PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Induction of Adaptation to Stress in Rats by Repeated Transcranial Electrostimulation

F. Z. Meerson, M. G. Pshennikova, B. A. Kuznetsova, A. D. Dmitriev, S. A. Radzievskii, E. Ya. Vorontsova, and M. V. Shimkovich

UDC 615.84.015.4:612.014.49].03.07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 117, № 1, pp. 16-18, January, 1994
Original article submitted June 7, 1993

A single transcranial electrostimulation of rats results, as does acute stress, in a fourfold elevation of plasma corticosterone, whereas after a course of several electrostimulations plasma corticosterone is not elevated and a threefold rise in plasma β-endorphin is recorded. Rats that undergoing a course of transcranial electrostimulations and then subjected to an immobilization stress do not show any rise in plasma corticosterone.

Key Words: *stress; transcranial electrostimulation; corticosterone; β-endorphin*

The adaptation developing in response to repeated moderate immobilization or emotional/pain stressors not only protects the body from severe stress but can also produce strongly marked protective cross-effects, raising the organism's resistance to hypoxia [5], to myocardial ischemia, repeated perfusions of the heart, and cardiac arrhythmia [7,12], and to the injurious effects of chemical agents [15], cold [11], and even radiation [1]. In order to put into better perspective the possible clinical uses of the protective cross-effects from such adaptation, we deemed it necessary to replace, in animal experiments, strong immobilization or emotional/pain stressors with milder ones that would not cause the animals to suffer pain or exhibit a defensive reaction. For this purpose we chose to apply transcranial electrostimulation (ES), which is used in physical therapy, and found that a course of ES sessions does indeed produce a cardioprotective effect against stress [9], myocardial ischemia, and reperfusion of the heart [8] as well as an antihypoxic effect at the organismic level [6]. Until recently, however, it remained unclear whether a course of multiple ES exerts protective effects by eliciting adaptation of the animals to the repeated "ministresses" or by some other mechanism.

The purpose of this study was to determine blood concentrations of a major stressor hormone, corticosterone, and the activity of the stress-limiting opioidergic system in rats after a course of transcranial ES.

MATERIALS AND METHODS

Male Wistar rats weighing 250±20 g were used. In these rats, plasma concentrations of corticosterone and β-endorphin after single or multiple transcranial ES were determined, as were the impact of an acute immobilization stress on their concentrations in rats that had undergone a single or multiple ES sessions. There were five groups of rats: intact controls (group 1); rats exposed to one ES session (group 2); those exposed to a course of multiple ES (group 3); those exposed to an immobilization stress lasting 1 h (group 4); and

Institute of General Pathology and Pathological Physiology, Russian Academy of Medical Sciences, Moscow

0007-4888/94/0001-0012$12.50

those exposed to this stress after a course of ES (group 5).

For ES, standard needles for facial acupuncture were used. The needles, connected to a Lasper CS-504 electrostimulator (Japan) designed for electroacupuncture in humans, were introduced into a particular site on the auricular concha of each ear. A course of ES consisted of 10 sessions lasting 10 min each on the first day and 20 min per day in the following nine days. ES was carried out with solitary sawtooth pulses of 1.5-2 mA and 1.5 msec in duration at a rate of 200 cpm. Such ES has been shown to impart a particular frequency to respiratory movements and, when repeated a number of times, to have beneficial effects on the oxygen-transporting systems of the body similar to those resulting from adaptation to periodic hypoxia [6]. The acute immobilization stress was produced by fixing the animals in the supine position for 1 h. The rats of all groups were decapitated as soon as the exposure to ES or stress was discontinued.

Rats that had undergone an ES course were stressed immediately after the last (10th) ES. Blood samples, collected into test tubes placed in ice and containing 50 μl EDTA, were centrifuged at 1500 g for 30 min; 1 ml of the plasma was then pipetted into each of two test tubes and kept frozen at -20°C. The plasma from one of the test tubes was used to measure corticosterone and that from the other, to measure β-endorphin. Corticosterone was determined by fluorimetry [16] and β-endorphin by radioimmunoassay [2].

The results obtained with these methods were evaluated on the premise that plasma corticosterone should rise 5- to 10-fold in response to a single exposure to stress and not at all after multiple exposures to the same stress because of the ensuing adaptation [4,10]. During the adaptation, stress-limiting systems of the body, including the opioidergic system, are usually activated, and this is accompanied by elevations in the blood and tissue levels of β-endorphin [3,7]. Accordingly, the rise in corticosterone observed after a single ES session was taken as the criterion of stress and no rise in this steroid together with activation of the β-endorphin system after multiple ES sessions, as the criterion of adaptation to the stress.

RESULTS

The results are summarized in Table 1. It can be seen that the rats exposed to only one ES session had plasma corticosterone concentrations approximately 4 times as high as the control rats (86.2± ±28.9 μg/100 ml vs. 24.8±4.2 μg/100 ml) and similar to those found in rats stressed by immobilization (103.1±50.1 μg/100 ml). Rats exposed to multiple ES showed increasingly lower corticosterone concentrations so that after the last (10th) session the concentrations were even below the control values (Table 1).

TABLE 1. Effect of Electrostimulation (ES) on Plasma Levels of Corticosterone and β-Endorphin

Group	Corticosterone, μg/100 ml	β-Endorphin, pmol/liter
Control ($n=5$)	24.8±4.2	178.42±19.2
Single ES ($n=7$)	86.2±28.9**	206.19±13.96
Multiple ES ($n=6$)	17.3±4.0	474.50±32.95**
Stress ($n=5$)	103.1±15.3**	308.33±18.72**
Multiple ES + stress ($n=6$)	20.6±1.9***	250.30±36.28*

Note. Asterisks indicate significant differences: *from control at $p<0.05$, **from control at $p<0.001$, ***from the stressed group at $p<0.01$.

These results indicate that ES causes corticosterone to be released into the bloodstream, which is a characteristic feature of stress reactions. Repeated ES led to the development of adaptation to the stressor, involving a progressive decrease in the stress reaction and a return to normal of blood corticosterone. This is confirmed by the results shown in the table: the immobilization-stressed rats that had undergone a course of ES, unlike those that had not, experienced no rise in this hormone. The exposure to multiple ES thus inhibited the stress reactions regardless of whether the stressor was the immobilization or the ES itself.

This phenomenon can be explained by data on blood concentrations of β-endorphin - one of the more potent transmitters of the opioidergic system. As shown in the table, the β-endorphin concentrations rose only slightly after one ES session but almost trebled after 10 sessions. The extinction of the stress reaction was thus accompanied by elevations in plasma β-endorphin as ES sessions were repeated. These findings agree with those of our previous study where activation of the opioidergic system, including a rise of β-endorphin in the hypothalamus, occurred in the course of adaptation to stress [3]. Taken together, our results indicate that ES is a stressor that induces stress adaptation when exposure to it is repeated a number of times.

In general, the currently available evidence suggests that the protection afforded by adaptation to stressors and in particular to repeated ESs may result from the operation of two basic mechanisms: activation of the body systems that limit the stress reaction, thereby preventing its various damaging effects [7,12]; and accumulation in the target or-

gans of stress proteins that possess dispersive properties and can thus prevent protein denaturation and the associated damage to cellular structures responsible for the so-called "adaptive stabilization of structures" [12,14]. This latter phenomenon, in turn, underlies numerous protective effects of stress adaptation [5,13].

REFERENCES

1. P. D. Gorizontov, O. I. Belousova, and M. I. Fedotova, *Stress and the Blood System* [in Russian], Moscow (1983).
2. A. D. Dmitriev, Yu. I. Golikova, and A. T. Kobylyanskii, *Neirokhimiya*, № 1, 66-68 (1982).
3. F. Z. Meerson, A. D. Dmitriev, *et al.*, *Vopr. Med. Khimii*, № 5, 32-34 (1985).
4. F. Z. Meerson, V. V. Malyshev, E. N. Ekimov, *et al.*, *Vopr. Med. Khimii*, № 1, 76-80 (1986).
5. F. Z. Meerson, T. D. Minyailenko, and V. P. Pozharov, *Byull. Eksp. Biol. Med.*, **115**, № 2, 132-135 (1993).
6. F. Z. Meerson, V. P. Pozharov, T. D. Minyailenko, *et al.*, *Ibid.*, № 4, 339-343 (1993).
7. F. Z. Meerson and M. G. Pshennikova, *Adaptation to Stressful Situations and Physical Loads* [in Russian], Moscow (1988).
8. F. Z. Meerson, S. A. Radzievskii, V. I. Vovk, *et al.*, *Kardiologiya*, № 10, 72-77 (1991).
9. S. A. Radzievskii, E. Ya. Vorotsova, and L. M. Chuvil'skaya, *Byull. Eksp. Biol. Med.*, **103**, № 8, 151-153 (1987).
10. K. Keim and E. Sigg, *Pharmacol. Biochem. Behav.*, **4**, № 3, 289-297 (1976).
11. A. Kurosyima, G. Habara, and A. Vehara, *Pflugers Arch.*, **402**, 402-408 (1984).
12. F. Z. Meerson, *Adaptive Protection of the Heart: Protecting against Stress and Ischemic Damage*, CRC Press, Boca Raton (1991).
13. F. Z. Meerson, *Protective Cross-Effect of Long-Term Adaptation*, in: *The III World Congress of the International Society for Adaptive Medicine, Tokyo, Japan, April 26-28* (1993), p. 55.
14. F. Z. Meerson, I. Yu. Malyshev, and A. V. Zamotrinskii, *Canad. J. Cardiol.*, **8**, № 9, 965-974 (1992).
15. J. Wallace and M. Cohen, *Amer. J. Physiol.*, **247**, G127-G132 (1984).
16. N. Zenker and D. E. Bernstein, *J. Biol. Chem.*, **231**, № 4, 695-701 (1958).

Effects of an Organophosphorus Compound on Pulmonary and Systemic Circulations

N. V. Sanotskaya, Ya. K. Kurambaev, D. D. Matsievskii, A. A. Khusinov, and V. A. Safonov

UDC 616.24-005+616.1-008.1]-02:546.18]-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 117, № 1, pp. 18-21, January, 1994
Original article submitted July 14, 1993

Shortly (30-90 min) after an intragastric administration of the organophosphorus pesticide Anthio to cats, their cardiac output begins to decrease and the right ventricular output decreased to a greater extent than the left. Blood is redistributed to the greater circulation with a diminution of blood flow in the pulmonary lobar vessels.

Key Words: *organophosphorus compounds; pulmonary circulation; systemic circulation; ultrasound*

Organophosphorus compounds (OPC) are widely used for pest control in agriculture as well as in the home. Pesticides, however, may have health-damaging effects on humans and animals if applied in excessive amounts. For example, OPC used against plant pests inhibit cholinesterase activity in the blood and various tissues, which has been shown to be a major factor in the mechanism of OPC action on biological structures [1-3]. As a result of the impaired catalytic function of cholinesterase, conversions of acetylcholine are disrupted, leading to its accumulation in organs

Laboratory for Pathophysiology of Respiration and Laboratory of Bioengineering, Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow

0007-4888/94/0001-0014$12.50