The use of a model of adoptive immunocytotherapy thus demonstrated, on the one hand, the immunosuppressor effect of excessively strong stimuli on the state of systems responsible for protecting the animal against growth of tumors. On the other hand, the arguments presented confirm the important role of NK cells in tumor immunocytotherapy. However, the possible role of regulatory cells (amplifiers) in the sensitivity of splenocytes to stress-induced depression of their therapeutic activity and the correction of these disturbances must be investigated in the future. The writer showed recently [4] that ability of splenocytes to produce interleukin-2 is sharply depressed in stress. This lymphokine is directly concerned in interferon production and NK cell activation.

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EFFECT OF BONE MARROW MYELOPEPTIDE MEDIATORS ON THE THRESHOLD SUMMATION INDEX AND BEHAVIORAL RESPONSE IN RATS

A. M. Vasilenko, G. M. Barashkov, and L. A. Zakharova

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The bone marrow cells of man and animals produce a mediator which causes a two-three-fold increase in antibody production at the peak of the immune response [1, 8]. This mediator is a thermostable substance of peptide nature with molecular weight of about 2 kilodaltons [5, 6]. Studies of the biological and physicochemical properties of this substance demonstrated its structural and functional heterogeneity [6, 9]. Besides immunostimulating activity, the bone marrow mediator also possesses analgesic and endorphin-like properties. Like morphine and certain endogenous opiates, it interacts with μ- and β- opiate receptors of the brain [10] and selectively inhibits cortical responses to nociceptive stimulation [9]. By analogy with neuropeptides, produced by cells of nerve tissue, the bone marrow mediators have been called myelopeptides.

The aim of this investigation was to continue the study of the analgesic action of myelopeptides, as reflected in their effect on the threshold-summation index (TSI) and behavioral responses in rats.

Central Research Institute of Reflex Therapy. Institute of Immunology, Minsitry of Health of the USSR, Moscow.

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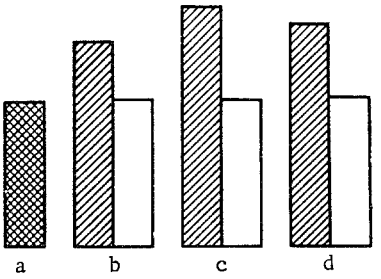

Fig. 1

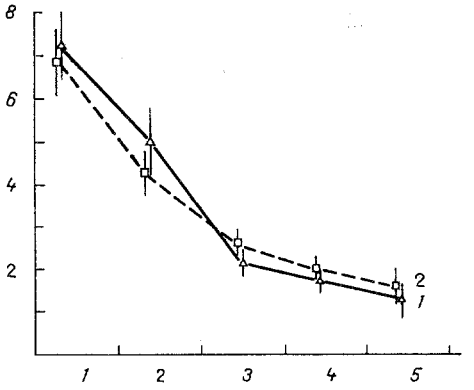

Fig. 2

Fig. 1. Changes in value of TSI (in relative units) after injection of myelopeptides. Shaded columns — injection of myelopeptides; unshaded — injection of physiological saline. a) Background (7.40 relative units), b) 20 min after injection of myelopeptides (10.30 ± 0.21 relative units) and physiological saline (7.48 ± 0.16 relative units), c) after 40 min (11.76 ± 0.32 and 7.52 ± 0.28 relative units respectively), d) after 60 min (11.21 ± 0.72 and 7.60 ± 0.41 relative units).

Fig. 2. Time course of distribution of burrowing reflex after injection of myelopeptides (1) and physiological saline (2). Abscissa, time (in min); ordinate, number of burrows studied.

TABLE 1. Behavioral Responses (in relative units) in Rats after Injection of Myelopeptides (M ± m, n = 70)

Parameter of behavioral response studied	Control	Expt.
Burrowing reflex	17,2±1,9	16,0±2,2
Motor activity	35,8±5,4	37,9±5,7
Number of groomings	3,4±1,8	3,6±2,3

EXPERIMENTAL METHOD

Myelopeptides were isolated from the supernatant of pig bone marrow cultures by gel-chromatography on Sephadex G-50 (medium), equilibrated with distilled water, pH 7.2. The dose of myelopeptides was estimated as their protein content, determined by Lowry's method. The experiments were carried out under free behavior conditions on 70 noninbred rats of both sexes weighing 190-210 g. Myelopeptides were injected intraperitoneally in a dose of 2 mg per rat. Rats of the control rat received an injection of the same volume of physiological saline. Values of TSI were determined 20, 40, and 60 min after injection into the rats [2, 4]. Changes in TSI under the influence of myelopeptides, after preliminary injection of naloxone in a dose of 100 μg/kg body weight into the rats, were studied in 10 experiments.

Behavioral responses of the rats were studied under "open field" conditions [7]. Orienting reactions were recorded: burrowing reflex, emotional reactivity determined as the number of groomings, investigative behavior, including motor activity of the rats, recorded as the number of squares crossed. Behavioral responses were studied 30-40 min after injection of the myelopeptides or physiological saline. All experiments were carried out in a room isolated from irrelevant stimulation for 5 min at the same time of day (5-8 p.m.), by a double blind method. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The analgesic action of the myelopeptides was assessed from the change in values of TSI, which reflects the ability of spinal and brain-stem structures to summate threshold impulses and the lability of the neural centers. As Fig. 1 shows, values of TSI of the experimental animals were increased 20 min after injection of the myelopeptides compared with the original

and control levels. Changes in TSI reached a peak after 40 min, the effect remained stable after 60 min, but by this time a tendency was observed for it to diminish.

Changes in TSI observed after injection of the myelopeptides and increasing with time indicate elevation of threshold of excitability of spinal and brain-stem centers. Intraperitoneal injection of naloxone in a dose of 100 μg/kg 10 min before injection of the myelopeptides prevented changes in TSI. A similar time course of TSI is characteristic of injection of moderate doses of narcotic analgesics into animals [11].

The writers showed previously that intravenous injection of bone marrow mediator in a dose of 10 mg/kg into experimental cats greatly reduced the amplitude of evoked potentials to nociceptive stimulation in the frontal association area of the cortex. A similar but rather weaker effect also was recorded in the somatosensory projection cortex, neurons of which contain fewer opiate receptors than those of the frontal cortex. The antinociceptive effect was abolished by naloxone [3].

The results of the present investigation show that myelopeptides can block the transmission of nociceptive impulses at the spinal and (or) brainstem level.

This hypothesis is confirmed by the results of investigation of the animals' behavioral responses. Figure 2 shows the dynamics of the distribution of orienting reactions of the control and experimental rats in time, assessed by means of the burrowing reflex. As Fig. 2 shows, injection of the myelopeptides did not alter the character of the natural dynamics of the orienting reactions. The results of a study of the other two behavioral responses — investigatinve motor activity and number of groomings — likewise revealed no difference between animals of the control and experimental groups (Table 1).

Myelopeptides thus possess marked analgesic properties but do not affect behavioral responses controlled by the cerebral cortex, a feature which distinguishes them in principle from known narcotic analgesics and the principal groups of endorphin-like substances [12]. This difference may perhaps be due to the structural-functional heterogeneity of the mediator. Besides opiates, the mediator also contains peptides which have other properties, such as immunoregulatory. The possibility cannot be ruled out thet they also exert a modulating influence on interaction between mediator and opiate receptors of nerve cells.

The fact that myelopeptides have both analgesic and immunostimulating activity, and have no visible effect on the basic behavioral responses opens up wide prospects for their use in clinical practice.

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