EMERGING RESEARCH FRONTS - 2009

April 2009

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Joseph L. Evans talks with *ScienceWatch.com* and answers a few questions about this month's Emerging Research Front Paper in the field of Biology & Biochemistry. The author has also sent along images of his work.

Article: Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction?
Authors: Evans, JL;Goldfine, ID;Maddux, BA;Grodsky, GM
Journal: DIABETES, 52 (1): 1-8 JAN 2003
Addresses: Med Res Inst, 444 De Haro St,Suite 209, San Francisco, CA 94107 USA.
Med Res Inst, San Francisco, CA 94107 USA.
Univ Calif San Francisco, San Francisco, CA 94143 USA.

SW: Why do you think your paper is highly cited?

Oxidative stress is a type of cellular inflammation that stems from chronic hyperglycemia. Oxidative stress had long been linked to the development of complications in type 1 and type 2 diabetic patients. Our paper, however, was the first to present evidence that oxidative stress, caused by hyperglycemia and previously unappreciated agents such as elevated free fatty acids, plays a major role in the development of insulin resistance and impaired insulin secretion—the major causes of type 2 diabetes (See Figure 1 to the right).

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Our paper offers a concise, complete, synthesis of a large body of work authored by many of the leading experts in the field. The paper presents a unifying hypothesis that ties together data from several diverse areas.

SW: Would you summarize the significance of your paper in layman's terms?

Both the early and late stages of type 2 diabetes are worsened and most likely caused by increased cellular inflammation due to oxidative stress. Treatments that reduce the oxidative stress and/or suppress the responses stimulated by oxidative stress can offer new therapeutic opportunities. These treatments should delay the onset and/or even prevent the development of diabetes and its complications.

SW: How did you become involved in this research and were any particular problems encountered along the way?

I first became involved in diabetes research in 1986 as a post-doctoral fellow

at Dartmouth Medical School, under the expert guidance of Professor Lee Witters. Since that time, my research efforts moved from academia to industry, but have continually and unwaveringly focused on identifying and developing new potential treatment approaches for type 2 diabetes and other metabolic disorders.

Success in this endeavor involves not only a thorough understanding of the drug development process, but also a comprehensive knowledge of the pathophysiology of the disease. This challenge has driven me towards a holistic viewpoint of both disease etiology and treatment, and ultimately resulted in some of the ideas put forth in this paper.

As for problems, there are always problems; it is the job of the scientist to find solutions. However, it has been an ongoing struggle for my collaborators and I to secure adequate funding for research described in this paper, as is often the case with new ideas.

Figure 1: +details

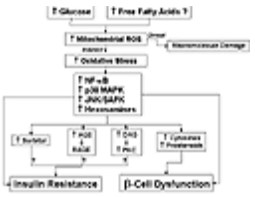
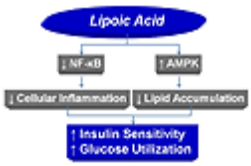


Figure 2:



SW: Where do you see your research leading in the future?

I firmly believe that this area of research will ultimately lead to safer and more efficacious treatments for type 2 diabetes than are currently available today. By targeting the cellular inflammation, these treatments will have a direct effect at improving insulin sensitivity, and reducing the deterioration of the insulin-producing beta cells.

One compound, in particular, that has shown great promise in this regard is alpha-lipoic acid. Although commonly thought of as an anti-oxidant, lipoic acid is a highly effective inhibitor of NF-kB activation (a primary inflammatory pathway) in humans. In addition, animal studies have shown that lipoic acid activates AMP-activated protein kinase in peripheral tissues, leading to reduced inflammation, reduced hepatic and muscle lipid accumulation, and increased glucose utilization and insulin sensitivity (See Figure 2 to the right above).

SW: Do you foresee any social or political implications for your research?

Absolutely. The US, along with the rest of the world, is experiencing an epidemic in diabetes and other metabolic diseases, especially the metabolic syndrome and obesity. There is not a country in the world that possesses a healthcare budget with sufficient funding to care for all the affected individuals after they develop the disease. The drain on the limited available health care resources is already being felt, and will only get worse.

The long-term solution is prevention and early intervention, before the debilitating complications of the disease arise. It is imperative for us as scientists and as citizens to convince our elected officials at both the state and federal levels to allocate significantly more resources to address the obvious need for improved therapy. These additional resources should be used to support academic research and development, along with providing increased support for small private business entities that are seeking to develop and commercialize these new treatments.

Joseph L. Evans, Ph.D.
Founder and President
P & N Development Ventures
Redwood City, CA, USA
Web

KEYWORDS: KAPPA-B ACTIVATION; ALPHA-LIPOIC ACID; RAT PANCREATIC-ISLETS; JUN NH2-TERMINAL KINASE; II DIABETES-MELLITUS; LONG-TERM EXPOSURE; L6 MUSCLE-CELLS; PROTEIN-KINASE; FATTY-ACID; ENDOTHELIAL-CELLS.

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Figures and descriptions:

Figure 1:

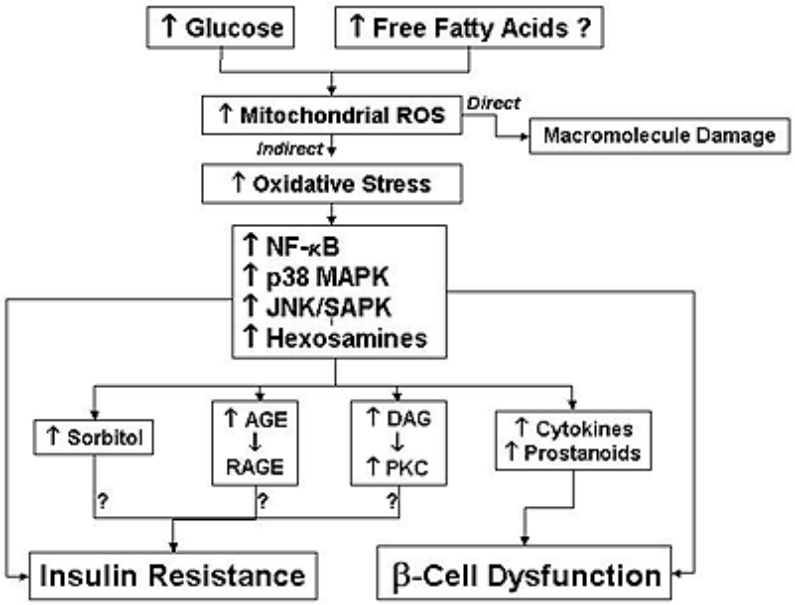

Figure 1:
Proposed general theory of how elevated glucose and possibly FFA levels contribute to the pathophysiology of diabetes via the generation of ROS and consequent activation of numerous stress-sensitive pathways. The causative link among hyperglycemia, mitochondrial ROS generation, oxidative stress, and the development of diabetic complications has been previously suggested (10,11,22). ROS (and RNS), by inflicting macromolecular damage, may play a key direct role in the pathogenesis of diabetes. ROS also function as signaling molecules (analogous to second messengers) to activate several stress-sensitive pathways (indirect role). In addition, in type 2 diabetes, there is growing evidence that activation of stress-sensitive pathways, such as NF-kB, p38 MAPK, JNK/SAPK, and hexosamine, by elevations in glucose and possibly FFA levels leads to both insulin resistance and impaired insulin secretion. Thus ROS and oxidative stress, induced by elevations in glucose and possibly FFA levels, may play a key role in causing insulin resistance and ß-cell dysfunction by their ability to activate stress-sensitive signaling pathways. The proposed sequence of events may also include other stress pathways, such as the increased production of AGE, sorbitol, cytokines, and prostanoids along with PKC activation. DAG, diacylglycerol.

Figure 2:

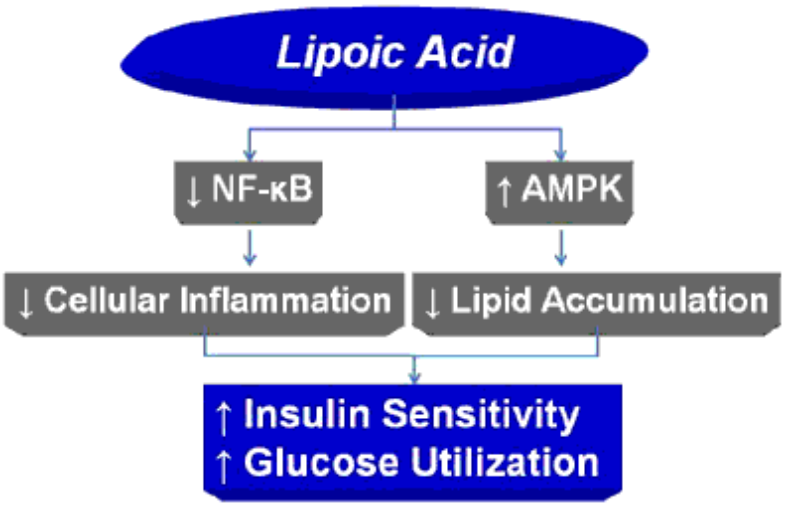

Figure 2:
a-Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to man. LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production. LA has been prescribed as pharmacotherapy in Germany for over thirty years for the treatment of diabetes-induced neuropathy. Both pre-clinical and clinical studies have established that LA suppresses the activation of NF-kB, a transcription factor that is a major mediator of the inflammatory response. The ability of LA to block the activation of NF-kB is clearly linked to its ability to protect cells from oxidative stress-induced insulin resistance. In animal studies, oral treatment with LA results in the activation of AMP-activated protein kinase (AMPK), the major cellular fuel sensor and an enzyme that is activated by the predominant anti-diabetic interventions of exercise, metformin, and thiazolidinediones. Activation of AMPK yields many beneficial effects on metabolism, especially the mobilization of lipid stores in skeletal muscle and liver. Reduced intracellular lipid reduces cellular inflammation, and increase the response of these tissues to insulin, i.e. LA increases insulin sensitivity. As a consequence of increasing insulin sensitivity, LA improves glucose utilization in patients with type 2 diabetes.

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