Dual mkk4 and mkk7 gene deletion in adult mouse causes an impairment of hippocampal immature granule cells

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Abstract
(1) Background: The c-Jun-NH2-terminal protein kinase (JNK) is a mitogen-activated protein kinase involved in regulating physiological processes in the central nervous system. However, the dual genetic deletion of Mkk4 and Mkk7 (upstream activators of JNK) in adult mice is not reported. The aim of this study was to induce the genetic deletion of Mkk4/Mkk7 in adult mice and analyze their effect in hippocampal neurogenesis. (2) Methods: To achieve this goal, Actin-Cre^{ERT2} (Cre$^{+/-}$), Mkk4$^{flox/flox}$, Mkk7$^{flox/flox}$ mice were created. The administration of tamoxifen in these 2-month-old mice induced the gene deletion (Actin-Cre^{ERT2} (Cre$^{+/-}$), Mkk4$^{\Delta/\Delta}$, Mkk7$^{\Delta/\Delta}$ genotype), which was verified by PCR, Western blot, and immunohistochemistry techniques. (3) Results: The levels of MKK4/MKK7 at 7 and 14 days after tamoxifen administration were not eliminated totally in CNS, unlike what happens in the liver and heart. These data could be correlated with the high levels of these proteins in CNS. In the hippocampus, the deletion of Mkk4/Mkk7 induced a misalignment position of immature hippocampal neurons together with alterations in their dendritic architecture pattern and maturation process jointly to the diminution of JNK phosphorylation. (4) Conclusion: All these data supported that the MKK4/MKK7–JNK pathway has a role in adult neurogenic activity.

Author keywords
Cre-LoxP; DCX; Hippocampus; MKK4; MKK7; PJNK