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# Neurotrophins and their receptors in early development of the mammalian nervous system

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Neurotrophins belonging to the class of growth factors and including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) are widely recognized as essential factors in the developing central nervous system (CNS). Neurotrophins are synthesized as precursor forms (proneurotrophins). Mature forms of neurotrophins exert their effect by binding to specific tyrosine kinases receptors (TrkA, TrkB and TrkC) as well as via the p75 receptor, a member of the tumor necrosis factor receptor superfamily while proneurotrophins interact with the receptor p75 or co-receptor complex of p75 and sortilin, that is a Vps10p domain-containing transmembrane protein. Expression of neurotrophins corresponds with the onset of neurogenesis in developing mammalian species. BDNF is low in early embryonic stages of development, while NT-3 highly expresses in the developing CNS. Expression of neurotrophins receptors mainly overlaps at early development. Data concerning early distribution of neurotrophins and their receptors in the nervous system and results in mice with targeted disruptions of neurotrophin or receptor genes show that neurotrophins and their receptors play distinct roles in control and regulation of the most crucial developmental processes such as proliferation, migration, differentiation, survival, apoptosis and synaptic plasticity.

Key words: BDNF, developing brain, NGF, NT-3, NT-4/5, p75, sortilin, TrkA, TrkB, TrkC

## NEUROTROPHINS AND THEIR RECEPTORS

### Neurotrophins

In the early 1950s Levi-Montalcini and Cohen (Levi-Montalcini and Hamburger 1951, Cohen et al. 1954) were first to describe the nerve growth factor (NGF) and for that discovery they won the Nobel Prize in Physiology or Medicine in 1986. Afterwards, several novel structurally homologous neurotrophic factors belonging to the nerve growth factor family termed neurotrophins were discovered in vertebrates. These were BDNF, NT-3, NT-4/5 (Barde et al. 1982, Phillips et al. 1990, Ibáñez et al. 1993). Other members of neurotrophins neurotrophin-6 (NT-6) and neurotrophin-7 (NT-7) were only cloned from some teleost species (Götz et al. 1994, Lai et al. 1998) and are not expressed in other vertebrate than teleost fishes.

Structure of all neurotrophins is highly conserved with the exception of NT-4/5 (Hallböök 1999) that shares only about 50% amino acid identity with other neurotrophins (Shooter 2001). An important common feature of all neurotrophins is the presence of six cysteine residues that enable formation of disulfide bridges. Neurotrophins are synthesized as pre-pro-proteins by both neuronal and non-neuronal cell types (Thoenen 1995, Seidah et al. 1996). Protein products of all genes encoding neurotrophin contain a signal peptide for protein secretion (pre-protein) and the precursor protein (pro-protein). When the hydrophobic region of the signal peptide is removed from pre-proneurotrophin at the N-terminal, the proneurotrophin is generated (Fig. 1). The proneurotrophin is either cleaved of the signalling peptide in the endoplasmic reticulum and converted to the mature neurotrophin or is transported to the plasma membrane and released in an unprocessed form (Seidah et al. 1996). In that case plasmin or another extracellular protease converts the

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precursor proneurotrophins to mature neurotrophins through proteolytic cleavage (Pang et al. 2004). Mature neurotrophins are secreted as homodimeric proteins into the extracellular space and act in a paracrine and/or autocrine way (Lu et al. 2005), controlling many crucial processes in development of the nervous system such as proliferation, migration, differentiation, survival, apoptosis and synaptic plasticity. All these processes lead to control neuronal numbers and dendritic growth.

**Neurotrophin receptors**

Neurotrophins interact with three distinct classes of receptors: three members of the tropomyosin receptor kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB and TrkC), the p75 neurotrophin receptor belonging to the tumor necrosis factor receptor (TNFR) superfamily and sortilin, a Vps10p domain-containg transmembrane protein. All neurotrophins mediate their effects via activation of one or more Trk recep-

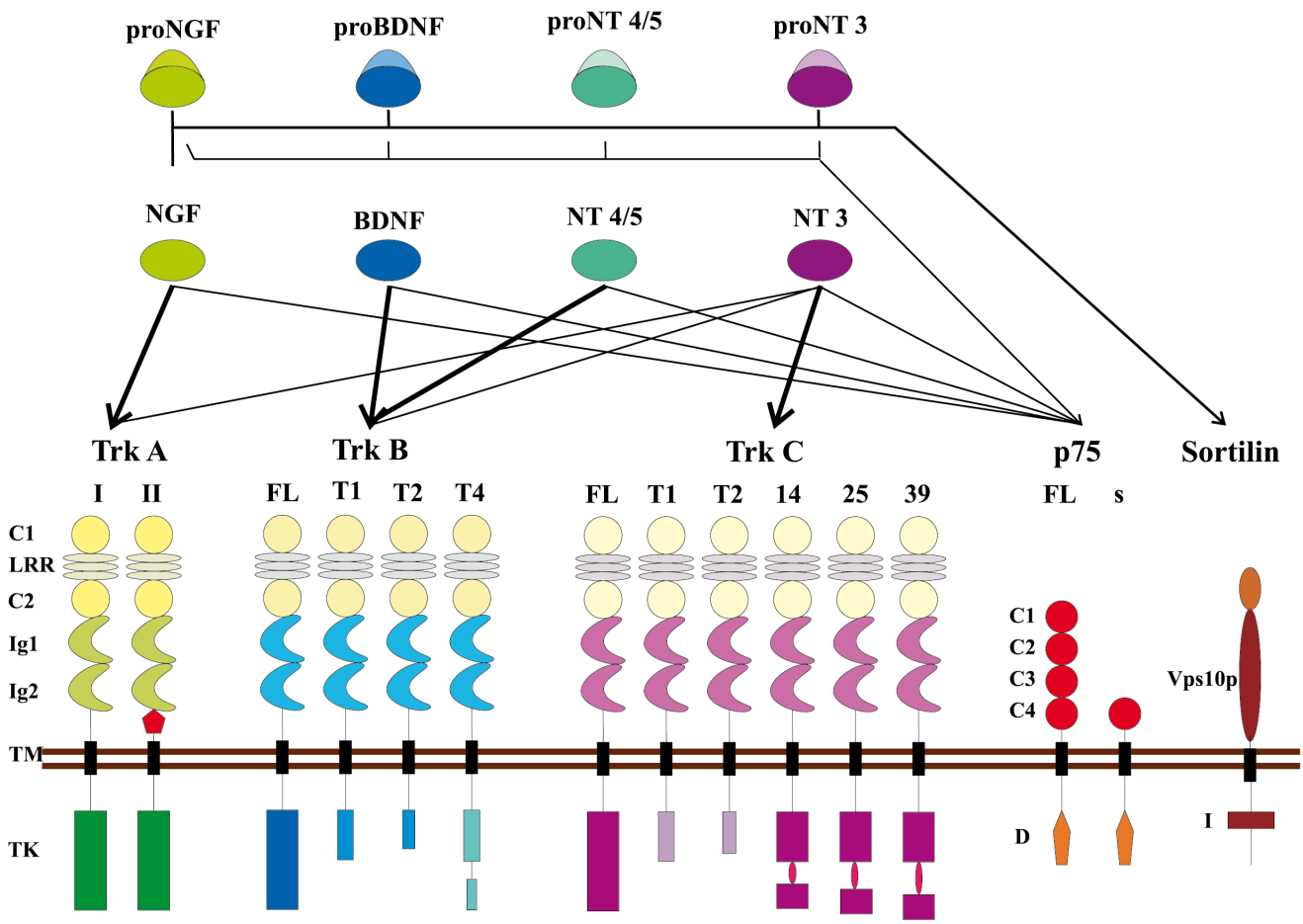


Fig. 1. Schematic design of neurotrophin receptors and their specific ligands. Neurotrophins bind to their receptors with high affinity (bold arrows) or low affinity (thin arrows). All isoforms of TrkA (I, II), TrkB and TrkC full length (FL), truncated (T1, T2, T3) and with insertion (14, 25, 39 - number of aminoacids) contain two cysteine rich regions (C1, C2), leucine rich region (LRR) and two immunoglobulin-like domains (Ig1, Ig2) in the extracellular region, the transmembrane domain (TM) and tyrosine kinase domain (TK) in the cytoplasmic region. Low affinity p75 neurotrophin receptor contains four cysteine rich regions (C1-C4) or one - C4 cysteine in the truncated form (s) in the extracellular region and D - "death" domain in the cytoplasmic part. Vps10p – extracellular domain of sortilin receptor, I – internalization motif in the cytoplasmic domain of sortilin.

tors. NGF activates the TrkA receptor, BDNF and NT-4/5 bind to the TrkB receptor and NT-3 activates predominantly the TrkC receptor but NT-3 can also bind to other Trk receptors. All these neurotrophins bind to the p75 receptor.

Proneurotrophins (precursor proteins) are also active as ligands of Trk receptors, but their binding elicits functional effects opposite to those elicited by binding of mature neurotrophins. All proneurotrophins interact with p75 or co-receptor complex of p75 and sortilin receptors inducing cell death or survival (Lee et al. 2001, Nykjaer et al. 2004, Teng et al. 2005).

Trk receptors

TrkA, TrkB and TrkC receptors belong to the family of receptor tyrosine kinases and neurotrophins are their common ligands. All Trk receptors consist of three structural regions: an extracellular ligand binding region that contains two cysteine-rich clusters, one of which is followed by three leucine-rich repeats and two immunoglobulin-like domains, a transmembrane region and the cytoplasmic region, where a tyrosine kinase catalytic domain is present (Fig. 1). The second immunoglobulin-like domain enables each of Trk receptors TrkA, TrkB and TrkC to bind selectively to their specific neurotrophins. However, other extracellular domains also regulate Trk catalytic activity (Arevalo et al. 2000). It has been shown that inhibition of N-glycosalytion of the extracellular domain which contains consensus sites for N-glycosylation induces activation of the Trk tyrosine kinase without binding of a ligand (Watson et al. 1999). Binding of a neurotrophin dimerizes the Trk receptor (Ohira et al. 2001), which activates the tyrosine kinase catalytic domain of the cytoplasmic region through its auto trans-phosphorylation for adaptor proteins (Huang and Reichardt 2003). Phosphorylation of tyrosine undergoes also outside of the tyrosine kinase domain at the C-terminus of the receptor.

Many isoforms of Trk receptors have been described, among them four isoforms of TrkA, eigth isoforms of TrkB and six isoforms of TrkC. The *trkA* locus encodes two isoforms, TrkA-I and TrkA-II (Fig. 1). TrkA-II contains an additional 6 amino acids-long insertion between the second immunoglobulin-like domain and the transmembrane region of the extracellular domain, while TrkA-I lacks that insertion (Barker et al. 1993). Both of them are biologically active receptors that recognize their specific ligand NGF and transduce functional signals. Two other isoforms are distinguished from the full-length isoforms by presence of only one leucine-rich region in the extracellular domain instead of three in the full-length TrkA or absent at all. These isoforms are expressed only in the thymus (Dubus et al. 2000). Distribution of the two TrkA splice variants has been investigated with *in situ* hybridization technique (Barker et al. 1993). High level of TrkA-II transcripts has been found in the sympathetic and dorsal root ganglia of the rat and human, the human trigeminal ganglia and rat brain whereas expression of TrkA-I was high in the non-neuronal tissue like kidney, lung. However in a neuronal cell line TrkA-II displays significantly higher activation by NT-3 (Clary and Reichardt 1994).

Various isoforms may be generated from the *trkB* and *trkC* genes by alternative splicing of transcripts of their exons (Fig. 1). Alternative mRNA splicing of *trkB* exons creates eight receptor isoforms. These isoforms that have truncated cytoplasmic domains lack the tyrosine kinase motif. The full length TrkB receptor is named $gp145^{trkB}$. Truncated forms lack most of the cytoplasmic domain of the full-length receptor but contain a short C-terminal sequences (Eide et al. 1996). The TrkB-T1 and TrkB-T2 trunctated isoforms differ from the full-length TrkB receptor by lacking the intracellular kinase domain. They have short intracellular tails of 23 and 21 aminoacids respectively whereas TrkB-T4, which has also been described as TrkB-T-ShC (Stoilov et al. 2002), is much longer than the other two truncated domains and contains a putative internalization sequence (Forooghian et al. 2001) as well as an Shc binding domain (Stoilov et al. 2002). Additional TrkB isoforms are distinguished from the full length TrkB receptor or TrkB-T1 that contain one (L1) or none (L0) of leucine-rich regions in the extracellular domain. The L1 and L0 variants are not biologically active and do not bind TrkB specific ligands such as BDNF, NT-3 and NT-4/5 (Armanini et al. 1995). High levels of expression of the TrkB-T1 and TrkB-T2 receptors has been found in neurons of the adult CNS (Carim-Todd et al. 2009) although expression of TrkB-T1 is also observed in glial cells such as astrocytes, oligodendrocytes and Schwann cells (Silhol et al. 2005). Truncated forms of TrkB receptors are also expressed in the choroid plexus and ependyma (Fryer et al. 1996).

Six TrkC isoforms have been identified so far (Fig. 1). They differ from the full length TrkC by trun-

cations or insertions in the intracellular domain. Two TrkC isoforms, TrkC-T1 and TrkC-T2 are characterized by truncated intracellular kinase domain that is replaced by distinct short C-terminal sequences (Valenzuela et al. 1993, Hapner et al. 1998). They were also named the TrkC-NC1 and TrkC-NC2 noncatalytic forms (Menn et al. 1998). Three other isoforms, TrkC-14, TrkC-25 and TrkC-39 are characterized by different length of insertions (14, 25 or 39 aminoacids) in the intracellular domain (Valenzuela et al. 1993, Tsoulfas et al. 1996, Menn et al. 1998). It has been shown that only the truncated isoforms are expressed in peripheral nerves and astrocytes, whereas TrkC insert isoforms are expressed in the CNS during the postnatal period and in the adult life (Tsoulfas et al. 1996). The full-length Trk receptors are the major forms early in development, whereas truncated forms predominate later.

TrkB and TrkC isoforms may modulate signal transduction either by formation of heterodimers with full-length receptors or by competitive binding of the available ligand. The truncated Trk receptors can inhibit the full-length Trk receptors either by acting as the dominant negative receptor or by forming non-functional heterodimers (Eide et al. 1996, Carim-Todd et al. 2009). Co-expression of the truncated and full-length isoforms has been shown for both TrkB and TrkC receptors (Eide et al. 1996, Palko et al. 1999). Truncated TrkC receptors may function as inhibitors of the TrkA or TrkB receptors, even though heterodimerization of different Trk receptors has not been demonstrated in vivo. The high degree of conservation of the intracellular domains of truncated receptors in evolution may suggest presence of other functions of these receptors (Hapner et al. 1998, Cheng et al. 2007, Islam et al. 2009). For example, truncated TrkB receptors may sequester ligands and limit their diffusion (Fryer et al. 1997). What more, after binding neurotrophins they may induce an increase in the rate release of acidic metabolites from cells (Baxter et al. 1997). Therefore, they may autonomously activate signalling cascades in a neurotrophin-dependent manner.

### p75

p75 belongs to the tumor necrosis factor family of receptors. It consists of an extracellular region that contains of four cystein-rich domains, a single transmembrane domain and the intracellular domain named death domain which is characteristic for all members of the tumour necrosis factor family receptors (Fig. 1). Activation of the cytoplasmic region leads to activation of NFkB which induces apoptosis (Liepinsh et al. 1997). The intracellular domain of this receptor can be phosphorylated. It can bind a number of death-signalling ligands and the PDZ domain containing proteins known for protein trafficking and receptor complex association (Roux and Barker 2002, Coulson et al. 2004). Therefore it was shown that p75 interacts with several proteins that transmit signals important for regulating survival, differentiation and synaptic plasticity (Underwood and Coulson 2008).

One truncated isoform of p75 has been identified. This isoform that was termed s-p75 has only one cysteine-rich repeat in the extracellular domain instead of four.

### Sortilin

A few years ago a novel neurotrophin receptor called sortilin has been described. Sortilin is a member of the family of Vps10p domain-containing transmembrane proteins and binds mature NGF, proNGF, proBDNF and proNT-3 (Nykjaer et al. 2004, Teng et al. 2005, Yano et al. 2009). NGF binds to sortilin with moderate affinity, as compared to its high affinity binding to TrkA and p75 (Hempstead et al. 1991). If sortilin is co-expressed with p75 and associates with it, then the affinity of this receptor complex to proNGF is increased. Nothing is known about the signalling pathways triggered by sortilin. It is not clear whether sortilin acts only as a co-receptor of p75 facilitating its binding to proNGF or if it can independently trigger a signalling cascade. If such independent function of sortilin exists, it has most probably a proapoptotic character (Schweigreiter 2006).

## EXPRESSION OF NEUROTROPHINS AND THEIR RECEPTORS DURING EARLY DEVELOPMENT OF THE NERVOUS SYSTEM

The level of expression of neurotrophins and their receptors is generally high throughout development of the mammalian CNS (Knusel et al. 1994, Kordower et al. 1994, Fryer et al. 1996, Tessarollo 1998, Quartu et al. 2003a, b, Beltaifa et al. 2005, Numan et al. 2005, Tang et al. 2010). During development neurotrophins

are expressed selectively at different stages in various structures of the nervous system (Table I), regulating different processes in various brain areas. It is worth to note, that almost all data relating to timing and localization of expression of neurotrophins and their receptors at early stages of development are derived from studies on rodents, carnivores and primates including human. Very few data are available on other species of mammals.

### Expression of NGF and TrkA during development

During development of the nervous system various processes such as neurogenesis, migration, growth of neuritis and forming connections, apoptosis, development of the neuronal dendritic field and their pruning occur in a sequential order and at specific developmental stages. Therefore timing of expression of neurotrophins and specific forms of their receptors defines the scope of developmental events they influence. It has been shown that NGF and its TrkA receptor are expressed during early or mid stages of development (Table I). In the rat PNS, e.g., in the trigeminal ganglion, the peak of NGF expression occurs at E12 (Arumäe et al. 1993), while in the human it takes place during 23$^{rd}$ week of gestation (Quartu et al. 1997). In the rat spinal cord NGF mRNA starts to be expressed at the stage E12 and it is detectable until E17.5 (Ayer-Lelievre et al. 1983, Elkabes et al. 1994). In primates expression of NGF in the CNS appears at comparatively later stages. In the monkey neocortex the NGF mRNA starts to be present at E120 till birth at E165 (Mori et al. 2006) and in the human neocortex at the 15-16$^{th}$ week of gestation (E105-112). Its expression in the hippocampus occurs even later, between 23$^{rd}$ and 28$^{th}$ weeks of gestation (Pizzuti et al. 1990, Quartu et al. 2003a).

Expression of TrkA receptors also occurs at early stages of brain development. Martin-Zanca and coauthors (1990) cloned the mouse *trk* proto-onconge (presently known as TrkA) and selected two of its putative exons for generating probes that were used in the Northern analysis and *in situ* hybridization. They found that in the mouse the TrkA mRNA could be first detected in the brain at the stage E8.5. The *trk*-specific band was first observed in Northern blots from brains of E9.5 embryos and its intensity increased until E13.5. Afterwards, its expression decreased to the level found in the adult. Analysis of expression of *trk* receptors with *in situ* hybridisation in E12.5-E14.5 mouse embryos showed the highest expression of *trk* mRNA in the sensory cranial and spinal dorsal root ganglia. Also in the rat expression of TrkA in the dorsal root sensory ganglia was first observed at E12.5 (Elkabes et al. 1994).

Development of expression of TrkA receptor was also investigated in mammalian species other than rodents (Table I). No data is available regarding presence the TrkA receptor in the monkey at earlier stages. In E133-135 fetuses of the macaque monkeys (*Macaca fascicularis*) NGF receptor immunoreactivity labeled with the monoclonal antibody against the human NGF receptor was visible in axons of the retinal ganglion cells, in Mueller glial cells of the retina and in the cerebellum (Schatteman et al. 1988). In the cerebellum the level of NGF receptor declined starting from E164 (Schatteman et al. 1988). In the rat cerebellum the NGF receptor was present during the first 20 days of postnatal development which is equivalent to the late prenatal period of the primate cerebellum (Quartu et al. 2003b). It has been shown that during late phases of the CNS development NGF is also involved in neuronal plasticity (Macias 2008, Badowska-Szalewska et al. 2009).

The role of NGF and TrkA receptors in the CNS development were also investigated in mice in which the *ngf* gene or *trkA* gene were knocked out (Crowley et al. 1994, Smeyne et al. 1994). Pups of the *ngf* (-/-) knockout mice were born alive but had a short life span (about 4 weeks) because of massive cell loss in the sensory and sympathetic ganglia (Crowley et al. 1994). These data provide direct information regarding the role of NGF in promoting cell survival of embryonic sensory neurons. NGF acts via the TrkA receptor and therefore the Trk-A null mice also die shortly after birth (Smeyne et al. 1994). TrkA knockout mice contained significantly fewer and smaller cholinergic neurons in the basal forebrain and striatum which indicates that the NGF/TrkA signalling plays an important role in maturation of neurons (Fagan et al. 1997).

### Expression of BDNF, NT-4/5 and TrkB during development

Expression of BDNF, NT-4/5 and TrkB receptors also occurs at early stages of development of the mammalian nervous system (Table I). At E10-E12 BDNF is present in the rat trigeminal ganglia (Arumäe et al.

1993). There are no data concerning expression of BDNF in the PNS of other mammalian species. Beginning from E13 BDNF immunoreactivity was also present in the CNS, especially in the neocortical subplate and developing cortical plate neuroblasts of the rat (Fukumitsu et al. 1998). The number of labeled cells increased till E18 when all cells of the cortical plate were labelled. In the macaque monkey expression of BDNF mRNA in the cerebral cortex was first detected at E121 (Huntley et al. 1992). The level of BDNF protein expression was low at that age and gradually increased afterwards (Mori et al. 2004).

Hayashi and coworkers (1999, 2000) investigated localization of TrkB-FL immunoreactivity in the developing hippocampal formation and cerebral cortex of the macaque monkey but only at two developmental stages (E140 and P7). At both stages the TrkB-FL protein was detected in the dentate gyrus, Ammon's horn, subiculum and the entorhinal cortex. In the prefrontal and visual cortices the number of cells immunopositive for the full-length TrkB was high at E140 and its expression has been maintained till the postnatal day 7. The truncated TrkB-T1 was also observed at late stages of the macaque pregnancy (Ohira et al. 1999). At E140 the level of truncated TrkB in the prefrontal cortex was about 7% of that in the adult macaque but in the hippocampus and cerebellum the level of expression of the truncated TrkB receptor was already high (Ohira et al. 1999). In the rat the truncated form of TrkB has not been detected before E15 and its expression was low until birth. Afterwards it increased gradually during neonatal development (Fryer et al. 1996). In human infants at the postnatal age 2 to 9 months BDNF and its TrkB receptor are expressed in the brainstem nuclei and hippocampus (Tang et al. 2010), but the time this expression begins is not known.

Mouse *trkB* cDNA has been cloned (Klein et al. 1989, 1990) and expression of its products during mouse embryogenesis was studied. Expression of *trkB* transcripts has been first visible at E9.5 in the neuroepithelium and neural crest cells that formed the dorsal root ganglia. At E13.5 *trkB* mRNA has been shown with the in situ hybridization in the lateral wall of the telencephalon, trigeminal nerve and the PNS (from sensory ganglia of the spinal cord to the visceral plexus). At that age and also at E16.5 particularly high levels of *trkB* expression in the CNS were visible in the olfactory lobe and ependymal layer of the fourth ventricle.

The full-length TrkB protein (TrkB-FL) is expressed in the brain during early embryonic development: in the rat at E13-14 (Knűsel et al. 1994, Freyer et al. 1996, Fukumitsu et al. 1998), in the mouse at E12.5 (Klein et al. 1989, 1990, Barnabé-Heider and Miller 2003, Bartkowska et al. 2007, Islam et al. 2009) and in the pre-term human newborns (Quartu et al. 2003a, b). In the rat E13 embryos TrkB immunoreactivity was strong in the cortical primordial plexiform layer and ventricular zone cells. Transient expression of TrkB that was observed at E18 in the cortical plate and subplate neurons disappeared at E20 (Fukumitsu et al. 1998). In the cingulate and entorhinal cortex expression of TrkB also appeared at E18 and increased till birth (Fryer et al. 1996) while expression of BDNF mRNA in the occipital cortex appeared only during postnatal development. At P10 the level of BDNF mRNA was still low and gradually increased until P30 (Schoups et al. 1995). Expression of NT-4/5 mRNA was found only in the rat trigeminal ganglia at E10-E11 (Arumäe et al. 1993, Ibáñez et al. 1993).

BDNF knockout mice were born alive but most of them died before the second postnatal week (Ernfors et al. 1994, Jones et al. 1994). They had poor motor coordination and body balance. Knockout of the *bdnf* gene resulted in cell loss of neurons in the sensory ganglia, including the vestibular ganglion (Bianchi et al. 1996), dorsal root ganglia, trigeminal ganglia (Ernfors et al. 1994), geniculate ganglia of the facial nerve (Patel and Krimm 2010) and the cranial and spinal sensory ganglia (Jones et al. 1994). In the *bdnf* (-/-) knockout mice the most affected structures in the brain were thalamus (Lotto et al. 2001), substantia nigra (Baker et al. 2005) and cerebellum (Schwartz et al. 1997).

*trkB* (-/-) knockout mice were born alive but majority of them died within 48 h after birth. These mutant mice had abnormalities in the facial motor nucleus and trigeminal ganglion hampering their suckling, which caused their death by starvation but abnormalities were also visible in other sensory ganglia of the head, like the vestibular and cochlear ganglia (Klein et al. 1993, Piñon et al. 1996, Silos-Santiago et al. 1997) and also in the dorsal root ganglia (Perez-Pinera et al. 2008). During early postnatal stage apoptotic cell death was significant in various brain regions of the TrkB mutant mice (Alcañtara et al. 1997, Holm et al. 2003). Knockout mice lacking both truncated and full-length isoforms of the TrkB receptor experienced less pronounced neuronal losses compared to animals with full-length TrkB knockout

Table I

The time of appearance of neurotrophins and their receptors expression in the developing CNS and PNS of mammalian species

| | NGF | TrkA | BDNF | NT-4/5 | TrkB | NT-3 | TrkC | p75 | Sortilin |
|---|---|---|---|---|---|---|---|---|---|
| **Neuroepithelium and neural tube** | | E9.5 m [21] | | | E9.5 m [17] | | E9.5 m [30] | | E9.5 m [13] |
| **Forebrain** | | E11-15 r [8]<br>14wg h [5] | | | E9.5 m [17] | | E13.5 m [30] | E13 r [18]<br>E56-64 mk [20]<br>14wg h [5] | |
| Subplate | | | E13 r [10] | | E13-18 r [8, 10] | E15 r [10] | E18 r [10] | E30 c [1], P2 f [1]<br>E54 mk [20]<br>14-26wg h [5, 19] | |
| Neocortex | E120 mk [23]<br>15-16wg h [24] | | E13-18 r [10]<br>E120 mk [14, 23] | E140 mk [22] | E13-18 r [8, 9, 10]<br>E140 m [12] | E18 r [10]<br>E120 mk [23] | E13-18 r [8, 10]<br>E11.5 m [30] | | E11.5 m [13] |
| Striatum and basal ganglia | | E13-18 r [8] | | | E15 r [9] | | | E15 rat [32]<br>P0 rat [4]<br>14wg h [5] | |
| Hippocampus | 23-28wg h [26] | | E18 r [8]<br>E120 mk [23]<br>23-28wg h [26] | 23-28wg h [26] | E13-18 r [8, 9]<br>E140 mk [11] | E18 r [8]<br>E120 mk [23]<br>23-28wg h [26] | E13-18 r [8]<br>E13.5 m [30] | 16-26wg h [5, 19] | E11.5-13.5 m [13] |
| Olfactory lobe | E15 r [3] | | | | E15 r [9]<br>E16 m [16] | | | E15 rat [32] | |
| **Midbrain** | | 14wg h [5] | | | E9.5 m [17] | | E11.5 m [30] | E15 r [32]<br>14wg h [5] | |
| **Pons and medulla** | E15 r [3] | 10wg h [5] | | | E9.5 m [17] | | E11.5 m [30] | E15 r [32]<br>10wg h [5] | |
| **Cerebellum** | 24wg h [27] | 14-24wg h [5, 28]<br>E133 mk [29] | 24wg h [27] | 24wg h [27] | 24wg h [28]<br>E9.5 m [17] | E16 r [8]<br>24wg h [27] | E13-18 r [8]<br>E11.5 m [30]<br>24wg h [28] | E7 r [7], E15 r [32]<br>14wg h [5] | E11.5-13.5 m [13] |
| **Spinal cord** | E12.5 r [6] | | | | E13-18 r [8]<br>E9.5 m [17] | E13-18 r [6, 8] | E13-18 r [8]<br>E11.5 m [30] | E7 r [7]<br>E15 r [32] | |
| **Sympathetic ganglia** | | | | | E10.5 m [17] | | E15.5 m [30] | E7 r [7]<br>E11 r [32] | |
| **Cranial ganglia** | E12 r [2]<br>23wg h [25] | E10-18 r [2, 6, 8]<br>E9.5 m [21, 31] | E12-18 r [2, 8]<br>23wg h [25] | E11-20 r [2, 15]<br>23wg h [25] | E11-18 r [2, 8]<br>E9.5 m [17] | E12-18 r [2, 6, 8]<br>23wg h [25] | E11-18 r [2, 6, 8] | E7 r [7]<br>E9.5 m [31] | E11.5 m [13] |
| **Spinal ganglia** | E12.5 r [6] | E13-18 r [8]<br>E9.5 m [21] | E13-18 r [8] | E13-20 r [15] | E13-18 r [8]<br>E9.5 m [17] | E13-18 r [8]<br>E12.5 r [6] | E13-18 r [8]<br>E11.5 m [30] | E7 r [7] | E11.5 m [13] |

c – cat, E – embryonal day, f – ferret, h – human, m – mouse, mk – monkey, P – postnatal day, wg – week gestation.

**1**.Allendoerfer et al. 1990, **2**.Arumae et al. 1993, **3.**Ayer-Lelievre et al. 1983, **4**.Buck et al. 1987, **5**.Chen et al. 1996, **6**.Elkabes et al. 1994, **7**.Ernfors et al. 1988, **8**.Ernfors et al. 1992, **9**.Fryer et al.1996, **10**.Fukumitsu et al. 1998, **11**.Hayashi et al. 1999, **12**.Hayashi et al. 2000, **13**.Hermans-Borgmeyer et al. 1999, **14**.Huntley et al. 1992, **15**.Ibanez et al. 1993, **16**.Klein et al. 1989, **17**.Klein et al. 1990, **18**.Koh and Loy, 1989, **19**.Kordower and Mufson 1992, **20**.Meinecke and Rakic 1993, **21**.Martin-Zanca et al. 1990, **22**.Mori et al. 2004, **23**.Mori et al. 2006, **24**.Pizzuti et al. 1990, **25**.Quartu et al. 1997, **26**.Quartu et al. 1999, **27**.Quartu et al. 2003a, **28**.Quartu et al. 2003b, **29**.Schatteman et al. 1988, **30**.Tesarollo er al. 1993, **31**.Wyatt and Davies 1993, **32**.Yan and Johnson, 1988.

(Luikart et al. 2003). Lack of the truncated TrkB caused also neurite abnormalities and reduced the length of dendrites in amygdalar neurons (Carim-Todd et al. 2009).

### Expression of NT-3 and TrkC during development

Pattern of developmental distribution of NT-3 and its TrkC receptor has been investigated in the rat embryo (Table I). In the cortex NT-3 immunoreactive cells were first present at E13 in the ventricular zone cells and primordial plexiform layer and at E15-E18 they were located in the subplate (Fukumitsu et al. 1998). Expression of TrkC was first observed in the rat at E13 in the primordial plexiform layer. At E18 it was visible in the subplate and in the deepest neuronal layer of the cortical plate (Fukumitsu et al. 1998).

In the mouse embryo expression of the TrkC mRNA was present from the earliest stages of neural tube formation, i.e. about E10.5 (Tessarollo et al. 1993). By E11.5 *trkC* expression was increased throughout CNS and *trk*C transcrips were present in the neocortex, striatum, pons, medulla, cerebellum and the mantle (postmitotic) layer of the spinal cord. In the human embryo TrkC was discovered in the cerebellum at the 24$^{th}$ week of gestation (Quartu et al. 2003b). The full-length form of TrkC was highly expressed during embryogenesis and at low level throughout postnatal development while expression of the truncated forms was low during early stages of development (Table I) and afterwards gradually increased to reach the mature levels by adolescence (Beltaifa et al. 2005).

NT-3-deficient mice displayed severe movement defects and most of them died shortly after birth (Ernfors et al. 1994). Mice lacking the *nt-3* gene experienced severe loss of the cranial and spinal sensory and sympathetic neurons (Fariñas et al. 1994, Ernfors et al. 1995, ElShamy et al. 1996, Liebl et al. 1997). The number of oligoprogenitors in these knockouts was lower (Kahn et al. 1999) and they had lower numbers of glial cells in the CNS. In the *nt-3* (-/-) mice proteins content in the myelin and myelin thickness were reduced (Woolley et al. 2008).

Mice lacking TrkC were born alive but died within 3 weeks after birth. *trkC* (-/-) mice showed abnormal behavior (Klein 1994) and they had reduced numbers of sensory neurons (Piñon et al. 1996, Liebl et al. 1997, Silos-Santiago et al. 1997). Mice lacking TrkC had also deficiencies in glial cells (Kahn et al. 1999).

### Expression of the p75 receptor during development

Expression of p75 has been shown at early developmental stages of the CNS and PNS (Table I). In the rat it was shown at E7 (Ernfors et al. 1988), particularly in the forming dorsal root ganglia. During subsequent days of development p75 was selectively expressed in the sympathetic and sensory ganglia and also in the forebrain (Buck et al. 1987). In the ventrolateral telencephalic wall the p75 receptor (described by the authors as the NGF receptor) immunoreactivity has been first found at E13 and its expression increased during following days (Koh and Loy 1989). In the monkey immunoreactivity for p75 was first visible at E56 in the embryonic cerebral wall, especially in the subplate which disappeared by birth (Meinecke and Rakic 1993).

In carnivores data about timing of expression of the p75 receptor in the nervous system during fetal period are known only for the cerebral cortex. Development of the cerebral cortex has been investigated in two carnivore species, the cat and ferret (Allendoerfer et al. 1990, 1994). NGF receptors (p75) on the subplate neurons were first labeled at E30 of the cat fetuses. They were then expressed there for about three weeks. Expression of the p75 receptor decreased at around E52 and disappeared at E60, when subplate neurons were starting to die out. Immunostaining for NGF receptors in the subplate neurons of the cerebral cortex in the ferret was established at the postnatal (P) day 2 that is developmentally equivalent to the developmental stage E43 in the cat. Kittens are born at the 65$^{th}$ gestational day, whereas ferret pups are born at the 41$^{st}$ gestational day, at much earlier stage of development (Luskin and Shatz 1985).

Mice lacking the *p75* gene had deficits in the PNS (Lee et al. 1992, Jahed and Kawaja 2005). They displayed behavioral impairment and loss of neurons in the basal forebrain (Peterson et al. 1999). On the contrary, Yeo and others (1997) showed that the size of neurons in the basal forebrain increased in the *p75* (-/-) knockout mice. These mice displayed also reduced apoptosis in the retina at E15.5.

### Expression of sortilin receptor during development

Expression of the sortilin receptor was observed in the developing nervous system (Table I). Transcripts of

sortilin were first detected at E7.5 in the ectodermal cell layer of the mouse embryo (Hermans-Borgmeyer et al. 1999). At E9.5 the hybridization signal was found in the neural tube. Later the sortilin gene was expressed in all areas of the CNS. Between E14.5 and E16.5 intensity of the signal decreased in proliferative zones but was still strong in the cerebral cortex and retina. During embryonal development of the retina sortilin coexpressed with p75 but at the postnatal day 6 only sortilin was expressed there. In the retinal neurons at E15 substantial amounts of sortilin receptors were localized in the intracellular membranes of the Golgi apparatus while at the postnatal period sortilin changed its localization and was placed on the cell surface (Nakamura et al. 2007). Beginning from E11.5 sortilin was also present in the peripheral nervous system, i.e. dorsal root ganglia and trigeminal ganglion (Hermans-Borgmeyer et al. 1999).

Sortilin knockout mice showed reduced neuronal apoptosis in the developing retina and in retinal cell culture (Nykjaer et al. 2004). Although sortilin deficiency did not affect developmentally regulated apoptosis in sympathetic neurons, it did prevent their age-dependent degeneration (Jansen et al. 2007).

## CONCLUSIONS

Onset of expression of neurotrophins (NGF, BDNF, NT-3 and NT-4/5) corresponds with the onset of neurogenesis in the neural tube during brain development of investigated mammalian species and is differentially regulated in later development. In spite of the fact that structure of neurotrophins and their receptors is very conservative, their functions are variable and complex, depending on cells they are expressed in and stage of development. What more, all neurotrophins are synthesized as proneurotrophins and all proneurotrophins are active ligands binding to the p75 receptor and activating either the apoptosis pathway or signal cascades that lead to cell survival.

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