REVIEWS

Neurochemical Relationships in the Action of Opioid Analgesics on Cerebral Cortex

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 132, No. 7, pp. 4-12, July, 2001
Original article submitted June 5, 2001

The experiments with unrestrained cats showed that opioid analgesics in near-analgesic doses decreased the amplitude of the primary test response recorded in the second sensorimotor zone of the cerebral cortex in 20-150-msec interval between the stimuli applied to thalamocortical fibers radiating from thalamic *n. VPL*. Application of test substances affecting certain neurotransmitter processes and microionophoretic application of drugs and neurotransmitters to cortical neurons showed that the inhibitory effect of opioid analgesics on cerebral cortex is probably realized through GABA-, serotonin-, β-adreno-, and cholinergic structures. The excitatory amino acids are also involved into this process.

Key Words: *opioid analgesics; cerebral cortex; neurotransmitters*

Elucidation of neurochemical mechanisms underlying the effects of various pharmacological agents on cerebral cortex (CC) is important for understanding general principles of their action and the development of rational strategy of the search for novel and more efficient neuro- and psychotropic preparations.

CC is the highest level of perception, evaluation, and processing of afferent information. It also participates in the formation of responses to afferent stimuli. Specifically, CC plays an important role in nociception and pain control; potentiation of inhibitory cortical influences can be involved in the realization of analgesic effect of many drugs [8]. Some cortical neurons respond to peripheral painful stimulation [13]. This stimulation enhances metabolism in some cortical areas [6]. The involvement of various neurotransmitter systems in nociceptive traffic at the supraspinal level was established [17,18]. However, the data on the effect of opioid analgesics on transmission of afferent signals to CC are contradictory [13]. This is due to the fact that most data were obtained in acute experiments on narcotized and immobilized animals, which makes interpretation of experimental data more difficult. Most studies with macroelectrode recording of bioelectric responses in CC were performed using single-stimulus technique. However, the time of perception and processing of afferent signal far surpasses the duration of a response evoked by a single stimulus. Therefore, paired stimulation of afferent pathways is a more adequate method allowing to study the effect of opioid analgesics on CC excitability. The optimal approach is to stimulate fibers originating from specific thalamic relay nuclei, because in this case the effect of subcortical structures on afferent traffic to CC can be eliminated. Preference in the choice of CC projection area should be given to sensorimotor area II, since it plays the leading role in the control of afferent signals to CC [1]. This choice is favored by the data indicating that this area is the central modulator of nociceptive sensitivity. This modulator quantitatively evaluates the nociceptive information and controls the nocifensive reactions [1,3].

Various methods are used to assess the neurochemical spectrum of the effects of opioid analgesics on CC. In experiments with macroelectrode recording

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0007-4888/01/1321-0613$25.00

the researchers combine the examined chemical agents with substances, which selectively modify specific neurotransmitter systems due to their potentiating (agonists, neurotransmitter uptake and utilization inhibitors) or inhibitory (antagonists, inhibitors of neurotransmitter synthesis) action. Similar approach makes it possible to assess the predominant contribution of each neurotransmitter and the corresponding receptor structures into the effects of opioid analgesics on afferent traffic in CC. In addition, the use of microiontophoretic technique for evaluation of the response of cortical neurons to examined preparations and their combinations with neurotransmitters and transmitter antagonists clarifies the neurochemical mechanisms underlying the effect of opioid analgesics in CC.

Stage I of the present study was performed on unrestrained cats. We examined the effect of opioid analgesics (morphine, fentanyl, pentazocine) and opioid peptides — pentapeptide FK 33-824 (Tyr-D-Ala-Gly-MePhe-Met(O)-ol) and tetrapeptidamide (Tyr-D-Ala-Gly-Phe-NH_2) on the recovery cycle of the primary responses (PR) in sensorimotor area II of CC, induced by paired suprathreshold electrical stimulation (interstimulus interval 20-500 msec) applied to thalamocortical radial fibers (TCRF) originating from thalamic *n. VPL*. The examined preparations produce different effects on various opiate receptors. Specifically, morphine is an agonist of μ- δ- and κ-receptors, the effect on μ-receptors being the most pronounced. The effects of fentanyl are similar to those of morphine, but this drug virtually does not affect κ-receptors. Pentazocine acts as δ- and κ-opiate receptor agonist and μ-receptor antagonist. Pentapeptide FK 33-824 and tetrapeptidamide interact predominantly with μ- and κ-receptors [14]. All examined preparations (used in near or above analgesic doses) and opiate antagonist naloxone (1 mg/kg) were injected intraperitoneally.

At stage II, we studied neurochemical regularities of the effect of morphine and FK 33-824 on the recovery cycle of PR in sensorimotor cortical area II of unrestrained cats. Analizator substances selectively affecting various neurotransmitter processes were used: GABA-positive agents (muscimol, sodium valproate, and aminooxyacetic acid), GABA-negative agents (thiosemicarbazide, bicuculline, picrotoxin), serotonin-positive agents (5-hydroxytryptophan and fluoxetine), and serotonin-negative agents (p-chlorophenylalanine and methysergide), catecholamine-positive agents (L-DOPA, apomorphine); catecholamine-negative agents (6-oxydopamine; α-methyl-p-tyrosine, phentolamine, phenoxybenzamine, yohimbine, propranolol), cholinepositive agent eserine and choline-negative agent hemicholinium-3.

Since these substances disturb the conduction of afferent impulses to CC, they were used in the doses that did not affect PR recovery cycle. Morphine, FK 33-824, naloxone, and analizator substances affecting the neurotransmitter processes were injected intraperitoneally (except 6-oxydopamine and hemicholinium-3 injected in 50-100 μl physiological saline into the lateral cerebral ventricle via a preliminary implanted cannula). To prevent effects of eserine, it was applied with methylatropine nitrate (12 mg/kg intraperitoneally).

Stage III of the experiment was performed on the cats narcotized with chloralose (20 mg/kg i.v.) and relaxed with pipecuronium (25 mg/kg/h i.v.). We studied the effects of morphine and FK 33-824 on evoked and spontaneous discharges in sensorimotor area II. Preliminary experiments showed that chloralose (20 mg/kg) does not change the PR recovery cycle. The firing of neurons in sensorimotor area II was recorded extracellularly. The neurons were identified with paired electrical stimulation of TCRF (interstimulus interval 80-100 msec). Seven-channel multibarrel microelectrodes (Medical Systems) were used. The central barrel was filled with NaCl (3 M), while the lateral barrels were filled with freshly prepared solutions of the examined agents, neurotransmitters, and their antagonists: morphine hydrochloride (0.05 M, pH 4.5), FK 33-824 (0.02 M, pH 4.0), naloxone (0.1 M, pH 4.0), GABA (1 M, pH 4.0), L-glutamate (1 M, pH 8.0), serotonin creatinine sulfate complex (0.04 M, pH 5.0), acetylcholine chloride (1 M, pH 4.0), dopamine hydrochloride (0.4 M, pH 5.0), isoproterenol (0.05 M, pH 5.0), phenylephrine (0.05 M, pH 5.0-5.5), bicuculline methiodide (0.05 M, pH 3.5), picrotoxin (0.05 M, pH 5.2), and propranolol (0.01 M, pH 4.5-5.5). One lateral barrel was filled with NaCl saline to control the pola-

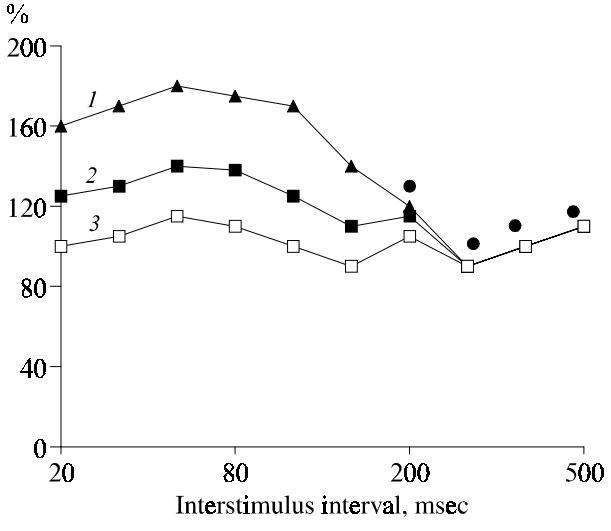

Fig. 1. Recovery cycle of primary responses (PR) in sensorimotor area II of cerebral cortex before (*1*) and after morphine injection in a dose of 3 (*2*) and 5 mg/kg (*3*). Ordinate: amplitude of testing PR. The amplitude of conditioning PR was taken for 100%. The points outside the plots are insignificant ($p>0.05$).

rizing effects induced by electric current. Microionophoresis of the above substances (except glutamate) was performed for 1-3 min using a NeuroPhore BH-2 microionophoreometer. The amplitude of ionophoretic current did not surpass 100 nA, while the value of cut-off current was 10-15 nA. Microionophoresis of glutamate was performed in 15-20-sec cycles with 1-min intervals.

We assessed the effects of morphine and FK 33-824 on spontaneous and evoked activity of neurons, the latter being induced by paired electrical stimulation of TCRF and glutamate application. In addition, interaction of these agents with neurotransmitters and their antagonists (manifested itself in evoked and spontaneous activity of the neurons in CC sensorimotor area II) was studied. In some experiments, morphine, FK 33-824, and naloxone were injected intravenously.

Effect of narcotic analgesics and opioid peptides on PR recovery cycle in sensorimotor zone II

Morphine (2-4 mg/kg) decreased the amplitude of testing PR in the sensorimotor area II in the period between conditioning and testing stimuli (20-150 msec). However, the amplitude of PR evoked by conditioning stimulation of TCRF virtually did not change (Fig. 1). Naloxone eliminated morphine effect on PR recovery cycle. When the dose was elevated to 5-8 mg/kg, morphine produced more pronounced changes in PR recovery cycle (Fig. 1). There was a certain increase in the amplitude of PR evoked by conditioning stimulation of TCRF: it was 225 and 270 μV for 3 and 5 mg/kg morphine, respectively, the baseline value being 220 μV. In doses of 10-15 mg/kg morphine provoked sporadic discharges in EEG and non-motivated motor activity of experimental animals accompanied by fixed stare. Naloxone eliminated these morphine-induced effects.

Fentanyl (0.11-0.20 mg/kg) and pentazocine (12-15 mg/kg) produced changes in PR recovery cycle similar to those induced by morphine. We did not use fentanyl in doses above 0.2 mg/kg because of the risk of respiratory arrest. Pentazocine (17-20 mg/kg) increased the amplitude of conditioning PR, and in the doses of 22-30 mg/kg it provoked seizures. Injection of naloxone during maximum manifestation of the described effects of opioid analgesics contributed into normalization of PR and behavior.

Similar to morphine, fentanyl, and pentazocine, FK 33-824 (0.7-2.0 mg/kg) decreased the amplitude of testing PR in the 20-150-msec interstimulus interval, but did not change the amplitude of PR evoked by conditioning stimulation of TCRF. In doses of 3-5 mg/kg FK 33-824 produced some increase in PR evoked by conditioning stimuli. Simultaneously, sporadic activity was observed in EEG, accompanied by motor excitation and fixed stare. Naloxone eliminated the changes in PR recovery cycle, increase in conditioning PR, sporadic EEG activity, and abnormal behavior caused by this pentapeptide.

Tetrapeptidamide inhibited the course of PR recovery cycle in sensorimotor area II. In doses of 10-20 mg/kg it decreased the amplitude of testing PR in the interval of 20-150 msec without changing the amplitude of PR evoked by conditioning stimulation of TCRF. Increasing the tetrapeptidamide dose to 25-35 mg/kg produced some increase in conditioning PR, sporadic activity in EEG, and motor excitation. In contrast to morphine and FK 33-824, the behavioral effect of tetrapeptidamide was manifested in pronounced aggressivity of the animals. Naloxone eliminated the effect of tetrapeptidamide on PR recovery cycle and the amplitude of PR evoked by conditioning stimulation of TCRF. In addition, it contributed to normalization of EEG and behavior (Table 1).

Thus, when used in near analgesic doses, the opioid analgesics (morphine, fentanyl, and pentazocine) and opioid peptides (FK 33-824 and tetrapeptidamide) decreased the amplitude of testing PR in the 20-150-msec interval between the stimuli applied to TCRF. This effect did not depend on the peculiarities of action of the examined opioids on opiate receptors.

Neurochemical regularities in the effects of morphine and FK 33-824 on recovery cycle of PR evoked by electrical stimulation of TCRF

GABA-agonist muscimol potentiated the effect of morphine and FK 33-824 on PR recovery cycle in sensorimotor area II. In addition, when applied against the background of muscimol, morphine and FK 33-824 decreased the amplitude of testing PR in the interval between conditioning and testing stimuli, which was longer than 150 msec. Naloxone restored interneuron transmission in sensorimotor area II disturbed by combined injections of muscimol+morphine or muscimol+FK 33-824. Similarly to muscimol, GABA-transaminase inhibitors sodium valproate and aminooxyacetic acid modulated the effect of morphine and FK 33-824. When injected in combination with sodium valproate and aminooxyacetic acid, naloxone retained ability to eliminate the effects of morphine and FK 33-824. Glutamate decarboxylase blocker thiosemicarbazide, $GAGA_A$-receptor antagonists bicuculline and picrotoxin pronouncedly diminished the effects of examined agents on PR recovery cycle in sensorimotor area II (Table 2).

Similar regularities in the interaction between GABA-ergic agents and narcotic analgesics were revealed in the study of the potency of some chemicals to modify

the analgesic effect of morphine [2,15]. It is noteworthy that GABAergic component in the effects of morphine and FK 33-824 is manifested at the level of $GABA_A$-receptors, because selective agonist (muscimol) and antagonists (bicuculline and picrotoxin) modify the effect of the test substances [4]. Morphine is known to decrease the number of high affinity sites for binding of GABA in CC. It is suggested that GABA-positive substances can prevent the decrease in GABA binding rate and prolong hyperpolarization in CC [2,4].

Therefore, our findings attest to participation of GABAergic system in the effect of morphine and FK 33-824 on CC excitability.

Serotonin precursor 5-hydroxytryptophan and fluoxetine (blocker of serotonin re-uptake) potentiated the inhibitory effect of morphine and FK 33-824 on PR recovery cycle. These agents changed the values of threshold doses, in which morphine and FK 33-824 suppressed PR recovery cycle. Addition of bicuculline (0.05 mg/kg) or picrotoxin (0.1 mg/kg) to combination of morphine+(5-hydroxytryptophan or fluoxetine) or FK 33-824+(5-hydroxytryptophan or fluoxetine) did not change the potentiating effect of 5-hydroxytryptophan and fluoxetine on the effect of morphine and pentapeptide FK 33-824. By contrast to 5-hydroxytryptophan and fluoxetine, the blockers of serotonin synthesis (p-chlorophenylalanine) and serotonin receptors (methysergide) attenuated the effect of morphine and FK 33-824 on testing PR (Table 2).

Morphine is known to elevate the cortical level of 5-hydroxyndole acetic acid, the major serotonin metabolite [16], and stimulate serotonin release in CC. This neurotransmitter potentiates the analgesic effect of the opioids [18]. It can be assumed that accumulation of serotonin in the brain caused by 5-hydroxytryptophan and fluoxetine is summed with serotonin released in CC induced by opioids, which potentiates the effects of morphine and FK 33-824. At the same time, morphine stimulates the release of GABA, a synergist of narcotic analgesics potentiating the effect of opioids on PR recovery [4]. In addition, GABA-positive substances decrease the content of serotonin in CC and the nuclei raphes, while bicuculline and picrotoxin eliminate the effects of the considered substances on this process [5]. To exclude the possible action of GABA on the effects of morphine and FK 33-824 used in combination with 5-hydroxytryptophan and fluoxetine, we used bicuculline or picrotoxin. Under these conditions, $GABA_A$-receptor antagonists did not change the potentiating effect of the above serotoninergic agents on the action of morphine and FK 33-824 on testing PR. Possibile participation of serotonin in the effect of examined substances is corroborated by experiments with p-chlorophenylalanine and methysergide. These serotonin-negative substances diminished the effect of morphine and FK 33-824 on PR recovery cycle.

Dopamine precursor L-DOPA and agonist of D_2-receptors apomorphine potentiated the effect of morphine and FK 33-824 on PR recovery cycle. Bicuculline (0.05 mg/kg) and picrotoxin (0.1 mg/kg) prevented, while haloperidol (1 mg/kg) did not change or slightly increased the potentiating action of L-DOPA and apomorphine on the effect of morphine and FK 33-824. 6-Hydroxydopamine destroying catecholami-

TABLE 1. Effect of Narcotic Analgesics and Opioid Peptides on PR Recovery Cycle in Sensorimotor Area II in Cerebral Cortex

Drug	Dose, mg/kg	ΔA1, %	ΔA2/A1, %	Seizure activity on EEG	Behavioral abnormalities	Antagonism to naloxone
Morphine	2-4	—	-20-30	—	—	+
	5-8	+10-15	-35-60	—	—	+
	10-15	+10-15	-35-60	+	+[1]	+
Fentanyl	0.11-0.15	—	-20-30	—	—	+
	0.2	—	-35-60	—	—	+
Pentazocine	12-15	—	-20-30	—	—	+
	17-20	+10-15	-35-60	—	—	+
	22-30	+10-15	-35-60	+	+[2]	+
FK 33-824	0.7-1	—	-20-30	—	—	+
	2	—	-35-60	—	—	+
	3-5	+10-15	-35-60	+	+[1]	+
Tetrapeptidamide	15-20	—	-35-60	—	—	+
	25-35	+10-15	-35-60	+	+[3]	+

Note. *A1* and *A2* are the amplitudes of conditioning and testing PR, respectively. Presence and absence of the effect are marked with (+) and (—), respectively. [1]Non-motivated motor excitation and fixed stare, [2]seizures, and [3]excitation with aggressivity.

nergic structures in the brain, diminished, while α-methyl-p-tyrosine (tyrosine hydroxylase inhibitor) slightly weakened the effect of morphine and FK 33-824. Phentolamine (α_1- and α_2-adrenoblocker), phenoxybenzamine (α_1-adrenoblocker), and yohimbine (α_2-adrenoblocker) did not modulate the effects of morphine and FK 33-824 on testing PR. However, propranolol (β_1- and β_2-adrenoblocker) diminished the effect of morphine and FK 33-824; the protective action of propranolol manifested in the 20-80-msec interval between the conditioning and testing stimuli (Table 2). It is possible that potentiating action of L-DOPA and apomorphine on the effects of morphine and pentapeptide FK 33-824 is not directly mediated via dopaminergic system, because haloperidol did not prevent the effects of L-DOPA and apomorphine. The capacity of bicuculline and picrotoxin to eliminate the potentiating effect of morphine and FK 33-824, observed under the action of L-DOPA and apomorphine, suggests participation of GABA in potentiation of the

TABLE 2. Interaction of Morphine (1-5 mg/kg i.p.) and Pentapeptide FK 33-824 (0.7-2.0 mg/kg i.p.) with Test Substances

Test substance	Dose, mg/kg	Effect	Threshold dose	PR recovery cycle
GABAergic:				
muscimol	1.2	Potentiation	Attenuation	Prolongation
sodium valproate	160	«	«	—
aminooxyacetic acid	10	«	«	—
thiosemicarbazide	6	Shortening	Potentiation	—
bicuculline	0.1	«	«	—
picrotoxin	0.4	«	«	—
Serotoninergic:				
5-hydroxytryptophan	50	Potentiation	Attenuation	Prolongation
+bicuculline	0.05	«	«	
+picrotoxin	0.1	«	«	«
fluoxetine	10	«	«	«
+bicuculline	0.05	«	«	«
+picrotoxin	0.1	«	«	«
p-chlorophenylalanine	200	Shortening	—	—
methysergide	1.5	«	—	—
Catecholaminergic:				
L-DOPA	80	Potentiation	Attenuation	—
+bicuculline	0.05	—	—	—
+picrotoxin	0.1	—	—	—
+haloperidol	1	Potentiation	Attenuation	—
apomorphine	0.5	«	«	—
+bicuculline	0.05	—	—	—
+picrotoxin	0.05	—	—	—
+haloperidol	1	Potentiation	Attenuation	—
6-hydroxydopamine*	0.25×2	Shortening	—	—
α-methyl-p-tyrosine	100	«	—	—
phentolamine	5	—	—	—
phenoxybenzamine	10	—	—	—
yohimbine	2	—	—	—
propranolol	1	Shortening	Potentiation	Attenuation
Cholinergic:				
eserine	1.5	«	—	«
hemicholinium*	0.005-0.007	Potentiation	—	—

Note. The test substances (except those marked by asterisk) were injected intraperitoneally. *Injection into lateral ventricle of the brain. Dash means the absence of interaction.

drug effect on PR recovery cycle. Such a possibility is quite probable, since L-DOPA and apomorphine enhance activity of glutamate decarboxylase and diminish activity of GABA-transaminase in the brain of experimental animals [11]. Attenuation of morphine and FK 33-824 effects by 6-oxydopamine can also be related to GABA-mediated processes. This hypothesis is corroborated by the data showing that in addition to a decrease in cerebral catecholamine level, 6-oxydopamine lowers the content of GABA in CC [18]. Moreover, when α-methyl-p-tyrosine was applied in cats in the dose of 100 mg/kg, which decreases catecholamine content in various cerebral subdivisions (CC included), it produced only insignificant changes in the effect of morphine and FK 33-824.

Eserine insignificantly attenuated the effects of morphine and FK 33-824 on PR recovery cycle, in the interval between the conditioning and testing stimuli did not surpass 80 msec. Eserine-induced potentiating of cholinergic transmission can attenuate the effect s of opioid due to inhibition of specific membrane binding of the test substances in CC. Hemicholinium-3 (a blocker of high-affinity choline uptake) potentiated the effect of examined agents on PR value (Table 2), probably due to potentiating of GABAergic transmission in the brain.

Therefore, the inhibitory action of morphine and FK 33-824 on afferent traffic to CC is mediated by GABA-, serotonin-, β-adreno-, and probably cholinergic structures. The dopaminergic processes can modulate the effects of the examined opioids via the GABA system.

Neurotransmitter spectrum of morphine and pentapeptide FK 33-824 effect on cortical neurons

Microionophoretically applied morphine (30-60 nA) diminished the potentiating effect of electrical stimulation of TCRF on discharge frequency in 12 (80%) of 15 examined neurons; 1 neuron did not respond to morphine, while activity of 2 (13%) neurons increased. FK 33-824 (40-70 nA) decreased the effect of electrical stimulation of TCRF by 9 (81%) of 11 examined neurons; one neuron did not respond to pentapeptide, and one neuron (9%) increased discharge frequency. Naloxone (30-40 nA) prevented both the potentiating and inhibitory influence of morphine and FK 33-824 on the effect of electrical stimulation of TCRF.

Morphine inhibited the responses of 27 (87%) of 31 examined neurons to microionophoresis of glutamate (80 nA), although 2 neurons did not respond to morphine and other 2 neurons (6%) increased the firing rate. FK 33-824 attenuated the potentiating effect of glutamate in 18 (86%) of 21 examined neurons, produced no changes in the response of 1 neuron, and increased the firing rate in 2 (10%) neurons. Naloxone restored the responses of neurons to glutamate.

Morphine inhibited spontaneous activity in 21 (75%) of 28 examined neurons. In 3 neurons the discharge frequency did not change, while in 4 (14%) neurons it increased. FK 33-824 inhibited the spontaneous discharges in 24 (82%) of 29 examined neurons, did not affect the firing rate of 3 neurons, and enhanced activity of 2 (7%) neurons. Naloxone prevented and eliminated both the inhibitory and potentiating effects of morphine and FK 33-824 on neuronal activity. Morphine (50 nA) and FK 33-824 (60 nA) more strongly inhibited the responses of CC neurons to microionophoretical glutamate than to electrical stimulation of TCRF. Spontaneous activity of CC neurons demonstrated pronounced resistance to the effect of these substances.

Although the combination of morphine (50 nA) or FK 33-824 (60 nA) with GABA (3-5 nA) did not change the spontaneous and evoked firing, it potentiated the final inhibitory effect of these substances. Application of morphine (less than 30 nA) or FK 33-824 (less than 40 nA) with GABA (3-5 nA) suppressed neuronal response evoked by electrical stimulation of TCRF or application of glutamate (80 nA), and moderated spontaneous activity. Similar regularity was observed when GABA (15 nA) was applied with morphine (less than 30 nA) or FK 33-824 (less than 40 nA). Bicuculline (45 nA) and picrotoxin (50 nA) diminished the effect of morphine and FK 33-824 towards all types of neuronal activity. These $GABA_A$-receptor antagonists diminished the effects of GABA+morphine or GABA+ FK 33-824 on the discharges. Combination of morphine (less than 30 nA) or FK 33-824 (less than 40 nA) with serotonin (20-25 nA) did not change the frequency of spontaneous and evoked discharges. Serotonin (20-25 nA) did not potentiate the effect of morphine (50 nA) or FK 33-824 (60 nA) on neurons. The test substances diminished the inhibitory effect of serotonin (40-60 nA) on spontaneous and evoked discharges (Fig. 2).

Dopamine (5 nA) did not modify the effects of morphine (50 nA) or FK 33-824 (60 nA). An increase of ionophoretic current to 20 nA led to summation of the inhibitory effect of dopamine and that of morphine (50 nA) or FK 33-824 (60 nA).

Propranolol (2-5 nA) did not change the effects of electrical stimulation of TCRF or those produced by microionophoresis of glutamate or phenylephrine (25 nA), eliminated the inhibitory effect of isoproterenol (50 nA), and attenuated the inhibitory effect of morphine or FK 33-824 on the neuronal activity.

Morphine (55 nA) and FK 33-824 (62 nA) decreased the potentiating effect of acetylcholine (50 nA) on neuronal activity (Fig. 2).

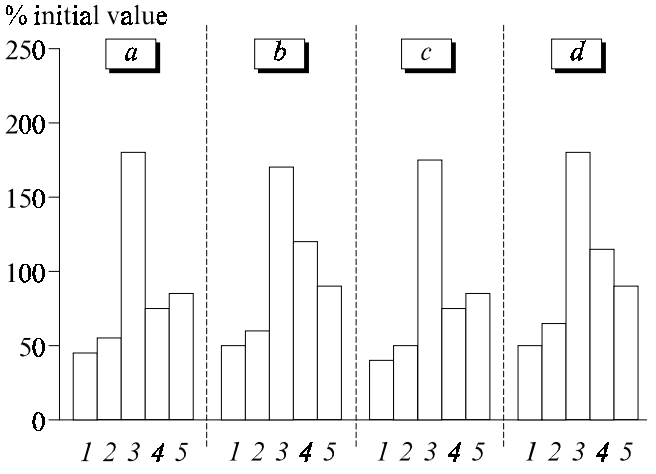

Fig. 2. Response of the neurons in sensorimotor area II in cerebral cortex to microionophoresis of neurotransmitters performed against the background action of morphine (55 nA, *a*; 3 mg/kg i.v., *b*) and FK 33-824 (62 nA, *c*; 2 mg/kg i.v., *d*). Microiontophoresis of glutamate (80 nA, *1*), acetylcholine (50 nA, *2*), GABA (20 nA, *3*), serotonin (50 nA, *4*), and dopamine (20 nA, *5*). *n*=26-27 (*a*, *c*) and *n*=6 (*b*, *d*).

Intravenous injection of morphine (3 mg/kg) and FK 33-824 (2 mg/kg) decreased the responses of neurons to electrical stimulation of TCRF and to microionophoretic glutamate or acetylcholine, potentiated responses to GABA or serotonin, and did not affect the reaction to dopamine (Fig. 2). Naloxone (1 mg/kg) restored the responses of neurons to glutamate, acetylcholine, GABA, and serotonin.

Thus, microionophoretic and intravenous application of morphine or FK 33-824 inhibited activity of the most examined neurons in sensorimotor area II of CC, evoked by electrical stimulation of TCRF or by glutamate microionophoresis. In addition, these substances reduced spontaneous activity of the neurons. The examined opioids attenuated the response of neurons to glutamate more strongly than to acetylcholine, did not modify the effects of dopamine, and potentiated those of GABA. Antagonists of $GABA_A$-receptors bicuculline and picrotoxin decreased efficiency of morphine and FK 33-824. Microionophoresis of morphine and FK 33-824 was accompanied by insignificant moderation of inhibitory effect of serotonin, while intravenous injection of these opioids potentiated the inhibitory effect of serotonin on cortical neurons.

Thus, when used in near analgesic doses, the examined preparations decrease the amplitude of testing PR in 20-150-msec interval between the stimuli applied to TCRF. This effect does not depend on peculiarities in the effects of these agents on various types of opiate receptors. Morphine and FK 33-824 have similar neurochemical spectrum of action on CC, and their effects probably mediated through the cortical GABA-, catecholamine-, and cholinergic systems. The examined opioids attenuate the processes mediated by excitatory amino acids in CC. Probably, this effect can be realized through various types of excitatory amino acid receptors [7,10]. The existence of these receptors in CC is well established [7]. The revealed regularities suggest that the effect of opioid analgesics on afferent traffic to CC is realized via attenuation of excitatory processes mediated by excitatory amino acids and acetylcholine, and via potentiation of GABAergic inhibition.

REFERENCES

1. R. A. Durinyan, *Usp. Fiziol. Nauk*, No. 1, 3-18 (1980).
2. V. V. Zakusov, R. U. Ostrovskaya, and V. M. Bulaev, *Vestn. Akad. Med. Nauk SSSR*, No. 5, 45-52 (1981).
3. V. K. Reshetnyak, *Advances in Science and Technology, Ser. Human and Animal Physiology* [in Russian], Vol. 29, Moscow (1985), pp. 39-103.
4. D. A. Kharkevich, V. P. Fisenko, and S. A. Kasparov, *Vestn. Akad. Med. Nauk SSSR*, No. 11, 41-55 (1984).
5. H. L. Fields and A. I. Basbaum, in: *Textbook of pain*, Eds. P. D. Wall and R. Melzack, Edinburgh (1999), pp. 309-330.
6. A. K. P. Jones and S. W. G. Derbyshire, *Prog. Pain Res. Management*, **3**, 154-172 (1994).
7. K. J. Karpenter and A. H. Dickenson, *Curr. Opin. Pharmacol*., No. 1, 57-61 (2001).
8. D. A. Kharkevich and V. V. Churukanov, *Eur. J. Pharmacol.*, **375**, 121-131 (1999).
9. Y. Lamour, J. C. Willer, and G. Guilbaud, *Exp. Brain Res*., **49**, 35-45 (1983).
10. J. K. Melichar, M. R. C. Daglish, and D. J. Nutt, *Curr. Opin. Pharmacol.*, No. 1, 84-90 (2001).
11. K. Noda, N. Mataga, M. Takashima, *et al., J. Pharm. Bio-Dyn.*, **5**, 44 (1982).
12. S. Ozava, H. Kamiya, and K. Tsuzuki, *Prog. Neurobiol.*, **54**, 581-618 (1998).
13. P. Rainville, G. H. Duncan, D. D. Price, *et al., Science*, **277**, 968-971 (1997).
14. H. P. Rang, M. M. Dale, and J. M. Ritter, in: *Pharmacology*, 4th Edition, London (1999), pp. 579-603.
15. S. P. Sivam and I. K. Ho, *Life Sci.*, **37**, 199-208 (1985).
16. U. Spampinato, E. Esposito, S. Romandini, *et al., Brain Res.*, **328**, 89-95 (1985).
17. T. L. Yaksh, *Acta Anaesthesiol. Scand.*, **41**, 94-111 (1997).
18. T. L. Yaksh, in: *Textbook of pain*, Eds. P. D. Wall and R. Melzack, Edinburgh (1999), pp. 253-308.