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EFFECT OF DELTA-SLEEP PEPTIDE ON INTERCENTRAL INTEGRATION IN EXPERIMENTAL EPILEPSY

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Peptides, among them delta-sleep peptide (DSP), possess a broad spectrum of action [11]. The therapeutic effect of DSP has been proved, especially under conditions of stress and in neuroses [3, 7], and this correlates with its ability to modify the convergent properties of brain structures [2] and mediator metabolism [2, 7], and to exert a modulating effect on pineal α_1-adrenergic receptors and on their responses to adrenergic agonists [8, 9]. The effect of DSP on epileptiform activity in the sensomotor cortex, induced by application of strychine and penicillin, has been demonstrated [5]. Meanwhile in epilepsy, the effect of DSP on processes developing in deep brain formations has not been explained, and the investigation described below was undertaken for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on cats with electrodes implanted into various brain formations: the auditory, visual, and motor areas of the cortex, caudate nucleus, centrum medianum of the thalamus, and the hippocampus of both hemispheres. The animals received an intramuscular injection of crystalline benzylpenicillin (Yugoslavia) in a dose of 400,000 U/kg, which induced epileptiform cyclic discharges, recorded simultaneously in all the brain structures tested, as well as myoclonic contractions of the muscles. Either before the appearance of epileptiform activity or when fully developed, these animals were given an intraperitoneal injection of DSP in doses of 25, 50, 75, and 100 μg/kg. The first three doses of DSP were given with intervals of 1-1.5 h between them, and with continuous monitoring of the EEG and evoked potentials (EP) of each brain structure. The largest dose of DSP was injected 2 days after injection of the smaller doses.

The recording electrodes were connected to a biopotentials amplifier ("Riz," Yugoslavia) with time constant of 0.05 sec and upper limit of the transmission band of 150 Hz. Evoked potentials (EP) were led from the output of the biopotentials amplifier to an analog-to-digital converter (ADC) of a type PDP P/40 computer, where they were averaged and the standard deviations were calculated in real time. The sampling interval was 2 msec and the epoch of analysis 200 msec. The results were displayed as print-outs of characteristics of EP in terms of assigned time limits (peak amplitudes, times until peaks), and also on a "Hewlett-Packard" graph plotter.

Evoked potentials were averaged to five flashes applied with time intervals varying from 2 to 3.5 sec. In this way the characteristics of EP were established for each brain structure before and during the action of penicillin, and again at different times after injection of DSP.

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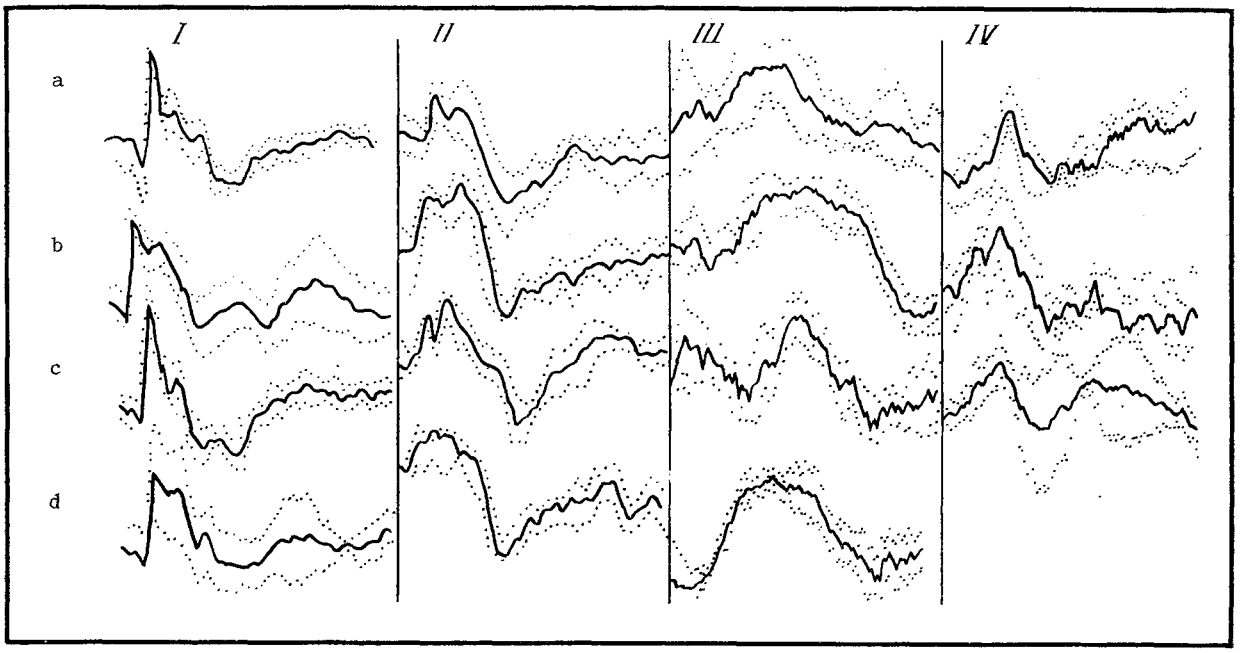

Fig. 1. Parameters and configuration of EP in various brain structures. I) Visual cortex, II) motor cortex, III) centrum medianum of thalamus, IV) caudate nucleus. a) Before injection of penicillin, b) 50 min after injection of penicillin, c) 30 min after injection of DSP, d) 1.5 h after injection of DSP.

EXPERIMENTAL RESULTS

Without dwelling in detail on a description of the epileptiform discharges themselves, induced in the brain structures by injection of penicillin, we may recall that their frequency, duration, and amplitude largely depend on the functional state of the animals [1]. In our experiments on conscious animals epileptiform cyclic discharges had a duration of between 1 and 1.5 sec and they appeared for 4 h or more with intervals of 8-25 sec. These discharges were accompanied by myoclonic contractions of the muscles. Correlation was observed between epileptiform activity and myoclonic contractions of the muscles.

Injection of DSP in doses of 25, 50, and 75 μg/kg after epileptiform discharges had already developed did not alter their character: as before the discharges affected all the brain structures tested. The temporal parameters of EP and their configuration remained unchanged, i.e., remained at the level of the characteristics of EP arising after injection of penicillin. Injection of DSP against this background in a dose of 100 μg/kg did not change the character of the EEG, but a tendency was observed in all brain structures for the temporal parameters of EP to be reduced, and their configuration closely resembled that observed initially (Fig. 1a, b, c). These changes in EP began 20-25 min after injection of the peptide and persisted for 25-40 min. After this time had elapsed, the parameters of EP reverted to those existing before injection of the peptide (Fig. 1d), i.e., following injection of penicillin.

In the second version of the experiments DSP was injected before epileptiform activity appeared. Under these conditions DSP in doses of 25, 50, and 75 μg/kg likewise did not change the parameters of the EEG or of EP. Injection of the peptide in a dose of 100 μg/kg induced two types of distortions of the initial EEG picture. In the first type, epileptiform discharges did not spread to all brain structures. In this case, slow-wave activity, lasting 5-8 sec, appeared periodically in the caudate nucleus and centrum medianum of the thalamus (Fig. 2b). In the second type, epileptiform discharges spread successively to the auditory and visual areas of the cortex, the hippocampus, and then to the motor cortex, caudate nucleus, and centrum medianum (Fig. 2c). No myoclonic contractions were exhibited in either of these two types.

Thus under chronic experimental conditions the antiepileptic action of DSP was more marked if it was injected before epilepsy developed. Under these conditions DSP caused the appearance of slow waves in the thalamic structures of the brain and the caudate nucleus.

Analysis of the distribution of epileptiform discharges among the brain structures after the two different versions of DSP injection demonstrates that the peptides, in a dose of 100 μg/kg, can interfere with the formation of the pathological intercentral integration that is characteristic of epilepsy, but cannot significantly modify pathological intercentral relations that are already organized. If DSP is injected before the development of epileptiform activity, its

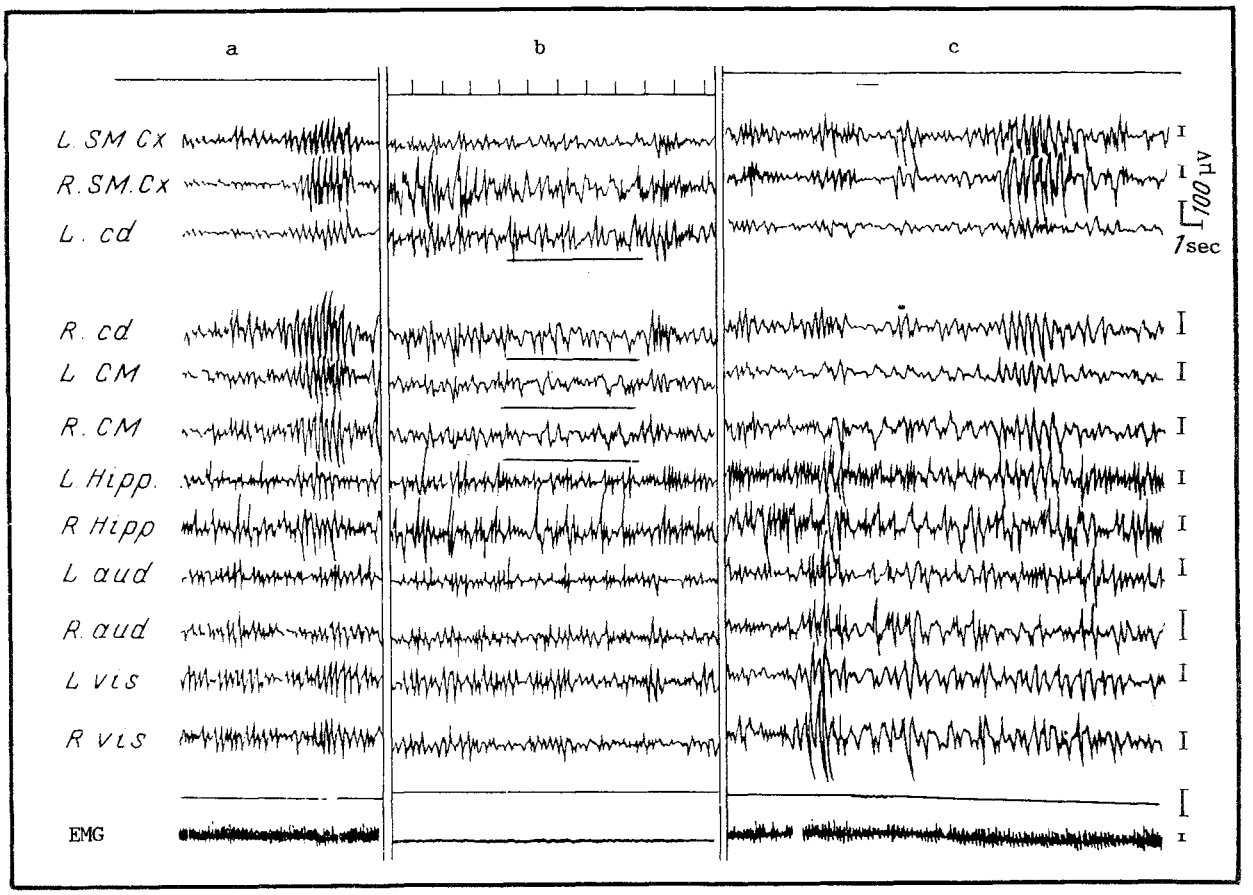

Fig. 2. Character of spread of epileptiform activity over brain structures when DSP injected before development of seizure discharges. a) EEG before injection of DSP, b, c) EEG after injection of DSP; b) slow activity appears in centrum medianum of thalamus and caudate nuclei, c) definite order of spread of epileptiform discharges can be observed over brain structures.

spread over the brain structures is prevented by slow waves appearing in the centrum medianum of the thalamus and in the caudate nucleus. Comparison of these facts with data indicating that slow-wave activity does not facilitate epileptiform discharges [4, 6], and also that delta sleep can potentiate or even provoke epileptiform activity [10], suggests that the slow-wave activity due to DSP and the slow-wave activity associated with natural sleep are different in their genesis. Further evidence in support of this view is given by differences in the response of the brain structures to photic and acoustic stimulation under conditions of slow-wave sleep and during the action of DSP [2].

Comparison of the action of DSP on neurophysiological processes in brain structures of intact animals during psychomotor excitation (evoked by chronic administration of L-dopa) and in epilepsy (connected with systemic injection of penicillin) indicates that a much larger dose of DSP is required in epilepsy for it to intervene in intercentral relations than during psychomotor excitation (25 and 100 μg/kg respectively). Meanwhile, under the conditions of the two forms of neuro-psychopathology examined above, DSP has a predominantly local action, directed in both cases to the thalamic structures of the brain, whereas in intact animals the effect of DSP is generalized in character. Admittedly, under conditions of psychomotor excitation DSP initially causes generalized inhibition of analogs of EP of sensory type in brain structures, but later it has a local effect, characterized by the appearance of slow waves in the intralaminar thalamic nuclei.

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CIRCENNIAL RHYTHM OF MYOCARDIAL ARYL SULFATASE ACTIVITY IN INTACT RABBITS

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There is evidence [1, 4] that some parameters of cardiac activity follow a distinct circennial rhythm. It is interesting to examine the principles governing analogous changes in lysosomal activity of the cardiomyocytes, for these organelles can play an important role in intracellular regeneration processes [3] and, consequently, they can determine both metabolism of the myocardium and its contractile function.

The aim of this investigation was to examine the state of the lysosomal apparatus of the cardiomyocytes of intact rabbits in the course of the year by the use of an enzyme histochemical reaction for detection of aryl sulfatase activity, regarded [5] as a selective method of enzyme histochemical identification of lysosomes.

EXPERIMENTAL METHOD

Experiments were carried out on 36 male Chinchilla rabbits weighing 2.5-3 kg. Every month (on the 21st-23rd of each month) three rabbits were killed by thoracotomy under superficial hexobarbital anesthesia, after which the heart was extracted. Aryl sulfatase activity was determined histochemically [2] in frozen sections of the left and right ventricles. Activity of the enzyme was assessed by counting the number of dark brown granules in 30 fields of vision (for each rabbit) under immersion magnification. The number of fields of vision (out of a total of 90) in which granules were found also was counted. The numerical data were subjected to statistical analysis by Student's test using a "Commodore 64" personal computer. The difference between mean values was taken to be significant at the $p \leq 0.05$ ($T \geq 2.0$) level. Correlation between the parameters was assessed as strong if the absolute value of the coefficient of correlation $r \geq 0.7$, as moderately strong if $r = 0.69$-0.3, and as weak if $r = 0.29$. The significance of the correlations was estimated by the usual statistical methods, based on our own program for the personal computer.

EXPERIMENTAL RESULTS

The results are given in Table 1.

The results in Table 1 are evidence that activity of the lysosomal enzyme aryl sulfatase in both left and right ventricles has a distinct circennial rhythm. Differences between mean values for neighboring months are not significant for the left ventricle during the periods February—May and September—October, and for the right ventricle during the periods February—April and June—August. At all other times the difference between the mean values is significant. Over the whole period of the investigation, except in September, the difference between the mean values for the number of granules in the left and right ventricles is significant.

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