Optogenetic Stimulation of Neural Grafts Enhances Neurotransmission and Downregulates the Inflammatory Response in Experimental Stroke Model.

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Abstract:

Compelling evidence suggests that transplantation of neural stem cells (NSCs) from multiple sources ameliorates motor deficits after stroke. However, it is currently unknown to what extent the electrophysiological activity of grafted NSC progeny participates in the improvement of motor deficits and whether excitatory phenotypes of the grafted cells are beneficial or deleterious to sensorimotor performances. To address this question, we used optogenetic tools to drive the excitatory outputs of the grafted NSCs and assess the impact on local circuitry and sensorimotor performance. We genetically engineered NSCs to express the Channelrhodopsin-2 (ChR2), a light-gated cation channel that evokes neuronal depolarization and initiation of action potentials with precise temporal control to light stimulation. To test the function of these cells in a stroke model, rats were subjected to an ischemic stroke and grafted with ChR2-NSCs. The grafted NSCs identified with a human-specific nuclear marker survived in the peri-infarct tissue and coexpressed the ChR2 transgene with the neuronal markers TuJ1 and NeuN. Gene expression analysis in stimulated versus vehicle-treated animals showed a differential upregulation of transcripts involved in neurotransmission, neuronal differentiation, regeneration, axonal guidance, and synaptic plasticity. Interestingly, genes involved in the inflammatory response were significantly downregulated. Behavioral analysis demonstrated that chronic optogenetic stimulation of the ChR2-NSCs enhanced forelimb use on the stroke-affected side and motor activity in an open field test. Together these data suggest that excitatory stimulation of grafted NSCs elicits beneficial effects in experimental stroke model through cell replacement and non-cell replacement, anti-inflammatory/neurotrophic effects.

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