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Neurotoxicity of Lindane and Picrotoxin: Neurochemical and Electrophysiological Correlates in the Rat Hippocampus In Vivo*

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In the present study, we compared in vivo changes of extracellular amino acid levels and nucleotide derivatives to a single *ip* dose of lindane (10–60 mg/kg) and picrotoxin (5 mg/kg) in the hippocampus of halothane anaesthetized rat by microdialysis-coupled HPLC analysis. Brain activity was monitored by EEG. The effects of lindane and picrotoxin on EEG pattern of rats as well as on hippocampal amino acid and nucleotide status were studied in 0–50 min, 50–100 min and 100–150 min periods post-dosing. Significant decreases in Glu and Asp were found after picrotoxin treatment. After 50–100 min post-dosing, hippocampal hypoxanthine and inosine levels increased to both lindane (10 mg/kg) and picrotoxin whereas xanthine and uridine levels increased to picrotoxin, only. Lindane elicited a dose-dependent occurrence of negative spikes accompanied with rhythmic activity at 4–5 Hz. The picrotoxin-induced 4–5 Hz activity did not display negative sharp waves and was accompanied by 10 Hz oscillations.

KEY WORDS: Lindane; picrotoxin; amino acids; nucleotides; EEG; microdyalisis.

INTRODUCTION

In vitro and in vivo data clearly supports that the antagonism of GABA-mediated inhibition is probably an important mechanism by which gamma-hexachlorocyclohexane (lindane) produces neuronal hyperexcitability and convulsions (1 and references cited there). Also, previous studies indicate that a global increase in transmitter release from presynaptic terminals probably does not occur during lindane intoxication (1 and references cited there). In vitro data have supported the hypothesis, as lindane decreases the evoked transmitter release of [^{3}H]D-aspartate (as a label for excitatory amino acids) from cultured granule neurons (2). Also, no detectable increase (3) but a decrease (4) of extracellular glutamate content was associated with the picrotoxin-induced seizures in the hippocampus. In the present study, we compared in vivo changes of extracellular amino acid levels to lindane and picrotoxin in the hippocampus by microdialysis-coupled HPLC analysis. In addition, since an increase in hippocampal adenosine release and metabolism associated with bicuculline-, kainic acid- and pentylenetetrazol-induced seizures has been evidenced (5) we attempted to measure changes in the extracellular concentrations of nucleotide derivatives to lindane and picrotoxin as well. EEG was also recorded to monitor brain activity.

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EXPERIMENTAL PROCEDURE

Microdialysis. Animal experiments were carried out as previously described (6) on the basis of local ethical rules in accordance with the Guidelines on the Use of Living Animals in Scientific Investigations 1984. Microdialysis probes were prepared as described earlier (7). Briefly, 5000 D cut-off hollow (Travenol, diameter 0.2 mm, length 3 mm) was adjusted into 24-gauge stainless steel tubing. Glass capillaries pulled from Jencons glass tubing were used for the inlet and outlet of the probe. These glass capillaries were guided by stainless steel tubes. Male Wistar rats (350–400 g, Toxicoop, Budapest, Hungary) were anaesthetized with 1% halothane in air and placed into a stereotaxic frame. The probes were implanted into the hippocampus (A: −5.2, L: 5, V: −8 mm) bilaterally, according to the atlas of Paxinos and Watson (8). To minimise tissue damage the final position of the probes was reached slowly, in not less than 15 min. We started to collect samples 120 min after the implantation of the microdialysis probe by perfusing nonpyrogenic, amino acid free, artificial cerebrospinal fluid (ACSF) containing 144 mM NaCl, 3 mM KCl, 1 mM $MgCl_2$ and 2 mM $CaCl_2$ (each from Sigma) in water, at a rate of 1.5 μl/min. The pH of ACSF was adjusted to 7.4 with NaOH prior to the microdialysis experiment started. To establish the ambient baseline amino acid and nucleoside concentrations, each experiment started with the collection of two control samples (75 μl). Drugs (lindane: 10, 20, 60 mg/kg, Aldrich; picrotoxin: 5 mg/kg, Sigma) were dissolved in 100% DMSO (Merck) and injected intraperitoneally (injected volume was 0.5 ml in all cases). To examine the effect of DMSO on amino acid and nucleoside levels, rats were injected intraperitoneally by the same amount of DMSO only. Three 75 μl samples were collected in every 50 minutes and kept in −20 C before measurement of amino acids and nucleosides from the same sample. After each experiment, the brain was removed and placed into 10% paraformaldehyde. Anatomical localisation of the dialysis probes were checked by histological analyses of Nissl-stained coronal sections.

Determination of the Concentration of Amino Acids in the Microdialysis Samples. To measure the amino acid concentrations, precolumn derivatization with OPA was used in the presence of mercaptoethanol at pH 10.4. Quantitative analysis of the OPA derivatized amino acids was performed in an automated HPLC (HP 1100 Series) with diode array detector at 338 nm (ref. 380 nm) on the basis of UV analysis of OPA derivated amino acids of Agilent Application Library (9). Separation of amino acids was performed by Agilent Hypersyl ODS reversed phase column (C18, 5μm spherical ODS, 200 × 2.1 mm, with 20 mm precolumn) with the following eluents: A: 0.1 M phosphate buffer containing 0.5% (vol/vol) tetrahydrofuran and 0.02% (vol/vol) tetraethylammonium hydroxide, pH 6.0); B: 70%; acetonitrile mixed with 0.1 M phosphate buffer adjusted to pH 6.0 with NaOH (reagents and solvents were from Sigma and Merck, respectively). The gradient profile was 8% B at 0 min, 24% at 9 min, 35% B at 20 min, 100% B at 22–28 min, 0% B at 29 min. The flow rate was 0.5 ml/min. External standards of 10 μM amino acids (Sigma) were injected after every 10 samples. Detection limits for amino acids were 1–5 pmol/10 μl sample (100 nM). Chromatograms were evaluated with Agilent ChemStation software.

Determination of the Concentration of Nucleosides in the Microdialysis Samples. Determination of nucleosides in the microdialysis samples was performed as described earlier (10,11). This method is sensitive and selective enough for the measurement of hypoxantine, xantine, uridine, inosine, guanosine, thymidine and adenosine in microdialysis samples (11). Separation was performed with HP1100 Series Chromatographic system on Agilent ODS Hypersyl reversed phase column (C18, 5 μm spherical ODS, 200 × 2.1 mm, with 20 mm precolumn) with the following eluents: A: 0.02 M formiate buffer, pH = 4.45, B: 0.02 M formiate buffer in 40% acetonitrile pH = 4.45. The gradient profile was 0% B at 0–10 min, 15% B at 20 min, 47% at 24 min and 0% at 28 min. The flow rate was 0.3 ml/min. UV detection was performed at 254 nm (ref 360 nm). Chromatograms were evaluated with Agilent ChemStation software.

EEG Recording. Stainless steel screw electrodes (1 × 5 mm) were implanted into the skull above the left frontal cortex (A: 3, L: 3), and above the left occipital cortex (A: −8, L: 1), the reference screw electrode was placed over the cerebellum (A: −10, L: 2). The recording was performed by Grass Model 8B EEG (gain 50 μV/mm, bandpass, 0.3–1000 Hz). EEG was continuously monitored on a Tektronix storage screen oscilloscope. Signal processing was done by CED 1401 AD converter of the Cambridge Electronic Devices (Cambridge, U.K.) using Signal 1.82 software. Sampling rate was 500 Hz and the digital samples were 30 s long. Data files converted to ASCII format were readable for MATLAB and ORIGINE 5.0 software.

Data Evaluation. Since diffusion of molecules into the microdialysis probe is complex, concentrations of amino acids and nucleotide derivatives in the dialysate are not identical with their extracellular concentrations (12) therefore concentrations of amino acids and nucleotide derivatives measured in microdialysis samples collected during various drug applications were related to averaged amino acid (nucleotide derivatives) concentration of control samples collected for 100 minutes previous to drug application and were given as percent changes. We obtained 3 data from each animal according to the time spent after the drug application: 0–50 minutes, 50–100 and 100–150 minutes. We averaged percent values obtained from different animals the same time after the drug application (mean ± SEM). We performed General Linear Model ANOVA (GLM ANOVA) in order to reveal the influence of different doses (10, 20 and 60 mg/kg) of lindane and 5 mg/kg dose of picrotoxin on amino acid and nucleoside concentrations and to describe the time course of the effect. To determine which differences between means were significant, Newman-Keuls multiple comparison procedure were used. Statistical calculations were carried out by NCSS Statistical Software (Utah, USA).

Wavelet analysis of EEG samples (unlike the traditional Fourier method) yields a time-frequency mapping of the signal. Since the EEG is a non stationary signal (its statistical parameters-such as auto correlation—are time dependent variants) the rearrangements of its oscillatory component can be tracked only by some adaptive power spectral estimation method like wavelet transform. As the wavelet power spectrum function has two independent variable (time and frequency) contour-plots are used for visualization of the EEG component fluctuations (13).

RESULTS

Changes in the Extracellular Concentration of Amino Acids in the Hippocampus after a Single Intraperitoneal Injection of Lindane or Picrotoxin. The concentration of Glu, Asp, Gln, Gly and Tau in the control dialysate samples remained constant for 2 hours

previous to drug application, and found to be: 0.3 ± 0.07 μM Glu, 0.2 ± 0.05 μM Asp, 26.6 ± 6.6 μM Gln, 1.5 ± 0.25 μM Gly, 2.7 ± 0.5 μM Tau, respectively. We examined the effect of intraperitoneal injection of different doses of lindane: 10 mg/kg (n = 4) and 20 mg/kg (n = 5) and 60 mg/kg (n = 3) together with a single dose of picrotoxin 5 mg/kg (n = 3) for 150 minutes. We compared all of our results to the data obtained from only DMSO injected rats (n = 3). The injection of DMSO alone had no effect on extracellular Asp, Glu, Gln, Gly and Tau concentration.

In agreement with half life for incorporation and elimination of lindane in blood and brain in awake rats (14), the extracellular concentration of Asp and Glu decreased in samples collected 100–150 min after the *ip* injection of 60 mg/kg lindane. However these effects were not significant according to the GLM ANOVA, the Students T-test showed significant differences at $p < 0.05$ level (Fig. 1). For Asp, the picrotoxin treatment (5 mg/kg) main effect was significant ($F_{4,21} = 3.71$, $p = 0.019$). In addition, significant differences were found among the following treatment means: picrotoxin *vs.* DMSO and picrotoxin vs. lindane dose 20 mg/kg. For Glu, the picrotoxin treatment main effect was significant ($F_{4,21} = 3.94$, $p = 0.015$). Also, there was a significant difference between picrotoxin and lindane dose 20 mg/kg. For both of Asp and Glu, the time main effect was not significant, ie. effects of different doses of the two drugs do not change in time (Fig. 1.).

For the other amino acids measured (Gln, Gly and Tau) there were no significant differences neither for dose nor for time factor after *ip* lindane or picrotoxin injection.

Changes in the Extracellular Concentration of Nucleosides and Nucleoside Metabolites after a Single Intraperitoneal Injection of Lindane or Picrotoxin in the Hippocampus. The dialysate concentration of the measured nucleosides and nucleoside metabolites in the control samples were: hypoxanthine: 0.5 ± 0.1 μM, xanthine: 1.8 ± 0.5 μM, uridine: 0.3 ± 0.03 μM, inosine: 0.2 ± 0.03 μM, guanosine: 0.06 ± 0.01 μM, thimidine: 0.1 ± 0.02 μM, adenosine: 0.3 ± 0.04 μM. When making comparisons for the effects of lindane and picrotoxin we used the data obtained from DMSO injected rats as control, since the extracellular concentrations of hypoxanthine, xanthine, uridine and adenosine slightly decreased spontaneously in DMSO treated rats.

The *ip* lindane (10, 20, 60 mg/kg) and picrotoxin (5 mg/kg) injections had no effect on the extracellular concentration of measured nucleosides and nucleoside metabolites in periods 0–50 and 100–150 min after drug injection (Fig. 2A and Fig. 2C). Change of xanthine concentration showed significant main effect for time factor ($F_{2,42} = 4.24$, $p = 0.02$; Fig. 2A,B,C). Multiple comparisons revealed the following significant differences (alpha = 0.05) for xanthine in samples collected 50–100 min after injection (Fig. 2B): picrotoxin *vs.* DMSO and picrotoxin *vs.* lindane (doses 10, 20 and 60 mg/kg). Although there were no significant main effects neither for dose nor for time associated with other nucleosides and their metabolites, we have found the following significant differences for *treatment* × *time*

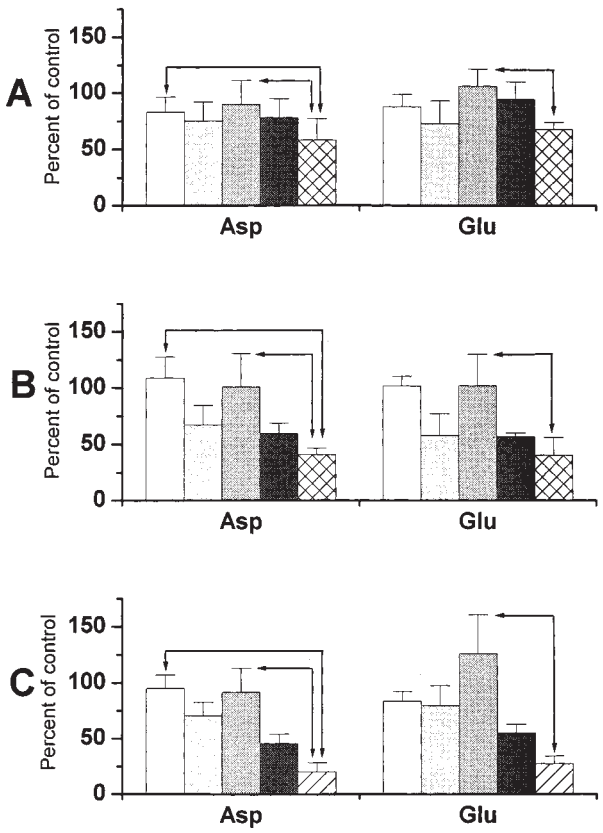

Fig. 1. The effect of *ip* injection of picrotoxin and different doses of lindane on the extracellular level of ASP and Glu in the hippocampus of halothane anaesthetized rats during 3 subsequent periods after drug injections: 0–50 min (**A**), 50–100 min (**B**) and 100–150 min (**C**) spent after the drug injection. White bars: *ip* injection of DMSO, light gray bars: *ip* injection of 10 mg/kg lindane dissolved in DMSO, gray bars: *ip* injection of 20 mg/kg lindane dissolved in DMSO, dark gray bars: *ip* injection of 60 mg/kg lindane dissolved in DMSO, crisscross hatched bars: *ip* injection of 5 mg/kg picrotoxin dissolved in DMSO. Data from experiments are expressed as mean percentage (±SEM) of control taken as the average concentration of two samples collected for two hours before the *ip* drug injection. Lines connecting different bars indicate significantly different values (GLM ANOVA).

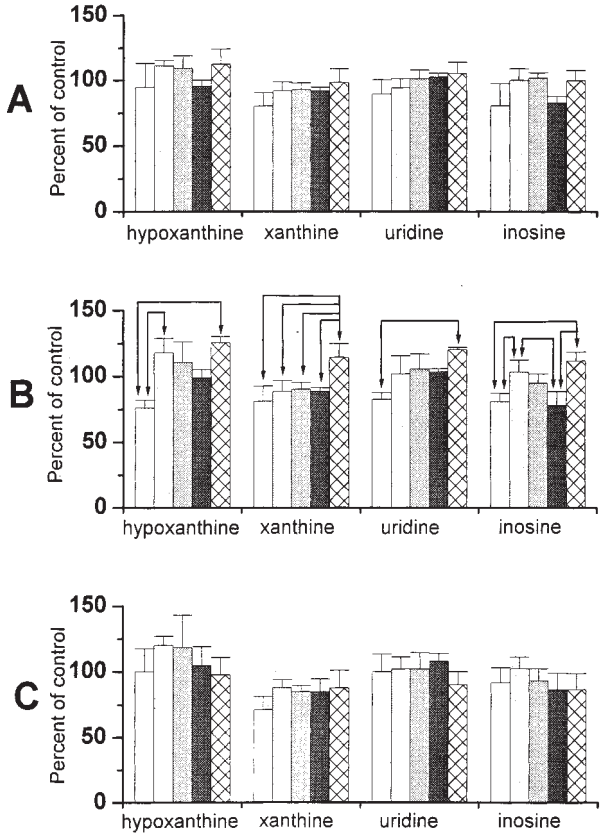

Fig. 2. The effect of *ip* injection of different doses of lindane and picrotoxin on extracellular concentrations of hypoxanthine, xanthine, uridine and inosine in the hippocampus of halothane anaesthetized rats during 3 subsequent periods after drug injections: 0–50 min. (**A**), 50–100 min (**B**) and 100–150 minutes (**C**). White bars: *ip* injection of DMSO, light gray bars: *ip* injection of 10 mg/kg lindane dissolved in DMSO, gray bars: *ip* injection of 20 mg/kg lindane dissolved in DMSO, dark gray bars: *ip* injection of 60 mg/kg lindane dissolved in DMSO, criss-cross hatched bars: *ip* injection of 5 mg/kg picrotoxin dissolved in DMSO. Data from experiments are expressed as mean percentage (±SEM) of control taken as the average concentration of two samples collected for two hours before the *ip* drug injection. Lines connecting different bars indicate significantly different values (GLM ANOVA).

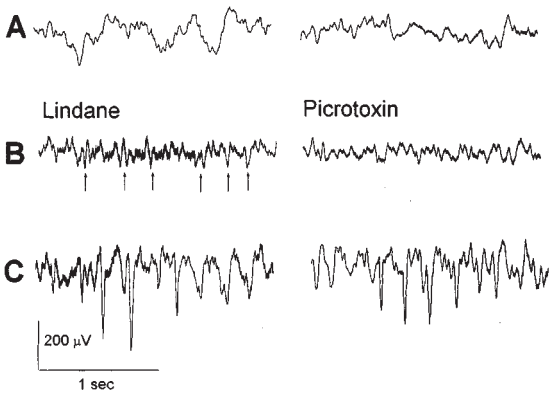

Fig. 3. Periods (2 s) of EEG recordings from halothane anaesthetized rats: control periods 10 minutes before drug treatment (**A**); periods with 4–5 Hz activity 10 min after *ip* injection of 20 mg/kg lindane or 5 mg/kg picrotoxin (**B**); epileptic bursts emerged 10 min after 20 mg/kg lindane and 40 min after 5 mg/kg picrotoxin injection (**C**). Arrows indicate the occurrence of negative sharp waves.

interactions 50–100 min after drug injections in the following cases (Fig. 2B): hypoxanthine (lindane dose 10 mg/kg *vs.* DMSO; picrotoxin *vs.* DMSO); uridine (picrotoxin *vs.* DMSO); inosine (lindane dose 10 mg/kg *vs.* DMSO; picrotoxin *vs.* DMSO; lindane dose 60 mg/kg *vs.* lindane dose 10 mg/kg; lindane dose 60 mg/kg *vs.* picrotoxin).

Effect of a Single Intraperitoneal Injection of Lindane on the EEG of the Halothane Anesthetised Rats. The EEG of the halothane anaesthetised rats before the *ip* drug application was dominated by slow-waves (1.0–1.5 Hz) in the delta frequency band (Fig. 3A, Fig. 4A). Injection of lindane *ip* (20 mg/kg in 0.5 ml DMSO) elicited sharp, negative spikes accompanied with rhythmic activity at 4–5 Hz (Fig. 3B) in contrast to *ip* injection of 0.5 ml DMSO whereby the slow-wave EEG pattern of halothane anesthetized rat was not changed. The effects of lindane were dose-dependent as to periods (10–30 s) of 4–5 Hz activity were observed 10–30 min and 5–120 min after the *ip* injection of 10 and 20 mg/kg lindane, respectively. The periodic patterns were transformed into a continuous appearance of 4–5 Hz EEG activity by the highest applied dose of lindane (60 mg/kg).

Both lindane and picrotoxin induced short epileptic seizures characterized by spike-wave discharges. Surprisingly, epileptic seizures occurred after the *ip* injection of 20 mg/kg lindane only and none of the rats receiving 60 mg/kg lindane showed epileptic pattern in their EEG. The bursts of spikes were not too long (about 2 s) and contained large amplitude negative spikes followed with relatively smaller amplitude positive waves (Fig. 3C). The epileptic spikes started about 10–20 min after the lindane application, periodicity with 5–10 min inter-burst intervals until about 50–70 min after the lindane application when the intervals between the bursts increased (10–30 min) but epileptic seizures occurred till the end of the experiment (150 min).

Picrotoxin showed EEG pattern somewhat similar to 20 mg/kg lindane-induced EEG changes as it elicited 4–5 Hz activity and epileptic bursts (2–5 s long) as well. However, the picrotoxin-induced 4–5 Hz activity did not display negative sharp waves (Fig 3B) and was accompanied by 10 Hz oscillations (Fig. 4C). The time course of picrotoxin effect was different as compared to lindane since the 4–5 Hz activity characterized

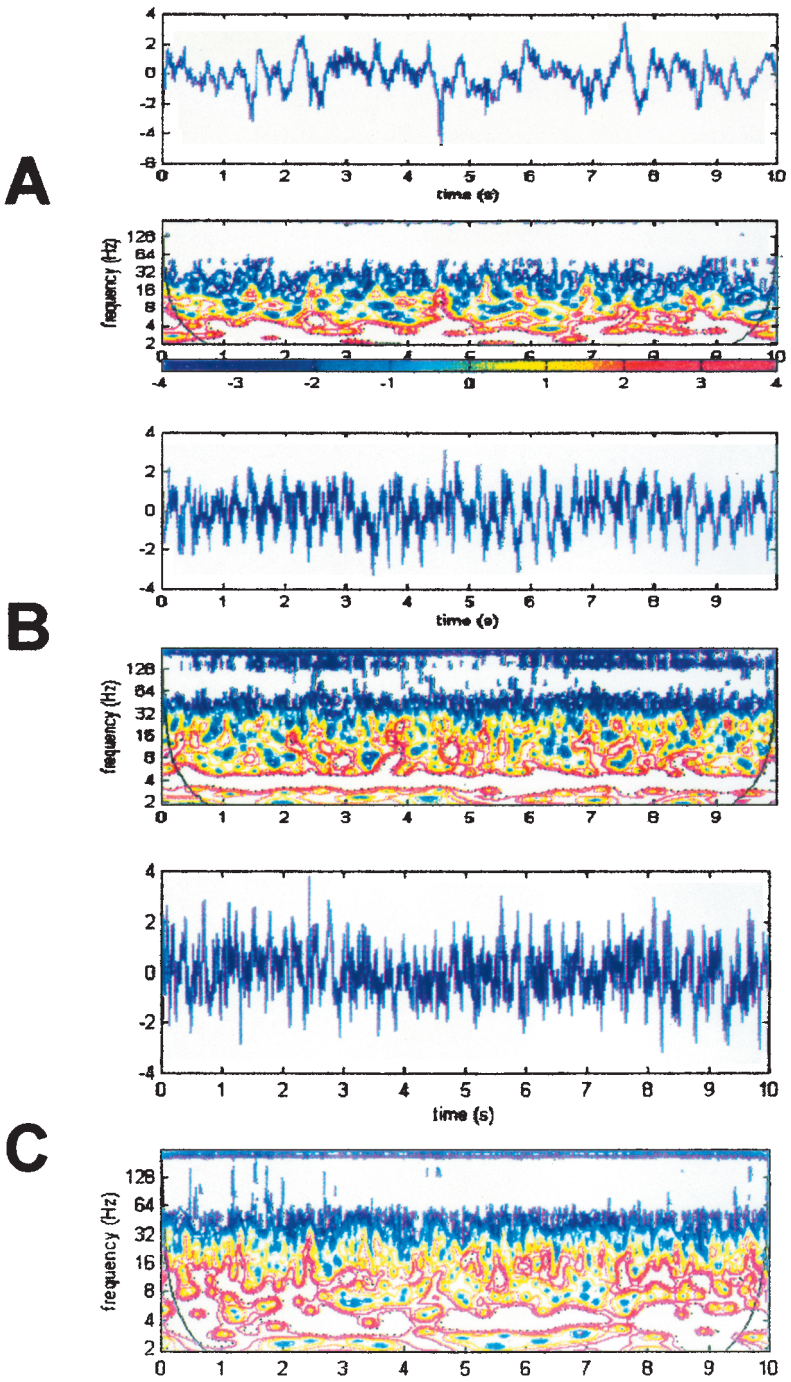

Fig. 4. Wavelet power spectrum for EEG periods (10 s) recorded before drug injection (**A**); after 60 min of *ip* injection of 60 mg/kg lindane (**B**); and after 10 min of *ip* injection of 5 mg/kg picrotoxin (**C**). Color code indicates increasing power from low (dark blue) through medium (light blue followed by green and yellow) to high (red) intensities.

the EEG pattern after 30–40 min of injection and the epileptic activity occurred in the last 100 min of the experiment. By comparison, picrotoxin (1 mg/kg *ip*) produced myoclonic seizures between 15–40 minutes after administration in the freely behaving rat (15). This finding suggest that the late onset of picrotoxin effect on the EEG pattern was most probably due to the halothane anesthesia applied in our experiment. Spectral analysis disclosed continuous and discontinuous 4–5 Hz rhythmic oscillations after 60 mg/kg lindane or

5 mg/kg picrotoxin injection, respectively (*cf.* Fig. 4B and 4C).

DISCUSSION

What mechanisms might possibly underlie the decrease of the extracellular level of Glu and Asp to picrotoxin? Several lines of evidence have indicated disinhibitory interactions of $GABA_A$ and $GABA_B$ receptors at the molecular level (16,17 and references cited there) including the possibility of presynaptic disinhibitory $GABA_A$-$GABA_B$ receptor interactions (16,18,19). Disinhibitory $GABA_A$-$GABA_B$ receptor interactions imply that a reduction of $GABA_A$ receptor-mediated inhibition would enhance $GABA_B$ receptor responses as well (20–24). It is possible therefore to speculate that the blockade of $GABA_A$ receptor by picrotoxin enhances presynaptic $GABA_B$ receptor function and subsequently generates a decreased extracellular level of Glu and Asp. Picrotoxin might also be suggested to act more specifically as an antagonist at an excitatory $GABA_A$ receptor. Support for this proposal includes the demonstration that glial cells are depolarized by GABA (25–27). Thus, one might conjecture that the impairment of an excitatory $GABA_A$ receptor by picrotoxin hyperpolarizes the glial membranes and subsequently enhances the glial uptake of Glu and Asp.

Lindane (20 mg/kg) did elicit epileptic spikes in the hippocampus of halothane anaesthetized rat, whereby changes in the extracellular level of Asp and Glu levels were not changed indicating, that the occurrence of spikes and changes of extracellular Asp and Glu levels were not associated. By contrast, epileptic bursts induced by 5 mg/kg picrotoxin were accompanied by a decrease of extracellular Asp and Glu. It is to note, that previous findings have suggested a close relationship between seizures elicited by intrahippocampal microdialysis of picrotoxin in freely moving rat and the decreased extracellular level of Asp and Glu (4). Differences in changes of the extracellular level of excitatory amino acids as well as the different oscillatory activity patterns to lindane and picrotoxin suggest, that in spite of behavioral similarities of lindane and picrotoxin actions in the brain, mechanisms activated by them could be different to some extent. DMSO (28,29) as well as halothane might be synergistic in combination with the low lindane dose explaining why higher dose of lindane did not elicited epileptic spikes as lower dose of lindane did. However, the other EEG correlate of lindane intoxication increased with dose raising the possibility that epileptic spikes were suppressed by the appearance of the *continuous* 4–5 Hz EEG activity.

In the present study, the most consistent and largest increases in purine levels generated by lindane (10 mg/kg) and picrotoxin (5 mg/kg), were for the adenosine metabolites (30) inosine, and hypoxanthine. In accordance with its suggested neuromodulatory function in the brain (11,31), extracellular level of uridine was increased by picrotoxin. Our results support and extend recent report of increased hippocampal inosine and hypoxanthine following seizure activity generated by bicuculline, kainic acid and pentylenetetrazol (5). By comparison, no increases in extracellular adenosine levels to lindane and picrotoxin treatments were observed. These results suggest that adenosine may be rapidly metabolised by adenosine deaminase (5). These findings support the hypothesis that an altered purine and pyrimidine metabolism is associated with lindane and picrotoxin intoxication. Augmented hippocampal purine metabolism was manifest to the lowest dose of lindane, even though the dose of lindane was increased by about one order of magnitude. This may be indicative of the acute tolerance to the behavioral effects observed with lindane (32). Further studies are needed to determine the precise relationship between the status of purine and pyrimidine metabolism and behavior during lindane intoxication.

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REFERENCES

1. Joy, R. M. and Albertson, T. E. 1987. Interactions of lindane with synaptically mediated inhibition and facilitation in the dentate gyrus. NeuroToxicology 8:529–542.
2. Damgaard, I., Nyitrai, G., Kovács, I., Kardos, J., and Schousboe, A. 1999. Possible involvement of $GABA_A$ and $GABA_B$ receptors in the inhibitory action of lindane on transmitter release from cerebellar granule neurons. Neurochem. Res. 24:1189–1193.
3. Obrenovitch, T. P., Urenjak, U., and Zilkha, E. 1996. Evidence disputing the link between seizure activity and high extracellular glutamate. J. Neurochem. 66:2446–2454.
4. Sierra-Paredes, G., Galán-Valiente, J., Vazquez-Illanes, D., Aguilar-Veiga, E., Soto-Otero, R., Mendez-Alvarez, E., and Sierra-Marcuno, G. 1998. Extracellular amino acids in the rat hippocampus during picrotoxin threshold seizures in chronic microdialysis experiments. Neurosci. Lett. 248:53–56.
5. Berman, R. F., Fredholm, B. B., Aden, U., and O'Connor, W. T. 2000. Evidence for increased dorsal hippocampal adenosine release and metabolism during pharmacologically induced seizures in rats. Brain Res. 872:44–53.
6. Nyitrai, G., Zs. Emri, V., Crunelli, A. K. Kékesi, Á. Dobolyi and G. Juhász 1996. Blockade of Thalamic $GABA_B$ Receptors

In Vivo Increases Excitatory Amino Acid Levels. Eur. J. Pharmacol. 318:295–300.
7. Juhász, G., Tarcali, J., Pungor, K., and Pungor, E. 1989. Electrochemical calibration of in vivo brain dialysis samplers. J. Neurosci. Methods, 29:131–137.
8. Paxinos G. and Watson C. 1997. The rat brain stereotaxic coordinates. Academic Press, Orlando.
9. Henderson, J. W., Ricker, R. D., Bidlingmeyer, B. A., and Woodward, C. 2000. Rapid, accurate, sensitive, and reproducible HPLC analysis of amino acids. Agilent Technologies, www.agilent.com/chem/supplies.
10. Dobolyi, Á., Reichart, A., Szikra, T., Szilágyi N., Kékesi A. K., Karancsi T., Slégel P., Palkovits M., and Juhász, G. 1998. Analysis of purine and pyrimidine bases, nucleosides and deoxynucleosides in brain microsamples (microdialysates and micropunches) and cerebrospinal fluid. Neurochem. Int. 32:247–256.
11. Dobolyi, Á., Reichart, A., Szikra, T., Nyitrai G., Kékesi A. K., and Juhász, G. 2000. Sustained depolarisation induces changes in the extracellular concentrations of purine and pyrimidine nucleosides in the rat thalamus. Neurochem. Int. 37:71–79.
12. Benveniste, H. and Huttemeier P. C. 1990. Microdialysis: theory application, Prog. Neurobiol., 35:195–215.
13. Torrence C. H. and Compo, G. P. 1998. Practical guide to wavelet analysis, Bull. Am. Meteorol. Soc. 79:61–78.
14. Tussel, J. M., Sunol, C., Gelphi, E., and Rodríguez-Farré, E. 1987. Relationship between lindane concentration in blood and brain and convulstant response in rats after oral or intraperitoneal administration. Arch. Toxicol. 60:432–437.
15. Dai, K. S. and Woolley D. E. 1991. Ro 5-4864, like picrotoxin, enhances EPSP-spike coupling in the freely behaving rat. Brain Res. Bull. 27:13–17.
16. Krogsgaard-Larsen, P., Frolund, B., Jorgensen, F., and Schousboe, A. 1994. $GABA_A$ receptor agonists, partial agonists, and antagonists. Design and therapeutic prospects. J. Med. Chem. 37:2489–2505.
17. Kardos, J. 1999. Recent advances in GABA research. Neurochem. Int. 34:353–358.
18. Kardos, J., Elster, L., Damgaard, I., Krogsgaard-Larsen, P., and Schousboe, A. 1994. Role of $GABA_B$ receptors in intracellular Ca^{2+} homeostasis and possible interaction between $GABA_A$ and $GABA_B$ receptors in regulation of transmitter release in cerebellar granule neurons. J. Neurosci. Res. 39:646–655.
19. Schousboe, A. 1999. Pharmacologic and therapeutic aspects of developmentally regulated expression of $GABA_A$ and $GABA_B$ receptors: cerebellar granule cells as a model system. Neurochem. Int. 34:373–377.
20. Newberry, N. R. and Nicoll, R. A. 1985. Comparison of the action of baclofen with gamma-aminobutyric acid on rat hippocampal pyramidal cells in vitro. J. Physiol. 360: 161–185.
21. Crunelli, V., Haby, M., Jassik-Gerschenfeld, D., Leresche, N., and Pirchio, M. 1988. Cl- and K-dependent inhibitory postsynaptic potentials evoked by interneurones of the rat lateral geniculate nucleus. J. Physiol. 399:153–176.
22. Connors, B. W., Malenka, R. C., and Silva, L. R. 1988. Two inhibitory postsynaptic potentials, and GABAa and GABAb receptor-mediated responses in neocortex of rat and cat. J. Physiol. 406:443–468.
23. Crunelli, V. and Leresche, N. 1991. A role for GABAb receptors in excitation and inhibition of thalamocortical cells. TINS 14:16–21.
24. von Krosigk, M., Bal, Th., and McCormick, D. A. 1993. Cellular mechanisms of a synchronised oscillation in the thalamus. Science 261:361–364.
25. Bormann, J. and Kettenmann, H. 1988. Patch-clamp study of γ-aminobutyric acid receptor Cl^- channels in cultured astrocytes. Proc. Natl. Acad. Sci. USA 85:9336–9340.
26. MacVicar, B. A., Tse, F. W., Crichton, S. A., and Kettenmann, H. 1989. GABA-activated Cl^- channels in astrocytes of hippocampal slices. J. Neurosci. 9:3577–3583.
27. Fraser, D. D., Duffy, S., Angelides, K. J., Perez-Velazquez, J. L., Kettenmann, H., and MacVicar, B. A. 1995. $GABA_A$/Benzodiazepine receptors in acutely isolated hippocampal astrocytes. J. Neurosci. 15:2720–2732.
28. Nakahiro, M., Arakawa, O., Narahashi, T., Ukai, S., Kato, Y., Nishinuma, K., and Nishinuma, T. 1992. Dimethyl sulfoxyde (DMSO) blocks GABA-induced current in rat dorsal root ganglion neurons. Neurosci. Lett. 138:5–8.
29. Joy, R. M. and Albertson, T. E. 1987. Factors responsible for increased excitability of dentate gyrus granule cells during exposure to lindane. Neurotoxicology 8:517–524.
30. Zimmermann, H. 1996. Extracellular purine metabolism. Drud Development Res. 39:337–352.
31. Kardos, J., Kovács, I., Szárics, E., Kovács, R., Skuban, N., Nyitrai, G., Dobolyi, Á, Juhász, G. 1999. Uridine activates fast transmembrane Ca^{2+} ion fluxes in rat brain homogenates. Neuroreport 10:1577–1582.
32. Llorens, J. Sunol, C., Tusell, J. M., and Rodriguez-Farré, E. 1991. Evidence for acute tolerance to the behavioral effects of lindane: concomitant changes in regional monoamine status. NeuroToxicology 12:697–706.