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Original Article

Royal jelly can modulate behavioral and histomorphometrical disorders caused by Parkinson's disease in rats

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Abstract

Introduction: The aim of present study was to investigate the effects of royal jelly (RJ) on the number of Nissl-stained neurons in caudate putamen unit (CPU) and substantia nigra pars compacta (SNC) and the thickness of gray (TGm) and white matter (TWm) of cerebral and cerebellar cortex in male rats with Parkinson's disease (PD).

Methods: Seventy five Sprague-Dawley adults' male rats were used. Rats were randomly divided into 5 groups: 1- control intact rats; 2- sham; rats received 0.02% ascorbic acid diluted in saline by CPU injection 3- PD induction without treatment; 4 and 5- PD induction + 100 or 200 mg/kg/day RJ for 21 days started 4 weeks after lesion induction. PD induction was carried out by unilateral injection of 6-hydroxydopamine in CPU. The apomorphine were done one week before lesion as well as, second, fourth and seventh weeks after lesion. Nissl-stained neurons of SNC and CPU were counted. The thickness of gray and white matter was measured by histomorphometry.

Results: data showed that RJ has corrected net contralateral turns of PD. RJ at both doses significantly (P<0.05) increased the number of Nissl-stained neurons in SNC and CPU in comparison to PD induction without treatment. RJ at low dose significantly (P<0.05) increased TGm and TWm of the cerebral cortex and it significantly (P<0.05) increased TGm but not TWm of cerebellum. RJ at high dose significantly (P<0.05) increased TGm and TWm in the cerebral cortex and cerebellum.

Conclusion: Results indicate that RJ can improve PD symptoms; this effect was associated with histomorphometrical disorders.

Keywords:
Parkinson's disease;
Dopamine;
Apomorphine;
Royal jelly;
Rat;
Histomorphometry

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Introduction

Parkinson's disease (PD) is a neurodegenerative disease accompanied by a group of motor and non-motor symptoms (Fathy and abdelkader, 2015) and is a protypic model of striatal dysfunction. The dopaminergic depletion is traditionaly considered as one of the underlying mechanisms that contributes to the cardinal motor symptoms of bradykinesia, rigidity and tremor (Jankovic, 2008). The dopaminergic neuronal death in PD may involve a complex interplay of genetic and extragenetic mechanisms (Olanow, 2007).

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In PD, the dopaminergic cell loss in the substantia nigra pars compacta (SNC) leads to a cascade of alterations affecting the entire basal ganglia circuit, consisting of both the direct and indirect pathways (Gerfen and Surmeier, 2011) and the levels of dopamine and its metabolites in the neocortical areas and hippocampus decrease. Diminution of cortical dopaminergic transmission may play a role in the mental impairment of some patients with PD (Scatton et al., 1982). The presence of dopaminergic innervation and dopamine D1–3 receptors in the cerebellum has been previously shown (Hurley et al., 2003; Giompres and Delis, 2005). The cerebellum receives a dopaminergic projection from the ventral tegmental area/SNC (Melchitzky and Lewis, 2000). Pathological changes in the cerebellum following dopaminergic degeneration were reported in patients with PD as well as animal models. It is well established that degeneration of nigrostriatal dopaminergic neurons causes dysfunction of both the basal ganglia–thalamic and cerebello-thalamic pathways in 6-hydroxydopamine-lesioned rats (Rolland et al., 2007). While cerebellar dysfunction might contribute to some motor and non-motor signs in PD, a possible approach for treating parkinsonian symptoms is an attempt to normalize cerebellar function. Surgical treatment such as deep brain stimulation of the subthalamic nucleus or globus pallidus improves the motor signs and normalizes cerebellar activation (Geday et al., 2009; Payoux et al., 2009).

Treatment of PD with administration of dopamine to the patient in the form of L-dopa in combination with a peripheral dopa decarboxylase inhibitor is considered as the gold standard procedure (Poewe et al., 2010). However, L-dopa therapy typically results in numerous side effects such as nausea, gastrointestinal bleeding, disturbed respiration, disorientation, anxiety and hallucination (Olanow et al., 2004). Dopamine is a monoamine derived from tyrosine and nutritional value of food can be an important factor affecting the production of dopamine (Choi et al., 2009 ; Miller and Heyland, 2010). Although dopamine is produced from enzymatic processes in particular neurons in the CNS, external or environmental factors can affect its production. Some foods contain tyrosine, which is a precursor of dopamine, as well as other amino acids that can be converted into tyrosine (Sasakia et al., 2012; Matsuyama et al., 2015).

Royal jelly (RJ) is a secretion of hypopharyngeal and mandibular glands of worker bees *Apis mellifera*, which is fed to the queen honeybee. RJ has a variety of biological activities towards various types of cells. For instance, RJ exhibits immunomodulatory properties (Oka et al., 2001). Antioxidative, antibacterial, anti-inflammatory and wound healing effects make RJ an ideal component of cosmetics and skin care products (Kohno et al., 2004). RJ can reduce blood sugar level via insulin-like peptides and other compounds (Batchelder, 2002). RJ is effective in premenopausal symptoms, osteoporosis as well as it improves hormonal equilibrium and fertility in men and women by increasing oocyte and sperm quality (Lewis, 2008).

RJ may influence the nervous system cellular performance and induction of brain- derived neutrophilic factor production. RJ also affects hippocampal long-term potentiation, so it facilitates restoration of the cognitive skills in mice (Hattori et al., 2011). RJ has the ability to induce neurites from cultured rat pheochromocytoma PC12 cells; also another *in vitro* study showed that RJ contains components that differently facilitate the differentiation of all types of brain cells (Hattori et al., 2006; Hattori et al., 2007). Sasaki (2016) reported that RJ contains not only tyrosine, but also other amino acid that can be converted into tyrosine. Thus RJ may contribute to the efficient enhancement of the brain dopamine in male and worker bees (Sasaki, 2016).

It is unclear wheather oral administration of RJ have an effect on brain of PD patients. In the present study we injected the 6-Hydroxydopamine (6-OHDA) unilaterally into the caudate putamen unit (CPU) to achieve retrograde dopaminergic cell loss in the substatia nigra. We assessed behavioral characteristics of motor deficits by applying apomorphine- induced rotation. It seems that PD induction leads to dopaminergic cell loss and so it can affect gray and white matter in cerebral cortex and cerebellum. Therefore we examined the influence of the 21 days oral administration of RJ, 4 weeks after PD induction on: 1- the rate of rotations induced by apomorphine; 2- the number of Nissl-stain neurons in SNC and CPU and 3- the thickness of white and gray matter of cerebral and cerebellum cortex.

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Materials and methods

Animals

seventy five Sprauge Dawley rats weighning 250-300g were used. Animals were maintained at standard tempreture (20-24ºC) with a 12/12 h light-dark cycle with free access to food and water. Institution's animal ethics were considered in housing conditions and experimental procedures. Animals were randomly divided into 5 groups (n=15 each): 1- control, intact rats; 2- sham, rats received 0.02% ascorbic acid diluted in saline; 3- induction of PD (rats received a single injection of 6-OHDA) without treatment; 4- induction of PD (rats received a single injection of 6-OHDA) + RJ 100 mg/kg/day orally for 21 days, started 4 weeks after lesion induction and 5- induction of PD (rats received a single injection of 6-OHDA) + RJ 200 mg/kg/day orally for 21 days, started 4 weeks after lesion induction.

Drugs

apomorphine hydrochloride (sigma-aldrich) was administered subcutaneously (0.2 mg/kg in 0.1% of ascorbic acid). Rats were recived a single injection of 6-OHDA (sigma-aldrich) 4 µl/rat (2.5 µg/µl in 0.15% of ascorbic acid). RJ (sigma-aldrich) was administered orally (100 and 200 mg/kg/day)(El-Nekeety et al., 2007).

Surgical procedure

to achieve unilateral lesion of the nigrostriatal system, rats received 6-OHDA injections into the right CPU. Rats were anesthetized using ketamine 100 mg/kg and xylazine 8 mg/kg and placed into a stereotaxic frame. Guide cannula was implanted in CPU (AP: 0.2 mm, L= -3mm and DV= 4.5 mm). After one week, 6-OHDA was injected through guide cannula by a 5µl Hamilton syring at the rate of 1 µl /min and needle was left in place for another 5 min after the injection before drawning back slowly. The position of 6-OHDA injection site in CPU were checked.

Behavioral test

Rats were received 0.2 mg/kg apomorphine in 0.1% of ascorbic acid by subcutaneous injection and one minute later was placed into a customized Plexiglas cylinder (37 cm height × 33 cm diameter). They were allowed to habituate to their environment for 10 min before apomorphine injection and to reduce the stress on the animals; their behavior was filmed for 30 minutes after apomorphine injection; turns contralateral and ipsilateral to the lesion was performed by a person who was unaware of the grouping system and the treatments. Results were expressed as ipsilateral turns/min minus contralateral apomorphine-induced turns/min. Apomorphine-induced rotations were measured one week before lesion and on second, fourth and seventh weeks after lesion.

Histomorphometric study

At the end of behavioral experiments, the rats were deeply anesthetized with a high dose of ketamine (150 mg/kg) and perfused through the ascending aorta with 200 ml of 0.9% saline followed by 500 ml of fixative solution containing 4% paraformaldehyde. Following perfusion, the brains were removed from the skull, the blocks of forebrian and brainstem were prepared, embedded in paraffin and then sections were cut at a thickness of 5 µM on a microtome and collected in buffer phosphate (0.1 M). Sections were Nissl-stained with 0.1 cresyl violet (Gulley and Wood, 1971). For histomorphometric studies, obtained slides from cerebral and cerebellar cortex were stained by hematoxylin and eosin (H&E) and Masson's Trichrome (MT) staining. Nissl stained neurons of the SNC and CPU were counted manually (light microscope; X400) using a superimposed grid to facilitate the procedure. Superimposed grid were composed of a scaled 40×40 square that a square of 19×19 of it was considered for neuron counting, then the number of neuron was multiplied in 100 and it was considered as the number of neurons in 1 mm^2. At least four sections representative of SNC and CPU sections were examined by scanning the entire extent on the ipsilateral side of 6-OHDA injection (right side of brain). Counting was done blinded to the treatment. Number of SNC and CPU neurons was expressed as the total count per mm^2 of each section (Fig. 1). Thicknesses of gray and white matter were measured by ocular micrometer and Olympus BX51 light microscope using Olysia software. At least four sections representative of gray and white matter sections were examined by scanning the entire extent on the ipsilateral side of 6-OHDA injection (right side of brain). All measurements were performed blinded to the treatment received.

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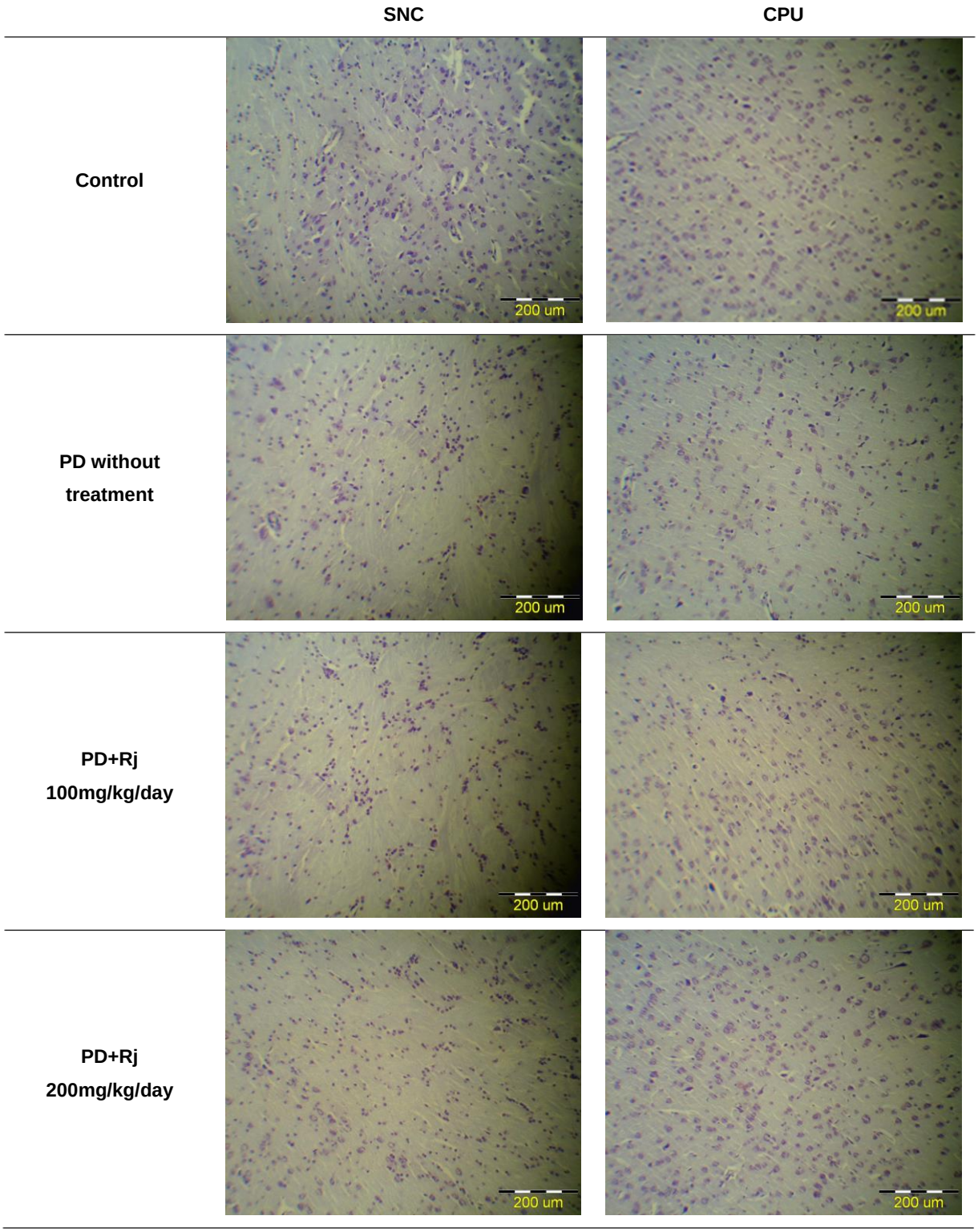

Fig.1. Photomicrograph were represented Nissl-stained neurons distribution in substantia nigra pars compacta (SNC) and caudate putamen unit (CPU) in groups.

Statistical analysis

data analysis was performed by SPSS software (version 21). For data analysis One way ANOVA and Tukey's test as post-hoc were used. Statistical significance level was $P<0.05$.

Results

The results of behavioral test (Fig. 2) showed that there was no significant difference between 3 groups in one week before lesion and the number of

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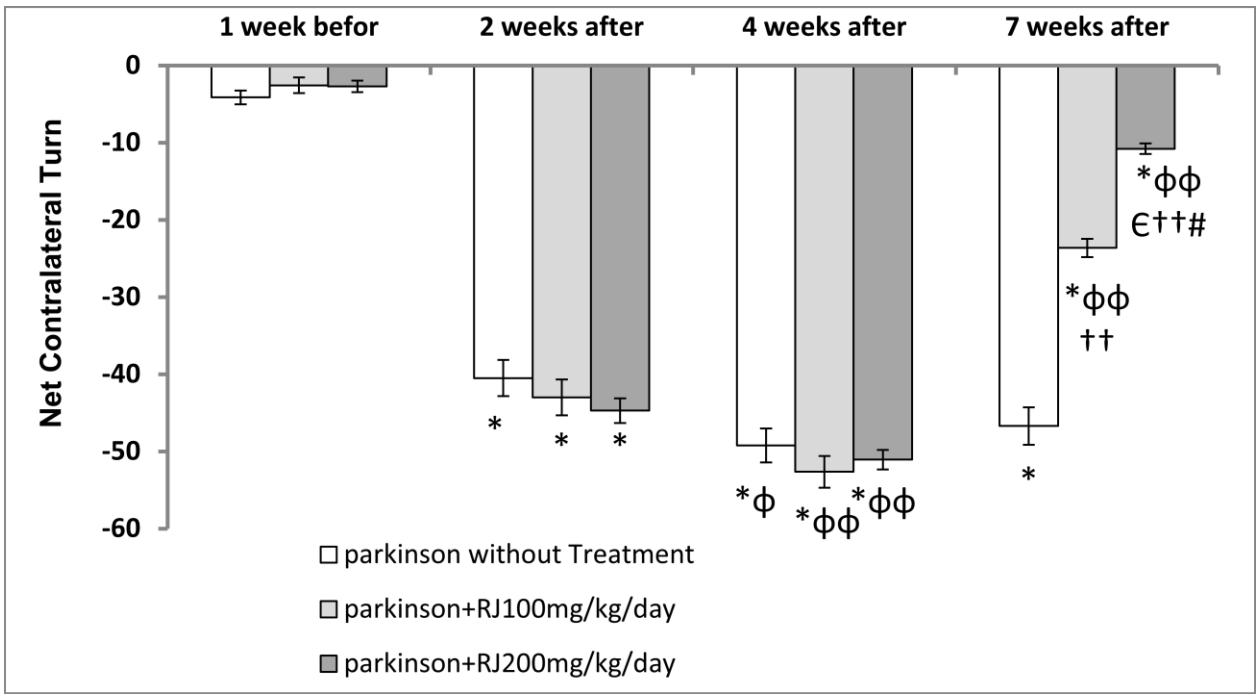

Fig.2. Rotation number (ipsilateral rotation - contralateral rotation) of PD rats induced by apomorphine.
* significant compared with 1 week before; † significant compared with PD without treatment. # significant compared with PD+ RJ 100mg/kg/day; ϕ significant compared with 2 weeks after; Є significant compared with 7 weeks after. * *P*<0.001; †† P<0.01; # *P*<0.05; ϕ *P*<0.01; ϕϕ *P*<0.001; Є *P*<0.01. RJ= Royal jelly

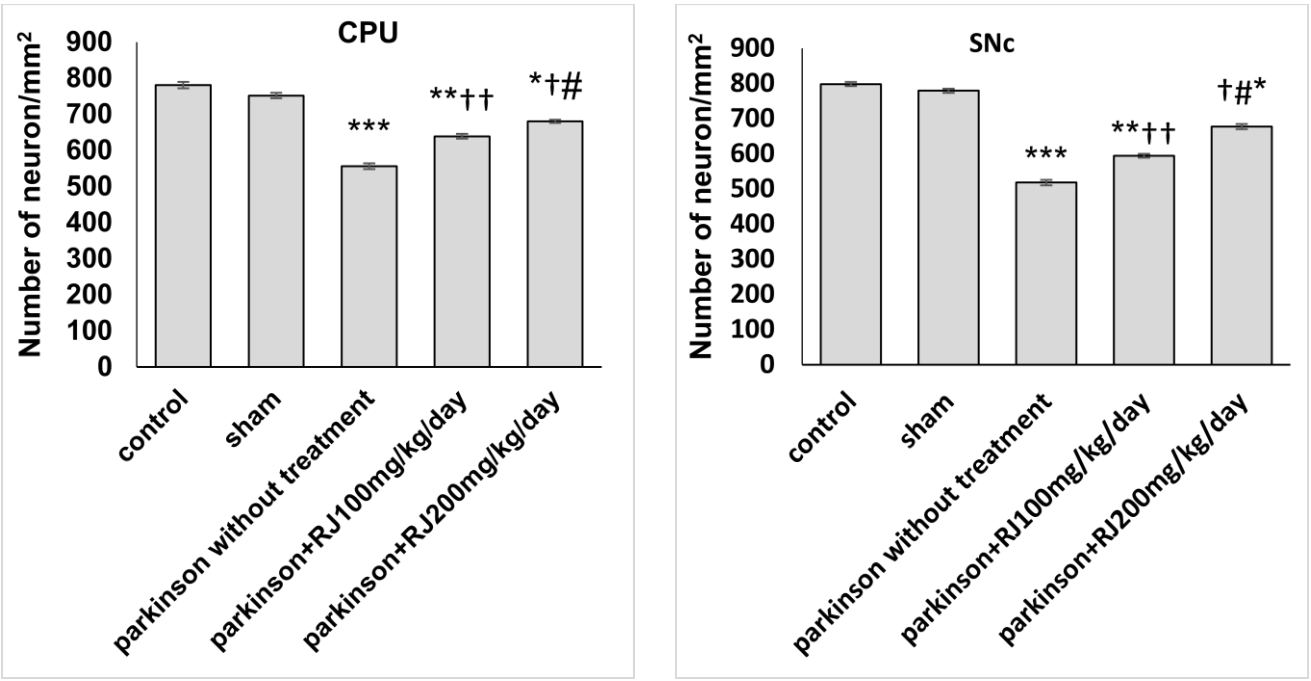

Fig.3. Effect of royal jelly on the number of Nissl-stained neurons in SNC and CPU in all groups. * significant compared with control and sham; † significant compared with PD without treatment; # significant compared with PD+ RJ100mg/kg/day. * *P*<0.05, ** *P*<0.01, *** *P*<0.001, † *P*<0.05, †† *P*<0.01, # *P*<0.05

rotations was very low in 3 groups. There was no significant difference between groups in second and forth weeks after lesion. In seventh week after lesion there was a significant (*P*<0.05) difference between groups and RJ at both doses significantly decreased the number of rotations in comparison with PD without treatment animals. The effect of RJ was dose dependent and in dose 200 mg/kg its effects were more pronounced than dose 100 mg/kg.

In comparison among weeks, in all groups in second,

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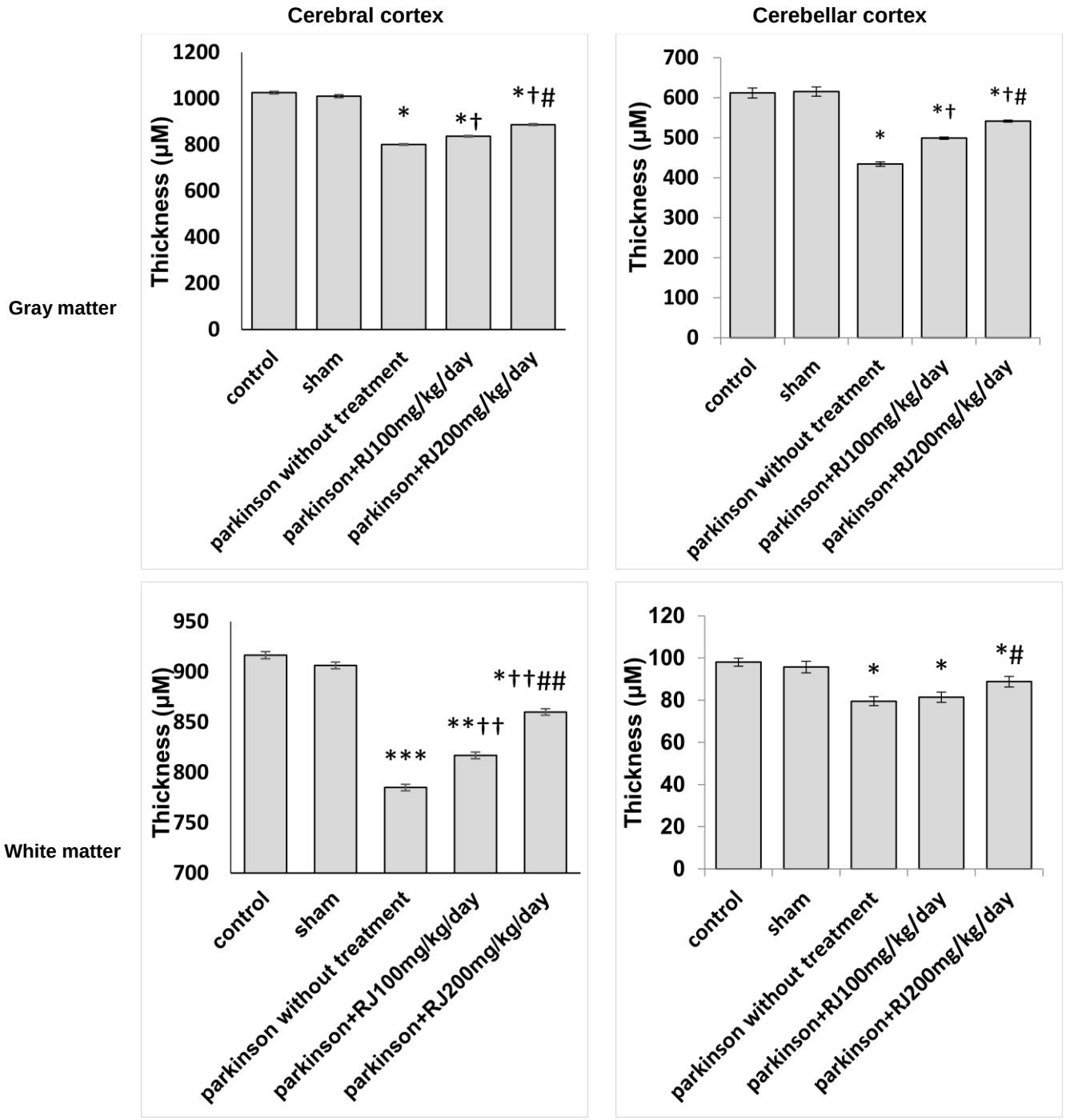

Fig.4. Effect of royal jelly on the thickness of gray and white matter in cerebral cortex and cerebellum cortex in all groups. * significant compared with control and sham; † significant compared with PD without treatment; # significant compared with PD+ RJ100mg/kg/day. * P<0.05, ** P<0.01, *** P<0.001, † P<0.05, †† P<0.01, # P<0.05

forth and seventh weeks after lesion the number of rotations were significantly higher than one week before lesion, also the number of rotations in 4th week were significantly (P<0.05) higher than second week rotations. In seventh week at both doses of RJ the number of rotations in comparison to second and forth week were significantly (P<0.05) lower.

The results of histological studies showed that the number of Nissl-stained neurons in CPU and SNC of all PD groups after 21 days of RJ treatment was significantly (P<0.05) lower than that of control and sham groups; but in RJ treatment groups the number of Nissl-stained neurons of SNC and CPU was significantly (P<0.05) higher than that of PD group without treatment (Fig. 3).

According to histomorphometric study, RJ at both

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doses significantly (P<0.05) increased the thickness of gray and white matter in cerebral cortex in comparison to PD without treatment. RJ at both doses significantly (P<0.05) increased the thickness of gray matter in cerebellar cortex in comparison to PD without treatment. RJ at 200 mg/kg significantly (P<0.05) increased thickness of white matter in cerebellar cortex (Fig. 4). But RJ at both doses were unable to fully offset the effects of PD. So white and gray matter thickness of cerebral and cerebellar cortex even after taking RJ at both doses were significantly (P<0.05) lower than the control and sham groups. The response to RJ was significantly (P<0.05) dose dependent in all experiments.

Discussion

In this study, the neuroprotective effect of oral administration of RJ was investigated in a model of PD. There is some unknown active component in RJ that can pass through the blood-brain barrier (Simuth et al., 2004). So, it seems that RJ would have neurotrophic action and/or neuroprotective effects on mature brain. To ensure that PD was correctly established, number of rotations induced by apomorphine in ipsilateral and contralateral to striatal lesion was measured. Previous studies have demonstrated that the unilateral damage of the nigrostriatal dopaminergic system through intrastriatal injection of 6-OHDA is followed by a reduction in the striatal dopaminergic level and an up-regulation of dopaminergic postsynaptic recptors at the same side. These changes produce a prominent functional and motor asymetry that can be evaluated by dopaminergic agonist like apomorphine. These rotations are considered as a reliable indicator of nigrostriatal dopamine depletion (Schwarting and Huston, 1996). Matsuyama et al. (2015) reported that consumption of RJ increases brain levels of dopamine and tyramine and promotes transition from normal to reproductive workers in queenless honey colonies.

In the present study, we tested whether the treatment with RJ (100 and 200 mg/kg/day) for 21 days, started 4weeks after experimental CPU lesion has protective effect on the number of Nissl-stained neurons in CPU and SNC in the ipsilateral to site of 6-OHDA injection and on behavioral recovery. In PD group without treatment Nissl-stained neurons in SNC and CPU were significantly reduced and RJ were increased Nissl-stained neurons in both SNC and CPU. Nissl-stained neurons in SNC are dopaminergic and Nissl-stained neurons in CPU are medium spiny neurons which are a special type of GABAergic inhibitory cell representing 95% of neurons within the human striatum. Medium spiny neurons that receive dopaminergic innervation express two types dopamin receptor D1 and D2 receptors (Yager et al., 2015). Progression of motor dysfunction in PD is correlated with reductions in various markers of nigrostriatal dipamine terminals within the same striatal territories (Ribeiro et al., 2002). Yoshikawa et al. (2004) in diffusion tensor MRI technique showed that 70-80% of dopaminergic neurons are lost before onset of PD.

neurotrophic and neuroprotective effects of RJ on the hippocampus of adult mouse brain were investigated (Hashimoto et al., 2005). Oral administration of RJ has led to the increase of the number of granular cells in the dentate gyrus (Hattori et al., 2011). Hashimoto et al. (2005) showed that oral administration of RJ selectively enhances the gene expression of glial cell- line derived neurotrophic factor (GDNF). Due to up-regulation of GDNF gene expression, RJ might also be protective for dopaminergic neurons, which are severely damaged in PD. GDNF is survival factor for cultured midbrain dopaminergic neurons. In an unpublished study, we observed that in PD rats were treated RJ 100 and 200 mg/kg/day, GDNF increased in SNC and CPU in comparison to untreated PD rats. So, it seems that increation of dopaminergic neurons in SNC and GABAergic neurons in CPU in the present study were through GDNF.

Pyrzanowska et al. (2014) reported that after administration of RJ 50 and 100 mg/kg, the level of dopamine in CPU was the same within RJ groups and control group animals, but the level of 3,4 dihydroxyphenyl acetic acid (dopamine metabolite) as well as dopamine turnover were increased in both RJ groups.

In the present study, RJ at both doses increased the thickness of gray and white matter in cerebral and cerebellar cortex in comparison to PD without treatment, however, the effect of 100 mg/kg RJ on white matter thickness was not significant. Kang et al. (2015) reported that extensive changes associated with motor symptoms in the gray matter volume was mainly located in the related area of movement,

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which had obvious relevance to the progression of PD. Jia et al. (2015) found even in patients with early-stage PD, gray matter volume loss in some region could be occurred. These regions included the frontal, temporal, parietal regions and the subcortical area in the caudate bilaterally. Bohnen and Albin (2011) demonstrated that severity of white matter lose burden is associated with worsening motor performance in PD independent of the degree of nigrostriatal dopaminergic denervation, as determined by PET imaging. They also found that comorbid white matter loss is a greater determinant of balance impairment than nigrostriatal dopaminergic denervation in PD. Hattori et al. (2012) reported that cognitive impairment in PD progresses followed by structural alterations in which white matter alteration precedes gray matter atrophy.

Conclusion

In the present study, 1- RJ could improve dopaminergic system dysfunction after seven week of PD induction. 2- RJ increased the number of Nissl-stained neurons in CPU and SNC of PD in comparison to PD group without treatment. 3- RJ increased the gray and white matter thickness in cerebral and cerebellar cortex. Our results indicate that RJ can improve PD symptoms; this effect was associated with an increase in number of Nissl-stained neurons in SNC and CPU as well as the white and gray matter thickness of cerebral and cerebellar cortex.

Acknowledgments

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Conflict of interest

All the authors can confirm that there is no financial or other relationship that would cause a conflict of interest.

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