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COMPLEX SYSTEMS BIOPHYSICS

The Effects of Low-Intensity Millimeter-Wavelength Radiation and Electromagnetic Shielding on Pain Sensitivity in Rats

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Abstract—Here, we studied changes in pain sensitivity in rats subjected to low-intensity millimeter-wavelength electromagnetic radiation (EMR MM) of 7.1 mm and 0.1 mW/cm^2 in the occipital-collar region with daily exposure of 30 min over 21 days. As well, this radiation was combined with moderate electromagnetic shielding (EMS) which had the following parameters. The shielding coefficients of the constant component of the magnetic field along the vertical and horizontal constituents were 4.4- and 20-fold, respectively, with an exposure of 22 h/day over 21 days. The pain sensitivity was estimated with algometric tests, that is, the hot plate, flick-tail, and algesimeter-pincher tests; these allowed observation of the pain impulse at different regulatory levels. The algological effects of both individual and combined EMR MM and EMS were demonstrated. It was shown that EMR MM has an antinociceptive property when combined with EMS, as well as a modulation effect caused by shielding during hyperalgesia. At the same time, shielding reduces the antinociceptive effect of EMR MM.

Keywords: pain sensitivity, millimeter-wavelength electromagnetic radiation, electromagnetic shielding

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The majority of non-biological environmental factors present electromagnetic radiation (EMR). Each region of this radiation spectrum plays its role in the evolution of living organisms and is involved in life-sustaining processes [1]. To support these data more information on the high sensitivity of biological systems to weak EMR of a nano- and pico-Tesla intensity is of significant interest [2–4]. However, electromagnetic effects of low-intensity factors on living organisms have been insufficiently studied.

The millimeter-wavelength range of EMR (EMR MM) is one of the low-intensity electromagnetic factors whose biological effects have been studied with significant efforts. These effects do not cause organismal structural changes, are completely absorbed in the skin, and result in profound biological responses [5–11]. Since the biological efficiency of EMR MM has been proven, this radiation is widely used in medicine to treat a variety of disorders of different origins [12, 13]. However, the mechanisms that underlie the effects of low-intensity EMR MM on biological objects are still to be revealed.

Active interference in organismal processes and studies on deprivation effects would facilitate our understanding of the ecological role of natural EMR. Experiments with the use of electromagnetic shielding (EMS) to significantly reduce static and alternating magnetic fields of different ranges are conventionally performed [14–16]. At the same time, the effects of weak EMS are not considered. The biological role of weak EMRs is of significant interest because their influence on all biosphere constituents cannot be underestimated. Studies on EMS effects draw the attention of researchers in many fields. This is associated with the necessity to investigate a number of basic problems, in particular, the important ecological role of the geomagnetic field and the factors responsible for shielding effects. Application of this knowledge to understand the harmful effects of these factors, as well as to prevent and correct them, is also important.

In nature, an effect of a single factor is rare, a combined effect of several factors whose influence can differ from that of single factors is more common. Moreover, in this case, the response of biological systems is substantially modified.

Thus, it is important to reveal the mechanisms of the influence of combined magnetic fields and modification of effects of superweak factors to solve current problems in physiology and biochemistry concerning the effects of EMR microdoses. This, in turn, allows

Abbreviations: EMR is electromagnetic radiation; EMR MM is millimeter-wavelength electromagnetic radiation; EMS is electromagnetic shielding; PRL_{tft} ispain response latency in a tail-flick test; F_{pul} is mechanical pain threshold; PRL_{hpt} is pain response latency in a hot plate test.

understanding the effects of weak EMR on organismal functions and results in the creation of an unambiguous basic concept: the mechanisms that underlie the effects of weak electromagnetic factors on organisms.

In this connection, the goal of this study was modification of pain sensitivity in rats with low-intensity millimeter-wavelength radiation and electromagnetic shielding.

MATERIALS AND METHODS

Experiments were performed with the common use facility in the Center of Experimental Physiology and Biophysics, Department of Human and Animal Physiology and Biophysics of the Tauric Academy of Vernandsky Crimean Federal University. Male rats of the Wistar line (120 mature animals with low activity and a low emotional level) were obtained from the Rappolovo Nursery of Laboratory Animals, Rappolovo, Leningrad Region. To determine the activity and emotional levels a special 45 × 45 cm working station with transparent propylene walls with a height of 20 cm was used. The station had an actimeter (Pan Lab Harvard Apparatus, Spain) with two infrared sensor frames designated for motion registration. Actitrack 2.0 software (Pan Lab Harvard Apparatus, Spain) was used to control the work station and collect data.

The animals were kept in the animal facility under the standard conditions of 18–22°C and a 12 h light–dark cycle on Rekhofiks MK 2000 litter based on maize ears with free access to water according to *GOST 33215-2014* of the Manual for the management of laboratory animals (Rules for room equipment and procedures) and adequate granulated food (*GOST R-50258-92*).

Regulation of pain sensitivity, depending on the affecting factor, is based on an integrative complex of mechanisms characterized by a selective and dynamic structure at neurochemical and neuromorphological levels. For this reason, the best way to obtain an objective estimate of pain sensitivity is the use of algometric tests.

The tail-flick test was used to estimate the perceptual pain component. Pain response latency in a tail-flick test (PRL_{tft}) was the principal characteristic. Light-thermal irritation was used to determine time period of the tail-flick reaction. These measurements were carried out with a LE7106 Tail-flick Meter unit (Pan Lab Panlab Harvard Apparatus, Spain). The tail of each rat placed in a fixator was subjected three times to light-thermal irritation with the subsequent calculation of the PRL_{tft} average represented in seconds. This test is based on the spinal reflex in response to local high-temperature irritation, which makes it possible to study pain sensitivity at the spinal level [17–19].

The algesimeter-pincher test (Randall-Selitto test) measures an applied force in grams (F_{pul}), which is the mechanical pain threshold that causes a response to gradually increasing pressure on the tail with a pincher [19]. This test was carried out with a BIO-RP-R Rodent pincher–analgesia meter (Bioseb, France). The tail of each rat placed in the fixator was squeezed three times with the subsequent calculation of the average pain threshold in grams.

The hot plate test was used to register pain response latency (PRL_{hpt}) which was determined according to the time (seconds) of limb flicking, licking, and/or vocalization. This test, which allows studying pain sensitivity at the supraspinal level, was performed with a Cold and hot plate CHP unit (Bioseb, France) [19, 20].

In total, three series of the experiments were performed with the tests as noted. In each series, the animals were divided in four groups of ten individuals each. The first group (control) was kept under the standard laboratory conditions. The second group was subjected to low-intensity EMR MM with a RAMED-EXPERT–01 unit (The Center of Radiophysical Methods of Diagnostics and Therapy, Institute of Technical Mechanics, NANU, Dnepropetrovsk; registration certificate 783/99, 14.07.14 issued by KNMT MOZ of Ukraine). The certificate of this equipment enables its use in medicine in Ukraine. The wave length was 7.1 mm, the radiation frequency was 42.3 GHz, and the power flow density was 0.1 mW/cm^2. To subject the animals to millimeter-wavelength radiation they were fixed in a transparent plexiglass chamber. The length and width of the chamber were regulated according to the size of the animal. The radiator was moved to an opening in the chamber, which corresponded to the radiator size, and fastened with plaster in the occipital–cervical region (contact radiation). The unit scheme and radiation are presented in Fig. 1 and Fig. 2. Exposure was carried out in the occipital–cervical region for 30 min [10] on a daily basis over 21 days.

The third group of animals (EMS-group) was placed in a chamber that shielded background magnetic fields for 21 days (23 h/day). The 2 × 3 × 2 m shielding chamber was made from two-layer iron of the Dynamo trademark. The shielding coefficient associated with the weakened magnetic field (S_B) was measured experimentally because of its low value.

For this purpose, the magnetic field value was measured within the chamber and out of it. The measurements were performed with both a ferroprobe magnetometer and an induction coil. The shielding coefficient at frequency f was calculated as the ratio of magnetic induction out of the chamber to that within the chamber (see Table 1).

Single- and two-component ferroprobe magnetometers were used for the low frequency region (10^{-4}–100 Hz). This equipment allowed simultaneous measuring of two mutually perpendicular projections of the magnetic field vector. The sensitivity threshold of the

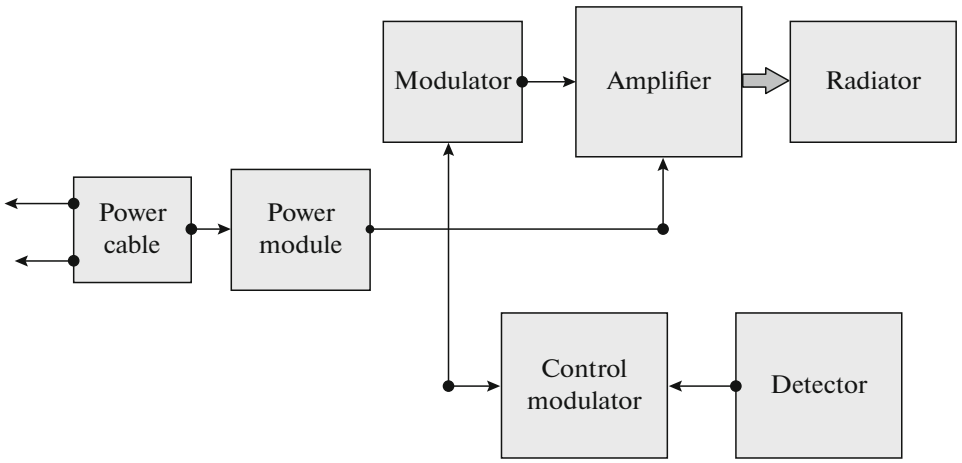


Fig. 1. The schematic circuit diagram of the Ramed Ekspert-01 unit.

magnetometers consisted 1 nT for each component and with a precision of ±3%.

Measurements of the hypomagnetic field in the high frequency region (15–100 kHz) were carried out in the shielding chamber with a measuring coil with the following characteristics: 500 turns, 10 cm inner diameter, 10.6 cm outer diameter, and U2-8 selective amplifier. The shielding coefficient of the magnetic field constant component measured with the ferroprobe magnetometer was 4.375 and 20.0 along the vertical and horizontal components, respectively. The spectral density of magnetic noise in the shielding chamber was measured in the region of ultralow and radio frequencies (Fig. 3).

The fourth group of animals was subjected to the combined effect of low-intensity millimeter-wavelength radiation and electromagnetic shielding (EMS + MM) for 21 days in the same way as the second and third groups.

The modification coefficient was used to evaluate the modifying effect of weak natural EMS to reduce the level of the millimeter-wavelength radiation:

$$MC_{EMS} = \frac{N_{EMS+MM} - N_{MM}}{N_{MM}},$$

$$MC_{MM} = \frac{N_{EMS+MM} - N_{EMS}}{N_{EMS}},$$

where MC is modification coefficient and N is nociception under the effect of the weak EMS and low-intensity (EMR MM) radiation. The modification coefficient equals zero if there is no modifying effect of the factor.

The results were treated statistically. The significance of the differences between the group averages of the independent samplings was estimated according to the Kruskal–Wallis nonparametric test. Statistica 10.0 software was used for statistical analysis.

RESULTS

The background values of pain sensitivity did not show intergroup differences. The nociception index in the control groups was changed insignificantly over 21 days and constituted, on average, 3.48 ± 0.20 s for the hot plate test; 4.00 ± 0.23 s for the tail-flick test; and 353.96 ± 64.31 g for the algesimeter-pincher test.

The second group animals subjected to low-intensity EMR MM showed a significantly higher antinociception level for the entire period compared with that of the control group. This suggests the development of pronounced algesia in response to the low-intensity physical factor.

As an example, the hot plate test resulted in a clear analgesic effect which was observed as longer PRL_{hpt} relative to the control for the entire observation period. According to [19, 20], this result suggests participation

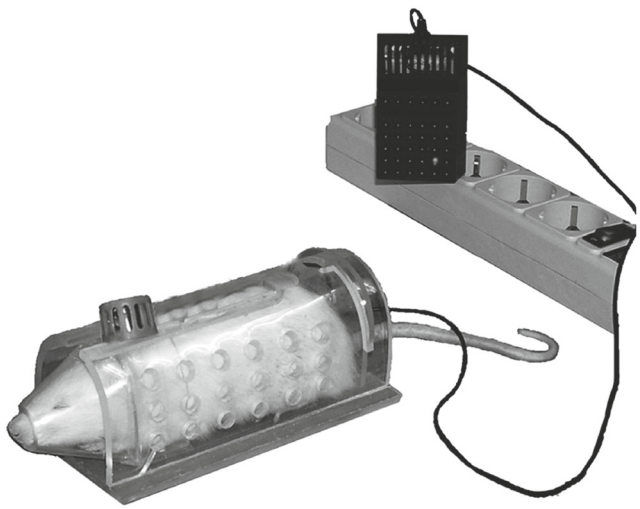


Fig. 2. The exposure of animals to low-intensity millimeter-wavelength electromagnetic radiation.

Table 1. The dependence of the shielding coefficient on the frequency of an alternating magnetic field

f, Hz	S_B	f, Hz	S_B	f, Hz	S_B	f, Hz	S_B
16	3.7	50	2.5	95	3.8	160	1.0
20	2.4	51	2.3	100	2.9	200	1.0
25	1.9	70	2.4	102	2.8	250	1.0
30	2.6	75	2.8	105	2.8	255	1.8
35	2.3	80	2.5	125	2.2	350	0.9
40	2.7	85	2.4	130	1.6	400	1.1
45	2.4	90	2.7	152	1.4	500	1.0

S_B is the shielding chamber coefficient; f is the alternating magnetic field frequency. The chamber was made from two-layer iron of the Dynamo trade mark.

of supraspinal mechanisms in regulation of pain sensitivity. Its maximum increase was registered on the 7th and 11th days and constituted 53.93% ($p < 0.01$) and 81.92% ($p < 0.005$), respectively, compared with the control group animals (Fig. 4a).

A clear analgesic effect was also found in the tail-flick test, which is a thermal model of acute pain [17–19]. The highest PRL_{tft} values were registered on the 1st, 7th, and 15th days of the exposure to the millimeter-wavelength radiation. These values were 30.56% ($p < 0.05$), 37.94% ($p < 0.05$), and 38.54% ($p < 0.05$), respectively, compared with the control animals (Fig. 4b). This suggests the participation of a perceptual component and a spinal mechanism in regulation of pain sensitivity in response to millimeter wavelengths.

In the Randall–Selitto test (algesimeter-pincher test) designated for determination of thresholds of mechanical pain sensitivity [19] the response to the mechanical pain factor was observed similar to the dynamics of the other algometric tests based on millimeter radiation. The F_{pul} maximum was registered on the 11th day (68.75%; $p < 0.005$) relative to the control (Fig. 4c).

According to the results of the different acute pain models, it can be suggested that low-intensity millimeter-wavelength radiation demonstrates an analgesic effect, which is consistent with our previous studies [10]. Moreover, a novel finding was that the nociceptive effect of EMR MM was exhibited for 21 days under the constant influence of this factor.

In the third group of animals, which were under influence of long-term EMS, phase changes in the pain sensitivity level in the different algological tests were observed, unlike the animals subjected to MM radiation.

As an example, in the tail-flick, hot plate, and algesimeter-pincher tests, lower characteristics of pain sensitivity were observed from the first to seventh days of shielding compared with the control rats (Fig. 4). This, in turn, suggests a lower pain threshold and the development of hyperalgesia compared with the control. The maximum decrease in the effect of the hypomagnetic environment relative to the control was registered in the hot plate test on the first day by 13.81%

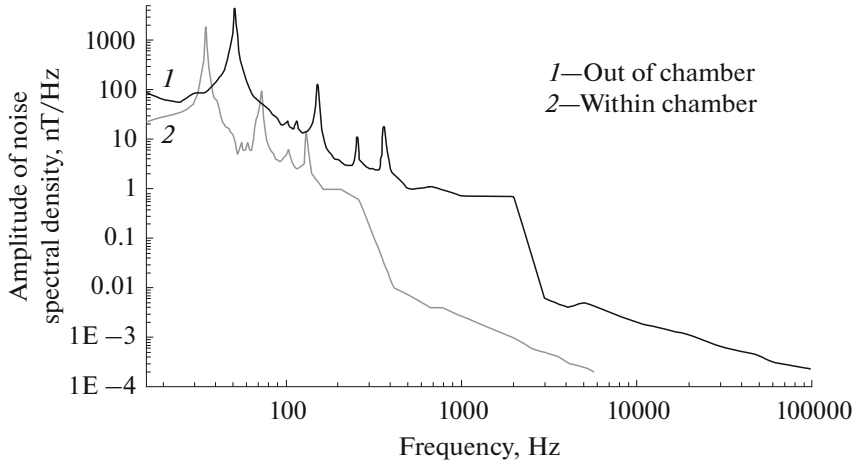


Fig. 3. The dependence of the spectral density of magnetic noise on the frequency in the range of 15 Hz to100 kHz within and outside of the chamber.

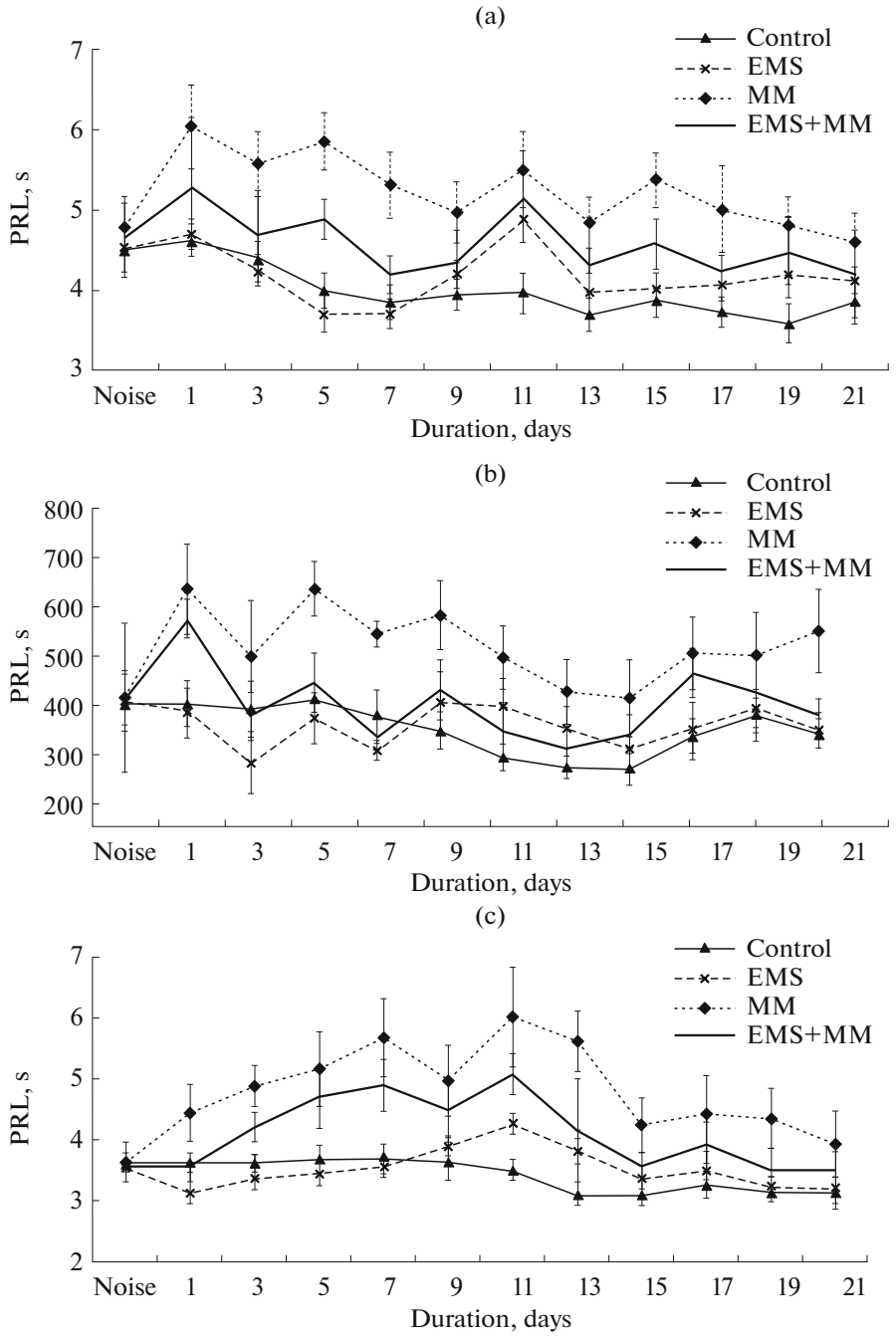


Fig. 4. The dynamics of nociception characteristics (PRL, pain reaction latency) upon individual and combined exposure to low-intensity millimeter-wavelength electromagnetic radiation (MM) and electromagnetic shielding (EMS) in rats subjected to the following tests: hot plate (a), flick-tail (b), and algesimeter-pincher (c).

($p < 0.05$); in the algesimeter-pincher test on the third day by 27.90% ($p < 0.05$); and in the tail-flick test on the fifth day by 7.30% ($p > 0.05$).

The pain reaction in the tests decreased after the ninth day of EMS. A gradual increase in the nociception characteristics relative to the background and those of the control group was observed. This suggests a higher pain threshold and the development of hypoalgesia. The maximum values of the PRL_{hpt}, PRL_{tft}, and F_{pul} tests were registered on the 11th day of shielding, which was higher by 23.12% ($p < 0.01$), 22.71% ($p < 0.01$), and 35.35% ($p < 0.01$), respectively, compared with those of the control group.

A gradually decreasing trend for the nociception characteristics and their shift to those of the control

group was registered after 15 days of exposure to the hypomagnetic environment.

All this suggests that rats that were subjected to weak EMS showed three-phase change in their pain sensitivity. The first phase, hyperalgesic, was observed between the first and seventh days. Next, the antinociceptive effect was developed, which is the second phase (11–15 days). Finally, the nociception characteristics were gradually decreased and became similar to those registered in the control group.

Our data on the development of the phase changes in pain sensitivity during EMS are consistent with results of the other researchers [21, 22]. However, the phase duration found in our study was significantly longer, which can be explained by the weaker shielding of the static and alternating magnetic fields.

The animals subjected to the combined effect of EMS and millimeter-wavelength radiation (EMS + MM) showed a higher nociception level compared with the control and EMS groups and lower characteristics compared with the rats subjected to isolated EMR MM.

As an example, beginning from the third day a significant PRL_{hpt} increase relative to the control was observed in the EMS + MM group. The maximum values were registered on the 7th and 13th days, 32.79% ($p < 0.01$) and 45.14% ($p < 0.01$), respectively. The highest PRL_{tft} value was observed on the 11th day, 29.72% ($p < 0.01$), while the F_{pul} maximum values were observed on the first (42.94%, $p < 0.01$) and 17th (37.41%, $p < 0.01$) days compared with the control group (Fig. 4).

The difference in these characteristics was statistically significant when they were compared with those of the second (MM) and third (EMS) groups. The maximum PRL_{hpt} increase was registered on the 5th (36.23%, $p < 0.01$) and 7th (37.64%, $p < 0.01$) days, while the F_{pul} values were increased to their maximum on the 1st (45.57%, $p < 0.01$) and 17th (33.45%, $p < 0.01$) days compared with the animals subjected to EMS alone.

Conversely, the second group animals (MM) showed significantly lower characteristics: on the 13th day for PRL_{hpt} (26.16%, $p < 0.05$); the 7th day for PRL_{tft} (21.15%, $p < 0.05$); and on the 7th day for F_{pul} (38.78%).

The dynamics of the modification coefficient under conditions of the combined EMS and MM radiation in the different pain tests clearly demonstrates that low-intensity EMR MM can result in antinociceptive and modulation effects upon hyperalgesion caused by shielding (Fig. 5).

DISCUSSION

Our results suggest changes in pain sensitivity in animals under the effect of low-intensity electromagnetic factors, which were EMR MM, EMS, and their combinations. The degree of these changes depends on the factor and its duration. The modification effects of pain sensitivity were revealed in rats with the low-intensity millimeter-wavelength radiation and electromagnetic shielding. It was found that EMR MM combined with EMS reduces the level of pain sensitivity, while EMS combined with EMR MM decreases the antinociceptive activity of EMR MM.

The comparison of these results with our previously published data allowed determination of the specific influence of the moderately weakened static and alternating components of geomagnetic fields, EMR MM, and their combinations. It also indicated the basic physiological mechanisms of the studied physical factors and their effects on pain sensitivity.

The opioid system is important in the mechanisms of electromagnetic factors that affect pain sensitivity and also includes EMS and low-intensity EMR MM. This was found in experiments with a nonselective inhibitor of opioid naloxone receptors. In particular, naloxone injections in rats led to a weaker antinociceptive EMR MM effect in the case of tonic, visceral, and acute thermal pains [10]. However, at different stages of prolonged EMR MM, the activity of this system was different. As an example, hyperalgesia was observed when this factor was applied to shells with additional naloxone injections for 1–3 days, which indicates the dependence of the antinociceptive effect of EMR MM on opioids in that time period. The hypoalgesic effect of EMR MM was completely inhibited by naloxone from 4 to 8 days, which also indicates dependence on the opioidergic system. Beginning of the ninth day, the effect was only partially opioid dependent since it was reduced but not completely eliminated by a nonspecific inhibitor of opioid receptors. Subsequently, the opioid significance decreased with more injections, which seems to be associated with the tolerance of the opioid system to prolonged EMR MM action [22]. EMRs of the other ranges have a similar effect [23]. Naloxone injections in animals isolated with an electromagnetic shield for 21 days enhanced the hyperalgesic EMS effect, which was observed as a trend for 3 days with its subsequent decrease. The developing hypoalgesic effect caused by combined EMS and EMR MM was completely eliminated on days 9–11 by naloxone, which suggests dependence on the opioid system. This effect progressively decreased, although it did not disappear completely, which suggests partial association of the hypoalgesic effect from the opioid system [22].

Thus, opioid dependence decreased with longer exposure to electromagnetic factors, which seems to be associated with the tolerance of the opioid system. The analgesic effect of the electromagnetic factors in this time period was possibly caused by other organismal antinociceptive systems. Our previous results that indicate that the hypoalgesic effect of EMR MM is

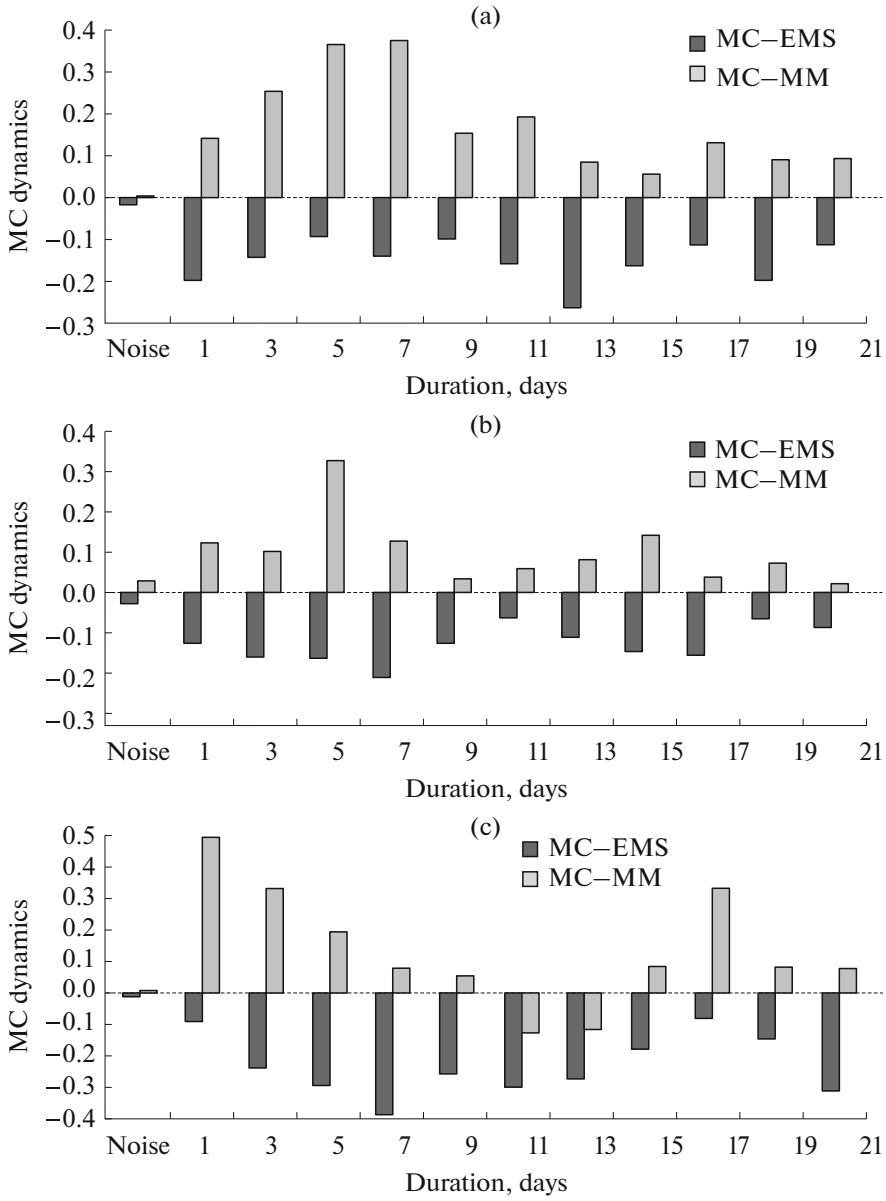


Fig. 5. The dynamics of the modification coefficient of electromagnetic shielding (EMS) and low-intensity millimeter-wavelength electromagnetic radiation (MM) applied individually and combined in the following tests: hot plate (a), flick-tail (b), and algesimeter-pincher (c).

caused by a variety of endogenic systems support this conclusion. In particular, melatonin plays the principal role in the mechanisms of the antinociceptive effect of EMR MM. We also revealed that this radiation results in a higher melatonin content in animal sera [24]. Opioid peptides are known to be physiological mediators of epiphyseal and extrapineal melatonin and are responsible for general coordination of the nervous, endocrine, and immune mechanisms, as well as for closed circuits between them and the pineal gland [25]. Moreover, we found that low-intensity EMR MM and exogenic melatonin affect changes in nociception induced by EMS similarly, which results in the reduction of the hyperalgesic effect [22]. These data are consistent with a melatonin theory of the effect of electromagnetic factors at the beginning of their action, which suggests that they suppress the release of this neurohormone [26]. This, in turn, causes reduction in β-endorphin production and in the sensitivity of opioid receptors, which leads to lower activity of the opioid system [27]. Hyperalgesia is the consequence of these processes, as can be seen under the conditions of individual EMS. It can be also suggested that the combined effect of EMS and EMR MM does not lead to lower melatonin release due to the modification effect of EMR MM. This is a reason

for the reduction of shield-dependent hyperalgesia caused by the additional action of EMR MM found in this study.

Our results indicate that the physiological mechanisms of the low-intensity effect of EMR MM on animals placed in the weakened electromagnetic field are associated with changes in the status of the opioidergic system and melatonin content. Therefore, it is natural to suggest that activation of these endogenic systems is a nonspecific organismal reaction to physiological factors of low intensity.

Thus, the results of this study allowed us to reveal modifying effects on pain sensitivity in rats using low-intensity millimeter-wavelength radiation and electromagnetic shielding. As well, the hypothesis on the corrective effect of EMR MM on shield-induced processes was verified and substantially expanded. Finally, the theoretical ideas on the basic physiological mechanisms that underlie the biological influence of these physical factors were experimentally confirmed.

CONCLUSIONS

(1) Effects of pain sensitivity modification in rats with the use of low-intensity millimeter-wavelength radiation and electromagnetic shielding were found. EMR MM in combination with EMS reduces the shield-induced changes in pain sensitivity. As well, EMS in combination with EMR MM decreases the antinociceptive activity of individual EMR MM.

(2) Animals exposed to low-intensity electromagnetic factors (EMR MM, EMS, and their combinations) demonstrated changes in pain sensitivity, whose degree depends on the factor and its duration.

(3) Low electromagnetic shielding resulted in a three phase change in pain sensitivity in all algometric tests used in this study: the first phase was hyperalgesia (1–7 days), the second phase was hypoalgesia (11–15 days), and the third phase was normalization and a shift of the nociception characteristics to the control (17–21 days).

(4) The animals exposed to low-intensity electromagnetic radiation in the millimeter range demonstrated significantly higher antinociception in all algometric tests over the entire observation period compared with the control group and the animals subjected to weak shielding.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare no conflict of interest.

Statement on the welfare of animals. This study was performed in accordance with *GOST R-53434-2009* of Basics of Relevant Laboratory Practice and rules of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes.

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