The Role of Oxidative Stress In Sleep Disorders

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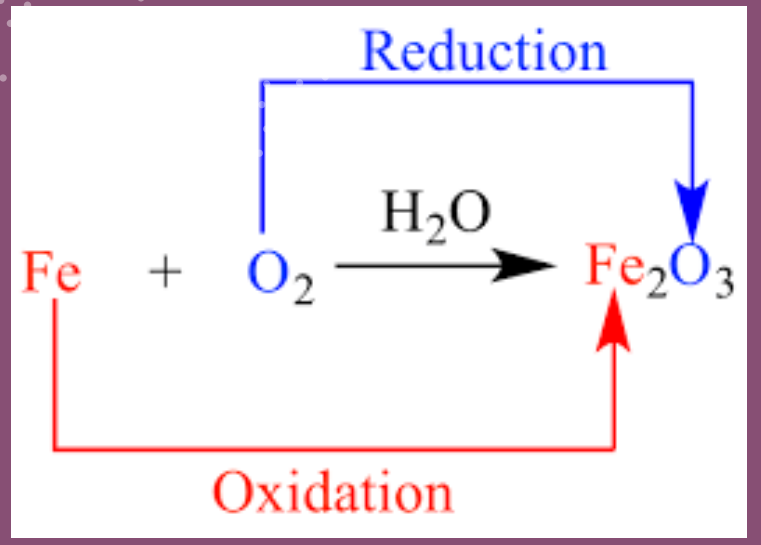
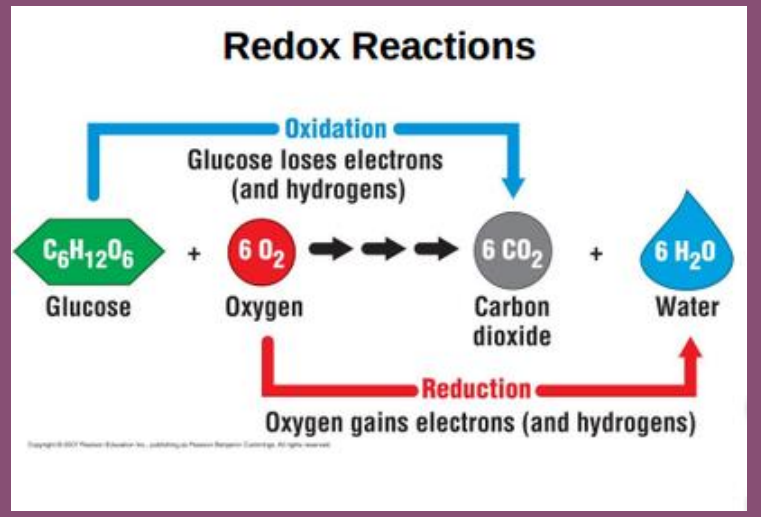
Objectives

- What is redox reaction
- What is oxidative stress
- Why is oxidative stress important to health
- Health conditions that oxidative stress impacts
- What is the circadian rhythm
- What is homeostatic processes involved with sleep
- Role of NRF2 in Sleep Disturbances
- Sleep and Neurological Disorders
- Role of Antioxidants in Sleep Disorders

Redox reactions (Oxidation-Reduction)

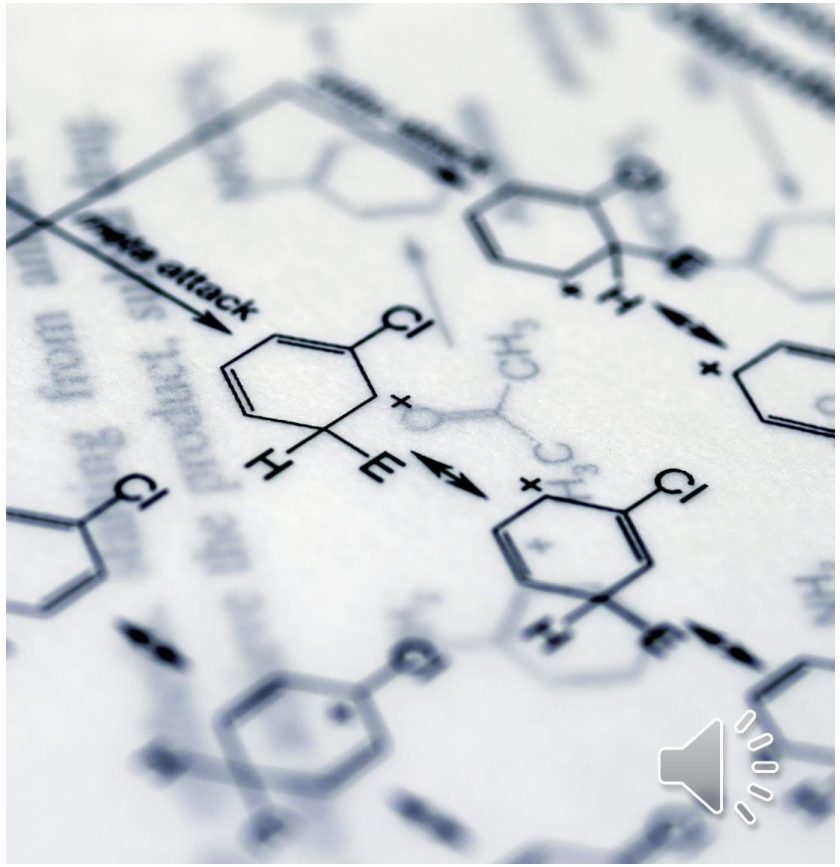
- It's a type of chemical reaction that involves a transfer of electrons between two species basically losing or gaining a electron
- Two simple examples of a redox reaction could be the rusting of iron and cellular respirations in humans





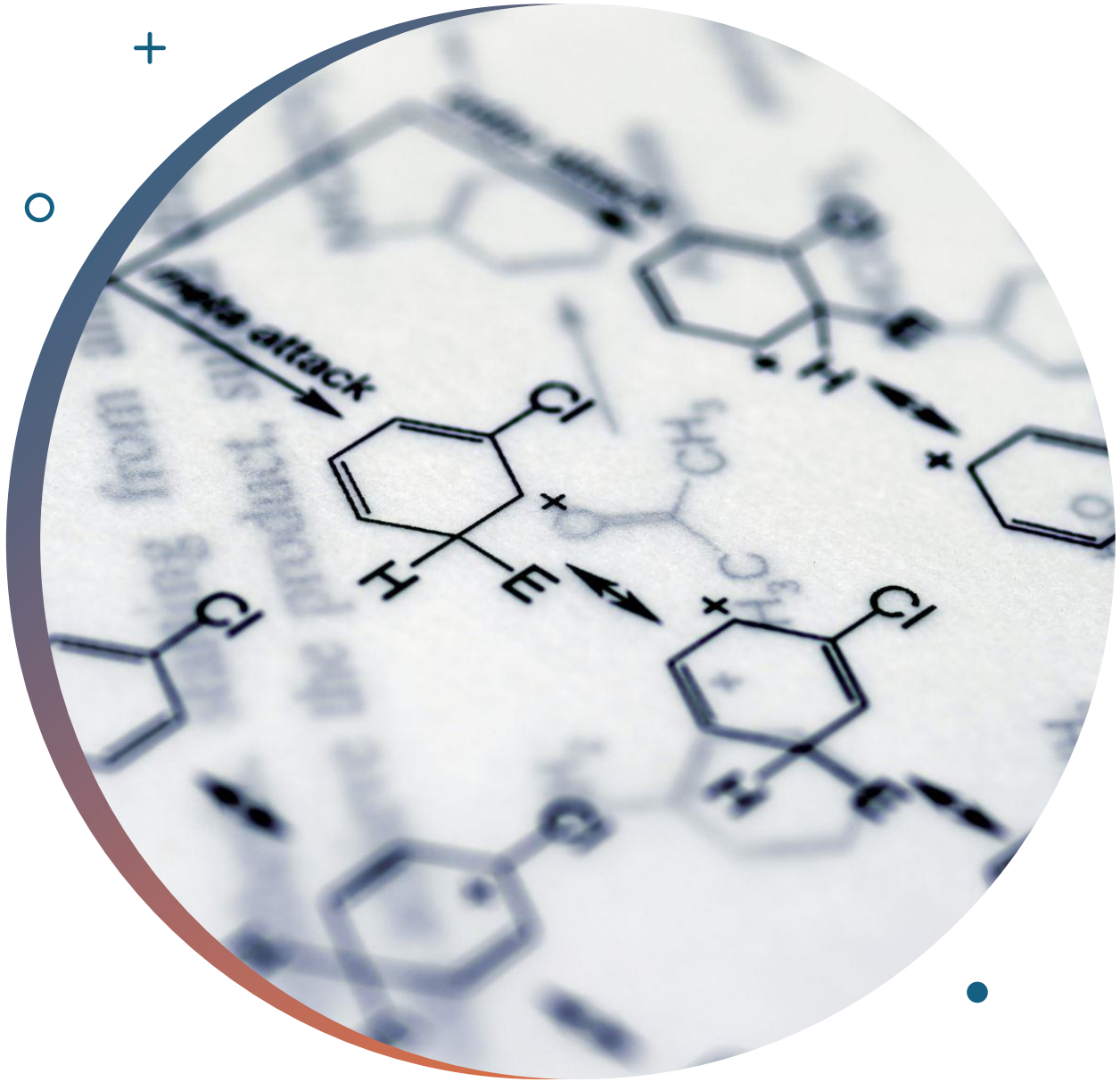
What is a free radical?

- During a redox reaction where an electron is either gained or lost it results in an odd number of electrons in the outer shell
- Examples include metabolic processes such as:
  - Cellular respiration (ATP production by mitochondria)
  - Phagocytosis (cell engulfs and destroys foreign substances or dead cells via proteins and superoxide, hydrogen peroxide, hypohalous acid, and hydroxyl radical
  - Prostaglandin synthesis (oxygenation catalyzed by the enzyme cyclooxygenase)
- External sources such as X-rays, ozone, cigarette smoke, air pollutants, and industrial chemicals
- Free radicals are also produced from refined sugar, carbohydrates, processed meats, and alcohol can produce free radicals



How does a free radical damage DNA?

- Free radicals damage DNA by directly reacting with the DNA molecule
- Chemical modifications to its bases and sugar backbone, which can lead to single-strand breaks, double-strand breaks, base modifications, and cross-links with other molecules
- Production of proteins and enzymes is altered or stopped
- Disrupting the DNA's structure and potentially causing mutations or cell death if not repaired properly



What is a free radical?

- Free radicals are unstable molecules within the body, often created as a byproduct of normal metabolism
- Unpaired electrons make them highly reactive and capable of damaging cell components like DNA, proteins, and lipids
- “Stealing" electrons from other molecules, leading to a chain reaction creating “Oxidative stress”
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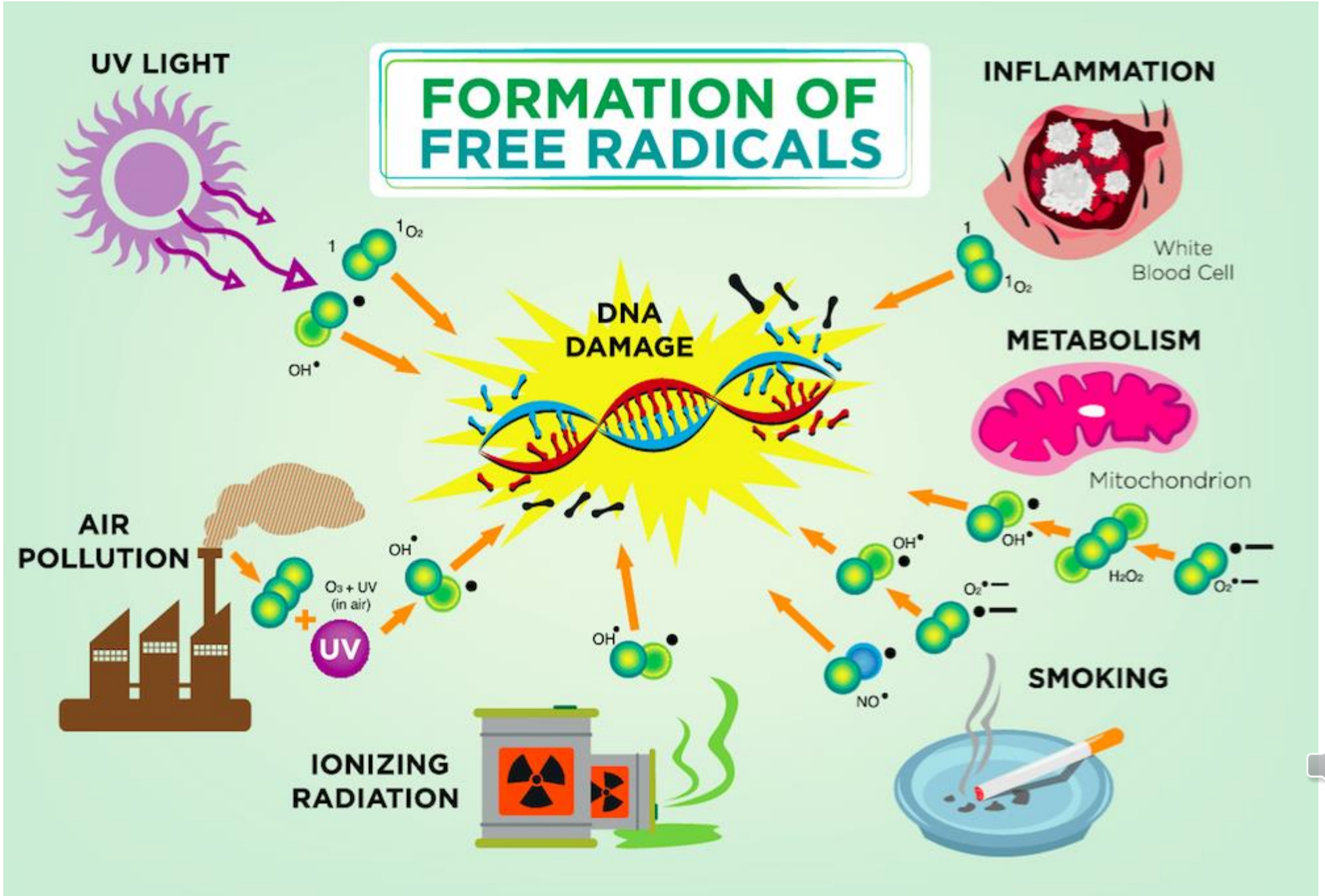
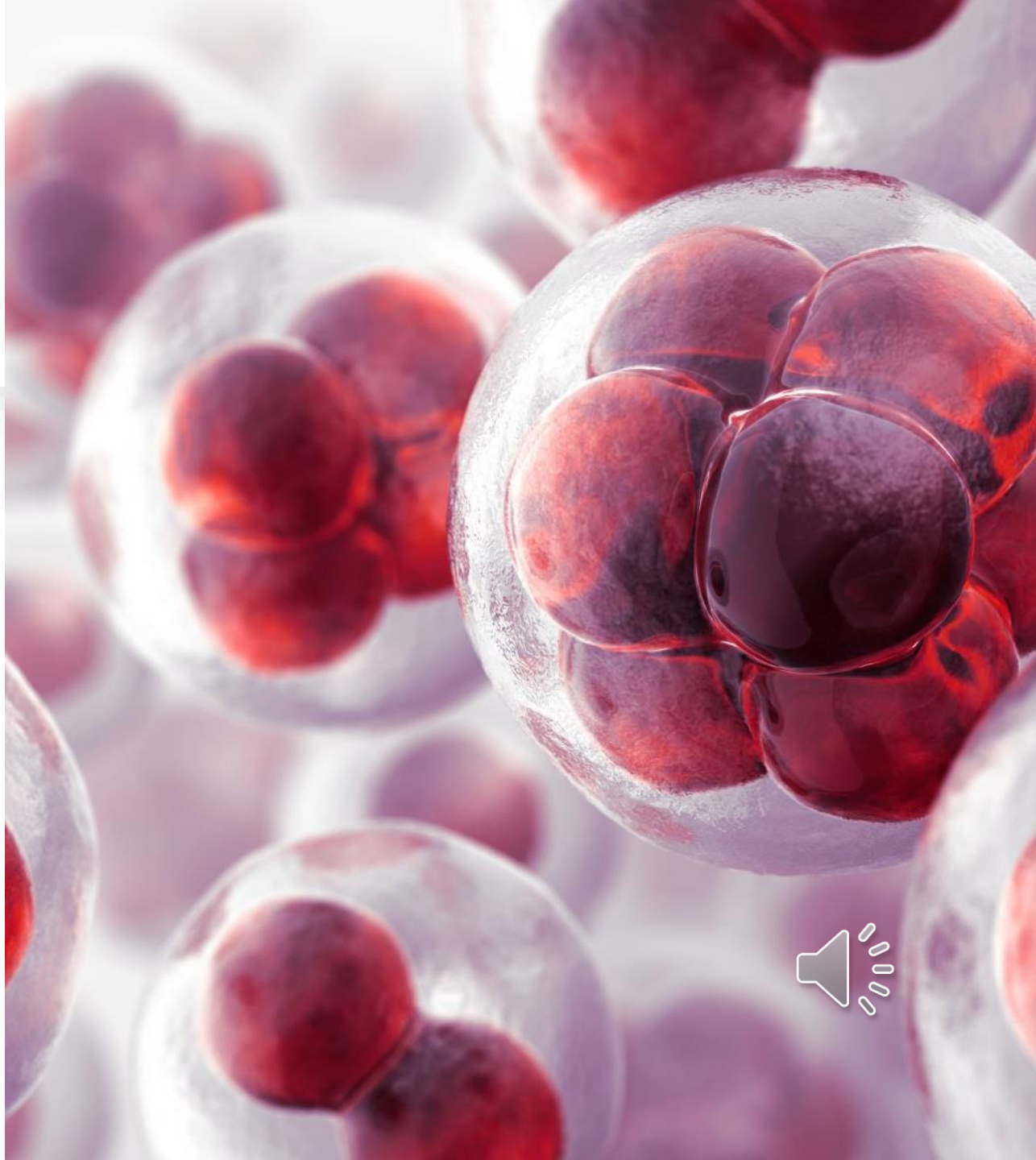

FORMATION OF FREE RADICALS
UV LIGHT
INFLAMMATION
White Blood Cell
DNA DAMAGE
METABOLISM
Mitochondrion
AIR POLLUTION
O3 + UV (in air)
UV
IONIZING RADIATION
SMOKING
NO
H2O2

Are all free radicals bad?

- Not all free radicals are bad many have beneficial physiological responses to the body
- For example:
  - Supporting our immune system,
  - Cell signaling
  - Facilitating physiologic processes like blood vessel dilation
  - Destroying invading bacteria through oxidative burst



Common free radicals produced in the body

- Superoxide: ($O_2^{-\cdot}$)
- Hydroxyl: ($OH\cdot$)
- Nitric oxide: ($NO\cdot$)
- Peroxyl: ($RO_2\cdot$)
- Hydrogen peroxide (H_2O_2)
- Peroxynitrite ($ONOO^-$)
- Hypochlorous acid ($HOCl$)
- Singlet oxygen
- Ozone

What is an antioxidant?

- A substance that is produced in the body or could be obtained from foods we eat or dietary supplements that neutralizes free radicals
- Scavenge free radicals from the body cells and prevent or reduce the damage caused by oxidation

What's the relationship between free radicals and antioxidants?

- Due to redox reactions in the body and the result in free radicals that are formed our bodies can balance out the free radicals with the use of antioxidants.
- Antioxidants are produced in the body, or they could be ingested by the foods we eat
- Antioxidants produced by the bodies include:
  - Glutathione
  - Alpha lipoic acid
  - Coenzyme Q10
  - Catalase (CAT)

Superoxide dismutase (SOD)

- The main purpose of this antioxidant is the conversion of the superoxide anion into hydrogen peroxide and water
- Produced in the body in the cytoplasm
- Found in foods that we eat such as broccoli, cabbage, Brussels sprouts
- Mutations of sod genes have been linked to neurodegenerative diseases such as Alzheimer's, ALS, Huntington disease, and Parkinson disease
- Current research is focusing on anti tumor, anti aging studies

Antioxidants not created in the body

Selenium	Polyphenols	Flavonoids	Vitamin C
Vitamin E	Beta carotene	Lycopene	Astaxanthin

What is oxidative stress

- Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) or free radicals in cells and tissues and the ability of a biological system to detoxify these reactive products
- Reactive oxygen species play an important role in several useful physiologic signaling processes
  - Cell growth
  - Differentiation
  - Immune response
  - Apoptosis or program cell death

Detrimental Effects of Oxidative Stress Human Health

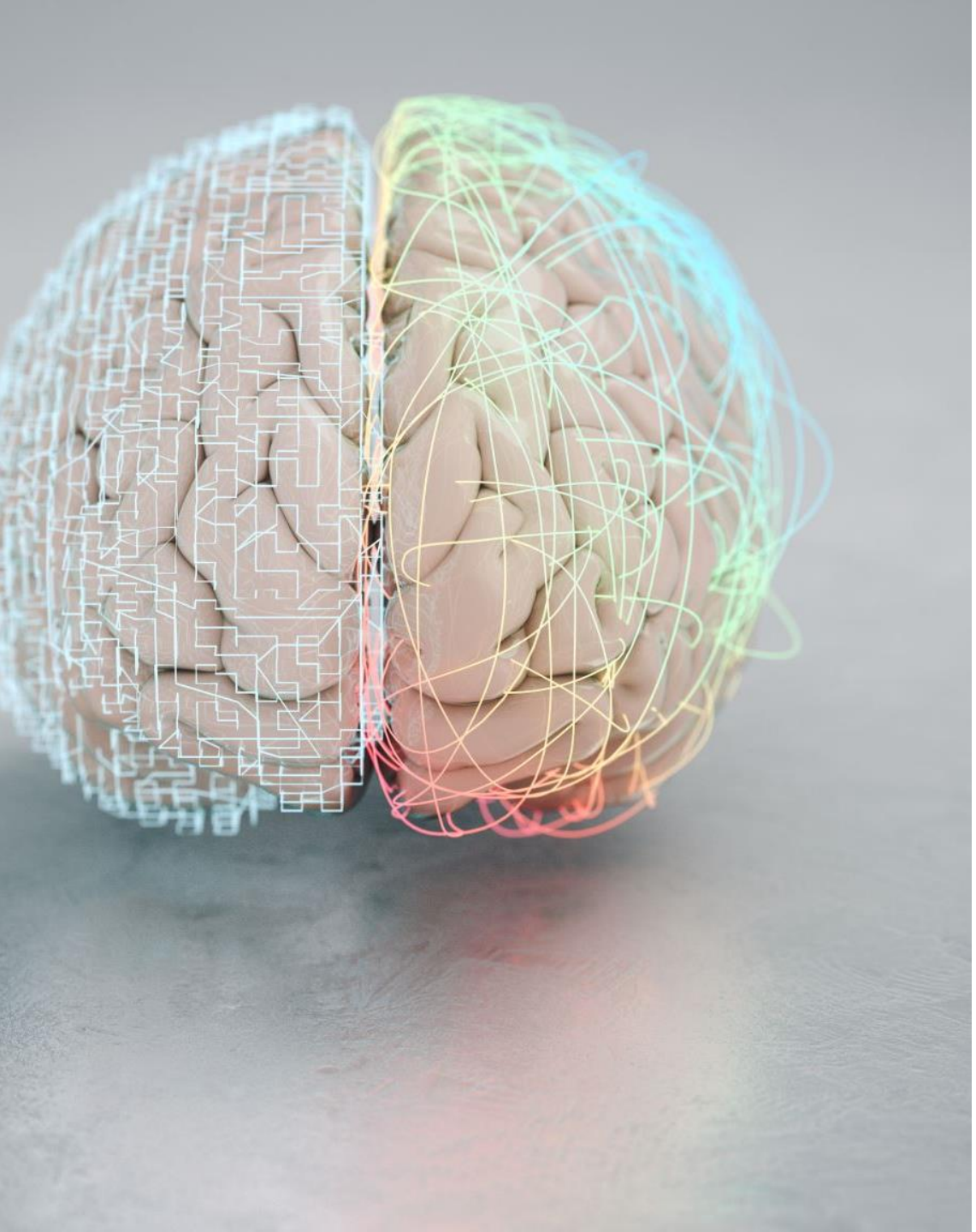
- Cancer and oxidative stress
- Cardiovascular disease and oxidative stress
- Neurological disease and oxidative stress
- Respiratory disease and oxidative stress
- Rheumatoid arthritis and oxidative stress
- Kidney disease and oxidative stress
- Sexual maturation and oxidative stress
- Sleep and oxidative stress

Sleep and oxidative stress

- Sleep is fundamental to brain function and systemic physiology
- Sleep impacts numerous parts of our systemic physiology such as metabolism, immunity, endocrine system, and cardiovascular system
- Sleep disturbance is associated with significant adverse health outcomes both in the short term and long term

Why do we need sleep?

- Waste removal (glymphatic system)
- Memory consolidation
- Brain plasticity
- Dreaming
- Blood glucose regulation
- Immune system support



Brain Plasticity Theory of Sleep

- A book was written by William James titled the “Principles of Psychology” and was written over 100 years ago. He is the first to mention the concept of “brain plasticity theory of sleep”
- The key points of the theory is that brain plasticity refers to the brain's ability to change and adapt its structure and function
- Major aspect of the theory is that sleep actively consolidated memories formed during wakefulness and is strengthened by neural connections associated with those experiences
- Sleep deprivation has been shown to impair memory function an oxidative stress seems to be the underlying physiologic cause

Free radical flux theory of sleep

- E Reimund 1994
- A theory of sleep is proposed in which cerebral free radicals accumulate during wakefulness and are removed during sleep.
- Removal of excess free radicals during sleep is accomplished by decreased rate of formation of free radicals, and increased efficiency of endogenous antioxidant mechanisms.
- Thus, sleep functions essentially as an antioxidant for the brain.

Restorative theory of sleep

- This theory speaks to the fact that sleep is required to repair and restore the body and mind during this time cellular repair
- During sleep and the body increases cellular division, protein synthesis, and growth hormone levels
- NREM and REM sleep is vital to restoring mental functions
- During times of oxidative stress cellular division, protein synthesis, and growth hormone levels are all decreased stop

Sleep regulation

- Circadian rhythm
- Neuroendocrine systems
- Sleep disturbances have a negative impact on the signaling pathways that regulate structural and synaptic plasticity
- This is evidenced by elevated serum levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor α (TNF-α), IL-6, and IL-17
- Most epidemiological evidence suggests that adults need an average of 7 to 8 hours of sleep

Sleep deprivation and oxidative stress What does the research say?

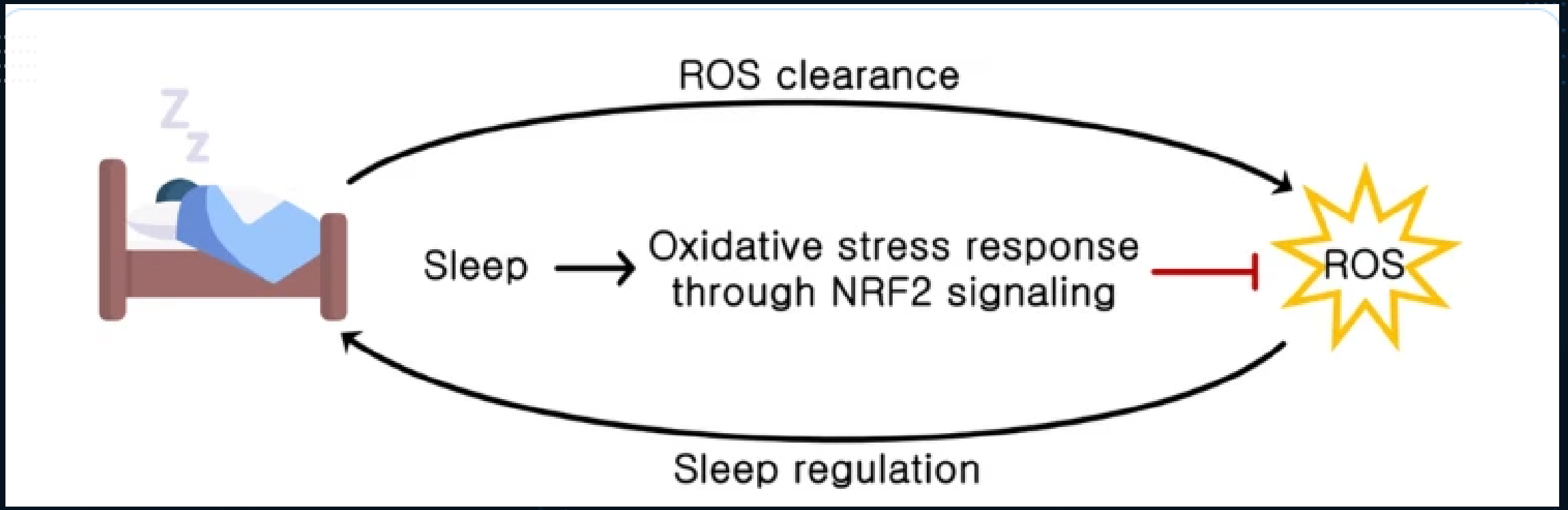
- Sleep is regulated by the circadian and neuroendocrine processes
- The circadian clock controls the timing of sleep, regulating the sleep–wake cycle and the distribution of sleep stages (i.e., rapid eye movement [REM] and non-rapid eye movement [NREM]) throughout the night
- Recent research has begun to reveal the molecular mechanisms by which redox signaling influences sleep–wake patterns.
- Evidence suggests that the cellular redox reactions plays a role in regulating neuronal activity and clock gene transcription in the suprachiasmatic nucleus (small region of hypothalamus that controls circadian rhythms).
- ROS produced by activated microglia and astrocytes may disrupt the function of the master clock, leading to circadian rhythm disturbances
- Night workers have been observed to exhibit elevated systemic markers of oxidative stress (e.g., plasma protein oxidation) and reduced antioxidant defenses when compared to their day worker counterparts

Evidence of the relationship between sleep deprivation and oxidative stress

- Majority of evidence originates from animal studies; two recent systematic reviews have attempted to elucidate the relationship between sleep and oxidative stress.
  - Villafuerte G, Miguel-Puga A, Murillo Rodríguez E et al (2015) Sleep deprivation and oxidative stress in animal models: a systematic review.
  - Neculicioiu VS, Colosi IA, Costache C et al (2023) Sleep deprivation induced oxidative stress in rat models: a scoping systematic review
- These reviews highlight the antioxidant effects of sleep in both brain and peripheral tissues, as well as the occurrence of oxidative stress following sleep deprivation

NRF2 or Nuclear factor erythroid 2-related factor 2

- What is a transcription factor?
  - Protein that regulates the transcription of genes, which is the process of copying DNA into RNA
- NRF2 or Nuclear factor erythroid 2-related factor 2
  - Regulates the cellular defenses against toxic and oxidative stress
  - Assist in the creation of proteins for antioxidant enzymes
  - Regulates numerous antioxidant genes by metabolizing proteins and enzymes
  - Vitamin C, vitamin E, glutathione, coenzyme Q10



Sleep and oxidative stress

- A bidirectional relationship between sleep and oxidative stress has been shown, indicating that sleep may play a protective role against the accumulation of reactive species during wakefulness and sleep deprivation.

Table 1 NRF2-dependent antioxidant genes and their enzymatic functions as discussed in this review

NRF2-dependent genes	Enzymatic function
Superoxide dismutase (SOD)	Catalyzes the dismutation of the superoxide radical (O_2^-) into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2)
Catalase (CAT)	Catalyzes the decomposition of hydrogen peroxide (H_2O_2) to water and molecular oxygen (O_2)
Heme oxygenase 1 (HO-1)	Catalyzes the degradation of heme to produce biliverdin and carbon monoxide (CO), two molecules with antioxidant effects
Glucose 6-phosphate dehydrogenase (G6PD)	Catalyzes the rate-limiting step of the oxidative pentose-phosphate pathway and generates nicotinamide adenine dinucleotide phosphate (NADPH)
6-phosphogluconate dehydrogenase (6PGD)	Produces NADPH by converting 6-phospho D-gluconolactone to D-ribulose 5-phosphate in the pentose-phosphate pathways
Malic enzyme 1 (ME1)	Catalyzes the conversion of malate to pyruvate while concomitantly generating NADPH from NADP
Isocitrate dehydrogenase 1 (IDH1)	Catalyzes decarboxylation of isocitrate to produce NADPH and 2-ketoglutarate
Thioredoxin (Trx) antioxidant system	Protects against oxidative stress through its disulfide reductase activity regulating protein dithiol/disulfide balance
Glutamate-cysteine ligase catalytic subunit (GCLC) and modifier subunit (GCLM)	Encode the subunits of the enzyme glutamate-cysteine ligase (GCL), which is the rate-limiting enzyme for the synthesis of the antioxidant glutathione (GSH)
Glutathione reductase (GR)	Catalyzes reduction of oxidized GSH and regeneration of reduced GSH
Glutathione peroxidase (GPx)	Reduces lipid hydroperoxides to their corresponding alcohols and H_2O_2 to water
Glutathione S-transferases (GST)	Catalyzes the conjugation of various substrates to GSH detoxifying endogenous compounds and enabling the breakdown of xenobiotics
NAD(P)H quinone oxidoreductase 1 (NQO1)	Flavin-containing quinone reductase that catalyzes two-electron reduction of quinones to hydroquinones
Peroxiredoxins (Prdx)	Regulate peroxide levels within cells, including H_2O_2 and peroxynitrite ($ONOO^-$)

Modulation of NRF2 in Sleep Disruption

NRF2 deficiency may contribute to sleep disturbances

There is hope and new research coming

Studies have shown that various molecules can supplement this deficiency

Potential remedies for NRF2 deficiency

- Ellagic acid (pomegranates, strawberries, raspberries, walnuts)
  - Polyphenolic compound found in various plants
  - Protect mice from memory loss and anxiety caused by sleep deprivation
  - Reduced the inflammatory response and oxidative stress caused by sleep deprivation
- Corilagin (isolated from plants such as pomegranate leaves and Chinese herbal medicine)
  - Ellagitannin that represents a derivative of ellagic acid
  - Inhibited NADPH oxidase 2 (NOX2) which increases sleep deprivation-induced oxidative stress
- Isoflavones (estrogen like compounds found in soybeans and legumes)
  - Phytoestrogens improved the cognitive performance of sleep-deprived animals
  - Increasing SOD activities
- Melatonin (St. John's Wort, Feverfew, nuts, bananas, grapes, coffee, or synthetically produced
  - Hormone responsible for regulating the sleep–wake cycle
  - Triggers the production of important anti oxidant enzymes, such as SOD and GPx

Table 2 Effects of NRF2 inducers in sleep deprivation models

Compounds	Models	Effects through NRF2 activation	References
Sulforaphane	Obstructive sleep apnea	•Modulation of endoplasmic reticulum (ER) stress •Protection of neurons from apoptosis •Reduction of the inflammatory response •Alleviation of cognitive impairment	Qiu et al. (2023)
Ellagic acid	Sleep deprivation	•Reduction of inflammatory response •Reduction of oxidative stress •Protection against memory impairment and anxiety in sleep-deprived mice	Wang et al. (2020a)
Corilagin	Sleep deprivation	•Inhibition of NADPH oxidase 2 (NOX2) levels •Reduction of malondialdehyde (MDA) levels •Restoration of glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities	Wang et al. (2020b)
Isoflavones	Chronic sleep deprivation	•Reduction of neuroinflammation •Restoration of SOD activities •Reduction of MDA levels	Lu et al. (2022)
Melatonin	Acute sleep deprivation	•Amelioration of memory loss •Reduction of hippocampal ferroptosis •Reduction of nuclear factor-κB (NF-κB) activation •Reduction of oxidative stress	Negi et al. (2011) and Wang et al. (2021)
Farnesol	Chronic sleep deprivation	•Activation of sirtuin 1 (SIRT1) •Activation of heme oxygenase-1 (HO-1) •Restoration of GPx activities	Li et al. (2023b)
Ketones	Chronic sleep deprivation	•Inhibition of ferroptosis •Reduction of lipid peroxidation •Improvement in neuronal repair ability •Activation of SIRT1	Yang et al. (2022)

Summary

- Sleep deprivation and oxidative stress is a serious issue
- Understanding the neurobiology of the brain is important into establishing important approach to handling this disorder
- NRF2 transcription factor seems to be the leading area of research regarding the oxidative stress caused by sleep deprivation
- Much research is being conducted and there are studies being conducted on how to deal with NRF2 deficiency

References

- Atrooz, F., & Salim, S. (2020). Sleep deprivation, oxidative stress and inflammation. *Advances in protein chemistry and structural biology*, *119*, 309-336.
- Davinelli, S., Medoro, A., Savino, R., & Scapagnini, G. (2024). Sleep and Oxidative Stress: Current Perspectives on the Role of NRF2. *Cellular and Molecular Neurobiology*, *44*(1), 52.
- He F, Ru X, Wen T. NRF2, a Transcription Factor for Stress Response and Beyond. Int J Mol Sci. 2020 Jul 6;21(13):4777. doi: 10.3390/ijms21134777. PMID: 32640524; PMCID: PMC7369905.
- Lu, C., Wei, Z., Jiang, N., Chen, Y., Wang, Y., Li, S., ... & Wang, F. (2022). Soy isoflavones protects against cognitive deficits induced by chronic sleep deprivation via alleviating oxidative stress and suppressing neuroinflammation. *Phytotherapy Research*, *36*(5), 2072-2080.