Graphical Review

Potential therapeutic effects of the simultaneous targeting of the Nrf2 and NF-κB pathways in diabetic neuropathy

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ABSTRACT

The Nuclear factor-2 erythroid related factor-2 (Nrf2) is a redox regulated transcription factor involved in the regulation of antioxidant defence systems. It drives the production of endogenous antioxidant defences and detoxifying enzymes. Nuclear factor-kappa light chain enhancer of B cells (NF-κB) is a transcription factor, involved in proinflammatory cytokine production, in addition to its immunological function. Both Nrf2 and NF-κB regulation are co-ordinated in order to maintain redox homeostasis in healthy cells. However, during pathological conditions this regulation is perturbed offering an opportunity for therapeutic intervention. Diabetic neuropathy is a condition, in which change in expression pattern of Nrf2 and NF-κB has been reported. This review aims to focus on the role of the Nrf2 and NF-κB in diabetic neuropathy and summarizes the therapeutic outcomes of various pharmacological modulators targeted at the Nrf2–NF-κB axis in diabetic neuropathy.

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Contents

Introduction ........................................................................................................................................... 394
Acknowledgement .............................................................................................................................. 397
References ........................................................................................................................................... 397

Introduction

Diabetes is one of the most debilitating conditions in patients affecting a substantial proportion of the world’s population. Diabetes can predispose an individual to metabolic, cardiovascular disturbances and obesity, and these pathologies are accompanied by vascular complications [1]. Hyperglycaemia-induced damage to the endothelial cells results in micro-vascular complications of the diabetes such as diabetic neuropathy, nephropathy and retinopathy and macro-vascular complications such as cardiomyopathy [2]. Diabetic neuropathy remains the most severe form of complication affecting 40–50% of people with both types of diabetes. The clinical features of diabetic neuropathy range from sensory deficit to allodynia and hyperalgesia. Diabetic neuropathy arises from the long term effects of hyperglycaemia induced damage to peripheral nervous tissue as well as the vasa nervorum [3].

The current knowledge of pathophysiological mechanisms of hyperglycaemia-induced diabetic neuropathy is substantial and recent advances made in field could lead to the development of some novel therapeutic strategies targeted at advance glycation end products (AGE), sorbitol accumulation, protein kinase C (PKC) activation and hexosamine pathway. The axis of pathophysiological factors responsible for diabetes and diabetic neuropathy converge at two of the most extensively studied pathways, oxidative–nitrosative stress and neuroinflammation (Fig. 1). Molecular studies have revealed the involvement of transcriptional regulators such as Nrf2-Keap1 and the NF-κB inflammatory cascade in the pathophysiology of many diseases [4].

NF-κB has been shown to respond to the cellular redox status since a reducing environment prevents its activation whereas
oxidative/nitrosative stress promotes phosphorylation and degradation of IκB [5]. Nrf2 increases intracellular GSH levels and GSH-dependent enzymes favouring a reducing environment thereby inhibiting Nf-κB. Li et al. demonstrated that Nrf2-deficient mice exhibit greater induction of pro-inflammatory genes regulated by NF-κB such as interleukins, TNF-α, iNOS and COX-2 pointing...
Towards the fact that Nrf2 deficiency enhances NF-κB-mediated pro-inflammatory reactions [6], Soares et al. showed that HO-1 inhibited the TNF-α dependent activation of NF-κB in endothelial cells. It has been postulated that HO-1 induced by the Nrf2-EpRE interaction inhibits the NF-κB dependent transcriptional apparatus. Inhibition of NF-κB downstream of IκB phosphorylation/degradation and nuclear translocation has been hypothesized to be the site of action of HO-1 [11]. These data further support the concept that the Nrf2 directed increase in the expression of HO-1 is one of the hubs for cross-talk between Nrf2 and NF-κB (Figs. 2 and 3).

Recent studies have shown that NF-κB suppresses the transcriptional activity of Nrf2. Liu et al. demonstrated that NF-κB p65 subunit repressed the beneficial effects of Nrf2 by promoting the localisation of transcription repressors, histone deacetylases with Nrf2/ARE and sequestering coactivators like CREB binding protein (CBP) [12]. Cells over-expressing NF-κB showed lesser expression of HO-1 which further confirms that NF-κB activation can act as a repressor of Nrf2 transcriptional activity. In a recent study, Yu et al. found that the N-terminal region of p65 subunit of NF-κB was physically associated with Keap1, and thus provide an additional mechanism for Nrf2–ARE inhibition. It was also suggested that NF-κB not only interacted with cytosolic Keap1 but also promoted nuclear translocation of Keap1 [13].

Previous studies with agents like curcumin [17], melatonin [18], resveratrol [19] and sulforaphane [20] have reported beneficial effects in ameliorating various functional (motor nerve conduction velocity and nerve blood flow), sensorimotor (thermal and mechanical hyperalgesia) and biochemical deficits in experimental diabetic neuropathy (Fig. 4). These agents also suppressed the increased activity and levels of NF-κB and associated proteins and hence protected against neuroinflammation in diabetic neuropathy. As expected, treatment with these agents increased the levels of Nrf2 and HO-1 which further modulating the redox regulation of pro-inflammatory signalling pathways. Additional studies to find any common co-activators or co-repressors shared by these transcription factors and co-regulation by upstream and downstream signalling in these cascades will enable a better appreciation of the crosstalk between these two transcription factors in diabetic neuropathy.

In summary, Nrf2 and NF-κB individually affect many signalling cascades to maintain a redox homeostasis; additionally they interact with each other to further modulate level of key redox modulators in health and disease. Studies with specific agents that might regulators the crosstalk between the two central pleiotropic transcription factors, Nrf2 and NF-κB, may be one of the prospective strategies that might aid in finding newer therapeutic choices for prevention and treatment of diabetic neuropathy.
expression of COX-2 and iNOS and reduced apoptosis. Reduced COX-2 activity in diabetic neuropathy leads to the development of neuropathic pain, production of proinflammatory cytokines, nerve damage, impaired motor nerve conduction velocity (MNCV) due to demyelination, impaired neuronal blood flow (NBF) and production of algogenic mediators and hence causes pain hypersensitivity. Reduced NF-κB activity results in increased oxidative stress in the neurons, which leads to the activation of PARP mediated neuronal apoptosis, AGE formation, PKC activation and alldynia and hyperalgesia due to the damage to the sensory fibres. However, this disturbed balance can be modulated pharmacologically to attenuate various deficits in diabetic neuropathy. The pharmacological modulation of NF-κB/Nrf2 axis by some pharmacological agents like Curcumin [17], Melatonin [18], Resveratrol [19] and Sulforaphane [20] produced beneficial effect by inhibiting NF-κB and activating Nrf2. The experimental outcomes of the studies of above mentioned compounds in streptozotocin (STZ) induced diabetic neuropathy model are manifested in the form of improved MNCV and NBF, decreased lipid peroxidation, IL-6, TNF-α, IL-1β, and allodynia and hyperalgesia due to the damage to the sensory fibres. However, this disturbed balance can be modulated pharmacologically to attenuate various deficits in diabetic neuropathy. The pharmacological modulation of NF-κB/Nrf2 axis by some pharmacological agents like Curcumin [17], Melatonin [18], Resveratrol [19] and Sulforaphane [20] produced beneficial effect by inhibiting NF-κB and activating Nrf2. 

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References

[1] J.M. Forbes, M.E. Cooper, Mechanisms of diabetic complications, Physiological reviews 91 (2011) 137–188.
[2] M. Brownlee, Biochemistry and molecular cell biology of diabetic complications, Nature 414 (2001) 813–820.
[3] J.L. Edwards, A.M. Vincent, H.T. Cheng, E.L. Feldman, Diabetic neuropathy: mechanisms to management, Pharmacology & Therapeutics 120 (2008) 1–34.
[4] G. Negi, A. Kumar, S.S. Sharma, Adopting Nrf2 and NF-κB from cancer: is there any role of the duo in diabetes? Nature Precedings (2011).
[5] A. Banning, R. Bigelins-Flohe, NF-kappaB, Nrf2, and HO-1 interplay in redox-regulated VCAM-1 expression, Antioxidants & Redox Signaling 7 (2005) 889–899.
[6] W. Li, T.O. Khor, C. Xu, G. Shen, W.S. Jeong, S. Yu, A.N. Kong, Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis, Biomedical Pharmacology 76 (2008) 1485–1489.
[7] M. Brownlee, The pathobiology of diabetic complications: a unifying mechanism, Diabetes 54 (2005) 1615–1625.
[8] Y. Tan, T. Ichikawa, J. Li, Q. Si, H. Yang, X. Chen, C.S. Goldblatt, C.J. Meyer, X. Li, L. Cai, Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress induced insulin resistance in cardiac cells in vitro and in vivo, Diabetes 60 (2011) 625–633.
[9] N.E. Cameron, M.A. Cotter, Pro-inflammatory mechanism in diabetic neuropathy: focus on the nuclear factor kappa B pathway, Current Drug Targets 9 (2008) 60–67.
[10] J. Scholz, C.J. Woolf, The neuropathic pain triad: neurons, immune cells and glia, Nature Neuroscience 10 (2007) 1361–1368.
[11] M.P. Soares, M.P. Seldon, L.P. Gregoire, T. Vassilevskia, P.D. Berberat, J. Yu, T.Y. Tsui, F.H. Bach, Haem oxygenase-1 modulates the expression of adhesion molecules associated with endothelial cell activation, Journal of Immunology 172 (2004) 3553–3563.
[12] G.H. Liu, J. Xu, X. Shen, NF-kappaB/p65 antagonizes Nrf2 activation and inflammation, production of proinflammatory molecules associated with endothelial cell activation, Journal of Immunology 172 (2004) 3553–3563.
[13] M. Yu, H. Li, Q. Liu, F. Liu, L. Tang, C. Li, Y. Yuan, Y. Zhan, W. Xu, W. Li, H. Chen, C. Ge, J. Wang, X. Yang, Nuclear factor p65 interacts with Keap1 to repress the Nrf2–ARE pathway, Cell Signaling 23 (2011) 883–892.
[14] E. Kansanen, S.M. Kuosmanen, H. Leinonen, A-L. Levonen, The Keap1–Nrf2 pathway: mechanisms of activation and dysregulation in cancer, Redox Biology 1 (2013) 45–49.
[15] N. Wakabayashi, S.L. Slocum, J.J. Skoko, S. Shin, T.W. Kessler, When NRF2 talks, who’s listening? Antioxidants & Redox Signaling 13 (2010) 1649–1663.
[16] M. Karin, Y. Yamamoto, Q.M. Wang, The IKK NF-kappaB pathway: a treasure trove for drug development, Nature Reviews Drug Discovery 3 (2004) 17–26.
[17] R.P. Joshi, G. Negi, A. Kumar, Y.B. Pawar, B. Munjal, A.K. Bansal, S.S. Sharma, SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: an insight into its mechanism for neuroprotection, Nanomedicine 9 (2013) 776–785.
[18] G. Negi, A. Kumar, S.S. Sharma, Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy; effects on NF-κB and Nrf2 cascades, Journal of PIneel Research 50 (2011) 124–131.
[19] A. Kumar, S.S. Sharma, NF-kappaB inhibitory action of resveratrol: a probable mechanism of neuroprotection in experimental diabetic neuropathy, Biochemical and Biophysical Research Communications 394 (2010) 360–365.
[20] G. Negi, A. Kumar, S.S. Sharma, Nrf2 and NF-κB modulation by sulforaphane counteracts multiple manifestations of diabetic neuropathy in rats and high glucose-induced changes, Current Neurovascular Research 8 (2011) 294–304.