Effect of the Tetrapeptide Tuftsin on the Bioelectrical Activity of Brain Structures in Cats with Different Functional States of the Central Nervous System

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The tetrapeptide tuftsin (Thr-Lys-Pro-Arg) injected intraperitoneally into cats altered the bioelectrical activity of sensory, motor, and limbicoreticular structures in the wakeful state, during two different phases of sleep, and also when the caudate nucleus was electrically stimulated. In wakefulness and during REM sleep, absolute values of the electroencephalographic power spectrum were increased in all the brain structures under study, while during slow-wave sleep they were increased in the sensorimotor cortical areas and decreased in the central medial thalamic nuclei and hippocampus. Tuftsin facilitated the genesis of slow waves in subcortical structures and the expression of theta waves in the hippocampus. It also increased the amplitude of evoked potentials and elongated spindles when the caudate nucleus was stimulated.

Key Words: *peptide; tuftsin; brain structures; wakefulness; sleep*

Regulation of functions in higher organisms is closely associated in many ways with the activity of biological modulators such as peptides. Studies designed to examine the actions of the same peptide in different functional states of the body are therefore of special significance, for they not only add to our understanding of how individual peptides act, but can also help in deciding whether particular peptides may be usefully employed in disorders of specific bodily functions.

A regulatory peptide that influences very diverse bodily functions is the tetrapeptide tuftsin (Thr-Lys-Pro-Arg). Tuftsin has been shown to be capable of altering motor activity [4,5], emotional reactivity [3,4], and patterns of response by various structures to sensory inputs [2], and to produce an analgesic effect not mediated by opioid receptors [12]. It also provokes alterations in nonspecific and specific immune responses [10]. Moreover, there is evidence that tuftsin influences metabolic transformations in brain structures, affecting in particular neurotransmitters and proteins [1].

The desire to gain better insight into how tuftsin acts on brain structures in various functional states of the central nervous system prompted us to undertake the present investigation, in which this compound was examined for its impact on the same brain structures of animals in the awake state, during different phases of sleep, and also when one of the most polyfunctional brain structures, the caudate nucleus, was activated.

MATERIAL AND METHODS

This study was conduced on cats with electrodes implanted in several brain structures (sensorimotor, auditory, and visual areas of the cortex, caudate nuclei, hippocampus, central medial thalamic nuclei, and superior colliculi). Bioelectrical activity

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from these structures was recorded with a 16-channel encephalograph (Ris) using a time constant of 0.05 sec and an upper pass band of 150 Hz, and with a tape recorder (Hewlett-Packard 3968A).

The electroencephalographic (EEG) tracings were subjected to analysis using fast Fourier transformation on a PDP 11/40 computer in order to see how absolute values of the EEG power spectra recorded for the brain structures under study would vary over time. To this end, the curves obtained were broken down into 12 epochs of 8 sec each and the EEG tracings per second were each divided into 128 dots. We analyzed segments of the curves plotted before tuftsin injection and those plotted over a 2-h period starting at minute 45 after injection during wakefulness, during the slow-wave and REM phases of sleep, and when the caudate nucleus was being stimulated. The left caudate nucleus was stimulated with electric current of the order of 100-200 μA at a frequency of 0.3 Hz. Tuftsin was injected intraperitoneally in a dose of 300 μg/kg.

RESULTS

Awake rats administered tuftsin became calmer and more sociable 1-1.5 h postinjection, and this effect persisted for 3 h or longer. No EEG changes could be detected visually in the structures under study with the exception of the hippocampus, which exhibited bioelectrical activity of markedly increased amplitude. However, as the spectral analysis of the curves showed, tuftsin increased absolute values of the EEG power spectrum in all structures, namely the sensorimotor, auditory, and visual cortical areas, central medial thalamic nuclei, caudate nuclei, hippocampus, and superior colliculi. The most pronounced changes in absolute values of the EEG power spectrum occurred in the hippocampus and thalamic nuclei (Fig. 1).

Natural sleep is divided according to EEG data into slow-wave and REM (or paradoxical) phases. Visually, slow waves during the first phase after tuftsin injection became more prominent, especially in the deep brain structures. During the REM phase after tuftsin injection, EEG amplitudes were patently increased in the sensorimotor cortical areas, caudate nuclei, hippocampus, and superior colliculi.

Analysis of the EEG power spectrum in each brain structure during the slow-wave phase of sleep showed that absolute values of the spectra increased in the sensorimotor cortical areas and caudate nuclei and decreased in the thalamic nuclei and hippocampus (Fig. 2). During the REM phase, absolute values of the EEG power spectrum increased

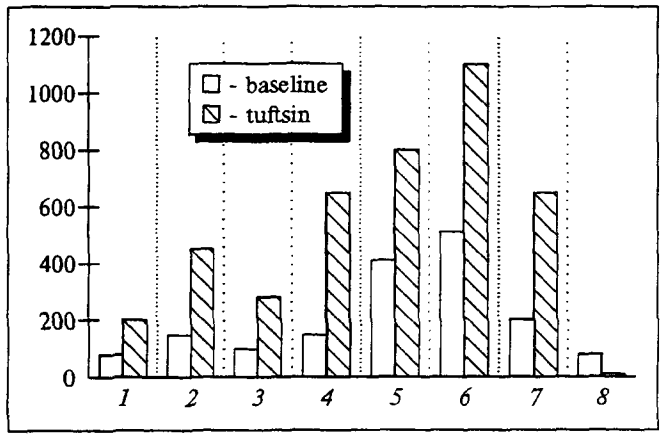


Fig. 1. Absolute values of EEG power spectrum (μW^2) in various structures of cat brain before (baseline) and 1 hr after tuftsin injection: sensorimotor cortical areas (*1* = left, *2* = right); caudate nuclei (*3* = left, *4* = right); medial thalamic centers (*5* = left, *6* = right); hippocampi (*7* = left, *8* = right)

after tuftsin injection in all brain structures (Fig. 3), i.e., the picture was similar to that observed for awake cats.

Stimulation of the caudate nucleus had a calming effect on the cats, which periodically fell into a drowse. Evoked potentials appeared with latencies of the order of 3-5 msec and spindles of 0.75 to 1.48 sec in duration with latencies of the order of 170-280 msec; the number of waves making up a spindle ranged from 8 to 14 (Fig. 4, *a*). Following tuftsin injection, caudate nucleus stimulation in these cats was accompanied by evoked potentials with increased (by 50%) amplitudes but the same latencies as before. The spindles became twice as long, but the number of waves making up a spindle remained unchanged (Fig. 4, *b*).

The greatest changes in the response to caudate nucleus stimulation in the tuftsin-injected cats were shown by deep brain structures.

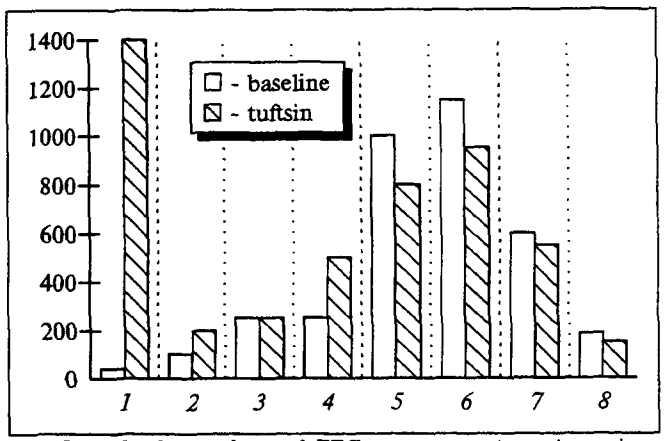


Fig. 2. Absolute values of EEG power spectrum in various structures of cat brain before (baseline) and 1 hr 45 min after tuftsin injection during slow-wave sleep. Same designations as in Fig. 1.

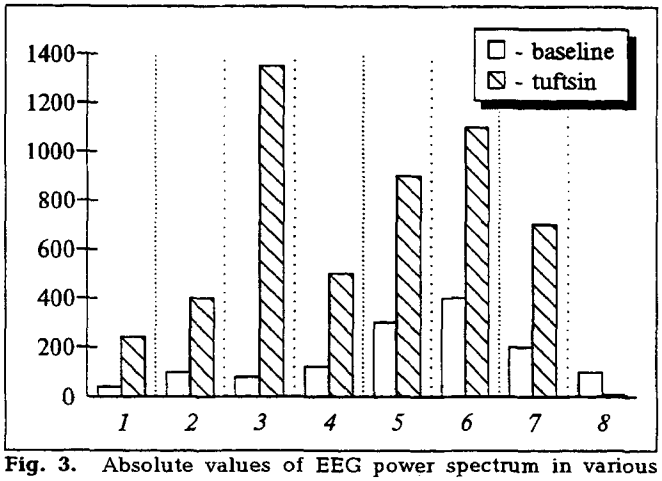
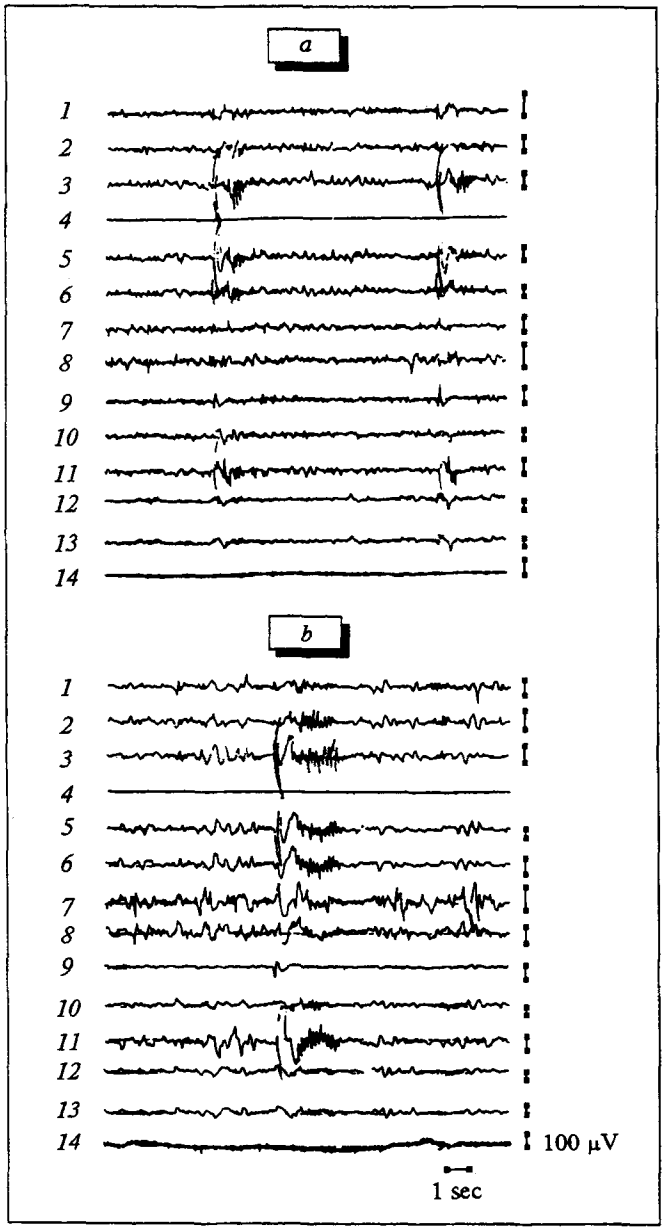


Fig. 3. Absolute values of EEG power spectrum in various structures of cat brain before (baseline) and 1 hr after tuftsin injection during REM sleep. Same designations as in Fig. 1.



Taken together, the results of this study indicate that tuftsin administration to awake animals results in virtually simultaneous increases in absolute values of the EEG power spectrum in the different brain structures. This peptide possibly provokes simultaneous changes in EEG parameters in functionally distinct brain structures by acting upon synchronizing mechanisms of the central nervous system. It influences both the spontaneous bioelectrical activity of cortical and subcortical/stem structures and the bioelectrical activity elicited by caudate nucleus stimulation. The diversity of brain structures where the EEG power spectrum is altered by tuftsin is commensurate with the wide range of emotional behavioral parameters undergoing alteration after its administration [3,4].

The changes in bioelectrical activity were greatest in the structures high in dopamine. In awake cats, shifts in EEG parameters were attended by a 25% depression (on average) of monoamine oxidase A activity and a 140 to 200% elevation of monoamine oxidase B activity in the sensorimotor cortical areas and particularly in the caudate nuclei, with little change in acetylcholinesterase activity [2].

According to cytochemical data [1], the first to undergo change under the influence of tuftsin is dopamine metabolism, this being followed by changes in other neutrotransmitter systems, including a decline in the utilization of serotonin (as indicated by lowered monoamine oxidase A activity) and acetylcholine.

The tuftsin-induced increases in absolute values of the EEG power spectra during the REM phase of sleep may be a consequence of elevated activity of the cholinergic and catecholaminergic systems, brought about by alterations in acetylcholinesterase and especially monoamine oxidase B activity, which may result in heightened reactivity of various cholinergic neurons [6]. The cholinergic systems of the brain are known to promote the awakening process as well as the synchronization of electrical activity of brain structures in the wakeful state.

Interference with neurotransmitter metabolism in general, and dopamine metabolism in particular, inevitably entails modulation of functional relationships among a wide range of brain structures.

Fig. 4. EEGs recorded from various structures of cat brain during stimulation of left caudate nucleus before (*a*) and 30 min after (*b*) tuftsin injection. *1* and *2*) right and left sensorimotor cortical areas; *3* and *4*) right and left caudate nuclei; *5* and *6*) right and left central medial thalamic nuclei; *7* and *8*) right and left hippocampus; *9* and *10*) right and left auditory cortical areas; *11*) superior colliculi; *12* and *13*) right and left visual cortical areas; *14*) electromyogram.

The dopamine projections of modulation may therefore alter relationships between the substantia nigra and caudate nuclei, which are connected with the sensorimotor cortex via the external segment of the globus pallidus and the thalamic nuclei. Information transfer by this route is subject to an inhibitory influence of subthalamic nuclei [11], which has an important bearing on the systemic effects of low dopamine doses [7,9]. On the other hand, the same subthalamic nuclei facilitate striatonigral information transfer, thereby exerting a considerable influence on the systemic consequences of dopamine agonists in high doses [9]. Inhibitory influences of the substantia nigra on the nonspecific thalamic nuclei and on the sensorimotor cortex have also been reported [8]. The experimental data apparently reflect specific relationships primarily between the caudate nuclei, internal segments of the globus pallidus, sensorimotor cortical areas, and substantia nigra under conditions of altered dopamine metabolism.

As the results of this study indicate, EEG parameters in different brain structures may undergo similar or contrasting changes under the influence of tuftsin depending on the functional states of these structures themselves. In other words, in the final analysis, it is the functional state of the organism that determines to a large extent how tuftsin will act.

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