB mRNA expression was found to be restricted to the outer syncytiotrophoblasts of the human placenta in an ideal position to be secreted into the maternal bloodstream. NKB concentrations in the plasma of 30 normotensive pregnant women were found to be low or undetectable throughout pregnancy, although a proportion exhibited a slight rise at term (less then 1 nmol/litre). Four women between weeks 9 and 14 also had concentrations equivalent to the highest at term. The eight women with pre-eclampsia examined in their third trimester were found to have considerably higher levels of NKB between 1 and 7 nmol/litre.

It is likely that NKB has a physiological role to play in establishing the early trophoblast. As trophoblastic invasion proceeds, it may be an important regulator of placental perfusion by serving to dilate the uterine spiral arteries. Evidence from the infusion of high doses of NKB into female rats would indicate that NKB might be involved in some of these haemodynamic events. These data suggest that, by causing vascular changes, NKB not only increases the maternal blood pressure but also shunts blood from certain organs, such as the liver and mesenteric beds, to the uterus and placenta. This was observed by a gain of 37% in rat uteri wet weight following the intravenous infusion of NKB (Page et al, 2000).

In the case of pre-eclampsia, it is proposed that if the defective trophoblast invasion does not rectify itself after the first trimester of pregnancy, then the placenta will start to secrete NKB into the maternal circulation in ever-increasing amounts. The incomplete invasion of the trophoblasts can lead to a situation where the uterine spiral arteries are unresponsive and cannot be dilated, and therefore an adequate blood supply to the placenta fails to occur. In most normal pregnancies, the incomplete invasion process will correct itself, and in these women small surges of NKB may be observed around this period of correction. The raised levels of NKB in the maternal circulation may then lead to maternal hypertension and damage to the kidneys and liver (*Figure 1*). At very elevated concentrations, NK1 receptors on platelets may be affected, eventually causing thrombocytopenia. The activation of NK1

receptors on neutrophils and monocytes would promote the distinctive inflammation and endothelial dysfunction of pre-eclampsia. High circulating concentrations could also be responsible for the cerebral complications of pre-eclampsia: high intravascular concentrations of SP have been shown to dilate cerebral blood vessels via NK1 receptors located on the endothelium (*Figure 1*).

TOWARDS AN UNDERSTANDING OF THE PATHOLOGY OF PRE-ECLAMPSIA

Attention has started to focus on the expression of the NK receptors in order to understand the physiological mechanism of NKB secretion from the placenta. The authors' group has been the first to look for the expression of the three main NK receptors in the human placenta, and consequently, they have conducted a study to look for each of the three receptors and also a fourth putative NK receptor (NK4) (originally cloned from the placenta) in both the placenta and the non-pregnant uterus. Evidence shows that, while both the placenta and uterus contain NK1 and NK2 receptors, only the uterus contains NK3 receptors, albeit being at a much lower level of expression (*Figure 2*). The study failed to find the fourth putative NK4 receptor. However, there is now evidence to suggest that this receptor may not even be of human origin (Sarau et al, 2000).

A full understanding of the expression of the tachykinins and their receptors throughout pregnancy and the human body will help to decipher the underlying pathology and effects of large doses of NKB in the circulation. Pre-eclampsia presents with a wide range of symptoms that can differ in severity between different patients, and this has made it very difficult to predict an outcome and therefore give appropriate treatment. Why does one patient develop severe hypertension only, while another patient develops the life-threatening seizures while having only a moderate raise in blood pressure? Should the hypertension, the seizures or both be treated? These questions cannot be answered effectively at the present time.

It is likely that some of these variations may be accounted for by NK receptor expression differences around the body of the affected individual. Some may have a higher density of NK1 receptors in the brain than the circulatory system and hence be more prone to seizures. Likewise, mutations in the NK receptors may allow NKB to have a higher affinity for NK1 and NK2 receptors than normal and so precipitate a stronger and enhanced reaction in certain pre-eclampsia affected organs and blood vessels. There is also the possibility that splice variants of the receptors exist.

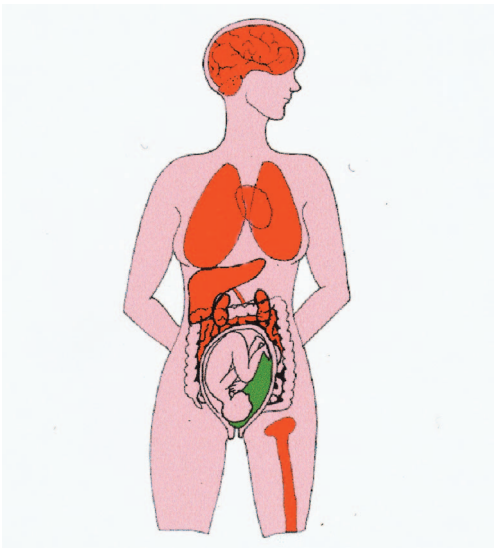
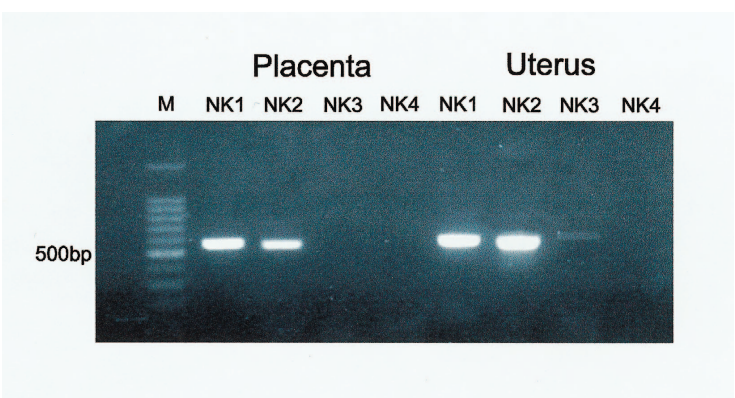


Figure 1. The secretion of large quantities of neurokinin B into the maternal bloodstream from the placenta has the capability of affecting a wide range of organs and tissues, producing a host of multiple symptoms.

CONCLUSIONS

A better understanding of the underlying factor(s) that led to the symptoms of pre-eclampsia could eventually lead to new targets to prevent or managed the disease, such as the use of NK antagonists. This could include the use of broad-spectrum NK antagonists or combinations of single NK antagonists. NKB could provide the first real predictive marker for pre-eclampsia, having the potential to uniquely predict and specifically accompany the clinical manifesta-

Figure 2. The polymerase chain reaction reveals the presence of NK1 and NK2 receptors in the placenta and NK1, NK2 and NK3 receptors in the non-pregnant uterus.



tions and being absent from other hypertensive disorders. Work is currently underway with the aim of designing a specific immunoassay that can be performed routinely in the clinical setting. In addition, large longitudinal studies are required to determine the diagnostic value of NKB at various stages of pregnancy. HM

Conflict of interest: none.

KEY POINTS

- To date, there is no widely accepted predictive test or therapeutic intervention to prevent or delay pre-eclampsia.
- The identity of the unknown placental factor causing pre-eclampsia has remained a much-debated medical mystery.
- Neurokinin B is a new placental hormone, levels of which are significantly elevated in the bloodstream of pre-eclamptic women.
- Neurokinin B may be able to provide the basis of a specific diagnostic test for pre-eclampsia.
- Treatment with neurokinin antagonists may prove an effective treatment for pre-eclampsia.

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