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Inhibition of Early Biochemical Defects in Prodromal Huntington's Disease by Simultaneous Activation of Nrf2 and Elevation of Multiple Micronutrients

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Abstract: Huntington's disease (HD) is a progressive fatal dominant hereditary neurodegenerative disease of the brain, which primarily affects the cortex and the striatum. The disorder is typified by an expansion of more than 35 repeats of the nucleotide triplet cytosine- adenine-guanosine (CAG) which codes for the amino acid glutamine in the huntingtin gene. Despite studies of several decades, there are no effective means to block or postpone the appearance of symptoms of HD. Analysis of these studies led us to propose that increased oxidative stress and chronic inflammation are earliest events in the pathogenesis of HD, and together with excessive glutamate release, participate in the progression of the disease. This review briefly describes evidence for the involvement of oxidative stress, chronic inflammation and glutamate in the pathogenesis of HD. It is proposed that attenuation of these biochemical abnormalities together, may delay the appearance of symptoms of HD. In order to achieve this goal, the simultaneous activation of the nuclear transcriptional factor-2/antioxidant response elements (Nrf2/ARE) pathway that would enhance the transcription of target genes coding for antioxidant enzymes and phase-2-detoxifying enzymes, and an elevation of the levels of antioxidant compounds by supplementation may be needed. Normal mechanisms of activation of Nrf2 requiring reactive oxygen species (ROS) may be impaired in HD, but certain antioxidant compounds can activate Nrf2 without ROS. Use of a combination of micronutrients that can activate the Nrf2/ARE pathway and enhance the levels of antioxidant compounds is suggested.

Keywords: Antioxidants, glutamate release, huntington's disease, inflammation, micronutrients, nuclear transcriptional factor Nrf2, oxidative stress.

1. INTRODUCTION

Huntington's disease (HD) is an autosomal dominant heritable neurodegenerative disease predominantly involving the striatum and cortex. The symptoms primarily include movement disorders, cognitive dysfunction and psychiatric problems. The prevalence of HD in the USA is around 1,550 new cases annually. It appears to be much less common in Asia [1].

In the huntingtin gene of normal people, the number of trinucleotide CAG repeats varies from 1-34; however, in HD the number of repeats of the trinucleotide CAG triplets is expanded to between 35 and 140 [2]. Individuals carrying 39-60 CAG repeats exhibit late onset HD, whereas those carrying more than 60 CAG repeats have earlier onset HD [3-5].

Despite several decades of research, there are no useful means of preventing or slowing the appearance of symptoms of HD. Existing therapies provide marginal relief. Therefore additional preventive and therapeutic approaches should be developed.

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Using animal models and human HD, some biochemical defects associated with this disorder have been identified. These include increased oxidative stress [6-11], mitochondrial dysfunction [12-14], chronic inflammation [15-18], elevated glutamate levels [19-21], higher density of gamma-aminobutyric acid receptors [22-24], reduced levels of dopamine receptors [25-29] and cannabinoids [30-32], transcriptional dysregulation [33, 34], and posttranslational modification of the HD protein [35, 36]. Although the temporal and causal relation between these changes and HD development and progression is not clear, critical examination of these data leads us to put forward a hypothesis that increased oxidative stress, prolonged inflammation and heightened glutamate discharge, primarily contribute to the development of HD. Previous attempts to improve the symptoms of HD have utilized individual antioxidants, such as vitamin E [37], vitamin C [38], N-acetylcysteine [39], alpha-lipoic acid [40], coenzyme Q10 [41-43], L-carnitine [44, 45], lycopene and epigallocatechin [46], melatonin [47], curcumin [48], resveratrol [49, 50] *Ginkgo biloba* [51], nicotinamide [52], probucol [53] and a combination of carnosine plus vitamin E and betaine [54]. Vitamin E had some benefits in early phase of this disease. In animal models of HD, studies with individual antioxidants reduced oxidative stress and some symptoms. It is possible that a single antioxidant

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does not adequately reduce oxidative stress, inflammation or glutamate release in humans. This review proposes that simultaneous enhancement of the levels of antioxidant enzymes and phase-2- detoxifying enzymes by activation of a nuclear transcriptional factor-2 (Nrf2), together with elevation of the levels of antioxidants compounds by dietary supplementation, may help to reduce these biochemical defects. Concurrent reduction in glutamate release may also be needed to improve clinical outcomes.

The normal mechanism of activation of the Nrf2 /ARE pathway by way of reactive oxygen species (ROS), can be impaired during chronic oxidative stress. This pathway must be activated for increasing the levels of cytoprotective enzymes (antioxidant enzymes and phase-2-detoxifying enzymes). The means of regulation of Nrf2 and identification of agents that activate the Nrf2/ARE pathway without the need for ROS are discussed here. A combination of micronutrients that can activate the Nrf2/ARE pathway, enhance the levels of antioxidant compounds, and reduce excessive release of glutamate simultaneously is also suggested.

2. SYMPTOMS OF HD

Generally, symptoms of HD are initially evident in the young adult and then a progressive worsening takes place. Signs include movement disorders, failure of cognitive function and psychiatric abnormality. The order of their appearance of these symptoms can be variable (http://www. healthcommunities.com/huntington-disease/symptoms.shtml).
Movement disorders include abnormal involuntary tics in various appendages and in the face. These are more pronounced when the patients are stressed. As the disorder advances, other difficulties appear, including, jaw clenching (bruxism), increasing failure of motor coordination, unclear speech, difficulty in swallowing, spasticity and dystonia. Weight loss also generally takes place. There is a progressive failure of memory, ability to answer questions and identify familiar objects. Intellectual deficits generally develop later as the disease becomes more advanced. Damage to the striatal region is found initially in HD, and degenerative changes in other cerebral areas including the cortex, and thalamus are found subsequently. The medium spiny projection neurons of the striatum degenerate early in the disease while interneurons are maintained relatively intact [37]. Depression is found early in the course of the disease and can include aggression, irritability, lethargy, and anhedonia. Bipolar manic-depressive disorder and psychotic sequelae including, hallucinations, and paranoia may also develop.

3. ANIMAL MODELS OF HD

Animal models of HD have been developed which can permit study the events underlying HD and allow the testing of new approaches to the treatment of HD. Both pharmacological and genetic strategies have been used. Quinolinic acid, agonists of the N-methyl-d-aspartate receptor site, and 3-nitropropionic acid, an inhibitor of mitochondrial dehydrogenase, can all induce changes in the striatum of experimental animals resembling those found in human HD [55-56]. Injection of quinolinic acid directly into the striatum leads to biochemical, histological and behavioral alterations in the rat that resemble those found in human HD, including elevated activity of NADPH oxidase that promotes superoxide anion generation in the striatal neurons. Quinolinic acid and 3-NP also increase the oxidative and nitrosylative stress that precede subsequent neurodegeneration.

A series of genetic mouse variants have been established in recent years that incorporate the defective human gene of construct excessive CAG triplet number into the mouse huntingdin gene. The neuropathology and behavior of these mice resemble those found in human HD. Transgenic HD mouse models expressing either short N-terminals fragments (R6/1 and R6/2) or the full length HD gene (YAC128) show a pattern of gene expression in striatal neurons paralleling that found in human HD [57].

4. EVIDENCE FOR ELEVATED OXIDATIVE STRESS AND PERSISTENT INFLAMMATION AS PRIMARY EVENTS IN THE DEVELOPMENT OF HD

Increased markers of oxidative stress, mitochondrial failure and persistent inflammation have been repeatedly found in brain tissues from HD patients [6]; however, it is difficult to conclude whether these biochemical defects are the cause or the consequence of the disease. Strongest support for the idea that the defects are at least in part, causal to HD comes from individuals possessing the aberrant HD gene but not yet with obvious disease symptoms and also from animal simulations of HD.

4.1. Increased Oxidative Stress in Asymptomatic and Symptomatic HD

Analysis of indices of oxidative stress in patients with HD found that levels of plasma lipid peroxidation increased and levels of glutathione decreased in HD patients relative to those of healthy controls. It is noteworthy that parallel changes in these parameters were already apparent before the appearance of disease symptoms in HD carriers [7]. The activities of proteolytic aminopeptidases, decreased in the plasma of both asymptomatic individuals possessing the HD gene and in those patients with active HD [58]. Such peptidases cause release of glutamate and aspartate from the proteins, thus increasing their concentrations. Elevated levels extracellular of these excitatory neurotransmitters secondarily promote cerebral oxidative damage. In HD patients, indices of free radical activity, including leukocyte 8- hydroxydeoxyguanosine and plasma malondialdehyde, are elevated relative to control subjects, while levels of Cu/Zn superoxide dismutase and glutathione peroxidase in red blood cells are depressed. Plasma MDA concentrations are proportional to the severity of HD [8]. An increase in the degree of mitochondrial DNA damage is apparent in brains from HD patients, and this may have been induced by HD protein. Postmortem analysis of brain tissues from HD victims shows levels of enzymes relating to oxidative phosphorylation to be depressed. This is most apparent in the basal ganglia [9] where indices of oxidative stress are also elevated. Furthermore, evidence of oxidized DNA bases was found in the plasma of patients with HD [59]. The levels of carbonyls, a marker of oxidized protein damage was increased, while aconitase, a protein involved in the energy metabolism decreased in the autopsied striatal tissue of HD patients [60].

Thus, heightened pro-oxidant activity may contribute to the pathogenesis of HD.

Increased oxidative stress leads to the accumulation of HD protein and this promotes neuronal death [61]. Oxidant events also inhibit the functioning of proteasomes in neurons expressing the abnormal HD gene. This inhibition of proteasome operation can be reversed by overexpression of the gene for Cu/Zn-superoxide dismutase [61].

4.2. Accumulation of HD Protein

Protein aggregation is one of the early neurodegenerative events in HD. The insoluble HD protein aggregates are toxic to neurons [62]. These aggregated forms of HD proteins promote generation of reactive oxygen species (ROS). Treatment with MW7 antibody to HD protein inhibited HD protein coalescence and diminished production of ROS [63]. In both the mouse model of HD and human HD, caspase-1 and caspase-3 are excessively activated and the degree of activation correlates with the state of development of neurological deficits [64]. Caspase-2 cuts the HD protein into smaller fragments which can easily aggregate. Since aggregated HD protein fragments are not readily removed, they gradually bring about neuronal cell death in both human HD transgenic HD mouse model containing the full-length human HD gene (YAC72 mice) [65]. Caspase inhibitors can delay the appearance of pathology in this transgenic HD mouse model.

4.3. Mitochondrial Dysfunction in Asymptomatic and Symptomatic Patients with HD

In asymptomatic individuals and patients with HD symptoms, the expression of genes for aconitase-2 (ACO-2) and 3-oxoacid CoA transferase-1 (OXCT-1) that regulate mitochondrial function, was low in peripheral leukocytes [10]. These changes can impair mitochondrial function that can enhance the formation of free radicals during oxidative phosphorylation. HD proteins accumulate in mitochondria leading to mitochondrial dysfunction [12]. This could be due HD proteins binding to the respiratory chains complexes leading to the inhibition of mitochondrial energy production, which is a characteristic feature of HD. Defective mitochondrial function has been found in the autopsied striatal tissues of HD patients [11]. Mitochondrial transcription factor A and peroxisome proliferator-activated receptor- co- activator gamma- 1alpha (PGC-alpha), an important regulator of energy metabolism and of mitochondrial synthesis are gradually decreased as the severity of HD is increasingly manifested [66]. The soluble and aggregated N-terminal fragments of HD protein inhibit mitochondrial axonal transport in hippocampal neurons in culture [67]. Oxidative damage to mitochondrial enzymes responsible for generating energy causing decrease in energy is found in the autopsied samples of HD brain striatum [68].

4.4. Chronic Inflammation in Asymptomatic and Symptomatic Individuals with HD

Inflammation occurs early in pathogenesis of HD and is already evident at the preclinical stages of HD. An increase in microglia activation has been found in asymptomatic HD carriers, using a non-invasive PET- based procedure as an index of inflammation [15]. Atrophy of the striatum, substantia nigra, and anterior prefrontal cortex are also found in asymptomatic HD carriers. Plasma concentrations of the inflammatory cytokine, interleukin-6 are already high in asymptomatic persons carrying the HD gene even 16 years before the appearance of symptoms of HD. Monocytes from those carrying the HD gene are hyperactive in their reaction to stimulation [16]. The cerebrospinal fluid from HD patients also shows elevation of immune activity. The immune activation facilitated by microglia may be critical in the development of HD. The levels of other inflammatory cytokines were high in the plasma of asymptomatic individuals carrying HD gene and their concentrations correlated with disease progression. Oxidative damage to DNA activates the IkB kinase ß (IKKß) involved in regulation of immune responses in the brain. This activation then initiates caspase-dependent cleavage of both wild-type and HD proteins causing increased formation of oligomeric peptides [69]. The N-terminal peptide fragments of huntingtin proteins can also activate IKKß, resulting in more fragmentation of the HD proteins and more insoluble oligomeric peptides that are toxic to neurons**.** Elevated IKKß activity is present in the brain of mouse model of HD, but it is initially confined to the striatum in the asymptomatic mice carrying HD protein. Inhibitors of IKKß subdue the toxic effects of HD peptides in the striatum [69]. Activated microglia are found in the regions of neuronal loss in the autopsied HD brain samples, and these cells can produce disproportionate amounts of neurotoxic materials, including free radicals, pro-inflammatory cytokines and prostaglandins. Using PET methodology with asymptomatic HD carriers, microglia activation was found to occur primarily in the striatum and cortex early in the development of HD [15, 18]. The density of activated microglia is higher around neurons producing aberrant HD proteins, in both brain tissue slices and in neuronal cultures. As neurodegeneration progresses, increased amounts of interleukin-6 and complement protein 1q are present [70]. Circulating pro-inflammatory cytokine IL-23 and the soluble human leukocyte antigen- G are increased in the advanced stages of HD and there is a relation between IL-23 levels and the severity of the disease [71]. Administration of an anti-inflammatory drug, Celecoxib, an inhibitor cyclooxygenase-2 to rats previously treated with quinolinic acid leads to behavioral and biochemical attenuation of damage cause by quinolinic acid. Thus, overall the progression of HD seems to involve activation of inflammatory responses in the brain [72]. Treatment with calcium channel, blockers verapamil and diltiazem, reduces oxidative damage and levels of pro-inflammatory cytokines (TNF-alpha and interleukin-6) and caspase-3 in a rat model of HD [73].

5. EXCITOTOXICITY IN HD

Free extracellular glutamate release also appears to play a part in the progression of HD. Activation of mGluR2/3 receptors present in the corticostriatal terminals inhibits the release of glutamate. Daily subcutaneous injections of LY379268, a mGluR2/3 receptor agonist, produce no apparent changes in normal mice. However, in a mouse model of HD (R6/2), it delays mortality, improves motor functions and enhances the survival of cortical and striatal neurons.

The protective effect of LY379268 is affected by up-regulation of the levels of brain- derived growth factor (BDNF) in cortical regions [74]. Glutamate-promoted excitotoxicity is one of the events involved leading to death of striatal neurons in HD. Treatment of a striatal cell line with N-methyl-d- aspartate (NMDA) a glutamate agonist, accelerates death in cells containing the aberrant HD gene (STHdh (Q111/Q111) relative to cells expressing wild-type huntingtin gene (STHdh (Q7/Q7) [19]. Using another mouse line replicating some features of HD (YAC128), striatal neurons exhibit heightened sensitivity to excitotoxicity prior the onset of the signs of HD [20]. Glutamate- effected stimulation of NMDA receptors may be the cause of much of the neuronal disruption found in HD. Striatal neurons containing a high density of NMDA receptors die relatively early in HD due to this excitotoxic effect. Correspondingly, injection of glutamate receptor agonists into the striatum of normal animals can produce HD–like pathology [21]. As HD progresses, there is reduced dopaminergic and glutamatergic neurotransmission [75] attributable to death of these neurons. Thus, restoring the equilibrium between dopaminergic and glutamatergic transmission may help in alleviating the clinical manifestations of HD [75]. The glutamate content of the extracellular fluid is increased in HD probably due to a decrease in the glutamate transporter protein-1-dependent reuptake of glutamate. Glutamate transporter -1 and glutamate-aspartate transporter are largely present in the astrocytes, and are important in maintaining low levels of extracellular free glutamate.

In the mouse model of HD, the rate of release of ascorbate into the extracellular fluid is also reduced [76]. Thus levels of extracellular ascorbate are decreased while those glutamate are increased in the extracellular fluid of the diseased striatum. Both of these processes could exacerbate the adverse milieu surrounding striatal neurons. In R6/2 mice, administration of ascorbate restores extracellular levels to the values found in normal wild-type mice, and also stabilizes neuronal function [76].

The proposed interactions between the deficits discussed above are summarized in Fig. (**1**).

6. REDUCTION OF PRO-OXIDANT EVENTS, CHRONIC INFLAMMATION AND EXTRACELLULAR GLUTAMATE LEVELS AS A THERAPEUTIC APPROACH

The nuclear transcriptional factor Nrf2 (nuclear factor-erythroid 2-related factor-2) can enhance the expression of genes for antioxidant enzymes, phase-2-detoxifying enzymes

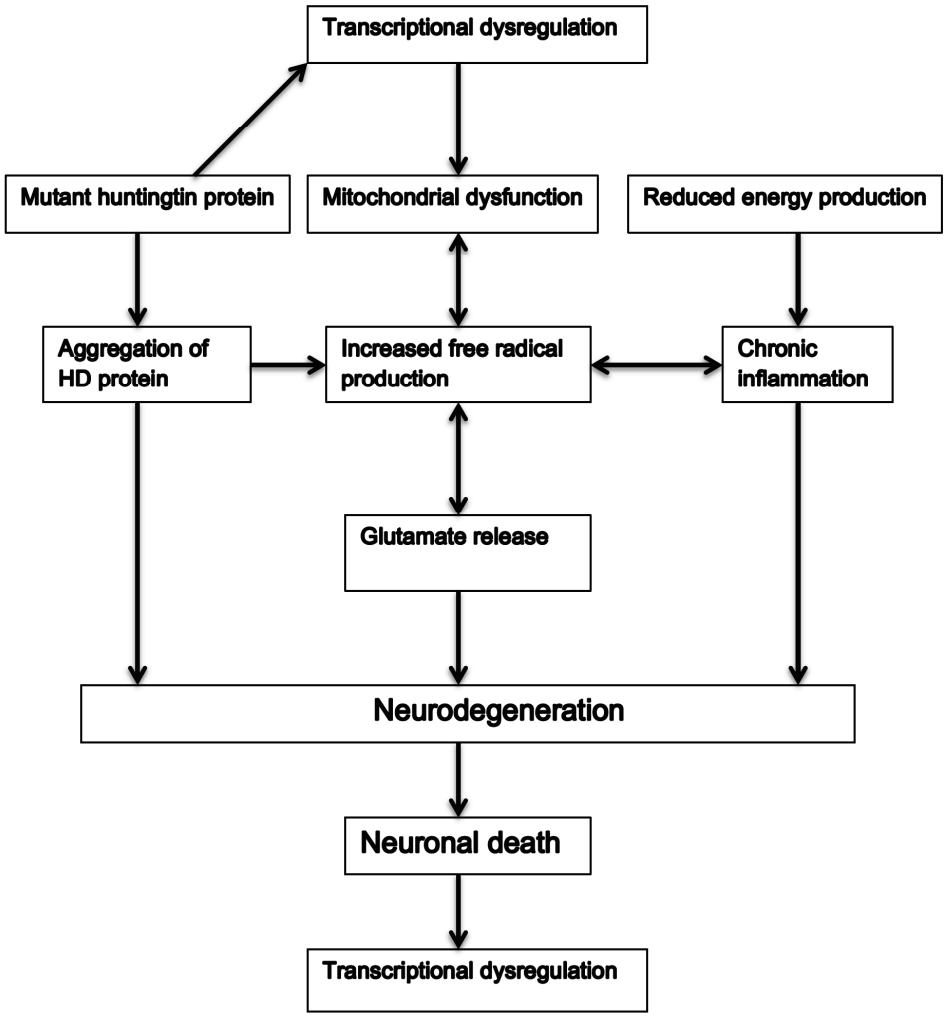


Fig. (1). Diagram of biochemical defects in Huntington's disease.

and mitochondrial enzymes. For this reason, the activation of Nrf2 is being used as a target in the development of new agents for treatment of several neurodegenerative diseases [77-80]. However, such activation alone may not suffice to reduce levels of oxidative stress sufficiently, because the levels of dietary and endogenous antioxidant compounds, which scavenge free radicals, can be depressed in the highly pro-oxidant environment of HD. Therefore, the levels of Nrf2 and antioxidant may thus need to be increased simultaneously. Antioxidant enzymes reduce free radical level by a mean that differs from that of antioxidant compounds, they catalyze the free radicals, while antioxidant compounds remove free radicals by direct scavenging. Elevated levels of antioxidant enzymes, together with dietary and endogenous antioxidants applied in combination, may most beneficially mitigate against pro-oxidant damage to the cell. In addition to increased oxidative stress, augmented accumulation of damaged proteins in the neurons plays a role in neuronal death. Thus, the levels of phase-2-detoxifying enzymes responsible for removing damaged molecules must also be increased.

In addition to scavenging free radicals, antioxidants can also reduce inflammation [81-85], and the release of glutamate [86-91] leading to a reduction of its neurotoxicity [91-93]. Vitamins B6, B12 and riboflavin can also curtail the release of glutamate [94, 95].

Since prolonged inflammation and excess extracellular glutamate are also key factors in the development of HD, it may be beneficial to reduce all these activities concurrently. Antioxidant compounds and B-vitamins may be increased by oral supplementation; however, increasing levels of antioxidant enzymes and phase-2-detoxifying enzymes requires an activation of Nrf2 leading to its translocation and binding to the nuclear antioxidant response elements (AREs).

7. THE ROLE OF Nrf2

7.1. Activation of Nrf2 by a ROS-dependent Mechanism During Acute Oxidative Stress

Normally, heightened ROS activates Nrf2, which dissociates itself from the Keap1- CuI-Rbx1 complex in the cytoplasm and translocates itself in the nucleus. After forming a heterodimer with a small Maf protein, this complex can then bind to the antioxidant response elements (AREs). This results in increased transcription of target genes coding for several antioxidant enzymes, phase-2-detoxifying enzymes and regulators of mitochondrial biogenesis [77, 78, 96-98]. Acute oxidative stress such as that observed during exercise is thought to activate Nrf2 by a mechanism that is dependent on ROS production [99]. Treatment with n-acetylcysteine (NAC) can actually block such ROS-initiated activation of Nrf2 [100]. Presumably, since NAC scavenges ROS effectively, insufficient ROS are present to promote activation of the Nrf2/ARE trajectory. This suggests that during acute oxidative stress, treatment with a single antioxidant may not be an effective means of preventing oxidative injury. In addition, repeated application of a solitary antioxidant before strenuous exercise may be harmful because it could be oxidized in a highly electrophilic environment, and in the absence of effective recycling, could then act in a pro-oxidant manner.

7.2. Impaired Binding of Nrf2 to ARE in Aged Animals

In order to enhance expression of antioxidant genes, activated Nrf2 must bind to the nuclear ARE. This binding capacity is reduced in aged rats but this depression can be reversed by administration of alpha-lipoic acid [101]. It is not yet known whether the ability of activated Nrf2 to bind to the ARE is normal in HD.

7.3. Defects in Normal Activation of Nrf2 by ROS During Chronic Oxidative Stress

Activation of Nrf2 becomes resistant to induction by ROS during prolonged oxidative stress yet activation by other means can still occur. Indeed, certain antioxidant compounds can activate Nrf2 without requiring ROS [102-104]. Consequently, such agents could be of use in reducing the progression of HD.

7.4. Regulation of the Levels and Activity of Nrf2

Nrf2 regulates the transcription of Keap1, and Keap1 reciprocally controls Nrf2 levels by modulating its proteosomal breakdown [105]. The immediate early response-3 (IER-3) gene, which responds to stress, can also modify Nrf2 activity. Deletion of this gene increases Nrf2 activity, while overexpression of IER-3 diminishes Nrf2 functioning [106].

The levels of Nrf2 are epigenetically controlled by methylation of the nucleotide residues CpG (cytosine-phosphate-guanosine) and by acetylation of histone3. Excessive methylation of CpG (107) and hyperacetylation of histone 3 [108] stimulate the expression of the Nrf2 gene, while reduced methylation and acetylation decrease it. Thus, pharmacological compounds that cause hypermethylation of CpG or hyperacetylation of histone3 may have utility in the mitigation of HD.

7.5. Reducing Oxidative Stress and Chronic Inflammation, and Improving Removal of Damaged Protein, by Activation of ROS-resistant Nrf2

Most antioxidant compounds inhibit oxidative damage in cells by scavenging free radicals directly, while some reduce it by also directly activating ROS-resistant Nrf2. Such agents include ascorbate [109] α-tocopherol and genistein [110], α-lipoic acid, [101], curcumin [111], resveratrol [112], omega-3-fatty acids [113, 114], glutathione [115], NAC [116], and coenzyme Q10 [117]. Several plant-derived materials in this group include epigallocatechin gallate, cafestol, lycopene and carnosol [118-120], allicin, present in garlic [121], sulforaphane, a component of cruciferous vegetables [122], and a range of kavalactones [123].

The activation of Nrf2 also suppresses chronic inflammation [124, 125] and increases the levels of phase-2-detoxifying enzymes for the removal of damaged molecules from the cells.

7.6. Nrf2 in Huntington's Disease

Abnormal HD protein disturbs the Nrf2 signaling route in striatal neurons expressing the HD gene, thus, promoting mitochondrial failure and increasing susceptibility to oxidative stress [126]. Treatment of animals with 3-nitropropionic

acid (3 -NP) also lowered the levels of cytoplasmic and nuclear Nrf2. Application of the complex II mitochondrial inhibitor dimethylfumarate to mouse models of HD (R6/2 and YAC128) is protective of cortical and striatal neurons, slows weight loss, and helps to maintain motor function. The mechanism underlying this appears to involve the Nrf2 signaling system [127]. Mice and cells with the Nrf2 gene deleted (Nrf2-/Nrf2-) are very susceptible to complex II inhibitors such as 3-nitropropionic and malonic acids, and administration of these can rapidly lead to death of striatal neurons. Intrastriatal insertion of astrocytes over-expressing Nrf2 is protective against the damage caused by these metabolic inhibitors [128]. After induction oxidative damage in rat striatal slices, with quinolinic acid, the Nrf2 pathway is rapidly upregulated, probably representing a protective response. Striatal sections derived from Nrf2-/- mice are more susceptible to the deleterious effects of quinolinic acid than those from Nrf2+/+ mice [129]. This suggests that stimulation of the Nrf2/ARE pathway may be of utility in the treatment of HD.

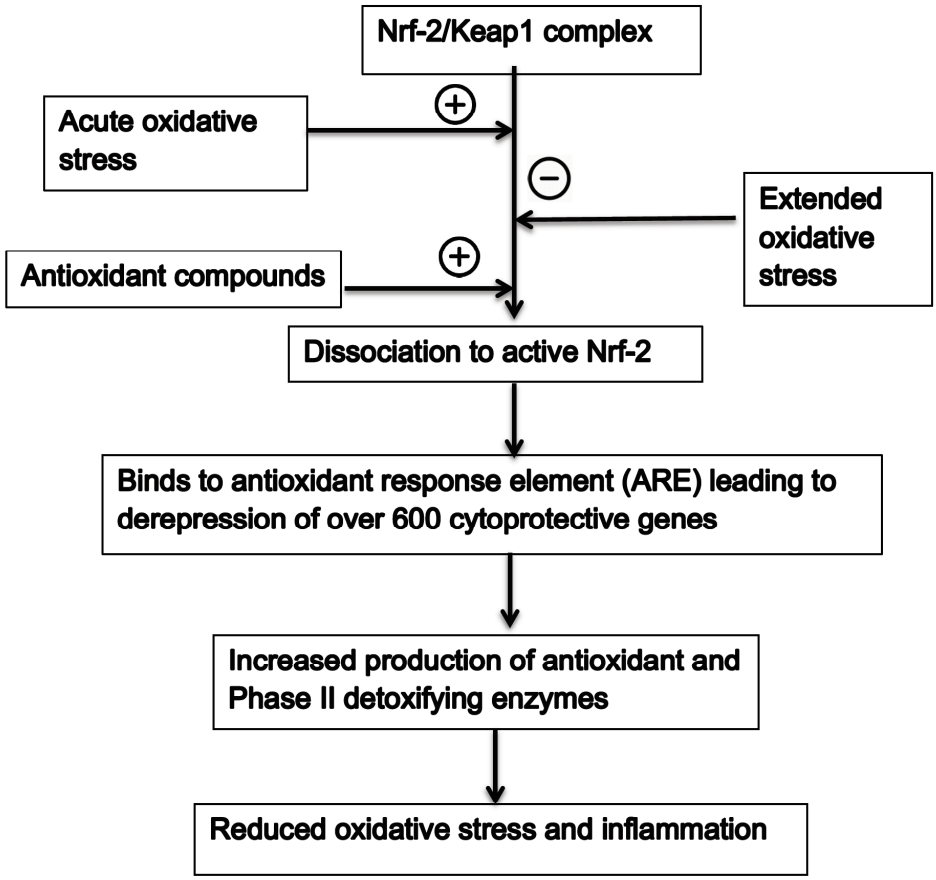
The means by which activated Nrf-2 acts broadly as a neuroprotectant are delineated in Fig. (**2**).

CONCLUSION

Increased pro-oxidant activity, chronic inflammation and excessive glutamate release pay an important role in the initiation and progression of HD. Diminution of these events may slow down the development of clinical symptoms of HD. Although the utilization of a single antioxidant improved some symptoms in animal models of HD, this strategy was ineffective in human HD. In order to optimally decrease oxidative stress, chronic inflammation and glutamate release, it may be necessary to simultaneously enhance the levels of antioxidant enzymes by activating the Nrf2/ARE pathway together with application of dietary antioxidant compounds. Using this multi-targeted approach, a preparation of micronutrients vitamins that would accomplish the above goal is proposed. These should include vitamin A, ascorbic acid, α-tocopherol, vitamin D, α-lipoic acid, coenzyme Q10, curcumin, resveratrol, omega-3-fatty acids, selenomethionine and several B-vitamins.

CONFLICT OF INTEREST

SCB has no conflict of interest. KNP consults with nutritional companies.



Nrf2 = Nuclear factor erythroid-2-related factor-2

⊕ = Activation ⊖ = Inhibition

Fig. (2). Diagram of the role of activation of Nrf-2 in protection of cellular elements.

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REFERENCES

[1] Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord 2012; 27: 1083-91.

[2] [No authors listed]. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993; 72(6): 971-83.

[3] Snell RG, MacMillan JC, Cheadle JP, *et al*. Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nat Genet 1993; 4: 393-7.

[4] Furtado S, Suchowersky O, Rewcastle B, Graham L, Klimek ML, Garber A. Relationship between trinucleotide repeats and neuropathological changes in Huntington's disease. Ann Neurol 1996; 39: 132-6.

[5] Ravina B, Romer M, Constantinescu R, *et al*. The relationship between CAG repeat length and clinical progression in Huntington's disease. Mov Disord 2008; 23: 1223-7.

[6] Browne SE, Beal MF. Oxidative damage in Huntington's disease pathogenesis. Antioxid Redox Signal 2006; 8: 2061-73.

[7] Klepac N, Relja M, Klepac R, Hecimovic S, Babic T, Trkulja V. Oxidative stress parameters in plasma of Huntington's disease patients, asymptomatic Huntington's disease gene carriers and healthy subjects : a cross-sectional study. J Neurol 2007; 254: 1676-83.

[8] Chen CM, Wu YR, Cheng ML, *et al*. Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington's disease patients. Biochem Biophys Res Commun 2007; 359:3 35-40.

[9] Browne SE, Bowling AC, MacGarvey U, *et al*. Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol 1997; 41: 646-53.

[10] Chang KH, Chen YC, Wu YR, Lee WF, Chen CM. Downregulation of genes involved in metabolism and oxidative stress in the peripheral leukocytes of Huntington's disease patients. PLoS ONE 2012; 7: e46492.E

[11] del Hoyo P, Garcia-Redondo A, de Bustos F, *et al*. Oxidative stress in skin fibroblasts cultures of patients with Huntington's disease. Neurochem Res 2006; 31: 1103-9.

[12] Browne SE. Mitochondria and Huntington's disease pathogenesis: Insight from genetic and chemical models. Ann N Y Acad Sci 2008; 1147: 358-82.

[13] Kim J, Moody JP, Edgerly CK, *et al*. Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Hum Mol Genet 2010; 19: 3919-35.

[14] Damiano M, Galvan L, Deglon N, Brouillet E. Mitochondria in Huntington's disease. Biochim Biophys Acta 2010; 1802: 52-61.

[15] Tai YF, Pavese N, Gerhard A, *et al*. Microglial activation in presymptomatic Huntington's disease gene carriers. Brain 2007; 130: 1759-66.

[16] Bjorkqvist M, Wild EJ, Thiele J, *et al*. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med 2008; 205: 1869-77.

[17] Pavese N, Gerhard A, Tai YF, *et al*. Microglial activation correlates with severity in Huntington disease: a clinical and PET study. Neurology 2006; 66: 1638-43.

[18] Politis M, Pavese N, Tai YF, *et al*. Microglial activation in regions related to cognitive function predicts disease onset in Huntington's disease: a multimodal imaging study. Human Brain Mapping 2011; 32: 258-70.

[19] Xifro X, Garcia-Martinez JM, Del Toro D, Alberch J, Perez-Navarro E. Calcineurin is involved in the early activation of NMDA-mediated cell death in mutant huntingtin knock-in striatal cells. J Neurochem 2008; 105: 1596-612.

[20] Graham RK, Pouladi MA, Joshi P, *et al*. Differential susceptibility to excitotoxic stress in YAC128 mouse models of Huntington disease between initiation and progression of disease. J Neurosci 2009; 29: 2193-204.

[21] Fan MM, Raymond LA. N-methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. Prog Neurobiol 2007; 81: 272-93.

[22] Rebec GV, Conroy SK, Barton SJ. Hyperactive striatal neurons in symptomatic Huntington R6/2 mice: variations with behavioral state and repeated ascorbate treatment. Neuroscience 2006; 137: 327-36.

[23] Rekik L, Daguin-Nerriere V, Petit JY, Brachet P. gamma-Aminobutyric acid type B receptor changes in the rat striatum and substantia nigra following intrastriatal quinolinic acid lesions. J Neurosci Res 2011; 89: 524-35.

[24] Cepeda C, Starling AJ, Wu N, *et al*. Increased GABAergic function in mouse models of Huntington's disease: reversal by BDNF. J Neurosci Res 2004; 78: 855-67.

[25] Yuen EY, Wei J, Zhong P, Yan Z. Disrupted GABAAR trafficking and synaptic inhibition in a mouse model of Huntington's disease. Neurobiol Dis 2012; 46: 497-502.

[26] Robinson P, Lebel M, Cyr M. Dopamine D1 receptor-mediated aggregation of N-terminal fragments of mutant huntingtin and cell death in a neuroblastoma cell line. Neuroscience 2008; 153 :762-72.

[27] Charvin D, Vanhoutte P, Pages C, Borrelli E, Caboche J. Unraveling a role for dopamine in Huntington's disease: the dual role of reactive oxygen species and D2 receptor stimulation. Proc Natl Acad Sci U S A 2005; 102: 12218-23.

[28] Pavese N, Politis M, Tai YF, *et al*. Cortical dopamine dysfunction in symptomatic and premanifest Huntington's disease gene carriers. Neurobiol Dis 2010; 37: 356-61.

[29] Esmaeilzadeh M, Farde L, Karlsson P, *et al*. Extrastriatal dopamine D(2) receptor binding in Huntington's disease. Human Brain Mapping 2011; 32: 1626-36.

[30] Ortiz AN, Osterhaus GL, Lauderdale K, *et al*. Motor function and dopamine release measurements in transgenic Huntington's disease model rats. Brain Res 2012; 1450: 148-56.

[31] Glass M, Dragunow M, Faull RL. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 2000; 97: 505-19.

[32] Van Laere K, Casteels C, Dhollander I, *et al*. Widespread decrease of type 1 cannabinoid receptor availability in Huntington disease *in vivo*. J Nuc Med 2010; 51: 1413-7.

[33] Blazquez C, Chiarlone A, Sagredo O, *et al*. Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. Brain 2011; 134: 119-36.

[34] ithell A, Johnson R, Buckley NJ. Transcriptional dysregulation of coding and non-coding genes in cellular models of Huntington's disease. Biochem Soc Trans 2009; 37: 1270-5.

[35] Buckley NJ, Johnson R, Zuccato C, Bithell A, Cattaneo E. The role of REST in transcriptional and epigenetic dysregulation in Huntington's disease. Neurobiol Dis 2010; 39: 28-39.

[36] Yanai A, Huang K, Kang R, *et al*. Palmitoylation of huntingtin by HIP14 is essential for its trafficking and function. Nat Neurosci 2006; 9: 824-31.

[37] Young FB, Butland SL, Sanders SS, Sutton LM, Hayden MR. Putting proteins in their place: palmitoylation in Huntington disease and other neuropsychiatric diseases. Prog Neurobiol 2012; 97: 220-38.

[38] Peyser CE, Folstein M, Chase GA, *et al*. Trial of d-alpha-tocopherol in Huntington's disease. Am J Psychiat 1995; 152(12): 1771-5.

[39] Rebec GV, Barton SJ, Marseilles AM, Collins K. Ascorbate treatment attenuates the Huntington behavioral phenotype in mice. Neuroreport 2003; 14: 1263-65.

[40] Sandhir R, Sood A, Mehrotra A, Kamboj SS. N-Acetylcysteine reverses mitochondrial dysfunctions and behavioral abnormalities in 3-nitropropionic acid-induced Huntington's disease. Neurodegenerative Dis 2012; 9: 145-57.

[41] Andreassen OA, Ferrante RJ, Dedeoglu A, Beal MF. Lipoic acid improves survival in transgenic mouse models of Huntington's disease. Neuroreport 2001; 12: 3371-3.

[42] Hickey MA, Zhu C, Medvedeva V, Franich NR, Levine MS, Chesselet MF. Evidence for behavioral benefits of early dietary supplementation with CoEnzymeQ10 in a slowly progressing mouse model of Huntington's disease. Mol Cell Neurosci 2012; 49: 149-57.

[43] Smith KM, Matson S, Matson WR, *et al*. Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice. Biochim Biophys Acta 2006; 1762: 616-26.

[44] Yang L, Calingasan NY, Wille EJ, *et al*. Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases. J Neurochem 2009; 109: 1427-39.

[45] Silva-Adaya D, Perez-De La Cruz V, Herrera-Mundo MN, *et al*. Excitotoxic damage, disrupted energy metabolism, and oxidative stress in the rat brain: Antioxidant and neuroprotective effects of L-carnitine. J Neurochem 2008; 105: 677-89.

[46] Vamos E, Voros K, Vecsei L, Klivenyi P. Neuroprotective effects of L-carnitine in a transgenic animal model of Huntington's disease. Biomed pharmacother 2010; 64: 282-6.

[47] Kumar P, Kumar A. Effect of lycopene and epigallocatechin-3-gallate against 3 nitropropionic acid induced cognitive dysfunction and glutathione depletion in rat: A novel nitric oxide mechanism. Food Chem Toxicol 2009; 47: 2522-30.

[48] Wang X, Sirianni A, Pei Z, *et al*. The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. J Neurosci 2011; 31: 14496-507.

[49] Hickey MA, Zhu C, Medvedeva V, *et al*. Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease. Mol Neurodegen 2012; 7: 12.

[50] Kumar P, Padi SS, Naidu PS, Kumar A. Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: Possible neuroprotective mechanisms. Behav Pharmacol 2006; 17: 485-92.

[51] Maher P, Dargusch R, Bodai L, Gerard PE, Purcell JM, Marsh JL. ERK activation by the polyphenols fisetin and resveratrol provides neuroprotection in multiple models of Huntington's disease. Hum Mol Genet 2011; 20: 261-70.

[52] Mahdy HM, Tadros MG, Mohamed MR, Karim AM, Khalifa AE. The effect of Ginkgo biloba extract on 3-nitropropionic acid-induced neurotoxicity in rats. Neurochem Int 2011; 59: 770-8.

[53] Hathorn T, Snyder-Keller A, Messer A. Nicotinamide improves motor deficits and upregulates PGC-1alpha and BDNF gene expression in a mouse model of Huntington's disease. Neurobiol Dis 2011; 41: 43-50.

[54] Colle D, Hartwig JM, Soares FA, Farina M. Probucol modulates oxidative stress and excitotoxicity in Huntington's disease models *in vitro*. Brain Res Bull 2012; 87: 397-405.

[55] Coban J, Bingul I, Yesil-Mizrak K. Effects of carnosine plus vitamin E and betaine treatments on oxidative stress in some tissues of aged rats. Curr Aging Sci 2013; 6: 199-205.

[56] Borlongan CV, Koutouzis TK, Sanberg PR. 3-Nitropropionic acid animal model and Huntington's disease. Neurosci Biobehav Rev 1997; 21: 289-93.

[57] Moresco RM, Lavazza T, Belloli S, *et al*. Quinolinic acid induced neurodegeneration in the striatum: a combined *in vivo* and *in vitro* analysis of receptor changes and microglia activation. Eur J Nucl Med Mol Imaging 2008; 35: 704-15.

[58] Kuhn A, Goldstein DR, Hodges A, *et al*. Mutant huntingtin's effects on striatal gene expression in mice recapitulate changes observed in human Huntington's disease brain and do not differ with mutant huntingtin length or wild-type huntingtin dosage. Hum Mol Genet 2007; 16: 1845-61.

[59] Duran R, Barrero FJ, Morales B, Luna JD, Ramirez M, Vives F. Oxidative stress and plasma aminopeptidase activity in Huntington's disease. J Neural Transm 2010; 117: 325-32.

[60] Johri A, Beal MF. Antioxidants in Huntington's disease. Biochem Biophys Acta 2012; 1822: 664-74.

[61] Sorolla MA, Reverter-Branchat G, Tamarit *et al*. Proteomic and oxidative stress analysis in human brain samples of Huntington disease Free Radic Biol Med 2008; 45: 667-78.

[62] Goswami A, Dikshit P, Mishra A, Mulherkar S, Nukina N, Jana NR. Oxidative stress promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death by mimicking proteasomal malfunction. Biochem Biophys Res Commun 2006; 342: 184-90. E

[63] Hoffner G, Soues S, Djian P. Aggregation of expanded huntingtin in the brains of patients with Huntington disease. Prion 2007; 1: 26-31.

[64] Hands S, Sajjad MU, Newton MJ, Wyttenbach A. *In vitro* and *in vivo* aggregation of a fragment of huntingtin protein directly causes free radical production. J Biol Chem 2011; 286: 44512-20.

[65] Sanchez Mejia RO, Friedlander RM. Caspases in Huntington's disease. The Neuroscientist 2001; 7: 480-9.

[66] Hermel E, Gafni J, Propp SS, *et al*. Specific caspase interactions and amplification are involved in selective neuronal vulnerability in Huntington's disease. Cell Death Diff 2004; 11: 424-38.

[67] McGill JK, Beal MF. PGC-1alpha, a new therapeutic target in Huntington's disease? Cell 2006; 127: 465-8.

[68] Tian J, Yan YP, Zhou R *et al*. Soluble N-terminal fragment of mutant huntingtin protein impairs mitochondrial axonal transport in cultured hippocampal neurons. Neurosci Bull 2014; 30: 74-80.

[69] Sorolla MA, Rodriguez-Colman MJ, Tamarit J, *et al*. Protein oxidation in Huntington disease affects energy production and vitamin B6 metabolism. Free Radic Biol Med 2010; 49: 612-21.

[70] Khoshnan A, Patterson PH. The role of IkappaB kinase complex in the neurobiology of Huntington's disease. Neurobiol Dis 2011; 43: 305-11.

[71] Kraft AD, Kaltenbach LS, Lo DC, Harry GJ. Activated microglia proliferate at neurites of mutant huntingtin-expressing neurons. Neurobiol Aging 2012; 33: 621 e17-33.

[72] Forrest CM, Mackay GM, Stoy N, *et al*. Blood levels of kynurenines, interleukin-23 and soluble human leucocyte antigen-G at different stages of Huntington's disease. J Neurochem 2010; 112: 112-22.

[73] Kalonia H, Kumar A. Suppressing inflammatory cascade by cyclo-oxygenase inhibitors attenuates quinolinic acid induced Huntington's disease-like alterations in rats. Life Sci 2011; 88: 784-91.

[74] Kalonia H, Kumar P, Kumar A. Attenuation of proinflammatory cytokines and apoptotic process by verapamil and diltiazem against quinolinic acid induced Huntington like alterations in rats. Brain Res 2011; 1372: 115-26.

[75] Reiner A, Lafferty DC, Wang HB, Del Mar N, Deng YP. The group 2 metabotropic glutamate receptor agonist LY379268 rescues neuronal, neurochemical and motor abnormalities in R6/2 Huntington's disease mice. Neurobiol Dis 2012; 47: 75-91.

[76] Andre VM, Cepeda C, Levine MS. Dopamine and glutamate in Huntington's disease: A balancing act. CNS Neurosci Therap 2010; 16: 163-78.

[77] Rebec Gv, Conroy SK, Barton SJ. Hyperactive striatal neurons in symptomatic Huntington R6/2 mice: Variations withbehavioralstate and repeated ascorbate treatment. Neuroscience 2006; 137: 326-36.

[78] Ajith TA, Padmajanair G. Mitochondrial Pharmaceutics: A review therapeutic strategy to ameliorate oxidative stress in Alzheimer's disease. Curr Aging Sci 2015; 8: 235-40.

[79] Tufekci KU, Bayin EC, Genc S *et al*. The Nrf2/ARE pathway: A promising target to counteract mitochondrial dysfunction in Parkinson's disease. Parkinson Dis 2011; 2011: 1-14.

[80] Dinkova-Kostova AT, Abramov AY. The emerging role of Nrf2 in mitochondrial function. Free Radic Biol Med 2015; 88: 179-88.

[81] Holmstrom KM, Baird L, Zhang Y, *et al*. Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. Biology Open 2015; doi:10.1242/bio.20134853

[82] Abate A, Yang G, Dennery PA, Oberle S, Schroder H. Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. Free Radic Biol Med 2000; 29: 1135-42.

[83] Devaraj S, Tang R, Adams-Huet B, *et al*. Effect of high-dose alpha-tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. Am J Clin Nutr 2007; 86: 1392-8.

[84] Fu Y, Zheng S, Lin J, Ryerse J, Chen A. Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol 2008; 73: 399-409.

[85] Lee HS, Jung KK, Cho JY, *et al*. Neuroprotective effect of curcumin is mainly mediated by blockade of microglial cell activation. Pharmazie 2007; 62: 937-42.

[86] Suzuki YJ, Aggarwal BB, Packer L. Alpha-lipoic acid is a potent inhibitor of NF-kappa B activation in human T cells. Biochem Biophys Res Commun 1992; 189: 1709-15.

[87] Zhu J, Yong W, Wu X, *et al*. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. Biochem Biophys Res Commun 2008; 369: 471-7.

[88] Dohare P, Hyzinski-Garcia MC, Vipani A, *et al*. The neuroprotective properties of the superoxide dismutase mimetic tempol correlate with its ability to reduce pathological glutamate release in a rodent model of stroke. Free Radic Biol Med 2014; 77: 168-82.

[89] Lu CW, Lin TY, Wang SJ. Quercetin inhibits depolarization-evoked glutamate release in nerve terminals from rat cerebral cortex. Neurotoxicology 2013; 39: 1-9.

[90] Hurtado O, De Cristobal J, Sanchez V, *et al*. Inhibition of glutamate release by delaying ATP fall accounts for neuroprotective effects of antioxidants in experimental stroke. FASEB J 2003; 17: 2082-4.

[91] Santos PS, Campelo LM, Freitas RL, Feitosa CM, Saldanha GB, Freitas RM. Lipoic acid effects on glutamate and taurine concentrations in rat hippocampus after pilocarpine-induced seizures. Arquivos de neuro-psiquiatria 2011; 69: 360-4.

[92] Chang Y, Huang SK, Wang SJ. Coenzyme Q10 inhibits the release of glutamate in rat cerebrocortical nerve terminals by suppression of voltage-dependent calcium influx and mitogen-activated protein kinase signaling pathway. J Agricul Food Chem 2012; 60: 11909-18.

[93] Schubert D, Kimura H, Maher P. Growth factors and vitamin E modify neuronal glutamate toxicity. Proc Natl Acad Sci U S A 1992; 89: 8264-7.

[94] Sandhu JK, Pandey S, Ribecco-Lutkiewicz M, *et al*. Molecular mechanisms of glutamate neurotoxicity in mixed cultures of NT2-derived neurons and astrocytes: Protective effects of coenzyme Q10. J Neurosci Res 2003; 72: 691-703.

[95] Yang TT, Wang SJ. Pyridoxine inhibits depolarization-evoked glutamate release in nerve terminals from rat cerebral cortex: a possible neuroprotective mechanism? J Pharmacol Expt Ther 2009; 331: 244-54.

[96] Hung KL, Wang CC, Huang CY, Wang SJ. Cyanocobalamin, vitamin B12, depresses glutamate release through inhibition of voltage-dependent Ca2+ influx in rat cerebrocortical nerve terminals (synaptosomes). Eur J Pharmacol 2009; 602: 230-7.

[97] Itoh K, Chiba T, Takahashi S, *et al*. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun 1997; 236: 313-22.

[98] Hayes JD, Chanas SA, Henderson CJ, *et al*. The Nrf2 transcription factor contributes both to the basal expression of glutathione S-transferases in mouse liver and to their induction by the chemopreventive synthetic antioxidants, butylated hydroxyanisole and ethoxyquin. Biochem Soc Trans 2000; 28: 33-41.

[99] Chan K, Han XD, Kan YW. An important function of Nrf2 in combating oxidative stress: detoxification of acetaminophen. Proc Natl Acad Sci USA 2001; 98: 4611-6.

[100] Muthusamy VR, Kannan S, Sadhaasivam K, *et al*. Acute exercise stress activates Nrf2/ARE signaling and promotes antioxidant mechanisms in the myocardium. Free Radic Biol Med 2012; 52: 366-76.

[101] Romanque P, Cornejo P, Valdes S, Videla LA. Thyroid hormone administration induces rat liver Nrf2 activation: suppression by N-acetylcysteine pretreatment. Thyroid 2011; 21: 655-62.

[102] Suh JH, Shenvi SV, Dixon BM, *et al*. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci USA 2004; 101: 3381-6.

[103] Ramsey CP, Glass CA, Montgomery MB, *et al*. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol 2007; 66: 75-85.

[104] Chen PC, Vargas MR, Pani AK, *et al*. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. Proc Natl Acad Sci U S A 2009; 106: 2933-8.

[105] Lastres-Becker I, Ulusoy A, Innamorato NG, *et al*. alpha-Synuclein expression and Nrf2 deficiency cooperate to aggravate protein aggregation, neuronal death and inflammation in early-stage Parkinson's disease. Hum Mol Genet 2012; 21: 3173-92.

[106] Niture SK, Kaspar JW, Shen J, Jaiswal AK. Nrf2 signaling and cell survival. Toxicol Appl Pharmacol 2010; 244: 37-42.

[107] Stachel I, Geismann C, Aden K, *et al*. Modulation of nuclear factor E2-related factor-2 (Nrf2) activation by the stress response gene immediate early response-3 (IER3) in colonic epithelial cells: A novel mechanism of cellular adaption to inflammatory stress. J Biol Chem 2014; 289: 1917-29.

[108] Khor TO, Fuentes F, Shu L, *et al*. Epigenetic DNA Methylation of Anti-oxidative Stress Regulator Nrf2 in Human Prostate Cancer. Cancer Prev Res 2014; 7: 1186-97.

[109] Yu S, Khor TO, Cheung KL, *et al*. Nrf2 expression is regulated by epigenetic mechanisms in prostate cancer of TRAMP mice. PloS One 2010; 5: e8579.

[110] Kim SR, Ha YM, Kim YM, *et al*. Ascorbic acid reduces HMGB1 secretion in lipopolysaccharide-activated RAW 264.7 cells and improves survival rate in septic mice by activation of Nrf2/HO-1 signals. Biochem Pharmacol 2015; 95: 279-89.

[111] Xi YD, Yu HL, Ding J, *et al*. Flavonoids protect cerebrovascular endothelial cells through Nrf2 and PI3K from beta-amyloid peptide-induced oxidative damage. Curr Neurovasc Res 2012; 9: 32-41.

[112] Trujillo J, Chirino YI, Molina-Jijon E, Anderica-Romero AC, Tapia E, Pedraza-Chaverri J. Renoprotective effect of the antioxidant curcumin: Recent findings. Redox Biol 2013; 1: 448-56.

[113] Kode A, Rajendrasozhan S, Caito S, Yang SR, Megson IL, Rahman I. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 2008; 294: L478-88.

[114] Gao L, Wang J, Sekhar KR, *et al*. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. J Biol Chem 2007; 282: 2529-37.

[115] Saw CL, Yang AY, Guo Y, Kong AN. Astaxanthin and omega-3 fatty acids individually and in combination protect against oxidative stress *via* the Nrf2-ARE pathway. Food Chem Toxicol 2013; 62: 869-75.

[116] Song J, Kang SM, Lee WT, Park KA, Lee KM, Lee JE. Glutathione protects brain endothelial cells from hydrogen peroxide-induced oxidative stress by increasing nrf2 expression. Exp Neurobiol 2014; 23: 93-103.

[117] Ji L, Liu R, Zhang XD, *et al*. N-acetylcysteine attenuates phosgene-induced acute lung injury *via* up-regulation of Nrf2 expression. Inhal Toxicol 2010; 22: 535-42.

[118] Choi HK, Pokharel YR, Lim SC, *et al*. Inhibition of liver fibrosis by solubilized coenzyme Q10: Role of Nrf2 activation in inhibiting transforming growth factor-beta1 expression. Toxicol Appl Pharmacol 2009; 240: 377-84.

[119] Chun KS, Kundu J, Kundu JK, Surh YJ. Targeting Nrf2-Keap1 signaling for chemoprevention of skin carcinogenesis with bioactive phytochemicals. Toxicol Lett 2014; 21:73-84.

[120] Jaramillo MC, Zhang DD. The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes Dev 2013; 27: 2179-91.

[121] Jeong WS, Jun M, Kong AN. Nrf2: a potential molecular target for cancer chemoprevention by natural compounds. Antioxid Redox Signal 2006; 8: 99-106.

[122] Li XH, Li CY, Lu JM, Tian RB, Wei J. Allicin ameliorates cognitive deficits ageing-induced learning and memory deficits through enhancing of Nrf2 antioxidant signaling pathways. Neurosci Lett 2012; 514: 46-50.

[123] Bergstrom P, Andersson HC, Gao Y, *et al*. Repeated transient sulforaphane stimulation in astrocytes leads to prolonged Nrf2-mediated gene expression and protection from superoxide-induced damage. Neuropharmacology 2011; 60: 343-53.

[124] Wruck CJ, Gotz ME, Herdegen T, Varoga D, Brandenburg LO, Pufe T. Kavalactones protect neural cells against amyloid beta peptide-induced neurotoxicity *via* extracellular signal-regulated kinase 1/2-dependent nuclear factor erythroid 2-related factor 2 activation. Mol Pharmacol 2008;73: 1785-95.

[125] Li W, Khor TO, Xu C, *et al*. Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. Biochem Pharmacol 2008; 76: 1485-9.

[126] Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. Mutat Res 2010; 690: 12-23.

[127] Jin YN, Yu YV, Gundemir S, *et al*. Impaired mitochondrial dynamics and Nrf2 signaling contribute to compromised responses to oxidative stress in striatal cells expressing full-length mutant huntingtin. PLoS ONE 2013;8: e57932.

[128] Ellrichmann G, Petrasch-Parwez E, Lee DH, *et al*. Efficacy of fumaric acid esters in the R6/2 and YAC128 models of Huntington's disease. PLoS ONE 2011; 6: e16172.

[129] Calkins MJ, Jakel RJ, Johnson DA, Chan K, Kan YW, Johnson JA. Protection from mitochondrial complex II inhibition *in vitro* and *in vivo* by Nrf2-mediated transcription. Proc Natl Acad Sci U S A 2005;102: 244-9.

[130] Bahramisharif A, van Gerven MA, Aarnoutse EJ, *et al*. Propagating neocortical gamma bursts are coordinated by traveling alpha waves. J Neurosci 2013; 33:18849-54.

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