# Peptide Correction of Disturbed Intercentral Relations

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Effects of peptides with opioid activity (δ-sleep peptide, tetrapeptidamide, and taftsin) are studied in animals with disturbed intercentral relations (psychomotor excitation or penicillin epilepsy). δ-Sleep peptide and tetrapeptidamide suppress brain structure responses to photo- and acoustic stimulants. All peptides alter the multisensory characteristics of the structures. In disease, peptidergic mechanisms regulate afferent flows to brain structures.

**Key Words:** *integration; neuropeptides; evoked potentials; monoamine oxidase A and B; myoclonic muscular contractions*

Pathological states of the central nervous system have been regarded as a result of discoordination between brain structures. However, this assumption is rather abstract and allows many interpretations. According to one of them, functional interactions (or integration) of brain structures is a principal scheme of distribution and regulation of afferent flows. Distortions of such a scheme lead to disease and its restoration to correction and compensation [6]. From this viewpoint we shall regard neuropsychotropic effects of δ-sleep peptides (DSP) and tetrapeptidamide possessing opioid activity and those of taftsin, a well-known stimulant of the central nervous system.

Systemic restructuring provoked by a single injection of each of these peptides to intact animals and animals with central nervous system diseases was assessed in higher animals by bioelectric activity of the brain: electroencephalogram, evoked potentials (EP), and their analogs or reproduced EP configurations between the signals.

## MATERIALS AND METHODS

Experiments were carried out on dogs and cats with chronically implanted electrodes. In dogs, the electrodes were implanted in the visual analyzer structures (fields $O_1$ and $O_2$), external geniculate body, motor field, caudate nucleus, pale globe, adjacent nucleus, and intralaminar nuclei of the thalamus. A defense habit was developed in dogs: a series of 6 light flashes (2 Hz) was combined with suprathreshold electrostimulation of the fore paw between the fifth and sixth flash.

Electroencephalogram and EP were recorded with a 9-circuit oscillographer (pass band up to 2000 Hz, time constant 1 sec). Similarity of EP analog configuration to configuration of EP recorded in response to sensory stimulator was the criterion for distinguishing EP analogs. The presence of EP analogs, their configuration, amplitude and time, and relation to the motor reaction were assessed.

In cats, the electrodes were implanted in sensorimotor, acoustic, and visual cortical zones, in caudate nuclei, hippocampus, central medial nuclei of the thalamus, and in anterior two-hillock area.

Electroencephalograms were recorded with a 16-channel encephalographer (RIS) with time constant 0.05 sec and upper pass band 150 Hz.

After stabilization of the habit in dogs, disease was induced.

For inducing a disease, the drugs were injected regularly until manifest side effects appeared: psychomotor excitation (L-DOPA in a daily dose of 15-25 mg/kg) or myoclonic convulsions (intramuscular benzylpenicillin in a dose of 400,000 U/kg).

Effects of some neuropeptides with opioid activity on the intercenter integration were examined: DSP (30 and 100 μg/kg), tetrapeptidamide (500 μg/kg), and taftsin (300 μg/kg). Effects of single and systemic administration of the peptides were studied in

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intact animals and in animals with nervous diseases (*a priori* distorted integration) in order to elucidate their corrective potentialities.

Reference data on the effects of each drug used in our study on the neuromediator systems (activities of enzymes responsible for utilization of biogenic amines: monoamine oxidase (MAO) A and B and acetylcholine esterase) obtained at the Department of Cytochemistry of the Institute of Brain were used in discussion of the findings in order to establish neurochemical correlations of intercentral relations.

## RESULTS

Ten minutes after DSP injection (30 μg/kg), the pattern of encephalogram corresponded to the slow-wave sleep stage: slow waves (3-4 Hz) predominate in all leads (Fig. 1). The level of awakening is not changed: active posture and orientation reaction are retained. Basic level of electroencephalogram is recovered after 60-70 min.

Ten minutes after injection of tetrapeptidamide in a dose of 500 μg/kg, the amplitude drops in all electroencephalogram leads without changes in its frequency characteristics. A morphine-like effect is observed: vomiting, salivation, and tremor.

The similarity between DSP and tetrapeptidamide effects consists in suppression of reactions of numerous brain structures to sensory stimulators. Slow waves of natural sleep disappear during photo- and phonostimulation, which is not observed during exposure to DSP (Fig. 1, *a*). Evoked potentials do not respond to flashes or clicks after treatment with tetrapeptidamide. These peptides similarly affect the neuromediator systems: 30 min after their injection, serotoninergic activity increases (MAO-A) and the adrenergic system is reciprocally suppressed (MAO-B). Judging from acetylcholine esterase activity, cholinergic processes are relatively stable during this period [1,3].

Suppression of brain reactions to light and sound stimuli may correlate with DSP and tetrapeptidamide effect on serotonin utilization. Similar changes in enzyme activity are observed in light deprivation [5].

It is noteworthy that the "filtering" effect of DSP, unlike that of tetrapeptidamide, does not involve afferentation induced by moving: slow electroencephalogram waves disappear during movement (Fig. 1, *b*).

Systemic administration of taftsin (300 μg/kg) also changes the typical pattern of bioelectric activity. A tendency to increase of the amplitude and duration of the major negative component of EP to light flashes develops in the cortical zone of visual analyzer, cortical motor zone, and caudate nucleus; small dispersion disappears in EP configuration. In other words, the ratio of afferent signals to these brain structures is changed. This process is compatible to restructuring at the mediator metabolism level. Thirty minutes after taftsin injection, MAO-A activity is suppressed in subfractions of synaptic membranes, synaptosomes, and mitochondria of caudate nucleus and cortical sensorimotor zone neurons, while the activity of MAO-B increases [4]. Taftsin gives rise to a tendency toward an increase in the content of dopamine and a decrease in the content of 5-hydroxyindolacetic acid, a serotonin metabolite [7].

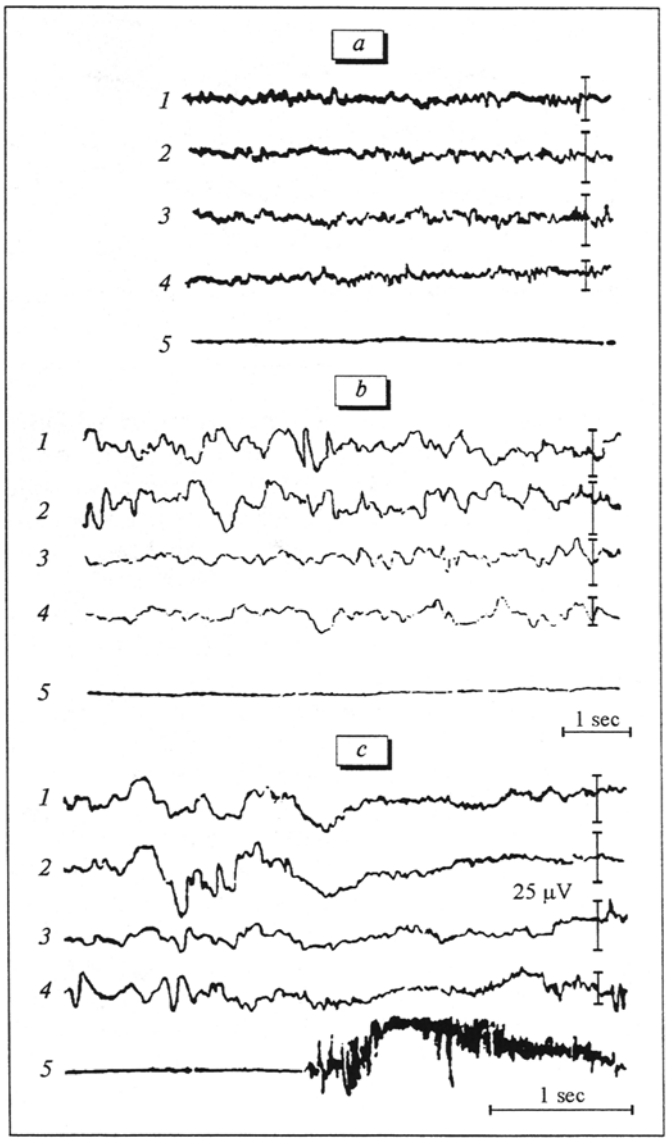


**Fig. 1.** Electroencephalogram changes in different structures of the brain caused by δ-sleep peptide (DSP). *a*) before DSP; *b*) 10 min after DSP, light flashes do not affect slow waves; *c*) 11-15 min after DSP, rising of the paw suppresses slow waves caused by DSP injection. Here and in Fig. 2: *1*) visual cortex; *2*) caudate nucleus; *3*) adjacent nucleus; *4*) motor cortex; *5*) electromyogram of the dog fore paw.

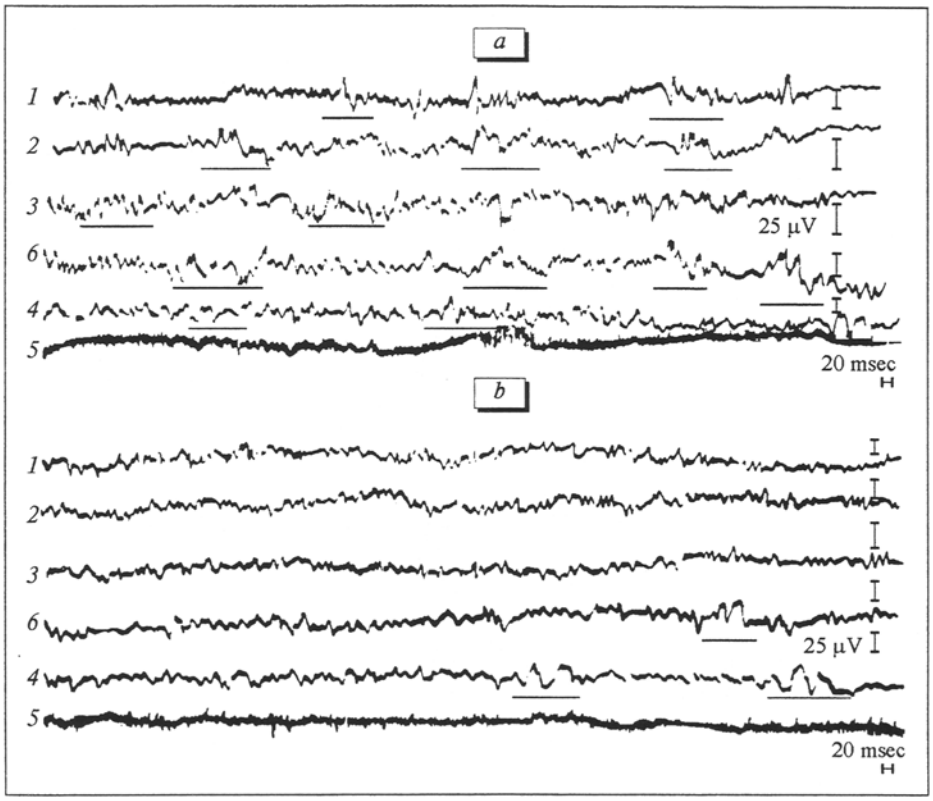


**Fig. 2.** Changes in evoked potential analogs caused by δ-sleep peptide (DSP) during exposure to L-DOPA: *a*) analogs of evoked potentials with both complex and simple configuration are recorded during exposure to L-DOPA; *b*) after DSP, only M-shaped analogs of evoked potentials are left. *6*) intralaminar thalamic nuclei.

Schematically, systemic administration of DSP, tetrapeptidamide, and taftsin can be represented as selective action on the convergent properties of brain structures. Such a "filtering" effect was used for correcting central nervous system abnormalities caused by afferent overexercise.

During regular chronic administration of L-DOPA, psychomotor excitation increased from episodes to a state of increased emotional excitation with outbreaks of unmotivated aggression. The number of EP analogs of different configuration was almost doubled in the cortical motor zone and in subcortical structures (caudate nucleus, pale globe, and adjacent nucleus). In intact animals with conditioned avoidance reaction, EP analogs with mainly complex M-shaped configuration were observed, i. e., effects of afferent complexes induced by movement predominated. During exposure to L-DOPA, EP analogs with both complex "motor" and simple configurations were recorded (Fig. 2, *a*). In other words, psychomotor excitation is associated with extra afferentation complexes which are not observed in health.

During combined exposure to L-DOPA and DSP, the "filtering" effect of DSP is superimposed on L-DOPA-induced afferent overloading of integration. Contralateral effects of L-DOPA and DSP were followed up at a subcellular level by changes in activities of enzymes responsible for the neuromediator utilization. L-DOPA stimulates dopaminergic and reciprocally suppresses serotonin- and cholinergic processes. By contrast, DSP activates serotoninergic and suppresses adrenergic systems [2,3].

After a single injection of DSP to animals with psychomotor excitation, the number of EP analogs dropped. The remaining EP analogs were characterized mainly by the M-shaped configuration (Fig. 2, *b*), i. e., afferent support of central integration normalized. Such an effect can be related to previously discussed DSP activation of the serotoninergic system.

Penicillin epilepsy was induced by intramuscular injection of crystalline benzylpenicillin in a dose of 400,000 U/kg. After its injection (40-45 min), electroencephalogram shows an epileptiform activity: cyclic epileptiform charges lasting for 1.0-1.5 sec at 8-25 sec intervals for 4 h. Epileptiform activity involves all examined structures of the brain and is associated with myoclonic muscular convulsions, which are then transformed into a generalized epileptic seizure and eventuate in death.

DSP in a dose of 100 μg/kg was injected intraperitoneally to animals with developing epileptiform electroencephalographic activity or before it.

Electroencephalogram did not change after DSP injection in the presence of epileptiform charges.

When DSP was injected before myoclonic seizures, two electroencephalographic patterns of peni-

cillin epilepsy were observed. In one of them, the epileptiform charges did not involve all brain structures, and 5-8-sec periods of slow-wave activity appeared in the caudate nucleus and the thalamic median center. In the other, epileptiform charges involved brain structures not all at once, but in succession: first the acoustic and visual zones of the cortex and hippocampus and then the sensorimotor zone of the cortex, caudate nucleus, and median center of the thalamus. Myoclonic seizures of muscles were not observed in any of the patterns. Dopamine and serotonin metabolism normalized under such conditions: MAO-A and MAO-B activities return to the initial levels [3].

Injection of taftsin (300 μg/kg) under the same conditions in the presence of developing epileptiform charges increased their frequency and duration and shortened the intervals between them.

If taftsin was injected before epileptiform electroencephalographic activity, the latent period before manifestation of the first cyclic charge was prolonged to 45-60 min. Nevertheless, as in the former case, epileptiform charges became more frequent and long.

It is noteworthy that irrespective of the conditions of taftsin injection, generalized epileptiform seizures did not lead to animal death. Biochemically, both variants of taftsin administration were associated with suppression of MAO-A activity [2,3]. Taftsin apparently does not influence the neurochemical processes triggered by penicillin. Penicillin affects mainly the GABAergic system, while taftsin modulates the dopamine- and serotoninergic systems [4].

Thus, the filtering effect of DSP and taftsin are manifested differently in penicillin epilepsy: both agents prevent the dissemination of epileptiform activity. Preventive injection of these peptides is an important factor in realization of this effect.

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