Annals of Biomedical Research
An open access journal
ISSN 2817-2094
eSciRes
Review Article
ABR-5-127

Do Glucocorticoids Play a Role in Patients with Temporal Lobe Epilepsy and, Depression and Anxiety? A Systematic Review

Glauber Menezes Lopim[1], Fabrizio dos Santos Cardoso[2,3] and Gerardo Maria de Araújo Filho[4]

[1]*Faculdade Ceres de Medicina, São José do Rio Preto, Brazil.*

[2]*Centro Universitário Redentor/Afya (UniREDENTOR), Itaperuna, Brazil.*

[3]*Hospital do Câncer de Muriaé, Fundação Cristiano Varella (FCV), Muriaé, Brazil.*

[4]*Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, Brazil.*

Abstract

Temporal Lobe Epilepsy (TLE) is one of the most frequent epilepsy syndromes associated with a high prevalence of psychiatric disorders (PD), particularly depression and anxiety. Stress levels associated with depression and anxiety can be related to alterations in glucocorticoid receptors, which play a role in hippocampal formation. In this study, we systematically reviewed the role of glucocorticoids acting by binding to their receptors in the temporal lobe of patients with TLE associated with depressive and anxiety disorders. The PubMed, PsycINFO, and Scielo databases were searched for relevant articles published in the last ten years. There have been relatively few published studies with different methodologies and contradicting conclusions regarding the association between TLE, depression, anxiety, and glucocorticoid receptors. Four articles were selected for this review after applying the inclusion and exclusion criteria. This indicates the necessity for more investigations into this topic.

Keywords: Temporal lobe epilepsy; Hippocampal sclerosis; Stress; Glucocorticoid receptors

Introduction

Temporal lobe epilepsy (TLE) is one of the most prevalent chronic epilepsy syndromes in adults [1-4]. It is drug-resistant, with positive results for seizure frequency after surgical procedures [5]. In addition, this disease is characterized by different patterns of loss of hippocampal neurons and in adjacent temporal lobe structures, particularly the loss of pyramidal cells in Ammon's horn [6].

TLE has been associated with psychiatric disorders, with prevalence rates ranging from 20-40% to 70% in drug-resistant patients. Among the most frequently diagnosed psychiatric comorbidities are major depression, anxiety, psychotic disorders, and personality disorders [7-10].

Different factors, such as stress, can precipitate seizures [11]. Studies have shown that 30 – 60% of patients with epilepsy self-report stress as a seizure precipitant [12-16]. Stress is characterized by a combination of physiological and psychological effects caused by a state of heightened arousal, awareness, and anxiety. Environmental or psychological stimuli can be described as stress-precipitating events for seizures in individuals with epilepsy, including sleep deprivation, changes in menstrual status, photosensitivity, substance abuse, and/or psychiatric disorders [17]. Studies have also observed that depressive and anxiety disorders are considered the most frequent psychiatric disorders in individuals with epilepsy [18-22]. Also, anxiety disorders are more prevalent in patients with drug-resistant TLE than in patients with other epilepsies [8,23].

Given the data cited above, we analyzed the studies that investigated the interaction of glucocorticoids with their receptors in psychiatric disorders in TLE patients.

Methods

The systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010).

Search Strategy

A comprehensive PubMed, PsycINFO, and Scielo databases search was conducted from their inception to December 2023 using a combination of terms related to investigating the role of glucocorticoid receptors active in patients with epilepsy and/or TLE associated with depression and/or anxiety. The following terminology was applied: (“epilepsy” OR "temporal lobe epilepsy") AND ("depression" OR "anxiety") AND ("cortisol" OR “glucocorticoid receptors” OR “mineralocorticoid receptors”).

Eligibility

In this study, only studies involving humans were conducted. Studies were included if: 1) report a quantitative analysis exploring the relationship between anxiety and/or depression, epilepsy/TLE, and glucocorticoid receptors; 2) present a relationship between the original data and the study question; 3) cross-sectional of prospective design; 4) were published in English in a peer-reviewed journal.

Identified these studies were selected and excluded by examining the titles, abstracts, or full-text articles. Studies that did not address the association between depression and/or anxiety, epilepsy/TLE, and glucocorticoids were excluded, or some of the items listed above.

Screening and Selection

Study screening was shared by two reviewers (GML and FC). The two reviewers independently assessed all titles and abstracts. Next, the full text of all potentially relevant articles was retrieved and assessed for inclusion by one reviewer (GML). At both stages, the discrepancies were resolved by a third reviewer (GAMF).

Author	Mental Disorder	Subjects	Results
Afifi et al., [45]	Depression	TLE patients with depression	Elevated levels of prolactin and cortisol, and reduced serum testosterone. Depressed patients had higher cortisol levels than nondepressed.
Busch et al., [43]	Depression	TLE patients	Higher cortisol levels were associated with impairment in tests of delayed verbal memory, weaker immediate and delayed visual memory, and greater trait anxiety. Patients with smaller hippocampal volumes showed impaired performance on a word list learning task.
Cano-López et al., [44]	Depression and anxiety	TLE patients with drug-resistant epilepsy.	Patients with low immediate and delayed memory performance showed higher cortisol levels. Memory performance was negatively related to cortisol levels and trait anxiety.
D'Alessio et al., [33]	Depression	TLE patients with depression	Reduced Glucocorticoid receptor (GR) expression in neuronal and glial cells. The reduced ratio between the number of GR/NeuN cells was correlated negatively with the depression severity.

Table 1: Summary of studies on the interaction of glucocorticoids with their receptors in psychiatric disorders in ELT patients.

Results

The electronic database search retrieved 68 articles. After removing duplicates, 61 articles remained, based on title and abstract. Of these, 40 did not meet the inclusion criteria. The full text of the remaining 21 articles was assessed for eligibility. Overall, four articles were eligible and included (see Table 1). Study characteristics of removing articles were one book chapter, one dissertation, 13 reviews that did not establish a relationship between the variables in the work question, and two that did not assess anxiety and/or depression and epilepsy (Figure 1).

Characteristics of the studies

The characteristics of the selected studies are demonstrated in Table 3.

Author	Subject	Epilepsy Assessment	Psychiatric/Neuropsychological Assessment	Analysis
Afifi et al., [45]	20 patients with epilepsy without depression; 20 patients with epilepsy; 20 healthy control	Not related	Ham-D	EEG; Blood samples (prolactin, testosterone, thyroid hormones, and cortisol
Busch et al., [43]	24 presurgical patients with drug resistant TLE epilepsy	EEG and MRI	RAVLT, MAC-S, CES-D and STAI	Salivary cortisol.
Cano-López et al., [44]	208 patients with characteristics based on side of seizure focus, epilepsy type and memory competence	Seizure history and semiology; video-EEG; MRI	WMS-III, STAI and BDI-II	Salivary cortisol

D'Alesio et al., [33]	26 hippocampal samples of patients with drug resistant TLE epilepsy	Video-EEG and MRI	Structured Clinical Interview, DSM-IV (AxisI), Global Assessment Scale of Functioning and Beck Depression Scale	Immunohistochemistry of GR protein expression

Table 3: Characteristics of studies selected: TLE (Temporal Lobe Epilepsy); EEG (Electroencephalogram); MRI (Magnetic Resonance Image); Video-EEG (Video- Electroencephalogram); Ham-D (Hamilton-D Scale); RAVLT (Rey Auditory Verbal Learning Test); MAC-S (Memory Assessment Clinics Self-Rating Scale); CES-D (Center for Epidemiologic Studies Depression Scale); STAI (State-Trait Anxiety).WMS-III (Wechsler Memory Scale- Third Edition); BDI-II (Beck Depression Inventory-II); DSM (Diagnostic and Statistical Manual of Mental disorder-IV AxisI).

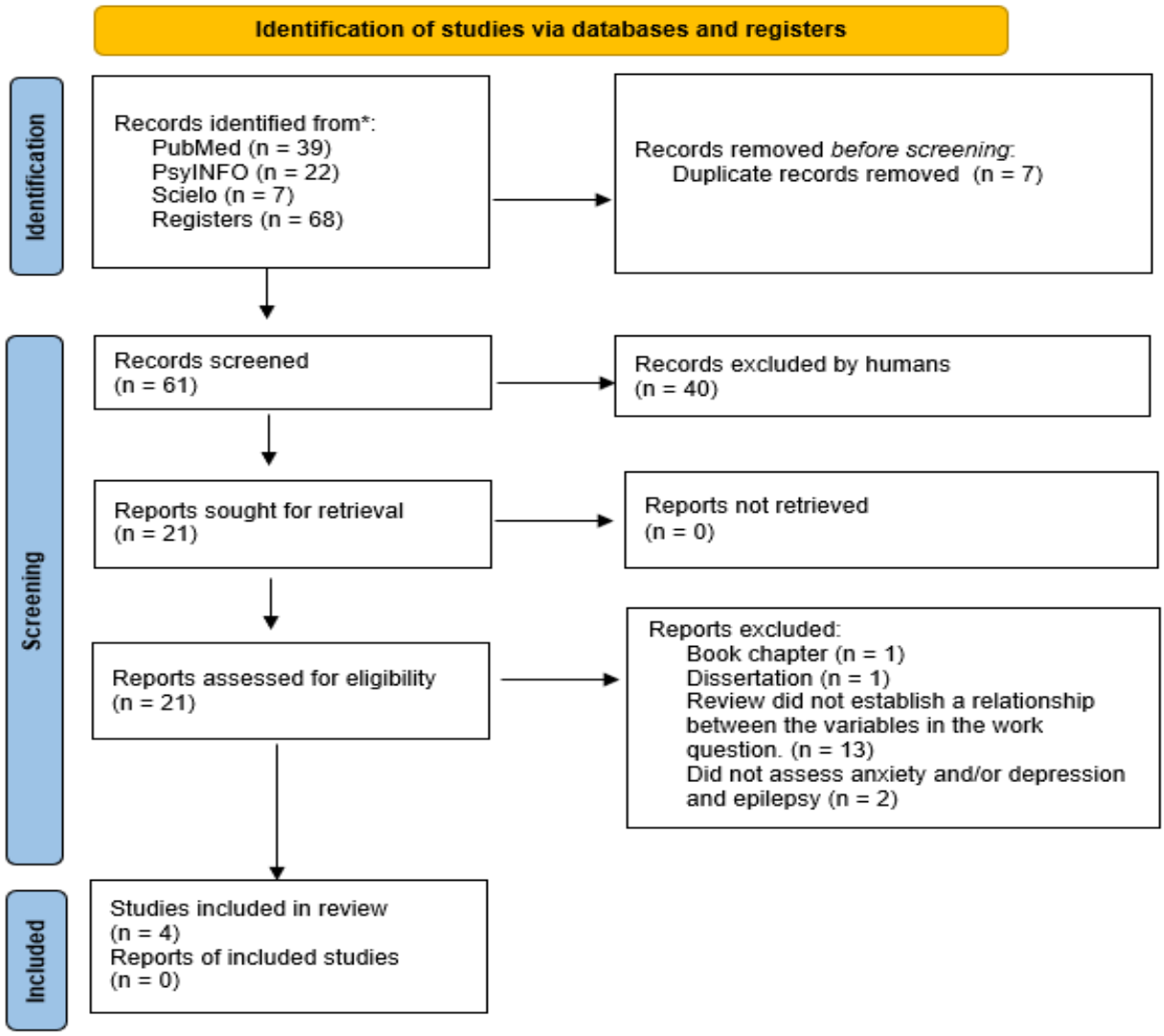

Figure 1: PRISMA diagram summarizing the screening process for included studies.

Discussion

The present study considered the possible role of glucocorticoids in patients with TLE associated with depressive and anxiety disorders. After the selection process, only four articles were eligible for inclusion.

Activation of the HPA axis in response to stress is essential for survival [24]. Once a stressful situation is initiated, hypothalamic neurons of the paraventricular neurons release corticotrophin-releasing hormone (CRH) directed towards the hypophyseal system, which in turn releases adrenocorticotrophic hormone (ACTH) from the anterior

pituitary gland. ACTH stimulates the adrenal cortex to synthesize and secrete GCs. GCs have two primary receptors, GR and MR, which act on the peripheral pathway and the brain (Figure 2) [24].

Given that GR and MR are almost identical (94%) in their DNA-binding domains, both bind to glucocorticoid-responsive elements in the DNA [25]. GCs in the brain affect memory [26], the aging process [27], and the stress response [28]. The actions of GCs are related to alterations in neurochemical transmission, for example, serotonin turnover (de Kloet et al., 1992), GABA uptake [29], and noradrenaline binding density [30], which triggers changes in neuroendocrine processes, behavior, mood [31], and seizure susceptibility [32].

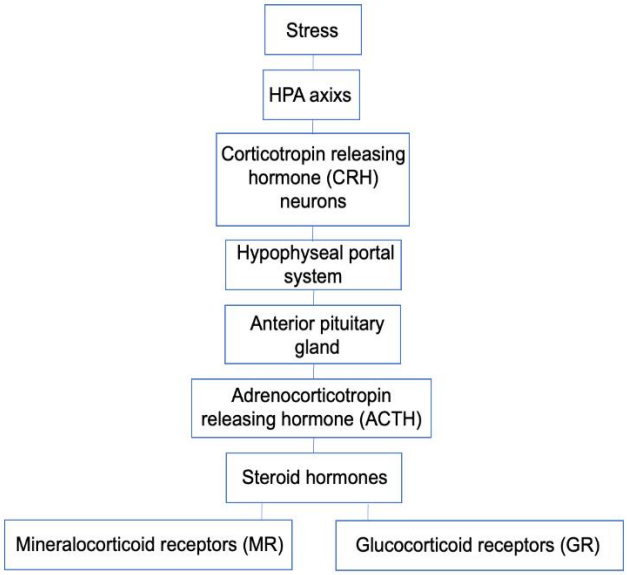

Figure 2: Steroid hormone signaling cascade in epilepsy.

In the study conducted by D'Alessio et al. [33], they analyzed GR expression in the hippocampal samples of three different groups: Control, TLE patients with depression (TLE + D), TLE patients without depression (TLE – D), those undergoing surgery for drug-resistant epilepsy, and a group of hippocampal sections from autopsy control cases. The psychiatric assessment was conducted by trained psychiatrists using a standardized protocol for patients with drug-resistant epilepsy. The results of this study revealed abundant GR immunoreactivity in the nuclei of granule cells in the dentate gyrus and pyramidal cells in the CA1 region of the control group. However, GR immunoreactivity decreased in TLE – D patients, while the lowest expression was found in TLE + D patients. In addition, the authors observed a negative correlation between GR+/NeuN+ cells and depression severity based on psychiatric history; however, no negative correlation was found when the time of assessment was analyzed. These data suggest that an increase in mood disorders is closely associated with increased GC in the hippocampus, thus reducing the number of neurons and causing HS. HS was initially recognized 180 years ago when Sommer and Bratz described it in a post-mortem series. They observed consistent patterns of neuronal loss, primarily restricted to a section of the hippocampal pyramidal cell layer immediately adjacent to the temporal horn of the lateral ventricle in a series of 90 post-mortem cases [34] (for historical review consult: [35]).

Subsequently, less severe neuronal loss occurs in the hilus and adjacent CA3 and neurons in the dentate gyrus's CA2, subiculum, and granular cell layer [36]. With advances in brain electrical recording techniques in the mid-20th century, HS was found to be associated with electrophysiological evidence of temporal lobe seizures [37] with more significant variability in the patterns and severity of neuronal loss [38] that occurs during bilateral sclerosis in 48%–56% of cases [39] and may vary from one patient to another [40]. Some authors have suggested that HS arises from injuries early in life, resulting in a brain lesion that is static and nonprogressive [41]. Other authors have noted that HS may have more than one cause, with the etiology involving a complex interaction between genetic background and environmental insults [42], described neuropathologically as being not just one entity but rather an association between the severity of cell loss with the relevant pattern [6].

Busch et al. [43] analyzed the relationships between late-night salivary cortisol levels and completed mood, anxiety, and memory measures in another study. Also, hippocampal atrophy was analyzed by MRI-based volumetric analyses. In contrast to the results found in the study of D'Alessio et al. [33]. These authors showed that cortisol was not related to current symptoms of depression and anxiety or hippocampal volumes. The difference between the findings can be attributed to the different methodologies used. D'Alessio et al. [33] used hippocampal tissue removed from patients with refractory epilepsy and performed immunohistochemistry to compare with hippocampal tissues of patients without epilepsy as a control group.

In contrast, the study conducted by Busch et al. [43] collected salivary samples provided at midnight, and MRI-based volumetric analyses determined the volume of the hippocampal structure. Another point cited by the authors in the discussion was the number of patients with clinically elevated cortisol levels (n = 3), which may have influenced the results.

Cano-López et al. [44] also used the method of saliva to analyze the cortisol in Fifty-two adults with drug-resistant epilepsy. The authors concluded that patients with low immediate and delayed memory performance and left-hemisphere focus showed higher cortisol levels, suggesting that memory deficits in PWE drug-resistant may be influenced by exposure to cortisol derived from chronic stress, and anxiety could contribute to increasing vulnerability to stress.

The last study selected, conducted by Afifi and colleagues [45], analyzed 40 patients (20 depressed, 20 non-depressed) and 20 healthy subjects. They showed that the effects of epilepsy and depression on cortisol may be additive.

Interestingly, we need to clarify that not only cortisol is associated with depression, anxiety, and epilepsy. Another factor is the disturbance of neurotransmitters; the neuroinflammatory process is also a relationship and can be explored more [46].

In conclusion, this review showed that only some studies have analyzed the relationship between TLE, depression, and anxiety after the search proposed in the methodology. These

studies presented different analysis methods, thus finding divergent results. Therefore, clinical studies with greater methodological rigor, or replicating the methods already used, are necessary to understand better how glucocorticoids act by binding to their receptors in the temporal lobe in patients with TLE associated with psychiatric disorders.

Conflict of Interest

The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

References

1. Schwartzkroin PA (1986) Hippocampal slices in experimental and human epilepsy. Adv Neurol 44: 991-1010.
2. Hauser WA, Annegers JF, Rocca WA (1996) Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 71(6): 576-586.
3. Picot MC, Baldy-Moulinier M, Daurès JP, et al. (2008) The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia 49(7): 1230-1238.
4. Blümcke I, Spreafico R, Haaker G, et al. (2017) Histopathological findings in brain tissue obtained during epilepsy surgery. New England Journal of Medicine 377(17): 1648-1656.
5. Engel J, McDermott MP, Wiebe S, et al. (2012) Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 307(9): 922-930.
6. Blümcke I, Thom M, Aronica E, et al. (2013) International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 54(7): 1315-1329.
7. Devinsky O (2003) Psychiatric comorbidity in patients with epilepsy: implications for diagnosis and treatment. Epilepsy Behav 4(4): 2-10.
8. Gaitatzis A, Trimble MR, Sander JW (2004) The psychiatric comorbidity of epilepsy. Acta Neurol Scand 110(4): 207-220.
9. Ertekin BA, Kulaksızoğlu IB, Ertekin E, et al. (2009) A comparative study of obsessive–compulsive disorder and other psychiatric comorbidities in patients with temporal lobe epilepsy and idiopathic generalized epilepsy. Epilepsy Behav 14(4): 634-639.
10. Nakahara S, Adachi M, Ito H, et al. (2018) Hippocampal pathophysiology: commonality shared by temporal lobe epilepsy and psychiatric disorders. Neurosci J 2018: 4852359.
11. Spector S, Cull C, Goldstein LH. (2000) Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. Epilepsy Res 38(2-3): 207-216.
12. Neugebauer R, Paik M, Hauser WA, et al. (1994) Stressful life events and with seizure frequency in patients epilepsy. Epilepsia 35(2): 336-343.
13. Frucht MM, Quigg M, Schwaner C, et al. (2000) Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 41(12): 1534-1539.
14. Nakken KO, Solaas MH, Kjeldsen MJ, et al. (2005) Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy & Behavior 6(1): 85-89.
15. Sperling MR, Schilling CA, Glosser D, et al. (2008) Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. Seizure 17(4): 302-307.
16. McKee HR, Privitera MD (2017) Stress as a seizure precipitant: identification, associated factors, and treatment options. Seizure 44: 21-26.
17. Basu T, Maguire J, Salpekar JA (2021) Hypothalamic-pituitary-adrenal axis targets for the treatment of epilepsy. Neuroscience letters 746: 135618.
18. Jansen C, Francomme L, Vignal JP, et al. (2019) Interictal psychiatric comorbidities of drug-resistant focal epilepsy: prevalence and influence of the localization of the epilepsy. Epilepsy Behav 94: 288-296.
19. Scott AJ, Sharpe L, Hunt C, et al. (2017) Anxiety and depressive disorders in people with epilepsy: a meta-analysis. Epilepsia 58(6): 973-982.
20. Gandy M, Sharpe L, Perry KN, et al. (2013) Rates of DSM-IV mood, anxiety disorders, and suicidality in Australian adult epilepsy outpatients: a comparison of well-controlled versus refractory epilepsy. Epilepsy Behav 26(1): 29-35.
21. Rai D, Kerr MP, McManus S, et al. (2012) Epilepsy and psychiatric comorbidity: A nationally representative population-based study. Epilepsia 53(6): 1095-1103.
22. de Araujo Filho GM, Gomes FL, Mazetto L, et al. (2012) Major depressive disorder as a predictor of a worse seizure outcome one year after surgery in patients with temporal lobe epilepsy and mesial temporal sclerosis. Seizure 21(8): 619-623.
23. Beyenburg S, Mitchell AJ, Schmidt D, et al. (2005) Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy Behav 7(2): 161-171.
24. de Kloet ER, Joëls M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6(6): 463-475.
25. Lombès M, Binart N, Oblin ME, et al. (1993) Characterization of the interaction of the human mineralocorticosteroid receptor with hormone response elements. Biochem J 292(2): 577-583.
26. Quirarte GL, Roozendaal B, McGaugh JL (1997) Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. Proc Natl Acad Sci U S A 94(25): 14048-14053.
27. McLay RN, Freeman SM, Harlan RE, et al. (1997) Aging in the hippocampus: Interrelated actions of neurotrophins and glucocorticoids. Neurosci Biobehav Rev 21(5): 615-629.
28. de Kloet ER, Rots NY, Cools AR. (1996) Brain-corticosteroid hormone dialogue: slow and persistent. Cell Mol Neurobiol 16(3): 345-356.
29. Miller AL, Chaptal C, McEwen BS, et al. (1978) Modulation of high affinity GABA uptake into hippocampal synaptosomes by glucocorticoids. Psychoneuroendocrinology 3(2): 155-164.
30. Weidenfeld J, Siegel RA, Corcos AP, et al. (1983) Effect of 6-hydroxydopamine on in vitro hippocampal corticosterone binding capacity in the male rat. Exp Brain Res 52(1): 121-124.

31. McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87(3): 873-904.
32. Joëls M (1997) Steroid hormones and excitability in the mammalian brain. Front Neuroendocrinol 18(1): 2-48.
33. D'Alessio L, Mesarosova L, Anink JJ, et al. (2020) Reduced expression of the glucocorticoid receptor in the hippocampus of patients with drug-resistant temporal lobe epilepsy and comorbid depression. Epilepsia 61(8): 1595-1605.
34. Sommer W (1880) Erkrankung des Ammonshorns als aetiologisches Moment der Epilepsie. Archiv für psychiatrie und nervenkrankheiten 10(3): 631-675.
35. Thom M, Mathern GW, Cross JH, et al. (2010) Mesial temporal lobe epilepsy: How do we improve surgical outcome? Ann Neurol 68(4): 424-434.
36. Thom M (2014) Hippocampal sclerosis in epilepsy: a neuropathology review. Neuropathol Appl Neurobiol 40(5): 520-543.
37. Sano K, Malamud N (1953) Clinical significance of sclerosis of the cornu ammonis: ictal psychic phenomena. AMA Arch Neurol Psychiatry 70(1): 40-53.
38. Margerison JH (1966) Epilepsy and the temporal lobes: a clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain 89(3): 499-530.
39. Thom M, Liu JY, Thompson P, et al. (2011) Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study. Brain 134(10): 2969-2981.
40. Hamelin S, Depaulis A (2015) Revisiting hippocampal sclerosis in mesial temporal lobe epilepsy according to the "two-hit" hypothesis. Rev Neurol (Paris) 171(3): 227-235.
41. Tasch E, Cendes F, Li LM, et al. (1999) Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. Ann Neurol 45(5): 568-576.
42. Walker MC (2015) Hippocampal sclerosis: causes and prevention. Semin Neurol 35(3): 193-200.
43. Busch RM, Frazier T, Chapin JS, et al. (2012) Role of cortisol in mood and memory in patients with intractable temporal lobe epilepsy. Neurology 78(14): 1064-1068.
44. Cano-López I, Hidalgo V, Hampel KG, et al. (2019) Cortisol and trait anxiety as relevant factors involved in memory performance in people with drug-resistant epilepsy. Epilepsy Behav 92: 125-134.
45. Afifi S, Fadel W, Morad H, et al. (2011) Neuroendocrinal study of depression in male epileptic patients. J Neuropsychiatry Clin Neurosci 23(2): 163-167.
46. Kanner AM (2017) Can neurochemical changes of mood disorders explain the increase risk of epilepsy or its worse seizure control? Neurochem Res 42(7): 2071-2076.

***Corresponding author:** Dr. Gerardo Maria de Araújo Filho, Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, Brazil; Email: filho.gerardo@gmail.com

Received date: January 31, 2024; **Accepted date:** March 13, 2024; **Published date:** March 29, 2024

Citation: Lopim GM, dos Santos Cardoso F, de Araújo Filho GM (2024) Do Glucocorticoids Play a Role in Patients with Temporal Lobe Epilepsy and, Depression and Anxiety? A Systematic Review. *Ann Biomed Res* 5(1): 127.