Wnt-3A and Sonic Hedgehog Signaling Pathways Underlie Melanocortin-Induced Neurogenesis in Stroke Conditions

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We previously found that, in stroke condition, melanocortin MC_4 receptor agonists induce neuroprotection and neurogenesis with subsequent long-lasting functional recovery (Giuliani et al. 2006, 2011, 2012). Here we investigated the molecular mechanisms underlying melanocortin-induced neurogenesis. Gerbils were subjected to transient global cerebral ischemia, then they were treated every 12 h, and until sacrifice, with 5-bromo-2'-deoxyuridine (BrdU; to label proliferating cells), and the melanocortin analog [Nle^4,D-Phe^7]α-melanocyte-stimulating hormone (NDP-α-MSH) or saline. NDP-α-MSH increased hippocampus dentate gyrus (DG) expression of Wnt-3A, ß-catenin, Sonic hedgehog (Shh), Zif268, interleukin-10 (IL-10) and doublecortin (DCX), as detected at days 3, 6 and 10 after the ischemic insult. Further, an elevated number of BrdU immunoreactive cells was found at days 3 and 10, and an improved histological picture with reduced neuronal loss at day 10, associated with learning and memory recovery. Pharmacological blockade of the Wnt-3A/ß-catenin and Shh pathways, as well as of melanocortin MC_4 receptors, prevented all effects of NDP-α-MSH. These data indicate that, in experimental brain ischemia, melanocortin MC_4 receptor agonist-induced neurogenesis is mediated by the canonical Wnt-3A/ß-catenin and Shh signaling pathways. Activation of these pathways is associated with up-regulation of the repair factor Zif268 and the neurogenesis facilitating factor IL-10, and it seems to address mainly towards a neuronal fate, as indicated by the increase in DCX positive cells. These findings could have important clinical implications.

References

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