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Peripheral to central: Organ interactions in stroke pathophysiology

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ABSTRACT

Stroke is associated with a high risk of disability and mortality, and with the exception of recombinant tissue-type plasminogen activator for acute stroke, most treatments have proven ineffective. Clinical translation of promising experimental therapeutics is limited by inadequate stroke models and a lack of understanding of the mechanisms underlying acute stroke and how they affect outcome. Bidirectional communication between the ischemic brain and peripheral immune system modulates stroke progression and tissue repair, while epidemiological studies have provided evidence of an association between organ dysfunction and stroke risk. This crosstalk can determine the fate of stroke patients and must be taken into consideration when investigating the pathophysiological mechanisms and therapeutic options for stroke. This review summarizes the current evidence for interactions between the brain and other organs in stroke pathophysiology in basic and clinic studies, and discusses the role of these interactions in the progression and outcome of stroke and how they can direct the development of more effective treatment strategies.

1. Introduction

Stroke is a neurological impairment attributed to acute focal injury in the central nervous system with a vascular origin, and includes cerebral ischemia, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Although it is a major cause of death and disability worldwide, there is no singularly effective treatment for stroke to date. Recombinant tissue-type plasminogen activator is currently the only agent recommended for treatment of ischemic stroke (F. Chen et al., 2014; Jauch et al., 2013). Most therapies that have appeared promising in experimental models have failed to produce results in patients. One reason for this is that the pathophysiological mechanisms underlying stroke are complex and have a global impact. The normal functioning of the human body depends on the interaction of all organs, and injury to one can impact the others and produce compensatory effects or secondary injury. Conversely, severe brain injury resulting from stroke, trauma, or infection can lead to multiple organ failure.

Interactions between peripheral organs can also exacerbate brain damage and affect the recovery of stroke patients. For instance, these patients are more likely to have chronic kidney disease (CKD), which is secondary to hypertension, small vessel disease associated with diabetes, and cardiovascular disease (Nongnuch et al., 2014). The present review presents evidence for crosstalk between the brain and other organs and discusses what is known about the clinical manifestations, pathophysiology, mechanisms, and treatment of stroke.

2. Brain and spleen

The brain and immune system interact during each stage of stroke. The spleen is the largest secondary immune organ in the body and functions in both innate and adaptive immunities. This section discusses how immune cells in the spleen are modulated by and recruited to the brain and contributes to neuroinflammatory damage and brain tissue repair (Fig. 1).

2.1. Splenic injury induced by stroke

Cerebral ischemia affects the total number of spleen cells and lymphocyte population size and function. Transient splenic atrophy in experimental models of ischemic stroke is characterized by a reduction in spleen size, reduction in splenocyte number, and induction of apoptosis (Offner et al., 2006b). The decrease in the splenocyte population is accompanied by increased efflux of immune cells—such as natural killer cells, monocytes, and cluster of differentiation (CD)4^+ and $CD8^+$ T cells—from the spleen into the peripheral circulation (Offner et al., 2006b; Seifert et al., 2012). Spleen and blood B cell populations are markedly reduced in experimental stroke, which may compromise the functioning of the humoral immune system (Offner et al., 2006b). Released immune cells infiltrate into the ischemic brain and exacerbate brain injury by secreting proinflammatory cytokines and chemokines (Ahmad and Graham, 2010; Offner et al., 2006a,b; Seifert et al., 2012).

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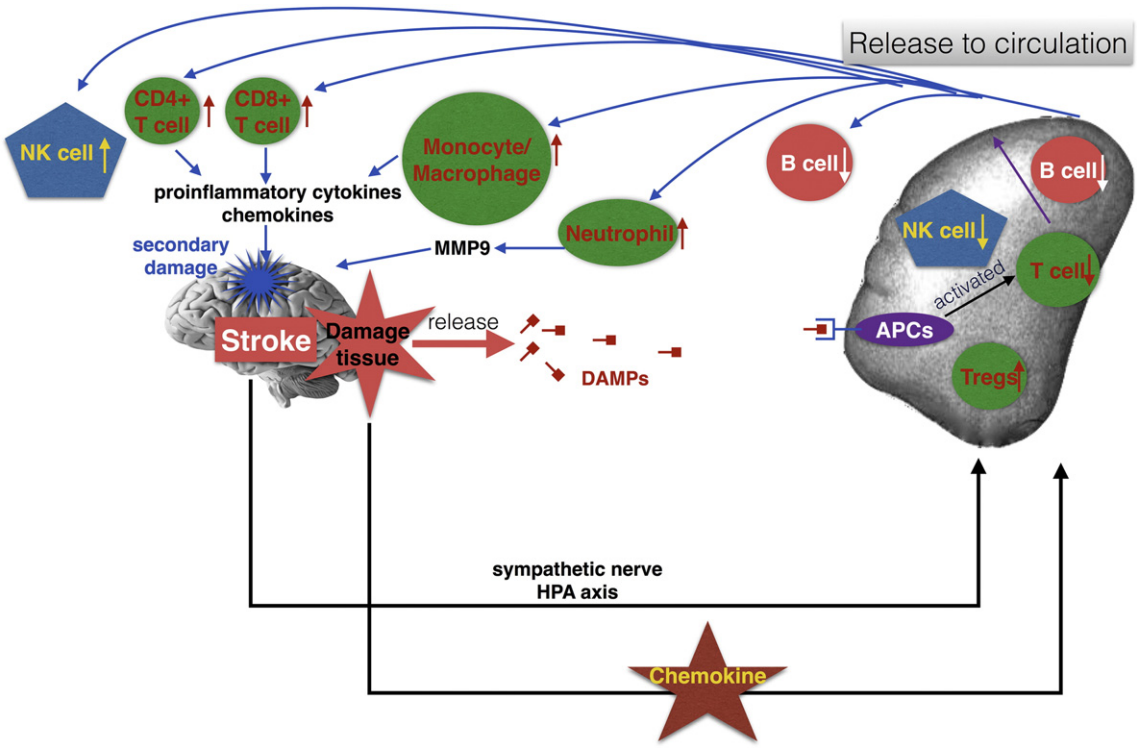

Fig. 1. Interactions between the brain and spleen in stroke pathophysiology. Black arrows indicate the effects of stroke on the spleen; blue arrows indicate the contribution of the spleen to stroke. APC, antigen-presenting cell; DAMP, danger-associated molecular pattern; NK, natural killer cell; HPA, hypothalamus–pituitary–adrenal axis; Treg: regulatory T cell.

Thus, splenic atrophy results not only from splenocyte apoptosis but also from the migration of cells from the spleen to the injured brain via the circulation.

In the early phase of ischemic injury, the immune system is activated by endogenous stress signals known as danger-associated molecular patterns (DAMPs) (Matzinger, 2002a,b) that include adenosine triphosphate, nicotinamide adenine dinucleotide, heat shock protein, and high-mobility group box 1 protein released from damaged cerebral tissue (Magnus et al., 2012). DAMPs are recognized by antigen-presenting cells and link innate and adaptive immune responses, leading to the recruitment of immune cells from the spleen to the brain (Famakin, 2014). Moreover, chemokines secreted from brain cells in the infarct area can travel through the blood and recruit immune cells from the spleen back to the ischemic lesion (Gan et al., 2014; Zhang et al., 2014). Additionally, the brain and spleen communicate via the activated sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis, which induces the release of catecholamines and steroids that alter spleen function (Schulze et al., 2014). Thus, the activation of the autonomic nervous system and HPA axis following stroke can trigger an efflux of immune cells from the spleen to the site of brain injury via DAMPs and chemokines derived from injured brain tissue.

2.2. Contribution of immunomodulatory therapies to stroke

Splenectomy has been proposed as a prophylactic intervention for cerebral ischemia (Izci, 2010). Evidence from rats has shown that splenectomy performed before cerebral ischemia can reduce infarct volume and decrease the numbers of activated microglia, macrophages, and neutrophils in brain tissue (Ajmo et al., 2008). However, it is unclear whether splenectomy has adverse secondary effects, given the role of the spleen in sustaining normal immune function. The immune response changes as stroke progresses; therefore, pharmacological and cell-based therapies that target the interaction between the brain and peripheral immune system have potential for stroke treatment (An et al., 2014; Pennypacker, 2014).

Immunomodulatory therapies involving specific immune cells are an alternative to splenectomy. Regulatory T cells (Tregs) and interleukin 10-producing regulatory B cells are specialized lymphocytes that exert neuroprotection following cerebral ischemia (Bodhankar et al., 2013; Offner and Hurn, 2012). Intravenous delivery of spleen-derived Tregs protects against ischemia by suppressing neutrophil-derived matrix metallopeptidase 9 production (Li et al., 2013a) without exacerbating post-stroke immunosuppression (Li et al., 2013b). Splenic $CD19^{+}$ B cells relieve brain injury in mice by reducing inflammatory cell infiltration in the ischemic brain, and also block ischemia-induced splenic atrophy, inhibit the pro-inflammatory activities of T cells and monocytes in the periphery, and enhance peripheral Treg and programmed death 1 expression in mice after middle cerebral artery occlusion (MCAO) (Bodhankar et al., 2013).

Most experimental and clinical studies on immune responses during stroke have focused on ischemic stroke; there is comparatively little information on hemorrhagic stroke, which has a distinct pathogenesis. In clinical trials, pharmacological intervention with fingolimod has been used to attenuate the immune response after ischemic stroke to minimize injury. In an MCAO model, cellular immune therapy has demonstrated effective neuroprotection without immunosuppression. An optimal pharmacological or cell-based intervention is one that can mitigate the splenic response to stroke and prevent neurodegeneration induced by the immune response without exacerbating post-stroke immunosuppression.

3. Brain and heart

The association between the brain and heart was first observed by topographic electrocardiography (Remond et al., 1957); later studies showed that cerebral vascular disorder induced changes in the electrocardiogram (Manning and Wallace, 1968). Since then, the interaction