Title

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Journal

Journal of the American Nutrition Association, 41(5)

ISSN

2769-7061

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Publication Date

2022-07-04

DOI

10.1080/07315724.2021.1910592

Peer reviewed

Journal of the American College of Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uacn20

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To cite this article: Kedar N. Prasad & Stephen C. Bondy (2021): Can a Micronutrient Mixture Delay the Onset and Progression of Symptoms of Single-Point Mutation Diseases?, Journal of the American College of Nutrition, DOI: 10.1080/07315724.2021.1910592

To link to this article: https://doi.org/10.1080/07315724.2021.1910592

Published online: 06 Jul 2021.

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION
https://doi.org/10.1080/07315724.2021.1910592

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REVIEW

Can a Micronutrient Mixture Delay the Onset and Progression of Symptoms of Single-Point Mutation Diseases?

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ABSTRACT

Single-point mutation diseases in which substitution of one nucleotide with another in a gene occurs include familial Alzheimer's disease (fAD), familial Parkinson's disease (fPD), and familial Creutzfeldt-Jacob disease (fCJD) as well as Huntington's disease (HD), sickle cell anemia, and hemophilia. Inevitability of occurrence of these diseases is certain. However, the time of appearance of symptoms could be influenced by the diet, environment, and possibly other genetic factors. There are no effective approaches to delay the onset or progression of symptoms of these diseases. The fact that increased oxidative stress and inflammation significantly contribute to the initiation and progression of these point mutation diseases shows that antioxidants could be useful. The major objectives are (a) to present evidence that increased oxidative stress and chronic inflammation are associated with selected single-point mutation diseases, such as fAD, fPD, and fCJD, HD, sickle cell anemia, and hemophilia; (b) to describe limited studies on the role of individual antioxidants in experimental models of some of these diseases; and (c) to discuss a rationale for utilizing a comprehensive mixture of micronutrients, which may delay the development and progression of symptoms of above diseases by simultaneously reducing oxidative and inflammatory damages.

KEY TEACHING POINTS

- Selected single-point mutation diseases and their pattern of inheritance
- Characteristics of each selected single-point mutation disease
- Evidence for increased oxidative stress and inflammation in each disease
- Potential reasons for failure of single antioxidants in human studies
- Rationale for using a comprehensive mixture of micronutrients in delaying the onset and progression of single-point mutation diseases

ARTICLE HISTORY
Received 20 February 2021
Accepted 25 March 2021

KEYWORDS
Single-point mutation diseases; pattern of inheritance; oxidative stress; chronic inflammation; micronutrients

Introduction

A single-point mutation includes substitution of one nucleotide with another, deletion of one nucleotide, or insertion of one nucleotide. Inheritance of genetic diseases with a single-point mutation exhibits autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive. The appearance of the symptoms of such single-point mutation diseases is inevitable; however, the time of detectable symptoms could be influenced by environmental, dietary, and genetic factors. Since these factors do not determine the inevitability of the appearance of the symptoms, single-point mutation disease should not be considered multifactorial.

A single-point mutation leading to the production of mutated protein has two possible harmful consequences. First, the mutated protein completely or partially loses its protective function. Second, the mutated protein may gain toxic function by producing harmful metabolites. The latter is demonstrated in familial Alzheimer's disease (fAD), in which toxicity of mutated amyloid precursor (APP) is mediated by its metabolite Aβ42, while the former is shown in familial Parkinson's disease (fPD), familial Creutzfeldt-Jacob disease (fCJD), Huntington's disease (HD), hemophilia, and sickle cell anemia. The above single-point mutation diseases involve primarily substitution of one nucleotide with another.

There are no effective strategies to delay the onset or progression of the symptoms of the above diseases. At this time, treatment of the such diseases starts as soon as one or more symptoms appear. It is not possible to correct the defect at the nucleotide level. Since increased oxidative stress and chronic inflammation are present before the onset and during progression of single-point mutation diseases, it is not certain whether these two biochemical defects cause the development and progression of these diseases or simply are consequences of the diseases or not related to the disease at all. Because antioxidants are known to reduce oxidative and inflammatory damage, they could be useful in delaying the initiation and progression of these diseases. This possibility was demonstrated in female *Drosophila melanogaster* in

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which a dominant single-point mutated Hopscotch (HOP) gene HOP (TUM-1) in which glycine is substituted with glutamic acid. This mutation increases the risk of leukemia-like tumor in female *D melanogaster* (1). The female flies carrying the mutated HOP (TUM-1) gene can be considered an excellent model of a single-point mutation disease, such as cancer. Irradiation of these flies with proton radiation markedly enhanced the incidence of cancer. Dietary supplementation with a mixture of antioxidants 7 days before and 7 days after irradiation markedly reduced cancer incidence in these female fruit flies (2). Thus, a mixture of antioxidants can prevent consequences of single-point mutation disease, such as cancer, in flies.

Another example of the utility of antioxidant N-acetylcysteine or vitamin E in addressing single-point mutation disease was demonstrated in *Caenorhabditis elegans* (nematodes). Administration of these agents fully prevented the life-shortening effect of gas-1(fc21) mitochondrial complex I mutation in which arginine is replaced by lysine, while coenzyme Q10, alpha-lipoic acid, and vitamin C only partially prevented the reduction in the life-span of these mutant nematodes (3).

Since increased oxidative stress and chronic inflammation are associated with single-point mutation diseases, such as fAD, fPD, fCJD, HD, sickle cell anemia, and hemophilia, supplementation with antioxidants may be useful in delaying the onset and progression of these diseases. However, very few investigations on this issue are available.

A few studies have demonstrated that individual antioxidants commonly used in clinical trials produced consistent benefits in experimental models of sporadic or single-point mutation diseases; however, such antioxidant approaches have yielded inconsistent results in humans varying from no effect to minimal beneficial effects to harmful effects. The references for these reports are listed later under appropriate sections.

The major objective of this review is to present evidence that increased oxidative stress and chronic inflammation are associated with selected single-point mutation diseases, such as fAD, fPD, fCJD, HD, sickle cell anemia, and hemophilia. This review presents the results of limited studies on the effects of individual antioxidants primarily in the experimental models of the above diseases. This review also discusses a rationale for utilizing a comprehensive mixture of micronutrients, which may delay the onset and progression of the symptoms of the above single-point mutation diseases by simultaneously reducing oxidative and inflammatory damages.

Patterns of inheritance of single-point mutation diseases

Autosomal dominant single-point mutation involves only one copy of a gene and is expressed in the first generation of offspring. Each affected individual has one affected parent carrying a single-point mutated gene. Some examples include fAD, fPD, fCJD, and HD. Autosomal recessive disease consists of single-point mutations in both copies of a gene and are expressed in the first generation. Some examples include sickle cell anemia. Each affected individual has both affected parents. X-linked single-point mutation can be dominant or recessive and expresses equally in both men and women. A characteristic of X-linked inheritance is that a father cannot pass an X-linked mutation to his son. Some examples of X-linked dominant single-point mutations are hypophosphatemic rickets and ornithine transcarbamylase deficiency, whereas X-linked recessive diseases include hemophilia A, hemophilia B, and Duchenne muscular dystrophy.

Characteristic of selected single-point mutation diseases

fAD

Approximately 5% to 10% of Alzheimer's disease (AD) cases are due to an autosomal dominant single-point mutation in the genes of APP, presenilin-1 (PS-1), and presenilin-2 (PS-2). About 5% of AD cases are due to single-point mutations in PS-1 and PS-2 genes (4). These mutations increase the production of Aβ42 peptides that play an important role in neuronal death (5). Individuals carrying these types of mutation show an early onset of AD symptoms.

fPD

Approximately 10% of Parkinson's disease (PD) cases have single-point mutations that cause an early onset of the disease (6). fPD shows both dominant and recessive modes of inheritance. For example, a single-point mutation in synuclein alpha (SNCA) or leucine-rich repeat kinase 2 (LRRK-2) is autosomal dominant, while a single-point mutation in the Parkin, Pink-1, or DJ-1 gene is autosomal recessive (7–9). Individuals carrying mutations in these genes show an early onset of PD symptoms.

fCJD

fCJD is an autosomal dominant single-point mutation disease in which lysine is substituted with glutamic acid in the mutated prion protein (PrPc) (10). Misfolding of normal PrPc into PrPsc causes disease phenotype. This disease is characterized by rapid mental deterioration, leading to dementia and death within a few months (11). The median age at the onset of the disease is 52 years.

HD

HD is a progressive, fatal, incurable disease. In the United States, incidence of HD is about 1599 new cases per year (12). A dominant single-point mutation in the wild-type huntingtin gene causes an increase in the number of trinucleotide cytosine-adenine-guanosine (CAG) coding for glutamine from 35 to over 140. The resulting polyglutamine tract is toxic to nerve cells in the brain (13). The higher the number of CAG, the sooner the HD symptoms would appear (14–16). The median age at onset of the disease is usually about 30 to 50 years.

Sickle cell anemia

This genetic disease affects approximately 100,000 people in the United States, out of which 70% of cases occur among African Americans. It is caused by a single-point mutation in which a single nucleotide changes from adenine to thymine, which leads to substitution of amino acid valine with glutamic acid in the beta-chain of the hemoglobin protein. The mutated hemoglobin is referred to as hemoglobin-S (Hb-S). The mutated Hb-S is devoid of oxygen-carrying capacity and easily polymerizes to assume "sickle" configuration. The red blood cells carrying Hb-S have reduced lifespan, leading to blood vessel occlusion, tissue ischemia, infarction, and premature hemolysis (17). This disease appears around 5 months of age.

Hemophilia

This is a single-point mutation disease in which blood does not clot properly due to inadequate amounts of coagulation factors VIII and IV. This disease is caused by a single-point mutation in the gene located on the X chromosome, which produces abnormal coagulation factors VIII and IV and interferes with blood clotting (18). The median age at the onset of symptoms varies depending upon the severity of the disease. It is 1 month for severe symptoms, 8 months for moderate symptoms, and 36 months for mild symptoms.

Oxidative stress and chronic inflammation associated with single-point mutation diseases

Limited investigations on the role of oxidative stress and chronic inflammation in single-point mutation diseases, which have been conducted, are described here.

Oxidative stress in fAD

The wild-type APP, PS-1, and PS-2 genes exhibit several cellular functions for protection and survival. One of these protective mechanisms involves protection against oxidative damage. A single-point mutation in APP, PS-1, or PS-2 genes increases oxidative stress (19) by enhancing the cleavage of mutated APP into Aβ42 (20, 21). Aβ42, which plays a major role in the pathogenesis of AD (22, 23), causes neuronal death by generating free radicals (24, 25). This is further supported by the fact that treatment of neuronal cells in culture with alpha-tocopherol (26) or coenzyme Q10 (27, 28) prevented Aβ42-induced toxicity. This is an example of gain in toxic function of a mutated protein though its metabolite. The fact that the markers of oxidative damage and inflammation were elevated in fAD before the appearance of neurological impairments such as cognitive dysfunction further suggests that these biochemical defects play a significant role in the initiation of this genetic disease (29).

Oxidative stress in fPD

The wild-type SNCA, LRRK-2, Parkin, Pink-1, and DJ-1 genes and their respective proteins have more than one function, but they all share a common function in protecting nerve cells against oxidative damage. A single-point mutation in the SNCA or Parkin gene enhanced the levels of markers of oxidative damage, such as malondialdehyde, 4-hydroxynonenal, 3-nitrotyrosine, and accelerated neuronal death induced by MPP+ (1-methyl-4-phenylpyridinium), a neurotoxin used to induce in experimental models of fPD (30, 31). A single-point mutation in the LRRK-2 gene increased the levels of markers of oxidative stress in the cerebrospinal fluid (32). A single-point mutation in Pink-1 or DJ-1 increased oxidative stress in experimental models of fPD (33, 34). This an example of loss of protective function of a mutated protein. Animal models of fPD show that increased oxidative stress could also be associated with asymptomatic individuals carrying a mutated gene in fPD (35).

Oxidative stress in fCJD

The wild-type prion gene PRNP codes for PrPc, which is a copper-binding protein exhibiting superoxide dismutase activity that protects against oxidative damage (36). Loss of this function in mutated PrPsc protein causes increased levels of markers of oxidative stress in fCJD (37–40). Increased levels of lipid peroxidation were found in the brain of infected with PrPsc (41). Elevated levels of lipid peroxidation were also present in the cerebrospinal fluid and plasma in patients with Creutzfeldt-Jacob disease (42). This an example of loss of protective function of a mutated protein.

Oxidative stress in HD

The wild-type huntingtin protein plays an important role in the neurogenesis, development, and survival of neurons of the cortex and midbrain, which are most affected in HD. Mutated huntingtin protein causes mitochondrial DNA (mtDNA) damage as well as depletion of mtDNA leading to increased oxidative stress (43). This an example of loss of protective function of a mutated protein. However, the fact that the higher the number of trinucleotides CAG, the sooner the HD symptoms would appear (14–16) suggests gain in toxic function of a mutated protein. Thus, mutated huntingtin protein exhibits both loss of protective function and gain of toxic function. Increased levels of oxidative stress are also found in asymptomatic individuals carrying mutated Huntington gene (44) as well as in patients with established HD (45, 46).

Oxidative stress in sickle cell anemia

Increased levels of oxidative stress also are found in patients with sickle cell anemia, which is due to auto-oxidation of hemoglobin-S, ischemic reperfusion injury, activation of xanthin oxidase system, and the presence of excessive amounts of free hemoglobin that catalyzes the Fenton reaction in the presence of iron (47–51). This demonstrates a loss of protective function by mutated hemoglobin protein. These changes indicate a loss of protective function of a mutated protein.

Table 1. Loss and gain function of mutated proteins leading to increased oxidative stress in single-gene mutation diseases.

Type of disease	Mutated gene site	Consequences	Gain/loss of function	Oxidative stress
Familial PD	Parkin and Pink-1	Dopaminergic death	Loss	Increased
Familial PD	DJ-1	Dopaminergic death	Loss	Increased
Familial PD	SNCA	Dopaminergic death	Loss	Increased
Familial PD	LRKK-2	Dopaminergic death	Loss	Increased
Familial AD	APP, PS-1, PS-2	More Aβ42, neuronal death	Gain	Increased
Familial CJD	PRNP	Neurological damage	Loss	Increased
HD	Huntingtin	Mitochondrial damage	Loss/gain	Increased
SCA	Hemoglobin	Auto-oxidation	Loss	Increased
Hemophilia A	VIII factor	Blood coagulability fails	Loss	Increased
Hemophilia B	IX factor	Blood coagulability fails	Loss	Increased

PD = Parkinson's disease; AD = Alzheimer's disease; SNCA = synuclein alpha; LRRK-2 = leucine-rich repeat kinase 2; PINK-1, PTEN-induced kinase-1; APP, amyloid precursor protein; PS-1, presenilin-1; PS-2, presenilin-2; CJD, Creutzfeldt-Jacob disease; HD, Huntington's disease; SCA, sickle cell anemia; Aβ42, beta amyloid 42; PRNP, prion gene; PrPsc, mutated prion protein; mtDNA, mitochondrial DNA.

Oxidative stress in hemophilia

Deficiency in coagulation factor VIII leads to hemophilia A, while deficiency of coagulation factor IX causes hemophilia B. Hemophilia A is more common than hemophilia B. Accumulation of misfolded coagulation factor VIII protein in the lumen of endoplasmic reticulum activates the unfolded protein to become misfolded, which causes increased oxidative stress and apoptosis *in vitro* and *in vivo* (52). Treatment with an antioxidant reduced misfolded coagulation factor VIII–induced oxidative stress and enhanced its secretion *in vitro* and in mice (52) (Table 1).

Increased chronic inflammation in single-point mutation diseases

There are no significant data on the changes in the levels of markers of inflammation in most diseases mentioned in this report. Oxidative stress and inflammation are closely linked. Acute inflammatory responses involving cells of innate and adaptive immunity and anti-inflammatory cytokines play an important role in the healing of oxidative damaged cells. As soon as the restorative processes are complete, acute inflammatory events are turned off. However, if oxidative damage of cells is not remedied, chronic inflammation responses occur. Such inflammatory responses release reactive oxygen species (ROS), pro-inflammatory cytokines, adhesion molecules, and complement proteins, all of which contribute to the degeneration and death of cells. Increased levels of markers of inflammation together with synaptic loss are found in asymptomatic individuals carrying mutated APP or PS-1 gene (53, 54).

Role of antioxidants in delaying the onset and progression of single-point mutation diseases

There is some evidence that the action of certain mutated proteins can be prevented by antioxidants. For example, mutation in the APP gene causes increased cleavage of mutated APP into more Aβ42 peptides (also called beta-amyloid peptides), which contribute to the pathogenesis of AD (22, 23). Beta-amyloid peptides cause neuronal death by generating free radicals (24, 25). This is supported by the fact that treatment of neuronal cells in culture with alpha-tocopherol (26) or coenzyme Q10 prevented Aβ42-induced toxicity (27, 28). In fAD, increased markers of oxidative damage and inflammation were elevated before the appearance of neurological impairments such as cognitive dysfunction (29). Therefore, it is likely that treatment with antioxidants may delay the onset and progression of the symptom of fAD.

In fCJD, treatment with resveratrol (55), Mn-SD/catalase mimetic, EUK-189 (56), pomegranate (57), or epigallocatechin gallate (58) protected neurons from the toxic effects of mutated prion protein PrPsc.

Patients with sickle cell anemia experience deficiency in several micronutrients (59, 60). Administration of a single antioxidant such as vitamin C or alpha-tocopherol has been useful in improving some of the symptoms of sickle cell anemia (61–63). In another clinical study, administration of high doses of vitamin C and alpha-tocopherol increased the markers of hemolysis but did not improve anemia (64). Thus, the use of a single antioxidant in this disease produced inconsistent results. In addition, such an approach may not correct other micronutrient deficiency in this disease.

Using mouse model of hemophilia, treatment with an antioxidant reduced misfolded coagulation factor VIII–induced oxidative stress and apoptosis and enhanced the secretion of coagulation factor VIII *in vitro* (52).

Basis for advocating administration of a mixture of micronutrients in concert

Failure of antioxidants in human diseases

Although the use of a single antioxidant produced impressive results in cell culture and animal models of sporadic AD (65), it was ineffective in treating patients with AD (66, 67) and sporadic PD (68, 69) as well as HD (70). Supplementation with a single antioxidant produced minimal benefits in early phase of sporadic AD (66, 71). Administration of beta-carotene alone in male heavy tobacco smokers increased the risk of lung cancer (72). These studies suggest that administration of a single antioxidant is unlikely to provide any significant protection against increased oxidative and inflammatory damages in single-point mutation diseases and may in fact be harmful.

Potential causes of failure of single antioxidants

Some possible reasons for the failure of a single antioxidant to yield expected benefits that were observed in animal models are described here.

a. The selected single-point mutation diseases describe in this report are associated with high levels of markers of oxidative damage. Administered single antioxidants in a high oxidative environment of such patients would be oxidized, which then would act as a pro-oxidant rather than as an antioxidant.
b. Different antioxidants are distributed in varying amounts in various organs. Even within the cell, they are distributed in different amounts in the subcellular compartments. Administration of a single antioxidant cannot accumulate equally in all organs and all parts of the cell in sufficient amounts to provide adequate protection against oxidative stress.
c. Alpha-tocopherol is a more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure (73). Therefore, administration of one antioxidant may not provide adequate protection again oxidative damage in the whole body.
d. Elevation of both the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds are essential for optimally reducing oxidative stress. This is due to the fact that antioxidant enzymes and antioxidant compounds reduce oxidative damage by different mechanisms. For example, antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes destroy H202 by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant cannot achieve this goal.
e. Administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cell against enhanced oxidative stress.
f. Different antioxidants increase the production of different protective proteins in the cells by altering the expression of different microRNAs (74). For example, some antioxidants can activate nuclear factor erythroid 2-related factor 2 (Nrf2) by upregulating miR-200a which inhibits its target protein Keap1, whereas others can activate Nrf2 by downregulating miR-21 which binds with 3'-UTR Nrf2 mRNA (75). Thus, different antioxidants activate Nrf2 by different mechanisms. The utilization of a single antioxidant cannot accomplish this goal.

There are no studies on the effectiveness of individual or multiple antioxidants in either fAD or fPD. As discussed in the above paragraphs, administration of a single antioxidant has been ineffective in patients with HD, produced inconsistent results in patients with sickle cell anemia, and yielded some beneficial effects in experimental models of fCJD and hemophilia. A systematic study to evaluate the role of multiple antioxidants should be conducted in animal models of fAD, fPD, fCJD, HD, sickle cell anemia, and hemophilia as well as patients with these diseases.

Necessity for utilizing multiple antioxidants

The failure of individual antioxidants to yield expected benefits in human diseases led us to propose that in order to simultaneously reduce oxidative stress and inflammation, the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds should be elevated at the same time (76). Oral supplementation with a mixture of antioxidant compounds can enhance their levels in the body; however, increasing the levels of antioxidant enzymes requires an activation of a nuclear transcriptional factor Nrf2. A brief description of steps needed to activate Nrf2 is presented here.

Activation of Nrf2

Under normal physiological conditions, ROS is required to activate Nrf2. Activated Nrf2 dissociates itself from the Keap1-CuI-Rbx1 complex in the cytoplasm and migrates to the nucleus, where it heterodimerizes with a small Maf protein and binds with antioxidant response element (ARE), leading to increased transcription of cytoprotective enzymes including antioxidant enzymes (77–81).

During the prolonged oxidative stress commonly observed in human chronic diseases, activation of Nrf2 becomes resistant to ROS (82–84). This is evidenced by the fact that increased oxidative stress continues to occur in chronic diseases despite the presence of Nrf2. However, some antioxidants such as alpha-tocopherol and genistein (85), alpha-lipoic acid (86), curcumin (87), resveratrol (88, 89), omega-3-fatty acids, (90, 91), glutathione (92), n-acetylcysteine (93), and coenzyme Q10 (94) can activate this ROS-resistant Nrf2.

Activation of Nrf2 alone is not adequate to enhance the levels of antioxidant enzymes. Activated Nrf2 must then bind to ARE in order to promote the transcription of antioxidant enzymes. The binding ability of Nrf2 to ARE is impaired in old rats, and treatment with alpha-lipoic acid reverses this defect (86).

Attenuation of chronic inflammation by activated Nrf2 and antioxidants

It has been reported that activation of Nrf2 decreases oxidative stress as well as inflammation (95, 96). Many antioxidant compounds also attenuate inflammation (97–102).

Figure 1 illustrates some major pathways by which antioxidant and anti-inflammatory agents can be protective. Such compounds can do the following:

a. Activate ROS-resistant Nrf2, leading to increased levels of antioxidant enzymes that would protect cell by reducing oxidative damage.
b. Regulate the expression of pro-inflammatory cytokines by inhibition of transcriptional factor NF-kB (103).
c. Activate SIRT1 (silent information regulator 1), a member of the sirtuin family (104).
d. Inhibit mammalian target of rapamycin (105).

Proposed mixture of micronutrients for delaying the onset and progression of symptoms of single-point mutation diseases

A comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl

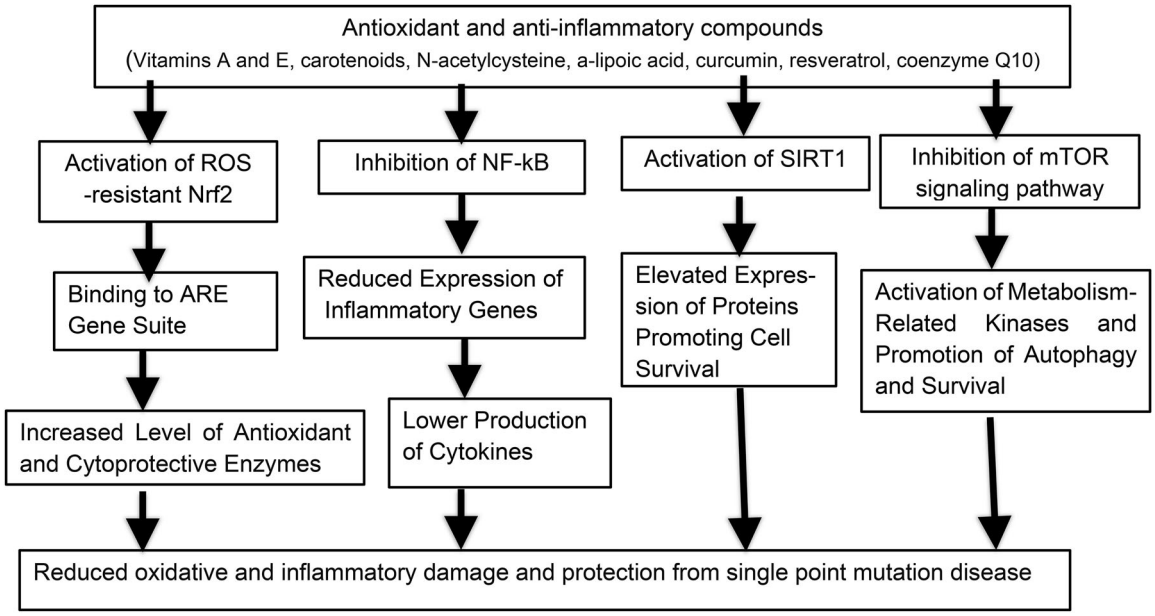

Figure 1. Potential protective pathways in single point-mutation diseases.
ARE = antioxidant response element; ROS = reactive oxygen species, Nrf2 = nuclear factor erythroid 2-related factor 2, SIRT1 = NAD-dependent deacetylase sirtuin-1, mTOR = mammalian target of rapamycin.

acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, all B-vitamins, and minerals selenomethionine, and zinc for reducing the risk of sporadic AD and sporadic PD has been proposed (65, 76). This micronutrient mixture may increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and enhancing the levels of dietary and endogenous antioxidant compounds at the same time. It is suggested that such a micronutrient mixture may delay the onset of symptoms of single-point mutation diseases by simultaneously addressing the reduction of oxidative stress and chronic inflammation. Such a micronutrient mixture may improve the efficacy of standard therapy in reducing the rate of progression of eye diseases.

The issue of whether a mixture of micronutrients has produced beneficial effects in any human diseases has been verified in two clinical studies. For example, administration of a commercial preparation of multiple micronutrients reduced the risk of cancer in men by about 10% (103) and delayed the progression of HIV disease, thus delaying the time period for initiating antiviral therapy (104). Therefore, it is likely that the proposed micronutrient mixture may delay the onset and progression of the symptoms of single-point mutation diseases. Preclinical and clinical studies on the efficacy of the proposed micronutrient mixture alone or in combination with standard therapy should be tested in each of the single-point mutation diseases.

Conclusions

At this time, there are no effective strategies to delay the onset of the symptoms of a single-gene mutation disease. Increased oxidative stress has been reported in single-point mutation diseases, such as fAD, fPD, and fCJD disease as well as in HD, sickle cell anemia, and hemophilia. Although environmental, dietary, and genetic factors may influence the time of onset of the symptoms, increased oxidative and inflammatory damage significantly contributes to the development and progression of the disease symptoms. Therefore, antioxidant treatment may be useful in delaying the onset and progression of these diseases. In order to maximize antioxidant utility and avoid problems incurred by solely using one antioxidant, use of a comprehensive mixture of micronutrients containing dietary and endogenous antioxidant compounds is suggested. Such a micronutrient mixture can increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and the levels of dietary and endogenous antioxidant compounds and thereby may delay the onset and progression of the symptoms of single-point mutation diseases by simultaneously improving redox status and curtailing chronic inflammation.

Disclosure statement

The author is chief scientific officer of Engage Global of Utah. This company sells nutritional products to consumers. SCB has no conflict.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

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