Polish Journal of Occupational Medicine and Environmental Health, Vol. 5, No 1, 55-69, 1992

A COMPARISON OF CHANGES IN SPONTANEOUS (EEG) AND EVOKED BRAIN ACTIVITY INDUCED BY CHLORPHENVINPHOS AND PHYSOSTIGMINE IN RATS AND RABBITS

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Key words, EEG, Flash evoked potential, Spectral analysis, Chlorphenvinphos, Physostigmine, Cholinesterase

Abstract: The effects of single i.p. injections of two cholinesterase inhibitors, chlorphenvinphos (CVP) and physostigmine, on hippocampal and cortical EEG and flash evoked potentials in occipital cortex were compared in rabbits and rats. A comprised method of spectral analysis was employed for evaluation of changes in EEG. The obtained results showed that in both species the changes in hippocampal and cortical EEG after administration of CVP were relatively small or neglible in comparison with those after physostigmine administered in doses resulting in comparable (or even lesser) inhibition of blood cholinesterase (ChE). Neither CVP nor physostigmine resulted in significant changes in the morphology of the flash evoked potentials. The data do not confirm the suggestion that brain electrical activity is the most sensitive index of neurotoxicity resulting from exposure to organophosphate ChE inhibitors.

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INTRODUCTION

The general use of organophosphorous compounds (OPs) requires very precise recognition of the health effects resulting from exposure to these compounds. OPs are esterase inhibitors. Acute symptoms of poisoning by OPs are attributable to inhibition of the activity of cholinesterase (ChE) and the resultant hyperactivity of the peripheral and central cholinergic system. According to the literature (14), they appear in the exposed subjects only in cases when ChE activity (as measured in blood plasma and in hemocytes) falls below 50% of the normal value. That has been reflected in the hygienic standards adopted by some countries. Results of some tests performed on animals (rats), however, suggest that changes in bioelectric brain activity may appear even after OP administration in doses which do not cause

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CORE

evident lowering of ChE activity (4). During our earlier tests of chlorphenvinphos (phosphoric acid, 2-chlor- 1, 2, 4, -di- chlorphenyl/vinyl diethyl ester CVP) in rabbits we found, by means of visual EEG analysis, that a single intraperitoneal administration of 22–250 mg/kg of CVP resulted in the domination of low-amplitude cortical activity and in the increase of the percentage content of rhythmical hippocampal theta activity (RSA). Those effects were evident, however, only when ChE activity fell well below 50% of the normal value (7). Such a result did not confirm what was hypothesised: the exceptional sensitivity of EEG used as an indicator of the state of poisoning by OPs. Three possible causes of that discrepancy include: insufficiently precise analysis, animal species, and the specificity of the compound. Our present study was aimed at determining the significance of those causes. To achieve this objective, we compared the effects of acute exposure to CVP on the cortical and hippocampal EEG in rabbits and rats.

EEG change evaluation was based on the results of spectral analysis. Flash-evoked visual potentials were also preexamined. Encephalographic effects of exposure to CVP were compared in both species with those resulting from exposure to physostigmine, a classical ChE inhibitor.

MATERIALS AND METHODS

Animals

The studies were performed on male, New Zeland, white 6 months old rabbits (n = 16) and male IMP-DAK outbred rats 4–5 months old (n = 24) weighing 300–350 g. The animals were prepared for the test by surgical implantation of bipolar electrodes to the dorsal hippocampus (both sides), to the cortex of the anterior part of the hemispheres and to the occipital cortex. The design of the electrodes and the details of the surgery are discussed elsewhere (6). The animal convalesced for 6 weeks.

Compounds and method of exposure

The following compounds were used in the study: physostigmine sulphate from Sigma Co. and chlorphenvinphos (CVP) from the Organika chemical plant, Jaworzno, Poland. Physostigmine was dissolved in water (aqua pro injection) and administered intraperitoneally in doses of 0.1 mg/kg, 0.2 mg/kg and 0.4 mg/kg (rabbits) and 1.0 mg/kg (rats). Sterile olive oil was used as the solvent to prepare the CVP solution. CVP was administered to the rabbits in doses of 14, 33 and 50 mg/kg body weight and to the rats in doses of 1.0 and 3.0 mg/kg body weight.

Experimental conditions

Spontaneous bioelectric activity (EEG) and evoked activity, [flash visual potentials (EPs)], in rabbits were recorded from the same animals during the same experiment. During recording, the rabbit remained in a small dark chamber and faced the lamp of a Ridan FOS-50 photostimulator placed at a distance of 20 cm. EEG and EPs recordings on rats were, for technical reasons, taken on different

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individuals. During EEG recording, the animals remained in a plastic container and during EPs recording were placed in a chamber with mirror walls and floor. The bioelectric activity was recorded on an 8 – channel electroencephalograph in the 0.5–32 Hz (EEG) and 15–1200 Hz (EP) bands. Electroencephalograph amplifier outputs were connected to the measuring unit of a computer-based system for bioelectric brain activity recording and analyzing.

An AT microcomputer (IBM clone) was used as the central unit of the system. In rabbits, EEG and EPs were recorded and analysed on the same apparatus. In rats, EEG were recorded and analysed using the computer system, and EPs were recorded and analyzed using an Anops-5 digital analyzer. The behavior of the animals during recording was observed by means of a closed industrial TV system.

Procedure

Rabbits. Before the proper experiment, all rabbits were tested for the quality and value of their EPs in relation to the stimulus (flash) intensity. The potentials were evoked using flashes which intensity varied from 0.1Ws to 0.6Ws in 0.1Ws increments. An optimum flash intensity value was selected for each rabbit, so that all essential components would appear in a given potential without causing saturation. The value was usually 0.2 – 0.3Ws.

Each experimental session comprised the following steps:

1. A control stage, which included:

a) recording and performing spectral analysis of 4 blocks of 1 min sections of EEG from the frontoparietal cortex and hippocampus. Each block was composed of eight 1 min EEG sections. The interval between sections within a block was 2 sec and between successive blocks was 4 min;

b) recording of averaged evoked potentials from the occipital cortex (50 flashes of predetermined intensity every 5 seconds, 500 msec transients.);

c) main stage, starting with CVP administration.

2. After the administration, the procedure included:

a) recording of averaged EPs immediately after the administration;

b) EEG recording and analysis,

c) recording of averaged EPs three times each hour.

For physostigmine, the course of each session was similar to that described above, with the exception that the experiments were terminated earlier, usually after 2 hours from the start.

Rats. EEG recording and analyzing procedure was identical to that used for rabbits, with the exception that EPs were not recorded during the experiment. EPs were recorded in 8 rats selected for their response from among all rats which had been operated. The flash intensity used in the experiment was selected in a way similar to that for the rabbits.

Each rat was first tested for its response to the intraperitoneal administration of olive oil (control test) and then, after seven days, for its response to intraperitoneal administration of CVP diluted in olive oil. In each case, EPs were recorded five times: before the injection, after 30 minutes of adaptation to the experimental situation, immediately after the injection, then 30 minutes, 1 hour, 2 hours, 3 hours

and 24 hours after the injection. Each recorded (and analyzed) potential was an average of 50 responses to flashes triggered at a frequency of 0.2 Hz.

Evaluation of EEG records

Our system of EEG recording and analysing enables automatic determination of the output power (energy) in any predetermined frequency bandwidth within a 0.5 Hz–32 Hz range. A suitable program procedure makes possible "on line" evaluation of the percentage distribution of power within the EEG spectrum, and the results are recorded in tabular form on a disk.

The cortical EEG was analysed in the following frequency bands: 1–4 Hz, 4–8 Hz, 8–13 Hz, 13–21 Hz, 21–32 Hz. For the hippocampal EEG, the corresponding frequency bands were: 1–4 Hz, 4–7 Hz, 7–10 Hz, 10–13 Hz, 13–21 Hz, 21–32 Hz. The results obtained for each individual were subjected to a statistical analysis. The differences between the consecutive 8-minute EEG blocks were estimated, independently for each frequency band, using the Kruskall Wallis analysis of variance and the Conover test for multiple comparison (15). The changes occurring after injection were considered to be significant if the energy share in a given band significantly differed in, at least, four consecutive blocks for CVP and, at least, in two for physostigmine from that found in all blocks before the injection.

Evaluation of the evoked activity

Amplitude and peak latency in the averaged evoked potentials recorded from the occipital cortex (rabbit and rat), were estimated. Because of certain differences between subjects in the morphology of the response, only those peaks were analysed which could be identified in the majority of the EPs recorded in a given species. The value of the latency was used to identify a given peak.

The changes occurring after the injection in a given animal were considered to be significant if the measured values of a given peak exceeded the variability range determined during the pre-injection period, and the variation trend (increasing or decreasing) was the same in, at least, two consecutive measuring periods for CVP and in, at least, one for physostigmine.

ChE determination

Data concerning ChE activity in blood 3 hours after i.p. CVP exposure in doses 14 mg/kg and 33 mg/kg in rabbits, and 1.0 mg/kg and 3 mg/kg in rats as well as 20–25 min after 1.0 mg/kg physostygmine in rats, were obtained in our earlier studies. For the present study they were supplemented by ChE determinations in rabbits 3 hours after CVP in dose 50 mg/kg ($n = 4$) and 20–25 min after physostygmine, in dose 0.1 mg/kg ($n = 2$), 0.2 mg/kg ($n = 4$) and 0.4 nmg/kg ($n = 4$) The Sachsse method, described in detail in our earlier work (12), was employed.

RESULTS

The effect of administration of CVP and physostigmine on EEG

Rabbits. The effects of CVP at the dose of 14 mg/kg were studied in seven rabbits, at 33 mg/kg in two rabbits and at 50 mg/kg in two rabbits. The effects of physostigmine

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were studied in five rabbits: at 0.1 mg/kg (n = 1), at 0.2 mg/kg (n = 2) and at 0.4 mg/kg (n = 2).

After the injection of CVP at 14 mg/kg, a significant decrease in total power of cortical activity was observed in three out of the seven rabbits, but the decrease persisted throughout the recording period only in one animal. In the latter rabbit, an essential but short-lasting (1.5 h) decrease in the activity at the 1–4 Hz band, an increase in the activity at the 4–8 Hz band and an increase in the activity at the 21–32 Hz band, were observed. In the remaining six animals, no significant changes in the spectral power distribution of the cortical EEG were noted. For hippocampal EEG, a significant increase in the total power after the injection was observed in four rabbits. (Two of these were the same in which the decrease in the total power of the cortical activity had been observed.) The activity in the 1–4 Hz band significantly increased only in one animal, in the 4–7 Hz band it was not changed in any of the rabbits, and in the 7–10 Hz band it was significantly lower in three of the rabbits. In the remaining bands analyzed, the activity was not changed significantly. A short-lasting (to approx. 1.5 h after the injection) decrease in the total power and a decrease in the activity in the 1–4 Hz band in the cortical EEG, and an increase in the power in the 4–7 Hz band in the hippocampal EEG was observed in one of the two rabbits which received CVP at 33 mg/kg. There were no changes in the other rabbit after the injection.

After the injection of CVP at 50 mg/kg, in one of the two rabbits there was a prolonged decrease in the total power and an increase in the cortical EEG activity at the 21–32 Hz band. No changes were observed in the hippocampal activity. In the other rabbit, the cortical activity was not changed, but there was a significant change (a decrease) in the total power of the hippocampal EEG and a significant but short-lasting decrease of the 4–7 Hz activity content in the spectrum.

In the rabbit which received physostigmine at a dose of 0.1 mg/kg, no changes in the cortical activity were observed, and in the hippocampal EEG the only effect was a significant increase of the 4–7 Hz activity share in the spectrum.

In both the rabbits which were injected physostigmine at 0.2 mg/kg, there was first a significant decrease and then, about one hour after the injection, a significant increase of the total power in the cortical EEG, a significant decrease of the 1–4 Hz activity and an increase in the 21–32 Hz band. In the hippocampal EEG, a significant increase of the total power, a decrease of the activity in the 1–4 Hz and 7–10 Hz bands, and an increase in the 4–7 Hz band were observed. With the exception of the increase of the power in the cortical EEG, the remaining effects disappeared within two hours after the injection.

In the rabbits which received physostigmine at 0.4 mg/kg, the changes were similar to those described above with the exception that the decreasse of the total power in the cortical EEG persisted for a longer time. As a result, the bi-phasic character of changes in the total power of the cortical activity was less distinct.

The effects of CVP and physostigmine on the distribution of the power in the neocortical and hippocampal EEG spectrum in rabbits are illustrated in Figs 1 and 2.

Rats. Eight rats were used to study the effect of CVP on the neocortical and hippocampal EEG, of which four received 1.0 mg CVP, and the other four 3.0 mg CVP per 1 kg of body weight. The effects of physostigmine at the dose of 1.0 mg/kg were studied in four rats.

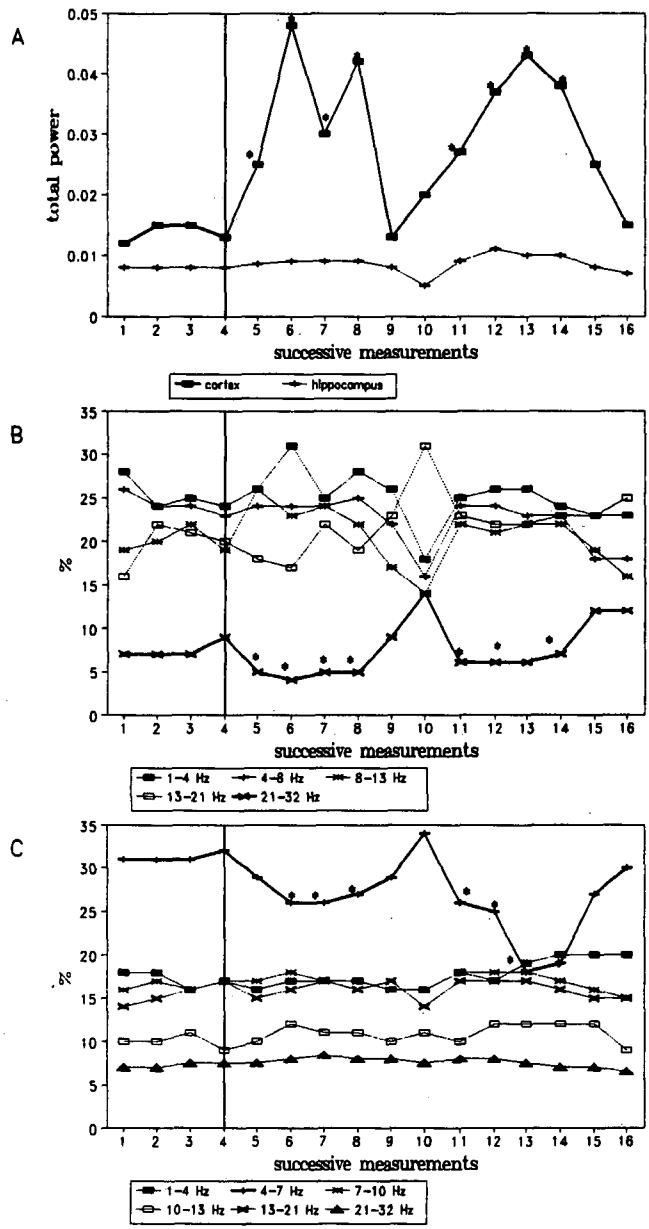

Fig. 1. Effect of 50 mg/kg CVP (i.p.) on cortical and hippocampal EEG in a rabbit;
a – changes in total power, b – changes in distribution of power between selected frequency bands of the cortical EEG, c – changes in distribution of power between selected frequency bands of the hippocampal EEG.
The vertical line separates the pre- and post-exposure periods of recording. Each point represents results of analysis of 8 min EEG sample. Successive measurements vere made every 15 min. Values differing significantly from those before exposure are marked by*.

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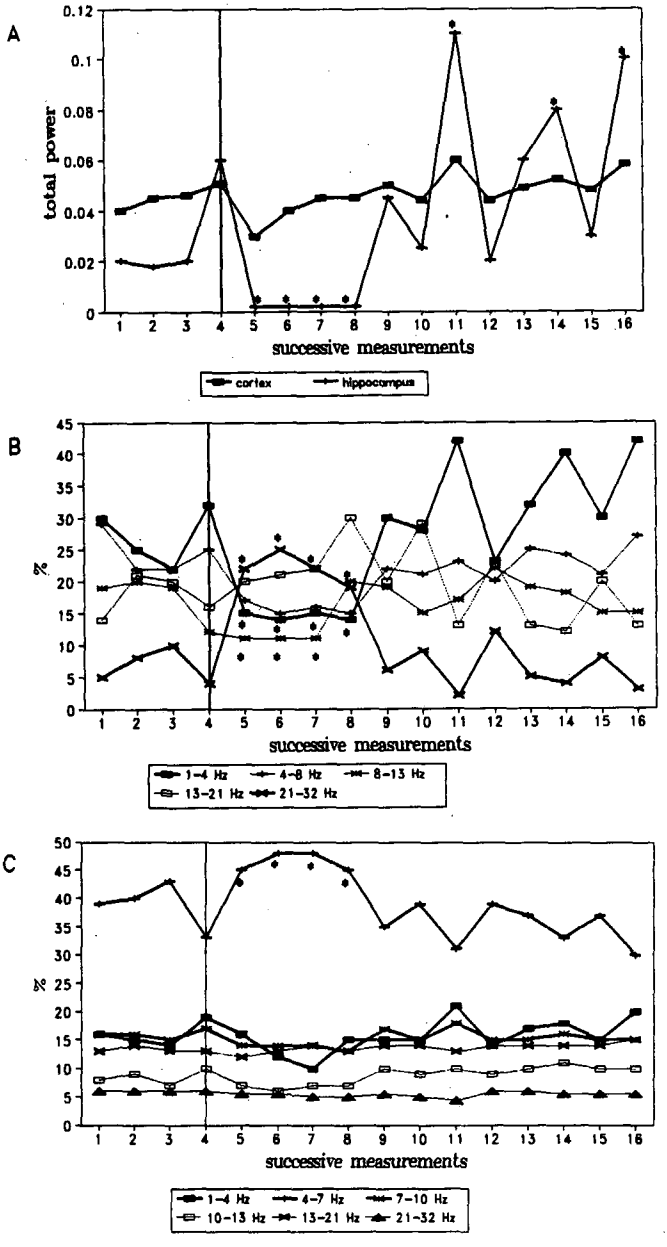

Fig. 2. Effect of 0,2 mg/kg physostigmine (i.p.) on cortical and hippocampal EEG in rabbit.
a — changes in total power, b — changes in distribution of power between selected frequency bands of the cortical EEG, c — changes in distribution of power between selected frequency bands of the hippocampal EEG.
The vertical line separates the pre- and post-exposure periods of recording. Each point represents results of analysis of 8 min EEG sample. Successive measurements vere made every 15 min. Values differing significantly from those before exposure are marked by*.

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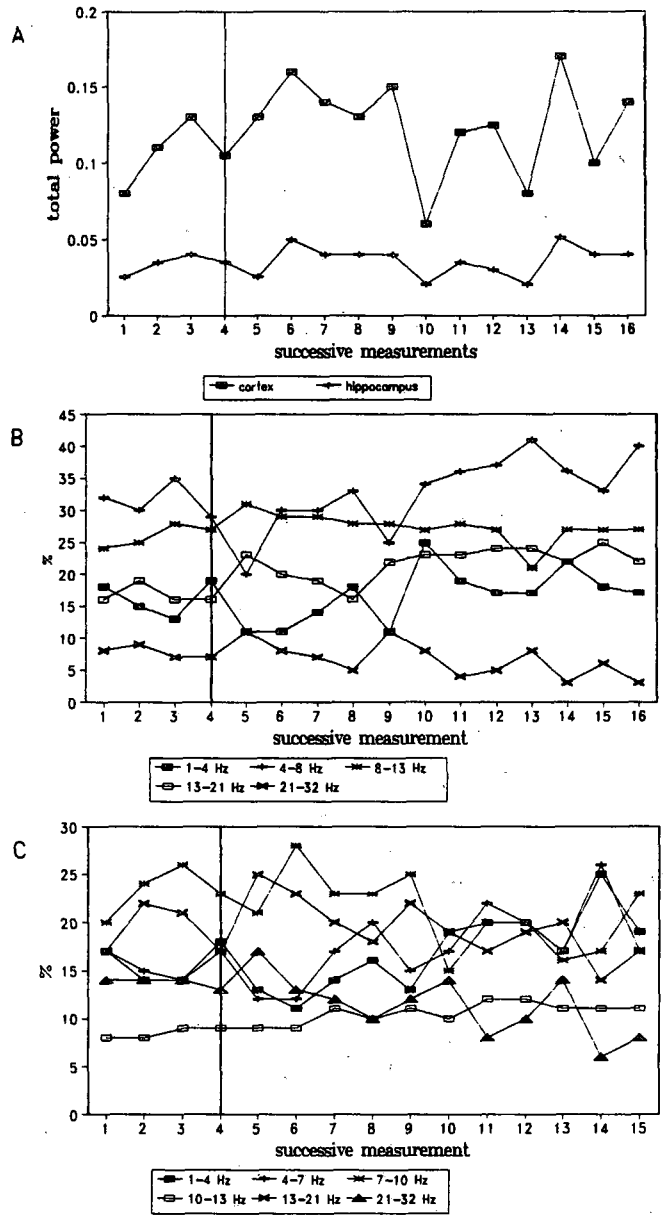

Fig. 3. Effect of 3,0 mg/kg CVP (i.p.) on cortical and hippocampal EEG in a rat.
a – changes in total power, b – changes in distribution of power between selected frequency bands of the cortical EEG, c – changes in distribution of power between selected frequency bands of the hippocampal EEG.
The vertical line separates the pre- and post-exposure periods of recording. Each point represents results of analysis of 8 min EEG sample. Successive measurements vere made every 15 min. Values differing significantly from those before exposure are marked by*.

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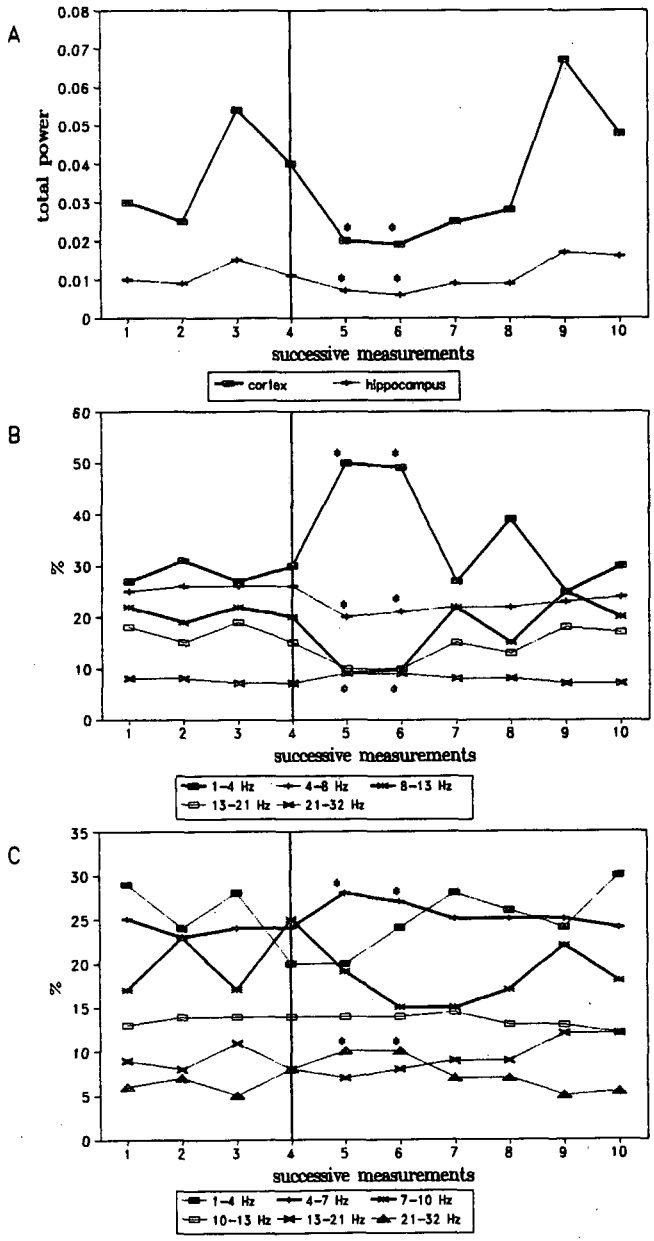

Fig. 4. Effect of 1,0 mg/kg physostigmine (i.p.) on cortical and hippocampal EEG in a rat.
a — changes in total power, b — changes in distribution of power between selected frequency bands of the cortical EEG, c — changes in distribution of power between selected frequency bands of the hippocampal EEG.
The vertical line separates the pre- and post-exposure periods of recording. Each point represents results of analysis of 8 min EEG sample. Successive measurements vere made every 15 min. Values differing significantly from those before exposure are marked by*.

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Following the injection of 1.0 mg/kg CVP, significant changes were found to occur only in two rats: in one, there was a prolonged (throughout the recording period) increase in the total power of the cortical EEG, unaccompanied by changes in power distribution. The changes detected in the other rat concerned the hippocampus only and involved a prolonged decrease of the total power and a decrease of the 21 – 32 Hz activity.

In the group of the animals which received CVP at 3.0 mg/kg changes were observed only in one rat and involved an increase of the total power in both investigated areas. The distribution of power within the spectrum remained unchanged.

Injection of physostigmine at a dose of 1.0 mg/kg resulted in changes occurring in all animals, the scope of the changes, however, being different. A decrease in 8 – 13 Hz activity in the cortical EEG, and an increase of 1 – 4 Hz activity, as well as an increase of the 4 – 7 Hz activity and a decrease in the 7 – 10 Hz band of the hippocampal EEG, occurred in all of the animals. Changes of the total power in the cortical EEG occurred in three rats. In two cases they included two phases, a decrease followed by an increase, and in one case, there was only an increase at the end of the recording period. A bi-phasic change in the total power was observed also in the hippocampal EEG of one rat, and in two rats there was only a decrease of the power.

Figs 3 and 4 illustrate the effect of CVP and physostigmine on the neocortical and hippocampal EEG spectrum in the rat.

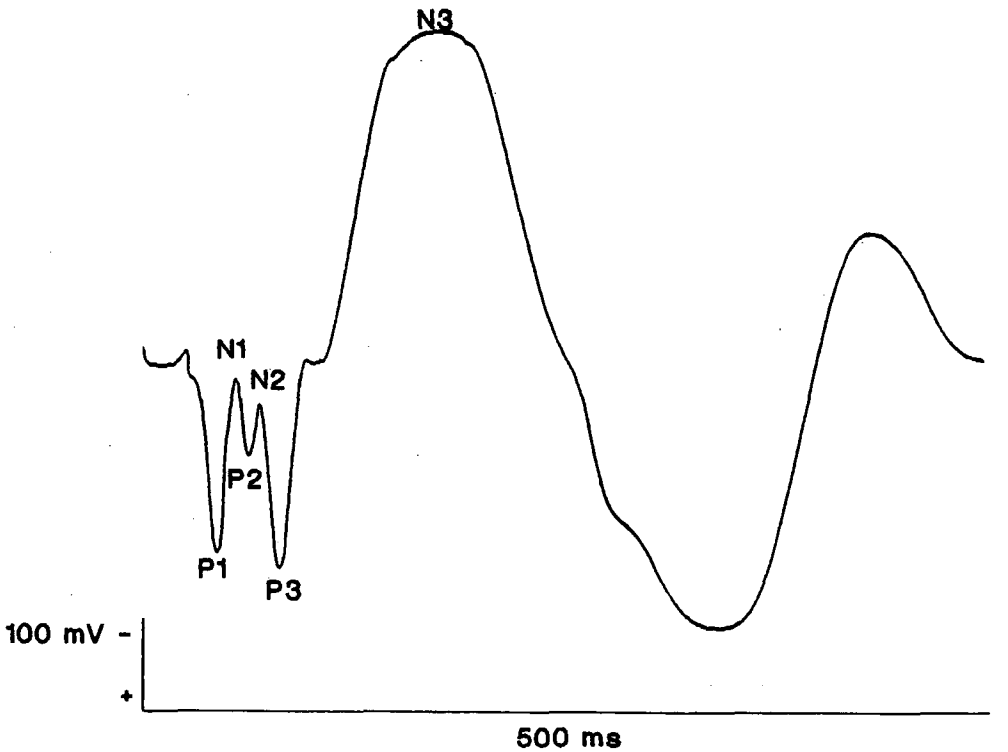

Fig. 5. An example of the averaged (n = 50) flash evoked potential recorded from the posterior cortex in a rabbit.

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The effect of CVP on the visual evoked potentials

Rabbits. The morphology of the potentials recorded from the rabbit occipital cortex was complex. In all cases, four peaks P1, N1, P2, N2 lasting to 10 msec each, could be identified. A slow electropositive 45–50 msec wave with 80–90 msec peak latency, denoted P3, was another common element. A small negative peak appeared on its positive-going slope. All that was followed by a series of slow afterdischarges. It was the negative phase of the first of those afterdischarges which could be identified in all cases. Fig. 5 shows a typical averaged potential recorded from the rabbit occipital cortex.

No significant changes in the latency of any of the peaks were found to occur in any of the rabbits. Significant (according to the adopted criterion) changes of

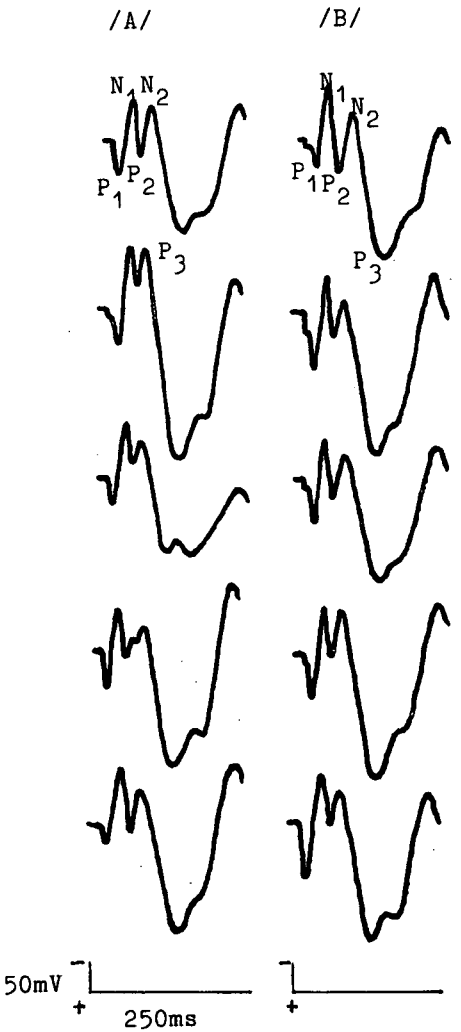

Fig. 6. Changes in the averaged (n = 50) flash evoked potentoial recorded from the posterior cortex in a rat after oil (A) and CVP (B) injection.

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amplitude following the injection of CVP were found only in two rabbits, of which one received CVP at 14 mg/kg, and the other at 50 mg/kg. In the first of those rabbits there was an increase of the P1 and N1 peak amplitude, and in the other there was an increase of the amplitude of all positive peaks, and of the N1 peak. The effect persisted for the whole recording period (3 hours).

No changes were observed following the injection of physostigmine at the dose of 0.1 mg/kg. In all rabbits which received physostigmine at the doses of 0.2 mg/kg and 0.4 mg/kg, the amplitude of the first discharge was reduced, the amplitude of both negative peaks (N1 and N2) was increased, and the P3 peak was lower.

Rats. Fig. 6 shows the most frequent waveforms of the averaged visual flash EPs in the rat occipital cortex. The morphology of the EPs was similar to that described by other authors (11).

Table I. A comparison of the effect of chlorphenvinphos (CVP) and physostigmine on cholinesterase (ChE) activity in blood.

Compound dose (mg/kg)	ChE activity in percent of control value* (mean and standard deviation) plasma	erythrocytes
CVP	**RATS**	
1.0 (n = 4)	55.5 (±30.9)	64.2 (±32.3)
3.0 (n = 4)	8.0 (±10.9)	11.7 (±14.4)
physostigmine 1.0 (n = 4)	47.1 (±17.9)	49.0 (±14.6)
CVP	**RABBITS**	
14.0 (n = 5)	68.9 (± 14.3)	67.0 (± 14.7)
33.0 (n = 9)	53.0 (±17.0)	50.3 (±15.1)
50.0 (n = 4)	13.7 (±12.2)	7.6 (±10.9)
physostigmine 0.1 (n = 2)	117.0 (±22.4)	77.0 (±27.8)
0.2 (n = 4)	99.0 (±17.3)	79.0 (±17.9)
0.4 (n = 4)	102.0 (±19.1)	70.0 (±18.4)

* – the value refer to activity measured 3 hrs after the injection of CVP and 25–30 min, after the injection of physostigmine.

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Out of the eight rats selected for EP testing, two received CVP at the dose 3.0 mg/kg, four at 1.0 mg/kg and two at 0.5 mg/kg. Both animals which received CVP at 3.0 mg/kg died within 24 hours after the administration. EP changes in those rats involved gradual decline of the peaks.

In the 3-hour period after the injection, significant changes were present in both rats which received 0.5 mg/kg CVP, and in two of the four rats which received 1.0 mg/kg CVP. In all those cases, the changes involved a reduction of the amplitude of one or both negative peaks. Only in one (1.0 mg/kg) rat, was the effect detectable as late as the next day.

Biochemical tests. In rats CVP and physostigmine inhibited ChE activity in plasma as well as in erythrocytes. In both these compartments the inhibition induced by 1.0 mg/kg physostigmine was slightly higher than that observed after 1.0 mg/kg CVP but lower than that after 3 mg/kg CVP.

In rabbits plasma and erythrocyte ChE, both appeared vulnerable to CVP. Physostigmine, however, inhibited only erythrocyte ChE. What is more, the inhibition of erythrocyte ChE by the highest dose of physostigmine (0.4 mg/kg) did not exceed that induced by the lowest dose of CVP (14 mg/kg). The values are presented in Table 1.

DISCUSSION

The results of our present study can be summarized as follows:

1. The changes in the neocortical and hippocampal EEG spectrum of the rabbits after intraperitoneal injection of CVP at the doses of 14, 33, or 50 mg/kg body weight were small, often disappearing within 3 hours, and occurred only in some of the animals. No dose-effect relationship was observed. The changes in the spectrum of both tested brain areas, if present, had a form suggesting a moderate increase of electroencephalographic arousal.

2. Intraperitoneal administration of physostigmine to rabbits at the doses of 0.1, 0.2. and 0.4 mg/kg in all animals resulted in cortical and hippocampal EEG spectrum changes characteristic of the electroencephalographic arousal. There was a clear dose-effect relationship, and the changes disappeared within 1–2 hours after the injection.

3. Administration of CVP to rats at doses of 1.0 and 3.0 mg/kg body weight resulted in noticeable changes of the spectrum in some of the animals only. The changes involved an increase of the total power of the cortical EEG and were not accompanied by changes of power distribution in the spectrum. There was no dose-effect relationship.

4. Intraperitoneal administration of physostigmine to rats at the dose of 1.0 mg/kg in all animals resulted in changes which pointed to an increase of electroencephalographic arousal and which were more manifested in the hippocampal EEG spectrum.

5. In both investigated species, intraperitoneal administration of CVP affected cortical evoked potentials in some of the individuals only, and it was not possible to determine the dominant trend of changes.

According to the literature, activation of the central cholinergic system in animals results in electroencephalographic arousal, i.e. domination of fast, low amplitude activity in the cortex and theta rhythm in the hippocampus (2, 3, 9). In the results of the spectral analysis, the encephalographic arousal response is manifested by a reduction of the total power of the recording and by changes in the percentage power distribution in the cortical spectrum (reduction in the 1–4 Hz band and increase in the 21–32 Hz band) and in the hippocampal spectrum (power increase in the 4–7 Hz band). In our experiments, a situation like that prevailed essentially in all animals, both rabbits and rats, which received physostigmine, and only in some of animals which received CVP. Those results are surprising when compared with the results of the biochemical tests (Table 1). They are, however, consistent with the results of our earlier studies in which we have shown that CVP efficiency in producing changes of the hippocampal and cortical EEG activity was relatively low when compared with its capacity to reduce ChE activity (7, 8). Conventional methods involving visual analysis of EEG recordings taken after the injection of CVP showed evident changes which occurred only when ChE activity was reduced by 50%. The digital methods of the analysis employed by us in our recent work, although more precise, gave similar results. It is, therefore, reasonable to suppose that the results of the performed investigations are dependent not only on the precision of the test methods employed, but primarily on the specificty of the investigated chemical compound under study.

The low efficiency of CVP in producing the state of electroencephalographic arousal may be one of the reasons for the small and unexplicit changes in the evoked activity. The strict relationship between the morphology of the evoked potentials and the level of arousal has been often asserted (10, 13, 15). In our work, however, there were no evident changes after the injection of rabbits with physostigmine either. It is not possible, therefore, to exclude that superposition of the effects resulting from the change in the excitability of the area from which the potential was taken and of the effects caused in the eye (pupil contraction) and behavioral changes (reduction of mobility), was the primary reason of the ambivalence of the changes in the evoked activity, both after the injection of CVP and physostigmine.

Based on our earlier electroencephalographic observations (7) we have sug-gested that CVP is not only a ChE inhibitor but also an antagonist of cholinergic receptors. The results of the electroencephalographic tests seems to support that suggestion. OPs compounds are known to be both agonists and antagonists of the cholinergic receptors (1, 5). According to some authors, the type of a specified OP interaction with the receptor may significantly affect a compound's toxicity, especially at higher doses (1).

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Received for publication: January 25, 1992
Accepted for publication: March 10, 1992

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