Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20140427

Research Article

To study the oxidative stress induced by lindane in epileptic rats brains and their modulation by neurosteroids

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Received: 27 February 2014
Accepted: 07 March 2014

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ABSTRACT

Background: Lindane is pesticide has been shown to affect the nervous system adversely. Previous work has shown that lindane is proconvulsant and neurosteroids (NS) has been shown to be neuroprotective against lindane-induced convulsions. As the mechanisms of lindane in epileptogenesis is not completely understood. The present study was designed to investigate the oxidative stress parameters of lindane toxicity in epileptogenesis and their modulation by NS like allopregnanolone (AP), and 4′-chlorodiazepam (4′-CD) in pentylenetetrazole (PTZ) kindling methods.
Methods: Kindling was induced by injecting PTZ (30 mg/kg; s.c.) on alternate days i.e., 3 times in a week. Lindane was also administered (15 mg/kg p.o) on alternate days for 6 weeks. AP (2.5 mg/kg, intaperitoneal [i.p.]) and 4′-CD (0.5 mg/kg, i.p.) single dose was given in kindled rats before lindane.
Results: Following per oral administration of lindane for 6 weeks produced significant oxidative stress in epileptic brain. There was an increase in brain malondialdehyde (MDA) level and decrease in reduced glutathione (GSH) levels. AP (2.5 mg/kg, i.p.) and 4′-CD (0.5 mg/kg, i.p.) single dose administration were not able to reverse the effect of chronic exposure of lindane.
Conclusion: The result of the present study provides evidence that oxidative stress produced in the brain after chronic exposure of lindane may be the mechanism of epileptogenesis. Though NS have been shown to be neuroprotective, but they failed to reverse chronic oxidative stress produced by lindane. Further studies are required to demonstrate interaction of NS with lindane in oxidative stress.

Keywords: Epilepsy, Neurosteroids, Lindane, PTZ

INTRODUCTION

By definition, pesticide is any substance or mixture of substances intended for preventing, repelling, destroying or mitigating any pest. There is mounting concern regarding the toxic effects of pesticides specifically organochlorine pesticides like Lindane. It had been used for agricultural, domestic and human application. Lindane was an ingredient of shampoo and was used to remove head lice. Due to its long half-life, persistent in the environment and bio accumulation potential through food chain resulted adverse effect to human health.[1] Lindane had been shown to be neurotoxicant because it accumulates in brain due to lipophilic nature and slow rate of biotransformation.[2] Lindane has been reported to induce oxidative stress in hepatic,[3] testicular,[4] and neuronal tissue[5,6] of rats. At present oxidative stress mechanisms of lindane in epilepsy not widely documented. Lindane has been shown to stimulate the brain by increasing neurotransmitter release from neurons and alter the activity of membrane associated enzymes, like acetylcholine-esterase and Na^+/K^+ ATPase.[7] Lindane toxicity results in mixed type of seizure grand mal, petit mal, and myoclonus.[8] Exposure to pesticides can induce oxidative stress, by increased production of free radicals that further accumulate in the cell and alter antioxidant defense mechanisms. Excessive production of reactive oxygen species (ROS) can causes oxidative modification of lipid, proteins, and DNA. Endogenous non-enzymatic (glutathione, GSH) and enzymatic (superoxide dismutase), catalase, GSH peroxidase, detoxify these ROS and protect cells. Due to continuous exposure of pesticides, level of these endogenous antioxidants decreases, leading to accelerated cell death.[9]

The neurosteroids (NS) can be defined as the steroid hormones synthesized from cholesterol in the nervous system, independent of the endocrine glands. The

examples of important NS are allopregnanolone (AP) and allotetrahydrodeoxycorticosterone (THDOC), pregnenolone sulfate (PS) and dehydroepiandrosterone sulfate (DHEAS), etc.[10] NS alter neuronal membrane excitability rapidly by modulation of neurotransmitter receptors like gamma-aminobutyric acid ($GABA_A$), nicotininc, muscarinic, N-methyl-D-aspartate, sigma, kainate, glycine, serotonergic and neuropeptide receptors.[11] NS are known to be involved in various physiological and pathological states such as behavior, stress, depression, anxiety, convulsions, memory, and neurodegenerative disorders.[12] There are some compounds which enhances synthesis of NS in brain like 4′-chlordiazepam (4′-CD) which is known as NS synthesis enhancer was also used in the study. Some reports have shown antioxidant property of AP, 4′-CD in rat brain in memory and cognation.[11-13] Previous work has demonstrated the anticonvulsant effect of NS in lindane induced convulsion. Interaction of NS and lindane with oxidative stress, which is involved in development of epilepsy has not been documented widely. We hypothesized that oxidative stress produced by lindane play a role in development of various neurological diseases particularly in epilepsy. Antioxidant effect of NS may modulate the oxidative stress parameters. Thus, the study was designed to investigate mechanisms of oxidative stress produced by lindane in epileptic rats and their reversal by antioxidant NS AP and 4′ CD.

METHODS

Animals

Male Wistar rats weighing between 150 and 200 g were used for the study. Animals were procured from Central Animal House, University College of Medical sciences, Delhi and maintained on natural light-dark cycle; 23 ± 1°C temp and 50 ± 2% humidity. The animals were housed under standard laboratory conditions and bulk fed with pellet diet and water ad libitum. The animals were acclimatized to laboratory conditions prior to experimentation.

Permission was taken from Institutional Animal Ethics Committee and the care of the animals was done as per "CPCSEA Guidelines for laboratory animal facilities".

Drugs and chemicals

Lindane, AP, and pentylenetetrazole (PTZ) were purchased from Sigma chemicals (USA). 4′-CD procured from Fluka (USA). All other chemical used were laboratory grade. Lindane was given per orally (p.o.) with ground nut oil as vehicle. To limit the weight gain of animals due to ground nut oil consumption, the concentration of lindane was maintained so that no animal receive more than 0.5 ml oil per day any time during study periods. AP and 4′-CD were administered by i.p. route. The vehicle for them was distilled water with two drops of Tween −80 added per 10 ml of suspension. Concentration was maintained so that each animal received 0.5 ml/100 g of suspension.

Groups

Animals were randomly divided into ten groups for chronic study having 10 rats/group

Group 1: Control group; vehicle for Lindane (ground nut oil, p.o.) on alternate day (3 days in week) for 6 week.
Group 2: Lindane; 15 mg/kg, (p.o.) on alternate day for 6 weeks.
Group 3: Vehicle for Lindane (p.o.) on alternate day for 6 weeks followed by AP; 2.5 mg/kg, (i.p.).
Group 4: Vehicle for Lindane (p.o.) on alternate day for 6 weeks followed by 4′-CD; 0.5mg/kg, (i.p.).
Group 5: PTZ; 30 mg/kg, (s.c.) on alternate days for 6 weeks.
Group 6: PTZ; 30 mg/kg, (s.c.) on alternate days for 6 week followed by AP; 2.5 mg/kg, (i.p).
Group 7: PTZ; 30 mg/kg, (s.c.) on alternate for 6 week followed by 4′-CD; 0.5 mg/kg, (i.p).
Group 8: PTZ; 30 mg/kg, (s.c.) and Lindane; 15 mg/kg, (p.o.) alternate with each other for 6 week
Group 9: PTZ; 30 mg/kg, (s.c.) and Lindane; 15 mg/kg, (p.o.) alternate with each other for 6 week followed by AP; 2.5 mg/kg, (i.p.).
Group 10: PTZ; 30 mg/kg, (s.c.) and Lindane; 15 mg/kg, (p.o.) alternate with each other for 6 weeks followed by 4′-CD; 0.5 mg/kg, (i.p.).

PTZ-induced kindling

A subconvulsive dose of PTZ; 30 mg/kg, s.c. was administered on alternate days, 3 times a week till kindling took place i.e., period of 6 week. The lindane groups also received 15 mg/kg lindane p.o. along with PTZ on alternate days. All animals were observed after injections, for any manifestations of convulsive episodes.

The evaluation of seizures activity was done as follows:

- Stage 0: No response
- Stage 1: Ear and facial twitching, severing, abnormal writhing
- Stage 2: Myoclonic jerks
- Stage 3: Clonic fore limb convulsion
- Stage 4: Generalized clonic convulsions with tonic rearing and falling down episodes
- Stage 5: Generalized convulsion with tonic extension episodes and status epilepticus.

When the animal reached at stage 4 or 5 at 3 consecutive injections at 72 hr interval, it was defined as kindled and treatment was discontinued.[14] Rats fulfilled the kindling criteria after 6 weeks of lindane and PTZ administration. AP and 4′-CD were administered 15 min and 30 min before the PTZ injection in the kindled animals to see antiepileptic effect. After the seizure subsided rats were scarified to asses oxidative stress parameters.

Assessment of oxidative stress

Sacrificing the animal

At the end of treatment rats were sacrificed under ether anesthesia. Whole brain was gently removed from the cavity with the help of spatula. Soon after removal it was washed in ice cold sodium phosphate buffer. The brain was then blotted dry and weight was taken. Brains were further processed and estimation of oxidative stress done on the same working day.

Brain tissue was homogenized with 10 times (w/v) sodium phosphate buffer (7.4 pH, ice cold, mixture of KH_2PO_4, and Na_2HPO_4). The homogenate was centrifuged at 3000 rpm for 15 min. The parameters of oxidative stress used were malondialdehyde (MDA) and reduced GSH.

Estimations of MDA

MDA (indicator of lipid peroxidation) was estimated as described by Okhawa et al.[15]

Procedure

Acetic acid (20%, pH 3.5) 1.5 ml, thiobarbituricacid (0.8%), sodium lauryl sulfate (8.1%) 0.2 ml were added to 0.5 ml of supernatant obtained above. The mixture was heated at 100°C for 1h in boiling water bath. The mixture was cooled with tap water and 5 ml of butanol: pyridine (15:1 % v/v) and 1 ml of distilled water were added. The mixture was vortexed vigorously and was centrifuged at 4000 rpm for 10 min. Thereafter the organic layer was withdrawn and absorbance measured at 532 nm using a spectrophotometer.

Standard curve

Various samples of external standard tetra ethoxypropane (1-10 nmol) were subjected to the steps mentioned in the above procedure. The readings of absorbance were plotted against the concentration of MDA to produce a standard curve. The concentration of MDA was determined by the linear standard curve and expressed as nmol/g wet brain tissue.

Estimation of Reduced GSH

Reduced GSH was estimated by the method described by Ellman.[16] To 0.5 ml of the supernatant obtained above 1 ml TCA (5%) was added and the mixture centrifuged to remove the proteins. To 0.1 ml of this homogenate, 4 ml of phosphate buffer (pH 8.4), 0.5 ml of DTNB and 0.4 ml double distilled water were added. The mixture was vortexed and absorbance read at 412 nm within 15 min.

Standard curve

Various concentrations of standard GSH (5-50 µg) were subjected to the steps mentioned above. The readings of absorbance were plotted against the concentration of GSH to produce standard curve. The concentration of GSH was determined by linear standard graph and expressed as µg/g wet brain tissue.

Data analysis

All results were expressed as mean ± standard error of the means. Difference between treatment group for MDA and reduces GSH levels were analyzed using one-way ANOVA with *post hoc* Tukey test, using SPSS v13 software. $p < 0.05$ were considered significant.

RESULTS

MDA

There was a marked and significant ($p < 0.001$) increase in the brain MDA levels in the lindane treated group as compared to the control group which indicates that lindane does cause oxidative stress and increases lipid peroxidation. Furthermore, there was significant ($p < 0.001$) increase in MDA levels in PTZ plus lindane treated group as compared to lindane alone group. The MDA levels were significantly lowered ($p < 0.001$) in the AP and 4′-CD treated groups as compared to lindane group. However, AP and 4′-CD single dose did not show any effect on the brain MDA levels when compared with control group. AP (2.5 mg/kg i.p.) and 4′-CD (0.5 mg/kg i.p.) single dose failed to modulate the chronic effect of lindane on MDA levels in kindled brain (Table 1).

Reduced GSH

A significant decrease was found in brain GSH levels of lindane treated groups. The GSH levels were significantly ($p < 0.001$) reduced in group which received lindane along with PTZ when compared to only lindane-treated group. There was no significant difference of GSH levels in AP and 4′-CD group as compared to control group. AP (2.5 mg/kg i.p.) and 4′-CD (0.5 mg/kg i.p.) single dose also failed to increase GSH levels in brain. Further, they failed to modulate the decrease in GSH levels produced by PTZ and lindane treatment (Table 2).

DISCUSSION

Pesticide induced oxidative stress as a possible mechanism of toxicity has been focus of toxicological research for the last few decades. Yet for certain pesticides mechanism leading to oxidative stress is partially understood. Pesticide induced

Table 1: Effect of lindane and neurosteroid on brain levels of MDA (nmol/g) in PTZ - kindled rats.

Group	Treatment (mg/kg, route)	MDA (nmol/g wet brain tissue) (mean±SEM)
Control	Vehicle for lindane, p.o. + vehicle for NS	171.23±1.87
Lindane	15 mg/kg, p.o. on alternate day	505.73±1.57[a]
PTZ	30 mg/kg, s.c.	495.62±2.65[a]
PTZ + lindane	30 mg/kg, s.c. + 15 mg/kg, p.o	593.53±3.83[a,b]
AP	2.5 mg/kg, i.p.	166.87±1.33[b]
4′-CD	0.5 mg/kg, i.p.	168.58±2.26[b]
PTZ + AP	30 mg/kg, s.c. + 2.5 mg/kg, i.p.	500.16±1.91[a]
PTZ + 4′-CD	30 mg/kg, s.c.+ 0.5 mg/kg, i.p.	498.86±1.97[a]
PTZ + lindane + AP	30 mg/kg, s.c. + 15 mg/kg, i.p. + 2.5 mg/kg, i.p.	575.50±3.78[a,b]
PTZ + lindane + 4′-CD	30 mg/kg, s.c. + 15 mg/kg, i.p. + 0.5 mg/kg, i.p.	574.94±2.79[a,b]

[a]$p < 0.001$ as compared to control group, [b]$p < 0.001$ as compared to lindane treated group. Comparison was done using one-way ANOVA followed by Tukey's *posthoc* test

Table 2: Effect of lindane and neurosteroid on brain levels of GSH (µg/g) in PTZ - kindled rats.

Group	Treatment (mg/kg, route)	GSH (µg/g of wet brain) (mean±SEM)
Control	Vehicle for lindane, p.o. + vehicle for NS	390.43±4.52
Lindane	15 mg/kg, p.o. on alternate days	203.47±1.94[a]
PTZ	30 mg/kg, s.c.	202.46±1.77[a]
PTZ + lindane	30 mg/kg, s.c. + 15 mg/kg, p.o	164.40±2.26[a,b]
AP	2.5 mg/kg, i.p.	402.26±2.27[b]
4′-CD	0.5 mg/kg, i.p.	394.30±3.58[b]
PTZ + AP	30 mg/kg, s.c. + 2.5 mg/kg, i.p.	210.45±2.86[a]
PTZ + 4′-CD	30 mg/kg, s.c. + 0.5 mg/kg, i.p.	213.78±1.169[a]
PTZ + lindane + AP	30 mg/kg, s.c. + 15 mg/kg, i.p. + 2.5 mg/kg, i.p.	174.24±2.17[a,b]
PTZ + lindane + 4′-CD	30 mg/kg, s.c. + 15 mg/kg, i.p. + 0.5 mg/kg, i.p.	170.63±1.71[a,b]

[a]$p < 0.001$ as compared to control group, [b]$p < 0.001$ as compared to lindane treated group. Comparison was done using one-way ANOVA followed by Tukey's *posthoc* test

oxidative stress is the final manifestation of a multiple step path way resulting in an imbalance between oxidant and prooxidant defense mechanisms. Pesticide intoxication induces derangements of certain antioxidant mechanisms in different tissues, including alteration in antioxidant enzymes and GSH redox system.[17] Lindane is an organochlorine pesticides produces its toxicity by generation of oxidative stress in various tissues such as liver, reproductive organs, and neural tissue.[3-6] It affect brain function adversely in the form of cognitive derangements, seizures and epilepsy. The exact role of lindane in epileptogenesis is needs to be explored further. NS are steroids synthesized within the brain and modulate neuronal excitability by rapid non-genomic actions. NS such as AP and THDOC, PS, and DHEAS.[10] They have been shown neuroprotective in epilepsy, anxiety, stress, and other neurobehavioral disorders.[18] Acute effects of NS are not related to interactions with classical steroid hormone receptors that regulate gene transcription. They modulate brain excitability primarily by interaction with neuronal membrane receptors and ion channels, principally GABA-A receptors[19] and therefore provide tremendous opportunities for developing therapeutic approaches.[20] In recent few years AP and 4′-CD had been investigated for their antioxidant potentials.[21]

Thus present study was hypothesized to evaluate the oxidative stress produced by lindane using PTZ kindling model of epilepsy and possible repair of oxidative derangements by NS single dose administration. Parameters of oxidative stress were included to find out the effect of lindane and NS in modulating oxidative activity in the present experimental set-up. Assessment of oxidative stress was done in kindled rats using MDA and GSH as parameters of oxidative stress.

PTZ induced kindling model of epileptogenesis is well-known standard method for development of epilepsy used in the present study Since PTZ has been reported to cause enhanced oxidative stress during convulsions.[22]

In the present study, lindane showed marked increase in oxidative stress in brain which was assessed by measuring brain MDA and GSH levels. These results are in accordance with the previous reports.[23,24] MDA, a product of lipid peroxidation is increased during xenobiotic-induced oxidative stress. The assay of MDA is often considered as an index of oxygen free radical generation. High levels of MDA in lindane exposed rats indicate that this compound enhances

lipid peroxidation and produces oxidative stress. The group of rats that received PTZ alone in chemical kindling also showed a significant increase in the MDA levels as compared to the control group. This finding is in accordance with the previous reports by other workers who have shown oxidative potential of PTZ. There was marked increase in MDA levels in the group of animals received lindane along with PTZ as compared to control group showing possibility of lindane exhibiting lipid peroxidation in brain in rats.

GSH is the most prevalent and important intracellular antioxidant. This compound is able to scavenge both singlet oxygen and hydroxyl radicals. Levels of GSH were decreased in the lindane group when compared to control group. The decrease in GSH level was marked in groups of rats which received PTZ along with lindane in kindled rats as compared to control group indicating there by the potential of lindane to cause oxidative stress. In our study AP and 4′-CD in the dose used failed to produce any effect on MDA and GSH levels per se. They did not modulate the oxidative stress produced by PTZ and lindane in kindled rats in the administered doses. Although the antioxidant property of various NS such as DHEA, PROG, and AP also have been hypothesized.[25] The lack of antioxidant property of AP and 4′-CD in kindled rats in this set up could be due to insufficient dose used for insufficient period of time to revert oxidative stress caused by lindane and PTZ. There is need to further demonstrate antioxidant effects of NS in modulating the chronic oxidative effects if lindane in the process of epileptogenesis.

CONCLUSION

Lindane chronic administration resulted in marked derangement in oxidative parameters in epileptic brain. This was manifested by marked increase in MDA levels and significant decrease in reduced GHS level. Thus, it proved the hypothesis that oxidative stress in brain produced by lindane leads to development of epilepsy. AP and 4′-CD in the single dose shown to protect convulsions in earlier studies but failed to modulate MDA and GSH in rat brain, also these agents were ineffective in counteracting the oxidative changes induced by lindane and PTZ. Finally, the data suggest that possibility for further investigation regarding mechanisms involved in neuroprotective role of NS against the neurotoxic effects of lindane particularly in epilepsy.

Funding: Funded by University College of Medical Sciences
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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doi: 10.5455/2319-2003.ijbcp20140427
Cite this article as: Tanwar K, Mediratta PK, Banerjee BD, Sharma KK. To study the oxidative stress induced by lindane in epileptic rats brains and their modulation by neurosteroids. Int J Basic Clin Pharmacol 2014;3:389-94.