ACTION OF OPIATE PEPTIDES AND NARCOTIC ANALGESICS ON THE CEREBRAL CORTEX

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The use of opiate peptides, possessing analgesic properties [5], is accompanied by changes in interneuronal transmission of excitation at different levels of the CNS [2, 3]. It has been suggested [15] that these peptides play a role in some manifestations of psychotic disturbances. Nevertheless the use of narcotic analgesics may also lead to disturbances of behavior in experimental animals [8, 16]. The analgesic effect of morphine-like compounds and their effect on behavior are known to take place through the participation of the cerebral cortex; hence the interest in the study of the action of opiate peptides and narcotic analgesics on the cerebral cortex of animals under conditions of free behavior.

The object of this investigation was to study primary responses (PR) of the cerebral cortex in cats to single and paired stimulation of fibers of the thalamocortical radiation (TCR), applied with different intervals between stimuli. Stimulation of the fibers of TCR enables the influence of deep brain structures on the conduction of the afferent volley to the cerebral cortex to be excluded [6].

The effects of two opiate peptides, obtained synthetically – FK 33-824 (Tyr-D-Ala-Gly-MePhe-Met(0)-01)* and the tetrapeptide (Tyr-D-Ala-Gly-Phe-NH_2)† – which induce analgesia in experimental animals when administered systemically [10, 12], were investigated. Similar experiments were carried out with the narcotic analgesics morphine, fentanyl, and pentazocine.

EXPERIMENTAL METHOD

Experiments were carried out on cats of both sexes weighing 3-3.5 kg. The animals were anesthetized with pentobarbital sodium (40-50 mg/kg, intraperitoneally), and bipolar nichrome electrodes (interelectrode distance 50 μ) were inserted stereotaxically into fibers of TCR at a depth of 5-7 mm from the surface of the 2nd somatosensory area of the cortex. Monopolar recording nichrome electrodes were applied to the surface of the 2nd somatosensory (gyr. ectosylv. ant.) and association (gyr. suprasylv. ant.) areas of the cortex, and the reference electrode was secured in the frontal bone. The animals were used in the chronic experiments not earlier than 6-8 days after the operation. Threshold, above-threshold, and supramaximal square stimuli with a duration of 0.1 msec and with different intervals between stimuli (20-500 msec) were applied to the fibers of TCR. To plot the graph of the recovery cycle of PR, the amplitude of the second (testing) response as a percentage of the amplitude of the first (conditioning) response, taken as 100%, was calculated. The opiate peptides and narcotic analgesics were administered in close to or above the analgesic doses (Table 1). Naloxone, an antagonist of the opiate peptides and narcotic analgesics, was used in a dose of 1 mg/kg. All the drugs were injected intraperitoneally.

EXPERIMENTAL RESULTS

The recovery cycle of PR in the 2nd somatosensory area of the cortex obtained during stimulation of fibers of TCR consisted of a period of an increase in PR to the second (testing) stimulus, lasting 200 msec, followed by a decrease in amplitude of PR below 100% when the interval between stimuli was 300-350 msec,

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TABLE 1. Comparative Characteristics of Opiate Peptides and Narcotic Analgesics

Substance	Dose of substance, mg/kg	A_1		A_2/A_1		Paroxysmal discharges on EEG	Analgesic doses, mg/kg	Literature citation
		sII	assoc.	sII	assoc.			
FK 33-824	0,4—0,5	—	—	—	↓	—	ED_{50}0.4 (mouse)	[15]
(Tyr-D-Ala-Gly-MePhe-Met(O)d)	0,7—1	—	—	↓	↓↓	—		
	2	—	—	↓↓	↓↓	—	ED_{50}0.7 (rat)	[15]
	3—5	↑	↑	↓↓	↓↓	+		
Tetrapeptide	10—12	—	—	—	↓	—	ED_{50}1 (rat)	[13]
(Tyr-D-Ala-Gly-Phe-NH_2)	15—20	—	—	↓	↓↓	—		
	25—35	↑	↑	↓↓	↓↓	+	ED_{50}9 (mouse)	[X]
Morphine	1—1,5	—	—	—	↓	—	ED_{50}1.8 (mouse)	[15]
	2—4	—	—	↓	↓↓	—		
	5—8	↑	↑	↓↓	↓↓	—	ED_{50}1.3 (rat)	[15]
	10—15	↑	↑	↓↓	↓↓	+	ED_{50}3.5 (rat)	[11]
							2 (cat)	[2]
Fentanyl	0,05—0,1	—	—	—	↓	—	ED_{50}0.013 (rat)	[11]
	0,11—0,15	—	—	↓	↓↓	—		
	0,2	—	—	↓↓	↓↓	—		
Pentazocine	7—10	—	—	—	↓	—	20 (rat)	[10]
	12—15	—	—	↓	↓↓	—		
	17—20	↑	↑	↓↓	↓↓	—		
	22—30	↑	↑	↓↓	↓↓	+		

Legend. ↑) Increase by 7-12%; ·↓) decrease by 20-30%; ↓ ↓) decrease by 30-45%; +) effect present; -) effect absent; sII) 2nd somatosensory area of cortex; assoc.) association area of cortex; X) data of O. N. Chichenkov; A_1) amplitude of 1st (conditioning) response; A_2/A_1) ratio of amplitude of 2nd (testing) response to amplitude of 1st (conditioning).

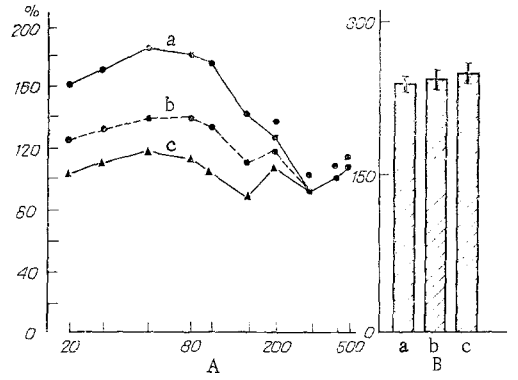

Fig. 1

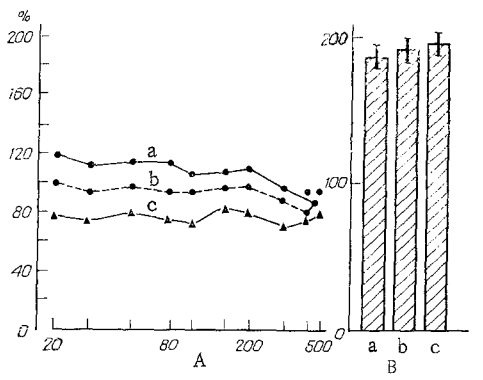

Fig. 2

Fig. 1. Effect of FK 33-824 on PR arising in 2nd somatosensory area of cat cortex during above-threshold (5-7 V) stimulation of fibers of TCR. A) Recovery cycles of PR before (a) and after application of FK 33-824 in doses of 0.8 mg/kg (b) and 2 mg/kg (c). Abscissa, intervals between conditioning and testing stimuli (in msec); ordinate, amplitude of testing PR (in % of amplitude of conditioning PR); B) amplitude of averaged (in μV) PR of 2nd somatosensory area of cortex to single above-threshold stimulation of fibers of TCR before (a) and after administration of FK 33-824 in doses of 0.8 mg/kg (b) and 2 mg/kg (c). Results indicated by dots are not statistically significant ($P > 0.05$).

Fig. 2. Effect of FK 33-824 on PR arising in association area of cat cortex during above-threshold (5-7 V) stimulation of fibers of TCR. Legend as in Fig. 1.

and gradual recovery of the amplitude of PR with an increase in the interval between stimuli to 500 msec. This pattern of change in the recovery cycle in the control was maintained whatever the strength of stimulation applied to the fibers of TCR.

The recovery cycle of PR in the association cortex was characterized by a longer (300-350 msec) but less marked phase of increase of PR to the second (testing) stimulus.

Substance FK 33-824 reduced the amplitude of the testing PR in the 2nd somatosensory area of the cortex to stimuli separated by an interval of 20-150 msec. This effect appeared particularly clearly in response to above-threshold stimulation of the fibers of TCR. This action of FK 33-824 occurred when the substance was given in doses of 0.7-1 mg/kg. Meanwhile, the amplitude of PR arising in response to conditioning stimulation

of the fibers of TCR remained virtually unchanged (Fig. 1). Naloxone abolished the effect of FK 33-824 on the recovery cycle of PR.

In the association area of the cortex FK 33-824 evoked similar changes in the recovery cycle of PR (in the interval 20-300 msec), but they arose when this opiate peptide was given in smaller doses (0.4-0.5 mg/kg). Under these circumstances the amplitude of PR to conditioning stimulation of TCR likewise was unchanged (Fig. 2).

With an increase in the dose of the compound to 2 mg/kg the intensity of changes in the recovery cycles of PR in both zones of the cortex increased. FK 33-824 (3-5 mg/kg) evoked some increase in amplitude of single PR both in the 2nd somatosensory area and in the association area of the cortex. At the same time paroxysmal discharges were found on the EEG and unmotivated motor excitation of the animals developed. The paroxysmal discharges on the EEG and the motor excitation were abolished by naloxone.

The tetrapeptide, like FK 33-824, had the power of inhibiting the course of recovery cycles of PR in the 2nd somatosensory and association areas of the cortex. This compound, in doses of 10 to 20 mg/kg, reduced the amplitude of the testing PR in both areas of the cortex but had no effect on the amplitude of PR obtained in response to single stimulation of TCR. An increase in the dose of the tetrapeptide to 25-35 mg/kg led to some increase in single PR and to the appearance of paroxysmal discharges on the EEG and motor excitation of the animals. Naloxone abolished the effect of the tetrapeptide on recovery cycles of PR and on the amplitude of single PR and returned the EEG and the animals' behavior to normal.

Morphine (1-4 mg/kg), fentanyl (0.05-0.2 mg/kg), and pentazocine (7-15 mg/kg) evoked changes in the recovery cycles of PR similar to those produced by the opiate peptides studied; in this case also PR of the association area of the cortex obtained upon testing stimulation of the fibers of TCR were highly sensitive to the action of these narcotic analgesics. Morphine in a dose of 5-8 mg/kg and pentazocine in a dose of 17-20 mg/kg evoked a paroxysmal response in the cats. The use of naloxone against the background of the maximal intensity of the above-mentioned effects of morphine and the other narcotic analgesics studied led to normalization both of the course of the recovery cycles of PR in both cortical areas and of the amplitude of single PR, EEG, and the animals' behavior.

This investigation thus revealed the ability of opiate peptides FK 33-824 and tetrapeptide, and also of narcotic analgesics morphine, fentanyl, and pentazocine, in near-analgesic doses, to weaken the phase of exaltation of the testing PR in the interval of 20-150 msec in the 2nd somatosensory area and in the interval 20-300 msec in the association area of the cortex.

Since changes in the testing response compared with the conditioning can serve as a criterion of the relations between excitation and inhibition [4, 7] in the cortex, it can be tentatively suggested that the compounds tested have a marked inhibitory effect on depolarization processes. Evidence in support of this view is given by the data of Satoh et al. [13], who showed the presence of antagonism between morphine and the excitatory mediators acetylcholine and L-glutamate on cortical neurons in a microiontophoretic study. The predominant influence of morphine on depolarization processes in the cortex is connected with a reduction in the slow negative potential following both PR and the direct cortical response, during local and systemic administration of the drug [1]. A direct inhibitory action of encephalins and morphine has also been observed on cortical unit activity [14]. However, the possibility of weakening of depolarization processes connected with the ability of compounds of the morphine group to raise the GABA level in different parts of the CNS likewise cannot be ruled out [9].

The substances tested, in above-analgesic doses, caused an increase in PR in response to single stimulation of the fibers of TCR, together with the appearance of paroxysmal discharges on the EEG and motor excitation of the animals. These effects can evidently be regarded as specific for the substances tested, for they were completely abolished by naloxone, which blocks opiate receptors. Furthermore, certain other opiate peptides have a similar effect to that of FK 33-824, tetrapeptide, morphine, and pentazocine on the EEG and behavior of animals.

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