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Research Article



Parkinson`s disease: MIF-1`s modulation on cannabinoids` effect on nociception

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Abstract

Parkinson`s disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra, but it is now clear that its pathogenesis is underlined by interaction of different mediatory systems. The endocannabinoid system (ECS) is vastly distributed in the central nervous system and represents a potential therapeutic approach for a number of neurologic diseases, PD among them. MIF-1`s modulating action on ECS is also of interest as well as ECS and peptides combined effect on pain perception in PD. Cannabinoids` and MIF-1`s interactions were estimated in a rat model of 6-hydroxydopamine hemiparkinsonism by Paw pressure test. Anandamide influenced pain perception in control animals as well as in animals with experimental PD. MIF-1 modulated ECS in PD-animals compared to controls. Our conclusion is that MIF-1 interacts with ECS and modulates pain perception in 6-hydroxydopamine hemiparkinsonism model in rats.

Keywords: Parkinson`s disease, MIF-1, cannabinoid system, pain perception, 6-hydroxydopamine hemiparkinsonism

Introduction

Parkinson`s disease (PD) affects between 1 and 3% of the population over 50 years of age. It represents a chronic incurable progressive neurodegenerative disease characterized predominantly by motor disturbances – tremor, rigidity, bradykinesia, and postural disorders.³³ The pathological hallmark of PD is specific degeneration of dopaminergic neurons in the substantia nigra pars compacta (McNamara et al., 2010; Lanciego et al., 2012). The basal ganglia represent a complex integrative system in the central nervous system (CNS) comprising substantia nigra, putamen, nucleus caudatus, nucleus accumbens, and globus pallidus. The effectiveness of such a system depends on the synaptic transmission representing itself the outcome of interaction (and integration) of different neurotransmitters and neuromodulators Graybiel et al., 1990; Lovinger, 2010). Animal studies suggested that basal ganglia play also a role as a sensory analyzer integrating and focusing adequate

sensory impulses, and finally modulating motor performance (Boecker et al., 1999). Such a sensorimotor integration links sensory input to the motor output producing adequate voluntary movements (Abbruzzese et al., 2003; Machado et al., 2010), and probably accounts for the pathogenesis of bradykinesia in PD.

Over the last decade researchers have focused their interest on purely sensory functions in PD. Along with motor dysfunctions 75% of PD patients manifest also sensory disorders with pain among them (Chaudhuri et al., 2006; Defazio et al., 2008). Living organisms possess a complex mechanism to control pain sensations. The antinociceptive pathways integrate two interrelated components – an opioid and a non-opioid one (Mogil et al., 1996).

The opioid component is connected with the opioid system – consisting of the opioid receptors (μ -, κ -, δ -,

-, -) and their endogenous ligands (-endorphins, enkephalins, and dynorphin) (Reed et al., 1994; Kieffer, 1995). The non-opioid component of analgesia integrates different neuromodulator/neurotransmitter systems - the adrenergic, the serotonergic, the nitric-oxide, and the endocannabinoid (ECS) systems.

Experimental data support the importance of the ECS in the central and the peripheral nervous system. The ECS consists of two types of cannabinoid receptors (1, 2), their endogenous ligands, and the enzyme systems involved in their synthesis and degradation (Howlett, 2002; Finn, 2010).

1 predominates in the brain and especially in the basal ganglia. It has been proven in the last years that the endocannabinoids exerted an important role in the striatum: they influenced its normal functions, interacted with dopamine and mediated the changes after dopamine depletion (Fernandez-Ruiz, 2009; Lovinger, 2010). It has also been proved that endocannabinoids levels in the striatum increased after dopamine depletion (Gubellini et al., 2002; Lovinger, 2010). The role of endocannabinoid and peptidergic neurotransmissions in the pathogenesis of motor dysfunctions in PD has also been confirmed (Brotchie, 2003; Sagredo et al., 2007; Garsia-Arencibia et al., 2009).

Melanocyte-stimulating hormone release inhibiting factor-1 (MIF-1), also known as PLG based on its amino acid structure (Pro-Leu-Gly-NH₂), is an endogenous brain peptide that exerts a variety of pharmacological effects on the central nervous system (Pan et al., 2007). It is the first peptide with proven anti-opioid effects (Mishra et al., 1983). Clinical studies have shown that MIF-1 can alleviate symptoms in PD probably due to a modulating effect on the dopaminergic neurotransmission (Mishra et al., 1990, 1997; Drucker et al., 1994; Rodrigues et al., 2002).

The dopaminergic neurotransmission is undoubtedly crucial to the pathogenesis of motor dysfunctions in PD, and it is also important in modulating pain perception and natural analgesia within supraspinal striatal and extra-striatal regions. Yet there are some evidences suggesting that other non-dopaminergic basal ganglia neurotransmitter systems may account for proper sensorimotor integration (Dray, 1981; Defazio et al., 2008; Machado et al., 2010) and thus influence the sensorimotor integration. In this regard

the ECS represents an interesting item, because of its involvement, on one hand, in pain perception, and on the other, in modulating neurotransmission in PD (Fox et al., 2002; Sagredo et al., 2007; Garsia-Arencibia et al., 2009).

In the present study we evaluated the modulating effect of MIF-1 on pain perception after injection of CB-1 agonist anandamide. The experiments were performed in a rat model of 6-hydroxydopamine (6-OHDA)-induced parkinsonism which is one of the most common animal models of PD. 6-OHDA is a hydroxylated analog of natural dopamine that selectively destroys catecholamine neurons. It also leads to production of reactive oxygen species that damage proteins, lipids and DNA, cause mitochondrial inhibition and impairment, and ATP deficiency (Kumar et al., 1995; Blum et al., 2001; Dauer et al., 2003).

Materials and Methods

Animals

The experiments were carried out on male Wistar rats (200-240 g at the beginning of study), housed individually in polypropylene cages (40 × 60 × 20 cm, 8–10 rats in each) at a temperature-controlled colony room maintained at 21 ± 3 °C under 12:12 h light/dark cycle with lights on at 6:00 a.m. The animals were given free access to tap water and standard rat chow. All procedures 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

Rats were anesthetized with intraperitoneal injection of 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). 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 and 2 µl of the solution was microinjected through Hamilton micro-syringe (Hamilton, Reno, NV) at the following coordinates: AP +4.4 mm, ML 1.2 mm relative to bregma, and DV -7.5 mm from the dura over a period of 2 min (rate 0.5

µl /min) 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.

Drugs and treatment

All drugs were obtained from Sigma. Anandamide (arachidonoyl ethanolamide, AEA) at a dose 1mg/kg was dissolved in DMSO and injected intraperitoneally (i.p.). MIF-1 was dissolved in sterile saline solution (0.9% NaCl) and i.p. injected at a dose 1mg/kg 10 min after AEA.

Nociceptive test

Paw-pressure test (Randall-Sellito test)

The changes in the mechanical nociceptive threshold of the rats were measured by analgesiometer (Ugo Basile). Increasing pressure (g) was applied to the

hind-paw and the value required to elicit a nociceptive response (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.

Statistical analysis

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 0.05 were considered to indicate statistical significance.

Results

Left-sided injection of 6-OHDA led to right-sided hemiparkinsonism (RSHP). The right paws of the animals were regarded as RSHP-paws, while the homolateral to the lesion ones were regarded as auto-controls (AC). Animals with saline microinjection were taken in consideration as controls.

Estimation of pain thresholds of the control animals, the AC, and the RSHP without any substances administrated showed that AC and RSHP had higher values than controls with RSHP being the highest (Fig. 1).

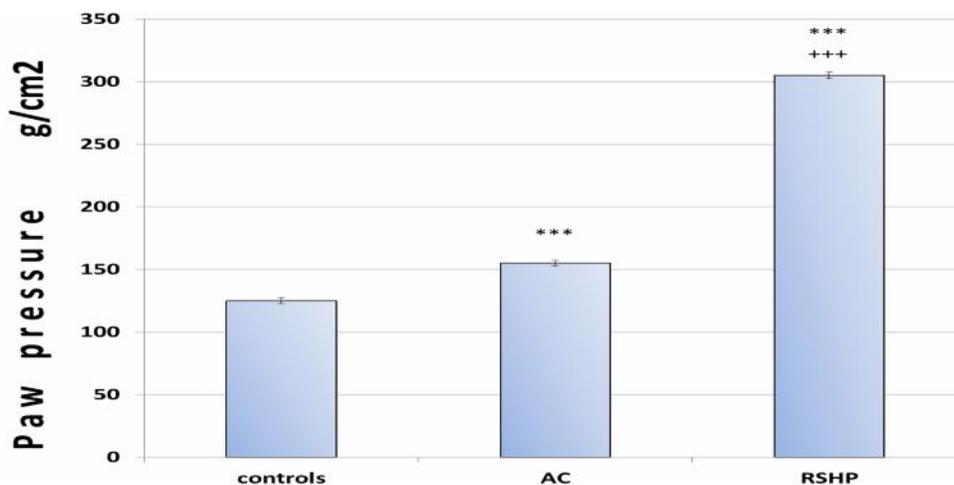


Fig. 1. Pain thresholds of control animals, left auto-control-paws (AC) and right 6-OHDA-hemiparkinsonian paws (RSHP) before evaluated substances administration. The results are represented as mean values ± S.E.M. AC and RSHP were compared to controls (***)p<0.001); RSHP were compared to AC (++)p<0.001).

Effects of cannabinoid mediatory system on pain perception were estimated 10 min after AEA administration.

After AEA injection the pain thresholds of AC and RSHP increased in respect to the control values. AC+AEA values were higher than AC on the 10th min (Fig. 2), and similarly RSHP+AEA were higher than RSHP (Fig. 3).

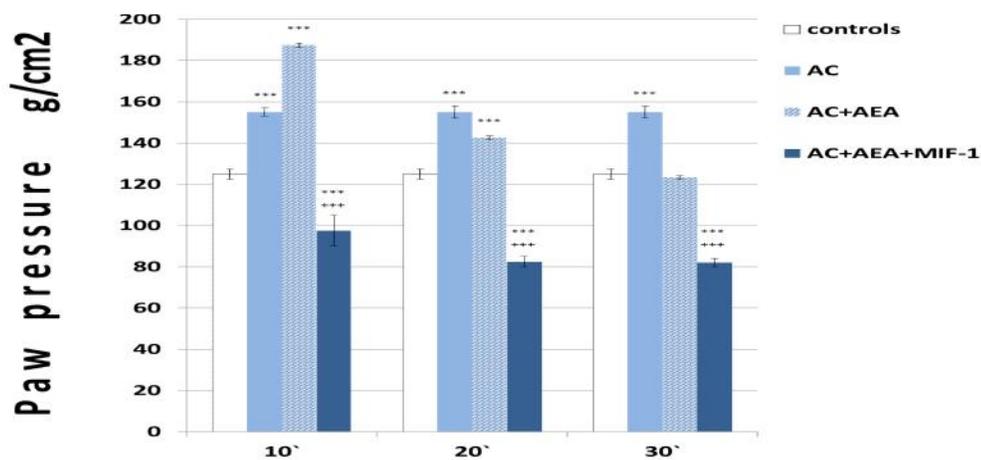


Fig. 2. Effects of AEA (1.0 mg/kg, i.p.) and MIF-1(1.0 mg/kg, i.p.) on the pain threshold of the auto-control (AC) paws in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. AC, AC+AEA, and AC+AEA+MIF-1 were compared to controls (**p<0.001); AC+AEA+MIF-1 were compared to AC+AEA (+++ p<0.001).

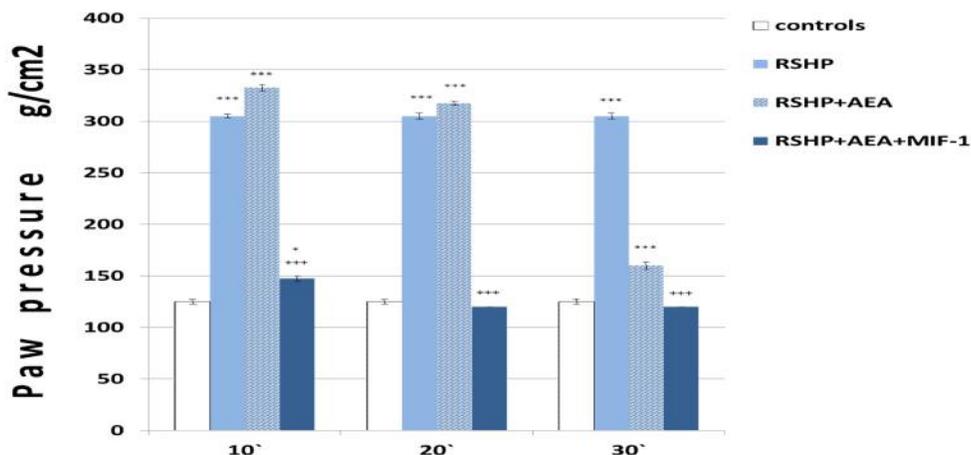


Fig. 3. Effects of AEA (1.0 mg/kg, i.p.) and MIF-1 (1.0 mg/kg, i.p.) on the pain threshold of the lesioned paws in animals with experimental 6-OHDA-RSHP. The results are represented as mean values ± S.E.M. RSHP, RSHP+AEA, and RSHP+AEA+MIF-1 were compared to controls (**p<0.001; *p<0.05); RSHP+AEA+MIF-1 were compared to RSHP+AEA (+++ p<0.001).

In a third series of experiments MIF-1 was administered 10 min after AEA and its modulating effect on nociception in rats with 6-OHDA-RSHP was estimated. MIF-1 administration after AEA in animals with experimental RSHP led to a statistically relevant decrease in pain thresholds of both AC- and lesioned

paws compared to AC- and lesioned paws in animals with AEA without the peptides (Fig. 2 and 3).

AC+AEA+MIF-1-thresholds decreased for the whole estimated period and were lower than controls, AC, and AC+AEA. A tendency toward hyperalgesia was observed (Fig. 2).

RSHP-paws thresholds showed a statistically relevant decrease in respect to RSHP and RSHP+AEA for the whole experimental time (Fig. 3).

Discussion

Parkinson`s disease is a degenerative neurological disease presenting with motor and non-motor signs and symptoms. It is difficult given the complexity of the disorder to delimitate changes in pain perception from pure motor dysfunctions. Because of the complex interconnection and interrelation between sensory input and motor output underlying motor activity, our purpose was more to establish whether MIF-1 could modify the individual effect of cannabinoids.

Administration of MIF-1 after AEA led to decrease in pain thresholds of AC-paws and a tendency toward hyperalgesia was observed, while RSHP-paws` thresholds were driven toward the control values.

MIF-1 is an allosteric modulator of dopaminergic transmission (Tan et al., 2013; Bhagwanth et al., 2013). In contrast to orthosteric ligands, allosteric ones bind to a site on the receptor topographically distinct from the active site, to subtly modulate its activity. Thus a fine-tuning mechanism of receptor`s activity is provided, different than just turning it on or off, as do orthosteric modulators. Additionally, the maximum effect of an allosteric ligand is set by the levels of endogenous ligand present.

Many researchers found that the endocannabinoid transmission (recording CB1 receptors or endocannabinoid levels) is overactive in the basal ganglia in different rat models of PD (Mailleux et al., 1993; Romero et al., 2000; Di Marzo et al., 2000; Gubellini et al., 2002). Other authors reported no changes (Herkenham et al., 1991), reductions (Silverdale et al., 2001), or dependency on a chronic levodopa cotreatment (Zeng et al., 1999). Given the evidences of increased endocannabinoid transmission experimental protocols have been developed using CB1 antagonists in order to evaluate their potential therapeutic usage. Some of the trials demonstrated an improvement in motor abilities of the animals (Di Marzo et al., 2000; El-Banoua et al., 2004), but others did not (Meschler et al., 2001). A clinical study was also performed but no efficacy of rimonabant in PD was demonstrated (Mesnage et al., 2004). Lack of

definite proofs for improvement of motor skills after blockage of CB1 receptors gave us the idea to search for a more complex involvement of cannabinoid receptors in impaired neurotransmission in PD. The combination of CB1 agonist (instead of antagonist) with the modulating MIF-1 peptide led to pain thresholds comparable to the control values. An extremely audacious hypothesis may be proposed: could increase of endocannabinoid transmission be an adaptive mechanism in the attempt to decrease the damage caused by dopamine depletion? The activation of CB1 receptors has been reported to inhibit glutamate release (Fernández-Ruiz et al., 2005). Thus the blockade of the receptors would increase glutamate release. But González and al. (González et al., 2006) found no changes in glutamate contents in the caudate-putamen by the application of 6-hydroxydopamine and by the treatment with rimonabant. Could it be that, along with the allosteric modulation of dopamine receptors by MIF-1, cannabinoids exert a modulation effect on neurotransmission?

More researches are needed in order to elucidate the complex interrelations between different mediator/modulation systems underlying sensory-motor deregulation in PD.

Conclusion

Parkinson`s disease presents with a complex pathogenesis including derangement in many of the mediating and modulating systems. Many systems - the dopaminergic, the cannabinoid, the opioidergic, as well as systems utilizing adenosine, glutamate, GABA, serotonin, take part in the basal ganglia circuits. Such a constellation implies an extremely cautious interpretation of experimental data but gives the opportunity for differential approaches to Parkinson`s disease by targeting the different mediatory systems alone and in combinations.

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