Neurotropic Effect of Myelopid on the Motor Activity of Rats: Stereotypical Movements, Locomotion, and Grooming

L. M. Lepekhina and L. A. Bibikova

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It is shown that myelopid, a new immunoregulating preparation isolated from bone marrow, modulates motor activity in rats and, consequently, possesses neurotropic activity. Presumably, the activating effect of myelopid on stereotypical movements is realized via stimulation of presynaptic receptors and subsequent activation of dopamine of the mesolimbic system, since this effect is abolished by the M-cholinoreceptor blocker atropine. The inhibitory effect on scratching may be a result of the inhibitory influence of myelopid on preganglionic sympathetic neurons of the spinal cord, since it was abolished by the blocker of ganglionic H-cholinoreceptors hexonium.

Key Words: *neurotropic effect; motor activity; myelopid; atropine; hexonium*

Myelopid, a new imunocorrecting preparation isolated from bone marrow, is an opioid neuropeptide. It affects nerve structures which are part of the nociceptive and antistress systems, exhibits analgetic activity, and plays an important role in stress responses. Myelopids are regarded as transmitters form a link between the immune and nervous systems, i.e., they are immunotransmitters. Their influence on the organism is polyfunctional [1].

We studied the neurotropic effect of myelopid on motor activity, which is known to be governed by central and peripheral mechanisms of nervous activity. It has ben reported that myelopid does not affect the following reflexes: washing,the "burrowing reflex", and exploratory behavior [4]. The aim of this study was to find out whether myelopid affects stereotypica behavior, locomotion, and grooming, and if so, to define possible ways of realizing these effects, using a pharmacological approach.

I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Medical Sciences; S. M. Kirov Military-Medical Academy, St. Petersburg. (Presented by N. P. Bekhtereva, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

Experiments were performed on albino male rats (age 3 months, weight 180-200 g) divided into two groups: experimental (n=11) and control (n=4). Myelopid was injected intraperitoneally in a dose of 0.5 mg/kg in 0.4 ml normal saline (5 rats). A similar volume of normal saline was injected in control animals (n=4). The mechanism of myelopid influence was analyzed with the use of the M-cholinoreceptor blocker atropine (0.5 mg/kg, 3 rats) and the blocker of H-cholinoreceptors hexonium (20 mg/kg, 3 rats).

For the recording of motor activity rats were placed in a plexiglas actograph with a piezoelectric sensor at the bottom. After amplification and transformation, the oscillations of the actograph bottom were recorded with an electrical encephalograph [3]. The following parameters were determined from actograms: 1) the total number of all movements - stereotypical ones (the number of sniffings and forepaw shufflings) and episodes of grooming (licking, washing, fur biting, and scratching) - during a 1-h period; 2) the total number

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of each kind of movement during a 1-h period; 3) the duration of each movement; 4) rhythm of paw or head movements during these activities (except locomotion).

RESULTS

The analysis of different movements showed that myelopid has the strongest effect on sniffing movements (their number increased by 766.7% compared with intact animals) and shufflings with the fore paws (a 160% increase in the number). The number of lickings increased by 80%, while the number of washings, shakings, and fur bitings did not change significantly, increasing by 10.9, 8.3, and 10.8%, respectively. Under the influence of myelopid the number of grooming scratching movements decreased significantly (by 90%, Fig. 1). Since the number of washings, shakings, and fur bitings remained as before while the number of lickings and scratchings changed in the opposite direction, the total number of grooming movements remained unchanged: 52.0±7.0 *vs.* 50±6.0 in the control. The total number of all movements increased (83.0±6.0 vs. 55.5±4.0 in intact rats, $p<0.05$). Analysis of other parameters of motor activity: the duration of individual movements and their rhythm revealed no changes related to myelopid administration.

Blocking of M-cholinoreceptors with atropine weakened the stimulatory effect of myelopid on stereotypical movements and abolished its effect on locomotion and on scratching movements. At the same time, atropine did not alter the inhibitory effect of myelopid on scratching, which was abolished by hexonium (Fig. 2). According to published data, activation of stereotypical behavior is indicative of dopaminergic stimulation. The increase in the sensitivity of the dopamine receptors induced by apomorphine or enhanced secretion of dopamine from nerve endings under the influence of amphetamines stimulates stereotypical behavior [9]. Dopamine is known to be confined to the extrapyramidal and mesolimbic systems of the brain. Destruction of some nuclei of the mesolimbic system (*nucleus accumbens septi, tuberculum, olfactorum, and central amygdalae*) differentially reduces or eliminates individual stereotypical movements. For example, the low intensity stereotypical behavior (sniffing and forepaw shuffling)is selectively and completely eliminated after destruction of *n. accumbens septi*, while destruction of *central amygdalae* eliminates the higher-intensity stereotypical behavior (crawling, biting, and licking of the actograph walls [7-9]. Consequently, the observed changes in stereotypical behavior of rats are associated with the mesolimbic system, namely, with *n. accumbens septi*.

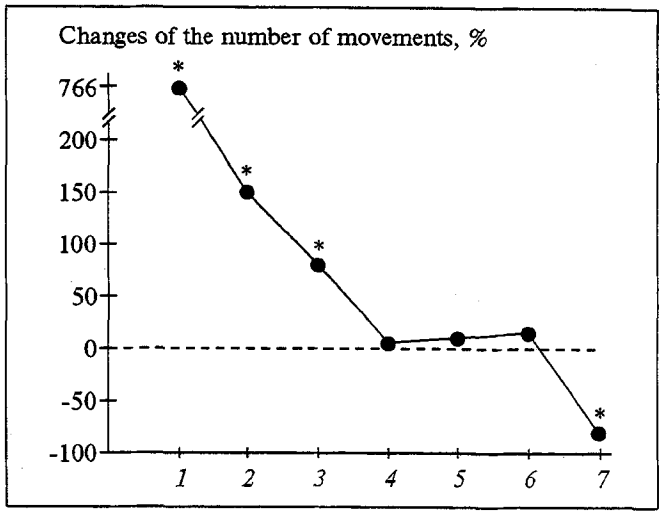

Fig. 1. Effect of myelopid on stereotypical movements, locomotion, and grooming. Abscissa: *1*) sniffing, *2*) locomotion, *3*) licking, *4*) washing, *5*) self−shaking, *6*) fur biting, *7*) scratching. Asterisk indicates statistically significant differences at $p<0.05$.

Published data mention that opaminergic innervation of *n. accumbens septi* plays a crucial role in modulating locomotor activity. Local injection of dopamine or apomorphine in *n. accumbens septi* activates not only sniffing behavior but also locomotion. On the other hand, injection of dopamine in *n. caudatus* (extrapyramidal system) inhibits locomotion, whereas apomorphine has no effect on

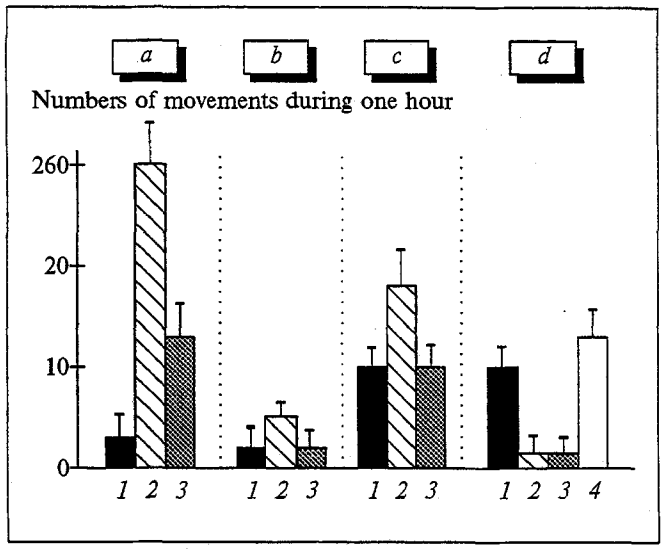

Fig. 2. Effect of myelopid on stereotypical movements, locomotion, and grooming after administration in combination wilt atropine and hexonium. *a*) sniffing; *b*) locomotion; *c*) licking; *d*) scratching. Abscissa: *1*) number of movements in intact rats; *2*) number of movements under the influence of myelopid; *3*) myelopid and atropine, *4*) myelopid and hexonium.

stereotypical behavior [8,9,11,13,14]. From the literature it may be surmised that the stimulation of exploratory behavior (sniffing) and of locomotion after myelopid injection is due to activation of mesolimbic dopaminergic innervation, specifically, of *n. accumbens septi*, but not of extrapyramidal innervation. Opiate receptors do not modulate the release of dopamine from the striatum [12].

The activating effect of myelopid on stereotypical behavior and locomotion of rats was abolished by atropine, indicating that this effect is mediated by the M-cholinoreceptors. This is consistent with the published data on functional relationship between the cholinergic and dopaminergic systems in *n.accumbens septi*. Presynaptic M-cholinoreceptors modulate and stimulate dopaminergic activity. This effect is blocked by atropine [5].

The inhibitory effect of myelopid on scratching was abolished by hexonium, a preparation that blocks ganglionic nicotine-sensitive cholinergic receptors and prevents the conveying of a stimulus from preganglionic to postganglionic spinal neurons. Hexonium activated scratching. Similarly to hexonium, extirpation of cervical sympathetic ganglia leads to activation of scratching in rats [2]. It follows that the inhibitory effect on scratching is mediated by sympathetic ganglionic spinal neurons. These neurons stimulate the neurons of cervical sympathetic ganglia [6]. However, in the presence of inhibitory descending influences their activity is inhibited and they become conductors of these these inhibitory influences. Immunohistochemical studies have shown that enkephalin fibers are functionally and morphologically closely associated with preganglionic spinal neurons. Enkephalins inhibit stimuli in sympathetic preganglionic neurons [15]. Consequently, inhibition of a stimulus in such neurons can be regarded as one of the ways in which myelopid participates in activating inhibitory descending influences on scratching.

The hypothalamo-spinal pathway, which starts in the giant neurosecretory cells of the paraventricular nucleus, may be the source of inhibitory descending influences on scratching movements. Its terminals end on preganglionic sympathetic spinal neurons, and its transmitters (vasopressin and oxytocin) elicit an inhibitory effect at these terminals [10,16]. Opiates are known to potentiate the release of vasopressin, and thus myelopid could modulate (potentiate) the inhibitory effect of the hypothalamo-spinal pathway. This is another possible way in which myelopid acts to inhibit scratching movements. The hind limbs of rats cannot accomplish scratching and locomotor movements simultaneously. The ability of myelopid to inhibit scratching movements and to activate locomotion and exploratory behavior (sniffing) is particularly important in stress.

Thus, myelopid modulates the locomotor activity of rats and adaptive behavior, and consequently it exhibits neurotropic activity.

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