Journal Club

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# BDNF Signaling Potentiates Transmission of Information from the Basolateral Amygdala to Infralimbic Prefrontal Cortex during Conditioned Taste Aversion Extinction

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Review of Xin et al.

Conditioned taste aversion (CTA) is a form of associative learning in which a palatable taste [e.g., saccharin; conditioned stimulus (CS)] is paired with a toxic unconditioned stimulus (e.g., injection of lithium chloride), resulting in a reduced preference for the CS. Extinction is a form learning in which a conditioned response to the CS is weakened through repetitive presentations of the CS alone. A recent report by Xin et al. (2014) in *The Journal of Neuroscience* examines the importance of brain-derived neurotrophic factor (BDNF) signaling in CTA extinction.

BDNF in the infralimbic prefrontal cortex (IL) was previously shown to be involved in conditioned fear extinction learning (Sotres-Bayon and Quirk, 2010). Specifically, after extinction training, rats showed reduced freezing in response to fear-conditioned stimuli (i.e., increased extinction) following infusion of exogenous BDNF into either hippocampus or IL. The BDNF-induced increase in extinction was also found independent of extinction training, which suggests that BDNF alone can produce extinction. The reduction in freezing was blocked by infusing BDNF-neutralizing antibodies into IL immediately before infusing exogenous BDNF into the hippocampus (Peters et al., 2010). This work revealed the importance of BDNF-dependent communication between brain areas where BDNF activity is also important for plasticity, and it implicates IL as a critical region facilitating conditioned fear extinction learning.

Xin et al. (2014) showed similar involvement of BDNF signaling during CTA extinction learning in the basolateral amygdala (BLA) and IL, two areas involved in this process (Bahar et al., 2003; Maroun et al., 2012). Additionally, they showed the importance of BDNF-dependent communication from BLA to IL and that IL is a critical region facilitating extinction learning. The similarities and differences between hippocampal–IL and BLA–IL mechanisms suggest a principle of operation that might be examined in other types of learning.

Xin and colleagues (2014) used behavioral, molecular, and pharmacological approaches to measure and manipulate BDNF mRNA and protein levels in the BLA and IL and examined the consequent effects on CTA extinction. During CTA extinction training, rats showed a reduction, compared with their initial aversion to the CS, by day 3 of 4. Because extinction training on day 2 led to the reduced aversion seen on day 3, molecular assays were performed on day 2. Using qRT-PCR, Xin et al. (2014) found increased BDNF mRNA in the BLA and IL 1.5 h after extinction; levels remained elevated at 6 h and returned to basal levels at 8 h. ELISA assay showed BDNF protein increased after extinction training shortly after the rise in mRNA levels (4 h) in the BLA and IL, with a return to baseline after mRNA levels dropped (12–16 h). No significant differences in BDNF mRNA or protein levels were seen in the central amygdala (CeA; CTA relevant) or hippocampus (CTA nonrelevant).

The neurotrophins BDNF and NT 4/5 bind to TrkB receptors, leading to receptor phosphorylation (p-TrkB), which then activates various signaling cascades resulting in cellular changes including synaptic plasticity (Minichiello, 2009). Xin et al. (2014) tested whether p-TrkB in the BLA and IL increased after extinction training. Increased p-TrkB was found in BLA and IL at 8 h, but also at 1 h after extinction training (before BDNF synthesis increased), suggesting activity-dependent release of pre-existing BDNF occurred. Increased p-TrkB was likely specific to BDNF because no significant differences were found in NT 4/5 mRNA levels 6 h after extinction.

The authors then examined the behavioral effects of manipulating BDNF during CTA extinction training. BDNF activity in the BLA or IL was modulated by bilaterally infusing a Trk receptor inhibitor (K252a), BDNF-neutralizing antibodies, or exogenous BDNF immediately

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after extinction training for each of the first 3 d. Inhibiting BDNF signaling in either BLA or IL reduced the CTA extinction rate. Conversely, increasing BDNF signaling in either area increased the CTA extinction rate. Although IL has been implicated in conditioned fear extinction (Sotres-Bayon and Quirk, 2010) and CTA extinction (Maroun et al., 2012), BDNF signaling in BLA and IL had not previously been established in CTA extinction.

Xin et al. (2014) inhibited BDNF signaling in the BLA or IL after extinction training and examined BDNF mRNA levels 1.5 h later. Inhibiting BDNF signaling in BLA or IL reduced local BDNF mRNA. Interestingly, inhibiting BDNF signaling in BLA also reduced BDNF mRNA expression in the IL. However, inhibiting BDNF signaling in IL had no effect on BDNF mRNA expression in the BLA. Thus, increased BDNF signaling in BLA after CTA extinction training produces BDNF-dependent communication to IL, resulting in increased BDNF expression in IL.

Because BDNF can have short- and long-term effects on cell signaling, it is important to understand how information about BDNF activity is transmitted from BLA to IL. Use of dual bilateral cannulation allowed Xin et al. (2014) to increase BDNF signaling in BLA, while simultaneously inhibiting BDNF signaling in IL in untrained rats. Within 20 min of increasing BDNF in BLA, p-TrkB levels were elevated in both BLA and IL; this effect was blocked in IL by inhibiting local BDNF signaling. The timing and sensitivity to BDNF inhibition seem to rule out the possibility that increased BDNF expression in IL could be due to transport of BDNF or the TrkB-BDNF complex from BLA. However, other rapid signaling mechanisms cannot be eliminated.

The same dual bilateral cannulation of BLA and IL was used to simultaneously increase BDNF in one brain region and inhibit BDNF signaling in the other immediately after CTA extinction training for each of the first 3 d. Inhibiting BDNF signaling in IL blocked the increase in CTA extinction rate induced by increasing BDNF in BLA. In contrast, increasing BDNF in IL increased the CTA extinction rate whether or not BDNF signaling was inhibited in BLA. This use of competing signals showed that although BDNF-dependent communication from the BLA to IL is essential for CTA extinction, it is local BDNF signaling in the IL that is critical for facilitating extinction learning.

BDNF signaling may lead to extinction through several different mechanisms of short-term activation and long-term synaptic changes that may differ depending on the brain region. BDNF-dependent communication from the BLA to IL was rapid, thus unlikely to involve gene transcription. BDNF secretion can lead to neuronal depolarization through intracellular calcium release or direct sodium channel activation (Minichiello, 2009), possibly triggering neural signal transmission. Rapid BDNF-related communication with IL is also a feature of hippocampal-dependent fear extinction. Increased BDNF in the hippocampus resulted in increased firing of IL neurons 30 min later (Rosas-Vidal et al., 2014). Similar to hippocampal–IL circuitry, we suggest that BDNF signaling in BLA could lead to rapid neuronal depolarization, resulting in BDNF release in the IL and subsequent downstream signaling.

Xin et al. (2014) blocked BDNF signaling in the IL after extinction training and found reduced extinction on the following days. This effect may be mediated by long-term synaptic plasticity and gene transcription necessary for learning. BDNF can activate intracellular cascades involving internal calcium release and/or mitogen-activated protein kinase, resulting in gene transcription (Minichiello, 2009). Future research should seek to delineate the effects of short-term and long-term synaptic changes during CTA extinction, as both are potential mechanisms of BDNF signaling.

Xin et al. (2014) showed the importance of BDNF in BLA–IL circuitry in CTA extinction, and others have focused on neuronal firing in the IL during extinction (Maroun et al., 2012; Rosas-Vidal et al., 2014). However, the effects of these circuits on downstream targets have not been extensively examined. The IL has been suggested to integrate contextual and emotional information via input from many neural areas (hippocampus, thalamus, amygdala), and can coordinate responses through diverse output projections, including the intercalated cell masses (ITCs) of the amygdala (Sotres-Bayon and Quirk, 2010). ITCs are clusters of GABAergic cells that receive input from the IL and modulate activity in their adjacent main-amygdalar nuclei. ITCs adjacent to BLA and CeA are involved in extinction of conditioned fear responses (Pape and Pare, 2010; Sotres-Bayon and Quirk, 2010). However, ITCs have not been examined in CTA extinction learning. BLA–IL BDNF signaling could strengthen the synaptic connectivity from IL to ITCs, which could modulate amygdalar output during extinction. BLA c-Fos expression is reduced over the course of CTA extinction learning (Mickley et al., 2004), possibly resulting from increased inhibition, but whether changes in ITC activity are involved is unknown. ITCs are heavily interconnected (Pape and Pare, 2010); thus, increased IL input could produce a variety of potential changes to amygdalar output.

The amygdalar circuitry involved in CTA extinction is a hippocampal-independent form of extinction learning that requires IL BDNF activity similar to that required for conditioned fear extinction. Both conditioned fear and CTA extinction learning require BDNF-dependent input to the IL from a subcortical location (the hippocampus or BLA, respectively). In both cases, the IL appears to be an essential brain region for facilitating extinction learning. Xin et al. (2014) expand our knowledge of BDNF contributions to extinction of aversive memory and rigorously demonstrate the necessity for BDNF-related corticopetal communication, which might also be important in other types of learning. They create exciting avenues of research into the IL and BDNF-dependent influences on downstream circuitry.

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