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Pharmacological regulation of descending cortical control of the nociceptive processing

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Abstract

Clinical and experimental data indicate that the cerebral cortex plays an important role in pain perception and endogenous antinociceptive system function. Moreover, the enhancement of descending inhibitory cortical control may be involved in the mechanisms of analgetic effect of some agents. The present study was designed to investigate the effect of cortical electrical stimulation (as a model of descending inhibitory control) on the behavioral and electrophysiological signs of nociceptive response, decipher the mechanisms involved therein and evaluate the action of central analgesics (both opioid and non-opioid) on descending cortical control. In acute experiments in cats the inhibitory cortical influence on neuronal activity produced by nociceptive stimuli (electrical stimulation of tooth pulp, C-fibers of afferent somatic nerves, afferent cardiac structures) was most marked after stimulation of the first and second sensory and fronto-orbital areas. In chronic experiments on rats cortical stimulation reduced behavioral signs of visceral pain (writhing test) and also delayed the development of neuropathic pain syndrome along with lowering its intensity. μ-Opioid receptor agonists (morphine, fentanyl) potentiated the inhibitory cortical effect on the evoked neuronal activity. Pentazocine, which has pronounced κ-receptor agonistic activity, was less effective. Naloxone eliminated the effects of both cortical stimulation and opioid analgesics. Serotonin receptor antagonist methysergide as well as *p*-chlorophenylalanine significantly decreased inhibitory cortical control and opioids effect. Monoamine re-uptake inhibitors with analgetic properties (imipramine, fluoxetine) potentiated the inhibitory effect of cortical stimulation. Adrenoceptor, dopamine, acetylcholine, GABA-receptor agents and antagonists of NMDA receptors had minor or no effect. Among non-narcotic analgesics, inhibitors of cyclooxygenase, metamysole and ketorolak increased only moderately the descending cortical control of nociception. Thus, the cerebral cortex is able to control the nociceptive processing in different pain syndromes (somatic, visceral or neuropathic pain). Opioidergic and serotonergic systems play the key role in this control. The effect over the cortical descending control is likely to be one of the components of the analgetic effect exerted by opioids and some other central analgesics.

Keywords: Opioid; Nonopioid analgesics; Cerebral cortex; Nociception control; Neurochemistry of cortical control

1. Introduction

Clinical observations and experimental data provide evidence of a substantial role of the cerebral cortex in the perception and control of pain (for a review, see Kenshalo and Willis, 1989). The main reasons that support cortex involvement in these processes are as follows. The injury of certain cortical areas is accompanied by hypo- or analgesia (Talairach et al., 1960; White and Sweet, 1969; Sweet, 1982), the electrical stimulation during surgical operation induced in patients a pain sensation or, inversely, decreased pain sensitivity (Albe-Fessard et al., 1985). In experiments, the removal or destruction of certain cortical areas produced in animals changes in behavioral and vegetative nociceptive responses: either reduction or enhancement (Berkley and Parmer, 1974). The electrical cortical stimulation inhibits the behavioral nociceptive reactions (Hardy, 1985), and in acute experiments—the spinal and suprasegmental neurons response to nociceptive stimuli (Coulter et al., 1974; Brown et al., 1977; Andersen, 1986). Neurons responsive to nociceptive stimulation were detected in the cortex (Lamour et al., 1982, 1983a,b).

Recent studies using positron emission tomography alone or in combination with magnetic resonance imaging generally support the conclusion that the painful stimulation of various types is associated with a significantly

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increased cerebral blood flow or local metabolism in some cortical areas (for a review, see Talbot et al., 1991; Jones and Derbyshire, 1994).

In the present study we examined the possible involvement of cortical control in the mechanism of analgesics action. An attempt was also made to evaluate the role of the cortex in endogenous antinociceptive system function and identify the neurochemical mechanisms responsible for the cortical descending effects.

2. Main details of methods: electrophysiological approach

Main part of the experiments was performed using the elctrophysiological techniques. This section presents only major items. The behavioral methods are briefly described in the sections below.

The electrical stimulation of the cortex was used as a model of descending cortical control. Acute experiments were carried out in chloralose-anesthetized and additionally flaxedil-immobilized cats. A bipolar electrode was used to produce the conditioning stimulation of the cortex. Single shocks or trains of impulses were applied. According to reported data the cortex is able to exert a dual effect upon the evoked neuronal activity: either stimulation or inhibition (Coulter et al., 1974; Yezierski et al., 1983). Similar results were also obtained from our previous experiments (Table 1). In our investigation the results were examined only with the inhibitory effect of cortex stimulation on the electrical activity in subcortical structures and spinal cord. Cortex stimulation parameters were chosen for each animal individually in the manner that the amplitude of evoked potentials or other electrical responses would make 70–80% of the basal level.

The afferent somatic nerves and tooth pulp were subjected to testing nociceptive stimulation. The nerves were stimulated using single electrical supramaximal stimuli at a strength sufficient for excitation of thin myelinated A-δ and non-myelinated C-fibers. Evoked potentials and unit (single neuron or a group of functionally similar neurons) activity after somatic nerve stimulation were recorded in suprasegmental structures involved in pain perception, and namely in ventrobasal complex of thalamus, posterior group of thalamic nuclei, medial and intralaminar nuclei (n.n. medialis dorsalis, centralis medialis, centralis lateralis, parafascicularis) as well as in the medulla (n. gracilis).

To assess the descending cortical effects on nociceptive processing at segmental level the activity of dorsal horn neurons (L_{6-7}) was recorded as response to supramaximal electrical stimulation of the superficial peroneal or sciatic nerves. According to the functional characteristics, all studied neurons are of a multireceptive type (they are activated by stimuli of various modalities including nociceptive). These neurons were located in laminae IV–V of the dorsal horn. Comparing to specific neurons which are mainly localized in the lamina I, the activity of these neurons is regulated to a greater extent by the descending pathways (Besson et al., 1982).

In the course of testing nociceptive stimulation of the tooth pulp the evoked potentials and unit activity were recorded in nuclei of the trigeminal complex (main sensory, oralis, interpolaris and caudalis).

To evaluate quantitatively the descending cortical effect and agents effects the amplitude of the evoked potentials was measured; the result was expressed as percent. The parameters of spontaneous and evoked unit activity, as the frequency of spike discharges, during cortical stimulation and then following drug administration were compared with the initial values and expressed as percent. In a series of experiments the post-stimulus histograms were examined. All the results were statistically analyzed using special computer programs. Some data were expressed as mean ± S.E.M.; the results were analyzed using Student's *t*-test or an analysis of variance (ANOVA).

All conditions for animals and procedures during experiments were in accordance with the Guidelines of the International Association for Study of Pain (Zimmerman, 1983).

3. The effect of cortical stimulation on electrical and behavioral signs of nociception

It appeared to be a benefit to begin the investigation with identification of the cortical areas able to exert the

Table 1
Effect of electrical cortical stimulation on the unit activity in thalamic nuclei

Structures	Number of neurons	Response to cortical stimulation[a]			
		Inhibition of spontaneous activity	Enhancement of spontaneous activity	Inhibition of evoked activity[b]	No effect
Parafascicular complex	187	89 (48%)	11 (5%)	47 (25%)	87 (47%)
Posterior group of nuclei	149	67 (45%)	10 (7%)	44 (29%)	72 (48%)

[a]Trains of electrical impulses were applied to S II.
[b]Activity was evoked by sciatic nerve stimulation.

most pronounced effect upon nociceptive impulses transmission at segmental and supraspinal levels. For this purpose, the decrease in amplitude of the evoked potentials, the degree of unit activity suppression and the structures where these events were recorded after electrical stimulation of different cortical areas were counted. Most obvious changes in the evoked activity (suppression by 30–45%) in the majority of tested structures were observed when stimulating the second somatosensory area (SII) and fronto-orbital cortex. The stimulation of the first somatosensory area (SI) and some areas of the visual cortex was less effective. The stimulation of other cortical areas either produced no effect or the changes were not significant. Within cortical areas where the stimulation inhibited the transmission of stimulus, the areas most effective with respect to certain subcortical structures were selected. Similarly to testing stimulation of the somatic nerves, under tooth pulp stimulation SII and fronto-orbital cortex stimulation inhibited most effectively the evoked activity in trigeminal complex nuclei. Conditioning stimulation of SI suppressed the trigeminal unit activity occasionally.

In spinal cord the conditioning stimulation of SII and fronto-orbital cortex suppressed the evoked discharges in studied neurons by 25–30%. The stimulation of other cortical areas had less effect.

In a series of experiments the cortical effects (electrical stimulation of SII and fronto-orbital cortex) were assessed in comparison with those produced by stimulation of the main structures of endogenous antinociceptive system—periaqueductal grey (PAG) and nucleus raphe magnus. It was shown that the descending inhibitory cortical effects upon the unit activity in trigeminal nuclei induced by tooth pulp stimulation are compatible, as to their degree, with the effects observed during stimulation of the above-mentioned structures of the midbrain and medulla.

The existence of corticobulbar and corticospinal projections to trigeminal complex and dorsal horn is well acknowledged (Brown et al., 1977; Besson, 1980; Besson et al., 1982). Furthermore, electrophysiological studies demonstrated the inhibitory and facilitating effects of cortical stimulation upon the neuronal activity in mentioned structures (Yezierski et al., 1983; Coulter et al., 1974). The intracortical stimulation has shown that most pronounced inhibition of spinal neuronal activity, induced by both nociceptive and non-nociceptive stimuli, occurred after the 3rd and, especially, the 5th and 6th cortical layers were stimulated (Brown et al., 1977). The bodies of pyramidal neurons, which axons form the corticospinal pathways, are located therein. In parallel, the depolarization of primary afferents was observed (Brown et al., 1977), and this is indication of an enhanced presynaptic inhibition. However, apart the direct cortical effect upon segmentary structures involved in nociception, other mechanisms exist. There are morphologic and electrophysiological evidences of the relationship between the cortex and the structures of midbrain (periaqueductal grey and others) and medulla (raphe nuclei and others) which play the pivotal role in brain antinociceptive system function (Besson et al., 1982; Duggan, 1985; Fields, 1987). These structures, in their turn, exert control over the nociceptive impulses via descending pathways (for a review, see Willis, 1988), as well as acting in rostral direction (Morgan et al., 1989).

Certain differences were shown in the nature and mechanisms of somatic and visceral pain formation (for a review, see Ness and Gebhart, 1990; Gebhart and Ness, 1991a,b). Two series of experiments were carried out to assess the cortical effects over the conduction of visceral nociceptive impulses.

In the electrophysiological tests designed as described above, the heart sinoatrial node, containing the rhythm-driving cells and afferent nervous plexus, was used as a provider of nociceptive impulses. The afferent impulses, including the nociceptive ones, are forwarded from the heart towards the CNS via the fibers of the two groups (Meller and Gebhart, 1992). The 1st group being integrated into the vagus nerve rami is reaching the solitary tract nucleus in the medulla. The fibers of the 2nd group enter the spinal cord as constituents of dorsal roots (T_1–T_2) and have either direct or indirect contact with the 5th layer neurons of the dorsal horn. The electrical stimulation of sinoatrial node generates a burst of afferent impulses with the nociceptive component. This observation is well supported by the fact that during sinoatrial node stimulation the evoked potentials of maximal amplitude were recorded with parameters just sufficient to give rise to vegetative components of nociceptive response—mydriasis and increased arterial pressure.

It was found that most substantial changes in potentials induced by nociceptive myocardial stimulation occur as result of conditioning cortex stimulation in posterior hypothalamus, non-specific thalamic nuclei and periaqueductal grey. More pronounced effect was observed after stimulation of SI and SII, associative areas in cruciate sulcus and anterior part of median suprasylvian gyrus.

The writhing test in rats induced by chemical stimulation of peritoneum, served as a model of behavioral nociceptive response of visceral genesis. Acetic acid solution was injected intraperitoneally. Response latency, the number of ‘writhings’ in a definite time span and the extent of their expression were examined. The electrodes were implanted in somatosensory area either in one or both hemispheres.

Cortical stimulation, started right after acid administration, prolonged the latent period of ‘writhings’ occurrence by 2–2.5 times (Fig. 1). In the course of the experiment the number of ‘writhings’ in the main animal group amounted to 30–40% as compared to the control (without cortical stimulation). Cortical stimulation also lowered the intensity of separate ‘writhings’ making them shorter and less expressed. The similar effect was observed when stimulating the cortex both unilaterally and bilaterally. After the stimulation was discontinued, the antinociceptive

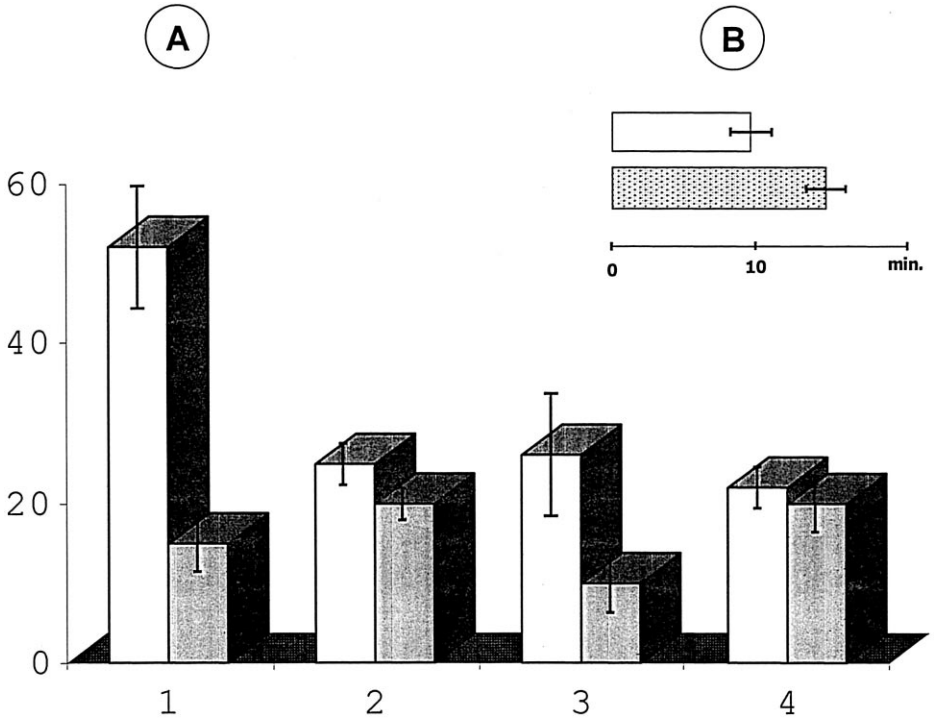

Fig. 1. Effect of cortical stimulation on the latency and course of 'writhing'. White columns: control animal group (without stimulating electrodes); black columns: main group (with electrodes for cortical stimulation). (A) number of 'writhings' (vertical scale) in a given time span: (1) throughout 30 min after acetic acid injection; cortical stimulation in the main group, (2) 31th–40th min; no stimulation in the main group, (3) 41th–50th min; cortical stimulation in the main group, (4) 51th–60th min; no stimulation in the main group. (B) latency of «writhings».

effect sustained for 5–10 min. Naloxone neither had influence upon the antinociceptive effect induced by cortical stimulation, nor affected the 'writhings' ongoing in the control group. Naloxone-induced blockade of the opioid receptors, however, completely eliminated the inhibitory effect induced by cortical stimulation in elecrophysiological experiments using the somatic or visceral testing stimulation (see below).

Considerable differences in the mechanisms responsible for acute pain and chronic pain syndromes including neurogenic, are well acknowledged (for a review, see Fields and Rowbotham, 1994). Therefore, it appeared beneficial to estimate the effect of cortical stimulation upon the development and expression of neuropathic pain syndrome produced in rats by sciatic nerve transection (Wall et al., 1979). To produce the neuropathic pain syndrome the

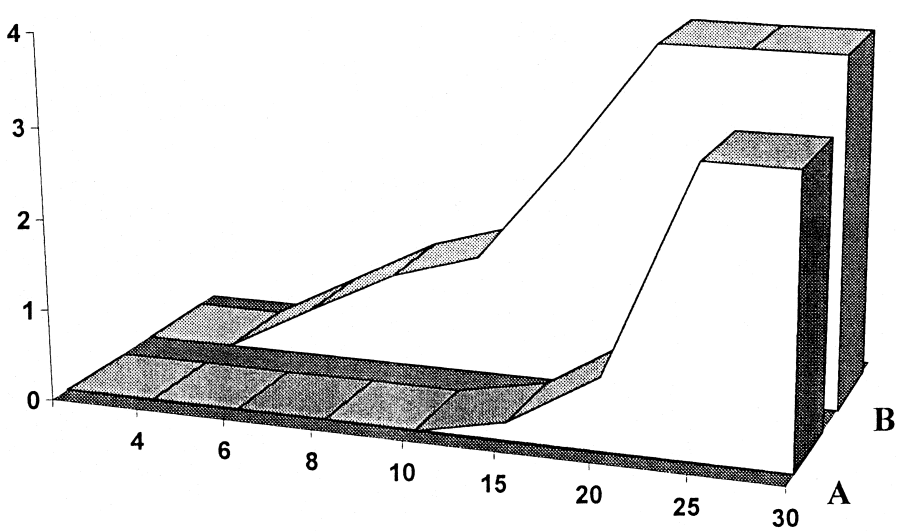

Fig. 2. Effect of electrical stimulation upon pain syndrome intensity after sciatic nerve section in the rat. (A) main animal group under cortical stimulation; (B) control animal group, Ordinate: pain syndrome intensity in points; abscissa: time (days) after sciatic nerve section.

sciatic nerve was cut and its central fragment was placed in a polyethylene capsule. Pain syndrome development was assessed basing on changes in animals behavior. An arbitrary rating scale was used to evaluate the intensity of nociceptive response. For stimulating the somatosensory cortex the electrodes were implanted into the hemisphere contralateral to the paw with the cut nerve. The stimulation was performed 5 min daily for 7 days starting from the 1st day after nerve section. The follow up of pain syndrome dynamics showed the slowed-down rate of its development: there was no progress during 7 days of stimulation and subsequent 6 days after the stimulation was discontinued. To this date (13th day of experiment) 90% of control animals demonstrated the signs of pain syndrome. Besides, the cortical stimulation reduced the intensity of the pain syndrome (Fig. 2). Thus, the descending cortical control was found to effectively suppress the nociception in both acute (somatic and visceral) and chronic pain syndromes.

4. Neurochemical analysis of descending cortical control of nociception; the effect of opioids

The inhibitory descending cortical effects were subjected to neurochemical analysis using the substances mainly acting upon opioidergic, adrenergic, dopaminergic, serotonergic and GABA-ergic mechanisms. These neurotransmitory processes were preferred in view of their involvement in formation of pain syndromes of different genesis and the function of the endogenous antinociceptive system (Wall and Melzack, 1994). The results of this series of experiments are summarized in Table 2. Most apparent changes in cortical control were detected after

Table 2
Neurochemical analysis of descending cortical inhibitory control of nociceptive processing in afferent pathways

Opioidergic system	
Stimulation of μ-receptors fentanyl	↑↑
Stimulation of κ-receptors pentazocine	↑
Inhibition of enkephalin inactivation thiorphan	⋮
Blockade of receptors naloxone	↓↓
Serotonergic system	
Stimulation of receptors quipazine	⋮
Re-uptake inhibition fluoxetine	↑
Inhibition of 5-HT synthesis p-chlorophenylalanine	↓
Blockade of receptors methysergide	↓
Adrenergic system	
Stimulation of receptors α_2 clonidine, β isoproterenol	0
Blockade of receptors α_1 prazosine, α_2 yohimbine, $\alpha_1\alpha_2$ phentolamine, β propranolol	0
Dopaminergic system	
Stimulation of receptors apomorphine	0
Blockade of receptors haloperidol	0
Cholinergic system	
Anticholinesterase agents physostigmine	⋮
Blockade of muscarinic receptors scopolamine	0
GABA-ergic system	
Stimulation of receptors $GABA\text{-}_A$ THIP	⋮↓
$GABA\text{-}_B$ baclofen	⋮
Blockade of receptors $GABA\text{-}_A$ bicuculline	↑
$GABA\text{-}_B$ phaclofen	0
Excitatory amino acids system	
Blockade of NMDA receptors dizocilpine	0

⋮ mild effect; | moderate effect; ‖ strong effect; ↑ increase; ↓ decrease; 0 no effect.

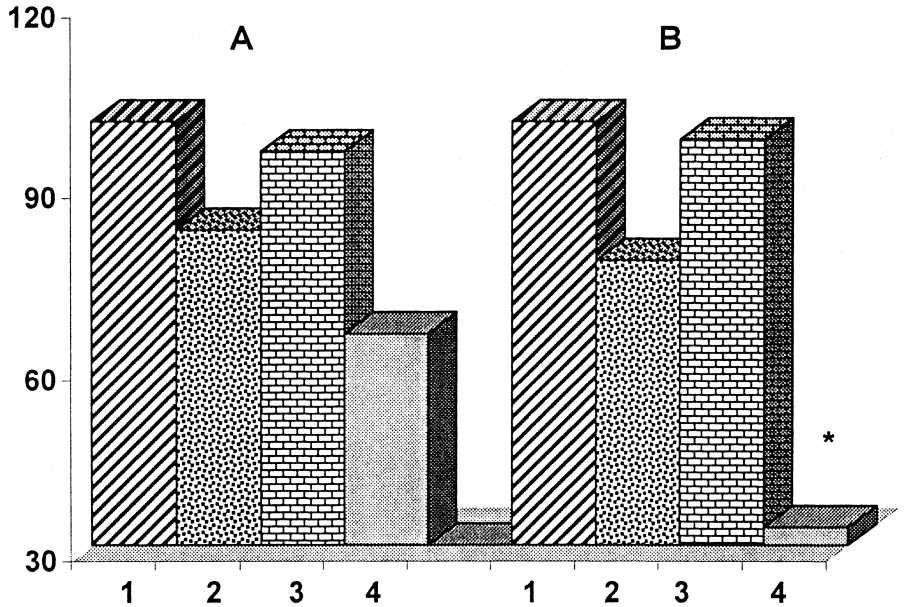

Fig. 3. Effects of morphine upon multireceptive neurons activity ($n = 6$) in dorsal horn (lamina V) and conditioning cortical stimulation (in percent). (A) Spontaneous activity. (B) activity induced by sciatic nerve stimulation; (1) initial activity, (2) activity under cortical stimulation, (3) activity after morphine administration (0.5 mg/kg, i.v.), (4) activity under stimulation and morphine action, * significant differences as compared to pretreatment parameters; $p < 0.05$.

opioid receptors stimulation. Thus, opioid μ-receptor agonist morphine (0.5–1 mg/kg, i.v.) significantly magnified (by 50% and more) the effect of cortical stimulation on the potentials evoked by somatic nerve stimulation in ventrobasal complex, posterior group of thalamic nuclei, medial and intralaminar thalamic nuclei and n. gracilis. Similar effect was observed when the potentials evoked by tooth pulp stimulation in the nuclei of trigeminal complex were recorded.

When the neuronal activity was recorded in the above structures using the microelectrodes, morphine increased the effect of cortical stimulation by 15–85%.

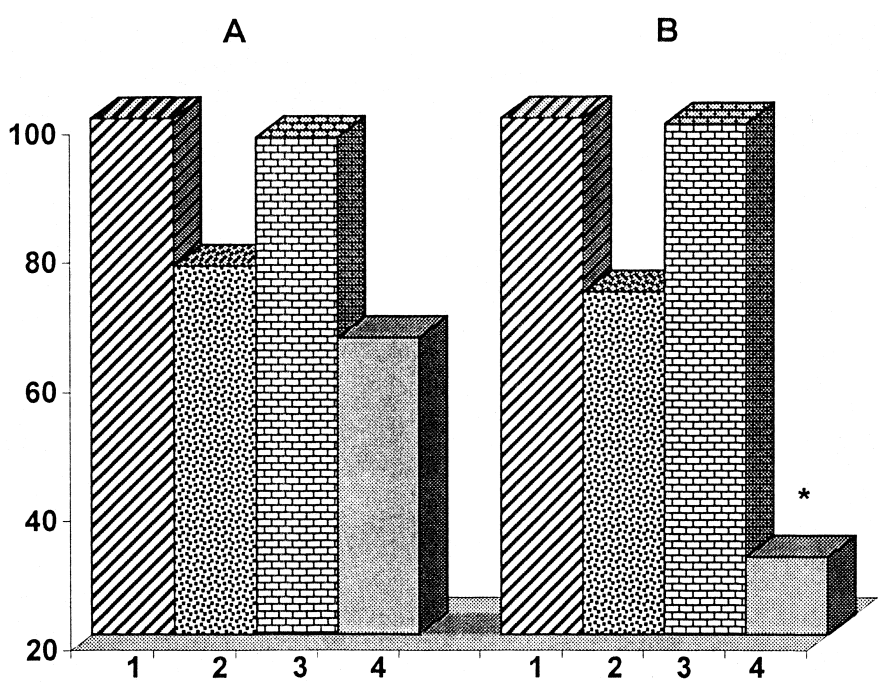

Fig. 4. Effects of fentanyl (0.005 mg/kg) on unit activity ($n = 8$) in nucleus caudalis of trigeminal complex and conditioning cortical stimulation (in percent). Same legend as for Fig. 3.

Morphine was also found to enhance the inhibitory descending cortical effects upon the activity of multireceptive neurons in the dorsal horn (Fig. 3). It is important to note that at tested doses morphine had no direct effect on the amplitude of evoked potentials and spontaneous unit activity, minor changes occurred in the evoked neuronal activity. Naloxone eliminated the effect of morphine. Fentanyl (0.001–0.01 mg/kg, i.v.) produced an effect similar to that of morphine (Fig. 4).

Unlike morphine, pentazocine (3–5 mg/kg, i.v.) exerted less pronounced action: the effects of cortical stimulation on evoked potentials and unit activity in the majority of experiments increased by 10–45%. In 20% of all cases when the unit activity was recorded (in dorsal horn and supraspinal structures) after somatic nerves or tooth pulp stimulation no rise in corticofugal effects was observed. Naloxone abolished the effect of pentazocine.

The obtained results provide evidence that the opioid agonists morphine and fentanyl significantly augmented the inhibitory descending cortical effects upon the transmission of somatic nociceptive impulses. Along with that, pentazocine in which spectrum of receptor activity the

Table 3
Neurochemical analysis of opioid analgesics action on descending cortical control of nociceptive processing in afferent pathways

Opioidergic system	
Blockade of receptors	
naloxone	↓↓
Serotonergic system	
Stimulation of receptors	
quipazine	0
Re-uptake inhibition	
fluoxetine	↑
Inhibition of 5-HT synthesis	
p-chlorophenylalanine	↓
Blockade of receptors	
methysergide	↓
Dopaminergic system	
Stimulation of receptors	
apomorphine	0
Blockade of receptors	
haloperidol	0
Cholinergic system	
Anticholinesterase agents	
physostigmine	0
Blockade of muscarinic receptors	
scopolamine	0
GABA-ergic system	
Stimulation of receptors	
$GABA\text{-}_A$ THIP $GABA\text{-}_B$ baclofen	0
Blockade of receptors	
$GABA\text{-}_A$ bicuculline	↑
$GABA\text{-}_B$ phaclofen	0
Excitatory amino acids (EAA) system	
Blockade of NMDA receptors	
dizocilpine	0

interaction with opioid κ-receptors prevail, exerted significantly lower effect upon the corticofugal mechanisms.

One of the constituent in the mechanism of analgetic action produced by morphine and other analgesics is their interaction with the opioid receptors located in the presynaptic membrane of primary non-myelinated dorsal afferents (Dickenson, 1994). As a result, the release of nociceptive signal transmitters (substance P and others) is reduced. The interaction at a level of primary afferents forms, probably, the basis of opioid analgesics-induced enhancement of cortical inhibition. Furthermore, stimulating the opioid receptors in the postsynaptic membrane of dorsal horn interneurons, morphine contribute to membrane hyperpolarization and suppresses their activity (Duggan, 1985; Dickenson, 1994). Opioid analgesics enhances the inhibitory descending effects of midbrain and medulla structures upon nociceptive impulses transmission at segmental level (Dickenson, 1994). Cortical stimulation-induced burst of impulses after reaching the periaqueductal grey, raphe nuclei and other structure being under the action of opioid analgesics, is able to significantly increase the descending inhibitory effects of these structures. Finally, the presence of opioid receptors, mainly of μ-subtype, in the cortex was recognized (Williams and Zieglgansberger, 1981). The application of opioid receptor agonists to the cortex leads to inhibition of the evoked electrical activity in spinal cord and some subcortical structures (Hernandez et al., 1985). Opioid analgesics administration may crucially increase the activity of cortical structures—generators of descending inhibitory impulses.

The blockade of 5-HT receptors (methysergide) notably decreased the inhibitory effect of cortical stimulation, whereas the stimulation of serotonergic transmission in the CNS by inhibiting the neurotransmitter re-uptake (fluoxetine) moderately enhanced the corticofugal inhibitory effect.

The methods employed in this study revealed no valuable involvement of adrenergic, dopaminergic and cholinergic mechanisms in the effects of electrical cortical stimulation.

The usage of GABA-ergic substances showed the changes in cortical control to be opposite in case of $GABA_A$-receptors stimulation (THIP) and, namely, the inhibitory effects on evoked activity of most multireceptive neurons increased, whereas the action over specific nociceptive neurons activity lowered.

5. Neurochemical analysis of opioid analgesics effects on the descending cortical control

The neurochemical analysis was performed to evaluate of the action produced by opioid analgesics with different spectra of receptor activity over the corticofugal mechanisms involved in nociceptive processing. The agonists and antagonists of 5-HT receptors, adreno- and cholinoreceptors as well as GABA-ergic substances were used.

The examination of morphine, fentanyl and pentazocine actions provided similar results (Table 3). The adrenergic and dopaminergic agents had no valuable influence on opioid analgesics effects upon the corticofugal control. 5-HT receptor antagonist methysergide reduced the effects of opioid analgesics after testing stimulation of somatic nerves and tooth pulp in all studied structures during both evoked potentials and unit activity recordings. Fluoxetine increased the effect of opioids in case of microelectrode recording of the neurons activity.

Scopolamine and physostigmine had no significant effect on opioids action. Tetrahydroisoxazolo-pyridine-3-ol (THIP), baclofen, bicuculline potentiated the effect of opioids over the corticofugal inhibitory control during recording of the activity of some neurons in dorsal horn and supraspinal structures. Faclofen had no significant effect.

Thus, the serotonergic mechanisms, having system of periaqueductal grey and the raphe nuclei as an anatomical and physiological substrate, are responsible for the enhancing effect on corticofugal inhibition of nociceptive impulse transmission under the action of opioid analgesics. GABA system was shown to play a certain role in this effect.

6. Effects of non-opioid agents with analgetic properties on the descending cortical control

It appeared of interest to assess the effects of non-opioid central agents possessing analgetic properties on the descending cortical control (Table 4).

Of the non-narcotic analgesics metamizole, ketorolak and acetaminophen were tested. The performed experiments showed that metamizole (20–60 mg/kg, i.v.) potentiated (by 10–20%) the inhibitory action of cortical stimulation over the potentials evoked by somatic nerves stimulation in ventrobasal complex, posterior group of thalamic nuclei, medial and intralaminar thalamic nuclei. Similar effect was observed when the potentials evoked by tooth pulp stimulation were recorded in the nuclei of trigeminal complex. No changes in potentials of n. gracilis were detected.

When the electrical activity in the above structures was recorded using the microelectrodes after somatic nerves or tooth pulp stimulation, metamizole increased the effects of cortical stimulation by 10–30% in 2/3 of studied neurons. Metamizole was also shown to potentiate the inhibitory corticofugal effect on the activity of miltireceptive and specific nociceptive neurons in the dorsal horn (Table 5).

Metamizole had no direct effect on the amplitude of evoked potentials and spontaneous neuronal activity, minor changes occurred in the evoked unit activity. Naloxone failed to eliminate the effect of metamizole.

Table 4
The action of analgesics and some agents with analgetic properties on descending cortical inhibitory control of nociceptive processing in afferent pathways

Opioid analgesics	
morphine, fentanyl	↑↑
pentazocine	↑
Sodium channels blockers (antiepileptic drugs)	
carbamazepine, phenytoin	0
Monoamine-reuptake inhibitors (antidepressants)	
imipramine, fluoxetine	↑
α_2-Adrenomimetics	
clonidine	0
GABA-$_B$ receptor agonists	
baclofen	⇡
NMDA receptor antagonists	
ketamine	0
Nonnarcotic analgesics	
metamizole, ketorolak	↑
acetaminophen	0

Unlike metamizole, ketorolak (1–5 mg/kg, i.v.) had little effect on the inhibitory effect of cortical stimulation over the evoked potentials in subcortical structures, including the trigeminal complex. In experiments with the unit activity recording (spinal cord and supraspinal structures) following somatic nerves stimulation after ketorolak injection in 65% of all cases no rise in corticofugal effects was observed. The effect of ketorolak on the unit activity in trigeminal complex was similar to that of metamizole.

Acetaminophen at doses up to 100 mg/kg had no influence upon the effects of cortical stimulation.

At present, the occurrence of an analgetic effects of non-narcotic analgesics metamizole, ketorolak and acetaminophen is mainly attributed to their central action (Buckley and Brogden, 1990; McCormack, 1994; Bjorkman et al., 1994; Lemina and Churukanov, 1995). Metamizole and ketorolak, in contrast to acetylsalicylic acid and other non-steroid anti-inflammatory drugs, have relatively minor effect on prostaglandines synthesis in the peripheral tissues. Acetaminophen has actually no such an effect. In parallel, these agents by inhibiting the cyclooxygenase in the CNS, reduce the content of prostaglandines in the spinal cord. Besides, there is evidence that the non-narcotic analgesics exert an effect on the processes in CNS which occur with nitric oxide involvement.

With respect to findings obtained from the present investigation about the enhancement of corticofugal mechanisms, it shall be noted that there are reports about metamizole-induced potentiation of the descending inhibitory effects produced by periaqueductal grey and raphe nuclei on nociceptive responses (Carlsson et al., 1986).

Table 5
The action of metamizole on unit activity (multireceptive neurons in the dorsal horn) and effect of conditioning electrical cortical stimulation, in % ($M \pm m$)

Unit activity	Control	Metamizole 25 mg/kg ($n = 6$)
Spontaneous	100	95.4 ± 3.8
Evoked by sciatic nerve stimulation	100	96.2 ± 5.2
Spontaneous under cortical stimulation	83.5 ± 3.4	79.1 ± 3.5
Evoked under cortical stimulation	73.5 ± 3.1	56.8 ± 2.4[a]

[a] Significant differences as compared to pretreatment parameters; $p < 0.05$.

Sodium channels blockers (carbamazepine, phenytoin), NMDA receptor antagonist ketamin, α_2-adrenomimetic clonidine, $GABA_B$ receptor agonist baclofen caused no significant changes in corticofugal effects. The antidepressants, inhibitors of neuronal re-uptake imipramine and fluoxetine produced more pronounced action. The enhancement of cortical inhibition under the effect of the latter agents seems likely to be the result of serotonergic transmission stimulation at the segmental and supraspinal levels.

7. Conclusion

Over the period of the 70s–80s extensive studies provided a body of data which allowed to frame the concept of the brain endogenous antinociceptive system (for review, see Besson et al., 1982; Wall and Melzack, 1994). This system includes the segmental structures, medulla (raphe nuclei and others), midbrain (periaqueductal grey and others), thalamic nuclei, hypothalamus. The discovery of endogenous antinociceptive system formed a basis to explain the mechanism of opioids action (Dickenson, 1994). The involvement of cortex in the function of this system is beyond any doubt (Kenshalo and Willis, 1989). However, the role of cortex in nociception control has yet to be further investigated.

The data presented provide a clear evidence supporting the role of the cortex in the nociception control demonstrated in different models of pain syndromes (somatic, visceral and neuropathic pain). It has been shown that the descending inhibitory cortical control is firstly effected via opioidergic and serotonergic systems. The increase in inhibitory cortical control of nociception as result of opioids effect is quite compatible to their action on the periaqueductal grey—raphe nuclei system.

The effect of antidepressants and some non-narcotic analgesics on the inhibitory cortical control is likely to be a valuable component of their analgetic profile.

The data presented have a good practical potential in view of recent reports on the efficacy of the electrical cortical stimulation for the treatment of central and neuropathic pain syndromes (Meyerson et al., 1993; Tsubokawa et al., 1993; Tsubokawa, 1995; Canavero and Bonicalzi, 1995).

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