Arch Biol Sci. 2019;71(3):403-408 https://doi.org/10.2298/ABS181209021D

Folic acid supplementation alleviates behavioral manifestations of lindane-induced seizuress

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Received: December 9, 2018; **Revised**: January 31, 2019; **Accepted**: February 1, 2019; **Published online**: April 1, 2019

Abstract: Lindane is a scabicide and pesticide that can exert neurotoxic effects such as tonic and clonic seizures that are refractory to many antiepileptic drugs. Folic acid stands out as a potential substance worth testing for its neuroprotective and in certain experimental models anticonvulsive effects. The aim of the present study was to examine the potential therapeutic value of folic acid supplementation on the behavioral characteristics of lindane-induced seizures. Adult male Wistar rats were divided into the following groups: Controls: dimethyl sulfoxide-injected (C_1), saline-treated (C_2); lindane (4 mg/kg; 6 mg/kg; 8 mg/kg; L_4; L_6; L_8, respectively); folic acid 15 mg/kg (F) and F administered 30 min prior to L_4, L_6, or L_8 (L_4F; L_6F; L_8F, respectively). Convulsive behavior was assessed by the incidence of seizures, seizure latency and seizure severity. Lindane administration has shown a tendency of proportional increase in seizure incidence, decrease in seizure latency and increase in seizure intensity. Pretreatment with folic acid significantly prolonged the latency period and decreased the frequency of grade 4 seizures in the L_8F group when compared to the L_8 group. We concluded that folic acid alleviates the behavioral manifestations of lindane-induced seizures and that it can be applied as a potential adjuvant in lindane-poisoned patients; however, further research is still needed.

Keywords: lindane; folic acid; seizures; rat; intoxication

INTRODUCTION

Lindane (γ-hexachlorocyclohexane), an environmentally present xenobiotic, has come into the focus of research for its frequent intoxications and extensive utilization in agriculture and human and veterinary medicine [1,2]. This organochlorine pesticide and scabicide has been banned in many countries, but still remains a potential hazard, especially in undeveloped and developing countries. Lindane intoxication exerts effects on multiple organ systems, including the central nervous, cardiovascular, respiratory and gastrointestinal systems [3-10]. The most prominent and important of its neurotoxic effects are seizures [11-13]. Administered orally or intraperitoneally, lindane evokes tonic and clonic seizures in a dose-dependent manner [14,15]. Additionally, it has been reported that lindane-evoked seizures are refractory to many conventional and novel antiepileptic drugs [16]. Therefore, this model may be used as a suitable model for testing the potential antiepileptic effects of various drugs.

Folates are members of the water-soluble B vitamin group and its requirements solely depend on nutritional intake. Folates are naturally present in a variety of foods; however, absorption of the dietary form of folate is only 50%, in contrast to 85-95% absorption of its synthetic form, and therefore many countries have followed the United States of America in ordering food supplementation with folic acid [17-19]. Since folate is the only methyl group donor in the central nervous system (CNS), it has an important role in a variety of physiological processes, such as DNA synthesis and neuroplasticity; however, being a methylating agent it is also a suspected candidate for producing epigenetic modifications [20].

A growing number of rodent and human studies have shown the correlation between folate deficiency and major depression, schizophrenia, cerebrovascular and neurodegenerative diseases including Alzheimer's and Parkinson's diseases [21-24]. Supplementation with this vitamin can significantly attenuate the clini-

cal features of stroke and various neurodegenerative disorders. Researches have shown that folic acid and its active metabolites exert antioxidative, antiinflammatory, antiapoptotic, antidepressant and neuroprotective effects [25-27]. In the pursuit of novel additional supplements or drugs, folic acid stands out as a potential substance worth further testing in experimental epilepsy models. On the other hand, some studies documented folic acid properties such as inducing hyperexcitability, altering synapse density, worsening of seizure frequency and enhancing seizures in kindling model of epilepsy [28,29].

In view of these considerations, the aim of the present study was to examine the effect of acute folic acid administration on the behavioral characteristics of lindane-induced seizures in adult rats.

MATERIALS AND METHODS

Animals and experimental conditions

All experimental procedures were carried out in accordance with the European Council Directive (86/609/EEC) and were approved by the Animal Care Committee of the University of Belgrade (298/5-2). Adult 2-month-old Wistar male rats (170-200 g), obtained from the Military Medical Academy Breeding Laboratories, Belgrade (Serbia), were used in the experiments. The animals were housed in transparent plastic wire-covered cages (55x35x15 cm) with free access to food and water. They were kept in a sound-attenuated chamber under controlled ambient conditions (22-23°C, 50-60% relative humidity, 12/12 h light/dark cycle with light switched on at 8 a.m.); all experiments were performed during the light period. The acclimatization period lasted for 7 days.

Drugs

All drugs were of analytical purity and purchased from Sigma-Aldrich Chemical Co., USA.

Study Design and Experimental Procedures

The animals were divided into following groups: (i) controls: dimethyl sulfoxide (DMSO)-injected (C_1, 0.5 mL/kg, n=10), saline-injected (C_2, 0.9% NaCl, n=10); (ii) lindane 4 mg/kg (L_4, n=10); (iii) lindane 6 mg/kg (L_6, n=11); (iv) lindane 8 mg/kg (L_8, n=11); (v) folic acid 15 mg/kg (F n=10), and (vi) folic acid (F) 30 min prior to lindane (L_4, L_6, L_8): L_4F (n=10), L_6F (n=10) and L_8F (n=10), respectively. Each rat was used only once. Lindane was dissolved in DMSO and folic acid in saline (pH adjusted to 7.4). All substances were freshly dissolved and administered intraperitoneally (i.p.) in a volume of 0.1 mL/100 g rat body weight.

Behavioral recording

Behavioral manifestations of lindane-induced epilepsy in rats were recorded. The animals placed in separate transparent plastic cages (55x35x15 cm) were observed for 30 min after lindane administration for the occurrence of convulsive behavior. This was assessed by the incidence of seizures (the number of convulsing animals out of the total number of rats), seizure latency (time between lindane administration and first seizure sign) and seizure severity. Seizure severity was determined by a modified descriptive rating scale reported by our group [30] with grades defined as follows: grade 0 – no seizures, grade 1 – head nodding, lower jaw twitching; grade 2 – myoclonic body jerks (hot plate reaction), bilateral forelimb clonus with full rearing (Kangaroo position); grade 3 – progression to generalized clonic convulsions followed by tonic extension of fore and hind limbs and tail, and grade 4 – prolonged severe tonic-clonic convulsions lasting over 10 s (status epilepticus). For rats without seizures, 30 min latency time was scored.

Statistical analysis

The significance of the differences in the incidence of seizures and seizure grade distribution was evaluated by Fisher's exact probability test. Since the normal distribution of the data on seizure latency and seizure severity has not been estimated by the Kolmogorov-Smirnov test, nonparametric analyses (Kruskal-Wallis ANOVA and the Mann-Whitney U test) were used to determine the statistical significance of the differences between the groups (*$p<0.05$, **$p<0.01$). The results were expressed as medians with 25th and 75th percentiles.

RESULTS

Normal gross behavioral activity without signs of convulsions was observed in all rats from the control (C_1, C_2) and folic acid (F) groups. Convulsions were

observed in all animals treated with lindane. The incidence of seizures showed a tendency to increase proportionally with an increase in lindane dose (from 40% in L_4 up to 73% in L_8; p>0.05), but statistical significance was not attained (Fig. 1). Folic acid administration decreased seizure incidence, but without statistical significance (Fig. 1).

Median seizure latency was significantly shorter in the L_6 and L_8 groups compared to the L_4 group (p<0.05) (Fig. 2). Pretreatment with folic acid significantly prolonged the median latency period to the first seizure episode in the L_8F group [13.5 (9.0-30.0) min], compared to the L_8 group [5.0 (4.0-30.0) min] (p<0.05) (Fig. 2).

Lindane increased the median seizure grade in a dose-dependent manner, with the lowest grade recorded in the L4 (grade 0); in the L6 median grade it was grade 2 (p>0.05), while the dominant seizure manifestation in L8 was grade 4 (p<0.05) (Fig. 3). Median seizure episode severity was decreased by folic acid administration in the L_8F [2.0 (0-3.0)], compared to the L_8 [4.0 (0-4.0)] group, but without statistical significance (Fig. 3).

In order to conduct a detailed analysis of seizure severity, we examined the statistical significance of seizure episode severity distribution. Analysis of the seizure grade distribution revealed the differences between the groups. In the L_4 group, the majority of seizures were grade 1 (40%), while the dominant manifestations of convulsive behavior in the L_8 were grade 4 (54.5%, p<0.05, Table1). In the L_6 group, grade 2, grade 3 and grade 4 convulsions were equally represented (18.2%), while after folic acid supplementation the dominant seizure manifestations were grade 2

Table 1. Seizure severity distribution in experimental groups.

Grade (%)	Experimental groups					
	L_4	L_4F	L_6	L_6F	L_8	L_8F
0	60	80	36.4	40	27.3	40
1	40	10	9.1	0	0 $^{+}$	0
2	0	10	18.2	60$^{\#}$	18.2	30
3	0	0	18.2	0	0	30*
4	0	0	18.2	0	54.5^{+}	0*

The significance of the differences between the groups was estimated by Fisher's exact probability test (*p<0.05 vs L_8, +p<0.05 vs L_4; # p<0.05 vs L_6). For the details refer to the Fig. 1 legend.

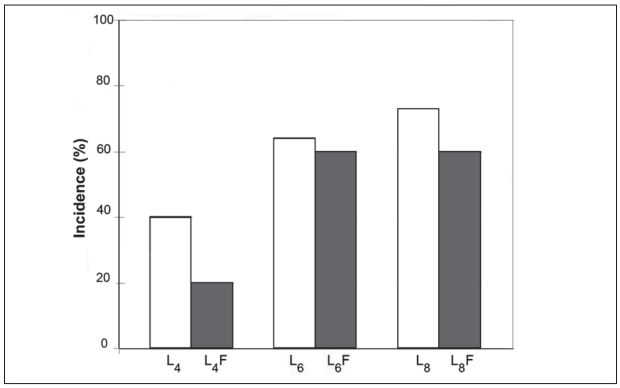

Fig. 1. The effects of acute folic acid administration on the incidence of seizures. The significance of the differences between the groups was estimated by Fisher's exact probability test (*p<0.05). L_4, L_6, L_8 – lindane i.p., doses 4 mg/kg, 6mg/kg, and 8 mg/kg, respectively. L_4F, L_6F and L_8F – rats pretreated with folic acid (15 mg/kg, i.p.) 30 min before administration of L_4, L_6, L_8.

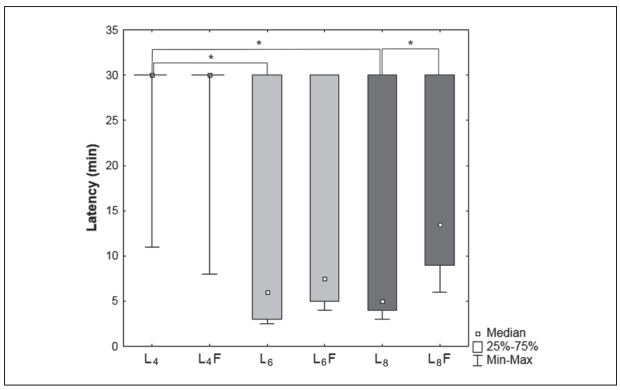

Fig. 2. The effects of acute folic acid administration on seizure latency. The significance of the differences between the groups was estimated by the Kruskal-Wallis ANOVA and the Mann Whitney U test (*p<0.05). For the details refer to the caption to Fig. 1.

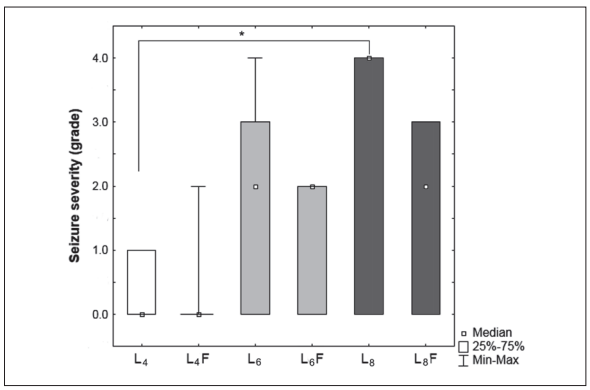

Fig. 3. The effects of acute folic acid administration on severity of seizures induced by lindane. The significance of the differences between the groups was estimated by the Kruskal-Wallis ANOVA and the Mann Whitney U test (*p<0.05). For the details refer to the caption to Fig. 1.

(L_6F, 60%, $p<0.05$). In the L_8F group, pretreatment with folic acid decreased the occurrence of grade 4 seizures (0%, $p<0.05$) and increased the occurrence of grade 3 (30%, $p<0.05$) and grade 2 seizures (30%, $p>0.05$) compared to the L_8 group (G4 54%, G3 0%, G2 18.2%, respectively) (Table 1).

DISCUSSION

Human exposure to lindane results from its continued use in treating lice and scabies infestations and its use for decades as a general insecticide. The production and agricultural use of lindane was banned in 2009, but a specific exemption allows its continued use as a second-line pharmaceutical treatment for lice and scabies [31]. Lindane is a well-known neurotoxin with rapid action. When administered either orally or intraperitoneally, lindane evoked tonic and clonic seizures in a dose-dependent manner [9,13]. Lindane is primarily a GABAA receptor antagonist, which increases neuronal firing rates causing seizures in experimental animals [7,15]. Lindane binds to the picrotoxin site in the chloride channel of GABAA receptor, thereby inhibiting its function [32]. Additional mechanisms include interfering with enzymes like Na^+/K^+-ATPase, Mg^{2+}-ATPase and acetylcholinesterase, changes in neurotransmitter levels and alterations of the central monoaminergic system [3,7,33]. Studies have also shown the potential role of excitatory amino acids in the central effects of lindane and its powerful oxidant effect, as well as a role in calcium mobilization [3,4,34].

Folic acid, also known as vitamin B9, is the synthetic molecule of its naturally occurring form, folate, which belongs to the essential vitamin group. Folic acid is essential for nucleic acid synthesis and methylation of DNA, proteins, phospholipids, and neurotransmitters. The complex relationship between folic acid and epileptic seizures is insufficiently understood. Early studies from the mid-1980s have suggested that folic acid acts as pro-epileptic agent and increases excitability of hippocampal neurons [35]. On the other hand, chronic use of anticonvulsant drugs is associated with low folate and B12 vitamin plasma levels [36]. Folate deficiency presents a prevalent problem and has been linked with cerebrovascular insult and neurodegenerative conditions like dementia. Folate deficiency increases homocysteine levels in the CNS, which may exert direct prooxidative and neurotoxic effects, probably by increasing the concentration of cytosolic calcium [37]. Furthermore, acute supplementation with folic acid decreases the overall excitability of the CNS and has an anticonvulsive effect [28].

In our present study we have also documented dose-dependent seizure behavior in all lindane-treated groups. Our results show that a very large dose of folic acid does not induce convulsions, which is in accordance with multiple studies that have demonstrated that folic acid does not possess pro-epileptic properties in a less than supraphysiological dose [38]. Namely our results show that i.p. pretreatment with folic acid had a general anticonvulsive effect and prolonged median latency to the first seizure episode in the L_8F group as compared to the L_8 group ($p<0.05$). Furthermore, folic acid showed a tendency of decreasing seizure incidence and seizure episode severity, but without statistical significance. In-depth analysis of seizure grade distribution revealed a significant reduction in the occurrence of G4 seizures in the L_8F group compared to the L_8 group ($p<0.05$). Folate is also required to maintain low levels of homocysteine in the CNS and previous results from our laboratory have shown that folic acid given acutely in large doses significantly decreased seizure incidence and prolonged seizure latency in homocysteine-induced epilepsy, which correlates with the present findings [28].

Lindane-induced seizures are refractory to numerous classical antiepileptic drugs such as carbamazepine, phenytoin, felbamate and lamotrigine, gabapentin and vigabatrin [16]. The effectiveness of folic acid in treating lindane-induced seizures could be explained by the fact that they share the same target – the NMDA receptor. The findings of our previous studies have proved that NR2B NMDA agonists are effective in preventing lindane-induced convulsions [39], while several studies demonstrated that folic acid acts as a potent antagonist of NMDA receptors [27,40]. Literature points to the role of oxidative stress as a potential mechanism responsible for complex interaction between lindane and folic acid. Previous studies have shown that lindane intoxication induced lipid peroxidation and decreased superoxide dismutase (SOD) activity in the cerebral cortex, the hippocampus, and the thalamus, which may partially explain the neurotoxic effects of lindane [41]. On the other hand, studies have shown

that folic acid prevents oxidative stress in the CNS by preventing the reduction of antioxidant enzymes, catalase and glutathione peroxidase, and by decreasing the levels of malondialdehyde and superoxide anion [26,42].

Dietary therapies represent a potentially valuable adjunct to other conventional epilepsy treatments. We conclude that folic acid alleviates the behavioral manifestations of lindane-induced seizures in rats. Based on these findings, a potential adjuvant for lindane-poisoned patients is proposed; however, further investigations aimed at gaining a better understanding of the relevant biological mechanisms and examination of the potential beneficial or adverse effects are necessary.

Funding: This work was supported by the Ministry of Education, Science and Technological Development of Serbia, Grant #175032.

Author contributions: EDj, DH, OS and ARM designed the experiment, performed the experiments and drafted the manuscript. NS, DS, ZG and VC contributed to the behavioral studies and the draft of the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest disclosure: The authors do not have conflicting interests.

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