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The journal has had 5 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 1107. (17.12.2013).

Conflict of interest: None declared. Received: 05.01.2014. Revised 15.04.2014. Accepted: 25.04.2014.

BEHAVIORAL DISTURBANCES INDUCED IN RATS VIA THE INTRANIGRAL INJECTION OF LEPTIN

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Summary
Introduction: Leptin action on brain structures might be helpful for better understanding of mechanism of this hormone neurotropic effects realization.
Materials and methods. Experiments have been carried out on Wistar rats (250-320 g) with the help of the EEG-, actometry recording and "open field" indices registration after microinjection of leptin (5-50 ng) into reticular part of substantia nigra (SNR). Besides, severity of picrtoxon-induced generalized seizures (2 mg/kg, i.p.) have been estimated after intra-SNR leptin administration.
Results. It was shown that bilateral intraSNR leptin injection (50 ng) resulted in oligo-akinesia, muscle tonus enhancement, decrease of wakefulness period and increase of deep slow-wave sleep and paradoxal sleep. Unilateral leptin administration (5; 25 and 50 ng) into SNR resulted in the appearance of dose-dependent contralateral circlings, which were blocked by naloxone (1.0 mg/kg). Haloperidol (1.0 mg/kg) caused the potentiation on keeping of uncomfortable position in animals with bilateral intraSNR leptin administration, while naloxone (1.0 mg/kg) markedly reduced this index. Analogous leptin intrastriatal injection failed to induce the same behavioral disturbances. Intranigral leptin administration was followed by decreasing of seizure susceptibility to i.p. picrotoxin administration (2,0 mg/kg).
Conclusion: leptin intraSNR induced opiate-depended behavioral disturbances of behavior, and also caused antiseizure action.
Key words: leptin, substantia nigra, circlings, naloxone, seizures.

Leptin is known as a hormone secreted by adipocytes in proportion to fat mass, acts via the long form of the leptin receptor (LepRb) to regulate energy homeostasis [1]. Neuronal specific deletion of LepR promotes hyperphagia and obesity [2], and restoration of neuronal LepRb in LepR-deficient mice normalizes food intake and body weight [3], indicating that leptin's effects on energy balance are achieved via brain LepRb. Last time antiepileptic properties of hormone have been established [4, 5] along with the realization of

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ketogenic antiepleptogenic effects via leptin elaboration [6]. But, controversial data with the emphasis on proepileptogenic action of leptin upon penicillin-induced seizures also have been delivered [7]

Hence, multiple mechanisms involvement is supposed to underlay neurotropic effects of leptin, namely effects upon 5-HT and GABA-ergic systems as well as modulation of opioid system with the involvement of pituitary- suprarenal axis [5, 8, 9, 10, 11]. Most of affected systems are known as those ones with antiepileptogenic activity, and cannabinoid CB1 receptor – dependent neurotropic mechanism of action might be suspected as a responsible for the facilitation of penicillin-induced epileptogenesis [7].

Thus, controversial effects of leptin upon epileptic activity justify further investigations of action of this neuropeptide on different models of epileptic syndrome. Meanwhile effects of intranigral (reticular part of substantia nigra) administration of leptin/ other compounds might be regarded as discriminative test on pro- or antiepileptiogenic properties of investigated copmpounds [12]. Taking into consideration ability of leptin to modulate mesolimbic dopaminergic system [13, 14, 15, 16], it was of interest to investigate behavioral effects induced via intranigral neuropeptide administration as well. Thus, Bilateral reduction of SN dopamine output underlies behavioral deteriorations, which are regarded as an experimental equivalent of Parkinsonian disease [17]. Inhibition of the dopaminergic neurons activity of SN pars compacta might be achieved via pharmacological modulation of SN reticular (SNR) neurons [18]. Thus, bilateral stimulation of GABA-A or GABA-B receptors with muscimol and baclofen in SNR counteracted the evoked dopamine release [19]. Besides, baclofen reduced, while muscimol intensified locomotor activity after intraSNR administration [19].

Hence **the objective** of present work was to investigate behavioral disorders induced by intraSNR leptin, with the emphasis on leptin - induced effects upon locomotion, sleep-wakefulness cycle, and antiseizure activity.

Materials and methods

a) Animals

The experiments were carried out on male Wistar rats with a weight of 250-320 g. All animals were kept at a constant room temperature of 22^{o}C with 12 a hr artificial dark/light cycle and free access to a standard diet and tap water.

Procedures involving animals and their care were conducted according to University guidelines that comply with international laws and policies [European Community Council Directive 86/609, OJ L 358, I, December 12, 1987; National Institute of Health *Guide for Care and Use of Laboratory Animals*, US National Research Council, 1996].

b) General surgery

Stainless steel guide cannulas (external diameter 0.5 mm) were implanted into the SNR and striatum under hexenal anesthesia (100 mg/kg) in accordance with the rat brain atlas [20]: (AP=-4.0; L=2.5; H=8.0 and AP=0.8; L=3.0; H=4.5, correspondently). The cannulas were implanted bilaterally so that they did not cross the upper boundary of the structure under investigation.

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In order to identify the various stages of sleep recording electrodes were implanted into the hippocampus (AP=-4.0; L=2.5; H=3.5), sensorimotor cortex and the neck muscles; an indifferent electrode was attached to the nasal bones. Quick-soliding dental plastic material was used for the fixation of the cannulas and electrodes to the skull. After the operations the rats were caged in groups of 5-10 animals. Starting one week after surgery, the rats were handled daily and adapted to the experimental setup.

c) Experimental schedule

Investigations were then started 1-2 weeks after the surgery. All observations were performed from 11.00 am to 5.00 pm. The number of rats in each group was 5-12. The analysis of circlings was confined to estimate the number of rotations. Analysis was performed during the 20 min period following the leptin injection into the left SNR. Locomotive activity was evaluated quantitatively by means of seismorecorded data registration for a period of 2 minutes after the placement of the animal on a movable floor. In addition "open field" data was determined by calculating the number of squares crossed during a period of 2 minutes after placing the animal in the center of the area3. Catalepsy was evaluated by determining the duration of retention of an uncomfortable posture [21]. Muscle tonus was estimated by clinically testing and recording the resistance of muscles for passive limb adduction. The number of animals with stereotype behavior (i.e. sniffing, licking, and gnawing) was noted as an informative index for the identification of stereotype behavior [21].

The investigations of the sleep-wakefulness cycle were conducted during 4 hrs by means of electrographical and behavioral indices recorded after the animals had been placed inside a sound-isolated box, with a constant level of artificial illumination. Actometry and EEG-recordings were then carried out via signals sampling at 256 samples/s using a data acquisition board (National Instruments, USA), and stored for off-line analysis. The signals were band pass filtered, only frequencies between 0.5-40 Hz. were allowed to pass. The polygraph records were inspected visually and epochs containing artifacts discarded. Actometry recording was performed during the sleep-wakefulness cycle investigation. EEG was evaluated minimally during 50 seconds [22]. The standard duration of the separate phases was ultimately determined manually. Two phases of slow sleep were determined in the next way1: the light phase was characterized by the appearance of unstable, relatively low-amplitude activity with separate theta and delta waves, the occurrence of which did not exceed 180 mcV; single alpha-rhythm spindles were also noted at this stage. The second phase - the deep slow wave stage was characterized by an increase in the number and amplitude of theta and delta waves: up to 200 mcV. The latency in both falling asleep and paradoxal sleep were also determined.

d) Leptin administration

Microinjections of leptin were conducted under mild ether anesthesia after fixing the animals in a stereotaxic device. Recombinant murine leptin (5; 25; 50 ng) (Pero Tech EC, London) was dissolved in saline in a volume of 1.0 mcl and was administered at the speed of injections of 0.5 mcl/min using the Hamilton microsyringe. Analogous administration of saline was performed to rats in control the groups. Haloperidol ("Gedeon Richter", Hungary) and

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naloxone ("Sigma", USA) were injected i.p. in a dose of 1.0 mg/kg, 10 min before the leptin administration.

e) Histology

At the end of experiments, the rats were anesthetized with pentobarbital sodium and perfused with paraformaldehyde. Frozen sections (32 μm) of the brain were then prepared and every alternate section mounted on gelatin- coated slides, stained with neutral red, covered with cover- slip, and examined by light microscopy. In all rats used in the analysis of the data the cannula traces and electrodes were identified at the appropriate location.

f) Data Analysis

For data analysis, when appropriate, parametric statistic (Student's t-test, analyses of variance) or the non- parametric statistic (Wilcoxon U-test) were used. Krusckall-Wallis test was used in case of seizure severity estimation. P values <0.05 were considered as statistically significant.

Results

1. Circlings after unilateral leptin injection.

Leptin administration into the left SNR caused the manifestations of contralateral circlings, the intensity of which depended on the dose peptide used. Circlings were observed for 1-5 min following the leptin administration, and their maximal intensity was observed during 2-4 min after the moment of their appearance. Circlings disappeared by the 10th-13th min after the beginning of the observation (Table 1).

Table 1.

Effects of leptin and its combination with naloxone and haloperidol on the indices of the circling behavior

	N of rats	Number of circlings (20 min) mean±SEM		
		Ipsi	Contra	P values ipsi vs contra
Saline, 1.0 mcl	8	0.63±0.5	1.1±0.6	>0.05
Leptin, 5.0 ng	8	0.7±0.5	3.4±0.6	<0.05
Leptin, 25 ng	7	1.1±0.6	5.0±1.0	<0.01
Leptin, 50 ng	7	1.6±0.9	9.1±1.6(*)	<0.01
Leptin, 50 ng + i.p. naloxone (1.0 mg/kg)	7	1.7±0.7	1.0±0.9	>0.05
Leptin, 50 ng + i.p. haloperidol (1.0 mg/kg)	7	0	0	>0.05

(*) - P<0.05 when compared with leptin 5.0 ng group (ANOVA test).

Periodical sniffings were observed in 2 out of 8 animals and 3 animals demonstrated chewing

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during their circlings. These reactions did not differ from those in the control group, where stereotype sniffings were recorded in 3 out of 7 rats. After the placement of the rats in an uncomfortable position (on the side or back) they retained it for 17.9±3.2 sec a significantly longer period in comparison with the analogous data obtained from the animals in the control group (1.4±0.2 sec; $F(1,12)=26.46$, $p<0.001$; Table 2).

Table 2.
Effects of leptin and its combination with naloxone and haloperidol on the duration of uncomfortable position maintenance.

	Time of "uncomfortable position", M±m, sec	P, vs control group
Saline, 1.0 mcl, N=7	1.42±0.16	--
Leptin 50 ng, N=7	17.9±3.2	<0.001
Leptin 50 ng + i.p. naloxone (1.0 mg/kg)	1.38±0.18	>0.05
Leptin, 50 ng + i.p. haloperidol (1.0 mg/kg)	179±35	<0.001

P was calculated using the ANOVA test.

After the preliminary naloxone administration the animals failed to keep the uncomfortable posture imposed to them ($F(1,12)=0.03$, $p>0.05$; Table 2) and neither was circling behavior observed (Table 1). Stereotype sniffings and gnawings were displayed by 3 out of 7 rats. The leptin injection which was administered after a preliminary dose of haloperidol, resulted in much longer retention of uncomfortable posture - 179±35 sec ($F(1,12)=25.74$, $p<0.001$; Table 2). When the animals eventually regained a vertical position, markedly reduced locomotive activity was recorded - the rats remained immobile during all the period of observation (Table 1). Paroxysmal gnawings were observed in 2 out of 8 rats and 2 rats displayed stereotype sniffings.

2. Behavioral changes after bilateral intranigral leptin administration.

3-10 min after the leptin injection into the SNR paroxysmal arrest reactions with a duration of 10-20 sec to 5.0-6.5 min were observed. After the placement of the rats into the center of the "open field", 4 out of 10 animals remained as placed throughout observation (2 min). The average number of squares crossed decreased significantly in comparison with the analogous index in the animals of the control group which decreased respectively from 547±130 to 129±46; $F(1,18)=9.01$, $p<0.01$; Fig.1,A) as well as with its initial value in the

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animals of the experimental group. Furthermore, a significant decrease in vertical bars was observed (Fig.1,A) compared both with the background level and with the activity in the control group (from 27.3±2.5 to 10.9±4.5 ($F(1,18)=10.15$, $p<0.01$).

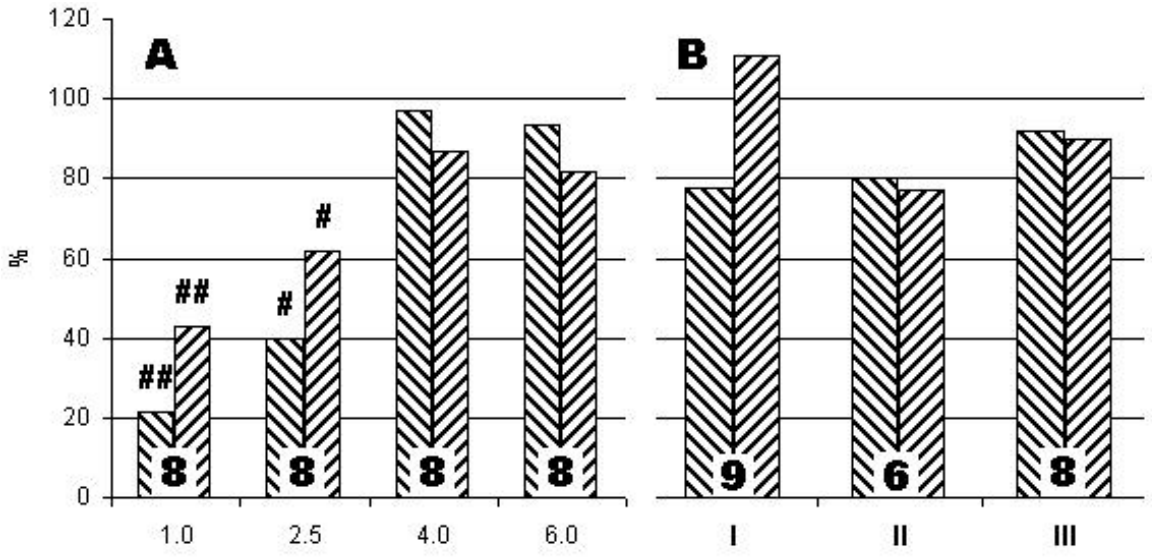

Fig. 1. The influence of leptin injection into SNR and caudate nuclei on locomotor activity of animals
A: Ordinate: the locomotor activity related pertaining to the indices of horizontal and vertical activity in animals treated with saline (control, 100%); Abscissa: time after pharmacons administration (hours).
B: Ordinate: the same as in "A"; Abscissa: I - leptin intra SNR administration in dose of 25,0 ng; II- and III- leptin administration into rostral part of n.caudatus in dosage of 5,0 and 25,0 ng correspondently.
The number of experimental animals are presented inside the bars.
#-P<0,05 and ##-P<0,01 in comparison with the control group.

During locomotion the slowing-down of motor functions, restricted limb movements and decrease in size of steps taken were registered. Significant resistance in passive limb adduction and increase in muscle tonus occurred. Ptosis, periodical gnawing and sniffings were registered in 3 out of 8 animals. The above mentioned behavioral disturbances were observed during a period of 60-80 min after the leptin microinjections with a continual decrease in the indices investigated later on. The absence of differences between the experimental and control groups as well as with the initial level was observed 3.5-6.0 hrs from the moment of leptin intra-SNR administration (Fig.1,A). An intranigral leptin administration in a dose of 5 ng as well as a

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leptin injection into the rostral parts of the nucleus caudatus in a dose of 10 ng did not result in a significant decrease of locomotive activity in the animals (Fig.1,B) and did not alter their behavior.

The sleep-wakefulness cycle investigations carried out on 5 rats with intranigral leptin microinjections revealed a significant decrease in active wakefulness ($F(1,18)=36.13$, $p<0.001$) and prolonged deep slow wave sleep and paradoxal sleep ($F(1,18)=11.08$, $p<0.01$ and $F(1,18)=8.00$, $p<0.05$), correspondently, compared to the analogous indices of the animals in the control group (injected intranigrally with saline) (Fig. 2. A).

These changes were recorded in the background of the decrease in locomotive activity (Fig. 2. B).

3. Leptin effects upon seizure susceptibility to picrotoxin administration.

Picrotoxin (2,0 mg/kg) produced first convulsive reactions at average 22,1± 1,0 min after dosage in control animals (saline injected into SNR). The intensity of seizures increased over the next 10-15 min, and generalized convulsive attacks occurred in 15 of 17 rats with latent period 35,0± 1,5 min. The mean intensity of convulsions was 4,0±0,1 points. The other two rats had clonic convulsions of the entire trunk and hind lambs.

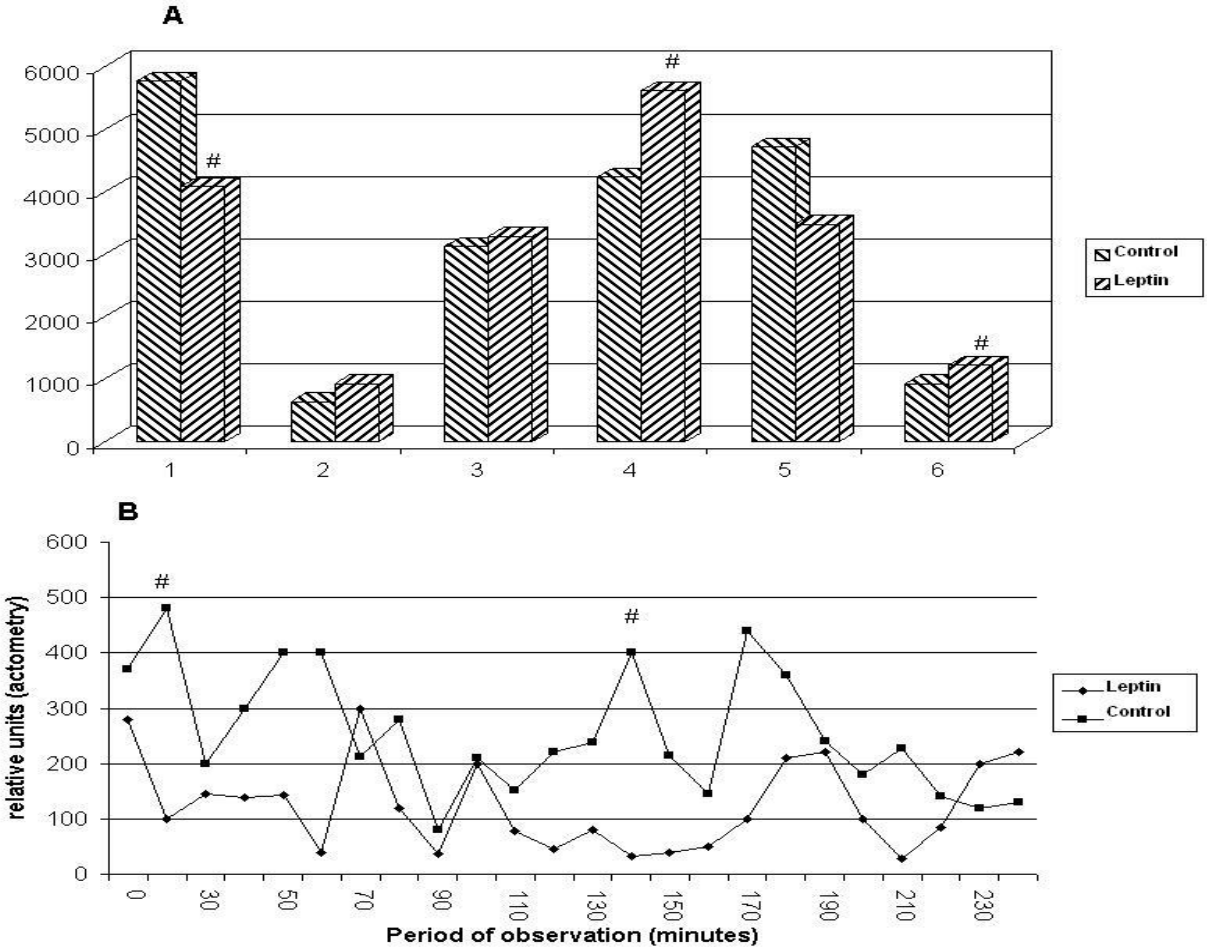

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Fig. 2. A. Ordinate: seconds; Absciss: I- wakefulness; II- latency of sleep precipitation; III- superficial, and IV- deep stages of slow-wave sleep; IV- latency of paradoxal sleep precipitation; VI- paradoxal sleep.
Fig. 2. B. Ordinate: actometry data; Abscissa: time after pharmacons administration (minutes).
#-P<0,05 in comparison with the control group.

Convulsant treatment of rats given bilaterally intranigrally leptin led to the formation of seizures with a latent period which was 24% greater than that in control animals ($F(1,25)=6.61$, $p<0.05$) (Fig. 3). Rats showed intense clonic convulsions of the muscles of the trunk and hindlimbs; two of ten animals developed generalized convulsive seizures. The latency of generalized clonic-tonic fits exceeded that one in control group by 61,0% ($F(1,25)=62.80$, $p<0.001$). The mean severity of seizures was 20% lower than that in control animals ($H=14.52$, $p<0,001$).

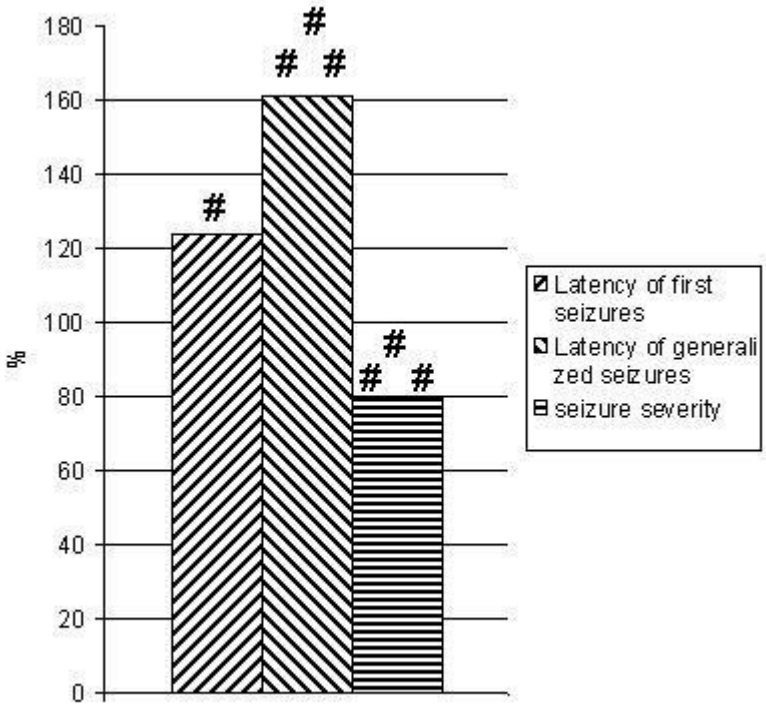

Fig. 3. Seizure manifestations induced by picrotoxin (2,0 mg/kg. i.p.) administration to rats treated intranigrally (SNR) with leptin (25,0 ng).
Ordinate- indices under investigation in % pertained to corresponded ones in the control group of animals (100 %).
#-P<0.05; ###-P<0,001 in comparison with the control group.

Discussion

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Our investigations showed that unilateral leptin administration into the SNR caused contralateral rotations of a dose-dependent character. The efficacy of naloxone in relatively low dosage (1.0 mg/kg) in preventing any circlings suggests that the opioid mechanisms activated by the intranigral leptin are in favor for their development. Haloperidol was also effective in this way. But the simultaneous participation of dopaminergic mechanisms as alternative cause of the circlings could hardly be suggested because the haloperidol and leptin-treated animals retained their uncomfortable posture significantly longer than those treated with separately administered drugs. It might be that the locomotive disabilities influenced with the circlings. Therefore, the potentiation of haloperidol-induced catalepsy by intra-SNR leptin could be supposed and the neuroleptic mode of leptin-induced effects could be suggested. Such a property is in accordance with modulative action of leptin upon mesolimbic dopaminergic system [15, 16]

It should be noted that stereotypic sniffings and gnawings were observed after the application of haloperidol following the intranigral opioid peptides administration [23, 24]. Therefore, the participation of opioid mechanisms in such behavioral changes is not to be excluded. In the case of intranigral leptin injection a significant decrease in wakefulness and increase in deep slow-wave sleep, as well as paradoxical sleep occurred. This data testifies to the fact that SNR structures do take part in the occurrence of deep slow-wave sleep and paradoxal sleep, which are known to enlarge after systemic leptin administration. The activation of the mechanisms of paradoxal sleep is shown to cause anticonvulsive effects [25, 26]. According to [25] the turn on-off mechanisms of paradoxical sleep are determined by noradrenergic brain systems. On the other hand, it was shown that the antiepileptic effects of intranigral muscimol are blocked by yohimbine (alpha-2-adrenoreceptor antagonist), resulting in the disinhibition of noradrenergic terminals [23, 27]. Thus, it could be assumed that the antiseizure effect of intranigral leptin administration, together with the application of other drugs, may be achieved via the paradoxal sleep mechanisms disinhibition as a result of the presynaptic inhibition of corresponding noradrenergic mechanisms. From the viewpoint of the above discussion the ability of leptin to modulate dopaminergic activity [13 - 16] is of great interest.

Hence, the participation of the opiatergic, and catecholaminergic and serotoninergic mechanisms in the creation of behavioral effects of intra-SNR administered leptin might be supposed. Besides, leptin is co-localized in neurons with galanine, which is known as a potent endogenous antiepileptic substance [28].

The above- mentioned scheme of consequences is congruent with the antiepileptic mechanisms realized via action of different substances upon SNR: Just, for the causing antiepileptic effects such mechanisms as activation of GABA mediation [23, 27, 29], kappa-opioid receptors [12] along with blocking of excitatory mechanisms [24] should be mentioned**.** Mentioned induction of neurotransmitter-involved mechanisms is attracted for the explanation of action of each of peptide.

Conclusions:

1. Leptin intranigrally (pars reticulata) induced oligo-akinesia, muscle tonus

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enhancement, decrease of wakefulness period, increase of deep slow-wave sleep and paradoxal sleep. Unilateral leptin administration resulted in the appearance of dose-dependent contralateral circling.

2. Leptin – induced circling are abolished by naloxone, while ability to keep of uncomfortable posture is enhanced with haloperidol administration, which is in favor for opiatergic and neuroleptic mechanisms involvement in leptin- induced effects.

3. Intranigral leptin prevented picrotoxin- insuced generalized seizures.

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Conflict of interest: None declared. Received: 05.01.2014. Revised 15.04.2014. Accepted: 25.04.2014.

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