



SOPHIA SUNDARARAJAN

TZD treatment in acute ischemic stroke results in activation of inflammatory cells, reduced infiltration of leukocytes into damaged brain, and reduced expression of toxic inflammatory genes.

Exploring New Treatments to Prevent Injury During Stroke

Stroke is the third leading cause of death and the leading cause of disability in the United States. Despite this, only very limited treatments are available to prevent injury during stroke. The laboratory of **Sophia Sundararajan, M.D., Ph.D.**, assistant professor of neurology, is focused on understanding mechanisms of injury in acute ischemic stroke in order to develop potential therapies for this devastating disease.

Stroke is characterized by a robust inflammatory response which begins soon after the onset of injury. This response is characterized by the activation of inflammatory cells within the brain as well as the activation and infiltration of leukocytes (white blood cells) from the blood. Activation of these cells leads to the release of toxic molecules within the blood vessels and tissue of the brain which worsens injury.

A class of medications, already FDA approved for the treatment of type 2 diabetes, called thiazolidinediones (TZDs), has been shown in models of disease to suppress inflammation. TZDs exert their effects by binding peroxisome proliferator-activated receptor (PPAR) gamma. Dr. Sundararajan's research team has found that PPARgamma is present in the brain and that TZD treatment during stroke causes PPARgamma to bind DNA, which is the first step in regulating gene expression.

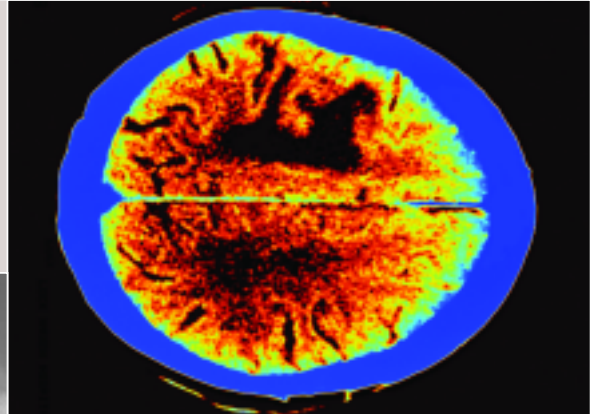
"We find that TZD treatment in acute ischemic stroke results in activation of inflammatory cells, reduced infiltration of leukocytes into damaged brain, and reduced expression of toxic inflammatory genes. Importantly, TZD treatment results in a smaller stroke and improved neurologic behavior following stroke in an animal model," notes Dr. Sundararajan.

Most recently, the researchers have been exploring whether oral treatment at doses similar to those used to treat diabetes are also effective in reducing injury after stroke and when during the course of stroke, TZDs need to be administered to protect the brain. These findings have important implications for the design of clinical trials to test TZDs in human stroke.

<http://alzlab.case.edu/landreth/pages/sophia.html>



JOSEPH C. LAMANNA



Loss of Oxygen to the Brain: Identifying Responses to Cerebral Hypoxia

With a focus on energy demand, energy metabolism, and blood flow in the brain, the laboratory of **Joseph C. LaManna, Ph.D.**, professor and chairman of the Department of Anatomy at the School of Medicine, as well as professor in the Departments of Neurology, Physiology/Biophysics, and Neuroscience, is actively investigating the role of these mechanisms in the tissue response to pathological insults such as stroke, hypoxia, and seizures. The lab's most recent research has centered on brain response to hypoxia and cerebral edema.

Cerebral hypoxia can be caused by any event that interferes with the brain's ability to receive or process oxygen. One of the more common and serious stresses challenging the body, it can be the result of limited oxygen in the environment, such as that experienced at high altitudes. Dr. LaManna's lab is studying acute mountain sickness, as well as the effects of returning to a normal atmosphere. In addition, his team is investigating severe, intermittent hypoxia due to periods of cessation of breathing during the night, often the result of sleep disorders. Reduced brain oxygen can also result from inadequate blood flow to the brain, caused by a stroke or cerebral edema, an excess accumulation of water in the brain.

Using a rat model, the research team examines the effects of both acute and chronic hypoxic conditions on brain metabolism and blood flow. By studying the physiological mechanisms which are triggered by hypoxia, they are able to determine which are successful adaptive responses and which might be responsible for further pathology.

Such adaptive responses to hypoxia include an acute transient increase in blood flow, increased red blood cell volume (hematocrit), and activation of hypoxia-inducible factor-1 that is responsible for initiating angiogenesis, the growth of new blood vessels. Chronic responses involve systemic, central metabolic and vascular processes such as brain angiogenesis. Of special interest is the growth and arrangement of small brain capillaries and the control of resting and responsive local tissue blood flow.

"In the mammalian central nervous system, the effects of hypoxia must be understood with respect to the unique features of both cerebrovascular and metabolic physiology. The more we understand the structural and functional adaptations of the brain to chronic exposure to a hypoxic environment, the better prepared we will be to prevent and treat these conditions," notes Dr. LaManna.

<http://www.case.edu/med/anatomy/brainlab>