The Neuroscientist

Is Altered BDNF Biosynthesis a General Feature in Patients with Cognitive Dysfunctions?
Davide Carlino, Maurizio De Vanna and Enrico Tongiorgi
Neuroscientist published online 14 December 2012
DOI: 10.1177/1073858412469444

The online version of this article can be found at:

Published by:

⑤SAGE

Additional services and information for *The Neuroscientist* can be found at:

Email Alerts: http://nro.sagepub.com/cgi/alerts

Subscriptions: http://nro.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - Dec 14, 2012

What is This?

Is Altered BDNF Biosynthesis a General Feature in Patients with Cognitive Dysfunctions?

Davide Carlino[1], Maurizio De Vanna[1], and Enrico Tongiorgi[2]

Abstract

Severe cognitive deficits are a frequent outcome of both neurodegenerative and neurodevelopmental disorders. In the attempt to define new clinical biomarkers, current research trends aim at the identification of common molecular features in these pathologies rather than searching for differences. Brain-derived neurotrophic factor (BDNF) has attracted great interest as possible biomarker because of its key role in synaptic remodeling during cognitive processes. BDNF undergoes proteolytic processing and studies in animal models have highlighted that different forms of learning and memory require either the proBDNF precursor or the mature BDNF form. Significantly, an altered expression of BDNF forms was found in postmortem brains and serum from patients with schizophrenia, Alzheimer's disease and mood disorders. Based on these studies, this review puts forward the hypothesis that abnormalities in proBDNF or mBDNF biosynthesis may correspond to different cognitive dysfunctions in these brain diseases, while the role of truncated BDNF remains unknown.

Introduction

Cognitive dysfunctions are a general feature of many neurodegenerative and neurodevelopmental disorders (Archer and others 2011). In the past three decades, several studies investigating cognitive functioning in schizophrenia and Alzheimer's disease (AD) have demonstrated that cognitive impairment influence quality of life and global performance significantly more than other behavioral or psychotic symptoms (Nuechterlein and others 2011).

A current major hypothesis is that cognitive disturbances may be associated with altered trophic support of neuronal activity and survival by various growth factors, including neurotrophins (Arancio and Chao, 2007). Among the growth and trophic factors that are able to provide both an effect on synaptic activity and neuronal survival, the neurotrophin brain-derived neurotrophic factor (BDNF) has attracted great interest. BDNF is a member of the family that includes nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT-4/5). BDNF is highly expressed in the central nervous system (CNS) and is crucial for dopaminergic (Guillin and others 2001), glutamatergic (Carvalho and others 2008), and serotonergic (Mossner and others 2000) neurotransmission; moreover, it has a pivotal role in synaptic remodeling during cognitive processes (Schinder and Poo 2000).

The aim of this review is to examine studies that investigated BDNF in animal models of learning and memory and in clinical conditions such as schizophrenia, AD, and mood disorders in order to establish whether abnormalities of its biosynthesis may represent a common molecular mechanism underlying cognitive deficits.

BDNF Biosynthesis

BDNF is initially synthesized in the endoplasmic reticulum as a precursor protein (proBDNF) of 32 kDa, which is proteolitically cleaved to generate either a truncated form of 28 kDa (truncated BDNF) or the mature form of 13.5 kDa (mBDNF; Fig. 1). mBDNF is naturally found

[1]Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
[2]Department of Life Sciences, University of Trieste, Trieste, Italy

Corresponding Author:
Davide Carlino, Psychiatric Clinic, Department of Medical, Surgical and Health Sciences, BRAIN Centre for Neuroscience, University of Trieste, via Paolo de Ralli 5, Trieste, 34127 Italy
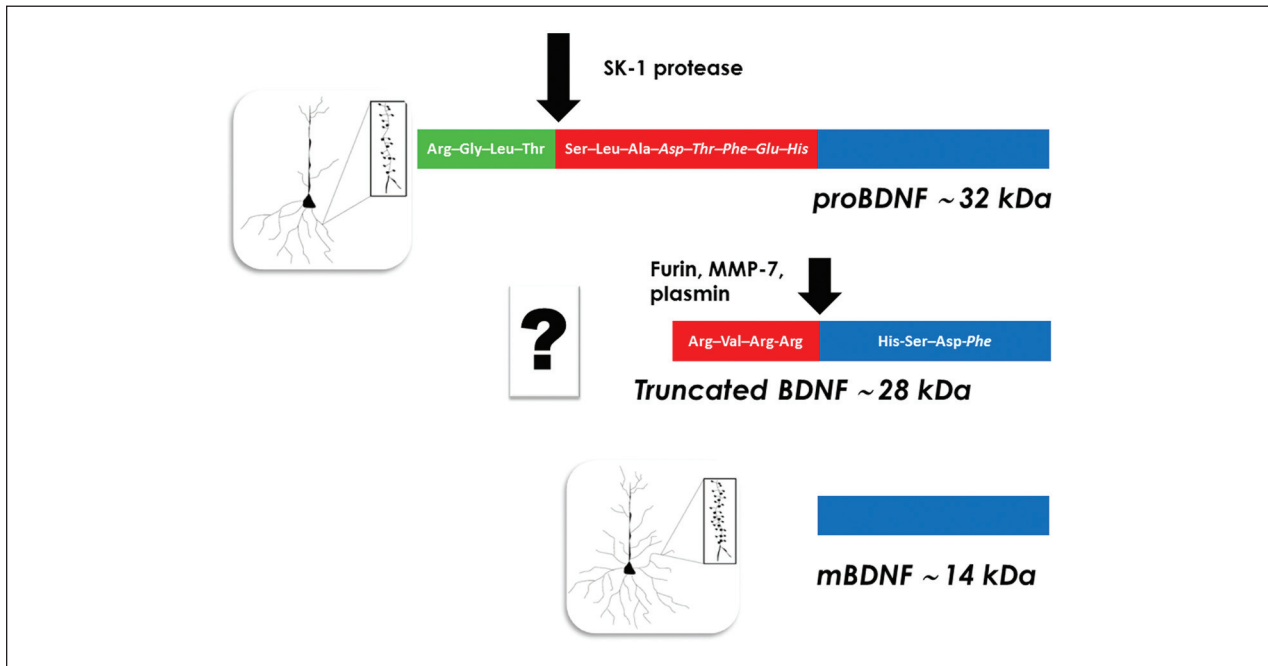Email: davide.carlino@tiscali.it

Figure 1. Proteolytic forms of BDNF: processing and physiological effects on neurons. Cleavage site Arg-Gly-Leu-Thr ↓ Ser-Leu-Ala-Asp, which generates the 28-kDa truncated BDNF form, is processed by the SKI-1 protease only, whereas the cleavage site Arg-Val-Arg-Arg ↓ His-Ser-Asp, which generates mature BDNF (mBDNF), can be recognized by three proteases, furin, MMP-7, and plasmin (MMP-7 = matrixmetalloprotease-7; SK-1 = subtilisin/kexin-isozyme-1). Insets on the right illustrate the biological functions of the different BDNF forms. ProBDNF, acting through p75 receptor and sortilin, causes reduction in spine density, cell death, and long-term depression (LTD). Truncated BDNF is not further processed into mBDNF, and therefore is considered a true final proteloytic product whose biological role is still unknown; nor are its receptor(s). Mature BDNF, by activating TrkB receptor induces increased spine density, cell survival, and long-term potentiation (LTP).

as a dimer of two 13.5 kDa subunits, leading to a dimeric molecule with a total mass of 27 kDa, which should not be confused with a monomer of truncated BDNF of 28 kDa. To produce mBDNF, the precursor proBDNF is processed through a cleavage after the arginine residues 125 or 128 at the recognition site 125-RVRR-128 either by furin in the trans-Golgi (Mowla and others 2001), or extracellularly, by plasmin or matrixmetalloprotease-7 (Lee and others 2001; Fig. 1). Conversely, truncated BDNF is generated by a cleavage of proBDNF at threonine 57 by the specific Ca^{2+}-dependent serine proteinase membrane-bound transcription factor site-1 protease (MBTFS-1), also known as subtilisin/kexin-isozyme 1 (SKI-1; Seidah and others 1999; Fig. 1). Since truncated BDNF is not further processed into mBDNF, it is considered a true final proteolytic product.

Mature BDNF and proBDNF Elicit Opposite Biological Effects in Vitro

It has long been thought that only secreted mBDNF was biologically active, whereas proBDNF was an inactive precursor localized intracellularly. However, recent studies have revealed that mBDNF and proBDNF may elicit opposite biological effects (Greenberg and others, 2009; Fig. 1). Specifically, the interaction between mBDNF and TrkB receptor promotes cell survival whereas binding of proBDNF to the p75 receptor triggers apoptotic processes (Koshimizu and others 2009; Teng and others 2005; Woo and others 2005). In addition, mBDNF and proBDNF have different effects on morphological neuroplasticity. Indeed, in the hippocampus mBDNF supports dendritic spines formation whereas proBDNF induces spine pruning (Koshimizu and others 2009; Teng and others 2005; Woo and others 2005; Fig. 1).

Classical studies in the early 1990s have demonstrated that BDNF is up-regulated after induction of synaptic long-term potentiation (LTP) in vitro (Patterson and others 1992). In the same decade, BDNF-TrkB receptor interaction was shown to be required to induce and maintain LTP at the level of the neuromuscular junction (Lohof and others 1993) and hippocampal CA3-CA1 synapses (Kang and Schuman, 1995). Although these early studies did not specify if proBDNF or the mature form was involved, the role of mBDNF/TrkB signaling in LTP induction and maintenance was confirmed by subsequent

studies involving BDNF knock-out mice. In these animal models, LTP is severely impaired (Korte and others 1995) but may be recovered by bath or virus-mediated addition of mBDNF (Korte and others 1996; Patterson and others 1996).

More recently, evidence that the antagonism of proBDNF and mBDNF is also relevant for the balance between long-term depression (LTD) and LTP at synapses is emerging (Fig. 1). Indeed, it has been observed that addition of mBDNF to acute slices may block LTD induced both by GABA$_A$ receptor activation in hippocampus (Akhondzadeh and Stone, 1999) and low-frequency stimulation in visual cortex (Akaneya and others 1996; Kinoshita and others 1999). In each of these in vitro models, TrkB receptor mediated the effect of mBDNF (Akhondzadeh and Stone, 1999; Sermasi and others 2000). Moreover, a direct demonstration of the role of proBDNF and its interaction with p75 during LTD has been provided by the studies of Woo and others (2005). These authors showed that activation of p75(NTR) by proBDNF led to enhanced NR2B-dependent LTD and NR2B-mediated synaptic currents while deletion of p75(NTR) in mice selectively impaired the NMDA receptor-dependent LTD, without affecting other forms of synaptic plasticity. These findings were corroborated by a recent study by Nagappan and others (2009), who used antibodies that selectively detect proBDNF or mBDNF to show that low-frequency stimulation in cultured hippocampal neurons induced predominantly proBDNF secretion while high-frequency stimulation preferentially increased extracellular mBDNF.

A role for proBDNF conversion in mBDNF in LTP has been also suggested by the analysis of protease knock-out mice (Scamuffa and others, 2006). It has been observed that BDNF and the tissue plasminogen activator (tPA, a serine protease) is implicated in the late-phase of long-term potentiation (L-LTP). In both tPA and plasminogen knock-out mice, the conversion of proBDNF in mBDNF by plasmin via the tPA-dependent activation of plasminogen is reduced. In these mice, the late phase of LTP (>100 minutes after theta-burst stimulation) is severely impaired and can be rescued by addition of mBDNF but not proBDNF suggesting the existence of a direct link between tPA and BDNF and LTP in hippocampus (Pang and others 2004).

Role of pro/mBDNF in Animal Models of Learning and Memory

Following the discovery of the role of BDNF in hippocampal LTP, several laboratories investigated the role of BDNF in spatial learning tasks such as the Morris water maze, in which the hippocampus plays a major role in remembering the position of a platform located just beneath the water surface. These studies showed that reduction of BDNF

levels by antisense oligonucleotide ablation or using heterozygous BDNF+/− knock-out transgenic mice lead to impaired spatial learning and memory retention, two functions that are associated with hippocampal-related memory (Gorski and others 2003; Linnarsson and others 1997; Ma and others 1998). More recently, a few investigations have been conducted to determine the role of proBDNF and mBDNF in other models of learning and memory as well.

Fear conditioning is a form of learning in which an aversive stimulus (e.g., an electrical shock) is associated with a neutral context (e.g., a room) or stimulus (e.g., a tone), resulting in the expression of fear responses to the originally neutral stimulus or context. The molecular mechanisms underlying long-term fear memory are very similar to those involved in LTP in the hippocampus (Costa-Mattioli and others 2007; LaLumiere and others 2005; Raymond 2007; Rodrigues and others 2004). This form of conditioning can undergo a mechanism of reconsolidation, that is, a form of renewal of the memory trace that occurs at each recall. However, under conditions of recall, fully consolidated memories become labile and may result in either reconsolidation or extinction. Extinction occurs when the neutral stimulus is presented several times without the noxius unconditioned stimulus leading first to attenuation and then extinction of the response to the unconditioned stimulus. Using intrahippocampal infusions of tPA-STOP, an inhibitor of proteolytic processing of proBDNF in mBDNF by plasminogen, Barnes and Thomas (2008) demonstrated that acquisition and extinction of contextual fear memory (CFM) requires an increase and a decrease, respectively of proteolysis of proBDNF in the hippocampus. In particular, these authors showed that formation of CFM is associated with increased tPA-dependent proteolytic processing of proBDNF in mBDNF. In contrast, increased proBDNF in the CA1 of the hippocampus sustained extinction. In addition, when proBDNF was decreased by the half by infusion of antisense oligonucleotides in hippocampal CA1 6 hours after conditioning or by pretreatment with tPA-STOP, animals showed reduced freezing behavior (the read-out of effective CFM) suggesting that proteolytic processing of BDNF is required for the consolidation phase. However, it seems that BDNF processing regulates the acquisition, consolidation and extinction of fear memory, but not memory reconsolidation. Indeed, in the dentate gyrus of the hippocampus there were no changes in proBDNF concentrations 6 hours after memory recall, suggesting that reconsolidation is a BDNF-independent memory process (Barnes and Thomas 2008; Lee and others 2004). It remains to be investigated if alterations in neuronal activity during the period analyzed may have changed the release of mBDNF/proBDNF without altering the total amount of protein.

The role of proBDNF conversion in mBDNF in the learning acquisition phase has been confirmed in adult rats undergoing several weeks of voluntary exercise in which mBDNF and tPA levels resulted increased, indicating enhanced processing of proBDNF (Ding and others 2011). Exercise improved the learning ability in the Morris water maze, because the latency to reach the hidden platform in trained rats was significantly shorter than in the sedentary group across all days of the assay (Griesbach and others 2009). In 5HT2C receptor knock-out mice (5HT2C−/−), mBDNF is constitutively upregulated in hippocampus whereas proBDNF is unchanged. However, 5HT2C-/- mice did not show any improvement in learning performance in the radial arm maze or the passive avoidance assays (Hill and others 2011). In these knock-out mice, however it is difficult to dissect out the role of the mutation on other neuronal signaling networks from those on BDNF.

Altered Processing of BDNF in Brains of Patients with Cognitive Dysfunctions

As described in the previous paragraphs, in vitro and in vivo investigations have highlighted that LTP initiation and maintenance, as well as learning acquisition and consolidation require proBDNF conversion in mature BDNF. On the opposite, elevated levels of proBDNF and reduction of its proteolytic processing are necessary for LTD and memory extinction. Accordingly, it can be predicted that any deficit in mature BDNF biosynthesis will affect memory formation and maintenance, while decreased levels of proBDNF are expected to impair LTD and inhibitory learning, such as extinction, and therefore affect the ability of the brain to modify and update the existing memories.

Studies on BDNF protein levels in postmortem brains provide interesting observations on BDNF processing (Table 1; Fig. 2). Peng and others (2005) found a 21% and 30% decrease in the amount of proBDNF in mild cognitive impairment (MCI) and AD patients, respectively, compared with healthy subjects; furthermore, a 40% decrease was found in end-stage AD patients (Michalski and Fahnestock 2003). Also, mBDNF was reduced by 34% and 62% in MCI and AD groups, respectively (Peng and others 2005). Thus, the decrease of mBDNF and proBDNF may precede the decline of choline acetyltransferase activity, which typically occurs later in AD. Both proBDNF and mBDNF levels were positively correlated with cognitive measures, such as the Global Cognitive Score and Mini Mental State Examination score (Peng and others 2005).

Weickert and others (2003) detected significantly reduced levels of mBDNF (>40% reduction) in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia compared with normal controls. Total BDNF protein levels within the DLPFC did not correlate with dosage and duration of antipsychotic medications, age of onset or length of duration. These findings were replicated in the study carried out by Wong and others (2010), who found a 23% reduction in mBDNF immunoreactive levels in post-mortem brains from patients with schizophrenia. The expression of the 32 kDa proBDNF and the 28 kDa truncated BDNF proteins was reduced by 14% and 10.4%, respectively, in patients with schizophrenia versus controls, although only the reduction in proBDNF protein reached the statistical significance. The authors observed a significant positive correlation between proBDNF, but not mBDNF, and age (Wong and others, 2010). It should be pointed out that although there was no correlation between age and BDNF levels, in postmortem brains from patients with AD proBDNF levels were also weakly associated with age (Peng and others 2005; Fig. 2).

In support of these findings, Karege and others (2005) reported that mBDNF was significantly reduced in the DLPFC of a mixed group of patients, including some patients with schizophrenia. However, this finding was not replicated in Dunham and others (2009). The discrepancy between these two studies could be related to the fact that the anti-BDNF antibody used by Dunham and coworkers was unable to recognize mature BDNF in Western-blot. In the same study, Dunham and others (2009) of the Stanley Consortium found that major depressive disorder (MDD) and bipolar disorder (BPD) patients had reductions in proBDNF in the right hippocampus. In addition, they found also reductions in p75 receptor density in the same hippocampal areas. In conclusion, data from postmortem brain analysis suggest that cognitive impairment in AD and schizophrenia is correlated with decrease in both mBDNF and proBDNF suggesting deficits in several mechanisms of learning and memory at the same time.

A possible interpretation of these data came from the study of Holt and others (2009) who showed that patients with schizophrenia have impaired extinction memory. As described in the previous paragraphs, extinction is a type of memory which in animal models was shown to require increased expression of proBDNF. Thus, in schizophrenia, MDD, and BPD, the observed decrease in proBDNF may be related to abnormally heightened neural and emotional response to innocuous stimuli by limbic brain regions involving prefrontal cortex, hippocampus, and amygdale, which under normal conditions can encode extinction (Holt and others, 2009).

Table 1. Studies on BDNF Protein Forms in Humans

Authors	Sample Collection	Subjects	Neuropsychological Assessment	Antibodies/ Chemicals	Principal Findings
Michalski and Fahnestock 2003	Postmortem parietal cortex samples	AD = 7; hc = 8	MMSE	Santa Cruz Biotechnology	Reduction proBDNF 40% in parietal cortex
Weickert and others 2003	Postmortem DLPFC	Schizophrenia	—	Chemicon	A significant reduction in mBDNF mRNA (mean = 23%) and protein (mean = 40%) in the DLPFC of patients with schizophrenia compared with hc.
Peng and others 2005	Postmortem parietal cortex samples	MCI = 17; AD = 17	MMSE, CGS	Santa Cruz Biotechnology	proBDNF decreased 21% and 30% in MCI and AD, respectively. mBDNF was reduced 34% and 62% in MCI and AD, respectively. proBDNF and mBDNF levels were positively correlated with cognitive measures such as the GCS and the MMSE score.
Karege and others 2005	Postmortem hippocampus, ventral PFC, entorhinal cortex samples	Suicide victims = 30; drug-free non-suicide subjects = 24	—	Promega	A significant decrease regardless of diagnosis in mBDNF levels in the hippocampus and PFC but not in the entorhinal cortex was found in suicide victims drug-free compared with non-suicide controls. In drug-treated suicide victims, mBDNF levels were not significantly different from non-suicide controls.
Dunham and others 2009	Postmortem hippocampus samples	Schizophrenia, MDD, BPD	—	Santa Cruz Biotechnology	In schizophrenia, although mean proBDNF densities were lower than controls in most subregions, they did not reach significance.
Wong and others 2010	Postmortem hippocampus, DLPFC, parietal cortex samples	Schizophrenia patients = 71; hc = 71	—	Santa Cruz Biotechnology	mBDNF protein expression is reduced in the DLPFC of patients with schizophrenia (23%).
Carlino and others 2011	Serum samples	Schizophrenia patients = 40; hc = 40	Trail Making Test A, B, Digit Span, Letter-Number Sequencing, Digit Symbol Coding subtests of WAIS. The IQ was determined using the short form of the WAIS. PANSS	Promega	A slight reduction in serum BDNF levels in SZ patients with respect to hc. Increased serum proBDNF and mBDNF and reduced truncated BDNF in SZ with respect to hc. Patients with an increase in proBDNF or mBDNF higher than the hc mean + 2 SD also had >2 SD reduction of truncated BDNF. Reduced truncated BDNF correlated significantly with higher positive and lower negative PANSS scores and a worst performance in all cognitive assays but not with antipsychotic type.
Yoshida and others 2012	Serum samples	MDD patients = 69; hc = 78	SIGH-D; WHOQOL-BREF; SASS; CogState battery	Adipo Bioscience	mBDNF in patients with MDD were significantly lower than those of hc. In contrast, there was no difference in the serum levels of proBDNF between patients and hc. Neither proBDNF nor mature BDNF serum levels was associated with cognitive impairment

PANSS = Positive and Negative Syndrome Scale; WAIS = Wechsler Adult Intelligence Scale; NPV = negative predictive value; PPV = positive predictive value; MCI = mild cognitive impairment; AD = Alzheimer's disease; NCI = no cognitive impairment; hc = healthy controls; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; MMSE = Mini Mental State Examination; GCS = Global Cognitive Score; SIGH-D = Structured Interview Guide for the Hamilton Depression Rating Scale; WHOQOL-BREF = World Health Organization Quality of Life–Short Version; MDD = major depressive disorder; BPD = bipolar disorder; SASS = Social Adaptation Self-Evaluation Scale.

BDNF Serum Levels in Patients with Cognitive Dysfunctions

The possibility of repeated, non-invasive measures of serum or plasma BDNF prompted great interest in the use of this biomarker in clinical practice. Several studies documented decreased serum concentration of total BDNF in AD patients with respect to subjects with other types of dementia or healthy controls (Einat and others 2003; Forlenza and others 2010; Laske and others 2007; Lee and others 2009) However, results are not conclusive, as serum total BDNF levels in AD did not correlate with age or scores in MMSE or Functional Assessment Staging (Yasutake and others 2006). In Laske and others (2006), serum BDNF levels did not predict AD or MCI-related cognitive deterioration, even if the presence of the Met allele of the Val66Met polymorphism in the BDNF gene was a significant predictor of cognitive impairment for these patients. In contrast, other investigators reported on increased BDNF levels in patients with MCI and early AD (Angelucci and others 2010). However, recent clinical trials demonstrated that lithium and a cholinesterase inhibitor (donepezil) were able to increase serum BDNF levels in patients with early AD (Leyhe and others 2009;
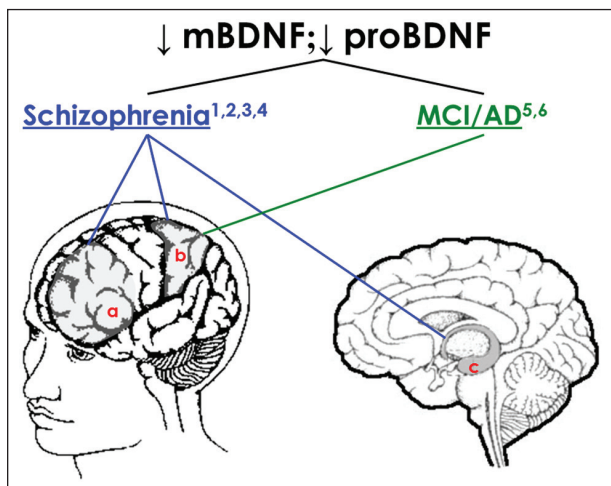
Figure 2. Primary results of postmortem studies investigating precursor forms of BDNF in humans.
[1]Weickert and others (2003); [2]Dunham and others (2009); [3]Wong and others (2010); [4]Karege and others (2005); [5]Michalski and Fahnestock (2003); [6]Peng and others (2005).
[a]Dorsolateral prefrontal cortex (DLPFC); [b]parietal cortex; [c]hippocampus/enthorinal cortex
MCI = mild cognitive impairment; AD = Alzheimer's disease.

Figure 3. Serum BDNF forms in chronic schizophrenic patients with cognitive impairment. In schizophrenic patients from group 1, with shorter disease duration, truncated BDNF is reduced and proBDNF precursor is increased, most likely as a result of a reduced cleavage, whereas mBDNF is normal. In patients from group 2, with longer duration of illness, truncated BDNF is also reduced but proBDNF has no significant variations with respect to healthy controls, most likely because of a compensatory increase of cleavage to generate mBDNF. As group 2 patients had longer disease duration with respect to those in group 1, this compensatory mechanism may occur after a prolonged pathological condition (Carlino and others 2011).

Diniz and others 2009). Also, in other diseases, the relationship between circulating total BDNF levels and cognitive impairment is unclear. Indeed, plasma BDNF is higher in Down syndrome patients than in controls, indicating that cognitive deficits in these patients are not related with a reduction in total BDNF protein levels (Dogliotti and others, 2010).

More promising are recent studies investigating separately proBDNF and mBDNF levels in serum. Using two ELISA kits able to recognize mBDNF or proBDNF, Yoshida and others (2012) found reduced mBDNF levels in the serum of MDD patients with respect to healthy donors, whereas proBDNF levels were not different. However, correlation of BDNF values with cognitive assessment using a CogState battery did not reveal any significant relationship between mBDNF or proBDNF levels and cognitive impairment. The lack of any interaction between cognitive scores and serum BDNF levels might be explained by the fact that the ELISA kits used presented low sensitivity (about half of the sera initially collected were below threshold). Moreover, MDD patients and healthy controls showed very small differences in scores of the cognitive scales (Yoshida and others 2012). Extinction memories were not tested in these patients.

Similar to AD, in schizophrenia also, analysis of total BDNF serum concentrations generated quite heterogeneous findings (Green and others 2011). Therefore, in a recent study, we measured serum levels of mBDNF, proBDNF, and truncated BDNF in patients with chronic
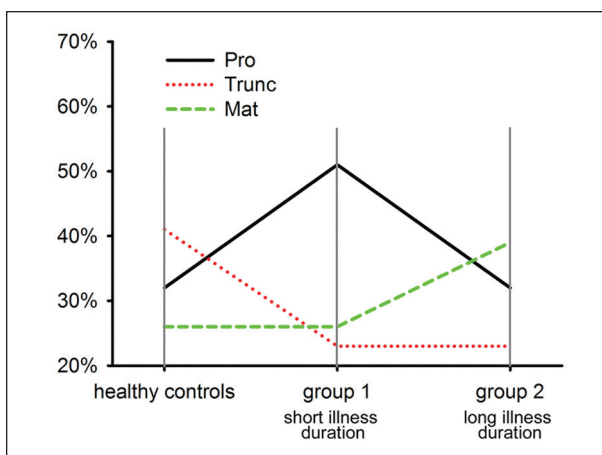
schizophrenia (Carlino and others 2011; Fig. 3). Two thirds of the patients analyzed showed reduced truncated BDNF levels and displayed significantly worst cognitive performance in comparison with those with no alterations in the proportion of the three different BDNF forms (Table 1; Fig. 3). With respect to healthy donors, all these patients had either increased proBDNF (Group 1) or increased mBDNF (Group 2) levels but not both (Fig. 3). In addition, irrespective of mBDNF or proBDNF serum levels and exposure to antipsychotic treatment, patients with schizophrenia showing decreased truncated BDNF concentrations were similar for clinical phenotype and impaired cognitive functioning (Carlino and others 2011). Hence, this study put forward the idea that the dosage of serum truncated BDNF may be used as an empirical method to predict cognitive impairment in patients suffering from schizophrenia. Indeed, considering a cut-off at 2 SD from the mean value of truncated BDNF in healthy controls (i.e., when truncated BDNF is less than 23.79% of total BDNF in the serum), the test showed remarkable parameters with sensitivity of 67.5%, specificity 97.5%, positive predictive value 96.4%, and negative predictive value 75%. We concluded that all patients with truncated BDNF less than 23.79% are likely to show cognitive impairment. The possible clinical implications of using

serum BDNF as a biomarker of cognitive impairment derive from a study by Vinogradov and others (2009) who showed that BDNF levels could be significantly increased in the serum of clinically stable, chronically ill schizophrenia patients who underwent a cognitive training.

Conclusions

Taken together, these findings support the view that biosynthesis of mBDNF and proBDNF (and possibly, truncated BDNF) forms is an important mechanism underlying brain remodeling and cognitive functions. Pathological alterations in BDNF processing may have an additive and/or multiplicative effect on brain's structure, thus perpetuating neurodegenerative events in schizophrenia as well as in AD. Accordingly, a reduced capability of the brain to synthesize mBDNF may result in memory loss and learning impairment, whereas decreased levels of proBDNF may produce aberrant behavioral reactions because of deficits in the governance of emotional memory, while deficits in both mBDNF and proBDNF may produce a disturbance of several cognitive domains. At the moment, the role of truncated BDNF in cognitive impairment remains unclear. More experiments are required to clarify its biological function.

Expanding Buckley and others' (2007) point of view on the role of BDNF in schizophrenia, we suggest that alterations in BDNF biosynthesis may be considered both a "biochemical footprint" of cognitive dysfunctions in neurodevelopmental and neurodegenerative diseases and a plausible endophenotype of "cognitive distress," as a result of injured processing of information. Further investigations should be planned to corroborate this hypothesis. In particular, larger sample sizes are needed and first-episode patients with schizophrenia or MCI should be recruited and monitored with respect to levels of BDNF proteolytic products along illness evolution.

Authors' Note

Maurizio De Vanna and Enrico Tongiorgi contributed equally to this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Akaneya Y, Tsumoto T, Hatanaka H. 1996. Brain-derived neurotrophic factor blocks long-term depression in rat visual cortex. J Neurophysiol 76(6):4198–201.

Akhondzadeh S, Stone T. 1999. Prevention of muscimol-induced long-term depression by brain-derived neurotrophic factor. Prog Neuropsychopharmacol Biol Psychiatry 23(7):1215–26.

Angelucci F, Spalletta G, di Iulio F, Ciaramella A, Salani F, Colantoni L, and others. 2010. Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients are characterized by increased BDNF serum levels. Curr Alzheimer Res 7(1):15–20.

Arancio O, Chao MV. 2007. Neurotrophins, synaptic plasticity and dementia. Curr Opin Neurobiol 17:325–30.

Archer T, Kostrzewa RM, Beninger RJ, Palomo T. 2011. Staging neurodegenerative disorders: structural, regional, biomarker, and functional progressions. Neurotox Res 19(2): 211–34.

Barnes P, Thomas KL. 2008. Proteolysis of proBDNF is a key regulator in the formation of memory. PloS ONE 3(9):e3248.

Buckley PF, Mahadik S, Pillai A, Terry A, Jr. 2007. Neurotrophins and schizophrenia. Schizophr Res 94(1–3):1–11.

Carlino D, Leone E, Di Cola F, Baj G, Marin R, Dinelli G, and others. 2011. Low serum truncated-BDNF isoform correlates with higher cognitive impairment in schizophrenia. J Psychiatr Res 45(2):273–9.

Carvalho AL, Caldeira MV, Santos SD, Duarte CB. 2008. Role of the brain-derived neurotrophic factor at glutamatergic synapses. Br J Pharmacol 153(Suppl 1):S310–24.

Costa-Mattioli M, Gobert D, Stern E, Gamache K, Colina R, Cuello C, and others. 2007. eIF2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory. Cell 129(1):195–206.

Ding Q, Ying Z, Gómez-Pinilla F. 2011. Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. Neuroscience 29(192):773–80.

Diniz BS, Pinto JA Jr., Gonzaga ML, Guimarães FM, Gattaz WF, Forlenza OV. 2009. To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 259(4):248–56.

Dogliotti G, Galliera E, Licastro F, Corsi MM. 2010. Age-related changes in plasma levels of BDNF in Down syndrome patients. Immun Ageing 25(7):2.

Dunham JS, Deakin JFW, Miyajima F, Payton A, Toro CT. 2009. Expression of hippocampal brain derived neurotrophic factor and its receptors in Stanley consortium brains. J Psychiatr Res 43:1175–84.

Einat H, Yuan P, Gould TD, Li J, Du J, Zhang L, and others. 2003. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. J Neurosci 23(19):7311–6.

Forlenza OV, Diniz BS, Teixeira AL, Ojopi EB, Talib LL, Mendonça VA, and others. 2010. Effect of brain-derived neurotrophic factor Val66Met polymorphism and serum levels on the progression of mild cognitive impairment. World J Biol Psychiatry 11(6):774–80.

Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. 2011. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 16(9):960–72.

Griesbach GS, Hovda DA, Gomez-Pinilla F. 2009. Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. Brain Res 1288:105–15.

Gorski JA, Balogh SA, Wehner JM, Jones KR. 2003. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience 121(2):341–54.

Greenberg ME, Xu B, Lu B, Hempstead BL. 2009. New insights in the biology of BDNF synthesis and release: implications in CNS function. J Neurosci 29(41):12764–7.

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. 2001. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature 411(6833):86–9.

Hill RA, Murray SS, Halley PG, Binder MD, Martin SJ, van den Buuse M. 2011. Brain-derived neurotrophic factor expression is increased in the hippocampus of 5-HT(2C) receptor knockout mice. Hippocampus 21(4):434–45.

Holt DJ, Lebron-Milad K, Milad MR, Rauch SL, Pitman RK, Orr SP, and others. 2009. Extinction memory is impaired in schizophrenia. Biol Psychiatry 65(6):455–63.

Kang H, Schuman EM. 1995. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 267(5204):1658–62.

Karege F, Vaudan G, Schwald M, Perroud N, La Harpe R. 2005. Neurotrophin levels in postmortem brains of suicide victims and the effects of ante mortem diagnosis and psychotropic drugs. Brain Res Mol Brain Res 136(1–2):29–37.

Kinoshita S, Yasuda H, Taniguchi N, Katoh-Semba R, Hatanaka H, Tsumoto T. 1999. Brain-derived neurotrophic factor prevents low-frequency inputs from inducing long-term depression in the developing visual cortex. J Neurosci 19(6):2122–30.

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. 1995. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci U S A 92(19):8856–60.

Korte M, Griesbeck O, Gravel C, Carroll P, Staiger V, Thoenen H, and others. 1996. Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. Proc Natl Acad Sci U S A 93(22):12547–52.

Koshimizu H, Kiyosue K, Hara T, Hazama S, Suzuki S, Uegaki K, and others. 2009. Multiple functions of precursor BDNF to CNS neurons: negative regulation of neurite growth, spine formation and cell survival. Mol Brain 2:27.

LaLumiere RT, Nawar EM, McGaugh JL. 2005. Modulation of memory consolidation by the basolateral amygdala or nucleus accumbens shell requires concurrent dopamine receptor activation in both brain regions. Learn Mem 12:296–301.

Laske C, Stransky E, Leyhe T, Eschweiler GW, Maetzler W, Wittorf A, and others. 2007. BDNF serum and CSF concentrations in Alzheimer's disease, normal pressure hydrocephalus and healthy controls. J Psychiatr Res 41(5):387–94.

Laske C, Stransky E, Leyhe T, Eschweiler GW, Wittorf A, Richartz E, others. 2006. Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm 113(9):1217–24.

Lee JG, Shin BS, You YS, Kim JE, Yoon SW, Jeon DW, and others. 2009. Decreased serum brain-derived neurotrophic factor levels in elderly Korean with dementia. Psychiatry Invest 6(4):299–305.

Lee JL, Everitt BJ, Thomas KL. 2004. Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 304(5672):839–43.

Lee R, Kermani P, Teng KK, Hempstead BL. 2001. Regulation of cell survival by secreted proneurotrophins. Science. 294(5548):1945–8.

Leyhe T, Eschweiler GW, Stransky E, Gasser T, Annas P, Basun H, and others. 2009. Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. J Alzheimers Dis 16(3):649–56.

Linnarsson S, Björklund A, Ernfors P. 1997. Learning deficit in BDNF mutant mice. Eur J Neurosci 9(12):2581–7.

Lohof AM, Ip NY, Poo MM. 1993. Potentiation of developing neuromuscular synapses by the neurotrophins NT-3 and BDNF. Nature 363(6427):350–3.

Ma YL, Wang HL, Wu HC, Wei CL, Lee EH. 1998. Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience 82(4):957–67.

Michalski B, Fahnestock M. 2003. Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Mol Brain Res. 111(1–2):148–54.

Mossner R, Daniel S, Albert D, Heils A, Okladnova O, Schmitt A, and others. 2000. Serotonin transporter function is modulated by brain-derived neurotrophic factor (BDNF) but not nerve growth factor (NGF). Neurochem Int 36(3):197–202.

Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG, and others. 2001. Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. J Biol Chem 276(16):12660–6.

Nagappan G, Zaitsev E, Senatorov VV Jr., Yang J, Hempstead BL, Lu B. 2009. Control of extracellular cleavage of ProBDNF by high frequency neuronal activity. Proc Natl Acad Sci U S A 106(4):1267–72.

Nuechterlein KH, Subotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, and others. 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr Bull 37(Suppl 2):33–40.

Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, and others. 2004. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306(5695):487–91.

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. 1996. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16(6):1137–45.

Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. 1992. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron 9(6):1081–8.

Peng S, Wuu J, Mufson EJ, Fahnestock M. 2005. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem 93(6):1412–21.

Raymond CR. 2007. LTP forms 1, 2 and 3: different mechanisms for the "long" in long-term potentiation. Trends Neurosci 30(4):167–75.

Rodrigues SM, Schafe GE, LeDoux JE. 2004. Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. Neuron 44(1):75–91.

Scamuffa N, Calvo F, Chrétien M, Seidah NG, Khatib AM. 2006. Proprotein convertases: lessons from knockouts. FASEB J 20(12):1954–63.

Schinder AF, Poo M. 2000. The neurotrophin hypothesis for synaptic plasticity. Trends Neurosci 23(12):639–45.

Seidah NG, Mowla SJ, Hamelin J, Mamarbachi AM, Benjannet S, Touré BB, and others. 1999. Mammalian subtilisin/kexin isozyme SKI-1: a widely expressed proprotein convertase with a unique cleavage specificity and cellular localization. Proc Natl Acad Sci U S A 96(4):1321–6.

Sermasi E, Margotti E, Cattaneo A, Domenici L. 2000. Trk B signalling controls LTP but not LTD expression in the developing rat visual cortex. Eur J Neurosci 12(4):1411–9.

Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, and others. 2005. ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25(22):5455–63.

Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. 2009. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? Biol Psychiatry 66(6):549–53.

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. 2003. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol Psychiatry 8(6):592–610.

Wong J, Hyde TM, Cassano HL, Deep-Soboslay A, Kleinman JE, Weickert CS. 2010. Promoter specific alterations of brain-derived neurotrophic factor mRNA in schizophrenia. Neuroscience 169(3):1071–84.

Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA, and others. 2005. Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8(8):1069–77.

Yasutake C, Kuroda K, Yanagawa T, Okamura T, Yoneda H. 2006. Serum BDNF, TNF-α and IL-1b levels in dementia patients: comparison between Alzheimer's disease and vascular dementia. Eur Arch Psychiatry Clin Neurosci 256(7):402–6.

Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraishi T, and others. 2012. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. PLoS One 7(8):e42676.