DEVICES FOR NON-INVASIVE TRANSCRANIAL ELECTROSTIMULATION OF THE BRAIN ENDORPHINERGIC SYSTEM: APPLICATION FOR IMPROVEMENT OF HUMAN PSYCHO-PHYSIOLOGICAL STATUS

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SUMMARY

Here, we describe the clinical application of devices for non-invasive and selective transcranial electrostimulation (TES) of the antinociceptive system; and, their endorphinergic and serotoninergic neurotransmitter components. Our data is based on a large number and variety of experimental and clinical studies. The process of development and a brief description of these devices are presented. We also demonstrate the high efficacy of TES treatment for reduction of psycho-physiological disturbances elicited by stress of different intensities and a variety of other factors.

STATE OF THE ART

During the last century, transcranial electrostimulation (TES) was proposed as a method to elicit electronarcosis /1/, electrosleep /2/ and electroanalgesia /3/. Many attempts in several countries were made to introduce these methods into clinical practice /4/. Despite the breathless expectations based on TES methodology (i.e., non-pharmacalogic, easily controlled, with few side effects); the practical results of TES applications were quite negative. In hindsight, it is understandable because there were: no suitable experimental models, little knowledge of the optimal parameters for treating specific abnormalities, or well-controlled studies; that, acceptance of TES into the clinical area was slow, if at all.

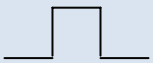
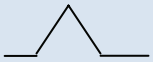
Our general aim was to develop the method of non-invasive, selective activation of the brain antinociceptive system with its endorphinergic and serotoninergic mechanisms by means of TES. Some data were presented previously /5, 6/. The specific aim of this paper is to describe the process of development of TES devices and its applications for reduction of psycho-physiological disturbances elicited by stress of different intensity and some other factors. This study was accomplished according to the established order of GMP, GLP and GCP.

MATERIALS AND METHODS

Development of devices

In the long history of TES, several different electrical regimens were introduced rather arbitrarily. To make a choice of optimal regimen for stimulation of antinociceptive system,

Table 1. Characteristics of impulses studied in screening experiments to elucidate of its optimal parameters for transcranial electroanalgesia

Impulse shape	Frequency (Hz)		Width (msec)		Combination with DC
	Range	Steps	Range	Steps	
	40 - 100	1 – 5	0.1 – 5.0	0.05	Yes
	100 - 3500	10 -50	0.1-1.0	0.1	No
	40 -250	10	0.1 –5.0	0.2	Yes / No

broad screening experiments were performed with non-traumatic pain models in several species of animals and volunteers with registrations of emotional, motor and autonomic pain-related events. The shape of impulses, range of frequencies, impulse width and the steps of its changes are presented in Table 1. All parameters studied were within the limits of ones of previously described devices for electrosleep and electroanalgesia /2, 3/. It was found that optimal stimulation antinociceptive system to elicit analgesic effect and maximal β-endorphin release are produced by rectangular impulses only of narrow band parameters of frequency and width slightly different for different species. The optimal parameters for humans were respectively 77.5 Hz and 3.5-4.0 msec. The relationship between the TES analgesic and other effects and impulse frequencies was very sharp and had rather "quasiresonance" shape. For example: ± 2 Hz frequency deviations from resonance point reduced effects at about 50 %, ± 4 Hz deviations abolished TES effects /6/. These data gave the basis to exclude an individual adjustment of frequency and impulse width for concrete patient in devices..

It was also found that constant voltage impulses are effective in combination with DC in ratio 1:2 only. Contrary constant current impulses of the equal amplitude had the same efficacy without additional DC. This result gave an opportunity to reduce significantly the level of current applied. In comparison between the analgesic efficacy of present TES regimen and regimen described by A.Limoge /7/ it was elucidated that the first one is much more effective. Further improvements of electrical regimen were directed to diminution of local irritating action on the skin under electrodes and increase the TES efficacy in population of patients. To realize the first aim the bipolar impulse with zero net charge (Fig.1A, phase "a" is equal phase "b") was used. For the second aim the stochastic frequency modulation was introduced in the limits of the width of "quasiresonance" curve at the 50% level of its height (Fig.1,A).

On the basis of these results the development of some models of devices named later as TRANSAIR (abbreviation - **TRAN**scranial **S**timulator for **A**nalgesia, **I**mmunity and **R**epair) and adjusted for out-and indoor usage were developed and manufactured (Fig.1,B).

Experimental studies

The immobilization and cold stress of different intensity in rats were used as a model estimation of possible TES antistress effect. The intensity of stress-related events before and after TES were estimated immunocytochemically in neurons of brain cortex and several brainstem nuclei activation by immediately early gene (C-Fos) expression /8/ and morphologically by measurement of number and shape of gastric ulcers /9/. TES was performed by regimen specially adjusted for rats /10/.

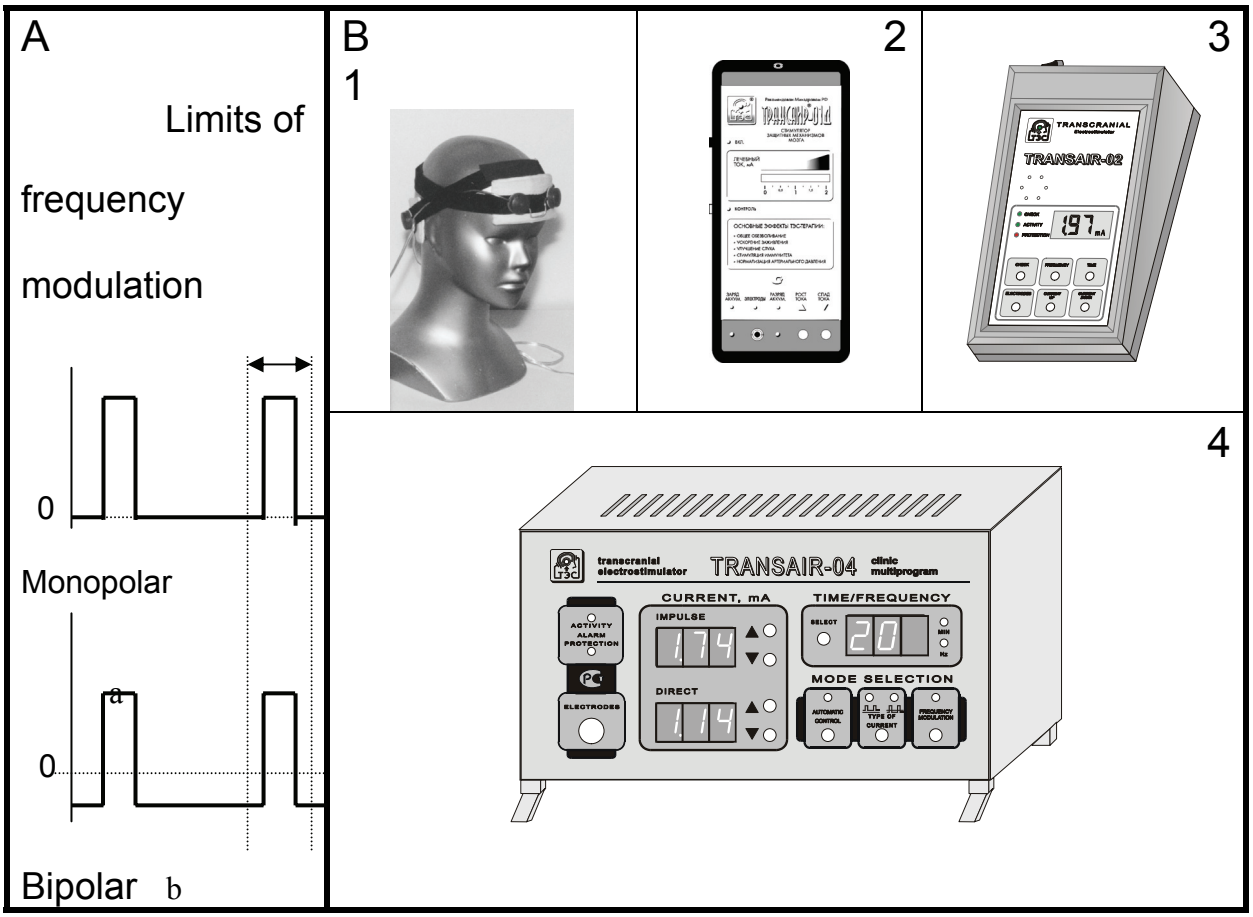


Fig. 1. Output current impulses (A) of TES devices (B).

A. Shape of impulses and limits of frequency modulation.

B. Different TRANSAIR models:

1- Headset of electrodes. 2- TRANSAIR – 02, the simpliest for outdoor usage, monopolar output impulse, rechargeable battery. 3- TRANSAIR – 01, for practitioners, mono- and bipolar output impulses, LCD, timer, frequency control, alarm and protection systems, plug in. 4- TRANSAIR – 04, for hospitals and outpatients clinics, mono- and bipolar output impulses with or without frequency modulation, LD indicators, timer, automatic control, alarm and protection systems, verbal dialogue with user in process of adjustment of parameters, plug in.

Human studies

The blind and placebo-controlled (passive and active placebo) studies were produced to estimate the TES effects on stress-related events, affective disorders, and accompanied psycho-physiological and autonomic disturbances of different intensity in several groups of volunteers and patients. Some subjective verbal and non-verbal tests and objective tests were used for estimation of initial level psycho-physiological status and it changes after TES sessions (Table 2).

Table 2. Groups of volunteers and patients with stress-related events, affective disorders and accompanied psycho-physiological disturbances and tests its estimation.

No	Groups of volunteers and patients	Types of stress and fatigue	n	Tests and number of indexes (n)
1	Workers	Everyday stress and fatigue	141	*Subjective tests* – non-verbal: VAS, Color Lusher's test (4). *Subjective tests* – verbal: Self-estim. test (3), Spilberger's test (2), Quality of life. *Objective tests*: Correction test with Landolth's rings (8), Critical frequency of flashing merger, Reaction on moving object, Circulation tests (4), Breathing tests (3), Heart rate variability – two tests (9)
2	Soldiers	Stress and fatigue during the 1st year of military service	24	
3	Servicemen	Stress and fatigue in real field battle conditions	65	
4	Rescue workers	Professional stress and fatigue	12	
5	Relatives of the losts	Stress – syndrome of "terrible bereavement"	67	
6	Patients	Fatigue during depression	18	
7	Patients	"Chronic fatigue" syndrome	27	
8	Patients	Stress in postabstinence syndrome	247	
9	Patients	Posttraumatic stress (heavy thermal burns)	207	

RESULTS

Experimental studies

It was demonstrated that after even one TES session (30-60 min, current 1.0-1.2 mA) substantially reduced the number of neurons activated after immobilization and marked by C-Fos staining. This effect was found in 9 cortex areas of 12 studied especially in deep cortex layers. The reduction of stress-related C-Fos expression was also observed subcortical structures: in 4 of 6 thalamic nuclei and in 6 of 10 hypothalamic nuclei.

One TES session had curative and preventive effects on gastric ulcers elicited by immobilization in cold environment stress. Numbers and severity of ulcers in treated animals were substantially lower in comparison with untreated ones. TES effects were naloxone reversible that support of its endorphinergic nature. Thus experimental data presented gave the basis for clinical application of TES antistress effect.

Human studies

All groups of volunteers and patients included are into Table 2. In the members of the groups 1-4 stress of different level was elicited by the conditions of professional activity including groups 3-4, which had some level of danger of death. Members of 5^{th} group had un-escapable stress as a relatives of lost in mass disaster. Members of group 6-7 have mainly high level of fatigue. In group 8 patients after treatment alcohol and heroin withdrawal were included. Patients of group 9 had posttraumatic stress disorders. In all cases it was demonstrated that fatigue, stress and other accompanied psycho-physiological disturbances were significantly improved or abolished after 2-5 TES sessions. The TES effects were more pronounced in cases of heavier disturbances.

DISCUSSION

It is well known that deficit of endorphins play important role in stress and affective disturbances of human psycho-physiological status. TES devices are effective for activation of the brain endorphinergic structures and its practical application is the effective homeostatic FES method for reduction of stress-related event and other psycho-physiological disturbances. Therefore, TES is an effective tool to greatly improve the quality of life.

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