AURO
WELLNESS

TOPICAL GLUTATHIONE

The Role of Glutathione in Enhancing Mental Resilience and Reducing Stress

NAYAN PATEL, PHARMD

OBJECTIVES

- Impact of Oxidative Stress on Mental Health
- Glutathione as a Potent Antioxidant
- Mechanism of Topical Glutathione
- Integrating Glutathione into Daily Lifestyle for Enhanced Resilience

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MENTAL WELLNESS

MENTAL WELLNESS

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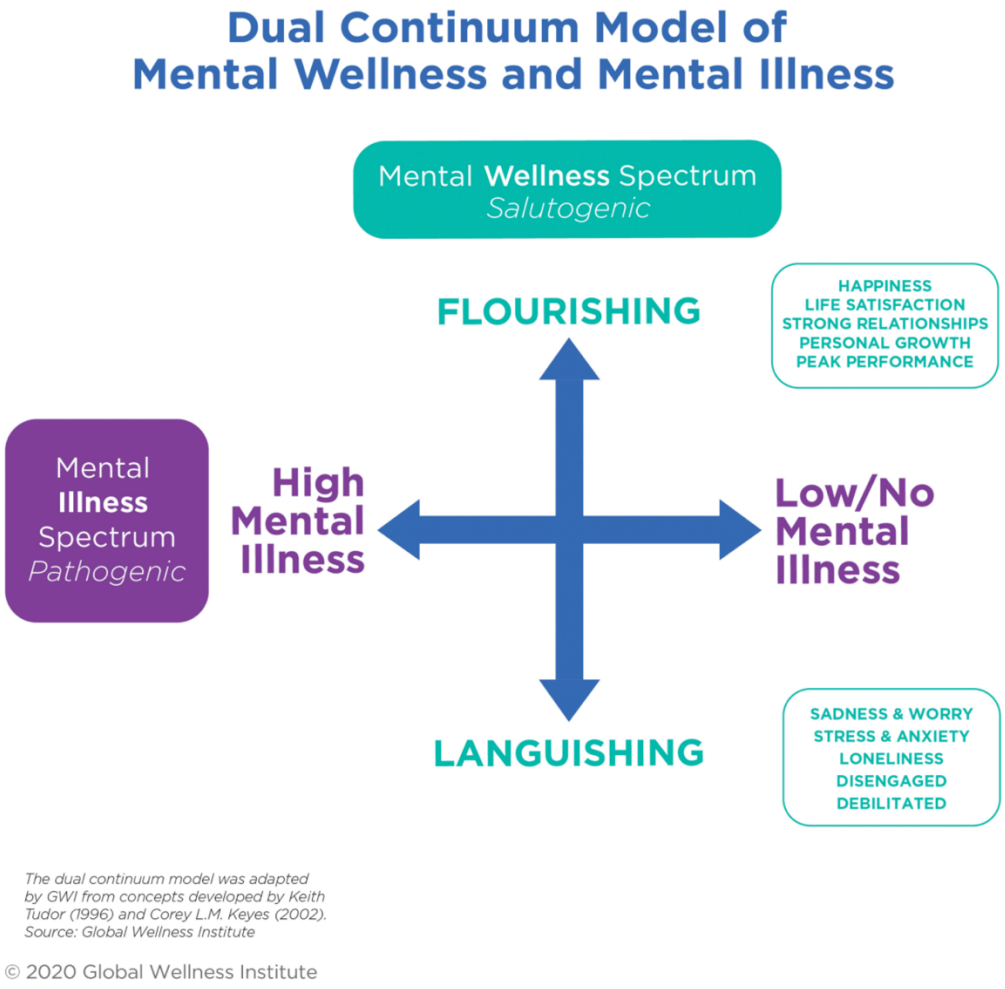
MENTAL WELLNESS AND MENTAL ILLNESS



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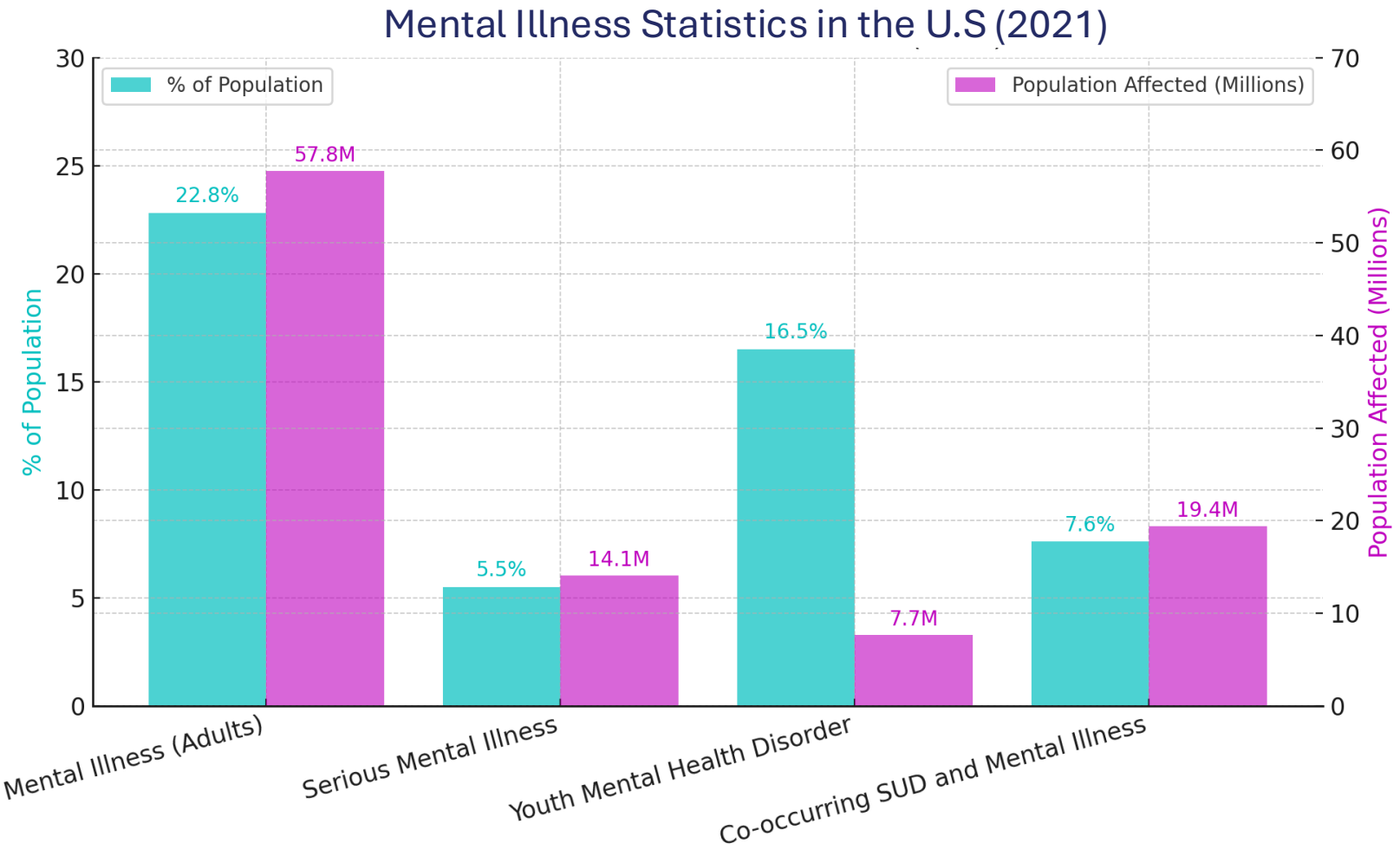
MENTAL ILLNESS STATUS IN THE US



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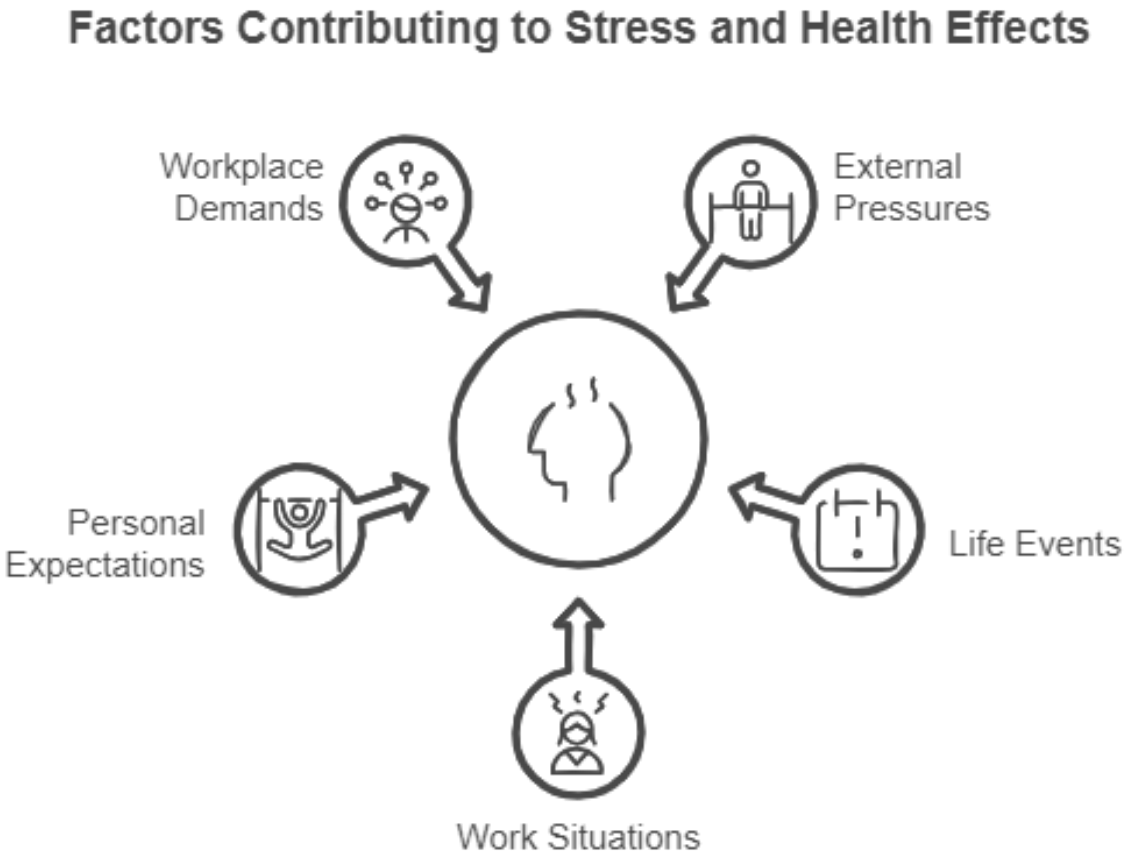
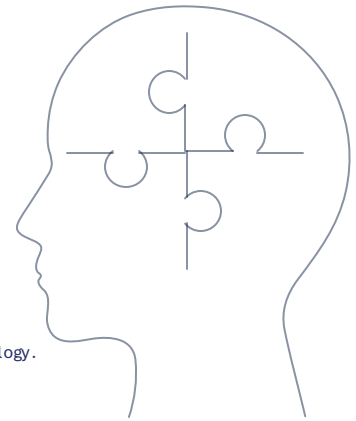
IMPACT OF STRESS ON MENTAL WELLNESS





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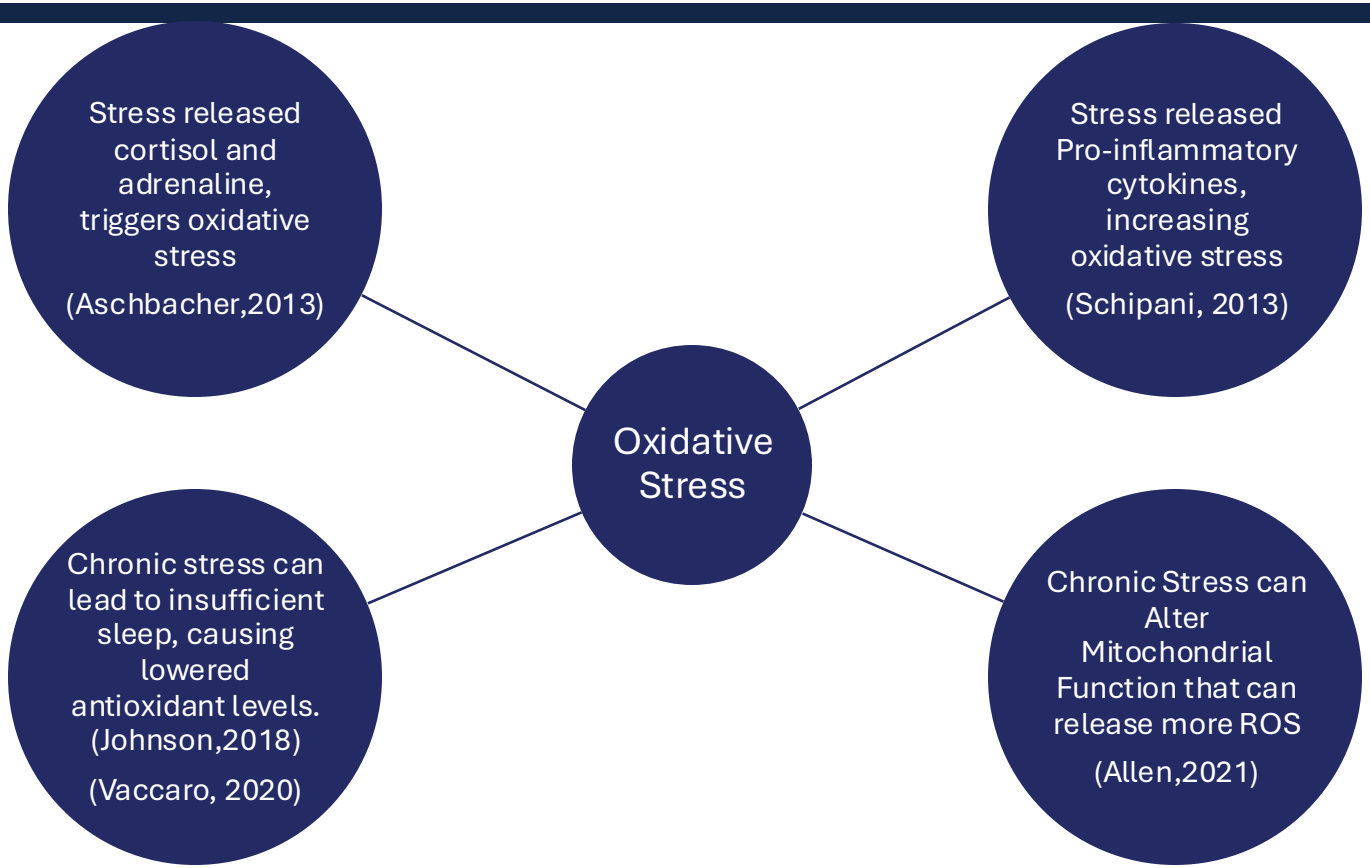
CONNECTION OF STRESS AND OXIDATIVE STRESS



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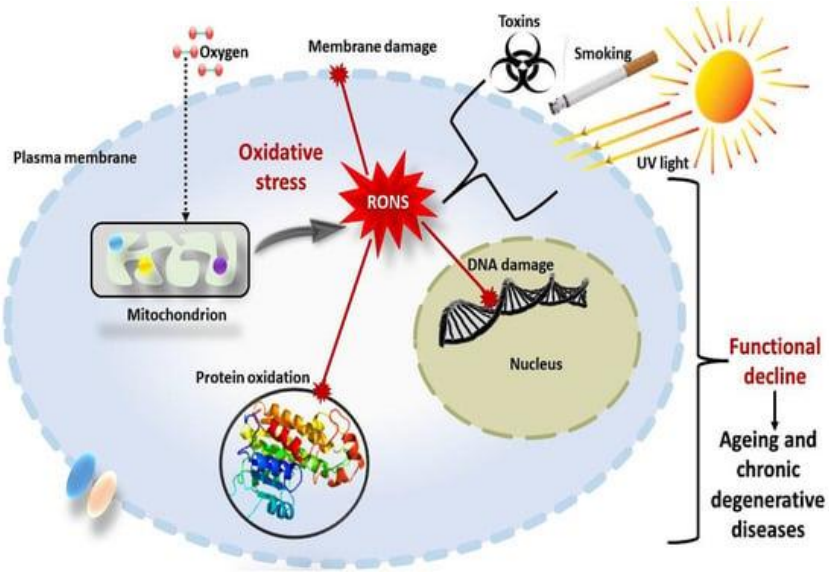
AURO WELLNESS

OXIDATIVE STRESS

OXIDATIVE STRESS

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms

When mitochondria utilize oxygen to generate energy, they also produce potentially harmful byproducts known as oxygen **free radicals** (or generated by pollution, radiation, and smoking).



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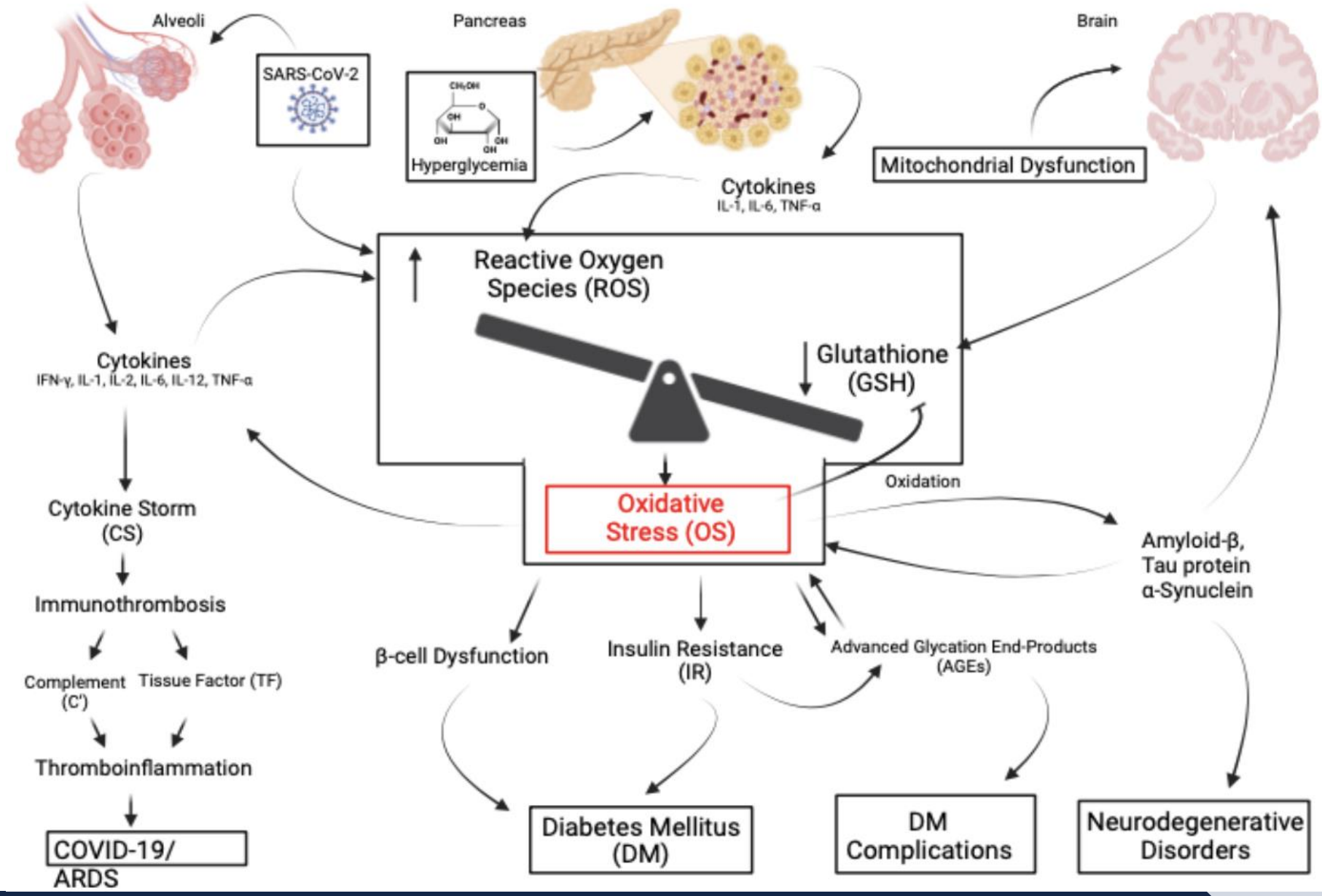

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Imbalance in ROS & Antioxidants.

CAUSES OF OXIDATIVE STRESS

Mitochondrial Dysfunction: Impaired mitochondrial function can lead to increased ROS production, as mitochondria are a major source of ROS in cells. (Kowalzik et.al,2021).

Nitrosative Damage: Peroxynitrite, formed by the reaction of NO with superoxide, can nitrify proteins and other cellular molecules, leading to dysfunction and contributing to inflammation and cell death. (Moon et. Al, 2008)

Accelerated Aging: The accumulation of oxidative and nitrosative damage contributes to the aging process by impairing cellular repair mechanisms, reducing cellular function, and promoting chronic inflammation. (Albano et. Al, 2022)

Chronic Inflammation: Persistent oxidative and nitrosative stress can lead to chronic inflammation, which further accelerates aging and contributes to the development of age-related diseases. (Kumar, et.al 2023)

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CAUSES OF OXIDATIVE STRESS

Metabolic Disorders: Metabolic disorders, such as diabetes and obesity, can disrupt cellular metabolism, leading to increased ROS production. (Oyendrin et. Al,2023)

Ageing: Aging is associated with a decline in antioxidant defense mechanisms and increased ROS production, contributing to age-related diseases. (Pithan, 2022)

Ischemia-Reperfusion Injury: When blood flow is temporarily blocked (ischemia) and then restored (reperfusion), it can cause a sudden burst of ROS, leading to tissue damage. (Minami et. Al, 2019)

Inadequate Antioxidant Defense: Insufficient levels of antioxidants, such as vitamins C and E, glutathione, and enzymes like superoxide dismutase, can result in an imbalance between ROS production and antioxidant defense. (Almeida, 2021)

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DISEASES LINKED WITH OXIDATIVE DAMAGE

- Asthma (Umit M Sahiner MD, 2011)
- Autoimmune disorders (rheumatoid arthritis, lupus, psoriasis, contact dermatitis, Crohn's disease) (Mannuncci,2021)
- Cancer (Hayes,2020)
- Cardiovascular diseases (atherosclerosis, coronary artery disease, arrhythmia, cardiomyopathy) (Singal, 1998)
- Neurodegenerative disorders (Alzheimer's, Parkinson's, ALS, Huntington's (Jie Li, 2013
- Viral disease (common flu, HIV/ADIS, herpes, shingles) (Pohanka, 2012)
- Stroke (Singal, 1998)

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AURO WELLNESS

OXIDATIVE STRESS AND NEURODEGENERATION

OXIDATIVE STRESS AND NEURODEGENERATION - OVERVIEW

- Biological tissues require oxygen to meet their energetic demands. However, the consumption of oxygen also results in the generation of free radicals that may have damaging effects on cells.

- The central nervous system (CNS) is particularly vulnerable to oxidative stress due to its high oxygen consumption, weakly antioxidative systems and the terminal-differentiation characteristic of neurons. Thus, oxidative stress elicits various neurodegenerative diseases.

- Reactive oxygen species (ROS) accumulate and damage neurons in neurodegenerative diseases like Parkinson's Disease (Dexter,1989), Alzheimer Disease (Butterfield,2002) (Hensley,1998), and Amyotrophic Lateral Sclerosis (Pederson,1998) (Beal 1997).

- Signs of oxidative stress, including lipid peroxidation and protein oxidation, are present in brain tissue from PD (Dexter,1989), AD (Butterfield,2002) (Hensley,1998), and ALS patients (Pederson,1998) (Beal 1997).

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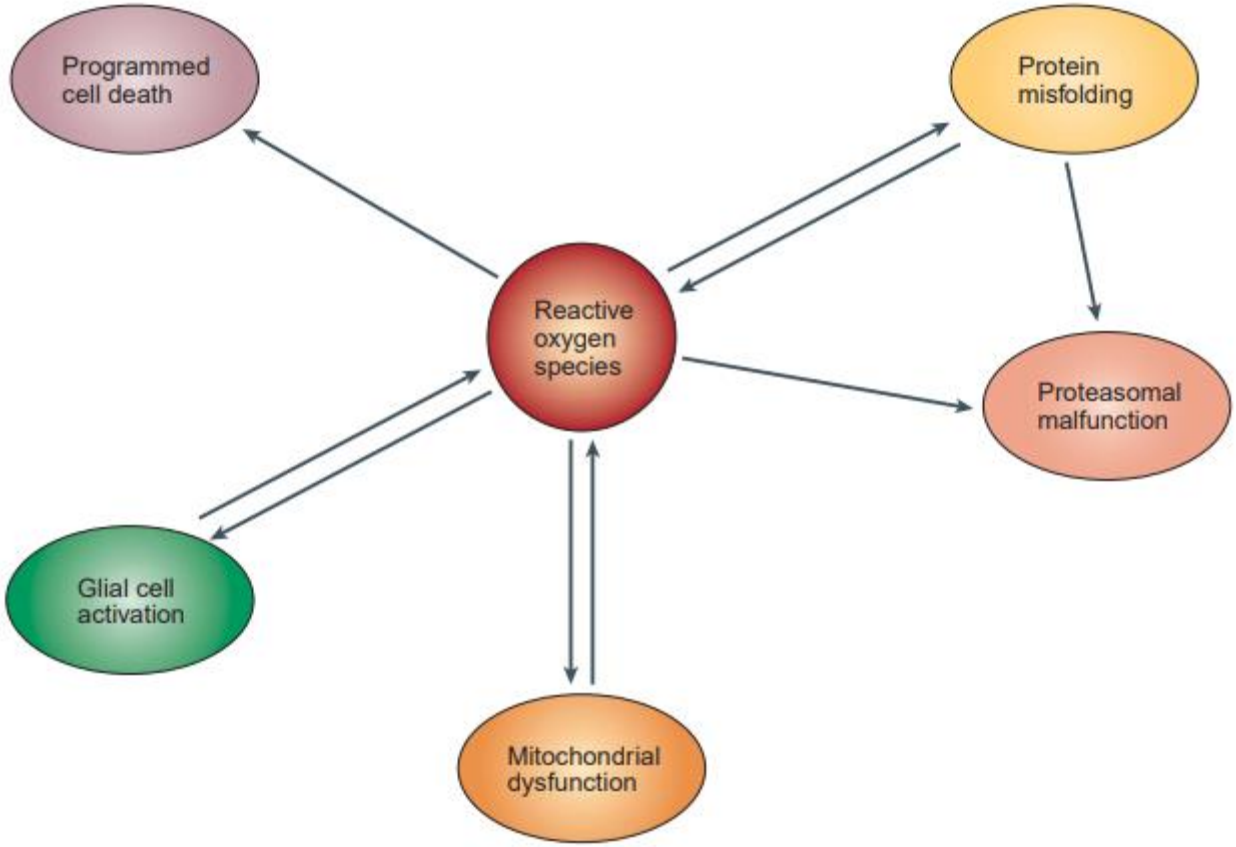
OXIDATIVE STRESS AND NEURODEGENERATION – ROLE OF ROS



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OXIDATIVE STRESS AND NEURODEGENERATION – DISEASES

- COGNITIVE DECLINE
  - PARKINSON'S DISEASE
  - ALZHEIMER'S DISEASE
- MOOD DISORDERS
  - MAJOR DEPRESSIVE DISORDER

OXIDATIVE STRESS LEADING TO PARKINSON'S DISEASE

Result and Discussion

Oxidative stress in Parkinson's disease stems from the dysregulation of cellular redox activity, with the resultant accumulation of reactive oxygen species (ROS) playing a key role in neuronal damage and disease progression

Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease

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Abstract

Parkinson's disease prevalence is rapidly increasing in an aging global population. With this increase comes exponentially rising social and economic costs, emphasizing the immediate need for effective disease-modifying treatments. Motor dysfunction results from the loss of dopaminergic neurons in the substantia nigra pars compacta and depletion of dopamine in the nigrostriatal pathway. While a specific biochemical mechanism remains elusive, oxidative stress plays an undeniable role in a complex and progressive neurodegenerative cascade. This review will explore the molecular factors that contribute to the high steady-state of oxidative stress in the healthy substantia nigra during aging, and how this chemical environment renders neurons susceptible to oxidative damage in Parkinson's disease. Contributing factors to oxidative stress during aging and as a pathogenic mechanism for Parkinson's disease will be discussed within the context of how and why therapeutic approaches targeting cellular redox activity in this disorder have, to date, yielded little therapeutic benefit. We present a contemporary perspective on the central biochemical contribution of redox imbalance to Parkinson's disease etiology and argue that improving our ability to accurately measure oxidative stress, dopaminergic neurotransmission and cell death pathways in vivo is crucial for both the development of new therapies and the identification of novel disease biomarkers.

KEYWORDS
antioxidant, oxidative stress, Parkinson's disease, reactive oxygen species

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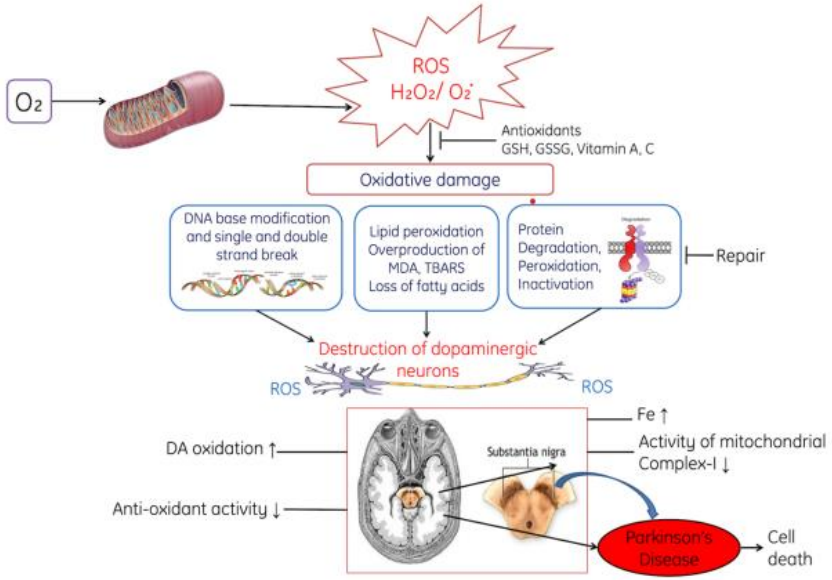
Trist BG, Hare DJ, Double KL. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell. 2019 Dec;18(6):e13031. doi: 10.1111/acel.13031. Epub 2019 Aug 20

OXIDATIVE STRESS LEADING TO PARKINSON'S DISEASE

Result and Discussion

Oxidative stress can cause **oxidative damage to DNA, leading to base modifications** and **DNA fragmentation**. In lipids, ROS can **trigger peroxidative damage**



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OXIDATIVE STRESS LEADING TO ALZHEIMER'S DISEASE

Result and Discussion

Oxidative stress plays a key role in Alzheimer's disease by **promoting β-amyloid** deposition, **tau hyperphosphorylation**, and **neuronal loss.**

Brain is vulnerable to oxidative damage (consumes 20% of the oxygen supplied by the respiratory system), antioxidants may offer potential in treating AD.

Review

Oxidative stress in Alzheimer's disease

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Oxidative stress plays a significant role in the pathogenesis of Alzheimer's disease (AD), a devastating disease of the elderly. The brain is more vulnerable than other organs to oxidative stress, and most of the components of neurons (lipids, proteins, and nucleic acids) can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation, and β-amyloid (Aβ) peptides. Oxidative stress participates in the development of AD by promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons. The relationship between oxidative stress and AD suggests that oxidative stress is an essential part of the pathological process, and antioxidants may be useful for AD treatment.

Keywords: Alzheimer's disease; oxidative stress; β-amyloid; tau; metals; antioxidants

Introduction

The human brain, although it constitutes only 2% of the body weight, consumes ~20% of the oxygen supplied by the respiratory system[1]. The high energy-consumption of the brain means that it is more susceptible to oxidative stress than any other organ. As the basic functional unit of the brain, the neuron is particularly vulnerable to oxidative in the blood reflect such stress in the brain[8, 9]. Currently, many blood markers of oxidative stress have been identified in AD patients or related animal models, including protein carbonyls and 3-nitrotyrosine[10, 11], 8-hydroxydeoxyguanosine (8-OHdG), 8-hydroxyguanosine (8-OHG), malondialdehyde (MDA)[12], 4-hydroxynonenal (4-HNE), and F2-isoprostanes (F2-IsoPs)[13-16]. Apart from the intracellular accumulation of free radicals, changes

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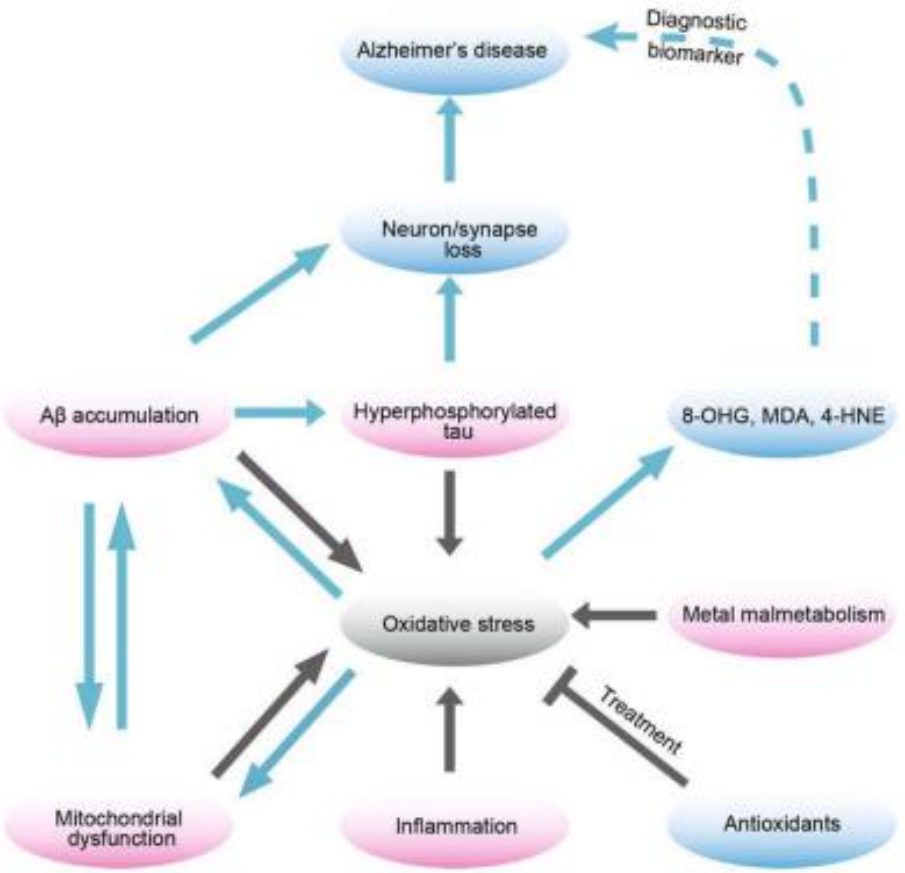
Chen Z, Zhong C. Oxidative stress in Alzheimer's disease. Neurosci Bull. 2014 Apr;30(2):271-81. doi: 10.1007/s12264-013-1423-y. Epub 2014 Mar 24. PMID: 24664866; PMCID: PMC5562667.

OXIDATIVE STRESS LEADING TO ALZHEIMER'S DISEASE



PROPOSED PREVENTIVE MEASURE

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Chen Z, Zhong C. Oxidative stress in Alzheimer's disease. Neurosci Bull. 2014 Apr;30(2):271-81. doi: 10.1007/s12264-013-1423-y. Epub 2014 Mar 24. PMID: 24664866; PMCID: PMC5562667.

OXIDATIVE STRESS LEADING TO MAJOR DEPRESSIVE DISORDER

Result and Discussion

SOD activity was significantly (F(1,33)=6, p=0.022) **reduced in MDD patients compared to healthy controls**

MDD patient's GPx activity was significant for recurrent depression (F(1,34)=17, p=0.0002)

Malondialdehyde, was significantly higher (first episode (F(1,33)=15, p=0.0002) **in MDD patients compared to healthy controls.**

Research report

The relevance of oxidative stress status in first episode and recurrent depression

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ABSTRACT

Oxidative and nitrosative stress (O&NS) could play an important role in the pathophysiology of major depression (MDD). The aim of the present work was to evaluate the specific activity of the main peripheral antioxidant defences (superoxide dismutase—SOD and glutathione peroxidase—GPX) and the level of malondialdehyde—MDA (a lipid peroxidation maker), in depressed patients, as compared to an age-matched control group. Also, we were interested to see if there are any differences between first episode vs. recurrent depression groups, in terms of oxidative stress markers. Additionally, we want it to investigate the effects of different antidepressant medication (mirtazapine, venlafaxine, tianeptine and escitalopram) on oxidative status of depressed patients. Our results showed an increased oxidative stress status in the serum of patients with MDD, expressed by a significant decrease of both SOD and GPX specific activities and a significant increase of the lipid peroxidation marker MDA, as compared to the control group. When we analyzed the oxidative stress status in depressed patients based on chronicity we observed significant decrease of SOD and GPX specific activities in recurrent depression group, as compared to the first episode group. Moreover, a very significant increase in MDA concentration was observed in recurrent depression patients, as compared to the first episode group.

Our work provides additional evidences of increased oxidative stress in MDD, expressed by altered antioxidant enzyme activity and increased levels of lipid peroxidation. Also, it seems that sub-classifying depression into different subtypes, based on chronicity, can predict differences in the levels of some various oxidative stress markers.

References:
Stefanescu C, Ciobica A. The relevance of oxidative stress status in first episode and recurrent depression. J Affect Disord. 2012 Dec 20;143(1-3):34-8.

OXIDATIVE STRESS LEADING TO MAJOR DEPRESSIVE DISORDER

Result and Discussion

Plasma MDA: ~57.20% increase in MDD patients compared to control healthy participants

Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder

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Recent data from several reports indicate that free radicals are involved in aetiopathogenesis of many human pathologies including neuropsychiatric disorders such as schizophrenia, bipolar disorder etc. In the present study, we aimed at determining and evaluating levels of malondialdehyde (MDA), a product of lipid peroxidation, and antioxidant enzyme (superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity levels in patients diagnosed with schizophrenia ($n = 25$) and bipolar disorder ($n = 23$). The control group was composed of 20 healthy subjects. There was a significant increase in MDA levels of patients with schizophrenia and bipolar disorder compared with controls. SOD and GSH-Px activity levels were significantly higher in the schizophrenic group compared with controls. SOD activity levels in bipolar the group were significantly higher than controls whereas there were no significant changes in GSH-Px activity levels in the bipolar group and controls. Significant differences between lipid peroxidation product and antioxidant enzyme (SOD and GSH-Px) activity levels in schizophrenic and bipolar disorder patients compared with controls leads us to believe that these differences are related to the heterogenities in aetiologies of these disorders.

KEY WORDS — MDA; SOD; GSH-Px; schizophrenia; bipolar disorder

INTRODUCTION

There is an enormous amount of convincing data indicating that reactive free radical species are involved in initiation and development of many different forms of human pathologies. Predominantly superoxide, degenerative diseases have also been investigated. Free radicals have been considered important primarily in the pathogenesis of neuroleptic treatment complications, such as tardive dyskinesia in psychiatric disorders.[1]

Free radicals are produced in many different ways,

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THERAPEUTIC STRATEGIES TO OVERCOME OXIDATIVE STRESS

Physical Activity Level
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Dietary Habits
(Vibha Rani, G. D.,2016)

Antioxidant Supplementation
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ROS & ANTIOXIDANTS

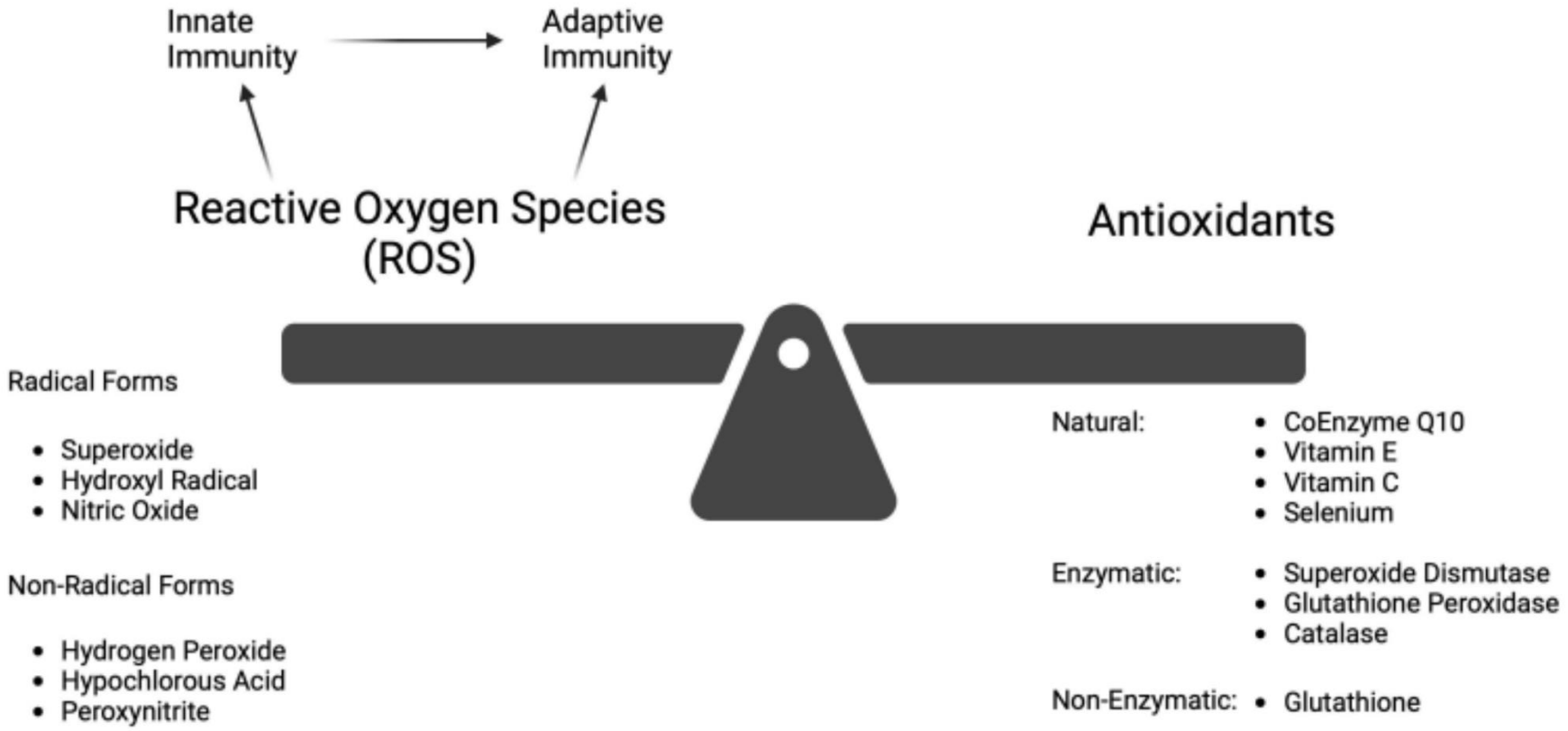

Figure 1. This illustrates the beneficial role of reactive oxygen species (ROS) when it is in physiologic balance with antioxidants. These include activating innate immunity and augmenting adaptive immunity. It should be noted that peroxynitrite and nitric oxide are co-existing reactive nitrogen species (RNS).

COMPARATIVE EFFECTIVENESS OF DIFFERENT ANTIOXIDANT

Antioxidant	Mechanism of Action	Effectiveness Against Oxidative Stress	Notes
Glutathione (Heather,2003)	Quenches free radicals and detoxifies harmful substances	Effective in neutralizing oxidative stress; Promotes Cell Proliferation; Modulates Immune Response; Detoxify Toxins	Often considered the body's master antioxidant.
Vitamin C (Hamza,2017)	Donates electrons to stabilize free radicals	Scavenges free radicals; Regenerates other anti-oxidant; Protect against environmental Stress	Water-soluble; can boost collagen production.
Vitamin E (Chow,1991)	Protects cell membranes from oxidation	Membrane Protection; Cellular Damage Protection; Supports Immune Function,	Fat-soluble; works synergistically with Vitamin C.
Coenzyme Q10 (Beyaz,2022)	Neutralizes free radicals and supports energy production	Beneficial for cardiovascular health and improving energy metabolism; Neutralizes free radicals	Important for ATP production in cells.
Alpha Lipoic Acid (Sztolsztener,2022)	Increases Antioxidant Enzyme such as GSH; reduce inflammatory enzymes	Scavenges free radicals; has anti-inflammatory effects	Unique in its ability to function in both water and fat environments.

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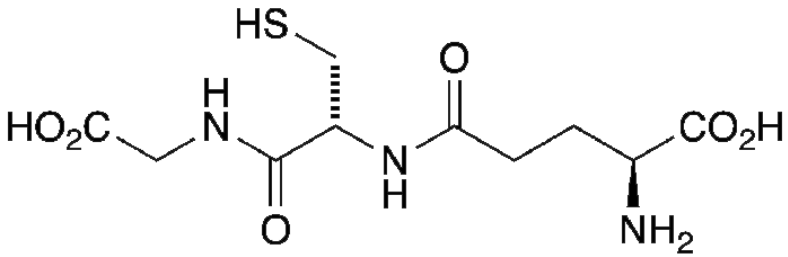
Ching Kuang Chow. (1991). VITAMIN E AND OXIDATIVE STRESS . Free Radical Biology and Medicine,, 17.
Pala R, Beyaz F, Tuzcu M, Er B, Sahin N, Cinar V, Sahin KThe effects of coenzyme Q10 on oxidative stress and heat shock proteins in rats subjected to acute and chronic exercise J Exerc Nutrition Biochem. 2018 Sep 30;22(3):14-20
Klaudia Sztolsztener, K. H. (2022). α-lipoic acid ameliorates inflammation state and oxidative stress by reducing the content of bioactive lipid derivatives in the left ventricle of rats fed a high-fat diet,. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease,, 13.

AURO
WELLNESS

GLUTATHIONE

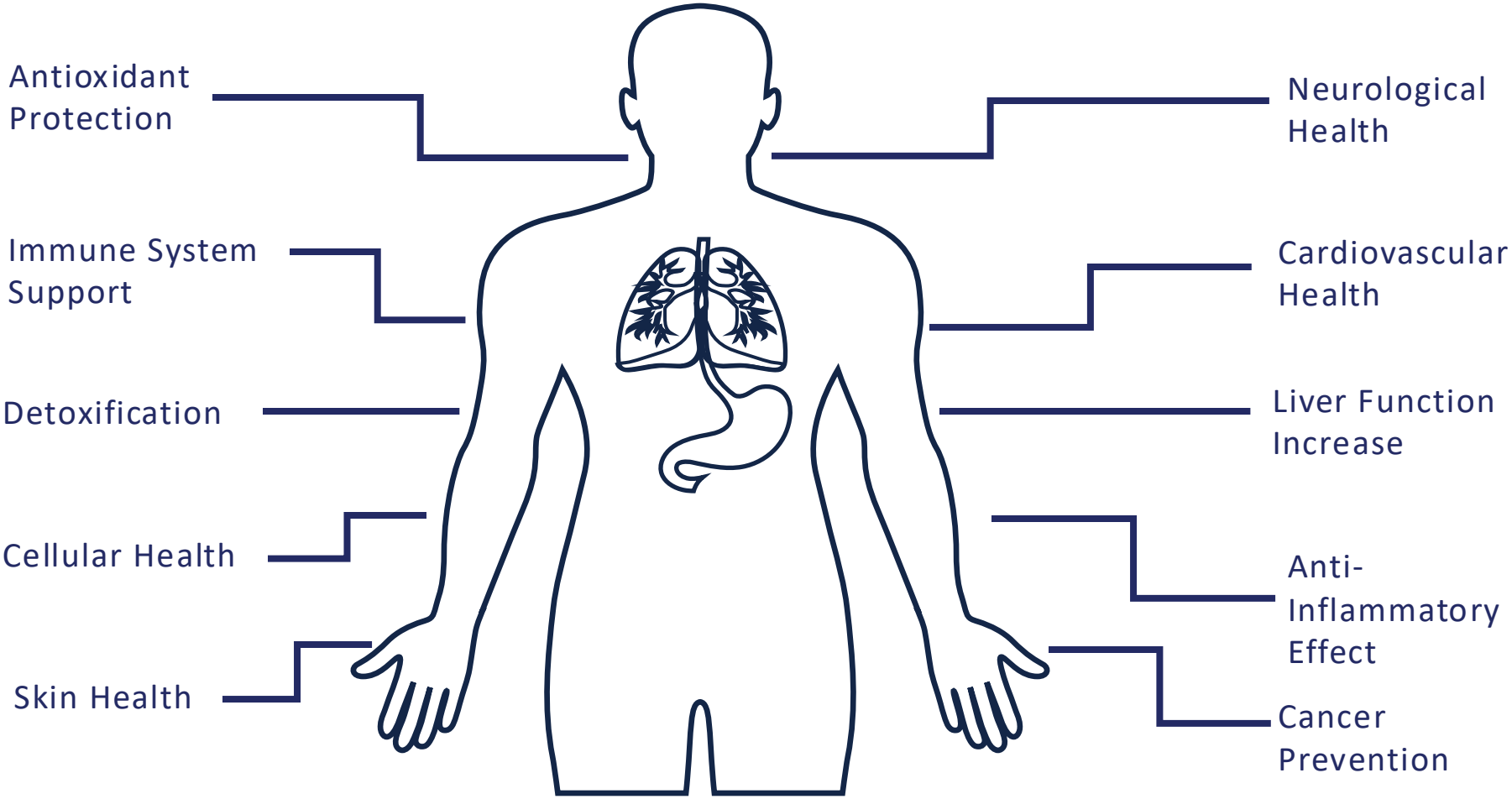
WHAT IS GLUTATHIONE?



- The primary endogenous antioxidant.
- The key detoxifying agent in the body.
- The most abundantly synthesized molecule within human cells.
- A fundamental tripeptide, consisting of three amino acids.
- Difficult to enhance intracellular levels during periods of increased demand

References:
Edio Maldonado, S. M. (2023). Aging Hallmarks and the Role of Oxidative Stress. Antioxidants, 37.
HEATHER JEFFERIES, J. C. (2003). GLUTATHIONE. BASIC SCIENCE REVIEW, 5

BENEFITS OF GLUTATHIONE



References: Michelle Alpert, D. (2005). The Diverse Benefits of Glutathione. Mary Ann Liebert, 5.

GLUTATHIONE OPTIMIZATION

- Physiological requirement remains constant throughout life, although endogenous synthesis declines with age
- Most effective method to maintain physiological homeostasis and minimize the accumulation of harmful substances
- Senescence is an unavoidable biological process, its adverse effects can be mitigated

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HEATHER JEFFERIES, J. C. (2003). GLUTATHIONE. BASIC SCIENCE REVIEW, 5

WHAT DOES GLUTATHIONE ACTUALLY DO?

1

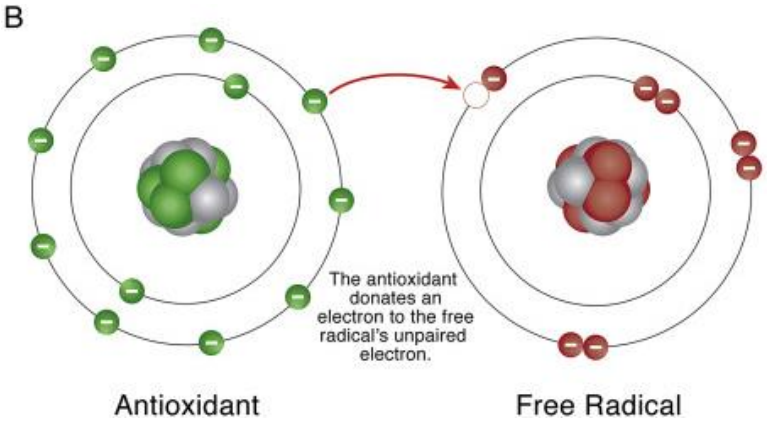
Neutralize free radicals that are continuously generated in the body.

2

Remove toxic substances, such as alcohol, from the body.

3

Maintain internal physiological cleanliness by reducing the buildup of harmful compounds.



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AURO WELLNESS

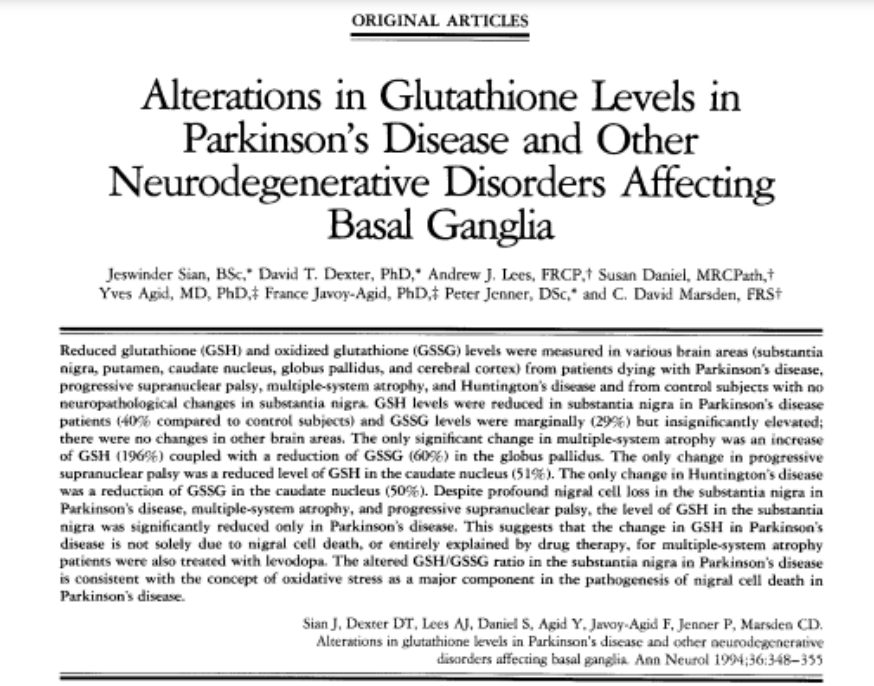
GLUTATHIONE AND NEURODEGENERATIVE DISORDERS

LITERATURE: GLUTATHIONE AND PARKINSON'S DISEASE

Result and Discussion

Glutathione (GSH) levels in the substantia nigra were reduced by 40% compared to control subjects, while glutathione disulfide (GSSG) levels were elevated by 27%,

Suggests that oxidative stress, as indicated by the altered GSH/oxidized glutathione (GSSG) ratio, plays a crucial role in the pathogenesis of Parkinson's disease, rather than cell death alone or drug therapy effects.



ORIGINAL ARTICLES

Alterations in Glutathione Levels in Parkinson's Disease and Other Neurodegenerative Disorders Affecting Basal Ganglia

Jeswinder Sian, BSc,* David T. Dexter, PhD,* Andrew J. Lees, FRCP,† Susan Daniel, MRCPath,†
Yves Agid, MD, PhD,‡ France Javoy-Agid, PhD,‡ Peter Jenner, DSc,* and C. David Marsden, FRS†

Reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were measured in various brain areas (substantia nigra, putamen, caudate nucleus, globus pallidus, and cerebral cortex) from patients dying with Parkinson's disease, progressive supranuclear palsy, multiple-system atrophy, and Huntington's disease and from control subjects with no neuropathological changes in substantia nigra. GSH levels were reduced in substantia nigra in Parkinson's disease patients (40% compared to control subjects) and GSSG levels were marginally (29%) but insignificantly elevated; there were no changes in other brain areas. The only significant change in multiple-system atrophy was an increase of GSH (196%) coupled with a reduction of GSSG (60%) in the globus pallidus. The only change in progressive supranuclear palsy was a reduced level of GSH in the caudate nucleus (51%). The only change in Huntington's disease was a reduction of GSSG in the caudate nucleus (50%). Despite profound nigral cell loss in the substantia nigra in Parkinson's disease, multiple-system atrophy, and progressive supranuclear palsy, the level of GSH in the substantia nigra was significantly reduced only in Parkinson's disease. This suggests that the change in GSH in Parkinson's disease is not solely due to nigral cell death, or entirely explained by drug therapy, for multiple-system atrophy patients were also treated with levodopa. The altered GSH/GSSG ratio in the substantia nigra in Parkinson's disease is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in Parkinson's disease.

Sian J, Dexter DT, Lees AJ, Daniel S, Agid Y, Javoy-Agid F, Jenner P, Marsden CD. Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol 1994;36:348–355

References:
Sian J, Dexter DT, Lees AJ, Daniel S, Agid Y, Javoy-Agid F, Jenner P, Marsden CD. Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol. 1994 Sep;36(3):348-55.

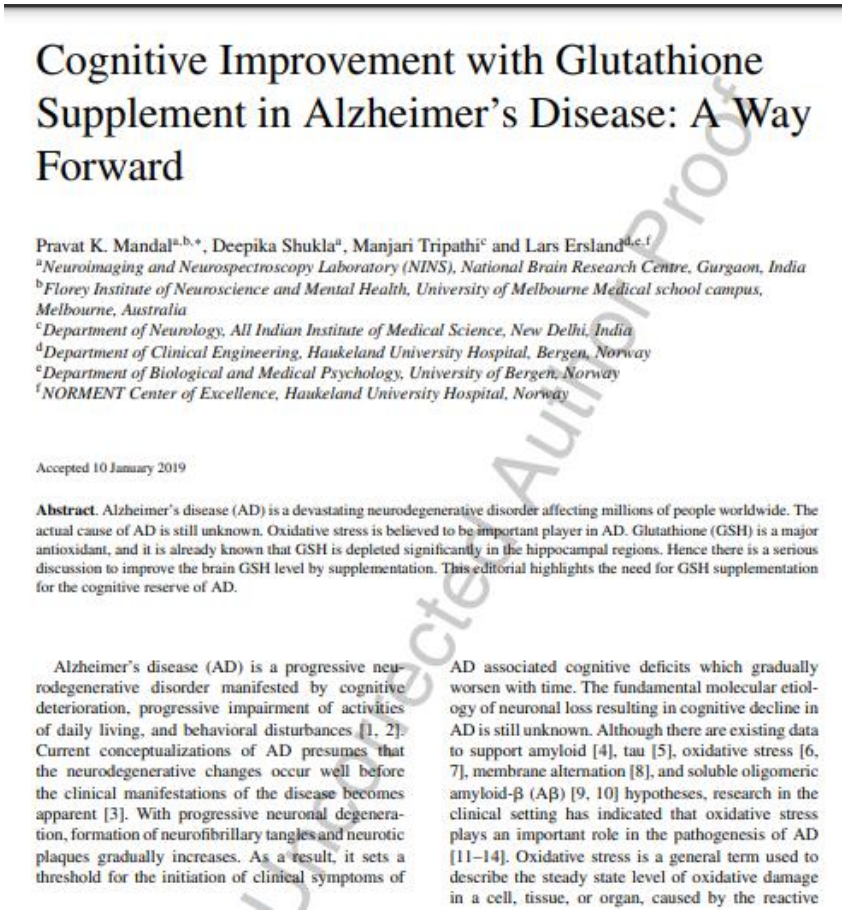
LITERATURE: GLUTATHIONE AND ALZHEIMER'S DISEASE

Result and Discussion

Decreased intracellular blood GSH in MCI and both intra- and extracellular GSH in AD. Brain GSH is reduced in AD and MCI in specific subgroups.

Showed significantly lower brain GSH in AD

Significant decreases in both intracellular and extracellular GSH in Blood GSH



Cognitive Improvement with Glutathione Supplement in Alzheimer's Disease: A Way Forward

Pravat K. Mandal[a,b,*], Deepika Shukla[a], Manjari Tripathi[c] and Lars Ersland[d,e,f]
[a]*Neuroimaging and Neurospectroscopy Laboratory (NINS), National Brain Research Centre, Gurgaon, India*
[b]*Florey Institute of Neuroscience and Mental Health, University of Melbourne Medical school campus, Melbourne, Australia*
[c]*Department of Neurology, All Indian Institute of Medical Science, New Delhi, India*
[d]*Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway*
[e]*Department of Biological and Medical Psychology, University of Bergen, Norway*
[f]*NORMENT Center of Excellence, Haukeland University Hospital, Norway*

Accepted 10 January 2019

Abstract. Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting millions of people worldwide. The actual cause of AD is still unknown. Oxidative stress is believed to be important player in AD. Glutathione (GSH) is a major antioxidant, and it is already known that GSH is depleted significantly in the hippocampal regions. Hence there is a serious discussion to improve the brain GSH level by supplementation. This editorial highlights the need for GSH supplementation for the cognitive reserve of AD.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder manifested by cognitive deterioration, progressive impairment of activities of daily living, and behavioral disturbances [1, 2]. Current conceptualizations of AD presumes that the neurodegenerative changes occur well before the clinical manifestations of the disease becomes apparent [3]. With progressive neuronal degeneration, formation of neurofibrillary tangles and neurotic plaques gradually increases. As a result, it sets a threshold for the initiation of clinical symptoms of AD associated cognitive deficits which gradually worsen with time. The fundamental molecular etiology of neuronal loss resulting in cognitive decline in AD is still unknown. Although there are existing data to support amyloid [4], tau [5], oxidative stress [6, 7], membrane alternation [8], and soluble oligomeric amyloid-β (Aβ) [9, 10] hypotheses, research in the clinical setting has indicated that oxidative stress plays an important role in the pathogenesis of AD [11–14]. Oxidative stress is a general term used to describe the steady state level of oxidative damage in a cell, tissue, or organ, caused by the reactive

References:
Mandal, P. K., Shukla, D., Tripathi, M., & Ersland, L. (2019). Cognitive Improvement with Glutathione Supplement in Alzheimer's Disease: A Way Forward. Journal of Alzheimer's Disease, 1–5.

LITERATURE: GLUTATHIONE SUPPLEMENTATION ON PARKINSON'S DISEASE

Result and Discussion

GSH may have the ability to slightly improve
motor function in patients with PD

Compared with the control groups, serum GSH-Px levels were significantly higher in the GSH groups

The dose of GSH (300 vs. 600 mg/d) may be one of the factors influencing motor function in patients with PD

Potential use of glutathione as a treatment for Parkinson's disease

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DOI: 10.3892/etm.2020.9557

Abstract. The aim of the present study was to assess the efficacy and safety of glutathione (GSH) for the treatment of Parkinson's disease (PD). The PubMed, Cochrane Library, OvidSP, Web of Science, China Science and Technology Journal Database, Chinese National Knowledge Infrastructure and China Wanfang Standards Database databases were systematically searched from the inception dates to October 1st, 2019, using the key words'glutathione' or 'GSH' and 'Parkinson' or 'Parkinson's disease' or 'PD'. The quality of the included articles was assessed using the bias risk assessment tool of the Cochrane systematic evaluator manual (version 5.1.0). Pooled analysis of the relevant data was performed using RevMan 5.3 software and subgroup analysis was performed to determine the impact of the dosage (300 vs. 600 mg) on the outcome measures. A total of seven randomized controlled trials involving 450 participants were included in the meta-analysis. The results of the present study indicated a statistically significant difference between the GSH and control groups, in terms of the Unified Parkinson's Disease Rating Scale (UPDRS) III [standard mean difference (SMD), -0.48; 95% CI, -(0.88-0.08); P=0.02] and GSH peroxidase (SMD, 1.88; 95% CI, 0.52-3.24; P=0.007). However, the differences in the UPDRS I (SMD, -0.04; 95% CI, -0.25-0.16; P=0.70) and UPDRS II (SMD, 0.03; 95% CI, -0.17-0.24; P=0.77) score and in side effects were not statistically significant between the groups. Subgroup analyses revealed that

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease associated with aging, which is characterized by the selective loss of nigrostriatal dopaminergic neurons (1-3). PD is the second most common neurodegenerative disease in the world with a prevalence that is estimated to reach between 8.7 and 9.3 million by 2030 (4). To date, the pathophysiology of PD remains to be fully elucidated, though studies indicate that oxidative stress may be one of the mechanisms contributing to PD (5). There is currently no cure for PD; thus, further research into the development of novel treatment strategies is critical (6). Increasing evidence has demonstrated that oxidative stress has an important role in the events contributing to the degeneration of dopaminergic neurons (7), and that redox reactions are a possible source of oxidative stress in nigral dopaminergic neurons (8). Glutathione (GSH) is a ubiquitous thiol tripeptide that protects against oxidative stress-induced damage by neutralizing reactive oxygen species (5). GSH deficiency has been identified as an early event in the progression of PD (9). Therefore, supplementing GSH may effectively improve the symptoms of PD. In recent years, a number of clinical trials have sought to investigate the effects of GSH treatment for PD (10-12). Regrettably, the sample size of these studies was small and the clinical evidence is insufficient (10-12). To the best of our knowledge, no previous meta-analyses have

References:
Wang HL, Zhang J, Li YP, Dong L, Chen YZ. Potential use of glutathione as a treatment for Parkinson's disease. Exp Ther Med. 2021 Feb;21(2):125.

LITERATURE: GLUTATHIONE AND COGNITIVE IMPAIRMENT, ALZEIMER'S, and PARKINSON'S

Result and Discussion

Treatment with N-Acetyl-L-Cysteine (a precursor of Glutathione production), an antioxidant that activates the GSH system and has immune-regulatory properties, has shown clinical efficacy in clinical trials in people with MCI, Alzheimer's disease, and Parkinson's disease

Oxidative stress and antioxidant defenses in mild cognitive impairment: a systematic review and meta-analysis.

Running title: Oxidative stress in mild cognitive impairment

Gallayaporn Nantachai, M.Sc.[a,b], Asara Vasupanrajit, M.Sc.[a], Chavit Tunvirachaisakul, M.D., Ph.D.[a, c], Marco Solmi, M.D., Ph.D. [d,e,f,g,h], Michael Maes, M.D., Ph.D.[a,c,i,j,*]

[a] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[b] Somdet Phra Sungharaj Nyanasumvara Geriatric Hospital, Department of Medical Services, Ministry of Public health, Chon Buri Province, Thailand.

[c] Cognitive Impairment and Dementia Research Unit, Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

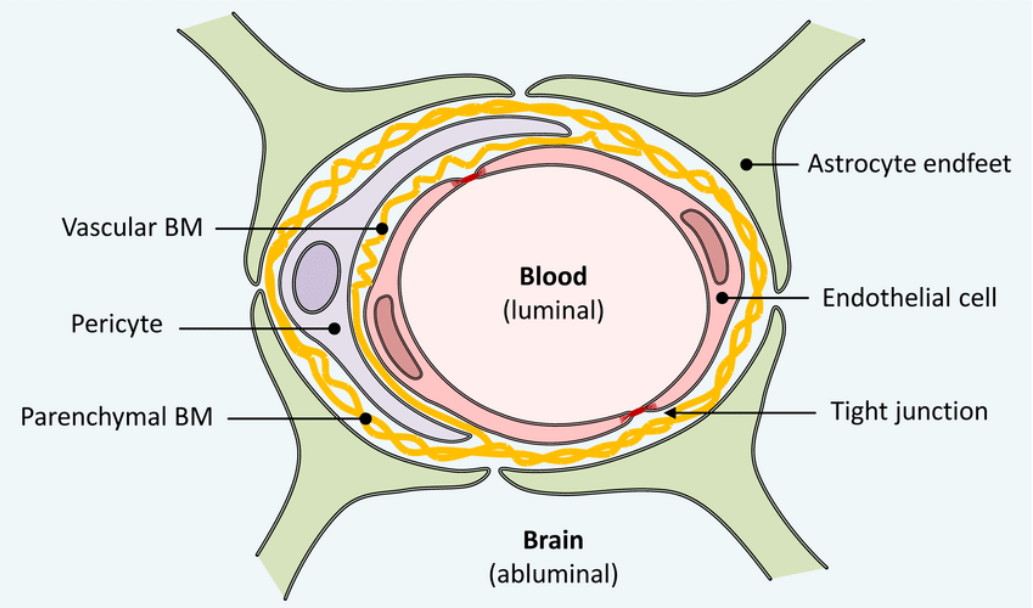
References:
Gallayaporn Nantachai, M. A. (2021). Oxidative stress and antioxidant defenses in mild cognitive impairment: a systematic review. MedRvix, 41..

AURO WELLNESS

CHALLENGES ON GLUTATHIONE THERAPY FOR NEURODEGENERATION

BLOOD BRAIN BARRIER

The blood-brain barrier (BBB) is a selective semi-permeable membrane between the blood and the interstitium of the brain, allowing cerebral blood vessels to regulate molecule and ion movement between the blood and the brain.



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Neumaier, Felix & Zlatopolskiy, Boris & Neumaier, Bernd. (2021). Drug Penetration into the Central Nervous System: Pharmacokinetic Concepts and In Vitro Model Systems. Pharmaceutics. 13. 1542. 10.3390/pharmaceutics13101542.

LITERATURE: PEPTIDE BRAIN UPTAKE

Uptakes of the tripeptides
TRH (L - pyroglutamyl - L - histidyl - L – proline amide) and **glutathione** (y-glutamyl-cysteinylglycine), were similarly less than **1%**

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Endocrinology

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Blood-Brain Barrier Restriction of Peptides and the Low Uptake of Enkephalins*

EAIN M. CORNFORD, LEON D. BRAUN, PAUL D. CRANE, AND WILLIAM H. OLDENDORF

Department of Neurology, Reed Neurological Research Center, School of Medicine, University of California-Los Angeles, Los Angeles, California 90024; and the Research Service, Brentwood Hospital, Veterans Administration, Los Angeles, California 90073

ABSTRACT. Blood-brain barrier penetration of leucine-enkephalin, methionine-enkephalin, and other peptide-like compounds was measured after intracarotid injection of three isotopes and was found to be nonsaturable over the nanomolar range of concentrations tested. No significant differences in brain regional extraction of leucine enkephalin (or morphine or heroin) were observed. In contrast to previous reports, the brain extraction of enkephalins was minimally low (E = 2–3%) and about the same order of magnitude as other putative neurotransmitters. Brain extractions of other peptide-like compounds were similarly small: TRH, E = 1%; glutathione, E = 0.5%; β-alanyl histidine, E = 1%; and thioacetyl coenzyme A, E = 2%. Extraction of the nondiffusible reference dextran was determined to be 1%, suggesting that the blood brain barrier tends to restrict peptide penetration. (*Endocrinology* **103:** 1297, 1978)

THE TRANSPORT of peptides by saturable carrier systems in bacteria and mammalian intestines has been reported by many workers (1–4). A group of recently isolated endogenously occurring peptides (endorphins and enkephalins—"endogenous opiates") (5–8) have been the subject of recent attention because of their morphine-like actions (7, 9–11) and addictive properties (12). Many peptides (13–15), including enkephalins (16), once thought to be restricted to a single tissue are now known to be common to both intestine and brain. *In vitro* studies suggest dipeptide transport occurs in mouse brain slices (17) and more recently it has been suggested that peptides (18) and enkephalins (19)

inability of enkephalins to show analgesic properties after systemic administration is said to be their inability to cross the BBB (12).

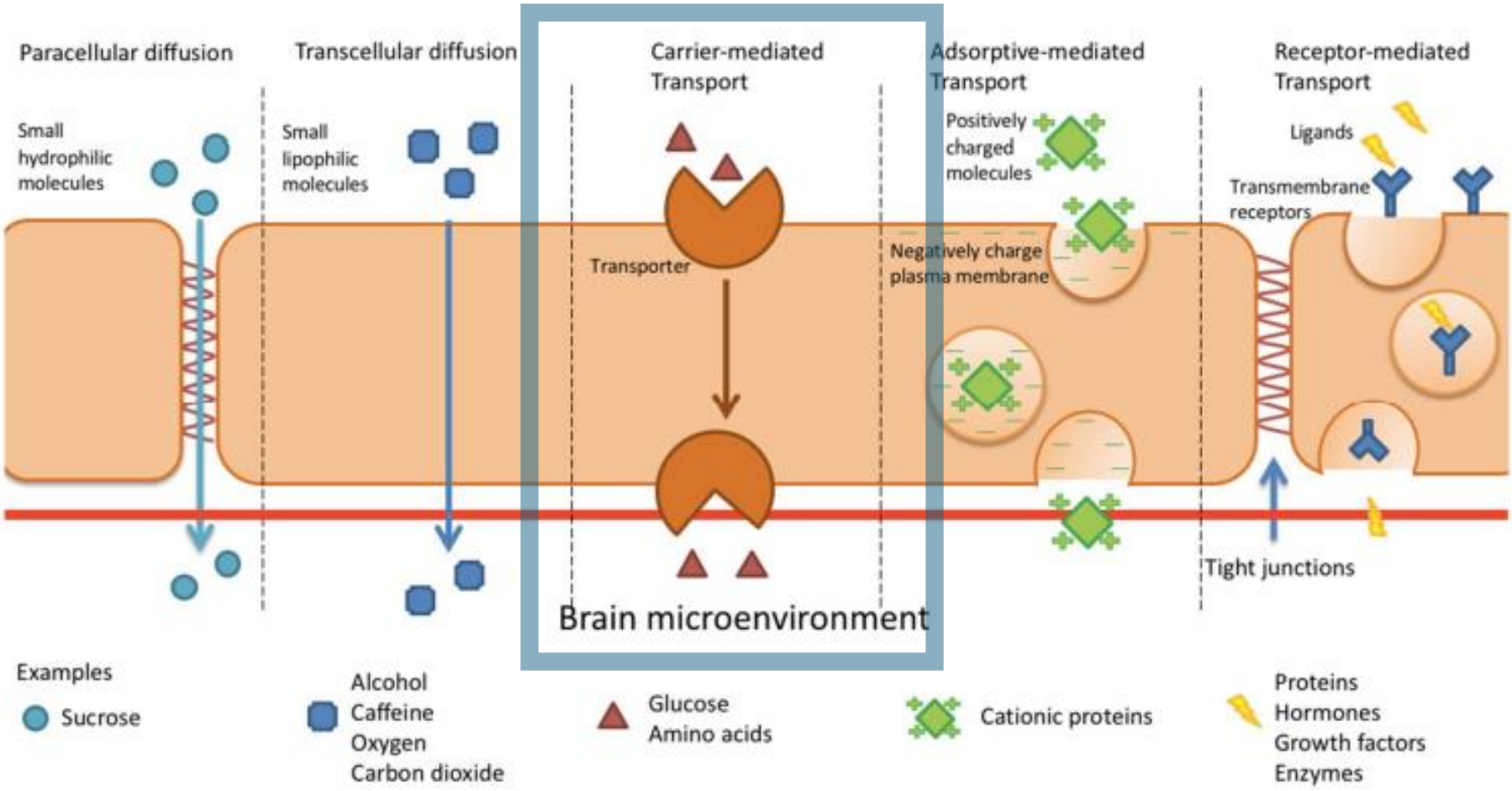
In the present study, we have employed the intracarotid injection method to reexamine BBB penetration of pentapeptide enkephalins as well as certain other small peptides, and report that the uptake of these compounds is very low and similar to that of other putative neurotransmitters, such as monoamines and acetyl choline.

Materials and Methods

Adult Wistar SPF rats (250–350 g), obtained from a commercial supplier (Hilltop Laboratories,

References:
Cornford EM, Braun LD, Crane PD, Oldendorf WH. Blood-brain barrier restriction of peptides and the low uptake of enkephalins. Endocrinology. 1978 Oct;103(4):1297-303. doi: 10.1210/endo-103-4-1297. PMID: 744146.
Aoyama, K. Glutathione inthe Brain. Int. J. Mol. Sci. 2021, 22,5010

BLOOD BRAIN BARRIER PENETRATION MECHANISM



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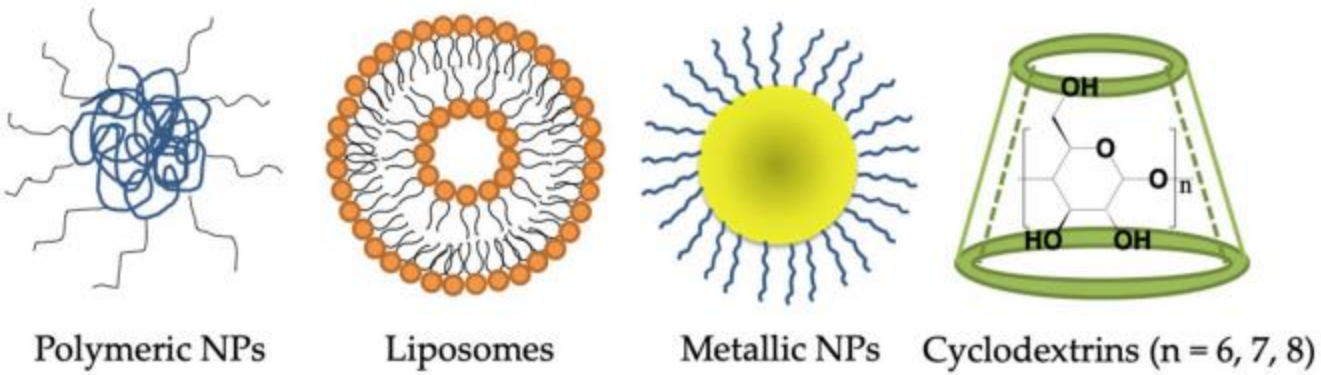
Wong KH, Riaz MK, Xie Y, Zhang X, Liu Q, Chen H, Bian Z, Chen X, Lu A, Yang Z. Review of Current Strategies for Delivering Alzheimer's Disease Drugs across the Blood-Brain Barrier. Int J Mol Sci. 2019 Jan 17;20(2):381.

NANOTECHNOLOGY-BASE DRUG DELIVERY SYSTEMS



Polymeric NPs Liposomes Metallic NPs Cyclodextrins (n = 6, 7, 8)

Cyclodextrins act as carriers by forming non-covalent host-guest complexes with lipophilic molecules. This interaction enhances the solubility, stability, and bioavailability of the guest molecules. CDs facilitate the delivery of therapeutic agents (e.g., doxorubicin) across biological barriers like the blood-brain barrier (BBB).

References:
Wong KH, Riaz MK, Xie Y, Zhang X, Liu Q, Chen H, Bian Z, Chen X, Lu A, Yang Z. Review of Current Strategies for Delivering Alzheimer's Disease Drugs across the Blood-Brain Barrier. Int J Mol Sci. 2019 Jan 17;20(2):381.

LITERATURE: CROCETIN-CYCLODEXTRIN COMPLEX

CRT-γ-CD complex was able to penetrate the BBB and concentration of CRT was determined after administration (5mg/kg) for half hour, which was about 200ng/g of brain.

Proves that the used of γ-CD was able to facilitate the CRT across the BBB and reach the brain

Delivering Crocetin across the Blood-Brain Barrier by Using γ-Cyclodextrin to Treat Alzheimer's Disease

Ka Hong Wong[1], Yuning Xie[1], Xiao Huang[1], Kazunori Kadota[1,2], Xin-Sheng Yao[3], Yang Yu[3], Xiaoyu Chen[1], Aiping Lu[1,4] & Zhijun Yang[1,4*]

Crocetin (CRT) has shown various neuroprotective effects such as antioxidant activities and the inhibition of amyloid β fibril formation, and thus is a potential therapeutic candidate for Alzheimer's disease (AD). However, poor water solubility and bioavailability are the major obstacles in formulation development and pharmaceutical applications of CRT. In this study, a novel water-soluble CRT-γ-cyclodextrin inclusion complex suitable for intravenous injection was developed. The inclusion complex was nontoxic to normal neuroblastoma cells (N2a cells and SH-SY5Y cells) and AD model cells (7PA2 cells). Furthermore, it showed stronger ability to downregulate the expression of C-terminus fragments and level of amyloid β in 7PA2 cell line as compared to the CRT free drug. Both inclusion complex and CRT were able to prevent SH-SY5Y cell death from H_2O_2-induced toxicity. The pharmacokinetics and biodistribution studies showed that CRT-γ-cyclodextrin inclusion complex significantly increased the bioavailability of CRT and facilitated CRT crossing the blood-brain barrier to enter the brain. This data shows a water-soluble γ-cyclodextrin inclusion complex helped to deliver CRT across the blood-brain barrier. This success should fuel further pharmaceutical research on CRT in the treatment for AD, and it should engender research on γ-cyclodextrin with other drugs that have so far not been explored.

References:
Wong, K.H., Xie, Y., Huang, X. et al. Delivering Crocetin across the Blood-Brain Barrier by Using γ-Cyclodextrin to Treat Alzheimer's Disease. Sci Rep 10, 3654 (2020). https://doi.org/10.1038/s41598-020-60293-y

AURO WELLNESS

GLUTATHIONE-CYCLODEXTRIN COMPLEX

GLUTATHIONE CYCLODEXTRIN COMPLEX

- Currently have been in 2 clinical human trials and the findings were published in May and July of 2023
- All researchers of the study are faculty and students at Western University School of medicine

LITERATURE: COVID 19 and GLUTATHIONE-CYCLODEXTRIN COMPLEX

Result and Discussion

The G-C complex shows potential in mitigating the CSS and reducing viral load. It could prevent hospitalization if given early and may reduce hospital stays and mortality in severe cases. It also offers a potential solution for post-COVID syndrome and could be used effectively in outpatient settings, including for neonates and critically ill patients in the ICU.

ORIGINAL RESEARCH

The COVID-19 Illness: Addressing the Current Treatment Limitations and Care Gaps with a Novel Alternative and Complementary Agent—the Glutathione-Cyclodextrin Complex

Ray Yutani, DO, PharmD, MS, FACOFP; Viswanath Venketaraman, PhD

ABSTRACT

We are approaching the fourth year of the COVID-19 pandemic. Although great progress has been made in addressing the SARS-CoV-2 infection, there are significant treatment limitations and care gaps that need to be addressed in order to more effectively treat patients critically ill with COVID-19 and the large population of patients with post-COVID symptoms. We highlight the significance of the cytokine storm in the immunothrombotic process of COVID-19 illness. Finally, we present scientific evidence of the utility of a novel complementary therapeutic agent, the glutathione-cyclodextrin complex, that will likely address those limitations and close those gaps. If confirmed by rigorous clinical trials, the complex will have a significant impact on the treatment of the entire spectrum of COVID-19 illness and contribute to the control or resolution of the COVID-19 pandemic. (*Altern Ther Health Med.* [E-pub ahead of print.])

Ray Yutani, DO, PharmD, MS, FACOFP; Associate Professor of Family Medicine; Western University of Health Sciences/COMP, Pomona, California, USA. **Viswanath Venketaraman, PhD,** Professor of Microbiology/Immunology; Western University of Health Sciences/COMP, Pomona, California, USA.

Corresponding author: Ray Yutani, DO
E-mail: ryutani@westernu.edu

or proteolysis. Those that act through RNA-dependent RNA-polymerase (RdRp) are mutagenic, potentially teratogenic and are thereby contraindicated in individuals who are pregnant or plan to become pregnant.[4] Paxlovid® inhibits proteolysis and is more effective in reducing the incidence of hospitalization than RNA-directed antivirals. However, its use is complicated when treating individuals who are receiving other medications, due to its enhancement of cytochrome-mediated drug-drug interactions. Paxlovid use is also restricted to high-risk individuals

References:
Ray Yutani, D. P., & Viswanath Venketaraman, P. (2023). The COVID-19 Illness: Addressing the Current. The COVID-19 Illness: Addressing the Current, 8.

LITERATURE: EFFECTIVENESS of GLUTATHIONE-CYCLODEXTRIN COMPLEX

Result and Discussion

The GSH-CD complex demonstrated promising results in enhancing immune function against Mycobacterium avium and improving bacterial clearance. It presents a safe and effective alternative for GSH delivery, suggesting potential for broader application in treating mycobacterium infections..

antioxidants

MDPI

Article

Topical Absorption of Glutathione–Cyclodextrin Nanoparticle Complex in Healthy Human Subjects Improves Immune Response against *Mycobacterium avium* Infection

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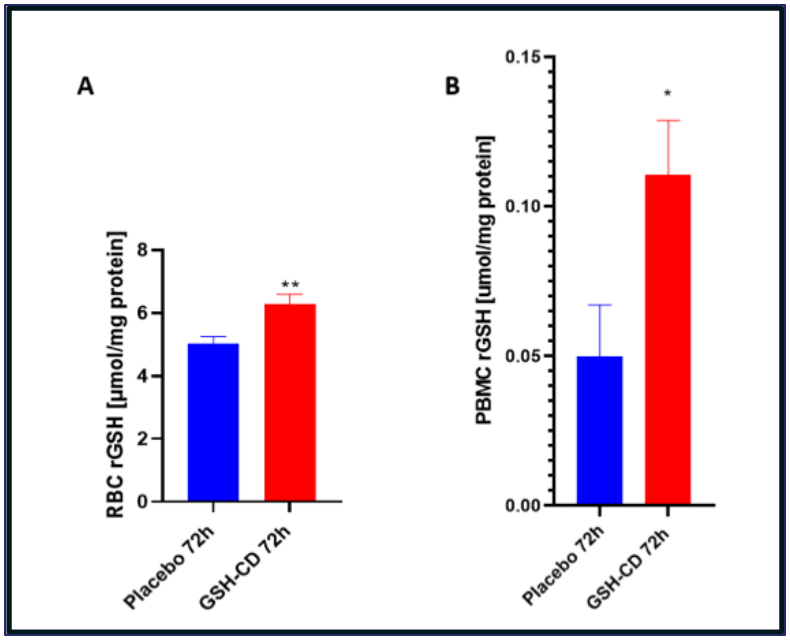
Abstract: Glutathione (GSH) is an important intracellular antioxidant responsible for neutralizing reactive oxygen species (ROS). Our laboratory previously demonstrated that the oral administration of liposomal GSH improves immune function against mycobacterium infections in healthy patients along with patients with HIV and Type 2 diabetes. We aim to determine if the topical application of a glutathione–cyclodextrin nanoparticle complex (GSH-CD) confers a therapeutic effect against mycobacterium infections. In our study, healthy participants received either topical GSH-CD (n = 15) or placebo (n = 15) treatment. Subjects were sprayed four times twice a day for three days topically on the abdomen. Blood draws were collected prior to application, and at 1, 4, and 72 h post-initial topical application. GSH, malondialdehyde (MDA), and cytokine levels were assessed in the processed blood samples of study participants. Additionally, whole blood cultures from study participants were challenged with *Mycobacterium avium (M. avium)* infection in vitro to assess mycobacterium survival post-treatment. Topical GSH-CD treatment was observed to elevate GSH levels in peripheral blood mononuclear cells (PBMCs) and red blood cells and decrease MDA levels in PBMCs 72 h post-treatment. An increase in plasma IL-2, IFN-γ, IL-12p70, and TNF-α was observed at 72 h post-topical GSH-CD treatment. Enhanced mycobacterium clearance was observed at 4 h and 72 h post-topical GSH-CD treatment. Overall, topical GSH-CD treatment was associated with improved immune function against *M. avium* infection. The findings of this pilot study suggest

References:
Kayvan Sasaninia , †. ,. (2023). Topical Absorption of Glutathione–Cyclodextrin Nanoparticle. Topical Absorption of Glutathione–Cyclodextrin Nanoparticle, 14.

LITERATURE: EFFECTIVENESS of GLUTATHIONE-CYCLODEXTRIN COMPLEX

- Glutathione levels in PBMC increased >100% within 72hrs



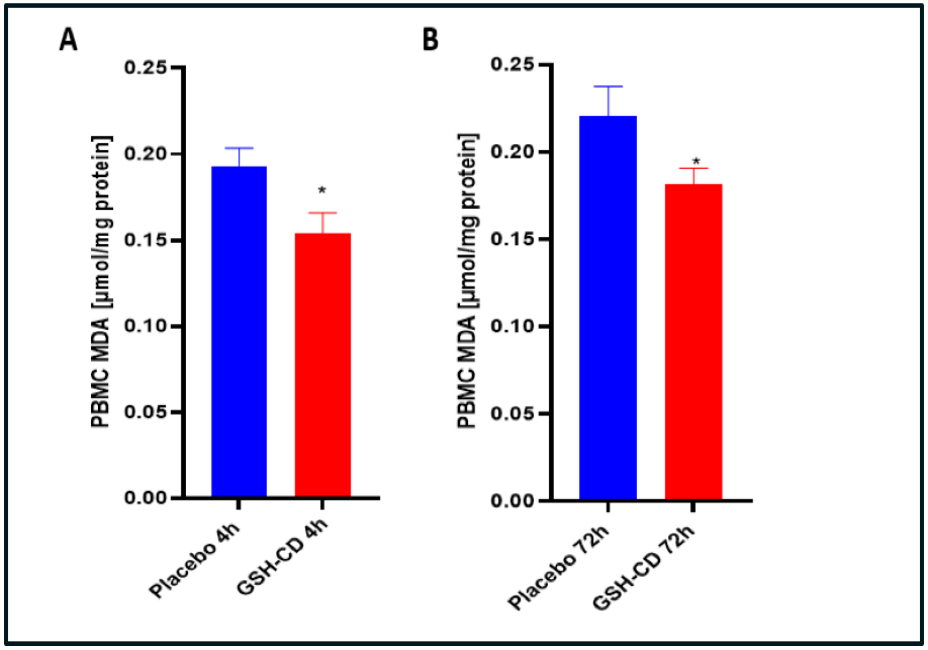
3. Results

3.1. Elevated Levles of Reduced GSH after GSH-CD Topical Treatment

References:
Kayvan Sasaninia, †. ,. (2023). Topical Absorption of Glutathione–Cyclodextrin Nanoparticle. Topical Absorption of Glutathione–Cyclodextrin Nanoparticle, 14.

LITERATURE: EFFECTIVENESS of GLUTATHIONE-CYCLODEXTRIN COMPLEX

- Oxidative Stress Reduced within 4 hrs measured as MDA

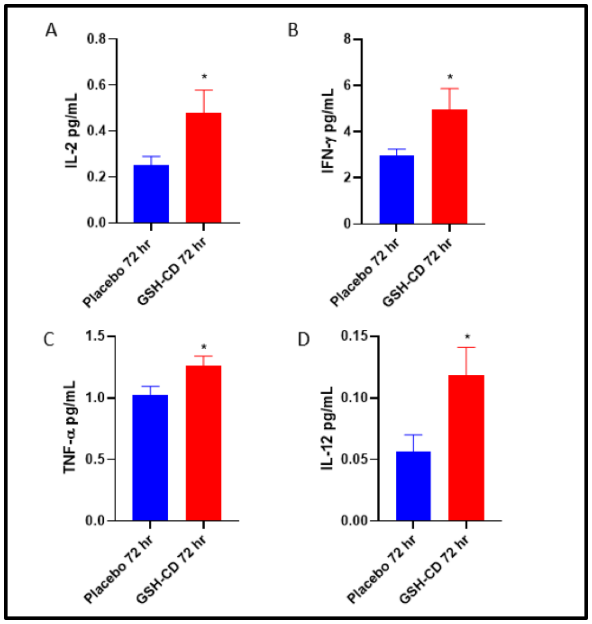


3.2. MDA Levels Are Decreased after Topical GSH-CD Treatment

References:
Kayvan Sasaninia †. ,. (2023). Topical Absorption of Glutathione–Cyclodextrin Nanoparticle. Topical Absorption of Glutathione–Cyclodextrin Nanoparticle, 14.

LITERATURE: EFFECTIVENESS of GLUTATHIONE-CYCLODEXTRIN COMPLEX

- IMPROVEMENT IN IMMUNE CYTOKINES WITHIN 72 HRS

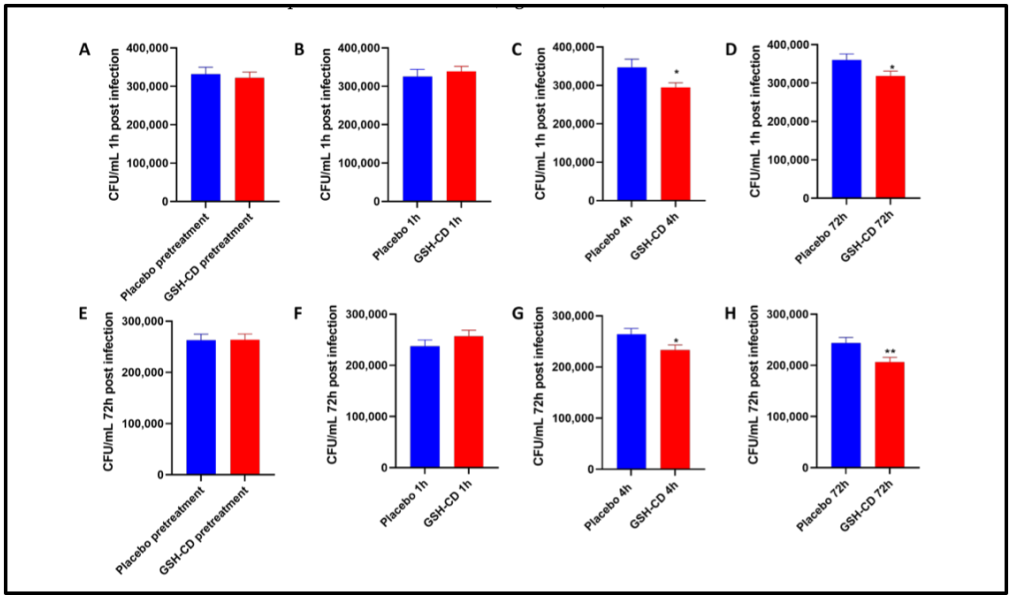


3.3. Increased Levels of IL-12, IL-2, IFN-γ and TNF-α in Plasma Post-Initial GSH-CD Treatment

References:
Kayvan Sasaninia , †. ,. (2023). Topical Absorption of Glutathione–Cyclodextrin Nanoparticle. Topical Absorption of Glutathione–Cyclodextrin Nanoparticle, 14.

LITERATURE: EFFECTIVENESS of GLUTATHIONE-CYCLODEXTRIN COMPLEX

- REDUCTION OF INFECTION WITHIN 4 HRS



3.4. Topical GSH-CD Treatment Is Associated with the Reduction in the Burden of M. avium (In Vitro)

References:
Kayvan Sasaninia †. ,. (2023). Topical Absorption of Glutathione–Cyclodextrin Nanoparticle. Topical Absorption of Glutathione–Cyclodextrin Nanoparticle, 14.

INCORPORATION OF GLUTATHIONE IN YOUR DAILY ROUTINE

- **Avoid toxins**
  - **Alcohol**
  - **Excessive exposure to sun**
  - **Pollution**
  - **Chemicals, solvents, pesticides, etc…**
- **Diet**
  - **Consume cysteine rich foods, ex. Whey proteins**
  - **Add selenium rich food like bazil nuts**
- **Reduce stress**
  - **Meditation**
  - **Exercise**
  - **Increase Your Vitamin C Intake**
- **Glutathione Supplementation**
  - **Topical – Patented Glutaryl™ of Auro wellness (best absorption)**
  - **IV, Oral caps, Liposomal liquid (low bioavailability)**

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Topical Glutathione

Glutaryl™ delivers effective dose of glutathione that can cause a rash at the site of application or parts of the body. Rash can be minimized by changing the application site or reducing the dose.

Rarely but sensitivity to any components of the product is also possible.

Dr. Nayan Patel: The Visionary Behind Topical Glutathione Innovation

“My dear friend Dr. Nayan Patel is at the forefront of the latest GSH research, and an expert on how to raise your glutathione levels to help revitalize your body and transform your health. He holds the patent for the transdermal Glutathione spray, Glutaryl, and is the author of his new book, The Glutathione Revolution. His book is a wealth of information and has been a game-changer in my personal health and wellness journey.”

- Tony Robbins

CONCLUSION

Glutaryl represents a groundbreaking innovation in glutathione administration, offering a unique topical delivery system that effectively enhances immunity. By revolutionizing the way glutathione is absorbed and utilized in the body, Glutaryl ensures higher bioavailability and optimal support for the body's antioxidant defense mechanisms, marking a significant advancement in applications for mental wellness and stress reduction.

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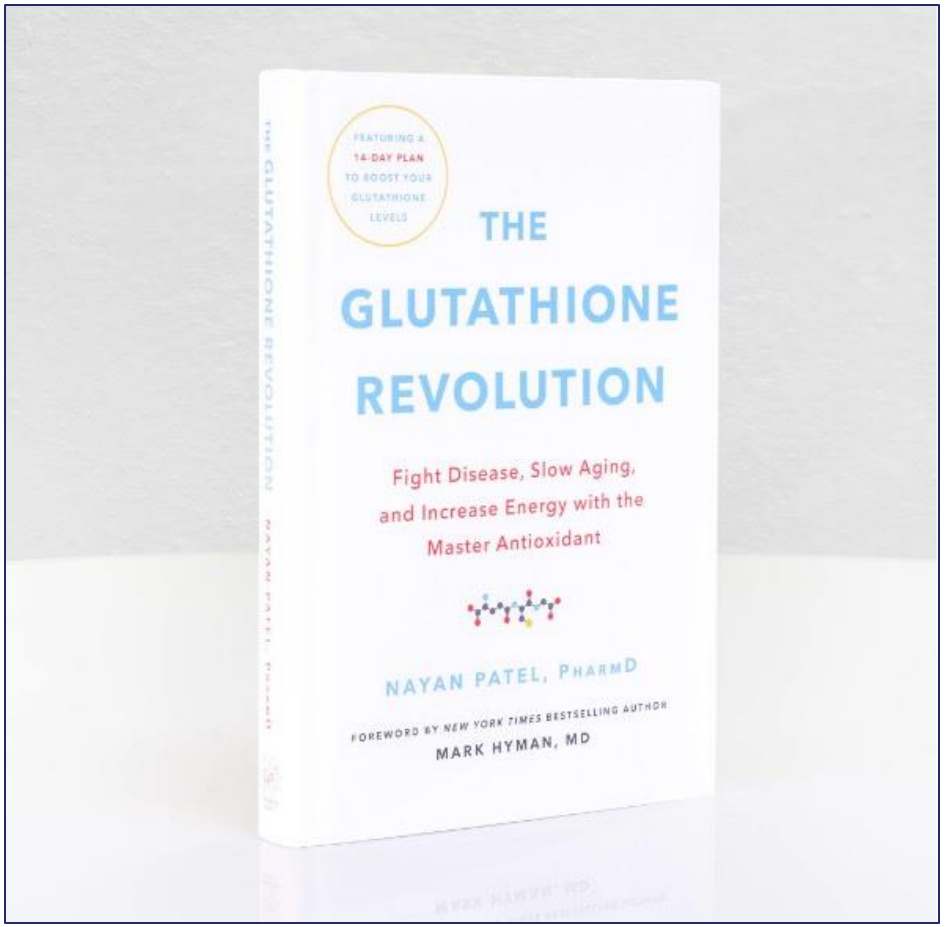

QUESTIONS?

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