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EDITORIAL

Regulation of brain-derived neurotrophic factor (BDNF) and its precursor proBDNF in the brain by serotonin

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Both serotonin (5-hydroxytryptamine) and brain-derived neurotrophic factor (BDNF) are known to modulate behavioral responses to stress and to mediate the therapeutic efficacy of the antidepressants through neuroplastic and epigenetic mechanisms [1]. It is well recognized that BDNF plays a key role in the pathophysiology of depression, as well as the therapeutic mechanisms of antidepressants [2, 3]. In this issue, Kronenberg et al. [4] reported that BDNF levels in the hippocampus and prefrontal cortex (PFC) were significantly elevated in tryptophan hydrolase-2 (*Tph2*) knock-out (KO) mice that lack brain serotonin, whereas no changes were observed in serotonin transporter (*Sert*) KO mice [4]. This study suggests the upregulation of BDNF in the brain by 5-HT deletion. However, in this study, the authors used commercial enzyme-linked immunosorbent assay (ELISA) kits (Promega) for determination of BDNF protein. This BDNF ELISA kit can recognize both BDNF (mature form) and its precursor proBDNF, due to the limited specificity of this particular BDNF antibody [5]. Thus, it seems that the values measured by this BDNF ELISA kit are total values of both proBDNF and BDNF (mature form) in these brain regions. Therefore, it is of great interest to measure proBDNF and BDNF (mature form) separately in the brain samples from *Thp2* KO mice.

BDNF (mature BDNF) is a 13-kDa polypeptide, which is initially synthesized as a precursor protein, preproBDNF, in the endoplasmic reticulum. Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to mature BDNF by intracellular and extracellular proteases (Fig. 1). Interestingly, BDNF (mature form) and BDNF propeptide (~17 kDa) are ~tenfold more abundant than proBDNF in the adult brain, and BDNF propeptide is stored in presynaptic dense core vesicles in the brain neurons (Fig. 1) [6], suggesting that BDNF propeptide may have physiological functions in the brain. It was initially thought that only secreted, BDNF (mature form) was biologically active, and that proBDNF, which localizes intracellularly, served as an inactive precursor. However, accumulating evidence shows that both proBDNF and BDNF (mature form) are active, eliciting opposing effects via the $p75^{NTR}$ and TrkB receptors, respectively, and that these three forms (proBDNF, BDNF (mature form), BDNF propeptide) might be important in several physiological functions (Fig. 1) [2, 3, 6]. Using Western blot analyses, we reported that both proBDNF and BDNF (mature form) were detected in the several brain regions, and that levels of proBDNF and BDNF (mature form) were altered in the brain regions including PFC, hippocampus, and nucleus accumbens (NAc) in rodent models (e.g., inflammation, repeat social defeat stress, learned helplessness) of depression [7–10]. It is likely that decreased levels of BDNF (mature form) in the PFC and hippocampus and/or increased levels of BDNF (mature form) in the NAc play a key role in the depression-like behaviors in rodents [7–10]. In addition, we also found an increase in proBDNF in the PFC of rats with depression-like phenotype and a decrease in proBDNF in the NAc of rats with depression-like phenotype [10]. Further detailed studies on the role of proBDNF–BDNF processing and transport in the PFC–NAc circuit should be needed. Nonetheless, it is of great interest to measure both proBDNF, BDNF (mature form), and BDNF propeptide in the brain regions since proBDNF–BDNF processing is involved in

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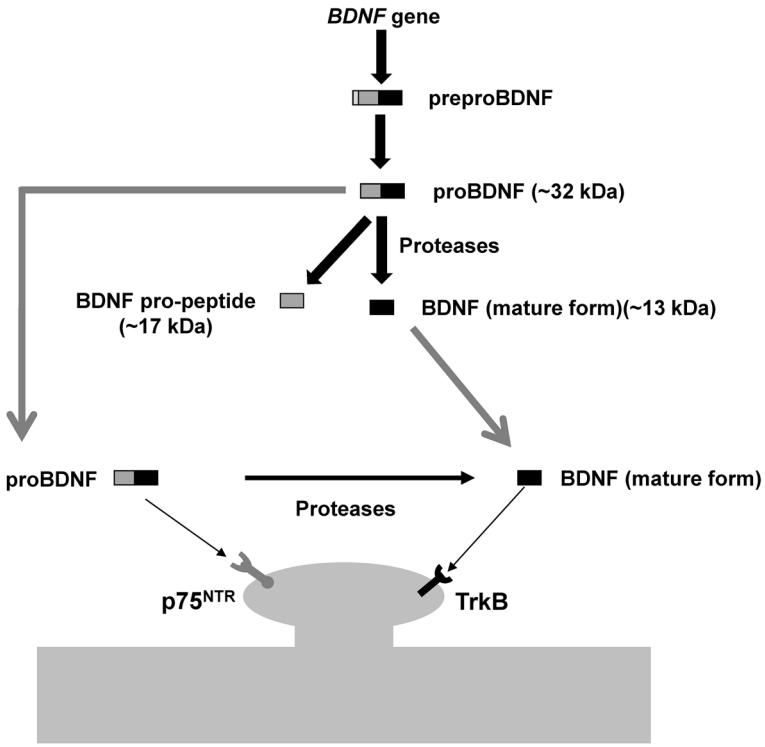

Fig. 1 Schematic representation of proBDNF, BDNF (mature form), and BDNF propeptide. The *BDNF* gene produced preproBDNF protein, and proBDNF (~32 kDa) is prepared from preproBDNF. Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to BDNF (mature form) (~13 kDa) by intracellular and extracellular proteases. BDNF (mature form) preferentially binds the TrkB receptor, and proBDNF binds to $p75^{NTR}$ [2, 3]. BDNF (mature form) and BDNF propeptide (~17 kDa) in the brain were ~tenfold more abundant than proBDNF [6]

the pathophysiology of neuropsychiatric disorders such as depression.

A recent meta-analysis of 179 associations ($N = 9484$ subjects) showed that serum levels of total BDNF (mature BDNF and proBDNF) in antidepressant-free patients with major depressive disorder were significantly (Cohen's $d = -0.71$, $p < 0.0000001$) lower than those of healthy controls [11], indicating that serum BDNF is a potential peripheral biomarker for depression. However, the BDNF ELISA kits used in the previous reports can recognize both proBDNF and BDNF (mature form), due to the limited specificity of the particular BDNF antibodies [5]. Using new commercially available human BDNF ELISA kits which differentiate between proBDNF and BDNF (mature form), we reported high concentrations of both proBDNF and mature BDNF in human serum [5].

In this issue, we also reported that healthy Jewish subjects in Israel showed very high serum levels of proBDNF compared to BDNF (mature form), although serum levels of BDNF (mature form) in the Jewish population were similar to other populations (Japanese and Swedish) [12]. In particular, serum levels of proBDNF in the Jewish population were markedly higher than in Japanese population, indicating ethnic difference of serum levels of proBDNF in human subjects [12]. Therefore, it would be of great interest to study ethnic differences in proBDNF–BDNF processing and subsequent pathways via $p75^{NTR}$ and TrkB signaling.

In conclusion, considering the high concentrations of proBDNF, BDNF (mature form), and BDNF propeptide in the brain and their putative opposing functions, we should measure levels of these three forms (proBDNF, BDNF (mature form), and BDNF propeptide) separately in the brain and blood.

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Compliance with ethical standards

Conflict of interest None.

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