Journal of Positive School Psychology http://journalppw.com
2022, Vol. 6, No. 6, 3511-3524

Effects Of Sodium Benzoate On Neuronal Response Of Pyramidal Neuron Of The CA1 Hippocampus In Rat Model Of Parkinson's Disease

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ABSTRACT

Introduction: Thinking and memory problems are among the most worrying potential symptoms of Parkinson's disease (PD). Sodium benzoate (NAB) is one of the compounds that is widely used in food and pharmaceutical industries and has been shown to have beneficial effects on the central nervous system, especially in the treatment of Alzheimer's and Parkinson's disease. The current study aimed at evaluating the effect of NAB on pyramidal neuron response in CA1 region of a rat model of PD.

Methods**:** In this experimental study, adult male Wistar rats were randomly divided into five groups: Substantia nigra pars compacta (SNc) lesion (the lesions were induced by IP injection of Rotenone 2mg/kg/19day/48h) and four groups of NAB (lesions plus 50, 100, 150 and 200 mg/kg ip of NAB). Spontaneous neural activity was recorded for all groups in the CA1 region of the hippocampus.

Results: The obtained results showed that IntraPeritoneal (IP) injection of NAB (100 mg/kg) increased neuronal spontaneous activity in the rat model of PD.

Conclusion: The current study results suggested that acute IP injection of NAB increased neuronal response in CA1 region of hippocampal in a rat model of PD.

Keywords: Electrophysiology, Parkinson's disease, Rats,Rotenone, Sodium benzoate

Introduction

Parkinson's disease, or agitated paralysis, is a common neurodegenerative disease that is more common between the ages of 55 and 65 (16). The main cause of Parkinson's disease is the destruction of dopamine-releasing neurons in the Substantia nigra pars compacta (SNc) in the

brain, resulting in impaired dopamine release (2). Symptoms of Parkinson's disease are divided into two categories: motor and non-motor. Unfortunately, one of the main non-motor symptoms of Parkinson's disease is memory disorders (1).

The hippocampus is known as the main place for memory formation and learning. The first time memory impairment was reported in Parkinson's patients, it was reported that about 50% of Parkinson's patients developed cognitive impairment and 90% developed dementia if the disease progressed (6). Dopamine is involved in many central nervous system functions such as emotion, motor behaviors, cognition and hormonal regulation (21). Dopamine has also been introduced as a potential substrate in synaptic plasticity and learning and memory mechanisms (20). Five subtypes of dopamine receptors are known. Some of them are located in the hippocampus and are involved in memory and learning. The dementia associated with Parkinson's disease has not yet been clearly defined and has been attributed to the pathology of Alzheimer's disease (3).

Due to the fact that during the early stages of Parkinson's disease, the most neuronal damage occurs in the SNc, less memory problems are seen. Due to the fact that outputs from the SNc and VTA regions are sent to the hippocampus, the dopamine secreted from this pathway in the hippocampal region affects memory, especially spatial positioning memory and learning. Decreased dopamine in the hippocampus is associated with decreased neurogenesis, synapsation, and subsequent severe memory impairment, so that the patient has problems in his daily life (15).

Sodium benzoate as the main substance extracted from cinnamon plant and used chemically in many food and pharmaceutical industries, inhibits the expression of Inos, inhibits the activation of glial cells and cytokines by regulating the pathway of mevalonate and activation Becomes RAS. It should be noted that this pathway is very important in causing inflammation and therefore probably effective compounds of cinnamon in preventing inflammation and is considered as a suitable option for intervening in disorders of the nervous system such as Alzheimer's and Parkinson's (11) .

Glial cell activation and pathogenesis-related neuroinflammation are implicated in several neurological disorders, including Parkinson's disease. Studies have shown that NAB is able to inhibit the expression of proinflammatory molecules in the culture medium of astrocytes and migroglia. NAB is mediated to inhibit the expression of NF-KB and nitric oxide synthase (iNOS) by 3-hydroxy-3-methyl coenzyme A malonate as well as farnesyl pyrophosphate in activated astrocytes. This suggests that NAB has anti-inflammatory effects by inhibiting cholesterol biosynthesis (8).

Levy bodies formation is a specific pathological feature of Parkinson's disease and alpha-synuclein accumulation is the main cause of Levy body formation. Although the mechanisms of levy accumulation have not yet been properly investigated, it has been shown that the use of sodium benzoate can somewhat slow down the process of alpha-synuclein accumulation and levy formation and thus play an important role in improving the symptoms of Parkinson's disease (19).

Studies have shown that nitric oxide is a negative regulator of DJ-1 and parkin as the two main proteins involved in Parkinson's disease, and sodium benzoate exerts protective effects on these two proteins by inhibiting nitric oxide (10).

Methods

Study animals

Adult male Wistar albino rats weighing 220±20 g were prepared and all experimental protocols were approved by the Ethics Committee of Shahid Chamran University of Ahvaz (Ahvaz, Iran) and tested according to the NIH guidelines for the care and use of laboratory animals (International Institute for Health Publications No. 23-80; revised in 1978). Mice were exposed to controlled humidity (50 ± 6%) and good light conditions (12 hours light/ dark cycle; light). The room temperature was set at 23±2 °C and food and water were freely available.

Study drugs

In the present study, Rotenone (Sigma Aldridge), which was dissolved in dimethyl sulfoxide (DMSO) and diluted with polyethylene glycol (PEG), as well as sodium benzoate (Sigma Aldrich) dissolved in sterile saline (0.9%) as a vehicle were used. The animals in the control group received saline. The drug was prepared immediately before injection and was administered in a volume of 2 ml/kg.

Experimental procedure

In the present study, single unit extracellular Recording of pyramidal neurons in the hippocampal CA1 region was performed in anesthetized animals. The experiments were performed in a completely quiet room at a normal room temperature of 25 1 1 ° C. A total of 40 male Wistar rats were used in this experiment. There were five groups (n = 8) as follows: 1. Substantia nigra pars compacta (SNc) lesion was lesion by IP rotenone injection of 2mg/kg/19day/48h. 2. lesions + 50 mg/kg of NAB (IP) 3.lesions + 100 mg/kg of NAB (IP). 4.lesions + 150 mg/kg of NAB (IP).5.lesions + 200 mg/kg of NAB (IP) . The recovery period for the lesion group was seven days. After recovery, they were prepared for 120 mins single-unit recording, ie after baseline recording (15 minutes), sodium benzoate or IP saline was injected and recording continued for 105 minutes thereafter. The change in firing activity of the recorded neurons after drug injection was calculated and interpreted as an indicator of the effect of the drug on the electrical properties of the neurons. The experimental design and groups of animals are shown in Figure 1.

Induced Parkinson's disease model

To create Model D, the animals were first anesthetized with ketamine (78 mg/kg, IP, Alfasan, Netherlands) and xylacin (3 mg / kg, IP, Alfasan, Netherlands) and then the SNC was destroyed by rotenone injection. One week after surgery, the animals were prepared for electrophysiological testing and single-unit recording. A histological specimen confirming the degradation of SNC of PD was presented (Figure 2).

Animal preparation and stereotactic surgery

Due to the fact that the use of ketamine for anesthesia blocks NMDA receptors and thus changes electrophysiological records. For this purpose, a substance that does not block brain receptors should be used to anesthetize animals. Urethane is a good material for this purpose. Animals were anesthetized with urethane (1.5 g/kg, IP; Sigma Aldrich, Germany) at supplemental doses (0.1 g/kg) every hour if needed to maintain a deep and stable level of anesthesia, as indicated by immobility. Response to strong tail pinching rats underwent tracheostomy to reduce respiratory impulses and maintain a stable airway waiting to be recorded. For this purpose, the hair on the front of the neck was shaved and an incision was made. The muscles and smooth tissue of the neck were then removed toward the trachea. A slit was made in the trachea and a polyethylene tube was placed in the lower part of the trachea and tightened with sutures. The animal was then gently placed in a stereotactic device (Stoelting, USA).

The animals' skins were cleaned to reveal the surface of the skull, and the Bregma spot was designated as a reference for stereotactics. A hole 2 mm in diameter was created above the CA1 region (AP -3.8 mm, ML ± 2.2 mm, DV -2.4 mm) of the hippocampus. Body temperature was maintained at 36-37 ° C for the entire experiment with a heat pad.

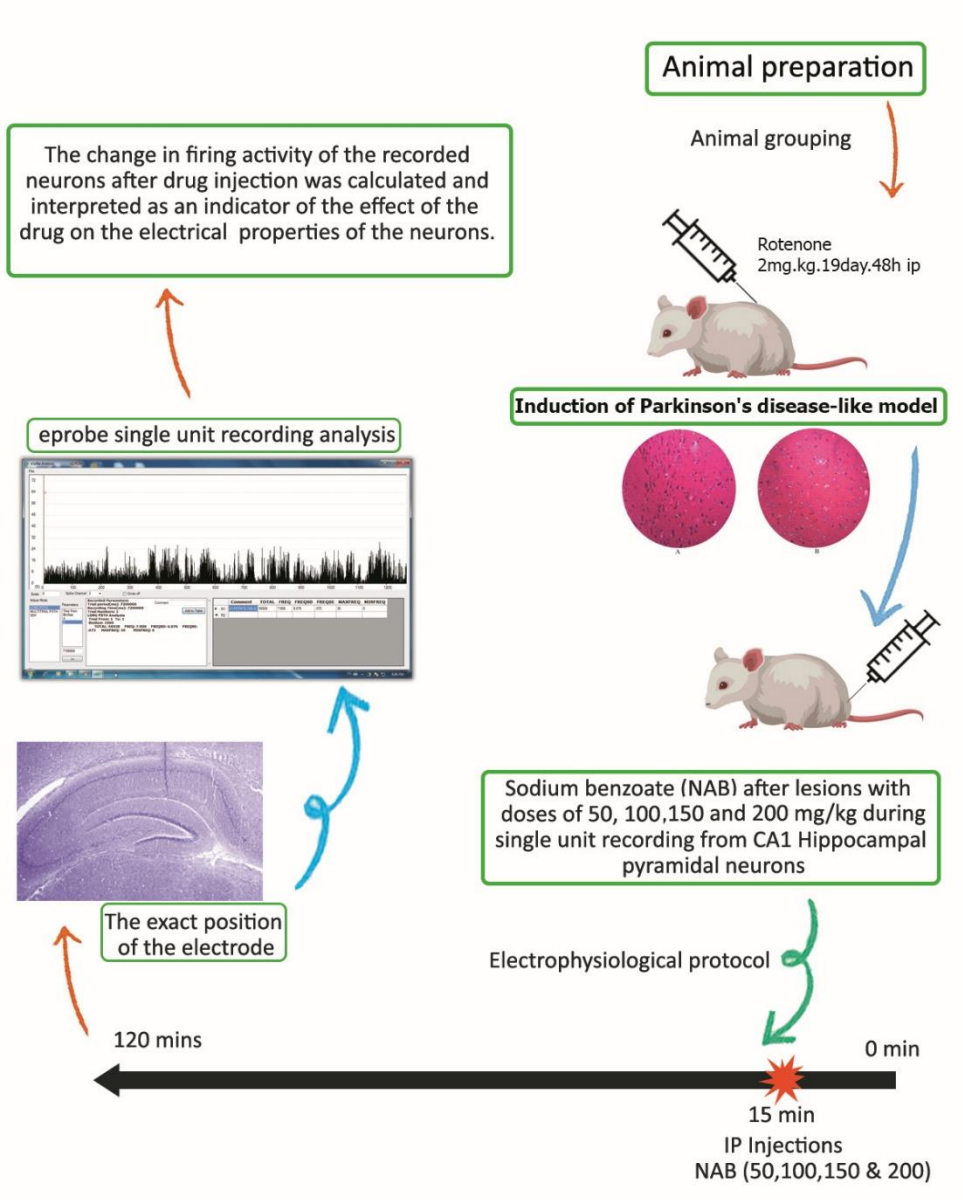

Figure 1. Experimental design.

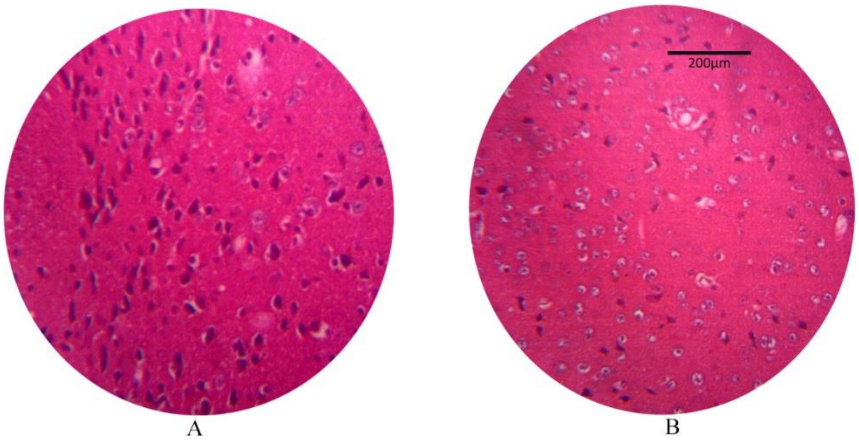

Figure 2. SNC lesions area by rotenone (A. Control, B. Rotenone)

Extracellular single-unit recording and data acquisition

Extracellular recording of individual neurons was performed using tungsten microelectrodes (coated with parylene, shaft diameter 127 μm, tip impedance 5 MΩ, Harvard device). The microelectrode was stereotactically transferred to the CA1 region of the hippocampus. Thereafter the electrode was moved slowly in the layer of pyramidal neurons using a microelectrode driver till a specific spike activity is recorded with a signal-to-noise ratio of >2 separation of the background activity.Spike signals were amplified (×10000 gain; 300 Hz, and 10 kHz for low and high filters, respectively) and displayed continuously on a storage oscilloscope as signals. The spike frequency was calculated and transmitted online in time bins of 1000 ms for the entire recording time by online sorter software (Spike; Science Beam, Tehran, Iran). The action potentials of the baseline activity were separated using a windows discriminator, which produced output pulses for single-units based on the spike height, which calculated the number of spikes per unit time. In this experiment, recording time for data gathering was 7200 s with bin size 1000 ms constantly stored on the hard disk and average frequency was computed by computer (7). According to the results, pyramidal neurons in CA1 region are known based on their spontaneous frequency of 8 or less (7). Recording continued for about 15 minutes due to the identification of a pyramidal neuron with a constant firing frequency and a constant spike amplitude and waveforms as the baseline. After 15 minutes, the drug was injected and the recording continued for about 105 minutes. In the present study, the discharge of each neuron over a 60-second time interval was calculated using a data acquisition program to generate a Peri-Stimulus Time Histograms (PSTHs) with a time interval of 15 minutes before injection to 105 minutes after drug injection. Data were analyzed offline using Windows Home Analysis software. In order to identify patterns of neural response to saline, sodium benzoate 50, 100, 150 and 200 mg/kg were administered, the entire perception period was cut into 60-second time buckets. Increasing or decreasing neuronal activity was considered as twice the standard time deviation from baseline activity for three consecutive points as a stimulatory or inhibitory response.

Histological confirmation

At the end of the electrophysiological recordings, the brains of the animals were removed and fixed in 10% formalin solution. Then, 20 μm sections were removed from near the electrode and the incisions were stained using hematoxylin and eosin (H&E). Finally, a microscope (Japan; Olympus EX51) was used to determine the recording location in the CA1 region of the hippocampus and the results were compared with references (Figure 3).

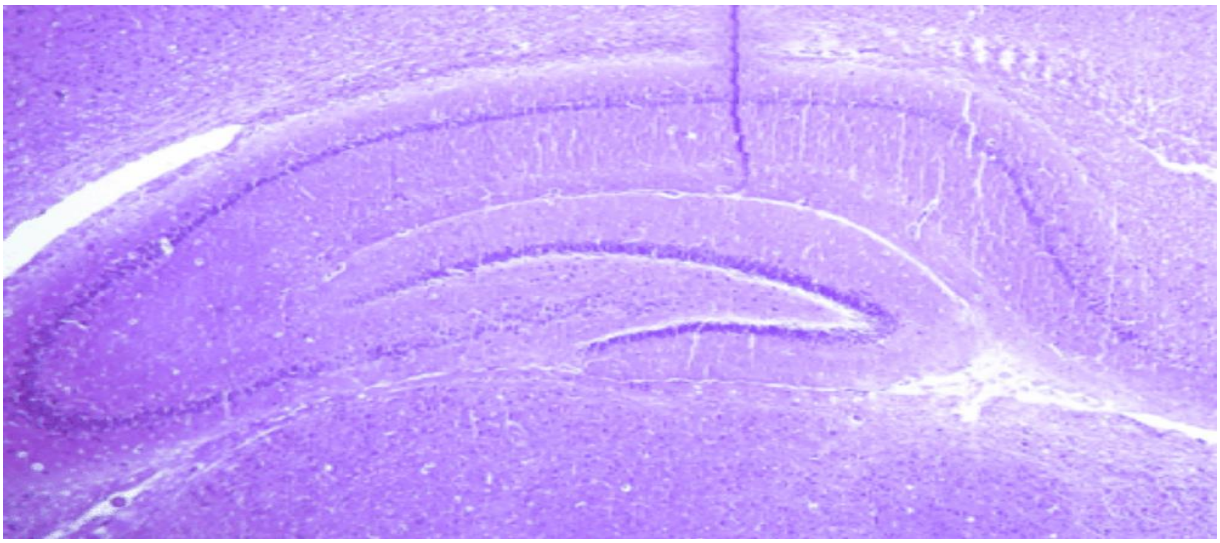

Figure 3. Histological confirmation of the location of the electrode in the CA1 area of the hippocampus

Statistical analysis

Data were recorded before and 105 minutes after IP administration of drugs. The obtained data were analyzed using SPSS software version 20. To evaluate the data, paired t-test was used to evaluate the effect of drug on nerve firing rate before and after drug injection. In addition, Graphpad Prism version 6.07 was used to plot the effect of the drug on the number of stimulatory, inhibitory and ineffective neurons. The data were presented as Mean ± Standard Error of the Mean (SEM). $P<0.05$ was considered statistically significant.

Results

Aiming at the effect of saline on electrical firing of pyramidal neurons in the CA1 hippocampus, 0.2 ml of saline was injected into the IP after basal recording and nerve firing was recorded for 105 minutes. From the obtained results, paired t-test was performed and the stimulatory response of neurons in the lesion group to saline injection did not show a significant increase in the frequency of neurons after injection compared to baseline activity (Figures 4 and 5).

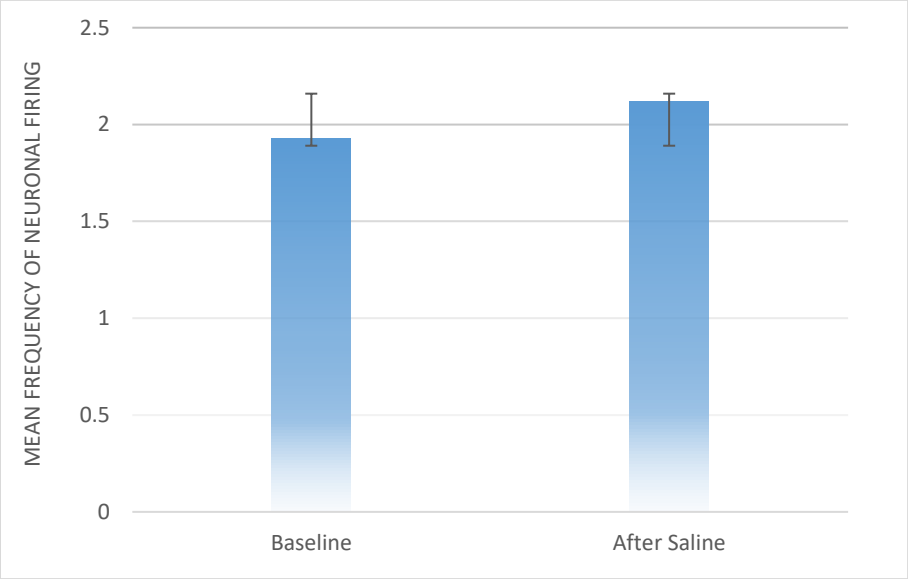

Figure 4. Effects of saline on the mean firing frequency of pyramidal neurons in CA1 region of the hippocampus compared to the baseline (t=-1.03, df=12; P>0.05).

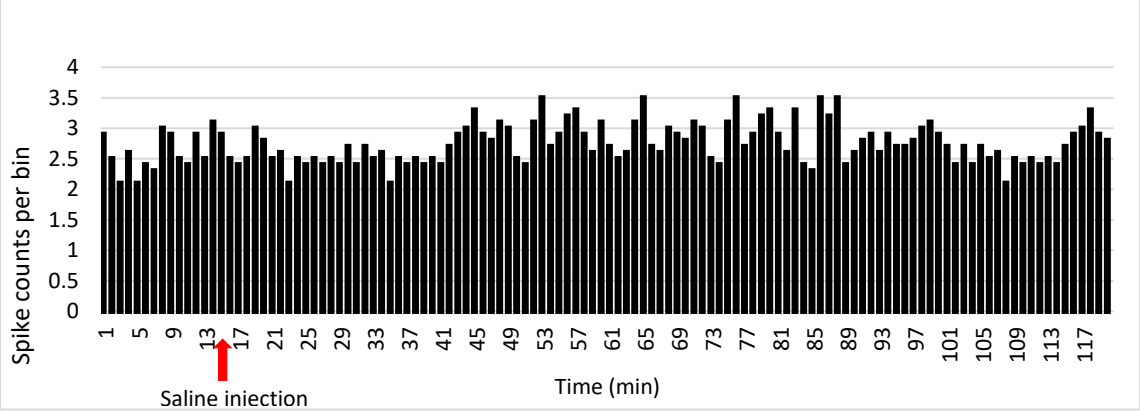

Figure 5. Histogram of electrophysiological recording pattern of spike CA1 neurons in baseline as well as after saline injection

In the present study, 12 neurons were recorded from 8 rats, of which saline was able to stimulate 2 neurons, inhibit 3, and also had no effect o,n 7 of them. Specifically, the effect of saline on neuronal stimulation was 38 to 54 minutes after epispasmodic injection. Also, the mean increase in the activity of pyramidal neurons in the CA1 region of the hippocampus showed that intraperitoneal saline injection was associated with a 20 to 50% increase in activity in 2 neurons and a 50 to 65% decrease in activity in 3 neurons.

The results of injection of sodium benzoate 50 mg/kg after lesion showed that t-test of paired samples did not show a significant increase in the frequency of neurons after injection compared to basal activity (t = -0.826, df = 18; P> 0.05) (Figure 6 & 7). In this group, 14 neurons from 8 rats were recorded and it was observed that sodium benzoate 50 mg/kg had no effect on 7 neurons, inhibited 3 neurons and stimulated 4 neurons (Figure 8). After injection of 50 mg sodium benzoate, stimulation of neuronal firing began within 42 to 58 minutes.

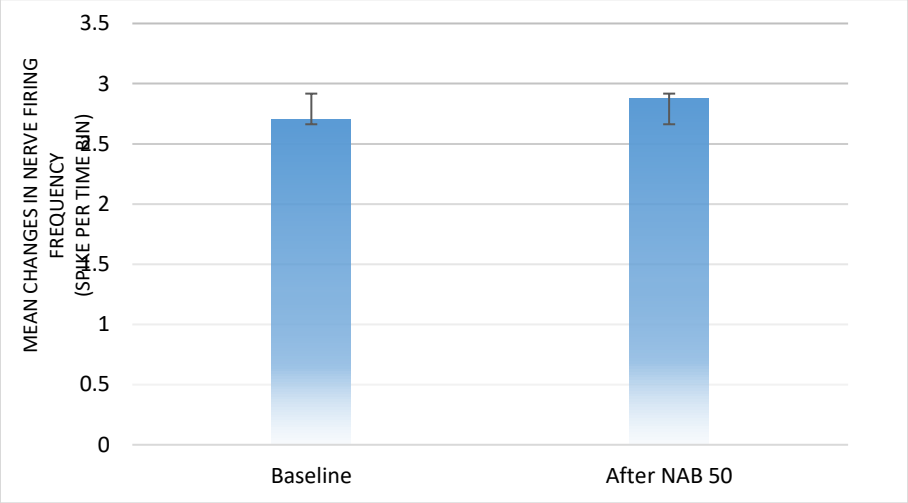

Figure 6. Effects of sodium benzoate 50 mg/kg on mean neuronal firing frequency (t = -0.826, df = 18; P> 0.05).

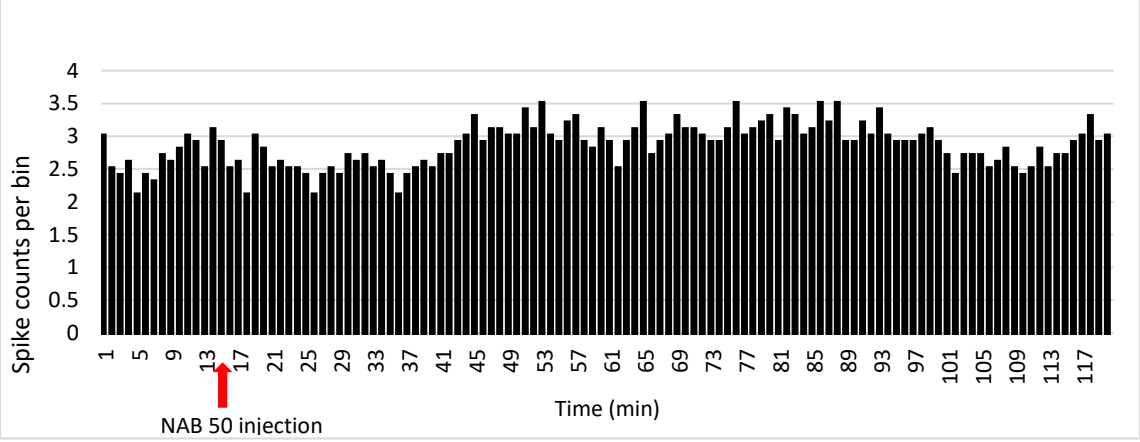

Figure 7. Histogram of electrophysiological recording pattern of spike CA1 neurons in baseline as well as after Sodium benzoate 50 mg/kg injection

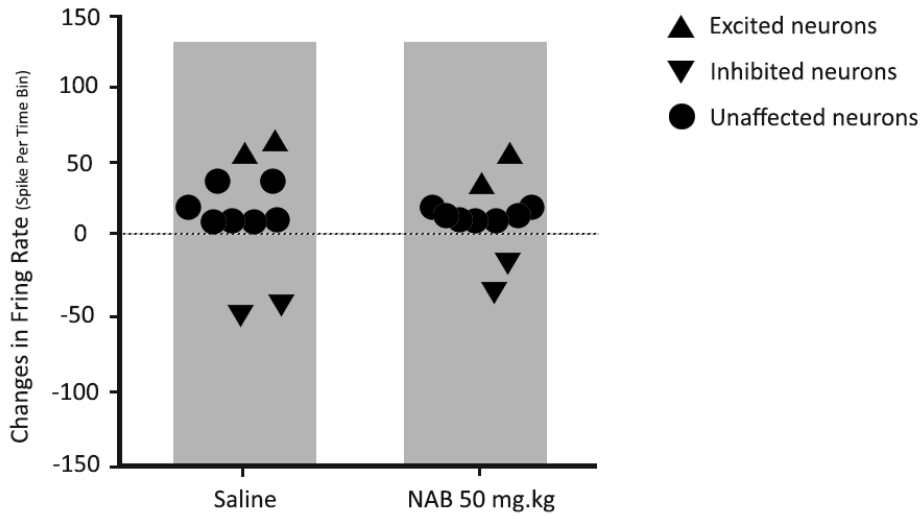

Figure 8.Scatterplot representing the response of pyramidal neurons to saline and sodium benzoate 50 mg/kg injection

Then, the group receiving sodium benzoate 100 mg/kg after the lesion showed a significant increase in the firing frequency of neurons in area A after injection compared to the basal neuronal activity in the t-test of paired samples (t = -1.723, df = 16; P <0.05). (Figure 9 & 10). Specifically, in this group of 8 mice, 12 neurons were recorded and it was found that 100 mg of sodium benzoate had a stimulatory effect on 7 neurons, had an inhibitory effect on 2 neurons and had no effect on 3 neurons (Figure 11). After injection of 100 mg sodium benzoate, stimulation was observed in the stimulation period of 42 to 58 minutes. In addition, injection of sodium benzoate 100 resulted in a 110 to 120% increase in 4 neurons, a 140 to 160% increase in 2 neurons, and a 270% increase in neural activity in 1 neuron.

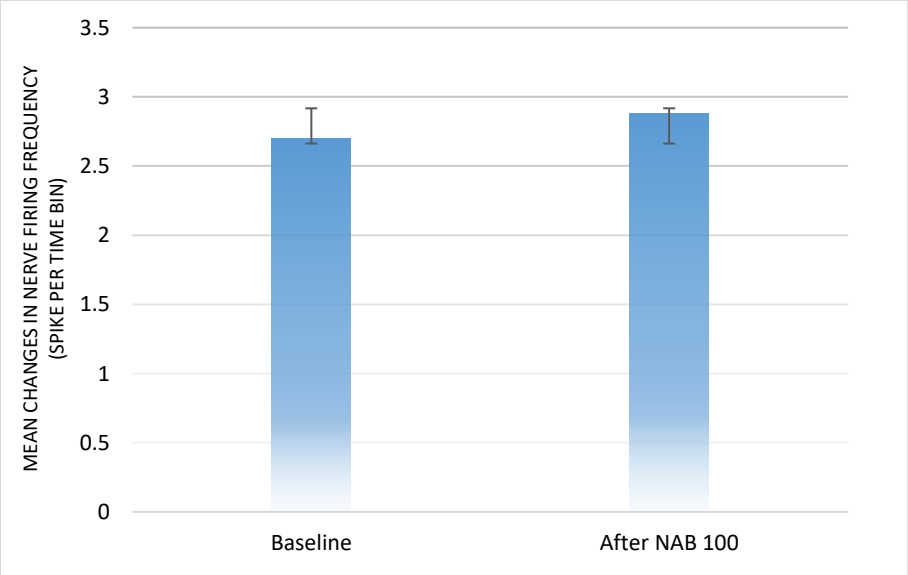

Figure 9. Effects of sodium benzoate 100 mg/kg on mean neuronal firing frequency (t = -0.826, df = 18; P> 0.05).

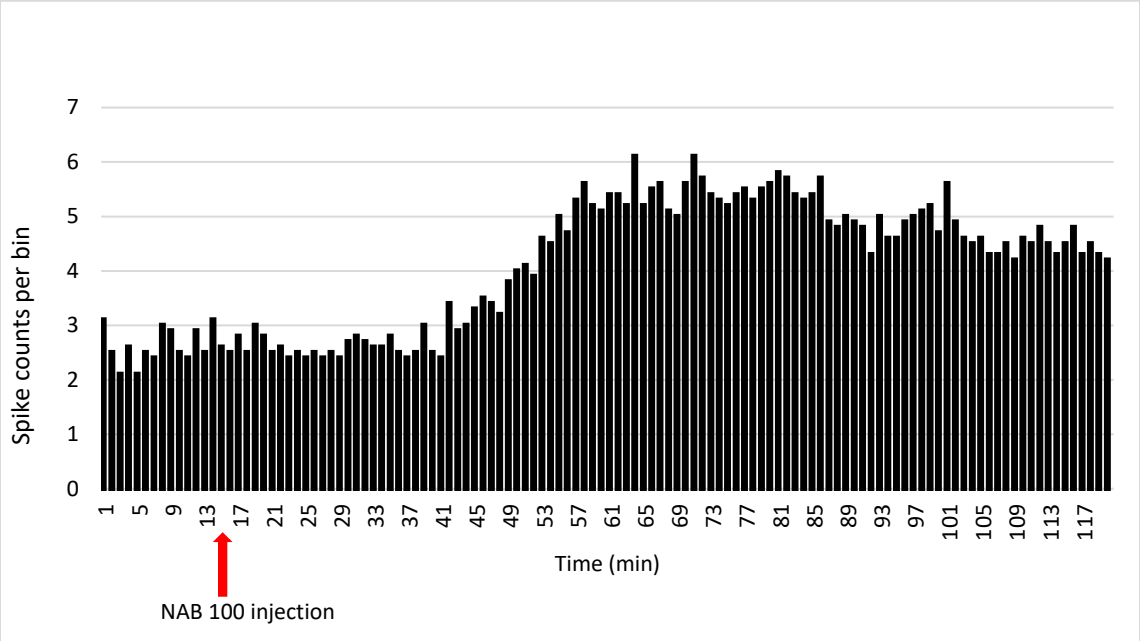

Figure 10. Histogram of electrophysiological recording pattern of spike CA1 neurons in baseline as well as after Sodium benzoate 100 mg/kg injection

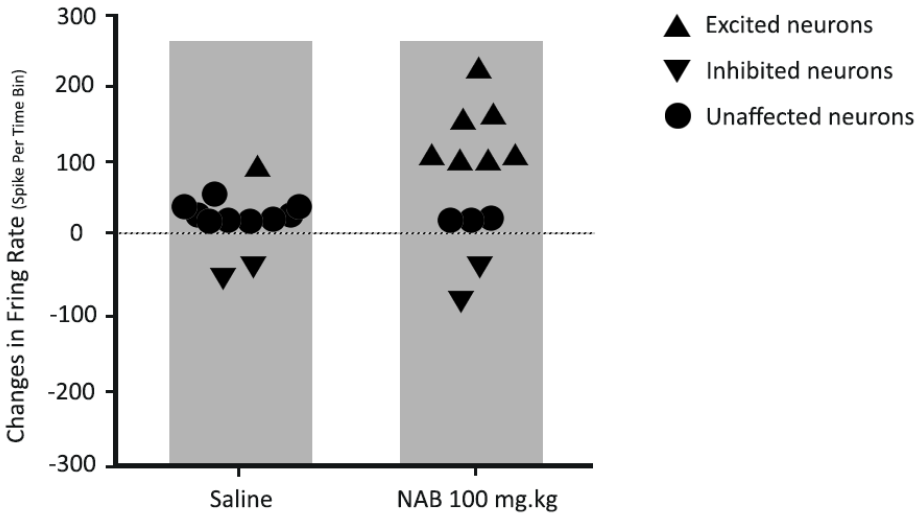

Figure 11.Scatterplot representing the response of pyramidal neurons to saline and sodium benzoate 100 mg/kg injection

The results of injection of 150 mg/kg sodium benzoate after lesion showed that no significant increase in neuronal firing frequency was observed compared to baseline activity in paired t-test ($t = -2.403$, $df = 17$; $P < 0.005$) (Figures 12 and 13). In this group of 8 mice, 13 neurons were recorded that 150 mg of sodium benzoate had a positive effect on 3 neurons, a negative effect on 4 neurons and no effect on 6 neurons (Figure 14). The onset of sodium benzoate stimulation was observed in a period of 43 to 56 minutes.

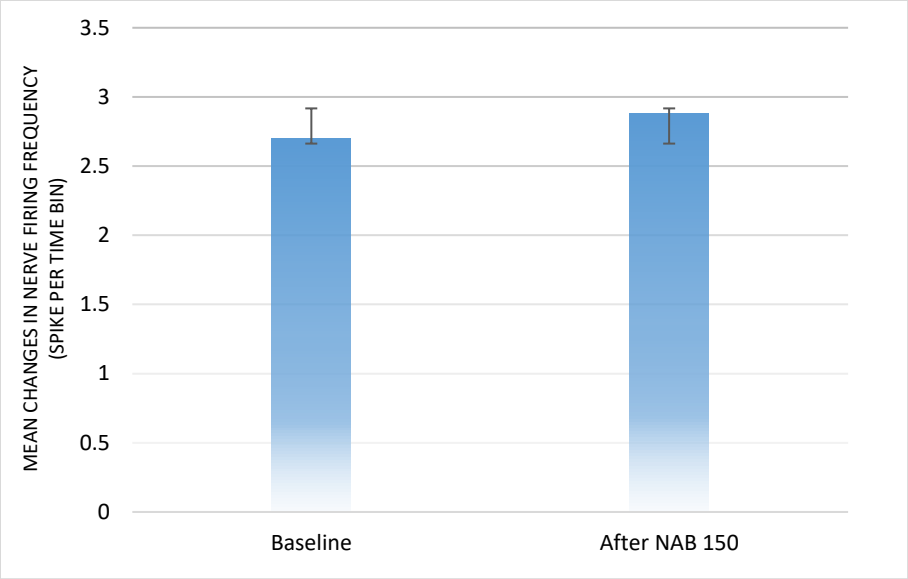

Figure 12. Effects of sodium benzoate 150 mg/kg on mean neuronal firing frequency (t = -0.826, df = 18; P> 0.05).

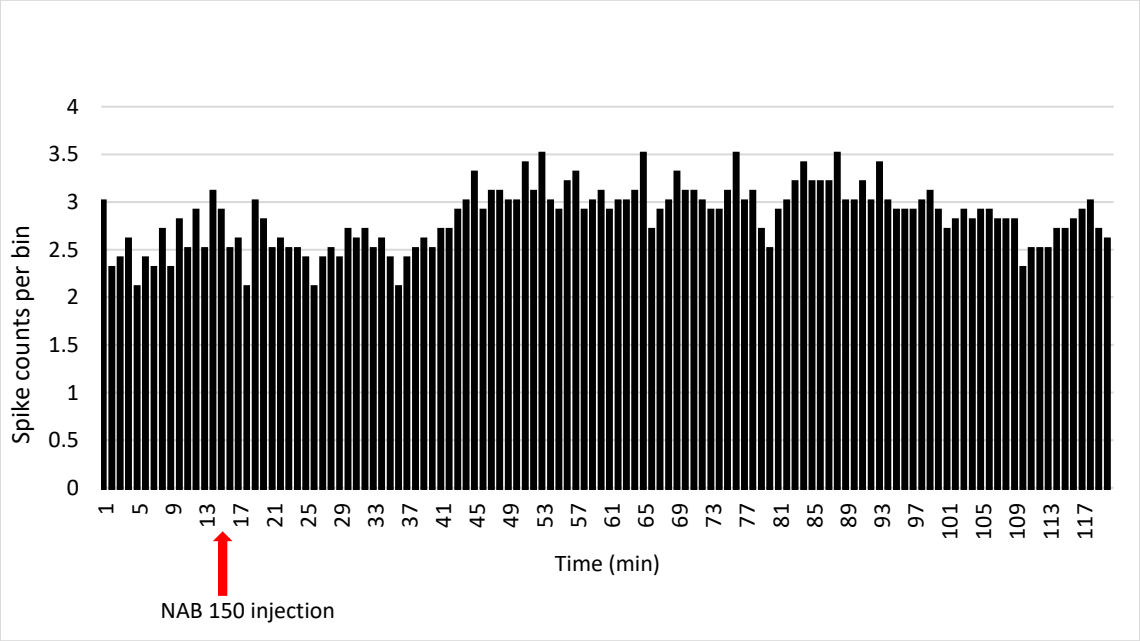

Figure 13. Histogram of electrophysiological recording pattern of spike CA1 neurons in baseline as well as after Sodium benzoate 150 mg/kg injection

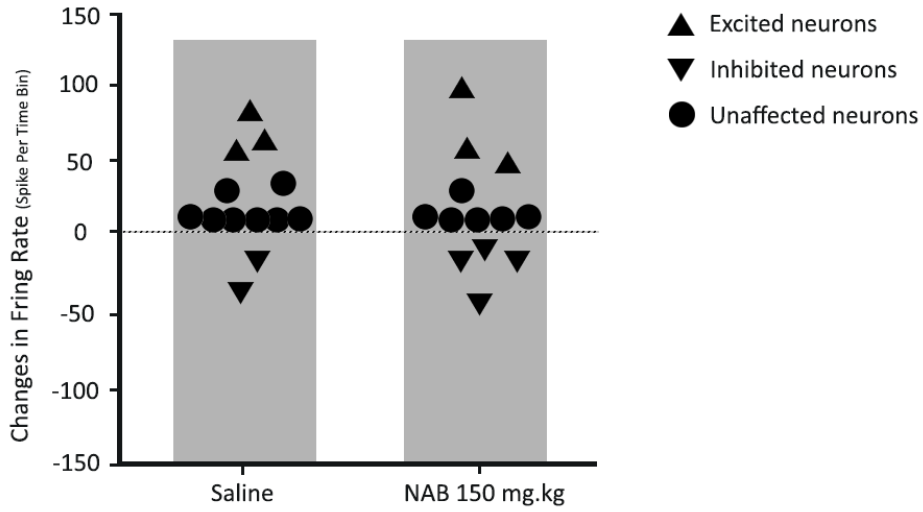

Figure 14. Scatterplot representing the response of pyramidal neurons to saline and sodium benzoate 150 mg/kg injection

The results of injection of 200 mg/kg sodium benzoate after lesion showed that no significant increase in neuronal firing frequency was observed compared to baseline activity in paired t-test (t = -1.742, df = 16; P <0.005) (Figures 15 and 16). In this group of 8 mice, 12 neurons were recorded that 150 mg of sodium benzoate had a positive effect on 2 neurons, a negative effect on 3 neurons and no effect on 7 neurons (Figure 17). The onset of sodium benzoate stimulation was observed in a period of 42 to 57 minutes.

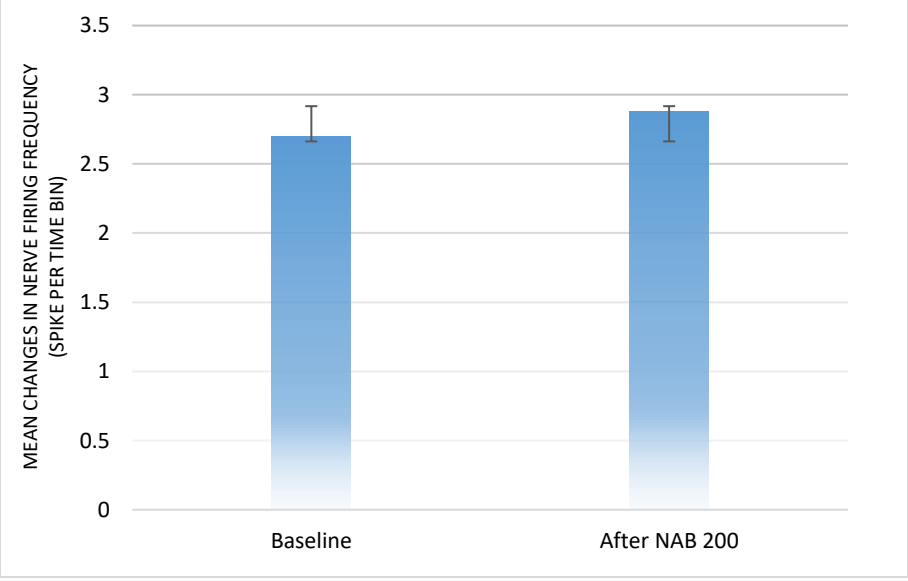

Figure 15. Effects of sodium benzoate 200 mg/kg on mean neuronal firing frequency (t = -0.826, df = 18; P> 0.05).

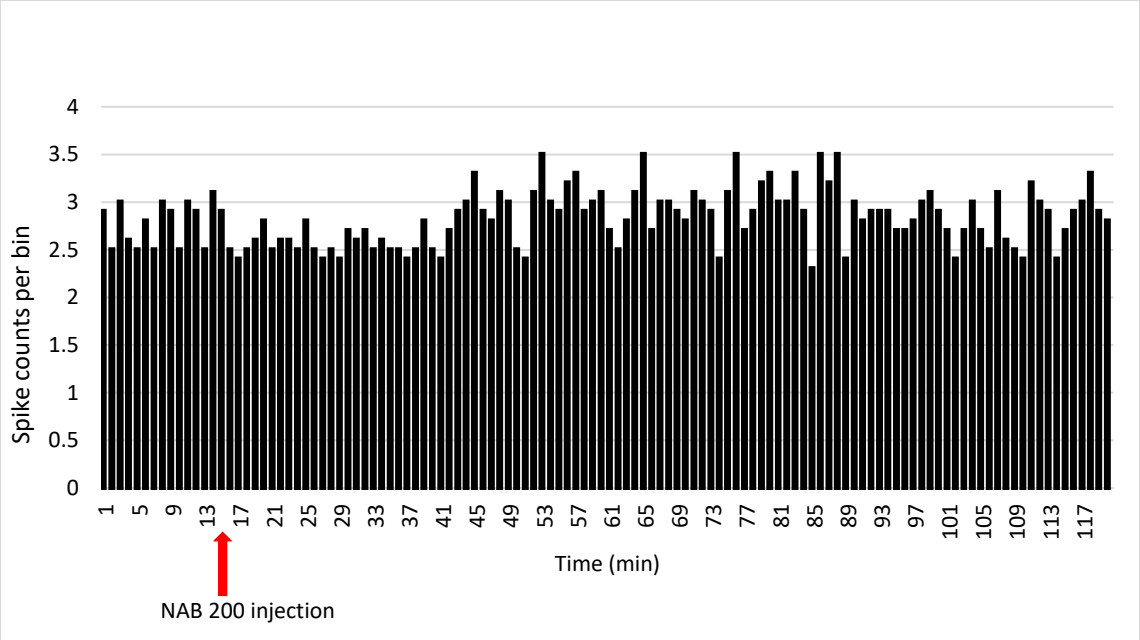

Figure 16. Histogram of electrophysiological recording pattern of spike CA1 neurons in baseline as well as after Sodium benzoate 200 mg/kg injection

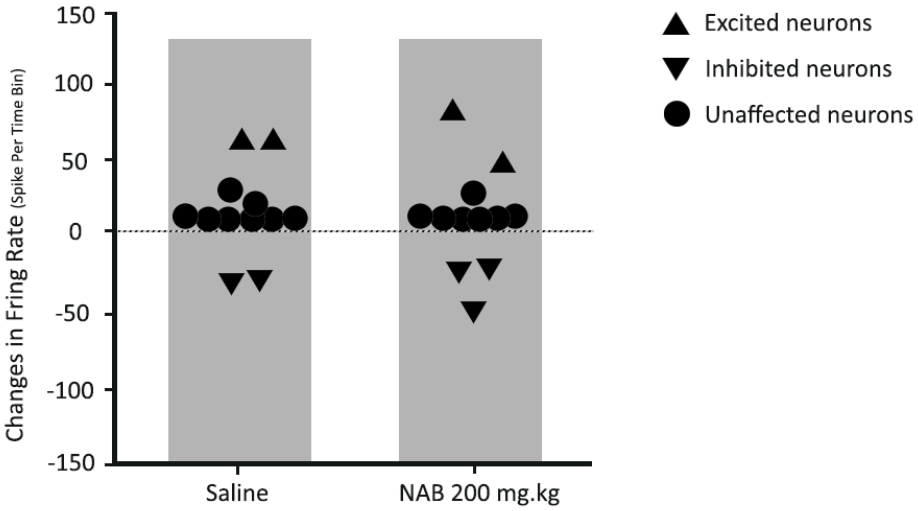

Figure 17. Scatterplot representing the response of pyramidal neurons to saline and sodium benzoate 200 mg/kg injection

Discussion

In the present study, saline and sodium benzoate were injected at 50, 100, 150, and 200 mg/kg in rotenone-induced Parkinson's disease mice, and sodium benzoate was found to increase spontaneous activity at 100 mg/kg. The pyramidal neurons become CA1, while the other values had no significant effect.

Sarbigi et al. (2019) reported that rotenone alters the electrical activity of the hippocampus and its associated behavioral changes. Rotenone mice showed a significant reduction in standing

movements during the 3 weeks compared to control animals (17).

In this regard, it has been reported that the use of cinnamon plant extract with sodium benzoate can improve the balance and endurance performance of Parkinson's disease animals on the Rotarod device compared to other groups. This effect of cinnamon plant is likely due to its protective effect on Genes such as DJ-1 and Parkin (10).

Sodium benzoate, as the main ingredient extracted from the cinnamon plant, inhibits the expression of Inos, inhibits the activation of glial cells and cytokines by regulating the mevalonate pathway, and activates RAS. It should be noted that this pathway is very important in causing inflammation and therefore probably effective compounds of cinnamon in preventing inflammation and is considered as a suitable option for intervening in disorders of the nervous system such as Alzheimer's and Parkinson's (11) .

In a study of male Parkinson's disease-like mice, Corlinus and colleagues reported that cinnamon extract had the ability to improve the animal's leg movements compared to the control group, indicating a positive effect of the plant (23).

Villin et al. Reported in 2019 that sodium benzoate reduces secondary brain weakness by inhibiting neuronal apoptosis and mitochondrial-mediated oxidative stress in a model of intracerebral hemorrhage, possibly by molecular mechanisms such as the DJ-1 / Akt pathways. / IKK / NFκB is done (18).

Modi et al. (2016) reported that oral treatment with cinnamon and NaB improved learning in mice. Its function is that NaB activates CREB in hippocampal neurons through protein kinase A (PKA), which is responsible for rearranging molecules associated with synaptic flexibility (12).

A study by Pahan et al. (2015) found that cinnamon and NaB, as its major metabolites, reduced glial inflammation, reorganized Tregs, suppressed Th17 and Th1 cells, inhibited inflammatory infiltration, and restored cerebral blood vessel integrity. , Spinal cord blood blockade and myelin protection in tezogenic mice with multiple sclerosis. Also in this study, it was found that oral treatment of cinnamon improves motor activity and inhibits the clinical symptoms of the disease in transgenic mice (13).

In a study, Jana et al. (2014) reported that the active ingredients of cinnamon extract are effective in regulating the function of nerve growth factors by activating CREB through protein kinase A. Due to the fact that nerve growth factors have been cited as the main factor in rescuing vulnerable neurons, their upstream regulation is of great importance for the health of the nervous system. Evidence shows that the compounds in cinnamon extract have a high potential for upstream regulation of nerve growth factors and can be used as a suitable option to protect neurons (9).

In a study by Patel et al. (2013), it was reported that sodium benzoate in cinnamon in the Parkinson's disease model of rats protects dopaminergic cells through GDNF astrocytes (14).

Darbinian et al. (2017) reported in a study that rotenone significantly reduced neural activity. It was also found that curcumin could ameliorate movement disorders and electrophysiological parameters in the hippocampal CA1 rye in rotenone-induced Parkinson's disease model rats and may be useful in the treatment of PD (5).

The results of the present study and according to the studies, it seems that sodium benzoate can at least partially improve the activity of pyramidal neurons in the CA1 region of the hippocampus in mice with Parkinson's disease and can be a suitable option for the treatment of diseases. Nervous including Parkinson's and Alzheimer's to be used.

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