NON-INVASIVE TRANSCRANIAL ELECTROSTIMULATION OF THE BRAIN ANTINOCICEPTIVE. SYSTEM AS METHOD OF FES: AN OVERVIEW

Valery P. Lebedev

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Abstract

The presented overview is devoted to elaboration and study of effects of a new non-invasive method of transcranial electrostimulation (TES) of the brain antinociceptive system. In experiments the optimal electrical regimen and optimal head electrodes position were estimated, and the "quasiresonance" characteristics of the brain antinociceptive system were revealed. By means of different approaches it was proved that effects of this type of TES are homeostatic and resemble the effects of direct electrical stimulation of the antinociceptive system. The main TES curative effects were estimated in animal experimental pathological models. As a result of experimental studies special devices for TES were developed and recommendations for practical TES application as a method of treatment and prophylaxis were established. 18-year practical usage of new TES method according our recommendation for non-pharmaceutical treatment of several types of pathology in more than 300 hospitals and outpatient clinics in Russia demonstrated the high level of efficacy without side effects. The results were proved by double-blind passive and active placebo-control.

Keywords: transcranial electrostimulation, antinociceptive system, endorphins, serotonin, homeostasis, non-pharmaceutical treatment.

1. Introduction

Electrostimulation of the brain through the skull (transcranial electrostimulation - TES) was firstly introduced in 1902 in France by Leduc [5] for electronarcosis and in 1947 in Russia by Giliarovsky [1] for electrosleep. It seemed very attractive to elicit narcosis or sleep without of usage of any medications and presence of respective its side effects. Unfortunately broad studies of electronarcosis with different approaches produced in France, Russia, USA, Japan, India etc. during more than 70 years gave no opportunity to elaborate clinically acceptable method without heavy side effects [9]. Metanalysis of the results of several double-blind studies also demonstrated the absence of reproducible sleep events during and after "electrosleep" stimulation [8].

Trying to elicit electronarcosis by focal brain electrostimulation Reynolds [7] found in medial part of the brain stem some areas activation of which elicited deep antinociceptive effects with reduction of pain reactions without changing other ones. In further extensive studies it

was revealed the structures included in antinociceptive system (ventro-medial hypothalamus, periaqueductal grey of midbrain, raphe nuclei of pons and medulla) and neurotransmitter mechanisms of its operation (mainly endorphins and serotonin - [3]).

The aim of present study was to reinvestigate if it could be possible to stimulate the antinociceptive system by the current applied on the skull surface. The following main events should be estimated: 1) optimal electrodes position on the skull to direct current pathways to the structures of the antinociceptive system; 2) characteristics of current for adequate activation of antinociceptive system; 3) neurotransmitter mechanisms involved; 4) main curative effects and clinical usage; 5) development of practically applied devices.

2. Results

2.1. Optimal electrodes position for TES. As it was demonstrated by MRI [2] that sagittaly applied impulse current only (electrodes on the forehead and on mastoids behind ears) can reach the antinociceptive system by means of two intracranial pathways via cerebrospinal fluid (CSF) through the connected in series basal cisternas and lateral ventricles - 3rd ventricle - 4th ventricle. Interconnections between two pathways at the level of the bottom of the 3rd ventricle and lateral recessus of the 4th ventricle were observed.

2.2. Optimal characteristics of impulse current for TES. Because the analgesia is one of the most important effect of the direct stimulation of the antinociceptive system the reduction of pain was used as indicator of its activation during and after TES. Quantitative estimation of acute pain level and pain tolerance and its reduction were performed in

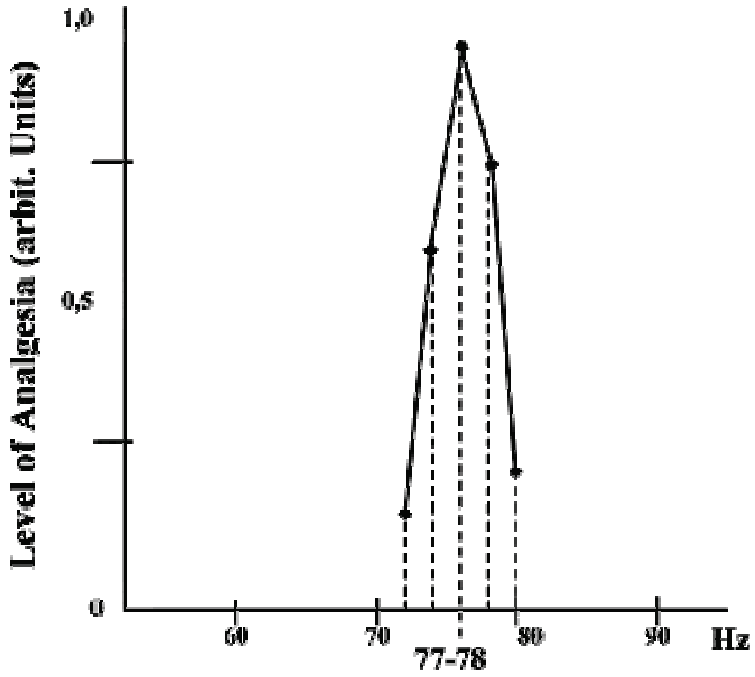

Fig. 1. Relation between frequency of TES and the level of analgesia.

screening experiments with different animal species (rat, mice, rabbit, turtle) and volunteers by means of registration of emotional, autonomic, motor escape reactions, and verbal report. The optimal characteristics of impulse current were found, and relations "effect - frequency of impulses" and "effect - impulse width" resembled rather sharp quasiresonance curve (Fig.1). As revealed in cross-over experiments the regimen elaborated is much more effective than one described by Limoge [6]. Elaborated type of stimulation increased consumption of [3H]-deoxyglucose (increase of carbohydrate metabolism of neurons correlates with increase of neuronal activity) in periaqueductal grey and decreased it in relay nuclei participated in ascending nociceptive impulsation and in somato-motor cortex.

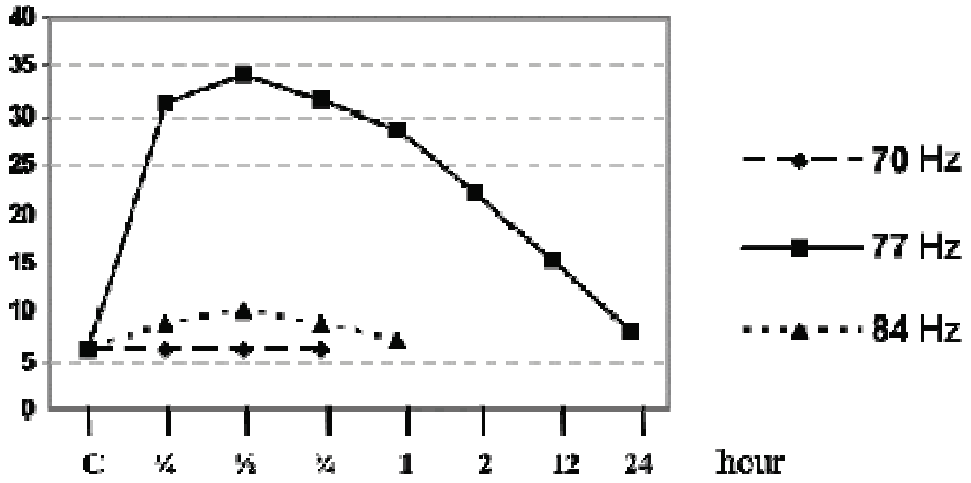

Fig. 2. Plasma beta-endorphin level after TES with different frequencies in rats (A) and in volunteers (B). A √ five different groups of rats in fifteen min after 20 min TES sessions. B √ follow-up in three groups of volunteers after one 30 min TES session. C √ control level on A and B.

2.3. Neurotransmitter mechanisms involved in TES effects. TES with elaborated regimen activated mainly endorphinergic and serotoninergic antinociceptive mechanisms . The increase of b -endorphin concentrations in the brain stem, spinal dorsal horns, in CSF and in the blood, and met-enkephalin - in CSF were demonstrated. The maximal b -endorphin release coincided with the optimal point of the regimen of transcranial electrostimulation (Fig.2). In correspondence with CSF opioid concentration growth the decrease of pain elicited substance P release in CSF was observed. Serotonin (5-HT) level in CSF was also increased. The effects of the TES were blocked by naloxone (opioid receptors blokers), 5,7-dihydroxy-triptamine and metergoline (5-HT antagonists) and was absent in animals with tolerance to morphine. Potentiation of the TES effects was elicited by enkephalinase blocker d-phenylalanine, 5-HT precursors, inhibitors of monoamineoxydase, and triptophanpyrrolase inhibitor milurit which prevents 5-HT precursor leakage via kinurenine metabolic pathway. Effects of cholinergic and GABA-ergic agonists and antagonists were rather limited.

2.4. Main curative effects and TES clinical usage. Majority of TES curative effects were estimated firstly in animal pathological models. All TES effects were naloxone-reversible. To verify the reality of clinical TES effects the double-blind active and passive controls were done.

Psycho-physiological effects only was estimated in healthy volunteers (several tests, questionnaires and computerized hart rate variability) manifested in reduction of fatigue, affectivity and stress events, increase of mood and adaptability. In general in different groups of patients treated by TES the increase of the "quality of life" and reduction of depression were observed. Preliminary studies demonstrated the obvious positive TES effects in treatment of the "chronic fatigue" syndrome in adults and pathological hyperactivity in children.

Analgesic effects broadly studied in screening experiments (see above) were practically used for relief of neurological and other types of pain syndromes and were more pronounced in cases of heavy pain (trigeminal neuralgia, postoperative pain). To exclude the morphine-like analgesic consumption TES was included as analgesic component of anesthesia during surgery.

Bloodpressure normalization based on experimentally revealed of TES endorphinergic effect on medulla vasomotor center used treatment of hypertension and vasomotor dystonia especially during preclimax.

TES of the brain endorphinergic structures reduced of *abstinence, craving* and other affective disorders connected with alcohol and opioid drug abuse.

TES accelerated *repair* of damaged tissu-es and used for treatment wounds and thermal burns, ulcers, myocardial infarction, sensorineural deafness, toxic hepatosis [4].

TES activated some specific and nonspecific mechanisms of *resistivity* and *immunity*. According these effects TES inhibited implanted tumor growth and it is a basis of TES usage for non-pharmaceutical analgesia in onco-logical patients with metastasis.

2.5. Practically applied devices. TES devices developed according "quasiresonance" peculiarities of the brain antinociceptive system. It means that it is not necessary to adjust the frequency and impulse width for concrete case. Nevertheless the frequency and impulse width stochastically change of its values inside the limits of quasiresonance curves (± 2 Hz and ± 0.25 msec respectively). To reduce the local unpleasant filling under electrodes the non-symmetrical bipolar impulses with zero net charge were used. Several models of devices with generic name as TRANSAIR (abbreviations of Transcranial Stimulator for Analgesia, Immunity, Repair) for therapeutics and anesthesiological applications developed and are manufactured by TES Center of the Pavlov Institute of Physiology.

3. Discussion and conclusions

The data devoted to elaboration and study of the method of TES based on the contemporary morphological, physiological, neurochemical and pharmacological data on the brain antinociceptive system and quantitative approach with placebo control. The main peculiarities of this method which is the example of FES are as follows:
- Multiple curative effects usually coincided with central and peripheral effects of endorphins;

- Several curative effects may appear simultaneously in concrete patient with multiple pathological processes;
- All TES effects have mainly homeostatic direction.

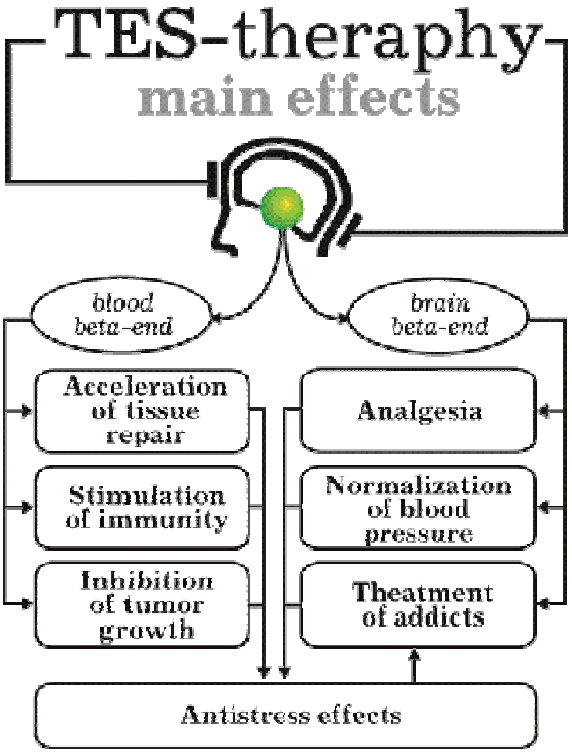

Fig. 3. Main effects of TES of the brain endorphinergic structures.

Thus according the data presented the non-invasive TES with regimen elaborated is a close analogue of invasive direct electrical stimulation of antinociceptive system.

18-year practical usage of new TES method and devices according our recommendation for non-pharmaceutical treatment of several types of pathology in more than 300 hospitals and outpatient clinics in Russia, Bulgaria and Israel supported our results and demonstrated the repeatability and high level of TES efficacy without side effects. The main part of presented results published in Russian only [10].

4. References

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