Diabetes drug spurs host defense

February 11 2015

Pioglitazone, a medication approved for treatment of type 2 diabetes, can help bypass genetic defects in chronic granulomatous disease to help white blood cells fight bacterial infections, according to researchers at National Jewish Health.

Patients with chronic granulomatous disease (CGD), a rare inherited disorder, lack a functional enzyme, known as NADPH oxidase, which impairs their ability to produce a variety of oxidant molecules, known as reactive oxygen species (ROS), in response to bacterial infection. Normally, ROS destroy bacteria by chemically reacting with their cell walls and other components. As a result of genetic mutation, CGD patients lack this early immune response and suffer ongoing and severe infections, especially of the lungs, liver, skin and lymph nodes.

Pioglitazone, an agonist of the signaling molecule PPAR?, has broad effects on cellular metabolism, which include mimicry of insulin, and anti-inflammatory activities. The medication is approved for treatment of type 2 diabetes and is being investigated for use in a variety of other disorders, primarily for its anti-inflammatory properties. Recent findings have suggested that it may also boost the production of ROS.

National Jewish Health Professor of Pediatrics, Donna Bratton, MD, and her colleagues reported in the February 2015 *Journal of Allergy and Clinical Immunology* that pioglitazone does indeed boost production of ROS in white blood cells by about 30 percent in a mouse model of chronic granulomatous disease and in white blood cells from CGD patients. They also found that pioglitazone enhanced the ability of the

cells from the CGD mouse model to kill Staphylococcus aureus and Burkholdia cepacia, two pathogens that are difficult to treat and common in CGD.

The researchers found that the additional ROS come not directly from NADPH oxidase, which is not functional in CGD patients, but from mitochondria, the energy producing organelles within the white blood cells.

"These findings demonstrate that pioglitazone can promote the production of ROS from mitochrondria of white blood cells," said Dr. Bratton. "While pioglitazone does not restore full ROS production, it does make a relevant contribution to host defense in mouse and cellular models of chronic granulomatous disease. We are looking forward to evaluating pioglitazone in patients with the disease."

Provided by National Jewish Health