

## Abstract

### Curcumin Inhibits the IKK:NF $\kappa$ B Pathway in Neural Circuits

by

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The study of how the brain acquires fearful memories has attracted considerable experimental attention, due in part by the promise of discovering novel therapeutic approaches for psychiatric disorders, such as post-traumatic stress disorder (PTSD), that are characterized by unusually strong and persistent traumatic memories. In recent years, extensive research has focused on studying the neural and molecular mechanisms by which fear memories are acquired, stored, and retrieved in the brain. Once acquired, fear memories may be attenuated using one of 2 procedures: 1) fear extinction, which involves repeated presentation of the fear-arousing stimulus in the absence of an aversive consequence, or 2) interference with the reconsolidation process. The discovery of novel pharmacological approaches that modulate the consolidation, reconsolidation, and extinction of fear memories may thus have considerable clinical significance.

Our lab has recently shown that a diet enriched with curcumin; a polyphenol compound found in the rhizome of the turmeric plant (*Curcuma longa*), impairs the consolidation and reconsolidation of an auditory Pavlovian fear memory. However, there remained a question as to

whether, 1) curcumin had any effect on the extinction of an auditory Pavlovian fear memory, and 2) if curcumin's effects were localized within the brain. Further, studies have shown extensive evidence for curcumin as an inflammatory inhibitor, specifically of the IKK:NF- $\kappa$ B inflammatory pathway. Therefore, the aim of this dissertation was to elucidate the mechanisms by which curcumin systematically affects the consolidation, reconsolidation, and extinction of an auditory Pavlovian fear memory, focusing on whether the IKK:NF- $\kappa$ B inflammatory pathway is implicated.

In Chapter 2, we find that direct infusions of curcumin into the lateral amygdala (LA), the primary site of acquisition and storage of fear memories in the brain, impairs training-related upregulation of the IKK enzyme, and impairs the consolidation of an auditory Pavlovian fear memory. In Chapter 3, we find that direct infusions of curcumin into the LA impairs retrieval-related upregulation of the IKK enzyme, and impairs the reconsolidation of an auditory Pavlovian fear memory. Surprisingly, in Chapter 4, we observe that a dietary source of curcumin facilitates the extinction of an auditory Pavlovian fear memory. Further, direct infusions of curcumin into the infralimbic cortex (IL), immediately after extinction training, facilitated the retention of an extinction memory. Interestingly, a dietary source of curcumin impairs the upregulation of the IKK enzyme. Collectively, we provide evidence that curcumin impairs the consolidation and reconsolidation, while facilitating the extinction, of an auditory Pavlovian fear memory. Further, all three behavioral effects are correlated with the downregulation of the IKK: NF- $\kappa$ B inflammatory signaling pathway.