FosB is essential for the enhancement of stress tolerance and antagonizes locomotor sensitization by ΔFosB

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Abstract

BACKGROUND:

Molecular mechanisms underlying stress tolerance and vulnerability are incompletely understood. The fosB gene is an attractive candidate for regulating stress responses, because ΔFosB, an alternative splice product of the fosB gene, accumulates after repeated stress or antidepressant treatments. On the other hand, FosB, the other alternative splice product of the fosB gene, expresses more transiently than ΔFosB but exerts higher transcriptional activity. However, the functional differences of these two fosB products remain unclear.

METHODS:

We established various mouse lines carrying three different types of fosB allele, wild-type (fosB(+)), fosB-null (fosB(G)), and fosB(d) allele, which encodes ΔFosB but not FosB, and analyzed them in stress-related behavioral tests.

RESULTS:

Because fosB(+/d) mice show enhanced ΔFosB levels in the presence of FosB and fosB(d/d) mice show more enhanced ΔFosB levels in the absence of FosB, the function of FosB can be inferred from differences observed between these lines. The fosB(+/d) and fosB(d/d) mice showed increased locomotor activity and elevated Akt phosphorylation, whereas only fosB(+/d) mice showed antidepressive-like behaviors and increased E-cadherin expression in striatum compared with wild-type mice. In contrast, fosB-null mice showed increased depression-like behavior and lower E-cadherin expression.

CONCLUSIONS:

These findings indicate that FosB is essential for stress tolerance mediated by ΔFosB. These data suggest that fosB gene products have a potential to regulate mood disorder-related behaviors.

Additional Information:

Epilepsy and depression show a high rate of comorbidity, making accurate diagnosis and resulting treatment of the conditions problematic. Therefore an increased understanding of the genetic and molecular basis for this comorbidity is of great value to the diagnosis and therapy of both disorders. Evidence suggests that adult hippocampal neurogenesis is associated with both depression and epilepsy. We reported that *fosB*-null mice exhibit depressive-like behaviors in the paper published in *Biological Psychiatry* 70(5):487-495, 2011. However, it has not yet been determined if the *fosB* gene also plays a role in epilepsy with depression, and/or adult hippocampal neurogenesis.

We have demonstrated that *fosB* products are expressed in neural progenitors of the dentate gyrus, as well as mature hippocampal neurons (1, 2), and that *fosB*-null mice display spontaneous epilepsy and impaired neurogenesis in the adult hippocampus (2). Moreover, microarray analysis shows that genes related to neurogenesis, depression and epilepsy are altered in the hippocampus of *fosB*-null mice (2). Thus, the *fosB*-null mouse is the first animal model to provide insight into the genetic and molecular basis of the comorbidity between depression and epilepsy with abnormal neurogenesis, all of which are caused by loss of a single gene, *fosB*. It will be important to determine if alterations in the *fosB* gene, or its expression, are associated with these disorders in humans. Consequently, *fosB* alterations may prove to be important for the diagnosis and therapy of these complicated disorders.

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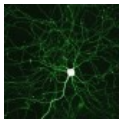

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