Synthetic Antioxidants as Potential Medical Remedies: An Update of the Past Decade of Pyridoindols

Potansiyel Tıbbi Çare Olarak Sentetik Antioksidanlar: Pridoindollerin Son On Yılına Güncel Bir Bakış

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ABSTRACT Diabetes mellitus, has long been recognized as a cause of accelerated aging, is a heterogeneous metabolic disorder characterized by hyperglycemia, which is often associated with complications such as cardiovascular disease, retinopathy, nephropathy and peripheral and autonomic neuropathy. In fact, aging and age-related diseases such as diabetes are accompanied by increased Oxidative Stress (OS) and accumulation of Advanced Glycation End products (AGEs). Unmitigated OS can lead to diminished cellular longevity, accelerated aging, and accumulated toxic effects for an organism. Consequences of oxidative stress are damage to DNA, lipids, proteins, accumulation of damaged molecules and disruption in cellular homeostasis. These damaged molecules also impair endothelial integrity and destroy membrane calcium current, leading to endothelial dysfunction, vascular smooth muscle proliferation and abnormal cardiovascular reactivity. Diabetes-induced oxidative stress increases AGEs formation. AGE modification of proteins leads to alterations in their normal functions by binding to intracellular or extracellular cell components, or through receptor binding. These interactions consequently can initiate a cascade of signal transduction pathways, which activate inflammatory responses, causing tissue injury. Such tissue injury contributes to the development of cardiovascular and other serious complications responsible for morbidity and mortality in diabetes. The increased amount of evidence on the harmful effects of hyperglycemia-induced oxidative stress on organ functions, the recent interest has focused on strategies to prevent, reverse or retard firstly oxidative stress and then its triggered harmful signaling. In this regard, stobadine, a synthetic and efficient antioxidant pyridoindole, has been studied largely, and found that it inhibits glyco-oxidative damage, decreases albuminuria, enzymuria, lipid peroxidation, matrix collagen cross-linking, plasma cholesterol, triglycerides, protein carbonylation and protein AGEs formation, and lead to a normalization in protein thiol, total thiol and non-protein thiol groups in different tissues of diabetic animals. Stobadine treatment of diabetic rats is characterized by retarded calcium accumulation in hearth. Stobadine is able to control mean arterial blood pressure, to prevent endothelial disturbances and to restore vascular reactivity abnormalities. This antioxidant protects metabolism, function and/or structure of heart, aorta, kidney, brain, liver, peripheral nerves, vas deferens and retina in streptozotocin-diabetic rats. Accumulating experimental evidence suggest that stobadine is a promising agent to prevent, delay or treat late diabetic complications.

Key Words: Aging, Experimental Diabetes, Oxidative Stress, Glycation, Antioxidant, Pyridoindol, Stobadine

ÖZET Diabetes mellitus, başlıca hiperglisemi ile karakterize metabolik bir sendrom olup, kardiyovasküler hastalıklar, retinopati, nefropati, periferal ve otonomik nöropati gibi çeşitli komplikasyonlara sıklıkla eşlik etmektedir ve hızlandırılmış yaşlanmanın önemli bir sebebi olarak tanınmaktadır. Gerçekte, "yaşlanma" ve "diyabet" gibi ilerleyen yaş ile ilişkili hastalıklarda, "oksidatif stres (OS)"de artış ve "ileri glikasyon son ürünleri (AGEs)"de birikme, organ yaşlanmasına aracılık eden önemli faktörlerdir. İflah olmayan OS'in, DNA, protein ve lipidlerde neden olduğu hasarlar, moleküllerin tunover'da ve onarım mekanizmalarında meydana gelen azalmalar, hasarlı moleküller hücrelerde giderek birikmesine ve doku fonksiyonlarının ilerleyen yaşla birlikte bozulmasına öncülük eder; örneğin, endotel disfonksiyonu, vasküler düz kas proliferasyonu, ve membran kalsiyum akımında bozulmaya neden olurlar ve bunlar sonuçta kardiyovasküler reaktivitenin değişmesiyle sonuçlanır. Diyabetin indüklediği OS aynı zamanda AGEs oluşumunu arttırır. Proteinlerde AGE'ler aracılığı ile oluşan modifikasyonlar da bu moleküllerin hücre içi ya da dışı komponentlere bağlanmalarını ya da reseptör bağlayıcı olarak normal fonksiyonlarını değiştirebilir. Bu etkileşmeler sonrasında inflamatuvar reaksiyonlar da tetiklenir. OS'in ve AGEs'lerin neden olduğu doku hasarları, diyabette morbidite ve mortaliteden sorumlu kardiyovasküler ve diğer komplikasyonların gelişmesini tetikleyen başlıca faktörlerdir. Hipergliseminin indüklediği OS'in organ fonksiyonları üzerindeki zararlı etkilerine yönelik bilimsel kanıtların giderek artıyor olması, araştırmacıların ilgisini OS'in önlenmesi, geciktirilmesi ya da geri döndürülmesi üzerine odaklamıştır. Bu bağlamda, pridoindol yapısında sentetik bir antioksidan olan stobadinin etkileri geniş çapta çalışılmış ve sonuç olarak bileşiğin, gliko-oksidatif hasarı inhibe ettiği, albuminüriyi, enzimüriyi, lipid peroksidasyonu, matriks kollagen çapraz bağlanmasını, plazma kolesterol ve trigliserit düzeylerini, protein karbonilasyonunu ve proteinlerle AGEs etkileşimini azalttığı, farklı dokularda protein tiyol, total tiyol, non-protein tiyol gruplarında iyileşmeye neden olduğu ve hipergliseminin şiddetini diyabetik deney hayvanlarında azalttığı gösterilmiştir. Stobadin ile tedavi edilen diyabetik deney hayvanlarında, kalpte kalsiyum birikimi azalmakta, ortalama kan basıncını düzelmekte, endotel hasarını önlemekte ve vasküler reaktivitedeki bozukluklar iyileştirilmektedir. Stobadin, kalp, aorta, böbrek, beyin, karaciğer, periferik sinirler, vas deferens ve retinayı, diyabetin neden olduğu metabolik, fonksiyonel ve yapısal değişikliklere karşı korumaktadır. Bu anlamda giderek artan deneysel kanıtlar, diyabetik komplikasyonların önlenmesi, geciktirilmesi ya da tedavi edilmesi bakımından stobadinin potansiyel terapötik bir ajan olabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Yaşlanma, Deneysel Diyabet, Oksidatif stress, Glikasyon, Antioksidant, Pridoindol, Stobadin

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MECHANISMS OF DIABETIC COMPLICATIONS

Aging and related chronic diseases such as diabetes mellitus are accompanied by increased Oxidative Stress (OS), which can directly affect the function of different tissues and organs. Since Advanced Glycation End products (AGEs) and OS are two mutually enhancing and tightly linked processes, it is likely that the accumulation of AGEs observed in the aging population is an important factor in the pathogenesis of the increased OS.[1] Hyperglycemia-induced metabolic abnormalities including redox imbalance, increased lipid peroxidation, AGEs formation and inflammation contribute to modifications in the receptor, enzyme or ion channel proteins. These result in impairments in their physiological functions and also signal transduction pathways such as abnormalities in the contractility of vascular smooth muscle and hearth, high blood pressure, nerve conduction velocity deficits and other tissue dysfunctions leading to complications as micro and macrovascular diseases, cardiomyopathy and neuropathy in diabetics.[2-7]

PREVENT, REVERSE OR RETARD OXIDATIVE STRESS IN ORDER TO MODIFY THE NATURAL HISTORY OF DIABETIC COMPLICATIONS

Since a linking element between hyperglycemia-induced metabolic disturbances and tissue function abnormalities is redox imbalance due to increased production of reactive oxygen species (ROS) and insufficiency in antioxidant defense, therefore recent research interest has focused on strategies to prevent, reverse or retard of OS in order to modify the natural history of diabetic complications.[8,9]

Oxidative stress is defined as an increase in the steady-state levels of ROS and may occur as a result of increased free radical generation and/or decreased anti-oxidant defense mechanisms. Increased basal production of $O_2^{\bullet-}$ and hydrogen peroxide (H_2O_2) in tissues has been shown in very early studies in diabetic animals.[10] Today we are clearly known that diabetes is a reason for an increased generation of oxygen-derived free radicals through autoxidation of glucose, AGE-formation, increased substrate flux through the polyol pathway, and stimulation of eicosanoid metabolism, sorbitol-diacylglycerol metabolism and NO synthase.[11]

A multitude of in vivo studies have been performed utilizing exogenous antioxidants in experimental diabetic models. The beneficial effects of treatment with exogenously added antioxidants on OS are measured through certain observable biomarkers. These markers include thiobarbituric acid reactants (TBARS) levels, malondialdehyde (MDA), F(2)-isoprostanes, and 4-hydroxynonenal as well as the enzymatic activities of catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase. Normalization of the levels of any of these markers, and ultimately, the balance of free-radical production/removal, would be an effective method to reduce ROS-induced damage. Many animal studies have been completed with this aim in mind and indeed have shown that diabetes-induced alterations of OS indicators can be reversed by antioxidant therapy. In different experiments of "the ADIC Study Group", we observed the effectiveness of exogenous antioxidant treatments in the recovery of oxidative stress markers and endogenous antioxidant enzyme activities in STZ-diabetic rats. Moreover, these recoveries have been associated with amelioration in vascular, cardiac and nerve metabolism and function.[2-4,12-22] Over the years, we focused on investigating the effects of the dietary supplemented antioxidants vitamin E, alpha-lipoic acid and vitamin A2-4.[12-22.]

PYRIDOINDOLS ARE EFFECTIVE IN THE PREVENTION OR IMPROVEMENT OF CELLULAR HOMEOSTASIS, METABOLISM AND TISSUE FUNCTIONS IN EXPERIMENTALLY-INDUCED DIABETES

In this context, in last decades our research area has focused on examining the effects of synthetic pyridoindole antioxidants on complications induced by experimentally models of diabetes. The experiments showed that stobadine is able to reduce hyperglycemia, hyperlypidemia, lipid hydroperoxides and/or other metabolic and cellular abnormalities associated with the functional and structural changes in myocardium, kidney, retina, liver, vasculature, nerve and other tissues in an in vivo model of streptozotocin-diabetic rats. Stobadine produced a vascular and endothelial protection in various model of ischemia/reperfusion. This antioxidant is also a neuroprotectan in models of free radical pathology in vivo and exerts antidysrhythmic, local anesthetic, alpha-adrenolytic, antihistaminic, myorelaxant and antiulcerogenic actions.[17-19,22,24-30] STZ-diabetic rats treated with stobadine were characterized by retarded calcium accumulation in the heart and attenuated cardiac protein glycation compared with untreated diabetic rats.[17] However, stobadine treatment was unable to af-

fect cardiac Ca^{2+},Mg^{2+}-ATPase activity,[17] but prevented diabetes-induced deterioration of cardiac Na^{+}, K^{+}-ATPase in the diabetic heart.[29] The combined treatment with stobadine and vitamin E was found to provide more benefits than the individual therapies in reducing both lipid peroxidation and cardiac abnormalities in diabetic animals.[17] This combination did not strengthen the protective effect of stobadine on the abnormal function of diabetic vas deferens[22] and leukocytes,[31] and contrary to our expectations, advanced the progression of the higher stages of cataract.[32] We observed that the inhibitory effect of in vivo stobadine treatment on Ca^{+2} entries through membrane-bound Ca^{+2} channels may account for its reducing effects on vasoconstriction and blood pressure.[33] In the model of doxorubicin-induced apoptosis of P815 cells, stobadine significantly increased cell viability and decreased the apoptosis rate as judged by flow cytometric analyses and by measuring caspase-3 and caspase-9 activities.[34] Furthermore, our preliminary findings suggest that STB and its analogues protected insulin release of INS-cell line stressed by H_2O_2 or cytokine cocktail, with potential therapeutic implications in the prevention of autoimmune diabetes.

CONCLUSION

STB was found to attenuate diabetes-induced pathological changes in different organs, to decrease albuminuria, enzymuria, lipid peroxidation and matrix collagen cross-linking, to reduce plasma cholesterol and triglyceride levels, and to diminish the severity of hyperglycemia in STZ-diabetic rats. Accumulating experimental evidence suggest that stobadine a promising agent to prevent, retard or treat diabetic complications.[17-19,22,24-34]

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