TRANSCRANIAL ELECTROSTMULATION OF THE BRAIN ENDORPHINERGIC SYSTEM AS AN EXAMPLE OF THE UNINVASIVE FUNCTIONAL ELECTROSTIMULATION OF THE BRAIN HOMEOSTATIC MECHANISMS: ACTIVATION OF TISSUE REPAIR

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Abstract.

Special electrical regimen and devices were developed for non-invasive transcranial stimulation of the brain antinociceptive endorphinergic structures. It was revealed in experiments and in clinical observations that stimulation of endorphin release effectively accelerates the repair processes in damaged tissues of different types.

INTRODUCTION

It is well known that opioid pep tides injected systemically or introcerebroventricularly are able to produce homeostatic effects on regulation of the several physiological mechanisms including the acceleration the growth and repair of damaged tissues of different types [1, 2]. The same effects can be reproduced by invasive direct electrical stimulation of the endorphinergic antinociceptive structures located in medial part of the brain stem [3, 4]. To increase of brain P-endorphin release we elaborate the uninvasive method of transcranial electrostimulation (TES) with special regimen for activation the brain endorphinergic structures according their quasiresonance characteristics [5, 6].

The aim of present paper is to review the possibilities and peculiarities of the TES effects on the regeneration processes of damage tissues of different types (skin and gastroduodenal epithelium, liver cells, connective tissue, peripheral nerve fibres) in experimental animal pathological models and in treatment of respective diseases in patients (P).

MATERIALS AND METHODS

Animal experiments.

All experiments were carried out in four groups of rats (R). The pathological models used are included in table I. In R of I and IV groups all surgery was done under deep pentobarbital anesthesia. In each group TES was produced by rectangular pulses (70 Hz - optimal for R, 3.5 msec, average current 0.8-1.2 mA, three 1 h daily sessions in a day) and delivered through subcutaneous needle electrodes on the forehead (cathode) and behind the ears (anodes). R were semirestrained (light ketamine anesthesia). As it was demonstrated previously these impulse parameters are optimal to elicit analgesia and the P-endorphin release in R [7, 8].

Clinical observations.

The groups of P pathology for TES treatment were selected mainly in accordance with positive results obtained in experimental pathological models (Table II). In P TES was delivered through the surface Ti electrodes (diameter 2.0 cm) applied on the skin of the forehead and both mastoids with thick wet cotton pads. Electrodes were fixed on the head of P by Velcro belts. TES in P was produced by rectangular pulses (77 Hz - optimal for humans [9], 3.5 msec, average current 1.0 - 5.0 mA, and session duration 30 - 45 min). In pilot studies the optimal protocol of treatment was estimated for different groups of P. For P of groups A and C there were about 15 daily sessions produced with current 2.5 - 5.0 mA. P of group B were treated twice a day during 7 — 10 days with current 1.5-3.0 mA. For P of group D the number of daily sessions and current were lower than for group C - 5 - 7 sessions and 1.0 -1.5 mA respectively.

Table I. Experimental models and methods used for estimation of the TES effects on the damaged tissue repair

Group of rats	Type of model	Damaging factor or intervention	Methods used for estimation of the repair processes
I	Standard skin wounds	Dissection of full layer skin flap on the back	Measurement of squares, light microscopy
II	Gastrodoudenal ulcers	Immobilization and cold stress, intoxication by alcohol and cisteamine	Measurement of squares, counting of number, calculation of the severity indexes
III	Toxic damage of liver cells	Poisoning by dichlorethane	Blood and liver biochemistry, light microscopy, micromorphometry
IV	Peripheral nerve trauma	Dissection and suturing of the sciatic nerve	Registration of single nerve fibers discharges

In P of A, B, and C groups the blood p-endorphin level was estimated by radioimmunoassay before and after the course of treatment and before and just after of 3-5 first sessions.

Table II. Groups of patients treated by TES

Group of patients	Diagnosis	Respective experimental model
A	Thermal burns, postoperative wounds	I
B	Gastric and duodenal ulcers	II
C	Acute myocardial infarction	No experimental model
D	Sensorineural hearing loss	IV

During sessions all P were conscious and had no unpleasant sensation, only light tingling especially under cathode which was reduced in some minutes in process of skin receptors adaptation . No side effects during or after sessions were observed. As a rule, after sessions P reported the improvement of self-filling , mood, reduction of stress, fatigue and pain relief, hi follow-up and psycho-physiological evaluations no any long term negative aftereffects were found. In all experiments and clinical observations the match controls were always used.

Devices.

TES treatment was produced by device named as TRANSAIR-01[1].The output parameters (constant amperage) of the portable battery operated or plug-in generator was preprogramed according the experimentally estimated sharp quasiresonance characteristics of brain endorphinergic system which were rather different in frequencies for R, humans and other animal species (mice, rabbits). The clinical application of TES with regimen elaborated and devices were approved by Russian Ministry of Health. Now the devices of TRANSAIR-01 type are broadly used in Hospitals and Outpatient Clinics in Russia. The therapeutic efficacy of TES regimen was also confirmed in Bulgaria and Israel.

RESULTS AND DISCUSSION

Experimental data,

in all groups of animals the significant acceleration of damaged tissue repair was observed. The opioid nature of effects was proved by naloxone reversibility and potentiation by enkephalinase inhibitors (D-leucine, D-phenylalanine).
The wound healing in R (group I) was accelerated up to 20-30% with active granulation at the bottom of wounds and very mild scars. The healing effect could be elicited by one TES sessions produced even a day before surgery. TES sessions with other frequencies (50, 90 Hz) were completely ineffective.

[1] TRANSAIR-01 was developed and manufactured by TES Centre of the Pavlov Institute of Physiology

In R of group II after TES sessions reduction of ulcer number up to 20-40% was observed and the severity indexes were decreased at about 2-5 times. The most prominent TES effect was found in cases of gastroduodenal ulcers elicited by pure ethyl alcohol. Prophylactic effect of TES sessions was also observed especially in R with stress induced ulcers.

In R with liver damage (group III) normalization or improvement of detoxification (thymol and bromsulfalein tests) function, synthetic (proteins, lipids, glucose, glycogen, cholinesterase) abilities and cytolysis events (alanine and aspartate aminotranspherases, alkaline and acid phosphatases, lactate dehydrogenase, ceruloplasmin). By means of light microscopy it was revealed that in the liver of treated animal fat degeneration of hepatocytes were found very rarely in comparison with control R. Necrotic areas were never observed. In the R with chronic poisoning and one month TES treatment no events of liver cirrhosis were found.

The first afferent single nerve fiber discharges in sciatic nerve (group IV) proximal to dissection level (focal mechanical hindpaw stimulation) were registered in treated R at the 12^{th} day after surgery in comparison with same events at $15\text{-}20^{th}$ days in control group. The same time difference of repair was found in reflexly activated efferent nerve fibers. It is important that in treated R even after 9 months after surgery the duration of action potentials in afferent fibres was significantly shorter in comparison with control.

Thus, experimental data demonstrated that TES treatment accelerates the repair processes in skin and gastroduodenal epithelium, connective tissue, hepatocytes (originated from duodenal epithelium) and peripheral nerve fibers. These effects could be elicited when some TES treatment was produced 1-2 days before damages (groups I and II). It means that TES treatment has a long term effects, as it was also demonstrated in group IV.

Surplus regeneration may be dangerous in successive malignancy. In connection with this possibility it was demonstrated in additional group experiments in R that TES treatment (with the optimal parameters for regeneration only) inhibited the growth of implanted tumor originated from the epithelium and connective tissue (carcinoma-256, sarcoma-45, hepatoma-27). This TES effect was also naloxone reversible.

Clinical data.

In P with thermal burns (group A) II-IIIAB levels of severity (up to 60% of body surface) the acceleration of healing during TES treatment was estimated as 20-30%. An important observation that in all P the significant analgesic and antistress effect was observed with increase of blood P-endorphin and somatotrophin and decrease of catecholamine levels. T-helpers and NK-lymhocytes were also activated.

Adult and children with gastric and duodenal ulcers (group B) were treated without any antihelicobacter medications. The velocities of gastric and duodenal ulcers healing (fibrogastroscopy) was about 4.15 ± 0.28 mm^2/day and 3.7 ± 0.37 (two daily TES sessions, 10 days) in comparison respectively with 1.17 ± 0.23 mm^2/day and 1.76 ± 0.58 mm^2/day in control group. The increase of blood P-endorphin level and normalization of gastrin level were constantly observed. In a two-three days of treatment all pain events and dyspeptic disorders were abolished. In follow the long term remission was found up of 81% P.

The TES treatment of acute myocardial infarction (group C) was started as usual in a 3-6 h after the beginning of heart attack. According the precordial polytopic ECG mapping the myocardial necrotic area was obviously smaller in TES treated P. More rapid scar formation was supported, as a demonstration of increased blood level of oxyproline — a collagen repair marker. TES treatment increased the heart contractility (with compensatory myocardial hypertrophy) and reduction up to 2 times of the cardiovascular insufficiency events at the end of observations. The increase of P-endorphin baseline level was found at the 3rd day of TES treatment and then each next TES sessions elicited more P-endorphin release. In control group of P no elevations of p-endorphin or oxyproline level were observed. TES treated P followed up to one year demonstrated significantly higher myocardial contractility than control group ones.

Sensorineural hearing loss (SNHL) based on impairment of neural structures of inner ear was effectively treated by TES (group D). The first effect in 50% of P with chronic SNHL (who were ineffectivly treated by medications by the years) was the reduction or abolishment of subjective tinnitus. After the 5-7 sessions the positive results (25-35 dB increase of hearing ability) was observed in 45% of P with chronic SNHL of different etiology. The prediction of positive TES effect with probability about 95% could be done in chronic SNHL by evaluation of of the presence of acoustic nerve excitability with focused ultrasound. The duration of remission was about 4 months. In cases of sudden SNHL the full restoration of hearing ability was found in 90% P just after two-three TES sessions.

CONCLUSIONS

TES of the brain endorphinergic structures is a new simple effective uninvasive scientifically based and clinicaly approved method for activation of endogenous homeostatic mechanisms involved in improvement of several functional and structural body disturbances e.g. by acceleration of repair processes in damaged tissues. The clinical study of TES treatment efficacy of liver pathology is in progress now.

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