The Shh Signaling Pathway is Upregulated in Multiple Cell Types in Cortical Ischemia and Influences the Outcome of Stroke in an Animal Model

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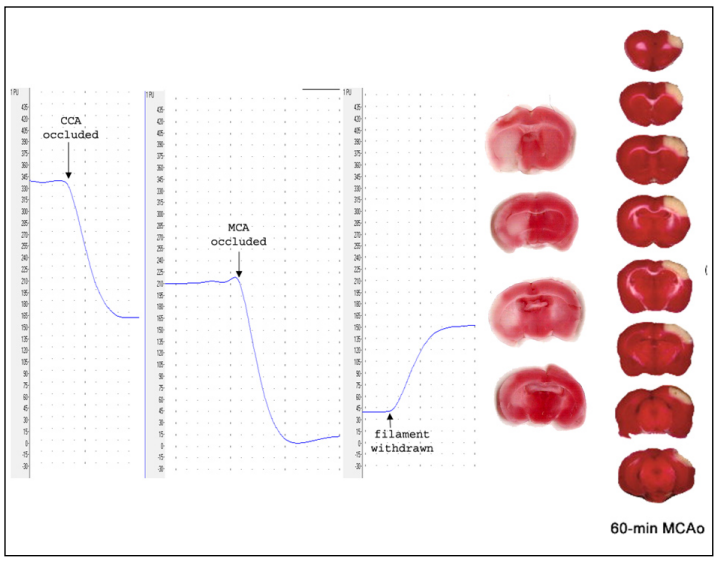
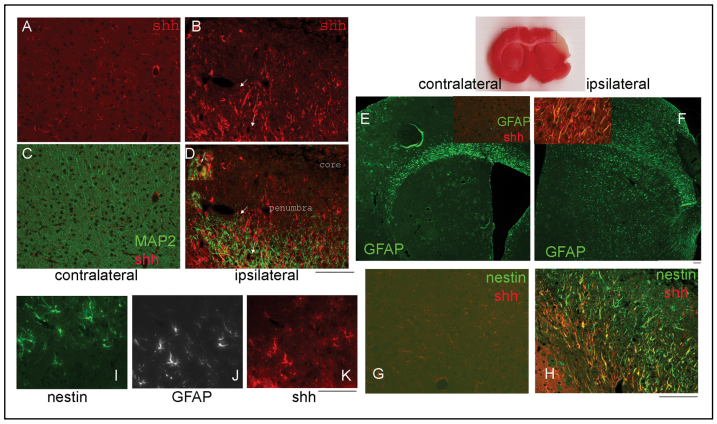
Introduction

Recently the sonic hedgehog (shh) signaling pathway has been shown to play an important role in regulating the repair and regenerative responses to brain injury, including ischemia. However, the precise cellular components that express and upregulate shh gene and the cellular components that respond to shh signaling remain to be identified.

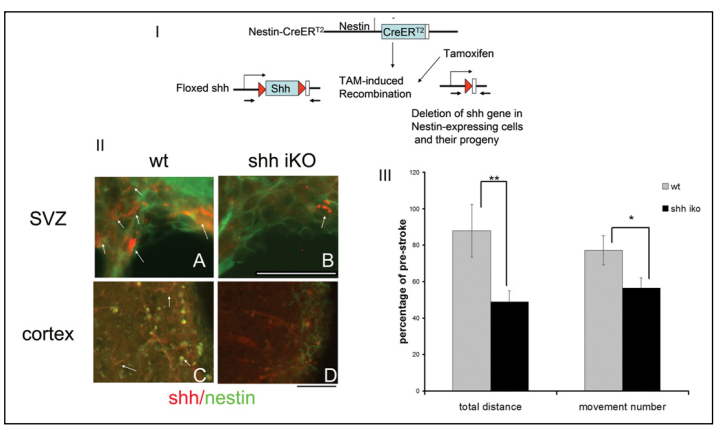


Methods

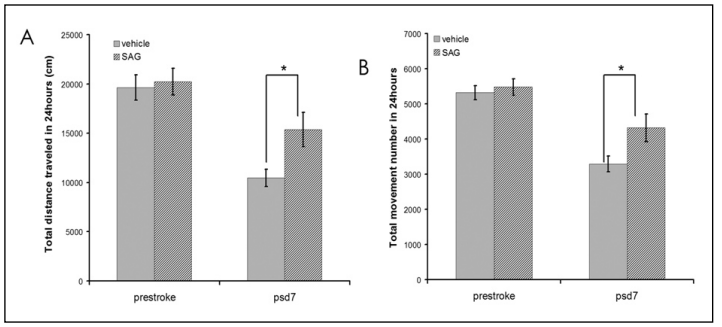
A cortical ischemic stroke model was utilized in a series of mice in which conditional deletion of the shh gene was accomplished. Behavioral deficits were analyzed and compared to animals treated with post-stroke shh signaling agonist treatment to placebo. Cortical ischemia was accomplished via an middle cerebral artery occlusion model. Laser doppler flowmetry is used to monitor cerebral blood supply during proximal and distal MCA occlusion. Two days after MCA ligation, animal brains are subjected to 2% triphenyltetrazolium chloride (TTC) staining.



Results: Distal MCAo induces shh expression in the cortical ischemic site. A and C) expression of shh and MAP2 in the contralateral side cortex. B and D) shh expression in the penumbra of the ipsilateral cortex. Arrow and inset showing shh+/MAP2+ cells. E) expression of shh and GFAP in the contralateral side cortex and striatum. F) upregulation of GFAP in both cortex and striatum in the ipsilateral side. Inset showing shh+/GFAP+ cells in cortex. G) basal expression of shh and minimal or no expression of nestin in contralateral side of cortex, H) shh and nestin upregulation near the penumbra in ipsilateral cortex. I,J.K) staining of nestin/GFAP/shh on same section. Scale bar = 100um



Conditional deletion of the shh gene both in SVZ and in penumbra nestin-expressing cells lead to



more severe behavioral deficits in shh iKO mice after stroke (total distance traveled= 87.9+14.6% of prestroke level for wt mice and 48.9+6.3% of prestroke level for shh iKO mice, p=0.020; Total movement number= 67.7+6.8% of prestroke level in wt and 50.0+8.5% in shh iKO mice, p=0.014). In contrast, animals given post-stroke treatment of shh signaling agonist demonstrated less deficits in behavioral function compared to vehicle treated mice.

Learning Objectives

Our findings suggest shh signaling pathway is important in pathological development and recovery in stroke animals. Modulation of shh pathway might provide a novel therapeutic strategy.

Conclusions

-shh signaling is upregulated in ischemic brain area in multiple cell types.
-Inducible conditional deletion of shh gene in SVZ and cortical nestin-expressing cells results in more severe behavioral deficits after cortical stroke.
-Post-stroke treatment of shh agonist results in less behavioral deficits in stroke mice.

References

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