Leukocytes, Macrophages and Secondary Brain Damage Following Cerebral Ischemia

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Summary

The involvement of white blood cells in microvascular derangement as a cause of secondary brain damage following cerebral ischemia is reviewed. Relevant data from the literature are arranged in the chronological sequence of the microvascular derangement of the brain that occurs after cerebral arterial occlusion (as based on our own experimental observations). The inflammatory processes which appeared to be elicited by polymorphonuclear leukocytes (PMNL) in the ischemic region of the brain may begin with adhesion of PMNLs to endothelial cells, followed by blood-brain barrier disruption, transudation/exudation, edema, necrosis, and scar formation. Stimulated by cytokines released from damaged neurons and axons, two types of macrophages (ameboid and ramified) appear, increase in number in the ischemic lesion, and engulf the debris of dead neurons, degenerated axons. Further, macrophages may release cytokines which stimulate healing processes, such as astroglial proliferation and revascularization, and release neurotoxins which could gradually kill surviving neurons. Even under such circumstances, individual leukocytes/macrophages are well regulated by specific mediators/cytokines. An urgent task is thus to find ways of controlling these key mediators/cytokines to reduce the inflammatory process and the extent of neuronal death for attenuating the secondary brain damage, without altering their beneficial effects.

Keywords: Microglia; ischemic microvascular derangement; immune reaction; inflammatory changes.

Introduction

In a variety of brain disorders, including ischemic stroke, the extent of irreversible tissue damage appears to be dependent largely on the degree of terminal vascular insufficiency in the injured region. The development of such microcirculatory derangement might well represent a final common pathway, which could account for the augmentation of injury by many non-specific factors. This article is a mini-review on the involvement of white blood cells in secondary brain damage. Up-to-date descriptions of relevant topics have appeared recently in two excellent overviews: one was provided by Kochanek and Hallenbeck [25] entitled “Polymorphonuclear leukocytes and monocytes/macrophages in the pathogenesis of cerebral ischemia and stroke”, and the other by del Zoppo and Garcia [8] entitled “Polymorphonuclear leukocyte adhesion in cerebrovascular ischemia”. The present review attempts to provide a broad outline of the white cell involvement in correlation with the various stages of ischemic microvascular derangement occurring in the brain. The overall framework for such microvascular derangement (Fig. 1) is based on observations [45,46,52] obtained by our photoelectric method [51,53] and cranial window technique applied to the cat cerebral cortex which was subjected to ischemia by middle cerebral artery occlusion (MCAO). Details of the inflammatory microvascular derangement relate to the work of Kulka [26], who examined microvascular changes in the ear of rabbits which sustained cold injury. Data on the involvement of polymorphonuclear leukocytes (PMNL) and monocytes/macrophages in ischemic tissue of the brain were collected from the literature, and have been arranged arbitrarily according to each stage of the cerebral microvascular derangement.

Microvascular Derangement

Figure 1 illustrates the sequential stages of the ischemic microvascular derangement during evolution of an infarct following cerebral arterial occlusion.

Stage 0: The scheme at the top left of Fig. 1 shows a microvascular unit consisting of an artery-microvascular-vein.
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Stage 1: Upon MCAO, the microvasculature shrinks. After stopping momentarily, the flow resumes sooner or later, and tends to recover in accordance with the development of collateral channels [45,46,52]. Leukocytes have been shown to participate in flow resistance through newly developing collateral channels even at an early stage due probably to their cellular shape [46,48,54]. Reperfusion by releasing the MCAO was found by Tanahashi [43] to produce various degrees of reactive hyperemia depending on the timing. He observed no change in CBV (cerebral blood volume) upon reopening within 1 min, and increases in CBV upon reopening after 1 min. Reperfusion produced multimodal individual time courses ranging from recovery after marked reactive hyperemia to severe postischemic hypoperfusion. No reflow was occasionally observed [43].

Stage 2: The CBV subsequently exceeds the preocclusive level (low perfusion hyperemia) due mainly to venous dilatation [24]. Direct observation reveals various changes in arterial diameter: simultaneous arterial dilation-constriction. This suggests a partial loss of vascular integrity, and a disruption of matching between flow and metabolism (e.g. misery perfusion syndrome).

Stage 3: By accumulation of surrounding extracellular fluid, the glial cells start to swell (cytotoxic edema) due to elevation of the osmotic potential in the cells (more than 200 mmHg) [50] induced by cell membrane damage. The neurons exhibit only slight swelling or even shrinkage due probably to partial rupture of the thin cell membrane [49]. The glial cells expand pushing aside surrounding structures and compressing the microvasculature. The blood-brain barrier (BBB) is disrupted with a delay of several hours after the occlusion. An increase in fluid permeability at the arterial side and absorption failure at the venous side of the microvasculature facilitate fluid retention in the tissue. Widening of the intercapillary distance, compression of vessels, focal leakage of plasma indicators, foggy, dark red areas of extravasated red cells, and marked aggregation of red cells are commonly observed. The experiments of postischemic hypoperfusion following reperfusion usually ran a similar course to that illustrating microvascular derangement after permanent occlusion.