Oxidative Signaling in Experimental Autoimmune Encephalomyelitis

Alison I. Bernstein and Gary W. Miller

Department of Environmental Health, Center for Neurodegenerative Disease, Rollins School of Public Health Emory University, Atlanta, Georgia 30322

To whom correspondence should be addressed. Fax: (404) 727-3728. E-mail: gary.miller@emory.edu.

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The article by Johnson et al. (2009) on the role of antioxidant signaling pathways in a model of experimental autoimmune encephalomyelitis (EAE) merits further discussion. This group hypothesized that alterations in oxidative signaling may be involved in the development of EAE and multiple sclerosis (MS). Their laboratory has performed extensive characterization of the nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE) pathway and the Nrf2 knockout mice. Building upon their previous studies, they have extended their characterization of the Nrf2-ARE system in an autoimmune inflammatory model of MS by crossing the Biozzi ABH mice with Nrf2 knockout mice. These hybrid mice allowed a direct test of their hypothesis and were crucial for the success of these studies. In this study, the authors demonstrate that the loss of Nrf2 exacerbates the development of EAE, suggesting that Nrf2 may represent a common pathway and that activation of Nrf2 may attenuate pathogenesis of autoimmune and neurodegenerative diseases.

Key Words: inflammation; auto-immune; oxidative stress.

The article by Johnson et al. (2009) on the role of antioxidant signaling pathways in a model of experimental autoimmune encephalomyelitis (EAE) merits further commentary. Indeed, we must start with a historical journey back to France (reviewed in Baxter, 2007). In 1885, after reportedly provoking a dog by poking it with a stick, 9-year-old Joseph Meister was severely bitten by the rabid animal. At this time in history, this meant certain death. His questionable behavior notwithstanding, young Joseph became the fortunate recipient of Louis Pasteur’s first rabies vaccine. Vaccines were prepared by isolating spinal cords of rabbits infected with rabies virus. The vaccine was used successfully in over 5000 patients. However, when some applications of the vaccine failed to save patients, the treatment was intensified by applying more virulent spinal cord preparations earlier. Treatment with these more intense vaccine preparations led to sporadic cases of paralysis in patients who had been vaccinated. These cases ranged from mild cases in which one or more muscle groups were affected to severe cases in which all four extremities were affected, swallowing and breathing were impaired, and resulting in a 30% mortality rate. These illnesses were distinct from rabies. Whereas rabies is characterized by a loss of nerve cells and no demyelination, these cases were characterized by lymphoid infiltrates and demyelination around blood vessels in the central nervous system with little loss of nerve fibers and cell bodies.

In the 1920s and 1930s, Thomas M. Rivers observed a parallel between the neurological symptoms associated with viral diseases, such as smallpox and measles, and the paralysis developed after rabies vaccination. He designed a series of experiments to determine the origin of the paralysis associated with rabies vaccination. He identified a connection between the antigenicity and antibody titer of the preparation injected into animals and the proportion of animals displaying muscle weakness, clumsiness, and myelin degeneration. When brain emulsions were mixed with Freund’s adjuvant to boost the immune response, a reaction could be induced in most recipient animals after only a few injections. Animals developed a relapsing and remitting course of illness. Histologically, acute lesions were found adjacent to blood vessels with lymphoid infiltrates. This association between brain-specific antibodies and pathology has been the basis of the model now known as EAE.

Since these early studies, EAE has been replicated in many species and is now the best characterized model of human autoimmune diseases and shares many features with human disease, including the degeneration of the myelin sheath, relative sparing of other nervous system tissues, the presence of multiple central nervous system (CNS) lesions, the predominantly perivascular localization of lesions, the maturation of lesions from inflammation to demyelination to gliosis and partial remyelination, and the presence of immunoglobulin in the CNS and cerebrospinal fluid. These characteristics are shared with many types of encephalitis, suggesting that these insults result in a common process of inflammation and immune response within the nervous system and that EAE represents a stereotyped response of CNS tissues to an
immunological stimulus after damage. EAE has been used as a model for multiple sclerosis (MS), and a number of clinical therapeutics have been developed in this system.

EAE can differ among species and strains. One of the most commonly used mouse strains for EAE is the Biozzi ABH mice. These mice were selectively bred by Guido Biozzi in 1972 to produce mice with a high antibody response to sheep red blood cells; these mice are susceptible to EAE and develop a chronic relapsing pattern of disease characterized by lymphocyte infiltration of the CNS, with demyelination being particularly evident in relapse (Amor et al., 2005). These mice have been extensively used in several experimental models of MS, allowing many aspects of disease to be addressed in a single mouse strain, circumventing issues of strain variance. Of relevance to the current study, these mice are susceptible to EAE induced by the myelin oligodendrocyte glycoprotein peptide 35-55 (MOG 35-55); immunization with MOG 35-55 leads to severe demyelination and chronic disease (Amor et al., 2005).

Johnson et al. hypothesized that alterations in oxidative signaling may be involved in the development of EAE and MS. The Johnson laboratory has performed extensive characterization of the nuclear factor erythroid 2–related factor 2–antioxidant response element (Nrf2-ARE) pathway and the Nrf2 knockout mice (Chen et al., 2009; Jakel et al., 2007; Li et al., 2004; Vargas and Johnson, 2009; Vargas et al., 2008). ARE is an enhancer element that is activated by the binding of its transcription factor Nrf2 and regulates transcription of cytoprotective and detoxification genes (Johnson et al., 2008). This group has shown that loss of Nrf2 exacerbates damage in a variety of disease models, including Parkinson’s disease, ischemia/reperfusion injury, Huntington’s disease, amyotrophic lateral sclerosis (ALS), and lupus (Calkins et al., 2005, 2009; Chen et al., 2009; Jakel et al., 2007; Li et al., 2004; Vargas et al., 2008). Based on work from this laboratory and others, targeting Nrf2 is now considered a strong candidate for novel therapeutics (Calkins et al., 2009).

Building upon their previous studies, the Johnson laboratory extends their characterization of the Nrf2-ARE system in an autoimmune inflammatory model of MS by crossing the Biozzi ABH mice with Nrf2 knockout mice. These hybrid mice allowed a direct test of their hypothesis and were crucial for the success of these studies. Crossing a knockout mouse strain onto the Biozzi ABH background can be invaluable technique in dissecting the pathways involved in EAE and human diseases, such as MS.

In this study, the authors demonstrate that the loss of Nrf2 exacerbates the development of EAE. Immunization with MOG 35-55 induced more severe EAE in mice lacking Nrf2; these mice displayed higher clinical scores of disease and greater incidence of disease than wild-type mice. In addition, a higher degree of demyelination, cell infiltration, and activation of astrocytes and microglia was seen in Nrf2-deficient mice. Furthermore, Nrf2 knockout mice showed a greater increase in cytokine and chemokine levels. From these data, the authors conclude that the Nrf2 can modulate an inflammatory response and that Nrf2 mediates protective mechanisms against EAE-induced neuroinflammation. The findings of this study are similar to previous studies from this group demonstrating that loss of Nrf2 also exacerbates toxicity in models of Parkinson’s disease, Huntington’s disease, ALS, lupus, and others (Calkins et al., 2005; Chen et al., 2009; Jakel et al., 2007; Li et al., 2004; Vargas and Johnson, 2009; Vargas et al., 2008). Together, these results suggest that Nrf2 may represent a common pathway and that activation of Nrf2 may attenuate pathogenesis of autoimmune and neurodegenerative diseases.

This study underscores the value of applying concepts and models of toxicology to the study of human disease. Over the past few decades, the field of toxicology has moved away from the LD50 study model (dose ‘em and count ‘em) to more mechanistic approaches that help identify how chemicals may be involved in certain disease processes. The field has made tremendous progress in this area. The present study highlights an even more daring and fruitful direction for the field of toxicology, i.e., the application of toxic mechanisms and models of injury to human disease even in the absence of an overt chemical exposure. Many of the pathogenic mechanisms that occur in either chemical-induced damage or human disease states are similar, and the investigators who have been studying those pathways are in a superb position to improve our understanding of said diseases. The article by Johnson et al. is a successful example of this new paradigm, and investigators in the field are encouraged to emulate these forward-thinking approaches.

REFERENCES


