A win in protection against ischemia-reperfusion injury?

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Central Message

Synthetic cannabinoid agonists may provide protection against ischemia reperfusion injury.

See Article page 494.

The human race has used plant-derived cannabinoids, most commonly referred to today as marijuana, for more than 6000 years.¹ The first record of the medical application of the strong anti-inflammatory effect of cannabinoids comes from the world's oldest pharmacopoeia, which was found in China.¹ During the early 1990s, the endogenous ligand for cannabinoid receptors, anandamide, was identified.² The name of the naturally occurring fatty acid derivative anandamide comes from the Sanskrit word *ananda*, which means bliss, delight, or joy, a description that very well reflects its strong anti-inflammatory, pain-relieving properties.² Recently, the therapeutic anti-inflammatory effect of synthetic fatty acid derivative WIN55212-2,

a nonselective cannabinoid agonist of cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors, has been explored. These cannabinoid receptors belong to the G-protein coupled receptor family and play a key role in downstream intracellular regulation of apoptosis and

FIGURE 1. Pathways of cannabinoid receptor-mediated protection against ischemia-reperfusion (IR) injury. Cannabinoid receptor ligand (WIN55212-2) binding to cannabinoid receptors may reduce apoptosis and decrease proinflammatory cytokines and nitric oxide (NO) by increasing cytosolic inhibitory $\text{kB}\alpha$, thus decreasing nuclear translocation of nuclear factor- kB (NF- kB) and decreasing nuclear translocation of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH)/Siah1 complex. CB1, Cannabinoid receptor 1; CB2, cannabinoid receptor 2; $\text{IkB}\alpha$, inhibitory $\text{kB}\alpha$; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species.

inflammation (Figure 1). CB1 receptors are located mostly in the central nervous system. In contrast, CB2 receptors are expressed mostly in the immune system, including the thymus, spleen, lymphatic nodes, and circulating leukocytes, where they mediate cytokine release.³ Some CB2 receptors are also present in nervous system tissue.⁴ In rat models, WIN55212-2 protected against ischemia-reperfusion (IR) injury in brain⁵ and heart⁶ tissue.

A fascinating article by Huo and colleagues⁷ focuses on the protective effect of WIN55212-2 against IR injury. The authors used WIN55212-2 in a rat model of spinal cord IR injury and demonstrated that WIN55212-2 decreased nuclear translocation of both glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and nuclear factor- κ B (NF- κ B).

The ubiquitous cytoplasmic enzyme GAPDH is an important mediator in apoptosis. It appears that GAPDH binds with Siah1 in response to IR injury followed by nuclear translocation of the GAPDH/Siah1 complex that, in turn, is associated with increased apoptosis.⁸ Huo and colleagues⁷ speculated that the inhibitory action of WIN55212-2 on the GAPDH/Siah1 cascade might be due to the suppression of nitric oxide production, given the observation that the protein expression of inducible nitric oxide synthase in the spinal cord of IR injury was reduced in the presence of WIN55212-2. They also demonstrated that WIN55212-2 decreased nuclear translocation of NF- κ B and increased cytosolic inhibitory κ B α , a marker of NF- κ B signaling activation.⁷ NF- κ B is a key mediator of inflammation in IR injury.^{9,10}

Huo and colleagues⁷ found that WIN55212-2 reduced the production of proinflammatory cytokines and reduced

apoptosis of spinal cord cells, resulting in improved neurologic outcome and spinal neuron survival. The effects of WIN55212-2 were reversed by a CB2 receptor antagonist (AM630), but not by a CB1 antagonist (AM251), strengthening the evidence for a key role of the CB2 receptor-mediated pathway. This elegant study is a significant step in our understanding of cannabinoid-induced protection and may lead to important clinical translation in surgery. The ancient saga of cannabinoid receptors continues!

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