Clinical Pharmacology & Biopharmaceutics
ISSN: 2167-065X
Mizui and Kojima, Clinic Pharmacol Biopharmaceut 2013, S1
DOI:10.4172/2167-065X.S1-004
Review Article
Open Access

BDNF and Synaptic Plasticity: The Recent Cell Biology for Understanding of Brain Disorders

Toshiyuki Mizui[1,2]* and Masami Kojima[1,2]

[1]*Bio-interface Research Group, Health Research Inst., National Institute of Advanced Industrial Science and Technology (AIST), Osaka, Japan*
[2]*Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency (JST), Kawaguchi, Japan*

Abstract

The cell biology of synaptic plasticity and neurotrophic factor has been extending to the understanding of pathological mechanisms of brain disorders. This knowledge could prove beneficial for the development of new therapies against brain diseases. Dendritic spines are actin-rich structures, which are part of most excitatory synapses in the central nervous systems. Recent studies have shown that the morphological plasticity of the spine plays a crucial role in higher brain functions, such as learning and memory. How neuronal activity modifies the morphology of the spines is an exactly prominent issue. Brain-derived Neurotrophic Factor (BDNF) is a traditional, yet fully characterized neurotrophic factor, and the key role in the adult brain is to modulate synaptic plasticity. This review focuses on recent advances in the research of dendrite spines, synaptic plasticity, and BDNF. Lastly, the recent research of BDNF for the development of new therapies, in particular, against depression is discussed.

Keywords: BDNF; TrkB; Synaptic plasticity; Spine; Morphology; Depression

Introduction

The brain exerts considerable structural and functional plasticity [1-3]. As an important interface between neurons, synapses are required for computation of circuits and information processing. Accumulating evidence indicates that once formed, synapses and dendrites can be maintained for long periods of time. However, they are eliminated or rewired to respond to environmental changes, as reported by Walsh and Lichtman (2003) [4]. The cell biology of neurons has been developed to the understanding of pathological mechanisms of brain disorders. This review article will pay an attention to the biological and pathological role of BDNF, which modulate synaptic plasticity in adult brain because this knowledge could prove beneficial for the development of new therapies against brain diseases. Dendritic spines are actin-rich structures, which are part of most excitatory synapses in the central nervous systems. Recent studies have shown that the morphological plasticity of the spine plays a crucial role in higher brain functions, such as learning and memory. This review focuses on recent advances in the research of dendrite spines, synaptic plasticity, and BDNF. Lastly, we will introduce recent reports demonstrating the role of BDNF in depression.

Dendrite Spines

The majority of excitatory synapses develop small protrusions on dendrites, called dendrite spines, which form the main platforms of synaptic input for neurons. Neurotransmitter receptors are largely localized at the surface of spines to counteract the presynaptic structure, axon terminals. Previously, consensus was that spine morphology is controlled for higher brain functions, such as learning and memory. Indeed, this notion has been supported by a significant number of studies. The strength of synaptic activity is controlled by the size and number of dendritic spines [5,6]. Activity-dependent remodeling and stability of spine structures is an important cellular mechanism for the maintenance and refinement of neuronal circuits [7,8]. Developing brain spines are structurally dynamic. Conversely, stable spines predominate during adult stages [2]. Interestingly, imaging studies demonstrate experience-dependent structural alterations of spines in animals [6,8], and spine genesis has a salient association with human cognitive function [9]. Moreover, autopsy studies of patients with dementia indicated a correlation between brain dysfunction and abnormal spine morphology [10,11]. Although synaptic function cannot be assessed from spine morphology, the regulatory mechanisms of spine morphogenesis, and the dynamics of spine morphology would provide insight into higher brain functions and their disorders.

Dendritic spines are actin-rich protrusions [12,13] and highly dynamic [14]. The dynamics are controlled by the architecture of their actin cytoskeleton [15]. The formation, maturation, and plasticity of spines depend on actin cytoskeleton remodeling [16,17]. Many of the key molecules controlling this process are members of the Rho-family of small GTPases [18-20], and several actin-binding proteins [21]. Most extracellular signals, affecting the organization of actin cytoskeleton in cells, converge inside the cells on Rho GTPases, such as RhoA, Rac1, and cdc42 [22,23]. The activation of RhoA-GTPase signaling, through the stimulation of glutamate receptors, could control actin cytoskeleton reorganization and spine morphology [24]. Rac activity also controls actin dynamics. The small GTPase activity itself is under the control of GEFs, which serve as activators of small GTPases [25]. Inhibition of the expression or function of upstream regulators of the actin cytoskeleton, including Rac-GEFs, Rac, and Rac targets such as PAK, cause the loss of spines [26-29]. The activation of these GTPase molecules leads to the assembly and organization of actin filaments in spines by controlling the activity of a variety of actin binding proteins. Many actin-binding proteins have been identified, such as Arp2/3, cortactin, ADF/cofilin, profilin, gelsolin, drebrin and neurabin [16,21]. Some actin-binding proteins inhibit the growth of actin filaments in spines by capping the growing

***Corresponding author:** Mizui T, Bio-interface Research Group, Health Research Inst., National Institute of Advanced Industrial Science and Technology (AIST), 1-8-31 Midorioka, Ikeda, Osaka, 563-8577, Japan, E-mail: t-mizui@aist.go.jp

Received November 27, 2012; **Accepted** March 20, 2013; **Published** March 26, 2013

Citation: Mizui T, Kojima M (2013) BDNF and Synaptic Plasticity: The Recent Cell Biology for Understanding of Brain Disorders. Clinic Pharmacol Biopharmaceut S1: 004. doi:10.4172/2167-065X.S1-004

ends of actins, whereas others exhibit opposite roles in the capping mechanism, or promote filament polymerization by the nucleation of new filaments [30]. This balancing mechanism is crucial for rapid control of actin dynamics within the spines.

The morphological changes in spines were shown in two electrophysiological models of synaptic plasticity, namely long-term potentiation (LTP) and long-term depression (LTD). LTP stimulation increased the density of spines [31], and enlarged existing spines [18]. LTD, which induces a long-lasting reduction in synaptic transmission by low-frequent stimulation, decreases spine density [32,33], and promotes spine shrinkage [34]. Previous studies indicate a correlation between the actin cytoskeleton, spine morphology, and synaptic strength [12,35-37]. Hippocampal pyramidal neurons increase and decrease the volume of dendritic spines during LTP and LTD, respectively [18,19,34]. Such activity-dependent spine morphology alterations, likely caused by the reorganization of the actin cytoskeleton, may contribute to the change in synaptic strength.

The Role of Brain-derived Neurotrophic Factor (BDNF) in Synaptic Plasticity

The morphology of dendritic spines is regulated by several molecular and cellular mechanisms [21,37]. In the central nervous system (CNS), BDNF plays a crucial role on the regulation of functional and structural plasticity. This paragraph focuses on this important aspect, and the reports are plenty. For more understating this part, the fantastic figures of several excellent reviews [38,39] could help the readers to understand these progresses.

In 1982, the group of Professor Barde et al. (1982) [40] reported the isolation of a new neurotrophic factor BDNF. Since this discovery, the biological role of BDNF for developing neurons has been shown extensively: BDNF promotes the differentiation and survival of developing neurons *in vivo* and *in vitro* [41]. In 1986, the group of Professor Chao reported on the first neurotrophin receptor p75NTR, which binds the neurotrophins with relatively low affinity [42]. In 1991, tropomyosin sensitive receptor kinases (Trks), were identified as the high-affinity receptors for the neurotrophin family of growth factors Reichardt [43]. Since these discoveries, Trk signaling, and BDNF-TrkB signaling has been characterized in plenty of brain functions: neuronal cell survival, neurite growth, cell migration, glutamate dependent spine, dendritic growth, synapse formation, stabilization, and potentiation. The Trk receptor tyrosine kinase family contains TrkA and TrkC, receptors for nerve growth factor (NGF) and neurotrophic factor 3 (NT-3), and TrkB, for BDNF and neurotrophic factor 4 (NT-4). The molecular properties of BDNF-TrkB signaling are beyond the scope of this article and are reviewed elsewhere [44]. There are several BDNF receptors (TrkB isoforms) in the mammalian CNS [43]. The full-length TrkB isoform causes tyrosine phosphorylation in the intracellular Trk domains, thereby exerting transduction of the BDNF/TrkB signaling. These events trigger the activation of mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), or phospholipase C gamma (PLCγ).

Electrophysiological studies have demonstrated that BDNF have a key role in synaptic plasticity [39,45]. BDNF far surpasses all other neurotrophins in its role in regulating LTP. Application of mature form of BDNF facilitates the early phase of LTP (E-LTP) in the hippocampus [46-48]. Inhibition of BDNF activity, by gene knockout or functional blocking using BDNF antibody or TrkB-immunoglobulin G, attenuates hippocampal E-LTP [46,48-50]. Impairment in BDNF knockout mice was rescued by acute application of recombinant BDNF [51,52]. Further evidence for the role of BDNF in LTP was illuminated [53]. Moreover, application of BDNF indicates the rapid enhancement of neurotransmitter release [54]. This effect is caused primarily by a presynaptic mechanism [55]. Postsynaptic effects of BDNF on dentate LTP in slice cultures and on NMDA (N-methyld-aspartate) receptors in cultured hippocampal neurons have been reported [56,57].

Like BDNF-TrkB signaling, L-LTP is known to induce gene expression through PI3K-Akt-mTOR and MAPK/Erk pathways [58]. Synaptic activity drives these signaling pathways that regulate the assembling of TrkB with synaptic proteins [59], gene transcription [60,61], protein translation [62], and trafficking of TrkB into synapses [59]. PI3K signaling regulates trafficking a postsynaptic density protein, PSD-95 to a synapse and cAMP regulates formation of synaptic PSD-95-TrkB complex [59,63]. BDNF-TrkB signaling regulates protein translation through both MAPK/Erk and PI3K-Akt-mTOR pathways [62].

Neuronal activity leads to the expression of over 300 genes [51], including brain-derived neurotrophic factor (BDNF), one of the major mediators of activity-dependent functions [39]. Regulation of BDNF has been studied in rodents thoroughly. Rat BDNF (rBDNF) gene was first described to have four promoters driving expression of transcripts containing different 5′ exons spliced to a single coding exon [52]. To date, it has been reported that rodent BDNF contains nine exons [64]. Cytoplasmic Ca^{2+} plays an important role, because it activates BDNF transcription through protein kinase cascades that lead to the activation of several transcription factors, including cyclic AMP response element binding protein (CREB) [58]. These reports support the important theory concerning the adult brain: the modulation of synaptic plasticity by BDNF.

Compared to that of LTP, few studies support the hypothesis that BDNF modulates LTD [38]. In the visual cortex, BDNF attenuates LTD in layer II/III synapses of young adult rats [65]. However, it was reported that pro- and mature neurotrophins activate different receptor/signaling to have opposing effects on neuronal survival [66]. proBDNF is a precursor form of BDNF. It was reported that the signaling of BDNF/TrkB and proBDNF/p75NTR promote neuronal survival and death, respectively [67,68]. There are reports showing that proBDNF may play a role in synaptic depression through p75NTR. The p75NTR mutant mice exhibit impairment in the behavioral tests of memory [69] and habituation [4]. Recently, it was demonstrated that proBDNF modulated hippocampal LTD through the activation of p75NTR [70]. The NMDA receptor-dependent LTD was pronounced at hippocampal synapses, but conversely and severely deficient in p75NTR-knockout animals [70,71].

The Possible Role of BDNF in the Regulation of Structural Plasticity

Given that the long-term changes in synaptic efficacy (LTP and LTD) lead to structural alterations of synapses, the bi-directional structural changes of synaptic structures may be controlled by the growth activity of BDNF. In line with this notion, it was shown that the exposure to BDNF led to axonal branching [72,73], dendritic growth [74,75], and refinement of synapses in an activity-dependent manner [76]. It was shown that long-term treatment of hippocampal slice with BDNF increases synapse number and spine density in apical dendrites of pyramidal neurons in the hippocampus [77], suggesting that BDNF acts on different types of spine, depending on spontaneous synaptic transmission. Moreover, BDNF regulation

of spine formation in the dendrites of hippocampal neurons is controlled by cyclic AMP (cAMP), a signaling molecule involved in L-LTP [59]. Thus, spontaneous neuronal activity and the consequent rise in the intracellular concentration of cAMP might be important for the spino-genesis exerted by BDNF.

The study of pro-neurotrophins has generated new focus into neurotrophin researches and disorders in the nervous system [78]. Using cultured hippocampal neurons, we demonstrated that proBDNF reduced the density of dendritic spines [68]. Then, the amplitude, but not the frequency, of spontaneous activity was significantly low in proBDNF-treated cultures [68]. While cultured neurons were used, this report suggests the role of BDNF processing in structural plasticity. There was more physiological study using slice cultures. Zagrebelsky et al. [79] demonstrated that the p75NTR negatively modulates dendrite complexity and spine density in hippocampal neurons.

Advance of BDNF Biology for the Development of New Therapies against Depression

Cell biology of BDNF has been developing, and is now aimed at the understanding of pathological mechanisms of brain disorders [80,81]. In particular, there are several studies indicating that BDNF is involved in depression. The initial reports showed that the expression of BDNF was decreased [82,83], and that antidepressant treatment rescued the expression of BDNF and led to the proposal of the "neurotrophin hypothesis of depression" [84]. Another important hypothesis is that the structure and function of synapses may be significantly impaired in depressed brain [84,85]. Thus, a bidirectional role of BDNF and proBDNF in structural and functional plasticity is also thought to be a tempting model [81] because it has been shown that proBDNF promotes synaptic depression and spine retraction [68,70].

A single sub-psychomimetic dose of ketamine, an ionotropic glutamatergic NMDAR (NMDA receptor) antagonist, produces fast-acting antidepressant responses in patients suffering from major depression [86-88]. Depressed patients report the alleviation of major depressive disorder symptoms within two hours of a single, low-dose intravenous infusion of ketamine, with effects lasting up to two weeks [86-88], while traditional antidepressants (serotonin re-uptake inhibitors) take weeks to reach efficacy. This delay is a major drawback to current therapies for major depressive disorder, and faster-acting antidepressants are needed, particularly for patients at risk of suicide [88]. Ketamine has the ability to produce rapid and long-lasting antidepressant responses in depressed patients.

Very recently, Autry et al. [89] demonstrated that ketamine and other NMDAR antagonists produce fast-acting antidepressant-like effects in mouse models, and, interestingly, these effects depended on the rapid synthesis of BDNF. The ketamine-mediated blockade of NMDAR deactivated eukaryotic elongation factor 2 (eEF2) kinase, resulting in the reduction in the phosphorylation levels of eEF2 and de-suppression of the translation of BDNF, indicating that the regulation of protein synthesis by spontaneous neurotransmission. The ketamine administration produced antidepressant-like effects in the forced swim test in mice [90,91]. These cellular and molecular findings would be a viable therapeutic mechanism approach for the development of fast-acting antidepressants.

As we described in this review, the cell biology of synaptic plasticity and BDNF has now fully developed and extended to the understanding of pathological mechanisms of brain disorders. This knowledge could prove beneficial for the development of new therapies against brain diseases.

Acknowledgement

The authors thank members of Kojima laboratory for helpful comments. T.M. and M.K. are supported by fellowship from CREST, JST. The funding organization had no role in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

References

1. Liston C, Gan WB (2011) Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. Proc Natl Acad Sci U S A 108: 16074-16079.
2. Grutzendler J, Kasthuri N, Gan WB (2002) Long-term dendritic spine stability in the adult cortex. Nature 420: 812-816.
3. Yang G, Pan F, Gan WB (2009) Stably maintained dendritic spines are associated with lifelong memories. Nature 462: 920-924.
4. Walsh MK, Lichtman JW (2003) In vivo time-lapse imaging of synaptic takeover associated with naturally occurring synapse elimination. Neuron 37: 67-73.
5. Kasai H, Fukuda M, Watanabe S, Hayashi-Takagi A, Noguchi J (2010) Structural dynamics of dendritic spines in memory and cognition. Trends Neurosci 33: 121-129.
6. Holtmaat A, Svoboda K (2009) Experience-dependent structural synaptic plasticity in the mammalian brain. Nat Rev Neurosci 10: 647-658.
7. Zuo Y, Yang G, Kwon E, Gan WB (2005) Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex. Nature 436: 261-265.
8. Alvarez VA, Sabatini BL (2007) Anatomical and physiological plasticity of dendritic spines. Annu Rev Neurosci 30: 79-97.
9. Ramakers GJ (2002) Rho proteins, mental retardation and the cellular basis of cognition. Trends Neurosci 25: 191-199.
10. Wisniewski KE, Segan SM, Miezejeski CM, Sersen EA, Rudelli RD (1991) The Fra(X) syndrome: neurological, electrophysiological, and neuropathological abnormalities. Am J Med Genet 38: 476-480.
11. Irwin SA, Galvez R, Greenough WT (2000) Dendritic spine structural anomalies in fragile-X mental retardation syndrome. Cereb Cortex 10: 1038-1044.
12. Nimchinsky EA, Sabatini BL, Svoboda K (2002) Structure and function of dendritic spines. Annu Rev Physiol 64: 313-353.
13. Bourne JN, Harris KM (2008) Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci 31: 47-67.
14. Matus A (2000) Actin-based plasticity in dendritic spines. Science 290: 754-758.
15. Zito K, Knott G, Shepherd GM, Shenolikar S, Svoboda K (2004) Induction of spine growth and synapse formation by regulation of the spine actin cytoskeleton. Neuron 44: 321-334.
16. Ethell IM, Pasquale EB (2005) Molecular mechanisms of dendritic spine development and remodeling. Prog Neurobiol 75: 161-205.
17. Cingolani LA, Thalhammer A, Yu LM, Catalano M, Ramos T, et al. (2008) Activity-dependent regulation of synaptic AMPA receptor composition and abundance by beta3 integrins. Neuron 58: 749-762.
18. Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H (2004) Structural basis of long-term potentiation in single dendritic spines. Nature 429: 761-766.
19. Okamoto K, Nagai T, Miyawaki A, Hayashi Y (2004) Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat Neurosci 7: 1104-1112.
20. Kopec CD, Li B, Wei W, Boehm J, Malinow R (2006) Glutamate receptor exocytosis and spine enlargement during chemically induced long-term potentiation. J Neurosci 26: 2000-2009.
21. Sekino Y, Kojima N, Shirao T (2007) Role of actin cytoskeleton in dendritic spine morphogenesis. Neurochem Int 51: 92-104.

22. Hall A (1998) Rho GTPases and the actin cytoskeleton. Science 279: 509-514.

23. Settleman J (1999) Rho GTPases in development. Prog Mol Subcell Biol 22: 201-229.

24. Schubert V, Da Silva JS, Dotti CG (2006) Localized recruitment and activation of RhoA underlies dendritic spine morphology in a glutamate receptor-dependent manner. J Cell Biol 172: 453-467.

25. Penzes P, Cahill ME (2012) Deconstructing signal transduction pathways that regulate the actin cytoskeleton in dendritic spines. Cytoskeleton (Hoboken) 69: 426-441.

26. Tashiro A, Minden A, Yuste R (2000) Regulation of dendritic spine morphology by the rho family of small GTPases: antagonistic roles of Rac and Rho. Cereb Cortex 10: 927-938.

27. Cahill ME, Xie Z, Day M, Photowala H, Barbolina MV, et al. (2009) Kalirin regulates cortical spine morphogenesis and disease-related behavioral phenotypes. Proc Natl Acad Sci U S A 106: 13058-13063.

28. Penzes P, Beeser A, Chernoff J, Schiller MR, Eipper BA, et al. (2003) Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. Neuron 37: 263-274.

29. Xie Z, Srivastava DP, Photowala H, Kai L, Cahill ME, et al. (2007) Kalirin-7 controls activity-dependent structural and functional plasticity of dendritic spines. Neuron 56: 640-656.

30. Okada H, Soderling SH (2009) Signaling through actin to regulate spine formation and function. The Open Neuroscience Journal 3: 97-107.

31. Muller D, Toni N, Buchs PA (2000) Spine changes associated with long-term potentiation. Hippocampus 10: 596-604.

32. Monfils MH, Teskey GC (2004) Induction of long-term depression is associated with decreased dendritic length and spine density in layers III and V of sensorimotor neocortex. Synapse 53: 114-121.

33. Bastrikova N, Gardner GA, Reece JM, Jeromin A, Dudek SM (2008) Synapse elimination accompanies functional plasticity in hippocampal neurons. Proc Natl Acad Sci U S A 105: 3123-3127.

34. Zhou Q, Homma KJ, Poo MM (2004) Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 44: 749-757.

35. Hering H, Sheng M (2001) Dendritic spines: structure, dynamics and regulation. Nat Rev Neurosci 2: 880-888.

36. Yuste R, Bonhoeffer T (2001) Morphological changes in dendritic spines associated with long-term synaptic plasticity. Annu Rev Neurosci 24: 1071-1089.

37. Kasai H, Matsuzaki M, Noguchi J, Yasumatsu N, Nakahara H (2003) Structure-stability-function relationships of dendritic spines. Trends Neurosci 26: 360-368.

38. Lu B, Pang PT, Woo NH (2005) The yin and yang of neurotrophin action. Nat Rev Neurosci 6: 603-614.

39. Poo MM (2001) Neurotrophins as synaptic modulators. Nat Rev Neurosci 2: 24-32.

40. Barde YA, Edgar D, Thoenen H (1982) Purification of a new neurotrophic factor from mammalian brain. EMBO J 1: 549-553.

41. Bibel M, Barde YA (2000) Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system. Genes Dev 14: 2919-2937.

42. Johnson D, Lanahan A, Buck CR, Sehgal A, Morgan C, et al. (1986) Expression and structure of the human NGF receptor. Cell 47: 545-554.

43. Reichardt LF (2006) Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci 361: 1545-1564.

44. Huang EJ, Reichardt LF (2003) Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem 72: 609-642.

45. Barco A, Patterson SL, Alarcon JM, Gromova P, Mata-Roig M, et al. (2005) Gene expression profiling of facilitated L-LTP in VP16-CREB mice reveals that BDNF is critical for the maintenance of LTP and its synaptic capture. Neuron 48: 123-137.

46. Korte M, Carroll P, Wolf E, Brem G, Thoenen H, et al. (1995) Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci U S A 92: 8856-8860.

47. Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381: 706-709.

48. Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, et al. (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16: 1137-1145.

49. Chen G, Kolbeck R, Barde YA, Bonhoeffer T, Kossel A (1999) Relative contribution of endogenous neurotrophins in hippocampal long-term potentiation. J Neurosci 19: 7983-7990.

50. Xu B, Gottschalk W, Chow A, Wilson RI, Schnell E, et al. (2000) The role of brain-derived neurotrophic factor receptors in the mature hippocampus: modulation of long-term potentiation through a presynaptic mechanism involving TrkB. J Neurosci 20: 6888-6897.

51. Lin Y, Bloodgood BL, Hauser JL, Lapan AD, Koon AC, et al. (2008) Activity-dependent regulation of inhibitory synapse development by Npas4. Nature 455: 1198-1204.

52. Timmusk T, Palm K, Metsis M, Reintam T, Paalme V, et al. (1993) Multiple promoters direct tissue-specific expression of the rat BDNF gene. Neuron 10: 475-489.

53. Lu B (2003) BDNF and activity-dependent synaptic modulation. Learn Mem 10: 86-98.

54. Lohof AM, Ip NY, Poo MM (1993) Potentiation of developing neuromuscular synapses by the neurotrophins NT-3 and BDNF. Nature 363: 350-353.

55. Gottschalk W, Pozzo-Miller LD, Figurov A, Lu B (1998) Presynaptic modulation of synaptic transmission and plasticity by brain-derived neurotrophic factor in the developing hippocampus. J Neurosci 18: 6830-6839.

56. Levine ES, Crozier RA, Black IB, Plummer MR (1998) Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing N-methyl-D-aspartic acid receptor activity. Proc Natl Acad Sci U S A 95: 10235-10239.

57. Kovalchuk Y, Hanse E, Kafitz KW, Konnerth A (2002) Postsynaptic Induction of BDNF-Mediated Long-Term Potentiation. Science 295: 1729-1734.

58. Klann E, Dever TE (2004) Biochemical mechanisms for translational regulation in synaptic plasticity. Nat Rev Neurosci 5: 931-942.

59. Ji Y, Pang PT, Feng L, Lu B (2005) Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. Nat Neurosci 8: 164-172.

60. Nguyen PV, Abel T, Kandel ER (1994) Requirement of a critical period of transcription for induction of a late phase of LTP. Science 265: 1104-1107.

61. Shaywitz AJ, Greenberg ME (1999) CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. Annu Rev Biochem 68: 821-861.

62. Sarbassov DD, Ali SM, Sabatini DM (2005) Growing roles for the mTOR pathway. Curr Opin Cell Biol 17: 596-603.

63. Yoshii A, Constantine-Paton M (2007) BDNF induces transport of PSD-95 to dendrites through PI3K-AKT signaling after NMDA receptor activation. Nat Neurosci 10: 702-711.

64. Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T (2007) Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res 85: 525-535.

65. Akaneya Y, Tsumoto T, Kinoshita S, Hatanaka H (1997) Brain-derived neurotrophic factor enhances long-term potentiation in rat visual cortex. J Neurosci 17: 6707-6716.

66. Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294: 1945-1948.

67. Teng HK, Teng KK, Lee R, Wright S, Tevar S, et al. (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25: 5455-5463.

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

69. Wright JW, Alt JA, Turner GD, Krueger JM (2004) Differences in spatial learning comparing transgenic p75 knockout, New Zealand Black, C57BL/6, and Swiss Webster mice. Behav Brain Res 153: 453-458.

70. Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, et al. (2005) Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8: 1069-1077.

71. Rösch H, Schweigreiter R, Bonhoeffer T, Barde YA, Korte M (2005) The neurotrophin receptor p75NTR modulates long-term depression and regulates the expression of AMPA receptor subunits in the hippocampus. Proc Natl Acad Sci U S A 102: 7362-7367.

72. Cohen-Cory S, Fraser SE (1995) Effects of brain-derived neurotrophic factor on optic axon branching and remodelling in vivo. Nature 378: 192-196.

73. Gallo G, Letourneau PC (1998) Localized sources of neurotrophins initiate axon collateral sprouting. J Neurosci 18: 5403-5414.

74. McAllister AK, Katz LC, Lo DC (1999) Neurotrophins and synaptic plasticity. Annu Rev Neurosci 22: 295-318.

75. Suzuki S, Kiyosue K, Hazama S, Ogura A, Kashihara M, et al. (2007) Brain-derived neurotrophic factor regulates cholesterol metabolism for synapse development. J Neurosci 27: 6417-6427.

76. Cabelli RJ, Hohn A, Shatz CJ (1995) Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. Science 267: 1662-1666.

77. Tyler WJ, Pozzo-Miller LD (2001) BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. J Neurosci 21: 4249-4258.

78. Chao MV (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci 4: 299-309.

79. Zagrebelsky M, Holz A, Dechant G, Barde YA, Bonhoeffer T, et al. (2005) The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. J Neurosci 25: 9989-9999.

80. Chao MV, Rajagopal R, Lee FS (2006) Neurotrophin signalling in health and disease. Clin Sci (Lond) 110: 167-173.

81. Martinowich K, Manji H, Lu B (2007) New insights into BDNF function in depression and anxiety. Nat Neurosci 10: 1089-1093.

82. Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 15: 7539-7547.

83. Smith MA, Makino S, Kvetnansky R, Post RM (1995) Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 15: 1768-1777.

84. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, et al. (2002) Neurobiology of depression. Neuron 34: 13-25.

85. Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455: 894-902.

86. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, et al. (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47: 351-354.

87. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, et al. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63: 856-864.

88. Price RB, Nock MK, Charney DS, Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 66: 522-526.

89. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, et al. (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475: 91-95.

90. Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, et al. (2012) Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. Biol Psychiatry 71: 996-1005.

91. Lindholm JS, Autio H, Vesa L, Antila H, Lindemann L, et al. (2012) The antidepressant-like effects of glutamatergic drugs ketamine and AMPA receptor potentiator LY 451646 are preserved in bdnf$^{+/-}$ heterozygous null mice. Neuropharmacology 62: 391-397.