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Review

Neurotrophins: Role in adverse pregnancy outcome

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ABSTRACT

Proper placental development is essential during pregnancy since it forms the interface between the maternal–foetal circulations and is critical for foetal nutrition and oxygenation. Neurotrophins such as nerve growth factor (NGF), brain derived neurotrophin (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) are naturally occurring molecules that regulate development of the placenta and brain. BDNF and NGF also involved in the regulation of angiogenesis. Recent studies suggest that the levels of BDNF and NGF are regulated by docosahexaenoic acid (DHA) which is an important omega-3 fatty acid and is a structural component of the plasma membrane. Oxidative stress during pregnancy may lower the levels of DHA and affecting the fluidity of the membranes leading to the changes in the levels and expression of BDNF and NGF. Therefore altered levels and expression of NGF and BDNF may lead to abnormal foetal growth and brain development that may increase the risk for cardiovascular disease, metabolic syndromes and neurodevelopmental disorders in children born preterm. This review discuss about the neurotrophins and their role in the feto-placental unit during critical period of pregnancy.

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1. Introduction

The placenta is known to make adaptations to ensure optimal foetal growth during pregnancy. It has been suggested that the placenta hold clues for predicting the individuals who would be at risk of developing chronic diseases in childhood or in adult life (Faye-Petersen, 2008). Studies also reports that children born with preterm delivery, low birth weight, intra uterine growth restriction (IUGR) and preeclampsia have been associated with metabolic and neurodevelopmental disorders. However, the mechanisms are not clearly understood.

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Growth factors like neurotrophins and cytokines are known to act in paracrine and/or autocrine manner through their receptors in the cell for the development of feto-placental unit (Guzeloglu-Kayisli et al., 2009). Neurotrophins are a family of polypeptide growth factors that influence proliferation, differentiation, survival and death of neuronal and non neuronal cells (Kim et al., 2004). The structure and function of these neurotrophins are described below

2. Types of neurotrophins and their structures

There are four major types of neurotrophins i.e. nerve growth factor (NGF), brain derived neurotrophin (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). Amongst these, BDNF and NGF are suggested to play an important role in placental and foetal growth and development (Zheng and Shao, 2012; Mayeur et al., 2010; Nico et al., 2008; Toti et al., 2006).

2.1. Nerve growth factor (NGF)

The biologically active NGF consists of a dimer of 13-kDa polypeptide chains, each of which has three intrachain disulfide bridges. The crystal structure of NGF has been resolved (McDonald et al., 1991). The NGF gene is located on human chromosome one and is expressed as two major splice variants (Edwards et al., 1988). NGF has two known receptors, receptor tyrosine kinase A (TrkA) and p75NTR (Gigante et al., 2003). Upon binding of NGF to TrkA, the receptor is subjected to a series of events that characterize Trk signalling. These include receptor dimerization and transphosphorylation of tyrosines leading to activation of kinase activity, followed by autophosphorylation of tyrosines outside of the activation loop. Subsequent phosphorylation and activation of accessory proteins lead to the generation of a cascade of receptor-independent signalling pathways (Ras (Rat Sarcoma), Phosphoinositide 3-kinase (PKC), Phospholipase C (PI3) kinase pathway) (Sofroniew et al., 2001).

2.2. Brain derived neurotrophic factor (BDNF)

The human *BDNF* gene has seven noncoding exons that are associated with distinct promoters and one coding exon that encode the mature BDNF proteins (Liu et al., 2005). BDNF protein shares about 50% amino acid identity with NGF, NT-3 and NT-4/5. It contains a signal peptide following the initiation codon and a pro-region containing an N-linked glycosylation site (Binder and Scharfman, 2004). It also shares a distinctive three-dimensional structure containing two pairs of antiparallel β-strands and cysteine residues in a cystine knot motif. Human *BDNF* transcripts are highest in the brain and several alternative *BDNF* mRNAs showed relatively high expression levels in nonneural tissues. For example, expression levels of transcripts containing exons VI and IXabcd were high in the heart, placenta, and prostate (Pruunsild et al., 2007).

BDNF binds to its specific receptor i.e. Trk B, although some nonselective binding also occurs (Thoenen, 1995). Ligand induced receptor dimerization results in kinase activation; subsequent receptor autophosphorylation creates specific binding sites for intracellular target proteins (PLC-γ1 (phospholipase C), p85 (the noncatalytic subunit of PI-3 kinase) and Shc (SH2-containing sequence)), which bind to the activated receptor via SH2 domains (Patapoutian and Reichardt, 2001; Barbacid, 1995). This activation can then lead to a variety of intracellular signalling cascades such as the Ras-MAP (mitogen-activated protein) kinase cascade and phosphorylation of cyclic AMP-response element binding protein (CREB) (Segal, 2003; Patapoutian and Reichardt, 2001).

2.3. Neurotrophin-3 (NT-3)

NT-3 is also a member of neurotrophin family and plays an essential role in the development of both the neural-crest-derived peripheral nervous system and the central nervous system (Chalazonitis, 2004). NT-3 has a high affinity for TrkC as a chemokine receptor (Chen et al., 2013) and also binds to TrkA and TrkB with low affinity (Skaper, 2008). It also has the same structure like other neurotrophins that contain a tertiary fold and cysteine knot. The NT3 promoter contributes to the dimer to form heterodimers (Robinson et al., 1995). The gene encoding human NT-3 (gene symbol designated *NTF3*) to chromosome 12 (Maisonpierre et al., 1991). The distribution of NT-3 messenger RNA and its biological activity on a variety of neuronal populations clearly distinguish NT-3 from NGF and BDNF.

2.4. Neurotrophin-4/5 (NT-4/5)

A fourth neurotrophin is NT-4/5 (also known as NT-4, NT-5) has been molecularly cloned from Xenopus (Ip et al., 1992). NT-4/5 contain six cysteine residues and also includes an insertion of seven amino acids between its second and third cysteines (Ip et al., 1992; Berkemeier et al., 1991) and its encoded gene is located on chromosome 19 in human. NT-4/5 shares a 95% amino-acid-sequence identity with BDNF and it is the only family member that has a truncated precursor region. NT-4/5 bind to the TrkB receptor corresponds with the onset of neurogenesis in the neural tube during brain development and is differentially regulated in later development (Bartkowska et al., 2010).

There are very limited studies that report the role of these neurotrophins in the development of the placenta.

3. Role of neurotrophins in the development of feto-placental unit

BDNF, NGF, NT-3 and NT-4/5 play a vital role during pregnancy in the mother, placenta and foetus (Fig. 1).

BDNF regulate the cytotrophoblast differentiation, proliferation and survival of the placenta (Kawamura et al., 2009, 2011; Mayeur et al., 2010). BDNF plays a key role in the regulation of angiogenesis and is reported to protect the endothelial progenitor cells by increasing the expression of superoxide dismutase (He and Katusic, 2012; Jiang et al., 2011). Changes in levels of neurotrophins can produce long lasting effects on neurotrophic processes (neuron number, synapse), which alter neuronal maturation and plasticity in later life (Vicario-Abejón et al., 2002). BDNF/TrkB-stimulated intracellular signalling is critical for neuronal survival, morphogenesis and plasticity (Numakawa et al., 2010).

It has been reported that both foetal and maternal tissues (trophoblast, amnion/chorion and maternal deciduas) express the NGF mRNA both in early gestation and at term (Toti et al., 2006). Role of NGF in mouse placentation during the post implantation period has been described (Kanai-Azuma et al., 1997). Furthermore, NGF and its receptors are suggested to play an important role during organogenesis (Miralles et al., 1998). NGF acts as an angiogenic factor by contributing to the maintenance, survival and function of endothelial cells by autocrine and/or paracrine mechanisms (Nico et al., 2008). In addition, NGF has been associated with functional activities of cells that include immune and endocrine systems and act as an inflammatory mediator (Berry et al., 2012).

There are very few studies, which have discussed the role of NT-3 and NT-4 in the development of the feto-placental unit. It has been hypothesized that NT-3 function in the regulation of placental and foetal brain development and for the maternal inflammatory responses (Casciaro et al., 2009). Kawamura et al. (2009) have