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Mini Review

Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: Old perspective with a new angle

Geeta Negi, Ashutosh Kumar, Rayanta P. Joshi, Shyam S. Sharma *

Molecular Neuropharmacology Laboratory, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Punjab, India

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ABSTRACT

Long-standing diabetes and complications thereof particularly, neuropathy stands for one of the major causes of morbidity across the globe. It is postulated that excessive production of reactive oxygen species is a key component in the development and progression of diabetic neuropathy. Oxidative damage is the most common concluding pathway for various pathogenetic mechanisms of neuronal injury in diabetic neuropathy. However despite optimistic preclinical data, it is still very ambiguous that why antioxidants have failed to demonstrate significant neuroprotection in humans. A growing body of evidences now suggests that strategies utilizing a more targeted approach like focusing on Nrf2 (a transcription factor modulating oxidative stress) may provide an enthralling avenue to optimize neuroprotection in diabetes and diabetic neuropathy. This review presents an emerging concept of Nrf2 in diabetic neuropathy; thus looking forward to newer strategies for combating the oxidant induced damage.

1. Introduction

The escalating prevalence of obesity, diabetes and metabolic syndrome at astounding rates in India and worldwide has been raising concern for last two decades. Between 1995 and 2030 the number of adult population affected by the diabetes is projected to grow by 170% [1]. Diabetic neuropathy is one of the most common and assorted complications of long standing diabetes. A detailed definition of DN says "a demonstrable disorder, either clinically evident or subclinical, that occurs in setting of diabetes mellitus without other causes for peripheral neuropathy [2]".

There are numerous acceptable pathogenetic factors which explain for the various deficits observed in diabetic neuropathy including aldose reductase pathway, advanced glycation end product formation, oxidative/nitrosative/carbonyl stress, increased protein kinase C activity, over-activation of poly ADP-ribose polymerase and inflammation [3–8]. While many of these pathways overlie and/or intersect with one or other pathways, together they produce a state of disparity between reactive species production and body's redox homeostasis, resulting in a condition termed as oxidative stress. Oxidative stress plays a major role in diabetes as well as in diabetic neuropathy. Nrf2 pathway has been implicated to play significant role contributing to the antioxidant defense of the body. Excess production of reactive oxygen species (ROS) is considered to cause abnormal axon morphology, altered neuronal membrane permeability along with causing functional modification of various cellular proteins [9–11]. Nrf2 and heme oxygenase-1 (HO-1, a phase II detoxifying enzyme) has been shown to possess protective effect against STZ induced diabetes and diabetic neuropathy [12]. In the present review, we have presented a contemporary outlook on most talked hypothesis of diabetic complications, oxidative stress and involvement of Nrf2 mediated modulation of antioxidant defense.

2. Oxidative stress in pathophysiology of DN: Classical perspective

Although hyperglycemia is considered to be a major pathogenic factor in the development of diabetic neuropathy, the mechanisms associated with this are not yet fully understood. Hyperglycemia unleash multiple pathways such as redox imbalances secondary to enhanced aldose reductase activity, increased advanced glycation end products (AGE) and altered protein kinase C (PKC) activity to induce oxidative stress (Fig 1). While specific inhibitors of any of these mechanisms ameliorate various diabetes-induced abnormalities *in vitro* and *in vivo*, common element linking all these pathways of hyperglycaemia-induced damage was a missing piece of puzzle for years. Oxidative stress has been found to be associated with the development of various abnormalities like reduced neurotrophic support, reduced axonal outgrowth, peroxynitrite damage to DNA, PARP overactivation etc. in DRG neurons and so could be the unifying mechanism

* Corresponding author. Address: Molecular Neuropharmacology Laboratory, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sec-67, S.A.S.Nagar, Mohali, Punjab 160062, India. Fax: +91 172 2214692.
E-mail address: sssharma@niper.ac.in (S.S. Sharma).

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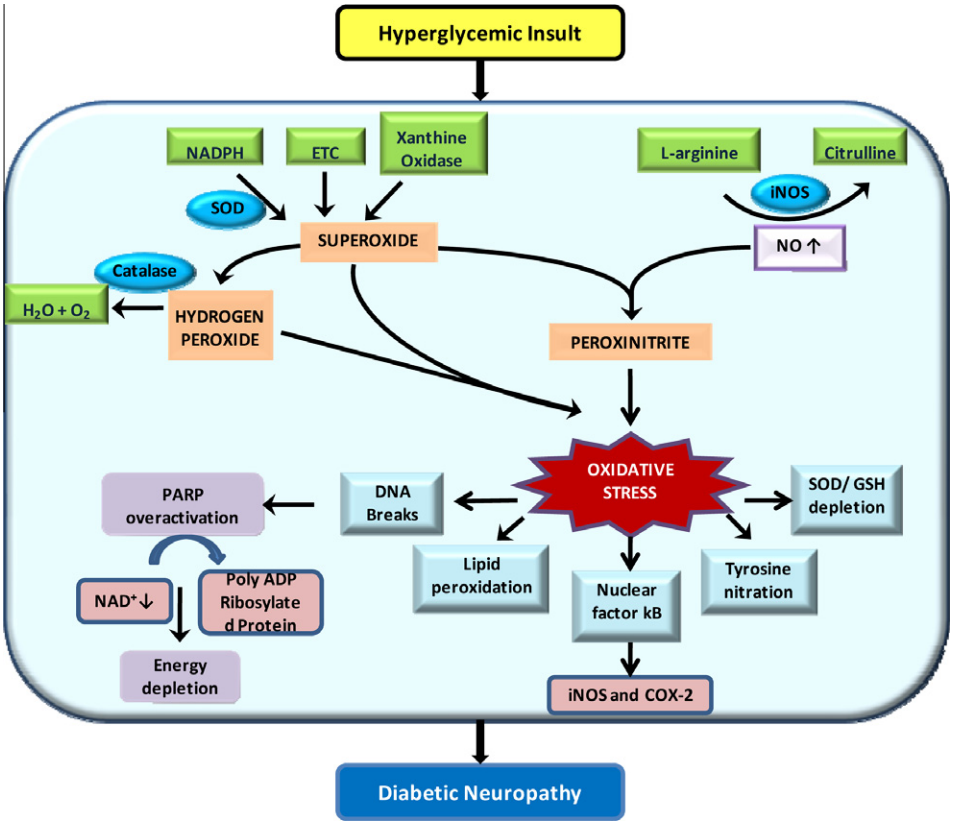

Fig. 1. Hyperglycemia activates many signaling mechanisms in cells. A unifying mechanism of neuronal injury in hyperglycemic condition is the production of ROS that impair protein and gene function. Under hyperglycemic conditions increased turnover of the mitochondrial energy-generating complexes occurs, which leads to escape of reactive intermediates. ETC: electron transport chain; GSH: reduced glutathione; PARP: poly ADP-ribose polymerase; SOD: superoxide dismutase.

that leads to nervous system damage in diabetes. Many up-to-the-minute studies have supported this hypothesis, including *in vivo* and *in vitro* measurement of oxidative-nitrosative stress and reduction in ROS levels by treatment with an antioxidant in sensory neurons and DRG [9,13–15].

One of the major pathways activated by elevated glucose levels i.e. polyol pathway depletes NADPH and NAD^+ levels which further reduces cellular glutathione, an endogenous antioxidant thereby weakening endogenous antioxidant defense. The biomarkers of oxidative stress were blunted by genetic ablation or by using inhibitors of aldose reductase which suggests that aldose reductase is also contributing to oxidative stress [16]. Glucose exist in equilibrium with their enediol, which can undergo autoxidation in the presence of transition metal forming enediol radical which can reduce molecular oxygen to form superoxide free radical and get oxidised to dicarbonyl compounds, thus contributing towards oxidative stress. These dicarbonyl compounds react with primary amino groups of proteins to form ketoimines which add to formation of AGE products [17]. RAGE (receptors for AGE) knockout mice were protected from excess mitochondrial and cytosolic superoxide which again points towards role of AGE in causing oxidant induced damage [18]. PKC, an important hyperglycemia activated enzyme has a unique structural feature that facilitates its regulation according to redox status of cell. Prooxidants react with regulatory domain to stimulate its activity while antioxidant reacts with catalytic domain and inhibits its activity. On activation, it triggers stress genes that phosphorylates transcription factors and thus alters the balance of gene expression [19,20]. As with some aldose reductase inhibitors, some of the PKC inhibitors have been shown to exhibit antioxidants effects. Bisindoylmaleimide, LY333531, ruboxistaurin, vitamin E, antisense oligonucleotides or peptide fragment inhibitors have demonstrated potential benefits in diabetic cardiovascular diseases [4]. Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme that is involved in DNA repair process. Recently it has been proved that PARP overactivation and oxidative stress are two inseparable pathways as well as reinforce each other in diabetic neuropathy [21,22]. Under physiological conditions, PARP activity is relatively low. However, under conditions of oxidative stress, excessive DNA single-strand breakage is triggered by ROS leading to overactivation of PARP [23]. Activated PARP initiates an energy consuming cycle resulting in rapid depletion of the intracellular pools of NAD^+ and ATP, hampering glycolysis and mitochondrial respiration, eventually leading to cellular energy crisis and cell death [24].

3. Transcription factor Nrf2: an emerging concept

Cells possess an array of antioxidant defense machinery to prevent or counterbalance the damage caused by reactive radicals. Important armors of antioxidant defense include superoxide dismutase, catalase, GSH, glutathione peroxidase, polyphenol, flavonoids. In addition to these, there is a family of enzymes which carry out the metabolic detoxification of highly reactive radicals and thus shield cells against excessive oxidative stress. These are phase II detoxifying enzymes which include glutathione S-transferase, UDP glucuronyl transferase, HO-1, NADPH-quinone oxidoreductase (NQO-1) and microsomal epoxide hydrolase. A cis-acting element termed antioxidant response element (ARE: 5′-NTGAG/CNNNGC-3′) regulates the levels of these detoxifying enzymes.

The transcription factor Nrf2 (NF-E2-related factor 2) has now been recognized as the crucial factor in the induction of phase II enzyme in response to stressful conditions through its interaction with ARE in the regulatory domains of its target genes [25–27].

Nrf2 is a member of cap 'n' collar basic region leucine zipper (CNC-bZIP) family of transcription factor. Nrf2 has been found to be ubiquitously present particularly in the organs involved in metabolic and detoxification processes. Kelch-like ECH associated protein 1 (Keap1) acts as a negative regulator of Nrf2 activity (Fig 2). Under unstressed conditions two molecules of Keap1 maintain Nrf2 in sequestered form in the cytosol. Keap1 molecule contains two major domains, a BTB domain (broad complex, tramtrack, and bric-a-brac) through which it is dimerized to another keap1 molecule and a Kelch (DGR) domain through which it is anchored to the F-actin cytoskeleton. Keap1 not only tethers Nrf2 in cytoplasm but also subject it to proteasomal degradation by bringing Nrf2 into the E3 ligase complex. Following interaction with E3 ligase, ubiquitination of Nrf2 occurs which is then degraded by the 26S proteasome. Thus in unstimulated conditions half life of Nrf2 is relatively very short (15 min) [27–29].

On the contrary, unsequestered Nrf2 is stable as it undergoes ubiquitination and proteasomal degradation at a much slower rate (half life >50 min). Encounter of the cell with reactive species results in the oxidation of cysteine thiol groups of Keap1 and brings in conformational changes in Keap1 dimer. This leads to the dissociation of Nrf2 from Keap1, allowing nuclear translocation of Nrf2. Once inside the nucleus, Nrf2 hetero-dimerizes with a small Maf protein for binding to a specific DNA-recognition sequence ARE. Interaction of Nrf2 with ARE results in the increased expression of antioxidant enzymes (HO-1; glutamylcysteine synthetase, γ-GCS and thioredoxin reductase 1) and phase II detoxifying enzymes (NQO1; glutathione S-transferases; UDP-glucuronyltransferases) [30–33].

4. Nrf2 and oxidative stress

As discussed earlier, oxidative stress plays a pivotal role in the pathophysiology of diabetic neuropathy and Nrf2 is considered as the axis of defense against oxidative stress, there is a definite correlation between pathogenesis of diabetic neuropathy and Nrf2 pathway. Protective effects of Nrf2 activators have been reported in experimental models for various diseases like diabetes, cerebral ischemia, cancer, neurodegeneration, atherosclerosis and numerous other inflammatory conditions [12,34–36]. Recently, many natural and synthetic compounds have been screened for their potential to activate Nrf2. Many of these have been found to be very effective in cancer chemoprevention, like oltipraz, quercetin, curcumin, ebselen, sulforaphane, celestrol, astaxanthine etc. [37,38]. Increased expression of Nrf2 also reduced VCAM-1 gene expression in vascular endothelial cells indicating its beneficial role in atherosclerosis [39,40]. A significantly higher levels of proinflammatory mediators were found in lungs of $Nrf2^{-/-}$ group in comparison with $Nrf2^{+/+}$ groups which suggests that Nrf2 deficiency is an important factor for asthma pathogenesis [41,42]. Nrf2 has also been implicated in providing protection to brain against oxidative stress and inflammation. Over-expression of Nrf2 in astrocytes conferred protection to neurons from oxidative stress. Activators of Nrf2 sulforaphane and *N*-acetyl-l-carnitine prevented inflammation mediated injuries in neurodegeneration and cerebral ischemia [34,43].

Nrf2 has been recently surfaced as an important target in diabetes and related complications. We studied Nrf2 and HO-1 expression in diabetic nerves and it was found to be down regulated in the sciatic nerve of diabetic animals when compared to normal control animals [12]. Other than studies from our group, evidences implicating decreased Nrf2 expression in diabetic neuropathy are relatively scarce. Still a plethora of studies have concluded the

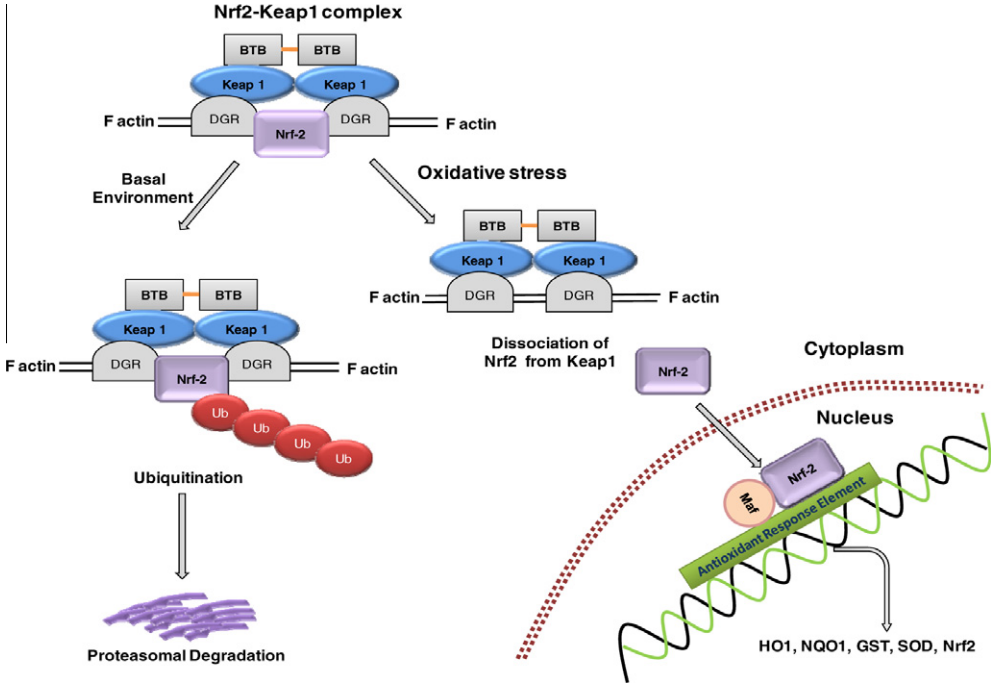

Fig. 2. A diagrammatic representation of Nrf2-Keap1 interaction and Nrf2 activation by oxidative stress. Keap1 act as negative regulator of the Nrf2 activation pathway and Nrf2 mediated antioxidant response. Under basal or unstimulated environment, two molecules of Keap1 keep Nrf2 sequestered in the cytoplasm. Keap1 molecules are dimerized through BTB domain and anchored to the F-actin cytoskeleton through a Kelch (DGR) domain. Keap1 complex also recruits the ubiquitin machinery to Nrf2, leading to proteasomal degradation of Nrf2. However, encounter with reactive oxygen species brings about a change in the conformation of Keap1 which results in the dissociation of Nrf2 from this inhibitory subunit. The free form of Nrf2, less prone to proteasomal degradation, translocates to the nucleus where it interacts with the antioxidant response element (ARE) to increase the expression of many antioxidant and detoxifying enzymes and proteins. BTB: broad complex, tramtrack, and bric-a-brac; DGR: double glycine repeat; Ub: ubiquitin; HO1: hemeoxygenase 1; NQO1: NADPH-quinone oxidoreductase 1; GST: glutathione S-tranferase; SOD: superoxide dismutase.

pivotal role of Nrf2 in diabetes and in the peripheral nerves. Nrf2 mediated HO-1 expression has been shown to reduce formalin induced inflammatory pain and thus can play putative role preventing sensorimotor alteration at peripheral sites [44]. Apart from neuropathy Nrf2 has been shown to possess neuroprotective effects in retinal ganglions [45,46]. Nrf2 is involved in retinal neuroprotection against many damaging stimuli by mechanisms including upregulation of thioredoxin system [47]. Pancreatic β-cell damage caused by cytokines and STZ was prevented by sulforaphane treatment or by overexpressing Nrf2 [48]. Nrf2 has also been reported to afford protection against STZ induced diabetic nephropathy as *Nrf2*$^{-/-}$ diabetic mice displayed higher ROS production and suffered greater renal injury when compared with *Nrf2*$^{+/+}$ diabetic mice [49,50]. Knockout of Nrf2 in cardiomyocytes incubated in high glucose media exhibited amplified ROS generation and subsequent apoptosis [51]. DRG and Schwann cells are highly susceptible to hyperglycemia mediated oxidative damage. DRG neurons were protected from H_2O_2 induced damage via activation of Nrf2 [15]. In our studies with antioxidants, we found that these antioxidants protected diabetic rats from various deficits in nerve function and executed their antioxidant functions through the activation of Nrf2-driven antioxidant enzymes [12]. Melatonin induced the expression of HO-1 in diabetic rats which translated in better protection against oxidative stress in diabetic neuropathy.

Recent progresses revealing Keap1–Nrf2 interaction, downstream signaling and antioxidant and phase II detoxifying enzymes expression regulated by Nrf2 are smoothening the progress of novel classes of chemopreventive agents which may also make their way to the management of diabetes related complications. Nrf-2 activators hold a potential for protection of peripheral nerves from a miscellany of stresses that originate from hyperglycemia and contribute to the burden of diabetes.

5. Antioxidants manipulate transcriptional activity of Nrf2

Treatment/prevention of diabetes related neuropathy hinge primarily upon the glycemic control. Antioxidants are surfacing out to be one of the successful strategies for treatment of diabetic neuropathy. The efficacy of many of the antioxidants has been recognized to be mediated through the induction of detoxifying and antioxidant genes based upon the study of animal model of diabetes. Resveratrol a polyphenolic antioxidant found in grapes proved to reverse the deficits associated with diabetic neuropathy via up regulating the expression of Nfr2 and HO-1 in the sciatic nerve of diabetic animals [52]. Vitamin E, one of the most experimented antioxidants in diabetic neuropathy has been proven to influence antioxidant enzymes and detoxifying enzymes regulated by Nrf2. Induction of Nrf2 activity by vitamin E depends on the form of the vitamin administered. α-tocopherol, which is most common form of vitamin E tested does not induce Nrf2 activity but γ-tocopherol does [53]. In addition to Nrf2, vitamin E also refurbished HO-1 expression in the kidney of diabetic animals [54]. Sulforaphane an antioxidant which gained attention through its excellent chemopreventive efficacy was found to be effective in diabetes as well. Sulforaphane prevented ROS production and also abrogated other biochemical deficits in human microvascular endothelial cells cultured in high glucose conditions [55]. Oltipraz another well known chemopreventive agent has shown its efficacy in diabetes. Aleksunes et al. showed that Nrf2 knock out diabetic mice had higher glucose levels as compared to wild type diabetic mice and treatment with oltipraz lowered blood glucose in wild-type but not Nrf2-null diabetic animal [56]. Thus Nrf2 is an essential component of glucose metabolism. Curcumin, a herb-derived polyphenolic compound, has been shown to possess multitude of biological response ranging from anti-oxidant, anti-inflammatory, anti-tumor, neuroprotective etc. Curcumin has also been demonstrated to exhibit antioxidant mechanism through Nrf2 activation [57] and is reported to protect against oxidant induced kidney damage by modulating Nrf2/HO-1 pathway [58]. Dimethyl curcumin (synthetic curcumin) has also been shown to modulate Nrf2/HO-1 in RAW264.7 macrophages [59].

Nrf2 pathway has gained importance in last few years and has been correlated in diverse conditions due to its role in neuroprotection, inflammatory diseases, and cancer prevention involving multiple organs. Oxidative stress has been correlated with the pathophysiology of diabetic neuropathy and is known to cross talk with the factors contributing towards its etiology. Nrf2 maintain balances controlling the antioxidant defense in the body which are at stake in variety of conditions including diabetes and diabetic neuropathy. The studies on transcription regulation by Nrf2 affecting the pathophysiology of diabetic neuropathy would probably provide a valuable futuristic avenue for drug development in diabetic neuropathy.

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References

[1] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (2010) (2010) 4–14.
[2] A.I. Vinik, R.E. Maser, B.D. Mitchell, R. Freeman, Diabetic Autonomic Neuropathy, Diabetes Care 26 (2003) 1553–1579.
[3] N.E. Cameron, M.A. Cotter, Pro-inflammatory mechanism in diabetic neuropathy: focus on the nuclear factor kappa b pathway, Curr. Drug Targets 9 (2008) 60–67.
[4] N. Das Evcimen, G.L. King, The role of protein kinase C activation and the vascular complications of diabetes, Pharmacol. Res. 55 (2007) 498–510.
[5] P.J. Oates, Aldose reductase, still a compelling target for diabetic neuropathy, Curr. Drug Targets 9 (2008) 14–36.
[6] S.S. Sharma, A. Kumar, R.K. Kaundal, Protective effects of 4-amino1, 8-napthalimide, a poly (ADP-ribose) polymerase inhibitor in experimental diabetic neuropathy, Life Sci. 82 (2008) 570–576.
[7] A.M. Vincent, J.L. Edwards, M. Sadidi, E.L. Feldman, The antioxidant response as a drug target in diabetic neuropathy, Curr. Drug Targets 9 (2008) 94–100.
[8] R. Wada, S. Yagihashi, Role of advanced glycation end products and their receptors in development of diabetic neuropathy, Ann. N. Y. Acad. Sci. 1043 (2005) 598–604.
[9] E. Zherebitskaya, E. Akude, D.R. Smith, P. Fernyhough, Development of selective axonopathy in adult sensory neurons isolated from diabetic rats: role of glucose-induced oxidative stress, Diabetes 58 (2009) 1356–1364.
[10] J.W. Russell, D. Golovoy, A.M. Vincent, P. Mahendru, J.A. Olzmann, A. Mentzer, E.L. Feldman, High glucose-induced oxidative stress and mitochondrial dysfunction in neurons, FASEB J. 16 (2002) 1738–1748.
[11] C. Figueroa-Romero, M. Sadidi, E.L. Feldman, Mechanisms of disease: the oxidative stress theory of diabetic neuropathy, Rev. Endocr. Metab. Disord. 9 (2008) 301–314.
[12] G. Negi, A. Kumar, S.S. Sharma, Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-kappaB and Nrf2 cascades, J. Pineal Res. 50 (2011) 124–131.
[13] A.M. Schmeichel, J.D. Schmelzer, P.A. Low, Oxidative injury and apoptosis of dorsal root ganglion neurons in chronic experimental diabetic neuropathy, Diabetes 52 (2003) 165–171.
[14] S.S. Sharma, A. Kumar, M. Arora, R.K. Kaundal, Neuroprotective potential of combination of resveratrol and 4-amino 1, 8 naphthalimide in experimental diabetic neuropathy: focus on functional, sensorimotor and biochemical changes, Free Radic. Res. 43 (2009) 400–408.
[15] A.M. Vincent, K. Kato, L.L. McLean, M.E. Soules, E.L. Feldman, Sensory neurons and schwann cells respond to oxidative stress by increasing antioxidant defense mechanisms, Antioxid. Redox. Signal. 11 (2009) 425–438.
[16] I.G. Obrosova, P. Pacher, C. Szabo, Z. Zsengeller, H. Hirooka, M.J. Stevens, M.A. Yorek, Aldose reductase inhibition counteracts oxidative-nitrosative stress and poly(ADP-ribose) polymerase activation in tissue sites for diabetes complications, Diabetes 54 (2005) 234–242.
[17] N. Ahmed, Advanced glycation endproducts–role in pathology of diabetic complications, Diabetes Res. Clin. Pract. 67 (2005) 3–21.

[18] A.L. Tan, K.C. Sourris, B.E. Harcourt, V. Thallas-Bonke, S. Penfold, S. Andrikopoulos, M.C. Thomas, R.C. O'Brien, A. Bierhaus, M.E. Cooper, J.M. Forbes, M.T. Coughlan, Disparate effects on renal and oxidative parameters following RAGE deletion, AGE accumulation inhibition, or dietary AGE control in experimental diabetic nephropathy, Am. J. Physiol. Renal Physiol. 298 (2010) F763–F770.
[19] J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes, Endocr. Rev. 23 (2002) 599–622.
[20] A.A. Sima, New insights into the metabolic and molecular basis for diabetic neuropathy, Cell Mol. Life Sci. 60 (2003) 2445–2464.
[21] G. Negi, A. Kumar, R.K. Kaundal, A. Gulati, S.S. Sharma, Functional and biochemical evidence indicating beneficial effect of Melatonin and Nicotinamide alone and in combination in experimental diabetic neuropathy, Neuropharmacology 58 (2010) 585–592.
[22] G. Negi, A. Kumar, S.S. Sharma, Concurrent targeting of nitrosative stress-PARP pathway corrects functional, behavioral and biochemical deficits in experimental diabetic neuropathy, Biochem. Biophys. Res. Commun. 391 (2010) 102–106.
[23] L. Virag, Structure and function of poly(ADP-ribose) polymerase-1: role in oxidative stress-related pathologies, Curr. Vasc. Pharmacol. 3 (2005) 209–214.
[24] I.G. Obrosova, V.R. Drel, P. Pacher, O. Ilnytska, Z.Q. Wang, M.J. Stevens, M.A. Yorek, Oxidative-nitrosative stress and poly(ADP-ribose) polymerase (PARP) activation in experimental diabetic neuropathy: the relation is revisited, Diabetes 54 (2005) 3435–3441.
[25] W. Wang, A.K. Jaiswal, Nuclear factor Nrf2 and antioxidant response element regulate NRH:quinone oxidoreductase 2 (NQO2) gene expression and antioxidant induction, Free Radic. Biol. Med. 40 (2006) 1119–1130.
[26] J. Alam, D. Stewart, C. Touchard, S. Boinapally, A.M.K. Choi, J.L. Cook, Nrf2, a cap n collar transcription factor, regulates induction of the heme oxygenase-1 Gene, J. Biol. Chem. 274 (1999) 26071–26078.
[27] A.K. Jaiswal, Nrf2 signaling in coordinated activation of antioxidant gene expression, Free Radic. Biol. Med. 36 (2004) 1199–1207.
[28] K.A. Jung, M.K. Kwak, The Nrf2 system as a potential target for the development of indirect antioxidants, Molecules 15 (2010) 7266–7291.
[29] N. Wakabayashi, S.L. Slocum, J.J. Skoko, S. Shin, T.W. Kensler, When Nrf2 Talks Who's Listening?, Antioxid Redox Signal. 13 (2010) 1649–1663.
[30] M. Kobayashi, M. Yamamoto, Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation, Antioxid. Redox Signal. 7 (2005) 385–394.
[31] W. Li, A.N. Kong, Molecular mechanisms of Nrf2-mediated antioxidant response, Mol. Carcinog. 48 (2009) 91–104.
[32] A.T. Dinkova-Kostova, P. Talalay, NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector, Arch. Biochem. Biophys. 501 (2010) 116–123.
[33] J.W. Kaspar, S.K. Niture, A.K. Jaiswal, Nrf2:INrf2 (Keap1) signaling in oxidative stress, Free Radic. Biol. Med. 47 (2009) 1304–1309.
[34] N.G. Innamorato, A.I. Rojo, A.J. Garcia-Yague, M. Yamamoto, M.L. de Ceballos, A. Cuadrado, The transcription factor Nrf2 is a therapeutic target against brain inflammation, J. Immunol. 181 (2008) 680–689.
[35] N. Tanaka, Y. Ikeda, Y. Ohta, K. Deguchi, F. Tian, J. Shang, T. Matsuura, K. Abe, Expression of Keap1-Nrf2 system and antioxidative proteins in mouse brain after transient middle cerebral artery occlusion, Brain Res. 1370 (2010) 246–253.
[36] Z. Ungvari, Z. Bagi, A. Feher, F.A. Recchia, W.E. Sonntag, K. Pearson, R. de Cabo, A. Csiszar, Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2, Am. J. Physiol. Heart Circ. Physiol. 299 (2010) H18–H24.
[37] J.D. Hayes, M. McMahon, S. Chowdhry, A.T. Dinkova-Kostova, Cancer chemoprevention mechanisms mediated through the Keap1-Nrf2 pathway, Antioxid. Redox Signal. 13 (2010) 1713–1748.
[38] M.K. Kwak, T.W. Kensler, Targeting NRF2 signaling for cancer chemoprevention, Toxicol. Appl. Pharmacol. 244 (2010) 66–76.
[39] X.L. Chen, G. Dodd, S. Thomas, X. Zhang, M.A. Wasserman, B.H. Rovin, C. Kunsch, Activation of Nrf2/ARE pathway protects endothelial cells from oxidant injury and inhibits inflammatory gene expression, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) H1862–H1870.
[40] X.L. Chen, S.E. Varner, A.S. Rao, J.Y. Grey, S. Thomas, C.K. Cook, M.A. Wasserman, R.M. Medford, A.K. Jaiswal, C. Kunsch, Laminar flow induction of antioxidant response element-mediated genes in endothelial cells. A novel anti-inflammatory mechanism, J. Biol. Chem. 278 (2003) 703–711.
[41] H.Y. Cho, A.E. Jedlicka, S.P. Reddy, T.W. Kensler, M. Yamamoto, L.Y. Zhang, S.R. Kleeberger, Role of NRF2 in protection against hyperoxic lung injury in mice, Am. J. Respir. Cell Mol. Biol. 26 (2002) 175–182.
[42] H.Y. Cho, S.P. Reddy, M. Yamamoto, S.R. Kleeberger, The transcription factor NRF2 protects against pulmonary fibrosis, FASEB J. 18 (2004) 1258–1260.
[43] V. Calabrese, A. Ravagna, C. Colombrita, G. Scapagnini, E. Guagliano, M. Calvani, D.A. Butterfield, A.M. Giuffrida Stella, Acetylcarnitine induces heme oxygenase in rat astrocytes and protects against oxidative stress: involvement of the transcription factor Nrf2, J. Neurosci. Res. 79 (2005) 509–521.
[44] A.O. Rosa, J. Egea, S. Lorrio, A.I. Rojo, A. Cuadrado, M.G. Lopez, Nrf2-mediated haeme oxygenase-1 up-regulation induced by cobalt protoporphyrin has antinociceptive effects against inflammatory pain in the formalin test in mice, Pain 137 (2008) 332–339.
[45] Y. Koriyama, K. Chiba, M. Yamazaki, H. Suzuki, K. Muramoto, S. Kato, Long-acting genipin derivative protects retinal ganglion cells from oxidative stress models in vitro and in vivo through the Nrf2/antioxidant response element signaling pathway, J. Neurochem. 115 (2010) 79–91.
[46] P. Maher, A. Hanneken, Flavonoids protect retinal ganglion cells from oxidative stress-induced death, Invest. Ophthalmol. Vis. Sci. 46 (2005) 4796–4803.
[47] M. Tanito, M.P. Agbaga, R.E. Anderson, Upregulation of thioredoxin system via Nrf2-antioxidant responsive element pathway in adaptive-retinal neuroprotection in vivo and in vitro, Free Radic. Biol. Med. 42 (2007) 1838–1850.
[48] M.Y. Song, E.K. Kim, W.S. Moon, J.W. Park, H.J. Kim, H.S. So, R. Park, K.B. Kwon, B.H. Park, Sulforaphane protects against cytokine- and streptozotocin-induced beta-cell damage by suppressing the NF-kappaB pathway, Toxicol. Appl. Pharmacol. 235 (2009) 57–67.
[49] T. Jiang, Z. Huang, Y. Lin, Z. Zhang, D. Fang, D.D. Zhang, The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy, Diabetes 59 (2010) 850–860.
[50] K. Yoh, A. Hirayama, K. Ishizaki, A. Yamada, M. Takeuchi, S. Yamagishi, N. Morito, T. Nakano, M. Ojima, H. Shimohata, K. Itoh, S. Takahashi, M. Yamamoto, Hyperglycemia induces oxidative and nitrosative stress and increases renal functional impairment in Nrf2-deficient mice, Genes Cells 13 (2008) 1159–1170.
[51] X. He, H. Kan, L. Cai, Q. Ma, Nrf2 is critical in defense against high glucose-induced oxidative damage in cardiomyocytes, J. Mol. Cell. Cardiol. 46 (2009) 47–58.
[52] A. Kumar, S.S. Sharma, NF-kappaB inhibitory action of resveratrol: a probable mechanism of neuroprotection in experimental diabetic neuropathy, Biochem. Biophys. Res. Commun. 394 (2010) 360–365.
[53] R. Pazdro, J.R. Burgess, The role of vitamin E and oxidative stress in diabetes complications, Mech. Ageing. Dev. 131 (2010) 276–286.
[54] D. Koya, K. Hayashi, M. Kitada, A. Kashiwagi, R. Kikkawa, M. Haneda, Effects of antioxidants in diabetes-induced oxidative stress in the glomeruli of diabetic rats, J. Am. Soc. Nephrol. 14 (2003) S250–S253.
[55] M. Xue, Q. Qian, A. Adaikalakoteswari, N. Rabbani, R. Babaei-Jadidi, P.J. Thornalley, Activation of NF-E2-related factor-2 reverses biochemical dysfunction of endothelial cells induced by hyperglycemia linked to vascular disease, Diabetes 57 (2008) 2809–2817.
[56] L.M. Aleksunes, S.A. Reisman, R.L. Yeager, M.J. Goedken, C.D. Klaassen, Nuclear factor erythroid 2-related factor 2 deletion impairs glucose tolerance and exacerbates hyperglycemia in type 1 diabetic mice, J. Pharmacol. Exp. Ther. 333 (2010) 140–151.
[57] E.S. Kang, G.H. Kim, H.J. Kim, I.S. Woo, S.A. Ham, H. Jin, M.Y. Kim, H.J. Kim, J.H. Lee, K.C. Chang, H.G. Seo, J.Y. Hwang, Nrf2 regulates curcumin-induced aldose reductase expression indirectly via nuclear factor-kappaB, Pharmacol. Res. 58 (2008) 15–21.
[58] E. Balogun, M. Hoque, P. Gong, E. Killeen, C.J. Green, R. Foresti, J. Alam, R. Motterlini, Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element, Biochem. J. 371 (2003) 887–895.
[59] S.O. Jeong, G.S. Oh, H.Y. Ha, B. Soon Koo, H. Sung Kim, Y.C. Kim, K.M. Lee, H.T. Chung, H.O. Pae, Dimethoxycurcumin, a synthetic curcumin analogue, induces heme oxygenase-1 expression through Nrf2 activation in RAW264.7 macrophages, J. Clin. Biochem. Nutr. 44 (2009) 79–84.