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Losartan pretreatment reduces neurodegeneration and behavioural symptoms in 6-hydroxydopamine induced unilateral rat model of Parkinson's disease

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Abstract

Losartan is an angiotensin II receptor antagonist which is mainly used to treat hypertension. It has been shown that angiotensin II involves in NADPH-dependent oxidase activation. In this study, the effect of losartan in 6-hydroxydopamine (6-OHDA)-induced rat model of Parkinson's disease was investigated. The rats were daily pre-treated i.p. with losartan (90 mg/kg), for the duration of six days before the 6-OHDA injection in the left substantia nigra pars compacta (SNC), until one day afterwards. Losartan administration caused a significant decrease in the rotational and rigidity score in the lesioned rats after 2 weeks. Furthermore, the pretreatment with losartan significantly lowered the value of the markers of oxidative stress after 24 h. Moreover, losartan protected SNC dopaminergic neurons against toxicity of 6-OHDA. The results therefore suggested that losartan pretreatment attenuated the symptoms of Parkinson's disease probably by preventing 6-OHDA induced oxidative stress and neurodegeneration.

Keywords: Losartan; Oxidative stress; Rotational behaviour; 6-Hydroxydopamine

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNC). Substantial studies show that inflammation, free radical formation and oxidative stress have an important role in the pathogenesis of PD or consider as a result of the neurodegeneration associated with PD [1–4]. Moreover, there is considerable evidence that the central renin–angiotensin system (RAS) might be linked to PD [5], and it has been demonstrated by several studies that microglial activation and/or NADPH-derived superoxide/peroxide have an important role in neurotoxin-induced dopaminergic cells degeneration in different animal models of PD [6]. Furthermore, in the SNC of the Parkinsonian patients, an increased expression of neuronal NAD(P)H quinone oxidoreductase was reported [7]. Angiotensin II as a proinflammatory compound [8] initiates the NADPH-dependent oxidase complex, an important source of superoxide [8–10], and blockage of the AT_1 receptor probably causes neuroprotection. In line with this hypothesis, several recent studies have been conducted with AT_1 receptor antagonists; a treatment with an AT_1 receptor antagonist, ZD 7155, in 6-OHDA rat model of PD reduced lipid peroxidation and protein oxidation in the striatum and the ventral midbrain, and had a neuroprotective effect on dopaminergic cells in the SNC [11]. Similar results on 6-OHDA induced dopaminergic cell loss and factors of oxidative stress were obtained with apocynin, an inhibitor of NADPH oxidase, suggesting that reduced activation of the NADPH oxidase complex results in neuroprotective effect of the AT_1 receptor antagonist [11]. An additional study demonstrated that losartan was able to protect

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dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity [12].

Angiotensin-converting enzyme (ACE) is a major component of enzymatic cascade which produces angiotensin II [13]. Therefore, inhibition of ACE may have an important role in pathogenesis of PD. This has been shown by reduction in MPTP-induced loss of dopaminergic cells in SNC and striatum in rats which received pre-treatment with the ACE inhibitor perindopril [14] and in another study similar results were obtained with captopril as another ACE inhibitor [15]. As well, neuroprotective effects of captopril were reported in a 6-OHDA rat model of PD [16].

This study was conducted to investigate, for the first time, the possible neuroprotective effect of losartan as an angiotensin II receptor antagonist drug used mainly to treat hypertension on 6-OHDA induced Parkinson's disease.

2. Materials and methods

2.1. Chemicals

In this study, ketamine, magnesium acetate tetrahydrate, sucrose, thiobarbituric acid, trichloroacetic acid, streptomycin sulfate, guanidine hydrochloride, apomorphine hydrochloride and xylazine were purchased from the Merck (Germany). The other chemicals were purchased from Sigma (USA).

2.2. Experimental procedure

In total, 48 adult male Wistar rats (200–250 g and about 5 months old) (purchased from Pasteur's Institute, Tehran) were used in the study. All experiments were carried out in accordance with NIH guidance for the care and use of laboratory animals. The rats were divided into 4 groups ($n = 12$). In each group 6 rats were killed 24 h after the lesion for biochemical tests and measurement of ACE activity and the other rats were used for behavioural tests and histopathological study 2 weeks after the lesion.

1. Sham-operated group (Sham); used as the normal (i.e., non-lesioned) control and received subcutaneous and intra SNC injections of saline.
2. Lesioned group (6-OHDA); 6-OHDA were injected into the left SNC (12.5 μg in 0.1% ascorbic acid in normal saline) [17].
3. Captopril treated lesioned group (6-OHDA + captopril); captopril was injected i.p. at dose of 5 mg/kg 144, 120, 96, 72, 48, 24 and 2 h before and 4 and 24 h after the lesion [16].
4. Losartan treated lesion group (6-OHDA + losartan); losartan was injected i.p. at a dose of 90 mg/kg 144, 120, 96, 72, 48, 24 and 2 h before and 4 and 24 h after the lesion [12,16].

During our experiment, we did observed no mortality by captopril or losartan and they were well-tolerated by the animals.

The rats were anesthetized with a combination of ketamine (100 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). Heads were placed in a stereotaxic apparatus (Stoelting, USA) after shaving. For injection in the SNC, stereotaxic coordinates were anteroposterior – 4.8 mm from the bregma, mediolateral – 2 mm from the midline, and dorsoventral – 8.3 mm from the skull. After drilling the skull, 4 μl of normal saline containing 12.5 μg of 6-OHDA and 0.1% vitamin C were injected in the left SNC using a 10 μl Hamilton syringe at the rate of 1 μl/min, and the cannula was left for 5 min after injection. Sham group only received saline [18].

2.3. Behavioural tests

2.3.1. Rotational test

The rats were tested for rotational behaviour by apomorphine hydrochloride (2.5 mg/kg, i.p.) 2 weeks after 6-OHDA injection. The test was performed in accordance with a method as previously described [19,20]. Briefly 1 min after the apomorphine hydrochloride (2.5 mg/kg) injection, the total rotation was counted in a cylindrical container (a diameter of 33 cm and a height of 35 cm). The number of contralateral (right) rotations was counted as positive scores .The net numbers of rotations were calculated as the positive scores minus the negative scores.

2.3.2. Morpurgo's test

The rats also were tested for muscular rigidity by the method described previously [21]; laying the animal on a flat surface, the rat received a score of 0.5 if it did not move when it was touched. After that the right paw of the rats put on a 3 cm high platform. If the animal did not take its paw off the platform after 10 s, it was given a score of 0.5. The same method was used for the left hand. In the next step, only the right paw of the rat was placed on a platform with a height of 9 cm. If the rat did not take its paw off the platform after 10 s, it received a score of 1. The last step was repeated for the left hand of the rats.

2.4. Biochemical analysis

2.4.1. Lipid peroxidation

Lipid peroxidation was assessed by determination of the concentration of thiobarbituric acid reactive substances (TBARS). The TBARS measurement was performed by a spectrophotometer measured at 532 nm using the published method [22]. The protein concentration of the sample was measured according to the Bradford method [23], with bovine serum albumin as the standard.

2.4.2. Protein oxidation

Protein oxidation was determined by measurement of protein carbonyl content. The protein carbonyl content was

assessed by a spectrophotometer at 370 nm according to a previously published method [24].

2.4.3. ACE activity in brain tissue homogenate

Brains tissues were homogenized and 10 μl of homogenate was incubated with 40 μl substrate (hippuryl L-histidyl L-leucine) in a thermo mixer (eppendorf – MTP model) for 30 min at 37 °C and 300 rpm. We measured enzyme product – hippuric acid – by HPLC (Shimadzu, pump: LC-10ADVP, detector: SPD-10AV, controller: SCL-10AVP, and class-VP software). 20 μl of each sample was injected into C18 column and washed by mobile phase (1:1 methanol and KH2PO4 0.1 M and pH = 3) with 1 ml/min flow rate and detected at 228 nm. One unit of enzyme activity is defined as nanomolar hippuric acid liberated per min at 37 °C per mg total protein.

2.5. Histological study

For each animal, mesencephalic sections (interaural 2.9–4.2 mm) were examined by a method as described previously [25,26]. Briefly, Nissl-stained neurons of SNC were counted manually (Light microscopy; 400×). At least two sections representative of each of four Paxinos–Watson plans (4.2, 3.8, 3.2, 2.97; interaural) were examined by scanning the entire extent on each side. Counting was done blind to the treatment received.

2.6. Statistical analysis

For the behavioural and biochemical tests, Kruskal–Wallis followed by the Mann–Whitney test was performed. The inter-group differences for the values of Nissl-stained neurons for the injected side were analyzed using one-way ANOVA and followed by Tukey test. In all analyses, the null hypothesis was rejected below the 0.05 level.

3. Results

All animals well tolerated surgical operations and there was also no significant change in weight of animals in each group.

3.1. Rotational test

Losartan and captopril reduced right rotation in the 6-OHDA-induced Parkinson's disease compared to the 6-OHDA group significantly (Fig. 1).

3.2. Morpurgo's test

The results showed a significant reduction of rigidity in the 6-OHDA + captopril and 6-OHDA + losartan groups compared to the 6-OHDA group ($p < 0.001$) (Fig. 2).

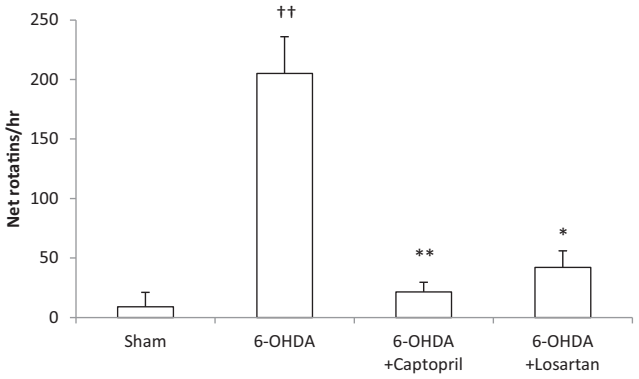

Fig. 1. Net total apomorphine-induced rotations in different groups (*$p < 0.05$, **$p < 0.01$ in comparison with the 6-OHDA group and ††$p < 0.01$ compared to the sham group).

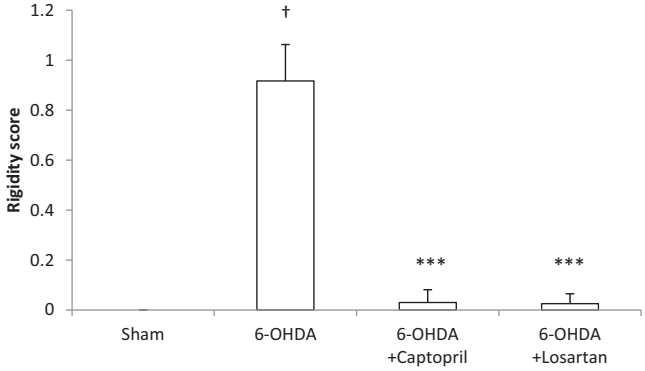

Fig. 2. The mean of rigidity grade in different groups (***$p < 0.001$ in comparison with the 6-OHDA group and †$p < 0.05$ compared to the sham group).

3.3. Lipid peroxidation

The results indicated that the 6-OHDA caused a significant increase in the amount of lipid peroxidation in the 6-OHDA group. Losartan and captopril reduced lipid peroxidation induced by 6-OHDA compared to the 6-OHDA group ($p < 0.05$) (Fig. 3).

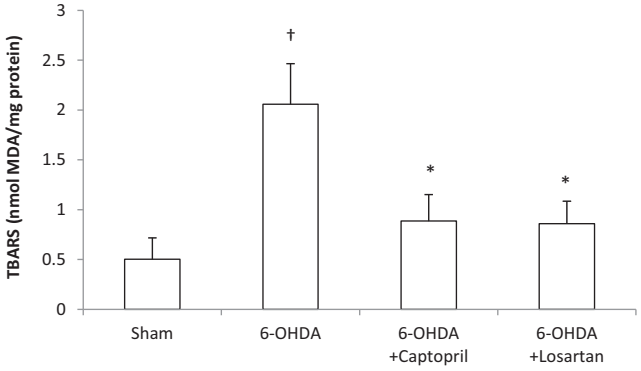

Fig. 3. TBARS content in homogenate of midbrain in different groups (*$p < 0.05$ in comparison with the 6-OHDA group and †$p < 0.05$ compared to the sham group).

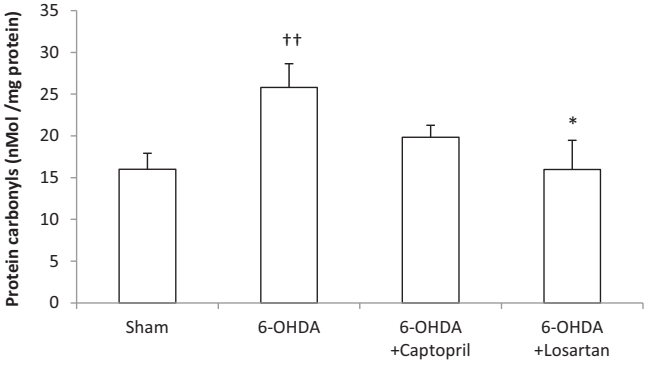

Fig. 4. Protein carbonyl content in homogenate of midbrain in different groups (*$p < 0.05$ in comparison with the 6-OHDA group and $^{\dagger\dagger}p < 0.01$ compared to the sham group).

3.4. Protein oxidation

The results indicated a significant reduction of carbonyl content in the 6-OHDA + losartan compared to the 6-OHDA group ($p < 0.05$) (Fig. 4).

3.5. Brain ACE activity

A significant reduction in the brain's ACE activity marker in the 6-OHDA + captopril group compared to the sham and 6-OHDA groups demonstrated by the results ($p < 0.05$) (Fig. 5).

3.6. Histopathological test

The rats subjected to injection of 6-OHDA into SNC showed a statistically significant reduction in the left side of SNC compared to the sham group ($p < 0.01$). Numbers of Nissl-stained neurons on the left side of SNC in the 6-OHDA + losatan and 6-OHDA + captopril were greater than the 6-OHDA group ($p < 0.05$) (Table 1 and Fig. 6).

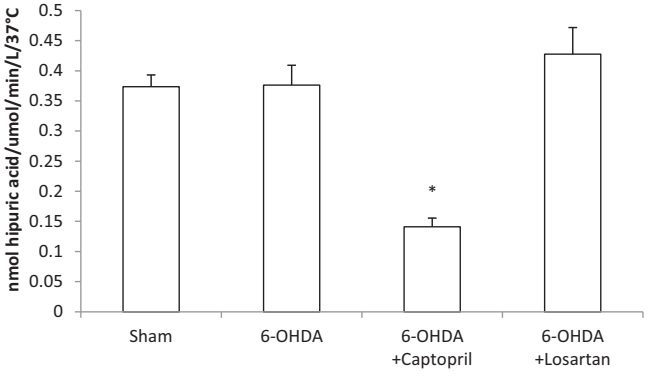

Fig. 5. ACE activity in homogenate of midbrain in different groups (*$p < 0.05$ in comparison with the 6-OHDA group).

4. Discussion

The results of the present study indicated that losartan at a dose of 90 mg/kg could result in a significant reduction in apomorphine-induced rotations, rigidity, oxidative stress markers and attenuated damage of substantia nigra dopaminergic neurons in the 6-OHDA lesioned rats. These results suggest the neuroprotective effect of losartan in 6-hydroxydopamine model of hemi-Parkinsonian rats.

The 6-OHDA-lesioned rat model has proven to be a valuable tool in evaluating the pharmacological action of new drugs on the dopaminergic system. The mechanism of 6-OHDA toxicity is complex and involves alkylation; rapid auto oxidization leading to the generation of hydrogen peroxide, superoxide, and hydroxyl radicals; and impairment of mitochondrial energy production [27,28]. All the mentioned processes result in dopaminergic cell apoptosis.

In this study we by the means of histopathological study showed that losartan as an antagonist of AT1 receptors can prevent consequently progress of dopaminergic neuronal loss. Stimulation of AT1 results in the release of reactive oxygen species (ROS), mainly the superoxide anion by the activation of their NADPH complex [16,29–31]. Then the produced ROS is converted into H_2O_2 by superoxide dismutase or it makes a combination with nitric oxide to generate peroxynitrite and promotes lipid peroxidation and protein oxidation [26,32]. Increase in ROS production or decrease in inactivation, bring about oxidative stress and finally apoptosis [14,33]. Treatment with losartan reduced the nigrostriatal superoxide content and suggesting a potentially important role for ARBs (angiotensin receptor blockers) in the treatment of PD [34]. Losartan was able to protect dopaminergic neurons against MPTP-induced neurotoxicity as well [12]. Hence the AT_1 receptor antagonist, losartan, can prevent oxidative stress caused by Parkinsonism-inducing neurotoxin, 6-OHDA.

This study also indicated the neuroprotective effect of captopril, an ACE inhibitor, in the 6-OHDA-induced PD model and as it was mentioned above; several previous studies have demonstrated this ability of captopril in the other models of PD as well [5,15,16]. ACE is an important compound of the enzymatic cascade which generates angiotensin II and inhibition of ACE by captopril that we indicated in this research can prevent the production of the angiotensin II and eventually prevents the formation of ROS, progression of oxidative stress and consequently dopaminergic cells death [5,16,35].

In this experiment the level of oxidative stress markers following the injection of the neurotoxin decreased by pretreatment with losartan and captopril and the pretreatment of captopril decreased the activity of brain ACE compared to the 6-OHDA group.

The possible explanation for the mechanism involved in AT_1 blockers' beneficial effects might be that they prevent chronic and/or toxic angiotensin II signaling via AT_1 receptors. An increased production of chemokines, cytokines and adhesion molecules and consequently the migration of

Table 1
Total number of Nissl-stained neurons on the left and right sides of SNC.

SNC	Sham	6-OHDA	6-OHDA + captopril	6-OHDA + losartan
Left (lesioned side)	118.63 ± 28††	50.45 ± 29**	72.11 ± 25†	73.9 ± 26†
Right (intact side)	110.54 ± 27	114.36 ± 19	111.7 ± 22	126.4 ± 15

Averaged total number of Nissl-stained neurons in sham-operated (sham), lesioned (6-OHDA), captopril treated lesioned (6-OHDA + captopril), losartan treated lesioned (6-OHDA + losartan) groups two weeks after the lesion.
** $p < 0.01$ in comparison with the sham group on the left side.
† $p < 0.05$ in comparison with the 6-OHDA group on the left side.
†† $p < 0.01$ in comparison with the 6-OHDA group on the left side.

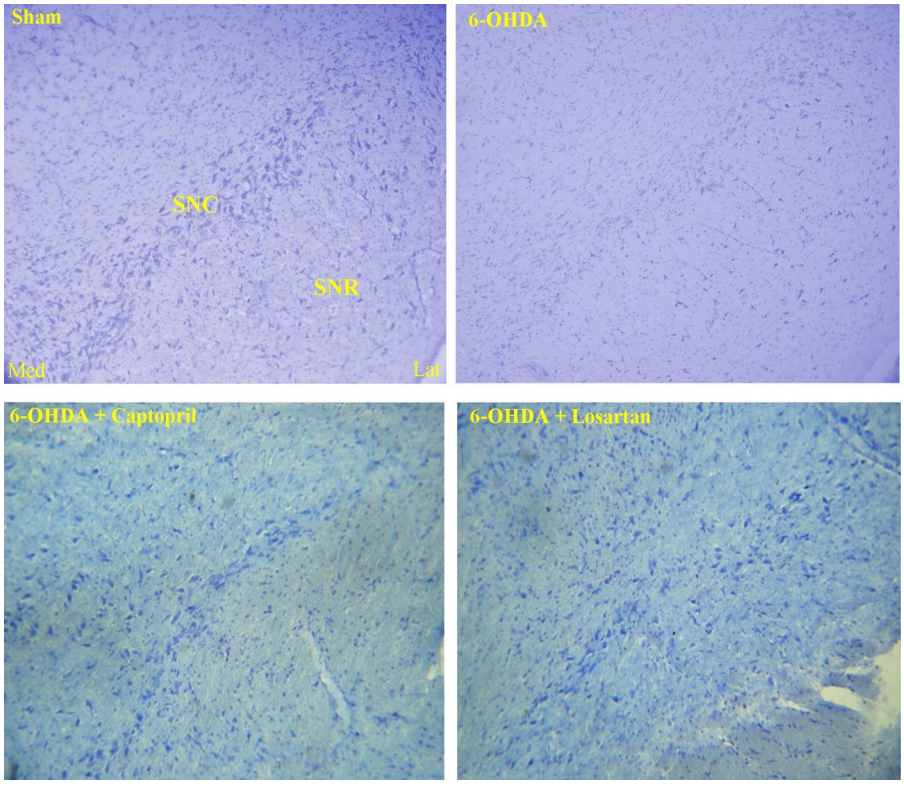

Fig. 6. Illustrative photomicrographs of typical coronal section through the midbrain showing Nissl-stained neurons in Sham, 6-OHDA, 6-OHDA + captopril and 6-OHDA + losartan groups on the left (lesion) side of SNC. A considerable reduction in the number of the dopaminergic neurons in SNC was observed in the 6-OHDA group but no such marked decrease was noted in the losartan + 6-OHDA group in comparison with the sham group. SNC, substantia nigra pars compacta. SNr, substantia nigra pars reticulate.

inflammatory cells were also taken place by the AT_1 receptors activation [36,37].

5. Conclusion

In conclusion, it was established by the means of behavioural and biochemical tests that pretreatment with the antagonist of AT_1 receptor, losartan as well as an ACEI captopril could prevent oxidative stress and the progress of the behavioural symptom of PD induced by 6-OHDA in rats. This data provides a potential basis for using losartan as novel treatments for PD in future.

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