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BRAIN RESEARCH

Research Report

Neurobehavioral basis of the impaired nurturing in mice lacking the immediate early gene *FosB*

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ABSTRACT

The transcription factor FosB is induced in neurons of the medial preoptic area (MPOA) during parenting, through activation of the extracellular signal-regulated kinase (ERK). *FosB* mutant (–/–) postpartum mice and virgin mice that are exposed to pups show defective nurturing behavior. The *FosB* (–/–) MPOA fails to fully up-regulate *SPRY1* and *Rad*, the feedback regulators of ERK and calcium signaling, respectively. Here we studied FosB function by examining the gene expression profiles and the behavioral characteristics of *FosB* (–/–) mice. We found that *FosB* (–/|–) mice exhibited not only decreased parenting but also decreased infanticide compared with (+/) littermates. We then performed gene expression analysis in the MPOA of *FosB* (–/–) mice compared with the wild-type littermates. We found up-regulation of glial fibrillary acidic protein *(GFAP)*, *C4*, and *Ela1* mRNA in the MPOA of *FosB* (–/–) mice; all of these gene products were implicated in general neuropathological conditions. Immunohistochemical analysis showed that up-regulation of GFAP was not restricted to MPOA but extended throughout the forebrain, including the cerebral cortex and striatum. Such pervasive GFAP up-regulation suggested that *FosB* (–/–) mice might have other behavioral abnormalities than nurturing. Indeed, these mice showed a clear alteration in emotionality, detected by the acoustic startle, elevated plus maze, and passive avoidance tests. These results suggest that *FosB* (–/–) mice have broader neurobehavioral dysfunctions, with which the nurturing defect might share the common mechanism.

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Abbreviations: ANOVA, analysis of variance; AOR, adjusted odds ratio; PPI, prepulse inhibition; CI, confidence interval; CNS, central nervous system; CORT, corticosterone; df, degree of freedom; ERK, extracellular signal-regulated kinase; FC, fold change; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAP, glial fibrillary acidic protein; IHC, immunohistochemical; GLM, generalized linear model; MPOA, medial preoptic area; MPOAdl, dorsolateral part of the MPOA; MTL, Montreal; PBS, sodium phosphate-buffered saline; qRT-PCR, quantitative real-time polymerase chain reaction; RIKEN, Rikagaku Kenkyuu Sho (The institute of Chemical and Physical Research)

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1. Introduction

Childhood abuse and neglect become risk factors for a wide range of mental disorders such as depression, anxiety disorders, and personality disorders (Heim and Nemeroff, 2001). Understanding the molecular, cellular, and neurobiological basis of parental behavior would be helpful for the prevention of child maltreatment. Because parental care, such as nursing, is essential for all mammalian infants to grow, the basic brain mechanism of parenting should be conserved among mammals. Therefore, we can expect to gain our knowledge about human parental behavior from basic research using other mammalian models.

The neural mechanism of parental behavior has been studied most extensively in rodents (Krasnegor and Bridges, 1990; Numan and Insel, 2003). Accumulating evidence supports the idea that the medial preoptic area (MPOA) of the hypothalamus plays a key role in the expression of parental retrieving behavior (i.e., gathering scattered pups into the nest) (Morgan et al., 1999; Numan, 1994). When a rat or mouse takes care of pups, c-Fos, which is an important molecule for AP-1 transcription activity (Herdegen and Leah, 1998), is induced in MPOA