Pharmacogn J. 2024; 16(2): 319-322
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Original Article

Hydrogen Sulfide and Cystathionine γ–Lyase with Oxidants and Antioxidants Levels for Patients with Epilepsy Diseases

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ABSTRACT

The research includes studying the levels of hydrogen sulphide (H_2S) and cystathionine γ–lyase (CSE) with some oxidants and antioxidants in the serum of patients with epilepsy disease in Mosul city which include: malondialdehyde (MDA), peroxynitrite (ONOO-), glutathione (GSH), total bilirubin (TSB), albumin (Alb) and uric acid (UA), were measured in the patient group who suffered from epilepsy disease in Mosul city, Samples reached (116), which included: (56) samples for epilepsy patients group, and (60) for control group. The results showed there was a significant decrease in the levels of H2S, CSE, GSH, and TSB and a significant increase in the levels of MDA, ONOO-, Alb and UA in serum for epilepsy patients when Compared with the control group. The study concluded that H_2S gas produced within the body and CSE suffer from low levels within the body, and they also decrease with the increase in the duration of the disease as a result of their use as protective functions in the body against epilepsy disease and developing it, by observing the levels of oxidants and antioxidants compounds and stimulating the body to increase their levels (H_2S, and CSE) in various ways can lead to improving the health condition of patients.

Key words: Epilepsy, Hydrogen sulfide, Cystationine γ–lyase, Oxidative stress.

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History

- Submission Date: 02-02-2024;
- Review completed: 16-03-2024;
- Accepted Date: 22-03-2024.

DOI : 10.5530/pj.2024.16.48

Article Available online

http://www.phcogj.com/v16/i2

INTRODUCTION

Epilepsy is one of the most prevalent and serious brain disorders. Over 70 million people worldwide suffer from epilepsy,[1] it is affects both sexes and all ages[2] with worldwide distribution characterized by recurrent epileptic seizures. An epileptic seizure is the clinical manifestation of an excessive electrical discharge of abnormal charges of nerve cells in a specific area of the brain.[3] Epilepsy either can be of unknown primary cause, which is the most common, or epilepsy (Secondary), which occurs when there is a cause such as brain damage or A severe blow to the head, or a stroke in which there is less oxygen in the brain, or meningitis, or brain pain, and others.[4]

When there is an imbalance between the production of oxidants and the antioxidant defence system, it is known as oxidative stress (OS), and the central nervous system is highly susceptible to it. because of the low concentrations or capacities of antioxidant enzymes and the high oxygen consumption, particularly in the brain, which makes it more susceptible to OS.[5]

OS plays an essential role in various types of neurological and non-neurological diseases such as Huntington disease, Alzheimer's disease, multiple sclerosis, Parkinson's disease, atherosclerosis, heart failure, cancer, chronic kidney disease, chronic obstructive pulmonary disease, and cardiovascular diseases,[6,7] it plays an important role as a cause of chronic disease and in neuropsychiatric conditions, such as depression and anxiety disorders, damage to the brain caused by OS has a strong potential to impair regular CNS functions.[8]

Hydrogen sulphide (H_2S) is an endogenous gaseous signal molecule in organisms and is the 3rd endogenous gasotransmitter followed by NO and CO is primarily produced by three enzymes, including cystathionine γ-lyase, cystathionine β-synthase and 3-mercaptopyruvate sulfurtransferase play important roles in both pathological and physiological effects[9]. In common neurodegenerative diseases such as Alzheimer's and Parkinson's disease, through the main mechanisms of antiapoptosis, antioxidation, and anti-inflammatory response can prevent or delay disease occurrence that H_2S may have effects as a smooth muscle relaxant and a neuromodulator, Several studies have shown that H_2S has a cardioprotective effect vasodilation, cell differentiation.[10,11]

Cystathionine γ – lyase CSE (EC 4.4.1.1) was first isolated and crystallized from rat liver,[12] and is a component of the Cys/Met metabolism that produces H_2S in mammalsThe final and second stage of the reverse transsulfuration of the methionine cycle is catalyzed by CSE, it is a major source of cysteine, which is a major constituent of proteins. It is also a precursor to H_2S and the antioxidant glutathione (GSH).[13]

Malondialdehyde (MDA) is known as an indicator of OS and is derived from the peroxidation of polyunsaturated fatty acids,[14] it can attack fatty, protein, and nucleic acids, resulting in numerous mutations and alterations in different body structures and tissues.[15] It is one of the most important products of the oxidation in the brain and its effect on the effectiveness and functions of the brain from During his ability to weaken nervous functions, the result of the occurrence of the condition of the OS.[16,17] Peroxynitrite (ONOO-) is a potent nitrogenous compound produced by the interaction of superoxide (O2•–) and nitric oxide (•NO) free radicals[18] that can cause many destructions to essential molecules within the body, which are proteins, fats, and nucleic acids[19] and therefore the ONOO- levels is a potential

Cite this article: Al-Taee KM, Al-Helaly LA. Hydrogen Sulfide and Cystathionine γ–Lyase with Oxidants and Antioxidants Levels for Patients with Epilepsy Diseases. Pharmacogn J. 2024;16(2): 319-322.

indicator of the occurrence of many illnesses including cardiovascular, immune, cancer and neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease.[20]

GSH is an endogenous antioxidant It is involved in metabolic and biochemical processes, including the synthesis of DNA, the protection of protein thiol groups, the stabilization of cell membranes, and the detoxification of xenobiotics.[21] It protects cells from damage brought on by reactive oxygen species, lipid peroxides, and nitrogen species (ROS, RNS).[22] Bilirubin (TSB) is an endogenous derivative of heme catabolism. The strongest natural antioxidants that prevent lipid peroxidation.[23] Uric acid(UA) is an important antioxidant produced during purine metabolism, that reduces OS by trapping the hydroxyl radical and the single oxygen in the aqueous phase.[24] This study is the first of its kind that focused on knowing the role of H_2S and CSE in epilepsy patients, as well as evaluating the OS by measuring oxidants and antioxidant compounds, In addition to studying the effect of the duration of illness on patients.

MATERIALS AND METHOD

The research involved (116) samples including (56) epilepsy patients in addition to (60) samples of healthy people as a control group. The samples were gathered from the Ibn Sina and Al-Salam Teaching Hospital in the city of Mosul, under the supervision of doctors specializing in neurological diseases, for the period between February and October 2022 and after recording the required information after recording the required information.

H_2S in serum was measured by Zhuo *et al.* method,[25] by the use of zinc acetate, N, N-dimethyl-p-phenylenediamine sulfate and $FeCl_3$, H_2S concentration was calculated against a standard curve created using sodium hydrosulfide hydrate (NaHS) solution. The assay for CSE involves measuring the rate of formation of α- ketobutyric acid from L-homoserine, it is determined by the method of Friedemann and Haugen.[26] The concentration of MDA in the serum was estimated using the modified method by researchers.[27] The method depends on the interaction of malondialdehyde with thiobarbituric acid (TBA). In 1998, Vanuffelen *et al.* created a modified method for determining ONOO-.[28] We used dithiobisnitrobenzoic acid (DTNB) to measure the GSH levels technique.[29] TSB is determined by using a kit manufactured by Biolabo (France).[30] Serum Alb is determined by using a kit manufactured by Biolabo (France).[31] Uricase is an enzymatic method that utilizes a kit (Biolabo/France) to estimate serum UA.[32]

Statistical Analysis

The data was statistically examined using the t-test. The data is shown as means with standard error (SE). The t-test was selected to compare two variables and determine the difference between the values that appeared through the (P) value, which occurs at ($P \leq 0.05$) a significant difference, and at ($P > 0.05$) a non-significant difference.

RESULTS

In current research, Comparing the mean values of H_2S and CSE between epilepsy patients and control groups as as noticed in Table (1), a significant decline in the levels of H_2S, and CSE was noticed in epilepsy patients (0.018±0.002) and (3.39±0.634) compared with the control group (0.027±0.004)and (7.54±1.18) respectively.

Table (2) shows the comparison of the levels of MDA, ONOO-, GSH, TSB, Alb and UA between epilepsy's patients and control group, a significant increase in the mean values of MDA, ONOO-, Alb and UA was noted in epilepsy's patients (5.45 ±0.284), (120.19±5.31), (58.72±4.22) and (461.71±18.15) as compared with control group (3.89±0.325), (82.13±4.84), (38.33±1.75) and (418.28±19.32), respectively while the results showed a significant decrease in levels of GSH and TSB inpatient group (7.60±0.369) and (0.383±0.041) compared with control group (10.27±0.163) and (0.70±0.034), respectively.

Table 1: H_2S and CSE in epilepsy patients as compared with the control group.

Parameters	Control group (n=60)	Epilepsy group (n=56)	p-value
H_2S (mol/L)	0.027±0.004	0.018±0.002	0.016*
CSE (U/L)	7.54±1.18	3.39±0.634	0.007**

Table 2: Biochemical Parameters in epilepsy patients versus control.

Biochemical Parameters (mean±SE)	Control group (n=60)	Epilepsy group (n=56)	p-value
MDA (µmol/L)	3.89±0.325	5.45±0.284	0.037*
ONOO-(µmol/L)	82.13±4.84	120.19±5.31	0.004**
GSH (µmol/L)	10.27±0.163	7.60±0.369	0.012*
TSB (mg/dL)	0.70±0.034	0.383±0.041	0.028*
Alb (g/L)	38.33±1.75	58.72±4.22	0.001**
UA (µmol/L)	418.28±19.32	461.71±18.15	0.042*

In this study, H_2S shows a high decrease in epilepsy patients, It acts as an antioxidant and cytoprotective agent against OS by reducing excessive amounts of oxidative species such as ROS and RNS,[33,34] it protects neurons by regulating anti-apoptotic responses, antioxidative, and anti-inflammatory. It has a physiological role in preserving homeostasis. Additionally, it protects against disorders of the central nervous system and inhibits neuroinflammation.[35]

CSE is one major H_2S-producing enzyme with L-cysteine as the main substrate in mammalian cells, The enzyme controls the body's H2S production, and reduced enzyme levels lead to a variety of neurodegenerative diseases.[36] Role of cystathionine γ -lyase in preserving the redox homeostasis in the brain, specifically concerning the involvement of mitochondrial It is necessary for neuroprotection because it maintains GSH levels and protein thiol homeostasis in the brain.[37] that the CSE/H2S system plays an important role in both health and diseases.[38]

The MDA level was elevated, these results match the results of a previous study that indicated an elevated level of MDA in the blood serum of epilepsy patients (39). The reason for the high level of MDA may be a sign of an increase in the lipid peroxidation process due to the increased oxidant compounds in patients. MDA is an unstable compound that can interact with other compounds in the body and is also an indicator of OS in cells and tissues.[40] Furthermore, it should be noted that increasing levels of toxic metals, such as lead and chromium, cause oxidant compounds to be produced, which as a result raises MDA levels.[41]

The significant increase in the concentration of ONOO may be caused by the increased concentration of the (•NO) radical in neurological disease patients, which interacts with the ($O_2^{\bullet-}$) anion radical. and increases the formation of ONOO-, Consequently, there is an increase in the production of oxidant compound products, which damage neurons and cause OS in patients.[42] Increased nitric oxide production has been suggested as an aggravating factor for numerous neurodegenerative diseases, including Parkinson's, Alzheimer's and amyotrophic lateral sclerosis disease.[43]

GSH levels fall in this study, These results match with previous study results showing that children with epilepsy had lower GSH levels than children without the condition.[44] When OS is partially responsible for neuronal injury it has crucial roles in the antioxidant defence system and the maintenance of redox homeostasis in neurons. The reduced GSH concentrations in the brain indicate continued OS and weakened

endogenous antioxidant defences. Patients with neurodegenerative diseases like Alzheimer's, epilepsy, and Parkinson's frequently have GSH depletion in their brains.[45]

The possible causes of the bilirubin decline include its role as an endogenous antioxidant and neuroprotective agent, other reports found a lower level of Bilirubin in neurological diseases such as Multiple sclerosis and Acute Ischemic Stroke.[46,47] A defect in the blood-brain barrier (BBB) may be the cause of elevated albumin levels. it has been demonstrated that BBB dysfunction and subsequent serum albumin extravasation contribute to epileptogenesis and the pathophysiology of epilepsy.[48]

The high level of UA is consistent with previous studies that showed high uric acid enhances epileptic seizures.[49] UA is a biomarker of OS and neuroinflammation which are factors in the pathogenesis of epilepsy. Therefore, manipulating uric acid can be beneficial in suppressing epileptic seizures.[50] Other parameters which potentially have a role in epilepsy and needs to be considered in further studies is the brain localized cytokine profile and oxygen supply which modulate pro-inflammatory/ anti-inflammatory markers balances in surrounding milieu.[51-53]

CONCLUSION

In conclusion, the study on the interplay between H2S and CSE with oxidants and antioxidant levels in patients with epilepsy diseases highlights the complex and intricate mechanisms underlying epileptic pathogenesis. The findings suggest that dysregulation of H2S and CSE may contribute to the OS and imbalanced redox status observed in epilepsy patients. Moreover, the study underscores the potential therapeutic implications of modulating H2S and CSE activity as a means to restore redox homeostasis and alleviate epileptic seizures. These results provide valuable insights into the underlying molecular mechanisms of epilepsy and may pave the way for the development of novel therapeutic strategies targeting the H2S/CSE pathway. However, further research is warranted to fully elucidate the precise role of H2S and CSE in epilepsy and to explore the therapeutic potential of targeting this pathway for the management of epilepsy diseases. Overall, this study contributes to our understanding of the complex interplay between H2S, CSE, oxidants, and antioxidants in epilepsy and sets the stage for future investigations aimed at improving the clinical outcomes for patients suffering from this debilitating neurological disorder.

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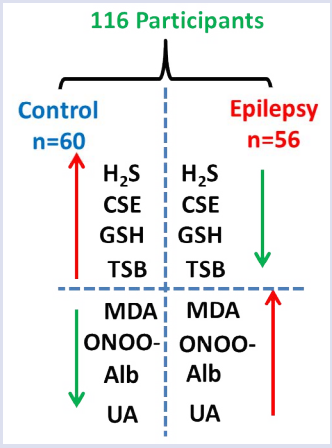
GRAPHICAL ABSTRACT



Cite this article: Al-Taee KM, Al-Helaly LA. Hydrogen Sulfide and Cystathionine γ–Lyase with Oxidants and Antioxidants Levels for Patients with Epilepsy Diseases. Pharmacogn J. 2024;16(2): 319-322.