Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Nrf2 Activators

Evidence Summary

Offers a potential mechanism to prevent age-associated ailments but will need to be targeted at multiple levels. The efficacy of current activators may decline with age, and novel activators are needed.

Neuroprotective Benefit: Activation may protect against oxidative stress related neuronal loss by upregulating a potent endogenous antioxidant pathway.

Aging and related health concerns: Endogenous Nrf2 activation capacity may decrease with age and exogenous Nrf2 activators may need to target multiple components to overcome the age-related decline and restore the antioxidant response.

Safety: Off-target effects of electrophilic Nrf2 activators could induce cell damage. Non-electrophilic activators may increase cancer risk, but their safety profile is not known.

What is it? Nuclear Factor (Erythroid-Derived 2)–Like 2 (Nrf2) is a transcription factor which serves as a master regulator of cellular homeostasis and is the main driver of the body's endogenous antioxidant pathway. Nrf2 is activated in response to oxidative stress and protects cells from oxidative damage. In animal models, loss of Nrf2 leads to mitochondrial dysfunction and is associated with aging and cognitive decline. Therefore, it has been hypothesized that maintenance of Nrf2 activation throughout life could be a preventative measure that provides for healthy aging.

Nrf2 Activation

Nrf2 is a basic leucine zipper transcription factor. Under basal conditions Nrf2 is bound in a complex with Keap1, which promotes the degradation of Nrf2 through the ubiquitin-proteasome pathway. The covalent modification of cysteine residues on Keap1 by traditional Nrf2 activators leads to the dissociation of this complex, which frees Nrf2 and allows its translocation into the nucleus. Once in the nucleus, Nrf2 binds to antioxidant response elements (AREs) in association with other transcription factors and regulates the expression of a series of antioxidant enzymes [1].

Neuroprotective Benefit: Activation may protect against oxidative stress related neuronal loss by upregulating a potent endogenous antioxidant pathway.

Association of Nrf2 levels and cognition:

A variety of animal models demonstrated that the loss of Nrf2 signaling is associated with cognitive decline, and models of neurodegenerative diseases also demonstrate a deficit in Nrf2 signaling, but there have been no definitive studies in humans [2]. The best available evidence comes from postmortem brain tissue. The levels of nuclear (active) Nrf2 were found to be decreased in the hippocampi of patients with Alzheimer's disease [3]. This loss of Nrf2 activation would then be expected to increase the susceptibility of the neurons to oxidative stress damage.

Evidence from Nrf2 activators:

There are many natural sources of Nrf2 activators found primarily in plants. However, these compounds have very poor bioavailability, thus the levels obtained by the diet are generally too low to exert significant Nrf2 induction, and the neuroprotective effects detected in epidemiological studies of nutrient-derived Nrf2 activators may be related to their action on other biological pathways. The more bioavailable synthetic Nrf2 activators have not been tested for preservation of cognition.

Aging and related health concerns: Endogenous Nrf2 activation capacity may decrease with age and exogenous Nrf2 activators may need to target multiple components to overcome the age-related decline and restore the antioxidant response.

Association of Nrf2 levels and aging:

Animal studies have indicated that Nrf2 pathway signaling declines with age, and that this decline makes cells more vulnerable to oxidative stress damage and likely contributes to the aging process [4]. Declines in Nrf2 have also been noted in the cells from people with a variety of age-associated diseases. In the premature aging disease, Hutchinson-Gilford progeria syndrome, the exacerbation of cell damage was shown to be due to mislocalization of Nrf2 and impaired induction of its antioxidant signaling pathway [5].

Lifespan: Whether maintenance of Nrf2 signaling can extend lifespan is unclear, since there have been conflicting results with different animal models [4]. Nrf2 activation can extend lifespan in *Drosophila* and *C. elegans*, but not in rodents, suggesting it is also unlikely to extend lifespan in humans.

Age associated deficits in Nrf2 activation:

Nrf2 induction (by the natural Nrf2 activator sulforaphane) has been shown to be impaired in primary lung cells (bronchial epithelial cells from a commercial supplier) from aged (60-69 years) relative to young (21-29 years) adults [6]. This was related to an increase in the expression of the Nrf2 negative regulator, Bach1, which inhibits binding of Nrf2 to AREs within the nucleus. In the context of submaximal exercise in older adults (≥ age 55), Nrf2 increased in the cytoplasm of peripheral blood mononuclear cells, but failed to localize to the nucleus and initiate target gene expression [7]. These studies suggest that traditional Nrf2 activators which act by releasing Nrf2 from Keap1 in the cytoplasm may be less effective in aged individuals and that they would need to be combined with other agents which would promote Nrf2 nuclear shuttling (kinase or acetylation regulators), and Nrf2 transcriptional activity (Bach1 inhibitor).

Safety concerns: Off-target effects of electrophilic Nrf2 activators could induce cell damage. Non-electrophilic activators may increase cancer risk, but their safety profile is not known.

Nrf2 signaling is upregulated in various cancers, and there is a concern that prolonged activation of Nrf2 could increase the risk for cancer [8]. However, many of the electrophilic Nrf2 activators have anti-cancer activity through their modification of other proteins.

Due to the poor bioavailability of naturally derived Nrf2 activating compounds, very high doses must be used to have any meaningful Nrf2 activation *in vivo*, which increases the risk for toxicity. Synthetic versions have been developed with greater potency and bioavailability, but due to their electrophilic nature, they still have relatively poor side effect profiles for chronic use. The activation of the pathway involves the generation of oxidative and/or electrophilic stress which itself can be damaging to cells. Additionally, off-target electrophilic activity can produce a variety of side effects in different tissues. There are extensive efforts underway to develop novel activators that offer higher potency with greater specificity for inhibiting the Keap1-Nrf2 interaction.

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