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Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease

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Abstract

Brain-derived neurotrophic factor (BDNF) is a small dimeric protein, structurally related to nerve growth factor, which is abundantly and widely expressed in the adult mammalian brain. BDNF has been found to promote survival of all major neuronal types affected in Alzheimer's disease and Parkinson's disease, like hippocampal and neocortical neurons, cholinergic septal and basal forebrain neurons, and nigral dopaminergic neurons. In this article, we summarize recent work on the molecular and cellular biology of BDNF, including current ideas about its intracellular trafficking, regulated synthesis and release, and actions at the synaptic level, which have considerably expanded our conception of BDNF actions in the central nervous system. But our primary aim is to review the literature regarding BDNF distribution in the human brain, and the modifications of BDNF expression which occur in the brain of individuals with Alzheimer's disease and Parkinson's disease. Our knowledge concerning BDNF actions on the neuronal populations affected in these pathological states is also reviewed, with an aim at understanding its pathogenic and pathophysiological relevance. © 2000 Elsevier Science Ltd. All rights reserved.

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Abbreviations: BDNF, brain-derived growth factor; ChAT, choline acetyltransferase; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; HIV, human immunodeficiency virus; MAPK, mitogen-activated protein kinase; NGF, nerve growth factor; NT, neurotrophin; NRIF, NT receptor interacting factor; NRSE, neuron-restrictive silencer element; $p75^{NTR}$, p75 neurotrophin receptor; PDGF, platelet-derived growth factor; PC, pro-protein convertase; PI3K, phosphatidylinositol-3′ kinase; rhBDNF, recombinant human BDNF; TH, Tyrosine hydroxylase; TNFR, Tumor necrosis factor receptor; TRAF6, TNFR-associated factor-6; Trk, tropomiosin receptor kinase; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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1. Introduction

The discovery of neurotrophins (NTs) followed an interesting series of experiments demonstrating that the survival of peripheral nervous system neurons during development depends on target availability and size. An excess number of sensory and sympathetic neurons is produced during early development, and then, programmed cell death occurs until the number of surviving neurons matches the size of the target (reviewed by Oppenheim, 1991; Hamburger, 1993). Strikingly, implanted tumoral tissue can serve as target for host embryonic peripheral nervous system neurons, and promotes survival and differentiation of sensory and sympathetic neurons (Bueker, 1948; Hamburger and Levi-Montalcini, 1949; Levi-Montalcini and Hamburger, 1951). Further work showed that the effect of tumors depended on the production of a diffusible agent, a protein which was finally named nerve growth factor (NGF) (Levi-Montalcini and Hamburger, 1953; reviewed by Levi-Montalcini, 1987; Hamburger, 1993). NGF could be isolated from mouse salivary glands (where it is highly concentrated), allowing the obtention of antibodies, with the demonstration that endogenous NGF is necessary for the development of some peripheral nervous system neurons in mammals (Cohen, 1960; Levi-Montalcini and Booker, 1960; Johnson et al., 1980). This discovery was followed by the demonstrations that target tissues of sympathetic and sensory neurons produce NGF (Davies et al., 1987), that peripheral neurons express NGF receptors (Sutter et al., 1979), and that NGF is retrogradely transported to their cell bodies (Dumas et al., 1979), findings that ultimately led to the concept of target-derived neurotrophic support (reviewed by Levi-Montalcini, 1987; Thoenen et al., 1987; Purves et al., 1988; Oppenheim, 1991). Cloning of mouse and human *NGF* genes was finally accomplished in 1983 (Scott et al., 1983; Ullrich et al., 1983). The NGF low-affinity and high-affinity receptors, whose existence was initially

demonstrated on the basis of physiological and ligand binding studies (Levi-Montalcini, 1987), have also been characterized at the genetic and molecular levels (Barbacid, 1994a, 1994b; Ultsch et al., 1999). Recent studies on genetically-modified mice lacking NGF, or its high-affinity receptor Tropomiosin receptor kinase A (TrkA), support that NGF is necessary for survival of peripheral sensory and sympathetic neurons (Crowley et al., 1994; Smeyne et al., 1994).

The earlier exciting discoveries on NGF physiology stimulated further work aimed at isolating other neurotrophic molecules. Brain-derived neurotrophic factor (BDNF) was purified from pig brain, thanks to its survival-promoting action on a subpopulation of dorsal root ganglion neurons (Barde et al., 1982). The amino acid sequence of mature BDNF has a strong homology with that of NGF (Leibrock et al., 1989; Rosenthal et al., 1991), a fact that encouraged the search of other sequence-related molecules, nowadays known as neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) (Ernfors et al., 1990a; Hohn et al., 1990; Jones and Reichardt, 1990; Kaisho et al., 1990; Rosenthal et al., 1990; Maisonpierre et al., 1990a, 1991; Berkemeier et al., 1991; Hallböök et al., 1991; Ip et al., 1992). The search for other sequence-related molecules still continues, and has recently led to the identification of new NTs in the bony fish (Götz et al., 1994; Nilsson et al., 1998; Lai et al., 1998) and lamprey (Hallböök et al., 1998). Thus far, only four NTs have been found in humans. All NTs bind the low-affinity receptor for NGF, at present known as p75 neurotrophin receptor ($p75^{NTR}$). In addition, other high-affinity NT receptors, structurally related to TrkA, have been identified. TrkB binds BDNF and NT-4/5, whereas NT-3 binds to TrkC, and with reduced efficacy, to TrkB (reviewed by Barbacid, 1994a, 1994b; Chao, 1994; Dechant et al., 1994).

As is the case for NGF, BDNF is necessary for survival of some peripheral sensory neurons, notably those in the vestibular ganglia and nodose-petrosum ganglia. Interestingly, part of the trophic effects of BDNF in the peripheral nervous system seem to depend on autocrine loops and paracrine interactions between adjacent neurons, since sensory neurons can express both BDNF and its high affinity receptor TrkB. These studies have been repeatedly reviewed before (Barde, 1989; Korsching, 1993; Davies, 1994; Klein, 1994; Snider, 1994; Lewin and Barde, 1996; Barde, 1999). In addition, BDNF is abundantly expressed in the central nervous system, specially in the hippocampal formation, cerebral cortex, and amygdaloid complex (Hofer et al., 1990; Ernfors et al., 1990a, 1990b; Wetmore et al., 1990; Phillips et al., 1990), and its expression increases until reaching a maximal level after birth (Maisonpierre et al., 1990b; Friedman et al., 1991a, 1991b; Schecterson and Bothwell, 1992). Then, the expression of BDNF seems not to decline with age (Lapchak et al., 1993b; Narisawa-Saito and Nawa, 1996; Katoh-Semba et al., 1997, 1998). These facts suggest essential roles for BDNF in the adult central nervous system.

The idea, that neuronal death in degenerative disorders can result from the lack of an endogenous trophic molecule, was in the mind of the research community at the beginning of the 1980s (Appel, 1981; Hefti, 1983). Following the knowledge acquired on NGF actions in the peripheral nervous system, the *target-derived neurotrophic support* concept was extended to populations of adult central nervous system neurons, in particular the cholinergic septal and basal forebrain neurons which degenerate in Alzheimer's disease (reviewed by Thoenen et al., 1987; Hefti et al., 1989 and more recently by Hefti, 1999). Septal and basal forebrain cholinergic neurons express both low- and high-affinity receptors for NGF, project to the hippocampal formation and cerebral cortex (the main central nervous system sites for NGF synthesis), and retrogradely transport NGF from these target structures to their cell bodies (Hefti, 1999). Destruction of the hippocampal formation or cerebral cortex leads to atrophy of septal and cholinergic neurons (Sofroniew et al., 1993; Burke et al., 1994; Skup et al., 1994), and similar effects can be obtained by administering immunotoxins directed against $p75^{NTR}$ (Heckers et al., 1994; Wenk et al., 1994), mutating the *Trk*A gene (Smeyne et al., 1994), the gene encoding for $p75^{NTR}$ (Vanderzee et al., 1996), or the NGF gene itself (Chen et al., 1997). Finally, NGF administration prevents cholinergic neuron atrophy caused by lesions of the septohippocampal and basal forebrain–cortical systems (Hefti, 1999). The compiled evidence led to the suggestion that NGF administration might produce some benefit to individuals with Alzheimer's disease (Hefti, 1999).

BDNF is more highly expressed and widely distributed than NGF in the central nervous system, and has survival promoting actions on a variety of central nervous system neurons including hippocampal and cortical neurons (Ghosh et al., 1994; Lowenstein and Arsenault, 1996; Lindholm et al., 1996), cholinergic neurons (Alderson et al., 1990; Knüsel et al., 1991), and nigral dopaminergic neurons (Hyman et al., 1991; Knüsel et al., 1991). Of course, these facts raised keen interest in BDNF as a potential therapeutic agent for Parkinson's disease and Alzheimer's disease, among other neurodegenerative disorders and non-degenerative pathologies. This interest has been intensified by reports demonstrating a reduced expression of BDNF in the brain of individuals with Alzheimer's disease (Phillips et al., 1991; Murray et al., 1994; Narisawa-Saito et al., 1996) and Parkinson's disease (Mogi et al., 1999; Parain et al., 1999).

This article reviews the distribution of BDNF in the

human control brain, and the reports revealing changes in BDNF expression in Alzheimer's disease and Parkinson's disease, with an aim to understand how an altered expression of BDNF can be involved in the pathogeny and pathophysiology of these diseases. There is a section that summarizes the knowledge acquired on BDNF molecular and cellular biology during the last decade, in order to render the review understandable for readers from other fields. Recent ideas about BDNF distribution within neurons, and on BDNF actions at the synaptic level are presented, to gain insight into the functional interactions between populations of central nervous system neurons which express BDNF and TrkB. Then, the distribution of BDNF in the human control brain, and the changes observed in Alzheimer's disease and Parkinson's disease are described. In addition, the actions of BDNF on the neuronal populations affected by both diseases are reviewed more extensively, to offer a broad panorama on the mechanisms through which an altered BDNF expression can be involved in the pathogeny and pathophysiology of Alzheimer's and Parkinson's diseases.

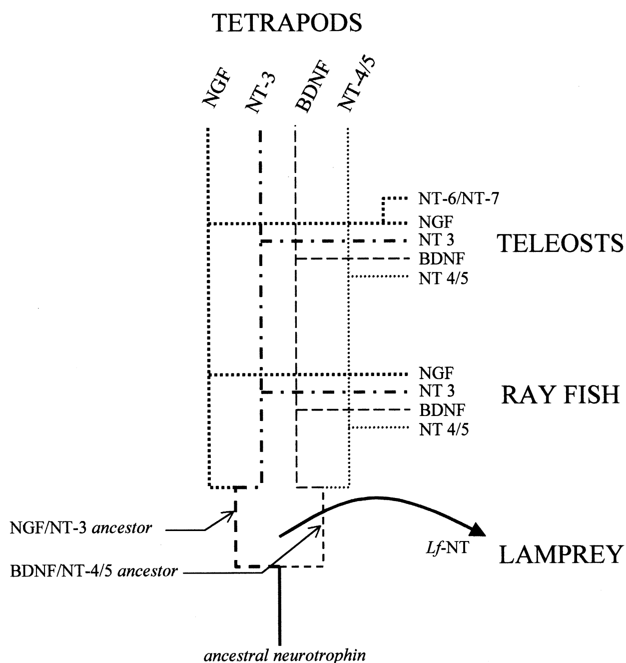

Fig. 1. Putative phylogenetic tree of the four neurotrophins found in humans (modified from Hallböök et al., 1998 with permission from Lippincott, Williams & Wilkins). The four neurotrophins could have evolved from a common neurotrophin ancestor after two subsequent duplications that occurred at early vertebrate stages.

2. Molecular and cellular biology of BDNF

2.1. BDNF is a member of the neurotrophin family

As outlined in the Section 1, BDNF is a member of the NT family, the other human members are NGF, NT-3 and NT-4/5. All four genes coding for NTs have been found in fish, amphibians, reptiles, and mammals (Isackson et al., 1991a; Götz and Schartl, 1994; Hallböök et al., 1998). The sequence of the mature form of human BDNF (hBDNF) is identical to that of porcine, rat and mouse BDNF (Hofer et al., 1990; Rosenthal et al., 1991), shows 90% identity as compared to teleost fish BDNF (Götz et al., 1992), and is more closely related to a recently described lamprey NT (*Lf*-NT) than NGF (Hallböök et al., 1998), indicating that BDNF structure has been more conserved than NGF structure during vertebrate evolution (Götz et al., 1992, 1994; Hallböök et al., 1998) (Fig. 1). Phylogenetic analysis suggests that all NTs have evolved from a common *NT ancestor* gene, which has suffered an early duplication more than 460 million years ago, giving rise to BDNF/NT-4/5 and NGF/NT-3 ancestor NTs. A subsequent duplication has probably originated the four NTs noticed in mammals (Hallböök et al., 1998) (Fig. 1). To date, no NT homolog has been found in non-vertebrates. A recent report (van Kesteren et al., 1998), describing a receptor tyrosine kinase related to vertebrate Trk high-affinity receptors for NTs in the snail *Lymnaea stagnalis* (*L*trk), suggests the existence of a NT-related endogenous ligand in invertebrates.

The mature form of hBDNF is about 50% identical to human mature NGF, NT-3 and NT-4/5. Conserved features among NTs include: (1) a presumptive signal peptide following the initiation codon (Leibrock et al., 1989; Ernfors et al., 1990a; Hohn et al., 1990; Jones and Reichardt, 1990; Kaisho et al., 1990; Rosenthal et al., 1990; Maisonpierre et al., 1990a, 1991; Berkemeier et al., 1991; Hallböök et al., 1991; Ip et al., 1992); (2) a pro-region, including an N-linked glycosylation site, and a proteolytic cleavage site for furin-like proteases followed by the mature sequence (Bresnahan et al., 1990; Seidah et al., 1996a, 1996b); (3) a distinctive three-dimensional structure determined by two pairs of anti-parallel β-strands, and six cysteine residues forming three disulfide bridges, referred to as the *cystine knot motif* (Angeletti and Bradshaw, 1971; McDonald and Hendrickson, 1993; Sun and Davies, 1995; Ibáñez, 1998). The cystine knot motif has been studied in crystals of NGF (McDonald et al., 1991), and it consists of two clustered cystine bridges and a short amino acid chain forming a ring through which a third cystine bridge passes. The cystine knot and the anti-parallel β-strands give NT molecules an unusual elongated three-dimensional fold, which is also typical of other growth factors like transforming growth fac-

tor β2 (TGFβ2), platelet-derived growth factor BB (PDGF-BB) and vascular endothelial growth factor (VEGF), this suggesting a common evolutionary origin (McDonald and Hendrickson, 1993; Sun and Davies, 1995; Ibáñez, 1998).

The mature active forms of NTs are very stable non-covalently associated homodimers, with molecular weights around 28 kDa (Bothwell and Shooter, 1977; McDonald et al., 1991; Radziejewski et al., 1992; Jungbluth et al., 1994; Ibáñez, 1998). The hydrophobic interactions between monomers, as suggested by studies on crystallized NGF (McDonald et al., 1991; Wiesmann et al., 1999), involve highly conserved residues in all NTs, suggesting the possibility of heterodimer formation. Actually, genetically-manipulated cells that express BDNF and NT-3 can form non-covalently linked BDNF/NT-3 heterodimers, which display reduced biological activity relative to mixtures of BDNF and NT-3 homodimers (Jungbluth et al., 1994; see also Arakawa et al., 1994; Heymach and Shooter, 1995; Robinson et al., 1995). Dimerization seems to be an essential requisite for NT receptor activation, and is a feature characterizing other growth factors as well (reviewed by Ibáñez, 1998).

2.2. Expression of the BDNF gene can be regulated by physiological signals, and insults, in the central nervous system

As can be expected from a molecule probably involved in the development and maturation of the nervous system, BDNF expression shows distinct modifications during fetal and early postnatal development (Maisonpierre et al., 1990b; Friedman et al., 1991a, 1991b; Schecterson and Bothwell, 1992). In particular, there is an exciting body of work showing that BDNF could be implicated in activity-dependent maturation of the visual cortex (Allendoerfer et al., 1994; Cabelli et al. 1995, 1997; Galuske et al., 1996).

Interestingly, modifications of BDNF expression also occur in response to a series of events, in the adult central nervous system. It was clearly stated that BDNF expression can be regulated in an activity-dependent manner in the adult mammalian brain. Soon, after BDNF discovery, it was reported that BDNF mRNA expression increases several times in the rodent hippocampal formation after seizures (Zafra et al., 1990; Ballarín et al., 1991; Ernfors et al., 1991; Gall et al., 1991; Isackson et al., 1991b). Increases in BDNF mRNA expression were found not only after long-lasting or recurrent seizures, but also after brief episodes of hippocampal epileptiform activity (Ernfors et al., 1991; Isackson et al., 1991b), and were not restricted to the hippocampal formation, but involved widespread regions of the cerebral cortex and the amygdaloid complex (Ballarín et al., 1991; Ernfors et al., 1991; Gall et al., 1991; Isackson et al., 1991b; Zafra et al., 1991; Dugich-Djordjevic et al., 1992). Confirmatory reports demonstrated increases in BDNF protein in the hippocampal formation after seizures (Nawa et al., 1995; Smith et al., 1997; Yan et al., 1997a). Remarkably, BDNF is increased in the hippocampus and temporal neocortex from individuals with temporal lobe epilepsy (Mathern et al., 1997; Takahashi et al., 1999).

Subsequent work has established that experimental paradigms specifically designed to simulate physiological changes in bioelectrical activity, can modify BDNF expression. Electrical stimulation with parameters that induce long-term potentiation induces BDNF expression in the hippocampal formation (Patterson et al., 1992; Castrén et al., 1993; Dragunow et al., 1993). Even spontaneous changes in bioelectrical activity, or changes in activity induced by pharmacological manipulations, modify BDNF mRNA expression in vitro (Rutherford et al., 1997, 1998; Gorba et al., 1999b). Finally, it was clearly established that different forms of sensory stimulation induce changes in BDNF expression in relevant central nervous system structures, including light-induced changes in the visual cortex (Castrén et al., 1992), osmotic stimuli-induced modifications in the hypothalamic paraventricular nucleus (Castrén et al., 1995), and whisker stimulation-induced changes in the somatosensory cortex (Rocamora et al., 1996b).

BDNF expression can also be regulated by neurotransmitters and hormones. In good agreement with the idea that BDNF expression is regulated by bioelectrical activity, there is an evidence showing that glutamate receptor agonists induce, whereas $GABA_A$ receptor agonists inhibit, BDNF expression (Zafra et al., 1990; reviewed by Lindholm et al., 1994 and Marty et al., 1997). Other synaptic mediators and hormones involved in the regulation of BDNF expression in the central nervous system are acetylcholine (Lapchak et al., 1993d; Knipper et al., 1994; French et al., 1999), serotonin (Nibuya et al., 1995; Vaidya et al., 1999b; Zetterstrom et al., 1999), nitric oxide (Xiong et al., 1999), thyroxine (Lüesse et al., 1998), glucocorticoids and mineralocorticoids (Chao et al., 1998b; Schaaf et al., 1998), and sexual steroids (Gibbs, 1999).

Further work has demonstrated that BDNF expression in the central nervous system can be modified by insults, including an increased expression following hypoxia-ischemia and hypoglycemic coma (Lindvall et al., 1992; Merlio et al., 1993; Korhonen et al., 1998; recently reviewed by Hughes et al., 1999; Nikolics, 1999), an increased expression in interneurons located close to axotomized cortical projection neurons (Wang et al., 1998), and a reduced expression after stress (Smith et al., 1995; reviewed by Altar, 1999).

The mechanisms linking the diverse extracellular sig-

nals with changes in BDNF expression have been elucidated to some extent. The rat's *BDNF* gene has a complex structure, including four 5′ exons, each one preceded by a separate promoter, and one 3′ exon encoding the mature protein. Alternative usage of the promoters and differential splicing give rise to four types of mRNAs, with different 5′ exons and the common 3′ exon, which have singular anatomical and functional patterns of expression (Timmusk et al., 1993; Bishop et al., 1994; Nakayama et al., 1994). All BDNF transcripts are expressed in the central nervous system, although regional variations in expression exist. Exons I, II and III, and in a much lesser degree exon IV, are regulated in an activity-dependent manner in the central nervous system (Timmusk et al., 1993; Falkenberg et al., 1992b; Metsis et al., 1993).

Recent reports revealed several mechanisms of regulation of *BDNF* gene expression. Activity-induced expression of the *BDNF* gene in cultured neurons involves promoter III, which is regulated by calcium influx through voltage-stimulated calcium channels via calcium/calmodulin dependent kinase IV and the transcription factor CREB (Shieh et al., 1998; Tao et al., 1998). In vivo, however, calcium/calmodulin-dependent protein kinase inhibition blocks activity-induced expression of exon I, but not of exon III (Murray et al., 1998). Promoter I is also activated in an activity-dependent manner by a mechanism involving calcium influx through voltage-stimulated calcium channels, in cultured neurons (Tabuchi et al., 1998). Furthermore, basal and activity-induced expression of promoters I and II in neurons, in vivo, can be suppressed by the neuron-restrictive silencer element (NRSE). NRSE is a negative regulatory element that prevents the expression of neuronal genes (Timmusk et al., 1999). Interestingly, activity-induced expression of *BDNF* exons I and II is negatively modulated by adrenal steroids in vivo (Lauterborn et al., 1998). Other specific elements in the BDNF gene involved in the regulation of BDNF expression are currently under study (Sohrabji et al., 1995; Timmusk et al., 1995; Bishop et al., 1997; Hayes et al., 1997; Tabuchi et al., 1999).

Activity-induced changes in BDNF expression have a very short latency, suggesting that BDNF can function as an immediate-early gene. In good agreement with this hypothesis, activity-induced expression of the different BDNF mRNAs is differently affected by protein synthesis inhibition. Anisomycin significantly attenuated the activity-induced increases in exon I- and II-containing BDNF mRNAs, but has no effect on exon III- and exon IV-containing transcripts, in mature forebrain neurons. Thus, activity-induced expression of BDNF exons III and IV can be considered as an immediate-early gene response (Lauterborn et al., 1996; see also Hughes et al., 1993 and a review by Hughes et al., 1999).

The human *BDNF* gene has been mapped to chromosome 11 (Maisonpierre et al., 1991; Ozcelik et al., 1991), more precisely, to a region involved in a genetic disorder known as the WRAG (Wilms tumor, aniridia, genito-urinary abnormalities, mental retardation) syndrome (Hanson et al., 1992; Rosier et al., 1994), suggesting that the deletion of the *BDNF* gene can contribute the patients' mental retardation. Recent studies are aimed to characterize in detail the human *BDNF* gene and its chromosomal environment (Guillemot et al., 1999).

2.3. BDNF seems to be stored in vesicles and subject to regulated release

From sequence data it could be predicted that all mature NTs result from post-translational processing of precursors containing an hydrophobic signal peptide followed by large pro-regions. The pro-NTs are more than twice the size of the mature forms (typically 28–35 kDa molecules) (Seidah et al., 1996a, 1996b; Marcinkiewicz et al., 1998; Haubensak et al., 1998), and all contain a consensus type I cleavage site for furin-like pro-protein convertases (PCs) (Seidah et al., 1996a, 1996b, 1998). Furin is a member of a family of endoproteases related to bacterial subtilisin and yeast kexin serine-proteases. The other known mammalian members of the subtilisin/kexin-like convertase family are named PC1/3, PC2, PACE4, PC4, PC5/6 and PC7/PC8, some of them having isoforms generated by alternative splicing (reviewed by Nakayama, 1997; Seidah et al., 1998).

Among the PCs, furin, PACE4, PC5/6 and PC1/3 are able to promote cleavage of pro-BDNF into mature BDNF (being furin the more efficient), when each convertase is co-expressed with full-length cDNA for hBDNF in cell lines. Similarly, furin, PACE4 and PC5/6, can process pro-NGF and pro-NT3 (Seidah et al., 1996a, 1996b). While furin and some other PCs are involved in processing pro-proteins within the *trans*-Golgi network, allowing the subsequent constitutive release of their active forms (Dubois et al., 1995; Mori et al., 1999; Mowla et al., 1999), PC1, PC2 and probably other PCs seem to cleave pro-proteins in granules after they bud from the *trans*-Golgi network, allowing regulated release of the mature forms (Rouille et al., 1995; Nakayama, 1997; Haubensak et al., 1998; Mowla et al., 1999). Thus, the kind of convertases expressed by a cell, their level of expression, and the mechanisms that regulate their expression, can potentially influence processing of pro-NTs by cells. The regional and cellular localization of the various convertases in the central nervous system and the mechanisms regulating their expression are just beginning to be elucidated (Schafer et al., 1993; Dong et al., 1995; Marcinkiewicz et al., 1997).

NGF has been shown to be released both constitutively and in a regulated manner by different cells (Barth et al., 1984; Edwards et al., 1988; Blöch and Thoenen, 1995, 1996; Heymach et al., 1996; Carstén Möller et al., 1998; Griesbeck et al., 1999; Mowla et al., 1999). This seems to be the case for BDNF and other NTs as well. Early studies by Goodman et al. (1996) showed that BDNF is targeted to the regulated pathway of secretion in a pituitary cell line transfected with a hBDNF cDNA. In these cells, BDNF-immunoreactivity colocalizes with chromogranin A (a marker of dense-core vesicles), and BDNF release can be induced by depolarization with high potassium in a calcium-dependent manner (see also Carstén Möller et al., 1998). The authors further demonstrated calcium-dependent stimulated release of BDNF from primary cultured hippocampal neurons, which were previously infected with an Herpes Simplex viral vector containing a hBDNF cDNA. A small amount of BDNF seemed to be released constitutively both by the transfected pituitary cell line and infected hippocampal neurons. Fawcett et al. (1997) have subsequently demonstrated that BDNF is present in a synaptosomal vesicular fraction obtained from rat cortical extracts. Localization of BDNF to vesicles was also observed by Haubensak et al. (1998) in primary cultured rat cortical neurons. The authors demonstrated that a fusion protein consisting of BDNF and green fusion protein colocalizes with secretogranin-II (a marker of secretory granules of the regulated pathway) in the soma and dendrites, but also in axons, of cultured cortical neurons. Furthermore, they showed a patchy staining corresponding to endogenous BDNF-like immunoreactive material in neurites of cultured cortical neurons (see also Tongiorgi et al., 1997). Finally, Mowla et al. (1999) studied cultured hippocampal neurons, Schwann cells, and cell lines expressing the full-length coding regions of pro-BDNF, and found that newly synthesized BDNF is retained within cells, in vesicles localized to cell processes, and that its release can be induced by exposing cultures to a medium with a high potassium concentration. Besides, inhibition of furin (which is involved in processing of constitutively secreted proteins) did not affect processing pro-BDNF, while cold-blocking (a procedure that impairs exit of proteins from the *trans*-Golgi network) was effective. Consequently, there is little doubt that BDNF can be sorted to the regulated pathway of secretion in neurons.

2.4. BDNF binds to low- and high-affinity receptors

The biological actions of NTs are mediated by two classes of membrane receptors (reviewed by Barbacid, 1994a, 1994b; Chao, 1994; Dechant et al., 1994; Bothwell, 1995). All NTs bind with similar affinities ($K_d \sim 10^{-9}$ M) to a protein nowadays named as NT receptor p75 ($p75^{NTR}$). Furthermore, NTs bind with distinct selectivities to three highly related receptor protein–tyrosine kinases, known as high-affinity ($K_d \sim 10^{-11}$ M) NT receptors TrkA, TrkB and TrkC. NGF specifically binds to TrkA, BDNF and NT-4/5 to TrkB, and NT-3 binds preferentially to TrkC but also to TrkB and TrkA with lower efficacy (Hempstead et al., 1991; Kaplan et al., 1991; Klein et al., 1991a, 1991b, 1992; Lamballe et al., 1991; Soppet et al., 1991; Squinto et al., 1991; Ip et al., 1992).

The characterization of an oncogene isolated from a colon carcinoma (Martin-Zanca et al., 1986), led to the identification of the corresponding proto-oncogene, which codes for a 140 kDa membrane glycoprotein containing a cytoplasmic protein–tyrosine kinase domain (Martin-Zanca et al., 1989). The oncogene was designated *trk* because of its structure, consisting of two fused sequences coding for a tropomyosin isoform and a receptor protein–tyrosine kinase. Ensuing work established that the protein encoded by the *trk* proto-oncogene was the high-affinity receptor mediating the main biological actions of NGF (TrkA; Hempstead et al., 1991; Kaplan et al., 1991; Klein et al., 1991a; reviewed by Dechant et al., 1994; Barbacid, 1994a, 1994b; Snider, 1994). Two other closely related genes which are highly expressed in the brain have subsequently been identified in mammals, *trkB* (Klein et al., 1989) and *trkC* (Lamballe et al., 1991), and found to encode for proteins binding BDNF, NT-4/5 and NT-3 (Klein et al., 1991b; Lamballe et al., 1991; Soppet et al., 1991; Squinto et al., 1991; Ip et al., 1992; Klein et al., 1992).

The *trkB* gene can give rise to several different transcripts in rodents, among which there are two mRNAs encoding the "full-length" or catalytic form of TrkB, the receptor mediating the main biological actions of BDNF (Dechant et al., 1994; Barbacid, 1994a, 1994b; Snider, 1994). Other transcripts give rise, at least, to two isoforms of TrkB which lack a large part of the intracellular domain and do not display protein–tyrosine kinase activity, known as "truncated" TrkB receptors (Klein et al., 1990a; Middlemas et al., 1991).

Full length Trk receptors have a complex structure, including a transmembrane region, an extracellular portion involved in NT binding, and an intracellular portion with protein–tyrosine kinase activity. The extracellular region includes a leucine-rich domain flanked by two cysteine-rich clusters, followed by two immunoglobulin-like domains (Schneider and Schweiger, 1991), one of which is essential for NT binding (Urfer et al., 1995; Haniu et al., 1997; Ultsch et al., 1999). Among the high-affinity Trk receptors, TrkB is the more promiscuous, since it binds BDNF, NT-4/5 and NT-3 (Klein et al., 1991b; Lamballe et al., 1991; Soppet et al., 1991; Squinto et al., 1991; Ip et al.,

1992; Klein et al., 1992). Two mechanisms have been described that can increase its selectivity for BDNF. First, a splice variant of the catalytic form of TrkB, lacking a part of the extracellular portion (catalytic TrkB "short") displays high affinity for BDNF, but interacts poorly with NT-4/5 and NT-3. Catalytic TrkB short is expressed by embryonic neurons (Strohmaier et al., 1996). Second, co-expression of $p75^{NTR}$ and TrkB in a cell line augments the specificity of TrkB for BDNF, compared with NT-3 and NT4/5 (Bibel et al., 1999).

NT binding leads to activation of full-length Trk receptors by a two-step process, consisting of ligand-induced receptor dimerization, and autophosphorilation of tyrosine residues in the intracellular region (Schlessinger and Ullrich, 1992). The activated receptors become able to interact and phosphorilate several intracellular targets (Segal and Greenberg, 1996). Among the proteins that can be activated by autophosphorilated Trk receptors are phospholipase C-1γ (Obermeier et al., 1994; Stephens et al., 1994); the adapter proteins Shc, rAPS and SH2-B (Obermeier et al., 1994; Stephens et al., 1994; Qian et al., 1998); phosphatidylinositol-3′ kinase (PI3K; Kaplan and Stephens, 1994; Stephens et al., 1994); Fyn, a protein–tyrosine kinase involved in regulation of cell adhesion and synaptic plasticity (Iwasaki et al., 1998); the brain immunoglobulin-like molecule with tyrosine-based activation motifs (BIT, also known as SHPS-1 and SIRPα; Ohnishi et al., 1999); and fibroblast growth factor receptor substrate 2 (FRS2; Easton et al., 1999). In turn, these activated proteins lead to activation of the Ras/mitogen-activated protein kinase (MAPK) signaling pathway and phosphorilation of extracellular signal-regulated kinases (ERKs) (Kaplan and Stephens, 1994), to an increase in intracellular calcium concentration and subsequent activation of calcium/calmodulin-dependent kinases and casein kinase 2 (Blanquet and Lamour, 1997; Finkbeiner et al., 1997; Blanquet, 1998), CREB phosphorylation (Finkbeiner et al., 1997), and further activation of phosphatidylinositol-3′ kinase (Baxter et al., 1995). The picture is further complicated by the existence of endogenous substances that can block activation of Trk receptors (see for example Hu and Koo, 1998).

A recent study has addressed the question of the ultrastructural localization of catalytic TrkB receptor immunoreactivity in the adult rat hippocampal formation, by means of electron microscopy (Drake et al., 1999). Catalytic TrkB-immunoreactivity was observed along axons, in synaptic terminals, and in the plasma membrane of dendritic spines. Localization of catalytic TrkB in synaptic terminals is consistent with the presumed role of TrkB receptors in mediating retrograde transport of BDNF to neuronal cell bodies (Bhattacharyya et al., 1997; Watson et al., 1999; see Section 2.6), and the reported actions of BDNF on presynaptic function (see Section 4.1.4). The presence of catalytic TrkB receptors on dendritic spines is consistent with previous findings which reported the presence of functional catalytic TrkB receptors in isolated postsynaptic densities (Wu et al., 1996). In conjunction with the data summarized in Section 2.3 relative to BDNF localization in vesicles and its regulated release, these work suggest that the synapses are the main site of action of BDNF in the central nervous system (see Section 4.1.4).

Although catalytic TrkB is considered as the receptor mediating the main biological actions of BDNF, one of the truncated forms of TrkB (TrkB.T1) is the predominant isoform in the adult brain (Escandón et al., 1994; Allendoerfer et al., 1994; Armanini et al., 1995). At the moment of their discovery, the truncated TrkB receptors were postulated to function as cellular adhesion molecules regulating synaptic plasticity and axonal outgrowth, to modulate signaling by catalytic TrkB through formation of heterodimers, and to regulate the extracellular availability of its endogenous ligands (Klein et al., 1990a; Middlemas et al., 1991). At present, there is some evidence supporting these predictions. When the catalytic form of TrkB is co-expressed with either TrkB.T1 or TrkB.T2 in the same cells, BDNF signaling is impaired as consequence of the formation of receptor heterodimers (Eide et al., 1996; Nikina et al., 1996), supporting that the truncated forms of TrkB can act as negative modulators of BDNF signaling. There is also evidence indicating that BDNF binds to truncated TrkB receptors in ependymal and leptomeningeal cells, and is subsequently internalized. This mechanism regulates the availability of endogenous BDNF in the central nervous system during development (Biffo et al., 1995), and limits the penetration of exogenous BDNF into the brain parenchyma after intraventricular administration (Yan et al., 1994). Glial cells also internalize BDNF bound to truncated TrkB receptors, and can store and subsequently release the sequestered BDNF molecules (Rubio, 1997; see Section 2.5). Consequently, glial cells can regulate the availability of BDNF and influence its biological actions on neurons (Fryer et al., 1997; see Section 2.5). Interestingly, truncated TrkB receptors are up-regulated in glial central nervous system cells after injury (Beck et al., 1993b; Frisén et al., 1993; Merlio et al., 1993; Venero and Hefti, 1998). Finally, recent evidence suggests that truncated TrkB receptors can mediate ligand-induced signal transduction in transfected cell lines, by a non-elucidated mechanism, which involves their specific short intracellular aminoacid domain (Baxter et al., 1997).

As occurs with BDNF, TrkB expression is regulated by bioelectrical activity, hypoxia-ischemia and hypoglycemic coma, and axotomy. The expression of the

full length and truncated forms of TrkB is sensitive to these stimuli (Beck et al., 1993b; Frisén et al., 1993; Lapchak et al., 1993c; Merlio et al., 1993). Recent elegant studies have demonstrated that bioelectrical activity promotes dendritic targeting of BDNF and TrkB mRNAs, and increases BDNF and TrkB protein levels in the dendritic tree (Tongiorgi et al., 1997), suggesting that local autocrine loops can regulate the structure and function of selective portions of the dendritic arbor (Horch et al., 1998). Depolarization increases neuronal responsiveness to BDNF by another mechanism, a rapid translocation of intracellular TrkB receptors to the plasma membrane (Meyer-Franke et al., 1998).

Finally, it has been observed that prolonged exposure to recombinant-human BDNF (rhBDNF) produces a strong down-regulation of full-length TrkB receptors in vitro and in the adult rat hippocampus (Frank et al., 1996; Knüsel et al., 1997), a fact that must be considered during the design of therapeutic strategies based on BDNF administration.

$p75^{NTR}$ has a glycosylated extracellular portion containing four cysteine-rich clusters involved in ligand binding, a transmembrane region, and a short cytoplasmic sequence which lacks intrinsic catalytic activity (Chao, 1994; Bothwell, 1995; Ibáñez, 1998). It is structurally related to proteins of the tumor necrosis factor receptor (TNFR) superfamily, including the TNFRs type I and II, Fas antigen, lymphocyte antigens CD40 and CD30, and several other receptor proteins possessing non-catalytic intracellular regions known as "death domains" (Baker and Reddy, 1998).

The mechanisms of transduction mediating the biological effects of $p75^{NTR}$ in neurons are poorly understood. On the one hand, $p75^{NTR}$ can modulate cellular responses to NTs, by interacting with their high-affinity Trk. Modulation of Trk interaction with NTs has been considered as the main $p75^{NTR}$ mechanisms of action since the discovery of Trk receptors (Barbacid, 1994a, 1994b; Chao, 1994; Dechant et al., 1994; Chao and Hempstead, 1995; Bothwell, 1995). However, it was clearly established that $p75^{NTR}$ can induce cellular responses in the absence of Trk receptors, notably cell death, when it is activated by NGF (Carter and Lewin, 1997; Dechant and Barde, 1997; Frade and Barde, 1999). Efforts aimed at finding proteins able to directly interact with $p75^{NTR}$, have recently succeeded in identifying RhoA, a member of the Ras superfamily of GTP-binding proteins (Yamashita et al., 1999), tumor necrosis factor receptor-associated factor-6 (TRAF6, Khursigara et al., 1999), and a zinc finger protein named NT receptor interacting factor (NRIF, Casademunt et al., 1999). These proteins are presumptively the mediators of $p75^{NTR}$-induced changes in NF-κB and c-Jun kinase activities, and activation of the sphingomyelin cycle, which result in the biological effects of $p75^{NTR}$ activation. Interestingly, downstream intracellular events can be raised by the NGF-$p75^{NTR}$ receptor complex, but not by binding of other NTs to $p75^{NTR}$ (Carter and Lewin, 1997; Dechant and Barde, 1997; Chao et al., 1998a). Startlingly, recent results showed that intracellular events and apoptotic cell death can be induced in cell lines and cultured neurons by binding of β-amyloid to $p75^{NTR}$ (Yaar et al., 1997; Kuner et al., 1998).

In the peripheral nervous system, BDNF-induced activation of $p75^{NTR}$ seems to produce apoptotic death of sympathetic neurons (Bamji et al., 1998). However, $p75^{NTR}$-deficient mutant mice do not display the characteristic alterations observed in BDNF- and TrkB- deficient mice, suggesting that $p75^{NTR}$ is not essential for most of the biological actions of BDNF in vivo (Barbacid, 1994a, 1994b; Snider, 1994).

2.5. BDNF is present in neurons and glia

The high sequence homology among NTs precluded the rapid development of highly specific anti-BDNF antibodies. To obtain them, the preferred strategy consisted in raising antibodies directed against fragments of the BDNF mature sequence which show low homology with the sequences of other NTs. Other groups preferred to develop antibodies against the complete mature from of the protein. Several independently developed anti-BDNF antibodies were raised and used to stain brain tissue sections, in order to study the cellular and regional distribution of BDNF in the central nervous system. Despite the high homology between the NTs and the different technical approaches used, it is not surprising that the various published reports have provided some discordant results.

It is widely accepted that BDNF mRNA is expressed by neurons (see below). However, some disagreement exists regarding the subcellular localization of the BDNF protein (cytoplasmic or nuclear, somatodendritic or axonal). The first report, describing the localization of BDNF protein in rat brain tissue sections, stressed that BDNF-immunoreactivity is present in the nucleus of hippocampal neurons (Wetmore et al., 1991; see also Wetmore et al., 1993; Schmidt-Kastner et al., 1996a). The authors also noticed the presence of BDNF immunoreactive material in the cell body cytoplasm and dendrites of neurons, and proposed that pro-BDNF can be processed differentially, originating as a mature secretory form, or an alternative product which is translocated to the nucleus. These results were obtained with antibodies directed against a synthetic peptide with an amino acid sequence corresponding to a region of the BDNF protein showing low homology with other NTs. Interestingly, two other research teams have independently developed antibodies directed against the same syn-

thetic peptide. On the one hand, Furukawa et al. (1998) reported neuronal nuclear and somatodendritic staining in rat brain tissue sections, and further demonstrated nuclear staining with another anti-BDNF antibody, raised against a different part of mature BDNF. On the other hand, Kawamoto et al. (1996) did not find nuclear staining with their antibody. Both research groups additionally localized BDNF-immunoreactivity to the neuronal cell body cytoplasm and dendrites. Localization of BDNF protein to a nuclear fraction obtained from rat hippocampal homogenates was reported by Katoh-Semba et al. (1997). The authors used two different anti-BDNF antibodies, and further showed nuclear staining of hippocampal neurons in rat brain tissue sections. Experiments performed by other researcher groups, with polyclonal antibodies directed against rhBDNF, failed to show any nuclear staining, but consistently showed somatodendritic localization of BDNF protein in rat brain tissue sections (Dugich-Djordjevic et al., 1995; Conner et al., 1997; Yan et al., 1997a). With these efforts by all groups in order to discard cross-reactivity of their antisera with other NTs, and the care was taken to prove specificity of tissue labeling, it can be suggested that in the nucleus and the somatodendritic compartment of neurons, different epitopes of the BDNF protein are accessible for antibody binding. It should be mentioned, however, that recent in vitro studies aimed at studying the intracellular trafficking of BDNF using methods to tag the translated product, failed to reveal BDNF protein targeting to the nucleus

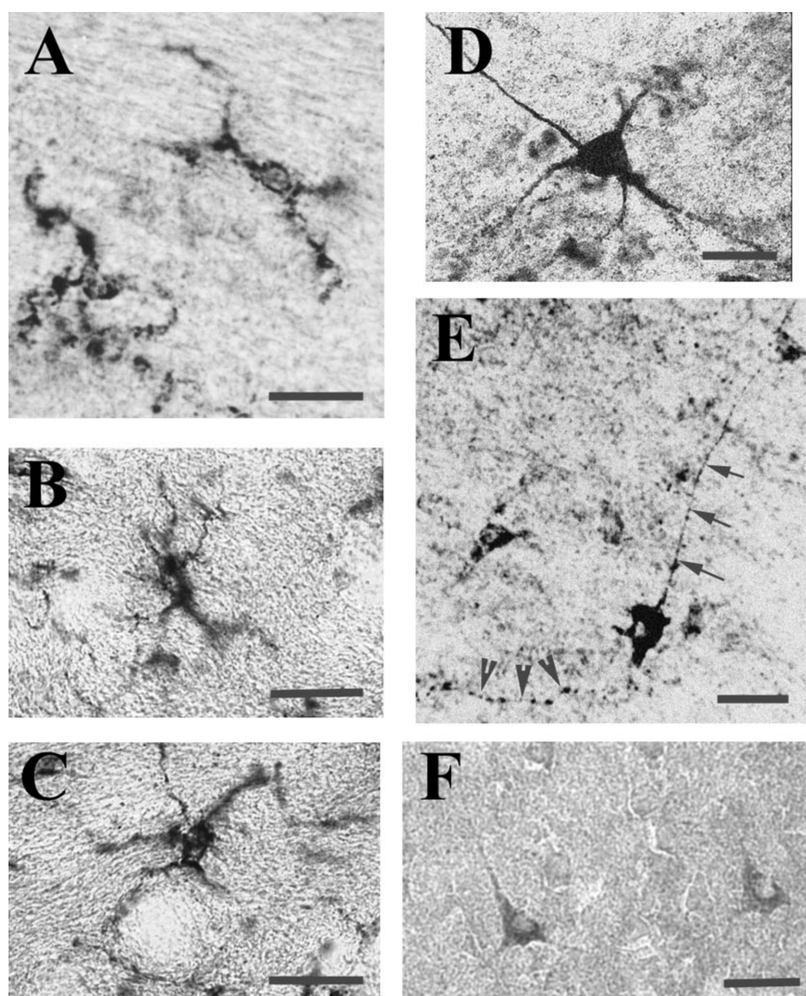

Fig. 2. High-power microphotographs illustrating the typical aspect of glial cells (A, B, C) and neurons (D, E, F) in control human brain tissue sections, immunostained with antibodies directed against human recombinant BDNF. Labeled glial cells in the brain stem. In (A), lightly labeled cell bodies with delicate processes resembling microglia or oligodendroglia. This was the most frequent kind of glial labeling pattern observed. Strongly, immunoreactive astrocyte-like cells were also found (B, C). Neurons in the claustrum were among the most strongly labeled (D). Note the somatodendritic distribution of the protein. Neurons with an "inverted' pyramidal morphology projecting their axons to the cortex (black arrowhead) were occasionally observed in the white matter immediately adjacent to the cortex and deep layer VI (E). Varicose fibers were frequently found in the cortex (white arrow in E). In (F), large pyramidal neurons in the deep layers of the entorhinal cortex. In most glial cells and neurons BDNF-immunoreactivity is clearly excluded from the nucleus. Scale bars: A, B, C, 10 μm; C, D, F, 50 μm.

(Carstén Möller et al., 1998; Haubensak et al., 1998; Mowla et al., 1999).

Studies in cultured neurons emphasized that BDNF protein is localized to the somatodendritic compartment of neurons in cultured cells. In cultured rat hippocampal neurons, Goodman et al. (1996) was able to localize BDNF-immunoreactivity in MAP2 (microtubule associated protein type 2, a marker of the somatodendritic domain) immunoreactive processes. Haubensak et al. (1998) provided further evidence localizing BDNF-immunoreactivity to the somatodendritic compartment of cultured rat cortical neurons, and showed co-localization of BDNF-immunoreactivity with an axon specific protein (Tau) in a minority of cells. The authors stressed that BDNF was excluded from the nucleus. Immunocytochemical studies of BDNF-immunoreactive neurons in adult brain tissue section, confirmed labeling of dendrites and axons, in rodents (Dugich-Djordjevic et al., 1995; Schmidt-Kastner et al., 1996a; Kawamoto et al., 1996; Yan et al., 1997a; Conner et al., 1997; Yan et al., 1997; Friedman et al., 1998; Furukawa et al., 1998), monkeys (Kawamoto et al., 1999b) and humans (Ferrer et al., 1999; Kawamoto et al., 1999a; Murer et al., 1999a; Parain et al., 1999) (Fig. 2).

Several workers have demonstrated BDNF mRNA expression in rodent cultured glial cells. Acheson et al. (1991) reported BDNF expression by Schwann cells in culture, whereas Rudge et al. (1992) and Condorelli et al. (1994) reported low levels of BDNF mRNA in primary rat astroglial cultures (but see Rubio, 1997). Elkabes et al. (1996) demonstrated that rodent microglia express BDNF mRNA in vitro. There is strong evidence supporting that other NTs are expressed by glial cells as well (Mallat et al., 1989; Lu et al., 1991; Rudge et al., 1992; Zafra et al., 1992; Zhou and Rush, 1993; Byravan et al., 1994; Condorelli et al., 1994; Schwartz and Nishiyama, 1994; Arendt et al., 1995; Elkabes et al., 1996).

However, early experiments looking for BDNF protein distribution in rodent brain tissue sections failed to detect BDNF-immunoreactivity in glial cells (Wetmore et al., 1991, 1993; Dugich-Djordjevic et al., 1995; Schmidt-Kastner et al., 1996a; Kawamoto et al., 1996). Our own anti-BDNF antibody did not reveal glial labeling in the adult rat brain (Conner et al., 1997; Yan et al., 1997a), nor in embryonic rat mesencephalic cultures containing neurons and astrocytes (Murer et al., 1999b). Intriguingly, in our experiments in the postmortem human brain, we consistently observed BDNF-immunoreactive glial cell bodies and processes in control and pathological brains, although the degree of glial labeling varied considerably among individuals (Murer et al., 1999a; Parain et al., 1999) (Fig. 2). Glial immunoreactive cells in the human brain showed different morphologies. The most frequent glial labeling pattern consisted of a delicate peripheral immunoreactive band which delineated the cell body and extended to fine processes. The aspect of these cells remembered that of microglia or oligodendroglia (Fig. 2(A)). Consistent with this idea, these cells were prominent in the white matter. Other cells showed an intense cell body labeling and multiple strongly stained processes, resembling astroglia (Fig. 2(B) and (C). In our own material, immunoreactive glial cells were ubiquitously distributed, but particularly abundant in the white matter. Interestingly, BDNF-deficient mice show a defect in central nervous system myelination (Cellerino et al., 1997).

There are other reports showing glial BDNF-immunoreactivity in human brain tissue sections. Soontornniyomkij et al. (1998) studied the brain of humans with immunodeficiency virus (HIV) encephalitis and found BDNF-immunoreactive microglia/macrophages in brain lesions, but did not report labeling of glial cells in control brains. A previous report of this group (Achim and Wiley, 1996) demonstrated that in vitro human fetal microglia increases BDNF mRNA expression following HIV infection. BDNF-immunoreactive material was found in GFAP-immunoreactive astrocytes in human control striatal sections by Kawamoto et al. (1999a), however, and in cultures, human embryonic astrocytes express BDNF mRNA (Moretto et al., 1994). Kerschensteiner et al. (1999) also showed weak BDNF-immunoreactivity of astrocytes in the control human brain. The authors also reported BDNF protein expression in inflammatory cells forming perivascular infiltrates in postmortem tissue sections from individuals with post-infectious leukoencephalitis and multiple sclerosis. The labeled cells were identified as T cells and macrophages by studying specific antigens in serial sections. In two cases of multiple sclerosis, they also found BDNF-immunoreactive macrophages in actively demyelinating lesions. In vitro, human $CD4^+$ T cells, $CD8^+$ T cells and B cells express BDNF mRNA, constitutively release BDNF to the culture medium, and increase BDNF release under stimulated conditions. Stimulated human monocytes also express BDNF mRNA in cultures, and release BDNF protein (Kerschensteiner et al., 1999). Finally, Ferrer et al. (1999), reported BDNF-immunolabeling of reactive astrocytes in the cerebral cortex of patients with old cerebral infarcts.

Our contrasting findings showing BDNF-immunoreactive glia in the control human brain but not in the healthy rat brain (Yan et al., 1997a; Murer et al., 1999a), led us to hypothesize that premortem conditions could have induced BDNF expression in human glial cells. This hypothesis is consistent with findings showing increased BDNF expression after hypoxia-ischemia and hypoglycemic coma (Lindvall et al., 1992; Merlio et al., 1993) or stress (Smith et al.,

1995). However, a recent detailed report on BDNF protein distribution in the monkey brain, using an anti-BDNF peptide antibody (Kawamoto et al., 1999b), describes widely distributed BDNF-immunoreactive microglia-like cells and occasional BDNF-positive astrocyte-like cells, resembling closely the pattern as seen by us in the control human brain. Furthermore, Dreyfus et al. (1999) also found labeling of astrocytes (GFAP (glial fibrillary acidic protein) positive cells) and other non-GFAP positive cells in the white matter of the rat spinal cord, and Furukawa et al. (1998) reported BDNF-immunoreactive oligodendrocytes in the rat brain white matter. Thus, it seems that BDNF protein is present in resting mammalian glial cells.

It should be pointed out that presence of BDNF protein in glial cells do not necessarily imply glial synthesis of BDNF, but alternatively, it could indicate BDNF internalization, or the presence of receptor-bound BDNF. Glial cells were found to express the truncated and the catalytic forms of TrkB (Frisén et al., 1993; Rudge et al., 1994; Roback et al., 1995; Nakajima et al., 1998). In an elegant series of experiments, Rubio (1997) demonstrated that cultured mouse astrocytes express the non-catalytic truncated form of TrkB, which mediates exogenous BDNF internalization and storage. The stored BDNF molecule is not degraded intracellularly, but released to the culture medium. The author proposed that astrocytes and other cells expressing the truncated form of TrkB regulate the bioavailability of BDNF. This hypothesis has been tested in co-culture systems consisting of non-neuronal cells expressing or not the non-catalytic form of TrkB, and neuroblastoma cells expressing full length TrkB (Fryer et al., 1997). In this system, non-neuronal cells expressing truncated TrkB became able to internalize BDNF and inhibited BDNF-induced differentiation of neuroblastoma cells. Interestingly, truncated TrkB receptors are up-regulated in glial central nervous system cells after injury (Beck et al., 1993b; Frisén et al., 1993; Merlio et al., 1993; Venero and Hefti, 1998), suggesting that glial modulation of BDNF availability might be implicated in regulating post-injury axonal sprouting and other reparative processes.

Finally, evidence from in vitro and animal studies support that BDNF expression and release by glial cells can be regulated by different signals and injury (Condorelli et al., 1994; Inoue et al., 1997; Miwa et al., 1997; Elkabes et al., 1998). Ceccatelli et al. (1991) reported an increased BDNF mRNA signal in white matter tracts of rats after colchicine treatment, suggesting that glia could express BDNF under conditions of severe metabolic stress, and Batchelor et al. (1999) reported induction of BDNF mRNA expression in activated microglia in the injured adult rat striatum. There is also evidence showing that BDNF can regulate glial function. Cultured microglia was found to express p75^{NTR} and all Trk high-affinity receptors for NTs and respond to BDNF (Roback et al., 1995; Elkabes et al., 1996; Nakajima et al., 1998). Furthermore, it was found that in vivo, BDNF administration prevents astroglial activation and macrophage infiltration that follows global ischemia (Kiprianova et al., 1999).

2.6. Retrograde and anterograde transport of BDNF

Earlier efforts in NGF cellular biology (reviewed by Levi-Montalcini, 1987; Thoenen et al., 1987), showed that BDNF is retrogradely transported by peripheral and central nervous system neurons (reviewed by Altar and DiStefano, 1998; von Bartheld, 1998 and Mufson et al., 1999). As is the case for NGF, locally applied BDNF can be taken up by axons and retrogradely transported to neuronal cell bodies in the adult mammalian central nervous system (DiStefano et al., 1992; reviewed by Mufson et al., 1999). To our knowledge, however, a formal demonstration of the existence of retrograde axonal transport of endogenous BDNF in the mammalian central nervous system is lacking. Both p75^{NTR} and TrkB seem to be able to mediate retrograde transport of BDNF, at least in the peripheral nervous system (Curtis et al., 1995, 1996a; von Bartheld et al., 1996; Bhattacharyya et al., 1997; Watson et al., 1999).

Recent findings demonstrated that BDNF is anterogradely transported in the central nervous system, a fact that has considerably expanded the concept of neuronal-derived trophic support, and sustains the hypothesis that BDNF can have actions at the synaptic level (see Section 2.4). This work has been recently reviewed by Altar and DiStefano (1998) and Mufson et al. (1999), and will be briefly summarized here. The distribution of exogenous BDNF protein following localized brain injections, is compatible with BDNF anterograde transport from cell bodies to nerve endings. Thus, after injections of BDNF into the amygdala, a dense BDNF-immunoreactive fiber plexus was found in an important amygdaloid complex target field, the bed nucleus of the stria terminalis (Sobreviela et al., 1996). Exogenous BDNF is also anterogradely transported from a neostriatal nucleus to the archistriatum in birds (Johnson et al., 1997; see also von Bartheld et al., 1996 and Akutagawa and Konishi, 1998). A comprehensive anatomical work by Conner et al. (1997) showed that BDNF protein is abundantly expressed by axon-like processes in some central structures lacking BDNF mRNA expression. BDNF mRNA is not expressed in the rat central nucleus of the amygdala, where a dense BDNF-immunoreactive fiber plexus is present. Lesions of the pontine parabrachial nuclei eliminated the BDNF-immunoreactive fiber plexus from the central nucleus of the amygdala.

Similarly, the dense BDNF-immunoreactive neuropile of the medial habenula (where BDNF mRNA is not expressed) disappeared after lesions of the septum. These results strongly suggested the existence of anterograde axonal transport of BDNF (Conner et al., 1997). In another interesting study, Smith et al. (1997) exploited the fact that seizures increase the expression of BDNF in the hippocampus, to compare the localization of changes of mRNA and protein expression at the cellular level. They found that seizures increase the expression of BDNF mRNA in the granule cells of the dentate gyrus, whereas BDNF-immunoreactivity increases in mossy fibers, that is, in the axons of the granule cells projecting to the CA3 hippocampal pyramidal layer. Destruction of the CA3 pyramidal layer, a putative source of retrograde BDNF for mossy fibers, did not affect the increase in BDNF protein as observed in mossy fibers after seizures. More direct evidence supporting the anterograde transport of endogenous BDNF was provided by Altar et al. (1997). The authors found that most striatal BDNF proceeds from the cerebral cortex, and secondarily, from the substantia nigra pars compacta, the two main striatal afferent nuclei. In rats treated with colchicine, an axonal transport blocker, the striatal content of BDNF falls, whereas that of the cortex and substantia nigra increases. Besides, the striatal BDNF content is severely reduced by lesions of the cortex (see also Kokaia et al., 1998), and in a lesser degree, by nigral lesions.

Evidence regarding a functional role of anterogradely transported BDNF in the central nervous system, however, is scarce. The experiments by Johnson et al. (1997) in birds, provided indirect evidence for a role of anterogradely transported BDNF in the developmental regulation of survival of archistriatal neurons. Similarly, the experiments by Altar et al. (1997) suggested that anterogradely transported BDNF regulates the expression of striatal peptides during development. Finally, there are studies showing a functional role of BDNF in the adult mossy fiber–CA3 pyramidal neuron synapse, suggesting that anterogradely transported BDNF can be involved in normal synaptic function (Scharfman, 1997) and epileptogenesis (Binder et al., 1999; Scharfman et al., 1999). A recent report by Fawcett et al. (1998) provided evidence supporting a trophic action of anterogradely transported BDNF in the developing rodent central nervous system. The authors demonstrated the co-localization of BDNF and dopamine-β-hydroxylase in noragrenergic axons. In addition, they used transgenic mice overexpressing BDNF selectively in noradrenergic neurons, to demonstrate trophic effects of anterogradely transported BDNF in noradrenergic nuclei target fields. Thus, these mice showed increased expression of BDNF in locus coeruleus neurons, increased activation of TrkB receptors in the cerebral cortex (a major target field of locus coeruleus neurons), and changes in cortical architecture. These mice also display trophic changes in facial nucleus motoneurons (Fawcett et al., 1998), and an increased number of substantia nigra dopaminergic neurons (Alonso-Vanegas et al., 1999), structures which possess an important afferent noradrenergic innervation.

2.7. Conclusion

The impressive amount of experimental results on BDNF molecular and cellular biology compiled during the last 10 years has considerably expanded our conception about how NTs act in the brain. Particularly interesting is the accumulated evidence suggesting a role for BDNF in modulation of synaptic activity in the adult brain.

BDNF synthesis is regulated by bioelectrical activity (Patterson et al., 1992; Castrén et al., 1993; Dragunow et al., 1993). Then, BDNF can be sorted to the regulated pathway of secretion, and anterogradely transported to dendrites and axon terminals, where it is released in an activity-dependent manner (Blöch and Thoenen, 1995, 1996; Goodman et al., 1996; Mowla et al., 1999). BDNF can also be retrogradely transported from processes to the cell body, and induce nuclear responses (Bhattacharyya et al., 1997; Mufson et al., 1999; Watson et al., 1999). Catalytic TrkB receptors are present both in the pre- and post-synaptic membranes (Wu et al., 1996; Drake et al., 1999). Many neurons co-express both BDNF and TrkB (Kokaia et al., 1993; Miranda et al., 1993). Consequently, BDNF can potentially be involved in: (1) a kind of neurotransmitter-like axo-dendritic communication; (2) in autocrine loops and paracrine interactions between neighbor cells; (3) in a more classic mechanism for a trophic factor, that is, retrograde communication from dendrites to axon terminals. Through these mechanisms BDNF might induce trophic actions including survival promotion and recovery from injury (see for example, Lindholm, 1994; Nikolics, 1999), have more subtle effects in the structure and function of synapses including a role in long-term potentiation and dendritic arbor modeling (reviewed by Lo, 1995; Thoenen, 1995; Altar et al., 1997; McAllister et al., 1999), and even directly induce very short-latency excitatory potentials and action potential firing (Kafitz et al., 1999).

3. Distribution of BDNF in the adult human brain

In this section the anatomical distribution of BDNF in the adult human control brain is reviewed. The description is mainly based on our own immunocyto-

chemical studies (Murer et al., 1999a), and fragmentary data provided by several other research groups on BDNF protein or mRNA distribution in discrete brain regions. In addition, we compare the distribution of BDNF protein between human, monkey and rat brain. Information about BDNF mRNA distribution (proceeding mainly from studies performed in rats) is also included. Finally, available data on the distribution of TrkB and the receptor protein mediating the main biological actions of BDNF are briefly reviewed, in order to comprehend the possible functional and trophic BDNF-mediated interactions between neurons in the human central nervous system.

A brief summary of the relevant studies, providing information about the ditribution of BDNF in the human brain, is presented in Table 1.

Table 1
The more relevant reports regarding BDNF in the human brain

Distribution of BDNF in the human brain	
Phillips et al. (1990)	mRNA in hippocampus, cortex, amygdala
Phillips et al. (1991)	mRNA in hippocampus
Duberley et al. (1997)	Protein in motor cortex
Kawamoto et al. (1996)	Protein in spinal cord
Nishio et al. (1998a)	Protein in substantia nigra
Nishio et al. (1998b)	Protein in spinal cord
Ferrer et al. (1999)	Protein in hippocampus, cortex
Kawamoto et al. (1999a, 1999b)	Protein in striatum, globus pallidus
Murer et al. (1999a)	Protein in brain, brain stem
Parain et al. (1999)	Protein in substantia nigra
Quartu et al. (1999)	Protein in hippocampus
Soontornniyomkij et al. (1999)	Protein in cerebral cortex and hippocampus
Modifications of BDNF expression and distribution in neurodegenerative disorders	
Phillips et al. (1991)	mRNA reduction in hippocampus, in Alzheimer's disease
Murray et al. (1994)	mRNA reduction in hippocampus, in Alzheimer's disease
Narisawa-Saito et al. (1996)	Protein reduction in entorhinal cortex, no change in dentate gyrus, in Alzheimer's disease
Amoureux et al. (1997)	mRNA reduction in cerebral cortex, in Alzheimer's disease
Connor et al. (1997)	Protein reduction hippocampus, in Alzheimer's disease
Duberley et al. (1997)	Protein, no change in motor cortex, in amyotrophic lateral sclerosis
Hock et al. (1998)	mRNA, no change in parietal cortex and cerebellum in Alzheimer's disease
Nishio et al. (1998b)	Protein reduction in motorneurons, in amyotrophic lateral sclerosis
Ferrer et al. (1999)	Protein reduction in motor cortex and hippocampus, labeling of plaques, in Alzheimer's disease
Kawamoto et al. (1999a, 1999b)	Protein, no change in striatum in Parkinson's disease, increase in striatum in multiple system atrophy
Mogi et al. (1999)	Protein, reduction in substantia nigra in Parkinson's disease
Murer et al. (1999a)	Protein, labeling of plaques in Alzheimer's disease
Parain et al. (1999)	Protein, reduction in substantia nigra in Parkinson's disease
Soontornniyomkij et al. (1999)	Protein, no labeling of plaques in Alzheimer's disease
Modifications in other pathologies	
Mathern et al. (1997)	mRNA increase in dentate granule cells, in temporal lobe epilepsy
Korhonen et al. (1998)	Protein increase in CSF in neonatal asphixia
Soontornniyomkij et al. (1998)	Protein increase in microglia/macrophages in HIV encephalitis
Kerschensteiner et al. (1999)	Protein in inflamatory cells, in multiple sclerosis
Takahashi et al. (1999)	Protein increase in temporal neocortex, in temporal lobe epilepsy
Expression of BDNF in cultured human fetal glial cells	
Moretto et al. (1994)	mRNA in astrocytes
Achim and Wiley, (1996)	mRNA in microglia, induction by HIV
Effects of BDNF on cultured human fetal neurons	
Kato and Lindsay, (1994)	Increases ChAT activity in spinal cord neurons
Zhou et al. (1994)	Increases survival of mesencephalic dopaminergic neurons
Othberg et al. (1995)	Increases survival of mesencephalic dopaminergic neurons
Spenger et al. (1995)	Survival promotion, mesencephalic dopaminergic, GABAergic and serotoninergic neurons
Barnea et al. (1996)	Induces autophosphorilation of TrkB in cortical neurons
Kaddis et al. (1996)	Increases survival of mesencephalic dopaminergic neurons
Studer et al. (1996)	Increases differentiation of mesencephalic dopaminergic neurons
Thajeb et al. (1997)	Increases survival of mesencephalic dopaminergic neurons
Hoglinger et al. (1998)	Increases survival of mesencephalic dopaminergic neurons
Zhou et al. (1998)	Induces dopaminergic phenotype in cortical neurons
Barnea et al. (1999)	Induces somatostatin production in cortical neurons
Pliego-Rivero et al. (1999)	Induces dopaminergic phenotype in cortical neurons
White et al. (1999)	Promotes survival and differentiation of neuroprogenitor cells

3.1. Technical considerations

As summarized above (Section 2.5) the different available antibodies provided somewhat divergent information regarding the subcellular localization of BDNF in neurons, more specifically, regarding labeling of the nucleus and axons. There are several reason, beyond deficient antibody specificity, that can explain the contrasting results. Some antibodies might be recognizing epitopes that are only available before complete BDNF folding (particularly anti-BDNF peptide antibodies), and consequently, revealing the protein in the cell body but not in cell processes. Besides, BDNF can form complexes with different intracellular proteins in different subcellular compartments, and therefore, expose different epitopes in different compartments. As could be expected, the different antibodies also provided somewhat different results in the analysis of the distribution of BDNF protein at the regional level.

There are other facts that complicate the description of the distribution of BDNF in the brain. In as much as extracellular BDNF is internalized by neurons and retrogradely transported, the presence of the protein in a cell does not necessarily imply that the cell synthesizes BDNF. Furthermore, synthesized BDNF could be preferentially targeted to neuronal processes, including the axon, or rapidly secreted, resulting in low levels of the protein in the cell body. To overcome this problem, available data on the distribution of BDNF mRNA is also included in the following sections.

Finally, the distribution or level of expression of BDNF in the control human brain can differ from that in the rodent brain, for motives distinct than species differences, like death-related changes in BDNF expression occurring only in humans, resulting from hypoxia-ischemia, hypoglycemia, stress, or medication.

3.2. Cerebral cortex, hippocampal formation

Soon after the discovery of BDNF, high levels of BDNF mRNA expression were noticed in the rodent (Hofer et al., 1990; Ernfors et al., 1990a, 1990b; Wetmore et al., 1990) and human (Phillips et al., 1990) hippocampal formation and cerebral cortex. The presence of BDNF-immunoreactivity and mRNA expression in cortical and hippocampal neurons was subsequently confirmed by several research groups, in humans (Phillips et al., 1991; Murray et al., 1994; Connor et al., 1997; Duberley et al., 1997; Ferrer et al., 1999; Murer et al., 1999a; Quartu et al., 1999; Soontornniyomkij et al., 1999), monkeys (Huntley et al., 1992; Hayashi et al., 1997; Okuno et al., 1999; Kawamoto et al., 1999b), and rats (Wetmore et al., 1991; Ceccatelli et al., 1991; Castrén et al., 1995; Dugich-Djordjevic et al., 1995; Kawamoto et al., 1996; Schmidt-Kastner et al., 1996a; Conner et al., 1997; Yan et al., 1997; Friedman et al., 1998; Furukawa et al., 1998). The following description of BDNF protein distribution is based on our own data from human control brain material (Murer et al., 1999a, 1999b),

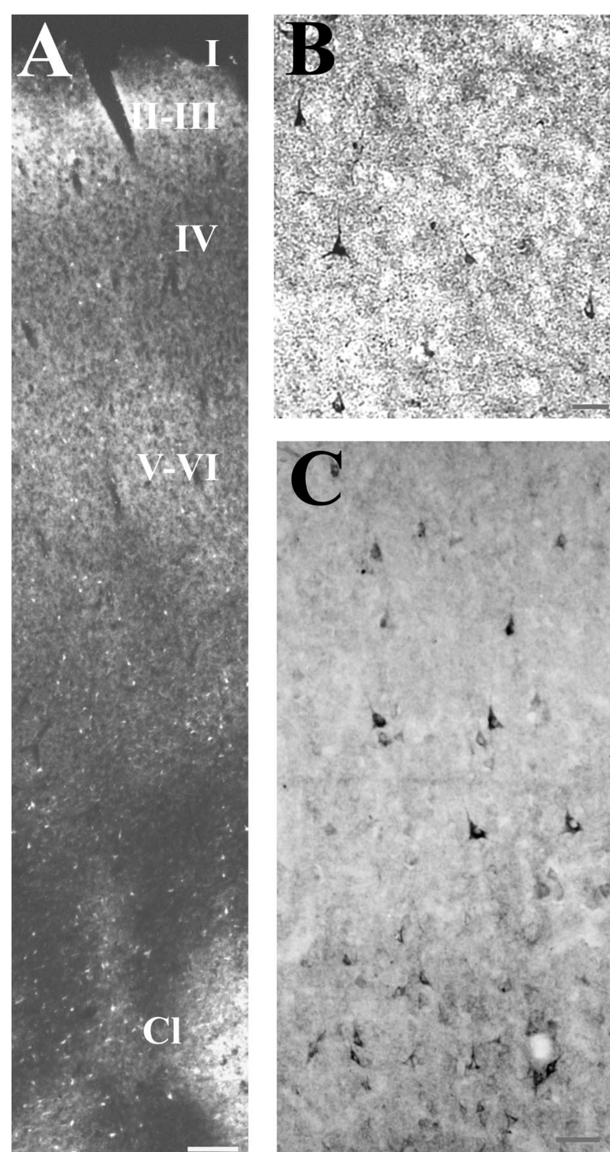

Fig. 3. (A) Low-power microphotograph of the insular cortex showing the distribution of BDNF-immunoreactivity. Note the preferential staining of the deep and superficial cortical layers, the strong staining of the claustrum, and the presence of BDNF-immunoreactive cell bodies in the white matter adjacent to the deep cortical layers. BDNF-immunostaining in the cortex is distributed both in neuronal cell bodies and the neuropile. Scale bar: 0.5 mm. (B) High power microphotograph of deep layer pyramidal neurons containing BDNF in the insular cortex. (C) High power microphotograph of deep layer pyramidal neurons containing BDNF in the temporal cortex. Note the exclusion of BDNF from the nucleus. Scale bars: 100 μm. Cl: Claustrum.

which was processed with the polyclonal anti-rhBDNF antibody developed by Q. Yan and his colleagues (Yan et al., 1997a), and is in general agreement with most previously published work.

BDNF-immunostained cell bodies with a pyramidal morphology (Figs. 2 and 3) were present in all cortical regions examined, including the primary visual cortex and other occipital areas, the motor and somatosensory cortex, the insular cortex, and cortex of the temporal pole (Murer et al., 1999a). Non-pyramidal neurons were rarely stained. Pyramidal BDNF-immunoreactive neurons were preferentially located in layers V–VI and II–III, and seemed to be more abundant in some cortical regions (insular and temporal cortex, Fig. 3) than others (primary motor and sensory cortices). BDNF-immunoreactive neurons were also noticeable in the white matter immediately adjacent to the cortex (Fig. 3). Occasionally, a kind of BDNF-immunoreactive neuron, pyramidal in shape but having an inverted cell body orientation with the axon projecting to the cortex, was observed in deep layer VI and the adjacent white matter (Fig. 2(E)).

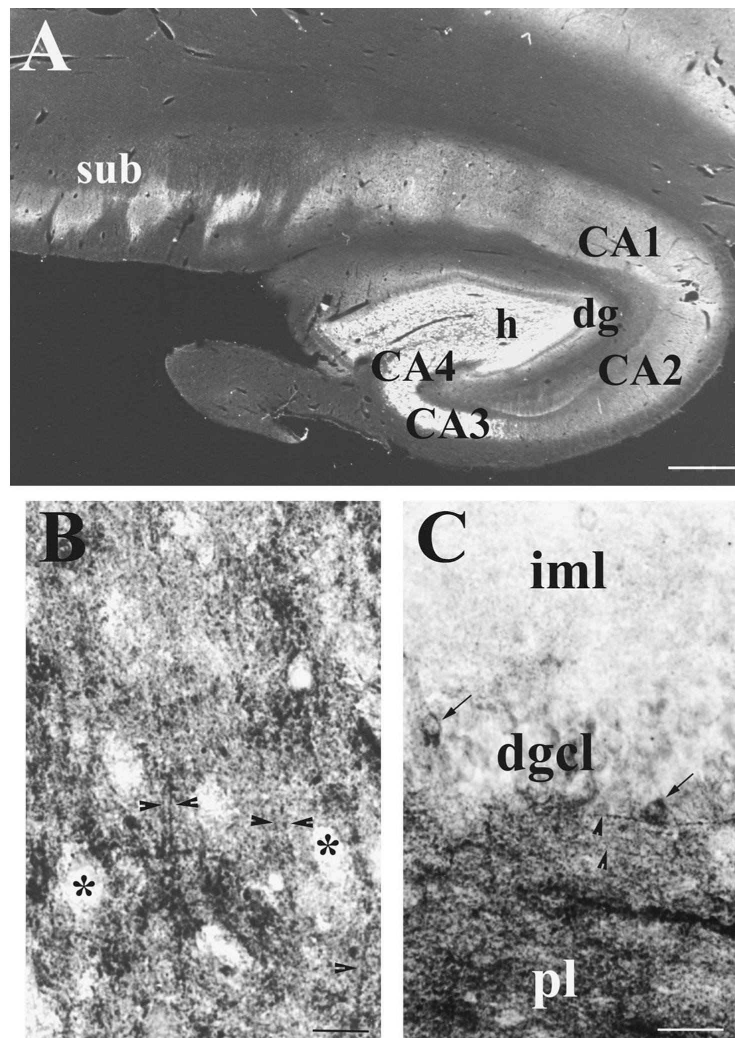

Fig. 4. (A) The human control hippocampus stained with anti-rhBDNF antibodies. Low-power microphotograph of the hippocampus of a control subject. BDNF is particularly abundant in the hilar region of the dentate gyrus, and the CA3 and CA4 hippocampal fields, suggesting labeling of the mossy fiber system. Within the molecular layer, BDNF-immunoreactivity was confined to the inner part, and was weak in the outer two-thrids, suggesting slight to no labeling of entorhinal afferent fibers. Scale bar: 1 mm. (B) BDNF-immunoreactivity in the CA3/CA4 hippocampal fields. Mossy fiber staining is so dense that virtually reveals the presence of non-immunoreactive pyramidal cell bodies (asterisks). The white arrowheads indicate BDNF-immunoreactive axon-like fibers which are probably ensheathing the proximal dendrites of pyramidal neurons. (C) High-power microphotograph showing the distribution of BDNF-immunoreactivity in the dentate gyrus. The arrows indicate strongly immunostained dentate gyrus granule cells. Note that most granule cells show weak labeling. A dense plexus of BDNF-immunoreactive mossy fibers can be observed in the polymorph layer and hilar region. The white arrowheads indicate stained axon-like fibers. Scale bars: 25 μm. Mofidied from Murer et al. (1999a) with permission. dg: dentate gyrus; dgcl: dentate granule cell layer; h: hilar region; iml; inner molecular layer; pl: polymorph layer; sub: subiculum.

In the adult human control hippocampal formation, a minority of neurons displayed a strong cell body BDNF-immunoreactivity. The density of labeled perikarya seemed to be higher in the granule cell layer of the dentate gyrus than in the Ammon's horn (Fig. 4). Within the latter, the density of immunoreactive pyramidal cell bodies was lowest in CA1. Intensely labeled axon-like fibers were present in the polymorph layer and hilar region of the dentate gyrus, and in the pyramidal layer of fields CA3 and CA4 (Fig. 4(B) and (C)). In fields CA3 and CA4, the intensity of neuropile staining revealed the location of non-labeled pyramidal neuronal cell bodies. The disposition of BDNF-immunoreactive axon-like fibers in the CA3 and CA4 fields strongly suggested that they were in close contact with the proximal dendrites of pyramidal neurons (Fig. 4(B)). In conjunction, the anatomical distribution of BDNF in the hippocampal formation supports that a large part of hippocampal BDNF is contained in the mossy fiber system, that is, in the axons of dentate gyrus granule cells which make synaptic contacts on the proximal dendrites of pyramidal neurons in the Ammon's horn after traversing the polymorph layer and hilar region of the dentate gyrus (see Conner et al., 1997 and Yan et al., 1997a, for a detailed description in the rat brain).

Moderately intense neuropile staining was also found in the inner molecular layer of the dentate gyrus (Fig. 4(C)). The two outer thirds of the molecular layer were almost devoid of labeling, however, suggesting scarce or no BDNF in afferent fibers arriving from the entorhinal cortex (the perforant path). In the molecular layer, labeled neuronal profiles were rarely found.

High-affinity receptors for BDNF are present in the human cerebral cortex and hippocampal formation. The mRNA for the catalytic form of TrkB is intensely and widely expressed in neurons of the human cerebral cortex, and pyramidal and granule cell layers of the hippocampus, but not in the hilus (Benisty et al., 1998). Similarly, Allen et al. (1994) found intense TrkB mRNA expression in pyramidal neurons and the granule cell layer of the adult human hippocampus. Ferrer et al. (1999) reported that a majority of neurons in the human frontal cortex and hippocampus, mainly pyramidal in shape, are immunoreactive for the catalytic form of TrkB. Similar findings were reported by Soontornniyomkij et al. (1999). These results are in good agreement with studies showing intense and widespread mRNA and protein expression of the catalytic form of TrkB in the rodent cerebral cortex and hippocampal formation (Merlio et al., 1992; Kokaia et al., 1993; Altar et al., 1994b; Miranda et al., 1993; Cellerino et al., 1996; Yan et al., 1997b; Drake et al., 1999).

BDNF and TrkB are co-expressed by neurons in the rat cerebral cortex and hippocampal formation. Kokaia et al. (1993) reported that almost all neurons expressing BDNF mRNA in the hippocampus and cerebral cortex, also contain full-length TrkB mRNA. Similar findings have been reported by Miranda et al. (1993), Giehl and Tetzlaff (1996) and Giehl et al. (1998). This result strongly suggests the existence of autocrine/paracrine functional interactions, probably involving pyramidal neurons, in both the cerebral cortex and hippocampal formation. Recent studies showed that BDNF and TrkB are targeted to distal dendrites of pyramidal neurons, suggesting the existence of short autocrine loops involving small districts in the dendritic tree of a single cell (Tongiorgi et al., 1997; Horch et al., 1999). Besides, cortical and hippocampal BDNF can function as target-derived neurotrophic factor for both local circuit neurons, cortical, and hippocampal afferent neurons. It has been shown that cortical and hippocampal interneurons express full-length TrkB but not BDNF, in rodents (Cellerino et al., 1996; Rocamora et al., 1996a; Zachrisson et al., 1996; Drake et al., 1999; Gorba and Wahle, 1999a; Pascual et al., 1999), suggesting that BDNF produced by pyramidal cortical neurons can affect the function of local circuit neurons (reviewed by Marty et al., 1997). Immunoreactivity for the catalytic form of TrkB has been located to excitatory-type axon terminals in the rat hippocampal formation by means of electron microscopy (Drake et al., 1999). Finally, it has been shown that BDNF can be anterogradely transported by cortical and hippocampal neurons to their target regions, suggesting further mechanisms of BDNF action. Anatomical rat and human studies agree in that the hippocampal mossy fibers, that is, the axons of dentate gyrus granule neurons projecting to CA3 pyramidal neurons, contain BDNF (Conner et al., 1997; Yan et al., 1997a; Smith et al., 1997; Murer et al., 1999a, 1999b), whereas the dendrites of CA3 pyramidal neurons contain catalytic TrkB (Yan et al., 1997b; Drake et al., 1999; Ferrer et al., 1999), suggesting an action of axonal BDNF on dendrites of CA3 pyramidal neurons.

3.3. *Amygdala, claustrum, septum, basal forebrain*

In our control human brain material, the claustrum was one the structures showing the most intense BDNF-immunoreactivity (Figs. 5(A) and 6(A). As in other brain regions, the intensity of cell labeling varied, with some neurons showing a strong cytoplasmic and dendritic staining, and others displaying a weak immunoreactivity (Figs. 2(D) and 5(B)). BDNF-immunoreactive axon-like processes were also visible in the claustrum. In situ hybridization studies revealed the presence of BDNF mRNA (Phillips et al., 1990), and the mRNA for the catalytic form of TrkB (Benisty et al., 1998), in the human claustrum.

BDNF protein abounds in the human amygdaloid complex (Fig. 5(A)). Macroscopically, labeling intensity is very high in the central amygdaloid nucleus, which presents, at the microscopic level, a dense fiber plexus and only scattered neuronal cell bodies. A very dense BDNF-immunoreactive fiber plexus is also present in the bed nucleus of the stria terminalis (Fig. 6(A)). The lateral nucleus of the amygdala shows plenty of BDNF-immunoreactive neuronal cell bodies, and a lightly labeled fiber plexus (Fig. 5(B)). The basal and cortical amygdaloid nuclei showed intermediate levels of both immunoreactive cell bodies and fibers. BDNF mRNA was detected in the human amygdala by Phillips et al. (1990). We are not aware of any report describing the presence of TrkB mRNA or protein in the human amygdala.

The available information regarding the presence of BDNF and TrkB in the rodent (Ceccatelli et al., 1991; Castrén et al., 1995; Kawamoto et al., 1996; Conner et al., 1997; Yan et al., 1997a, 1997b; Furukawa et al., 1998) and primate (Kawamoto et al., 1999b) claustrum and amygdala is in general good agreement with the human data as presented above. There is some information regarding the fiber plexuses in the central nucleus of the amygdala and bed nucleus of the stria terminalis, compiled from experiments performed in rats. Conner et al. (1997) have demonstrated that BDNF mRNA is poorly expressed in the central

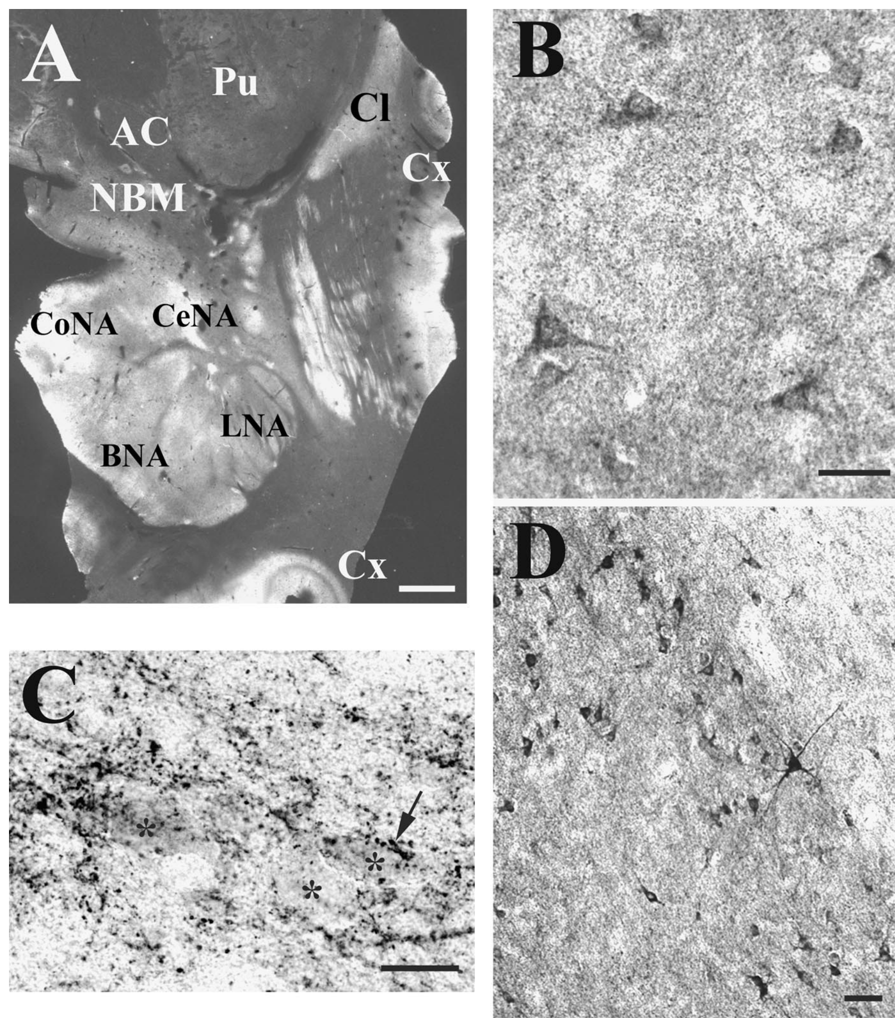

Fig. 5. (A) Low-power microphotograph showing BDNF-immunolabeling in the amygdala and basal forebrain. Note the patchy labeling in the putamen, and the laminar distribution of BDNF-immunoreactivity in the cerebral cortex. Scale bar: 5 mm. (B) BDNF-immunoreactive neuronal cell bodies in the lateral nucleus of the amygdala. Note the different intensity of staining displayed by adjacent neurons, and that BDNF-immunoreactivity is excluded from the nucleus. Scale bar: 50 μm. (C) The large cholinergic neurons of the basal forebrain did not display BDNF-immunoreactivity (asterisks). Presumptively cholinergic cell bodies in the nucleus basalis of Meynert were often in close proximity to BDNF-immunoreactive axon terminals. Scale bar: 50 μm. (D) Strong staining of neuronal cell bodies and fibers was found in the claustrum. Scale bar: 50 μm. AC: anterior commisure; BNA: basal nucleus of the amygdala; CeNA: central nucleus of the amygdala; Cl: claustrum; CoNA: cortical nucleus of the amygdala; Cx: cerebral cortex; GP: globus pallidus; LNA: lateral nucleus of the amygdala; NBM: nucleus basalis of Meynert; Pu: putamen. Modified from Murer et al. (1999a) with permission.

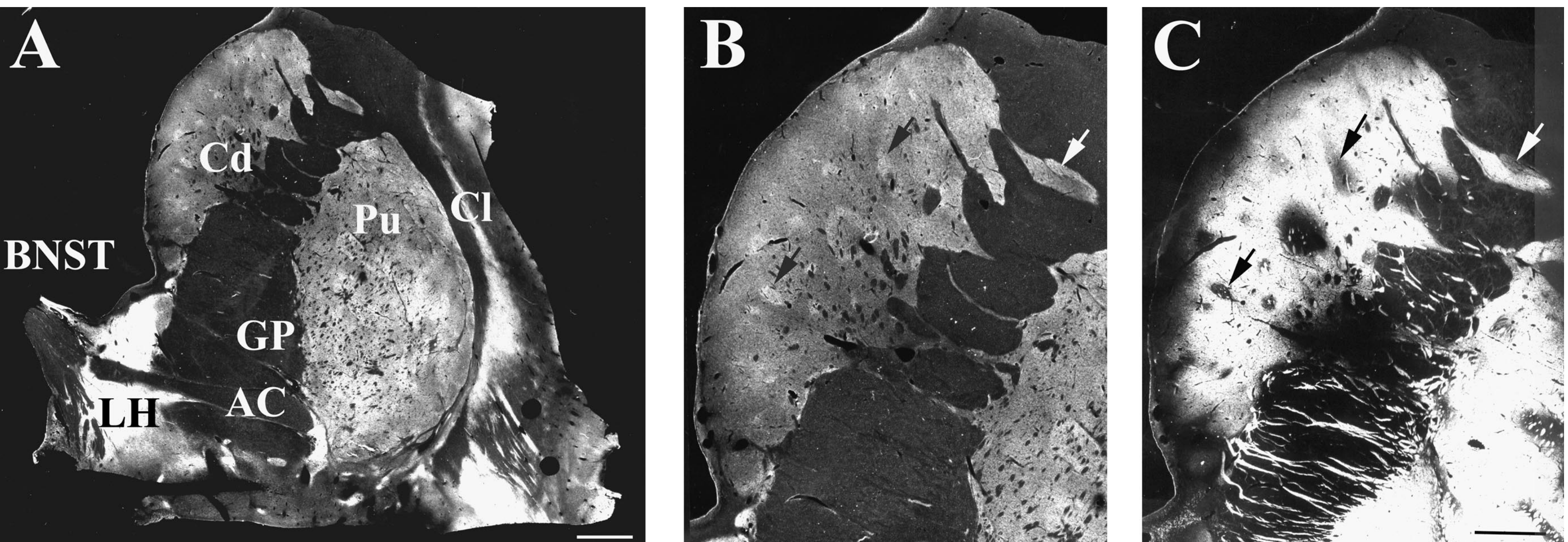

Fig. 6. (A) Low-power microphotograph showing BDNF-immunostaining in the caudate nucleus and putamen. Note the heterogeneous pattern of labeling in the caudate nucleus. The claustrum and bed nucleus of the stria terminalis exhibit strong staining. The globus pallidus did not display BDNF-immunoreactivity. Scale bar: 5 mm. (B and C) In the caudate nucleus, calbindin-poor striosomes (arrowheads in C) showed a strongest BDNF-immunoreactivity (arrowheads in B) than the calbindin- rich striatal matrix. AC: anterior commisure; BNST: bed nucleus of the stria terminalis; Cl: claustrum; GP: globus pallidus; LH: lateral hypothalamus; Pu: putamen. Scale bar: 2.5 mm. Reproduced with permission, from Murer et al. (1999a).

nucleus of the amygdala, and that the BDNF-immunoreactive fibers in this nucleus almost disappear after lesions of the pontine parabrachial nuclei, suggesting that BDNF in the central nucleus of the amygdala is contained in afferent axons. In addition, BDNF mRNA is not expressed by neurons in the bed nucleus of the stria terminalis in the rat (Conner et al., 1997). The BDNF-immunoreactive fibers in the bed nucleus of the stria terminalis are probably axons of amygdala projecting neurons, since BDNF-containing fibers were found in the bed nucleus after administration of exogenous BDNF in the amygdala (Mufson et al., 1999).

In our human material, the large cell bodies of presumptively cholinergic neurons of the nucleus basalis of Meynert and the septum, were devoid of BDNF-immunoreactivity (Fig. 5(C)). There were scarce, small neurons, showing an intense immunolabeling, in these regions (Murer et al., 1999a). The large, presumptively cholinergic neurons, were closely apposed to BDNF-immunoreactive fibers of unknown origin (Fig. 5(C)). Several studies agree in that cholinergic neurons of the nucleus basalis of Meynert express TrkB mRNA and protein in the human brain (Salehi et al., 1996; Boisiére et al., 1997; Benisty et al., 1998), suggesting that they receive BDNF support, probably from the afferent fiber system described above, or in a target-derived manner.

To our knowledge, there are no reports demonstrating the presence of BDNF mRNA in basal forebrain human cholinergic neurons. Rat studies show that a minority of cells in the basal forebrain express BDNF mRNA, but many cells contain BDNF mRNA in the medial septum (Ceccatelli et al., 1991; Castrén et al., 1995; Conner et al., 1997; Yan et al., 1997a). The study of Miranda et al. (1993) reports that less than 5% of the cells in the septum and diagonal band coexpress BDNF and $p75^{NTR}$ mRNAs, or BDNF and TrkA mRNAs. Since most cholinergic basal forebrain and septal cholinergic neurons express these receptors (see the review by Hefti (1999) for references), it seems that BDNF is synthesized by a minority of cholinergic neurons projecting to the cerebral cortex and hippocampal formation. One monkey study and several rat reports described BDNF-immunoreactivity in presumptively cholinergic neurons, however, in the septum and basal forebrain (Kawamoto et al., 1996; Furukawa et al., 1998; Kawamoto et al., 1999b). Colocalization studies of BDNF mRNA and markers of cholinergic phenotype are required to accurately determine how many septal and basal forebrain cholinergic cells synthesize BDNF.

3.4. Basal ganglia

Direct observation of forebrain tissue sections immunostained with anti-rhBDNF antibodies (Murer et al., 1999a) revealed an intermediate level of staining of the caudate nucleus, putamen and nucleus accumbens (Fig. 6(A)). BDNF-immunoreactivity had a nonhomogeneous appearance, with patches of intense labeling surrounded by areas of near background staining, which were more clearly visible in the caudate nucleus. To determine whether these patches of intense BDNF-immunoreactivity correspond to striosomes, Murer and colleagues compared staining patterns between BDNF-immunolabeled and acetylcholinesterase-labeled or calbindin-labeled adjacent sections, and showed that acetylcholinesterase poor/calbindin poor regions (striosomes) were stained more intensely with anti-rhBDNF antibodies than acetylcholinesterase rich/calbindin rich regions (Fig. 6). Strongly stained axons with varicosities were observed both in striosomes and matrix, but the density of the BDNF-immunoreactive fiber plexus was greater within striosomes. BDNF immunoreactive neuronal cell bodies were rarely found in the striatum, but occasional astrocyte-like cells were observed, preferentially within the patches of strong BDNF-immunoreactivity. Recent reports by Kawamoto et al. (1999a, 1999b) are consistent with the description provided above. The authors used an anti-BDNF peptide antibody, and found infrequent labeling of neuronal cell bodies in the human and monkey striatum, but numerous BDNF-immunoreactive fibers. Likewise, in the adult rat brain, BDNF protein seems to be present in striatal fibers but not in striatal neuronal cells bodies (Dugich-Djordjevic et al., 1995; Kawamoto et al., 1996; Conner et al., 1997; Yan et al., 1997a), even after colchicine treatment (Altar et al., 1997), and levels of BDNF mRNA are be very low in the rodent striatum (Wetmore et al., 1990; Ceccatelli et al., 1991; Castrén et al., 1995; Schmidt-Kastner et al., 1996a; Conner et al., 1997).

The origin of striatal BDNF immunoreactive fibers was studied by Altar et al. (1997) in the rat. After colchicine treatment, staining of BDNF-immunoreactive fibers in the rat striatum was reduced, whereas staining of cell bodies in major striatal afferent structures (cerebral cortex and substantia nigra) increased. Cortical lesions decreased striatal BDNF protein by 66%, and destruction of the mesotelencephalic dopaminergic system reduced BDNF protein levels by 14%. Consequently, Altar and colleagues concluded that most striatal BDNF is contained in axons of cortical and, secondarily, of nigral neurons. The mRNA for the catalytic form of TrkB is expressed by human striatal neurons (Allen et al., 1994; Benisty et al., 1998), both by cholinergic interneurons and putative medium spiny neurons (Boisiére et al., 1997). TrkB mRNA and protein are likewise expressed by rat striatal neurons (Merlio et al., 1992; Yan et al., 1997b). Therefore, it seems that BDNF is synthesized by cortical and nigral

neurons, transported anterogradely through corticostriatal and nigrostriatal axons into the striatum, and released to act on striatal neurons (Altar, 1999).

In our material (Murer et al., 1999a), no clear labeling of cell bodies or fibers could be evidenced in either segment of the pallidum (Fig. 6). BDNF-immunoreactive fibers, but not neuronal cell bodies, were stained in the subthalamic nucleus. The mesencephalic dopaminergic cell groups showed many BDNF-immunoreactive neurons (Fig. 9(A)). Many neuromelanin-containing cell bodies were in close proximity to strongly immunoreactive nerve terminals and fibers (Fig. 7(D)), and the nigral neuropile showed a high density of labeled neurites (Figs. 7(D) and 9(A)).

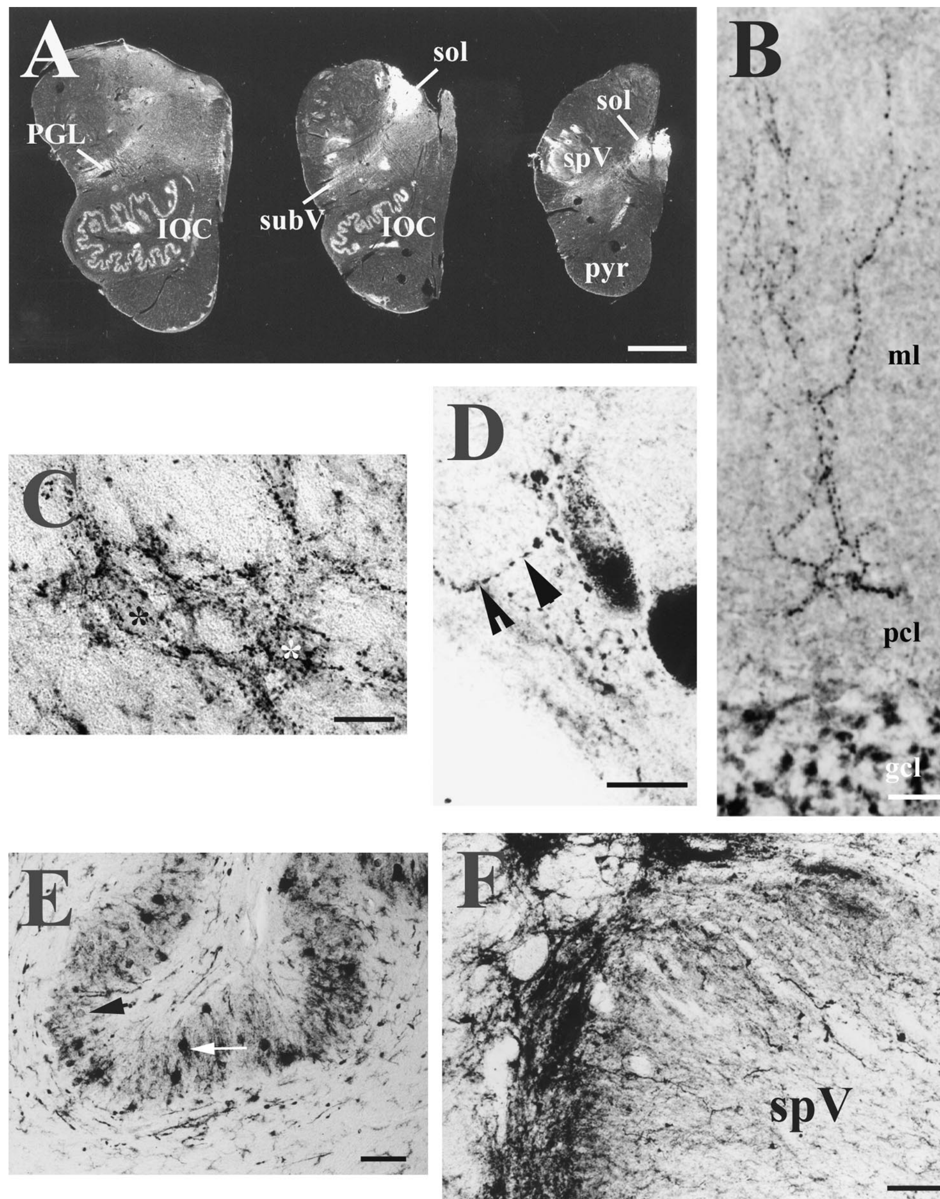

Fig. 7. (A) Low power microphotographs of three different levels of the medulla, showing BDNF-immunoreactivity in the inferior olivary complex, the nucleus of the solitary tract, the reticular paragigantocellular nucleus, the subtrigeminal nucleus and the spinal trigeminal nucleus. Scale bar: 2.5 mm. (B) In the cerebellum, the granule cells were BDNF-immunoreactive, but most Purkinje were not. Note presence of BDNF-immunoreactive fibers in the molecular layer. Scale bar: 50 μm. (C) Presumptive cholinergic, non-immunoreactive neuronal cell bodies (asterisks), were completely ensheated by BDNF-immunoreactive fibers and nerve terminals in the pedunculopontine nucleus pars compacta. Scale bar: 25 μm. (D) Varicose fibers (black arrowheads) were often seen in close proximity to neuromelanin-containing pars compacta neurons. Scale bar: 25 μm. (E) Some neurons showed an intense BDNF-immunoreactivity (white arrow) while others were devoid of labeling (black arrow) in the inferior olivary complex. Scale bar: 25 μm. (F) A dense plexus of fibers, probably representing primary afferent axons, was observed in the spinal trigeminal nucleus. Scale bar: 50 μm. Modified with permission, from Murer et al. (1999a). gcl: granule cell layer; ioc: inferior olivary complex; ml: molecular layer; pcl: Purkinje cell layer; pgl: paragigantocellular nucleus; pyr: pyramids; sol: nucleus of the solitary tract; spV: spinal trigeminal nucleus; subV: subtrigeminal nucleus.

Recent quantitative immunohistochemical studies by Nishio et al. (1998a) and Parain et al. (1999) stated that about 65% of the mesencephalic dopaminergic neurons were immunoreactive for BDNF (Table 2). BDNF-immunoreactivity (Dugich-Djordjevic et al., 1995; Kawamoto et al., 1996; Conner et al., 1997; Yan et al., 1997a; Furukawa et al., 1998; Kawamoto et al., 1999b), and BDNF mRNA expression (Wetmore et al., 1990; Ceccatelli et al., 1991; Seroogy et al., 1993;Castrén et al., 1995; Schmidt-Kastner et al., 1996a; Conner et al., 1997) have also been observed in rat and monkey nigral neurons. Seroogy et al. (1994) (see also Seroogy and Gall, 1993) verified the dopaminergic nature of BDNF-containing nigral neurons in double labeling experiments, demonstrating the colocalization of BDNF mRNA and tyrosine hydroxylase in the rat mesencephalon. Consistent with this description, specific lesions of mesencephalic dopaminergic neurons produced a decrease in nigral BDNF mRNA in the rat (Venero et al., 1994a).

In the rat, most nigral dopaminergic neurons express TrkB mRNA and protein (Merlio et al., 1992; Altar et al., 1994b; Yan et al., 1997b; Numan and Seroogy, 1999), suggesting co-expression of BDNF and its high-affinity receptor in the same neurons. TrkB is expressed by human nigral dopaminergic neurons (Allen et al., 1994; Nishio et al., 1998a; Benisty et al., 1998). Nishio et al. (1998a) found that about 70% of neuromelanin-containing mesencephalic neurons are immunoreactive for TrkB and 70% are immunoreactive for BDNF, implying the co-existence of both proteins in a large proportion of human dopaminergic neurons. The expression of BDNF and TrkB in the same neurons/neuronal population suggests the existence of autocrine/paracrine trophic loops in the substantia nigra.

Table 2
Number of neuromelanin-containing neurons expressing or not BDNF protein in control and parkinsonian brains (Parain et al., 1999)[a,e]

	A8	VTA	SNpc
Pigmented BDNF + neurons			
Control	11.2 ± 2.7	91.0 ± 44.5	1020.0 ± 99.1
Parkinsonian	16.4 ± 5.8	59.2 ± 13.2	97.8 ± 36.7[b]
Pigmented BDNF − neurons			
Control	8.2 ± 2.0	53.0 ± 25.9	542.2 ± 49.1
Parkinsonian	19.2 ± 10.0	66.8 ± 12.6	129.4 ± 25.7[c]
BDNF + /BDNF − ratio			
Control	1.99 ± 0.82	2.03 ± 0.58	1.98 ± 0.32
Parkinsonian	1.71 ± 0.77	1.01 ± 0.21	0.75 ± 0.16[d]

[a] Data are mean ± SEM of five cases per group.
[b] $p < 0.0001$.
[c] $p < 0.0001$.
[d] $p = 0.0098$, vs. control brains. Student's t test.
[e] Experiments were performed on postmortem brain tissue from individuals with no known history of neurological or psychiatric illness, and patients with clinical and neuropathological diagnosis of Parkinson's disease. Patients and control subjects did not differ significantly for their mean age at death (mean ± SEM: patients 75.2 ± 7.4; controls 69.5 ± 9.4) and the mean interval from death to freezing of tissue (mean ± SEM: patients 23.3 ± 8.2; controls 22.3 ± 5.3). Reproduced with permission (Parain et al., 1999).

In the human substantia nigra, a dense plexus of BDNF-immunoreactive neurites exists (Murer et al., 1999a; Parain et al., 1999), formed by the proximal dendrites of nigral neurons and by axon-like fibers (Figs. 7(D) and 9(A)). The origin of the BDNF-immunoreactive axon-like structures in the substantia nigra is not known, but is probably not of striatal origin, since striatal neurons do not express BDNF mRNA. Nigral BDNF-immunoreactive fibers are probably of lower brain stem origin (see Section 3.5).

3.5. Cerebellum and brain stem

In our human material (Murer et al., 1999a), a minority of Purkinje cells showed weak cell body immunoreactivity. A more strong immunolabeling was observed in granule cells, and in axon-like, varicose fibers, which run perpendicularly to the cortical surface (Fig. 7(B)). These fibers seemed to envelop the proximal unstained dendrites of Purkinje cells (Fig. 7(B)). BDNF-immunoreactive neuronal cell bodies were found in the inferior olivary complex (Fig. 7(A) and (E)), suggesting that the fibers in the cortical molecular layer were climbing fibers. Alternatively, these fibers might proceed from the locus coeruleus, which express BDNF mRNA in rodents (see below). At present, there is no evidence favoring one or the other interpretation.

In contrast with our findings, Kawamoto et al. (1999b) did not show BDNF-immunoreactivity in the granule cell layer, but found strong labeling of Purkinje cells, and confirmed the presence of BDNF-immunoreactivity in the inferior olivary complex. Intriguingly, in the rat, our anti-rhBDNF antibody did not produce any staining (Conner et al., 1997). Other reports in the rat describe BDNF-immunoreactivity in Purkinje cells, but not in granule cells (Dugich-Djordjevic et al., 1995; Kawamoto et al., 1998; Furukawa et al., 1998). To our knowledge, there are no reports on BDNF mRNA distribution in the human cerebellum. In the rat, BDNF mRNA is displayed by granule cells, but not Purkinje cells (Wetmore et al., 1990; Rocamora et al., 1993; Castrén et al., 1995). In good agreement with the human distribution, neurons in the inferior olivary complex display both BDNF mRNA (Rocamora et al., 1993; Castrén et al., 1995; Conner et al., 1997; Yan et al., 1997a) and protein (Kawamoto et al., 1996; Conner et al., 1997; Yan et al., 1997a) in rodents.

Allen et al. (1994) reported the presence of full-

length TrkB mRNA in all granule cells, but not in Purkinje cells, in the human adult cerebellum. Similar findings were reported by Benisty et al. (1998), who stressed the intensity of TrkB mRNA labeling in the granule cell layer, its absence in Purkinje cells, and the presence of some TrkB mRNA containing cells in the molecular layer. In the rodent cerebellum, TrkB-immunoreactivity (Schwartz et al., 1997; Yan et al., 1997b), and TrkB mRNA (Klein et al., 1990b; Alvarez-Dolado et al., 1994; Gao et al., 1995), was observed both in granule and Purkinje cells.

The reasons for the discrepant results of different research groups regarding the regional localization of BDNF and TrkB proteins and mRNAs in the cerebellar cortex are not clear, giving the consistent results observed in other brain structures. It seems possible that important species differences in the distribution of BDNF and TrkB exists specifically in the cerebellum, or that distinct mechanisms of BDNF and TrkB intracellular trafficking and cell to cell BDNF-mediated communication are functional in the cerebellum. Studies on the distribution of BDNF mRNA and TrkB-immunoreactivity in the human cerebellum will contribute to give an answer to this puzzle.

We did not found BDNF-immunoreactive cell bodies in the human locus coeruleus (Murer et al., 1999a). However, locus coeruleus neurons display BDNF mRNA (Ceccatelli et al., 1991; Castrén et al., 1995; Conner et al., 1997; Yan et al., 1997a, 1997b; Fawcett et al., 1998), and BDNF-immunoreactive cell bodies (Kawamoto et al., 1996; Furukawa et al., 1998) in rodents. Besides, Kawamoto et al. (1999b) reported BDNF-immunolabeling of cell bodies in the primate locus coeruleus. In mice, BDNF-immunoreactivity colocalizes with dopamine-β-hydroxylase in fibers, suggesting that BDNF is anterogradely transported from the locus coeruleus to target structures, like the substantia nigra and cerebral cortex (Fawcett et al., 1998; Alonso-Vanegas et al., 1999; see Section 2.6). It seems possible that in the human locus coeruleus BDNF is rapidly targeted to processes, and very low amounts of protein remain in cell bodies.

Little information exists on BDNF and TrkB distribution in the human lower brain stem, beyond the data already discussed by Murer et al. (1999a). The readers are referred to this manuscript for information on the lower brain stem (see also Fig. 7).

4. Brain-derived neurotrophic factor in Alzheimer's disease and Parkinson's disease

The expression of BDNF in the human central nervous system is altered by several pathological processes, including neurodegenerative diseases (see below), epilepsy (Nawa et al., 1995; Mathern et al., 1997; Takahashi et al., 1999), and hypoxia-ischemia, and hypoglycemia (Lindvall et al., 1992; Merlio et al., 1993; Korhonen et al., 1998). The following section examines evidence demonstrating changes in BDNF expression in Alzheimer's disease and Parkinson's disease (see also Table 1). When available, evidence on modifications of the expression of TrkB is also reviewed. Then, the most relevant in vitro an in vivo studies, reporting the actions of BDNF on vulnerable neuronal populations in Alzheimer's disease and Parkinson's disease, are commented. This information is reviewed in an attempt to envisage the relevance that altered BDNF expression might have in the pathogeny/pathophysiology of the different diseases. Subsections are devoted to the analysis of BDNF effects on survival and differentiation of relevant neuronal populations, of BDNF actions on fully developed healthy neurons and injured neurons, and also to studies which suggest that altered BDNF expression could have consequences on synaptic function, neuronal gene expression, and behavior.

4.1. Alzheimer's disease

4.1.1. Altered expression of BDNF in Alzheimer's disease

In 1991, Phillips and colleagues reported a selective reduction of BDNF mRNA expression in the hippocampal formation of individuals with Alzheimer's disease. The authors studied the in situ hybridization signal of BDNF, NGF and NT-3 mRNAs, in hippocampal tissue sections of nine patients with Alzheimer's disease and six control individuals. They found important reductions of BDNF mRNA in the pyramidal layer of the hippocampus proper and the granule cell layer of the dentate gyrus. No change was found for NGF and NT-3 mRNAs. Phillips and colleagues further studied BDNF mRNA abundance with an RNAase protection assay in an independent set of hippocampal samples, and found a 2-fold reduction of the BDNF transcript, in patients relative to control individuals. A reduced expression of BDNF mRNA in the hippocampal formation of individuals with Alzheimer's disease was confirmed by others (Murray et al., 1994). More recently, the availability of antibodies directed against rhBDNF or BDNF peptides allowed the study of BDNF protein in brain samples from individuals with Alzheimer's disease. By means of a two-site enzyme immunoassay, Narisawa-Saito et al. (1996) found that BDNF protein content was not significantly reduced in dentate gyrus samples from patients, nor in motor cortex samples, although a significant decrease was observed in the entorhinal cortex. Another study (Connor et al., 1997) found an important reduction in the number of BDNF-immunoreactive neuronal cell bodies in the granule cell layer of the dentate gyrus

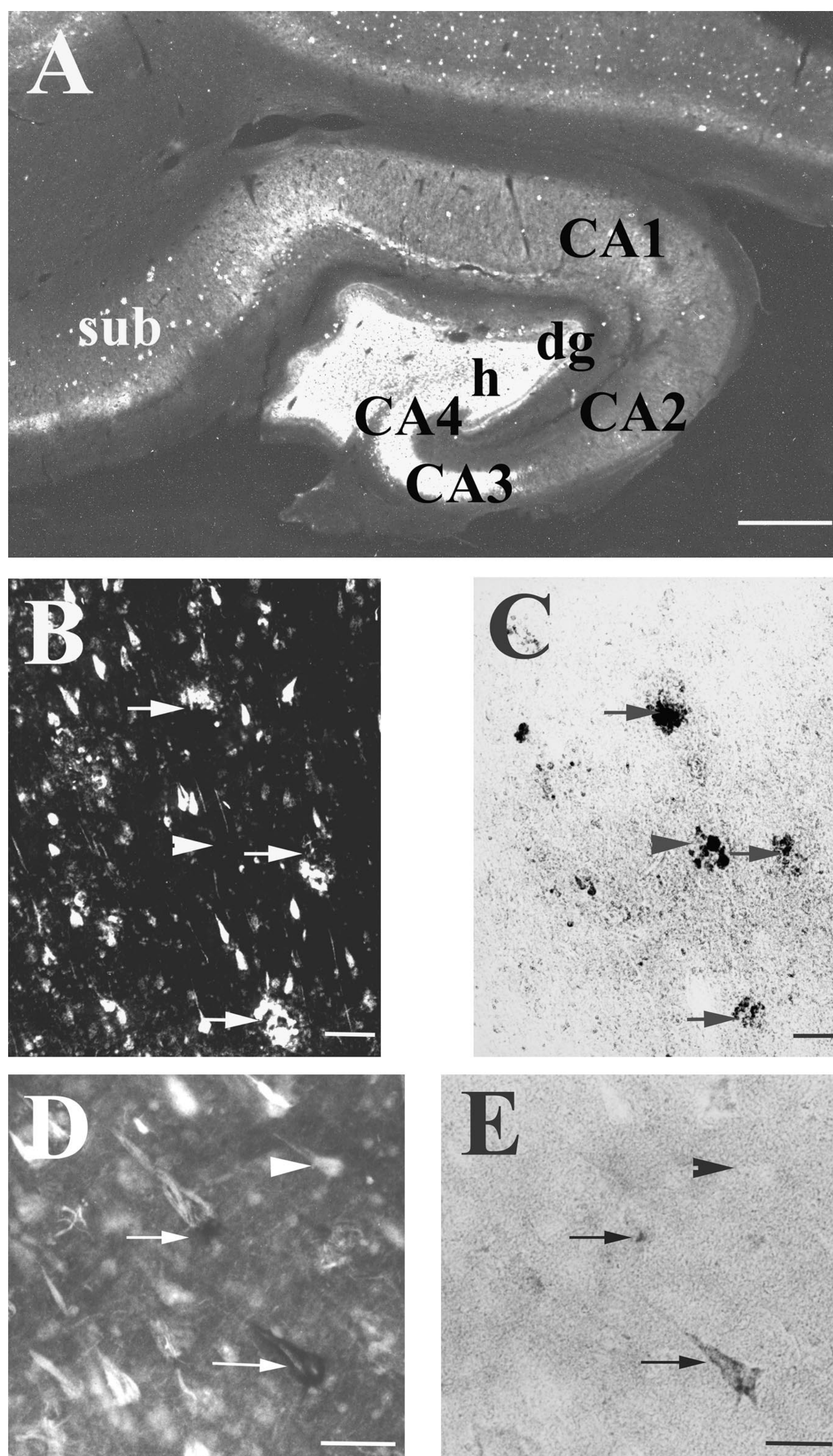

Fig. 8. BDNF-immunoreactivity in the brain of individuals with Alzheimer's disease. (A) Low-power microphotograph of the hippocampus showing that the general pattern of BDNF-immunolabeling was similar to that of control brains. Note labeling of senile plaques. Scale bar: 1 mm. (B and C) Many BDNF-immunoreactive deposits (white arrows in B) were associated to thioflavine-S fluorescent material (white arrows in C), whereas others seemed to not have any relation with thioflavine-S deposits (arrowhead in B and C). Scale bars: 50 μm. (D and E) Pyramidal neurons showing a massive neurofibrilary degeneration were devoid of BDNF-immunoreactivity (arrowheads in D and E). Many BDNF-immunoreactive pyramidal cells with discrete thioflavine-S fluorescent deposits in the apical cytoplasm, or neurons displaying a massive neurofibrilary degeneration which still showed a discrete BDNF-immunoreactivity in the basal cell body cytoplasm (white arrows in D and E) were also found. Scale bars: 25 μm. Reproduced from Murer et al. (1999a) with permission. dg: dentate gyrus; h: hilar region; sub: subiculum.

and hilar region, of individuals with Alzheimer's disease. Cell counts of BDNF-immunoreactive neurons in temporal lobe sections from individuals with Alzheimer's disease, revealed a non-significant decrease in the CA1 field and a significant reduction in the temporal cortex of patients relative to controls (Connor et al., 1997). Furthermore, relative optical density measurements showed reduced BDNF immunostaining in the hilar region of the Alzheimer's disease dentate gyrus compared to the control hilar region (Connor et al., 1997). In another recent study, Ferrer et al. (1999) used anti-BDNF peptide antibodies and found a decreased BDNF signal in Western blots performed on frontal cortex samples from patients. Besides, the authors described a reduced intensity of BDNF-immunoreactivity in tangle-bearing and non-tangle-bearing cortical and hippocampal neurons of patients, and strong BDNF-immunolabeling of dystrophic neurites surrounding senile plaques. In our tissue samples from patients with Alzheimer's disease (Murer et al., 1999a), it was evident that BDNF-containing cortical neurons are not spared by the degenerative process, since they often showed thioflavine S labeled neurofibrillary deposits (tangles) and reduced BDNF-immunoreactivity (Fig. 8(D) and (E)). Furthermore, deposits of BDNF-immunoreactive material resembling senile plaques were observed in the hippocampal formation, subiculum, entorhinal cortex, and other cortical areas in all samples from patients (Fig. 8(A)). After double staining with thioflavine S and anti-rhBDNF antibodies, some of these deposits displayed an intensely fluorescent core, whereas other BDNF-immunoreactive deposits showed almost no fluorescent material. In plaques, BDNF-immunoreactivity was excluded from the amyloid central core (Fig. 8(B) and (C)). Plaques with a dense fluorescent core and no associated BDNF-immunoreactive material were also observed. To our knowledge, no study of BDNF expression in the basal forebrain of individuals with Alzheimer's disease has been published.

Studies on the expression of TrkB in the brain of patients with Alzheimer's disease provided data on the hippocampal formation and cerebral cortex, but also on the basal forebrain. Boisière et al. (1997) examined the expression of catalytic TrkB mRNA at the cellular level by in situ hybridization, in brain tissue sections including the striatum and basal forebrain of individuals with Alzheimer's disease and controls. The sections were immunostained for choline acetyltransferase (ChAT), the enzyme involved in acetylcholine synthesis, in order to identify striatal and basal forebrain cholinergic neurons. No change in TrkB mRNA was observed in basal forebrain cholinergic neurons, nor in striatal cholinergic and non-cholinergic neurons. However, Salehi et al. (1996) found that the proportion of basal forebrain neurons showing TrkB-immunoreactivity was significantly reduced from 75% in control brains to 40% in individuals with Alzheimer's disease. Ferrer et al. (1999) studied the expression of catalytic and truncated forms of TrkB protein in the frontal cortex and hippocampal formation of patients and controls. In Western blots of frontal cortex samples, they found a marked decrease of catalytic TrkB content in all patients studied, and an increase of truncated TrkB in some cases. Immunocytochemical studies on brain tissue sections showed a reduced catalytic TrkB-immunostaining in the cerebral cortex and hippocampal formation of individuals with Alzheimer's disease relative to controls. Furthermore, the authors found that neurofibrillary tangles occur in cortical and hippocampal neurons showing catalytic TrkB-immunoreactivity. Allen et al. (1999) confirmed a profound decrease in catalytic TrkB protein expression in the frontal and temporal cortices of individuals with Alzheimer's disease. Increased immunoreactivity for the truncated form of TrkB was also reported by Connor et al. (1996), both in the hippocampal formation and other regions of the temporal lobe. Connor et al. (1996), but not Ferrer et al. (1999), found truncated TrkB-immunoreactivity in senile plaques. The study of Connor et al. (1996), however, should be considered cautiously, since they failed to reveal immunoreactivity for the full-length form of TrkB in the control human brain, in striking contrast with most human and animal studies (see Section 3.2).

In summary, the bulk of the available evidence suggests that individuals with Alzheimer's disease have a reduced BDNF mRNA and protein content in the hippocampal formation, temporal cortex, and probably other cortical areas, that BDNF protein forms deposits in relation with senile plaques, and that neurons expressing BDNF and/or TrkB are not protected from degeneration in Alzheimer's disease. It seems that reductions in the expression of catalytic TrkB also occur in the cerebral cortex and hippocampus of patients, and possibly in the basal forebrain, but evidence on TrkB expression is still fragmentary and somewhat contradictory.

4.1.2. BDNF promotes survival and differentiation of hippocampal, cortical, and basal forebrain cholinergic neurons in vitro

Almost all studies on BDNF expression in postmortem human tissue from individuals with Alzheimer's disease were focused on the cerebral cortex and hippocampus. Nothing is known about BDNF expression in the basal forebrain of patients with Alzheimer's disease. In contrast, there are several in vitro and animal studies reporting BDNF effects on forebrain cholinergic neurons. Shortly after BDNF discovery, Alderson et al. (1990) showed that BDNF promotes survival of rat embryonic septal cholinergic neurons in culture.

BDNF increased the activity of the enzymes involved in acetylcholine synthesis and degradation, ChAT and acetylcholinesterase. These findings were confirmed first by Knüsel et al. (1991), and then by several different research groups (Nonomura and Hatanaka, 1992; Friedman et al., 1995; Nonomura et al., 1995; Abiru et al., 1996, Ha et al., 1996, 1999; Nonner et al., 1996; Hashimoto et al., 1999).

The effects of BDNF on cultured hippocampal neurons has likewise been the subject matter of several research reports. Ip et al. (1993) did not found any survival promoting effect of BDNF on embryonic hippocampal neurons, even though cultured hippocampal neurons express TrkB and show phenotypic changes after exposure to BDNF, such as an increased expression of c-Fos, calbindin, and AChE. Similar findings, that is, BDNF-induced intracellular events in the absence of survival-promoting activity, have been reported by Marsh and Palfrey (1996) in highly enriched cultures of rat hippocampal pyramidal neurons. Lowenstein and Arsenault (1996) found evidence of increased survival of hippocampal dentate granule neurons in cultures treated with exogenous BDNF. The effect of BDNF on survival was evident when dentate granule cells were plated at low density. The authors also found evidence suggestive of an autocrine/paracrine effect of endogenous BDNF (produced by the cultured cells) on differentiation of dentate granule neurons. These results are consistent with those of Lindholm et al. (1996), who showed that cultured hippocampal neurons die spontaneously when are plated at low (but not at high) density. Spontaneous death of hippocampal neurons plated at low density can be prevented by administration of BDNF. Furthermore, the authors found increased death rates for cultured hippocampal neurons from BDNF knockout mice relative to wild-type mice, and a survival promoting action of exogenous BDNF on cultured pyramidal neurons lacking the BDNF gene, suggesting an autocrine/paracrine effect of endogenous BDNF on survival of hippocampal pyramidal neurons. Consequently, it seems that when plated at high density, hippocampal neurons can survive and differentiate, thanks to the existence of functional autocrine/paracrine trophic loops in the culture. Exogenous BDNF has a noticeable effect only when hippocampal neurons are plated at low density, and autocrine/paracrine loops are presumptively not functional. As summarized above (see Section 3.2), a large part of hippocampal pyramidal and dentate granule cells co-express both BDNF and TrkB.

The existence of functional BDNF-dependent autocrine/paracrine trophic loops in cultures is supported by studies by Ghosh et al. (1994), performed on embryonic rat cortical neurons. Addition of anti-BDNF antibodies (but not of antibodies to other NTs) to the culture medium reduced survival of cultured cortical neurons, and prevented the survival-promoting action of high potassium-induced depolarization. The effect of depolarization on survival was mediated by activation of voltage-sensitive calcium channels, and increased synthesis of BDNF by cultured cells. The authors proposed that autocrine/paracrine loops involving changes in BDNF expression mediate activity-dependent survival of cortical neurons during development.

In addition to increasing survival, BDNF has several other effects on cultured hippocampal and cortical neurons. Application of BDNF increases spontaneous firing rates (Levine et al., 1995a), regulates dendritic spine density (Murphy et al., 1998), increases axonal complexity (Patel and McNamara, 1995; Lowenstein and Arsenault, 1996), and potentiates synaptic transmission (Leßmann et al., 1994; Levine et al., 1995b; Bartrup et al., 1997; Leßmann and Heumann, 1998), in cultures of rat cortical and hippocampal neurons. The mechanisms affecting synaptic transmission in hippocampal/cortical cultures might involve enhanced glutamate release (Takei et al., 1997, 1998; Li et al., 1998a, 1998b), enhanced synaptic vesicle exocitosis (Bradley and Sporns, 1999), increased expression of AMPA glutamate receptors (Narisawa-Saito et al., 1999), modulation of NMDA glutamate receptor function (Jarvis et al., 1997; Levine et al., 1998), and modulation GABAergic neuronal function (Bartrup et al., 1997; Rutherford et al., 1997).

Exogenous BDNF has actions on cultured non-pyramidal, non-granule, hippocampal and cortical neurons as well. Thus, BDNF was shown to promote differentiation (neuritic extension and peptide expression) of non-pyramidal hippocampal neurons, in rat organotypic cultures (Marty et al., 1996a, 1996b), and to regulate phenotype and function of GABAergic neurons in rat cortical cultures (Widmer and Hefti, 1994; Marty et al., 1996a, 1996b; Pappas and Parnavelas, 1997; Rutherford et al., 1997; Murphy et al., 1998) and of somatostatin-producing neurons in cultures derived from the human fetal cortex (Barnea et al., 1999). In addition, Shetty and Turner (1998) found that exogenous BDNF promotes differentiation of hippocampal stem cells into hippocampal pyramidal neurons, and increases survival of recently differentiated hippocampal pyramidal neurons.

In summary, in vitro studies support that BDNF promotes survival and differentiation of hippocampal, and basal forebrain cholinergic neurons. There are also some studies aimed at determining if exogenous BDNF protects cultured basal forebrain and hippocampal/cortical neurons against insults, like energy deprivation, growth factor deprivation, excitotoxins, calcium overload, elevated concentrations of free radicals, and others deleterious factors (Shimohama et al.,

1993; Chen and Mattson, 1994; Chen et al., 1994; Mattson et al., 1995; Ha et al., 1996; Nonner et al., 1996; Pringle et al., 1996; Kew and Sofroniew, 1997; Kume et al., 1997; Ahn et al., 1998; Mitchell et al., 1998; Ohgoh et al., 1998; Hetman et al., 1999; Kim et al., 1999b; Nitta et al., 1999; Noh et al., 1999; Takei et al., 1999; Tremblay et al., 1999), most of them showing a beneficial effect of BDNF. There are, however, no convincing arguments supporting that these experimental situations reflect in any way the mechanisms leading to neuronal damage in Alzheimer's disease. Furthermore, recent evidence suggest that BDNF can enhance the toxic effects of some deleterious agents on rodent cultured neurons. Energy deprivation-induced damage of cortical neurons (Koh et al., 1995), free radical-mediated damage of cortical and striatal neurons (Gwag et al., 1995; Park et al., 1998), NMDA-induced degeneration of hippocampal and cortical neurons (Koh et al., 1995; Prehn, 1996), and zinc-induced death of cortical neurons (Kim et al., 1999a), are all increased by a pretreatment with BDNF. Differences in culture conditions can explain the contrasting (e.g., protective versus deleterious) effects of BDNF on paradigms aimed at damaging cultured neurons (Behrens et al., 1999). Accordingly, Samdani et al. (1997) reported that NTs can enhance or reduce NMDA-induced damage of rodent cortical neurons, depending on culture conditions. To our knowledge, it has not been reported if BDNF protects basal forebrain or hippocampal neurons against insults of more relevance for the understanding of Alzheimer's disease pathophysiology, like amyloid-β-peptide toxicity.

4.1.3. Does BDNF promote survival of injured hippocampal, cortical, and basal forebrain cholinergic neurons in vivo?

There are several reports showing that BDNF protects hippocampal and basal forebrain cholinergic neurons from injury. However, the experimental paradigms used to produce injury seem to not have any close relationship with the poorly understood mechanisms producing neuronal death in Alzheimer's disease.

A tenacious effort was performed since the discovery of BDNF, to determine if forebrain cholinergic neurons can be protected from injury in vivo by exogenous administration of BDNF. Several research groups chose the transection of septo-hippocampal cholinergic axons at the fimbria as model, which produces a well characterized degeneration of cholinergic cell bodies in the septum and basal forebrain. The rationale of this series of studies was that axotomized basal forebrain cholinergic neurons degenerate as consequence of the lack of endogenous target-derived (hippocampal/cortical) trophic support. Basal forebrain cholinergic neurons retrogradely transport exogenous BDNF from the hippocampus or neocortex to their cell bodies (reviewed by Mufson et al., 1999). Consequently, it has been proposed that a replacement therapy with neurotrophic molecules would prevent death of the axotomized neurons. An early attempt by Knüsel et al. (1992) provided exciting results. Intraventricular administration of rhBDNF for 20 days, beginning the day of fimbria transection, significantly increased the number of remaining ChAT-immunoreactive neurons in the septum. Subsequent reports support that BDNF administration produces a partial protection of basal forebrain cholinergic neurons after axotomy (Morse et al., 1993; Widmer et al., 1993; Koliatsos et al., 1994; Venero et al., 1994b; Williams et al., 1996). None of these studies included any behavioral examination of the animals, however, remaining the question of the existence of functional protection or recovery unanswered.

Other researchers tried to determine if exogenous BDNF can protect forebrain cholinergic neurons from degeneration induced by direct destruction of their target cells. Burke et al. (1994) destroyed the rat hippocampus with an injection of ibotenic acid, and then treated the rats for 27 days beginning the day of the lesion, with repeated intraventricular injections of BDNF. The authors reported a significant protective effect of BDNF on basal forebrain cholinergic neurons (as assessed by counts of ChAT-immunoreactive and $p75^{NTR}$-immunoreactive cells), and a BDNF-induced sprouting of cholinergic processes in the residual hippocampal formation. In contrast, Skup et al. (1994) failed to find any protective effect of intraventricular administration of BDNF on nucleus basalis magnocelularis neurons, in rats with cortical lesions induced by devascularization. The dose and duration of the BDNF regime used by Skup and colleagues were smaller than in the other studies.

In summary, most studies coincide in that BDNF administration provides partial protection to basal forebrain cholinergic neurons against damage induced by axotomy or target cell destruction. It must be mentioned, however, that all studies comparing the protective effects of BDNF and NGF on forebrain cholinergic neurons, found that the former is not as effective as NGF (Knüsel et al., 1992; Morse et al., 1993; Widmer et al., 1993; Burke et al., 1994; Koliatsos et al., 1994; Skup et al., 1994; Venero et al., 1994b; Williams et al., 1996).

Likewise, several studies indicate that exogenous BDNF protects hippocampal and cortical neurons from injury. Administration of BDNF protects hippocampal/cortical neurons from ischemic (reviewed by Nikolics, 1999) and excitotoxic injury (reviewed by Lindholm, 1994). Less is known about the role of endogenous BDNF in promoting survival of lesioned adult central nervous system neurons. A recent series of experiments by Giehl and colleagues provided

strong evidence for a role of endogenous BDNF in promoting survival of axotomized cortical projection neurons in the rat. Intraparenchymal administration of rhBDNF, started the day of axotomy and continued for 7 days, almost completely prevented the death of axotomized corticospinal neurons during the first week after the lesion (Giehl and Tetzlaff, 1996). Fourteen days of rhBDNF infusion promoted survival of axotomized neurons for at least 42 days (Hammond et al., 1999). Intraparenchymal infusion of anti-BDNF neutralizing antibodies for 7 days had no effect on survival of unlesioned corticospinal neurons, but increased death of axotomized corticospinal neurons (Giehl et al., 1998). Interestingly, this results indicates that adult neurons, which do not require endogenous BDNF support for survival in the healthy central nervous system, can become dependent on endogenous BDNF support after injury. Giehl and colleagues further demonstrated that most corticospinal neurons express TrkB mRNA, and about half of them express BDNF mRNA, suggesting that an autocrine/paracrine loop involving endogenous BDNF and TrkB receptors supports survival of axotomized corticospinal neurons (Giehl and Tetzlaff, 1996; Giehl et al., 1998). In another recent study, Larsson et al. (1999) found evidence suggestive of a protective effect oendogenous BDNF after global ischemia in rats. Intraventricular infusion of TrkB-Fc fusion protein (which scavenges endogenous TrkB ligands) during one week before and one week after induction of global forebrain ischemia, selectively increased death of CA4 pyramidal neurons, dentate gyrus interneurons, and striatal cholinergic neurons.

Finally, recent studies suggest that administration of BDNF can potentiate the toxic effect of some deleterious agents in vivo. Seizures induced by systemic administration of kainic acid produce a well characterized loss of hippocampal pyramidal neurons in rats. Intrahippocampal administration of rhBDNF was not protective in this paradigm, but instead, increased seizure-induced pyramidal cell loss in the CA3 field (Rudge et al., 1998). This result is consistent with recent studies showing that BDNF can potentiate excitotoxin-induced neuronal damage in hippocampal cultures (see Section 4.1.2).

4.1.4. Short- and long-term changes in hippocampal, cortical, and basal forebrain cholinergic neuronal function related to BDNF

There is evidence showing that exogenous BDNF increases function of basal forebrain cholinergic neurons in rats. Koliatsos et al. (1994) reported a modest effect of 2-week BDNF administration on cholinergic markers in the intact rat forebrain. Furthermore, implantation of engineered cells that secrete BDNF in the forebrain of healthy rats, increases expression of ChAT, AChE and $p75^{NTR}$ in the nucleus basalis magnocelularis and the striatum (Martinez-Serrano et al., 1996). Similar findings were observed after viral vector BDNF gene transfer to the adult rat basal forebrain (Klein et al., 1999b). Healthy rats expressing vector-derived BDNF showed 50% more basal forebrain cholinergic neurons than rats receiving the virus without the BDNF gene. Finally, there is a study that analyzed the effect of BDNF administration on basal forebrain cholinergic neurons which survived to an insult (Dekker et al., 1994). Basal forebrain cholinergic neurons were lesioned with ibotenic acid, and the NT treatment was started 2 weeks later, that is, once all the vulnerable neurons had degenerated. Intraparenchymal infusion of BDNF for 4 weeks did not improve cortical ChAT activity, and did not have any effect on the number or size of remaining cholinergic cell bodies in the basal forebrain. It seems possible that the remaining forebrain system was in an hyperactive compensatory state before BDNF administration, and consequently, was unable to respond to exogenous BDNF administration. Some findings suggest that BDNF could have acute effects on basal forebrain cholinergic function as well. Knipper et al. (1994) found that BDNF increases acetylcholine release from rat hippocampal synaptosomes, which presumptively include axonal endings of septo-hippocampal cholinergic neurons.

The action of endogenous BDNF, if any, on basal forebrain cholinergic neurons is almost not known. Putative sources of endogenous BDNF for basal forebrain cholinergic neurons include their main target nuclei (hippocampal formation and cerebral cortex), basal forebrain afferent fibers containing BDNF, and BDNF provided by neighbor cells. Autocrine mechanisms seem to be less important for basal forebrain cholinergic neurons, since most of them do not synthesize BDNF (see Section 3.3). Homozygous mice with a targeted deletion of the *BDNF* gene do not differ from wild-type mice in the appearance of basal forebrain cholinergic neurons (Jones et al., 1994; Ernfors et al., 1995), suggesting that endogenous BDNF is not necessary for basal forebrain cholinergic neuron development. Mice without functional copies of the *Trk*B gene show increased numbers of pycnotic (presumptively apoptotic) nuclei in the septum, 2 weeks after birth (Alcántara et al., 1997), suggesting that TrkB signaling is important for postnatal survival of septal neurons (but the authors did not report the neurochemical phenotype of the apoptotic neurons). Unfortunately, the state of the adult basal forebrain cholinergic system was not explored in any of the studies examining the effects of antisense oligonucleotides directed against the BDNF transcript. There are also reports examining the effects of the destruction of target structures, like the hippocampus and cerebral cortex, on basal forebrain cholinergic neurons.

Destruction of the cerebral cortex or hippocampus leads to degeneration and/or atrophia of forebrain cholinergic neurons (Sofroniew et al., 1993; Burke et al., 1994; Skup et al., 1994). Furthermore, survival and differentiation of cultured basal forebrain cholinergic neurons is improved when they are co-cultured with cortical neurons (Ha et al., 1996, 1999). Some of the effects derived from target destruction can be prevented by BDNF administration (Burke et al., 1994; Ha et al., 1996, 1999), but this fact can not be taken as unequivocal evidence of a trophic role of endogenous BDNF.

The hippocampus is the brain region containing the highest concentrations of BDNF and TrkB. The cerebral cortex also express abundantly BDNF and TrkB. In addition, the hippocampal and cortical BDNF content increases during rodent postnatal development, and remains elevated during the entire lifespan (Maisonpierre et al., 1990b; Friedman et al., 1991a; Lapchak et al., 1993b; Ringstedt et al., 1993; Escandón et al., 1994; Fryer et al., 1996; Narisawa-Saito and Nawa, 1996; Katoh-Semba et al., 1997, 1998), suggesting a more important role for BDNF in the fully developed central nervous system than during embryogenesis and fetal life. This fact is also suggested by studies in genetically modified mice lacking endogenous BDNF or TrkB, which show no gross morphological alterations in the central nervous system at the time of birth (Ernfors et al., 1994; Jones et al., 1994; Conover et al., 1995; Minichiello and Klein, 1996; Alcántara et al., 1997; Silos-Santiago et al., 1997). Little is known, however, about the actions of endogenous BDNF on survival and function of hippocampal and cortical neurons in the adult mammalian brain.

Experiments performed on genetically-modified BDNF-deficient mice shed some light into the role of endogenous BDNF in hippocampal and cortical development and differentiation, in the early postnatal period (homozygous mutants die during the first weeks after birth). The hippocampal formation and cerebral cortex of BDNF mutant mice showed no gross cytoarchitectural abnormalities (Ernfors et al., 1994; Jones et al., 1994; Conover et al., 1995), but alterations of peptide expression were noticed, including reduced expression of neuropeptide Y, parvalbumin and calbindin in interneurons (Jones et al., 1994; Altar et al., 1997). The thickness of the cerebral cortex of mutants was reduced relative to controls (Jones et al., 1994; Conover et al., 1995), and a deficit in central nervous system myelination has also been noticed in BDNF-deficient mice (Cellerino et al., 1997). Interestingly, recent studies suggest that an excess of BDNF during development can severely affect the formation of the cerebral cortex (Fawcett et al., 1998; Ringstedt et al., 1999).

Consistent with these findings, the hippocampal formation and cerebral cortex develop normally in mutants lacking *Trk*B receptors (Minichiello and Klein, 1996; Alcántara et al., 1997; Silos-Santiago et al., 1997), but hippocampal and cortical neurons are of smaller size in the mutants (Alcántara et al., 1997). TrkB mutants showed an increased number of pycnotic nuclei (presumptively apoptotic neurons) in the dentate gyrus, and also in hippocampal CA1 and CA3 fields, cerebral cortex, and other brain areas (Alcántara et al., 1997). Minichiello et al. (1999) developed a conditional TrkB mutant mice in which knockout of the *Trk*B gene occurs during postnatal development, and only in the forebrain. These mutants show a normal hippocampal and cortical cytoarchitecture, and no evidence of increased rates of neuronal death, but they show a mild deficit in myelination in the hippocampus. Comparison of results from the different TrkB and BDNF mutants suggests an important role of TrkB and BDNF for development, differentiation and survival of hippocampal and cortical neurons until the early postnatal period, but not for neuronal survival in the adult hippocampal formation and cerebral cortex.

BDNF has more subtle effects on neuronal structure and function. An interesting series of reports stressed the ability of BDNF to modify dendritic architecture, including dendritic spine turnover (reviewed by McAllister et al., 1999). Application of rhBDNF to ferret postnatal visual cortex slices for 36 h alters dendritic complexity of pyramidal neurons, producing distinct patterns of dendritic modifications (increasing or decreasing dendritic complexity) in different cortical layers (McAllister et al., 1995, 1996). Incubation of the slices with different Trk–IgG fusion proteins (which neutralize endogenous NTs), allowed McAllister et al. (1997) to demonstrate that endogenous BDNF has selective effects on the architecture of the dendritic arbors of visual cortex pyramidal neurons. A very recent report by Horch et al. (1999) suggests that BDNF destabilizes dendritic arbors of cortical pyramidal neurons, therefore increasing dendritic plasticity. The studies were performed in ferret postnatal visual cortex slices co-transfected with the green fusion protein and BDNF genes, allowing repeated examination of individual BDNF-overexpressing pyramidal neurons. After 24–48 h, dendrites of BDNF-overexpressing neurons showed massive dendritic sprouting and a reduced number of dendritic spines, an effect that was dependent on TrkB activation through an autocrine loop (Horch et al., 1999).

Experiments have been performed based on the supposition that BDNF is involved in the axonal sprouting which follows lesions or neuronal overactivity in the adult brain, providing conflicting results. Lesions of hippocampal afferents and paradigms inducing hippocampal overactivity and seizures, known for their

ability to induce axonal sprouting, are accompanied by changes in the expression of BDNF and the truncated and catalytic forms of TrkB, in rats and humans (Beck et al., 1993b; Lapchak et al., 1993c; Merlio et al., 1993; Nawa et al., 1995; Suzuki et al., 1995; Guilhem et al., 1996; Elmér et al., 1996, 1997; Schmidt-Kastner et al., 1996b; Mathern et al., 1997; Goutan et al., 1998; Inoue et al., 1998; Vezzani et al., 1999). The existence of a close correlation between changes in BDNF and TrkB expression and axonal sprouting is, however, a matter of dispute. Results from experiments aimed at finding direct evidence of a relationship between BDNF and axonal sprouting in the adult brain are also contradictory. Bender et al. (1998) studied sprouting of the hippocampal mossy fiber system in slice cultures from early postnatal wild-type mice and BDNF-deficient mice, and did not found any impairment in BDNF knockout mice, suggesting that BDNF is not essential for mossy fiber sprouting. This finding is consistent with studies in adult mice heterozygous for a deletion of the BDNF gene, which showed increased kindling-induced mossy fiber sprouting in mutants relative to wild-type mice (Kokaia et al., 1995). In contrast, Vaidya et al. (1999a) reported decreased mossy fiber sprouting in hetrozygous BDNF-deficient mice following chronic electroconvulsive seizures, and Guilhelm et al. (1998) found that infusion of an antisense oligonucleotide directed against the BDNF transcript prevented hippocampal hypertrophic changes induced by kainic acid. Infusion of rhBDNF in the normal hippocampal formation does not, however, induce sprouting (Guilhem et al., 1996; Vaidya et al., 1999a). Consequently, a general role for BDNF in axonal sprouting induced by lesions and overactivity in the mature brain seems unlikely, even if BDNF and TrkB regulate axonal arborizations and formation of axon-dendritic contacts in the cerebral cortex and hippocampus during the early postnatal development (Cabelli et al., 1995; Galuske et al., 1996; Cabelli et al., 1997; Martinez et al., 1998).

As could be expected after results from in vitro studies (see Section 4.1.2) intracerebral administration of rhBDNF modifies synaptic transmission and alters the expression of neuronal peptides in vivo. One of the more interesting actions of BDNF is its capacity to produce long-lasting changes in synaptic function and structure (reviewed by Jankowsky and Patterson, 1999; Lu and Chow 1999; and McAllister et al., 1999). A role for endogenous BDNF in long-term potentiation was suggested by experiments showing that stimulation paradigms recognized for their ability to induce long-term potentiation, enhance BDNF mRNA expression in hippocampal neurons (Patterson et al., 1992; Castrén et al., 1993; Dragunow et al., 1993), and that BDNF can be released in an activity-dependent manner by hippocampal neurons (Blöchl and Thoenen, 1995; Goodman et al., 1996). Kang and Schuman (1995) subsequently demonstrated that transient application of BDNF to hippocampal slices produces a strong and sustained enhancement of synaptic efficacy in the Schaffer collateral–CA1 synapse, and that the effect is probably mediated by Trk receptors. Furthermore, Korte et al. (1995) found that long-term potentiation is impaired in the Schaffer collateral–CA1 synapse of slices from mutant mice lacking BDNF. The deficit in long-term potentiation of BDNF knockout mice could be reversed by acutely treating the slices with rhBDNF (Patterson et al., 1996), or by restoring BDNF expression in the CA1 region by means of virus-mediated gene transfer (Korte et al., 1996), suggesting that the deficit in long-term potentiation is not consequence of unrelated developmental alterations of BDNF-deficient mice. In good agreement with these conclusion, conditional mutant mice with a postnatal TrkB forebrain deficiency also show impaired long-term potentiation (Minichiello et al., 1999). In slices from normal rodents, function-blocking antibodies directed against TrkB (Korte et al., 1998), TrkB–IgG fusion proteins which binds endogenous BDNF and NT-4/5 (Figurov et al., 1996; Kang et al., 1997; Korte et al., 1998; Chen et al., 1999), and function-blocking antibodies directed against BDNF (Chen et al., 1999), all produce an impairment of long-term potentiation. Besides, long-lasting potentiation of synaptic activity has been reported to occur in the intact adult rat hippocampus after local infusion of rhBDNF (Messaoudi et al., 1998). Acute intrahippocampal infusion of rhBDNF in the hippocampal formation of anesthetized rats increased the field excitatory postsynaptic potential induced by stimulation of the perforant path. Finally, BDNF has been found to produce long-lasting functional synaptic modifications in the visual cortex as well (Akaneya et al., 1996, 1997; Carmignoto et al., 1997; Huber et al., 1998; Kinoshita et al., 1999).

Recent studies suggest a more general role of BDNF in synaptic transmission. Hippocampal excitatory transmission shows increased fatigue in hippocampal slices from immature rats having a low content of endogenous BDNF (Figurov et al., 1996), and in hippocampal slices from BDNF-deficient mice (Pozzo-Miller et al., 1999), and the deficit can be reverted by adding rhBDNF. Furthermore, hippocampal synapses in the CA1 field of mutant mice showed a reduced number of vesicles docked at presynaptic active zones, and a reduced content of synaptophysin and synaptobrevin (proteins involved in vesicle docking and fusion), suggesting that BDNF is involved in synaptic vesicle mobilization, availability, docking and/or fusion (Pozzo-Miller et al., 1999). A reduced density of synaptic terminals, synaptic vesicles docked to presynaptic active zones, and reduced expression of synaptic-

associated proteins, has also been noticed in TrkB mutants (Martinez et al., 1998). Consistent with these findings, BDNF promotes the release of acetylcholine and glutamate from hippocampal synaptosomes (Knipper et al., 1994).

BDNF has also postsynaptic actions which can explain its role in potentiating excitatory transmission in the hippocampal formation. BDNF promotes phosphorilation of NMDA glutamate receptors in adult rat hippocampal synaptoneurosomes and isolated postsynaptic densities (Suen et al., 1997; Lin et al., 1998). Besides, BDNF treatment of rat hippocampal slices reduces $GABA_A$-mediated inhibitory synaptic potentials in CA1 pyramidal neurons (Tanaka et al., 1997; Frerking et al., 1998). Finally, a very recent report by Kafitz et al. (1999) demonstrates that application of BDNF near the cell body of rat hippocampal pyramidal neurons elicits action potential firing. The effect of a nanomolar concentration of BDNF is as rapid and potent as that of a micromolar concentration of glutamate, the prototypic excitatory neurotransmitter. BDNF excitation seems to be mediated by Trk receptors, and involves reversible activation of a sodium conductance by a membrane-delimitated pathway. The startling findings of Kafitz and colleagues suggest that BDNF might function as a conventional neurotransmitter in the hippocampus (see also Altar and DiStefano, 1998).

Exogenous BDNF also regulates the expression of neuropeptides in cortical and hippocampal neurons in vivo (Nawa et al., 1994; Croll et al., 1994; Marty et al., 1997). During an interesting study aimed at determining if exogenous BDNF can affect in an age-dependent manner the expression of neuropeptides, Croll et al. (1999b) found that BDNF upregulates cortical and hippocampal neuropeptide Y and cortical somatostatin, and reduces expression of hippocampal dynorphin, both in young and aged rats. In contrast, BDNF infusion selectively reversed age-related atrophy of cholecystokinin-containing cortical interneurons.

4.1.5. Behavioral evidence relating BDNF expression to cognitive performance

Several experiments aimed at demonstrating a role for BDNF in learning and memory have been published recently. The first reports were disappointing. Fisher et al. (1994) examined the effect of intraventricular infusion of NTs (a 4-week treatment) on spatial memory in aged rats, and failed to find any beneficial effect of BDNF. The other NTs were able to reverse the age-related memory impairment. Similar results were reported by Pelleymounter et al. (1996), who found that intraventricular/intrahippocampal infusions of BDNF did not improve learning of the Morris water maze, whereas NGF partially reversed age-related deficits in spatial learning. In addition, Ma et al. (1999) reported that chronic infusion of rhBDNF into the dentate gyrus of rats does not improve retention performance in an inhibitory avoidance learning task.

Two studies performed in BDNF knockout mice attained contrasting conclusions. Montkowski and Holsboer (1997) reported that mice carrying a null mutation of one copy of the *BDN*F gene (3 months old), do not differ from wild-type mice in their performance in the Morris water maze or the elevated plus maze. Linnarsson et al. (1997), in contrast, found strong learning deficits (also in the Morris water maze) in heterozygous BDNF mutants. Young mutants (6–8 weeks old), required twice the number of days needed by wild-type mice to acquire an equivalent level of performance, but did not show any problem in retention. Aged mutants (10 months old) were completely unable to learn the task. Several differences between both studies, including number of training sessions and control of mice genetic background, can explain the conflictive results, and seem to favor the conclusion advanced by Linnarsson et al. (1997). The learning deficit in BDNF mutants, if any, cannot be unequivocally attributed to functional hippocampal or cortical changes, even if BDNF mutants show impaired hippocampal LTP (Korte et al., 1995), and a strong, age-dependent, reduction of cortical/hippocampal BDNF mRNA expression (Linnarsson et al., 1997), since BDNF-mutants show other central and peripheral nervous system deficits (Ernfors et al., 1994; Jones et al., 1994; Conover et al., 1995; Liu et al., 1995; Schwartz et al., 1997). A very recent report (Minichiello et al., 1999), demonstrating severe deficits in spatial learning tasks in mice with an homozygous TrkB deletion restricted to the forebrain and occurring during postnatal development, seem to support an essential role for forebrain TrkB signaling in learning. These conditional TrkB mutants have severe deficits in hippocampal LTP (like BDNF knockout mice). Finally, recent evidence from transgenic animals suggests that an increased expression of BDNF can have deleterious effects on learning, as well. Croll et al. (1999a) developed mice which overexpress BDNF diffusely in the brain, and found that they have a profound passive avoidance deficit, which resolved with age as BDNF expression declined to near normal levels.

Other experiments aimed at determining if endogenous BDNF has a role in learning and memory, were based in approaches aimed at blocking released BDNF protein, or impairing BDNF translation. Ma et al. (1998) studied inhibitory avoidance learning, and found that those rats showing full task retention display increased BDNF mRNA expression in the hippocampal dentate gyrus. Repeated intrahippocampal injections of an oligonucleotide directed against the BDNF transcript, when performed during training, decreased dentate gyrus BDNF mRNA expression,

reduced hippocampal LTP, and impaired retention. Further work by Ma et al. (1999) showed that the marked improvement in retention of inhibitory learning induced by corticotrophin-releasing factor is mediated by endogenous BDNF. Johnston et al. (1999) demonstrated that pre-training intracerebral injections of anti- BDNF antibodies, impaired the formation of a long-term memory track for an aversive stimulus in chicks. In contrast, injections of rhBDNF increased retention, even for weaker aversive stimulation (but see Ma et al., 1999). In another study of this kind, Mu et al. (1999) found that intraventricular infusion of anti-BDNF antibodies for a week before training, slowed learning of the Morris water maze.

There are other reports which indicate a relationship between levels of BDNF expression and learning and memory performance. Falkenberg et al. (1992b) reported increased levels of BDNF mRNA in the hippocampus of rats housed in enriched environments, and that higher levels of hippocampal BDNF mRNA correlated with better spatial learning abilities. Kesslak et al. (1998) reported an specific increase in hippocampal BDNF mRNA during training in the water maze. In contrast, Croll et al. (1998) did not found any relationship between cognitive performance of aged rats and level of BDNF expression in the forebrain. This latter result is consistent with a majority of studies showing no decrease or even increases in rat hippocampal BDNF and TrkB content during aging (Lapchak et al., 1993b; Escandón et al., 1994; Narisawa-Saito and Nawa, 1996; Katoh-Semba et al., 1997, 1998). A recent study reported a decreased expression of BDNF mRNA in the hippocampus and cerebral cortex of aged primates, however (Hayashi et al., 1997).

In conclusion, there is evidence indicating that disruption of endogenous BDNF signaling impairs learning and memory in animals. However, administration of BDNF seems to not reverse aging-related learning and memory deficits. Furthermore, a widespread increase of endogenous BDNF produces learning deficits. It seems possible that the physiological role of BDNF in learning depends on exquisitely regulated spatial and temporal changes in BDNF expression and release, which can not be mimicked by increasing diffusely BDNF expression or extracellular concentration.

4.1.6. Mechanisms through which altered BDNF expression could be involved in the pathogenesis and pathophysiology of Alzheimer's disease

Putative endogenous sources of BDNF for hippocampal neurons include BDNF released from their own dendrites (autocrine/paracrine loops), from axonal endings of afferent hippocampal and extrahippocampal neurons (anterogradely transported BDNF), and from target fields (retrogradely transported BDNF). As summarized in Section 3.2, most granule neurons in the dentate gyrus and pyramidal neurons in the hippocampal CA3 field express both BDNF and TrkB, suggesting the existence of autocrine/paracrine loops. Furthermore, the mossy fibers probably constitute the most important BDNF source for CA3 pyramidal neurons (Smith et al., 1997; Conner et al., 1997; Yan et al., 1997a; Murer et al., 1999a, 1999b). Putative extrahippocampal BDNF sources for hippocampal neurons include afferent fibers coming from the amygdala and parahippocampal cortex, regions where projecting neurons express BDNF mRNA (see Sections 3.2 and 3.3). Finally, BDNF might function as a classical retrograde neurotrophic factor for hippocampal neurons, since exogenous BDNF is retrogradely transported from several hippocampal target fields to the cell bodies of hippocampal neurons (reviewed by Mufson et al., 1999). Autocrine/paracrine loops are probably a major source of endogenous BDNF for cortical pyramidal neurons, a part of which express both BDNF and TrkB (Section 3.2). Pyramidal cortical neurons can also transport BDNF retrogradely from their axon terminals to the cell bodies (reviewed by Mufson et al., 1999). Finally, most cortical and hippocampal interneurons express TrkB, but do not express BDNF, suggesting that BDNF acts as a classical target-derived neurotrophic factor for these cells (reviewed by Marty et al., 1997). It seems that under pathological circumstances, interneurons can upregulate BDNF expression and presumptively become an endogenous source of BDNF (Wang et al., 1998). The endogenous sources of BDNF for basal forebrain cholinergic neurons probably include target-derived BDNF and BDNF contained in afferent fibers (see Section 3.2) There is strong evidence suggesting that most of these sources of endogenous BDNF, and BDNF signaling through TrkB receptors, are disrupted in Alzheimer's disease (see Section 4.1.1).

There is no evidence indicating that healthy hippocampal, cortical, and basal forebrain cholinergic neurons in the adult mammalian brain are absolutely dependent on endogenous BDNF support for survival. Nevertheless, there is substantial evidence suggesting that the death of injured adult neurons in these regions can be prevented by BDNF (Section 4.1.3). But the paradigms of injury utilized in these studies do probably not reflect closely enough the poorly understood mechanisms leading to neuronal death in Alzheimer's disease.

Consequently, it is not possible to make a confident statement about what consequences could a reduction in *endogenous* BDNF content have on the ongoing degenerative process in Alzheimer's disease.

Reduced endogenous BDNF can contribute to Alzheimer's disease pathophysiology through other mechanisms. It is widely accepted that BDNF plays

a role in modulating synaptic plasticity, both at the functional and structural levels (Lo, 1995; Thoenen, 1995; McAllister et al., 1999; Section 4.1.4). Loss of synaptic contacts in the hippocampus and cerebral cortex is one the most important neuropathological findings in the brain of individuals with Alzheimer's disease (Terry et al., 1991). Consequently, it seems possible that altered synaptic plasticity resulting from reduced endogenous BDNF content contributes to cognitive impairment in Alzheimer's disease (Section 4.1.5). Of utmost importance, it has recently been proposed that the primary defect in Alzheimer's disease is a perturbation in neuronal plasticity, which ultimately leads to all the neuropathological and clinical manifestations, including formation of amyloid plaques and neurofibrilary tangles, neuronal death, synaptic contact loss, and cognitive deterioration (Mesulam, 1999).

Interestingly, a recent report established a relationship between BDNF signaling through TrkB receptors and presenilin-1. Mutations in the gene encoding for presenilin-1 cause an inherited, autosomal dominant, early onset form of Alzheimer's disease. Recent studies suggest that mutated presenilin-1 influences intracellular processing of β-amyloid precursor proteins in a manner that determines an increased production of amyloidogenic Aβ peptides (Hardy, 1997). Remarkably, cultured cortical neurons from mice lacking the presenilin-1 gene accumulate β-amyloid precursor proteins, display an altered post-translational maturation of TrkB, and a severe deficit in TrkB autophosphorilation in response to BDNF. The deficit in intracellular protein processing of membrane and secretory proteins in cells lacking presenilin-1 is not ubiquitous, but highly selective (Naruse et al., 1998). Thus, it seems possible that the role of BDNF in the pathogeny and pathophysiology of Alzheimer's disease is just beginning to be comprehended.

4.2. Parkinson's disease

4.2.1. BDNF expression is reduced in the substantia nigra in Parkinson's disease

Parain et al. (1999) have recently demonstrated a reduced expression of BDNF protein in the substantia nigra of individuals with Parkinson's disease. The authors reported that about 65% of all melanized neurons in the SNpc were immunoreactive for BDNF in controls, whereas in patients, only 10% of the pigmented neurons were BDNF immunoreactive (Table 2, Fig. 9). Among the structures studied, reduced BDNF protein expression occurred specifically in the substantia nigra pars compacta, the neuronal group most severely affected in Parkinson's disease. Pigmented neurons in the A8 region, which was not affected by the disease, showed no altered proportion of BDNF-immunoreactive neurons. This result can be explained by, at least, two different hypothesis: (1) expression of BDNF in the remaining nigral neurons fell below the level of detection of the immunocytochemical procedure used; (2) BDNF-immunoreactive nigral neurons were preferentially targeted by the cell death process. The authors further reported that most patients pigmented neurons presenting Lewy bodies showed BDNF-immunoreactivity (Fig. 9). The significance of the presence of Lewy bodies in remaining nigral neurons of patients is uncertain (for reviews see Lang and Lozano, 1998 and Trojanowski et al., 1998), but if it is related to the cause of cell death in Parkinson's disease, the results of Parain and colleagues might indicate that BDNF immunoreactive melanized neurons are preferentially targeted by the cell death process. In

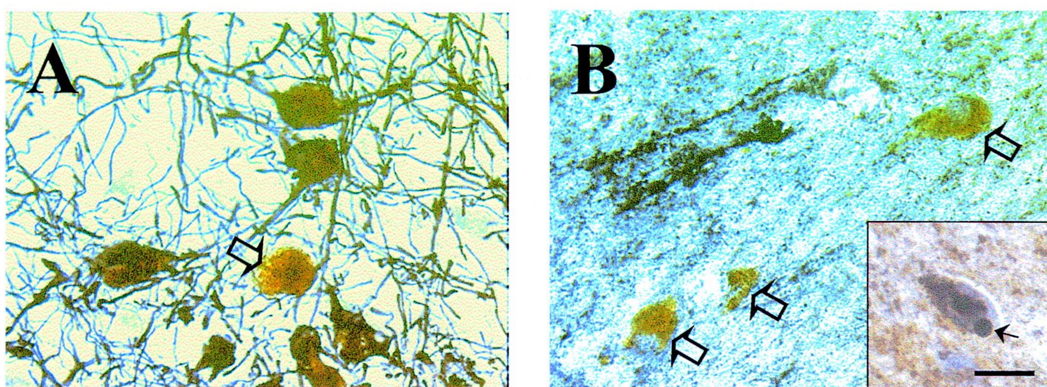

Fig. 9. (A) High-power microphotograph illustrating the type of labeling observed in the substantia nigra in the control human brain. An unlabeled melanized cell is signaled with an arrow. Most pigmented cells were BDNF immunoreactive, and there was also a dense labeling of neurites. (B) Remaining pigmented cells were rarely BDNF-immunoreactive in mesencephalic sections from patients with Parkinson's disease (arrows). Inset: a BDNF-immunoreactive neuron in the substantia nigra of a patient showing an ubiquitin-immunoreactive inclusion (Lewy body) in the cytoplasm (arrow). Scale bar: 50 μm. Modified from Parain et al. (1999), inset reproduced with permission.

any case, it seems clear that expression of BDNF does not protect nigrostriatal neurons from injury in Parkinson's disease.

Another recent report provides further evidence supporting a reduction of BDNF protein content in the brain of patients with Parkinson's disease (Mogi et al., 1999). The authors used a sensitive enzyme-linked immunosorbent assay to measure the concentration of BDNF protein in several regions of the brain of control individuals and patients. They found an important reduction of BDNF concentration in the caudate nucleus (24% of the control value), putamen (18% of the control value) and substantia nigra (55% of control value), and non-significant decreases in the two other areas sampled, the frontal cortex and cerebellum. Another report by Kawamoto et al. (1999a), failed to detect any reduction in the density of striatal BDNF immunoreactive neurites in the putamen of patients with Parkinson's disease. The reason for the seeming discrepant results on striatal BDNF in patients is not clear. In any case, the important decrease in striatal BDNF content observed by Mogi and colleagues seems not to merely reflect the loss of BDNF protein contained in dopaminergic striatal afferents, in as much as most striatal BDNF is contained in cortical afferents (Altar et al., 1997).

To our knowledge, only one report exists on the expression of TrkB receptor in the brain of patients with Parkinson's disease (Benisty et al., 1998). Benisty and colleagues studied the expression of TrkB mRNA at the cellular level in substantia nigra and ventral tegmental area neurons, and found no difference in expression between controls and patients with Parkinson's disease. To our knowledge, there are no reports on levels of TrkB protein expression in Parkinson's disease.

The possibility that reduced expression of BDNF in Parkinson's disease were a consequence of chronic therapy with levodopa cannot be completely ruled-out. However, the available evidence does not support this conclusion. The effect of levodopa administration on BDNF expression has been studied by Okazawa et al. (1992), who found that levodopa increases the expression of BDNF mRNA in the striatum of healthy mice. In addition, the expression of BDNF is not changed in cultured mesencephalic dopaminergic neurons after levodopa administration for 7 days (M.G. Murer and P.P. Michel, unpublished observations). Finally, rats lesioned with 6-OHDA and treated for 6 months with levodopa do not differ from 6-OHDA-lesioned rats treated with vehicle, in BDNF protein expression, at the striatal or nigral levels (M.G. Murer and R. Raisman-Vozari, unpublished results).

4.2.2. BDNF promotes survival of dopaminergic neurons and protects them from toxin-induced damage in vitro

Early reports by Hyman et al. (1991) and Knüsel et al. (1991) showed that BDNF prevents the spontaneous death of dopaminergic neurons in rat primary mesencephalic cultures. The authors reported that most tyrosine hydroxylase (TH) immunoreactive neurons die during the first week in control primary mesencephalic cultures. Administration of BDNF protein increased several times the number of surviving TH-immunoreactive neurons after 7–9 days in vitro. Hyman et al. (1991) further demonstrated that BDNF administration protects TH-immunoreactive neurons from the selective toxin MPP^+ (1-methyl-4-phenylpyridinium). These results raised interest in BDNF as a putative novel therapeutic agent for Parkinson's disease.

The survival promoting action of BDNF on rat embryonic and early postnatal mesencephalic dopaminergic neurons in vitro has been confirmed by several different research groups (Beck et al., 1993a; Hyman et al., 1994; Studer et al., 1995; Krieglstein et al., 1996; Ostergaard et al., 1996; Hoglinger et al., 1998; Engele, 1998; Sautter et al., 1998; Feng et al., 1999; Murer et al., 1999b) (Fig. 10). These reports also demonstrated that BDNF promotes differentiation of rat embryonic dopaminergic neurons. Cultured dopaminergic neurons treated with BDNF show increased TH activity, dopamine uptake and dopamine content, release more dopamine upon depolarization, and display an increased cell body size and higher neuritic complexity (Beck et al., 1993a; Hyman et al., 1994; Studer et al., 1995; Blöchl and Sirrenberg, 1996; Ostergaard et al., 1996; Feng et al., 1999). The protective effect of BDNF in vitro against specific toxins like MPP^+ and 6-OHDA, has likewise been confirmed (Beck et al., 1992; Spina et al., 1992; Fadda et al., 1993; Son et al., 1999). The survival promoting action of BDNF has additionally been recorded in human embryonic mesencephalic dopaminergic neurons, in different culture conditions (Table 1). Furthermore, BDNF increases dopamine content and TH activity (Zhou et al., 1994; Othberg et al., 1995), and dopaminergic cell body size, neuritic development and neuritic complexity (Studer et al., 1996), in human embryonic mesencephalic cultures.

As summarized above (Section 3.4), a large number of dopaminergic mesencephalic neurons seem to express both BDNF and TrkB, suggesting the existence of autocrine and paracrine trophic loops supporting survival and function of the mesotelencephalic system. In vitro evidence favoring the existence of these autocrine/paracrine mechanisms was provided by Lau et al. (1998). The authors have treated rat primary mesencephalic cultures with an antisense oligodeoxynucleotide against the BDNF transcript, and found a sig-

nificant reduction of the number of TH-immunoreactive neurons and [^{3}H] dopamine uptake relative to cultures treated with an scrambled oligodeoxynucleotide, suggesting that BDNF synthesized by cultured cells supports survival of dopaminergic neurons. The source of BDNF was not investigated, nor BDNF protein presence in the culture media, remaining the exact mechanism of survival promotion to be elucidated. Similarly, Zhou et al. (1997) found that addition of anti-BDNF antibodies to the culture medium reduces survival of embryonic mesencephalic TH-immunoreactive neurons. Experiments by Middlemas et al. (1999) in a neuroblastoma cell line supports the existence of autocrine loops involving BDNF and TrkB in the process of differentiation of catecholaminergic cells. In contrast, Murer et al. (1999b) failed to find any effect of treating cultures with function-blocking anti-rhBDNF antibodies on survival of TH-immunoreactive neurons in rat primary mesencephalic cultures.

4.2.3. Does BDNF promote survival and recovery of injured dopaminergic neurons in vivo?

The above summarized findings stimulated research aimed at determining whether BDNF administration can protect mesencephalic dopaminergic neurons from damage induced by toxins or axotomy in vivo.

In the first experiments of this kind, Knüsel et al. (1992) axotomized mesencephalic dopaminergic neurons at the medial forebrain bundle in rats, and subsequently administered rhBDNF for 18–20 days by repeated intraventricular or intranigral infusions. The authors failed to find any protective effect of the treatment on mesencephalic TH-immunoreactive neurons, and did not examine any behavioral parameters. Subsequently, Lapchak et al. (1993a) reported that chronic intranigral administration of BDNF does not prevent the decline in striatal dopaminergic function that follows axotomy of mesostriatal dopaminergic axons. A similar paradigm was used later by Hagg (1998). The author, however, has evaluated the integrity of the nigrostriatal system both by using TH as a dopaminergic marker, and by retrogradely labeling nigral cell bodies from the striatum with a fluorescent tracer. Interestingly, Hagg found a strong survival promoting effect of BDNF on retrogradely labeled nigral neurons, but not on TH-immunoreactive nigral neurons. In the experiments of Hagg, an important number of the rescued retrogradely labeled nigral neurons had undetectable levels of expression of TH, a finding that can explain the negative findings reported previously by Knüsel et al. (1992) and Lapchak et al. (1993a). Unfortunately, Hagg did not report on any behavioral examination of the animals.

Initial experiments intended to detect a protective action of BDNF on nigral damage induced by high doses of 6-OHDA showed no beneficial effects (Altar et al., 1994a; Lucidi-Phillipi et al., 1995). More promising results were obtained with models of "early parkinsonsim", where rats receive lower doses of 6-OHDA or MPP$^+$ in the striatum. Shultz et al. (1995) studied the effect of repeated intrastriatal injections of rhBDNF on damage induced by intrastriatal administration of 6-OHDA, and found evidence of behavioral improvement in pharmacological tests, and moderate sparing of striatal dopaminergic nerve endings around the injection site. Hung and Lee (1996) further reported a protective effect of direct nigral infusion of BDNF against reductions in striatal dopamine content induced by MPTP in mice. Levivier et al. (1995) demonstrated that striatal grafts of fibroblasts genetically engineered to produce BDNF, protected dopaminergic nerve terminals and cell bodies against damage induced by intrastriatal administration of 6-OHDA. Similar findings were reported by Frim et al.

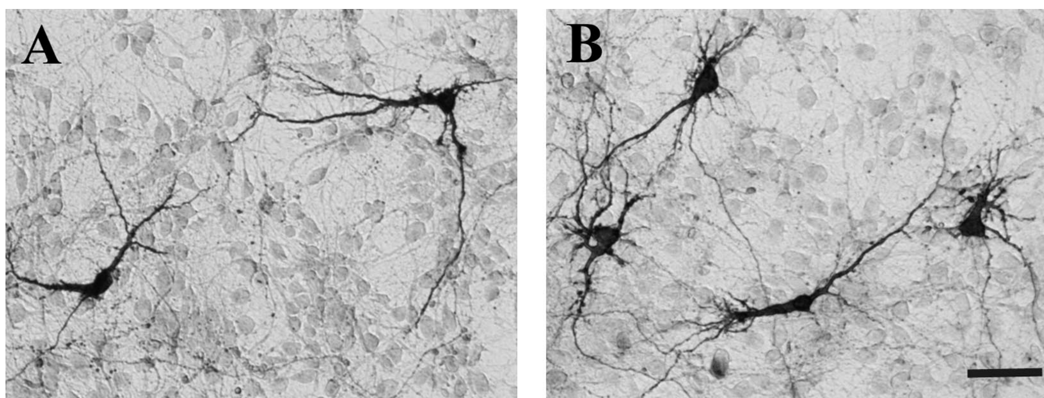

Fig. 10. Tyrosine hydroxylase immunoreactive embryonic neurons in rat mesencephalic primary cultures. (A) control condition (7 days in vitro). (B) after a 7-day treatment with rhBDNF (20 ng/ml). The treatment increased the number of tyrosine hydroxylase immunoreactive neurons by 50%. After Murer et al. (1999b). Scale bar: 20 μm.

(1994) and Galpern et al. (1996), but they implanted the engineered fibroblasts dorsal to the substantia nigra, and induced the lesion by injecting MPP^+ intrastriatally. A preliminary report by Tsukahara et al. (1995) showed a protective effect of intrathecal infusion of BDNF against the toxic action of systemic MPTP in monkeys. The authors found that BDNF administration delayed the emergence and attenuated the parkinsonian signs, and reduced damage in the substantia nigra, but they studied only three monkeys in the treated and control groups. Very recently, Klein et al. (1999a) reported that expression of a transgene containing the BDNF gene in the mesencephalon of rats did not prevent the 6-OHDA-induced loss of TH-immunoreactive cell bodies in the substantia nigra.

In summary, there is a body of work suggesting that exogenous BDNF administration can increase survival and/or promote recovery of injured mesencephalic dopaminergic neurons at least in some experimental conditions. It seems that the experimental approach used to increase BDNF content locally in the central nervous system is a critically determinant animal outcome. At least two important deficits can be detected in most of the studies summarized above: (1) scarcity of behavioral investigations, with most reports studying only pharmacologically-induced behavior; (2) examination of the integrity of the mesotelencephalic dopaminergic system relying on detection of the expression of dopaminergic markers. Critical experiments demonstrating a correlation between improvement in spontaneous motor function, degree of expression of dopaminergic markers, and degree of anatomical completeness of the mesotelencephalic system, are lacking.

4.2.4. BDNF regulates the expression of striatal peptides and nigrostriatal function

Besides its putative role in promoting survival of adult dopaminergic neurons after injury, BDNF can influence basal ganglia function in several different ways. Most evidence proceeds, however, from studies looking at actions of exogenous BDNF on basal ganglia function, remaining the functional significance of endogenous BDNF poorly understood.

There is strong, although somewhat contradictory evidence, demonstrating actions of BDNF on intact adult dopaminergic neurons. After a 2 week supranigral unilateral infusion of BDNF, intact rats develop a contralateral turning response to the dopamine releasing drug amphetamine (Altar et al., 1992), reflecting a disbalance between the dopaminergic systems of both hemispheres. Presumptively, the effect of BDNF resulted from changes in the infused nigrostriatal system, which are reflected in an increased dopamine turnover in the ipsilateral striatum. Further results from Altar and colleagues (Martin-Iverson et al., 1994; Martin-Iverson and Altar, 1996) showed that rats infused with BDNF above the substantia nigra, exhibited more spontaneous locomotor activity, a contralateral postural bias, and an increased behavioral response to amphetamine, all changes being consistent with an increased dopaminergic activity. Analysis of the electrophysiological activity of nigral dopaminergic neurons in infused animals showed that BDNF increases their firing rate (Shen et al., 1994). Reports from other laboratories suggest, instead an antidopaminergic effect of chronic supranigral infusion of BDNF. Hagg (1998) found that BDNF reduces the expression of TH protein in intact nigral neurons, and Lapchak et al. (1993a) reported reduced striatal dopamine uptake and dopamine uptake sites, reduced striatal dopamine content and TH activity, and reduced TH mRNA expression by dopaminergic neurons, in healthy rats treated locally with BDNF. Finally, Lau et al. (1998) showed an increase in nigral dopamine content after intranigral administration of an antisense oligonucleotide directed against the BDNF transcript.

In contrast with the large series of experiments performed to determine if exogenous BDNF can rescue injured mesencephalic dopaminergic neurons, little or no evidence exists on the effect of endogenous BDNF on survival of dopaminergic neurons in the adult mammalian brain. Mice lacking both functional copies of the BDNF gene (Ernfors et al., 1994; Jones et al., 1994) do not show a major loss of mesencephalic dopaminergic neurons, indicating that endogenous BDNF is not essential for survival of dopaminergic neurons during development. These mice die early after birth, however, leaving unanswered the question of whether endogenous BDNF is required or not for dopaminergic cell survival in adulthood, or if it has any protective effect against injury or aging-related cell loss. An interesting report by Alonso-Vanegas et al. (1999) suggests that overexpression of BDNF during development can reduce developmental cell death of mesencephalic dopaminergic neurons. The authors used a transgenic mouse that overexpress BDNF in noradrenergic and adrenergic neurons as a consequence of the fusion of the BDNF gene to the promoter of the dopamine-β-hydroxylase gene. The number of mesencephalic dopaminergic neurons increased significantly in transgenic mice. The mechanism suggested by Alonso-Vanegas and colleagues for the trophic effect of overexpressed BDNF was that increased anterograde transport of BDNF via the coeruleo-nigral pathway protects developing mesencephalic neurons from programmed cell death. A trophic effect of the coeruleo-nigral pathway on nigral dopaminergic neurons has been suggested on the basis of functional evidence before. Notably, the coeruleo-nigral pathway seems to partially protect mesencephalic dopaminergic neurons from toxin-induced damage in monkeys and

rodents (Mavridis et al., 1991; Marien et al., 1993; Bing et al., 1994; Fornai et al., 1996).

Evidence regarding the existence of functional autocrine/paracrine trophic loops in the adult ventral mesencephalon is lacking. To our knowledge, only one report exists (Lau et al., 1998) examining the effects of reducing BDNF synthesis in vivo with antisense oligodeoxynucleotides, on mesencephalic dopaminergic neuronal function in adult rats. The authors found an unexpected increase in dopaminergic function after antisense injections in the substantia nigra. Unfortunately, they report important non-specific effects of the control oligodeoxynucleotide, and consequently, their findings should be considered cautiously.

Indirect evidence on the existence of functional nigral autocrine/paracrine loops can be derived from studies relating BDNF expression to vulnerability to damage. There is limited evidence suggesting that mesencephalic dopaminergic neurons expressing BDNF are less vulnerable to injury in animals. This is an important issue, since the pattern of dopaminergic neuronal degeneration in Parkinson's disease suggests a preferential vulnerability of some dopaminergic neuronal groups (Gibb and Lees, 1991; Hirsch et al., 1992). Hung and Lee (1996) studied the relationship between expression of BDNF mRNA and susceptibility to MPP^+-induced damage in mesencephalic dopaminergic cell groups, and reach the conclusion that higher BDNF mRNA expression in the medial mesolimbic pathway can explain its reduced vulnerability to the toxin. Nishio et al. (1998a) found, in the control human mesencephalon, that NTs and their Trk receptors (including BDNF and TrkB) are preferentially expressed by medial dopaminergic neurons, which are relatively preserved in Parkinson's disease. It has also been reported that dopaminergic neurons projecting to the striatal matrix are more vulnerable to MPTP toxicity in dogs and monkeys (Turner et al., 1988; Moratalla et al., 1992). In the control human brain, BDNF-immunoreactivity is higher in striosomes than in the matrix (Murer et al., 1999a), suggesting a mechanism through which nigrostriatal neurons projecting to striosomes can be less vulnerable to MPTP toxicity. Interestingly, the nigrostriatal dopaminergic projection to the striosomes seems to be preferentially targeted in Parkinson's disease, despite higher expression of BDNF protein in striosomes relative to the matrix. Thus, immunohistochemical studies on the distribution of the plasma membrane dopamine transporter in striatal postmortem tissue sections from patients with Parkinson's disease demonstrated preservation of immunolabeled patches (suggesting preserved nigrostriatal dopaminergic nerve endings) in the putaminal matrix (Miller et al., 1997). Furthermore, analysis of the degenerative process in the mesencephalon of patients suggested that nigral dopaminergic neurons projecting to striosomes are preferentially affected by the disease (Gibb and Lees, 1991; Hirsch et al., 1992). These facts support that endogenous BDNF does not protect nigrostriatal neurons from the etiologic factor/s in Parkinson's disease.

Further relationships between BDNF and the pathophysiology of Parkinson's disease can result from a diminished action of endogenous nigral BDNF on other populations basal ganglia neurons. For example, nigral GABAergic neurons could be influenced by locally released BDNF from nigral dopaminergic neurons. In addition, BDNF seems to be anterogradely transported by nigral neurons to the striatum (Altar et al., 1997), and destruction of the mesotelencephalic dopaminergic system results in an increased expression of TrkB mRNA in the striatum (Numan and Seroogy, 1997), suggesting a role for endogenous nigral BDNF in the regulation of striatal function. In agreement with this suggestion, BDNF has been shown to modify the expression of peptides in striatal and nigral GABAergic neurons in culture conditions (Hyman et al., 1994; Mizuno et al., 1994; Ventimiglia et al., 1995; Ivkovic and Ehrlich, 1999), in animals with a null mutation in the gene encoding for BDNF (Altar et al., 1997; Ivkovic and Ehrlich, 1999), and in adult healthy animals infused with rhBDNF (Croll et al., 1994; Sauer et al., 1994, 1995; Arenas et al., 1996).

4.2.5. Mechanisms through which altered BDNF expression could be involved in the pathogenesis and pathophysiology of Parkinson's disease

The above reviewed experiments on BDNF and the nigrostriatal dopaminergic system suggest several mechanisms through which an altered BDNF expression can be involved in Parkinson's disease pathophysiology.

First, it must be considered if BDNF is involved in the compensatory mechanisms that take place in the basal ganglia of patients. The clinical signs in Parkinson's disease do not fully develop until the striatal dopamine content falls to about 20% of the control value. Putative compensatory mechanisms affecting the remaining nigral neurons include increased firing rate, dopamine synthesis, and dopamine release (Zigmond et al., 1992). These effects have been shown after nigral administration of BDNF in the intact rat, and in rats with a partial lesion of the nigrostriatal system (Altar et al., 1992; Martin-Iverson et al., 1994; Shen et al., 1994; Shultz et al., 1995; Martin-Iverson and Altar, 1996). The expression of BDNF in the remaining nigral neurons of patients is reduced, however, suggesting that autocrine/paracrine mechanisms are not involved in these compensatory changes. It remains possible that coeruleo-nigral-derived BDNF cause the compensatory changes in the remaining

nigral neurons. However, we are not aware of any animals studies addressing this question.

Second, a reduced expression of BDNF by remaining nigral neurons might result in a reduced autocrine/paracrine trophic support and increased cell death. Even if there is some data suggesting the existence of this kind of trophic support in cultures of mesencephalic dopaminergic neurons (Lau et al., 1998; Middlemas et al., 1999), no conclusive evidence has yet been provided indicating that endogenous nigral BDNF protects dopaminergic neurons from injury in vivo, nor suggesting that endogenous nigral BDNF is necessary for dopaminergic cell survival in the mature brain.

Third, the degeneration of locus coeruleus neurons that occurs in Parkinson's disease (Fearnley and Lees, 1997) can private remaining mesencephalic dopaminergic neurons from anterogradely transported BDNF, and increase nigral cell death. This possibility is suggested by reports demonstrating an increased vulnerability of nigral dopaminergic neurons to toxin-induced damage after locus coeruleus lesions (Mavridis et al., 1991; Bing et al., 1994; Fornai et al., 1996), in conjunction with the work of Alonso-Vanegas (1999), showing an increased number of mesencephalic dopaminergic neurons in mice overexpressing BDNF in noradrenergic neurons. It remains to be determined if the protective effect of the locus coeruleus against toxin-induced damage in the adult brain is related to anterograde transport of BDNF through the coeruleo-nigral pathway. Besides, the status of BDNF expression by remaining locus coeruleus neurons in patients with Parkinson's disease is not known, nor the density of BDNF-containing fibers in the ventral mesencephalon of patients.

Fourth, it is possible that the striatal post-synaptic changes observed in Parkinson's disease are to some extent due to the lack of anterogradely transported nigral BDNF. However, the effects of selective experimental manipulation of nigral BDNF production on striatal function in the adult brain are not known.

In summary, the lack of comprehensive experiments aimed at understanding the actions of endogenous BDNF on dopaminergic neuronal survival and basal ganglia function, prevents a more profound and less speculative analysis of BDNF involvement in the pathophysiology of Parkinson's disease. The results of this kind of studies are enthusiastically awaited, given that BDNF therapy is at present a tangible possibility for patients. The facts that TrkB mRNA expression in melanized mesencephalic neurons of patients with Parkinson's disease is normal, whereas BDNF expression in remaining nigral neurons is reduced, in conjunction with animals studies showing that injured dopaminergic neurons respond to exogenous BDNF in vivo, suggest that patients could find some benefit from a rationally designed BDNF therapy.

5. Conclusion

Our knowledge about the anatomical distribution and physiology of BDNF has grown enormously during the last decade, and suggests that BDNF is not only important for the normal development of the peripheral and central nervous system, but that also has relevant actions in the adult central nervous system, and might be involved in the pathogeny and pathophysiology of central nervous system diseases, notably Alzheimer's disease and Parkinson's disease. Among the advances in the field attained during the last decade, we can mention: (1) the unraveling of some fundamental aspects of BDNF intracellular trafficking, including its anterograde transport, and its sorting to the regulated pathway of secretion; (2) the fact that BDNF expression is under the control of physiological and injury-related signals; (3) the disclosure of BDNF influences on synaptic plasticity, at the functional and structural levels; (4) the discovery of the survival-promoting action of BDNF on injured neurons in the adult brain; (5) the description of BDNF distribution in the human central nervous system, and of the modifications of BDNF expression occurring in some pathological states. The challenge for the next decade is to gain insight into the role of endogenous BDNF in the pathogeny and pathophysiology of Alzheimer's and Parkinson's diseases, in order to rationally decide if patients can expect to obtain some relief from a therapy aimed at reversing the modifications in the expression of BDNF which occur during these pathological states.

Note added in proof

Holsinger et al. (2000) further confirmed levels of BDNF mRNA are reduced in the brain (parietal cortex) of individuals with Alzheimer's disease. Ferrer et al. (2000) reported that BDNF protein is not decreased in frontotemporal dementia. This fact suggests that the decrease in BDNF expression which occurs in Alzheimer's disease is not a phenomenon common to all kinds of dementia. Murray et al. (2000) provided additional evidence demonstrating an increased expression of BDNF mRNA in dentate granule cells from hippocampal samples of epileptic humans.

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