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The effects of hydrogen sulfide synthesis inhibition in lindane-induced seizures in rats: a behavioral and EEG study

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Abstract: Lindane-induced seizure in rats is a model of refractory generalized epilepsy. Hydrogen sulfide (H_2S) is a gasotransmitter with different physiological and pathological roles. Cystathionine-β-synthase (CBS) is a major enzyme responsible for H_2S production in the brain. The aim of this study was to investigate the effects of H_2S production inhibition using aminooxyacetate (a CBS inhibitor) on behavioral and EEG manifestations of lindane-induced seizures. Male *Wistar* rats with previously implanted EEG electrodes were intraperitoneally (i.p.) treated with 4 mg/kg lindane and observed for convulsive behavior and EEG manifestations during the next 30 min. Aminooxyacetate (5, 15 and 25 mg/kg, i.p.) or saline, was injected 30 min prior to lindane. Convulsive behavior was assessed by seizure incidence, latency time and severity (grades 0-4). The number and duration of ictal periods in the EEG were also analyzed. Seizure incidence was higher in rats treated with aminooxyacetate (AOA) before lindane, but not significantly when compared with those treated only with lindane. However, AOA significantly decreased the latency time and augmented the severity of lindane-induced seizures in a dose-dependent manner. EEG analysis revealed an increased number and duration of ictal periods in rats receiving AOA prior to lindane. H_2S production inhibition aggravated lindane-induced seizures, which showed a functional relationship between H_2S and the effects of lindane.

Keywords: aminooxyacetate; cystathionine-β-synthase; EEG; hydrogen sulfide; lindane

INTRODUCTION

Epilepsy, one of the most common chronic neurological disorders, is caused by sudden, hypersynchronous and excessive activity of neurons. It is often characterized by specific motor manifestations appearing as seizures [1].

Lindane (γ-hexachlorocyclohexane) is an organochlorine pesticide and scabicide widely used in agriculture and human and veterinary medicine. The use of lindane is present today, especially in developing countries. Symptoms of intoxication caused by lindane range from headache and vertigo to convulsive seizures and death [2]. The basis of the proconvulsive properties of lindane lies in several different mechanisms that are still not fully understood [3] and the blockage of γ-aminobutyric acid type A ($GABA_A$) receptor is thought to be the major mechanism [4].

Due to the limitations of clinical studies, the results gained from animal-based experiments can help in the selection of promising drugs and their combinations, but also in the clarification of mechanisms underlying epileptic activity [5]. In order to scrutinize the mechanisms of lindane effects and the possibility of anticonvulsive therapy, an experimental model of lindane-induced seizure in rats has been developed [6]. Lindane-induced seizures are challenging from a therapeutic viewpoint since these seizures are refractory to numerous classical antiepileptic drugs [7]. Therefore, this model is believed to be suitable for the exploration of refractory epilepsy.

Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) belong to the family of gas transmitters. Until recently, H_2S has been considered only as a toxic gas. Nowadays, researchers are mainly interested in H_2S created by mammalian enzymes under physiological conditions and its involvement in the mechanisms of various pathological conditions. Namely, there are indications that H_2S participates in the pathogenesis of

diseases in the CNS, particularly in the development of Parkinson's disease, Alzheimer's disease, stroke, traumatic brain injury as well as some others [8,9].

Endogenous H_2S is produced from L-cysteine by the activity of two enzymes, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) [10]. Increased expression of CBS was mainly detected in the cerebellum and hippocampus of rats compared to the cortex and brain stem while no expression of CSE was found in the brain [11]. Thus, the key enzyme responsible for H_2S production in the brain is CBS, which in humans and rats takes the form of a homotetramer [12]. H_2S at physiological concentrations facilitates the induction of long-term potentiation (LTP) in the hippocampus; however, at high concentrations it inhibits the synaptic response. This points to neuromodulatory effects of H_2S in the brain [11] and the possibility of its involvement in mechanisms of initiation and development of epileptic activity. It is possible to modulate the concentration of H_2S in a dose-dependent manner for experimental purposes with aminooxyacetate or hydroxylamine as selective inhibitors of CBS [13,14].

Therefore, the aim of this study was to determine the effects of AOA, a widely-used CBS inhibitor, on the behavioral and EEG manifestations of seizures induced by lindane in adult male rats and to elucidate the role of H_2S in the mechanisms of lindane-induced epileptic activity.

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. Adult, two-month-old male *Wistar albino* rats, obtained from the Military Medical Academy breeding laboratory (Belgrade, Serbia), were used in the experiments. The animals were housed individually in transparent plexiglass cages (55x35x30 cm) with access to food and water *ad libitum* during the entire experiment. They were kept under controlled ambient conditions (22-24°C, 50±5% relative humidity, 12/12h light/dark cycle with the light turned on from 8:00 to 20:00 h). Animals were used only once during the experiment. The acclimatization period to the laboratory ambience lasted for 7 days.

Study design and experimental procedures

The following experimental groups were formed based on literature data [14] and our preliminary experiments by a random distribution of rats: (i) control (C; 0.9% NaCl, n= 6); (ii) aminooxyacetate (AOA; 25 mg/kg, n= 6); (iii) lindane (L; 4 mg/kg, n= 9); (iv) AOA (5, 15 or 25 mg/kg) 30 min prior to L application: AOA5+L (n= 8); AOA15+L (n= 8) and AOA25+L (n= 8).

All drugs (Sigma Aldrich Co., USA) were freshly dissolved in saline and administered intraperitoneally (i.p.) in a volume of 0.1 mL/100 g rat body weight.

EEG electrode implantation

Upon being anesthetized (pentobarbital sodium 50 mg/kg, i.p.), three gold-plated recording electrodes were implanted in a stereotaxic apparatus over the frontal (2 mm rostrally to bregma and 2 mm from the median line), parietal (2 mm rostrally to lambda and 2 mm laterally to the median line) and occipital (2 mm caudally to lambda) cortices for further EEG recordings. The electrodes were fixed to the skull using dental acrylic cement. A one-week recovery period was allowed prior to further experiments. Also, 24-hour habituation to the recording environment was allowed to all animals.

Convulsive behavior assessment

Convulsive behavior was monitored for 30 min after lindane administration. The following parameters were assessed: incidence, latency period and seizure severity. Incidence was defined as the number of convulsing rats in a group and expressed as a percentage. The latency period was defined as the time between lindane administration and first seizure sign. Seizure severity was assessed by a modified descriptive scale with grades from 0 to 4, defined as follows: 0 – no seizure; grade 1 – head nodding and lower jaw twitching; grade 2 – myoclonic body jerks (hot-plate reaction) and bilateral forelimb clonus with full rearing (kangaroo position); grade 3 – progression to generalized clonic convulsions followed by tonic extension of fore and hindlimbs and tail; grade 4 – status epilepticus [15].

EEG registration and analysis

An 8-channel EEG apparatus (RIZ, Zagreb, Croatia) with a sampling frequency of 512 Hz/channel and 16-bit A/D conversion was used for EEG recording in freely moving rats. The signals were digitized using a SCB-68 data acquisition card (National Instruments Co, Austin, Texas, USA). Ambient noise was removed using a 50 Hz notch filter and the cutoff frequencies were set at 0.3 Hz and 100 Hz for the high-pass and low-pass filters, respectively. Data acquisition and signal processing were performed with LabVIEW platform software developed in the laboratory (NeuroSciLaBG) [3,16]. All EEG recordings were visually monitored and screened for ictal activity and stored on a disk for subsequent analysis. The rats were removed from the recording chamber and returned to their home cage at the end of the 30-min recording sessions.

Ictal periods in the EEG were defined as follows: (i) spontaneous and generalized spiking activity; (ii) lasting >1 s, and (iii) amplitude of at least twice the background EEG activity [3]. The number and duration of ictal periods were calculated during a 30-min period after lindane administration. All ictal periods were detected visually.

Data analysis

The statistically significant difference in incidence was determined by Fisher's exact probability test. Since the normal distribution of the data regarding latency periods and their severity, as well as the number and duration of ictal periods in the EEG, were not determined by the Kolmogorov-Smirnov test, non-parametric Kruskal-Wallis ANOVA and Mann Whitney U tests were applied for further data assessment of statistically significant differences between groups (*P<0.05, **P<0.01). The results were expressed as medians with 25th and 75th percentiles.

RESULTS

Convulsive behavior analysis

Rats injected with AOA at the highest applied dose, as well as rats in the control groups, did not show any signs of convulsive behavior. Seizure behavior was recorded in all animals treated with lindane. The greatest number of animals with seizures was in the group treated with AOA at the dose of 25 mg/kg prior to the subconvulsive dose (4 mg/kg) of lindane (AOA25+L, 75%). The incidence of seizures exhibited a tendency to increase after AOA administration in a dose-dependent manner (Fig. 1). Although the incidence of seizures was higher in group AOA25+L compared to group L, the recorded difference (75% vs 33.33%) did not reach statistical significance (P>0.05, Fig. 1).

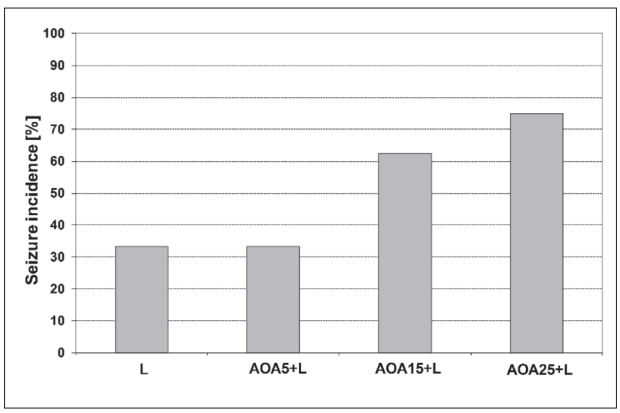

Fig. 1. The effect of aminooxyacetate on the incidence of lindane-induced seizures in rats. Seizure incidence was defined as the number of rats with seizures out of the total number of rats in the group, expressed as the percentage. Seizures were induced by lindane (L, 4 mg/kg, n=9). Aminooxyacetate (AOA 5, 15 and 25 mg/kg) was administered 30 min prior to L (AOA5+L, AOA15+L and AOA25+L, n=8 in each). The statistical significance of the differences between the groups was estimated by Fisher's exact probability test.

Aminooxyacetate decreased the latency period of seizures induced by lindane, but only significantly at the dose of 25 mg/kg (P<0.05). The reductions achieved with the other two doses of AOA were not statistically significant (P>0.05) (Fig. 2A).

When seizure intensity was analyzed, it was determined that the aminooxyacetate increased the severity of seizures induced by lindane in a dose-dependent manner. The intensity of seizures was significantly higher in AOA15+L and AOA25+L in comparison to the L group (P<0.05, Fig. 2B), as well as in the AOA25+L group when compared to the AOA5+L group.

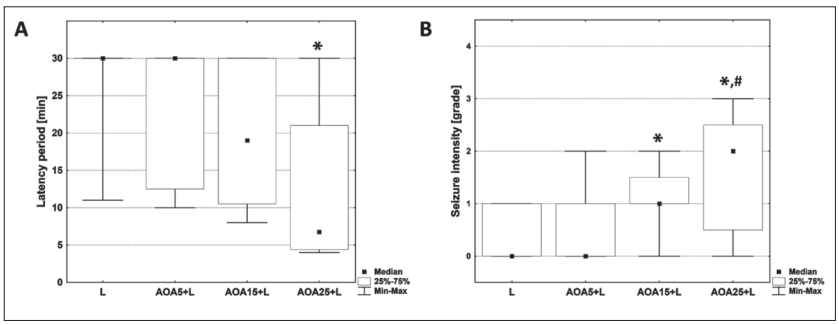

Fig. 2. The effect of aminooxyacetate on the latency period of lindane-induced seizures in rats (**A**) and their severity (**B**). **A** – The latency period defined as the time between lindane administration and the first seizure sign. **B** – The severity of seizure episodes determined by a descriptive rating scale with the following grades: 1 – head nodding, lower jaw twitching; 2 – myoclonic body jerks (hot plate reaction), bilateral forelimb clonus with full rearing (kangaroo position); 3 – progression to generalized clonic convulsions followed by tonic extension of fore and hindlimbs and tail; 4 – prolonged severe tonic-clonic convulsions lasting over 20 s (status epilepticus) or frequently repeated episodes of clonic convulsions for an extended period of time (longer than 5 min). The significance of the differences between the groups was estimated by the Kruskal-Wallis ANOVA and Mann-Whitney U test (**P*<0.05 vs L, #*P*<0.05 vs AOA5+L). For details refer to the caption to Fig. 1.

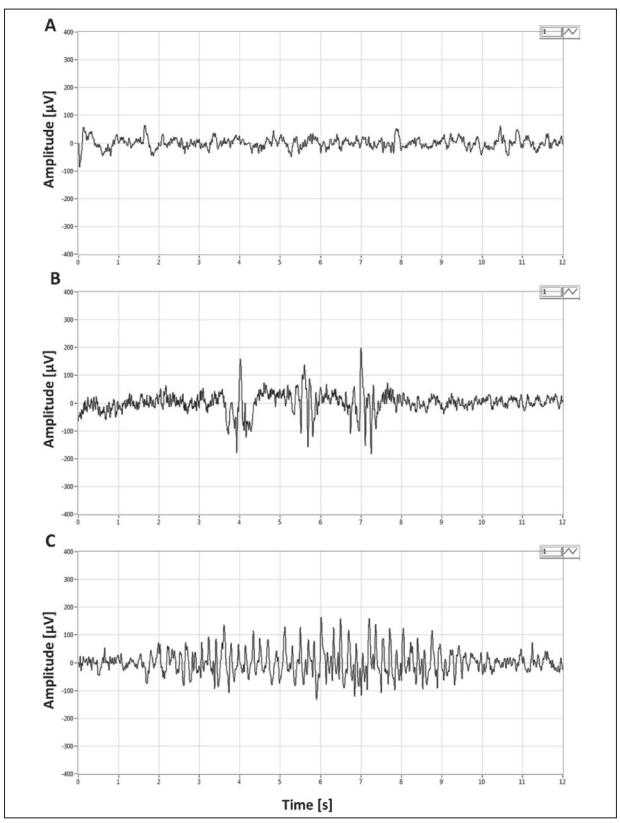

Fig. 3. Representative EEG tracings. **A** – control group 15 min after saline treatment; **B** – lindane group 15 min after lindane administration; **C** – AOA25+L group 15 min after lindane administration**.** Note baseline activity without signs of epileptiform discharges in **A**, isolated spikes and waves in **B**, and the ictal pattern in **C**. Lead: left frontal – right parietal cortex. For details refer to the caption to Fig. 1.

EEG analysis

EEG recordings in rats from control groups and rats treated only with the highest dose of AOA showed no signs of ictal activity (baseline EEG recording, Fig. 3A). Injection of lindane induced the appearance of isolated spikes and waves (Fig.3B), while AOA pretreatment induced ictal periods consisting of a series of high-amplitude spikes (EEG ictal period, Fig. 3C). The number and duration of these ictal periods were quantitatively analyzed.

Off-line analysis of ictal periods exposed the differences between these groups. The number of ictal periods per rat was significantly higher in the AOA25S+L group than in the L group ($P<0.05$, Fig. 4A). The same holds true for the duration of ictal periods (AOA25+L vs L, $P<0.05$, Fig. 4B).

DISCUSSION

The results of this study showed that systemic administration of aminooxyacetate, a selective CBS inhibitor [14,17], showed a tendency to increase the incidence of lindane-induced convulsions, significantly increasing their intensity and, at the same time, shortening the latent period until the occurrence of the seizure. The EEG analysis that was performed in this study showed that AOA significantly increased the number and duration of lindane-induced EEG ictal periods at subconvulsive doses.

Lindane, whether administered intraperitoneally or orally, leads to tonic and clonic seizures in a dose-dependent manner [3,16]. These seizures are associated with a characteristic EEG pattern. There are many different mechanisms, such as blockage of $GABA_A$ receptors [4], which could explain the convulsive effect of lindane, but they are not fully understood. On the other hand, it has been proven that H_2S mitigates damage to the hippocampus by preventing the loss of $GABA_B$ receptors during recurrent febrile seizures

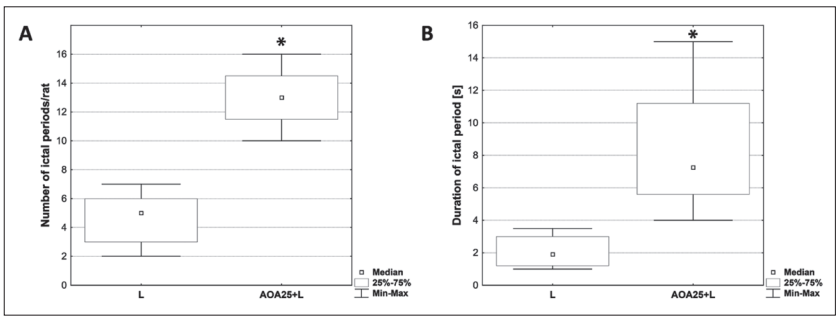

Fig. 4. The number (**A**) and duration (**B**) of ictal periods during EEG recordings of 30 min upon lindane administration. The significance of the differences between the groups was estimated by Kruskal-Wallis ANOVA and Mann-Whitney U test (**P*<0.05 vs L). For details refer to the caption to Fig. 1 and Fig. 3.

[18,19]. In this manner, H_2S can achieve a balance between excitation and inhibition during seizures, facilitating the occurrence of hyperpolarization. These findings [20] are in concordance with the results of this study. Recently, the involvement of NO-mediated signaling mechanisms in lindane-induced seizures was proven [3], thus demonstrating the involvement of gasotransmitters in lindane seizures and providing a clue that other gasotransmitters like H_2S could contribute to these mechanisms [21].

Lindane-induced seizures could only be partially antagonized by carbamazepine, phenytoin, felbamate, lamotrigine, gabapentin and vigabatrin [22] and acute high-dose administration of alcohol and ifenprodil to rats [23,24], showing that lindane-induced seizures are extremely refractory to conventional and new antiepileptic drugs. These findings favor lindane convulsions as a model of refractory seizures. Therefore, investigations into the mechanisms involved in lindane proconvulsive effects are of particular importance.

There are several possible ways to explain the results of this study, which showed potentiation of lindane-induced seizures after the administration of aminooxyacetate, i.e. a selective CBS block. The anticonvulsive effects of H_2S may be achieved via activation of K^+ channels in the hippocampus [25] since these channels have a role in the control of epileptic seizures [26]. Moreover, H_2S activates Cl^- channels and increases the influx of Cl^- in the cells, leading to a decrease in excitability [27]. It was shown that H_2S also contributes to protection from oxidative stress, one of the mechanisms that may be involved in epileptogenesis. Namely, it has been demonstrated that H_2S stimulates the enzyme γ-glutamylcysteine synthetase (γ-GSC), thus causing an increase in the level of glutathione, which is an antioxidant [28]. Also, H_2S has an effect on numerous Ca^{2+} channels and regulates neurotransmitter release and gene expression [29]. On the other hand, it is believed that intracellular Ca^{2+} mobilization is involved in lindane neurotoxicity [4]. Also, the physiological level of H_2S in the brain protects the CNS against oxidative stress, neuroinflammation and neurodegenerative diseases [30,31]. H_2S could also be a potent neuroprotective agent [32].

However, there are findings that point to a proconvulsive role of H_2S. Namely, the latest research on the role of H_2S in the pathogenesis of seizure-like events showed that NaHS, a donor of H_2S, activated voltage-dependent Na^+ channels, which increased the number and amplitude of the action potentials [33]. Similar results are presented in other studies [34], indicating that H_2S can act as a proconvulsant. H_2S-induced sulfhydration is another mechanism for establishing a proconvulsive state since ion channels and receptors for excitatory amino acids become activated [35]. Recent studies have shown that H_2S simultaneously activates NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors involved in the pathogenesis of seizures [36-38]. This contests our hypothesis about the anticonvulsive property of H_2S. Obviously, H_2S has an ambiguous role in epileptogenesis that depends on many factors. The most important among them include different models of epilepsy, different concentrations of H_2S in different experiments, as well the unclear role of numerous H_2S metabolites produced in the body.

In this study, using aminooxyacetate as an inhibitor of the CBS enzyme, we demonstrated that lowering H_2S levels in the brain creates preconditions for the proconvulsive effects of lindane. The effects of aminooxyacetate potentiated lindane-induced seizures in adult rats, which can be seen in all tested parameters of behavioral and EEG characteristics. In this manner, it has been shown that there is a functional relationship between H_2S and the effects of lindane.

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Author contributions: NŠ, ARM, EDj and DH designed the experiment, performed the experiments and drafted the manuscript. ŽG and EDj contributed to the experimental studies and drafted the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest disclosure: The authors declare that they have no conflict of interest.

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-82.
2. Nolan K, Kamrath J, Levitt J. Lindane toxicity: a comprehensive review of the medical literature. Pediatr Dermatol. 2012;29(2):141-6.
3. Hrnčić D, Rašić-Marković A, Djuric D, Šušić V, Stanojlović O. The Role of nitric oxide in convulsions induced by lindane in rats. Food Chem Toxicol. 2011;49(4):947-54.
4. Costa LG. The neurotoxicity of organochlorine and pyrethroid pesticides. Handb Clin Neurol. 2015;131:135-48.
5. Löscher W. Single versus combinatorial therapies in status epilepticus: Novel data from preclinical models. Epilepsy Behav EB. 2015;49:20-5.
6. Vučević D, Hrncić D, Radosavljević T, Mladenović D, Rasić-Marković A, Loncar-Stevanović H, Djurić D, Macut D, Susić V, Stanojlović O. Correlation between electrocorticographic and motor phenomena in lindane-induced experimental epilepsy in rats. Can J Physiol Pharmacol. 2008;86(4):173-9.
7. Kaminski RM, Tochman AM, Dekundy A, Turski WA, Czuczwar SJ. Ethosuximide and valproate display high efficacy against lindane-induced seizures in mice. Toxicol Lett. 2004;154(1-2):55-60.
8. Kumar M, Sandhir R. Hydrogen sulfide in physiological and pathological mechanisms in brain. CNS Neurol Disord Drug Targets. 2018;17(9):654-70.
9. Kashfi K. The role of hydrogen sulfide in health and disease. Biochem Pharmacol. 2018;149:1-4.
10. Kimura H. Hydrogen sulfide and polysulfides as biological mediators. Mol Basel Switz. 2014;19(10):16146-57.
11. Kimura H. Signaling molecules: hydrogen sulfide and polysulfide. Antioxid Redox Signal. 2015;22(5):362-76.
12. Mendes MI, Colaço HG, Smith DE, Ramos RJ, Pop A, van Dooren SJ, Tavares de Almeida I, Kluijtmans LA, Janssen MC, Rivera I, Salomons GS, Leandro P, Blom HJ. Reduced response of Cystathionine Beta-Synthase (CBS) to S-Adenosylmethionine (SAM): Identification and functional analysis of CBS gene mutations in Homocystinuria patients. J Inherit Metab Dis. 2014;37(2):245-54.
13. Powell CR, Dillon KM, Matson JB. A review of hydrogen sulfide (H2S) donors: Chemistry and potential therapeutic applications. Biochem Pharmacol. 2018;149:110-23.
14. Donatti AF, Soriano RN, Sabino JP, Branco LGS. Involvement of endogenous hydrogen sulfide (H2S) in the rostral ventrolateral medulla (RVLM) in hypoxia-induced hypothermia. Brain Res Bull. 2014;108:94-9.
15. Stanojlović O, Rasić-Marković A, Hrncić D, Susić V, Macut D, Radosavljević T, Djuric D. Two Types of Seizures in Homocysteine Thiolactone-Treated Adult Rats, Behavioral and Electroencephalographic Study. Cell Mol Neurobiol. 2009;29(3):329-39.
16. Stanojlović O, Nikolić T, Hrnčić D, Radonjić N, Rašić-Marković A, Mladenović D, Petronijević N. Ontogenetic influence on rat susceptibility to lindane seizure after pretreatment with phencyclidine. Environ Toxicol Pharmacol. 2013;35(2):161-70.
17. Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci Off J Soc Neurosci. 1996;16(3):1066-71.
18. Han Y, Qin J, Chang X, Yang Z, Bu D, Du J. Modulating effect of hydrogen sulfide on gamma-aminobutyric acid B receptor in recurrent febrile seizures in rats. Neurosci Res. 2005;53(2):216-219.
19. Wiles DA, Russell JL, Olson KR, Walson PD, Kelley M. Massive lindane overdose with toxicokinetics analysis. J Med Toxicol. 2015;11(1):106-109.
20. Han Y, Qin J, Chang X, Yang Z, Tang X, Du J. Hydrogen sulfide may improve the hippocampal damage induced by recurrent febrile seizures in rats. Biochem Biophys Res Commun. 2005;327(2):431-6.
21. Gupta YK, Dahiya AK, Reeta KH. Gaso-transmitter hydrogen sulphide: potential new target in pharmacotherapy. Indian J Exp Biol. 2010;48(11):1069-77.
22. Tochman AM, Kamiński R, Turski WA, Czuczwar SJ. Protection by conventional and new antiepileptic drugs against lindane-induced seizures and lethal effects in mice. Neurotox Res. 2000;2(1):63-70.
23. Mladenović D, Hrncić D, Vucević D, Radosavljević T, Loncar-Stevanović H, Petrović J, Susic V, Djuric D, Stanojlović O. Ethanol suppressed seizures in lindane-treated rats. Electroencephalographic and behavioral studies. J Physiol Pharmacol. 2007;58(4):641-56.
24. Hrncić D, Rasić-Marković A, Susić V, Djurić D, Stanojlović O. Influence of NR2B-selective NMDA antagonist on lindane-induced seizures in rats. Pharmacology. 2009;84(4):234-9.
25. Dawe GS, Han SP, Bian JS, Moore PK. Hydrogen sulphide in the hypothalamus causes an ATP-sensitive K+ channel-dependent decrease in blood pressure in freely moving rats. Neuroscience. 2008;152(1):169-77.
26. Yamada K, Inagaki N. Neuroprotection by KATP channels. J Mol Cell Cardiol. 2005;38(6):945-9.
27. Kimura Y, Dargusch R, Schubert D, Kimura H. Hydrogen sulfide protects HT22 neuronal cells from oxidative stress. Antioxid Redox Signal. 2006;8(3-4):661-70.
28. Kimura Y, Kimura H. Hydrogen sulfide protects neurons from oxidative stress. FASEB J Off Publ Fed Am Soc Exp Biol. 2004;18(10):1165-1167.
29. Tan BH, Wong PT-H, Bian J-S. Hydrogen sulfide: a novel signaling molecule in the central nervous system. Neurochem Int. 2010;56(1):3-10.

30. Shefa U, Kim M-S, Jeong NY, Jung J. Antioxidant and Cell-Signaling Functions of Hydrogen Sulfide in the Central Nervous System. Oxid Med Cell Longev. 2018;2018:1873962.
31. Paul BD, Snyder SH. Gasotransmitter hydrogen sulfide signaling in neuronal health and disease. Biochem Pharmacol. 2018;149:101-9.
32. Chen WL, Niu YY, Jiang WZ, Tang HL, Zhang C, Xia QM, Tang XQ. Neuroprotective effects of hydrogen sulfide and the underlying signaling pathways. Rev Neurosci. 2015;26(2):129-42.
33. Luo Y, Wu PF, Zhou J, Xiao W, He JG, Guan XL, Zhang JT, Hu ZL, Wang F, Chen JG. Aggravation of seizure-like events by hydrogen sulfide: involvement of multiple targets that control neuronal excitability. CNS Neurosci Ther. 2014;20(5):411-9.
34. Chao D, He X, Yang Y, Balboni G, Salvadori S, Kim DH, Xia Y. Hydrogen sulfide induced disruption of Na+ homeostasis in the cortex. Toxicol Sci. 2012;128(1):198-208.
35. Hou XY, Hu ZL, Zhang DZ, Lu W, Zhou J, Wu PF, Guan XL, Han QQ, Deng SL, Zhang H, Chen JG, Wang F. Rapid Antidepressant Effect of Hydrogen Sulfide: Evidence for Activation of mTORC1-TrkB-AMPA Receptor Pathways. Antioxid Redox Signal. 2017;27(8):472-88.
36. Rogawski MA. Revisiting AMPA receptors as an antiepileptic drug target. Epilepsy Curr. 2011;11(2):56-63.
37. Frasca A, Aalbers M, Frigerio F, Fiordaliso F, Salio M, Gobbi M, Cagnotto A, Gardoni F, Battaglia GS, Hoogland G, Di Luca M, Vezzani A. Misplaced NMDA receptors in epileptogenesis contribute to excitotoxicity. Neurobiol Dis. 2011;43(2):507-15.
38. Yakovlev AV, Kurmasheva ED, Giniatullin R, Khalilov I, Sitdikova GF. Hydrogen sulfide inhibits giant depolarizing potentials and abolishes epileptiform activity of neonatal rat hippocampal slices. Neuroscience. 2017;340:153-65.