Treatment for Ischemic Stroke: A New Approach from the Ancient Art of War

Zhe-Qi Xu, Chong Liu & Ding-Feng Su

Department of Pharmacology, Second Military Medical University, Shanghai, China

doi: 10.1111/cns.12492

Ischemic stroke is the leading cause of death in women and the second leading cause of death in men, based on the recent estimate of the World Health Organization (http://gamapserver.who.int/gho/interactive_charts/mbd/leading_cod/2012.asp).

Ischemic stroke is also the leading cause of long-term disability [1]. Intravenous fibrinolysis is the first-line therapy recommended by the latest guidelines for ischemic stroke, but is limited by the narrow therapeutic window [2,3]. As a result, novel treatment is urgently needed.

Inflammatory responses are important pathological processes which protect the host from a vast variety of damage, including infection, trauma, and tissue necrosis. However, it is a double-edged sword. Many types of cytokines and complements could damage normal tissues [4,5]. Upon ischemic stroke, the necrotic brain tissue releases a variety of chemokines, including cytokines, especially interleukin-8 (IL-8) and complements (like C5a), which ignite local inflammation by microglia [6,7]. Also, the chemokines released into peripheral circulation trigger a strong systemic inflammatory response which in turn deteriorates ischemic stroke. Oxidative stress caused by inflammation also contributes to neuronal necrosis and apoptosis [8]. Activated neutrophils and monocytes release free radicals, particularly reactive oxygen species (ROS), into infarcted tissue [9]. The sudden burst of the generation of ROS upon ischemic stroke exceeds the capacity of endogenous antioxidant defense system [8]. In addition to the increase of ROS in extracellular space, ROS generation in neuronal cells is also induced by the activation of N-methylaspartate (NMDA) receptors and the resulting calcium influx [10].

Current therapeutic strategies for ischemic stroke focus on recanalization; systemic inflammation is largely ignored. Inspired by the ancient art of war called *Besiege Wei to Rescue Zhao*, we believe that systemic inflammation represents a viable approach to develop novel treatments for ischemic stroke.

In 354 BC, the Warring States Period of ancient China, General Juan Pang, from the vassal state of Wei, led almost all his forces to attack the vassal state of Zhao. Zhao was too weak to fight against Wei that its capital Handan was nearly occupied. At the critical moment, Zhao asked its ally, vassal state of Qi, for military aid. The prince of Qi assigned general Ji Tian and general Bin Sun to the rescue. Instead of joining the fight with Zhao directly, the two generals attack Wei. General Juan Pang had to retreat his army from Zhao, and Zhao was rescued. This renowned strategy was recorded in *Art of War*.

By analogy in the context of ischemic stroke, systemic inflammation is Wei, and ischemic brain is Zhao. Indeed, such a strategy is supported by evidence from the studies of ischemic stroke after removal of the spleen, the largest immune organ in the body (about 25% of the total lymphoid tissues), and a critical site for cellular immunity and humoral immunity. Upon ischemic stroke, resident macrophages in the spleen are stimulated to secrete a large quantity of inflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-6) into peripheral blood. Zhang and colleagues reported that splenectomies at 2 weeks before permanent middle cerebral artery occlusion (MCAO) could reduce infarct size by >50% smaller in rats, most likely through decreasing levels of inflammatory cytokines [11].

Recently, evidence indicates that a combination of anisodamine and neostigmine could control inflammation and increase the survival rate in endotoxin shock mice [12,13]. A study from the identical laboratory showed that a combination of neostigmine and anisodamine could protect against ischemic stroke [14]. In this report, Qian et al. showed that treatment with neostigmine/anisodamine combination results in a dramatic reduction of the infarct size (from $42.0 \pm 6.9\%$ of hemisphere to $15.6 \pm 3.3\%$ of the hemisphere) and a decrease of neurological deficit score in rats undergone MCAO [14]. A subsequent study showed the neostigmine/anisodamine combination therapy could decrease the production of pro-inflammatory cytokines in macrophages and inhibit the neuronal apoptosis in the ischemic penumbra [15], which may throw a light on targeting systemic inflammation in treatment of ischemic stroke.

In summary, systemic inflammation is an important part of the entire pathologic processes triggered by ischemic stroke. Inspired by ancient art of war, we propose to attenuate systemic inflammation in the treatment of ischemic stroke. Neostigmine, anisodamine, and other similar agents could be considered as the intervention in future clinical trials.

Disclosure

The authors declare no conflict of interests.

Funding

Project supported by the State Key Program of National Natural Science of China (Grant No. 81230083).

References

- Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2009;**58**:421–426.
- Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:3754–3832.
- Hong KS, Bang OY, Kim JS, et al. Stroke statistics in Korea: Part II stroke awareness and acute stroke care, a report from the Korean stroke society and clinical research center for stroke. *J Stroke* 2013;**15**:67–77.
- Tao AF, Xu ZH, Chen B, et al. The pro-inflammatory cytokine interleukin-1 β is a key regulatory factor for the postictal suppression in mice. *CNS Neurosci Ther* 2015;**21**:642–650.
- Kim JY, Kim N, Yenari MA. Mechanisms and potential therapeutic applications of microglial activation after brain injury. *CNS Neurosci Ther* 2015;**21**:309–319.
- Nilupul Perera M, Ma HK, Arakawa S, et al. Inflammation following stroke. *J Clin Neurosci* 2006;**13**:1–8.
- Kaushal V, Schlichter LC. Mechanisms of microglia-mediated neurotoxicity in a new model of the stroke penumbra. *J Neurosci* 2008;**28**:2221–2230.
- Manzanero S, Santoro T, Arumugam TV. Neuronal oxidative stress in acute ischemic stroke: Sources and contribution to cell injury. *Neurochem Int* 2013;**62**:712–718.
- Alexandrova ML, Bochev PG. Oxidative stress during the chronic phase after stroke. *Free Radic Biol Med* 2005;**39**:297–316.
- Jara-Prado A, Ortega-Vazquez A, Martinez-Ruano L, Rios C, Santamaria A. Homocysteine-induced brain lipid peroxidation: Effects of NMDA receptor blockade, antioxidant treatment, and nitric oxide synthase inhibition. *Neurotox Res* 2003;**5**:237–243.
- Zhang BJ, Men XJ, Lu ZQ, et al. Splenectomy protects experimental rats from cerebral damage after stroke due to anti-inflammatory effects. *Chin Med J (Engl)* 2013;**126**:2354–2360.
- Liu C, Shen FM, Le YY, et al. Antishock effect of anisodamine involves a novel pathway for activating alpha7 nicotinic acetylcholine receptor. *Crit Care Med* 2009;**37**:634–641.
- Sun L, Zhang GF, Zhang X, et al. Combined administration of anisodamine and neostigmine produces anti-shock effects: Involvement of alpha7 nicotinic acetylcholine receptors. *Acta Pharmacol Sin* 2012;**33**:761–766.
- Qian J, Zhang JM, Lin LL, et al. A combination of neostigmine and anisodamine protects against ischemic stroke by activating alpha7nAChR. *Int J Stroke* 2015;**10**:737–744.
- Liu AJ, Zang P, Guo JM, et al. Involvement of acetylcholine-alpha7nAChR in the protective effects of arterial baroreflex against ischemic stroke. *CNS Neurosci Ther* 2012;**18**:918–926.