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Aldose reductase inhibition decelerates optic nerve degeneration by alleviating retinal microglia activation

Mishal Rao¹, Yu-Kai Huang^{1,4,5}, Chia-Chun Liu¹, Chandler Meadows¹, Hui-Chun Cheng¹, Mengli Zhou¹, Yu-Chih Chen⁶, Xin Xia⁷, Jeffrey L. Goldberg⁷, Andrew M. Williams¹, Takaaki Kuwajima¹ & Kun-Che Chang^{1,4,5,8}

As part of the central nervous system (CNS), retinal ganglion cells (RGCs) and their axons are the only neurons in the retina that transmit visual signals from the eye to the brain via the optic nerve (ON). Unfortunately, they do not regenerate upon injury in mammals. In ON trauma, retinal microglia (RMG) become activated, inducing inflammatory responses and resulting in axon degeneration and RGC loss. Since aldose reductase (AR) is an inflammatory response mediator highly expressed in RMG, we investigated if pharmacological inhibition of AR can attenuate ocular inflammation and thereby promote RGC survival and axon regeneration after ON crush (ONC). *In vitro*, we discovered that Sorbinil, an AR inhibitor, attenuates BV2 microglia activation and migration in the lipopolysaccharide (LPS) and monocyte chemoattractant protein-1 (MCP-1) treatments. *In vivo*, Sorbinil suppressed ONC-induced Iba1⁺ microglia/macrophage infiltration in the retina and ON and promoted RGC survival. Moreover, Sorbinil restored RGC function and delayed axon degeneration one week after ONC. RNA sequencing data revealed that Sorbinil protects the retina from ONC-induced degeneration by suppressing inflammatory signaling. In summary, we report the first study demonstrating that AR inhibition transiently protects RGC and axon from degeneration, providing a potential therapeutic strategy for optic neuropathies.

Central nervous system (CNS) axons and neurons are incapable of spontaneously regenerating in mammals¹. Injury or insult to CNS axons causes irreversible damage leading to neurological and neurodegenerative disorders². The optic nerve (ON) is a sensory nerve critical for vision. The ON transmits signal from the eye to the brain through axons of retinal ganglion cells (RGCs), which reside in the nerve fiber layer of the neural retina. Unmyelinated RGC axons exit the eyes globe at the ON head (optic nerve head). Posterior to the ONH, the axons are myelinated by supporting oligodendrocytes, a type of glial cell. Given their delicate structure, ON axons are vulnerable to insult.

Unlike other vertebrates³, mammals cannot spontaneously regenerate damaged axons of RGC after ON injury due to various inhibitory factors^{4,5}. Since RGCs are critical for vision, knowing what other cells influence RGCs and RGC axon survival, especially when injured, is essential. Other than neuronal cells, the mammalian retina contains three types of glial cells: Müller glia (MG), astrocyte glia (ASG), and retinal microglia (RMG)⁶. ASG cell bodies and processes are found in the nerve fiber layer and closely interact with RGCs and their axons in the ONH⁷. RMG, the primary immune cells in the retina that respond to stress, are found at varying densities in every retinal layer, including the ganglion cell layer (GCL), where they interact with RGCs⁸. Since the eye is

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Aldose Reductase Inhibition

**Henry Weiner, Roger S.
Holmes, Bendicht Wermuth**



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Aldose Reductase Inhibition Dushan Dvornik, J.D. Ward, 1987 **The Potential Role of Aldose Reductase Inhibition in the Treatment of Diabetic Neuropathy** David Elwyn Price, 1990 **Molecular Mechanisms of Action of Functional Foods and Nutraceuticals for Chronic Diseases** Shima Abdollahi, Syam Mohan, Yashwant V. Pathak, 2023-04-19

There has been a global rise in the incidence of chronic illnesses which may be partially attributed to the lengthening of the average human lifespan. Functional foods and nutraceuticals have a potential role to play in the development and maintenance of health. They can assist the body in its battle against inflammation and chronic illnesses. *Molecular Mechanisms of Action of Functional Foods and Nutraceuticals for Chronic Diseases* addresses the effects and mechanism of functional foods in relation to chronic diseases such as obesity, cardiovascular diseases, diabetes, cancer, etc. This volume, like the first volume *Applications of Functional Foods and Nutraceuticals for Chronic Diseases*, inspires new thought processes and a paradigm shift in research and development. *Key Features* discusses the molecular mechanism of action, the range of toxicities exerted by these food components for functional foods for addressing chronic conditions. It enhances scientists and industrial personnel knowledge of functional foods and in the management of chronic diseases. It presents research on the role of functional foods/nutraceuticals in preventing and treating chronic diseases through epigenetic modulation. It explores various subjects such as epigenetics, immunological, metabolic, technological, and neurodegenerative aspects affected by functional foods in chronic diseases. The world's leading wellness centers for chronic diseases are using functional foods and nutraceuticals in their practice and discovering their useful applications, and this second of two volume set is another great reference for practitioners, scientists, and clinicians in the management of chronic diseases. Contributors hail from different geographical locations around the world and have many years of research and scholarly experience in functional foods, nutraceuticals, and biology.

The Polyol Paradigm and Complications of Diabetes Margo P. Cohen, 2012-12-06. In the last decade, it has become increasingly evident that the clinical and morphologic changes underlying many of the complications of diabetes, including cataract formation, retinopathy, nephropathy, neuropathy, and macrovascular disease, are preceded by a variety of disturbances of biochemical and physiologic origin. Dr. Cohen has recently written a superb monograph entitled *Diabetes and Protein Glycosylation: Measurement and Biologic Relevance*, in which she thoroughly explores how enhanced nonenzymatic glycosylation in uncontrolled diabetes underscores the pressing need for maintenance of long-term euglycemia. In the present volume, *The Polyol Paradigm and Complications of Diabetes*, she reviews in a most succinct and thorough manner how another biochemical mechanism involving the polyol pathway is involved in the pathogenesis of such diabetes complications as retinopathy, neuropathy, nephropathy, and cataract formation. Dr. Cohen gives us a clearly written and comprehensive monograph reviewing the chemistry of the polyol pathway and of the aldose reductase inhibitors and the pathophysiologic significance of increased polyol pathway activity in a variety

of tissues affected by VIII Foreword diabetes mellitus She insightfully describes the relationship of increased polyol pathway activity to altered metabolism of inositol containing phospholipids and to changes in various tissue concentrations of myo inositol Finally she provides us with a careful review of the existing experimental and clinical studies with a variety of different aldose reductase inhibitors that have been and are being performed in the hope of preventing or reversing long term complications of diabetes

Diabetic Retinopathy Elia Duh, 2008-10-08 Diabetic retinopathy is the most common microvascular complication of diabetes It remains a major cause of new onset visual loss in the United States and other industrialized nations In Diabetic Retinopathy Elia Duh and a panel of internationally recognized experts comprehensively assess the current state of knowledge regarding the clinical management of DR as well as its underlying mechanisms The authors outline the current understanding of diabetic retinopathy from the perspective of clinical practice while reviewing the multifactorial pathogenesis and pathophysiology of DR from the standpoint of biomedical research Also included is a discussion of emerging concepts relating to the management and treatment of DR Informative and highly practical Diabetic Retinopathy provides ophthalmologists diabetologists endocrinologists and internists with a highly readable guide not only to understanding diabetic retinopathy but also to its optimal clinical management

Enzymology and Molecular Biology of Carbonyl Metabolism 3 David W. Crabb, Henry Weiner, Bendicht Wermuth, 2012-12-06 The Fifth International Workshop on the Enzymology and Molecular Biology of Carbonyl Metabolism was held at Purdue University in June 1990 This represents the fifth time that I had the privilege of organizing the scientific program It was the first time that I actually hosted the meeting I wish to salute my four previous co organizers and the thousands of scientists who have hosted other meetings It is much easier to arrange the scientific program and edit the proceedings No local organization could occur without the help of ones research group and in this case my wife I sincerely thank Esther and my research group for their advise and help At this Workshop similar to the preceeding ones much new information was presented It was apparent how molecular biological techniques were influencing the direction of the research on the three families of enzymes discussed It also was apparent that not all biochemical problems could be solved by using these techniques Many of the presentations showed how important advances still could be made using more traditional biochemical approaches

Microcirculation Ronald F. Tuma, Walter N. Duran, Klaus Ley, 2011-04-28 This reference is a volume in the Handbook of Physiology co published with The American Physiological Society Growth in knowledge about the microcirculation has been explosive with the field becoming fragmented into numerous subdisciplines and subspecialties This volume pulls all of the critical information into one volume Meticulously edited and reviewed Benefit Provides investigators a unique tool to explore the significance of their findings in the context of other aspects of the microcirculation In this way the updated edition has a direct role in helping to develop new pathways of research and scholarship Highlights the explosive growth in knowledge about the microcirculation including the biology of nitric oxide synthase NOS endothelial cell signaling angiogenesis cell adhesion molecules lymphocyte

trafficking ion channels and receptors and propagated vasomotor responses Benefit Microcirculatory biology has become fragmented into numerous sub disciplines and subspecialties and these reference reintegrates the information in one volume

Diabetes Mellitus Oluwafemi Oguntibeju, 2013-01-23 The fundamental treatment and management goals in diabetes mellitus are to control and normalize blood glucose levels and to prevent diabetic complications It also includes maintaining normal growth and development and normal body weight Proper diet regular exercise weight control and different therapeutic agents are the mainstays of diabetic care and management Weight reduction and exercise have been shown to improve tissue sensitivity to insulin and allow its proper use by target tissues It is obvious that medical management and goals of therapy for diabetes mellitus have changed since the publication of the Diabetes Control and Complications Trial in 1993 Recent studies have shown that the risk of developing retinopathy can decrease by 76% in properly managed diabetic patients when compared to control group and that clinical and laboratory signs and symptoms of nephropathy and neuropathy can also decrease by 54 to 60% Modern approaches to the management of diabetes mellitus embrace holistic options and this book addressed various approaches in the management of diabetes mellitus

Enzymology and Molecular Biology of Carbonyl Metabolism 4 Henry Weiner, David W. Crabb, T. Geoffrey Flynn, 2012-12-06 The Sixth International Workshop on the Enzymology and Molecular Biology of Carbonyl Metabolism was held outside of Dublin Ireland at the end of June 1992 Prof Keith Tipton Chairman of the Biochemistry Department at Trinity College kindly agreed to host the meeting On behalf of all of us who attended I wish to extend our sincere thanks to the whole Tipton family for making us feel so welcome in Ireland It has been a decade since the first workshop was held in Bern Switzerland The scope of the meetings reflected somewhat the changes that have occurred in biochemistry during the past decade At the first meeting primarily enzymes and their properties were discussed At this last meeting many of the talks centered on gene regulation as well as more traditional aspects of enzymology and metabolism During the past decade site directed mutagenesis to probe for the active site of an enzyme has become part of traditional enzymology this was virtually unheard of at our first meeting Many of the presenters now used this tool to study some aspect of structure and function of one of the three carbonyl metabolizing enzymes

Annual Report - National Eye Institute National Eye Institute, 1987 Effects of Aldose Reductase Inhibition on Diabetic Nephropathy Laurie Ann O'Daniel, 1987

Nutrition and Eye Health John Lawrenson, Laura Downie, 2020-01-03 Blindness and visual impairment impact significantly on an individual's physical and mental well being Loss of vision is a global health problem with approximately 250 million of the world's population currently living with vision loss of which 36 million are classified as blind Visual impairment is more frequent in the elderly with cataract and age related macular degeneration AMD accounting for over 50% of cases globally Oxidative stress has been strongly implicated in the pathogenesis of both conditions and consequently the role of nutritional factors in particular carotenoids and micronutrient antioxidants have been investigated as possible preventative or therapeutic strategies Dry eye

syndrome DES is one of the most common ophthalmic conditions in the world DES occurs where the eye does not produce enough tears and or the tears evaporate too quickly leading to discomfort and varying degrees of visual disturbance There has recently been a great deal of interest in the potential for oral or topical supplementation with essential fatty acids EFAs specifically omega 3 and omega 6 fatty acids as an adjunct to conventional treatments for DES The objective of this Special Issue on Nutrition and Eye Health is to publish papers describing the role of nutrition in maintaining eye health and the use of nutritional interventions to prevent or treat ocular disease A particular but not exclusive emphasis will be on papers reviews and or clinical or experimental studies relating to cataract AMD and DES

Diabetes R. D. G. Leslie, David C. Robbins, 1995-03-09 This significant new publication provides a summary and overview of the most recent scientific advances in diabetes research and highlights the role of these developments in advancing clinical practice Diabetes is one of the major causes of morbidity and mortality in the developed world and its prevalence elsewhere is on the increase It affects in excess of 100 million people worldwide Recent scientific advances have clarified our understanding of the causes and consequences of this devastating disease These scientific developments are playing an increasingly important role in clinical practice and could well lead the way to the prevention of complications and even a cure for the disease An international and authoritative team of authors draws together this knowledge and the most recent developments to provide an up to date account which will benefit researchers and clinicians

Current Bibliographies in Medicine, 1988 **Disease Prevention Research at NIH** Ronald L. Gordner, 1993 Scientific Directory and Annual Bibliography National Institutes of Health (U.S.), 1991 Each issue lists papers published during the preceding year

Advances in Drug Research Bernard Testa, 2013-10-22 Each volume in this distinguished series presents authoritative reviews both generally on topics of broad interest in drug research and specifically on novel and established therapeutic classes Acknowledged experts contribute in areas such as drug design clinical and molecular pharmacology drug metabolism and mechanisms of action Reviewers have consistently praised **Advances in Drug Research** for its comprehensive and lucid summaries of up to date knowledge

Advances in Ganoderma Research and Application: 2012 Edition, 2012-12-26 **Advances in Ganoderma Research and Application 2012 Edition** is a Scholarly Paper that delivers timely authoritative and intensively focused information about Ganoderma in a compact format The editors have built **Advances in Ganoderma Research and Application 2012 Edition** on the vast information databases of ScholarlyNews You can expect the information about Ganoderma in this eBook to be deeper than what you can access anywhere else as well as consistently reliable authoritative informed and relevant The content of **Advances in Ganoderma Research and Application 2012 Edition** has been produced by the world's leading scientists engineers analysts research institutions and companies All of the content is from peer reviewed sources and all of it is written assembled and edited by the editors at ScholarlyEditions and available exclusively from us You now have a source you can cite with authority confidence and credibility More information is available at <http://www.ScholarlyEditions.com>

Prevention of Type 2 Diabetes Manfred Ganz, 2005-09-01 This book provides a unique and comprehensive synopsis of the prevention and early diagnosis of Type 2 Diabetes. It features articles by key opinion leaders in diabetes from North America, Europe, and the Asia Pacific region who describe the gravity of the problem and the important issue of screening, including contributions on the perspectives of the International Diabetes Federation and the World Health Organization. Once patients at risk have been identified, the key issue is to prevent their progression to full-blown diabetes. Several chapters address this, particularly the difficult task of changing people's behaviour. Prevention of the complications associated with diabetes involves more targeted interventions, which are discussed by experts in the relevant areas. This book offers both a global perspective and local solutions. Key contributors include Paul Zimmet and Pierre Lefèvre, President of the International Diabetes Federation, who has written a chapter and a foreword. Praise from the reviews: An excellent resource for professionals who want a good means for getting up to speed on the prevention angle. It is all-inclusive from many perspectives, authorship of chapters, rich reference lists, and content. This book is a one-stop source for understanding the state of current prevention knowledge about type 2 diabetes. **DIABETES TECHNOLOGY THERAPEUTICS** This is a timely and helpful treatment of an important public health topic. I am unaware of any other contemporary books which address exactly this issue. **DOODY'S HEALTH SERVICES** An ambitious title written by some of the world's leading diabetologists; it takes a very careful approach. **PEDIATRIC ENDOCRINOLOGY REVIEWS** PER **Enzymology and Molecular Biology of Carbonyl Metabolism** 5 Henry Weiner, Roger S. Holmes, Bendicht Wermuth, 2013-06-29 Since the inception of these meetings in 1982, they have always been a satellite of the International Society for Biomedical Research on Alcoholism meeting. At our 1992 meeting in Dublin, we learned that the next ISBRA meeting would be held in Brisbane. Of all our previous meetings, I was very concerned, Australia. As the scientific organizer about holding a meeting in the Southern Hemisphere, for fear that many of our potential participants would not travel that far, I am pleased to say that I was proven to be incorrect. Nearly 90 scientists from a dozen countries participated at our seventh conference. At this meeting, like at all our previous ones, much new information about the three enzyme systems was presented. Of equal importance was, like at all our previous meetings, the extreme openness of the participants to discuss ideas, future directions, and unpublished data. On behalf of all the participants, I wish to express our sincere thanks to our Massey University colleagues for the excellent organization of this Palmerston North, New Zealand meeting. These included Kathryn Kitson, Michael Hardman, Paul Buckley, Trevor Kitson, and Len Blackwell. At this meeting, a few new innovations were introduced. Though posters are common at many meetings, bush walks and visits to nature preserves to see kiwi birds. Our hosts were able to secure support from the International Union of Biochemistry, are not

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