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REVIEW

BDNF pro-peptide: physiological mechanisms and implications for depression

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Abstract

Most growth factors are synthesized as precursors and biologically active forms are generated by proteolytic cleavage of the pro-domain. However, the biological functions of pro-domains are ill-defined. New roles were recently reported for the pro-domain of brain-derived neurotrophic factor (BDNF), a well-known growth factor in the brain. Interestingly, the pro-domain of BDNF (BDNF pro-peptide) is localized at presynaptic termini, where it facilitates long-term depression (LTD) in hippocampal slices, implicating it as a novel synaptic modulator. BDNF binds its pro-peptide with high affinity in a pH-dependent manner and when bound to BDNF, the BDNF pro-peptide cannot facilitate hippocampal LTD, representing a new mechanism of regulation. The BDNF pro-peptide is present in human cerebrospinal fluid (CSF) and levels were significantly lower in patients with major depressive disorder (MDD) than in controls. Notably, male MDD patients exhibit significantly lower levels of CSF pro-peptide than females. These findings demonstrate that the BDNF pro-peptide is a biologically important synaptic modulator and is associated with MDD, particularly in males.

Keywords BDNF pro-peptide · Proteolytic processing · Long-term depression · Synaptic modulator · Major depressive disorder

Introduction

Growth factors control many cellular functions including proliferation, differentiation and cell migration. In the nervous system, neurotrophins (NTs), including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4), exert their biological activities by binding to their cognate tyrosine kinase receptors (NGF to tropomyosin receptor kinase A (TrkA), BDNF and NT-4 to tropomyosin receptor kinase B (TrkB) and NT-3 to TrkC) and to a common low-affinity neurotrophin receptor ($p75^{NTR}$) (Chao 2003; Reichardt 2006). The discovery of NT family proteins provided pivotal insight into the formation of neuronal networks, memory and learning in the adult brain and the spatial and temporal nature of their action (Bibel and Barde 2000; Park and Poo 2013). Interestingly, NTs are responsible for long- and short-term actions (Lu 2003a; Park and Poo 2013). Long-term trophic actions depend on gene regulation, whereas short-term effects on developing neurons and synaptic events are controlled by intracellular effectors activated by NT signaling (Lu 2003a; Park and Poo 2013). The biological actions, signaling mechanisms and transcriptional and translational control of NTs are detailed in other publications and in other chapters in this special issue.

This review focuses on post-translational mechanisms, proteolytic processing of the BDNF precursor and the resulting BDNF pro-peptide by-product (Fig. 1, red). We describe the biological activities of the BDNF pro-peptide. As shown in Fig. 1, the BDNF pro-peptide is a by-product generated from the precursor of BDNF via proteolytic processing and knowledge on the by-product was minimal until recently.

However, recent reports demonstrated that this pro-peptide (BDNF pro-peptide, Fig. 1) enhances synaptic depression in hippocampal LTD (Mizui et al. 2015) and promotes retraction

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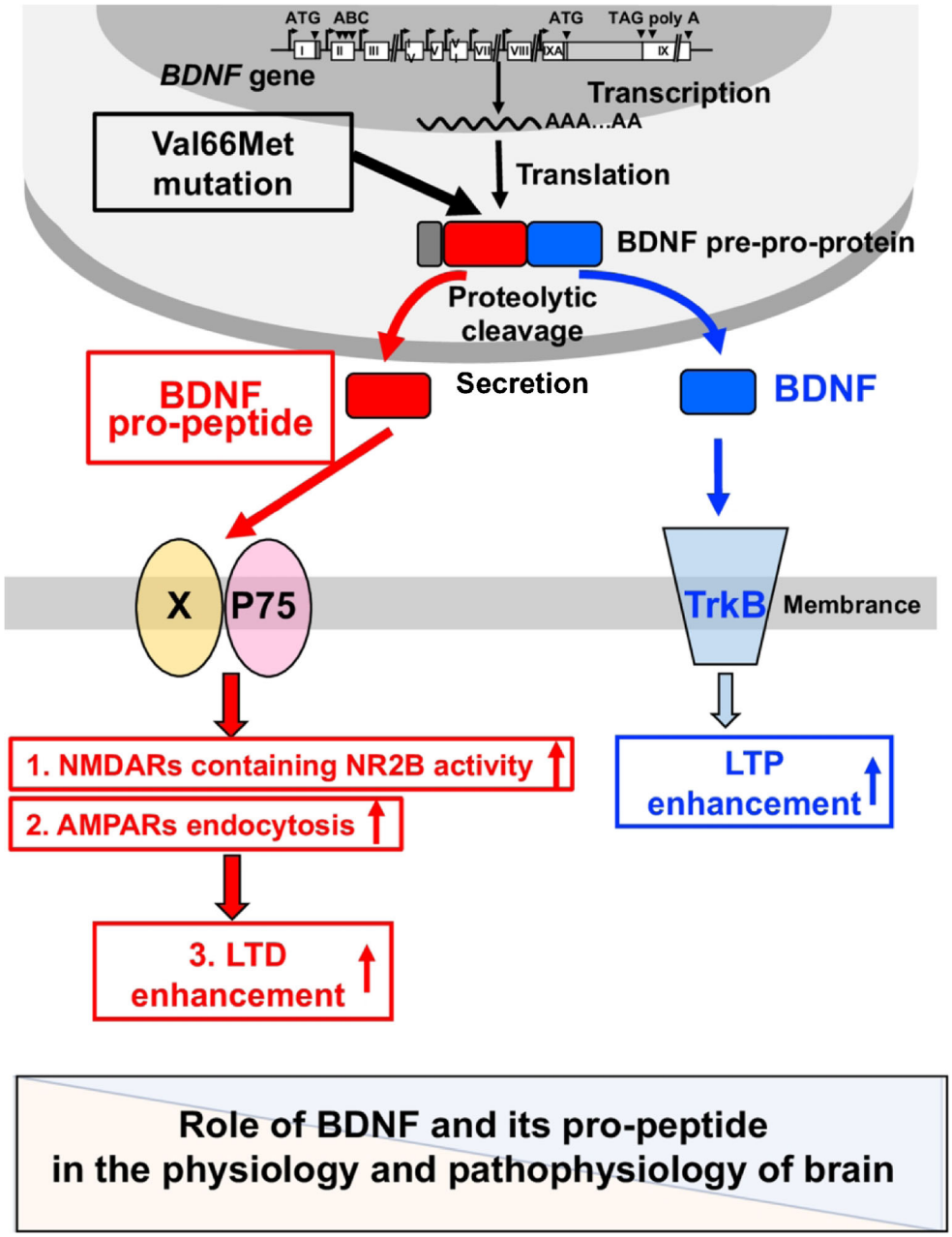

Fig. 1 Distinct actions of BDNF (brain-derived neurotrophic factor) and its pro-peptide in synaptic plasticity. BDNF is initially synthesized as a pre-pro-protein precursor (BDNF pre-pro-protein), which contains a signal sequence (gray, 18 amino acids), a pro-domain (red, 112 amino acids) and the mature BDNF peptide (blue, 119 amino acids). First, the signal sequence is cleaved off immediately upon entry into the ER to generate the BDNF pro-protein (pro-BDNF), which is subsequently transported into the TGN. The Val66Met BDNF polymorphism (indicated by bold black arrow) affects brain functions and the activity-dependent secretion of BDNF. The BDNF pro-peptide is generated by proteolytic processing of pro-BDNF (precursor BDNF) at presynaptic dense-core vesicles and secreted from cultured hippocampal neurons. BDNF and its pro-peptide enhance LTP (long-term potentiation) and LTD (long-term depression). The receptors TrkB and $p75^{NTR}$ are responsible for signaling by the respective ligands. Signaling by the BDNF pro-peptide is blocked by inhibitors of $p75^{NTR}$. Thus, other receptor components (indicated by X) may be required. The BDNF pro-peptide-induced facilitation of LTD requires the activation of the pathway involving NMDA and AMPA receptors (indicated by 1., 2. and 3.). The physiological and pathophysiological roles discussed in this review are indicated. Exactly how the ligands function in healthy and disordered brains is an interesting question

of dendritic spines in cultured hippocampal neurons (Guo et al. 2016). We subsequently explain that BDNF pro-peptide levels are decreased in the cerebrospinal fluid (CSF) in male patients suffering from major depressive disorder (MDD), suggesting that CSF BDNF pro-peptide levels are associated with this disease (Mizui et al. 2019).

Synthesis, processing, intracellular targeting and secretion of BDNF into the extracellular space

Most secretory proteins are initially synthesized as precursor proteins in the endoplasmic reticulum (ER) and subsequently translocated into a series of intracellular organelles including the Golgi complex, trans-Golgi network (TGN) and secretory vesicles and finally secreted into the extracellular space (Halban and Irminger 1994).

Similar to other growth factors and neuropeptides, BDNF is initially synthesized as a pre-pro-protein precursor (BDNF pre-pro-protein Fig. 1) in the ER and contains a signal sequence (18 amino acids), a pro-domain (112 amino acids) and the mature BDNF peptide (119 amino acids) (Leibrock et al. 1989).

First, the signal sequence is cleaved off immediately upon entry into the ER to generate the BDNF pro-protein (pro-BDNF), which is subsequently transported into the TGN. The N-terminal fragment of pro-BDNF can be processed by soluble pro-hormone convertases (PC1 and PC2) (Seidah et al. 1990; Smeekens and Steiner 1990) and membrane-anchored furin (Roebroek et al. 1986a, b) in either the TGN or the vesicle lumen. In non-neuronal cells such as Schwann cells, neurotrophins are cleaved by furin and secreted (Lu 2003a; Lessmann and Brigadski 2009). However, in excitable cells such as neurons, neuropeptides are cleaved by PC1 and PC2 (Rouille et al. 1995).

The subcellular localization and maturation of these PCs has been detailed previously (Nakayama 1997). The active furin is localized in the TGN but freshly synthesized pro-furin is first converted into the active mature form by autocatalytic cleavage of the pro-peptide in the ER. This pro-peptide cleavage is a prerequisite for the exit of furin molecules out of the ER (Creemers et al. 1995; Molloy et al. 1994; Takahashi et al. 1995). Furthermore, to achieve the complete release of this pro-peptide and conversion to the bioactive form, furin requires exposure to the acidic conditions of the intracellular organelle that contains Ca^{2+}. Furin exhibits proteolytic activity over a broad pH range between 6.0 and 8.5, with peak activity at 7.0. Meanwhile, to convert the precursor protein into the mature form, PC1/2 is localized in the TGN and possibly also in secretory granules. However, to achieve full activity, PC1/2 requires a relatively acidic environment (pH 5.0–6.5) and > 10 mM Ca^{2+} (reviewed in Nakayama (Nakayama, 1997)). Thus, furin and PC1/2 may require specific microenvironments for maximal bioactivity, such as the TGN for furin and secretory granules for PC1/2.

The role of TGN in the intracellular processing of pro-BDNF is of particular interest. In the TGN, following pro-BDNF processing, the resulting BDNF is transported into granules by a specific mechanism (discussed below). We recently demonstrated that BDNF binds to its pro-domain with high affinity using surface plasmon resonance on a Biacore instrument (Uegaki et al. 2017), suggesting that BDNF and its pro-domain move in concert with each other. It was also reported that the Golgi-resident targeting receptor sortilin binds to the BDNF pro-domain and undergoes intra-Golgi sorting of BDNF to the regulated secretion pathway (Chen et al. 2005). A previous report demonstrated that the vesicle membrane-resident sorting receptor, carboxypeptidase E (CPE) controlled transportation of BDNF into secretory granules (Lou et al. 2005). They also showed that four amino acid residues (isoleucine at position 16, glutamic acid at position 18, isoleucine at position 105 and aspartic acid at position 106) in mature BDNF were important for targeting of BDNF to the regulated secretory pathway. Thus, the sequences of both the pro-domain and the mature BDNF peptide appear to regulate processing of the BDNF precursor and its targeting to secretory granules.

Based on these mechanisms, BDNF may be transported via the regulatory pathway and secreted into the extracellular space in response to depolarization signals. Additionally, an imaging study using a BDNF-GFP fusion protein showed that depolarization-induced BDNF secretion is dependent on Ca^{2+} influx (Kolarow et al. 2007). Importantly, it was demonstrated that BDNF was endogenously released from cultured hippocampal neurons in a neuronal activity–dependent manner (Balkowiec and Katz 2000; Matsumoto et al. 2008). Thus, these findings highlight the importance of neuronal activity in the secretion of BDNF, as well as the enhancement of synaptic transmission and synaptic plasticity (Park and Poo 2013).

BDNF pro-domain and Val66Met polymorphism

Previously, it was reported that the BDNF pro-domain acts as a molecular chaperone that assists the folding of the BDNF protein (Kolbeck et al. 1994). In 2003, we demonstrated that the Val66Met polymorphism (Fig. 1, black arrow), in which valine 66 in the pro-domain of human BDNF is replaced with a methionine, affects brain functions and the activity-dependent secretion of BDNF (Egan et al. 2003). Since this report, there have been a number of studies showing that the Val66Met genetic variant of the BDNF gene is associated with susceptibility to brain disorders (Tsai 2018). Furthermore, a link between the Val66Met mutation and brain functions was shown using knock-in mice harboring the Val66Met mutation (Chen et al. 2004).

However, Dieni et al. (2012) recently suggested that the BDNF pro-domain has additional synaptic functions. The

authors performed immunocytochemical and electron microscopy studies and detected signals from BDNF and its pro-domain in dense-core vesicles in excitatory presynaptic termini in the adult mouse hippocampus. These results suggest that the BDNF pro-domain (BDNF pro-peptide) is released in an intracellular vesicle-dependent manner. Interestingly, this report also provided a basis for an anterograde mode of BDNF action in the central nervous system (CNS) distinct from the retrograde model of NGF in the peripheral nervous system (PNS).

Dieni et al. (2012) further determined the amount of BDNF, precursor BDNF (pro-BDNF) and its pro-peptide and BDNF and its pro-peptide were found to be ~10-fold more abundant than pro-BDNF, at least in the adult mouse brain. These findings suggest that most pro-BDNF molecules are cleaved in regulated secretory vesicles.

Thus, these reports raise new hypotheses: (1) the BDNF pro-domain may exert distinct roles in addition to acting as a molecular chaperone to assist the folding of BDNF (Kolbeck et al. 1994) and (2) in general, post-translational mechanisms, including proteolytic cleavage of precursor proteins, may mediate diverse actions for neurotrophic factors such as BDNF.

BDNF pro-peptide enhances hippocampal LTD

Since the BDNF pro-peptide is present in dense-core vesicles in excitatory presynaptic termini (Dieni et al. 2012), we wondered whether it may be a synaptic modulator like the BDNF protein (Mizui et al. 2015). To test this, we performed an electrophysiological study with hippocampal slices and found that the BDNF pro-peptide, a portion of pro-BDNF (Fig. 1, red), can enhance hippocampal LTD (Mizui et al. 2015). For LTD induction, low-frequency stimulation (LFS; 1 Hz, 900 pulses, 15 min) was applied to Schaffer collaterals of hippocampal slices derived from 4-week-old mice and field excitatory postsynaptic potential (fEPSP) slopes were recorded in the CA1 area. A 30-min treatment with recombinant BDNF pro-peptide facilitated LTD without affecting basal transmission. For synapse facilitation, sub-nanomolar concentrations of BDNF pro-peptide were sufficient. Moreover, application of BDNF pro-peptide to *Bdnf*$^{-/-}$ hippocampal slices enhanced LTD, demonstrating that the BDNF pro-peptide elicits LTD independently of an interaction with endogenous BDNF (Mizui et al. 2015).

Furthermore, BDNF pro-peptide-induced hippocampal LTD is involved in the activation of the p75^{NTR} receptor and GluN2B/N-methyl-D-aspartate (NMDA) receptor subunit 2B-containing receptors. Our imaging study showed that the BDNF pro-peptide activates endocytosis of the NMDA-induced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, an important mechanism for LTD expression (Mizui et al. 2015).

These findings demonstrate that the BDNF pro-peptide is a facilitator of hippocampal LTD and regulates the mechanism required for promoting synaptic depression.

Impact of Val66Met polymorphism on BDNF pro-peptide-induced LTD

Since the report of Egan et al. (2003), a body of clinical and psychological evidence has shown that the Val66Met BDNF polymorphism increases susceptibility to a variety of brain disorders and influences brain functions (Tsai 2018). The molecular impact of the Val66Met polymorphism on neurons has also been explored. Firstly, hippocampal slices prepared from mice harboring the Val66Met mutation are defective in N-methyl-D-aspartate receptor (NMDAR)-dependent plasticity (Ninan et al. 2010) and unexpectedly, we demonstrated that BDNF pro-peptide harboring the Met mutation rescued hippocampal LTD (Mizui et al. 2015). BDNF pro-peptide-induced endocytosis of GluA2, a known mechanism underpinning LTD, can be reversed by BDNF pro-peptide harboring the Val66Met mutation (Mizui et al. 2015). These reports reveal the mechanisms underlying the impact of the common Val66Met BDNF polymorphism on synaptic functions.

DNF interacts with its pro-peptide with high affinity

The primary sequence of the BDNF pro-peptide is highly conserved among species (Lu 2003b). However, BDNF and its pro-peptide are basic and acidic, respectively, with an isoelectric point (pI) of 9.6 and 5.2 (Leibrock et al. 1989, Uegaki et al. 2017), which suggests that they may have distinct biological properties but are able to interact in an electrostatic manner. We tested this putative interaction using surface plasmon resonance and biochemical methods. To this end, we immobilized recombinant BDNF pro-peptide on a Biacore sensor chip and passed BDNF solution over the chip (Uegaki et al. 2017). Administration of BDNF led to a rapid and reversible binding response that occurred in a BDNF concentration-dependent manner. The dissociation constant K_D (concentration at half-maximal binding) was 42.1 nM, demonstrating a high-affinity interaction between BDNF and its pro-peptide. To elucidate the specificity of binding, we tested the effects of NGF, NT-3 and NT-4, all of which share significant amino acid sequence similarity with BDNF. However, the Biacore assays showed that these three NTs failed to bind strongly to the BDNF pro-peptide. Thus, these results confirmed the specificity of the high-affinity binding between BDNF and its pro-peptide (Uegaki et al. 2017).

BDNF Val66Met polymorphism stabilizes the interaction between BDNF and its pro-peptide

Accumulating evidence suggests that the BDNF Val66Met polymorphism affects human brain function (Tsai 2018). We tested the impact of this polymorphism on the interaction between BDNF and its pro-peptide using recombinant BDNF pro-peptide with Val or Met immobilized on a Biacore chip (Uegaki et al. 2017). Interestingly, compared with the Val-BDNF pro-peptide, the Met pro-peptide appeared to be released from the BDNF protein very slowly and in a BDNF concentration-dependent manner. Quantitative analysis revealed that the rate of association and dissociation was decreased by 10- and 100-fold, respectively, following replacement of Val with Met. This provided the first evidence that the Val66Met BDNF polymorphism stabilizes the molecular interaction between BDNF and its pro-peptide.

Met-BDNF pro-peptide binds stably to BDNF over a wide pH range

BDNF is transported from acidic intracellular organelles to the neutral extracellular space (Lessmann and Brigadski 2009). It was reported that the Val66Met BDNF polymorphism affects the intracellular trafficking of BDNF (Egan et al. 2003; Chen et al. 2004). Thus, we raised the question of whether binding between BDNF and its pro-peptide is sensitive to pH (Uegaki et al. 2017). Interestingly, under all conditions tested, the Met-BDNF pro-peptide was released more slowly from BDNF than the Val-type pro-peptide and the association and dissociation with BDNF appeared to be independent of pH. These results suggest that the Met mutation enhances the stability of binding within the BDNF/pro-peptide complex over a wider pH range (pH 6.5–7.4), and highlight the influence of the common Val66Met polymorphism on BDNF action.

Interaction between BDNF and its pro-peptide affects the physiological role of BDNF

Exactly what happens when BDNF and its pro-peptide interact with each other is of clear importance. Interestingly, when pre-incubated with BDNF for 30 min, the BDNF pro-peptide attenuates the ability of BDNF to inhibit hippocampal LTD. Furthermore, this attenuation is not rescued by treatment with a REX $p75^{NTR}$ antagonist (Uegaki et al. 2017). The BDNF pro-peptide itself allows facilitation of hippocampal LTD and this enhancement requires the activation of $p75^{NTR}$, while BDNF rescues LTD (Mizui et al. 2015). Thus, by sustaining the binding of BDNF, the BDNF pro-peptide might inhibit BDNF action.

BDNF and MDD

MDD is a widespread psychiatric illness with core symptoms including depressed mood, anhedonia, difficulties in concentrating and appetite and sleep abnormalities. MDD is a chronic, recurring illness that affects more than 20% of the world's population (Ferrari et al. 2013). However, the pathophysiology of MDD remains poorly understood. In 1996, Nibuya et al. (1995) first demonstrated that chronic antidepressant treatment can increase BDNF levels in the rat hippocampus, indicating a role for BDNF in depression. Since this report, altered BDNF levels have been measured in patients with psychiatric disorders including MDD and brain postmortem and blood BDNF measurements in depressed patients have demonstrated the important pathophysiological role of BDNF in depression (Duman and Monteggia 2006). Postmortem studies on suicide victims with depression revealed lower BDNF expression in the hippocampus (Dwivedi et al. 2003) and the prefrontal cortex (Karege et al. 2005).

Drug-naive patients with depression often display decreased BDNF, while patients treated with antidepressants exhibit increased BDNF (Shimizu et al. 2003). Furthermore, a significant correlation was found between changes in BDNF level after antidepressant medication, accompanied by altered depression scores (Brunoni et al. 2008).

Diagnostic role of BDNF in blood and cerebrospinal fluid

Blood BDNF levels may be useful as a biomarker for depression (Tsai 2018). BDNF is abundant in platelets and other peripheral tissues but it remains unclear how blood mBDNF levels reflect those in the brain. BDNF in the CSF is mainly produced by the brain parenchyma and it directly reflects brain activity (Slavik and Dolezal, 2012). In Alzheimer's disease, for example, the level of phosphorylated tau in CSF is diagnostic of the intensity of neurodegeneration and the severity of acute neuronal damage in the brain (Blennow, 2017).

Pathophysiological role of CSF BDNF pro-peptide in MDD

Recently, we investigated whether the BDNF pro-peptide is present in human CSF using western blotting (Mizui et al. 2019). Interestingly, CSF BDNF pro-peptide levels are significantly lower in patients with MDD than in controls. Notably, BDNF pro-peptide is significantly lower in male but not in

female patients with schizophrenia and MDD than in same-sex controls. This was the first report comparing CSF BDNF pro-peptide levels in male patients with MDD, schizophrenia and healthy controls. Furthermore, CSF BDNF pro-peptide levels may reflect impaired BDNF function in the brains of patients with MDD and may therefore be an effective biomarker of psychiatric disorders.

While the mechanism underlying the decrease in BDNF pro-peptide is not yet understood, a potential explanation can be offered. Since BDNF expression is decreased in MDD patients and animal models of depression and because BDNF expression is controlled by neuronal activity (Park and Poo 2013), low BDNF pro-peptide levels in CSF may be the result of lower neuronal activity in the depressive brain (Castren and Kojima 2017).

A recent postmortem study indicated that BDNF pro-peptide protein levels are significantly decreased in the cerebellum of patients with MDD and schizophrenia (Yang et al. 2016). The reasons for these localized differences are not yet clear but it would be interesting to investigate whether BDNF pro-peptide protein levels are altered in other brain regions, since the results may shed light on the pathophysiological role of the BDNF pro-peptide in the brain.

The CSF BDNF pro-peptide is present at significantly lower levels in male but not female patients with MDD than in controls. However, the total CSF protein concentration did not differ between males and females (Mizui et al. 2019), indicating that gender is related to the reduction in BDNF pro-peptide level. Indeed, differences in the severity of psychiatric disorders such as schizophrenia and MDD between sexes have been reported (Cyranowski et al. 2000). Additionally, amenorrheic women possess significantly lower BDNF levels than fertile females (Begliuomini et al. 2007). Further investigations to elucidate the mechanisms underlying sex differences in CSF BDNF pro-peptide levels are clearly needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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