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The neuroprotective mechanisms and effects of sulforaphane

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Abstract:

Sulforaphane (SFN) is a phytochemical found in cruciferous vegetables. It has been shown to have many protective effects against many diseases, including multiple types of cancer. SFN is a potent activator of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response element (ARE) genetic pathway. Upregulation of Nrf2-ARE increases the availability of multiple antioxidants. A substantial amount of preclinical research regarding the ability of SFN to protect the nervous system from many diseases and toxins has been done, but only a few small human trials have been completed. Preclinical data suggest that SFN protects the nervous system through multiple mechanisms and may help reduce the risk of many diseases and reduce the burden of symptoms in existing conditions. This review focuses on the literature regarding the protective effects of SFN on the nervous system. A discussion of neuroprotective mechanisms is followed by a discussion of the protective effects elicited by SFN administration in a multitude of neurological diseases and toxin exposures. SFN is a promising neuroprotective phytochemical which needs further human trials to evaluate its efficacy in preventing and decreasing the burden of many neurological diseases.

Keywords:

Antioxidant, autism spectrum disorder, broccoli sprouts, epilepsy, isothiocyanate, neurodegenerative disease, nuclear factor erythroid 2-related factor 2, phytochemical, schizophrenia

Introduction

Sulforaphane (SFN) is a phytochemical whose precursor glucoraphanin is found in cruciferous vegetables, with the highest concentrations in broccoli sprouts.^[1] SFN belongs to the group of plant-derived compounds called isothiocyanates. It is known for being a powerful inducer of the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway which plays a major role in upregulating cellular defenses to oxidative stress.^[2] SFN has been studied intensely regarding its ability to decrease the risk of various cancers and reduce the damage associated with varying forms of oxidative stress.^[3]

More recently, a variety of preclinical research regarding the role of SFN in neuroprotection has been conducted with very promising results. Only a few human trials regarding the protective effects of SFN in the nervous system have been done; however, SFN has very strong antioxidant and anti-inflammatory properties which allow it to dramatically reduce cytotoxicity in the nervous system, with apparently very little toxicity of its own within the therapeutic range.^[4] Animal studies suggest that SFN supplementation could be disease-modifying for many common, debilitating central nervous system (CNS) diseases including Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and others.

To fully assess the research that has been completed regarding the neuroprotective effects of SFN, a literature search was done using MEDLINE for relevant articles

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published as of January 2019. The literature search included the following keywords: SFN, neuroprotection, neurodegeneration, nervous system, neuron, brain, neurogenesis, and Nrf2. Resulting articles were reviewed for relevance to the topic of neuroprotection. The dates of included publications range from 2004 to 2018. This review focuses on the research that has been completed regarding the neuroprotective properties of SFN in various disease states and toxin exposures. The mechanisms underlying SFN's protective properties will be discussed first, followed by the effects seen in various disease models.

Mechanisms of Neuroprotection

SFN is a well-known powerful inducer of the Nrf2-ARE pathway, which has been coined the "guardian of redox homeostasis."^[5,6] The activation of the Nrf2-ARE pathway leads to upregulation of many downstream products involved in protection against oxidative stress, including NAD(P)H quinone oxidoreductase 1, heme oxygenase 1, glutathione (GSH) peroxidase 1,^[7] and gamma-glutamylcysteine synthetase, an important rate-limiting enzyme which controls the rate of GSH synthesis.^[8] The adequate availability of reduced GSH is vital to avoid the damage induced by free radicals.^[8] SFN increases GSH release by up to 2.4-fold in cultured astrocytes^[8] and has been shown to reduce oxidative stress in multiple disease states in cultured cells and animal models.^[9-14] A brief study in humans revealed that SFN increases the amount of GSH in the brain after 7 days of administration, which provides evidence that the antioxidant pathways activated by SFN are present in humans.^[15] The Nrf2 pathway is vital for many of SFN's protective effects, as evidenced by a lack of neuroprotection from multiple toxins when SFN is given with an inhibitor of gamma-glutamylcysteine synthetase^[16] or in Nrf2-knockout mice.^[17,18] Nrf2-ARE plays a vital role in the protective effect of SFN against many diseases, including Parkinson's disease, neuropathy, Friedrich's ataxia, stroke, and Alzheimer's disease.^[19-23]

Besides its promotion of antioxidant defenses, SFN also significantly lessens inflammatory responses to pathologic states, thus reducing the amount of damage done due to the body's immune response.^[24] SFN reduces damage to neurons mediated by microglia by promoting polarization of microglia from the M1 to the anti-inflammatory M2 type,^[25,26] thus down regulating the mRNA and proteins levels of multiple inflammatory mediators, including tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, cyclooxygenase 2, and inducible nitric oxide synthetase.^[5,11,24,27,28] Furthermore, SFN decreases the activation of multiple mitogen-activated protein kinases and other inflammatory mediators, including nuclear factor κ B, RIPK3, and MLKL, resulting in reduced

neuronal apoptosis and necrosis.^[24] Interestingly, when the immune system is needed such as when cancer is present, however, SFN inhibits the ability of glioblastoma multiforme to create a supportive immunosuppressed environment by disallowing the transformation of monocytes into myeloid-derived suppressor cells.^[29] SFN also reduces cleavage of caspase-1 and caspase-3,^[12,30-33] increases the production of the anti-inflammatory cytokines IL-4 and IL-10,^[25,34] and reduces the amount of gliosis, apoptosis, and necrosis in response to toxins.^[11,17,23,27,31,35,36] The reduction of neuroinflammation plays a prominent role in protecting against many toxins, as well as neuronal damage associated with Alzheimer's disease, Parkinson's disease, epileptic seizures, cerebral infarction, hepatic encephalopathy, Huntington's disease, and spinal cord injury.^[9-11,17,25,26,30,37,38] Oxidative stress and inflammation are major causes of cellular damage in a vast array of neurological diseases, and so by reducing both of these factors, SFN has major promise for helping protect against this damage.

Autophagy, a process used by cells to degrade damaged organelles and harmful proteins,^[19] is also upregulated by SFN in neurons.^[19,23,39,40] One study found that the promotion of autophagy by SFN is partially dependent on the Nrf2-ARE pathway, as indicated by Nrf2-knockout mice expressing fewer autophagy genes as well as the rescue of this expression by infection with an Nrf2-expressing lentivirus.^[19] However, a separate study found that Nrf2 knockdown did not influence autophagy.^[40] SFN produces oxidative stress itself, which is necessary for the upregulation of autophagy, evidenced by a lack of this upregulation when neurons are co-treated with SFN and the potent antioxidant N-acetyl-L-cysteine.^[40] The upregulation of autophagy by SFN plays a role in its neuroprotection in many neurodegenerative diseases by increasing the breakdown of the harmful proteins that characterize these diseases, including Alzheimer's disease,^[19] Parkinson's disease,^[23] and prion diseases.^[39]

SFN also protects mitochondrial function in neurons.^[22,41-44] Neurons, which are highly metabolically active and rely on oxidative phosphorylation to keep up with energy demands, depend on healthy mitochondria.^[43] The Nrf2-ARE pathway activates multiple genes which promote mitochondrial biogenesis, protect the function of mitochondrial complex I, II, and IV, and inhibit the decrease in adenosine triphosphate (ATP) generation caused by toxins.^[42] The upregulation of antioxidant defenses by the Nrf2-ARE pathway also works to protect the mitochondria from damage.^[43] Mitochondrial protection plays a role in reducing damage due to epileptic seizures,^[44] chemotherapy-induced neuropathy,^[5] models of Huntington's disease,^[42] neurodegenerative diseases,^[43] and carbon monoxide exposure.^[41]

Neurogenesis, the production of new neurons from neural stem cells, is critically important for learning and memory, and it is dysregulated in many neurodegenerative diseases.^[3] SFN increases neuronal expression of brain-derived neurotrophic factor, which promotes neuron generation^[3] and upregulates Wnt signaling in neural stem cells, which then increases stem cell proliferation and their differentiation into neurons.^[45]

Neuroprotection in Disease and Toxin Exposure

Table 1 provides a tabular view of the major evidence for the neuroprotective effects of SFN, categorized by disease.

Neurodegenerative Diseases

SFN has many potential benefits in preventing and modifying the course and symptom burden of multiple neurodegenerative diseases. In the brains of transgenic mouse models of Alzheimer's disease, SFN reduces the amount of amyloid beta (A β) and phosphorylated tau proteins as well as their aggregation.^[9,46] It also reduces memory deficits in mouse models.^[9,46] The degradation of abnormal protein aggregates is likely promoted by the pro-autophagy pathways activated by SFN.^[19] The oxidative stress that the aggregated proteins cause in Alzheimer's disease is also reduced with SFN supplementation.^[9,46,47] SFN in a toxin-induced Alzheimer's mouse model led to sparing of cholinergic neuron loss in the hippocampus and medial septal region of the brain.^[48] SFN also protects cultured neural cells from the toxicity of methylglyoxal, a precursor of advanced glycation end products (AGEs) which is associated with Alzheimer's disease.^[12] Neural cell death due to A β exposure is also reduced with SFN supplementation by the activation of proteasomes.^[49] Similarly, SFN may also prevent or slow the process of normal brain aging and memory problems.^[50] Memory is protected by SFN when animals are exposed to various toxins, including streptozocin,^[31] MG132 (an inhibitor of proteasomes),^[50] and scopolamine.^[51]

Parkinson's disease also benefits from SFN administration. In mouse models of Parkinson's disease induced by various neurotoxins, including rotenone,^[23] 6-hydroxydopamine,^[32,36,52] 5-S-cysteinyl dopamine,^[53] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine,^[17] SFN administration protects neurons and reduces neuronal cell death of nigrostriatal dopaminergic neurons.^[23,32,52] SFN also reduces motor deficits in toxin-induced animal models.^[23,32] Brain slice culture of rat nigrostriatal area also shows protection from toxin-induced Parkinson's damage.^[54] This protection is thought to be dependent on Nrf2 activation, with antioxidation and autophagy both

participating in reducing damage.^[23,32,55] SFN may also protect cells from damage in prion diseases by activating autophagy to degrade the misfolded proteins.^[39] Furthermore, in animal models of Huntington's disease, SFN reduces striatal damage, decreases neuron death, and improves mitochondrial function.^[27,42] SFN has a protective role in many neurodegenerative diseases that do not have any known cures, which makes it a quintessential agent for nervous system health. Research in humans is lacking, however, so its ability to decrease the risk of neurodegenerative diseases is unknown.

Stroke and Injury

Hypoxic-ischemic injury, hemorrhage, and traumatic spinal cord injury also cause great amounts of damage to the nervous system, including the primary event as well as the secondary damage due to the resulting inflammatory reaction and oxidative stress from reperfusion.^[30] In hypoxic-ischemic injury such as infarction, SFN pre- and co-treatment reduces infarct volume and improves the neurological function in animals with induced infarcts.^[30] Protection is also seen in cultured neurons exposed to ischemia.^[33,56] The same appears to be true for immature, developing nervous systems in the hypoxic conditions resulting from chronic placental insufficiency as well as infarct, with SFN administration reducing the loss of white matter, improving neurological function,^[57] and decreasing delayed neuronal cell death.^[56] Reduction in multiple inflammatory markers and immune cell activation is also seen with SFN use in ischemic injury.^[30,57,58] In the setting of intracerebral hemorrhage, SFN also improves neurological function^[20] and decreases the amount of damage due to free hemoglobin by inducing haptoglobin production in the brain.^[56,59]

SFN is also protective in spinal cord injury in multiple animal models, including traumatic, contusive, and compressive cord injury models.^[38,60,61] Reductions in contusion volume, increased viable axons caudal to the lesion, and decreased neuronal cell death result from SFN administration.^[38,60,61] Improvements in motor function and coordination are also seen with SFN use in spinal cord-injured animals.^[38,60] The same is true in traumatic brain injury in mice and rats, with SFN administration leading to decreased neuronal cell death, decreased contusion volume, and improvements in neurological function.^[18]

Epilepsy

Epileptic seizures damage neurons by inducing oxidative stress in seizure locations.^[10] In animal models, SFN administration, when combined with the anti-oxidant N-acetylcysteine, reduces the frequency of seizures, improves cognitive function, and decreases hippocampal cell death.^[10] Low-dose SFN alone also potentiates the

Table 1: Summary of major findings related to the neuroprotective effects of sulforaphane in various neurologic disease states

Topic	Article	Model	Effect	
Neurodegeneration				
	AD	Hou <i>et al.</i> , 2018; Lee <i>et al.</i> , 2018	Mouse transgenic AD	Reduced amount of A β and phosphorylated tau and their aggregation in the brain; reduced memory deficits
		Zhang <i>et al.</i> , 2014	Mouse aluminum and D-galactose-induced AD	Reduced cholinergic neuron loss in hippocampus and septum
Memory		Angeloni <i>et al.</i> , 2015	Cultured neurons with methylglyoxal	Reduced cell death
		Park <i>et al.</i> , 2009	Cultured neurons with A β	Reduced cell death
		Wang <i>et al.</i> , 2016	Rat streptozotocin-induced DM	Reduced apoptosis of hippocampal neurons; reduced memory impairment
PD		Sunkaria <i>et al.</i> , 2018	Mouse MG132 exposure	Protection against loss of spatial memory and memory consolidation
		Lee S <i>et al.</i> , 2014	Mouse scopolamine exposure	Protection against memory loss; increased level of ACh in hippocampus
		Zhou <i>et al.</i> , 2016	Mouse rotenone-induced PD	Improved locomotor activity; reduced dopaminergic neuron loss in brain
Prion diseases		Morrioni <i>et al.</i> , 2013	Mouse 6-hydroxydopamine-induced PD	Improved motor coordination; reduced neuron apoptosis
		Morrioni <i>et al.</i> , 2018; Deng <i>et al.</i> , 2012	Mouse 6-hydroxydopamine-induced PD	Reduced dopaminergic neuron loss
		Vauzour <i>et al.</i> , 2010	Cultured cortical neurons with 5-S-cysteinyl-dopamine	Reduced neuron loss
		Jazwa <i>et al.</i> , 2011	Mouse MPTP-induced PD	Reduced loss of nigral dopaminergic neurons
		Siebert <i>et al.</i> , 2009	Nigrostriatal culture of rat brain exposed to 6-hydroxydopamine	Reduced neuron loss
HD	Lee JH <i>et al.</i> , 2014	Human neuroblastoma cells exposed to PrP	Reduced cell death	
Stroke and injury		Luis-García <i>et al.</i> , 2017	Rat quinolinic-acid-induced HD	Reduced mitochondrial dysfunction
		Jang <i>et al.</i> , 2016	Mouse 3-NP-induced HD	Improved neurological behavior; reduced animal death; reduced neuron loss
Epilepsy		Yu <i>et al.</i> , 2017	Rat 60 min occlusive injury	Improved neurological function scores; reduced infarct volume
		Wu <i>et al.</i> , 2012	Cultured rat cortical neurons 1 h glucose-oxygen deprivation	Reduced cell death and injury
		Soane <i>et al.</i> , 2010	Cultured primary mouse immature hippocampal neurons exposed to oxygen-glucose deprivation	Reduced delayed neuronal death
		Soane <i>et al.</i> , 2010	Cultured primary mouse immature hippocampal neurons exposed to hemin	Reduced neuron loss
		Black <i>et al.</i> , 2015	Rat surgically-induced IUGR	Improved neurocognitive function in offspring; protection against loss of white matter and hippocampal neurons in offspring
		Yin <i>et al.</i> , 2015	Rat induced basal ganglia hemorrhage	Improved neurological function
		Zhao <i>et al.</i> , 2009	Mouse and rat induced ICH	Reduced neuron damage
		Mao <i>et al.</i> , 2011	Mouse compressive SCI	Improved locomotor function; reduced neuron loss
		Wang <i>et al.</i> , 2012	Rat mechanical SCI	Reduced contusion volume; improved motor coordination
		Benedict <i>et al.</i> , 2012	Rat contusive SCI	Improved locomotor function; increased 5-HT axons
Epilepsy		Hong <i>et al.</i> , 2010	Mouse and rat TBI	Improved neurological function; reduced contusion size; reduced neuron loss
		Pauletti <i>et al.</i> , 2017	Rat electrically-induced epilepsy, co-treatment with N-acetylcysteine	Reduced frequency of seizures; reduced hippocampal neuron loss; improved cognitive function
		Socała <i>et al.</i> , 2017	Mouse electrically-induced seizure	Potential of anti-convulsant effect of carbamazepine; at high concentrations, caused reduced seizure threshold
	Carrasco-Pozo <i>et al.</i> , 2015	Mouse epilepsy and SE models	Increased ATP production; anticonvulsant effect	

Contd...

Table 1: Contd...

Topic	Article	Model	Effect
Diabetes and neuropathy	Negi <i>et al.</i> , 2011	Cultured peripheral neurons	Improved conduction velocity and blood flow
	Negi <i>et al.</i> , 2011	Rat streptozocin-induced DM	Improved pain behavior
	Yang <i>et al.</i> , 2018	Mouse oxaliplatin-induced neuropathy	Improved pain sensation; improved mitochondrial function in DRG
	Di <i>et al.</i> , 2016	Rat nitroglycerin-induced hyperalgesia	Reduced tactile threshold
	Wang <i>et al.</i> , 2016	Rat streptozocin-induced DM	Reduced apoptosis of hippocampal neurons; reduced memory impairment
	Ren <i>et al.</i> , 2018	Mouse streptozocin-and high fat diet-induced DM-associated retinopathy	Improved ONL thickness; reduced retinal cell apoptosis
Psychosis	Shirai <i>et al.</i> , 2015	Mouse PCP-induced model of schizophrenia	Improved cognitive function
	Mas <i>et al.</i> , 2012	Human dopaminergic neuroblastoma cells exposed to antipsychotic medications and dopamine	Reduced cell death
	Shiina <i>et al.</i> , 2015	Human patients with schizophrenia	Improved accuracy component of one card learning task
GBM	Kumar <i>et al.</i> , 2017	Cultured human monocytes in glioma-conditioned media	Increased mature dendritic cell development; reduced harmful monocyte transformation
Friedrich's ataxia	Petrillo <i>et al.</i> , 2017	Cultured frataxin-deficient motor neurons	Increased neurite number and amount of extension
Hepatic encephalopathy	Hernandez-Rabaza <i>et al.</i> , 2016	Rat ammonia-induced encephalopathy	Improved learning; improved motor coordination
	Hernandez-Rabaza <i>et al.</i> , 2016	Rat ammonia-induced encephalopathy	Improved spatial learning
Herpes encephalitis	Schachtele <i>et al.</i> , 2012	Mouse HSV encephalitis	Reduced neuronal damage; reduced neuroinflammation
ASD	Singh <i>et al.</i> , 2014	Human men with ASD	Improved measures of aberrant behavior, social responsiveness, social interaction, and verbal communication
	Bent <i>et al.</i> , 2018	Human children with ASD	Improved measures of social responsiveness
Toxins	Bi <i>et al.</i> , 2017	Rat carbon monoxide exposure	Improved mitochondrial function; reduced hippocampal neuron damage
	Innamorato <i>et al.</i> , 2008	Mouse LPS exposure	Reduced inflammatory markers in brain
	Townsend <i>et al.</i> , 2017	Mouse LPS exposure	Reduced inflammatory markers in hippocampus
	Dwivedi <i>et al.</i> , 2016	Rat okadaic acid exposure	Improved memory; reduced neuron apoptosis in cortex and hippocampus
	Wang <i>et al.</i> , 2013	Zebrafish larvae cadmium exposure	Reduced olfactory tissue damage
	Ishihara <i>et al.</i> , 2012	Cultured rat hippocampus exposed to TBT	Reduced cell death
	Chang <i>et al.</i> , 2010	Cultured rat spinal cord exposed to glutamate	Reduced glutamate-associated neuronal damage
	Shavali <i>et al.</i> , 2008	Human neuroblastoma cells exposed to arsenic and dopamine	Reduced cell death
Pearson <i>et al.</i> , 2016	Cultured mouse neurons exposed to various neurotoxins	Reduced biochemical damage	

AP β : Amyloid β , AD: Alzheimer's disease, ACh: Acetylcholine, ASD: Autism spectrum disorder, DM: Diabetes mellitus, GBM: Glioblastoma multiforme, HD: Huntington's disease, HSV: Herpes simplex virus, ICH: Intracerebral hemorrhage, IUGR: Intrauterine growth restriction, LPS: Lipopolysaccharide, MPTP: Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, ONL: Outer nuclear layer, PCP: Phencyclidine, PD: Parkinson's disease, PrP: Prion protein, SCI: Spinal cord injury, SE: Status epilepticus, TBI: Traumatic brain injury, TBT: Tributyltin, 3-NP: 3-nitropropionic acid, DRG: Dorsal root ganglion, ATP: Adenosine triphosphate, 5-HT: 5-hydroxytryptamine (serotonin)

anti-seizure effects of carbamazepine, thus increasing the seizure threshold.^[62] SFN also raises the seizure threshold to protect against seizure occurrence.^[44] High-dose SFN, however, can decrease the seizure threshold.^[62] The administration of SFN in status epilepticus reduces lipid peroxidation in the hippocampus by protecting mitochondrial function and thus allowing the generation

of more ATP in the energy-starved state induced by prolonged seizure.^[44]

Diabetes and Neuropathy

AGEs are well-known neurotoxins that form due to high glucose concentrations as seen in diabetes

mellitus (DM) and can cause peripheral neuropathy, cognitive dysfunction, and retinal damage.^[12,28,63] In cultured peripheral neurons, SFN improves multiple parameters of AGE-induced neuronal damage, including the normalization of conduction velocity and blood flow.^[28] In animal models of DM-induced neuropathy, pain behavior is lessened with SFN administration.^[28] Protection from neuropathy due to other causes, such as the chemotherapeutic drug oxaliplatin- and nitroglycerin-induced trigeminal nerve pain, is also conferred by SFN.^[22,64] In the CNS, SFN prevents AGE formation^[65] and prevents memory dysfunction in DM animal models.^[31] Retinal degeneration due to AGEs is also reduced with SFN administration.^[63] Multiple mechanisms are at play in protection from AGE-induced damage, including the induction of thioredoxin,^[63] increased generation of GSH,^[12] decreased cleavage of caspase-3,^[31] and induction of the detoxifying glyoxalase-1^[12] which decreases AGE formation.^[65]

Psychosis

The role of SFN in psychotic disorders is multifaceted and not yet fully elucidated. Both pre- and post-exposure administration of SFN in animals exposed to phencyclidine, a psychosis-inducing agent, reduces damage to the prefrontal cortex and improves cognitive dysfunction.^[66] The Nrf2 gene also has a genetic association with cognitive impairments in schizophrenic patients, thus implying that the Nrf2 pathway and SFN may play a key role in psychosis in humans.^[66] Furthermore, treatment with antipsychotic drugs including haloperidol, risperidone, and paliperidone causes neuronal damage due to the formation of oxidative stress.^[14] SFN reduces this oxidative stress in dopaminergic neurons and thus may prevent some of the untoward effects associated with the treatment of psychotic disorders.^[14] A small study of seven human patients with schizophrenia found that 8 weeks of SFN administration resulted in significant improvement in one of the three components of a test assessing working memory, but the study size may have limited its power to find other significant improvements.^[1]

Other Diseases

As if the above protective effects are not enough, SFN also protects against neuronal damage in a variety of other diseases. Damage due to oxidative stress is reduced in models of Friedreich's ataxia, with SFN leading to an increased number of neurites, indicating increased plasticity.^[21] As briefly discussed previously, SFN may have a role in upsetting the immunosuppressed environment that protects glioblastoma multiforme.^[29] In hepatic encephalopathy

in animals, SFN lowers the inflammatory response to hyperammonemia and normalizes cognitive function and coordination.^[25,26] SFN administration also reduces neuronal damage induced by oxidative stress in mice with herpes encephalitis.^[7] Research regarding SFN use in autism spectrum disorder (ASD) is one area where some human studies have been done. A randomized controlled trial in human men with ASD revealed that 18 weeks of SFN administration improves multiple types of behavior, including reducing aberrant behaviors by 34%, increasing social responsiveness by 17%, as well as improving social interaction and verbal communication behaviors.^[67] A small study in children with ASD had similar results, with 12 weeks of SFN administration resulting in significantly improved social responsiveness, although this study found only a nonsignificant improvement in aberrant behavior.^[68] With such a wide array of disease protection, SFN may be utilized in many ways to help reduce nervous system disease burden.

Toxins

Many neurotoxins exist with a variety of unique mechanisms of toxicity. The neuroprotection conferred by SFN appears to be quite broad, as evidenced by the reduction of neuronal damage in the setting of various toxin exposures. These include all the toxins used to induce models of disease mentioned above, as well as carbon monoxide,^[41] lipopolysaccharide found in Gram-negative bacteria,^[5,37] the memory-impairing chemical okadaic acid,^[11] scopolamine,^[51] cadmium,^[69] the pesticide tributyltin,^[13] the excitotoxicity-inducing agent threohydroxyaspartate,^[70] arsenic,^[35] and multiple fungicides associated with genetic changes seen in autism, aging, and neurodegeneration.^[71] This broad scope of protection makes SFN a very useful tool to prevent or reduce neurotoxicity due to environmental or pharmaceutical toxin exposure.

Limitations and next steps

Several limitations are present in the currently available research. Nearly all SFN research regarding neuroprotection has been conducted with cultured neurons or animal models, apart from small trials regarding schizophrenia and ASD. While the results of this preclinical data are powerful, SFN use in humans with the diseases discussed will be crucial in understanding how well this animal research translates to human neurobiology. Without long-term prospective human cohort studies or controlled trials, it is difficult to assess whether the neuroprotection conferred by SFN will prevent the incidence of disease and burden of symptoms in preexisting disease. Another limitation is regarding the combination of SFN and antioxidants. Some researchers suggest that the concomitant use of SFN with antioxidants such as N-acetyl-L-cysteine

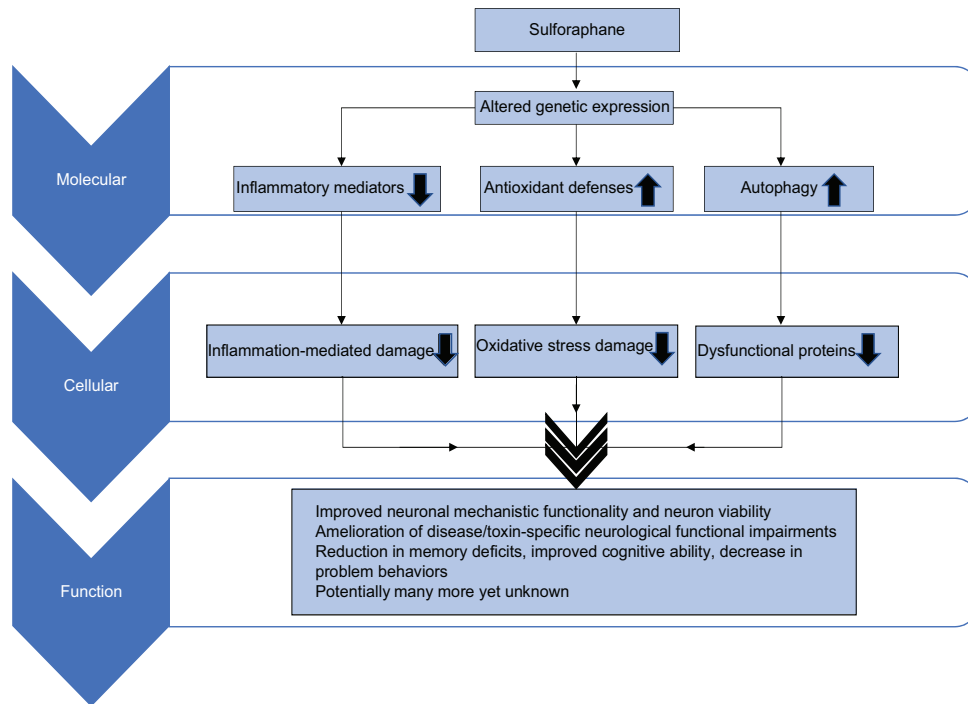


Figure 1: A schematic view of the effects of sulforaphane in the nervous system. Sulforaphane provides neuroprotective effects by altering genetic expression of various damaging or protective mediators, which reduces cellular damage and harmful protein accumulation, finally resulting in multiple functional neurological improvements in many neurological disease states and toxin exposures

reduces some the protective effects of SFN, specifically regarding the induction of autophagy.^[40] However, other research suggests that the combination can be more beneficial than either alone.^[10] This concept needs to be more fully elucidated to determine whether SFN with or without antioxidants will be most beneficial in each disease.

Further, only a few of the studies discussed mention possible neurotoxic effects of SFN, such as lowering the seizure threshold.^[62] Some researchers have concluded that SFN is a goitrogen because it can reduce uptake of iodine into the thyroid, but a human safety trial did not show reductions in thyroid function after SFN administration.^[4] Determining ideal dosages to maximize protection without causing detrimental effects will also be an important aspect of human trials.

Future research needs to address SFN use in humans with neurological diseases and disorders. This includes randomized controlled trials and longitudinal studies to assess the practical efficacy of SFN in neuroprotection. Research assessing the role of SFN as part of a multimodal treatment plan will also be important since SFN appears to have differential effects based on the concurrent treatments. Other research could look for even more efficacious Nrf2 activators or attempt to create them, like a melatonin-SFN hybrid molecule which may provide even further neuroprotection.^[72] There are currently multiple clinical trials ongoing regarding the effects of

SFN supplementation in patients with schizophrenia and patients with ASD.^[73] Hopefully, more researchers find SFN to be a worthy compound to assess in other diseases as well.

Conclusion and Perspective

SFN is a powerful antioxidant and anti-inflammatory phytochemical with great promise in its ability to protect the nervous system from many diseases and toxins and reduce the symptomatic burden of multiple pervasive diseases [Figure 1]. Research regarding long-term use in humans and disease outcomes will be important to determine its clinical utility. SFN, found naturally in high concentrations in broccoli sprouts, is a powerful example of how important food is to our health, and we must remember that while simple things like broccoli do not seem as powerful as human-made pharmaceuticals, they can truly be as or more important. The area of phytochemical use in prevention and damage reduction of neurological diseases is blossoming and may well be an important next step in reducing the risk of the many diseases we have assumed inevitable or incurable.

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Conflicts of interest

There are no conflicts of interest.

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