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BDNF: linking fear learning to memory consolidation

Marie-H. Monfils*, Kiriana K. Cowansage* & Joseph E. LeDoux

Center for Neural Science, New York University, New York, USA, 10003

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Running Title: BDNF and fear memory

Address correspondence to: Marie-H. Monfils

Center for Neural Science,

4 Washington Place, Room 809,

New York University,

New York, NY, USA,

10003-6621

e-mail: monfils@cns.nyu.edu

* These authors contributed equally

Abstract

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays an important role in synaptic plasticity. In this issue of Molecular Pharmacology, Ou & Gean thoroughly describe the molecular cascade by which fear learning leads to an increase in BDNF expression in the lateral amygdala (LA). Calcium influx through NMDA receptors and L-VDCC channels, which occurs in the LA during fear conditioning, activates PKA and CaMKIV. Each induces phosphorylation of CREB, which binds to the BDNF promoter, leading to BDNF expression in the LA, and contributes to fear memory consolidation.

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The activity-dependent modification of synapses, a process known as synaptic plasticity, permits the brain to generate efficient neural networks that facilitate advantageous behavioral adaptations. Although an extensive body of research has demonstrated the importance of synaptic strengthening in the beneficial functions of learning and memory, recent evidence also suggests that a host of pathologies, including mood disorders and drug addiction, engage overlapping mechanisms. Thus, the elucidation of molecular pathways involved in driving these physiological changes has broad clinical implications (Malenka & Bear, 2004; MacKinnon & Zamoiski, 2006).

The neurotrophins, a family of structurally related proteins known for their role in promoting neuronal differentiation and survival during development (Levi Montalcini, 1987; Leibrock et al., 1989; Barde, 1994), have recently surfaced as playing an important role in mediating synaptic plasticity (Schinder & Poo, 2000; Lu, 2003; Lu, 2004; Bramham & Messaoudi, 2005; Arancio & Chao, 2007). In the current issue of Molecular Pharmacology, Ou and Gean (2007) investigated the mechanism by which one member of this family, brain derived neurotrophic factor (BDNF), mediates fear memory consolidation in the amygdala. BDNF and its main receptor, TrkB, are fast emerging as major regulators of synaptic transmission and plasticity in the adult brain. In mammals, BDNF is synthesized, stored, and released from excitatory glutamate (Lessman et al., 2003) and, in some populations, dopamine-containing neurons (Berton et al., 2006).

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Past investigations into the role of BDNF in plasticity have predominantly focused on the hippocampus, a structure traditionally associated with learning and memory. In that structure, TrkB receptors have been specifically localized to the pre- and post-synaptic elements of glutamatergic synapses (Drake et al., 1999), and co-immunoprecipitate with the transmembrane NMDA receptor protein, which allows calcium entry into the cell in response to detection of coincidental rises in both pre-synaptic glutamate and post-synaptic voltage (Aoki et al., 2000). Because this calcium influx is necessary for the initiation of cellular changes, the co-localization of NMDARs with BDNF and its receptor, TrkB, at synaptic junctions sets the stage to synchronize bidirectional synaptic optimization.

Much evidence indicates that learning initiates alterations in glutamate-dependent excitatory synaptic transmission, which subsequently stabilize through structural changes at postsynaptic sites on dendritic spines (for review, see Lamprecht & LeDoux, 2004). Direct infusion of BDNF into the hippocampus enhances synaptic strength, both *in vitro* (Kang & Schuman, 1995; Levine et al., 1995) and *in vivo* (Messaoudi et al., 1998), as well as modulates the induction of long-term potentiation (Patterson et al., 1996; Messaoudi et al., 2002) and structural changes in dendritic spines (Alonso et al., 2004). Recent work by Tyler and colleagues (2002) also suggests that BDNF activation is necessary for the learning-induced modification of hippocampal spines, which may also involve the activation of TrkB (von Bohlen und Halbach et al., 2006). Furthermore, Bekinschtein et al. (2007) recently demonstrated that BDNF-dependent storage of long-

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term memories occurs within hours after acquisition of an associative learning task, suggesting that BDNF is likely to be involved in memory stabilization.

Despite the traditional popularity of the hippocampus in all matters of learning and memory, there is increasing empirical support for the role of another structure—the amygdala—in the types of synaptic changes facilitated by BDNF. In particular, mounting evidence now indicates a role for BDNF signaling in the basal and lateral nuclei of the amygdala (Rattiner et al., 2004a; Ou & Gean, 2006), areas known to be necessary for the formation of learned fear associations (LeDoux et al., 2000). Because the amygdala has been implicated in many pathologies, including post-traumatic stress (Garakani et al., 2006), anxiety (Rauch et al., 2006), and autism spectrum disorders (Baron-Cohen et al., 2000; Bachevalier & Loveland, 2006), considerable efforts have been devoted to the characterization of this circuitry as a central site for emotion-induced neuronal plasticity (LeDoux, 2000; Maren, 2001, Paré et al., 2004; Wilensky et al., 2006). A number of studies have shown, using Pavlovian fear conditioning paradigms, that the physiological basis for such changes begins with the relay of sensory information from the medial geniculate nucleus of the thalamus (MGm) to the lateral amygdala (LA), where the initial association is made via an LTP-like mechanism, followed by the intra-amygdala transfer of signals to the central nucleus of the amygdala (CEm) which facilitates the expression of a fear response by way of projections to brainstem and hypothalamic targets (Davis, 1997; Paré et al., 2004; LeDoux, 2000). Together, these findings support the notion that changes in synaptic strength are required for the acquisition of emotional memories. At a more profound level, however, our knowledge

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of these larger-scale anatomical modifications remains bound by our more limited comprehension of the molecular machinery governing those changes.

A recent study found temporally-specific increases in BDNF gene expression to occur in the basal/lateral portion of the amygdala (BLA) after paired stimuli that supported learning, but not after exposure to neutral or aversive stimuli alone (Rattiner et al., 2004a). BDNF signaling through TrkB receptors was also found to be necessary for the consolidation of fear memories (Rattiner et al., 2004a). In agreement with Rattiner et al.'s findings (2004), Ou & Gean (2006) reported increases in BDNF protein expression and activation of TrkB receptors in the amygdala. Their study further revealed that intra-amygdala infusion of a TrkB ligand scavenger or the inhibition of Trk receptors impaired fear memory assessed 24 hours after training. In addition, they showed that BDNF phosphorylates mitogen-activated protein kinase (MAPK), and this is blocked by the Trk receptor inhibitor K252a (Ou & Gean, 2006). The BDNF-induced phosphorylation of MAPK occurs via Shc binding to the TrkB receptor, which leads to the activation of Ras, Raf, MEK, and MAPK. BDNF also phosphorylates MAPK via activation of PI-3 kinase (see figure 1).

In the current issue of molecular pharmacology, Ou & Gean (2007) extend their earlier work to a characterization of the molecular cascades underlying fear conditioning that exert transcriptional and translational control over BDNF expression in the amygdala. Consistent with the previous work of Rattiner et al. (2004b), they show a significant increase in BDNF exon I- and III-containing mRNA in the amygdala of fear

conditioned rats. Inhibition of protein synthesis and translation, using intra-LA anisomycin or actinomycin D, respectively, attenuates this increase in fear-conditioning-induced BDNF expression. Further, they demonstrate that the increase in BDNF depends on the activation of NMDA receptors as well as L-type voltage-dependent calcium channels (L-VDCC), the blockade of which significantly attenuates BDNF expression. A similar reduction was also apparent following the pharmacological inhibition of PKA and CaMKIV activity. In addition, through the use of DNA affinity precipitation and chromatin immunoprecipitation (ChIP) assays, Ou & Gean (2007) demonstrate a specific increase in the binding of phosphorylated cAMP response element binding protein (p-CREB) to exon I and III promoters after fear conditioning. Interestingly, they found that sequestration of endogenous BDNF during fear conditioning by infusion of a TrkB IgG did not affect the BDNF protein level increases typically observed one hour after conditioning. This suggests that whereas BDNF signaling through TrkB receptors in the amygdala is required for long-term memory (Rattiner et al., 2004a; Ou & Gean, 2006), it is not necessary to regulate the increase in BDNF protein levels induced by fear conditioning (Ou & Gean, 2007).

Many of the most common psychiatric disorders that afflict humans are emotional disorders, a number of which involve the activation of fear circuitry in the brain. In order to develop suitable treatments for anxiety-related disorders, it is necessary to develop a better understanding of the molecular mechanisms that underlie their development and manifestation. Ou & Gean's (2007) findings elegantly illustrate that calcium influx through NMDA receptors and L-VDCC channels, known to occur during fear

conditioning, activates PKA and CaMKIV, each inducing CREB phosphorylation. In turn, phosphorylated CREB binds to the BDNF promoter, leading to an increase in BDNF expression in the amygdala, and likely contributes to fear memory consolidation (see Figure 1). Ou & Gean's (2007) study describes a tight molecular cascade linking the initial physiological events that take place during fear conditioning to the expression of BDNF- a potent modulator of synaptic plasticity that could lead to the restructuring of synapses in the LA. Taken together, these findings implicate the BDNF signaling cascade in the amygdala as a potential target for novel pharmacological interventions.

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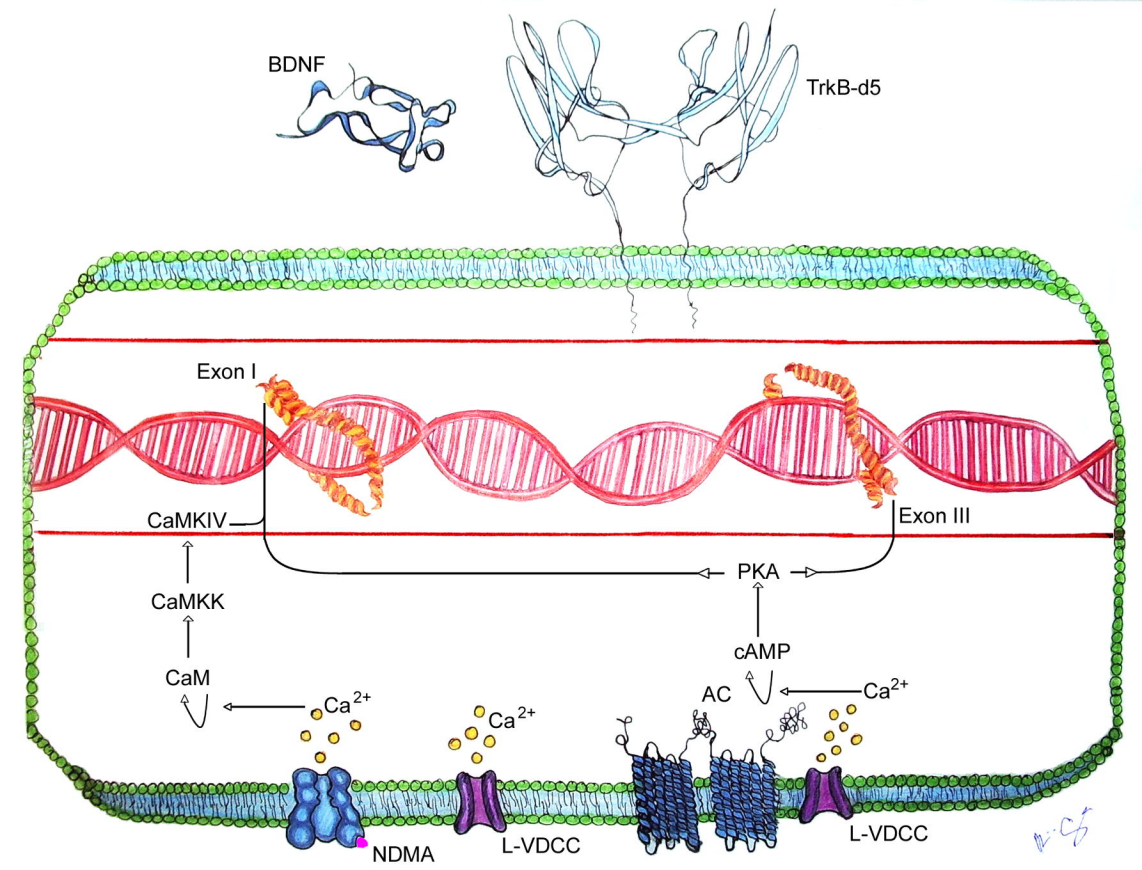
Figure caption

Figure 1. Brain-derived neurotrophic factor (BDNF) signaling cascade involved during fear conditioning. Calcium influx through NMDA receptors and L-VDCC channels, which occurs in the lateral amygdala (LA) during fear conditioning, activates adenyl cyclase (AC) and protein kinase A (PKA). Activated PKA translocates to the nucleus and induces CREB phosphorylation. Increase in intracellular calcium also activates CaMKIV, and leads to phosphorylation of CREB at ser-133. Activated CREB binds to the BDNF promoter, leading to BDNF expression in the LA, and contributes to fear memory consolidation (from Ou & Gean, 2007). Fear conditioning is also associated with binding of BDNF to TrkB receptors. This results in the association of Shc and TrkB receptor [structure of ligand binding domain after the work of Ultsch et al (1999)], and leads to the activation of Ras, Raf, MEK, and MAPK (not shown here). BDNF also phosphorylates MAPK via activation of PI3 kinase (from Ou & Gean, 2006) (not shown here).


BDNF
TrkB-d5
Exon I
Exon III
CaMKIV
CaMKK
CaM
PKA
cAMP
AC
Ca^{2+}
Ca^{2+}
Ca^{2+}
NDMA
L-VDCC
L-VDCC