Chapter 17
TGF-β in Brain Disorders

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Abstract Transforming growth factor beta (TGF-β) is known to regulate numerous cell functions in the nervous system development, adult maintenance, and degeneration. TGF-β carries roles in neurons and glia and is involved in the regulation of proliferation, differentiation, neuron survival and death, as well as orchestrating its response to lesion. In the context of brain disorders the current understanding of TGF-β action is discussed for brain tumors, neurodegenerative disease, such as Alzheimers' and Parkinson's disease, in insults such as ischemia, stroke, and vascular damage, as well as changes in neuronal activity, such as hyperactivity as seen in epilepsy, or in neuronal depression.

Keywords Cell cycle regulation • ECM • Neuroprotection • Cell death • Blood • Neurons • Astrocytes • Microglia • Myelination • Neurogenesis

Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
Alk	Activin-receptor like kinase
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursos protein
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
Cdk	Cyclin-dependent kinase
CNS	Central nervous system

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CNTF	Ciliary neurotrophic factor
CSF	Cerebrospinal fluid
E	Embryonic day
ECM	Extracellular matrix
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
Fox	Forkhead box
GDNF	Glial cell line-derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GFRα	GDNF receptor
Id4	Inhibitors of DNA binding/differentiation
TIEG	TGF-β immediate early gene
IL	Interleukin
Kir	Inward recitfying potassium channels
MGP	Matrix GLA protein
MHC	Major histocompatobility class
MMP	Matrix metalloproteinase
MPP+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Multiples sclerosis
NGF	Nerve growth factor
PAI	Plasminogen activator inhibitor
PD	Parkinson's disease
PDGF	Platelet-derived growth factor
PNS	Peripheral nervous system
SOD	Superoxide dismutase
TGF- β	Transforming growth factor β
TβR	TGF-β receptor
TNF-α	Tumor necrosis factor α
TRAF	TNF-α receptor associated factor
t-PA	Tissue plasminogen activator
VEGF	Vascular endothelial growth factor

17.1 Introduction

The isolation and characterization of transforming growth factors-β (TGF-β) by Anita Roberts has introduced a versatile extrinsic signaling molecule affecting numerous events in the life of almost each cell (Roberts and Sporn 1990; Derynck et al. 1985). Best characterized events include the regulation of cell cycle, composition of the extracellular matrix (ECM), and thereby cell migration or differentiation, as well as regulation of cell survival and death. Imbalance of TGF-β availability is therefore likely to affect tissue development, maintenance, and homeostasis. This certainly also accounts for the nervous system. Once accepted that TGF-β is also expressed in the nervous system, the functional contribution of TGF-β is now more

and more understood in numerous events in the development of the nervous system, its maintenance, and consequently also in the context of many brain diseases. This review will discuss the current knowledge of TGF-β in brain development and function and consequently in brain disorders.

Brain disorders include brain tumors, neurodegenerative disease, such as Alzheimers' disease and Parkinson's disease, insults such as ischemia and stroke, and vascular damage, as well as changes in neuronal activity, such as hyperactivity as seen in epilepsy, or neuronal depression.

17.2 TGF-β Expression in the Central Nervous System

Localisation of TGF-β isoforms in mice and rats has been performed by immunohistochemistry and in situ hybridization studies demonstrating a widespread distribution of TGF-β2 and TGF-β3 during development (Flanders et al. 1991; Pelton et al. 1991a, b; Unsicker et al. 1991). TGF-β1 is confined to meninges and choroid plexuses. During mouse development TGF-β2 and -β3 immunoreactivities become first detectable along peripheral nerves, in radial glial cells and along the central nervous system (CNS) axon tracts at embryonic age (E)12. Neuronal cell bodies become immunoreactive from E15 onwards. Most notably, TGF-β immunoreactivity is not detectable in the ventricular zone throughout the neural tube, suggesting that TGF-β may not be involved in the regulation of cell division of neural stem cells during development (Flanders et al. 1991). In contrast, on day E16, cells in the subventricular zone, subplate, and lamina I of the cortex stain positive for TGF-β. As they develop, astrocytes are also immunoreactive for TGF-β2 and -β3. In the adult nervous system both neurons and astroglia are immunoreactive for TGF-β2, -β3. Immunoreactive neuron populations include cortical layers 2, 3, and 5, hippocampus, piriform cortex, retinal ganglionic cells, hindbrain aminergic neurons, as well as spinal and hindbrain motoneurons (Unsicker et al. 1991). TGF-β1 is most prominent within the choroid plexus and meninges, it may, however, be expressed in other cells below levels of detectability. Upon lesioning, TGF-β1 may by upregulated in astrocytes as well as in neurons in vivo. TGF-β1 becomes also detectable in tissue culture, possibly mimicking a lesion-like situation. In primary neural tissue culture, treatment with all three TGF-β isoforms usually results in identical responses, suggesting that the recombinant proteins used have similar affinities for their shared receptor complex (Krieglstein and Unsicker 1994; Massague 2000).

In addition to the distribution of TGF-β within the peripheral nervous system (PNS) and CNS, its subcellular localization and mode of secretion is of importance in order to elaborate on its possible functions. Taking PC12 cells as a model to study sorting in the trans-Golgi network, Specht et al. (2003) could show that TGF-β2 may be sorted and released to a large proportion via the regulated path of secretion. Secretory vesicles provide a milieu of pH 5, which is suitable for TGF-β activation within the vesicle, enabling release of active TGF-β (Specht et al. 2003). Activity-depended release of TGF-β2 may suggest a function as a modulator for synaptic plasticity (Lacmann et al. 2007).

17.3 TGF-β in Brain Tumors

The role of TGF-β in cancer biology is complex and involves both aspects of tumor suppression (Bartholin et al. 2013; Seoane 2006) as well as tumor promotion (Wendt and Schiemann 2013; Joseph et al. 2013; Roberts and Wakefield 2003).

TGF-βs are well known for their capacity to regulate cell proliferation in a context-dependent manner. There are at least four scenarios in which regulation of cell proliferation is an important issue in nervous system development and maintenance: (a) neurogenesis, (b) proliferation of neuroblasts (neural crest cells), (c) proliferation of glial cells during development or upon lesioning, and (d) upon transformation in tumors.

Neurogenesis in the neural tube requires definite exit of the cell cycle to generate postmitotic neurons. In the past years there is increasing evidence for the role of TGF-β in developmental and adult neurogenesis (Vogel et al. 2010; Aigner and Bogdahn 2008). For some years there was indirect evidence available that neural stem cells in the neuroepithelium need to be protected from the action of TGF-β, in order to prevent premature growth retardation (Seoane et al. 2004; Hanashima et al. 2002). Seoane and coworkers have demonstrated on the basis of protein interaction analysis in human HaCaT keratinocytes that expression of the cyclin-dependent kinase (cdk) inhibitory protein 1 (p21Cip1) is regulated by TGF-β-dependent Smad complexes in combination with the Forkhead box (Fox) family member FoxO. This FoxO-Smad complex is inhibited by FoxG1, which has been shown to be essential for proliferation of telencephalic progenitor cells (Xuan et al. 1995). Indeed, FoxG1 mutants, which display reduced proliferation of telencephalic progenitor cell, premature differentiation and early depletion of the progenitor population (Xuan et al. 1995) show high levels of p21Cip1 expression in TGF-β-sensitive progenitor cells (Seoane et al. 2004). Exit from the cell cycle during terminal differentiation, as required for neurogenesis, has been described to be regulated by Ink4d and Kip1 inhibitors of cyclin-dependent kinases (Zindy et al. 1999; Cunningham and Roussel 2001). P27Kip1 has been identified as a TGF-β-dependent target gene; however, there is no evidence for a TGF-β-dependent regulation of p19Ink4d. This suggests that TGF-β may serve as an extracellular regulator to induce cell cycle arrest at the G1 phase in neural stem cells but may probably not be sufficient to regulate cell cycle exit required for terminal differentiation. In mouse hippocampal progenitor cells, TGF-β causes induction of p21Cip1 and downregulation of Cdk activators Ccnd1 and Ccnd2, leading to cell cycle exit and neuronal differentiation (Vogel et al. 2010). Along this line, TGF-β2/-β3 double knockout mice display increased cell proliferation and reduced numbers of neurons in the developing cerebral cortex and hippocampus, as the progenitor cells failed to differentiate into neurons because they did not exit cell cycle. Furthermore, TGF-β1 has been implicated as a negative modulator of adult neurogenesis (Wachs et al. 2006).

By affecting the cell cycle prior to terminal differentiation, TGF-β may, of course, regulate proliferation of neuroepithelial cells, including neuroblasts, neural crest cells, and glial progenitors (Zhang et al. 1997a; Anchan and Reh 1995).

Furthermore, TGF-β2 has been shown to regulate cell proliferation in neural crest-derived chromaffin cells (Rahhal et al. 2004) with the capacity of lifelong proliferation.

Tumors of the CNS include primitive neuroectodermal tumors, such as gliomas and medulloblastomas (Fogarty et al. 2005; Nieder et al. 2003). They derive from dividing glial cells, or neural stem and progenitor cells. Glial brain tumors are further classified using grades I–IV to express the likelihood of increased growth and malignancy. CNS tumors are characterized by rapid and infiltrative growth, angiogenesis, and immune suppression. Due to the proliferative behavior of brain cells, brain tumors show a high occurrence not only during development affecting children but also during adulthood. Particularly adult neural stem cells with the capacity to provide new neurons and glia in regions with high plasticity, following injury, or in the context of specific diseases, may escape their physiological control machinery and transform into brain cancer stem cells (reviewed in Aigner and Bogdahn 2008).

Id4 (inhibitors of DNA binding/differentiation) has been shown to serve important functions in neural stem cell differentiation and its deregulation has been implicated in glial neoplasia (Dell'Orso et al. 2010). Deregulation could occur via functional point mutations or epigenetic silencing. Martini and coworkers (2012) were able to show that epigenetic silencing of Id4 via hypermethylation resulted in reduced expression of matrix GLA protein (MGP), TGF-β1 and vascular endothelial growth factor (VEGF) which was associated with a more favorable clinical outcome. However, there are many possibilities to circumvent this effect. First, as TGF-β actions are context-dependent, the presence of certain mitogens, such as TGF-α/epidermal growth factor (EGF) or platelet-derived growth factor (PDGF) may turn TGF-β into a growth stimulating factor (Roberts et al. 1981; Leof et al. 1986; Seoane 2006). Secondly, transformed cells may become insensitive to TGF-β due to overproduction of TGF-β or due to mutations of TGF-β receptors, their signaling components, or even their target genes responsible for G1 arrest (for example Rich et al. 1999; Lyons et al. 1990; Markowitz et al. 1995; Hahn et al. 1996; Seoane et al. 2004; Rich 2003 for review).

TGF-β´s ability to regulate ECM composition puts TGF-β at high risk in the regulation of tumor invasion and metastasis. In this context TGF-β has been shown to regulate integrin expression, for example integrin $\alpha_V\beta_3$ which has been shown to play a role in glioma propagation (Uhm et al. 1999). TGF-β has also been shown to upregulate matrix metalloprotease 2 (MMP-2) and MMP-9 expression at the cell surface (Rooprai et al. 2000) that may interact with $\alpha_V\beta_3$ integrin (for review, see Platten et al. 2001).

TGF-β is a potent immunosuppressive cytokine (Wahl and Chen 2003; Roth et al. 2012; Hau et al. 2011). Brain tumors are well known for their immunosuppressive properties allowing them to escape from the host's immune surveillance. TGF-β2 and TGF-β3 are considered master molecules that upon secretion mediate this immunosupressive environment. This immunosuppressive role has been attributed to TGF-β2, which is also the preferentially expressed isoform by many glioblastomas, grade IV gliomas (Bodmer et al. 1989; Hau et al. 2011). On this basis, TGF-β2-specific antisense gene therapy strategies have been established to make

tumor cells accessible to an effective anti-tumor immune response and counteract TGF-β-dependent tumor metastasis (Hau et al. 2009; Jachimczak et al. 1993; Lou 2004). Along this line, there is extensive research going on to identify TGF-β signaling inhibitors for cancer therapy (DaCosta et al. 2004; Yingling et al. 2004; Lahn et al. 2005).

17.4 Vascular Damage in the CNS

The blood–brain barrier (BBB) generates the specific milieu of the brain by building a tight boundary and thereby separating the components of the circulating blood from the brain. After injury or in neurologic diseases including trauma, ischemia/stroke, or Alzheimer's disease (AD), leakage of the BBB results in the entry of blood constituents into the brain (Abbott et al. 2006). Plasma proteins such as albumin, immunoglobulins, amyloid-β, and fibrinogen, and vascular cells such as erythrocytes and leucocytes, leaking into the brain have been associated with inflammation and restriction of repair (for review, see Beck and Schachtrup 2012). Schachtrup and coworkers (2010) identified TGF-β as a vascular-derived protein. Specifically, they could demonstrate that the plasma-derived protein fibrinogen acts as a carrier of latent TGF-β. Its activation is mediated via avβ6 and avβ8 integrins present on the surface of astrocytes.

Increased levels of TGF-β1 has been described in human brains during trauma, multiple sclerosis (MS), Parkinson's, AD, and stroke patients (Lippa et al. 1995). In patients suffering from severe head injury, high levels of TGF-β1 could be detected in the cerebrospinal fluid (CSF) within 1 day after injury (Csuka et al. 1999; Morganti-Kossmann et al. 1999). These observations strongly suggest that lesion-induced, vascular-derived TGF-β contributes to the corresponding degeneration and regeneration processes (Beck and Schachtrup 2012).

TGF-β has been profoundly investigated for its role in orchestrating the response to brain lesions (for review, see Flanders et al. 1998). With regard to astrocytes, this includes regulation of astrocytic growth, astroglial scar formation, and anti-inflammatory responses. In most contexts studied, TGF-β inhibits the growth of astrocytes (Flanders et al. 1993; Hunter et al. 1993). Most importantly, TGF-β counteracts mitogenic signals by astroglial mitogens such as fibroblast growth factor-2 (FGF-2) or PDGF. However, effects may vary depending on astrocyte culture conditions in vitro or may be brain region-dependent in vivo (Labourdette et al. 1990; Johns et al. 1992). TGF-β may also affect cell adhesion, migration, and ECM production by astrocytes, all being important steps in the cascade of shaping the reactive astrocyte phenotype. TGF-β-treated astrocytes show a slight increase in actin content, the appearance of actin stress fibers, a slight increase in the glial fibrillary acidic protein (GFAP), and an increased production of laminin and fibronectin (cf. Baghdassarian et al. 1993). Thus, treatment of cerebral wounds with anti-TGF-β2 antibodies was shown to lead to a marked reduction of glial scarring (Logan et al. 1999). Many effects of TGF-β on astroglia are anti-inflammatory

and immunosuppressive, as TGF-β modulates the expression of important cytokines involved in CNS immune reactions. These include upregulation of interleukin-6 (IL-6) and nerve growth factor (NGF) (Spittau et al. 2012; Aderka et al. 1989; Lindholm et al. 1992), blocking interferon-γ mediated upregulation of major histocompatibility class (MHC) II (Dong et al. 2001), and the tumor necrosis factor α (TNF-α) and interleukin-1 β (IL-1 β)-mediated upregulation of intercellular adhesion molecule-1 (Shrikant et al. 1996).

17.5 TGF-β in Neuronal Survival and Death

TGF-β has been shown to promote survival of several neuronal populations in vitro (Krieglstein et al. 1995; Poulsen et al. 1994; Martinou et al. 1990). However, it is now well established that TGF-β may modulate the neurotrophic capacities of numerous growth factors including neurotrophins, such as NGF, brain-derived neurotrophic factor (BDNF), as well as ciliary neurotrophic factor (CNTF) (Krieglstein and Unsicker 1996) and, most importantly, glial cell line-derived neurotrophic factor (GDNF; Krieglstein et al. 1998b). GDNF was shown to crucially depend on TGF-β to exert its neurotrophic activities on peripheral as well as mesencephalic dopaminergic neurons in vitro. In vivo, GDNF's neuroprotective effect on target-deprived pre-ganglionic sympathetic neurons, as well as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned nigrostriatal dopaminergic neurons, also depends on the presence of TGF-β (Schober et al. 1999, 2007). GDNF/TGF-β cooperativity on chick ciliary ganglionic neurons has now been characterized in detail, whereby TGF-β is required for appropriate GDNF receptor (GFRα1) recruitment to the plasma membrane (Peterziel et al. 2002). Interestingly, TGF-β does not cooperate with Neurturin, a closely related factor to GDNF, and does not promote the recruitment of GFRα2 to the plasma membrane, suggesting high specificity in TGF-β/GDNF cooperativity (Peterziel et al. 2007).

Depending on the cellular context, TGF-β has also been shown to regulate ontogenetic neuron death. Upon immunoneutralization of all TGF-β isoforms in ovo (E6–E10), ontogenetic cell death of chick parasympathetic ciliary ganglionic neurons, sensory dorsal root ganglionic neurons as well as lumbar spinal motoneurons could be prevented (Krieglstein et al. 2000). Similarly, TGF-β regulates ontogenetic morphogenetic cell death in the developing retina of chick and mouse embryos (Dünker et al. 2001; Dunker and Krieglstein 2003). Another classical model for morphogenetic cell death during embryogenesis represents the removal of interdigital tissue to form individual fingers. Similarly, double deletion of TGF-β2 and -β3 in the mouse resulted in lack of cell death (Dunker et al. 2002). Furthermore, induced neuron death following embryonic limb bud ablation in chick embryos resulted in a significant neuroprotection upon immunoneutralization of TGF-β (Krieglstein et al. 2000). Together, these data suggest that TGF-β is a key regulator of ontogenetic cell death in vivo. Mechanistically, we recently identified that TGF-β-induced apoptosis in oligodendroglial progenitor cells (OLI-neu; Schuster et al. 2002) is characterized

by downregulation of Bcl-xl. Furthermore, Fractin is produced as a caspase-specific cleavage product in oligodendroglial cells during TGF-β-mediated apoptosis, whereby Fractin binding to Bcl-xl induced downregulation of Bcl-xl protein levels (Schulz et al. 2009). Sorrentino and collaborators (2008) were able to show that the intracellular apoptotic cascade can be initiated via the type I receptor of TGF-β (TβR-I) and receptor-engaged TNF-α receptor associated factor 6 (TRAF6). Although TGF-β-induced apoptosis and underlying signaling pathways have been well characterized in many cells types, little is known about TGF-β-induced apoptosis in neurons (Schuster and Krieglstein 2002; Sanchez-Capelo 2005).

17.6 Cerebral Ischemia

Cerebral ischemia is caused by either a blood clot occluding a blood vessel in the brain (focal ischenia) or a more general reduction in brain blood flow (global ischemia) leading to insufficient blood flow and reduced oxygen levels in the respective brain areas, thus leading to death of brain tissue. Neuronal cell death may occur as necrosis or apoptosis. Thrombolysis is the approved treatment of stroke. TGF-β1 expressed at low levels in adult brain is rapidly upregulated following insults such as cerebral ischemia, excitatory injury, or traumatic brain injury (Klempt et al. 1992; Knuckey et al. 1996; Yamashita et al. 1999; Morganti-Kossmann et al. 1999; Zhu et al. 2000; Boche et al. 2003; Krieglstein 2006; Pál et al. 2012). TGF-β1 upregulation was observed primarily in microglial cells and in astrocytes, while TGF-β2 upregulation was seen in neurons. TGF-β3 was not upregulated; however, the levels of both TGF-β2 and TGF-β3 decreased subsequently. These data suggest a distinct spatiotemporal requirement of TGF-β isoforms action during cerebral ischemia (Pál et al. 2012). As TGF-β is a good candidate to organize the response of neurons to degeneration as well as mediating anti-inflammatory reactions, its neuroprotective potential has been widely analyzed (for review, see Flanders et al. 1998; Böttner et al. 2000; Dobolyi et al. 2012). Specifically, TGF-β1 applied either as recombinant protein or by adenoviral-based overexpression has been shown to reduce infarct size after focal cerebral ischemia and to prevent hippocampal neuronal damage after global ischemia (Gross et al. 1993; Prehn et al. 1993; Zhu et al. 2002; for review, see Buisson et al. 2003; Dhandapani and Brann 2003). Furthermore, TGF-β may also mediate tolerance of ischemic preconditioning towards subsequent ischemic insult (Boche et al. 2003). The molecular mechanism(s) by which TGF-β protects neurons from ischemic cell death relies on a signaling crosstalk between neurons and astrocytes (Prehn et al. 1994; Docagne et al. 1999) and involves the maintenance of Ca^{2+} homeostasis, modulation of the t-plasminogen activator (tPA)/plasminogen activator inhibitor (PAI-1) axis, as well as inhibition of pro-apoptotic pathways, such as Bad and caspase-3 (Zhu et al. 2001, 2002) and upregulation of anti-apoptotic proteins such as Bcl-2 (Prehn et al. 1994). An additional TGF-β-dependent anti-apoptotic pathways involving NF-κB activation has been described (Zhu et al. 2004). This pathway seems to be downstream of ALK1 (activin receptor-like kinase

1), an alternative TGF-β type I receptor first described on endothelial cells, which has been shown to be upregulated in neurons in an injury-dependent manner (Konig et al. 2005). Injury-dependent upregulation of ALK1, with signaling preference towards Smad1, may also explain numerous opposing effects of TGF-β in brain development and lesions.

17.7 Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative brain syndrome characterized by a progressive decline in learning and memory, thinking, language, judgment, and other higher brain functions. Currently about 18 million people worldwide suffer from AD and it is estimated that in 2025, 34 million will be affected. The statistical risk of occurrence is 1.4 % at the age of 60 and doubles every 5 years thereafter (WHO; Huang and Mucke 2012).

AD is characterized by considerable brain shrinkage resulting in a large loss of brain weight and volume. The extent of brain volume loss suggests more general mechanisms such as shrinkage and loss of neuronal processes, including degeneration of specific neuron populations (Huang and Mucke 2012). Along this line, aberrant neuronal network activity, dysfunction, and loss of synapses may describe the cognitive decline in AD.

TGF-β has been implicated in the regulation of neurite outgrowth, transmitter synthesis as well as synapse formation (Krieglstein et al. 2011). TGF-β has been reported to cause neurite sprouting and elongation of hippocampal axons as well as promoting re-elongation of injured axons of hippocampal neurons in vitro (Ishihara et al. 1994; Abe et al. 1996). In the mouse neocortex, TGF-β can direct neuronal polarity by initiation of axon formation and neuronal migration via site-specific phosphorylation of the polarity protein Par6 (Yi et al. 2010). Extracellular signaling factors such as Wnt and TGF-βs are recognized as target-derived signals in synaptogenesis (Salinas 2005; Packard et al. 2003). In chick ciliary ganglionic neurons, developmental expression of K_{Ca} channels coincides with synaptogenesis. Dryer and coworkers have shown that target-derived TGF-β1 regulates the developmental expression of Ca^{2+}-activated K^+ currents in vitro and in vivo (Cameron et al. 1999). The acute effect of TGF-β1 relies on the translocation of K_{Ca} channels from intracellular stores to the plasma membrane involving signaling via the Ras GTPase, extracellular regulated kinases (Erk), and phosphoinositide 4′ (PI4) kinase (for review, see Dryer et al. 2003). In conclusion, TGF-β may well be suited to modulate synaptic plasticity and cognition (for review, see Krieglstein et al. 2011).

The pathogenesis of AD is focusing on amyloid β (Aβ) peptides, the main constituent in plaques, derived from amyloid precursor protein (APP) upon proteolylic cleavage (De Strooper et al. 2010; Bertram et al. 2010). There are several lines of evidence suggesting that TGF-β1 may contribute to the pathology of Alzheimer's disease, particularly through promoting Aβ precursor expression and Aβ deposition (Burton et al. 2002; Wyss-Coray et al. 1997a, b; Flanders et al. 1995;

van der Wal et al. 1993). Mice overexpressing TGF-β1 in astrocytes develop AD-like vascular and meningeal abnormalities with age (Gaertner et al. 2005). These chronic alterations could be correlated with reduced brain tissue perfusion, leading to an increased amount of fibrillar and soluble Aβ peptides. However, in brain parenchyma, astroglial TGF-β1 expression leads to a reduction of overall Aβ as well as decreased numbers of dystrophic neurites (Wyss-Coray et al. 2001). The reduced plaque burden in brain parenchyma is thought to depend on TGF-β-dependent microglial activation and microglial Aβ-clearance. Furthermore, a genetic association study of three polymorphisms of the human TGF-β1 gene with AD suggests that there is no correlation between TGF-β1 and AD on the basis of TGF-β1 gene variability (Araria-Goumidi et al. 2002).

Most recently, bioactive TGF-β has been shown to be associated with lipoproteins, specifically those containing ApoE3, but not ApoE4 (Tesseur et al. 2009). Association of TGF-β1 with lipoproteins may facilitate its diffusion and signaling and possibly also other biological functions of TGF-β1. This observation is of particular interest in this context as ApoE4 has been genetically linked with late-onset AD (Bertram et al. 2010). As TGF-β1 is a neuroprotective agent and may be beneficial in the AD condition, for example through reduction of plaque burden, the preferential binding of TGF-β1 to ApoE3 versus ApoE4 may put ApoE4 carriers on higher risk for developing AD (Tesseur et al. 2009).

Several lines of evidence suggest impairment of TGF-β-activated Smad signaling, with ectopic localization of phosphorylated Smad2/3 within amyloid plaques and neurofibrillary tangles (Lee et al. 2006; Tesseur et al. 2006; Ueberham et al. 2006; Chalmers and Love 2007a, b). Furthermore, AD patients have been shown to have reduced plasma levels of TGF-β1 (Mocali et al. 2004; Juraskova et al. 2010) as well as reduced neuronal expression of the TGF-β type II receptor (TβRII) (Tesseur et al. 2006). Lack of TβRII signaling via neuronal expression of kinase-deficient TβRII in AD transgenic mice promoted Aβ deposition and loss of dendrites (Tesseur et al. 2006), while Aβ may downregulate expression of TβRII via induction of miR-106b (Wang et al. 2010). Finally, injection of synthetic Aβ in combination with blocking TGF-β signaling via application of the TβRI kinase inhibitor SB431542 significantly increased the vulnerability of hippocampal neurons to Aβ, leading to neuronal degeneration (Caraci et al. 2008).

Together, as TGF-β1 signaling is beneficial in the AD environment, rescuing TGF-β1 levels and TGF-β signaling may represent a new strategy for neuroprotection in AD (Caraci et al. 2012).

17.8 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by a progressive loss of nigrostriatal neurons and in consequence by marked reduction of striatal dopamine resulting in impaired voluntary movement (for review, see Braak et al. 2004; Dunnett and Björklund 1999). In addition to the loss of neurons, a further

morphologic hallmark of PD is the presence of Lewy bodies and Lewy neurites (Forno 1996). The formation of these proteinaceous inclusions involves interaction of several proteins, including α-synuclein (Spillantini et al. 1998). The etiology of PD is likely due to combinations of environmental and genetic factors (for review, see, for example, Valente et al. 2012; Gasser et al. 2011).

TGF-β2 and TGF-β3 are expressed in adult nigral dopaminergic neurons (Unsicker et al. 1991), and TGF-β1 and -β2 were elevated in biopsies of PD patients (Nagatsu et al. 2000). TGF-βs have been shown to promote midbrain dopaminergic neuron survival in vitro and in vivo (Krieglstein and Unsicker 1994; Poulsen et al. 1994; Roussa et al. 2004), as well as protection against 1-methyl-4-phenylpyridinium (MPP+) intoxication (Krieglstein et al. 1995; Roussa et al. 2009). Most importantly, TGF-β cooperates with GDNF to promote dopaminergic neuron survival (Krieglstein et al. 1998b). GDNF is well known as a potential therapeutic agent coping with PD (for review, see Björklund and Lindvall 2000). However, also in vivo GDNF-dependent neuroprotective effects are based on the cooperativity with TGF-β, as shown in the MPTP-mouse model, an animal model of PD (Schober et al. 2007). This neuroprotective strategy has already been used incidentally by grafting extra-adrenal chromaffin cells obtained from Zuckerkandl's organ in parkinsonian rats (6-hydroxydopamine model). The behavioral improvements of parkinsonia deficts were in addition to the supply of catecholamines attributed to the release of the survival promoting proteins GDNF and TGF-β1 (Fernandez-Espejo et al. 2005).

Most recently, a new animal model for PD has been introduced. Viral transformation of rats with α-synuclein showed a slow progression of nigral dopaminergic neurons (Ulusoy et al. 2010). Most interestingly, GDNF, for long considered as the gold standard in neurotrophic-based neuroprotection of PD, is not able to rescue α-synuclein-mediated degeneration of dopaminergic neurons (Decressac et al. 2011).

17.9 Epilepsy

Epilepsy is a common neurological disorder affecting 0.5–2 % of the population worldwide. Epilepsy is characterized by seizures resulting from abnormal neuronal activity. So far, there is no cure known for the disease. The mechanisms leading to the disease are only poorly understood. However, epilepsy is often seen following brain trauma, ischemic or infectious brain injury, or drug and alcohol misuse. These conditions may be accompanied by vascular damage and leakage of the blood–brain barrier (see above).

Cacheaux et al. (2009) have identified the involvement of TGF-β signaling in epileptogenesis. The group has previously demonstrated that serum albumin causes epileptic field potentials when exposed to brain slices in vitro (Ivens et al. 2007). Serum albumin was taken up by astrocytes leading to down regulation of inward-rectifying potassium (Kir 4.1) channels, resulting in reduced buffering of extracellular potassium in neuronal hyperexcitability and epileptiform activity. As the albumin uptake was shown to occur in a TGF-β receptor-mediated mechanism,

blocking of the TβR in vivo reduced the likelihood of epiletogenesis in albumin exposed brains (Ivens et al. 2007). In follow-up experiments, the group was able to show that TGF-β1-mediated signaling is sufficient to induce epileptoforming activity (Cacheaux et al. 2009). These data strongly link the TGF-β pathway with epileptogenesis and identify the TGF-β pathway as a therapeutic target for the prevention of injury-induced epilepsy (Friedman 2011).

17.10 Depression

Major depressive disorder is a mental disorder characterized by low mood, low self-esteem, and reduced interest in enjoying pleasure. There is no clinical test for depression. Patients are treated with antidepressant drugs, which improves their mental condition after several weeks of treatment. Most antidepressant medications directly or indirectly increase the levels of one or more of the monoamines, such as serotonin, noradrenaline, and dopamine, in the synaptic cleft between neurons in the brain, suggesting that depression may be the consequence of reduced synaptic activity. In addition to neurotransmitters, also neuropeptides and neurotrophic factors such as BDNF and TGF-β have been shown to be released in an activity-dependent manner (Thoenen 1995; Specht et al. 2003; Lacmann et al. 2007). Notably, KCl stimulation caused Smad translocation into the nucleus and induced TGF-β-inducible early gene (Tieg1) expression, demonstrating that activity-dependent released TGF-β may exert autocrine actions and thereby activate the TGF-β-dependent signaling pathway (Lacmann et al. 2007). These results suggest an activity-dependent release and gene transcription of TGF-β in mouse hippocampal neurons in vitro as well as subsequent autocrine functions of the released TGF-β within the hippocampal network. TGF-β is also known to have a prominent role in long-term synaptic facilitation in isolated Aplysia ganglia (Zhang et al. 1997b). Within minutes, TGF-β1 stimulated MAPK-dependent phosphorylation of synapsin, which appeared to modulate synapsin distribution, and resulted in a reduced magnitude of synaptic depression (Chin et al. 2002). Most recently, Fukushima and coworkers (2007) were able to show that TGF-β modulates synaptic efficacy and plasticity in dissociated rat hippocampal neurons. Together, increasing evidence suggests that TGF-β may be involved in synaptogenesis, modulation of synaptic transmission, and synaptic plasticity.

The delayed effects of antidepressants are thought to depend on indirect mechanisms, including the regulation of gene expression, for example antidepressant-induced upregulation of BDNF signaling, which then in turn promotes adaptive neuronal plasticity through effects on gene expression. Wibrand and coworkers (2006) identified five genes (Neuritin, Narp, Tieg1, Carp, and Arl4d) that are co-upregulated with Arc during BDNF-LTP. Tieg1 is a TGF-β-dependent immediate early gene that has also been shown to be upregulated in hippocampal neurons by TGF-β (Lacmann et al. 2007). As TGF-β has been shown to cooperate with BDNF in several scenarios, it may be quite likely that BDNF and TGF-β are the key players in antidepressant-mediated restoration of neuronal plasticity in patients suffering from major depressive disorders.

17.11 Motoneuron Disease

Amyotrophic lateral sclerosis (ALS) is a fatal disease, leading to paralysis and death. It is characterized by loss of motoneurons. Some ALS cases are due to mutation of the superoxide dismutase 1 (SOD1). TGF-β is a prominent motoneuron survival factor (McLennan and Koishi 2002; Martinou et al. 1990). Using SOD1 knockout mice as a model for ALS application of TGF-β2 caused a rapid and marked but transient improvement in the motoric performance of the mice (Day et al. 2005). In the past years, all components of the TGF-β signaling system have been localized in the presynaptic terminal of the neuromuscular junction, whereby TGF-β ligands are synthesized and localized on the postsynaptic side (McLennan and Koishi 2002; Toepfer et al. 1999). Furthermore, it has been shown that TGF-β2 alters the characteristics of the neuromuscular junction by regulating presynaptic quantal size (Fong et al. 2010).

Appropriate myelination is an important aspect of neuronal activity. Oligodendroglial cells are the myelinating cells of the CNS and Schwann cells of the PNS. Oligodendrocytes arise from a bipotential progenitor cell, the O2A progenitor. TGF-β restricts their PDGF-driven proliferation and induces oligodendroglial differentiation (McKinnon et al. 1993) but may also induce apoptosis (Schuster et al. 2002). In the PNS, TGF-β mediates developmental cell death of Schwann cells (Parkinson et al. 2001) and blocks Schwann cell myelination and expression of myelin-related proteins (Awatramani et al. 2002 and references therein). However, in adult mice TGF-β seems to stabilize compact myelin, as TGF-β1-null mice have grossly abnormal myelin (Day et al. 2003). Ski, a repressor of Smad-mediated TGF-β signaling controls Schwann cell proliferation and myelination, whereas absence of Ski abolished the formation of peripheral myelin, and myelinating Schwann cells upregulate Ski in development as well as during remyelination upon injury (Bonnon and Atanasoski 2012; Atanasoski et al. 2004).

17.12 Conclusions

TGF-β is a multifunctional and versatile molecule, effecting development, adult maintenance as well as aging of the brain. Although the prototype of a superfamily TGF-β is acting in the nervous system in a highly specific manner. In the context of brain tumors TGF-β is acting very much the way it as expected to by regulating cell cycle, adhesion, and immunosuppression. However, in all other disease scenarios TGF-β action is much more versatile reaching from orchestrating astrocyte and microglia activation to regulating growth factor responsiveness, uptake and release mechanisms, activity-dependent gene expression, and nerve myelination. TGF-β responsiveness may be mediated via alternative TβR-1 usage and may be blocked via the miRNA-dependent downregulation of TβR-II. A new and fascinating aspect is also evident from the modes of TGF-β delivery within the body through transport via lipoproteins or via fibrinogen. In conclusion, the role of TGF-β within brain

disorders, either as cause or as key molecule orchestrating responses is only at the beginning of its understanding. Major open issues regard the specific action of individual TGF-β isoform, the context-specificity, the role of TGF-β activation to regulate TGF-β function and complexity of TGF-β signaling and crosstalk. This knowledge will then be also helpful to explain opposing actions of TGF-β such as promotion of survival/protection as to induction of cell death.

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