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RESEARCH ARTICLE

Postischemic Brain Infiltration of Leukocyte Subpopulations Differs among Murine Permanent and Transient Focal Cerebral Ischemia Models

Wei Zhou[1]*; Arthur Liesz[1]*; Henrike Bauer[2]; Clemens Sommer[2]; Bernd Lahrmann[3]; Nektarios Valous[3]; Niels Grabe[3]; Roland Veltkamp[1]

[1] Department of Neurology, University Heidelberg, Heidelberg.
[2] Department of Neuropathology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz.
[3] Hamamatsu Tissue Imaging and Analysis center, BIOQUANT, University Heidelberg, Heidelberg, Germany.

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Corresponding author:
Roland Veltkamp, MD, Department of Neurology, University Heidelberg, INF 400, 69120 Heidelberg, Germany (E-mail: *roland.veltkamp@med.uni-heidelberg.de*

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* These authors contributed equally.

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Abstract

Cellular and humoral inflammations play important roles in ischemic brain injury. The effectiveness of immunomodulatory therapies may critically depend on the chosen experimental model. Our purpose was to compare the post-ischemic neuroinflammation among murine permanent and transient middle cerebral artery occlusion (MCAO) models. Permanent MCAO was induced by transtemporal electrocoagulation and 30 minutes or 90 minutes transient MCAO was induced by intraluminal filament in C57BL/6 mice. Infiltration of leukocyte subpopulations was quantified by immunohistochemistry and fluorescence-activated cell sorting. Cerebral cytokine and adhesion molecule expression was measured by real-time polymerase chain reaction (RT-PCR). Neutrophil infiltration was noted at 24 h after transient MCAO, but did not further increase until 5 days in the permanent MCAO model. Few T cells were observed in both MCAO models at 24 h, but permanent MCAO demonstrated much more infiltrating T cells at 5 days. Pronounced microglial activation was evident at 24 h and 5 days after permanent but not after transient MCAO. The number of invading NK cells and expression of MHCII on CD11b+ cells did not differ among the three groups. Five days after MCAO, the expression of IL-1, TNF-α and IFN-γ and of the adhesion molecules ICAM-1 and VCAM-1 was significantly higher in the permanent than in the transient MCAO groups. Cellular and humoral inflammation differs substantially among commonly used MCAO models. Neuroinflammation is more pronounced after permanent electrocoagulatory MCAO compared with 30 minutes and 90 minutes filament-MCAO.

INTRODUCTION

Brain damage after ischemic stroke results from a variety of parallel and sequential processes, including excitotoxicity, calcium dysregulation, oxidative stress, inflammation and pro-apoptotic stimuli (26). Inflammatory mechanisms and the interaction of activated immune cells with the ischemic brain tissue are currently under intensive investigation because they are believed to contribute substantially to secondary brain damage and potential repair mechanisms (12). Moreover, their delayed kinetics makes them amenable to therapeutic interventions. Key features of the neuroimmunological response to brain ischemia are early microglial activation (21) and subsequent recruitment of circulating leukocytes to the ischemic brain (12, 22). Indeed, several cells residing physiologically in the brain, including microglia, astrocytes, neurons and endothelial cells, are activated after ischemia and secrete a plethora of pro-inflammatory mediators, including IL-1β and TNF-α (3, 30). These mediators facilitate adhesion by endothelial activation and migration of circulating leukocytes to the ischemic brain (37).

The failure of multiple therapeutic strategies for stroke patients despite very promising preclinical data has prompted an intensive search for underlying reasons (9). An important possible explanation is that many key targets, including inflammatory mediators, had a different and sometimes even opposing impact on outcome in different phases after ischemia (28, 32, 41). Moreover, considerable discrepancies become evident when different animal models of ischemia are investigated. Because pathophysiological processes differ depending on early reperfusion of the ischemic tissue, the STAIR committee recommends that a new therapy is tested both in permanent and transient animal models (1).

Although modulation of immune cells either by depletion (6, 18, 39), systemic arrest or attenuated cerebral immigration (19, 36, 40) is a promising target for brain protection in experimental studies, the basic immunological processes in different ischemia models require a better description and understanding. For example, the effectiveness of endogenous and therapeutic immunomodulation depended at least in part on the animal model under investigation in two of our recent extensive studies (17, 19). Interestingly, anti-inflammatory strategies were more effective in