

# Simultaneous Activation of Nrf2, Elevation of Antioxidants and Reduction in Glutamate Level: An Essential Strategy for Prevention and Improved Management of Neurodegenerative Diseases

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## Abstract

Despite extensive research on the biochemical and genetic defects in Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and post-traumatic stress disorders (PTSDs), there are no effective preventive strategies; and the treatment methods remain unsatisfactory. The reviews of these studies suggested that enhanced production of free radicals, persistence inflammation were one of the earliest events in the development and progression of these diseases. Excess release of glutamate occurred in HD and PTSD earlier than in AD and PD. Glutamate together with excess free radicals and pro-inflammatory cytokines participate in the progression of these diseases. Thus, reducing simultaneously these biochemical defects may prevent, and together with standard therapy, enhance the care of neurodegenerative diseases. Previous studies using primarily individual antioxidants produced variable outcomes ranging from transient benefits in the early phase of the disease to no effect. In order to optimally attenuate oxidative stress, persistence inflammation and glutamate, it is necessary to simultaneously increase the cellular levels of cytoprotective enzymes including antioxidant enzymes, antioxidant compounds that are derived from the diet and made in the body and reduce glutamate level. Enhancement of antioxidant compounds and attenuation of glutamate level are achieved by supplementation with antioxidants and B-vitamins; however, increasing the cellular levels of antioxidant enzymes needs an activation of Nrf2 that is ROS-dependent and ROS-independent. In neurodegenerative diseases, Nrf2 is not activated by ROS; however, antioxidants activate ROS-independent Nrf2. This commentary briefly describes the genetic and epigenetic factors that regulate the activation of Nrf2, and proposes a micronutrient mixture that may simultaneously activate ROS-independent Nrf2, increase the cellular levels of antioxidants, and decrease the release and toxicity of glutamate. This micronutrient mixture may simultaneously and optimally reduce oxidative, chronic inflammation and glutamate, and thus, may prevent and together with standard therapy, enhance the care of these neurodegenerative diseases.

**Keywords:** Oxidative stress; Chronic inflammation; Glutamate release; Prevention; microRNAs

## Introduction

There are several types of neurodegenerative disease; however, this commentary focuses on Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and post-traumatic stress disorders (PTSDs). Despite extensive research during past decades on the biochemical and genetic defects in these diseases, there are no effective preventive strategies except for modifications in the diet and lifestyle; and treatment approaches are unsatisfactory. Nevertheless, several biochemical and genetic abnormalities were identified and reviewed [1-5]. For example, cellular and genetic defects in AD include: (a) enhanced production free radicals, (b) persistence inflammation, (c) abnormal mitochondrial function, (d) (e) cholesterol levels, (f) increased production of A $\beta$ 1-42 peptides generated from the amyloid precursor protein (APP) and (g) up regulation and down regulation of microRNAs, (h) inhibition of proteasome activity, and (i) mutations in genes, such as APP, presenilin-1 and presenilin-2 [1,2]. In PD, biochemical and genetic abnormalities include increased oxidative damage, persistent inflammation, mitochondrial dysfunction, and glutamate level. Mutation in DJ-1, alpha-synuclein, PINK-1 or PARKIN gene associated with familial PD impairs mitochondrial function that can increase oxidative stress [3]. HD is an autosomal dominant heritable neurodegenerative disease characterized by an expansion of more than 35 repeats of the nucleotide triplet cytosine-adenine-guanosine (CAG) that codes for the amino acid glutamine in the huntingtin protein. Biochemical abnormalities in HD and PTSD include increased production of free radicals, mitochondrial dysfunction, persistence inflammation, and glutamate level [4,5]. The

studies discussed in these reviews suggested that increased oxidative stress precedes other abnormalities. Oxidative damage, if not repaired, induces chronic inflammation that produces pro-inflammatory cytokines, additional free radicals, complement proteins and adhesion molecules all of which are neurotoxic. Thus, increased oxidative stress and chronic inflammation initiate the development of these neurological diseases. These reviews also revealed that excess release of glutamate occurred earlier in HD and PTSD than in AD and PD. Transcranial magnetic stimulation (TMS) technique have identified cortical hyper excitability in patients with AD [6], mild cognitive impairment [7], vascular dementia [8] and obstructive sleep apnea syndrome, restless legs syndrome, insomnia, and sleep deprivation [9]. Cortical hyper excitability could be due to release of excess glutamate. Increased glutamate levels together with excess free radicals and pro-inflammatory cytokines participate in the progression of these diseases. Thus, increased oxidative damage, pro-inflammatory cytokines and glutamate level are common biochemical defects in these neurological

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diseases. This commentary suggests that simultaneous reduction of these biochemical defects may prevent and together with standard therapy, enhance the treatment of these neurodegenerative diseases.

The central question is how to simultaneously attenuate oxidative damage, chronic inflammation, and glutamate level. Previous studies using primarily single antioxidants in AD [1,2], PD [3], HD and PTSD level [4,5] have yielded variable results ranging from transient benefits in the early disease phase to no effect. One of the reasons could be that supplemented single antioxidant does not simultaneously decrease all three biochemical defects. Furthermore, it is known that a single antioxidant is oxidized in the presence of a high oxidative environment of patients with these diseases, and then behaves as a pro-oxidant that could be neurotoxic. In order to avoid these problems, this commentary suggests that it is essential to increase simultaneously the cellular levels of cytoprotective enzymes including antioxidant enzymes, and antioxidant compounds derived from the diet and endogenously made in order to maximally reduce oxidative stress and chronic inflammation. Certain B-vitamins prevented the release of glutamate [10,11] and certain antioxidants [12-14] reduced the release and toxicity of glutamate. The cellular levels of antioxidant compounds and B-vitamins can be enhanced by an appropriate supplementation; however, increasing the cellular levels of antioxidant enzymes requires an activation of a nuclear transcriptional factor Nrf2.

### Methods of Activation of Nrf2

Since increasing the cellular levels of antioxidant enzymes and other cytoprotective enzymes needs an activation of Nrf2, this nuclear transcriptional factor is briefly described. The Nrf2 (nuclear factor-erythroid-2-related factor 2) belongs to the Cap 'N' Collar (CNC) family that has a conserved basic leucine zipper (bZIP) transcriptional factor. Under normal physiological conditions, Nrf2 is bound to Kelch-like ECH protein 1 (Keap1) which is considered as an inhibitor of Nrf2 [15]. Keap1 protein acts as an adaptor to connect Nrf2 to the ubiquitin ligase Cul-Rbx1 complex in order to be degraded by the enzymes proteasomes. This allows maintenance of the steady levels of Nrf2 in the cytoplasm. Nrf2-keap1 complex is primarily located in the cytoplasm. Keap1 behaves as a sensor for ROS/electrophilic stress that causes dissociation of Nrf2 from the Keap1 protein in the cytoplasm.

### Activation of Nrf2 requiring ROS-stimulation

Under normal conditions, excessive production of free radicals occurs during aerobic exercise. To protect against oxidative damage, ROS activates Nrf2 which then separates itself from the Keap1-Cul-Rbx1 complex and migrates to the nucleus where it heterodimerizes with a small Maf protein. The binding of Nrf2 with the ARE causes increased transcription of target genes coding for cytoprotective enzymes including antioxidant enzymes [16-19]. Thus, in response of acute oxidative stress, Nrf2 is activated by ROS to protect the neurons from oxidative damage.

### Binding of Nrf2 with antioxidant response element (ARE)

Activation of Nrf2 by ROS alone may not be enough to enhance the cellular levels of antioxidant enzymes. Activated Nrf2 must bind with the ARE in the nucleus for increasing the transcription of its target genes coding for cytoprotective enzymes. It has been reported that the binding ability of Nrf2 with ARE was impaired in aged rats; however, supplementation with alpha-lipoic acid restored the binding ability of Nrf2 with ARE [20].

### Activation of Nrf2 not requiring ROS-stimulation

Activation of Nrf2 by ROS-stimulation becomes impaired during chronic oxidative stress found in patients with neurodegenerative

diseases [21-23]. This is supported by the fact that increased oxidative damage occurs in neurodegenerative diseases despite the presence of Nrf2.

### Genetic and Epigenetic Regulation of the Levels and Activity of Nrf2

Keap1 regulates the cellular levels of Nrf2 by maintaining its degradation by the enzymes proteasomes, whereas Nrf2 controls the cellular levels of Keap1 by regulating its transcription [24]. A multifunctional stress response gene, immediate early response-3 (IER-3) gene also controls the activity of Nrf2. Silencing of IER-3 gene enhances Nrf2 activity, whereas increased expression of IER-3 reduces it [25]. The cellular levels of Nrf2 are controlled epigenetically by methylation of CpG (cytosine-phosphate-guanosine) and acetylation of histone3. Hypermethylation of CpG and hyperacetylation of histone3 enhance the transcription of Nrf2, whereas hypomethylation of CpG and hypoacetylation of histone3 reduce it [26].

### MicoRNAs Regulating the Activation of Nrf2

Although changes in the expression of microRNAs are being investigated in neurodegenerative diseases, this section focuses on the functions of microRNAs in regulating Nrf2 activation. MicroRNAs (miRs) are evolutionarily conserved small non-coding single-stranded RNAs of about 22 nucleotides in length, and are present in all living organisms including humans [27-30]. Each microRNA binds to its complementary sequences in the 3'-untranslated region (3'-UTR) of the target mRNA that prevents the formation of its protein. Thus, microRNAs play a key role in regulating cell function. It appears that specific microRNAs may regulate the activation of Nrf2 by decreasing the levels of Keap1. The complex of Keap1-Nrf2 in the cytoplasm prevents activation of Nrf2. Overexpression of miR-200a reduced Keap-1 levels in the cells allowing Nrf2 to migrate to the nucleus where it binds to the ARE that enhanced the expression of target genes coding for cytoprotective enzymes including antioxidant enzymes [31].

### Antioxidant Compounds Regulating Activation of Nrf2

During persistence oxidative stress, activation of Nrf2 becomes resistant to ROS-stimulation. Antioxidant compounds activate Nrf2 without requiring stimulation by ROS. Some of them are listed here.

### Antioxidant compounds activate Nrf2 without requiring ROS-stimulation

Some of them include vitamin E and genistein [32], alpha-lipoic acid [20], curcumin [33], resveratrol [34,35], omega-3-fatty acids, astaxanthin [36,37], glutathione [38], NAC [39], coenzyme Q10 [40] and several plant-derived phytochemicals with antioxidant activities, such as epigallocatechin-3-gallate, carexol, kahweol, cinnamonyl-based compounds, zerumbone, lycopene and carnosol [41,42] genistein, allicin, a major organosulfur compound found in garlic [43], genistein [32], sulforaphane, an organosulfur compound, found in cruciferous vegetables [44] and kavalactones (methysticin, kavain and yangonin) [45].

### L-carnitine-induced activation of Nrf2 requiring ROS-stimulation

Treatment of cells with L-carnitine activates Nrf2 that requires ROS-stimulation [46]. This could be due to the fact that L-carnitine treatment may generate transient ROS.

## Reducing Oxidative Stress Levels

Activation of Nrf2 may not be sufficient to optimally reduce oxidative stress, because antioxidant compounds are also decreased during chronic oxidative stress [47-49]; therefore, their levels must also be simultaneously elevated.

## Reducing Inflammation levels

Activation of Nrf2 [50,51] and some individual antioxidant compounds reduced chronic inflammation [52-58].

## Reducing glutamate levels

Some antioxidants decrease the release of glutamate as well as its neurotoxicity [12-14]. In addition, certain B-vitamins can also decrease the release of glutamate [10,11].

## Proposed Micronutrients for Reducing the Risk of Developing Neurodegenerative Diseases

Because of failure to produce consistent benefits by individual micronutrients in prevention or improved management of neurodegenerative diseases, and because a single antioxidant cannot simultaneously decrease oxidative stress and chronic inflammation, a comprehensive micronutrient mixture is proposed. This mixture of micronutrients has multiple dietary antioxidant compounds (vitamin A, natural mixed carotenoids, vitamin C, vitamin D, vitamin E, curcumin, resveratrol), endogenous antioxidants (alpha-lipoic acid, L-carnitine, and coenzyme Q10) and a synthetic antioxidant N-acetylcysteine (NAC), omega-3-fatty acids and all B-vitamins. This micronutrient mixture may maximally decrease oxidative damage and persistence inflammation by simultaneously increasing the cellular levels of antioxidant enzymes through activation of the Nrf2/ARE pathway, and elevating the levels of antioxidant compounds. The same micronutrient mixture may also reduce the release and the toxicity of glutamate.

## Prevention of Neurodegenerative Diseases

### Primary prevention

The major focus of primary prevention is to protect healthy individuals from developing neurological diseases. Individual of 65 years or older, and those carrying specific gene mutation who have no symptoms of the disease are suitable subjects for the primary prevention study. At present, there are no strategies to prevent or delay the appearance of the symptoms of the disease in individuals carrying mutated genes. The proposed micronutrient mixture may be effective in preventing or delaying the appearance of the symptoms of neurodegenerative diseases in these individuals. This possibility was indirectly supported by an experiment on the fruit flies described here.

The gene HOP (TUM-1) is essential for the development of *Drosophila melanogaster* (fruit fly). A mutation in this gene markedly increases the risk of developing a leukemia-like tumor in female flies. In collaboration with Dr. Bhattacharya of NASA Moffat Field, CA, we observed that whole-body irradiation of these flies with proton radiation dramatically increased the incidence of cancer compared to that observed in un-irradiated female flies. Treatment with a mixture of multiple antioxidants before and after irradiation blocked the incidence of proton radiation-induced cancer in female fruit flies [59].

### Secondary prevention

The major focus of secondary prevention is to prevent or slow the rate of the progression of neurodegenerative disease after exposure to

agents that enhance the risk of the disease. Individuals who have been exposed to such agents, but have not developed any symptoms of the disease, and are not taking any medication, are suitable subjects for the secondary prevention study. The micronutrient mixture suggested for the primary prevention study is also proposed for the secondary prevention study.

## Proposed micronutrient strategy in combination with standard care

The patients with neurodegenerative disease who are receiving standard care are suitable for this study. The micronutrient mixture suggested for the primary prevention study is also proposed together with standard therapy for the treatment study.

## Conclusion

Published studies suggest that increased production of free radicals, persistent inflammation and glutamate level are important in the development and progression of all neurodegenerative diseases discussed in this commentary. Some antioxidant compounds may activate ROS-independent Nrf2, but this may not be enough to maximally decrease oxidative damage, persistent inflammation and glutamate release. This could be due to the fact that the cellular levels of antioxidant compounds derived from the diet and endogenously made are also depleted in the environment of high oxidation found in patients with neurodegenerative disease. Their cellular levels must also be simultaneously increased. The proposed micronutrient mixture may maximally decrease oxidative damage and chronic inflammation by simultaneously increasing the cellular levels of antioxidant enzymes through activating the Nrf2/ARE pathway, and antioxidant compounds derived from the diet and endogenously made. Such a micronutrient mixture may also reduce the release and toxicity of glutamate. The efficacy of this mixture of micronutrients should be tested in the primary prevention, secondary prevention, as well as together with standard care, in the treatment of neurodegenerative diseases.

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