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A study to examine the effects on epilepsy and memory of different embelin and resveratrol dosages given to mice

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Abstract

Drugs already on the market "work symptomatically, and one-third of patients are resistant to them, thus finding novel compounds that can control the epileptogenesis process is critical. To find out if Embelin (EMB) and Resveratrol (RESV) affect" epileptogenesis in mice given pentylenetetrazole (PTZ), researchers undertook this investigation.

For embelin and "resveratrol, independent studies were conducted. In an acute investigation, EMB (5, 10 and 20 mg/kg p.o.) and (RESV (10, 20 and 40 mg/kg p.o.) were given to Swiss albino mice. Various neurological and neurobehavioral tests were performed on the rats on the seventh day, including the Increasing Current Electroshock Test (ICES), PTZ-induced seizures, passive avoidance reaction, raised plus maze test, and forced swim test (FST). In a chronic trial, PTZ at a dosage of 25mg/kg i.p. every other day was delivered to promote kindling, while EMB and RESV at all three doses were given daily. When kindling had developed, the seizure score was tracked continually until the study's conclusion, when cognition tests and the FST were administered. A method called Elisa was used to measure the amounts of pro-inflammatory biomarkers such as IgL1, IgL1-Ra, IL-6, and TNF- in the kindled animals' hippocampus and cortex after they were" killed GABA, glutamate, and dopamine were also assessed in the kindling brains of the experimental animals using a validated LC-MS/MS technique followed by UHPLC, as well as oxidative stress markers such as MDA levels, GSH, GPx, and nitrite content.

Both EMB and RESV "significantly raised the seizure threshold current (STC) in the ICES experiment when compared to the control and phenytoin. Only RESV, not EMB, enhanced the delay to myoclonic jerks and generalised seizures in the PTZ-induced seizure test. EMB and RESV exhibited no signs of behavioural impairments in any of the neurobehavioral tests (acute and chronic), such as step down latency, transfer latency, and the forced swim test, although both drugs were shown to be memory- and antidepressive-protecting. During" the PTZ-induced kindling experiment, both EMB and RESV were able to reduce the mean seizure score to a safe "level. RESV outperformed EMB in terms of efficacy. IL-1, IL-1Ra, IL-6 and TNF- were discovered to be increased after kindling and both EMB and RESV were able to reduce their levels following application of the vaccines. The neurotransmitters GABA, glutamate, and dopamine were all regulated by EMB and RESV in kindling mice whose brains had been stimulated. Oxidative stress was reduced in the kindled rats when treated with EMB" or RESV.

Keywords: embelin; resveratrol; kindling; epileptogenesis; inflammatory biomarkers; IL-1β; IL- 1Ra; IL-6; TNF-α; GABA; glutamate; dopamine; cognition; depression; oxidative stress

Introduction

The disease of the central nervous "system (CNS) epilepsy affects around 70 million individuals worldwide (Houinato et al., 2013). Epilepsy is distinguished by a persistent propensity to have seizures, which have neurological, psychological, cognitive, and social implications. As well as epilepsy, there are a number of co-morbid conditions such as anxiety and depression as well as memory loss, mental retardation, and" learning difficulties. Individuals with epilepsy are considerably over-represented in cognitive and behavioural co-morbidities, and these co-morbidities have severe implications that reduce quality of life.

Many modern "antiepileptic medicines (AEDs) have been developed through the drug development process that work largely on ion channels to control neuronal excitability. One-third of epileptic patients continue to have seizures despite the availability of AEDs (Martinc et al., 2014). Because both monotherapy and polytherapy fail to control seizures in these individuals, they need more severe treatment. Additionally, it is becoming increasingly important to monitor the occurrences of side effects including neurological disturbances, cognitive impairment, and metabolic changes linked to AEDs (Deckers et al., 2001). However,

the underlying brain abnormalities are minimally changed by the currently available AEDs, which operate symptomatically and reduce seizures (Saha and Chakrabarti, 2014). Epilepsy-related mortality is also a big global problem, with epilepsy sufferers being twice as likely to die as the average person (Koshal and Kumar, 2016). New AEDs that can control seizures by altering the underlying pathophysiology are therefore urgently required. When the brain undergoes epileptogenesis, it transforms" into an epileptic brain due to alterations in many places such membrane channels, neuronal cell signalling pathways, neurotransmission, and synaptic connections. This alteration results in a chronic condition of irritability and irritability. "Epilepsy and hyperexcitabilty of the epileptic brain are both caused by changes in the amounts of neurotransmitters in the brain (Koshal and Kumar, 2016). A neurotransmitter called Gamma amino butyric acid (GABA) inhibits hyperexcitability by increasing glutamate, which in turn increases seizure activity by increasing hyperexcitability. GABA appears to be reduced during seizure activity and allows increased excitatory neurotransmitter glutamate to pass through. It is now widely accepted that GABA serves as the brain's primary inhibitory neurotransmitter. To keep an inhibitory tone that counterbalances neuronal excitement, GABA is concentrated" in short-axon interneurons that synapsese on cell bodies and proximal axons (Treiman, 2001). The imbalance of GABA and glutamate "neurotransmitters may be the underlying mechanism for the onset and" development of seizures in healthy people.

Glutamine is a precursor of "GABA in neurons and glutamine in astrocytes, both of which are excitatory neurotransmitters produced by glutamate. Astrocytes and neurons compartmentalise and metabolise glutamate differently, using various enzymes, and they deal with exogenous and endogenous glutamate in different ways. Human brain tissues and epileptic animal models have shown elevated glutamate levels, and glutamate-induced excitotoxicity is known to cause neuronal death in epilepsy (Cho, 2013). Dopamine is an important neurotransmitter that has been linked to seizure" activity regulation in mouse brains.

There is "evidence to suggest that dopamine affects the way epileptiform discharges are modulated. Dopamine has been found to impact seizure start in several epilepsy models in vivo and in vitro, according to several research. To protect an animal from seizures, the dopaminergic system in the hippocampus has to be activated. Stomach injection of SCH 23390 in rats lowered seizure threshold and reduced the severity, suggesting a function for hippocampus dopaminergic receptors in seizure threshold reduction (Goda et al., 2008). Seizure treatment focuses on blocking neuronal ion channels and GABA" and glutamate receptors. More sophisticated models of epileptogenesis raise more concerns than prior research that focused on neurons (Shimada et al., 2014). "Epileptic's aetiology may be connected to both neuronal and non-neuronal components including glial cells, peripheral leucocytes, and inflammatory cytokines, according to research in animals and" epilepsy patients.

According "to research, seizures are caused in part by an inflammatory process in the brain (Vezzani, 2014). Seizures may be more common in individuals with chronic inflammatory issues than in the general population, according to some research. Antiepileptic" drugs (AEDs) are not "working for epileptic patients, and their plasma cytokines have a pro-inflammatory character, which comes from the brain (Rao et al.). Many studies have shown that chemoconvulsants and electroshock increase the expression of inflammatory cytokines in the body. Mice and rats have had increased levels of the pro-inflammatory cytokines interleukin (IL)-1, interleukin (IL)-6, and tumour necrosis factor-alpha (TNF-), all of which have been linked to increased inflammation (Vezzani, 2014). Seizures enhanced the rat hippocampus slice release of TNF- and IL-6 as well (Vezzani et al., 2002). Seizures" have been linked to an increase in the brain's "interleukin-1 receptor type 1 (IL-1R1), which mediates the biological response to IL-1. IL1-Ra has been demonstrated to be an effective antagonist of IL-1 when expressed in astrocytes, where it decreases seizure susceptibility" (Vezzani, 2014).

Literature Review

There are no geographical, "cultural, or racial barriers to epilepsy, which is a neurological disorder that affects people of all ages (Singh and Trevick, 2016). This illness has neurobiologic, cognitive, psychological, and social implications, and is classified as an epilepsy as a disorder of the brain characterised by a persistent propensity to create epileptic seizures (Fisher et al., 2005). History of epileptic seizures dates back to the Mesopotamian and Indian Vedic eras. Epilepsy and epileptic seizures have been documented since 4000 BC in Mesopotamian literature and the Indian Vedas (Singh and Trevick, 2016). The" seizure was blamed on the moon deity. A history of epileptic seizures may be found not just in ancient Greece and Rome, but also in ancient China and Egypt. A guy with a history of brain trauma suffered a seizure, according to an ancient Egyptian papyrus.

It's no coincidence that the word "epilepsy" originates from the Greek word for "seized" or "attacked" (Fisher et al., 2005). "Epilepsy was originally documented by Hippocrates almost 2500 years ago. He dismissed the idea that epilepsy is caused by a divine intervention and instead determined that excessive phlegm in the body leads to aberrant brain consistency (Novarino et al., 2013). During mediaeval times, divine etiologies retook precedence over Hippocratic views on epileptic convulsions, which had fallen out of favour. Extreme masturbation was thought to be a cause of epilepsy as early as the mid-nineteenth" century. As a result of this idea, the first effective anticonvulsant (i.e. bromides) was developed.

Either one or "all of these symptoms may be present during a seizure depending on the kind. Excessive neuronal firing or depolarization causes seizures, which are described as a temporary alteration in the patient's clinical condition. Seizures might be brought on by stress or be completely unrelated to it" (Fisher et al., 2014).

Throughout 70 "million individuals around the world are affected with epilepsy. Like underdeveloped nations in Africa, Asia, or Latin America, 90% of epilepsy patients live (Houinato et al., 2013). In developing nations, epilepsy has a median prevalence of 1.54% (range: 0.48–4.96%) in rural areas and a prevalence of 1.03 percent (range: 0.28–3.8%) in urban areas, according to a research (Ngugi et al., 2010). Epilepsy affects an estimated 2.4 million individuals worldwide each year. New instances of the disease occur on a yearly basis in high-income nations between 30 and 50 per 100,000 individuals. This number might be up to twice as high in nations with low and medium incomes. To some extent, this" is attributable to the greater risk of endemic diseases like malaria and neurocysticercosis (NCC); the higher frequency of "traffic accidents and birth accidents; and differences in the medical infrastructure as well as access to health programmes and services. Around 90% of the population lives in low- and middle-income nations with inadequate resources, according to the World Bank's categorization" system.

Approximately 4 to 10 people "out of every 1000 in developed nations are affected with epilepsy (Bell and Sander, 2001). Epilepsy prevalence rates are greater in poor and tropical nations, with estimates ranging from 14 to 57 cases per 1,000 people (Burneo et al., 2005, Carpio and Hauser, 2009). However, in other parts of the globe, particular infectious illnesses as NCC are frequently the cause of epilepsy. The higher incidence rates of epilepsy in underdeveloped nations is probably linked to methodological issues in those studies (Ndimubanzi et al., 2010). Epilepsy is more common in youngsters and the elderly in industrialised countries, with a U-shaped curve. In contrast, epilepsy tends to peak in developing nations in early adulthood (Ndimubanzi" et al., 2010).

Research Gap

In the field of neurology, epilepsy "is a frequent and severe condition. Until yet, the medicines that have been found merely treat the symptoms. Until now, we only have a few AEDs that don't have severe adverse

effects including cognitive impairment, depression, or behavioural abnormalities, which makes it difficult for people with epilepsy to lead a normal life. Hence, the most important strategy is to discover such a moiety that may modify the pathophysiology and minimise epilepsy's co-morbidities. According" to popular wisdom, epilepsy is caused by a dysregulation of excitatory and inhibitory brain chemicals. Epilepsy's fundamental cause may potentially be due to inflammation and oxidative stress in the brain, according to new study. In other words, this "research shows how EMB and RESV affect brain inflammation, neurotransmitter changes, and oxidative stress caused by" epileptogenesis.

The neuroprotective effect of EMB and RESV "was investigated in the current study for epilepsy, as well as a potential mechanism. The seizure threshold current equivalant to phenytoin was raised by EMB in the ICES experiment in a dose-dependent manner. This suggests that it could be able to keep electrical seizures at bay. As a result, our findings are in line with those of a previous study that looked at the extract of Embelia ribes Burm and found that embelin protected against the MES test. Emelin suppressed HLTE, reduced stupor duration, and provided mortality protection comparable to phenytoin in this research (Mahendran et al., 2011). New medicines are tested to see if they affect generalised tonic-clonic seizures or partial seizures using ICES and MES (Rathor et al., 2014). Embelin may thus be a new chemical with preventive effects against electro-convulsions based on our study's findings and supporting evidence. EMB" failed to protect against myoclonic jerks and generalised seizures in the "PTZ-induced seizure test. An earlier research on embelin, on the other hand, found that it might help control PTZ-induced epilepsy in rats (Mahendran et al., 2011). PTZ blocks the GABA receptor by its action on it. Since of this, it may be concluded from the findings that embelin acute study administration failed to show an impact on the GABA receptor because PTZ" inhibited it.

To see if it can "help prevent electrical seizures, researchers tested RESV on an ICES model and found that it dramatically raised the seizure threshold for hind limb extension (HLE) seizures in comparison to the vehicle-treated group. Higher dosages of RESV enhanced the delay to myoclonic jerks and generalised seizures in the acute investigation on PTZ-induced seizures. Previous research suggests that resveratrol may lower the frequency of seizures in rats produced by PTZ dosage dependently (Gupta et al., 2002a). Researchers discovered that RESV had a protective effect against kainic acid-induced convulsions, as seen by lower convulsion frequency and enhanced CA1 and CA3 neuron function inside the hippocampus (Gupta et al., 2002b, Wu et al., 2009). Because of this, the results of this study confirm previous findings about the neuroprotective properties of RESV in epilepsy. To evaluate the efficacy of drugs on generalised tonic-clonic and partial seizures, the ICES test is widely used, while the PTZ-induced seizure model is well-known for testing drugs against absence seizures (Rathor et al., 2014; Sehar et al., 2015). The observed" effects of RESV on the ICES and PTZ-induced seizure models indicate that it could suppress both generalised and absence seizures. valproic acid and lamotrigine are two therapeutically authorised medications widely used in generalised and absence seizures, respectively (Mikati and Holmes, 1997).

Research Objective & Methodology

To study the effects of different dosages of embelin and resveratrol on epilepsy models, cognition, and mouse behaviour.

Chemicals

Cayman "Chemical Co. in the United States provided the trans-resveratrol. Sigma Aldrich in St. Louis, Missouri, USA provided Embelin, PTZ, the Griess" Reagent System, and other chemicals.

Animals

We utilized "healthy Swiss albino male mice (N=120), weighing between 20 and 35 g. Six to eight mice were housed in a propylene cage with husk bedding, and the atmosphere was strictly regulated (temperature: 22 2 8°C, humidity: 50–55 percent, natural light and dark cycle) to ensure the safety of the animals. We utilised polypropylene cages (43cm x 28.6 cm x 15.5 cm) and provided unrestricted access to pellet feed and water. A minimum of one hour before the trials began, animals were brought into the laboratory for acclimation. All studies were carried out between the hours of 9:00 a.m. and 5:00 p.m., during the day's light" phase.

Drug administration Protocol

Embelin and "resveratrol were weighed and dissolved in double-distilled water with 1% carboxy methyl cellulose (CMC). Water was used to dissolve the PTZ compound. The animals in the control group were given a daily oral dose of a 1% CMC suspension in double-distilled water. Prior investigations used EMB and RESV dosages of 5, 10, and 20 mg/kg iv and p.o./day, respectively, in an acute trial. EMB was given for five days while RESV was given for seven days (Saha and Chakrabarti, 2014, Mahendran et al., 2011). Until embelin and resveratrol developed kindling in the chronic" research (PTZ-kindling experiment), the same dosages were utilised for both compounds. All medications were administered at a rate of 10 ml/kg.

Experimental design Acute study

The acute effects of "EMB and RESV on seizure and cognition were studied in mice split into six groups, with six animals in each group. As a control, one group received EMB dosages of 5, 10, and 20 mg/kg p.o., while the other groups received RESV doses of 10, 20, and 40 mg/kg p.o., at varying concentrations. A phenytoin 25mg/kg/day positive control group was also included in the ICES trial. All tests were carried" out one hour following the injection of EMB/RESV on the seventh day of dosing.

Increasing current electroshock (ICES) test

EMB and RESV "were evaluated for their effect on seizures using the ICES test, which was previously developed. Each mouse received a linearly escalating dose of 2 mA/2 sec of electric shock starting at a current of 2 mA through ear electrodes in a single train of pulses lasting 0.2 seconds. The seizure threshold current was found to be the current at which tonic hind limb extension (HLE) occurred. We discontinued electric shocks early if we did not see tonic HLE up to a current of 30 mA, and this cut-off current was employed" in the analysis.

EMB and RESV were tested to see how they affected memory. The shock-free zone was created by placing "an inverted petridish in the centre of a grid floor of a continuous avoidance device (SFZ). A 20-volt electric shock was administered to mice when they were on the petridish (SFZ) as they stepped down from the petridish (SFZ). A petridish (SFZ) was used to train animals to stay on it for 60 seconds. After the training session, the step-down delay was measured in seconds and referred to as the acquisition latency. After a 24-hour break, the animals were tested once more, this time without the use of electric shock. Retention latency is the measurement of the time it takes the mouse to step down. a time limit of 600 seconds was set for the animal that didn't get up within that time (Agarwal et al., 2011). The same experiment was performed on kindling mice to see if RESV/embelin had" any long-term effects on them.

Animals treated "with EMB and RESV underwent this test to see if they showed any signs of depression. The animals were put through two trials in which they had to swim up to 15 cm in a cylinder filled with water (25° C) that was 40 cm high and 18 cm in diameter. The first trial was followed by a 24-hour break before the second. One experiment lasted 15 minutes, whereas the other barely took 5 minutes. During the

second experiment, the total time spent immobile was recorded (Porsolt et al., 1978). In addition, the kindling" experiment was repeated with the same results.

Data Analysis & Findings

The seizure "threshold was raised by EMB at dosages of 5, 10, and 20 mg/kg (STC). EMB 10 (p 0.05) and EMB 20 (p 0.01) groups showed a dose-dependent increase in STC compared to control. A significant seizure threshold current was observed when phenytoin (PHT - 25mg/kg) served as a positive control (p0.01), compared to the control group, and was non-significant when compared to EMB 10mg/kg and EMB 20 mg/kg, indicating complete protection from hind limb extension (HLE) of EMB 10 mg/kg and 20 mg/kg groups against PHT (Table 6). Animals in the EMB 5 mg/kg group outlived those in the control group by 66.66 percent. However, in the ICES test, EMB at dosages of 10" and 20 mg/kg, as well as phenytoin treatments, provided 100 percent protection against death.

The delay to "myoclonic jerks and generalised seizures in the diazepam-treated group vs the control was highly significant in the PTZ-induced seizure trial. The delay for myoclonic jerks and generalised seizures was not increased by EMB at any of the three dosages compared to control and diazepam. There are 7 tables in all. In the PTZ-induced seizure trial, the death rate was 33.33 percent in the control group and 50 percent in the EMB 5 and 10 mg/kg groups. Diazepam, the positive control, and EMB, at a dosage" of 20 mg/kg (66.66%), provided 100 percent protection from death in the trial.

The "vehicle+PTZ group had an increase in convulsive behaviour resulting to a Racine score of up to 4 on generalised tonic-clonic seizures after receiving repeated sub-convulsant doses of PTZ (25 mg/kg) every other day for five weeks" (i.e. 35 days, 18 injections).

As compared to the vehicle +PTZ-treated group, EMB administration at dosages of 10 and 20 mg/kg substantially and dose-dependently reduced the onset of PTZ-induced kindling (P0.05 and P0.01, respectively.

Conclusion

PTZ-induced "kindling experiments showed that lipid peroxidation increased in the vehicle +PTZ treated group after PTZ treatment and glutathione peroxidation increased as well as NO generation and GSH levels decreased. These results are consistent with earlier research. A reduction in lipid peroxidation, increased glutathione peroxidation, and decreased NO generation were all linked to embelin and resveratrol therapy in the ignited animals. As a result, embelin and resveratrol appear to be able to counteract the ignited animals' increased lipid peroxidation, glutathione peroxidation, NO generation, and reduced GSH levels. In a rat model of sporadic dementia caused by intracerebroventricular streptozotocin, chronic treatment of embelin dose-dependently reduced MDA and nitrite levels and restored levels of the antioxidant enzyme glutathione (Arora and Deshmukh, 2017). Using an Ischemia-Induced Brain Damage model in rats, embelin therapy decreased lipid peroxidation and enhanced total thiol content and glutathione-S-transferase activity in brain homogenates (Thippeswamy et al., 2011). It follows that embelin may have antioxidant effects" in kindling, as shown by the data of this study.

When seizures were "induced after administration of PTZ, prototypic inflammatory cytokines such as IL-1, IL-6 and TNF-—were upregulated, as evident in the vehicle + PTZ treated group in our study, and a cascade of downstream inflammatory events like production of IL1-Ra in significant amounts in response to IL-1 production may have begun to inhib. Now, if we hypothesise the mechanism from seizure generation to seizure It's possible that glutamate was reabsorbable and elevated in the brain because of PTZ-induced kindling and inflammatory indicators. GABA and dopamine levels would also be low as a result. These occurrences would have triggered an increase in glutamatergic neurotransmission, as well as free radical

production in neuronal cells. As a result, the burden of oxidative stress may have increased, as evidenced by higher MDA levels, increased GPx activity, lower GSH levels, and higher nitrite content. As shown in the current study, increased levels of inflammatory mediators such as IL-6, IL-1, IL-1Ra, and TNF-, as well as an increase" in oxidative stress, were found in the vehicle + PTZ treated animals. These findings suggest that increased levels of glutamate and decreased levels of GABA and dopamine were the result of these inflammatory events. "EMB and RESV therapy may have reduced inflammation in this study since the levels of IL-6, IL-1, IL-1Ra, and TNF- in the EMB and RESV treated rats were considerably lower. It is possible that the decreased amounts of inflammatory mediators contributed to the GABA and glutamate neruochemical imbalance. However, this may not be" enough to induce persistent kindling and oxidative stress.

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