# THE ROLE OF THE ENDOGENOUS OPIOID SYSTEM IN THE CONTROL OF HEART RATE VARIABILITY UNDER COGNITIVE LOADS OF VARIOUS LEVELS

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**The aim of the investigation** is to study the role of the endogenous opioid system (EOS) in the control of the heart rate under cognitive loads of different levels.

**Materials and Methods.** There has been given a brief historical background of the study of the role of endogenous opioid system (EOS) in regulation of body functions. A comparable analysis of the heart rate variability dynamics was carried out in drug-addicts with reduction of EOS receptor apparatus and healthy volunteers in the context of cognitive loads of different levels. 135 individuals were examined: 64 patients of the narcologic clinic with addiction to opiates composed an experimental group, and 71 healthy students were included into the control group. A measured cognitive load was formed using hardware-software complex Handtracking (Russia). Long-term continuous monitoring of heart rate was carried on by means of mobile telemetry.

**Results.** The psychophysiological markers of EOS activity during interactive communication with information images were determined on the basis of parameters of the heart rate variability and threshold characteristics of cognitive functions. It was established, that control and experimental samples were statistically significantly different by the frequency-domain indices of the heart rate variability in the stationary context of rest and in solving cognitive tasks ($p<0.05$), i.e. reduction of the mode of the autonomic regulation of heart rate and lack of adaptative alterations in the structure of the heart rate in case of changing the external information context, were characteristic of the examined drug-addicts. The most informative functional tests, the data of which make it possible to identify most effectively the condition of EOS and to develop noninvasive methods of diagnosing narcotization and addiction, were selected from the suggested contexts. Methods of collecting physiological data, minimizing the risks of cognitive context distortion, implying involvement of resources of the cognitive system in the process of measuring or interaction with an expert, were used for the first time.

**Key words:** endogenous opioid system; heart rate variability; cognitive functions.

**Background.** Endogenous opioid system (EOS), discovered 40 years ago [1–6], immediately draw the attention of the investigators owing to its evident antinociceptive properties [7–9]. Along with the revealing of the leading role of EOS in the formation of various clinical forms of depressing pain sensitivity (medicamental, acupunctural, electrostimulating, and others), there was found an essential contribution of this system in the development of the so-called stress-analgesia [10–13], occurring in response to some injury or its threat. There was also raised a question on the influence of EOS on the visceral systems, providing a physiological (but not information) component of the stress-reaction, and a significant role that the opioid peptides played in the regulation of cardiovascular, respiratory and other systems in the conditions of damaging actions was found out [14]. In the 80-s of the last century the first data were published on antishock effect of blockers of opiate receptors [15–26], received from the experiments on different kinds of animals (mice, rats, guinea pigs, rabbits, cats, dogs, and so on) using various experimental models of shock (hemorrhagic, electropain, endotoxic, exotoxic, occlusion, spinal, etc.). An application of opiate antagonists for antishock therapy was patented [27, 28], and became implemented in the reanimatologic clinical practice. However, the proper medical aspects of EOS problems pushed to the background investigations of tiny mechanisms of the

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effect of opioids on the regulation of visceral functions under extreme loads, including information ones.

Stress is a basic extreme condition. It may be the main component of the extreme condition, a forming factor, and a response on the extreme action [29]. It is known that H. Selye argued that the shock is an extreme degree of stress [29]. It is widely believed that the question about the mechanisms of extreme functional states have been studied in detail. But it is far from being true. For example, for many decades the basic physiologic mechanisms of stress (and a more extent of shock) have traditionally been reduced to the emergency activation of two neuroendocrine complexes: the sympathetic-adrenal-medullary system and hypothalamic-pituitary-adrenal system [30–33]. No doubts, that these two systems, providing various components of nonspecific activation of psychic, motor, metabolic and visceral functions, form mainly the first two stages of stress: anxiety and resistance. At the same time, the mechanisms of the third stage of stress — the stage of exhaustion — are studied superficially, which is, in many ways, connected with the "hypnosis" of the classic idea about it as a period of complete disintegration of regulatory and executive mechanisms [33–36]. In contrast to this misconception, the works of one of the authors of this article [37–39] prove convincingly that the stage of exhaustion is also a regulated process, similar to the first two stages of stress, only EOS becomes the basic neuroendocrine control system, providing minimization of the energy consumption and transfer of the organism to hypobiotic mode [37–39]. Besides, EOS is present at all three stages of the stress-reaction with different extent of dominance. These statements are supported by the results of numerous experiments on animals and calculations on the neuro-like mathematical model, though, no doubts, investigations using noninvasive methods of monitoring functional state of an individual in the condition of daily life, and primarily, under cognitive loads, are sure to be of great importance.

In recent decades a high informativity and reliability of noninvasive technique analysis of heart rate variability especially aimed at monitoring of the functional states of a man not only in laboratories, but in the daily life conditions as well, became quite evident [40–43]. Attempts are being made to use this method for the assessment of the level of emotional, cognitive loads, stress, and so on [44–50]. However, these attempts do not always give adequate results, which is linked not only with the well-known problems of noisiness and instationarity of the recorded signals [51], but with an underestimation of the EOS role in regulation of the heart rate. This problem has been deeply analyzed only in the clinical aspect. Thus, multiyear studies of the Tomsk cardiologic school [52–55] has demonstrated antiarrhythmic and suppressive action of opioid peptides on the heart activity; an experience of the foreign investigators reveals negative chrono-, dromo-, and ionotropic effects in stimulation of opiate receptors, and a reverse situation in case of introduction of naloxon — an opiate receptor antagonist [56–59]. It is quite evident, that the lack of systematic studies of EOS contribution to the rhythmogenic regulation of the heart activity becomes one of the main obsticle in the way of the search of dynamic markers of the cognitive loads of various levels. The work performed is designed to facilitate the elimination of this serious gap in the knowledge of the fundamental mechanisms of cognitive processes.

**The aim of the investigation** is to study the character of autonomic provision of cognitive loads associated with disorders of endogenous opioid system activity.

**Materials and Methods**. A complex of methods, directed to the study of the dynamic aspects of EOS activity in the functional system, providing cognitive, affective, and behavioral reactions in interaction with information images of the virtual computer medium, has been used in the investigation (Fig. 1). A comparative analysis of the vegetative regulation dynamics in the context of the controlled cognitive loads was carried out for two clusters: cluster 1 were people with a physical form of drug addiction, in which the opiate receptor matrix was reduced and functions of EOS were suppressed; cluster 2 included healthy persons with undamaged apparatus of the opiate receptors and an adequate EOS activity.

Methods of physiological data collection, minimizing the risks of cognitive context distortion, connected with the involvement of the cognitive system resources in the process of measurement or interaction with an expert, were applied. A long-term continuous monitoring of heart rate (heart rate variability) was realized using mobile telemetry technique [60–62]. The monitoring technology is based on wireless sensor networks, transmitting a signal from the compact low power-consuming sensor platform BioHarness (USA), which includes cardiosignal sensors, a receiver-transmitter, memory module and processor. The signal from the platform is transmitted

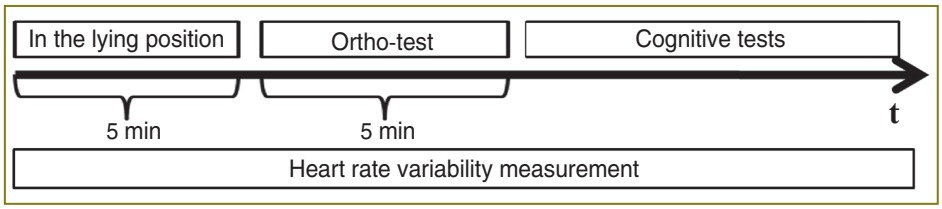


**Fig. 1.** The scheme of the experiment. Continuous measuring of the autonomic regulation dynamics in conventionally healthy individuals and post-abstinent drug users during successive change of behavioral contexts: at rest, under orthostatic load, and performing a series of cognitive tests

through Bluetooth to the smartphone. The smartphone transmits the signals via GPS to the distant Internet server. Hardware-software complex Handtracking (Russia) formed a measured cognitive load and measured threshold characteristics of the individual's cognitive load relative to the audio and visual stimuli in different dynamic contexts [63]. A set of 6 functional trials was implemented and readings of the reactions were recorded for the following contexts:

1. *Tests for sensomotor coordination*. Measured parameters: the time of sensorimotor reaction in response to the presented series of sound clicks with the interval between the stimuli from 300 ms to 5 s. The level of the load is specified by the value of the interval between stimulus and a number of stimuli in the set. In the given investigation the subjects being tested underwent 4–8 series of clicks in each experiment. In each series 10 stimuli were presented with a constant interval between stimulus, the duration of stimulus presentation was 23 μs. The experiment finished up in the series in which the subject under test made more than 3 mistakes. Omission of the stimuli, or an early reaction to the stimulus were considered to be a mistake.

2. *Stroop's test on cognitive conflict*. Measured parameters: time of reaction and a number of errors in different proportions of verbal and visual information.

The examenees underwent 4 series in the test: 1) the color of the letters in the word is black — it is necessary to choose an icon, the color of which matches the semantics of the word; 2) the color of the letters coincides with their semantics — it is necessary to select the icon of the pertaining color; 3) the color of the letters in the word and their semantics do not coincide — it is necessary to select the icon, the color of which matches the word semantics; 4) the color of the letters of the words and their semantics do not coincide — it is necessary to choose the icon, the color of which matches the color of the word letters. Each series contained 10 stimuli.

3. *Computer campimetry*. Measured parameters: a function of color differentiation reflecting the association between the shade of the color stimulus and a threshold of color differentiation within the color HLS model. Measurement of color differentiation thresholds was performed according to the H scale from 0 to 250 standard units with a step of 10 standard units.

4. *Computer laterometry*. Measured parameters: thresholds of lateralization of dichotic stimulus, direction of functional intrerhemisphere asymmetry, coefficient of interhemisphere asymmetry.

5. *Test "Clocks with a turn"*. Measured parameters: an error of reproducing the position of the clock hands relative to the task; dynamics of mistakes in repeated tasks in the cycles with a feedback, informing about the error magnitude. 10 tasks were presented to the tested subjects — from 0 to 12 hours, the initial deviation of the stimulus — amounted to 1 h 30 min, a stimulus length — 40 mm, width — 2 mm, the way of control — joystick.

6. *Test "Angle of the line slope"*. Measured parameters: errors of line orientation control relative to the pattern, error dynamics in the process of control, differential thresholds according to the angle of the line slope in the range of 0–180° with an increment of 22.5°. The level of the load is set by a coefficient of correlation between the manipulator displacement and the change in the angle of the line slope: the higher is the coefficient the more difficult it becomes to control the object. The people being tested were presented 9 stimulus patterns, the initial deviation of the controlled stimulus from the pattern stimulus was 15°, the time of the controlled stimulus holding — 5000 ms, stimulus length — 50 mm, stimulus thickness — 1 mm.

The heart rate with the labeling of the start and finish of each test was being continuously recorded in the course of the functional tests. Additionally, 5-minute record of the heart rate in the lying position was made, and a standard orthotest (a clinical model of the physical stress) was carried on for each participant of the study.

Fourier transform with a smoothing window was used to assess fast changes in the modes of the autonomic regulation, coordinated by the time scale with the dynamics of the information images, and new algorithms of heart rate variability data analysis, providing the study of microstructure of dynamics of R–R-intervals on the basis of isolated very high-frequency components of the heart rate variability (HRV) spectrum were developed. Previously poorly investigated [64] a very high frequency region of the spectrum (0.45–5.0 Hz), reflecting short-term regulatory effects on the heart rate has been analyzed during frequency-domain analysis of R–R-interval variability apart from the classic frequency bands (0.04–0.6 Hz). New methods of analyzing enable the researchers to obtain information about functional state from the records with 10 s duration, 30 times exceeding the time resolution relative to traditional methods, in which the analysis of the records lasting not less than 300 s is considered correct.

Statistical analysis was performed using the following methods: cluster analysis (clasterization by K-means method), analysis of variance (multidimensional method of repeated measures analysis of variance), correlation analysis. The results were statistically processed using Microsoft Excel and Statistica 6.0 programs.

Thus, owing to the comparative analysis of the context-depended HRV and threshold characteristics of the human cognitive system between the samples of healthy and drug-addictive subjects, we got an opportunity to reveal autonomic and cognitive correlates of the physical EOS activity in the context of the measured cognitive loads.

The sample comprised: an experimental group (n=64) consisting of the opiate-addicted patients of the narcologic clinic (in the post-withdrawal period), and a control group (n=71) including students-psychologists of the Faculty of Social Sciences of Lobachevsky State

University of Nizhni Novgorod. Informed written consent was obtained from all subjects for participation in the study.

**Results.** Autonomic regulation of the heart rate in drug-addicts was characterized by a significant reduction of all basic HRV parameters relative to the control group: a total power of HRV spectrum in the experimental group was almost 5 times lower; powers in the range of low frequencies (0.04–0.15 Hz) — 4 times lower, and in the range of high frequencies (0.15–0.6 Hz) — 10 times

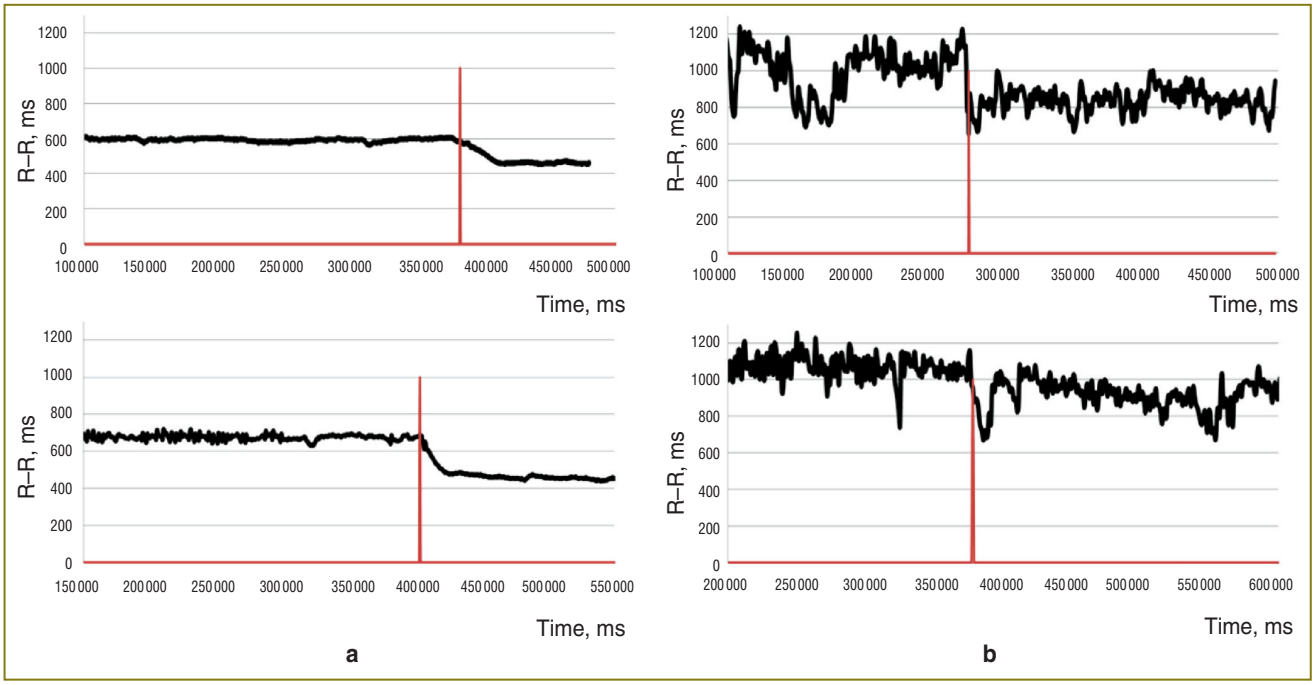


**Fig. 2.** Reduction of autonomic regulation of heart rate in drug-addicts. Dynamics of RR-intervals for the tested drug-addicts (*a*) and healthy people (*b*); the beginning of orthostatic test is shown by a red marker

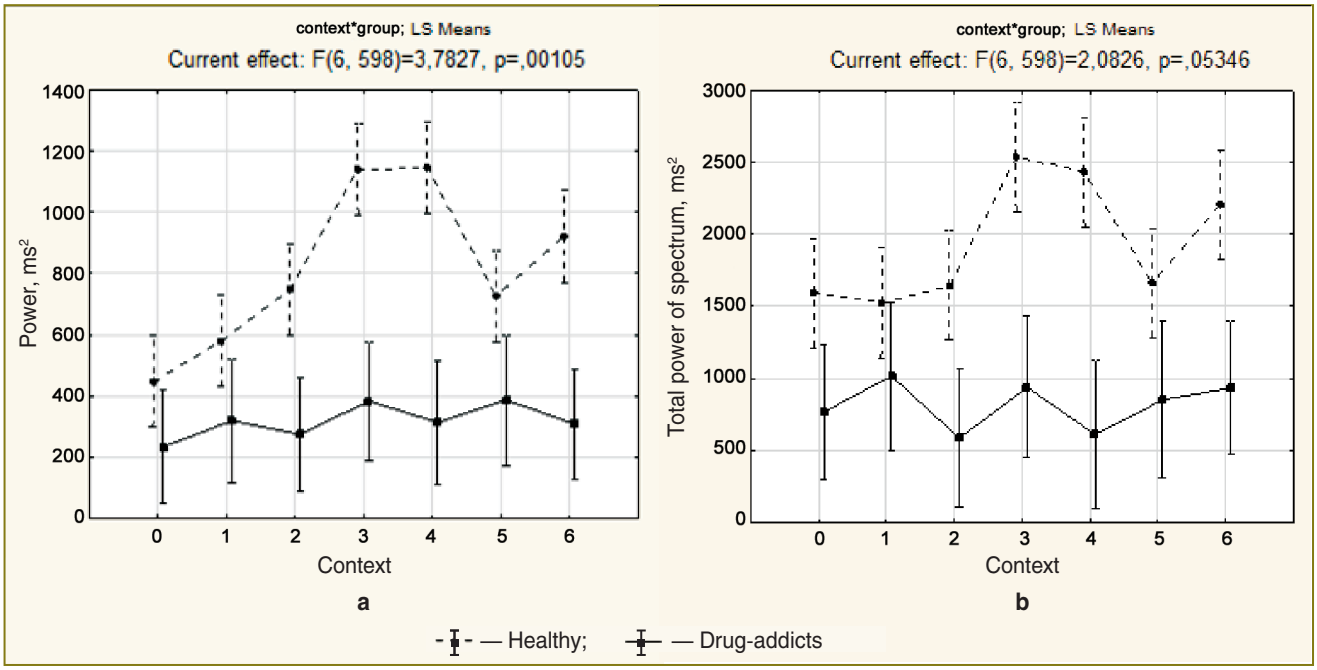


**Fig. 3.** Dynamics of heart rate variability parameters (*a* — LF, ms²; *b* — TP, ms²) in 6 trials: *0* — lying down; *1* — computer laterometry; *2* — computer campimetry; *3* — Stroop's test; *4* — "Clock" test; *5* — test "Control of the line slope angle"; *6* — measurement of the sensorimotor reaction time. The difference of parameter variance in the contexts according to F-criterion in the group of healthy students is significant (p=0.02), in the group of drug-addicts the difference is insignificant (p=0.08), the differences of parameters between the groups are significant (p<0.01, t-test)

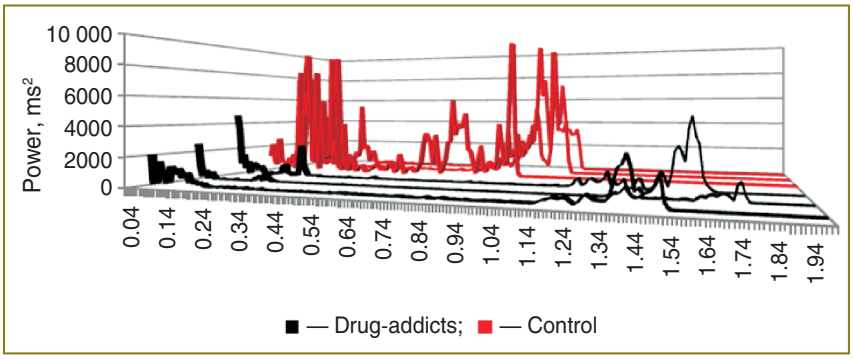


**Fig. 4.** Examples of heart rate variability spectra of the tested individuals from the control group and the group of drug-addicts

Table 1

**Mean values and standard errors in mean of the very high-frequency HRV spectrum region in groups of healthy controls and drug-addicts**

| Group | Spectrum parameters | | | |
|---|---|---|---|---|
| | Mode of the peak frequency | Peak frequency | Minimum frequency | Maximum frequency |
| Drug-addicts | 1320.33±1796.09 | 1.51±0.11 | 1.41±0.11 | 1.58±0.10 |
| Healthy | 8067.17±4772.20 | 0.85±0.12 | 0.76±0.13 | 0.93±0.12 |

lower, which reflected the reduction of activity of sympathetic and parasympathetic parts of the autonomic nervous system, respectively. Besides, index of the autonomic balance, which shows the excess of the power of sympathetic regulation of heart rateover the power of the parasympathetic one, was essentially higher in the drug-users ($p<0.05$, t-test ). Dynamics of R–R-intervals in the experimental group differed considerably from the control one — high values of heart rate and essential reduction of HRV were observed.

Notably, that in 90% of the patients heart rate disturbances in the form of tachycardia, arrhythmia, extrasystole were recorded (Fig. 2).

In the HRV dynamics during functional trials a high degree of plasticity of the readings was revealed in healthy examinees in the course of information context change. The analysis of variance (linear models with repeated measurements) showed statistically significant differences of variance ($p<0.05$) of HRV parameters in the context of various trials (Fig. 3).

Examples of spectra of RR-intervals for the tested subjects of both groups are presented on Fig. 4. It is seen, that, firstly, the peak frequency in the very high frequency range of HRV (0.45–5.0 Hz) for the drug-addicts is higher than for the control group. Secondly, the power of very high frequency component of the spectrum is considerably lower in the group of drug-users.

Visually observed differences were confirmed by the statistical comparison of the sample parameters of the very high frequency band of HRV spectrum ($p<0.05$, Student criterion). Using the parameter values from this range, i.e. calculating the power of the peak (maximum) frequency, peak frequency, minimum frequency, maximum frequency, we performed cluster analysis by K-means method, resulted in distinguishing two clusters significantly different by these parameters. The first cluster contains 100% of the tested persons from the sample of the control group, the second one — 84% of the tested people from the group of drug-addicts. Thus, the authors succeeded in distinguishing the borders of the parameters of the very high-frequency HRV spectrum region, specific for both of the samples (Table 1).

**Discussion**. Drug-addicts compared with the control group have a reduced activity of the central and autonomic contours of heart rate regulation with a dominant activity of the sympathetic part of the autonomic nervous system. This effect agrees with the previously obtained investigation data [65, 66], in which introduction of naloxon — opiate receptor blocker — was used as an experimental model of EOS activity reduction. Introduction of naloxon leads to the increase of heart rate and decrease of HRV. On the other hand, EOS activity intensified with the help of acupuncture or transcranial stimulation methods improves the balance of processes of autonomic regulation of heart rate [67].

A novel and important aspect of the findings of the study performed became the demonstration of the absence of the adaptive alterations of the heart rate in the drug users in switching the tasks in the context of cognitive loads. In the drug-addict sample the changes of the autonomic regulation mode are minimal, that show the decrease of the degrees of freedom, when implementing of functional system, which is aimed at the achievement of the useful adaptation result in the specific tasks.

Mechanisms of opioid peptide participation in the heart rate control may be the basis of possible explanations of the effects described (Table 2). The data of this Table are based on the investigations of Yu.B. Lishmanov et al., who showed, that endogenous opioid peptides, being agonists of the central and peripheral opiate receptors, play a key role in the implemention of the adaptation processes [52–55, 68].

As a result of actualization of such an aspect of drug-addict condition, physicians of narcologic clinics may be recommended to refer these patients to cardiologic examination, and to apply in the practice of narcologic rehabilitation, in addition to psychoactive medications, cardiotropic preparations, e.g. beta-adrenoblockers, which relieve the effects of sympathoadrenal hyperactivation.

Table 2

**Mechanisms of opioid peptide participation in the formation of heart adaptation [52–55, 68]**

| Participation of the opioid peptides in cardiac rhythm control | |
|---|---|
| Via central opiate receptors | Via peripheral opiate receptors |
| Decrease of stress-hormone level (adrenaline, noradrenaline, ACTH) | |
| Change of the tonus of the sympathetic and parasympathetic links of ANS | Decrease of cAMP/cGMP ratio in myocardium |
| | Activation of myocardium protein synthesis |

Here: ACTH — adrenocorticotropic hormone; ANS — autonomic nervous system; cAMP — cyclic adenosinemonophosphate; cGMP — cyclic guanosinemonophosphate.

The revealed parameters of very high frequency region of HRV spectrum (0.45–5.0 Hz), being informative for differentiation of drug-addict patients and healthy examinees, may be used in future for non-invasive diagnosis of drug addiction.

It is necessary to underline, that a coordinated analysis of the parameters of autonomic regulation of heart rate and the parameters of efficacy of cognitive processes in drug users is of crucial importance for determining the EOS role in realization of cognitive functions.

**Conclusion.** Suppression of the regulatory function of the endogenous opioid system reduces the adaptability of autonomic regulation of heart rate. In drug-addicts there is no changes of the autonomic regulation mode in case of target task switching in the context of cognitive loads of different levels. Two possible mechanisms are likely to explain this effect. Firstly, one of the basic neurochemical brain systems — endogenous opioid system — is excluded from the structure of the neuro-humoral regulation of the heart rate. Accordingly, the system of heart rate control is reduced. Secondly, the disturbance of the endogenous opioid system results in the elimination of inhibitory (limiting) mechanisms, making effects of sympathoadrenal hyperactivated. Thus, suppression of the endogenous opioid system leads to disorders of adaptation processes under cognitive loads.

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