Evaluation of the in vivo antihypertensive effect and antioxidant activity of HL-7 and HL-10 peptide in mice

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Abstract
Background The tendency to use bioactive peptides has increased in recent decades, and research would be essential for recognizing the therapeutic effects of peptides present in animals or food resource. In this study, the in vivo antioxidant and antihypertensive properties of peptides HL-7 with the sequence of YLYELR and HL-10 with the sequence of AFPYYGHHLG were identified from scorpion venom of H. lepturus were evaluated.

Methods and results To study the in vivo effects of peptides, D-galactose-induced and DOCA salt-induced mice models were used. The results of the antioxidant assay for both peptides showed that the activity of serum and liver catalase (CAT), as well as superoxide dismutase (SOD) enzymes, was significantly decreased in the D-galactose-induced group (NC), while MDA levels were increased in serum and the liver tissue samples (p < 0.01). Compared with the D-galactose-induced mice, the peptide treated mice group had a higher activity of antioxidant enzymes namely CAT and SOD, as well as a lower lipid peroxidation level. Also, the results of antihypertensive activity for both peptides showed that systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the mice treated with the HL-7 and HL-10 peptides were significantly reduced in a dose-dependent manner (p < 0.01). The administration of the HL-7 peptide at doses of 2 mg/kg BW (LP1), 5 mg/kg BW (-IP1) and 15 mg/kg BW (HP1) significantly diminished the mean arterial blood pressure (MAP) by 11 mmHg, 31 mmHg and 40.47 mmHg, respectively. Accordingly, treatment of mice with the HL-10 peptide at doses of 2 mg/kg BW (LP2), 5 mg/kg BW (IP2) and 15 mg/kg BW (HP2) considerably lowered the MAP by 8 mmHg, 18.3 mmHg and 21.93 mmHg, respectively.

Conclusion Our findings suggest that both the HL-7 and HL-10 peptides could be potentially utilized as antihypertensive and antioxidant components.

Keywords Peptide · Antioxidant enzymes · Hypertension · Animal model

Introduction

Oxygen reactive species (ROS) cause a lot of damage to macromolecules such as DNA, protein, and lipids [1]. The antioxidant activity of intracellular defense system deals with the damage caused by free radicals. Antioxidant agents inhibit lipid peroxidation by reducing free radicals, stopping the production of radicals, and subsequently decomposing peroxides [1]. In some situations, such as inadequate ROS removal, antioxidant defense system fails to protect cells against oxidative stress [1]. Hence, the presence of synthetic and natural antioxidants seems necessary to prevent the deleterious effects of oxidative stress [2].

Intracellular antioxidant enzymes include primary and secondary antioxidants [3]. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which cause inactivation of ROS, are considered the primary antioxidant enzymes. Secondary antioxidant enzymes consisted of glutathione reductase (GR), glucose 6-phosphate dehydrogenase (G6PD), and glutathione S-transferase (GST) maintain their proper function through direct detoxification of ROS and continuous supply of nicotinamide adenine dinucleotide phosphate (NADP) and glutathione (GSH) for primary antioxidant enzymes [4]. The superoxide anion produced by oxidation of molecular oxygen is converted into hydrogen peroxide (H₂O₂) by SOD enzyme. In the next step, CAT enzyme converts H₂O₂ into water [5].
Hypertension is the cause of cardiovascular disorders that affects 25% of the world’s population [6]. Hypertension is one of the most important reasons for atherosclerosis, myocardial infarction, and left ventricular hypertrophy [7, 8]. The metabolic pathway of rennin-angiotensin plays a role in controlling blood pressure. High blood pressure is one of the curable factors in the prevention of cardiovascular disease (CAD), so Angiotensin Converting Enzyme (ACE) is an important target for the treatment of CAD [9, 10]. Captopril, Lisinopril, and enalapril have been identified as antihypertensive drugs with an inhibitory effect on ACE. However, such drugs have unwanted side effects [11]. Therefore, the tendency to use bioactive peptides has increased in recent decades, and research would be essential for recognizing the therapeutic effects of peptides present in animals or food resource. Some peptides isolated from scorpion venom can enhance bradykinin effect through the mechanism of ACE inhibition, which is shown for peptides with the activity of reducing blood pressure in scorpion venom of Tityus serrulatus (Peptide T) [12] and Buthus occitanus (Peptide K12) [13].

To date, no study has been conducted to show the antioxidant and antihypertensive effects of peptides isolated from Hemiscorpius lepturus scorpion venom. In the previous study, the antihypertensive and antioxidant effects of peptides coined as HL-7 and HL-10 were evaluated in vitro [14, 15].

The aim of this study was to measure the antioxidant activity of CAT and SOD enzymes, as well as the evaluation of MDA levels in serum and liver samples of D-galactose-induced mice to observe whether the HL-7 and HL-10 peptides are capable of modulating the elevated levels of ROS. Moreover, the antihypertensive potentials of those peptides were assessed in mice with hypertension induced by DOCA-salt.

Materials and methods

Chemicals

Ascorbic acid, D-galactose, trichloroacetic acid (TCA), thiobarbituric acid (TBA), desoxycorticosterone acetate (DOCA), catalase (CAT), hydrogen peroxide (H$_2$O$_2$), and pentobarbital sodium were obtained from Merck Chemicals Co. (Darmstadt, Germany). The SOD assay kit was applied for the measurement of SOD activity (Beyotime, Shanghai, China).

Peptide synthesis

Solid-phase method and standard 9-fluorenlymethoxycarbonyl protection chemistry were used for the synthesis of HL-7 and HL-10 peptides with 95% purity (GL Biochem Shanghai Ltd. Shanghai, China).

Animal procedures

All experiments were performed on male mice weighing 20–30 g. All stages of the experiment were conducted in accordance with the ethics committee of the University of Mashhad. The protocols of the current study were confirmed by the National Committee for Ethics in Biological Research (No. IR.UM.REC.1397.063). Mice were maintained under the same light conditions (12 h light/dark cycles), temperature (22 ± 2 °C), and humidity (60% ± 5) without any restrictions to gain access to water and food. In general, the experiments were carried out in two steps: at the first stage, the antioxidant enzymes were measured and the second stages the blood pressure of animals was examined.

Antioxidant measurement

In the first step, 30 healthy mice (8-week-old) weighing 20.0 ± 2.0 gr were randomized into the control (n = 6) and aging-induced groups (n = 24). Mice in the control received a physiological saline solution (0.9% NaCl) (10 ml/kg BW) daily by subcutaneous injection for 21 days. Aging was induced by injection of 120 mg/kg of D-galactose though subcutaneous injection once daily for 21 days. Mice in the negative control (NC) group received a subcutaneous injection of D-galactose (120 mg/kg) for 21 days. The D-galactose was dissolved in physiological saline solution (0.9% NaCl). Mice in the positive control (PC) group received ascorbic acid (10 mg/kg BW) and D-galactose through subcutaneous injection for 21 days. The peptide groups coined as the P1 and P2 groups were treated with 15 mg/kg BW of the HL-7 and HL-10 peptides, respectively by subcutaneous injection and also received D-galactose through subcutaneous injection for 21 days. Treatments were performed once a week for 4 weeks.

Serum and liver homogenate preparation and biochemical assays

After 4 weeks, mice were anesthetized with pentobarbital sodium, and the activity of CAT and SOD enzymes, as well as the levels of MDA, were measured in the liver and serum of mice. In order to separate the serum, blood was centrifuged at 300 rpm at 4 °C for 15 min. The obtained serum samples were stored at −20 °C for further analysis. After sacrificing mice, liver tissues were minced on ice by a razor blade and placed in a falcon. Then, 10 ml phosphate buffer (10 mM) was added to the falcon. The tissues were homogenized on the ice three times for 30 s [5].
The activity of CAT was measured according to the method of Weydert and Cullen (2010) in which the decomposition of H$_2$O$_2$ is recorded at 240 nm at room temperature [5]. A decrease in absorbance was measured every 30 s in a 2-min period using the spectrophotometry method. The activity of CAT enzyme was expressed as mK/mg protein. The analysis of SOD activity was carried out using the SOD assay kit (Beyotime, Shanghai, China). The measurement of SOD enzyme is monitored on the basis of the production of superoxide ions (by xanthine oxidation) and the reaction with tetrazolium forming a formazan color which is absorbed at 450 nm. One unit of SOD alludes to the amount of enzyme reducing the absorbance by up to 50% at 450 nm. The activity of SOD enzyme was expressed as U/mg protein [16]. MDA is a crucial factor in the determination of the amount of lipid peroxidation. MDA, as a lipid peroxidation product, reacts with TBA and the pink-colored products are absorbed at 535 nm. The TBA reaction was used to measure MDA levels in serum and liver. MDA content was expressed as nmol/mg protein [17].

Assessment of blood pressure

In the second step, 36 mice were divided into six groups (n = 6) to evaluate the effect the HL-7 and HL-10 peptides. The induction of hypertension in mice was implemented by desoxycorticosterone-DOCA-salt method [18]. In hypertension group, hypertension was induced by the subcutaneous injection of desoxycorticosterone (8 mg/kg/week) for 21 days. Additionally, 1% NaCl and 3% potassium chloride were added to drinking water for mice. Captopril was utilized in our experiments as a positive control to be able to compare the potency of peptides in comparison with a well-accepted drug. The peptide groups coined as the LP1, IP1, HP1 and LP2, IP2, HP2 groups were treated with the HL-7 and HL-10 peptides, respectively by subcutaneous injection and also received desoxycorticosterone through subcutaneous injection for 21 days. The experimental groups included control (water), positive control (captopril at a dosage of 5 mg/kg BW), LP1 (HL-7 peptide at a dosage of 2 mg/kg BW), IP1 (HL-7 peptide at a dosage of 5 mg/kg BW), HP1 (HL-7 peptide at a dosage of 15 mg/kg BW), LP2 (HL-10 peptide at a dosage of 2 mg/kg BW), IP2 (HL-10 peptide at a dosage of 5 mg/kg BW), and HP2 (HL-10 peptide at a dosage of 15 mg/kg BW) by subcutaneous injection. The systolic blood pressure (SBP) and the diastolic blood pressure (DBP) of the mice were measured in awake mice by the tail cuff method before administration and also 2, 4, 6, 8, and 24 h after administration. This is a non-invasive blood pressure measuring system, which was clinically validated to assess blood pressure in mice and rats. It determines the tail blood volume, using a volume pressure recording sensor and occlusion tail-cuff. The values of SBP and DBP were taken as the average of 8–12 reading. The rats are kept at 38 °C for 20 min before measurement. To minimize stress on mice, all recordings are done by one person in the same situation.

Statistical analysis

The results were expressed as mean ± SD. The analysis of the obtained data was performed using the Mstat C and JMP packages. The comparison between groups was made by Duncan Multiple Range Test. Also, for multiple pairwise comparisons with a control group, we use the Dunnett test. The results were analyzed based on a significance level of 5%.

Results

Antioxidant tests

The in vivo antioxidant activity of the HL-7 and HL-10 peptides was evaluated through D-galactose-induced mice model.

Antioxidant enzymes

CAT enzyme

The results of the present study showed that the mean activity of CAT enzyme in D-galactose-induced mice was significantly reduced compared with the control group (control) (p < 0.01), which indicated the progression of aging in the D-galactose-treated group (Fig. 1). The serum activity of CAT in the D-galactose-treated group (2.57 mK/mg protein)
was significantly lower than the negative control group (7.65 mK/mg protein). Accordingly, as shown in Fig. 1, the activity of CAT in the liver tissue of the D-galactose-treated group was significantly lower (1.99 mK/mg protein) than that of the negative control group (7.53 mK/mg protein). In line with this, the activity of CAT significantly changed from 7.53 mK/mg protein in the negative control group (NC) to 1.99 mK/mg protein in the D-galactose-treated group when assayed in the liver tissue (Fig. 1). The activity of CAT enzyme in the ascorbic acid-treated group (PC) and peptides-treated groups, P1 (HL-7) and P2 (HL-10), was significantly increased in both serum and liver samples compared with the D-galactose-induced mice (p < 0.01), indicating the improvement of antioxidant defense system in mice receiving ascorbic acid and the HL-7 and HL-10 peptides. The CAT activity in serum and liver homogenates of the P1 group was close to the PC group, and the activity of CAT enzyme in the P2 group (HL-10 peptide) was lower than the PC and P1 groups, while its activity was higher than the D-galactose-treated group (NC) (Fig. 1).

**SOD enzyme**

The analysis of variance of the obtained data showed that the activity of SOD enzyme in the D-galactose-induced mice was significantly decreased compared with the control group (p < 0.01), based on the Dunnett test, where as the activity of SOD in the PC, P1, and P2 groups was significantly higher than the D-galactose group (NC); however, the activity of SOD was lower in all four groups in comparison with the control group (Fig. 2). In all groups, the activity of CAT was higher in serum samples. An increase in the activity of serum SOD enzyme in the PC and P1 groups was approximately 2.5 folds higher than the D-galactose-treated group (NC). Correspondingly, the activity of SOD was 2 folds higher in the P2 group when compared with mice induced by D-galactose (NC). The activity of SOD in the P2 group was lower than the P1 group, and its activity was higher in the PC group compared with the P1 group (Fig. 2).

**MDA levels**

The analysis of the obtained results showed that treatment with D-galactose (NC) caused a significant increase in liver and serum levels of MDA (p < 0.01), based on the Dunnett test, which showed the highest amount in the liver sample of the D-galactose-treated group (Fig. 3). Compared with the control group, the MDA level in the PC and the peptide groups, P1 and P2, was decreased in serum and liver homogenates (Fig. 3). The concentration of MDA was nearly the same in the PC and P1 groups, while MDA level was higher in the P2 group than that of the PC and P1 groups (Fig. 3).

**Assessment of blood pressure**

The in vivo antihypertensive effect of the HL-7 and HL-10 peptides was evaluated through sub cutaneous injection of peptides to mice and eventually the measurement blood pressure by tail cuff pressure measurements. The antihypertensive effect on peptides HL-7 and HL-10 was measured over a 24-h period and the greatest decrease was associated with 8 h after injection (Table 1). The results showed that the induction of hypertension by DOCA-salt was performed effectively, so that in all animals with hypertension, systolic blood pressure (SBP) was higher than 145 mmHg (Table 1). Before and after the injection, control group had no effect on the values of the SBP and DBP. The results showed that an subcutaneous injection of the HL-7 and
HL-10 peptides at doses of 2, 5 and 15 mg/kg BW caused a significant decrease in blood pressure in mice with hypertension compared with the control group (p < 0.01). The highest reduction was related to the HL-7 peptide, so that at doses of 2, 5 and 15 mg/kg BW, the mean arterial blood pressure (MAP) was decreased by 11 mmHg, 31 mmHg and 40.47 mmHg, respectively (Figure S2). Before the injection, the values of the SBP and DBP were 158.1 ± 8 mmHg and 129.0 ± 3 mmHg, respectively in the HP1 group (a group supposed to receive the HL-7 peptide at a dose of 15 mg/kg BW) (Table 1). The values of the SBP and DBP were decreased to 118.3 ± 4 mmHg (−39.8 mmHg) and 88.5 ± 6 mmHg (−40.8 mmHg), respectively (Table 1 and Fig. 4). The values of the MAP in the P2 peptide groups at doses of 2 mg/kg BW (LP2), 5 mg/kg BW (IP2) and 15 mg/kg BW (HP2) reached 128 mmHg (−8 mmHg), 118 mmHg (−18.3 mmHg) and 104.1 mmHg (−21.93 mmHg), respectively, which were greater than that of the PC group at a dose of 5 mg/kg BW [113 mmHg (−24.5 mmHg)] (Figs. 4 and 5). The HL-10 peptide at doses of 5 and 15 mg/kg BW showed a great antihypertensive activity very close to 5 mg/kg BW captopril (Figs. 4 and 5).

**Discussion**

Oxygen reactive species (ROS) cause lipid peroxidation and subsequently damage to vital intracellular components, including proteins REF (Related Elongation Factor). Oxidative stress is increased as living organisms become aged; hence, the use of antioxidants is necessary in order to reduce the harmful effects of oxidative stress associated with aging [19, 20]. To date, no research has been established to investigate the activity of antioxidant peptides extracted from the scorpion venom against oxidative stress. Hence, in this study, D-galactose-induced mice was used to evaluate the antioxidant activity of the extracted peptides namely HL-7 and HL-10 from *H. lepturus* scorpion venom. The results showed that the activity of CAT and SOD enzymes was decreased significantly in D-galactose-induced mice when compared with the control group (p < 0.01), while the level of MDA, as the product of lipid peroxidation, was increased in the D-galactose-treated groups (Figs. 1 and 2).
CAT REF. CAT reacts with H$_2$O$_2$, neutralizes the oxygen radicals produced by balancing between the production and the elimination of reactive oxygen species. This enzyme is capable of eliminating superoxide radicals and oxygen [5]. In this study, the HL-7 and HL-10 peptides prevent a decrease in the activity of CAT and SOD both in the serum and liver of D-galactose-induced mice. The HL-7 peptide had a higher rate of antioxidant and anti-aging effect in comparison with the HL-10 peptide. A number of studies have shown that the antioxidant activity of peptides can be attributed to the presence of the high numbers of hydrophobic amino acids [24]. Research has shown that the main ingredient in bee venom is a 26-amino acid peptide called melittin. This peptide was extracted by high-performance liquid chromatography (HPLC). The results showed that melittin was the main compound in the venom, which caused high antioxidant properties in the bee venom (Apis dorsata) extract. Therefore, bee venom extract can have potential applications in cosmetic products [25]. Reports have shown that animal venoms have a high selectivity for molecular purposes and consequently potential therapeutic properties due to their enzymes, proteins and bioactive peptides. Hossam Ebaid et al. (2014) found that Samsum ant (Pachycondyla sennaarensis) venom was a powerful antioxidant agent that scavenged oxygen free radicals and thus neutralized CCL4-Induced Nephrotoxicity in vivo [26]. In the present study, due to the high hydrophobicity of the HL-7 peptide (42%) in comparison with the peptide HL-10 (30%), the antioxidant activity of the HL-7 peptide was more pronounced over the peptide HL-10. In line with this, studies have indicated that there is an inverse relationship between antioxidant potency and the molecular weight of peptides. In the present study, the HL-7 peptide possessed a lower molecular weight (927.30 Da) and a higher antioxidant activity compared with the HL-10 peptide (1161.41 Da).

In our previous study, the antihypertensive effect of the HL-7 and HL-10 peptides was reported in vitro, and the IC$_{50}$ values of those peptides were 9.37 μM and 17.22 μM, respectively. The results of the molecular docking confirmed the experimental results and showed that both peptides, as competitive inhibitors, inhibit ACE by binding to the active sites of the enzyme [15]. In order to test whether the previous report can be replicated when the HL-7 and HL-10 peptides are used in vivo, we applied both peptides in DOCA salt-induced mice model to monitor their potency and ability in the reduction of the blood pressure. We also compared the antihypertensive potentials of peptides with captopril, which is considered a well-accepted drug against hypertension. Our findings showed that the HL-7 and HL-10 peptides resulted in a significant decrease in the blood pressure in hypertensive mice compared with the control group in a dose-dependent manner. The highest reduction was found in the MAP at doses of 2, 5 and 15 mg/kg BW of the HL-7 peptide (Figure S2). This result is valuable because the MAP values of mice treated with the HL-7 peptide were significantly lower than captopril at a dose of 5 mg/kg BW. Mice treated with the HL-10 peptide at doses of 2, 5 and 15 mg/kg BW, exhibited a lower change in the blood pressure when compared with the control mice which received captopril and those treated with the HL-7 at three doses of 2, 5 and 15 mg/kg BW (Figs. 4 and 5). An isolated peptide from the venom of Tityus serrulatus scorpion (peptide T) was recognized as the first peptide with bradykinin-potentiating activity [11]. It has also been reported that the bradykinin-potentiating activity of peptide K12 isolated from the venom of Buthus occitanus scorpion is probably due to the inhibition of ACE...
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Conclusion

In this study, the in vivo antioxidant and antihypertensive effects of the HL-7 and HL-10 peptides were evaluated on mice induced by the administration of D-galactose and DOCA salt, respectively. The results showed that both peptides, as antioxidant agents, increase the activity of antioxidant enzymes (CAT and SOD) and reduce MDA levels through the upregulation of antiaging factors in mice treated with the HL-7 and HL-10 peptides. Also, the measurement of the blood pressure implicated that both peptides had a higher rate of antihypertensive activity in comparison with captoril in hypertensive mice. Hence, the HL-7 and HL-10 peptides can be considered valuable candidates for the future drug design.

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Declarations

Conflict of interest Zahra Setayesh-Mehr, Leila Vafadari Ghasemi and Ahmad Assoodeh declare that they have no conflict of interest.

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