Neuroscience 189 (2011) 156–169

MEMORY OF FEARFUL EVENTS: THE ROLE OF FIBROBLAST GROWTH FACTOR-2 IN FEAR ACQUISITION AND EXTINCTION

B. M. GRAHAM[a]* AND R. RICHARDSON[b]

[a]*Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, 149 13th St. Charlestown, 02129 Boston, MA, USA*

[b]*School of Psychology, UNSW, 2052, Sydney, Australia*

Abstract—Research during the past decade has led to a tremendous growth in our understanding of how fear memories are acquired and subsequently inhibited on a neural and molecular level. Such research has contributed to significant developments in the treatment of anxiety disorders, and has considerably advanced our understanding of the neurobiology of learning and memory in general. A number of recent studies have examined the role of growth factors in the formation of long-term memory for fearful events, due to their ability to cause morphological neural changes in response to environmental stimulation. In this review we first describe physiological evidence that fibroblast growth factor-2 (FGF2) receptors are highly expressed in the neural circuitry regulating fear acquisition and extinction, and that FGF2 modulates the molecular signals known to be involved in the formation of fear memories. Then we present emerging behavioral research that demonstrates that exogenous FGF2 can enhance the formation of fear conditioning and extinction memories. Finally, we briefly discuss how research into the role of FGF2 in learning and memory may be of clinical benefit, particularly in the treatment of anxiety disorders.

Key words: fibroblast growth factor-2, fear conditioning, fear extinction, anxiety, memory, long-term potentiation.

Contents

*Corresponding author. Tel: +1-617-643-1156; fax: +1-617-726-4078.
E-mail address: bmgraham@nmr.mgh.harvard.edu (B. M. Graham).
Abbreviations: BDNF, brain-derived neurotrophic factor; BLA, basolateral complex of the amygdala; BNST, bed nuclei of the stria terminalis; cAMP, cyclic adenosine monophosphate; CeA, central nucleus of the amygdala; CREB, cAMP response element binding protein; CS, conditioned stimulus; ERK, extracellular signal-regulated kinase; *Fgfr1*, FGF receptor-1; FGF2, fibroblast growth factor-2; IL, infralimbic region of the prefrontal cortex; LTP, long-term potentiation; LVGCCs, L-type voltage gated Ca^{2+} channels; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mPFC, medial prefrontal cortex; NMDA, N-methyl-D-aspartate; PKC, calcium/phospholid-dependent protein kinase; PND, postnatal day; TrkB, tyrosine kinase B; US, unconditioned stimulus.

The neurobiology underlying fear memories, both their acquisition and inhibition (i.e., extinction), has become increasingly well characterized over the years. This has had a number of clinical applications, including the development of drugs that interfere with the consolidation/reconsolidation of fearful memories and drugs that enhance the acquisition and/or consolidation of fear extinction memories (for a recent review see Graham et al., in press). However, most of the documented neurobiological changes that characterize fear memories are relatively transient, which leads to the question of how these memories persist. One approach to this issue which has recently started being explored has focused on the role of growth factors in memory formation. Growth factors cause structural changes within the brain and therefore may be in part responsible for the persistence of fear memories. One example is brain-derived neurotrophic factor (BDNF), which has been comprehensively reviewed in a number of recent papers (Cunha et al., 2010; Lu et al., 2008). Another example is fibroblast growth factor-2 (FGF2). Although FGF2 has received much less attention than BDNF regarding its potential role in learning and memory, a vast body of research has demonstrated that FGF2 modulates, and is modulated by, the molecular processes that underlie fear memories. Further, recent research has shown that systemic FGF2 modulates both fear acquisition and extinction memories. The purpose of this review is to describe the neural, molecular, and behavioral evidence that suggests that FGF2 is involved in the regulation of fear memories.

The most common ways of modeling fear acquisition and inhibition in the laboratory are through Pavlovian fear conditioning and fear extinction, and as such, this review

0306-4522/11 $ - see front matter
doi:10.1016/j.neuroscience.2011.05.041