Original Article

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Effect of Ursodeoxycholic Acid on Pentylenetetrazole Kindling and Kindling Induced Memory Impairment in Rat

M. Naderi (MD) [1], A. Jand (MD)[2], Y. Jand (MD)[2], T. Rahjoo (MSc)[1], M.R. Palizvan (PhD)[•1]

1.Department of Physiology, Faculty of Medicine, Arak University of Medical Science, Arak, I.R.Iran

2.Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Epilepsy is one of the common diseases of the brain that about 30-40% of patients with epilepsy experience recurent attacks due to drug resistance. Recently, the beneficial effects of Ursodeoxycholic acid on brain disorders have been considered. The aim of this study was to evaluate the effect of Ursodeoxycholic acid(UDCA)on the Pentylenetetrazole (PTZ) induced kindling, and related learning and memory impairments on Morris water maze.

METHODS: This experimental study was done on 32 male Winstar rats divided into 4 groups. The first(n=7)and the second (n=9) groups have received three injections of 0.5 ml NaCl or 50 mg/kg of UDCA respectively and third(n=7) and fourth(n=9) groups have received fifteen injections of 0.5 ml NaCl or 50 mg/kg of UDCA respectively. All injections were given intraperitoneally(ip)(every 48 hours). In all groups, chemical kindling were started after third injections. Twenty-four hour after the last injection, spatial memory was investigated in the Morris water maze.

FINDING: Fifteen injections of UDCA significantly reduced the seizure stage from 3.5±0.17 to 3.08±0.11 and duration of stages five from 12.38±1.2 to 8.61±0.58 and increased time to reach the stage five seizures from 1021.65±72.07 to 1252.41±49.63 as compared to control group. However, three injections of UDCA have no effect on the kindling process. However, three time administration of UDCA significantly increased reference memory from 18.72±1.2 s to 26.11±1.8 s.

CONCLUSION: Ursodeoxycholic acid inhibits chemical kindling and improves kindling induced memory impairment.

KEY WORDS: *Epilepsy, Pentylenetetrazole, Spatial learning, Ursodeoxycholic acid*

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•Corresponding author; M.R. Palizvan (PhD)

Address: Department of Physiology, Faculty of Medicine, Arak University of Medical Science, Basij Square, Sardasht, Arak, I.R.Iran.

Tel: +98 86 34173502

E-mail: dr.palizvan@arakmu.ac.ir

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Introduction

Seizure is a common brain disorder, and about 65 million people worldwide are suffering from the disease. Approximately 30 to 40% of patients have seizure despite using anti-seizure drugs (1-5). Temporal lobe seizure is one of the most common types of seizures in adults. Previous studies have shown that 70% of those who are resistant to anti epilepsy drugs have a pathology in the temporal lobe (6), and among the many pathologies that follow from seizures, the most common is the disappearance of neurons, which impair memory and learning (7). Kindling is a process in which seizures occur in animals with frequent subthreshold stimulation (8). Studies have shown that after kindling in the hippocampus neurons, cell death occurs due to apoptosis (9).

It has also been shown that multiple pathways inducing apoptosis, including increased ROS activity and cytochrome C release, are involved in the kindling pathogenesis (7, 10-14). Cheng et al. showed that taking Edaravone with reduced apoptosis decreases seizure-induced neurological damage and reduces seizure (15). Ursodeoxycholic acid is one of the bile acids that improve the clinical and biochemical parameters of liver disease (16, 17).

Other studies have shown that it plays an important role in altering apoptosis amount in cells (17,18). Several mechanisms have been proposed to reduce apoptosis by bile acids, which include reducing the release of cytochrome C from mitochondria and reducing the apoptosis induced by FAS ligands (19, 20). On the other hand, the protective effects of bile acids have been shown in various brain diseases such as Parkinson's, Alzheimer's, and Huntington's (16, 20-23). Due to the protective role of ursodeoxycholic acid on diseases such as Parkinson & Huntington and the effect of this drug on cell apoptosis, it seems that the drug should have improvement effects on epileptic models and learning impairment caused by them. Therefore, the purpose of this study was to investigate the effect of intraperitoneal injection of ursodeoxycholic acid on chemical kindling and its learning impairment.

Methods

Animals: In this experimental study, 32 male Wistar rats weighing 250-200 grams were used. The mice were kept in an animal house of the school of Medicine with free access to water and food in the conditions of 12 hours of light and 12 hours of darkness at 24 °C. All ethics based on the animal's work ethics approved by the Ethics Committee in Arak University of Medical Sciences with code IR.ARAKMU.REC.453.1395 were observed. The rats were randomly divided into 4 groups. In the first group (n=7), 0.5 ml sodium chloride (NaCl) solution (1.02% with pH equaled 4.8), in the second group (n=9) 50 mg/kg UDCA (Loghman Pharmaceutical Company) soluble in saline (due to not solving UDCA in saline, as in previous studies, a solution of 0.12% NaCl and ph=8.4 was used (24-26) was injected. Intraperitoneal injections included three injections every 48 hours. In the third group (n=7), 0.5 ml of NaCl solution (1.02% with PH equal to 4.8) and in the fourth group (n=9) 50 mg/kg of UDCA in saline solution (1.02% with PH equal to 8.4) was injected 15 times every 48 hours (Fig 1). Due to the possibility of death in UDCA recipient groups, the number of animals at the start of the tests in these groups was 9.

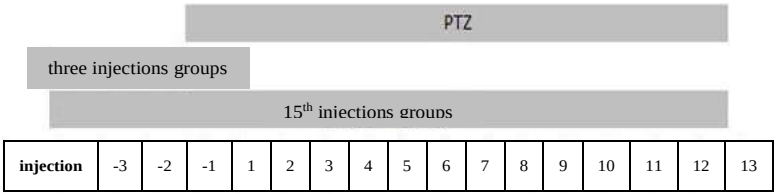

Figure 1. Schematic schema of the test protocol and how to inject drugs. UDCA injection started six days earlier (three injections) from PTZ, and after three injections of UDCA or saline, PTZ injections and the creation of kindling in animals began

Behavioral tests:

Chemical Kindling: Chemical Kindling was started in all groups after three injections. Six hours after UDCA or NaCl injection, pentylenetetrazole (37.5 mg/kg) was injected intraperitoneally (13 injections, every 48 hours) into mice, and then animal behavior were monitored for 20 minutes and their seizure responses to classified the zero stage: no response - stage one: facial and ears muscle contraction - stage two: backward contraction wave - stage three: myoclonic jerks and standing on the legs - stage four: falling to the side - Stage five: falling down and generalized Tonic-clonic seizures. The seizure stage, the time of animal arrival to stage two and five, and the time the animal stayed in the stage five of seizures in the animal was examined (27).

Morris water maze: Morris water maze was used to evaluate the spatial learning. The water maze is made

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up of a black cylindrical water tank with a diameter of 140 cm and a height of 60 cm, filled to a height of 52.5 cm. A removable black platform (30 cm high and 10 cm in diameter) and placed in a certain position from the pool, which was about 5.2 cm below the water. The pool was in a room that signs were mounted outside the maze on the wall. On top of pool, a camera was put (Delux PC Camera, AMCAP) that recorded the movements of the animal during the test.

The whole experiment consisted of four days of training and one test day, and each training day included four times, that animals were put in water at a time interval of 10 minutes. To train, the maze was divided into four equal parts, so around the maze four-point A, B, C, and D were created that each time; rats were put in water from one of these places. These points were randomly selected and each of the four points was used every day.

The mouse had 60 seconds to find the platform. If it found the platform during this time, it was allowed to sit on the platform for 10 seconds, and if during that 60 seconds the animal could not find the platform, it was slowly guided by hand to the platform and then it was allowed to sit on the platform for 10 seconds and then left the pool. On the fifth day, the probe was tested in such a way that the platform was removed from the pool and all animals were released from point B into the pool. Within 60 seconds, the latency and distance traveled in target quadrant (the part where the platform was previously located) were measured (28). Thus, the duration of finding the hidden platform per day as short-term memory or working memory and the duration of the animal's swimming in target quadrant in the probe test was considered as a long-term reference memory. Data is presented as mean±standard error. Student's t-test was used to compare the results of chemical kindling after verifying the normal distribution of data using Kolmogorov-smirnov test, and to compare the results of Morris water maze, analysis of variance with repeated observations was used. Student's t-test was used to evaluate the difference in time and distance traveled in target quadrant on the fifth day (Probe test) and $p<0.05$ was considered significant.

Results

The results of the comparison of the mean weight of the rats in each group showed no significant difference between the groups. Comparison of the results of seizure parameters in two groups of saline control showed that there was not a significant difference between the variable of attack stage, the time to reach the second stage of seizure and the time to reach the fifth stage of stress, but the mean time of stage five of seizure was significantly higher following 15 injections of saline (12.37±1.24 seconds) compared to 3 times saline injections (8.4±1.09 seconds) (p=0.026).

Comparison of cumulative mean of seizure parameters following 3 times UDCA and saline injections showed that there were no significant difference between the two groups in the attack stage variables (p=0.122), the time of arrival to the second stage (p=0.908), the time to reach the fifth stage (p=0.153) and also the time remaining of animal in the fifth stage of seizure (p=0.767) (Table 1).

Table 1. Comparison of seizure parameters following three times injections of UDCA and saline

group Stages	Saline (3 injection) Mean±SEM	Ursodeoxycholic acid (3 injection) Mean±SEM	P-value
Attack stage	3.42±0.28	2.89±0.18	0.122
Time to reach the second stage of seizure	307.88±54.9	315.67±40.38	0.908
Time to reach the stage five seizures	1181.09±71.6	1314.41±55.11	0.153
The time remaining in the fifth stage of seizure	8.43±1.09	8±0.92	0.767

The comparison of the mean attack stage in the two groups showed that the attack stage following UDCA injection was 3.08±0.17, which was significantly lower than saline (3.53±0.11) (p=0.038) (Fig 2). Comparison of cumulative mean of arrival time to the second stage of seizure in groups of 15 times UDCA and saline injections showed no significant difference between them (p=0.396). Comparison of cumulative mean arrival time of animal to fifth stage of seizure following intraperitoneal injection of PTZ in two groups of 15 times injection with t-test showed that the mean time to reach the fifth stage of seizure was 1252.41±63.49 in the UDCA group which was significantly higher than this time (1021.65±72.07 seconds) in the saline recipient group (p=0.014) (Fig3). Comparison of cumulative mean of animal survival

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time in fifth stage of seizure showed that this time in UDCA group (15 injections) (8.61±0.58 seconds) was significantly lower compared to saline (15 injections) (12.37±1.24 seconds) (p=0.012) (Fig 4).

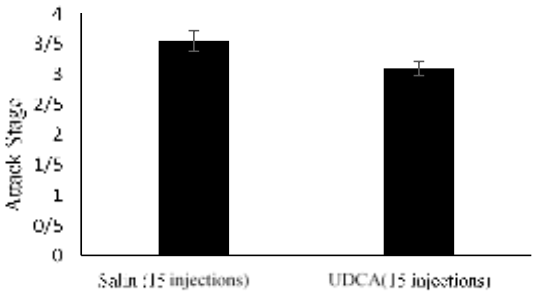

Figure 2. Comparison of the cumulative mean of the attack stage followed by 13 PTZ injections in two groups of UDCA injection (n=9, 15 injections) and saline (n=15, 15 injections) (p=0.038)

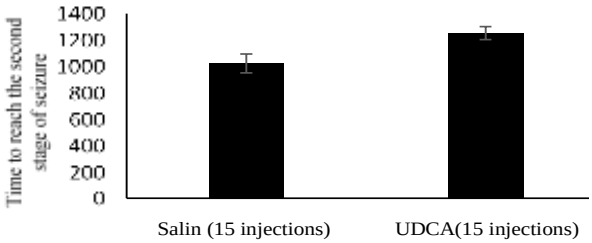

Figure 3. Comparison of cumulative mean of arrival time to fifth stage of seizure following 13 PTZ injections in two groups of UDCA (n=9, 15 injections) and saline (n=15, 15 injections) (* p=0.014)

Comparison of mean time and distance traveled to finding the platform in four days of training showed that in both groups of UDCA (3 injections) and saline (3 injections) time and distance for finding the platform were reduced individually with repeated days of training (p=0.0001 ،F (1.12) =24.11). On the other hand, the comparison of two groups of three injections of saline and UDCA in terms of time (p=0.34, F (1.12)=1.09) and distance (p=0.209, F(1.12)=1.88) for finding the platform showed that there was no significant difference between them.

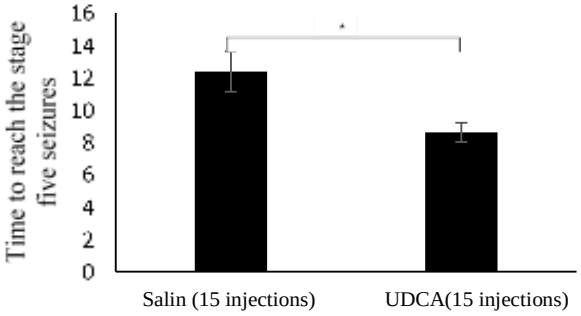

Figure 4. Comparison of cumulative mean time of fifth stage of seizure following 13 PTZ injections in two groups of UDCA (n=9, 15 injections) and saline (n=15, 15 injections) (* p=0.012)

Comparison of the mean time and distance traveled to finding the platform in four days of training showed that in both groups of UDCA (15 injections) and saline (15 injections), the time (p=0.0001, F (1.11)=28.36) and the distance (p=0.0001, F (1.11)=16.92) necessary to find the platform were decreased by repeating the training days. On the other hand, the comparison of time (p=0.735, F=(1.11) =0.1) and distance (p=0.376, F (1.11)=0.85) required to find the platform showed no significant difference between the two groups.

The mean time of presence in the target quadrant in the probe test in the UDCA group (3 injections) was 26.11±1.8 seconds, which was significantly more than that of the saline recipient (3 injections) with a mean time of 18.72±1.2 seconds (p=0.006) (Fig 5). Comparison of the mean time of presence in a target quadrant in the probe test in two groups of UDCA (15 injections) and saline (15 injections) showed that there was no significant difference between them (p=0.583) (Fig 5).

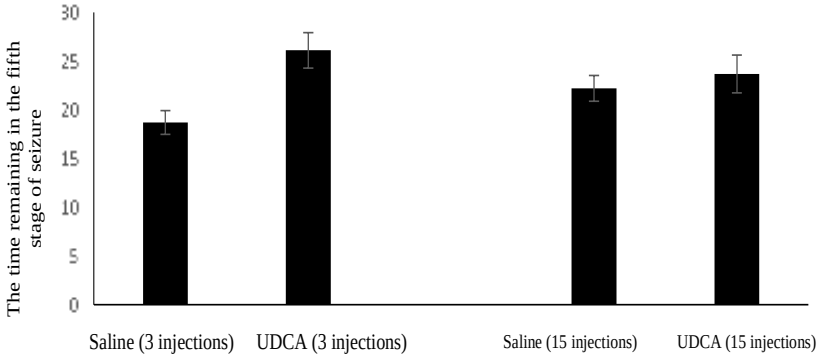

Figure 5. Comparison of the mean of presence time in target qudrant in the probe test in Morris water maze in two groups of UDCA and saline (3 and 15 times injection) followed by 13 PTZ injections (p=0.006)**

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Discussion

The results showed that while three consecutive injections of UDCA did not have an effect on inhibiting the chemical kindling process with pentylenetetrazole, injection of this drug for one month reduced the mean attack time, increased time to reach the fifth stage of seizure, and shortened the time of the fifth stage of seizure. On the other hand, studying the memory and learning of rats by using Morris water maze showed that three UDCA injections had no effect on short-term memory, but significantly increased the reference memory. Analysis of the results of 15 times UDCA injections on learning showed no significant effect on memory and learning.

The first point about the effects of UDCA on brain disorders is the possibility of its passing through the blood brain barrier. Researches have shown that 50 mg/kg UDCA and its conjugate form (TUDCA) from endogenous bile acids can pass through the blood brain barrier (30, 29). Parry et al. also showed that administration of UDCA in a dose-dependent manner increased its level in the blood and cerebrospinal fluid in patients (30).

Along with these results, our research also showed that UDCA intraperitoneal injection inhibits seizure and improves memory in mice resulting from its passage through the blood-brain barrier. Our results also showed that the time of the fifth stage of seizure was significantly higher in saline group (15 injections) than saline (3 injections). Perhaps this is due to the difference in the number of injections. While the first group received three saline injections, the mice in the second group received 15 saline injections.

Therefore, further injections may affect the seizure through stress. Along with these results, previous studies have shown that chronic stress increases seizures in animals (32, 31). Another finding from the study is that injection of UDCA for one month inhibits the kindling process. One of the mechanisms by which pentylenetetrazole can cause seizures is increase of apoptosis in neurons (34, 33, 9).

Previous studies have shown that UDCA prevents the effects of apoptosis induced in neurons by 3-nitropropionic acid. It also reduces mitochondrial dysfunction in the striatum and elimination of neurons by 3-nitropropionic acid (35, 29). In another study, UDCA reduced apoptosis by reducing the risk of ischemic damage in the mouse brain (16). Castro et al. also found that UDCA reduces apoptosis due to excessive glutamate uptake in neurons (36). It seems that the effect of 15 UDCA injections on inhibiting the kindling is due to inhibition of apoptosis in these mice. On the other hand, the results showed that three times UDCA injections did not inhibit kindling. This difference is probably due to the fact that UDCA does not have long-term effects in controlling the seizure phenomenon, however, UDCA can decrease seizure manifestation in the short term. Due to the fact that the group received three injections of UDCA, did not received PTZ, these inhibitory effects were absent. Another possibility is that three times of UDCA injection has not produced sufficient concentration to exert inhibitory effects. In this regard, a study that examined the level of UDCA in the brain following intraperitoneal injection concluded that UDCA levels in the brain following acute and chronic injection were 2 and 6 times, respectively (29).

Study of memory and spatial learning results showed that although none of the UDCA injection protocols had no significant effect on learning, three times UDCA injections improved the memory of animals in the Morris Water maze test. In line with our results, previous studies have shown that UDCA injection does not affect the Alzheimer's model and memory impairment due to hypoxia (37, 38). On the other hand, contrary to our findings, three times UDCA injections resulted in improved reference memory, while 15 times injection did not have any effect on the reference memory.

The previous results showed that 14 UDCA injections improved memory in memory impairment of Alzheimer's model due to hypoxia (37, 38), and learning disorder due to microcystin-leucine-arginin (39). This difference is probably due to differences in memory impairment and learning models. The results of the study showed that chronic UDCA consumption reduces the potential risks for chemical kindling, but its short-term use does not have an effect on the kindling process, but it prevents memory impairment caused by chemical kindling with pentylenetetrazole.

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