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Protective Effect of Rutin on Cognition Impairment Caused by Levetiracetam.

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KEYWORDS

Rutin, Levetiracetam, Diphenylhydantoin, Acetylcholinesteras, Cognitive functioning.

ABSTRACT:

Objective: To investigate how levetiracetam and rutin, as opposed to levetiracetam and piracetam, affects mice's ability to control their seizures and their cognitive and motor abilities.

Materials and Methods: Utilizing the increasing current electroshock seizure (ICES) test, levetiracetam and piracetam's combined effect on convulsions was assessed. While motor capabilities were screened utilizing a rolling roller equipment and counting the number of arm entries on a plus maze, cognitive functions in mice were evaluated by means of spontaneous alternation in behavior on a plus maze. The Ellman et al. method was used to quantify the activity of brain acetylcholinesterase (AChE).

Results: The research demonstrated that rutin, when given in addition to levetiracetam, dramatically reversed the drug's lowering of spontaneous alternation without affecting levetiracetam's effectiveness against In both short-term and long-term research, ICES. Moreover, it undid the rise in AChE activity brought on by levetiracetam.

Conclusion: In summary, rutin mitigated the cognitive deficit brought on by levetiracetam while maintaining its antiepileptic effectiveness.

INTRODUCTION

Compared to more readily available medications, levetiracetam is a more recent anticonvulsant medication with a number of advantages. It is widely used as an adjuvant therapy for partial, myoclonic, and tonic-clonic seizures as well as a monotherapy treatment for epilepsy in the event of partial seizures[1]. Along with its many potential uses, the medication is well-known for treating a number of neurologic and psychiatric disorders, including Alzheimer's disease, autism, bipolar disorder, anxiety disorders, and Tourette syndrome[2–3]. Nonetheless, the drug's most detrimental side effects are the behavioral deficits it causes [3]. Complete seizure control without interfering with cognitive functions is commendable for effective convulsion treatment. For efficient treatment for convulsions it is praiseworthy to have complete seizure control without interrupting any cognitive effects. To obtain a nominal or nonexistent memory deficit with AED therapy, it may be advantageous to combine adjuvant nootropic compound use with antiepileptic medication therapy. It is imperative to choose a better strategy that addresses the mental instability while also providing seizure prevention. One of the well-known nootropics, piracetam (PIM) (2-oxo-1-pyrolidone acetamide), is particularly well-known for its antimyoclonic (4-6) and particular antiamnesic (in numerous experimental examples) (7-9) properties. Additionally, it has been demonstrated to have a protective effect against learning deficit and kindling-induced neuronal death caused by pentylenetetrazol (PTZ) (10,12). However, in the MES model, it does not exhibit anticonvulsant action (7). Nonetheless, significant neuroprotection has been observed in experiments (11, 12). Thus, it was discovered through a variety of experimental techniques that PIM is a potent nootropic drug. To obtain a nominal or nonexistent memory deficit with AED therapy, it may be advantageous to combine adjuvant nootropic

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MATERIAL AND METHODS

Animals

The 24-34-g Swiss albino mice were kept in cages in groups of ten at a temperature between 23 and 300 degrees Celsius, with a natural light-dark cycle. They have free access to tap water and a conventional pellet diet. The CPCSEA Ethics Committee has accepted the study (project no. 164, Nov. 2023). Strict adherence to ethical guidelines was maintained throughout the entire experiment process.

Drugs and dosing schedules

Two hours before each observation, injections of levetiracetam, which is branded as "Levroxa," at doses of 8, 12, and 22 mg/kg body weight in a volume of 10 ml/kg body weight were administered intravenously (26). Piracetam, the nootropic standard, or "Nootropic" syrup, was administered orally in doses of 125, 250, and 500 mg/kg body weight in a volume of 10 ml/kg body weight. The same protocol was followed every time, starting one hour before the experiment. A volume of 10 ml/kg body weight of distilled water was administered to the control groups. For 21 days, chronic studies were conducted. Following two hours of Levetiracetam and one hour of Piracetam administration, all observations were completed on day 21. In long-term research, medication was given between 10 and 12 A.M. (26).

Increasing Current Electroshock Seizures (ICES)

The Kitano et al. (27) modified Marwah et al. (28) approach was utilized to evaluate the anticonvulsant impact of the ICES medicines. Using an electroconvulsometer, a single train of pulses lasting 0.2 seconds was administered to each mouse, starting with a current of 2 mA electroshock via ear electrodes. The intensity of the pulses increased linearly with time, from 2 mA to 2 sec. Seizures threshold current (STC) was defined as the current at which tonic Hind Limb Extension (HLE) appeared. Electroshock was stopped when a current of 30 mA showed no tonic HLE.

Spontaneous Altered Behavior (SAB) on a plus maze

The tendency of animals, including single-celled organisms, to alternate their non-reinforced (Dember & Richman, 1989) choices of T- or Y-maze arms on successive trials, after an initial trial or turn, is known as spontaneous altering behavior (SAB). It is a natural inclination for rats to exhibit alternation. Nootropics modify the behavioral impairment brought on by medications, and vice versa. As a result, improved cognition is indicated by a shift in vacillation and vice versa. Using a plus maze, the Itoh et al. (29) protocol was followed for the assessment of cognitive functions, and Ragozzino et al. (30)'s method was applied for SAB. Potential swap = number of entries for arms –4

Spontaneous alteration behavior (SAB) generally refers to the tendency of animals, even single-celled organisms, to alternate their non-reinforced (Dember & Richman, 1989) choices of T- or Y-maze arms on subsequent trials, following an initial trial or turn. Rodents naturally show the tendency of alternation. Impairment of behavior caused by the drugs is altered by with nootropics and vice versa. Therefore, change in the vacillation shows improved cognition and vice versa. The assessment of cognitive functions was performed using a plus maze following the procedure proposed by Itoh et al (29) and

Journal of Chemical Health Risks

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the method proposed by Ragozzino et al.(30) was used for SAB. The 50-centimeter-tall maze was constructed of wood, painted gray, and included four symmetrical arms (23.5 X 8 cm) with 10-centimeter walls surrounding the central platform (8 X 8 cm). Mice were housed in the middle platform and then permitted to roam freely. For five minutes, each arm's entry sequence and count were noted during the observation period. Alternation was described as entry into four distinct arms on overlapping quintuple sets.A quintuple set is made up of the choices for five arms in a row within the entire set of arm choices; for example, a quintuple set with the possibilities for arms A, B, C, and B was not regarded as an alternation (26).

Using the method described above, the % alternation was computed as follows:

Following the above procedure percentage alternation was calculated as follows:

Percentage alternation = Actual no. of alternation/Possible no. of alternation X 100

Possible alternation = no. of arms entries –4

The number of arm entries was also recorded separately to determine the motor influence on the observed effects.(26)

Rolling roller apparatus

The neurological impairment brought on by the medications was assessed using the methodology described by Dunham et al (31). The animals were placed on the roller, which had a setting of 5 revolutions per minute. The testing period lasted one minute. Under typical circumstances, the animal may counterpoise itself throughout the duration. Therefore, the animal's inability to maintain equilibrium on the roller during the one-minute test period was indicative of a neurological deficiency.

Estimation of brain acetylcholinesterase (AChE) activity

The Ellman et al. approach (32) was followed in order to measure the AChE activity throughout the entire brain.The foundation of this technique is the creation of yellow color due to thiocholine's reaction with dithiobisnitrobenzoate ions.Using a spectrophotometer, the rate at which thiocholine is formed from acetylcholine iodide in the presence of tissue cholinesterase was determined. Following the application of 5, 5'-dithionitrobenzoic acid (DTNB) to the sample, the optical density (OD) of the yellow-colored chemical generated during the reaction was measured at 412 nm every minute for three minutes (26). The Folin method was applied to estimate the amount of protein. The calculation for the AChE activity (26) was done using the following formula.

R = δ O.D X Volume of Assay (3 ml)/ E X mg of protein

Where R= rate of enzyme activity in ‘n’ mole of acetylthiocholine iodide hydrolyzed / minute / mg protein

δ O.D = Change in absorbance / minutes

E = Extinction coefficient = 13600 /M/cm Statistical analysis

The expressionof data was done as mean+SEM. P values <0.05 were considered significant.

RESULTS

Increasing Current Electroshock Seizures (ICES)

In acute tests, Levetracetam demonstrated 100% protection against ICES at a dose of 22 mg/kg, i.v. by completely eliminating HLE. There was no protection observed at considerably lower dosages (8 mg/kg, p.o.), but at a lower dose of 12 mg/kg, i.v., there was 50% protection (Table 1). On ICES, PIM and rutin at doses that improved memory calculated from Table 1 were shown to be ineffective (Table 1).

Spontaneous Alteration Behavior

Acute studies

At a dose of 12–22 mg/kg, intravenous, the cognitive effect was demonstrated by the annihilation of percentage alternation on the plus maze. Levetracetam and PIM didn't show much of a reaction at lower dosages—8 mg/kg and 125 mg/kg, po, respectively—but at higher doses, both of them exhibit promising outcomes (Table 1). Additionally, when the combined effects of PIM (250 mg/kg) and Levetracetam (12 mg/kg, p.o.) were seen, the outcomes were quite comparable to those of the control group, meaning that there was no alteration in any effect on ICES and no confounding effect on memory (Table 1).

Chronic studies

The long-term research revealed the substantial impairment that Levetracetam (12 mg/kg, i.v. X 21 days) caused, which resulted in a decrease in the percentage alternation. However, the combination of PIM (125 mg/kg, PO for 21 days) and Levetracetam (125 mg/kg, PO for 21 days) along with Rutin (125 mg/kg, IV for 21 days) treated the patient's condition and reversed the decline (Table 2).

Rolling roller apparatus:

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In both acute and long-term trials, as well as when used in combination, there was no evidence of a motor deficit at any dosage of Levetracetam, PIM, or Rutin.

Whole brain AChE activity

There was no discernible variation in the total brain AChE activity when Levetracetam (8 mg/kg, p.o.) was compared to the control. However, there was a noticeable acceleration in AChE activity as compared to control when the dose was increased to 12 mg/kg p.o. Neither PIM nor Rutin significantly changed brain AChE activity at lower doses (125 mg/kg, p.o.). However, p.o. considerably reduced AChE levels at a dose of 250 mg/kg. AChE levels were comparable to control when Levetracetam (12 mg/kg, i.v.) was combined with PIM (250 mg/kg, p.o.) and Levetracetam (12 mg/kg, i.v.) with Rutin (250 mg/kg, p.o.) (Table 3).

DISCUSSION

The current investigation shown that levetiracetam (12–22 mg/kg, intravenously) negatively impacted cognitive function in both acute and long-term trials. Despite this, the dosages against ICES were discovered to be ED50 and ED100. These findings corroborated those obtained from PHT and Sod.valproate investigations on cognitive processes (33–39). PIM's antimyoclonic activity (4-6) and nootropic property (7-9) are well-established facts that have produced impressive effects over spontaneous alternation behavior in a variety of investigations. Higher dosages of PIM have demonstrated a strong antiepileptic impact against ICES (26) as well as substantial nootropic effects on the MES model (7). Another well-known flavonoid is rutin, which has nootropic properties (19–25).Therefore, the goal of this investigation was to convince the effect. Thus in this study it was intended to persuade the effect of co administration of PIM and Rutin with a clinically established AED in antiepileptic therapy. In the present study the results showed that when co administration of PIM and Rutin with Levetracetam solemnly confiscated the Levetracetam produced cognitive impairment without interrupting it's the efficacy against ICES. Also in this study, Rutin was found to be pillared for the results as accessed with the combination of PIM. When lower dose of Levetracetam was given no significant data was obtained however enhancement in percentage alternation was witnessed (10, 26). Therefore, the purpose of this study was to demonstrate the benefits of co-administering PIM and rutin with a clinically proven AED in the treatment of epilepsy. The current study's findings demonstrated that co-administration of PIM and Rutin with Levetiracetam solemnly stopped the drug's ability to prevent ICES, but instead caused cognitive impairment. Rutin was also determined to be the study's mainstay for the outcomes when combined with PIM. No significant findings were obtained when a reduced dose of Levetiracetam was administered; however, a notable increase in percentage alternation was seen (10, 26). Using the rolling roller equipment for PIM and Rutin separately and in conjunction with Levetiracetam, no significant motor impacts were found.

Levetiracetam significantly increased "brain AChE activity" in the current investigation, whereas PIM and Rutin caused a decrease in "brain AChE activity," indicating that these medications had cholinergic system-related effects. Levetiracetam's disruption of the cholinergic system and subsequent reduction of brain ACh levels have an impact on memory and learning (2, 16, and 17). Thus, in this situation, our results confirmed a persistent report. It is noteworthy that Levetiracetam does not exhibit any impairment and does not raise aChE levels at lower doses. Rutin is a member of the flavonoid family, and many of its members have different effects on the cholinergic system. PIM is a member of the pyrrolidone's group, the majority of whose members influence the cholinergic system (8,11,24). PIM and rutin decreased the brain's AChE activity in our investigation. The co-administration of Levetiracetam and PIM Rutin appears to have enhanced the Levetiracetam-induced fast rise in total brain AChE level, indicating the opposing action of PIM/Rutin and Levetiracetam on the cholinergic system. This is an intriguing fact to note in this framework. To sum up the investigation, it can be claimed that PIM and Rutin reversed the negative effects on the cholinergic system when used in adjuvant therapy with Levetracetam. Ultimately, however, it is imperative to investigate Rutin's full potential for ameliorating Levetracetam-induced cognitive deficits and determining the appropriate course of action for the ongoing AED therapy.

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EFFECT OF ACUTE LEVETIRACETAM (LEVE), ACUTE PIRACETAM (PIM) AND ITS COMBINATION ON ICES AND SAB IN MICE (TABLE 1)

Group	Treatment	Dose (mg/kg)	ICES		SAB	
			Seizure threshold current(mA)	% protection	% alteration	No. of arm enteries
I	Distilled water	10 mg//kg	16.1 ±0.41	0	71.1±3.14	15±1.51
II	Leve	8	21.4 ± 1.39	0	63.1±2.4	14±1.01
III	Leve	12	29.4 ±2.16	50	53.7±2.8	15±1.10
IV	Leve	22	40 ±0.0	100	44.2±3.9	18±1.02
F 35.1104 df 3 p < 0.01				H 11.07 df 3 p < 0.01		
I(control)	Distilled water	10 ml/kg	15.2 + 0.33	0	79.0+ 6.04	16.2 + 1.75
V	PIM	125	15.8 + 0.85	0	79.3 ± 6.19	20.0 ± 2.860
VI	PIM	250	15.9 + 0.42	0	84.7 ± 6.27	16.8 ± 2.420
VII	PIM	500	16.6 + 1.74	0	86.9 ± 6.91	20.1 ± 1.900
H 8.64 df 3 P < 0.05						
VIII	Rutin	125	15.0±0.16	0	74.2±3.91	19.1±2.40
IX	Rutin	250	15.1±0.45	0	77.1±3.92	20.9±2.76
X	Rutin	500	15.7±0.89	0	80.5±4.07	21.8±2.85
H 7.49 Df 3						

Journal of Chemical Health Risks

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JCHR (2024) 14(1), 2554-2560 | ISSN:2251-6727

				P	<0.05	
III	Leve	12	29.4 ±2.16	50	53.7±2.8	15±1.10
VI	PIM	250	15.3 + 0.42	0	86.1 ± 4.72	16.8 ± 2.40
XI	leve + PIM	12+ 250	31.0± 1.06	50	71.4 ± 6.46	21.6 ± 1.9
XII	leve+ Rutin	12 +250	30.9± 1.02	50	69.4± 4.61	22.6 ± 1.84
			F 39.70		H 8.46	
			Df 3		df 3	
			P < 0.01		p < 0.01	

Values are mean + SEM, Values within parentheses are number of animals, ICES- Increasing current electroshock seizure, SAB-Spontaneous alternation behaviour. Seizure threshold current values were analysed using one-way ANOVA followed by Dunnett's test and alternation values by Kruskal–Wallis H test followed by a multiple range test, *P<0.05, † P<0.01 Vs control, ‡ P< 0.05 Vs Group III

EFFECT OF CHRONIC LEVETIRACETAM (LEVE) AND PIRACETAM (PIM) ON SAB (TABLE 2)

Treatment	Dose	% alternation	No. of arms enteries
Control	10 ml/kg	69.32 ± 4.14 (9)	11.25 ±0.75
LEVE	8	63.1±2.4	14±1.01
LEVE	12	53.7±2.8	15±1.10
PIM	125	76.2 ± 2.19	20.0 ± 2.860
Rutin	125	79.3 ± 2.06	21.7 ±2.09
LEVE+ PIM	12+ 125	80.1 + 3.09	17.9 ± 1.16
LEVE + Rutin	12+125	82.9 ± 3.06	19.9 ± 1.97

Values are mean+SEM, Values within parentheses are number of animals,AChE-whole brain AChE activity. *P<0.05 Vs control (multiple range test)

EFFECT OF ACUTE LEVETIRACETAM LEVE), ACUTE PIRACETAM (PIM) AND ITS COMBINATION ON ACHE ACTIVITY IN MICE (TABLE 3)

Treatment	Dose (mg/kg, p.o.)	AChE
Control (distilled water)		
LEVE	10 ml/kg	107.1 + 6.19
LEVE	8	109.0 + 7.16
PIM	12	187.6 + 11.06*
PIM	125	111.4 + 9.04
LEVE+PIM	250	96.3 + 7.41*
LEVE + Rutin	12+250	121.1 + 5.03
LEVE + leve	12+250	122.8+ 4.86
	H 17.17	
	Df 5	
	P <0.01	

Values are mean+SEM, Values within parentheses are number of animals, AChE-whole brain AChE activity. *P<0.05 Vs control (multiple range test)