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Neurovascular unit remodelling in the subacute stage of stroke recovery

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Abstract

Brain plasticity following focal cerebral ischemia has been observed in both stroke survivors and in preclinical models of stroke. Endogenous neurovascular adaptation is at present incompletely understood yet its potentiation may improve long-term functional outcome. We employed longitudinal MRI, intracranial array electrophysiology, Montoya Staircase testing, and immunofluorescence to examine function of brain vessels, neurons, and glia in addition to forelimb skilled reaching during the subacute stage of ischemic injury progression. Focal ischemic stroke (~100mm3 or ~20% of the total brain volume) was induced in adult Sprague-Dawley rats via direct injection of endothelin-1 (ET-1) into the right sensori-motor cortex, producing sustained impairment in left forelimb reaching ability. Resting perfusion and vascular reactivity to hypercapnia in the peri-lesional cortex were elevated by approximately 60% and 80% respectively seven days following stroke. At the same time, the normal topological pattern of local field potential (LFP) responses to peripheral somatosensory stimulation was abolished and the average power of spontaneous LFP activity attenuated by approximately 50% relative to the contra-lesional cortex, suggesting initial response attenuation within the peri-infarct zone. By 21 days after stroke, perilesional blood flow resolved, but peri-lesional vascular reactivity remained elevated. Concomitantly, the LFP response amplitudes increased with distance from the site of ET-1 injection, suggesting functional remodelling from the core of the lesion to its periphery. This notion was further buttressed by the lateralization of spontaneous neuronal activity: by day 21, the average ipsi-lesional power of spontaneous LFP activity was almost twice that of the contra-lesional cortex. Over the observation period, the peri-lesional cortex exhibited increased vascular density, along with neuronal loss, astrocytic activation, and recruitment and activation of microglia and macrophages, with neuronal loss and inflammation extending beyond the peri-lesional cortex. These findings highlight the complex relationship between neurophysiological state and behaviour and provide evidence of highly dynamic functional changes in the peri-infarct zone weeks following the ischemic insult, suggesting an extended temporal window for therapeutic interventions.

Keywords: focal ischemia, endothelin-1, preclinical stroke modelling, magnetic resonance imaging, arterial spin labelling, Montoya reaching task, intra-cranial electrophysiology, immunofluorescence
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