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Effects of nociceptin neurotransmitter system on nociception in 6-hydroxydopamine model of hemiparkinsonism in rat

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The aim of the present study was to investigate the analgesic effects of N/OFQ(1-13)NH_2, JTC-801 (a NOP receptor antagonist) and a newly synthesized analog on analgesia in a 6-hydroxidopamine model of hemiparkinsonism in rats.

The experiments were carried out on male Wistar rats (180-200g at the time of the surgery). Right-sided hemiparkinsonism has been induced by stereotaxic microinjection of 6-hydroxidopamine into the ventrolateral striatum. Experiments started 15 days after surgery. All the evaluated substances were injected intraperitoneally. Changes in nociception were measured by paw-pressure test and adopted as a sensitivity indicator.

The results showed that N/OFQ(1-13)NH_2 and the newly synthesized analog decreased the pain threshold compared to the control animals. JTC-801 led to a more expressed decrease in pain threshold compared to N/OFQ(1-13)NH_2 and the analog.

We tried to elucidate the participation of the nociceptinergic mediator system in the sensory disorders in Parkinson`s disease. The results obtained suggest that the effect is more a modulating one, since the NOP-receptor agonist and the antagonist led to unidirectional changes that differ in magnitude. We assume that the nociceptinergic system is involved in sensory modulation in the adopted model of hemiparkinsonism.

Keywords: nociceptin, N/OFQ(1-13)NH_2, JTC-801, NOP ligands, analgesia, Parkinson disease model

INTRODUCTION

Parkinson disease (PD) is the second most common age-related progressive neurodegenerative disease after Alzheimer's disease. Described first by James Parkinson in 1817 in his monograph "Essay on the Shaking Palsy", more than a century had to pass before its central pathological feature was discovered. In 1958 Arvid Carlsson made the discovery of dopamine (DA) in the mammalian brain. Then the pathologic hallmark of PD was established to be a degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Loss of SNpc neurons leads to striatal DA deficiency. This neurotransmitter regulates excitatory and inhibitory outflow of the basal ganglia [1, 2] and is responsible for the major symptoms of PD resulting from the depletion of striatal dopamine [2-4].

From a clinical point of view PD is characterized principally by the syndrome of bradykinesia, tremor, rigidity, and postural instability.

Along with the motor dysfunction there is an increasing recognition of non-motor symptoms in PD patients, some of which may precede the onset of motor symptoms by many decades. Non-motor symptoms such as pain, dementia, anxiety, and depression are common in PD [5].

As a common problem in PD pain can either be directly caused by PD or secondary - due to other reasons [6]. The exact mechanisms of the phenomenon have still to be elucidated.

Different studies report a prevalence of pain in PD between 40 and 85% [7-13]. The variation in prevalence rates may be related to inclusion criteria, to definition of pain or to differences in patient population across centers. Specific features of pain including its localization were evaluated in some studies [14, 15].

Pain is reported by nearly half of patients with PD and its prevalence is higher than in general population [8- 12]. Furthermore PD patients' cases are reported with pain symptoms antedating the onset of motor symptoms [10, 16]. Other non-motor dysfunctions, like olfactory dysfunction, are even considered as a useful diagnostic marker of preclinical PD, because pathological changes are recognized before the motor symptoms` development [17].

The heptadecapeptide Nociceptin/Orphanin FQ (N/OFQ) is an endogenous ligand of the opioid-like receptor named ORL_1 or N/OFQ peptide (NOP) receptor, a novel member of the opioid receptor family [18-20]. Through its receptor N/OFQ modulates a number of biological functions in the

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central and the peripheral nervous system [20, 21], and is relevant for the modulation of pain perception, locomotion, etc. Its receptor is expressed both spinally and supraspinally in the central nervous system [18, 19].

N/OFQ(1-13)NH_2 is the shortest sequence of the N/OFQ molecule preserving its biological effects [22].

The understanding of the role of the N/OFQ/NOP system depends upon the development of selective and highly potent ligands. Among them are N/OFQ related peptides and small peptides, identified by screening of peptide combinatorial libraries [23].

Based on the templates Ac-Arg-Phe-Met-Trp-Met-Lys-NH_2 (opioid receptor antagonist) [25] and Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH_2 (highly potent and selective NOP-receptor agonist) [24] new series of hexapeptides were recently synthesized and evaluated by our group [26, 27].

Our recent results showed that the presence of a N-methyl β^2-tryptophan residue in position 5 in Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH_2 modified the selectivity of the referent peptide. The same group in position 4 did not change the properties of Ac-Arg-Phe-Met-Trp-Met-Lys-NH_2, while the 5-methoxy β^2-tryptophan residue led to significant changes in peptides' selectivity and affinity [27]. Replacement of Trp with β^2-tryptophan analogues in position 4 of Ac-Arg-Phe-Met-Trp-Met-Lys-NH_2 led to increased and longer lasting analgesic effect [26].

The interrelations between N/OFQ, its receptor NOP, and PD are subjected to intense research [7, 9]. N/OFQ exerts an inhibitory control on locomotion through inhibition of DA neurons in the SN [28]. Literature data show that dopamine depletion in PD increases N/OFQ expression in SN [1, 29-31].

Most of the scientists investigating PD are still interested in motor dysfunctions and the possibility to influence them. Our interest was focused on sensory dysfunctions and how the nociceptin system influenced pain perception in a rat model of PD.

The effect of N/OFQ(1-13)NH_2, JTC-801 (NOP-receptor antagonist), and novel hexapeptides containing β^2-tryptophan analogues on nociception were evaluated in a rat model of hemiparkinsonism. The effects of the latter on nociception were compared to N/OFQ(1-13)NH_2.

EXPERIMENTAL

Animals

The experiments were carried out on male Wistar rats (200-240 g at the time of experiments). The rats were housed individually in polypropylene boxes with free access to food and water and maintained in a constant temperature environment (22 ±2ºC) on a 12 h light/dark cycle (lights on at 6.00 a.m.). The behaviour experiments were carried out between 10:00 a.m. and 1:00 p.m.

The experiments were carried out according to the ''Principles of laboratory animal care'' (NIH publication No. 85_23, revised 1985), and the rules of the Ethics Committee of the Institute of Neurobiology, Bulgarian Academy of Sciences.

Stereotaxic drug injection into the ventrolateral striatum

After intraperitoneal anaesthesia with a mixture of ketamine (75 mg/kg), acepromazine (0.75 mg/kg) and rompun (4 mg/kg), the animals were placed in a stereotaxic apparatus (Stoelting, USA). Burr hole was drilled at the following coordinates for ventrolateral striatum according to the stereotaxic atlas of Pellegrino and Cushman (1967) relative to bregma: posterior 1.1 mm; lateral 3.1 mm. 8 μg (free base weight) 6-OHDA (RBI) was dissolved *ex tempore* in 2 μl of 0.2% ascorbic acid with 0.9% normal saline. 2 μl of the solution was microinjected trough Hamilton micro-syringe (Hamilton, Reno, NV) at a depth of 6 mm below the dura over a period of 2 min (rate 0.5 μl /m) and the injection cannula was left in place for additional 30 seconds. The control group was microinjected with 2 μl saline into the same area. Immediately prior to sacrificing the animals were injected with 1 ml 2% Fastgreen dye through the injection cannula.

Injection sites were then anatomically verified post-mortem in 25 mm coronal brain sections cut through the hippocampus by an investigator, blind to the behavioural results. Results from animals with cannulas` placements outside the ventrolateral striatum area were excluded from the statistical analysis.

After the model of right hemiparkinsonism was performed a 15-days period was observed before the beginning of the experiments.

All the evaluated substances were dissolved in sterile saline (0.9% NaCl) solution and were injected intraperitoneally (i.p.). N/OFQ(1-13)NH_2 and the new hexapeptides were administered at a dose of 10 μg/kg, while JTC-801 was administered at a dose of 0.5 mg/kg. N/OFQ(1-13)NH_2 and JTC-801 were obtained by Sigma. The substituted NOP-

receptor ligands were synthesized in the Department of Organic Chemistry of the University of Chemical Technology and Metallurgy - Sofia [26].

Nociceptive test

Paw-pressure test (Randall-Selitto test). The changes in the mechanical nociceptive threshold of the rats were measured by the use of an analgesiometer (Ugo Basile). Increasing pressure (g) was applied to the hind-paw and the value required to elicit a nociceptive responses (a squeak or struggle) was taken as the mechanical nociceptive threshold. A cut-off value of 500 g was observed in order to prevent damage of the paw.

The results were statistically assessed by one-way analysis of variance ANOVA followed by t-test comparison. Values are mean ± S.E.M. Values of $p \leq 0.05$ were considered to indicate statistical significance.

The experimental procedures were carried out in accordance with the requirements of the Ethical Committee of the Medical University of Sofia.

RESULTS

Nociception in animals with right-side hemiparkinsonism (RSHP) was investigated. The left paw without 6-OHDA lesion was regarded as auto-control (AC).

In the first series of experiments N/OFQ(1-13)NH_2 or the NOP-receptor antagonist JTC-801 was applied to the animals. Measuring the pain threshold started 10 min after injection of the substances.

The left paw (AC) had the higher pain threshold as compared to the control group ($p<0.01$). Right paws showed higher pain threshold in comparison both to the control ($p<0.001$) and AC-paws during the whole time investigated (Fig. 1).

On the 10th min after N/OFQ(1-13)NH_2 administration at a dose of 10 μg/kg the pain threshold was decreased for AC- and RSHP-paws compared to AC- ($p<0.01$) and RSHP-paws ($p<0.01$) of animals without the substance respectively. The pain threshold for AC of animals with N/OFQ(1-13)NH_2 on the 10th min was comparable to the controls.

An additional decrease in pain thresholds was observed on the 20th min after N/OFQ(1-13)NH_2 administration for both AC- and RSHP-paws of animals with N/OFQ(1-13)NH_2 compared to the AC- ($p<0.001$) and RSHP-paws ($p<0.001$) of animals without the substance respectively.

Compared to the control animals on the 20th min the AC-paws in animals with N/OFQ(1-13)NH_2 showed a tendency toward hyperalgesia ($p<0.01$), while the pain threshold for RSHP-paws of the same animals was comparable to the controls (Fig. 1).

Hence, N/OFQ(1-13)NH_2 affected pain perception both in auto-control paws and the RSHP ones. The nociceptive effects were more pronounced and pain thresholds of both the estimated paws were lower than the controls on the 20th min of the evaluation (Fig. 1).

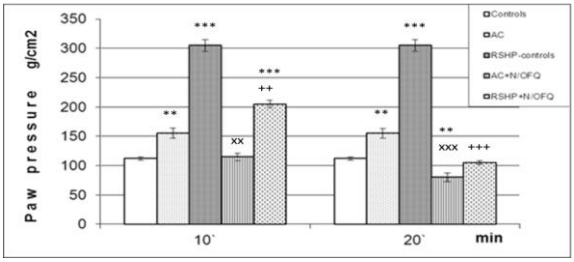


Fig. 1. Effects of N/OFQ(1-13)NH_2 (10 μg/kg, i.p.) on the pain threshold in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. AC and RSHP-animals were compared to controls ($^{***}p<0.001$; $^{**}p<0.01$); AC with N/OFQ(1-13)NH_2 were compared to controls ($^{**}p<0.01$) and to AC without the substance (^{xxx} $p<0.001$; ^{xx} $p<0.01$); RSHP-animals with N/OFQ(1-13)NH_2 were compared to controls ($^{***}p<0.001$) and to RSHP-controls (RSHP-animals without N/OFQ(1-13)NH_2) ($^{+++}p<0.001$; $^{++}p<0.01$).

Administration of the NOP-receptor antagonist JTC-801 at a dose of 0.5 mg/kg led to a statistically significant decrease in pain threshold both for AC- and the RSHP-paws (Fig. 2). In AC-paws of animals with JTC-801 the nociception increased compared to AC of animals without the substance. On the 10th min the pain threshold of RSHP-paws in animals with JTC-801 was significantly lower than RSHP-paws of animals without the antagonist administration, but higher than the control animals (Fig. 2).

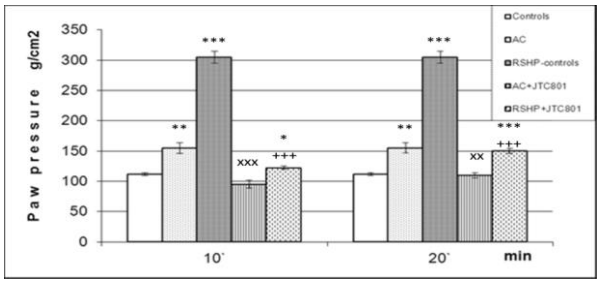


Fig. 2. Effects of JTC801 (0.5 mg/kg, i.p.) on pain threshold in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. AC and RSHP-animals were compared to controls

(***p<0.001; **p<0.01); AC with JTC801 were compared to controls (***p<0.001; **p<0.01) and to AC without the substance (^{xxx}p<0.001; ^{xx}p<0.01); RSHP-animals with JTC801 were compared to controls (***p<0.001; *p<0.05) and to RSHP-controls (RSHP-animals without JTC801) ($^{+++}$p<0.001).

On the 20th min the nociception for AC+JTC-801 was still comparable to the controls and higher than the AC without the antagonist. RSHP-paws of animals with JTC-801 showed lower pain thresholds than the RSHP-paws of animals without the antagonist; values were comparable to the AC (Fig. 2).

Hence, NOP-receptor antagonist JTC 801 affected pain perception of both AC- and RSHP-paws in animals with hemiparkinsonism. The nociceptive effect was most pronounced on the 10th in of the experiment.

Since both the NOP-receptor agonist and the antagonist JTC 801 led to a decrease in the pain thresholds for both AC- and RSHP-paws compared to animals without substances administration, an additional comparison was made for AC- and RSHP-paws with N/OFQ(1-13)NH$_2$ and JTC 801(Fig. 3).

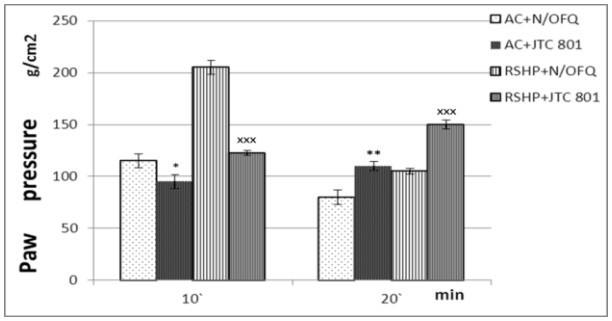


Fig. 3. Comparison between the nociceptive effects of N/OFQ(1-13)NH2 and JTC801 administrated in AC and RSHP-animals. The results are represented as mean values ± S.E.M. AC with JTC801 were compared to AC with N/OFQ(1-13)NH2 (**p<0.01; *p<0.05); RSHP-animals with JTC801 were compared to RSHP-animals with N/OFQ(1-13)NH2 (^{xxx}p<0.001).

The comparison between the nociceptive effects of N/OFQ(1-13)NH$_2$ and JTC 801 administered in animals with hemiparkinsonism showed that on the 10th min of the experiment both AC- (p<0.05) and RSHP-paws (p<0.001) of animals with the NOP-receptor antagonist had lower pain thresholds, while on the 20th min AC- (p<0.01) and RSHP-paws (p<0.001) of animals with the NOP-receptor agonist had the lower pain thresholds (Fig. 3).

An additional series of experiments was conducted with first JTC801 administration (0.5 mg/kg, i.p.) and 10 min later N/OFQ(1-13)NH$_2$ (10 μg/kg, i.p.) administration in animals with experimental RSHP. The results were represented in two figures – one for the AC-paws (Fig. 4) and one for the RSHP-paws (Fig.5).

On the 10th min of the experiment the Paw pressure test showed that the pain threshold for AC+ N/OFQ(1-13)NH$_2$ + JTC801 was comparable to the controls, the AC + N/OFQ(1-13)NH$_2$, and the AC + JTC801.

On the 20th min of the experiment the nociception for AC + N/OFQ(1-13)NH$_2$ + JTC801 was increased in respect to controls (p<0.001, AC without any substances (p<0.001), and AC with the antagonist (p<0.01), but was comparable to the AC with N/OFQ(1-13)NH$_2$ (Fig. 4).

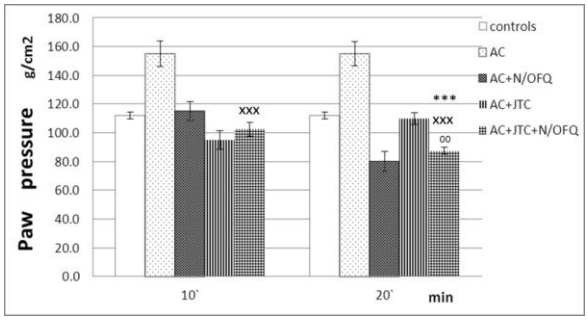


Fig. 4. Effects of N/OFQ(1-13)NH2 (10 μg/kg, i.p.) applied after JTC801 (0.5 mg/kg, i.p.) on the pain threshold in auto-control (AC) animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. AC-animals with both JTC801 and N/OFQ(1-13)NH2 were compared to controls (***p<0.001), to AC without any substances (^{xxx} p<0.001), to AC with N/OFQ(1-13)NH2 (without statistically relevant difference), and to AC with JTC801 (00p<0.01).

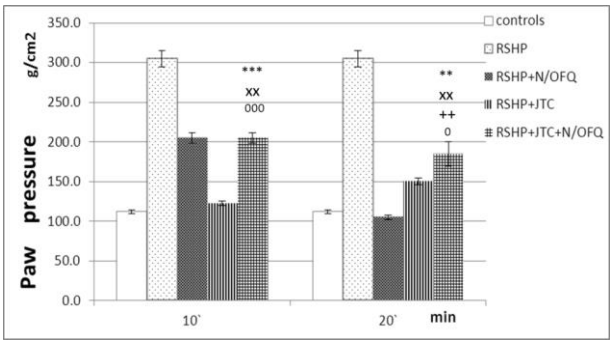


Fig.5. Effects of N/OFQ(1-13)NH$_2$ (10 μg/kg, i.p.) applied after JTC801 (0.5 mg/kg, i.p.) on the pain threshold in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. RSHP-animals with both JTC801 and N/OFQ(1-13)NH$_2$ were compared to controls (***p<0.001; **p<0.01); to RSHP without any substances (^{xx} p<0.01); to RSHP with N/OFQ(1-13)NH$_2$ ($^{++}$p<0.01), and to RSHP with JTC801 (^{000} p<0.001; ^{0} p<0.05).

As to RSHPpaws+N/OFQ(1-13)NH$_2$+JTC801, the pain threshold on the 10th min was comparable

to RSHP-paws of animals with N/OFQ(1-13)NH_2. The nociception for RSHP-paws in animals with both N/OFQ(1-13)NH_2 and JTC801 was decreased compared to the controls ($p<0.001$) and the RSHP-paws of animals with JTC801($p<0.001$), but increased in comparison to RSHP-paws of animals without any substances ($p<0.01$).

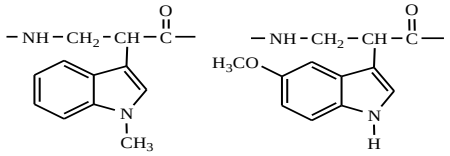
On the 20th min the pain threshold of RSHP-paws + N/OFQ(1-13)NH_2 +JTC801 was still lower than RSHP-paws of animals without any substances ($p<0.01$), but was higher than controls ($p<0.01$) and animals with the NOP receptor agonist ($p<0.01$) and antagonist ($p<0.05$) separately administered (Fig. 5).

In another series of experiments we investigated the effects on nociception of two newly synthesized hexapeptides modified in 4th position with β^2-tryptophan analogs containing methyl group (analog 1) and methoxy group (analog 2) in the indole functional group.

The novel hexapeptides containing β^2-tryptophan analogues have the following sequences:

Ac-Arg-Phe-Met-**X**-Met-Lys-NH_2

Where ***X*** is:



analog 1 analog 2

Analog 1`s administration in animals with hemiparkinsonism did not change AC-paws` pain threshold during the whole period of observation compared to AC-paws in animals without the substance. Analog 2`s administration led to a decrease in AC-paws` pain threshold compared to AC-paws of animals without the substance ($p<0.01$) only on the 20th min of the evaluated period (Fig. 6).

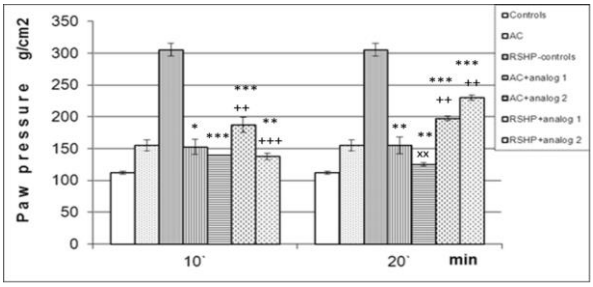


Fig. 6. Effects of hexapeptides 1 and 2 (10 μg/kg, i.p.) on pain threshold in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. AC with analogs 1 and 2 were compared to controls ($^{***}p<0.001$; $^{**}p<0.01$; $^{*}p<0.05$) and to AC without the substances ($^{xx}p<0.01$); RSHP-animals with analogs 1 and 2 were compared to controls ($^{***}p>0.001$) and to RSHP without the substances ($^{+++}p<0.001$; $^{++}p<0.01$).

Analogs` injection led to a statistically significant decrease in pain threshold of RSHP-paws compared to RSHP-paws of the animals without substances` administration. After analog 1 an increase of nociception was observed for the whole estimated period in RSHP-paws compared to the same paws in animals without the substance ($p<0.01$). On the 10th min analog 2 led to a more pronounced decrease in RSHP-paws` pain threshold compared to analog 1. On the 20th min a decrease in nociception was detected for RSHP-paws of animals with analog 2 compared to the same paws of animals with analog 1 and RSHP-paws of animals with analog 2 on the 10th min (Fig 6).

DISCUSSION

Pain is a frequently reported symptom in PD-patients [7-12]. It can be attributed to changes in sensory centers of the brain (primary pain) or can be caused by rigidity, dystonia or dyskinesia (secondary pain) [32].

Over the last decade researchers have extended their interest to objective alteration of sensory information processing. Patients with PD have altered central somatosensory processing [33]. Animal studies suggested that basal ganglia act as a sensory analyzer that integrates and focuses adequate sensory impulses, therefore modulating motor performance [34]. Although the degeneration of dopaminergic neurons in the SNpc is retained to be the pathologic hallmark of PD, and the regulating role of the dopaminergic system in excitatory and inhibitory outflow of the basal ganglia is well established [1, 2], some clinical trials report no correlation between motor symptoms, dopaminergic medication and pain [9, 10]. Some results also suggest that neurodegeneration of other non-dopaminergic basal ganglia neurotransmitter systems may be responsible for the sensory abnormalities in PD [33].

N/OFQ and its receptor represent a neuropeptide system that bears structural and functional analogies with classical opioid systems but possesses a pharmacological profile of its own [20]. NOP receptor expression and binding are widespread throughout the rodent and primate brain, supporting that the N/OFQ-NOP receptor system plays a substantial role in the modulation of central functions such as sensory nociceptive processing, learning and memory, reward, mood, feeding, stress, and movement [21, 35]. Preclinical

and clinical studies revealed a link between N/OFQ and Parkinson's disease [29, 36, 37].

Literature data suggest changes in N/OFQ-NOP receptor system in patients with PD, concerning NOP receptor gene expression [30], N/OFQ expression and release in the SN [31, 37], and N/OFQ levels in the cerebrospinal fluid of parkinsonian patients [37].

It`s known that N/OFQ is released from SN GABA neurons [38]. Exogenously administrated N/OFQ inhibits nigrostriatal DA transmission *in vivo* [39] and elevates glutamate (GLU) release in the SN reticulata *in vivo* [40]. Some data suggest an endogenous N/OFQ tone in the regulation of motor functions, and different selective antagonists [20, 41] improve nigrostriatal DA transmission and motor behavior, and inhibit glutamate release from substantia nigra [39, 40, 42].

Since most of the efforts were to establish the effect of N/OFQ on motor functions, our interest was to estimate potential changes in pain perception. Our results showed that experimental hemiparkinsonism in rats led to an increase in pain thresholds both for the paws unilateral (AC) and contralateral to the lesion (experimental-hemiparkinsonism-affected paws) as compared to control animals. Administration of the NOP-receptor agonist decreased the pain thresholds in auto-control paws as well as in experimental-hemiparkinsonism-affected paws of the animals. The pro-nociceptive effect of N/OFQ(1-13)NH_2 has been documented by other research groups [43], while others report the pro-analgesic effect of the substance [44, 45].

Acute pain activates C- and Aδ-nociceptive pain fibers, but the presence of the NOP receptor on them hasn`t been documented till now. Experimental data rather suggest that the receptor is transported to either the sensory projections endings in laminae II and III, or to the nerve terminals in peripheral tissues [46, 47]. Concentration of N/OFQ-immunoreactivity was detected in fibers that innervate the superficial layers of the dorsal horn and such immunoreactivity was not altered by unilateral dorsal rhizotomy, suggesting that N/OFQ is not predominantly produced in primary afferent neurons whose cell bodies are located in dorsal root ganglia, but rather is produced within the spinal cord [48]. Such observations support the idea that N/OFQ can modulate pain transmission by activating NOP-receptors located in the central nervous system.

An endogenous tone of the N/OFQ has been proposed since NOP-antagonists produced antinociception when given alone [49, 50]. Surprisingly, in our experiments JTC-801 administration alone also led to a decrease in pain threshold for paws both homo- and contralateral to the lesion. Such results can hardly be explained since literature data point out that NOP-receptor antagonists antagonized agonist`s effects independently whether pro-analgesic or pro-nociceptive [51]. A possible reason might be that disease-related changes in pain-perception account for the results observed.

A comparison between agonist`s and antagonist`s effect showed that the latter`s pro-nociceptive action occurred earlier, on the 10^{th} min, while N/OFQ(1-13)NH_2 had the more pronounced effect on the 20^{th} min of the experiment both with AC- and RSHP-paws. When N/OFQ(1-13)NH_2 was injected 10 min after JTC-801 the results obtained for the AC on the 20^{th} min were comparable to those for agonist`s alone administration, while for RSHP-paws such a relationship was obtained on the 10^{th} min. Additional experiments are needed to discover the complex interrelations underlying pain perception in parkinsonism.

As to the two newly synthesized hexapeptides, the parent molecule Ac-Arg-Phe-Met-Trp-Met-Lys-NH_2 was originally proved to act as an opioid antagonist. The substitution in position 4 with a 5-methoxy β^2-tryptophan residue conferred to the newly synthesized substance the characteristics of a weak NOP-receptor agonist, while the substitution in the same position with N-methyl β^2-tryptophan residue did not change the affinity of the parent molecule [27]. Despite nociceptin doesn`t interact with opioid receptors [21, 52] some authors showed that nociceptin antagonized some analgesic opioid effects [53] which suggests a potential interrelation between systems involved in nociception and additionally complicates the interpretation of the experimental data obtained. Our experiment showed that the effects of analog 1 (opioid receptor antagonist) on nociception both in AC- and RSHP-paws had no paragon with the dynamic curve of animals with N/OFQ(1-13)NH_2, but changes in pain perception were still observed compared to animals with N/OFQ(1-13)NH_2. Analog 2 (the one with affinity reverted to weak NOP-receptor agonist) showed for AC-paws a dynamic curve similar to the one for AC+N/OFQ(1-13)NH_2. In RSHP-paws such a similarity was not observed, probably due to disease`s influence over the pain perception pathways.

CONCLUSION

Our experiments tried to elucidate the participation of the nociceptinergic mediatory

system in the sensory disorders in Parkinson`s disease. The effect seemed to be more a modulating one, since NOP-receptor agonist and antagonist led to unidirectional changes that differ in magnitude.

Our data showed that administered alone JTC-801 led to a decrease in pain threshold for paws both homo- and contralateral to the lesion. These results are difficult to explain and aren`t supported by any other literature data since now. They point out that NOP-receptor antagonists antagonized agonist`s effects independently whether pro-analgesic or pro-nociceptive.

After analogs` injection in animals with experimental Parkinsonism a decrease in pain threshold was observed. Analog 1 increased nociception for the whole estimated period in RSHP-paws of the animals compared to RSHP-paws of the animals without the substance, while analog 2 led to a more pronounced decrease in pain threshold in RSHP-paws compared to analog 1 on the 10^{th} min. On the 20^{th} min a decrease in nociception was detected for RSHP-paws of animals with analog 2 compared to RSHP-paws of animals with analog 1 and RSHP-paws of animals with analog 2 on the 10^{th} min. The results showed that the effects of the two analogs were time-dependent.

The newly synthesized hexapeptides also suggest that there is a possible interrelation between opioid and NOP-receptor pathways in mediation of pain perception in Parkinson`s disease.

The authors declare no potential conflict of interest.

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ЕФЕКТИ НА НОЦИЦЕПТИНОВАТА НЕВРОТРАНСМИТЕРНА СИСТЕМА ВЪРХУ НОЦИЦЕПЦИЯТА ПРИ 6-ХИДРОКСИДОПАМИНОВ МОДЕЛ НА ХЕМИПАРКИНСОНИЗЪМ ПРИ ПЛЪХ

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(Резюме)

Целта на настоящето проучване бе изследване ефекта на N/OFQ(1-13)NH_2, JTC-801 (NOP-рецепторен антагонист), както и на новосинтезирани ноцицептинови аналози върху аналгезията при 6-хидроксидопаминов модел на хемипаркинсонизъм при плъхове.

Експериментите бяха проведени върху мъжки плъхове от породата Wistar (180-200 гр по времето на интервенцията). Десностранен хемипаркинсонизъм бе индуциран чрез стереотаксично микроинжектиране на 6-хидроксидопамин във вентролатералния стриатум. Експериментите започваха 15 дена след интервенцията. Изследваните субстанции се въвеждаха интраперитонеално. Промените в ноцицепцията се определяха посредством paw-pressure test.

Резултатите показаха, че N/OFQ(1-13)NH_2 и неговият новосинтезиран аналог понижават болковия праг в сравнение с контролните животни.

Чрез описаните експерименти бе направен опит за изясняване участието на ноцицептин-ергичната система в сетивните нарушения при Паркинсонова болест. Получените резултати показаха, че ефектът й е по-скоро модулаторен, тъй като както агонистът, така и антагонистът на NOP-рецептора показаха еднопосочно повлияване, но в различна степен. Приемаме, че ноцицептин-ергичната система модулира сетивността при изпозвания модел на хемипаркинсонизъм.