

Oligodendroglial Cells and Neurotrophins: A Polyphonic Cantata in Major and Minor

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Abstract Oligodendrocytes met neurotrophins in the early 1990s of the last century. Since then, their relationship underwent functional ups and downs partially dependent on the developmental stage of the oligodendroglial cells and the species, from which the cells were derived. This review provides a brief overview of oligodendroglial cells and neurotrophins, characterizes neurotrophin signaling during oligodendroglial development, and discusses the significance of proneurotrophins and sortilin for oligodendroglial death and survival. Furthermore, data are provided that TrkA, the tyrosine kinase competent NGF receptor, is localized to caveolin-containing microdomains on the oligodendroglial plasma membrane; an interplay of caveolin and NGF signaling via TrkA might be of functional importance. Finally, experimental evidence of studies is presented which support the idea that neurotrophins are promising candidates for improving oligodendroglial regeneration and remyelination.

Keywords Oligodendrocytes · Neurotrophins · Proneurotrophins · Sortilin · Caveolin

Prolegomenon

Glial cells were originally thought as ‘glue’ for keeping nerve cells in position. In the following, astrocytes, which entered the neural field historically ca. 40 years after the neurons and again ca. 40 years before the name ‘oligodendrocyte’ was coined (Althaus et al. 1984), have caught more interest than oligodendrocytes (OL); they have been accepted as courtiers of neurons suggested for and fulfilling a number of tasks

(Lugaro 1907; Fedoroff and Vernadakis 1986; Nedergaard et al. 2003; Benarroch 2005). In contrast, OL remained as being an essential but unattractive chip in the neural network; they were the jobber that enwrapped the axons with a myelin sheath. This view have begun to change: Developmental studies indicate that neurons, astrocytes, and OL have some properties in common; it has been found that neuronal and astroglial lineages might also give rise to oligodendroglial cells (Williams et al. 1991; Tominaga et al. 2005; Casper and McCarthy 2006; Carmen et al. 2007). In this context, it could not come to such a surprise that OL respond to neurotransmitters during their development, express receptors not only for these but also for growth factors, produce growth factors by themselves, and establish ion channels (Deadwyler et al. 2000; Soliven 2001; Du and Dreyfus 2002; Karadottir and Attwell 2007). Recent studies have added another fascinating facet to the tasks of OL by demonstrating trophic and protective influence of OL to neurons and axons (Du and Dreyfus 2002; Wilkins et al. 2003; Lappe-Siefke et al. 2003; Kassmann et al. 2007). Furthermore, OL and myelin abnormalities might play a role in diseases such as schizophrenia and Alzheimer dementias, which were long thought to originate from neuronal dysfunction alone (Noble 2004; Richter-Landsberg and Bauer 2004; Haroutunian and Davis 2007). Thus, the brain functions properly only when the orchestral network interacts at the right time and in harmony.

Oligodendroglial Cells, Neurotrophins, and their Receptors: A Brief Overview

Oligodendrocytes

Browsing OL literature, the first-glance assessment offers a coherent view of OL properties during oligodendroglial differentiation and maturation. An impression is aroused as

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if ‘the one type of oligodendrocyte’ exists independent of the mammalian species in which it resides. This erroneous conclusion is evoked by the overwhelming number of research articles concerning rodent OL. Publications about OL from other mammalian species such as human, non-human primates, or pigs comprise less than 10% of *in vitro* and *in vivo* investigations. These indicate that results acquired from rodent OL cannot easily be extrapolated (Althaus et al. 1994; Chandran et al. 2004; Miron et al. 2007). However, despite several species differences, OL have some principle pathways in common. In fact, the mammalian oligodendroglial lineage is generated via a time and space controlled process by which members of the sonic hedgehog (Shh)/Patched and Jagged/Notch family and basic-helix-loop-helix (bHLH) transcription factors such as Mash1 and Olig1/2 play a dominant role (Kagawa et al. 2001; Zhou and Anderson 2002; Xin et al. 2005; Fuccillo et al. 2006; Gao and Miller 2006; Nicolay et al. 2007; Wegner, this issue). Developmental stages, which are partly influenced by thyroid hormones, are passed from early bipolar oligodendroglial progenitors (some use the term ‘precursor’ for earlier cells; OLP) to multiprocessed mature OL, which include several differentiation steps of distinct antigenic characteristics and function (Hardy and Reynolds 1991; Pfeiffer et al. 1993; Althaus and Richter-Landsberg 2000; Baumann and Pham-Dinh 2001; Kagawa et al. 2001; Grinspan 2002; Richardson et al. 2006). The mature OL is assumed to be non-proliferating and capable of furnishing and maintaining myelin. Oligodendroglial processes contact axons and enwrap them. In contrast to Schwann cells, where a 1:1 relationship of internode to cell exists, OL can form multiple internodes. Morphological, biochemical, and physiological properties of OL change not only during development but also a local variability and biochemical subpopulations within the central nervous system (CNS) have been described (Butt et al. 1995; Du et al. 2003). Certainly, pathophysiological alterations such as injury, inflammation, aging, or culture conditions can influence the behavior of OL. Seemingly equivocal results in OL research might simply reflect the plasticity of oligodendroglial cells to react to an introduction of various environmental factors. The challenge is to filter those results that are of basic importance and which might be worth to be followed to acquaint more knowledge about diseases that go along with dysfunction and/or degeneration of OL and myelinating deficiencies.

Neurotrophins and their Receptors

Neurotrophins (NTs) constitute a group of six members that is involved in a variety of cellular processes of neural and non-neural cells within a physiological and pathophysiological context (Huang and Reichardt 2001; Sofroniew et al. 2001). NTs interact with two distinct types of trans-

membrane receptors, the Trks (tropomyosin related kinases) and p75^{NTR}, which lack an intrinsic catalytic activity (Chao and Hempstead 1995; Teng and Hempstead 2004; Reichardt 2006). The expression ratio of Trk/p75^{NTR} seems to determine the cellular effects of NTs; in cells in which the p75^{NTR}/Trk ratio is greater than 10:1, p75^{NTR} does independently signal upon binding of nerve growth factor (NGF; Schor 2005). P75^{NTR} is downregulated in the adult (with exceptions) but can be upregulated under pathological conditions (Dechant and Barde 2002; Blöchl and Blöchl 2007). The molecular mechanisms that control the cell-specific expression pattern of Trks and p75^{NTR} await further elucidation (Lei and Parada 2007). P75^{NTR} can interact not only with Trks but also with sortilin, LINGO-1, and NogoR (Mi et al. 2004; Lu et al. 2005; Nykjaer et al. 2005). While all members of NTs bind to p75^{NTR}, the binding of individual NTs is restricted to specific Trks: NGF is the ligand for TrkA, brain-derived neurotrophic factor (BDNF) and NT-4 for TrkB, and NT-3 for TrkC. Signaling downstream of Trk occurs after neurotrophin-mediated dimerization and subsequent autophosphorylation of Trk due to its intrinsic tyrosine kinase activity (Heumann 1994). Further propagation of the initial signal is provided by association of other proteins to the tyrosine-phosphorylated sites of Trk via their SH2 or PTB domain (Pawson et al. 1993; van der Geer and Pawson 1995). The major pathways induced by the Trk receptors are Ras, Rac, PI3-kinase, PLC- γ 1, and their downstream effectors (Reichardt 2006). Parts of the signaling cascades, such as the ERKs end in the cell nucleus, use transcription factors as substrate and alter gene expression (Pearson et al. 2001).

Signaling downstream p75^{NTR} is mediated by several adaptor proteins such as Traf6, NRIF, MAGE, and NRAGE (Roux and Barker 2002; Schor 2005; Reichardt 2006; Zampieri and Chao 2006; Blöchl and Blöchl 2007). Data indicate that the Chopper domain of the p75^{NTR} molecule is the critical death-inducing part (Coulson et al. 2004). P75^{NTR} signals via the generation of ceramide, which promotes both apoptotic and prosurvival pathways (Blöchl and Blöchl 2007). An apoptotic cascade involves JNK, phosphorylation of Bad, accumulation of cytochrome c within the cytosol, and activation of caspases (Bhakar et al. 2003; Weston and Davis 2007). Interestingly and less known is a transient mitogen-activated protein kinase (MAPK) activation via NTs and p75^{NTR}, a pathway that bypasses Raf (Lad and Neet 2003). In addition, p75^{NTR} might act as GDI displacement factor for RhoA (Yamashita and Tohyama 2003).

Altogether, signaling via Trk is largely linked to cell differentiation and survival (Zhang et al. 2000), whereas p75^{NTR} signals cell death, although prosurvival effects have also been reported (Schor 2005; Coulson 2006); a ‘yin and yang’ model of the action of NTs was proposed (Lu et al. 2005).

Processing and Secretion of Neurotrophins

Like other growth factors, NTs are derived from a precursor proform. They are generated from gene transcripts that contain hydrophobic signal sequences followed by pro-regions with a stretch of basic amino acids (Seidah et al. 1996, 1999; Mowla et al. 2001; Fig. 1). The signal sequence is removed within the endoplasmic reticulum resulting in proneurotrophins (pro-NTs) with a MW of 30–36 kDa. Higher molecular weight pro-NTs represent differential-glycosylated forms (Fahnestock et al. 2004a). The pro-NTs enter the Golgi apparatus and accumulate in the TGN. Further proteolytic processing of pro-NTs occurs in the TGN or in secretory vesicles by members of the proprotein convertase family such as furin (Nakayama 1997; Thomas 2002) to yield the mature form (NGF, 13.2–13.5 kDa; BDNF, 14.5 kDa; NT-3, 14 kDa; Seidah et al. 1996, 1999; Fahnestock et al. 2004b). Secretory vesicles of two different types, either small for the constitutive pathway or larger (with a diameter of 100–300 nm) for the regulated pathway, are used for protein transport to the plasma membrane (Lessmann et al. 2003). NGF and NT-3 were found to mainly sort to the constitutive pathway, whereas BDNF is released via the regulated pathway. However, inhibition of furin activity or overexpression of NTs (including formation of heterodimers) or signaling by NTs themselves can direct NTs to the regulatory pathway (Krüttgen et al. 1998; Mowla et al. 1999; Farhadi et al. 2000). Interestingly, an activity-dependent release of pro-NTs could involve a coordinated interaction of extracellular proteases (e.g., plasmin) and their inhibitors to regulate extracellular conversion of pro-NTs to the mature form (Bruno and Cuello 2006).

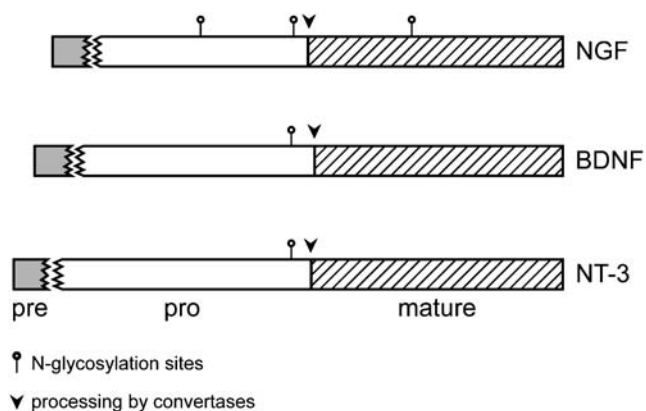


Figure 1 Schematic depiction of major proneurotrophins (pro-NTs): The signal (pre) sequence (gray) directs its pre-proneurotrophin to the endoplasmic reticulum, where it is cleaved off; further proteolytic processing of the resulting proneurotrophins (open plus hatched) with a MW of 30–36 kDa is executed by pro-protein convertases present in TGN and secretory vesicles; mature NTs (hatched) are released either by the constitutive or the regulated pathway (adapted from Jones and Reichardt 1990)

Proneurotrophins, Predominant Species in the Brain

Precursors of mature NTs have been identified already since two decades. The functional role of the prodomain was attributed to correct folding of the mature protein and sorting into the one or other secretory pathway. Interest in biological activity of pro-NTs was aroused with the finding of Fahnestock et al. (2001), who detected pro-NGF and almost no mature NGF in various areas of human, mouse, and rat brain tissue; whether present intracellular or secreted remained open. Similarly, a later study revealed pro-BDNF as the predominant species in human brains with weak staining for mature BDNF (Peng et al. 2005). Interestingly, pro-BDNF was found to be localized predominantly in nerve terminals (Zhou et al. 2004).

Oligodendrocytes and Other Cellular Sources of Neurotrophins in the CNS

In principle, neural and non-neural cells of the CNS could synthesize and release NTs being effective in a paracrine and/or autocrine way. Rodent OL have been reported to express a number of growth factors including NGF, BDNF, and NT-3 (Althaus and Richter-Landsberg 2000; Du and Dreyfus 2002). Neuronal signals were found to regulate the expression of NTs in OL of rat basal forebrains (Dai et al. 2001). However, NGF was not detectable in mature OL of injured rat spinal cord (Krenz and Weaver 2000). In mature pig OL, NGF mRNA was not detected in Northern blots (Althaus et al. 1997); the cells also remained negative for NGF immunocytochemically (Althaus and Klöppner 2006). In contrast, oligodendroglial progenitors derived from human embryonic stem cells expressed various growth factors including NGF, BDNF, and NT-3 (Zhang et al. 2006).

Cortical neurons and basal ganglia can produce NTs with regional variability (Krause et al. 2007). Strong evidence exists that astrocytes produce NTs (Althaus 2004). Various components such as interferon- β or dexamethason induce or suppress the expression and secretion of NTs by astrocytes (Althaus and Richter-Landsberg 2000; Allen and Dawbarn 2006; Reichardt 2006). Non-neural synthesis of NTs was detected in macrophages/microglia, in cerebral endothelial cells, in lymphocytes of inflammatory brain lesions, and in choroid plexus cells (Althaus 2004). In almost all reports of this kind, it remains to be investigated as to whether mature NTs or pro-NTs were released.

Oligodendrocytes Express Neurotrophin Receptors

OL of rodent, pig, non-human primate, and human origin express p75^{NTR} (Althaus and Richter-Landsberg 2000).

Relatively low levels of p75^{NTR} are upregulated in rat oligodendroglial progenitors and downregulated after the axon has been contacted (Cohen et al. 1996). Such a clear picture does not emerge for the Trks of rodent OL. Previous reports agreed that rat OL do not express TrkA (Kumar et al. 1993; Casaccia-Bonnel et al. 1996) but express TrkC (Kumar and deVellis 1996), which is downregulated when OL mature (Barres et al. 1994). Subsequent *in vitro* studies reported about a more complex situation: Full-length TrkC was present throughout oligodendroglial differentiation; TrkA_I was expressed in oligodendroglial progenitors with decreasing expression in differentiated OL, while the ‘neuronal’ TrkA_{II}, with the additional 18-bp insert, which confers binding to NT-3, was detected only in mature rat OL. In addition, truncated TrkB and TrkC isoforms were found (Cohen et al. 1996; Kumar and deVellis 1996). A slightly different picture was reported by Kavanaugh et al. (2000), where TrkC and TrkA were also demonstrated but with an increase of TrkA expression in more mature OL. A variation of the theme was noted by Robinson and Miller (1996) in that optic nerve OLP expressed TrkC, while those from the spinal cord did not. Basal forebrain OL also expressed TrkB in a subset of OL (Du et al. 2003).

Northern blots of mature pig OL revealed the presence of TrkA mRNA and p75^{NTR}; TrkA mRNA but not p75^{NTR} mRNA was upregulated during culturing and also by adding NGF to the culture medium. Transcripts of TrkA could not be revealed for cultured adult human OL, while p75^{NTR} was detected (Ladiwala et al. 1998). In contrast, others detected TrkA and p75^{NTR} (Althaus et al. 2001; Althaus 2004). A further source of information about the expression of neurotrophin receptors on human OL comes from MS lesions. However, no unique picture arises: A presence or even an upregulation of p75^{NTR} was detected at least in subsets of OL and OLP (and microglia) (Dowling et al. 1999; Chang et al. 2000); in contrast, Valdo et al. (2002) found immunoreactivity for p75^{NTR} on astrocytes while the vast majority of OL and OLP did not express p75^{NTR}. These groups could not detect TrkA, but TrkA mRNA and p75^{NTR} mRNA were shown to be expressed in human optic nerves affected by MS (Micera et al. 1999).

Localization of Trk on the Pig Oligodendroglial Plasma Membrane

Investigations of Simons and van Meer (1988) have shown that the plasma membrane is organized in lipid (cholesterol and glycosphingolipids)-rich domains. These membranous ‘platforms’ or ‘rafts’ are also designated as ‘detergent-resistant membranes’ because of their insolubility in Triton X-100 at 4°C (Kurzchalia and Parton 1999). The rafts,

though hotly debated (Pierce 2004), seem to compartmentalize signaling components (Simons and Toomre 2000). Trks are considered as growth factor receptors permanently associated with lipid rafts (Paratcha and Ibanez (2002). In this case, activation of receptors results in signaling via components of the signaling cascade already present in the rafts. Specialized forms of rafts are those that contain caveolin. A functional co-localization of neurotrophin receptors and caveolin-containing microdomains (CMD) were already shown for PC12 cells (Bilderback et al. 1999; Huang et al. 1999; Peiro et al. 2000).

Pig OL express caveolin-1, and as shown by confocal laser microscopy, TrkA and caveolin immunoreactivity was colocalized (Fig. 2). Furthermore, classical, flask-shaped caveolae could be observed by transmission electron microscopy (Fig. 2). Density gradient fractionation of oligodendroglial lysates according to Song et al. (1996) resulted in three fractions, which were enriched in caveolin, flotillin, cholesterol, and signaling components such as TrkA, p75^{NTR}, Erk1/2, and p21Ras; TrkA co-immunoprecipitated with caveolin. Oligodendroglial plasma membrane fractions (isolated via magnetic beads) were exposed to Triton X-100 at 4°C; TrkA and caveolin-1 partitioned in soluble and insoluble fractions. No translocation of TrkA to the detergent-resistant fraction occurred after NGF binding. This indicates that TrkA and caveolin are probably not exclusively organized in detergent resistant, lipid-rich rafts at the plasma membrane.

Neurotrophin Signaling in Oligodendrocytes

The picture that emerges for the signaling cascades induced in OL after binding of NTs to their respective receptors is as yet fragmentary, in particular for OLP. The major routes that operate in neuronal cells are also followed in mature OL. In general, NTs can elicit fast and long-term actions (Berninger and Poo 1998); the latter means fast signaling and running into sustained response. An example for an acute effect could be demonstrated by a rapid, transient increase of [Ca²⁺]_i in regenerating pig OL; this occurred within 2 min and was dependent on extracellular Ca²⁺ and on Ca²⁺ release from internal stores (Engel et al. 1994). The cells were able to respond to several NGF pulses within a time frame of minutes; whether p75^{NTR} contributes to this increase of [Ca²⁺]_i is unknown. A rapid effect of NTs on growth cone motility as described for neurons has as yet not been reported, but changes in p21Ras activity may trigger an acute response on the outgrowth of regenerating oligodendroglial processes via Rho proteins (Klopffleisch 2007).

Long-term actions are initiated via Trk or p75^{NTR}. Concerning Trk, the already well-known pathways (see above) are followed in OL by association of adaptor proteins to the respective docking sites (Althaus et al. 1997; Althaus

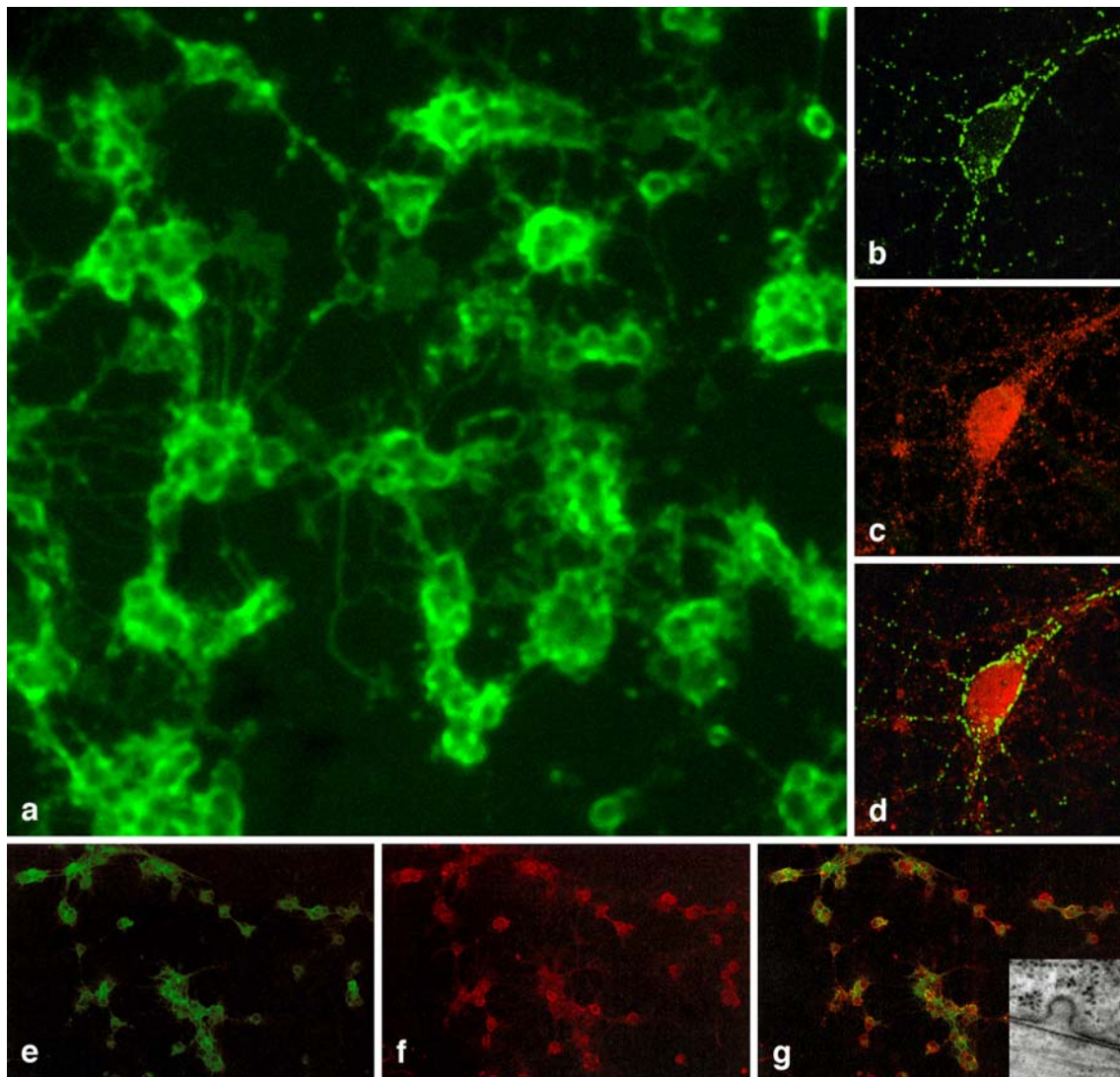


Figure 2 Mature pig oligodendrocytes (OL) express caveolin: Anti-MOG identified the isolated cells as mature OL (a); by using MOSP (anti-MOSP-IgM; Alexa Fluor 488-green conjugated anti-IgM as second antibody) as marker for OL (b) and anti-caveolin (IgG; Alexa Fluor 546-red conjugated anti-IgG as second antibody) (c) evidence was provided that OL express caveolin (d); confocal microscopy revealed when OL were double labeled with anti-TrkA (IgG; Alexa

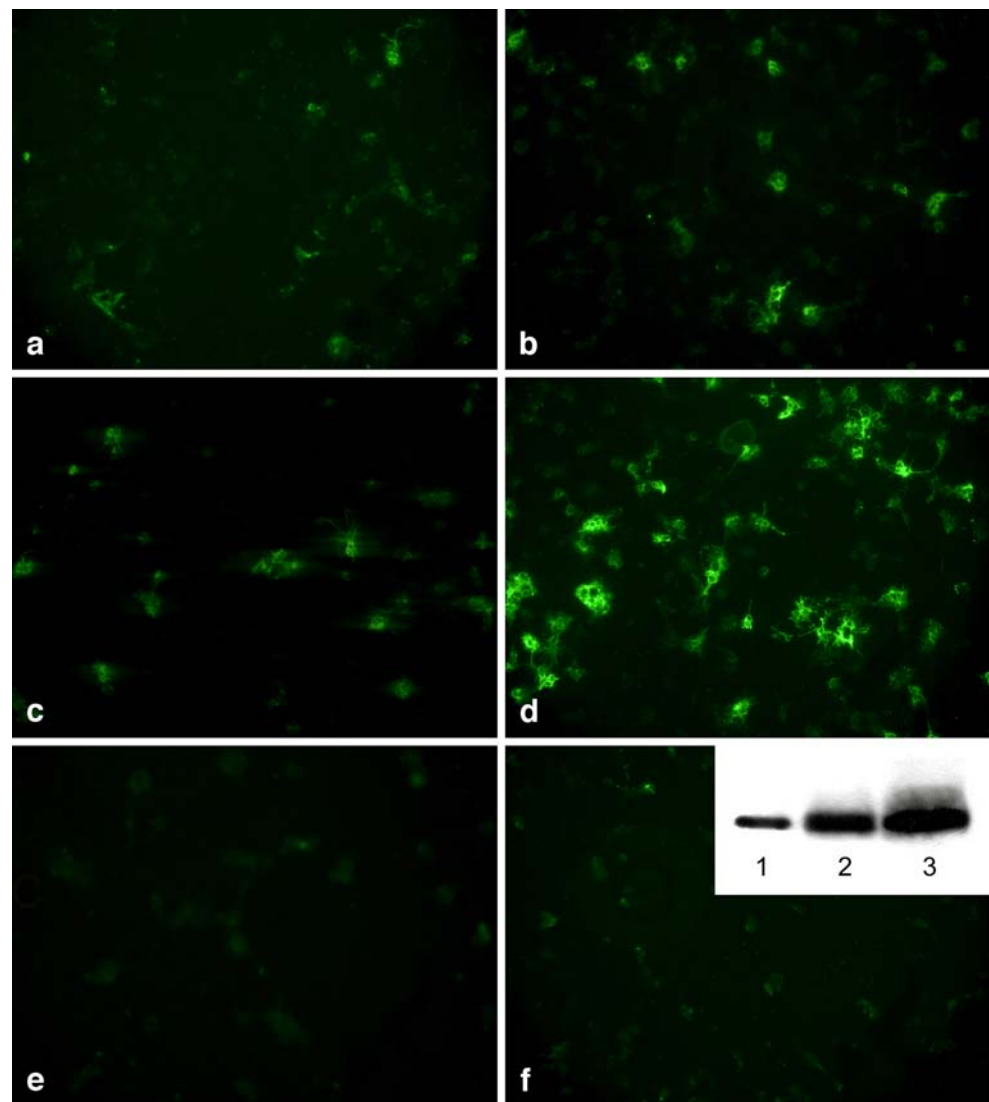
Fluor 488 conjugated anti-IgG as second antibody) (e) and anti-caveolin (IgM; Alexa Fluor 546 conjugated anti-IgM as second antibody) (f) that TrkA and caveolin largely co-localize (g=e+f merged); TEM of the oligodendroglial plasma membrane demonstrated the presence of caveolae of which a typical flask-shaped form is shown (g-inset)

and Richter-Landsberg 2000). They are responsible for the effects of NTs on survival, proliferation, and differentiation of OL. Major cascades downstream Trk are the MAPKs. Members of this family are the ERKs, which have been shown to be involved in oligodendroglial process extension and proliferation (Stariha and Kim 2001). The nuclear translocation of ERKs induces the expression of immediate-early genes. An indicator protein for such an effect is c-fos, which was detectable after 30 min, increased over 2 h, and was no longer visible immunocytochemically after 6 h (Althaus et al. 1997). The role of ERK5 and MEF2, which are also expressed in pig OL, remains to be investigated, but

both could be involved in regulating the intracellular concentration of c-Jun (Pearson et al. 2001) and in a neurotrophin-dependent survival of newly generated OLP as described for granule neurons (Shalizi et al. 2003).

The upregulation of caveolin by NGF and the reduced potential of NGF to stimulate oligodendroglial process regeneration after caveolin knockdown (Schmitz 2006) indicated a functional importance of CMD for neurotrophin signaling. In addition, caveolin was phosphorylated (caveolin-1pY14) when the cells were exposed to NGF (Fig. 3); c-Src, which might associate with TrkA (Tsuruda et al. 2004), seems to confer this phosphorylation (Schmitz 2006).

Figure 3 NGF induces phosphorylation of oligodendroglial caveolin: Pig OL were exposed to NGF, which induced phosphorylation of caveolin at tyrosine14 (Cav-pY14); labeling with anti-cav-pY14 showed that a few cells express phosphorylated caveolin under normal culture conditions (**a**); an increase of cav-pY14 can be observed during NGF exposure (**b** 10 min, **c** 1 h, **d** 6 h) immunocytochemically and by Western blotting (**f**-inset: *lane1*=control; *lane2*=cavpY14 10 min, *lane3*=6 h of NGF exposure); caveolin phosphorylation could be inhibited by PP2, an inhibitor predominantly of c-src kinases (**e**) and by K-252a, an inhibitor of TrkA phosphorylation (**f**)



Caveolin-1pY14 in turn could provide a further docking site for Trk signaling (Lee et al. 2000, 2006). Interestingly, cavtratin, a membrane permeable derivative of the caveolin-scaffolding domain (CSD; Song et al. 2007), inhibited NGF-induced TrkA phosphorylation and subsequent ERK activation.

A number of factors such as cell stress or TNF- α involve ceramide and SAPK/JNKs activation, which could finally result in cell death. The role of p75^{NTR} in this context will be discussed in more detail below. Previous results showed that rat OL, which expressed p75^{NTR} only, underwent cell death when treated with NGF (Casaccia-Bonnel et al. 1996) but were rescued when missing TrkA was introduced (Yoon et al. 1998). In this context, it is interesting to note that cultured human OL did not undergo cell death when exposed to NGF, although p75^{NTR} and no Trk was detected;

activation of JNK was not observed but, instead, a nuclear translocation of NF κ B (Ladiwala et al. (1998).

Oligodendroglial Development: Neurotrophins and Other Growth Factors

A number of growth factors, cytokines, and chemokines have been found to exert an effect on rodent OL during oligodendroglial development (Baumann and Pham-Dinh 2001; Grinspan 2002; Filipovic and Zecevic 2008). Their action is best investigated during the oligodendroglial stage of progenitors and immature OL and less when OL are mature. Their influence might be limited to a certain developmental window (depending on the expression of the specific receptor) and can be inhibitory or promoting; in

some cases, at least under *in vitro* conditions, a combination of their effects seems to be necessary to be effective (Barres et al. 1993). Most of the individual specific receptors are downregulated at the latest when OL mature.

Which roles do NTs play during oligodendroglial development? Previous *in vitro* studies gave conflicting results as to whether uncommitted neuroepithelial cells can be induced by NTs to give rise to a neuronal or glial lineage. In one report (Johe et al. 1996), none of the NTs tested (NGF, BDNF, and NT-3) had any significant effect on cell type determination, while in the other (Lachyankar et al. 1997), it was described that most of the cells expressed receptors for NTs. Exposing the cells either to NGF or BDNF produced neurons and astrocytes, whereas NT-3 induced GalC-positive OL. Obviously, additional environmental signals such as the extracellular matrix (Baron et al. 2005) modulate the expression and influence of growth factors. Murine embryonic stem-cell-derived neural progenitors gave rise to neurons and OL when cultured with Shh and NT-3, whereas PDGF and bFGF enhanced cell viability (Willerth et al. 2007). In this context, it is interesting to note that mice lacking functional TrkC were deficient in OL (Kahn et al. 1999). The effects of eight growth factors including NGF on the differentiation of cells derived from human embryonic stem cells (HESC) were investigated (Schuldiner et al. 2000). Their effects were divided into three categories, with NGF and HGF in one category allowing differentiation into the three embryonic germ layers. None of the growth factors directed differentiation exclusively to one cell type (Schuldiner et al. 2000). In other experiments, HESC did not differentiate to OLP under standard conditions (withdrawal of FGF) but, surprisingly, when PDGF-A was added to the culture medium (Zhang et al. 2001). Unfortunately, the timing of the expression of neurotrophin receptors on HESC was not investigated during a more elaborated procedure for obtaining cells of the oligodendroglial lineage (Nistor et al. 2005), as it was shown later that these cells produce NTs (Zhang et al. 2006) offering the possibility of an ongoing autocrine loop during differentiation.

The route of differentiation from OLP to mature OL is further accompanied by NTs. For rat optic nerve OLP, NT-3, but not NGF or BDNF, provided survival when combined with other growth factors (Barres et al. 1993) and was mitogenic when combined with PDGF and insulin (Barres et al. 1994). A proliferative effect of NT-3 in combination with insulin was also observed for rat brain OLP (Cohen et al. 1996). In addition, it was found that NT-3 promoted process formation and arborization of OLP and enhanced the presence of GalC-positive cells thereby influencing differentiation (Heinrich et al. 1999). Intracranial injections of NT-3 into the rat brain potentiated the proliferation of OLP *in vivo*

(Kumar et al. 1998). The so-called rodent neonatal O-2A progenitors, which develop into OL when transplanted *in vivo* (Espinosa de los Monteros et al. 1993), express TrkA and TrkC and p75^{NTR}; MAPK was activated by NGF and NT-3, however, more sustained by NT-3. NT-3 enhanced the proliferation and survival of O-2A cells, whereas NGF and NT4/5 needed the co-administration of FGF-2 and PDGF-AA (Cohen et al. 1996; Scarisbrick et al. 2000). Human OLP expressed markers equivalent to those of rodent OLP, and PDGF, NT-3, and GGF-2 promoted proliferation (Wilson et al. 2003). However, some evidence exist that human and rodent OLP respond to mitogens differently (Sato and Kim 1994; Filipovic and Zecevic 2008).

In the adult CNS, two types of OL are relevant: the mature OL and the so-called adult O-2A cell or, better to say, the adult OLP (Grinspan 2002). The latter stains positive for NG2 but constitutes only a small fraction with less than 1% of the total NG2 + population (Berry et al. 2002). Whether this adult OLP can be induced to proliferate remains controversial; at least, NT-3 was not mitogenic for adult OLP of the rat spinal cord (Engel and Wolswijk 1996). The number of OLP in the adult human brain was estimated to be 1–4% which contrasts to another statement that NG2 + OLP are as abundant in the normal human brain as astrocytes (Chang et al. 2000), but see above. Their proliferative response to NTs was tested with a negative result (Scolding et al. 1995).

The survival of mature OL derived from rodent brain is supported by NGF and NT-3 (Cohen et al. 1996). A fraction of mature OL from pig brain (15–20%) could be induced by NGF but not by PDGF and FGF to proliferate (Althaus et al. 1992). Several growth factors including NGF were tested for their ability to induce proliferation of adult human OL, however, with a negative result (Kim and Yong 1990). On the other hand, NGF promoted process regeneration (Althaus et al. 2001).

In summary, the developmental profile of the oligodendroglial lineage is best investigated in rodents. From the embryonic neuroepithelial cell on, the fate and further differentiation are determined by intrinsic and extrinsic cues. Under *in vivo* conditions, growth factors act probably in concert to achieve full effectiveness. NTs seem to function together with other growth factors, and no special task or key functions are apparent as described for Schwann cells in the PNS (Notterpek 2003). Some results in terms of NT-3 dysfunction (Barres et al. 1994; Kahn et al. 1999) indicate that NTs are components to which not only a supportive role (Grinspan 2002) should be conceded. Whether NTs contribute to cell death during oligodendroglial development via the early expressed p75^{NTR} remains to be investigated. Much less is known about the functions of NTs during the ontogenesis of OL from other mammalian species. One has to keep in mind that the set of growth factors

operating is apparently different to that of rodents (Althaus et al. 1994).

Oligodendroglial Survival and Cell Death In Vitro and In Vivo

Early on, a publication of Barres et al. (1993) suggested already that axons may control the levels of oligodendroglial survival factors during development and that oligodendroglial cell death was prevented by an exogenous delivery of such factors; these included NGF and NT-3 (Barres et al. 1994; Cohen et al. 1996). However, NTs are also protective in other conditions that cause oligodendroglial cell death. For example, NGF prevented TNF- α -mediated oligodendroglial cell death by activating the Akt pathway (Takano et al. 2000) while NT-3 and, to a lesser extent, NGF protected the cells against AMPA-GluR-induced excitotoxicity at least partially (Kavanaugh et al. 2000). It is interesting to note that AMPA does not induce a significant percentage of cell death of mature pig OL (Althaus et al., unpublished observation).

p75^{NTR} may operate in two different ways: either it cooperates with Trks or it may signal on its own. An example of the first possibility is given by the experiments of Du et al. (2006): TrkA, TrkB, and TrkC colocalized with p75^{NTR} on basal forebrain OL, whereby NGF and NT-3 used both receptor types for mediating their actions as demonstrated by p75^{NTR} knockout animals. A report about cell death of a cell line transfected with p75^{NTR} was the first indication that p75^{NTR} signals on its own (Rabizadeh et al. 1993). Oligodendroglial research met cell death signaling via p75^{NTR} and NGF with the experiments of Casaccia-Bonnel et al. (1996); a subsequent paper showed that introducing TrkA expression in OL rescued the cells (Yoon et al. 1998). Since publications at that time reported about an expression of only p75^{NTR} on human OL in vitro and on OL of MS lesions (see above), it was speculated that oligodendroglial cell death in MS might occur via p75^{NTR}. However, Ladiwala et al. (1998) could not observe oligodendroglial cell death when exposing the cells to NGF, and Althaus (2004) demonstrated an expression of TrkA on human OL. Nevertheless, a decisive imbalance of Trk to p75^{NTR} in favor of the latter could occur under pathological conditions, which would favor cell death rather than survival (Hennigan et al. 2007). Results of Starkey et al. (2001) are in contrast to this view: isolated OL from rat cerebrum and cultured for 16 h expressed p75^{NTR} and TrkC but not TrkA; cell viability was not influenced by exposure to NGF. Furthermore, cells overexpressing p75^{NTR} remained unresponsive to NGF. These authors concluded that upregulation of p75^{NTR} alone is insufficient to promote cell death; an additional induction of other downstream death signaling is required. Given that culture conditions can be regarded as pathologic, it is of

interest to note that, in mature pig OL, TrkA but not p75^{NTR} was upregulated (Althaus et al. 1997).

Cell death via p75^{NTR} occurred when cells were exposed to relatively high concentrations of NGF (Ibañez 2002). A new chapter of the p75^{NTR} story was opened with the finding that pro-NGF is a high affinity ligand for p75^{NTR} (Lee et al. 2001). The general conclusion was that the biological action of NTs depends on the proteolytic cleavage of their proforms either intra- or extracellularly: Proforms preferentially activate p75^{NTR} to mediate apoptosis, and mature forms promote survival via Trk receptors. A number of subsequent studies supported the view that pro-NTs play an important role within the CNS (and elsewhere) under physiological and pathological conditions (Twiss et al. 2006). From the oligodendroglial point of view, two reports should be mentioned. They provided evidence that pro-NGF induces oligodendroglial cell death either after rat spinal cord injury (Beattie et al. 2002) or during development of hypothyroid rat brains (Kumar et al. 2006). Astrocytes and microglial cells have been found as major sources for a release of pro-NTs (Srinivasan et al. 2004; Domeniconi et al. 2007; Yune et al. 2007), while Müller glia secreted mature NTs and proforms (Taylor et al. 2003).

A further remarkable step to connect p75^{NTR} to the action of pro-NTs was made by Nykjaer et al. (2004). Two findings of this report are of particular interest: first and most importantly, sortilin was identified as a decisive element, which led to an increase in the affinity of pro-NGF to p75^{NTR}, while pro-NGF per se binds equally well to p75^{NTR} and TrkA but with a tenfold lower affinity. A ternary complex of pro-NGF/sortilin/p75^{NTR} is built with pro-NGF as crosslinker (Nykjaer et al. 2004; Nykjaer et al. 2005) thereby transducing death signals efficiently. Second, wild-type pro-NGF induced apoptosis as effectively as a furin-resistant pro-NGF. While the expression of pro-NTs is largely linked to cell death, was the presence of pro-NGF differentially interpreted by others (Fahnestock et al. 2004b; Buttigieg et al. 2007). Their assumption is simply founded on the finding that pro-NGF and pro-BDNF are the dominant forms in normal CNS. They hypothesize that, while pro-NGF exhibits neurotrophic activity but is less active than mature NGF, pro-NTs serve for normal neurotrophic activity in most tissues; they are upregulated in injuries together with proteases, which cleave off the pro-sequence (Fahnestock et al. 2004a). In partial agreement with this idea of a condition-dependent cleavage of pro-NTs are findings of Bruno and Cuello (2006) who outlined a scenario in which an activity-dependent concerted action of released pro-NGF and proteases takes place. A cleavage-resistant pro-NGF, constructed differently to the one of Lee et al. (2001), stimulated neurite outgrowth of SCG neurons and PC12 cells and activated MAPK via TrkA phosphorylation (Fahnestock et al. 2004a). In accordance with these results are those by

Fayard et al. (2005), who constructed a furin-resistant pro-BDNF. Their data indicated that pro-BDNF binds to and activates TrkB. Another support came from investigations on mature pig OL (Althaus and Klöppner 2006). Pig OL rapidly processed non-mutated human recombinant pro-NGF (rhproNGF) and did not undergo cell death, although the cells expressed sortilin (Fig. 4) and p75^{NTR}. Hence, wild-type pro-NGF per se is not sufficient to induce cell death when OL concomitantly express TrkA. Of note is that experimental evidence pointed to an intracellular cleavage of rhproNGF; pig OL efficiently endocytosed exogenous rhproNGF (Fig. 4) and released mature NGF into the culture medium. Whether sortilin is an active participant in this endocytotic process remains to be answered. Furthermore, rhproNGF and mature NGF enhanced oligodendroglial processes regeneration and Erk1/2 activation similarly. Two different cleavage-resistant pro-NGFs (provided by M. Fahnstock and B. Hempstead) also stimulated Erk1/2 activation in pig OL (Fig. 4). However, one has to admit that higher concentrations were used as for inducing a morphological response via mature NGF.

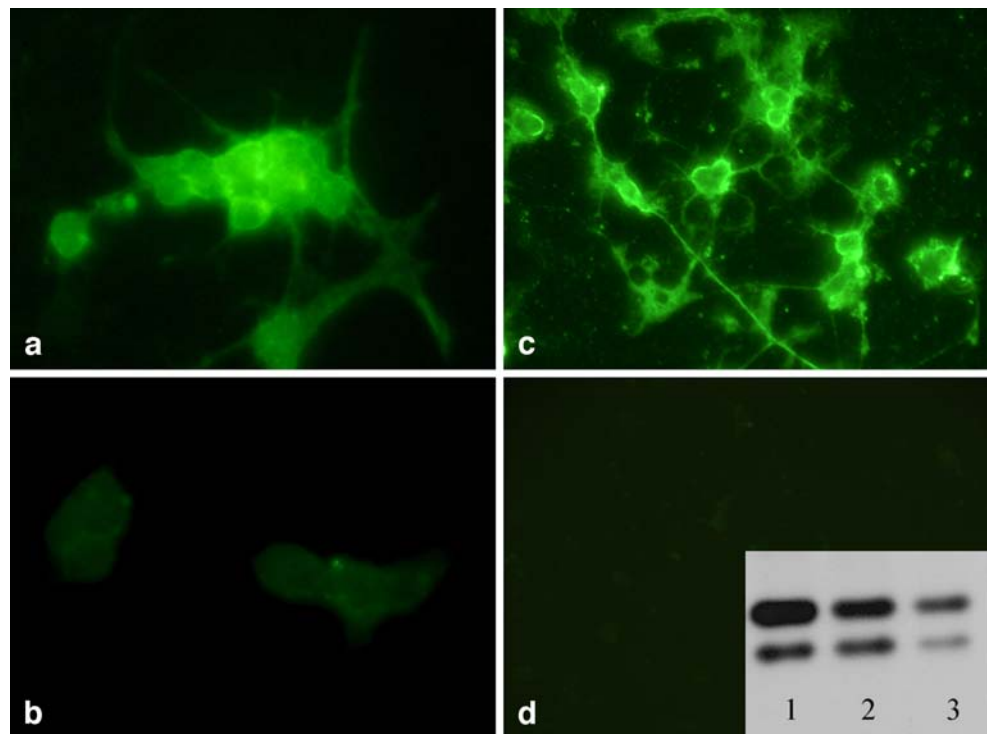
Two important points with relevance for studying oligodendroglial cell death under pathological conditions were raised in a short paper by Nakamura et al. (2007). First, they investigated the intracellular sortilin expression in mouse retinal ganglion cells (RGCs). The majority of sortilin (80–90%) resided in intracellular membranes (particularly in the Golgi apparatus), and the remaining was localized on the cell surface. In E15 retina, where sortilin was mainly detected in the plasma membrane colocalized with p75^{NTR}, pro-NGF

enhanced the death of E15 RGCs. In contrast, in the postnatal retina, where sortilin expression had changed to the intracellular region and colocalization with p75^{NTR} was lacking, cell death via pro-NGF was no longer observed. Second, an ischemic injury was set in the adult retina by occluding the retinal artery. Pro-NGF increased 24 h thereafter, but no change in the p75^{NTR}/sortilin expression pattern was observed; the ischemic injury was almost identical in wild-type and in p75^{NTR} knockout mice (Nakamura et al. 2007). Hence, a hypothetical scenario for a CNS injury could be: apoptosis occurs, p75^{NTR} and pro-NGF are upregulated to some extent; however, these findings are unrelated to each other because sortilin is not sufficiently expressed on the plasma membrane.

Neurotrophins Support Oligodendroglial Regeneration and Remyelination

Myelination and remyelination is a multi-step process: oligodendroglial (or Schwann cell in the PNS) processes contact axons and enwrap them spirally; finally, a partial compaction of the layers occurs, sparing inner, outer, and paranodal loops. Rarely, other structures than axons are myelinated. It indicates that not only several, specific positive and inhibitory factors (membrane-bound and diffusible) control myelin formation but also that unspecific components might be inherent (Althaus et al. 1987). Stimulating signals are necessary to allow and activate OL to synthesize myelin products, which exceed the own weight of the cells by far. In

Figure 4 Oligodendrocytes (OL) and pro-NGF: When mature regenerating OL (8 DIV) were exposed to pro-NGF, they became positively labeled for pro-NGF within 10 min as revealed by anti-pro-NGF (Chemicon) and an Alexa Fluor 488 (green) conjugated second antibody (a), no labeling was observed in controls (b no exposure to pro-NGF); the cells express sortilin as shown with anti-sortilin (IgG; BD Biosciences) (c), no staining in controls (d without first antibody), a predominant plasma membrane staining seems to be apparent; cleavage-resistant pro-NGF activated oligodendroglial ERK1/ERK2 by using NGF concentrations as for NGF-induced accelerated process regeneration (50 ng/ml) (inset: 1 mutated pro-NGF of M. Fahnstock; 2 mutated pro-NGF of B. Hempstead; 3 control; exposure time 6 h)



the light of recent results, an involvement of NTs and their receptors in myelination and remyelination of the CNS seems to be a route worth to be explored. An interesting facet was recently added by showing that NGF promoted myelination of TrkA-expressing sensory neurons (B-cells) of DRG by Schwann cells, whereas myelination by OL was inhibited (Chan et al. 2004); it contradicted the common held view that axonal signals are similarly valid for Schwann cells and OL. Some experimental details might evoke a comment: for example, although DRG cells of mice lacking p75^{NTR} show a predominant loss of small B-cells (Dreetz Gjerstad et al. 2002), cocultures of OL and DRG cells exhibited a similar inhibitory effect on myelination via NGF as the wild type; some subsets of DRG cells co-express TrkA, TrkB (Rifkin et al. 2000), and c-ret (Huang and Reichardt 2001). In addition, a negative finding of TrkA for OL is in contrast to the results of Cohen et al. (1996). Nevertheless, the conclusions drawn are intriguing: Firstly, NTs regulate myelination by a direct action on myelinating glial cells and, secondly, indirectly by influencing axonal signals. Candidates for these axonal signals could be growth factors such as BDNF, GDNF, or neuregulin, expressed in TrkA + DRG cells (Rosenberg et al. 2006). In this context, LINGO-1, already known as inhibitor of OLP differentiation (Mi et al. 2004), acts as an inhibitor of oligodendroglial differentiation also when expressed on axons, and NGF upregulates LINGO-1 expression on DRG cells (Lee et al. 2007). Whether these findings can be generalized to all neuronal/oligodendroglial interactions, and whether they can be extrapolated to other mammalian species, remains an open question.

Remyelination is thought to be a process in which myelination is recapitulated. *In vitro* and *in vivo* studies indicate that remyelination occurs and can be enhanced by growth factors. One of the first studies was performed by McTigue et al. (1998) who transplanted fibroblasts engineered to express BDNF and NT-3 into the injured spinal cord. This resulted in an enhanced axonal growth, OLP proliferation, and improved myelination. Similar experiments with similar results supported the view that NTs could help to improve remyelination (Cao et al. 2005; Girard et al. 2005). In another model, young-adult minipigs were used for producing demyelinated lesions in both sites of the corpus callosum via lysolecithin. In this model, after 10 days, almost completely demyelinated areas had developed at the site of injections. Superfusing these lesions either with NGF or with phosphate-buffered saline as control for another 10–12 days resulted in an intense remyelination for the NGF-superfused area (Althaus 2004). However, despite many examples of successful remyelination in animal models, pathological *in vivo* conditions in humans such as spinal cord injury and demyelination in MS still await a therapeutical breakthrough. NTs could certainly be an option to improve the situation (Althaus 2004; Villoslada et al. 2004) provided they are used at a time before local

alterations such as axonal loss or astrocytosis (Rice and Scolding 2007) impair any possible remyelination.

Conclusion

OL and neurons are phenomenologically unique cell types that have several basic features in common: Both cell types elaborate numerous processes with terminal ends being specialized in form and function. Beyond that, recent and ongoing research indicates that they also have a closer functional interrelation than previously thought. Without any doubt, research on mice and rats has provided a basic and closer insight into oligodendroglial differentiation and properties. However, these results cannot simply be extrapolated to the final target, the human being, in most cases. Hence, an animal model that fills the gap between rodents and humans is desirable. In this respect, the minipig can be very instrumental; it also meets the need to study a larger, practicable animal. Myelination in minipigs proceeds very similar to that in humans. Not to mention that BDNF was originally isolated from pig brain (Barde et al. 1982). Furthermore, a recent publication on porcine neural precursor cells, demonstrating many characteristics of their human counterparts (Schwartz et al. 2005), underlines that neurobiological research on porcine nervous tissue should be pursued, not least in terms of cell transplantation and research on activation of intrinsic progenitor cells.

The oligodendroglial lineage is relatively well investigated during its ontogenesis in rodents but, rather, fragmentary in porcine or human brains. The matter of aging has as yet rarely entered the field of oligodendroglial research, but an increase of proneurotrophins in aged tissues including nervous tissue was established (Bierl and Isaacson 2007). Growth factors influence OL during their development as they do with other cells. Neurotrophins play an important role in this concert. In contrast, the action of proneurotrophins during the differentiation period is less well investigated. In particular, it is of interest to know the role of p75^{NTR} and their co-receptors. Interestingly, sortilin exhibits the highest accumulation with ongoing development of the forebrain (Hermans-Borgmeyer et al. 1999). Some results support the idea that NTs are promising candidates for improving remyelination and thus ameliorating MS. A critical point for making a treatment with neurotrophins effective is the need to achieve a local concentration in a range of 1–10 ng/ml, which is way beyond the endogenous level (pg range; Lorigados et al. 2001). Several possibilities exist to circumvent the blood–brain barrier, which is impermeable for NTs under normal conditions (Althaus 2004; Blesch 2006). However, as the neurotrophin melody for OL runs in major and minor, proneurotrophins and p75^{NTR} should be considered as

possible targets in an eventual therapeutic concept adjusted to NTs (Soilu-Hänninen et al. 2000; Twiss et al. 2006).

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