Brain-Spleen Inflammatory Coupling: A Literature Review

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Recent evidence suggests a link between brain injury and the autonomic release of pro-inflammatory cytokines by resident macrophages in the spleen. This phenomenon, termed “brain-spleen inflammatory coupling,” has garnered attention from scientific and medical communities interested in developing novel treatments for traumatic brain injury (TBI). Cholinergic stimulation of the α7-subunit nicotinic acetylcholine receptor (α7NAchR) on splenic macrophages has been shown to inhibit their release of pro-inflammatory cytokines. This inhibition, mediated by the parasympathetic nervous system, has been shown to improve outcomes in animal models of sepsis, stroke, and TBI. As evidence of a beneficial role of splenic inhibition grows, new treatment strategies might be applied to many medical conditions involving neuroinflammation, a process that contributes to further neurological deterioration.

Located within the peritoneal cavity, the spleen monitors the circulation and removes foreign material in the blood that potentially threatens homeostasis. As the primary mediator of the mononuclear phagocyte system, splenic leukocytes in the red and white pulp prevent devastating infections by encapsulated bacteria and intracellular pathogens. It comes as a surprise, then, that the same organ that plays such a crucial role in preventing infection may simultaneously exacerbate the inflammatory response after brain injury. With this in mind, a fresh body of evidence has suggested a link between brain injury and the autonomic release of inflammatory cytokines by macrophages in the spleen (Figure 1). This phenomenon, termed “brain-spleen inflammatory coupling,” has garnered attention from scientific and medical communities seeking new treatments for ischemic and traumatic brain injuries.

Physicians and scientists readily acknowledge that the intricate mechanisms driving acute inflammation remain a mystery. Dr. Niels Jerne, a Nobel Prize–winning immunologist, once described the immune system as a network of interacting cells and antibodies, analogous to the communication among neurons, glia, and their neurotransmitters in the central nervous system (CNS) (Jerne, 1985). For decades, these systems were thought to function independently; however, scientists have discovered several physiologic processes linking them. In the 1980s, Damjanovich and colleagues discovered that lymphocytes possess excitable membranes that behave similarly to those of neurons (Damjanovich et al., 1989). Leukocytes have also been shown to express 2-adrenergic receptors, indicating they are sensitive to changes in autonomic output (Bruynzeel, 1984). These findings provided the framework for the development of theories describing neurotransmitter control of inflammation and the link between emotional states and immune status.

In a broad sense, inflammation is a paradox of complexity. For example, the CNS was once considered an “immune privileged” site due to the lack of sentinel lymphocytes in the brain (Medawar, 1948; Barker and Billingham, 1977; Prendergast and Anderton, 2009) and the apparent lack of cellular transport and selective molecular permeability through the blood-brain barrier. While this property holds true under normal physiologic conditions, acute injuries to the brain ignite a strong inflammatory response by endogenous neurons, astrocytes, and microglia. In addition, circulating lymphocytes and macrophages are found within the brain parenchyma even in the absence of damage to the blood-brain barrier (Dickson et al., 1993). Outside the brain, the systemic inflammatory response is often a normal reactive process driven by a vast array of cytokines, chemokines, stress hormones, and stereotypical cellular and vascular responses. However, when inflammation is left unchecked, it can be more deleterious than the primary injury itself. Immune cells must allow the body to respond properly to injury, but at the same time prevent collateral damage to uninjured cells.

This dichotomy is exemplified in the CNS, where a robust inflammatory response is mounted after ischemic and traumatic injury. Unfortunately, this often leads to significant neuronal death and edema, which can be fatal. While the primary and immediate consequences of mechanical trauma to neurons cannot be undone, secondary pathological sequelae, specifically brain swelling and inflammation, are considered targets for therapeutic intervention.

Proponents of the brain-spleen inflammatory coupling hypothesis point to the physiologic phenomenon of post-traumatic changes in autonomic output as the main mechanism driving the coupling (Borovikova et al., 2000; Tracey, 2002). Immediately after injury, damaged neurons and surrounding glia release locally acting, pro-inflammatory cytokines, which stimulate the posterior hypothalamus to increase systemic sympathetic output. This leads to numerous hormonal and systemic responses such as catecholamine release from the adrenal medulla, peripheral vasoconstriction, and positive chrono- and ionotropic stimulation of the heart. The cumulative effects of these changes contribute to the “fight-or-flight” response. Several authors have demonstrated that resident macrophages in the spleen and liver also express adrenergic/cholinergic receptors and...
are therefore sensitive to changes in autonomic output (Wang et al., 2003; Ajmo et al., 2009; Rosas-Ballina and Tracey, 2009). After acute brain injury, splenic macrophages are adrenergically stimulated to secrete massive amounts of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) into the peripheral circulation (Tracey, 2002). These inflammatory cytokines eventually reach and penetrate the disrupted blood-brain barrier and enhance the post-traumatic immunologic response.

Increased sympathetic tone leads to the release of pro-inflammatory cytokines and, conversely, this predicts that increased parasympathetic tone, or cholinergic stimulation, would be anti-inflammatory, perhaps by its effects on splenic macrophages (Vida et al., 2011). In 2000, Borovikova and colleagues demonstrated that direct electrical stimulation of the vagus nerve lowered the concentration of TNF-α in serum and prevented the progression of septic shock in rats during lethal endotoxemia (Borovikova et al., 2000). This was the first study to propose a pathway for CNS regulation of the immune response, or a “cholinergic anti-inflammatory pathway.” In 2002, Wang and colleagues determined that the nicotinic acetylcholine receptor α7 subunit (α7nAChR) was required for acetylcholine-mediated inhibition of mac-
roporphage TNF-α release (Wang et al., 2002). The highest concentrations of α7nAChR-macrophages were found in the liver and spleen.

Direct and indirect stimulation of nicotinic receptors have been shown to improve outcomes in animal models of sepsis (Wang et al., 2004; Huston et al., 2006; Pavlov et al., 2009). In 2009, Pavlov and colleagues demonstrated that oral administration of galantamine, a centrally acting acetylcholinesterase inhibitor, significantly reduced serum levels of TNF-α in rats (Pavlov et al., 2009). Galantamine indirectly increases vagal (cholinergic) stimulation of the α7nAChR, leading to this inhibition. Reduced serum levels of TNF-α were in turn proven to be protective in rats subjected to sepsis compared to untreated rats and α7nAChR-knockout rats treated with galantamine.

With parasympathetic attenuation of inflammation in mind, neuroscientists examined the anti-inflammatory effects of splenic inhibition in the context of ischemic and hemorrhagic stroke. A 2011 study using a middle cerebral artery occlusion model noted significantly reduced infarct size and improved survival in rats treated with 3,2,4 dimethoxybenzylidene, an agonist of the α7nACh receptor (Muhammad et al., 2011). Another recent study similarly demonstrated improved neurologic outcomes, reduced brain swelling, and decreased levels of inflammatory cytokines in a hemorrhagic stroke model using intraventricular muscarine, a selective vagal agonist (Lee et al., 2010). Furthermore, researchers at the University of South Florida noticed a greater than 80% decrease in infarct volume in rats splenectomized two weeks prior to permanent middle cerebral artery occlusion (Ajmo et al., 2008). Unlike the other studies demonstrating short-term improvements after injury, this study successfully demonstrated a long-term benefit from splenic inhibition.

In early 2011, researchers in China were the first to apply these principles to the treatment of experimental TBI. Li and colleagues successfully demonstrated that rats receiving immediate splenectomy after severe contusive brain injury had significantly reduced serum levels of pro-inflammatory cytokines, improved cognitive function, and decreased mortality compared with intact controls (Li et al., 2011). Although it is not practical to perform a splenectomy immediately after a head injury in a human subject, the authors of this study note that it might be warranted, when possible, to reduce the effects of secondary pathological sequelae. These results are consistent with the findings of the ischemic and hemorrhagic stroke studies, which further support the hypothesis that the spleen can exacerbate brain inflammation.

It should be mentioned that the administration of corticosteroids, which are potent anti-inflammatory agents, has not demonstrated positive outcomes after brain injury or stroke (Qizilbash et al., 2000; Edwards et al., 2005). For example, intravenous methyl prednisolone sodium succinate, a steroid that was once a mainstay therapy for TBI, was abandoned after being shown to worsen morbidity and mortality (Edwards et al., 2005). This suggests that the anti-inflammatory pathways affected by selective inhibition of brain-spleen coupling are more complex than merely the inhibition of pro-inflammatory cytokine release. Ajmo and colleagues hypothesize that the spleen responds to injury by transferring resident leukocytes into the vasculature, thus increasing the absolute number of immune cells in the peripheral circulation (Ajmo et al., 2008). These leukocytes eventually make their way to the brain, where they promote neuroinflammation. Thus, the prevention of leukocyte migration and cytokine release by cholinergic stimulation of the α7nAChR should lead to decreased morbidity and mortality after an acute brain injury (Ajmo et al., 2009).

Researchers and physicians who have taken note of this brain-spleen phenomenon are launching investigations into novel therapies for a wide range of degenerative conditions other than brain injury. One study revealed a contributing role of splenic macrophages in the development of Alzheimer’s disease (Subramanian et al., 2010). Outside the CNS, attenuation of brain-spleen coupling by cholinergic agonists could have potential for the treatment of rheumatoid arthritis (Bruchfeld et al., 2010). As evidence grows of a beneficial role of splenic inhibition, new treatment strategies can then be applied to many medical conditions.

CNS injuries from trauma and ischemia, such as TBI and stroke, remain among the leading causes of morbidity and mortality in developing nations around the world as well as in the United States (Faul et al., 2010; Maas et al., 2010). Therapies to reduce intracranial pressure, such as hyperventilation, barbiturate coma, and osmotic diuresis, are often used supportively to treat TBI patients. However, therapeutic interventions such as decompressive craniectomy, insulin, hypothermia, and corticosteroid administration remain controversial (Edwards et al., 2005; Godoy et al., 2010; Clifton et al., 2011; Cooper et al., 2011). Growing evidence of the beneficial effects of splenic inhibition across a variety of medical conditions is encouraging, and thus wide-ranging investigation is warranted. However, it is clear that splenic inhibition has particular promise in the development of novel therapies for TBI. There is reason to believe that the use of cholinergic agonists and inducers of parasympathetic tone or beta blockers (Ajmo et al., 2009) described here can be applied as both direct and indirect pharmacological approaches to improve outcomes after brain injury.
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