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NEUROPROTECTIVE PROPERITY OF *CENTELLA ASIATICA* AGAINST PENTYLENE-TETRAZOLE INDUCED EPILEPSY IN RAT BRAIN WITH PARTICULAR REFERENCE TO LIPID METABOLISM

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ABSTRACT: This study evaluated the anticonvulsant effect of different extracts of *Centella asiatica* (CA) with particular reference to lipid metabolism in different regions of rat brain. The rats were randomly divided into 4 groups having 6 in each group: *i.e.* Control group received saline, PTZ-induced epileptic group (60mg/kg b.w op/ 1 day), epileptic group pretreated with chloroform extract (CE), epileptic group pretreated with aqueous (AE) extract and epileptic group pretreated with diazepam (DP; Reference control) (2 mg/kg b.w/ip/ day). The CA extract is administered at the dose of 200 mg/kg body weight orally for one week. The experimental results were observed that the decreased content of phospholipids in the entire brain regions *i.e.* Cerebral cortex (CC), Cerebellum (CB), Hippocampus (HC) and Pons medulla (PM); total cholesterol, triglycerides and increased content of Lipid peroxidation in epileptic rats. The reversal changes were observed on pre-treatment with the chloroform extract of CA and diazepam. Hence, it is evident that the different bioactive factors of CA offered protection against PTZ-induced epilepsy.

INTRODUCTION: Cholesterol is an essential component for neuronal physiology not only during development stage but also in the adult life. Cholesterol metabolism in brain is independent from that in peripheral tissues due to blood-brain barrier [1]. Lipids serve several functions in the biological systems such as structural components of the membranes, storage and transport forms of metabolic fuel, protective coating on the surface concerned in cell recognition, species specificity and tissue immunity [2]. Epilepsy is a sudden surge electrical activity in the brain [3]. It is well known that the epileptic seizures result from excessive discharge in a population of hyper excitable neurons.

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Despite the multiple molecular mechanisms have been proposed in generating and spreading epileptic discharges, it has been well established that impaired GABAergic activity exaggerated glutamatergic neurotransmission primarily contribute to the various types of epilepsies [4]. Glutamate is required for normal brain function; the presence of excessive amounts of glutamate can lead to excitotoxic cell death [5].

Through the inhibition of inhibitory neurotransmitter (GABA), the resting membrane potential can be regulated and thus can reduce the probability of glutamate excitation [6]. Hopefully new antiepileptic drugs act on different neurotransmitter receptors or ion-channels will result in improved control of seizures and drugs that are active on ion-channels have greater potential in restoring the function of epileptic neurons to normalcy [7]. CA showed decrement in seizure score, improvement in learning deficits induced by PTZ and increased latencies in passive avoidance behavior [8].

It showed protection against electroshock induced convulsions, pentylenetetrazole and strychnine induced chemo convulsions [9]. It also showed a reduction in lipid peroxidation, spontaneous motor activity, potentiation in diazepam withdrawal-induced hyperactivity, hypothermia and potentiation of pentobarbitone sleeping time [10]. However, there are also anecdotal observations that multiple antiepileptic drugs regimens employed in ameliorating seizers generally met with partial success and suffer from substantial problems such as neurological disorders.

During the past few years, considerable progress has been made towards identifying active factors from indigenous medicinal plants for different human ailments including neurodegenerative disorders such as Alzheimer's disease, parkinsonism, epilepsy etc. *Centella asiatica* considerably increased the seizure threshold and reversed the neuro chemical abnormalities occurred in cholinergic system, monoamine neurotransmitter system and metabolism of glutamate and energy during PTZ- induced epilepsy. Keeping in view of this the present investigation is aimed at studying the modulations of lipid metabolism during PTZ-induced epilepsy and antiepileptic treatment with *Centella asiatica*.

MATERIALS AND METHODS:

Procurement and Maintenance of Experimental Animals: Male adult wistar rats weighing 150 ± 25 grams were used as the experimental animals in the present investigation. The rats were purchased from the Indian Institute of Science (IISc), Bangalore, maintained in the animal house of the department in polypropylene cages under laboratory conditions of 28 ± 2 ^{0}C temperatures with photoperiod of 12 hours light and 12 hours dark and 75 % relative humidity. The rats were fed with standard pellet diet (Hindustan Lever Ltd., Mumbai) and water *ad libitum*.

Ethical Guidelines: The rats were maintained according to the ethical guidelines for animal protection and welfare bearing the CPCSEA 438/01/A/CPCSEA/dt:17.07.2006 in its resolution No:09/(i)/a/ CPCSCA/ IAEC/ SVU/ WR/KSP/Dt. 04.03.2006.

Selection of Drug: Pentylenetetrazole (PTZ), an anticonvulsant drug, was selected for the present study. It was obtained as commercial grade chemical from Sigma chemicals, USA.

Collection of the Plant Material: *Centella asiatica* (CA) plant was collected from Tirumala hills and indentified by a botanist, Department of Botany, S.V. University, Tirupati. A voucher specimen was deposited in the herbarium of the Department of Botany, S. V. University, Tirupati (Voucher no. 1688).

Preparation of Plant Extracts: The active principles of the leaves of plant were extracted into Chloroform, since this solvent was predominantly used by several investigators for extracting anticonvulsant principle(s) from various plants [11, 12]. Powdered plant material was soaked in methanol for 2 days at room temperature and the solvent was filtered. This was repeated 3-4 times until the extract gave no coloration. The extract was distilled and concentrated under reduced pressure in the Buchi rotovapour R-114 yielding a gum-like residue, which was then suspended in water and extracted with chloroform.

Induction of Epilepsy: Convulsions were induced by an intraperitoneal (i.p.) injection of Pentylenetetrazole (60 mg/Kg body weight) in saline [13, 14].

Administration of Test Substance: Each fraction of CA extract (200 mg/Kg body weight) was dissolved in saline and given to the animals for one week prior to the injection of PTZ [15]. A gavage tube was used to deliver the substance by the oral route, which is the clinically expected route of administration of CA [14]. The volume of administration was kept at 1 ml/kg/ animal. Diazepam, an anticonvulsant drug, was dissolved in normal saline and given intraperitoneally (2 mg/Kg bw i.p.) for one week to the experimental animals (Reference control).

Drugs, Chemicals and Apparatus: All chemicals used in the present study were Analar grade (AR) and obtained from the following scientific companies: Sigma, Fisher (Pittsburg, PA, USA), Merck (Mumbai, India), Ranbaxy (New Delhi, India), Qualigens (Mumbai, India). Pentylenetetrazole and diazepam were obtained from Sigma Aldrich (St. Louis, MO, USA). In the present investigation Barnstead Thermoline water purification plant for nanopure water, Kubota KR

centrifuge and Hitachi U-2000 Spectrophotometer and other standard equipments were used for biochemical analyses.

Isolation of Tissues: The animals were sacrificed by cervical dislocation and different brain regions such as Cerebral Cortex (CC), Cerebellum (CB), Pons Medulla (PM) and Hippocampus (HC) were isolated, frozen in liquid nitrogen and were stored at -80 ^{0}C.

Experimental Design for Screening of Plant Extracts for Anticonvulsant Activity: The rats were randomly divided into 4 groups having 6 in each group: *i.e*. Control group received Saline, PTZ-induced epileptic group (60 mg/kg b.w./ i.p/ 1 day), Epileptic group pretreated with chloroform extract (CE) and epileptic group pretreated with Diazepam (DP; Reference control) (2 mg/kg b.w/i.p). The chloroform extract was administered at the dose of 200 mg/kg body weight orally for one week.

Biochemical Analysis: Phospholipids were estimated by the method of Zilversmidth and Davis [16]. The total cholesterol and triglycerides contents were estimated by the method of Natelson [17]. MDA levels were estimated by Ohkawa *et al*., [18].

Statistical Treatment of Data: All assays were carried out with six separate replicates from each group. The mean, standard error (SE) and Analysis of variance (ANOVA) were done using SPSS statistical software (11.5 ver.) for different parameters. Difference between control and experimental assays were considered as significant at $P<0.05$.

RESULTS:

Phospholipids: The phospholipids content was decreased significantly in all the brain regions in induced epileptic rats (PTZ), with highest decrease noted in the hippocampus (HC). Pretreatment with CA extract *i.e*. CE and diazepam (Reference control) were resulted in significantly increased phospholipids content in all the brain regions and highest increment is noted in HC (**Table 1**).

Total Cholesterol: When compared with saline control, PTZ-induced animals had significantly decreased the total cholesterol in all the brain regions, with highest decrease noted in the hippocampus (HC). Pre-treatment with CA extract *i.e*. CE and diazepam (Reference control) were resulted in significantly increased total cholesterol content in all the brain regions. (**Table 2**)

Triglycerides: The Triglycerides content was decreased significantly in all the brain regions in induced epileptic rats (PTZ), with highest decrease noted in the hippocampus (HC). Pre-treatment with CA extract *i.e*. CE, and were resulted in significantly increased Triglycerides content in all the brain regions and highest increment was noted in HC (**Table 3**).

Lipid Peroxidation: The malondialdehyde content was significantly increased in all the areas of brain during PTZ- induced epilepsy, the highest elevation was noted in hippocampus (HC). Meanwhile pre-treatment with the extract of CA, showed significant decrease malondialdehyde content in all the brain regions, the highest decrement was noted in HC (**Table 4**).

TABLE 1: CHANGES IN THE PHOSPHOLIPIDS CONTENT IN DIFFERENT REGIONS OF RAT BRAIN DURING PTZ- INDUCED EPILEPSY AND PRE-TREATMENT WITH DIFFERENT EXTRACTS OF *CENTELLA ASIATICA*

Brain Region	SC	PTZ	PTZ+CE	DP+PTZ
CC	48.398	30.256*	68.983*	71.471*
	±0.198	±1.016	±0.264	±0.657
		(-37.48)	(42.53)	(47.67)
CB	29.87	17.921*	40.348*	42.928*
	±0.358	±0.845	±0.385	±0.833
		(-40.00)	(35.07)	(43.71)
HC	18.057	10.360*	26.519*	26.975*
	±0.123	±0.818	±0.821	±1.187
	(-42.62)	(46.86)	(49.38)	(-42.62)
PM	21.281	13.056*	28.283*	30.820*
	±0.227	±0.720	±0.808	±0.511
		(-38.65)	(32.90)	(44.82)

All the values are mean, ± SEM of six individual observations. Values in '( )'parentheses are % change over saline control. *Values are significant at $P < 0.05$ in Scheffe test. (Values are expressed in mg of phospholipids/g wet wt of the tissue)

TABLE 2: CHANGES IN THE TOTAL CHOLESTEROL CONTENT IN DIFFERENT REGIONS OF RAT BRAIN DURING PTZ-INDUCED EPILEPSY AND PRE-TREATMENT WITH DIFFERENT EXTRACTS OF *CENTELLA ASIATICA*

Brain Region	SC	PTZ	PTZ+CE	DP+PTZ
CC	42.775	31.383*	60.994*	63.348*
	±0.456	±0.849	±0.507	±0.668
		(-26.63)	(42.59)	(48.09)
CB	80.271	42.425*	106.655*	116.196*
	±0.292	±0.942	±0.475	±0.551
		(-47.14)	(32.86)	(44.75)
HC	60.039	30.018*	93.453*	95.344*
	±0.719	±0.647	±0.617	±0.596
		(-50.00)	(55.65)	(58.80)
PM	97.279	60.815*	148.383*	143.658*
	±0.397	±0.616	±0.832	±0.933
		(-37.48)	(52.53)	(47.67)

All the values are mean, ± SEM of six individual observations. Values in '( )'parentheses are % change over saline control. *Values are significant at P < 0.05 in Scheffe test. (Values are expressed in mg of phospholipids/g wet wt of the tissue)

TABLE 3: CHANGES IN THE TRIGLYCERIDES CONTENT IN DIFFERENT REGIONS OF RAT BRAIN DURING PTZ- INDUCED EPILEPSY AND PRE-TREATMENT WITH DIFFERENT EXTRACTS OF *CENTELLA ASIATICA*

Brain Region	SC	PTZ	PTZ+CE	DP+PTZ
CC	0.396	0.292*	0.467	0.523*
	±0.021	±0.021	±0.022	±0.031
		(-26.26)	(17.99)	(31.95)
CB	0.555	0.389*	0.745*	0.744*
	±0.015	±0.011	±0.029	±0.017
		(-29.94)	(34.25)	(34.04)
HC	0.901	0.563*	1.257*	1.330*
	±0.023	±0.013	±0.012	±0.032
		(-37.51)	(39.56)	(47.64)
PM	0.458	0.316*	0.569	0.622*
	±0.014	±0.033	±0.008	±0.025
		(-30.90)	(24.23)	(35.85)

All the values are mean, ± SEM of six individual observations. Values in '( )'parentheses are % change over saline control. *Values are significant at P < 0.05 in Scheffe test. (Values are expressed in mg of triglycerides / g wet wt of the tissue)

TABLE 4: CHANGES IN THE LIPID PEROXIDATION CONTENT IN DIFFERENT REGIONS OF RAT BRAIN DURING PTZ-INDUCED EPILEPSY AND PRE-TREATMENT WITH DIFFERENT EXTRACTS OF *CENTELLA ASIATICA*

Brain Region	SC	PTZ	PTZ+CE	DP+PTZ
CC	29.866	40.566*	19.756**	17.356*
	±1.877	±1.252	±0.935	±1.077
		(35.82)	(-33.85)	(-41.88)
CB	62.794	84.221*	37.535*	33.320*
	±2.021	±1.187	±0.881	±1.477
		(34.12)	(-40.22)	(-46.93)
HC	122.01	180.124*	66.047*	56.399*
	±2.123	±1.474	±1.037	±1.649
		(47.63)	(-45.86)	(-53.77)
PM	96.751	131.165*	67.757*	56.605*
	±6.993	±1.101	±1.456	±1.150
		(35.57)	(-29.96)	(-41.49)

All the values are mean, ± SEM of six individual observations. Values in '( )' parentheses are % change over saline control. *Values are significant at P < 0.05 in Scheffe test. (Values are expressed in µ moles of malondialdehyde formed / gram wet wt of the tissue).

DISCUSSION: The treatment with extracts of *Centella asiatica* and diazepam restored the levels of cholesterol in different regions of brain of epileptic rats. The membrane micro domains are rich in cholesterol; the alterations in cerebral cholesterol in induced epilepsy could alter the cellular signaling pathways which possibly play a pivotal role in the neuro degeneration process [19]. Increase in cholesterol levels were reported in rats fed both CA extract and powder during H_2O_2 induced oxidative stress [20]. The decreased levels of triglycerides in different regions of brain during PTZ-induced epilepsy might be due to enhanced lipolysis through lipase activity. It is well established that glutamate excitotoxicity and oxidative stress contribute to neuronal degeneration in acute conditions such as stroke, epilepsy, trauma, hypoxia and hypoglycemia and chronic neuro-degenerative diseases such as Parkinson's disease, Alzheimer's and Huntington's disease [21].

Since the bioactive factors of CA significantly attenuate the glutamate induced excitation and oxidative stress, it is possible that the CA extract possibly ameliorate the deregulated lipid metabolism in general and cholesterol metabolism in particular, thus protecting the progressive cell damage that occurs in induced epilepsy [22]. Lipid peroxidation is a complex process generating reactive radicals, which is regarded as an etiologic or pathogenic factor in several diseases of central nervous system including epilepsy.

The cell membranes, enriched with polyunsaturated fatty acids (PUFAs), are more prone to free radical mediated lipid peroxidation. Lipid peroxidation of cell membranes causes a loss of the fluid properties of the membrane as well as increase in membrane permeability [23]. Lipid peroxidation products are constantly involved in some of the pathophysiological effects associated with oxidative stress in cell and tissues. Unlike reactive free radicals, aldehydes can produce lipid peroxidation products, which are rather long lived and can therefore diffuse from the site of their origin, reaching and attacking intracellular and extra cellular targets [24]. They disrupt various important structural and protective functions associated with bio-membranes in various *in-vivo* pathologic events and are implicated as a result of this oxidation [25].

The key functions of nerve cells, such as creation and maintenance of transmembrane potential, reception and subsequent transmission of signal, synthesis and regulation of signal transducers, and uptake and secretion of neurotransmitters are highly susceptible to excessive accumulation of endogenous products of lipid peroxidation in neuronal membrane structures.

Hence, lipid peroxidation is regarded as an etiologic or pathological factor in myriad number of neurological disorders such as Parkinson's disease, Downs's syndrome, schizophrenia, epilepsy *etc*. oxidative damage induced by lipid peroxidation has been recognized as key factor for the occurrence of many human diseases [26]. It has been hypothesized that COx enzyme induction leads to an increase in various prostaglandins, particularly PGE2 which facilitates the massive release of glutamate from nerve terminals and astrocytes and subsequently increase the free radical production leading to oxidative stress followed by apoptosis of GABAergic neurons ending in epileptic discharges [27].

Similar increases in MDA, XO and NO levels have also been recorded in the brains of mice treated with PTZ [28]. Liu *et al*., [29] have indicated that the made cassoside, the active constituent of CA, decreased nitric oxide (NO) levels and malanoldehyde (MDA) content in the burn skin tissue. Decreased MDA content and an increase in glutathione and catalase activities have been reported in rats treated with aqueous extract of CA in intra cerebroventricular streptozotocan model of Alzheimer 's disease in rats. Decreased lipid peroxidation and increased enzymatic and non-enzymatic antioxidants have been elucidated by the asiaticoside derived from CA [30].

CONCLUSION: The present findings in conjugation with the earlier reports it is speculated that the bioactive factors of CA has the propensity to a modulate excitotoxic glutamate induced oxidative impairments in the brain and may be efficiently employed as a neuroprotective adjuvant to abrogate the oxidative stress that occur during induced epilepsy. However, further in depth studies are required to understand the physiological mechanism of different bioactive compounds present in the CA extracts and to suggest that the

therapeutic modality of these compounds with particular reference of anticonvulsant and neuroprotective activity.

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