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A REVIEW OF THE IMPORTANCE OF GLUTATHIONE IN NEURODEGENERATIVE DISEASES

Innocent O. Imosemi*

Department of Anatomy, College of Medicine, University of Ibadan, Ibadan, Nigeria.

***Corresponding Author: Innocent O. Imosemi**

Department of Anatomy, College of Medicine, University of Ibadan, Ibadan, Nigeria.

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ABSTRACT

Neurodegenerative diseases, including Huntington's, Amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases are known to deteriorate neural function in the peripheral or central nervous system and eventually result in the death of the nerve cells. The glutathione system is particularly vital for cellular defense against reactive oxygen species found in the brain cells, working non-stop in the decontamination of radicals in reactions that do not require enzymes and acting as a substrate for numerous peroxidases. Growing evidence suggests that there are other vital roles glutathione can play in the brain, especially in the case of neurodegenerative disease; a few of which are antioxidant defense, the decontamination of xenobiotic, and the regulation of intracellular redox homeostasis. Findings from various studies are suggestive of the fact that oxidative stress is a facilitator involved in neurodegenerative processes and may be an important event activating numerous forms of cell death. This review places emphases on glutathione synthesis and homeostasis, its therapeutic effects and the importance of glutathione in neurodegenerative diseases.

KEYWORDS: Glutathione, oxidative stress, antioxidant defense, neurodegenerative diseases.

INTRODUCTION

For the past two to four decades with the worldwide increase in life expectancy, neurodegenerative disease that is popular among the elderly population has been a source of concern. Thus, causing the science community to centre more on age-related neurodegenerative disease research, the common of which are Parkinson's and Alzheimer's disease. The popularity of the aforementioned two is largely due to their irreversible nature and absence of effective means of managing the disease.[1] The progression of neurodegenerative disease is the slow but sure impairment in neural cells and neuronal loss, thus leading to impaired motor or cognitive function.

Glutathione (GSH) is popularly referred to as the biomarker for neurodegenerative diseases. It is the key antioxidant whose levels deplete with each passing year, particularly in the elderly and those suffering from neurodegenerative diseases. A good number of scientists have embarked on studies to gain a clearer understanding of the importance of running down of glutathione levels in neurodegenerative diseases so as to take advantage of developing GSH-based treatment. Glutathione is without doubt a vital cellular constituent, as it plays the first and foremost role guarding and shielding against any danger as a consequence of exposure to reactive oxygen specie (ROS) which is mainly found in the brain. It is worth noting that this protective layer or barrier is broken down as a result of GSH-dependent enzyme inactivation and GSH homeostasis disturbance, leading to cell becoming vulnerable to the harm caused by oxidative stress.[2]

Apart from the cytoprotective function of glutathione, it also carries out other important role in relation to brain function which provides a pharmacological base for the correlation between changes in glutathione homeostasis and the advancement of some neurodegenerative process. As a result, glutathione carry out significant functional roles in the central nervous system (CNS). It is produced by the serial action of Glutamate-Cysteine Ligase (GCL) and Glutathione synthetase.[3] Glutamate-Cysteine Ligase is made up of two sub units which play the role of catalyzing the creation of gamma-glutamylcysteine, which denotes the rate limiting reaction in the production of glutathione. A prolonged reduction in the level of glutathione in GCL modifier (GCLM) deactivates astrocytes and can bring about a reaction that has to do with changes in lysine acetylation and protein expression.[4] A lot of evidence proposes that glutathione reduction, factors in the start of neurodegenerative diseases. Transient reduction in *substantia nigra compacta* has been linked with neuro-inflammation in rats.[5]

Glutathione in its reduced form (L-g-glutamyl-L-cysteinyl-glycine, GSH) is known as a very rich non-protein thiol in the cells of mammalian animals and the

predominant low-molecular weight peptide in eukaryotic cells. At first it was labeled as a powerful reducing agent; though, a significant number of cellular functions have of late been attributed to glutathione, hence the growing level of scientific interest. Results from numerous researches have made it clear that apart from being a reducing agent, glutathione also plays the role of a key antioxidant, a mediator of a good number of physiological reactions and a reservoir of cysteine. The aim of this review is to summarize the importance of glutathione in neurodegenerative diseases.

Oxidative Stress in Neurodegenerative Diseases

Oxidative stress describes the imbalance between cellular levels of oxidants and antioxidants.[6] Oxidative stress has been implicated in neurodegenerative diseases, including Huntington's, Amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases, modifying DNA, protein and lipids, resulting in protein alteration, mitochondria dysfunction, glia cell activation, apoptosis and death.[7] The brain of a human being is made up of just 2% of the body's weight but makes use of 20% of the total oxygen consumption of the body. It is categorized among the most producing sites for the Reactive Oxygen Species (ROS), where the mitochondria transforms 4% of the oxygen it takes in, to an ion known as super oxide superoxide ion, which holds remarkably high reactivity, especially as a potent oxidizing agent and an architect of radical reactions . A tremendous amount of evidence shows a specific vulnerability of neurons to ROS due to their characteristic features such as high rate of oxygen consumption, high energy demands, low anti-oxidative defense and high levels of polyunsaturated fatty acids.[8]

In a situation whereby the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) are a minimal in comparison to those of other organs, the enzymatic system built to offer resistance to foreign bodies in the neuronal cells will not be strong enough. Furthermore, glutathione, as a vital anti-oxidant element, is found at short concentrations in the brain. These discoveries suggest the participation of ROS in neurodegenerative diseases.[9]

Numerous researches validated a strong participation of oxidative stress in the pathophysiology of neurodegenerative diseases by means of a range of mechanisms such as the initiation of oxidation of macromolecules such as lipids, proteins, nucleic acids, proteasome and mitochondrial dysfunction, amyloid β deposition, apoptosis and glial cell activation.[10] A systemic review demonstrated that these processes of neurodegeneration pass through numerous damaging cellular pathways. Any form of intrusion in these pathways has tremendous influence on pathogenesis.[11] Presently, researchers are focusing on the consequence of oxygen specie origin and development of neurodegenerative diseases and the usefulness of antioxidants as a likely means of managing neurodegenerative diseases.

Synthesis and Homeostasis of Glutathione

The concentration of glutathione in the brain is 2–3 mM, as likened to 5 μM of the cerebrospinal fluid and 15 μM of the blood.[12] Glutathione is produced in the brain cells by neurons and astrocytes, and it is equally essential for numerous vital antioxidant-related processes.[13] Certain evidence is suggestive of the fact that the transportation of glutathione across the blood brain barrier (BBB) is poor. On the other hand, it is likely that the blood is not the main source of cerebral glutathione.[14] Glutathione is ever-present molecule that is manufactured intracellularly irrespective of the cell or organ; however it is rich in liver and lung tissues. It is a linear tripeptide produced from the glycine, cysteine amino acids and glutamate reaching concentrations of 1 to 10 mM in a variety of cells. The reaction is catalyzed by γ-glutamylcysteine ligase and glutathione synthetase. The first reaction which is a reaction that requires ample amount of ATP, between cysteine and glutamate is mediated by γ-glutamylcysteine ligase. The product formed from this reaction is γ-glutamylcysteine. The second reaction is another reaction that needs a good amount of ATP, which is between Glycine and γ-GluCys to form glutathione. It is important to note that very little is known about exact mechanisms fundamental for the regulation of glutathione activity in comparison to those of as γ-glutamylcysteine.[15]

However, plasma glutathione levels on the other hand are somewhat low 0.01 mM, largely due to its quick catabolism. Intracellular glutathione can function as a monomer in its reduced state, or as a disulfide dimmer shaped as a result of its oxidation which ordinarily constitutes less than 1% of the total intracellular glutathione content. In addition, a significant portion of the entire intracellular glutathione is present as mercaptide, thioester, or other glutathione conjugates. It is freely spread in the cytosol, though it can be sorted in organelles such as the endoplasmic reticulum, peroxisomes, mitochondria and nuclear matrix at the end of its cystolic synthesis.[16]

In order for glutathione synthesis to take place, the Km value of γ-glutamylcysteine ligase for cysteine has to be ~0.15 mM, that for glycine is ~0.8 mM, with glutamate being ~1.7Mm.[17] The intracellular amino acid level differs with cell types and tissues, however the concentration of cysteine in the brain are kept at levels that are much lesser than those of glutamate of glycine[18], largely due to neurotoxicity.[19] It is thus safe to say that the intracellular level of cysteine is measured as the rate-limiting factor of glutathione synthesis in the brain. Usually, for keeping up glutathione homeostasis in the brain, two mechanisms are at play; the components of glutathione may be recovered or reprocessed during the turnover of glutathione in the brain cells, and

cysteine and other molecules comprising of it might be conveyed through the Blood Brain Barrier (BBB).[20]

In the synthesis of glutathione, the γ-carboxyl group of glutamate connects the cysteine residues rare peptide bond and the N-terminal glutamate. This specific peptide bond plays the role of safeguarding glutathione against cleavage by intracellular peptidases averting its hydrolysis and making glutathione firmly fixed in the cell, at least to a reasonable level. The C-terminal glycine residue in glutathione configuration averts its cleavage by the intracellular enzyme γ-glutamyl cyclotransferase. A very active practical element of glutathione is the cysteine residue. This residue is known to be responsible for thiol group. Moreover, as a result of the reaction of cysteine residues, the dipeptide bond is formed in the oxidized form of glutathione. Two residues of the already oxidized tripeptide, glutathione which are connected by disulphide bond form glutathione disulfide.[21]

Several plant extracts and nutraceuticals such as *Calotropis procera*[22], *Telfairia occidentalis*[23,24], *Carica papay*[25,26], *Lycopersicon esculentum*[27,28], *Ocimum gratissimum*[29], Honey[30], *Celosia argentea*.[31] *Camelia sinenses*[32] and *Cucumis sativus*[33] have been shown to increase the glutathione levels and antioxidant status of the CNS, which helps in protecting or ameliorating or mitigating oxidative stress-induced neurotoxicity.

Therapeutic uses of Glutathione

Usually in the advanced stages of a disease there appears to be an absence of the therapeutics capable of slowing down its advancement. Since ROS are critical agents in the processes of degenerative and inflammatory diseases, they are responsible for an interesting healing objective in Relapsing Remitting Multiple Sclerosis and Progressive Multiple Sclerosis.[34] Glutathione is active in the preservation of cellular redox homeostasis and the safeguard against reactive oxygen species. Going by the reduced glutathione levels and changes in glutathione allied enzyme actions in multiple sclerosis, upholding or bringing back glutathione levels signifies a capable Therapeutic approach.[35] Glutathione supply to the central nervous system is predominantly challenging. Very high measures of glutathione would be needed so as to get a therapeutic effect. As a result of the toxic outcome, the uninterrupted distribution of the precursor amino acid cysteine turned out to be unsuccessful.[36]

Though, ingesting glutathione orally does not seem to have a serious effect on the glutathione levels in the brain, numerous compounds can indirectly bring about the making of glutathione. For that reason, an alternative tactic entails using compounds that trigger the nuclear factor erythroid 2-related factor 2 (Nrf_2) pathways, as a majority of enzymes that are active in glutathione synthesis are prompted by Nrf_2 activation. A popular Nrf_2 activator that is proven to increase the concentration of glutathione and anti-inflammatory and antioxidant potential Monomethylfumarate.[37]

The glutathione analog YM 737 offers defense against cerebral ischemia in mice by hindering lipid peroxidation.[38] For the reason that the accessibility of cysteine limits the synthesis of glutathione in the neuron[39], compounds that can be broken down to cysteine could be employed as pro-drugs raise glutathione concentration in the neurons. In the case of the murine mutant wobbler, management with N-acetyl-L-cysteine led to a higher glutathione peroxidase concentration in the cervical spinal cord and a substantial decrease in the damage of motor neurons.[40] The therapeutic approach of using L-2-oxothiazolidine-4-carboxylate, fuels growth and regularizes glutathione concentrations in the tissue of rats given a diet lacking in sulfur amino acid.[41] Though, it is only cells that express 5-oxoprolinase that convert L-2-oxothiazolidine-4-carboxylate to cysteine. For the reason that cultured neurons lack the ability of making use of L-2-oxothiazolidine-4-carboxylate, as a glutathione precursor.[42] The detected rise of glutathione levels in the brain may be as a result of the metabolic rate of glial cells. It is important to note that any employing the use of therapeutic substances that results in the rise of brain cysteine levels is inappropriate due to the fact that in theory cysteine is poisonous for neurons.[43] On the other hand, the glutathione levels can be increased in the brain when dipeptide γ-glutamylcysteine is administered intracerebroventricularly.[44] In the production of glutathione, the brain can employ the use of cysteinylglycine or γ-glutamylcysteine.[45]

Though, a disruption of glutathione homeostasis has been drawn in, in the pathogenesis of numerous neurodegenerative diseases. It is still open to examination: if in certain illness or disorders, this is a major flaw or just a result of ROS generation; the level of glutathione in the brain can be increased carefully by making use of different management approaches; and an increase in the glutathione levels in the brain will have an end result of clinical advantage or neuroprotection.[46]

Glutathione in Aging

For neurodegenerative diseases the most consistent risk factor is normal aging. Evidence suggests that mitochondrial activity degenerates with age. The measurement of 8-hydroxy-2′-deoxyguanosine is evidence of the rise in oxidative damage to the DNA of mitochondria which is highly reliant on age. It is important to note that 8-hydroxy-2′-deoxyguanosine occurs as a result of the attack by a range of free radicals.[47] Antioxidants may play an instrumental role during the normal aging process. The amount of glutathione found in the cerebral spinal fluid of humans reduces during the aging process.[48] An imposed ectopic expression of glutathione extends the lifetime (Beal, 1995).[49] The results from related studies have that

glutathione has a major influence in the aging process and may highlight numerous changes in the normal aging process and the beginning of a good number of diseases.

Importance of Glutathione in Neurodegenerative Diseases

The key manipulator that activates the commencement of development of the popular neurodegenerative diseases is the collapse of balance between the antioxidant and ROS defense system.[2] Clinically, innate errors in glutathione associated enzymes are infrequent, although disorders in glutathione metabolism are common in certain neurodegenerative diseases exhibiting glutathione reduction and heightened levels of oxidative stress in the central nervous system. In a current study whereby nuclear magnetic resonance (NMR) spectroscopy was employed, it afforded a higher possibility of measuring glutathione levels in the brain of humans.[50] It is wise to say that the running down of glutathione levels precedes neurodegeneration.[51] Numerous *in vivo* studies conducted demonstrated a glutathione and a rise in ROS and reactive nitrogen specie (RNS) with the advancement of age in the brain.[52] Aging is also known to have a major impact Glutathione synthesis.[53] Oxidative stress which results to neuronal degeneration is enhanced by the depletion of glutathione.[46]

Importance of Glutathione in Alzheimer's disease

Alzheimer's disease of otherwise referred to as dementia is branded by a continuous loss of behavioral and cognitive functions which results to the diminishing of day-to-day and mundane activities. It is regarded as one of the most common neurodegenerative diseases with an estimated number of 45 million people suffering from it. The neuropathological diagnostic distinguishing quality of Alzheimer's disease is the buildup of neurotoxic Aβ oligomer peptides, which in combination with Tau protein, facilitates the progressive loss of nerve cells and neurologic function, as a result initiating dendritic changes, cholinergic denervation, synaptic connection and neuroinflammation. The existence of amyloid plaques, which is primarily made up of Aβ peptide, in the brain is the symbol of the disorder. The soluble Aβ oligomers obstruct the excitatory amino acid transporter (EAAT3) mediated cysteine uptake resulting in a loss of glutathione in cultured human neuronal cells.[54] As maintained by the brain examination of patients of Alzheimer's disease, who display abnormal EAAT3 buildup in pyramidal neurons of the hippocampus[55] with the advancement of the disorder.

The chief pathogenic factor in Alzheimer's disease is oxidative stress. As the running down of glutathione levels is of huge implication in oxidative stress, it will likely have a role in the development of the disease. In a new clinical study where NMR spectroscopy was employed, established that glutathione levels are exhausted in individuals suffering from Alzheimer's diseases when compared with healthy individuals.[56] The result from this study has profound implication in the clinical sector. Also when the blood of individuals suffering from the disorder was analyzed, it showed that a reduction in the concentration of glutathione in erythrocytes.[57] Going by these results, it is proposed that turbulences in glutathione metabolism pave the way for the beginning of Alzheimer's disease. Key risk factors for Alzheimer's disease are genetic polymorphism in the glutathione peroxidase-1 and glutathione S-transferase genes.[58] This is possibly the cause of reductions in the activities of glutathione S-transferase and glutathione peroxidase in Alzheimer's disease.[59]

Glutathione is a chief endogenous enzyme catalyzed antioxidant that carries out a central function in decontamination of ROS and the regulation of the intracellular redox environment.[60] The concentration of GSH in the brain is 1-2Nm[61], and its equilibrium at the intracellular level has been shown to be vital for the general well-being and running of the brain.[62] A variety of animal research have constantly demonstrated that the lack of glutathione in the brain result in oxidative stress-linked damage to the brain.[63] A good number of *in vitro* and *in vivo* researches have demonstrated that glutathione serves a neuroprotective function against numerous antioxidants.[64] According to findings glutathione could avert oxidative damage brought about by 4-hydroxyl-2-nonenal (HNE) and Aβ in cultured neuronal cells. It is also suggested that the running down of glutathione worsens oxidative insults roused by HNE and Aβ and for that reason speed up the advancement of the disease.

Importance of Glutathione in Parkinson's disease

Clinically, idiopathic Parkinson's disease is marked by the damage of dopaminergic neurons in the substantia nigra pars compacta, which usually results to pharmacological and clinical irregularities that portrays the disease. The origin of the neuronal loss is still unknown. Nevertheless, new progresses have been made in describing biochemical and morphological happenings in the origin and development of the disease. Generation of ROS and the act of inhibiting of excitotoxicity and oxidative phosphorylation are regarded as vital mediators of neuronal death in Parkinson's disease.[49]

Parkinson's disease is characterized by Tremor, Rigidity, Alkinesia, and Postural Instability (TRAP).[65] Just like in Alzheimer's disease it is characterized by loss of glutathione but in this case the loss is only in the substantia nigra.[66] Exactly like the case of patients suffering from Alzheimer's disease, no variation has been discovered in the concentrations of α-tocopherol (vitamin E) or ascorbate (vitamin C) in the *Substantia Nigra* between individuals suffering from Parkinson's disease and controls.[67] These findings are suggestive of the fact that a fundamental cause of Parkinson's disease is a disorder of glutathione metabolism. In the advancement of the condition of Parkinson's disease glutathione depletion is often times regarded as the initial

or earliest occurrence.[68] The aggregation of α -synuclein accelerates oxidative stress, which would also be enabled by glutathione disulphide.[69] For a patient with Parkinson's disease a fall in the ratio of glutathione to glutathione disulphide in the brain may increase the speed of Lewy body formation and oxidative stress.

Numerous reports that point out the involvement of ROS and oxidative stress might be one of the key influences of Parkinson's disease. Individuals suffering from Parkinson's disease have been reported to higher levels of proteins, oxidized lipids and DNA, alongside depleted levels of glutathione.[70] However the reasons for the depletion of glutathione levels are not obvious. Since there is no corresponding increase in glutathione disulfide (oxidized glutathione) it may not be clarified only by oxidative stress. On the other hand, no observable letdown of glutathione synthesis is detected, for the reason that in Parkinson's disease the function of γ-glutamylcysteine synthetase in the substantia nigra is regular.[71] Remarkably, there is a rise in the action of γ-glutamyltranspeptidase in Parkinson's disease.[72] This is the enzyme that plays the role of transferring γ-glutamyl moiety from a glutathione conjugate or glutathione itself to a molecule that will accept it.[73] Glutathione in the extracellular matrix plays the role of substrate of γ-glutamyltranspeptidase. The product of the aforementioned enzymatic reaction, dipeptide cysteinylglycine undergoes hydrolysis to give glycine and cysteine, which can then be made use of by neurons in glutathione synthesis. Due to the fact that neurons find it impossible to directly put glutathione into use, a rise in the activity of the enzyme γ-glutamyltranspeptidase may echo a compensatory up-regulation to make available dipeptide precursors for neurons to produce additional glutathione. Then again, the discharge of glutathione from the nigral glia and the rise in the action of the enzyme -γglutamyltranspeptidase may be the first stage in the pathogenesis of Parkinson's disease. In a situation whereby the cysteine is not employed in the production of glutathione, there is a high possibility for it to react with dopamine-0-quinone to give 5-Scysteinyldopamin.[74]

Importance of Glutathione in Schizophrenia

According to reports, a twenty seven percent drop was recorded in the cerebrospinal fluid of drug-free schizophrenic patients.[75] However a gap was observed with regards to the concentrations of serotonin, dopamine and their metabolites, as no difference was recorded in relation to that of their controls. *In Vivo* Proton Magnetic Resonance Spectroscopy was employed to validate the aforementioned results, which displayed a 52% reduction in the glutathione levels in the frontal cortex of individuals suffering from schizophrenia in comparison with controls. It is however debated that an initial reduction in the glutathione levels may clarify both the dopamine dysfunction and glutamate hypofunction hypothesis.

Importance of Glutathione in Multiple Sclerosis

This is a neural disorder categorized by the inflammatory-mediated removal of the myelin sheath from a nerve in the central nervous system. Though, it is open to question if multiple sclerosis is a neurodegenerative disease or not, long strands of evidence suggest neurodegeneration as the chief reason of irreversible neural incapacity in patients suffering from multiple sclerosis.[76] Neuronal deterioration is an eminent characteristic in the brain of individuals suffering from this disorder. Other features are reduced synaptic density, neuritic transaction, reduced neuronal density, and neuronal apoptosis.[77] Studies carried out using NMR Spectroscopy showed lower levels of glutathione in individuals suffering from multiple sclerosis in comparison to those of the controls.[78] In the pathogenesis of multiple sclerosis, oxidative stress factors a lot in oxidative stress[79], nevertheless, the clear-cut mechanism of running down of glutathione levels is still vague.

Importance of Glutathione in Huntington's disease

This is a disease named after George Huntington in 1872. It is a very deadly and autosomal dominant congenital progressive neurodegenerative disease which leads to neuronal degeneration in the striatum and decline of the thalamus and cerebral cortex. It is mostly characterized by the impairment of the both the cognitive and motor traits, psychiatric ailments and a significant change in personality.[80] In summary the disease is depicted by choreic movements which are a result of basal ganglia disorders. The lipid peroxidation levels in the plasma of individuals suffering from this disease are way higher and the glutathione levels appear to be depleted in comparison with those of the controls.[81] The result gotten from an in vitro study carried out with a knock-in mice model HD (HD140Q/140Q) wherein the Huntington gene of a human with 140 CAG repeats was introduced, showed depletion in the level of glutathione, with a noticeable elevation in the level of ROS.[82] The results of the study demonstrated Excitatory Amino Acid Transporter C1 dysfunction in the mice model, which lessened the absorption of glutathione resulting in the running down of glutathione in the neurons. Irrespective of the fact that Huntington's disease is well researched upon by experts and that the part played by oxygen species is well spotted, the pathways and origin and development of the disease are however still not clear.

Importance of Glutathione in Progressive Supranuclear Palsy

This is a good example of an aged related neurodegenerative disease. Patients of Progressive Supranuclear Palsy are known to exhibit the following symptoms; vertical supranuclear gaze palsy, Parkinsonism and quick postural shakiness. Recent studies show that Progressive Supranuclear Palsy patients have reduced levels of glutathione in the substantia nigra.[83] 4-hydroxy-2-nonenal, the product of lipid peroxidation results in the synthesis of crosslinked

glutathione related enzymes so as to weaken enzymatic function.[84] Glutathione peroxidase and 4-hydroxy-2-nonenal temporarily fuse together in the central nervous system of individuals suffering from Progressive Supranuclear Palsy, which results in the weakening of enzymatic function.[85] Though current studies have put forward evidence oxidative stress plays a pivotal role in the origin and development of Progressive Supranuclear Palsy.[86] However, the exact mechanisms of falling levels glutathione in the brain cells are not completely understood.

Importance of Glutathione in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis also referred to as Lou Gehrig's disease is another deadly progressive neurological disorder with a key feature of paralysis of the muscle which is as a result of the falling apart of motor neurons in the brainstem, brain and spinal cord. A contributing factor to this incidence is elevated levels of oxidative stress, causing a rise in the death of motor neurons. Mutations Zinc, Copper, Superoxide Dismutase gene happen to be frequently linked with hereditary amyotrophic lateral sclerosis.[87] This occurrence has been described in mice concealing different mutations such as Gly93Arg, Gly85Arg, and Gly37Ala. The aforementioned mutations are reported to result in neurodegeneration.[88] The presence of heavy metals may be a chief reason for the rise of ROS. It is detected that a parallel is drawn with specific Glutathione S-Transferase Pi-1 gene polymorphisms in the association between the risk of Amyotrophic Lateral Sclerosis and the exposure to lead.[89] Without a doubt the expression of the Glutathione S-Transferase Pi-1 variant Ile105Val is capable of increasing the impact of Lead on the advancement of amyotrophic lateral sclerosis.[90]

Other than oxidative stress associated with lessened scavenging of superoxide; result from other studies show that the running down of glutathione levels *in vitro* is complemented by motor neuron cell death[91], stimulating Amyotrophic Lateral Sclerosis. Glutathione and glutathione dependent enzymes seem to be dysregulated in amyotrophic lateral sclerosis. In a different study the glutathione content in red blood cells in individuals suffering from amyotrophic lateral sclerosis was considerably lower than that of the control; in the same way the activity of glutathione reductase also witnessed a significant drop.[92] The loss of the activities of glutathione and that of glutathione reductase occurs over a period of time.[93] The findings from the studies of glutathione peroxidase activities in of red blood cell samples extracted from individuals suffering from amyotrophic lateral sclerosis were varied with certain of them showing substantial decrease while the others exhibited no observable change (Cova et al., 2010).[94] A different study showed that the mRNA levels for Glutathione S-Transferase Pi underwent a major down regulation in the sensory cortex, motor cortex and spinal cord of individuals suffering from amyotrophic lateral sclerosis.[95] Dysfunction of the glutathione dependent enzymes or the enzymes responsible for the creation of glutathione may additionally deteriorate the defense barrier set by antioxidants amidst the reactive oxygen species-scavenging system which has been previously compromised, leading to greater harm and eventually cell death.

Importance of glutathione in Friedreich Ataxia

Friedreich Ataxia is a disease categorized by progressive degeneration of the central and peripheral nervous systems, cardiomyopathy, and the prevalence of diabetes mellitus. It was first defined by Nikolaus Friedrick and in 1863, before it got be universally recognized as a disease after his 1877 publication.[96]

Certain changes in glutathione homeostasis have a high possibility of contributing to neurodegenerative diseases; a good example being in Friedreich's Ataxia. There is a reduction in free glutathione in the red blood cells. It is an autosomal recessive disorder which is mostly as a result of trinucleotide repeat expansion of alpha 1, 4-glucosidase in the gene responsible for producing frataxin. Although the mutation is similar to that in Huntington's disease but there is substantial cellular difference. The earlier mentioned expansion leads to buildup of iron within the mitochondria, possibly creating a situation that boosts oxidative stress.[97] Individuals suffering from this disorder were discovered to have reduced glutathione levels in their red blood cells when compared to those of healthy individuals.[98] The result gotten from a different study showed that the spinal cords of individuals with Friedreich Ataxia have higher levels of glutathione in comparison to their controls.[99] This rise in glutathionylated proteins echoes an increased oxidative setting and probably elucidates the reduced quantity of free glutathione in individuals suffering from Friedreich Ataxia. When yeast Friedreich Ataxia model deficient of the frataxin homologue was analyzed, it displayed a major rise in the activity of glutathione peroxidase (GPx), signifying an upregulation of antioxidant capacity; but the concentration of NADPH was reduced. However a different study reported that overexpression of frataxin in 3T3 cells led to decreased vulnerability of *tert*-butyl peroxide, accredited to a rise in the activity of GPx.[100] With the two opposing results of the two studies it is evident that additional study is needed.

Importance of glutathione in Duchene Muscular Dystrophy

Duchene Muscular Dystrophy (DMD) is an upsetting muscle wasting disease which is as a result of deletions or mutations in the X-linked dystrophin gene, which leads to a deficiency of dystrophin protein, or the expression of extremely dysfunctional, shortened kinds of the dystrophin protein.[101] It is referred to as one of the most frequently happening disorders in 1 out of every 3500-5000 male babies.[102] It usually results in death at the early or late stages of teenage development, from

respiratory failure.[103] This is a disorder that is also linked with particular learning and developmental disabilities.

A mice lacking dystrophin was reported to have an hyperoxidative status plus a decrease in the total glutathione concentration, and an rise in the disulphide glutathione/glutathione ratio; rise in the activities of the enzyme glutathione reductase and peroxidase, and decreased concentration of hydrogen isocitrate together with aconitase and NADP (ICDH), two enzymes sensitive to deactivation by oxidative stress and are key in the making of glutathione.[104] Therefore, the progressive loss of muscle fibers in individuals suffering from Duchene Muscular Dystrophy might include a long-lasting oxidative injury that exceeds the ability of muscle regeneration.[105] Findings from a study embarked upon displayed that a decrement of glutathione levels was found in both the muscles and the blood of patients suffering from the disorder. A constant reduction in GSSG levels was also observed, resulting to a major disparity in the ratio of GSSG/GSG.[106] Oxidative stress might have a serious role to play in muscle degeneration that is common in Duchene Muscular Dystrophy and may have an impact on the development and severity of the illness. This is further reiterated by the result gotten from research carried out in part to analyze the plasma levels of three glutathione states, showed that concentration of blood glutathione was reduced in patients suffering from Duchene Muscular Dystrophy in comparison to their controls, whereas the concentration of glutathione in its oxidized form also witnessed a substantial rise. The findings from this study strongly clarifies the point that oxidative stress is very much involved in the resulting cascade to dystrophic pathology and point to glutathione as an active redox biomarker.[107]

CONCLUSION

Glutathione plays numerous important roles in certain cells of the body and it is uncommon to come across a situation where there are genetic-based disorders of glutathione related enzymes. However, what is common place is the running down of glutathione levels in the origin and development of most of the key neurodegenerative diseases. Results from recent studies demonstrate that glutathione depletion introduces or is usually before neurodegeneration. Neuronal glutathione depletion is thus the chief cause of neurodegenerative disease. Many neurodegenerative diseases have been shown to be correlated to depleted levels of antioxidants, most especially glutathione, leading to increase in free radicals generation and Reactive Oxygen Species. Many studies have also shown that treatment and therapies involving the use of glutathione helped in the recovery or prognosis of these neurodegenerative diseases, helping people suffering from such diseases, lead longer and healthier lives. It is worthy of note that additional research is essential in defining in more accurate terms the participation of disturbance of the grid of glutathione-dependent reactions in the neurodegenerative actions with the hope of providing fresh means of averting or regulating these events, as well proposing more real approach therapies for individuals suffering from neurodegenerative diseases.

Conflict of Interest

The author declares no conflict of interest.

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