A Neurochemical Framework to Stress and the Role of the Endogenous Opioid System in the Control of Heart Rate Variability for Cognitive Load

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Abstract— **This paper presents a complex analysis of the stress and shock phenomena. These specific reactions represent non-specific, protective, stepwise, multi-systemic, reduced psychophysiological responses to injury or threat. Finding psycho-physiological, neurochemical and patho-physiological mechanisms of stress and shock is an important task nowadays. It is relevant not only from the theoretical, but also from practical point of view, as every day thousands of people die from shock. At the beginning of 1980s, it has been suggested to look at stress and shock as processes based on similar mechanisms of hyperactivation of three neuro-endocrine systems: sympatho-adrenal system, hypothalamic-pituitary-adrenal axis and endogenous opioid system. The mechanisms of stress and shock are related to a significant reduction of regulatory mechanisms. On the basis of these theoretical concepts, we created an explicit psycho-physiological model of stress that describes in mathematical form, how neuro-endocrine input modulates cardiac responses during the first phase of stress reaction. Here, we give a comparative analysis of the heart-rate variability dynamics. This analysis was carried out for drug-addicts with reduction of endogenous opioid receptor apparatus, and for healthy volunteers in the context of cognitive loads of different levels. It is shown that such specific reactions as the reduction of the hart-rate autonomic regulation mode and the lack of adaptive variations in the heart-rate structure as response to the changing external information context, are typical for the examined drug-addicts.**

Keywords – stress; endogenous opioid system; heart rate variability; cognitive functions

I. INTRODUCTION

Stress (or general adaptive syndrome) is a nonspecific reaction to injury, according to the theory of H. Selye [1][2]. This theory was globally recognized over the past decades. However, many of its key points become questioned at the XXI century. E.g., the use of the term “adaptation” has led to confusion that any impact is stressor. Lack of attention to the results of researching the functions of the endogenous opioid system (EOS) has led to stagnation of studies of neurochemical stress mechanisms. Our methods include psycho-physiological, — Electro-encephalography (EEG), Event-Related Telemetry (ERT), Hart-Rate Variabitily (HRV), respirography, measurement of hemodynamic etc., — biochemical, radioimmunoassay, psychophysical (computer laterometry and campimetry), psychological, and mathematical approach. A total of 1850 animals (7 species) and 800 subjects participated in the studies.

Note that stress represents a simplified (reduced) reaction to an emergency, which provides decreasing individual deviations of psychological, physiological, biochemical, and other indicators from the normal value. This is the result of depleting the regulatory mechanisms: three neuroendocrine stress-protective systems have exclusive dominance. This standardization provides nonspecific protection that is optimal only in emergency situations [7].

It should be emphasized that the stress phenomenon itself appears to be wide-spread and rather normal for modern life. However, this actually represents a danger due to the possibility of stress-to-shock transition. Shock represents a special case of stress thus, they have similar physiological mechanisms [2][4]. However, the shock (in contrary to the stress) *always* leads to devastating and life-threatening consequences.

Stress is a basic extreme process. It may be the main component of the extreme condition, a forming factor, and a response to the extreme action. It is known that H. Selye had argued that the shock is an extreme degree of stress. It is widely believed, that the question about the mechanisms of extreme functional states has been studied in detail. But it is far from being true. E.g., for many decades, the basic physiologic mechanisms of stress (and particularly, shock) have traditionally been reduced to the emergency activation of two neuroendocrine complexes: the sympathetic-adrenal-medullary system (SAS) and hypothalamic-pituitary-adrenal (HPAS) system. No doubt, these two systems, providing various nonspecific patterns 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 — were studied superficially. This is to a big extent connected with the “hypnosis” of the classic idea to treat it as a period of complete disintegration of regulatory and executive mechanisms. In contrast to this misconception, it has been proven convincingly that the stage of exhaustion is also a regulated process similar to the first two stages of stress [7]. The only difference is that EOS becomes the basic

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neuroendocrine control system providing minimization of the energy consumption and transfer of the organism to hypobiotic mode. Besides, EOS does work in all three stress stages with different extent of dominance. These statements were supported by the results of numerous experiments on animals, as well as by calculations within the neuron-like mathematical model. However, the researches by means of noninvasive methods of monitoring functional state of an individual in the condition of daily life (and primarily, under cognitive loads), are undoubtedly very important.

The paper is organized as follows. In Section II, the problem of strict formalization of the stress process is discussed. In Section III, we present the neuron-inspired model of stress-protective systems. In Section IV, we present a complex of methods, directed to the study of the dynamic aspects of EOS activity in the functional system. In Section V, the psycho-physiological markers of EOS activity during interactive communication with information images are determined. Further working perspectives are discussed in Section VI.

II. FORMALIZATION OF THE STRESS PHENOMENON

In spite of various studies of the problem, some very important points concerning the definition and marker of the stress process should be clarified.

A. *Definition of Stress*

Classic postulates (H.Selye) read: «Stress (general adaptation syndrome) is a non-specific response of the body to the physical or psychological effects of violating its homeostasis»; «Stress is a reaction based on the interaction of two regulatory stress reactive systems: SAS and HPAS»; «Stress is adaptive response»; «Stress response has three stages: alarm, resistance, and exhaustion stages» [1][2].

Our postulates are somewhat different: «Stress is a nonspecific phase systemic protective reduced psycho-physiological reaction to injury or threat»; «Stress is a systemic reaction based on the dynamical interplay of three regulatory neuroendocrine systems: SAS, HPAS, and, most important, EOS»; «Stress is not an adaptive, but protective response»; «Stress is a phasic response. Stages of stress are associated with considerable dominance of one of the stress-protection systems: alarm stage – SAS domination, resistance stage – HPAS domination, exhaustion stage – EOS domination» [6]-[8].

B. *Markers of Stress*

Classic postulate (H.Selye) reads: the endocrine markers of stress correspond to increased levels of cortisol, epinephrine, norepinephrine, Adrenocorticotropic Hormone (ACTH), Corticotropin Releasing Hormone (CRH), etc.

Our postulate reads: the endocrine markers of stress are increased levels of enkephalins, endorphins, dynorphins, etc.

Neurophysiological marker is simultaneous increase of the autonomic balance index and fall in the total power spectrum of HRV [4][6][7].

Below, the results of the measurement of cardiovascular reactivity and cognitive functions of the opiate-dependent patients are presented.

III. THE THREE-COMPONENT MODEL

The algorithm is based on the hypothesis of dynamic interaction between SAS, HPAS and EOS (Fig. 1) and realized via the neuron-likely network equations.

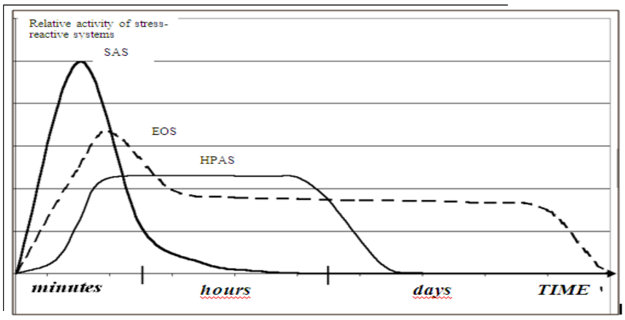


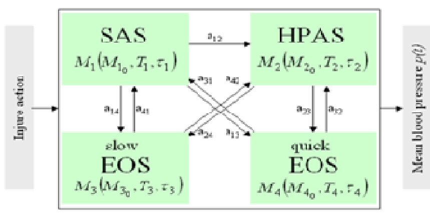
Figure 1. The qualitative characteristics of dynamics of the stress-protection systems (extracted from [6][7], short version).

In order to describe the neurochemical processes during the stress process, we use the model based on the neuron-likely network equations, which consists of four elements, representing SAS, HPAS and two components of EOS (quick and the slow ones), see Fig. 2. Model (1) has been realized as a discrete algorithm in the MATLAB environment; here:

M1 – SAS activity;
M2 – HPAS activity;
M3 – EOS slow component activity;
M4 – EOS quick component activity;
i – typical Mi activity period;
aji – the parameter indicating the influence of Mj on Mi;
Ti – the parameter of Mi self-excitation.

The activity of each Mi system is controlled by interaction with other three systems, and by the self-excitation. The values outside the interval are truncated to its ends.

The influence parameters aji and the typical periods i were chosen according to neurobiological data. In accordance with the activity attenuation and systems` depletion, the Ti parameters change with time.



$$\tau_i \frac{\partial M_i}{\partial t} = -M_i + F\left[\sum_j a_{ji} M_j + T_i\right] \quad (1)$$

$$p(t) = p_0 + \sum_j \alpha p_j \int_{t-\Delta t}^{t} \left(1 - \frac{(t-t')}{\Delta t}\right) M_j(t')dt' \quad (2)$$

a	M_1	M_2	M_3	M_4
M_1	0	0.4	0.2	0.9
M_2	0	0	0.5	0.6
M_3	-0.74	-0.965	0	0
M_4	-0.4	-0.45	0	0

Figure 2. The algorithm of functional system of stress.

The dynamics of R-R intervals in the stress process has been chosen as a test parameter for the model functioning. It is an integral characteristic of the functional state depending on the activity of the stress-protective systems. This parameter is used for indicating the severity of stress in experiments and clinical practice. The model calculations are in a good agreement with experimentally measured changes in R-R intervals during acute stress in healthy adults (Fig. 3).

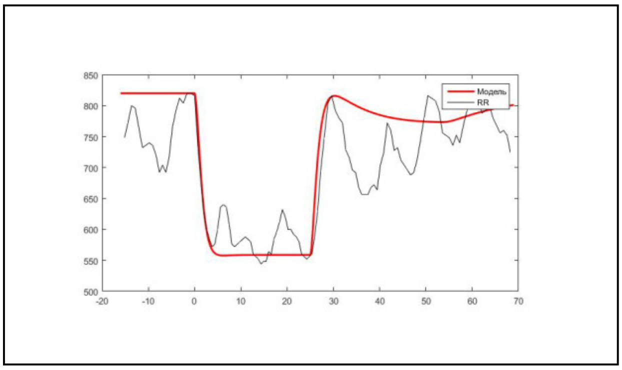


Figure 3. Examples of comparison of model calculation results (red line) with the experimental data during electrically induced pain stress.

These results were obtained within the neuron-based model suggested. It has been tested and proved to give stable results, which reproduce the interaction dynamics of neurochemical stress-protective systems, RR changes in stress and shock, and the elements of pharmacological correction of this integral body state. We hope that the suggested model can serve as a useful tool for further research of the neurobiological mechanisms of stress and shock at the system and cell level, and for finding the best methods for the extreme-states treatment.

IV. The Methods

Our information technology ERT provides long continuous collection, transmission, storage and preprocessing the time-synchronized recordings of heart-rate data and psycho-physiological test results [9][10] (Fig. 4). The optimum size and power consumption of the sensors of physiological signals, microprocessors and devices for radio signal reception and transmission were chosen. Data are transmitted to the Smartphone or personal computer via Bluetooth. Then, the data in processed form are transmitted via Global System for Mobile Communications (GSM) channels to a dedicated server system (StressMonitor WEB application) on the Internet. There, the preprocessing and spectral analysis of rhythmograms is performed in pseudo-time, allowing us to determine the initial point of the stress process with an accuracy of up to a few seconds. The result has the form of the spectrogram, which provides the possibility to determine automatically the place, time, and events associated with stress for a particular person in his everyday activity. Thus, the HRV spectral analysis corresponds to:

Total Power (0,015-0,6 Hz);

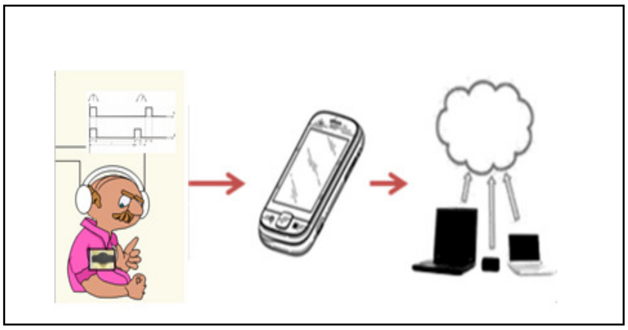


Figure 4. Mobile heart-rate telemetry system: WEB-application Stress Monitor.ru.

Low Frequency band (0,04-0,15 Hz) (LF);

High Frequency band (0,15-0,6 Hz) (HF); LF/HF ;

Very High Frequency band (0,6-2 Hz) [11]-[14].

For the purpose of the cognitive function study, a WEB-platform Apway.ru has been developed. It provides the universal framework for design and testing. Besides, a similar system has been constructed, with a computer being the source of the signal and current registrar (Fig. 5). The distortions and errors introduced by human into the managed attribute information on the image represent a characteristic of the cognitive system. The system includes a module for the stimulus formation in a wide range of amplitude-time values, a virtual measurement mode control panel, a module for registration of operator motor responses, a database, and a module for report generation in the form of tables and graphs. The efficiency of cognitive functions was estimated by the absolute and differential thresholds, and the sensorimotor coordination errors. We used the following computer tests: the computer laterometry, the computer campimetry, the Stroop task, the test “Clock face”, the simple sensorimotor activity.

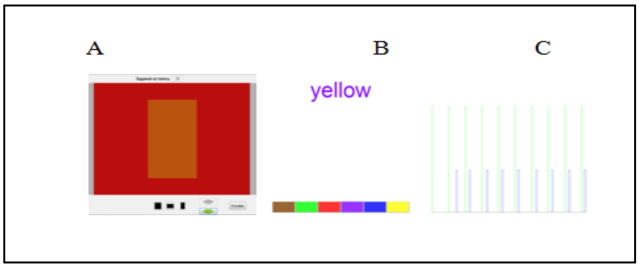


Figure 5. Cognitive simulator: WEB-platform Apway.ru: A - Color discrimination thresholds in shade (computer campimetry); B - Level of cognitive conflict (Stroop test); C - Tests for sensorimotor activity.

V. The Results

Two groups of subjects participated in the study: 54 opiate-dependent patients during opiate withdrawal (26 men and 28 women, with a mean age of 22.5 (±1.2)) and 25 healthy control participants (12 men and 13 women, with a mean age of 21.5 (±1.3)). An independent samples t-test revealed significant difference in frequency-domain indices of HRV ($p<.03$). The opiate dependent patients exhibited

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reduced LF, HF, TP (LFm=233.95; HFm=203.77; TPm=765.88) and increased LF/HF ratio (LF/HFm=1.87) in comparison with healthy control participants (LFm=447.37; HFm=700.94; TPm=1592.34; LF/HFm=0.98) in rest context. ANOVA (General Linear Models) revealed significant difference in frequency-domain indices of HRV between contexts different cognitive loads for healthy control participants ($F=15.48$, $p<.05$) but no this difference for opiate- dependent patients ($F=1$, $p>.05$) (Fig. 6).

The opiate-dependent patients respond to incentives with frequency 5 Hz without errors in tests for sensorimotor coordination. The healthy control participants respond without errors only to incentives with frequency no more 2.5 Hz.

However, the opiate-dependent patients demonstrated increased delay of motor component of reactions ($p<0.01$). The subjects could make an unlimited number of attempts during setting a predetermined time in the test “Clock face”. They turned to the next task, when the error of the set time seemed satisfactory to them. Most opiate-dependent patients were satisfied by the error of the set time from 0 to 2 (74%). Most healthy control participants were satisfied with the error of the set time from 2 to 4 (76%).

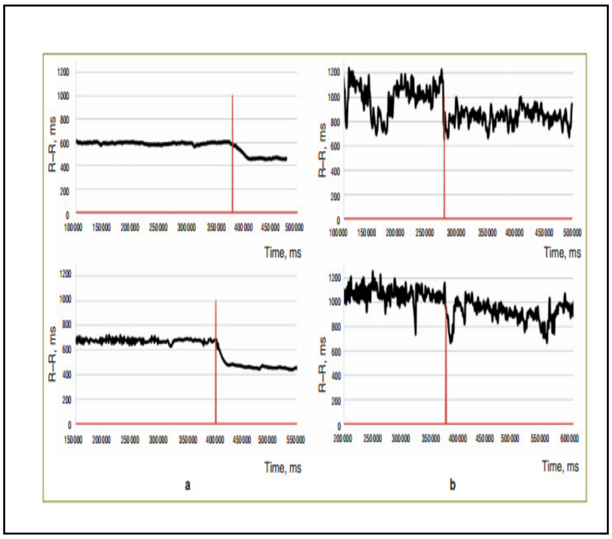

Figure 6. Reduction of autonomic regulation of heart rate in drug-addicts. Dynamics of RR-intervals for the tested drug-addicts (a) and healthy people (b); the beginning of orthostatic test is shown by a red marker.

The opiate-dependent patients are people with disorders of EOS. It is quite natural that the results of our study show cognitive and cardiovascular changes, which are associated with reduced activity of EOS.

VI. Conclusions

Summarizing all presented arguments, we can infer that:

- Stress is an integrative psycho-physiological response to injury or threat of injury. Its psychological component is assessment of the threat power and formation of protective strategies;
- Its physiological component provides the energy supply for cognitive and motor functions by enhancing the effect of regulatory systems SAS, HPAS, and EOS [3]-[5];
- Stress is a nonspecific reaction. It develops regardless of the type of stress factor and has the typical autonomic markers (e.g., the simultaneous increase in the autonomic balance index and decrease in the total power spectrum of HRV). This differs from a variety of specific regulation mechanisms for adequate load;
- Stress is not an adaptive response, but a protective reaction, in analogy with inflammation [6]. It is based not only on functional, but also on structural changes (e.g., the "Selye triad");
- Stress is a systemic response. It is based on the dynamic interaction of three stress-protection systems: SAS, HPAS, and (it is especially important) EOS;
- Stress is a three-step process. The stages of stress are associated with the dominance of one of the stress-protection systems: the alarm corresponds to the dominance of SAS, the resistance – HPAS, the exhaustion – EOS;

We believe that the proposed refinements (corrections) of the stress conception could provide rather clear understanding of the phenomenon and draw attention to the systemic aspects of the problem.

The proposed technology ERT has already proven its efficiency in a variety of natural, clinical and experimental contexts, — namely, in the study of the EOS role in control of HRV, in mapping stressful road infrastructure in metropolitan areas, in the study of spatial dynamics of stress in bus and private car drivers; in the study of autonomic regulation of patients with chronic headache; in the monitoring the stress of translators in course of simultaneous translating, etc.

We have shown that the disorders of EOS could result in:

- Increased operation speed in the case of simple sensorimotor reactions;
- Increased requirements to control accuracy;
- Decreased efficiency of central cardiac-rhythm-control system.

We can infer that the lack of adaptability of autonomic regulation during cognitive tasks is a specific feature of opiate-dependent patients. Thereby, EOS activity is represented in VHF component of HRV.

However, there are still the problems for further researches. In particular, it would be interesting to compare the results of our model with the stress\shock model presented by Chernavskaya [14].

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