Original Article

Zahedan Journal of Research in Medical Sciences

Journal homepage: www.zjrms.ir

Salvia Officinalis and Cisplatin Effects on Pentylenetetrazole Induced Seizure Threshold

Mir Hadi Khayate-Nouri,[1] Ali Namvaran-Abbasabad,*[2] Farzaneh Tavakkoli[2]

1. Department of Pharmacology and Toxicology, Tabriz Branch, Islamic Azad University, Tabriz, Iran
2. Young Researchers Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran

Article information

Article history:
Received: 18 June 2012
Accepted: 25 Sep 2012
Available online: 7 Jan 2013
ZJRMS 2013; 15(11): 1-3

Keywords:
Salvia officinalis
Cisplatin
Pentylenetetrazole
Seizure
Mice

*Corresponding author at:
Islamic Azad University,
Tabriz, Iran
E-mail:
ali.namvaran@gmail.com

Abstract

Background: Studies have shown that cisplatin have neuropathic effects and *Salvia* officinalis (SO) could have therapeutic effects on nervous system. The aim of this study was to investigate the effects of SO hydroalcoholic extract and cisplatin on pentylenetetrazole (PTZ) induced seizure in mice.

***Materials and methods*:** This is an experimental interventional study. For this purpose first group received normal saline, second group received SO extract, third group received cisplatin, in the fourth group received SO extract plus cisplatin and the subsequent seizure threshold was determined for each group.

***Results*:** The results showed that SO extract significantly ($p<0.05$) increased and in cisplatin group significantly ($p<0.05$) decreased seizure threshold. Simultaneous uses of cisplatin and SO extract caused to significantly increased seizure threshold ($p<0.05$) compared with cisplatin group.

***Conclusion*:** Considering different types of ingredients in SO extract which have beneficial effects on nervous system, it might be used to reduce cisplatin induced neuropathic effects. It seems that SO extract could be useful in cisplatin-induced seizure but further investigations are needed.

Introduction

An epileptic seizure, occasionally referred to as a fit, is defined as a transient symptom of abnormal excessive or synchronous neuronal activity in the brain. Epileptic drug therapy in most patients is based on experimental seizure classification and millions of people have uncontrolled epilepsy. Despite the many advances in the field of medicine and pharmacy, patients and epileptic seizure disorders always have been challenges physicians and researchers. In some cases, with recurrence, toxicity and side effects of drugs increased and the patient should have a long period of treatment to over [1]. Previous studies have shown that herbal medication could be useful for treating vincristine and cisplatin induced seizure, pain and side effects [2-4].

One of the most important genuses of Lamiaceae is genus Salvia. Fifty-eight species of this genus are documented in the Flora of Iran; 17 of them are endemic [5]. The plants of the genus salvia are generally known for their multiple pharmacological effects such as analgesic, hepatoprotective, hypoglycemic activities, and antiischemia. Numbers of these have exhibited effects relevant to potential treatment of CNS related disorders; the flavonoid apigenin for example has been shown to protect neurons against Aß induced toxicity. In addition to antioxidant activity many salvia species and their isolated constituents demonstrate anti-inflammatory properties [6, 7]. Previous study proved apigenin could have GABA like effects [8]. Cisplatin-based chemotherapy is the mainstay for the treatment of different tumors. Its clinical use is severely curtailed by dose-limiting renal toxicity, ototoxicity, and neurotoxicity [9]. In some cases treated with cisplatin seizure observed. It seems that drug effects on the nervous system as an encephalopathy in human [10], including in case report by Highley et al. Four of eight children with advanced neuroblastoma treated with a rapid delivery high dose intensity cisplatin based regimen developed acute neurological toxicity. Three had seizures and one developed transient blindness [11]. Cispltin can penetrate to central nervous system so it is used for treating central nervous metastasis. GABAergic system is one of the most important inhibitory systems in CNS and could be affected through using cisplatin chemotherapy.

This study was preformed because one of cisplatin-induced mechanisms is oxidative stress and SO contains different substances including antioxidants and flavonoids that could be useful in prevention and treatment. This study investigated the convulsant effects of cisplatin and anticonvulsant effects of Salvia officinalis in mice.

Materials and Methods

Animals: This is an experimental interventional study. Experiments were performed on 25-30g adult NMRI male mice in their 8-9 week, purchased from Razi Institute and randomly divided in four groups. Animals were housed in

a temperature and humidity controlled environment under a 12-hour light/dark cycle (lights on at 7 am). Food and water were available ad libitum. The National Institutes of Health guidelines for care and use of animals and Guidelines on Ethical Standards Experiments in Animals were followed. All efforts were made to minimize the number of animals which were used and their suffering degree.

The cisplatin-induced neuropathy model was conducted by intravenal (IV) injection in this experiment. Animals received single IV injections of cisplatin (2 mg/kg), saline (1 ml/kg/day) and SO hydroalcoholic extract (1 g/Kg/ Intraperitoneal) for 4 days, in last day extract were administered and after 30 minutes pentylenetetrazole - seizure test were preformed.

Animals were divided into 4 groups randomly (n=10), the first group received saline normal (Control group), the second group received SO hydroalcoholic extract (1 g/Kg/IP) (SO group), the third group received cisplatin (2 mg/kg/IV) (Cis group), the forth group received SO hydroalcoholic extract and cisplatin (Cis+SO Group).

Chemicals: PTZ were purchased from Sigma-Aldrich Company and dissolved in normal saline. Cisplatin was purchased from EBEWE pharma Ges.m.b.h. Austria.

Administration of test agent: Cisplatin was administered intravenously via tail vein. Normal saline and SO hydroalcoholic extract was administered intraperitonealy. Dose selection of each agent was based on the results of previous studies. To determine seizure threshold, PTZ solution (5 mg/ml) was infused in a constant rate of 0.5 ml/min into the lateral tail veins of mice. Infusion continued until the occurrence of upper limb clonic seizure and followed by full body tonic seizure. Minimum dose of PTZ (1 mg/kg of mice body weight) needed to create clonic seizure as an index of clonic seizure threshold was considered.

Extracting method: Dry SO leaves (*Salvia officinalis*) from Isfahan pharmaceutical company purchased and drench method used for extraction. For this purpose leaves mildly powdered. Fifty grams of SO powder and 500 ml of 70% ethylic alcohol mixed and after 48 hour (container were motivated for 5 minutes with 12 hours withdrawal time). The mixture leached and solvent extracted in rotary adjusted in 70ºC in medium round speed. The caliginous fluid was spread on a window and in 50ºC Oven and after drying the powder gathered and used in this experiment.

Data Analysis: The results analyzed using SPSS software 17. Group data are presented as mean±SEM and analyzed statistically using comparison *t*-test. The level for statistical significance was set at a *p*-value of <0.05.

Results

Seizure threshold obtained in mice that received normal saline as control was 35.52±0.87 mg/kg. Vehicles effect on seizure threshold showed that the vehicles used in this study didn't have significant effect on seizure threshold.

Intravenous administration of cisplatin caused decrease in PTZ-induced seizure threshold to 28.3±1.23. This decrease was statistically significant *(p<0.05)* compared with control group (Fig. 1).

Intra peritoneal injection of SO, 30 minutes before seizure test caused increase in threshold to 45.83±1.23. This increase was statistically significant *(p<0.05)* compared with control group. Injection of SO and cisplatin together (Cis+SO group), before PTZ-induced seizure threshold test have shown that seizure threshold was 32.46±1.72. This increase was statistically significant *(p*<0.05*)* compared with cisplatin group (Fig. 1).

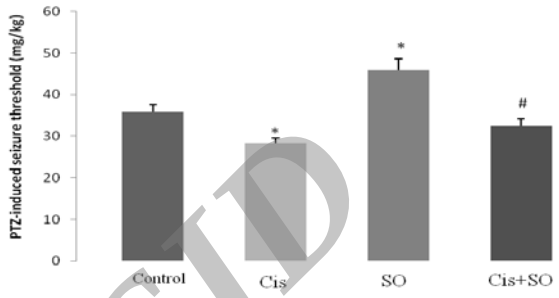

Figure 1. Effect of hydroalcoholic extract of *Salvia officinalis*, Cisplatin and Salvia officinalis-Cisplatin together on clonic seizure threshold in mice. Each line represents mean±SEM of 6 mice. Cis=cisplati group, SO= Salvia officinalis group. * *p*<0.05

Discussion

The results of present study have shown that SO extract could decrease cisplatin-induced neuropathic and epileptic effects in mice. Medical and therapeutic effects of traditional medicine and medicinal plants and harmless effects in many years is the major reason of using this kind of therapeutics. In this study the effect of SO hydroalcoholic extract on PTZ-induced seizure threshold was determined. $GABA_A$ receptor is prominent inhibitory neurotransmitter receptors in vertebrate central nervous system. It is well marked that PTZ acts on the position of picrotoxin action complex on GABA receptor. In this study, SO increased PTZ-induced seizure threshold. Since PTZ acts via $GABA_A$ receptor, it seems that an anticonvulsant effect of SO is through Gabaergic system. Other researchers showed with biochemical studies that SO extract containing apigenin that have GABA like effects [8] and it can increase GABA effects on $GABA_A$ receptors. Because GABA is an inhibitory neurotransmitter in brain it decreases activity in central nervous system.

Maklad et al. have shown that the extract of Salvia transsylvanica (same genus of *Salvia officinalis*, induced significant analgesic, antipyretic, antiepileptic, anti-inflammatory, antiulcerogenic, as well as tranquillizing activities. They also have shown that Salvia transsylvanica extract could control PTZ induced seizure dose dependently in mice. They used 500 mg/kg, 750 mg/kg and 1000 mg/kg of herb and their results showed that last dose (1000 mg/kg) could provide 100% protective effects against PTZ induced seizure. Positive control of their study was diphenylhydantoins that act with GABA system [12]. As our results showed it seems

there are beneficial relation between cisplatin decreased seizure threshold and GABAergic inhibitory system. The dosage of our article is as same as Maklad et al study and results showed that in this dose SO extract could have anticonvulsant effects. Recent studies have shown that Matricaria recutita could be an alternative approach for treating both cisplatin and vincristine induced seizure and side effects [3]. The possibility of same effects tested for SO extract in this study.

In present study the convulsant effects of cisplatin evaluated as cancer chemotherapy agent. Although it is generally held that the therapeutic effects of platinum-based anticancer drugs are mediated by DNA alkylation, the mechanism by which they produce neurotoxicity, a major dose-limiting side effect for this class of therapeutic agents, is not well understood. In the present study, we characterized the convulsant effects produced commonly used member of the platinum-based cancer chemotherapies, Cisplatin, a representative drug in this class, which has been clinically used for 4 decades. One of the mechanisms suggested for causing encephalopathy was neurons myelin peroxidation. Engender free radicals and lipid peroxidation following cisplatin drug use, is one of the main mechanisms for the neuropathy and neurons damage followed by encephalopathy that causes seizures in patients [10, 11, 13, 14]. Due to daily administration of SO extract in this study, it can be expected antioxidant effects of this plant overcome to side effects of this drug. Also because of substances that are effective in central nervous system, it seems generally the plant is useful to reduce convulsant symptoms caused by cisplatin. The results of our study showed that SO hydroalcoholic extract increased seizure PTZ-induced threshold in cisplatin received mice. Probably gabaergic inhibitory neurotransmitter system is responsible for the anticonvulsant effect. However, the role of anticonvulsant mechanisms in human is needed further investigation.

Acknowledgements

The authors sincerely acknowledge their gratitude to the efforts of Pharmacology department of veterinary collage, Islamic Azad University Tabriz branch.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of interest

The authors declare no conflict of interest.

Funding/Support

Islamic Azad University Tabriz branch, Tabriz-Iran.

References

1. Faingold CL. Emergent properties of CNS neuronal networks as targets for pharmacology: Application to anticonvulsant drug action. Prog Neurobiol 2004; 72(1): 55-85.
2. Namvaran-Abbas-Abad A, Khayate-Nouri MH, Tavakkoli F. Study of Matricaria recutita and Vincristine effects on PTZ-induced seizure threshold in mice. Res J Med Sci 2011; 5(5): 247-51.
3. Namvaran-Abbas-Abad A, Khayate-Nouri MH. Interactions between Matricaria recutita and cisplatin on PTZ-induced seizure threshold in mice. Feyz 2011; 15(3): 188-93.
4. Namvaran-Abbas-Abad A, Kayate-Nouri MH, Gharjanie A and Tavakkoli F. Effect of Matricaria chamomilla hydroalcoholic extract on cisplatin-induced neuropathy in mice. Chin J Nat Med 2011; 9(2): 126-31.
5. Rustayan A, Masoudi S, Monfared A and Komilizadeh H. Volstile constituents of three Salvia species grown wild in Iran. Flavor Fragrance J 1999; 14: 267-78.
6. Hernandez-Perez M, Rabanal RM, de la Torre MC and Rodriguez B. Analgesic, anti-inflammatory, antipyretic and haematological effects of aethiopinone, an o-naphthoquinone diterpenoid from Salvia aethiopis roots and two hemisynthetic derivatives. Planta Med 1995; 61(6): 505-9.
7. Namvaran-Abbas-Abad A, Khayate-Nouri MH, Tavakkoli F. Effect of Salvia officinalis Hydroalcoholic Extract on Vincristine-induced Neuropathy in Mice. Chin J Nat Med 2011; 9(5): 354-8.
8. Viola H, Wasowski C, Levi de Stein M, et al. Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. Planta Med 1995; 61(3): 213-6.
9. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 2007; 7(8): 573-84.
10. Steeghs N, de Jongh FE, Sillevis Smitt PA and van den Bent MJ. Cisplatin-induced encephalopathy and seizures. Anticancer Drugs 2003; 14(6): 443-6.
11. Highley M, Meller ST, Pinkerton CR. Seizures and cortical dysfunction following high-dose cisplatin administration in children. Med Pediatr Oncol 1992; 20(2): 143-8.
12. Maklad YA, Aboutabl EA, el-Sherei MM and Meselhy KM. Bioactivity studies of Salvia transsylvanica (Schur ex Griseb) grown in Egypt. Phytother Res 1999; 13(2): 147-50.
13. Blisard KS, Harrington DA. Cisplatin-induced neurotoxicity with seizures in frogs. Ann Neurol 1989; 26(3): 336-41.
14. Joseph EK, Levine JD. Comparison of oxaliplatin- and cisplatin-induced painful peripheral neuropathy in the rat. J Pain 2009; 10(5): 534-41.

Please cite this article as: Khayate-Nouri MH, Namvaran-Abbasabad A, Tavakkoli F. Salvia officinalis and cisplatin effects on pentylenetetrazole induced seizure threshold. Zahedan J Res Med Sci (ZJRMS) 2013; 15(11): 1-3.