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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

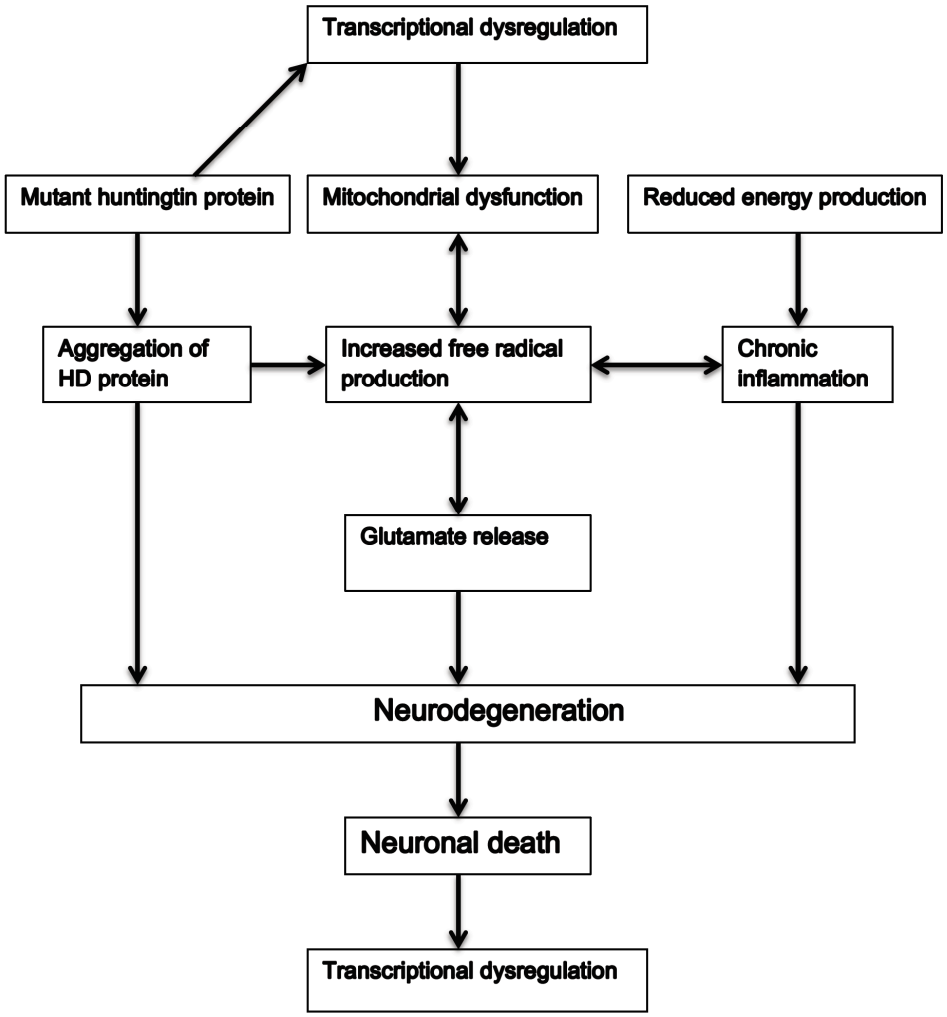


Fig. (1). Diagram of biochemical defects in Huntington's disease.

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.

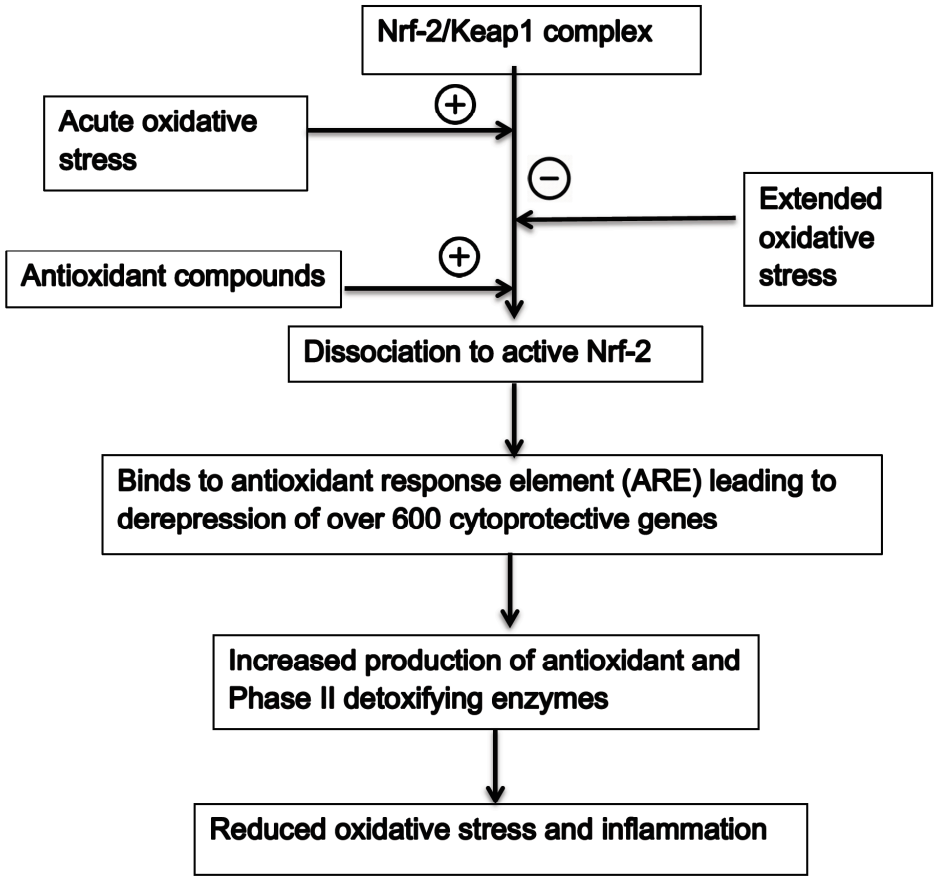
The means by which activated Nrf-2 acts broadly as a neuroprotectant are delineated in Fig. (**2**).

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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Declared none.

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